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Chiara Beneduce
Marta Bertolaso *Editors*

Personalized Medicine in the Making

Philosophical Perspectives from Biology to Healthcare

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Foreword: The Social Trends Institute

The Social Trends Institute (STI) is a nonprofit international research center dedicated to fostering understanding of globally significant social trends. People and institutions that support STI share a conception of society and the individual that commands a deep respect for the equal dignity of human beings, and for freedom of thought, as well as a strong desire to contribute to social progress and the common good. To this end, STI organizes Experts Meetings around specific topics in its areas of priority study and brings together the world's leading thinkers, taking an interdisciplinary and international approach. Currently, these priority research areas are family, bioethics, culture and lifestyles, governance, and civil society. Findings are disseminated to the media and through scholarly publications. Carlos Cavallé, Ph.D., is president of the Social Trends Institute. Founded in New York City, STI also has a delegation in Barcelona, Spain.

This volume, *Personalized Medicine in the Making: Philosophical Perspectives from Biology to Healthcare*, is the result of one such Experts Meeting held in Rome in February 2020, under the academic leadership of Marta Bertolaso and Chiara Beneduce. The meeting explored the concept of "personalized medicine" from a multidisciplinary point of view: social sciences and humanities were particularly involved to support scientific knowledge and practices related to a personalized approach in medicine.

The results of the research carried out in view of the abovementioned Experts Meeting are presented in this book. Without endorsing any particular viewpoint, STI hopes that as a whole, the contributions collected in this volume will deepen readers' understanding of the concept of "personalized medicine."

Barcelona, 2020 Tracey O'Donnell

Acknowledgments

The editors want to thank the Social Trends Institute (www.socialtrendsinstitute.org) for its generous financial and organizational support, which made possible the Experts Meeting "Personalized Medicine: A Multidisciplinary Approach to Complexity" (Campus Bio-Medico University of Rome, February 2–4, 2020). The present volume is based on the papers collected and extensively discussed during that conference.

Introduction

A Title as a Reading Guide

Selecting a title for a collective volume can be a hard task for editors. The title must properly reflect the volume's contents and aims, be as comprehensive as possible, and draw readers' interest. The choice of the title for the present volume has been a long journey, which would have not been possible without the support of every single scholar contributing to the book and to the discussion we had during the conference on which this volume is based.[1] The papers contained in this collection enter into greater detail regarding what constitutes "personalized medicine." The introductory summaries at the beginning of each book's section and the papers' abstracts will help the reader follow the papers' and sections' main lines of reasoning. This introduction aims to explain the major ideas implied by the book's title: *Personalized Medicine in the Making: Philosophical Perspectives from Biology to Healthcare*. In this way, we hope to show the main goals of our conference and book project on "personalized medicine" as a whole.

Personalized Medicine in the Making

It seems impossible to discuss "personalized medicine" without acknowledging its mutability. The features associated with "personalized medicine" are in constant interaction with new scientific and technological discoveries, changed social problems and needs, and further conceptual investigations. Thus, there is no standard, precise, definition of "personalized medicine." While great potential is attributed to personalized approaches in medicine, several key challenges have emerged. In other words, "personalized medicine" is a concept continuously *in-the-making*; it is

[1]The conference "Personalized Medicine: A Multidisciplinary Approach to Complexity" took place in Rome, at Campus Bio-Medico University, on February 2–4, 2020. Here the presentation of the conference from the website of the Social Trends Institute (STI). https://www.socialtrendsinstitute.org/expertsmeetings/bioethics/personalized-medicine-a-multidisciplinary-approach-to-complexity (last consulted on April 12, 2020).

a concept whose meanings, limits, potentialities, and challenges are constantly in question. The papers collected in this volume acknowledge this mutability, while at the same time identifying common themes and ideals as well as challenges facing "personalized medicine".

Rather than giving inventories of problems and shifting agendas, what we wished to work on was a wider reflection on the theoretical premises, frameworks, and tools of personalized medicine. In other words, the question we wanted to address was what are *the conditions for* an accountable personalization of treatments and healthcare policies. This reflection on theoretical foundations for personalized medicine will emerge in detail throughout the introductory summaries at the beginning of each section and from the single collected papers. We sum up central themes here.

A central theme of the papers in this volume is that a systemic and relational epistemology is required when dealing with the intrinsic complexity of living systems, from their biological to their social manifestation and actualization (see also, Green 2017; Bertolaso 2013, 2016; Leonelli 2015; Donati 2012). This means that (1) temporal dynamics and contextualization at the biological level are fundamental to understanding, treating, and, when possible, curing diseases. As the social dimension is concerned (2), a systemic and relational epistemology requires us to look at persons not in individual terms but as relational beings. The attention to both contexts is key to implementing personalized medicine effectively, starting from biomedical science and up to the development of personalized-medicine-oriented technologies and healthcare policies.

As for (1), recent research has demonstrated how time and contextual factors are key to understanding and treating complex diseases (Bizzarri 2018). Contributions collected in this book, especially the ones centered on biomedicine, point in this direction. An effective personalized approach should consider "disease as a 'historical' process, in which different spatially and timely distributed factors interact each other in a complex, non-linear way".[2] An effective personalized approach cannot ignore the interplay between biological determinants and personal life events taken as a nonlinear, complex process.

As for (2), what also emerges from our volume is that a person's historicity is made up of three dimensions, which should be seen in an integrated way: the genealogical one (our genetic setup, personal biographies, etc.); the specific roles and circumstances we live in and interact with during life, which shape our epigenetics (e.g., geographical conditions and food); and the contextual dimension (including how values, social, and cultural factors influence personal and collective behaviors and choices) (see also Bertolaso and Rocchi 2020; Bertolaso 2016).

When taking into account the integrated interplay of those dimensions, a key theme is that the ideal of "personal" in personalized health is essentially relational. That is to say, successful or effective "personalized" medicine cannot ignore that the person is a relational entity; or, at both the biological and social level, complex

[2]This quotation appeared in the conference version of the paper by Bizzarri et al. in this volume.

relationships within and between a person and their environment shape health outcomes. Attention to these relations is key to effective prevention efforts and increases the effectiveness of treatments.

Contextual factors, historicity, and relational dimension are essential theoretical categories for building more solid personalized-medicine approaches for the future. This is what, in one way or another, the papers collected in this volume help us to claim from several viewpoints: biomedical research (Anya Plutynski; Guglielmo Militello & Marta Bertolaso; Maël Montévil; Mariano Bizzarri et al.; Julia Tinland; Laura Dugo et al.); biomedical technologies (Sara Green et al.; Francesco De Pretis et al.; Edwin Morley-Fletcher; Liesbet Geris); and the ethical, social, and economical implications of personalized healthcare strategies (Xavier Guchet; Silvia Caianiello; Antonella Ficorilli; Maria Rosaria Brizi; Maria Sophia Aguirre; and Roger Strand).

Philosophical Perspectives

The concept of "personalized medicine" is one undergoing constant revision. This has clearly emerged in the past years, with a growing literature on personalized medicine that was not only strictly biomedical.[3] The contribution offered by this volume to the ongoing reflections on the concept of "personalized medicine" involves a clearly programmatic philosophical perspective, since the aim was to provide theoretical foundations for implementing personalized medicine. *Philosophical perspectives* is here intended in a broad sense. Our investigation is not only an ethical or bioethical inquiry into personalized medicine. Ethics is only one of the perspectives and expertise involved in this volume. Philosophy of science (philosophy of medicine and biology in particular) is the main branch to which most scholars contributing to this volume belong. In addition, natural and social scientists (biologists, food scientists, engineers, economists, and lawyers) were asked to contribute to this volume and were invited to apply a "philosophical" approach to their papers, by proposing a critical – broader – thinking of the empirical data coming out from their research.

This leads us to remark an important aspect of the volume's interdisciplinarity. The interdisciplinarity was among the first principles inspiring the project underlying this volume. Indeed, the original title of the conference on which the volume is based was *Personalized Medicine: A Multidisciplinary Approach to Complexity*. Both in the conference and the volume, we interlaced recent viewpoints on "personalized medicine" from different domains. This is because "personalized medicine" is a cross-disciplinary enterprise. Indeed, a central insight growing out

[3] Several examples can be made here, but see the publications by Vollman et al. (2015), Guchet (2016), Schildmann and Vollmann (2017), and Prainsack (2017) to savour from how many different perspectives, at the cross-road with biomedicine, the concept of "personalized medicine" can be approached.

of this conference was that *any* discussion on "personalized medicine" should involve, at the same time, biomedical sciences, techno-sciences, social sciences, and humanities. In other words, science and technology are not enough when dealing with the in-the-making concept of "personalized medicine." Social sciences, such as law and economics, and humanities, particularly philosophy (ethics and philosophy of science), are key to inquiring into theoretical foundations. Inquiry into such foundations – the "why" and not simply the "how" of personalized medicine – is necessary to guide scientific and technological research and practices.[4]

Personalized Medicine, Personalized Technology, and Personalized Healthcare Strategies

Science, technology, and healthcare strategies and policies, together with philosophical readings of them, are – or should be – intertwined when considering personalized medicine.[5] The last part of the title, "From Biology to Healthcare," helps to stress this comprehensive approach required to understand personalized medicine and reflects the division of our volume into three main sections: "Personalized Medicine: From Biology to Clinics," "Personalized Technology: From Epistemology to Data Management," and "Personalized Healthcare: From Ethics to Policies." This division and the sections' titles reinforce the interdisciplinary ideas growing out of our conference and book project as a whole. In particular, the labels "personalized medicine," "personalized technology," and "personalized healthcare" help us to highlight the specific contribution that a relational epistemology is able to offer in understanding biological and clinical actual or potential advancement, assessing relevant frameworks for technological innovation, and investigating effective impact of healthcare policies.

The volume offers a new contribution to the longstanding debate over how to define personalized medicine, and how best to conceptualize this notion. Alternative and/or complementary terms have been, in fact, attached to the lemma "medicine" as to better express the idea of "personalized medicine" (e.g., "individualized medicine,", "precision medicine," and the famous idea of "P4 medicine" – predictive, personalized, preventive, and participatory medicine).[6] Some suggest that we ought to jettison talk of "personalized" medicine altogether. Yet, keeping the term "personalized" can have a certain advantage, which we support in this book. It still makes sense to keep the term "personalized" if it implies and includes the meaning of "person" as a relational entity, as described above in (2).

[4] An invitation to integrate "the Social Sciences and Humanities with Science and Engineering" came expressively from the European Commission, about Horizon 2020. See Gilbert (2016).

[5] See above in this introduction.

[6] On definitions of "personalized medicine" and discussions on the definitions of "personalized medicine," see for example, Shleidgen et al. (2013), Redekop and Mladsi (2013), Gamma (2016), De Grandis and Halgunset (2016), and Lemoine (2017). Several of the papers collected in the present volume refer to (possible) definitions of "personalized medicine" and to the debate on those definitions.

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Part I

Personalized Medicine: From Biology to Clinics[1]

The contributions collected in this first section underline the relevance of reading "personalized medicine" against the background of the living being's complexity. Far from being based only on the patient's genomic profile, personalized medicine should be understood in the framework of the interplay and integration of multiple aspects, such as temporality, context, and interrelations of biological, biographical, social, and ethical factors. Philosophers and scientists contributing to this section address some aspects of this theoretical, relational, background as to strengthen personalized medicine's conceptualization and efficacy. In her paper (Why precision oncology is not very precise (and why this should not surprise us)), Anya Plutynski inquires the features and future of precision oncology by underlining the challenges implied by cancer's heterogeneity and complexity. Cancer is also the focus of the second paper of this section (The complexity of tumor heterogeneity: Limitations and challenges of the pharmacogenomics in cancer). Guglielmo Militello and Marta Bertolaso address the topic of tumor heterogeneity by considering its epistemological complexity and the practical consequences of such complexity for personalized medicine. Epistemology of biology, broadly intended, is instead the perspective by which Maël Montévil's paper (Conceptual and theoretical specifications for accuracy in medicine) approaches the concept of "personalized medicine" for this volume. Montévil stresses the central role of historicity of biological norms to reinforce epistemological foundations of accuracy and, consequently, precision in medicine. By going back to the case study of oncologic diseases and their treatments, the paper by Mariano Bizzarri, Andrea Pensotti, Alessandra Cucina, Noemi Monti, and Valeria Fedeli (Personalized treatments: Where patient's history and biological background meet) highlights how personalized cancer treatments should consider the multilevel interactions and the context- and time-dependent dynamics which make the tumor phenotype unpredictable from the tumor genotype. On these bases, personalized medicine should work according to the spacing-frame and timing-frame of each pathological condition. Therefore, "personalizing"

[1]The introductions to the volume's sections are by Marta Bertolaso and Chiara Beneduce.

medicine requires considering the complex interaction between biological traits and life events. Julia Tinland's paper (Personalised prevention: Increasing or decreasing over-medicalisation, overdiagnosis and overtreatment?) addresses two further case studies, one from psychiatry and, another, from oncology. The paper analyzes limits and potentialities related to a personalized approach in prevention. While the development of personalized prevention has been the target of serious criticisms due to the risk of overmedicalization, Tinland studies some epistemological strategies for de-escalating the risk of overdiagnosis related to it. The first thematic section of this volume closes with a viewpoint on personalized medicine and nutrition by Laura Dugo, Andrea Pensotti, and Vincenzo Fogliano (Making feasible personalized nutrition: Between science and daily habits). The authors identify technological devices and knowledge of biological data as key-elements for the development of a promising future for personalized nutrition. However, based on the multiple factors involved in the nutrition process, the authors stress the complex relationship between food and health, ultimately concluding that the success of personalized nutrition strongly depends on the human factor, i.e., the user motivation.

This section identifies the relevance of historicity, contextualization, and relationality as essential theoretical categories in order to understand health and illness. From biology to clinics, from medicine to nutrition, curing diseases in a personalized way thus requires a more attentive focus on the "relational" dimensions of the person.

Why Precision Oncology Is Not Very Precise (and Why This Should Not Surprise Us)

Anya Plutynski

Introduction: What Is Precision Oncology?

In 2015, President Obama launched his "Precision Medicine Initiative," an ambitious effort at funding research that would ensure that patients receive care "tailored to them". Though Obama granted that physicians have always sought to tailor care to individual patients, he argued that this initiative would launch a genuinely new kind of medicine. Care might be tailored to each patient in light of their genomic profile and personal characteristics, or perhaps, molecular and genetic characteristics of their particular disease.

The latter is seen as an especially promising avenue of research for cancer. Cancer is typically described as a "genetic" or "genomic" disease, in light of the fact that cancers are caused (in part) by genomic alterations that alter pathways in the cell governing cell birth and death. Each individual's cancer has a unique suite of genomic changes, which in principle could help physicians predict the course of disease, or anticipate response to treatment. Indeed, several molecular biomarkers are already standardly used to make decisions about treatment, or predict risk of recurrence (NCI 2019). So, the ideal of precision oncology is often taken to be the model for precision medicine more generally.

In 2015, Francis Collins, director of the NHGRI, (National Human Genome Research Institute), Collins, and his colleague, Varmus, commented on Obama's initiative: "Oncology is the clear choice for enhancing the near-term impact of

Dedicated to Karola Stotz

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precision medicine [. . .]. Research has already revealed many of the molecular lesions that drive cancers, showing that each cancer has its own genomic signature, with some tumor-specific features and some features common to multiple types" (Collins and Varmus 2015, 793).

As this passage suggests, advocates of precision oncology make the following fundamental assumptions: each individual's cancer has a distinctive genomic profile – or set of mutations particular to that disease. These mutations are called *drivers* of cancer – they play central roles in the origin and process of disease progression. Such genomic features and their products can, potentially, be used as biomarkers. Many have argued that such biomarkers will eventually replace diagnostic criteria such as site of origin, node status, size of tumor, or degree of differentiation of cells, in service of more accurate prognoses, and targeted (and less harmful) treatment. Molecular features are often characterized as more "precise" than the pathologists' assessments of grade and stage. Some cancer researchers speak of gross clinical features of cancer as soon to be, if not already – relatively obsolete.

This idea is not new; indeed, the hope for precision oncology was a deliberate outcome of investment in integrative research on cancer genomics and bioinformatics. In 2011, an ad hoc Committee of the National Research Council was convened to host a two-day workshop on the future of molecular medicine, and published *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease* – mapping out a plan for building an "Information Commons" and "Knowledge Network" for a new, "modernized" taxonomy of disease (NRC 2011) – one that draws upon the tools of "big data" and artificial intelligence. This more modern taxonomy would – in principle – remove any room for subjective or value-laden judgment in physicians' diagnoses, or patients' decisions (Table 1).

Table 1 This table defines and explains key terms in the chapter

Key terms	
Biomarkers	Measurable properties of a patient believed to be predictive of a particular clinical status. In cancer, biomarkers may be the presence or absence of a particular mutation, or, protein levels indicating the activity of a particular gene; "biomarker endpoints" are measures of endpoints used in clinical trials as a proxy for the actual clinical endpoint. Thus, "progression free survival" (PFS) is sometimes used as a "biomarker" for "overall survival" (OS), to reduce the time and cost needed to assess the relative efficacy of new treatments.
Functional categories of biomarkers	The U.S. FDA and NIH BEST (Biomarkers, Endpoints and other Tools) document (2015) identify seven: diagnostic, monitoring, assess pharmacodynamics and/or response to drug, predict which treatments are likely to benefit a particular patient, determine prognosis, detect safety, or assess susceptibility/risk. Hey et al. 2019b identify an eighth function: acting as surrogate measure or substitute for direct measure of outcomes.
Biomarker validation	Formal assessment showing that a measure or biomarker is a reliable indicator of patient's clinical status or outcome.

(continued)

Table 1 (continued)

Key terms	
Driver genes	Genes, mutations to which are thought to play an important role in cancer onset and progression
"p-medicine"	Lemoine's (2017) term for forms of medicine that link biomarkers to highly effective, specific therapies, through innovative means – including shared repositories of data, such as genomic databases, or a biological network.
Precision oncology	The use of molecular markers (including but not limited to presence and absence of particular mutations) in service of stratifying patients, diagnosis, prognosis, and tailoring therapy to molecular features of the cancer itself.
Adaptive trials	An adaptive clinical trial is a clinical trial that evaluates a medical device or treatment by observing participant outcomes on a prescribed schedule, and modifying parameters of the trial protocol in accord with those observations.
N-of-1 trials	In this case, a single patient is the entire trial. Random allocation can be used to determine the order in which an experimental and control intervention are given to a patient, a "randomized controlled" N-of-one trial. In cancer, a tumor may be sequenced, whole exome, genome, and/or RNA expression analysis, this information is analyzed to identify the distinct drivers in that patient's tumor, and then a search is conducted drugs known to target those drivers. Drugs are tested on the patient's tumor sample, either in cell culture or after being implanted into a mouse model (technically called a patient-derived xenograft), and if treatment is effective, it may be investigated in the patient, serially, over time.
Mabs	These fall in the class of "biologics": Monoclonal antibodies: drugs that target proteins, and in particular, antibodies. In the case of cancer, they bind to specific antigens associated with cancer cells, in order to induce immune response, or slow replication of cells, as in the case of trastuzumab for HER2neu breast cancer.
TKIs	Also fall in the class of biologics: Tyrosine kinase inhibitors inhibit the activity of kinases that enable signaling transduction – thus halting the activity of certain pathways associated with cancer. For instance, imatinib is a first line treatment for CML patients with a particular chromosomal abnormality.
"Accelerated" approval for "breakthrough" drugs	"Accelerated" approvals by the FDA are meant to expedite access to a drug, based on evidence of impact on a surrogate endpoint rather than evidence of impact on the actual clinical benefit the drug is intended to provide; "breakthrough" processes expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).
Curse of dimensionality	The greater the number of molecular biomarkers that influence whether a treatment will be effective, the higher the dimensionality of the space of possible treatment decisions (based on combinations of these drug-biomarker pairings), requiring many more observations to test for effectiveness.

There are many questions one could raise about this ideal for medicine. This paper will focus on how effective precision oncology has been so far, as well as whether we ought to expect the promises made on behalf of precision oncology to be borne out in the future. The philosophical analysis is informed by a review of the scientific literature, analyses of the aims and scope of precision oncology by philosophers, historians, and social scientists, as well as insights from interviews with researchers and clinicians, who work both in basic science behind and clinical applications of precision oncology.

Part of the challenge of assessing the effectiveness of precision oncology is that the term is not used consistently. Some accounts are so permissive that they include any and all novel methods that draw upon molecular data. Others limit precision oncology to the use of NGS (next generation sequencing), to guide targeted therapy (Prasad and Gale 2017). This latter definition is so restrictive that it would exclude anything developed prior to roughly 2008, effectively ruling out some of the most famous exemplars of successful precision oncology (e.g., Tamoxifen, Herceptin).

Given this ambiguity, several philosophers of medicine have weighed in on how best to define "p-medicine" more generally (Lemoine 2017; De Grandis and Halgunset 2016). Lemoine uses "p-medicine" as a general category for a variety of expressions ("personalized," "precision," "stratified," "individualized," "P4," "P5") that have been used in service of either imagining the future of medicine, or characterizing exemplary instances of success in "molecularized" approaches to medicine. Precision oncology is only one instance of p-medicine, but arguably inherits from p-medicine some of the same ambiguity. Lemoine argues that we ought to define "p-medicine" by looking to exemplars of "what has been achieved, not what we should consider it is 'by nature'" (2017). He takes mabs (monoclonal antibodies) as archetypal cases of success in p-medicine, not only because they are one of the most commonly cited exemplars, but also because they are the only case of a molecularly targeted therapy not "limited in principle to a narrow range of pathological conditions" (Lemoine 2017, p. 19).

I agree with Lemoine's emphasis on concrete exemplars of success, and in principle, I agree that if our aim is defining "p-medicine" generally, we ought to select exemplars that are not "limited to a narrow range of conditions." However, one distinctive aim of precision *oncology* is designing therapies or prognostic tools that are beneficial to patients in light of their cancers' unique molecular features. This creates a special challenge: both for defining precision oncology, and relatedly, for assessing effectiveness. Almost by definition, we should not expect a mode of intervention to target a wide range of conditions in precision oncology. Indeed, the wider range of conditions an intervention targets, the less it ought to serve as an instance of precision oncology.

The fact that precision oncology in principle involves developing prognostic tools and treatments unique to each patient yields a puzzle, also, in determining how we ought to measure "success" of such methods. Exactly because of the uniqueness of each cancer, we cannot and should not expect to conduct large randomized trials of novel prognostic tools or therapies. This has led to the controversial adoption of novel trial designs by the FDA (U.S. Food and Drug Administration) (Khan 2018),

which, while getting drugs to market faster and thus arguably benefiting patients more quickly, also raise a suite of both epistemic and moral questions about whether such trials provide sufficient evidence of benefit. While small trials of several hundred patients with shared molecular features are problematic in themselves, "N-of-1" trials raise further questions about generalizability. In other words, the challenges facing how best to define precision oncology are intertwined with the problems of how best to measure success, and adjudicate failures.

For the purposes of this paper, I'll adopt a middle ground that is (hopefully) neither overly inclusive, nor so exclusive as to rule out by definition some of the most celebrated cases. The aim of precision oncology is to identify and deploy genetic and molecular features of cancer in service of diagnosis, prognosis, and treatment. By identifying particular markers of molecular features of the disease in each cancer patient, researchers and clinicians hope to better predict likely disease course, and tailor treatments to each patient.

This roughly captures the typical characterization of the aim of precision therapy, as providing "the right drug, at the right dose, for the right patient, at the right time".[1] Carolyn Hutter, the former director of the Cancer Genome Atlas Project (TCGA), explained that molecular characterization of cancer may be used for two main ends: to distinguish aggressive from non-aggressive forms of disease, and, in the ideal case, there will be "that perfect mutation that informs the drug to give, and the drug to not give." (Hutter interview July 27, 2018). The aim of this paper is to consider why this goal has been so elusive, focusing on two key case studies: Avastin and TAILORx.

Some Preliminaries: Cancer Complexity and the Goals of Precision Oncology

The scientific and practical challenges facing both how best to measure and classify molecular features of cancer, and translate results to clinical medicine, are more daunting than the more optimistic visions of precision oncology suggest. Below, I identify the sources of such challenges, starting with the massive complexity and dynamic features of cancer itself, the "curse of dimensionality," and then turning to practical challenges facing biomarker identification and validation. Problems of reversal of "fast tracked" drugs, I will argue, are likely to plague much of this research.

First, however, it's important to note that cancer progression is a complex and dynamic process involving many factors in interaction. Cancers are not homogeneous, but heterogeneous populations of cells. Many tumors contain multiple

[1] Indeed, this slogan has even been deployed as a label for a clinical trial, the "Right Drug, Right Dose, Right Time Using Genomic Data to Individualize Treatment Protocol (RIGHT Protocol)" a study using pharmacogenomic testing to develop electronic health records infrastructure to deliver clinical decision support and study the effects of integrating preemptive pharmacogenomics testing into clinical practice (https://clinicaltrials.gov/ct2/show/NCT03803293).

subclones, and over time, these lineages of cells evolve in response to novel challenges (e.g., lack of oxygen supply), akin to branches in the tree of life, enabling invasion and metastasis, as well as the emergence of resistance to therapy (Greaves and Maley 2012). This makes reliance on a single biomarker, sampled at a single point in time, problematic as the sole criterion for prognosis, or treatment decisions. Thus, many clinicians and researchers suggest that multiple biopsies or samples of cells be taken over the disease course.[2]

Moreover, interactions among both molecular and structural features of a tumor shape and are in turn, shaped by, features in the tumor microenvironment over time (Bissell and Hines 2011). While the very concept of the tumor microenvironment is one in flux (see, Laplane et al. 2018), it's clear that a variety of factors apart from the cancer genome contribute to how a cancer progresses, and in turn, how likely a patient is to respond to targeted treatment. In addition, patients' age, treatment history, sex, stage of life (e.g., before or after menopause), metabolism, and other clinical characteristics, are likely to shape their response to therapy. Attention to these complex causal contributions to a cancer's evolution and interaction with its microenvironment is absolutely essential to developing lasting, effective therapies. In sum, cancer progression is not fully determined by static, fixed, molecular properties. Molecular features vary in their expression within the same tumor, and over time. Tumors with the same expression profiles can have different responses to the same drugs, both because of differences in the tissue or organ affected, presence or absence of further molecular features, and much else.

Drugs effective for some cancers with a particular genetic profile may also not be as effective in tumors arising in a different organ or tissue – for instance, a drug effective in skin may not be effective in the pancreas. Differences in non-genomic features of these tissues affect effectiveness of targeted therapy. Tissue microenvironment – e.g., the presence or absence of fibroblasts, blood supply to the stroma, etc. – can affect whether and how therapies arrive at the target. In sum, it should not surprise us that responses to therapy vary; and that treatment success is not uniform for patients who share a biomarker sampled at a single time. The presence of a shared biomarker is only one of several predictive factors in successful response to drugs targeting a specific molecular pathway.

It's important to emphasize also that gene expression is a matter of degree – and, given the heterogeneity of cells in a tumor, can vary in space and time. Yet, for the purposes of prognostic tests or treatment decisions, cut-off points for measures of expression of proteins must be chosen, either to stratify patient's risk of progression, or likelihood of benefiting from a particular drug. Choosing level of expression for such cut-offs thus requires complex processes of validation, and may also involve value-laden judgments about risk and benefit of over- and under-treatment. Line drawing problems in diagnosis and treatment decisions, in other words, will not be

[2]See also, Green et al. (in this volume), where a potential drug match for an organoid often leads to discussion at a tumor board meeting, as to whether the biopsy is sufficiently recent. To ensure acting on a match is warranted, they often need to re-biopsy patients.

eliminated by molecular profile data. Precision medicine is no less subject to the rule that variation is the norm in biology.

There are, indeed, many reasons apart from the complexity of cancer biology that precision oncology has not proven as effective in clinical practice as one might be led to believe in the light of its frequent mention in the news cycle. Some of these reasons have to do with "upstream" problems with the basic science, but many more have to do with the institutional organization of cancer research, and challenges facing translation. Initial sequencing of the cancer genome faced many challenges – from improving quality of the samples used, to improving read depth and coverage of sequencing,[3] to development of algorithms for analyzing the data in service of identifying actionable genes. Indeed, one core difficulty is that the very definition of what count as "actionable" genomic alterations varies substantially, making it difficult to implement large-scale genomic testing to enroll patients in clinical trials in the first place (e.g., Johnson et al. 2014; Meric-Bernstam et al. 2015; Schwaederle et al. 2015; Sholl et al. 2016). Drug design and testing is costly and (arguably) inefficient; most cancer drugs fail. Trial design is distinctive for therapies that are intended to target unique patient profiles, and even those that are approved by regulatory bodies run across many problems in translation (as in the Avastin case, discussed in some detail, below). In sum, not only is the genetics and biology of cancer prohibitively complex, but also the design and testing of precision therapies is enormously difficult, making "precision" as a goal elusive.

As we will see below, a central reason for the lack of uniformity of success has to do with *how we are assessing effectiveness*. Some of these are endemic to any research that is concerned with testing drugs that are intended to work for only small subpopulations of patients. But, some are problems with the design of trials, choice of endpoints, and consistency of tests for the presence and absence of biomarkers. For instance, critics of precision oncology have pointed out that early clinical trials often test an experimental group against a weak comparator that is infrequently used in practice (Tao and Prasad 2018), that many surrogates used as the end-point of clinical trials do not represent outcomes that are important for patients (Prasad et al. 2016), or, that clinical trials may use different levels of cut-off to designate molecular markers "present" or "absent", leading to inconsistent outcomes (Hey and Barsanti-Innes 2016). A further (but related) concern is whether clinicians are in a position to interpret results of commercially available screening tools, let alone apply such results to treatment decisions (Hey et al. 2019b).

It also deserves mentioning also that most patients are simply ineligible for many precision therapies as defined here; a recent study showed that only 5% of patients were eligible for treatment with precision therapies, out of over 500 whose cancers

[3]This criterion refers to the number of times a particular base position in the DNA is read during the sequencing analysis. The greater the coverage of a particular alteration, the more likely it is to be detected, which is especially important in tumor samples with low tumor content (where most cells in a biopsy or sample are not tumor cells, but stromal cells). By covering the same area of the gene fragment multiple times, the likelihood of picking up a variation of low allelic frequency is enhanced.

were tested (ECOG-ACRIN Research Group 2016). That is, a relatively small proportion of cancer patients have specific markers for which targeted therapies have been demonstrated to be effective.

In sum, there are good reasons to think that the "magic bullet" model is unlikely (by itself) to lead to lasting and effective treatments in cancer, especially for advanced (metastatic) disease. Even the most successful exemplars of precision therapies face problems with tolerance and lasting response to treatment. For instance, TKIs for CML (chronic myeloid leukemia) (tyrosine kinase inhibitors, such as imatinib, or Gleevec), targeting BCR-ABL1 fusion protein, have improved overall survival significantly – from 10-year OS from 10–20% to 80–90% in the last few decades. Yet resistance and intolerance to the drug is still a problem (Cortes et al. 2019).

Below, I consider two case studies in precision oncology that illustrate how heterogeneity, complexity, and dynamic interactions create a variety of challenges for implementing precision oncology. Yet, each new generation seem very much in the thrall of this picture of the future of cancer medicine. As Strand, and colleagues argue (in this volume), precision oncology as an imaginary or ideal seems to be far more at work here than the actual clinical practice of precision care. Perhaps more concerning, patients and families have been led to imagine that precision cancer care can and will be a panacea. This kind of optimism can be harmful – both to patients, and to the future of both upstream, and downstream, clinical research.

Two Case Studies: Avastin and TAILORx

Below I will consider two case studies in precision oncology: the approval and subsequent withdrawal of Avastin, and the recent TAILORx trial, and subsequent follow up. These cases illustrate both the limitations and potential successes of precision oncology.

First, Avastin received accelerated approval from the FDA in 2008, after a single, multi-center, open-label study showed improvement in progression free survival (PFS) for patients with HER2-negative metastatic breast cancer taking bevacizumab in combination with paclitaxel (Taxol) over Taxol alone (Miller et al. 2007). However, it was later withdrawn in 2011, when the evidence showed that while there was a statistically significant improvement in PFS (Progression Free Survival), there was no significant improvement in overall survival. Even after it was withdrawn, however, Medicare and Medicaid were approving payment for the drug. This case is illustrative of several challenges facing precision oncology, and the oversight and regulation of drug approval in the US.

Avastin's approval hinged upon improvements in PFS. When it was approved, there was no evidence that it would improve overall survival (OS). A recent metanalysis by Hey et al. (2019a), reviewed 52 studies of Avastin in patients with metastatic HER2-negative breast cancer, both before and after the FDA's accelerated approval. None found a significant association between PFS and OS. Of those 52 studies, only six showed statistically significant outcomes favorable to

the drug (namely, in PFS), but none showed overall survival benefit. Ten of these 52 studies were terminated, and in 14, trial results are unknown; one of these showed a statistically insignificant benefit in PFS in combination with another drug, but the toxicities were so significant that results did not indicate benefits to the drug. In other words, in multiple studies, with a total of 11,897 patient participants, there was no improvement in overall survival, and significant enough costs in terms of toxicities and quality of life to terminate a majority of trials. Arguably, this case shows a failure of oversight; though it also illustrates several challenges in designing and developing exactly this sort of targeted therapy.

First, while Hey et al. (2019a) argue that the FDA did use appropriate oversight in the sense that it withdrew approval when they should have, it seems well worth asking why as many as 37 trials with such nearly identical protocols were conducted between 2006 and 2009. Arguably, many more trials were conducted than were appropriate or necessary, given the minimal benefit demonstrated. Indeed, redundancy, or lack of coordination among researchers seems fairly common in precision oncology research (Carlisle et al. 2020).[4] This wastes valuable time, money, and arguably, causing potentially unnecessary harm (in the form of toxicities, or worth, early death), and unwarranted hope among participants in the trials. There is also a concern about either underreporting or inadequate reporting of toxic side effects, which preclude giving these drugs in combination with other therapies, for instance. Many trials prior to approval were discontinued, but it's not clear from the reporting of this data whether this was because of toxicity of the drug in some combinations with other therapies, or simply because of lack of evidence of benefit.

Second, in accelerated trials, approval for drugs often hinges on improvements in surrogate measures like progression free survival. But, several have raised concerns about whether PFS is a legitimate surrogate for outcomes that concern patients: namely, overall survival. Validating PFS as a surrogate for OS is difficult at best. Hey et al. (2019a) review the data, and show that even after seven clinical trials, it was unclear whether PFS was a good surrogate for overall survival in the case of metastatic breast cancer (BC). In principle, subsequent follow up for accelerated approval is expected to either validate PFS as a surrogate, or warrant removing the drug's approval. But, even though there is a mandate that the FDA conduct follow up research for accelerated trials, it seems that (a) there has not always been adequate follow up, given the rapid expansion of approval for drugs on the basis of these surrogate measures, and (b) it is not easy (or possible) to determine whether and if so, the surrogate is a valid measure of outcomes of interest. In this case, the follow up studies showed no benefit, and Avastin was withdrawn. But, even after withdrawal, Medicare and Medicaid was approving reimbursement for the drug.

[4]One reader suggested that this may be a consequence of the structure of incentives and institutional support for competitive grants for research on new drug's approval. There may be benefits in being the first institution or researcher to implement precision medicine, which make it more attractive to conduct (redundant) trials. Thanks to Green for this suggestion.

Even though the Avastin case is an instance of "success" in that it was (appropriately) withdrawn, there seems to be at least three kinds of concerns cases like this raise. First, there should have been more coordination of research, to avoid redundant or unnecessary trials. Second, there needs to be greater coordination of regulatory decisions and reimbursement decisions by Medicare and Medicaid. With greater investment in the process of translation to the clinic, this kind of organization of research could be more efficient, and ideally, less harmful. Third, the question of whether and why PFS is a valid surrogate ought to be considered in light of the widest array of relevant evidence, including the nature of the drug, and the disease. While PFS is often taken to be an unproblematic surrogate for OS, it seems that there is good reason to question this as a general rule.

Arguably, it's unsurprising that PFS was not a good surrogate for OS, particularly in the case of metastatic disease. Avastin targets one pathway, endothelial growth factor. In advanced solid tumors, there is likely to be a great deal of genetic variation – i.e., multiple lineages or subclones, and thus great potential for resistance to such drugs (Greaves and Maley 2012). Natural selection in response to a drug (for instance, in the case of antibiotic resistance) typically leads to a short-term response, followed by treatment failure. Targeting a single pathway is likely, by and large, to lead a cancer to return in a far more aggressive form. Particularly in a heterogeneous population of cells typical of metastatic disease, there will be ample variation available for natural selection, and thus ample opportunity for resistance to evolve. In this case, the response in the short term (PFS) may have been good, but overall response (OS) is likely to be poor. In short, these outcomes could have been predicted. Mathematical modeling of cancer's evolutionary dynamics has predicted responses such as these going back to the early 2000s (e.g., Nowak et al. 2004). If greater attention were paid to the evolutionary dynamics of advanced cancer, the outcomes of such trials could be predicted, and less confidence may have been placed in PFS as a proxy for OS. This could have saved thousands of women taking Avastin from unnecessary harm and unwarranted hope.

The second case study in some ways suggests a great benefit of genomic data, but in other ways highlights similar problems with oversight, translation, and the elusive benefit of genetic information. Using the 21-gene Oncotype DX assay (Genomic Health, Redwood City, CA), the recent Trial Assigning Individualized Options for Treatment (TAILORx) study demonstrated that the majority of women with ER+, HER2-negative, node-negative breast cancer derive no benefit from adjuvant chemotherapy (Sparano et al. 2018). In other words, they demonstrated that chemotherapy provides no benefit to 70% of women with early stage (node-negative, ER+, HER-2-negative) disease. The way the research study was framed in the news was that prior to the TAILORx study, many women were not receiving a benefit from chemotherapy; now, with greater understanding of the genetics associated with risk of recurrence, patients can avoid chemotherapy and its harmful effects, and clinicians can recommend treatment to only those patients who will likely benefit.

While this spin on the results of the trial seems very impressive, a closer look at the standard of care prior to the completion of TAILORx reveals a somewhat

more complicated story. Arguably, many of the women shown to benefit from the genetic assay would have opted out of chemotherapy anyway, and for good reason. In premarket studies, oncologists were already recommending the Oncotype-DX test as a way to urge women with low-risk profile to not take chemotherapy. That is, they were preferentially offering the test to women with low-risk disease – i.e., those who were ER+, node-negative, and HER2-neu negative – because oncologists knew already that such women were unlikely to benefit from chemotherapy. The test was used to provide patients with additional reassurance that chemotherapy was unnecessary. In other words, it was well known almost a decade prior to the TAILORx study that women with node-negative status, ER+ and HER2-neu profiles were at low risk of recurrence, and so oncologists were already not recommending chemotherapy for these patients (Oratz et al. 2007; Henry et al. 2009; Asad et al. 2008). Adjuvant! Online (Ravdin 1995), a program designed to generate treatment plans to women based on ER (estrogen receptor) status, age, node positive and negative status, and size of tumor, starting in the late 1990s, and early 2000s, would have already urged most women with node-negative cancer to opt out of chemotherapy, and opt either for surgery and radiation, or simply surgery and tamoxifen (Olivotto et al. 2005).

In sum, the genetic information was – more or less – redundant. So, while the TAILORx study is hailed as a celebrated victory for prognostic genetic testing, it is unclear whether it as a matter of fact led to any change in standard of care typical for practicing oncologists. Indeed, a recent review in NEJM (New England Journal of Medicine) showed that in terms of absolute risk of recurrence, imaging and other clinical data (stage, grade, patient age, ER status HER2-neu status) are *as if not more predictive of rates of recurrence*, and relative benefit of chemotherapy. Given that the test is expensive (approximately $4000 per patient in the United States), it's worth noting that imaging and histologic markers already available could be used to predict the overall chance of recurrence and ultimately obviate the need for the more expensive assay.

It is not surprising that the vast majority of node-negative, HER2-neu breast cancers are at lower risk of recurrence, and so that patients with this status are unlikely to benefit from chemotherapy. Such cancers were not expressing a protein that was known as early as the 80s to increase risk of recurrence. Indeed, anyone familiar with the development of genomic assays for cancer would already realize that the particular genes identified in the OncotypeDX assay were in fact identified as associated with some of the same risk factors associated with higher relative risk of recurrence well-known decades prior to the test: (e.g., one of the genes is associated with HER2-neu status, one of the best predictors of recurrence risk). According to Dialani et al. (2016), "combining imaging features (on mammographic, US, and MR images, whenever available) with tumor histologic grade and progesterone receptor and human epidermal growth factor receptor 2 status can reliably be used to identify tumors with high recurrence scores with a sensitivity of 89% and a specificity of 83%, thereby obviating OncotypeDX testing (Genomic Health) and thus potentially substantially reducing health care expenditures". A recent review of a subset of the TAILORx dataset showed that in terms of reduction of absolute risk, traditional

histologic and imaging data is equally as effective in predicting risk of recurrence and thus benefits of chemotherapy.

Upshots

Where do these case studies leave us? If, as some studies (Le Tourneau et al. 2015) suggest, the success of precision therapies is minimal, then why are so many scientists convinced of it potential? Are the successful cases unique? If so, what explains the relative success of these cases?

It seems clear that there are several central challenges facing precision oncology – not only with establishing and measuring effectiveness, but also, with regulation, design and implementation of research. First, arguably, the problem of precision oncology is a direct consequence of the complex and heterogeneous biology of cancer. As Shrager et al. (2019) characterize this problem, it's a consequence of what computer scientists call the "curse of dimensionality" problem. While this summary of the problem is somewhat oversimplified, it makes the nature of the fundamental epistemic challenge facing design and implementation of precision oncology very clear:

> Computer and cognitive scientists have long thought of problem solving in terms of the search for good solutions in a potentially very large space of possible solutions . . . Classically, this search space was not considered very large, so a fairly simplistic search strategy based on large clinical trials was effective. At the peak of the success of classical clinical trials, say 25 years ago, cancer was thought of as what might be called a "10 by 10" disease: there were ten types of cancer, corresponding to tissue of origin, crossed with roughly 10 types of chemotherapy. This way of thinking is represented by a 100-cell matrix . . . Each cell in this matrix represents a biomarker-treatment relationship which needs to be tested . . . and the search for the right treatment would involve conducting large, randomized trials for each of the ten chemotherapies . . . as our understanding of cancer has evolved – recognizing that there are potentially thousands of molecular biomarkers that influence whether a treatment will be effective . . . The space of possible treatment decisions is enormously larger . . . With thousands of molecular features, leading to tens of thousands of combinatorial subtypes, and hundreds of plausible combination therapies, there may be many millions of treatment-decision rules (i.e., matrix cells) that have to be tested . . . The number of dimensions that determine the size of this search space is called the "dimensionality" of the data, and the number of independent observations is sometimes referred to as the sample size, or "n" of a study. As a result of the combinatorial structure of the problem, each new feature grows the size of the search space exponentially (Shrager et al. 2019, p. 363).

Given the dimensions of the problem space, it is not surprising that success in precision oncology is elusive. The "low-hanging fruit," or instances where a single biomarker can be targeted effectively without recurrence, are likely to be rare. In particular, effective targeted therapy is particularly likely in cancers with low genomic complexity – e.g., cases of cancer driven by only a handful of driver mutations, and cancers with low heterogeneity. And, this is what we find: very rarely (e.g., in CML) have we found a single genomic feature that predicts with great precision how a patient is likely to respond to targeted therapy. This is because such

cancers are relatively simple (from a genomic perspective) (Lawrence et al. 2013). For more complex disease (indeed, in the vast majority of cancers), we ought to expect the effectiveness of novel precision cancer therapies to be limited.

Particularly in metastatic disease, even the most effective precision interventions are – by and large – not likely to be curative. I.e., "exceptional" responders are exceptional for a reason. Indeed, there are new research programs designed around determining why such responders do in fact respond so well. The vast majority of cancer deaths are in treatment-resistant, recalcitrant, or advanced stage disease – typically those identified relatively late in the game. Advanced tumors are likely to recur, or evolve resistance to both standard chemotherapies and targeted therapies, exactly because they have been subject to multiple rounds of therapy. Intratumor heterogeneity in advanced tumors makes the effectiveness of such therapies particularly precarious, because such tumors are more likely to evolve resistance to both standard chemotherapies and targeted therapies.

In the face of this challenge, researchers have attempted to develop methods that deploy AI and big data methods – like network models – that help reduce the number of dimensions of the problem. However, such methods are only successful (as Shrager et al. point out), when there are well-defined criteria of successful solutions of a problem, when the data concerning success is readily available, cheap and plentiful, when experts can teach AI using data from easy and cheap to run experiments, and when there are highly accurate simulators of the underlying processes. These conditions are not met in cancer research.

In sum, defining "success" – as we've seen – is a highly contested matter. As several critics of precision oncology have pointed out (Tannock and Hickman 2017; Prasad et al. 2016; Hey et al. 2019a), the endpoint measured in trials is often not "overall" survival, but typically "progression free survival" or "time to tumor growth." The latter are not the outcome patients are most concerned to intervene upon, and may or may not track the former. Follow up studies can improve upon this problem, but coordination of research is a problem, as we've seen with the FDA's rapid approval (and removal) of drugs. In addition, sometimes tests of novel therapies are not done against standard of care, such that results are not very informative for clinicians (Tao and Prasad 218).

As I've argued, there are further reasons to be concerned about the informational value of cancer biomarkers, or molecular data, in service of prognosis and treatment decisions. First, while gene expression is continuous, biomarkers are often "binned" as discrete variables, for the purposes of prognosis, diagnosis and treatment decisions. This means that two different cancers – say, one advanced stage metastatic breast cancer, and another a treatment naïve early stage cancer – could "score" the same in terms of gene expression profile, even though they are very different disease. This could lead to clinicians assigning the same drug to two very different patients (as has happened, in some ovarian cancers), leading to inconsistent results (e.g., Hey and Barsanti-Innes 2016).

To be sure, as in many contexts in medicine, a cut-off has to be made for continuous variables in making decisions about care. This is not a challenge unique to precision oncology; while it introduces some arbitrariness, as long as researchers

attend to the widest array of relevant evidence in making such decisions about cut-offs, it's not necessarily a devastating problem. The problem comes with the presupposition that molecular data trumps or obviate the need to attend to the many other variables that need to be taken into account. The key here is to use a wider array of information – not only more molecular data, but to sample a tumor at multiple time points, as well as attend to gross histological features of the tumor itself, to better understand the likely response to the drug. For, whether a drug gets to the target may have to do with some basic facts about the blood supply to a tumor, properties of the tissue in the surrounding organ, immune response, and patient metabolism. Prioritizing the genomic and molecular features of a tumor can lead to loss of important information.

Indeed, commercial tests of presence and absence of molecular variants are not always consistent in their results. A comparison of two commercially available next-generation sequencing platforms revealed rampant disagreements in mutation and recommended drugs for the same nine patients.

Another study found that different commercially provided tests for breast cancer patients arrived at divergent classifications of patients, depending in part on how many cores were taken of a tumor. In other words, intratumor heterogeneity (ITH) can lead to prognostic misclassification in of patients, because some tumors have regions of both indolent and aggressive disease (see also, Green et al. in this volume). Gene expression panels (GEPs) such as Oncotype Dx, MammaPrint, PAM50 (Prosigna), EndoPredict, and Breast Cancer Index (BCI) use a small number of selected genes. So, "in patients with highly heterogeneous tumors, multiple cores might be required to estimate risk prediction and that it might be a useful strategy to include both representative and atypical cores while selecting multiple samples to fully account for the ITH-driven variation in risk prediction." (Gyanchandani et al. 2016).

Further, many of these new drugs are tested in small populations of patients, and often patients with advanced cancers. Whether the results of such studies are relevant to the vast majority of patients (and particularly those with treatment naïve cancers) is unclear. Even when patients share the same biomarkers, the "same" cancer can have very different properties. So, what we discover about such therapies in trials may or may not be relevant to other patients.[5]

Last but certainly not least, cost of precision care makes many new diagnostic tests and therapies unavailable to a vast majority of patients. Last but not least, apart from questions about effectiveness, it's worth mentioning that the cost of newly approved agents is also staggering. The OncotypeDX test is prohibitively expensive for many patients, and it not apparently all that beneficial, over and above information already available (patient ER status, node status, etc.). Even the most

[5]For further discussion, see also: Green et al. (in this volume). Green notes: This is also a problem in PreCan. Incurable cancer patients with advanced cancers are the only ones "experimentally accessible" but it is a patient population group that is very different from the majority of cancer patients.

effective targeted therapies, however, are also routinely priced far outside the range available to most patients. The Institute for Clinical and Economic Review has released its Draft Evidence Report assessing the comparative clinical effectiveness of the PARP inhibitors (Poly ADP-Ribose Polymerase) (ICER 2017), and suggests that even in the best circumstances, maintenance therapy in recurrent disease would require discounts of approximately 50–80% on current list prices to meet acceptable thresholds ($50,000–150,000 per QALY (quality adjusted life years) gained) (cfr., Volpe et al. 2018). Similarly, for the TKIs for non-small cell lung cancer, costs would need to be reduced some 20–40% (depending on the drug) for current list prices to achieve $100,000 per QALY gained) (ICER 2016). In other words, the costs of these drugs – in some cases as much as $400,000 plus per year – would need to be reduced substantially to warrant their continued administration to patients, given the time and quality of life gained from treatment. This is genuinely disheartening, considering especially that many patients might be using up their life savings – or worse, suffering bankruptcy – to pay for such drugs.

It's not even clear (as in the case of TAILORx) that most patients are likely to benefit from what – for most – would be a prohibitively expensive test. Yet many patients clamor for such tests, even if they're unlikely to benefit. As mentioned above, very few patients overall are likely to benefit from precision oncology, as most cancer patients do not have actionable mutation. That is, most cancers are not even candidates for precision therapy. There simply are not (yet) targeted drugs likely to assist them (Marquart et al. 2018). Of course, this may well change with advances in biologics and immune therapies.

In sum, there are a variety of reasons why precision therapy has not been as successful as one might hope – some to do with cancer itself, and some to do with what and how we are testing novel cancer therapies, and last but not least, how approvals for novel therapies regulated and translated into the clinic.

Conclusions

To be clear, one ought not to downplay the significance of successes of precision oncology, both for researchers, and of course, for patients and their families. However, it's worth noting that many exemplars of successful precision oncology were developed and approved before the first human genome was sequenced in 2001. For instance, tamoxifen Herceptin (trastuzumab) for Her2+ BC, was approved by the FDA in 1998. The initial test for test for HER2-neu positivity used fluorescent in situ hybridization–based gene amplification, or immunohistochemistry, to demonstrate overexpression of the protein – not NGS (next generation sequencing). Imatinib was approved for targeted treatment in chronic myeloid leukemia in patients with the BCR-ABL rearrangement in in 2001, almost a full decade before the first cancer genome was sequenced. Gefitinib was approved by the FDA for treatment in 2003 for non–small cell lung cancer patients with a specific mutation to the epidermal growth factor receptor gene.

Some of these precision therapies are now part of the standard of care. HER2-neu is considered essential to classifying patients, not only in service of providing them with targeted therapies, but also for giving them prognoses of likely disease course. Small cell lung cancer patients with EGFR mutation benefit from a tyrosine kinase inhibitor, which can help them also to avoid aggressive and toxic chemotherapies. Some of these treatments improve outcomes significantly. Prior to the development of Imatinib, the median survival among patients with CML is about five years, but ranged from a few months to ten years or longer for those who have indolent, chemo responsive CML. With Imatinib, the 5-year estimated overall survival rate for patients who received imatinib as initial therapy (89%) is higher than that reported in any previously published prospective study of the treatment of CML (Druker et al. 2006). Molecular profile can help predict disease course for glioblastomas.

What the above case studies suggest is that in the vast majority of cases, the actual (as opposed to the hyped) benefit of precision oncology is rather minimal. As Strand and colleagues have emphasized (in this volume), personalized medicine presents a vision or imaginary of desired futures, but this state may be very far from reality. For instance, what TAILORx succeeded in showing, at best, is a substantial proportion of patients were overtreated. To be sure, this means that one thing that genetic profiling can do well is demonstrate lack of benefit of current treatment modalities. But, it turns out that clinicians already were aware that a variety of markers indicated low benefit of chemotherapy, and so the case of TAILORx did not (or should not have) radically changed the standard of care. At best, what it might do is prevent overenthusiastic (and ill informed) clinicians from overtreating patients with aggressive chemotherapy.

More seriously, it's not clear how much in absolute terms precision oncology yields benefits that matter. The endpoint measured in trials of new targeted treatments is typically not "overall" survival, but "progression free survival." That's a problem because patients by and large are not simply concerned with slowing the growth of a cancer for a few months, especially when these months of life are accompanied by substantial toxicities. This ought to be communicated to patients with end-stage disease who sign on for clinical trials, as so often such patients are subject to false hope.

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The Complexity of Tumor Heterogeneity: Limitations and Challenges of the Pharmacogenomics in Cancer Treatment

Guglielmo Militello and Marta Bertolaso

Introduction

Over the last two decades, pharmacogenomics has been attracting sizeable investments from both the public and the private sector. The primary purpose of pharmacogenomics is to identify the variant genes affecting drug response and to develop drugs that are based on the genetic profile of a patient. As such, pharmacogenomics is currently considered a fundamental lynchpin of personalized medicine, which is an application of molecular and/or genomic data in medicine in service of diagnosis, prognosis, or treatment. Pharmacogenomics has already been employed to study the precise dosing of drugs for the treatment of different pathologies (e.g., cardiovascular diseases, osteoarticular pathologies, psychiatric disorders) (Ranganathan 2008; Joyner and Paneth 2019).

A promising field of application of pharmacogenomics is the treatment of cancer, as carcinogenesis is thought to be caused or, at least, closely connected with genetic mutations. Thus, pharmacogenomics aims at discovering the molecular targets of anti-cancer drugs, in order to make them more effective. Nevertheless, tumor cells exhibit genetic and phenotypic *heterogeneity* that seriously interfere with the molecular targets of anti-cancer drugs. Indeed, genetic heterogeneity could enable tumor cells to bypass or halt the drug's progress, and phenotypic heterogeneity can

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make getting drug to target difficult (e.g., it can prevent the drugs from diffusing into a tumor).

It therefore seems that a successful application of pharmacogenomics to cancer treatment hinges on the knowledge of its levels of organization. Accordingly, the purpose of this paper is threefold: first, to analyze the levels of organization of tumor heterogeneity; second, to examine the complexity of intratumor heterogeneity; finally, to evaluate the consequences of such a complexity for the epistemology and scientific practice of pharmacogenomics in the context of personalized cancer medicine.

The philosophical literature usually considers "complexity" as a feature of *systems* (e.g., physical, biological, social systems) (Ladyman et al. 2013). However, since tumor heterogeneity is not a system, but rather a property (or *phenomenon*) of a system such as cancer, is it appropriate to define tumor heterogeneity as "complex"? In our view, the answer is *positive*, because (as we will argue in Sect. 4) tumor heterogeneity is a very complicated phenomenon both ontologically and epistemologically: it occurs at different organizational levels and involve heterogeneous entities that are causally interdependent, thus establishing an intricate network of causes and effects. As a consequence of such an ontological complexity, there is an *epistemological* complexity that mostly entails the difficulty in explaining the intricate network of causal relationships underlying genetic and phenotypic heterogeneity.

The understanding of the complexity of tumor heterogeneity will allow us to critically assess the limitations, the challenges, and the potentialities of the theoretical framework and research programs of pharmacogenomics in cancer treatment. We argue that tumor heterogeneity can adequately be addressed by considering the (causal) relationships between different levels of organization of cancer and it could also be stopped or, at least, slowed down by exploiting systemic properties of cancer. We suggest that a gene-based approach to anti-cancer drugs is neither the most effective nor the most relevant way to deal with tumor heterogeneity and cancer progression, and that pharmacogenomics may benefit from the tools of systems pharmacology.

The paper is organized as follows. Section 2 conducts a critical review of the main theoretical accounts of pharmacogenomics, focusing on its promises and its main obstacles. In the Sect. 3, we examine the levels of organization of tumor heterogeneity. Section 4 explores the complexity of tumor heterogeneity. Then, Sect. 5 evaluates how the complexity of intratumor heterogeneity affects the epistemological framework and the scientific practice of pharmacogenomics for cancer treatment. Finally, Sect. 6 makes some concluding remarks.

The Promises and the Obstacles of Pharmacogenomics: A Critical Review

From an historical point of view, the rise of personalized medicine is directly linked to the Human Genome Project,[1] the Human Haplotype Map Project,[2] and the development of -omics data such as genomics, transcriptomics, proteomics and metabolomics (Ghosh and Poisson 2009). Personalized medicine aims at integrating the data coming from genomics with the clinical data of individual patients in such a way as to create very specific therapies (and drugs) based on the genetic profile of each patient (Emmert-Streib 2013). As such, personalized medicine is usually regarded as an evidence-based medicine, because it relies on an evidence hierarchy (e.g., cohort studies, randomized control trials, meta-analyses), and also as a precision medicine, since it encourages a model of healthcare grounded on medical decisions, treatments, and drugs that are individually tailored (Joyner and Paneth 2019).

An essential aspect of personalized medicine is *pharmacogenomics,*[3] which aims at developing drugs on the basis of the genetic profile of a patient. The main *theoretical assumption* underlying pharmacogenomics is the idea that a drug is likely to be more efficacious and less toxic if the genetic profile of a patient is fully known and if the genetic variability associated with a certain disease and some drug response is perfectly understood (Karczewski et al. 2012). As such, drug therapy in pharmacogenomics entails a division of patients into smaller subpopulations each having specific genetic profiles. Pharmacogenomics has a twofold aim: firstly, to identify the *variant mutations* affecting the response to drugs in individual patients; secondly, to develop *new drugs* based on the discovery of new drug targets (Mancinelli et al. 2000).

The identification of genetic mutations combines different techniques that are aimed at studying not only the gene targets for some drugs but also the regulatory and signaling networks in which the gene is embedded. One of the most important methods is genome-wide associations studies (GWAS) that examine the correlation between single nucleotide polymorphisms (SNPs)[4] and phenotypic

[1]The Human Genome Project was an international research project, carried out between the 1990s and the early 2000s, that aimed at sequencing all the genes of the human genome.

[2]The Human Haplotype Map Project was an international project carried out between 2002 and 2009 that aimed at developing a haplotype map of the human genome so as to explain the main genetic variants causing diseases and responses to drugs (International HapMap Consortium 2003).

[3]The first steps towards pharmacogenomics can be traced back to the 1950s, as a number of scientists tried to merge genetics, biochemistry and pharmacology into a new scientific discipline (Mancinelli et al. 2000). Afterwards, the human genome project played a fundamental role in opening up a whole new field of research in pharmacogenomics (Ginsburg and Willard 2009).

[4]Single nucleotide polymorphisms are substitutions of single nucleotides in a certain DNA strain.

traits involved in human diseases (Lu et al. 2014).[5] Other techniques include expression methods, cheminformatics, and pathway discovery (Karczewski et al. 2012). Expression methods detect the genes involved in drug response by means of RNA expression data from microarrays or RNA-Seq[6] technique from drug-treated samples (Karczewski et al. 2012). Different expression profiles are then compared through the connectivity map, which shows the gene expression data of cell lines in terms of small molecules. A number of computational methods (i.e. cheminformatics) combine information about protein structure and small molecule structure for understanding potential drug targets.

Pharmacogenomics plays a fundamental role in the development of new drugs, as it can help to identify new potential gene targets of drugs. Through the use of next generation sequencing (a set of techniques aimed at sequencing the whole genome) in a certain cohort of patients, the current drug development efforts seek to pinpoint the genetic variants responsible for therapeutic vulnerability, to synthesize molecules that can inhibit the activated protein variants, and to identify additional patients who could eventually benefit from these targeted therapies (Mardis 2019).

Pharmacogenomics has brought some considerable benefits for the treatment of some pathologies (e.g., cardiovascular diseases, osteoarticular diseases), because the clinical trials of pharmacogenomics have made it possible a more precise dosing of some drugs (Ranganathan 2008; Joyner and Paneth 2019). However, pharmacogenomics has important *limitations* due to the "dynamic complexity of the human genome, multigenic disease origins, and involvement of numerous genes in drug response" (Mancinelli et al. 2000, p. 11). Indeed, most noninfectious diseases (e.g., cardiovascular, renal diseases, etc.) are the outcome of many gene variants working collectively in such a way that it is impossible to find a unique genetic cause (Kalow 2006). Accordingly, some doubts have arisen over the effectiveness of the personalized medicine and somebody has voiced a fear that "the concentration of research on personalized medicine might deprive other promising avenues of research of appropriate resources" (Tannock and Hickman 2016).

In the case of cancer cure, the application of pharmacogenomics to the treatment of malignant tumors reveals not only some potentialities, but also some important limitations. On the one hand, pharmacogenomics is a promise for the treatment of cancer, insofar as the creation of more effective anti-cancer drugs is believed to depend on the mechanistic understanding of their gene targets. A number of different parameters (e.g., SNPs, copy number variations (CNV), gene deletion and insertion) are evaluated to assess how anti-cancer drugs are metabolized in different

[5]GWAS usually employ control setups and the analysis of quantitative phenotype data. The former is an observational study that compares a set of healthy individuals with another set of individuals affected by a disease by analyzing the *alteration* of *allele frequency* in the SNPs of the ill patients. The latter is the quantitative analysis of biomarkers concentrations or gene expression in order to evaluate the amount of mutated phenotypes in the cluster of ill people (Bush and Moore 2012).

[6]RNA-seq stands for RNA sequencing which employs the technique of next generation sequencing for analyzing the presence and the concentration of RNA in a sample.

subpopulations of patients (Dhawan and Padh 2013). On the other hand, it has recently been shown, for example, that the percentage of US cancer patients that benefitted from pharmacogenomics is very low (Marquart et al. 2018).

A fundamental aspect of cancer cells that hinders pharmacogenomics lies in that the cells of the *same* tumor are extremely heterogeneous (intratumor heterogeneity).[7] A fundamental aspect of cancer cells that hinders pharmacogenomics lies in that the cells of the same tumor are extremely heterogeneous (intratumor heterogeneity). Basically, intratumor heterogeneity refers to the differences in gene expression (e.g., the expression of cell surface markers or growth factors), morphology (e.g., solid structures, tubular structures, alveolar structures), and other cellular capacities (e.g., metabolism, motility, immunological capacities) between the cells of the same tumor (Marusyk and Polyak 2010) often including mutations related to cell-cell communication and differentiation. A second sense of tumor heterogeneity is related to the genetic drift[8] of tumor cells, which "refers to the equally important source of cellular variability in cancer derived from genetic heterogeneity in a tumour that accumulates as cancer progresses. [. . .] The processes of increasing tumour heterogeneity imply the disruption of the correct processes of differentiation in the progenitor tumour cell with a concomitant loss of control on the genomic level of organization in tumour cells" (reviewed in Bertolaso 2016, p. 14). The heterogeneity that is generated in this way usually follows the previous one (i.e., functional heterogeneity) posing interesting questions about the fundamental organizational features that are actually compromised in cancer and their reciprocal temporal dependencies in causal terms.

A major consequence of intratumor heterogeneity is that tumor cells exhibit new adaptive behaviors by interacting in a new way with their microenvironment. When they are targeted by anticancer drugs, they develop resistance to single molecular targeted genes by means, for example, of epigenetic upregulation[9] of partially inhibited pathways, mutation of the gene target, or activation of alternative pathways (Tannock and Hickman 2016). Adaptive responses often involve multiple targets, and also it can be very difficult to combine targeted agents (Tannock and Hickman 2016). One of the most dramatic effects of tumor heterogeneity is that cancer cells, when treated with anti-cancer drugs, produce bottlenecks in which some drug-resistant cells survive, thus proliferating and generating metastasis (Marusyk and Polyak 2010). Anticancer treatments provide only a partial inhibition of some signaling pathways involved in tumor proliferation, and also they are extremely toxic and cannot be used in combination (Tannock and Hickman 2016).

[7] Another important dimension of the heterogeneity of cancer is the genetic and morphological differences between the cells of different tumors (inter-tumor heterogeneity). In spite of its importance, we focus in this paper on intratumor heterogeneity and on its epistemological and practical challenges to pharmacogenomics.

[8] Genetic drift is the change in the frequency of gene variants (alleles) in a population.

[9] Epigenetic regulation plays a pivotal role in the transcriptional regulation of cancer. More particularly, epigenetic upregulation of DNA repair genes entails the increase in gene expression, whereas epigenetic downregulation a decrease.

In view of the foregoing, the essential question for the application of pharmacogenomics to cancer treatment is whether it is possible to develop efficacious gene-based drugs in spite of intratumor heterogeneity (Tannock and Hickman 2016, p. 1292). For gene-based drugs to be successful, they should be able, firstly, to target the mutations driving tumor genomic instability and tumor heterogeneity, and secondly to inhibit the pathways of tumor progression (Tannock and Hickman 2016). We may speculate that the biological properties and the specific organization of tumor heterogeneity pose big challenges to the current epistemic paradigms and the overall scientific practice underlying pharmacogenomics. Thus, in order to better evaluate the obstacles and potentialities of pharmacogenomics in cancer treatment, we carefully analyze in the next section the levels of organization of tumor heterogeneity as they are represented in the scientific literature.

Levels of Organization of Intratumor Heterogeneity

It was not until the 1930s that the existence of morphological and functional heterogeneity of cancer cells was revealed, inasmuch as it was shown that the transplantation of one leukemia cell of mouse was able to originate new malignant leukocytes with new morphological and functional traits (Furth and Kahn 1937). During the 1950–60s, cytogenetic studies on the allelic assessment of metabolic isoenzymes[10] and immunoglobulins[11] as well as on DNA polymorphisms confirmed the idea that one single mutated cell gave rise to new malignant cells with different genetic and phenotypic profiles (Loponte et al. 2019). Since the 1970s, the genetic and phenotypic heterogeneity of cancer cells has been investigated within the theoretical framework of the "Somatic Mutation Theory" (SMT) which posits that carcinogenesis and the proliferation of cancer cells is caused by somatic mutations (i.e., alteration of the DNA sequence of the cells of a multicellular organism). At the end of the Nineties, an alternative explanation of tumor heterogeneity has been provided by the "Tissue Organization Field Theory" (TOFT) which states that the initiation and proliferation of cancer is determined by some tissue dysfunctionalities that affect the genetic organization of cells. Furthermore, systemic accounts of tumor heterogeneity have recently been provided by scholars studying cancer dynamics with the tools of Systems Biology. In both accounts, intratumor heterogeneity has inextricably been linked to the factors responsible for *carcinogenesis* and *tumor progression*; yet, their different explanations of the causes of cancer initiation and progression inevitably affect how they describe genetic and phenotypic heterogeneity. Thus, the next two subsections examine intratumor

[10] Isoenzymes (or isozymes) are enzymes with different amino acid sequences but catalyze the same chemical reaction.

[11] Immunoglobulins (or antibodies) are the proteins synthesized by the plasma cells of the immune system.

heterogeneity in the context of the SMT, firstly, and then in the TOFT and in the systemic models in cancer research.

Intratumor Heterogeneity from the Perspective of the SMT

Although the SMT has been formulated in distinct ways,[12] some biological assumptions form its innermost core. Firstly, neoplasms are characterized by *genetic mutations* that increase their proliferation rate. Secondly, the *cell* is regarded as the fundamental level to explain carcinogenesis and tumor progression. Thirdly, tumors stem from a single cell that has acquired multiple mutations and has the potential for unlimited proliferation. Finally, neoplasms arise when there are genetic mutations or increased expression in those genes (the *oncogenes*) regulating cell growth and differentiation (reviewed in Bertolaso 2016, p. 20). According to the SMT, *genetic* and *epigenetic* factors are the primary causes of intratumor heterogeneity, which in turn favor tumor evolution[13] and tumor progression.[14]

The genetic factors contributing to intratumor heterogeneity include changes in both the single genes (e.g., nucleotide polymorphisms, heterozygosity, splicing forms, etc.) and in the whole genome (e.g., copy number variation, microdeletions and inversions, aneuploidy, polyploidy, etc.) (Heng et al. 2009; McGranahan and Swanton 2017). Some studies have underlined that tumor heterogeneity is likely due not only to random genetic mutations, but also to the recurrent inactivation of the same tumor suppressor genes (Gerlinger et al. 2012; Swanton 2012). Furthermore, some genetic events (e.g., polyploidy, chromosomal instability) could explain the initial phases of tumor growth and intratumor heterogeneity, while other mutations (e.g., the mutations of p53[15]) could drive tumor growth and maintenance (Swanton 2012). Altogether, these genetic mutations effect a profound transformation in how a healthy cell synthesizes proteins, performs (genetic) regulatory mechanisms, and generates intra- and extra-cellular signals.

A huge variety of epigenetic mechanisms yield intratumor heterogeneity, the most important of which are changes in DNA methylation, reorganization of chromatin, variability in gene expression and microRNAs[16] (Heng et al. 2009;

[12] For a detailed discussion of the different accounts of the SMT, see Bertolaso (2016, pp. 17-41).

[13] By *tumor evolution*, we mean the dynamics of natural selection that underlie the progression of neoplasms.

[14] The expression *tumor progression* is employed in this paper to refer to the *growth* and *proliferation* of tumor cells. We will not use the term *development*, because this word usually relates to a gene-controlled process of self-organization both in time and space, whereas cancer progression is driven by stochastic events of gene replacement which do not follow regulated patterns. In spite of being correlative terms, tumor *progression* and tumor *evolution* designate different biological aspects of cancer dynamics.

[15] p53 is a protein that prevents cancer formation, thus functioning as a tumor suppressor.

[16] MicroRNAs are small non-coding RNA molecules, discovered in some viruses, plants, and animals, that are involved in RNA silencing and post-transcriptional regulation of gene expression.

Gerashchenko et al. 2013; Mazor et al. 2016). DNA methylation increases the genomic instability as indicated by the aberrant methylation of the promoter genes of CpG island[17] methylator phenotype that is involved in cell control and development (Gerashchenko et al. 2013, p. 1203). The remodeling of chromatin is due to post-translational modifications of histone proteins and modifies gene transcription. This has some important cellular effects, inasmuch as, for instance, the deacetylation of histones can negatively affect cell adhesion and intercellular contacts, thus generating different morphological structures within the tumor (Gerashchenko et al. 2013, p. 1203). MicroRNAs play an important role for the diversity of tumor cells, because variations in microRNAs determine an alteration in the regulation of cell cycle and differentiation of healthy cells, thus promoting cancer differentiation and progression (Gerashchenko et al. 2013).

The *tumor microenvironment* (e.g., the extracellular matrix,[18] fibroblasts,[19] immune cells,[20] blood vessels) occupies a prominent role in the origin of intratumor heterogeneity. Interestingly, and with some ambiguity, its role is discussed either in passive terms, so that the cells maintain the relevant properties that are responsible for cells' invasion (Hanahan and Weinberg 2011), or attributing to the microenvironment permissive properties. In this latter case, the microenvironment seems to create, in fact, an abnormal context that favors stress responses, genetic instability and the selection of more invasive phenotypes (Polyak et al. 2009; Marusyk et al. 2012; Spill et al. 2016; Lin and Lin 2019). In this sense, the tumor microenvironment may determine the epithelial-mesenchymal transition which is a process during which epithelial cells lose fundamental capacities such as cell-cell adhesion and cell polarity and gain migratory properties that allow them to become mesenchymal stem cells; thus promoting cancer progression (Polyak and Weinberg 2009). The tumor microenvironment also promotes the vasculogenic mimicry[21] in such a way that tumor can transport material among each other; thus facilitating tumor growth (Hendrix et al. 2003). In general, the tumor microenvironment radically modifies the functional organization of healthy cells in such a way that new environmental niches appear: for instance, the abnormal vascularization of malignant tumor cells determines a very irregular vascular architecture with inefficient blood vessels with considerable fluctuations of oxygen over time (Marusyk et al. 2012). The development of tumor heterogeneity is also influenced by some micro-environmental factors such as exposure stress (e.g., anti-cancer drugs), tissue specificity, nutrition

[17] CpG islands are DNA regions rich in cytosine and guanine. They can change their expression through methylation and, as such, they play an important role in epigenetics.

[18] The extracellular matrix is a three-dimensional structure consisting of extracellular macromolecules (e.g., collagen, enzymes, glycoproteins) the function of which is to provide surrounding cells with structural and biochemical support (Theocharis et al. 2016).

[19] Fibroblasts are cells synthesizing the extracellular matrix and collagen.

[20] Examples of immune cells are macrophages and lymphocytes.

[21] Vasculogenic mimicry is formation of micro-vessels by tumor cells.

status, alterations of the physiological conditions (e.g., alterations in the hormone and metabolic levels) (Heng et al. 2009; McGranahan and Swanton 2017).

Beyond such interesting information about the role of the microenvironment, a fundamental assumption underpinning the SMT is that intratumor heterogeneity is an important cause of *tumor evolution*, because it would favor the formation of more aggressive and adapted tumor cells (McGranahan and Swanton 2017; Merlo et al. 2006; Heng et al. 2009; Polyak et al. 2009; Ye et al. 2009). Indeed, it has been argued that the mutations in the gene structure and in the number of gene copies that characterize intratumor heterogeneity are fundamental causes of the *microevolution* of malignant tumor cells, because they represent a raw material for selection to act on genes and they also permit the change in allele frequency, thus determining the appearance of new genetic variants (Heng et al. 2009). An indirect, though important, source of microevolution is represented by epigenetic mechanisms, which control gene expression in such a way that genes improve their adaptive capacities to the selection pressures of the environment. As such, epigenetic mechanisms play an important role in cancer progression and in the response to anti-cancer drugs (Marusyk and Polyak 2010; Lin and Lin 2019). Likewise, tumor microenvironment promotes the selection of adapted cells by promoting different selective pressures on the same tumor, thus driving the evolutionary trajectories of tumor cells (Marusyk et al. 2012; Gerashchenko et al. 2013). It is interesting to observe that in this context the term "evolution" could be a bit problematic, because the "natural evolution of cancer" refers to the development of the disease in *absence* of any *external conditioning*. Nevertheless, a population of tumor cells behave and "evolve" under the action of constraints, such as those placed by the microenvironment, the treatment, and artificial (laboratory) constraints. Thus, the term "natural evolution" in the context of cancer should be taken with a grain of salt.

According to the SMT, intratumor heterogeneity is a fundamental cause of cancer progression in *space* and *time* because of the role played by genetic, epigenetic and environmental causes. Indeed, nucleotide changes, modifications of chromosomes, and epigenetic mechanisms determine an overall genomic instability and environmental factors may favor multiple rounds of *proliferation* of the clones, usually accompanied by *cell death* (Marusyk and Polyak 2010). Moreover, the assumption of anti-cancer drugs may favor the appearance of genetic and phenotypic variants that promote cancer progression instead of inhibiting it (Swanton 2012; McGranahan and Swanton 2017). Compared to "natural evolution", progression is a far more entangled process, as it depends from the combined interplay of a number of factors located at higher levels (tissues, organs, immune system and so forth) that constrain the progression of tumor cells.

In the light of the above, we can draw some important conclusions. First, SMT accounts share a *reductionist* account of tumor heterogeneity, because the relevant causes for understanding intratumor heterogeneity are identified with genetic and epigenetic mechanisms and only partially with the extracellular (or environmental) context. Secondly, the genetic, epigenetic, and environmental factors underlying tumor heterogeneity are important sources of the *microevolution* of malignant

tumor cells. However, a population of malignant tumor cells can scarcely undergo macroevolution, because tumor cells independently change their genetic profiles, thus not generating a population with a homogeneous genetic set-up. Thirdly intratumor heterogeneity plays a pivotal role in cancer *progression*, because it favors the development of multiple rounds of proliferation and the invasion of other tissues.

Intratumor Heterogeneity from the Perspective of the TOFT and the Systemic Models of Cancer

A different explanatory perspective on intratumor heterogeneity has been provided by the TOFT and some systemic models in cancer research. The common denominator of these theoretical frameworks is the acknowledgement that the genetic and epigenetic levels of the cells do not satisfactorily explain cancer dynamics and tumor heterogeneity. Especially when the focus (*explananda*) is on carcinogenesis, they suggest that cancer is a multi-level disease, the biological features of which can be understood by examining the different (hierarchical) levels of organization of the overall organism and their functional inter-dependencies.

According to the TOFT, carcinogenesis is not caused by genetic mutations, but rather by some single or multiple carcinogenic exposure acts that interfere with the normal biophysical and biochemical communication between the mesenchyme[22]/stroma[23] and the parenchyma[24] in a given morphogenetic field[25] (Soto and Sonnenschein 2004, 2011). According to the TOFT, the "default" state of a cell is *proliferation* (and *motility*) (Soto and Sonnenschein 2004). The origin and progression of malignant tumor cells is due to a *loss of constraints* at the tissue level in such a way that the proliferative and motile capacities of tumor cells are no longer inhibited.

Although Soto and Sonnenschein's theory does *not* give a *clear* account of the genetic and phenotypic *heterogeneity* of cancer, they seem to connect tumor heterogeneity with the disruption of the constitutive organization of the relationship between the parenchyma and the stroma. A correlation between tumor heterogeneity and an extensive alteration between parenchymal and stromal cells has been suggested by some research works (not necessarily adhering to the TOFT as an overall comprehensive theory about cancer) (Mueller and Fusenig 2004; Shtilbans 2013). This is consistent with the observation that much of tumor heterogeneity is found in their stromal compartments and that both neoplastic cells and stromal cells around them change progressively during the multistep transformation of normal tissues into high-grade malignancies (Hanahan and Weinberg 2011).

[22]The mesenchyme is a type of connective tissue mostly found during the embryonic development of bilateral animals.

[23]The stroma is a part of a tissue (or organ) with a connective role.

[24]The parenchyma is the functional part of an organ.

[25]A morphogenetic field is a group of cells involved in the morphogenesis of tissues and organs.

Another important perspective on intratumor heterogeneity is provided by systemic models[26] in cancer research which study tumor heterogeneity by considering the way in which the cell changes its functional states (Heng et al. 2009). As pointed out by Heng et al. (2009), the genetic and epigenetic mechanisms underlying tumor heterogeneity do not make sense if separated by the dynamics of the functional states of the cellular system.

From a systemic perspective, *tumor microenvironment* plays a pivotal role, in explanatory terms, both in tumor progression and in intratumor heterogeneity, since it is the biochemical *support* of the *morphogenetic field,* which drives epithelial cells towards differentiation and phenotype transformation (Nelson and Bissell 2006; Bizzarri and Cucina 2014). A deregulation in the balance between morphostats[27] and morphogens,[28] for example, would lead to further abnormalities in cell proliferation and tissue organization (Bizzarri and Cucina 2016). Intratumor heterogeneity would be the outcome of the complex cross-talk among stromal cells, epithelial cells, and tumor microenvironment: the interactions between epithelial cells and microenvironmental components (particularly stromal cells) change the extracellular matrix composition as well as its biochemical-biophysical features (Bizzarri and Cucina 2014). The change in the tumor microenvironment entails a structural and functional reorganization of the overall cell in such a way that the genetic and phenotypic changes of tumor cells (including their heterogeneity) must be understood in the light of this *cell-tissue continuum* (Nelson and Bissell 2006). For instance, it has been observed that alterations in the relationship between cytoskeletal filaments and proteins and the extracellular matrix have far-reaching consequences not only for the cell shape and tissue modeling, but also for the enhancement of cell proliferation and migration (Ingeber 2008; Bizzarri et al. 2015). It is widely accepted that cancer dynamics should be studied by considering both the tumor microenvironment and the "tumor organismal environment", which includes the immune system, the nervous system and the microbiome (see, Laplane et al. 2019).

To conclude, the TOFT and the systemic models underline the importance of the *cell-tissue continuum* to understand the origin, the progression, and the tumor heterogeneity of malignant tumor cells. This implies that the primary causes of tumor heterogeneity do not lie in genetic and epigenetic mechanisms, but rather in an overall structural and functional reorganization of the cell-tissue interactions that determine genetic and epigenetic mutations. Hence, the relationship between microenvironment and tumor cells is no longer a mere co-factor, but rather the constitutive context of tumor heterogeneity and cancer progression.

[26] An in-depth discussion of the systemic models in cancer research can be found in Bertolaso (2016, pp. 43-59).

[27] Morphostats are molecules, mostly produced by fibroblasts and macrophages, that regulate cell proliferation.

[28] Morphogens are molecules that govern the pattern of tissue development in the process of morphogenesis.

Tumor Heterogeneity as a Complex Phenomenon

The SMT and the systemic accounts[29] have differently explained tumor heterogeneity, considering it as the result of either genetic and epigenetic modifications or alterations at the tissue (and organ) level. In spite of this major difference, do these theoretical perspectives provide us with a *common* core concept of complexity of tumor heterogeneity? In order to answer to this question, we consider some features of tumor heterogeneity on which both accounts agree, despite somehow the different explanatory accounts: first, the relevance of *genome instability*; secondly, the role played by *tumor microenvironment*; thirdly, tumor heterogeneity as a fundamental feature of *tumor progression*; fourthly, the influence of tumor heterogeneity on the *spatial and temporal organization* of a metazoan; finally, tumor heterogeneity as a causal related aspect of the *loss of systemic regulation*.

A first convergence point between the SMT and the systemic accounts lies in recognizing *genome instability* as a major driver of tumor heterogeneity. Genome instability is a broad term referring to the high frequency of genetic mutations in a genome (e.g., changes in DNA sequences, chromosomal rearrangements, appearance of an abnormal number of chromosomes) that are at the origin of the continuous appearance of new genetic and phenotypic traits, and therefore *intratumor heterogeneity*, during cancer initiation and progression. Although the SMT and the systemic accounts agree that genomic instability is a fundamental cause of intratumor heterogeneity, they differently explain it[30]: according to the SMT, genome instability is mostly caused by random alterations at the gene level (e.g., modifications of DNA repair mechanisms) (Swanton 2012; McGranahan and Swanton 2017); the systemic accounts, instead, interpret genomic instability as the outcome of systemic alterations (e.g., alterations in the paracrine signals expression that lead to a failure in intercellular communication or the destruction of the extracellular matrix) (Nelson and Bissell 2006; Bizzarri and Cucina 2014).

There is a consensus between the SMT and the systemic accounts about the role played by *tumor microenvironment*, inasmuch as both theoretical perspectives agree that genetic and phenotypic heterogeneity are affected by the components of the extracellular environment (e.g., the extracellular matrix, fibroblasts, blood vessels). The SMT and the systemic accounts emphasize different but not mutually exclusive aspects of tumor microenvironment. According to the former, the tumor microenvironment provides tumor cells with a *structural support* and *nutrients*, thus determining an abnormal context that favor stress responses, genetic instability and the selection of more invasive phenotypes (Spill et al. 2016; Lin and Lin 2019). The latter considers tumor microenvironment as a *physical-chemical constraint* that drives the differentiation and the genetic and phenotypic transformation of epithelial cells (Bizzarri and Cucina 2014). Modifications in the tumor microenvironment

[29] Hereinafter, we use the term systemic accounts to refer both to the TOFT and to the models of systems biology.

[30] As pointed out by one referee, these views are not mutually exclusive.

(e.g., in the architecture of fibroblasts or extracellular matrix) trigger alterations in the gene expression of paracrine signals and their extracellular release, thus affecting intercellular communication and the coordination among the cells of a tissue which may in turn affect genome instability and the production of aberrant phenotypes (Bizzarri and Cucina 2014; Baghban et al. 2020; Brassart-Pasco et al. 2020). This difference is substantial in explaining tumor heterogeneity: for the SMT tumor microenvironment is a factor *promoting* tumor heterogeneity, but it has no priority over the genetic mutations; by contrast, the systemic accounts consider the modifications occurring in the tumor microenvironment as *a primary cause* of the appearance of intratumor heterogeneity.

Both the SMT and the systemic models reject the idea that intratumor heterogeneity is a *mere* stochastic molecular noise determining random variations in gene expression levels; in fact, these two theoretical perspectives recognize that, despite its randomness, the emergence of genetic and phenotypic heterogeneity is a *systematic cause* of *tumor progression* and, as such, it must be regarded as a *systemic property* of the pathophysiology of cancer. According to the SMT, the appearance of genetic heterogeneity in tumor cells represents a raw material upon which selection can act, thus determining the appearance of new (more adapted) genetic variants (Heng et al. 2009; Gerashchenko et al. 2013). The microevolution of tumor cells in turn favors the progression of cancer, inasmuch as tumor cells can respond to stress factors (e.g., anti-cancer drugs) more effectively (Heng et al. 2009). In the systemic models, the progression of cancer is enabled by the structural and functional changes in the tumor microenvironment and the appearance of genetic and phenotypic heterogeneity (Bizzarri and Cucina 2014).

Another convergence point between the SMT and the systemic models is the idea that intratumor heterogeneity alters the *functional integration* of cells, tissues, and organs of a metazoan. The reason is that the emergence of new genetic and phenotypic traits modifies the normal *spatial organization* of anatomical parts, thus interfering with the way in which the functions performed by these parts are integrated among each other. For example, an alteration in the gene expression of signaling pathways may alter epithelial cell polarity as well as cell size and shape (Etienne-Manneville 2008; Lee and Vasioukhin 2008). Furthermore, tumor heterogeneity affects the *temporal coordination* between the functions performed by different anatomical parts, thus determining a decoupling among them. For instance, the introduction of genetic and phenotypic variants in growth factor pathways may determine a loss of temporal coordination with metabolic processes, leading to an abnormal proliferation of tumor cells (Sever and Brugge 2015).

All in all, both the SMT and the systemic models recognize that intratumor heterogeneity produces an *inter-level dysregulation* during which the signaling and regulatory pathways underlying cell differentiation, apoptosis, and tumor proliferation become *uncoupled*, the relationship between the stroma and the parenchyma is radically altered, and organs are seriously compromised. As a result, the normal functional integration and the hierarchy of cells, tissues, and organs are progressively lost, thus undermining the systemic stability. The loss of a hierarchical organization during cancer initiation and progression is accompanied by the appear-

ance of *aberrant* and *unorganized* genetic and phenotypic heterogeneity which in turn upsets the proper balance between homeostasis and the maintenance of *ordered* functional heterogeneity (Bertolaso and Dupré 2018).

Now, what can we infer from the above-mentioned features to understand the complexity of tumor heterogeneity? In our view, tumor heterogeneity is *complex* inasmuch as a) it occurs at *different levels* involving *heterogeneous entities*; and b) these entities are *causally interdependent*, thus establishing an intricate network of causes and effects. Let us argue this salient point.

Tumor heterogeneity occurs at different levels because it is the *cause* of (e.g., the loss of spatio-temporal integration among the levels of a metazoan, the failure of systemic regulation) and, at the same time, the *effect* of (e.g., genomic instability, alterations in the tumor microenvironment) several dysfunctionalities encompassing different entities (e.g., nucleic acids, proteins, cells, tissues) at the different organizational levels (i.e., genes, cellular network, cell-cell interactions, tissue, organs, and organ systems) of a metazoan. As a result, the overall functional integration of a metazoan is compromised. Tumor heterogeneity entails an extremely *intricate network of causal relationships* where three thorny problems arise, all having far-reaching consequences for the explanation of tumor heterogeneity throughout cancer progression.

First, it is hard to sharply distinguish between the *primary* (or direct) and the *secondary* (or indirect) causes (if any) involved in the appearance of new genetic and phenotypic traits. The controversy between the SMT and the systemic accounts over the factors causing tumor heterogeneity (and carcinogenesis as well) is indicative of the difficulty of establishing which factors are primary or secondary causes of tumor heterogeneity. Apparently, it seems that genetic and epigenetic factors are as primary causes as systemic alterations (e.g., modifications in the parenchyma-stroma interactions), thus giving the impression that each organizational level is at the same time relevant to understand the emergence of tumor heterogeneity. This entails a disagreement over the more appropriate pharmacological treatments of tumor heterogeneity (and hence tumor progression): on the one hand, SMT accounts endorse a pharmacological approach that targets the proteins synthesized by oncogenes (e.g., trastuzumab targets the protein HER2 which is synthesized by the oncogene *HER2*); on the other hand, systemic accounts stress the importance of differentiated pharmacological therapies that target not only the genetic level but also the cellular and microenvironmental contexts (e.g., manipulation of cancer metabolism) (Yoshida 2015; Bizzarri et al. 2020a).

Secondly, a corollary of the difficulty of establishing a clear hierarchy of causes of tumor heterogeneity is that it is very problematic to exactly determine their *temporal dependence relations* (i.e., diachrony or synchrony, and what kind of reflexivity holds). This is manifest when we consider, for example, the temporal causal relation between genetic alterations, genomic instability, and tumor microenvironment: in spite of being considered causes of tumor heterogeneity, it is very difficult to determine the *exact* causal relation among them in terms of *temporal dependence*.

Finally, the lack of a consensus on the primary and secondary causes of tumor heterogeneity and on their temporal order poses great challenges to the interpretation and integration of *empirical data*. For example, since the (temporal) order of the causal relationships between genetic mutations, the alterations of regulatory, signaling, and metabolic pathways underlying intratumor heterogeneity is not well known, cancer research copes with a considerable difficulty in interpreting and integrating the empirical data coming from genomics, transcriptomics, proteomics, and metabolomics (Plutynski 2013; Boniolo and Campaner 2019).

Pharmacogenomics in the Light of the Complexity of Intratumor Heterogeneity

After having examined the organizational levels of tumor heterogeneity and its complexity, let us assess the impact of genetic and phenotypic heterogeneity on the epistemological framework and the scientific practice of pharmacogenomics, in order to understand the limits of this branch of personalized medicine and outline some strategies to cross them, thus revealing the potentialities of pharmacogenomics in cancer treatment.

The rationale behind pharmacogenomics is that the effectiveness of drug metabolism hinges on the genetic variations responsible for a certain disease. Accordingly, the main purpose of pharmacogenomics is the discovery of genetic (e.g., nucleotide polymorphisms or variations in the copy number of genes) and genomic variations (e.g., variations in the copy number of genes) behind a disease in order to understand how these modifications affect pharmacokinetics, pharmacodynamics,[31] and immunological responses, and therefore to find the correct dosage of a drug and its gene targets (Crews et al. 2012). Such a gene-based approach to pharmacology relies on the implicit assumption that (acquired or inherited) gene variations occur only *once* and that they do *not change* during a pathophysiologic process.

Nevertheless, what tumor heterogeneity teaches us is that cancer initiation and progression are characterized by a continuous change both in single genes, in allele frequency, and in the overall genome, leading to dramatic changes in the gene expression and phenotypic features of tumor cells. Furthermore, genetic variations are neither the only nor the principal causes of tumor heterogeneity, because many other modifications in the regulatory, signaling, metabolic pathways, as well as in the tissue and organ architecture play a fundamental role in cancer initiation and progression. This being the case, the epistemological premise of pharmacogenomics is seriously compromised because of a *continuously* changing genome that entails

[31] Pharmacokinetics is the study of how an organism affects a drug (e.g., drug metabolism and elimination), whereas pharmacodynamics is the study of how a drug affects an organism. Pharmacokinetics and pharmacodynamics are the main branches of pharmacology,

the *constant* appearance of new phenotypic variations and, therefore, new dynamics in the metabolism of drugs.

The weakening of the epistemological support of pharmacogenomics in cancer treatment is reflected in the limits of its *diagnostic* and *predictive capacities*. Since tumor heterogeneity is a major source of variability in tumor cells, a question arises as to whether a single sample from one specific tumor region is representative of the whole corresponding tumor. Regardless of the selection criteria, the analysis of a single sample reveals some genetic and phenotypic features that are unique to that single sample, and therefore not representative of the tumor as a whole (Cyll et al. 2017). A further problem is posed by pharmacogenomic biomarkers,[32] the discovery of which relies on genetic or transcriptomic analyses of single tumor biopsies taken from primary or metastatic lesions. Genetic and phenotypic heterogeneity may produce *biases* in tumor samplings and in the validation of biomarkers, because it may suggest incorrect causal relationships between (heterogeneous) genetic alterations and clinical outcomes in the discovery phase (Swanton 2012). For example, it has been shown that intra- and inter-tumor heterogeneity preclude the use of some predictive biomarkers (e.g., Prolaris and Decipher) on a single biopsy to administer a successful treatment (Cyll et al. 2017). Accordingly, as pointed out by Plutynski (in this volume), the informational value of cancer biomarkers is rather limited and this reduces their ability to predict the risk of recurrence or to make decisions about treatment.

As a further consequence of the epistemological fragility of pharmacogenomics determined by tumor heterogeneity, the *prognostic power* (and the clinical effectiveness) of pharmacogenomics is undermined. On the one hand, pharmacogenomics has produced positive results in cancer treatment, because the progression of many solid tumors has been shown to be slowed down by identifying and targeting some gene variants for receptor tyrosine kinases (e.g., EGFR, ERBB2, JAK2) (Lauschke et al. 2018). On the other hand, tumor heterogeneity causes additional mutations that lead to drug resistance "even in patients that are initially responsive to targeted therapy" (Lauschke et al. 2018, p. 8). Although some malignant tumors (e.g., chronic myeloid leukemia) have successfully been treated by inhibiting tyrosine kinases (e.g., by employing the imatinib), many anticancer drugs are mutagens that could potentially cause de novo drug-resistance mutations (Lauschke et al. 2018). The mutagenesis produced by anti-cancer drugs is due to the general genome instability of neoplasms, which is closely connected to the genetic and phenotypic tumor heterogeneity. Thus, although a number of anti-cancer drugs have been shown to improve the progression-free survival, they do not offer an overall survival benefit to patients (see, Plutynski in this volume).

[32]Biomarkers are measurable indicators of some biological state which can have a predictive, a diagnostic, or a prognostic value. In personalized cancer medicine, pharmacogenomic biomarkers are mutated genes (found in tumor cells) that are considered explanatorily relevant for the prediction and diagnosis of cancer, and for the identification of new potential therapeutic targets (see, Plutynski in this volume).

The main limitations of pharmacogenomics in the treatment of tumor heterogeneity and cancer progression can be understood in the light of a general theoretical paradigm that dominates the current pharmacology: the idea that *one* drug binds to *one* molecular receptor in order to cure *one* disease (the so-called one drug-one target-one disease approach). Such a theoretical perspective considers the molecular level (genes and receptors) as the most explanatorily relevant one, thus overshadowing other potentially relevant organizational levels (e.g., tissues) for the study and development of drugs. So that, pharmacogenomics is the product of such a conceptual framework, hence suffering from the same epistemological and practical limitations. It therefore seems that a new and perhaps more fruitful way to conceive pharmacogenomics demands a *change* in the *paradigm* of pharmacology: the transition from a *molecular*- to a *system*-based pharmacology in which the molecular level is not necessarily the most relevant one to drug discovery and action, but rather one of the several interconnected levels that underlie pharmacokinetics and pharmacodynamics (Bizzarri et al. 2020b). Let us address this fundamental point, which represents the pars construens of our argument concerning pharmacogenomics.

There are two related senses in which we can talk about a system-based pharmacology. First, the idea that pharmacokinetics and pharmacodynamics can be studied through the construction and the analysis of *network models* that study how different functional entities involved in drug response (e.g., transcription factors, enzymes, signaling molecules) interact among each other *over time* (Danhof 2016). Secondly, the view that *inter-level* relationships and *systemic* properties take priority over gene and molecular pathways, not in the trivial sense that the molecular level is not important, but rather that it (as well as the other organizational levels) is entirely dependent on the inter-level relationships and systemic properties[33] (Bizzarri et al. 2020b) because of a different causal dynamics that take place *in time* and that justify the epistemological relevance of adopting the natural history of the organism as a privileged viewpoint (Bertolaso 2016; Bertolaso and Dupré 2018).

Now, to what extent a system-based pharmacology could be a fruitful tool for the treatment of tumor heterogeneity and cancer progression? A first potential benefit of systems pharmacology is its *predictive* and *diagnostic power*, as it describes the effects of dynamic complex patterns of drug action (e.g., oscillatory patterns) on disease progression (e.g., the exponential progression patterns of cancer). Systems pharmacology studies pharmacokinetics and pharmacodynamics as *dynamical* systems, the evolution of which is predicted by solving a set of differential equations (Danhof 2016). Thus, since tumor heterogeneity is a dynamic process that enables tumor cells to develop new ways to respond to anti-cancer drugs, systems pharmacology could be extremely valuable to make more accurate predictions of how anti-cancer drugs are metabolized and which effects they may produce throughout cancer progression.

[33]This view is ontologically grounded on a relational view (e.g., Bertolaso 2016; Bertolaso and Dupré 2018) and on an organizational account (e.g., Mossio et al. 2009) of biological functions.

A second advantage of system-based pharmacology in cancer treatment is its *prognostic* value, because it seeks to target some entities and mechanisms that are at the root of *tumor heterogeneity* in at least three ways. First, whereas a molecular-based pharmacology develops drugs that target a single gene (or protein), the system-based one adopts a multi-target approach, thus opening up the possibility of using *new therapeutic strategies* also based on nonconventional mechanisms of action (Bizzarri et al. 2020b). For example, nonconventional strategies, such as foams and creams, have been starting to be employed in the cancer treatment in order to promote hydration, inhibit contractile tension, and reduce the local production of reactive oxygen species, thus reestablishing the normal epidermal barriers (Bizzarri et al. 2020b). Secondly, special emphasis is put on *homeostatic mechanisms* that can be exploited to control cellular states. For instance, it has been suggested that epithelial homeostatic mechanisms can be harnessed in order to foster the elimination of precancerous neighbors by epithelial cells (Lahvic and Hariharan 2019). Thirdly, there is an increasing effort to study *tumor microenvironment* with the tools of the computational models of systems pharmacology. For instance, there already exists a computational model that studies the temporal evolution of selected factors associated with immunoactivation or immunosuppression of the tumor microenvironment in order to improve cancer immunotherapy (Mpekris et al. 2020). All in all, these therapeutic strategies likely have the potential to undermine some fundamental (systemic) causes of tumor heterogeneity.

If considered in the context of a system-based pharmacology, pharmacogenomics gains a new *diagnostic* and *prognostic* significance. Indeed, if tumor heterogeneity can be blocked or, at least, slowed down by using a dynamic multi-target approach, then pharmacogenomics turns out to be useful to investigate which *genes* may interfere with or undermine the metabolism of anti-cancer drugs and to find the *correct dosage* of them. In this respect, the employment of pharmacogenomics makes sense only *after* that tumor heterogeneity has successfully been stopped (or slowed down) and always in synergy with systemic, and not only gene-based, pharmacological approaches to cancer.

Concluding Remarks

In the previous sections, after having explored the levels of organization of tumor heterogeneity from the perspectives of both the SMT and the systemic accounts, we have examined some characteristics of tumor heterogeneity that make it a *complex* phenomenon. We have argued that the complexity of tumor heterogeneity lies in that it is a nested phenomenon occurring at different organizational levels and exhibiting an intricate network of causal relations. Such a complexity has important consequences not only in the context of scientific research, but also in the clinical pharmacological treatment of cancer. Indeed, the genetic and phenotypic heterogeneity of tumor cells significantly weakens the epistemological premise of pharmacogenomics based on the idea that gene variations occur only once and that they do not change over time. This epistemological fragility entails

important limitations in the diagnostic, predictive, and prognostic capacities of pharmacogenomics.

We have argued that these epistemic and practical problems of pharmacogenomics are due to the epistemic limitations of the theoretical paradigm of classical pharmacology, which does not assess the complexity of systemic responses to drugs. Therefore, we have suggested that a potential fruitful way to conceive pharmacogenomics is within the theoretical framework of systems pharmacology which opens up the possibility of more accurate predictions of the dynamics of anti-cancer drugs and new (multi-target) pharmacological strategies for tumor heterogeneity and cancer progression. In the context of a system-based pharmacology, there are more concrete possibilities for successfully treating tumor heterogeneity and pharmacogenomics can be a useful tool for finding the genes affecting drug metabolism and for discovering the correct dosage of anti-cancer drugs.

We may now wonder which are the future challenges of pharmacogenomics in cancer treatment and what practical consequences could ensue from our thesis. First, a systemic framework for the pharmacokinetics and pharmacodynamics of anti-cancer drugs entails the challenging task of developing new computational models for the integration and interpretation of different data. Secondly, a biological and philosophical study on the concepts underlying the biological organization of cancer as a whole (e.g., functional integration, regulation, evolvability) will be required. Thirdly, translational research in personalized medicine will likely attract new public and private investments in order to convert the results of the systemic (computational) models of cancer into fruitful anti-cancer treatments. Finally, personalized cancer medicine would eventually relativize the (alleged) deterministic power of genetic mutations in favor of a systemic view of cancer. This may psychologically help oncological patients to consider cancer not as an inherited and inescapable disease, but rather as a very complex pathology that, if treated in a systemic way, could be cured.

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Conceptual and Theoretical Specifications for Accuracy in Medicine

Maël Montévil

Introduction

Medicine is not a science but an art that builds on sciences (Canguilhem 1972). It follows that modern medicine always took into account scientific evidence. In this perspective, the name "evidence-based medicine" is somewhat misleading. Moreover, this methodology was never supposed to build on scientific evidence alone. Instead, proponents of evidence-based medicine also acknowledge the physicians' experience (Sackett et al. 1996; Masic et al. 2008). A similar misnaming occurs for personalized and precision medicine. Since Hippocrates, medicine has always been personalized, and hopefully, medicine always aimed for a reasonable level of precision.

"Evidence-based medicine" and the more recent "personalized medicine" and "precision medicine" are notions that are partially misnamed — their name emphasizes a general aspect of medicine that is not specific to them. These names are less appropriate for philosophy and scientific reasoning than for marketing strategies targeting the medical community, patients, managers, and political deciders. They suggest that other approaches are lacking in the designated area: nobody defends a medicine that would ignore scientific evidence, would be imprecise, or would not take into account the individuality of patients.

Nevertheless, these different stances concerning medicine correspond to specific strategies for the organization and practice of medical care. These strategies are both epistemological and technological. To an extent, they aim to overcome the shortcomings of previous practices and introduce technological changes in therapeutic work. Thus, they are designed to be performative, not descriptive. More

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precisely, the changes introduced are organological in the sense of Bernard Stiegler (Stiegler and Ross 2017): they advocate a reorganization of human activities through their technological instruments of publication, measurement, cure, and care. Let us discuss each case briefly.

Evidence-based medicine has two main specificities. First, randomized trials are paradigmatic scientific evidence in this framework. Researchers use statistical tests to analyze the effect of a treatment by comparison with a former treatment or no treatment at all. Randomized trials aim to reduce biases by randomly constituting treatment groups and, when possible, hiding the nature of the treatment given to both patients and caregivers (to correct the placebo effect). In the vocabulary introduced in Montévil (2019a), this method defines symmetrizations, that is to say, the constitution of groups that are similar in a given sense, even though they are never genuinely equivalent biologically. Evidence-based medicine showed that several physiological reasoning leading to widespread prescriptions were actually harmful. For example, after head injuries, inflammation is a risk factor. However, a clinical trial showed that corticosteroids increased the risk of death and that the standard prescription was detrimental to patients (Edwards et al. 2005). Similarly, myocardial infarction can lead to arrhythmia; however, a clinical trial showed that drugs used to suppress it, encainide and flecainide, actually increase the risk of death (Echt et al. 1991). Second, evidence-based medicine was proposed in the 80s and emerged in the 90s and 2000s. At this time, biomedical research underwent massification and changed its means of publication progressively, from printed papers to digital media. In this context, it is physically impossible for physicians to follow all the relevant scientific literature even though they are traditionally ethically compelled to do so – physicians are required to provide the best possible care. For research to irrigate clinical works, a methodic approach was necessary. Evidence-based medicine proposes for physicians to catch up with the literature based on the cases encountered. It also organizes the literature by the publication of syntheses: reviews and statistical meta-analyses of randomized trials. Meta-analyses are computational summaries of published results, based on statistical computations (Sackett et al. 1996; Masic et al. 2008; Leon 2012).

Personalized medicine and precision medicine stem from a critique of randomized trials, and more specifically of the idea that individuals will exhibit a qualitatively similar response to a given treatment (Leon 2012; Cohen and Hersh 2004). For example, personalized medicine advocates the constitutions of subgroups that may display different responses — a method called stratification. However, by itself, stratification is far from new. For example, the definition of blood groups is a stratification — blood transfusion to a patient may kill or cure her depending on the compatibility of the receiver with the donor. For a large part, the specificity of personalized medicine stems from the introduction of high throughput, relatively low-cost measurement technologies, in particular genomics and sometimes proteomics or microbiome analysis — technics at the molecular and cellular level (The Personalized Medicine Coalition 2014). From this perspective, “personalized” would just mean adjusted to some genomic or other molecular-level

properties — a very reductionist stance that possesses fundamental limitations (Soto et al. 2016b; Bevilacqua 2019).

However, personalized medicine is also emerging when other technologies are being developed, such as cloud computing, especially the new database and deep learning technologies. The connection between personalized medicine and these technologies is undecided to no small extent. It remains at the level of prototypes and projects such as IBM Watson (Rhrissorrakrai et al. 2016) — a project that is seemingly not in good shape. The principal, certain applications of personalized medicine remain limited to specific cases of genetic correlations associated with the choice of a few drugs or the adjustment of drug doses (The Personalized Medicine Coalition 2014). As a result, it is critical to distinguish the real practices, and knowledge from the attempts at performative technological discourses pushed forward by several stakeholders. Let us emphasize that using high throughput methods requires statistical methods. When the latter does not build on the concept of machine learning, they use complex computational models built on classical concepts of statistical analysis.

In this context, the relationship between evidence-based medicine and personalized medicine also remains a matter of debate. For some authors, personalized medicine should be a further development of evidence-based medicine — a logical stance considering that current applications are limited to the use of new observables for the stratification of patient groups (Chow et al. 2018). For others, there is a paradigm shift between the two approaches. Randomized trials assume the homogeneity of the intended population; by contrast, personalized medicine would consider that populations are fundamentally heterogeneous (Leon 2012). The latter option culminates in the notion of $n = 1$ experiments, where an experiment is performed repeatedly on a single individual to provide clues on her response and find suitable treatments.

As mentioned above, the core of these approaches is technological, empirical procedures, where statistical computations are central. However, the bare use of statistical methods is a misuse. More than 800 statisticians defend the idea that the categorization of results by statistical significance (p-values) is damaging science and should not be performed anymore (Amrhein et al. 2019). Along the same line, the American Statistical Society felt compelled to produce a statement on the use of p-values, a unique situation since statements by scientific societies usually target non-academic actors, such as decision-makers (Wasserstein and Lazar 2016). Let us quote this statement:

> Practices that reduce data analysis or scientific inference to mechanical "bright-line" rules (such as "$p < 0.05$") for justifying scientific claims or conclusions can lead to erroneous beliefs and poor decision making. [...] Researchers should bring many contextual factors into play to derive scientific inferences, including the design of a study, the quality of the measurements, the external evidence for the phenomenon under study, and the validity of assumptions that underlie the data analysis. [...] The widespread use of "statistical significance" (generally interpreted as "$p < 0.05$") as a license for making a claim of a scientific finding (or implied truth) leads to considerable distortion of the scientific process.

Part of the (intellectual) context of a scientific experiment is the scientific framework in which it takes place, especially its theoretical and epistemological framework. By contrast with the idea that data and statistics could replace the scientific method (Anderson 2008), statisticians emphasize the role of hypotheses and the underlying scientific reasoning to interpret data and perform statistical analyses. Detailed analyses emphasize this point (Leonelli 2014; Montévil and Longo 2018). Evidence-based medicine and personalized medicine are lacking in that regard. Evidence-based medicine focuses on the generic concept of the randomized trial without addressing the theoretical background of such trials, especially the causal analysis of the treatment attempted. Existing personalized medicine builds mostly on genetic determinism, a somewhat outdated perspective; for example, in some cases, overall gene expression does not reflect radical phenotypic changes (Po et al. 2019). Moreover, the genocentric view can only analyze differences between individuals and groups; therefore, it is blind to general trends such as the current pandemics of non-communicable diseases, a critical topic for current public health (Moodie et al. 2013).

At this point, it is useful to introduce the conceptual difference between precision and accuracy. Let us start with a familiar image: shooting arrows at a target. Precision describes whether arrows hit a specific area of the target consistently, but not necessarily its center, while accuracy represents whether arrows hit the center of the target. In terms of classical measurement,[1] precision describes how consistent a measurement method is, while accuracy describes whether measurements correspond to the genuine theoretical target, for example, the right observables without systematic biases. Here, we emphasize that genuine scientific accuracy requires a theoretical framework, whereas precision makes sense in more lenient settings. Let us take a medical example. Heart rate, as defined by ECG patterns, may be measured with very high precision; however, this precision does not make much biological and medical sense since this rate is a non-stationary time series: its average changes over time, at all time scales. It is far more biologically accurate to obtain a reasonably precise measurement of the value of heart rate complemented by an analysis of its variability (West 2006; Longo and Montévil 2014). We want to emphasize that an excess of precision in reading instruments is considered bad practice in physics and that measurement reports are limited to significant figures, the digits that are assumed to be accurate accounts of the intended theoretical quantity. By contrast, further digits are noise from the measurement apparatus, and reporting them in publications is a bad practice that mixes significant figures and noise. Let us take a final example. In classical physics, both initial position and velocity measurements are required to make predictions. Without velocity, even extremely precise measurements of the initial position are inadequate to make predictions. Such measurements are insufficient and thus inaccurate for prediction purposes.

[1] In classical physics, a system has a state that can be measured with arbitrarily high precision, in principle. However, and again in principle, this precision is never perfect, which is why some systems can be at the same time deterministic and unpredictable.

In this context, we remark that precision medicine is well-named since it is driven by the precision and ease of use of molecular measurement technologies, and not by a rational understanding of health and disease. By contrast, we contend that it is impossible to progress towards accuracy in medicine without proper theorization. In this chapter, we will first review some aspects of the collective work of theorization that the "organism group" as performed. In 2013, Ana Soto created this transdisciplinary group in the context of her Blaise Pascale Chair in École Normale Supérieure. This group aims to investigate theoretical principles to understand organisms in the postgenomic era. Members are Ana Soto, Giuseppe Longo, Nicole Perret, Maël Montévil, Carlos Sonnenschein, Matteo Mossio, Arnaud Pocheville, and Paul-Antoine Miquel. Then, we will point to several theoretical specificities when addressing human health.

Theoretical Perspective on Organisms

In the introduction, we emphasized that theory seems to be excluded from medical paradigms such as evidence-based or personalized medicine. This lack of theorization has very practical consequences. For example, system thinking could bring about significant progress in biology and medicine (Noble 2017; Joly and Rondó 2017). In the NIH (National Institutes of Health) report on systems pharmacology by Sorger et al. (2011), the authors refer to the work of Noble (2002) and consider it a paradigmatic success. However, their scientific recommendations, surprisingly, do not include the central points of Noble's approach. The problem lies in the forceful choice of a molecular ontology to describe phenomena. In heart study, organ geometry and the properties of depolarization waves on this geometry are critical. They are not entailed by generic descriptions at the molecular level of the functioning heart since, among other reasons, these geometric properties are the diachronic results of ontogeny and not of the processes taking place in the adult beating heart. We think that assimilating the lessons of Noble's work is difficult despite its acknowledged success because of the overall lack of theoretical fluency in biology.

We call theoretical fluency the ability to recognize that any scientific statement depends on theoretical assumptions and an underlying epistemological framework. Theoretical fluency also requires acknowledging that a change of framework may be required either for empirical reasons or as a result of intrinsic contradictions of a theoretical framework or contradictions with other, established, and relevant theoretical perspectives. Of course, one may have a perspective of choice, but the progress of science requires the ability to acknowledge and analyze critically other theoretical perspectives and, when needed, to develop new ones. Otherwise, the adhesion to a perspective becomes a dogma that rational criticism cannot reach. Along this line, the lack of sound theoretical debates on carcinogenesis arguably hinders both scientific research and progress in medical care (Sonnenschein et al. 2014; Sonnenschein and Soto 2016; Montévil and Pocheville 2017).

In this situation, paraphrasing Noble (2008), a lot should be done to theorize properly biological organisms. To address current theoretical challenges in the study of organisms, Soto gathered an interdisciplinary group that proposed several new theoretical principles (Soto et al. 2016b). These principles aim to frame and guide both modeling and empirical works in biology. We argue that they also should be useful for medical practice and the critical analysis of scientific evidence — provided that evidence only makes sense in a theoretical framework that defines observables and concept(s) of causality.

The principle of variation posits that invariants underlying the descriptions of biological patterns are ultimately contingent; they have a historical origin and can change over time (Montévil et al. 2016a). This situation is in sharp contrast with theoretical physics' epistemology, where invariants are postulated and explain how objects change over time (Longo and Montévil 2017). In biology, we posit that there are no such invariants. Without underlying invariants, the nature of biological changes is radically different from the ones in physics, and we need to reassess critically the perspectives inherited from physics epistemology. Biological processes involve the emergence of novelties in a strong sense (Montévil 2019b). Accordingly, current biological patterns stem from the historical emergence of such novelties at all temporal levels (evolution and ontogenesis). Let us emphasize that the modelization of a system that is the result of history cannot always be performed with the same method as in anhistorical systems, like in physics (Montévil 2020). Moreover, contexts can change biological organizations without an underlying invariant to subsume these changes. The concept of biological context is then different from the concept of boundary conditions in physics. The latter assumes that the changes taking place inside the system follow equations, with their underlying mathematical invariants and invariant preserving transformations (symmetries). Without these theoretical entities, biological contexts have a deeper impact on an object than in physics. In a nutshell, biological objects become fundamentally contextual and historical.

This perspective alone is insufficient, and we need a specific way to account for biological patterns, that is, biological regularities. We call "constraints" the regularities shaping transformation processes. This action of constraints corresponds to a first kind of causation. More precisely, constraints are regularities in the sense that they are conserved at the time scale of the process they affect but can change at other time scales (Montévil and Mossio 2015). Most of them are far from thermodynamic equilibrium properties: they need to be actively sustained by the use of flows of matter, energy, and entropy from the organism's surroundings. However, organisms are not spontaneous self-organization of flows, unlike flames or cyclones. The latter are the generic result of stable equations once the proper flows are triggered. We insist that this is not a side property; instead, it is a fundamental component of physics' method to understand these phenomena. However, the assumptions of this method do not fit the principle of variation. Unlike "physical laws," which are postulated, constraints are fundamentally historical. As result constraints make possible the appearance of new constraints, a second kind of causation that we called enablement. In the context of the principle of variation, we cannot rely on

underlying, postulated invariants. Then, specific reasoning lines are required to justify their theoretical validity and to understand why some constraints last for an extended period. Natural selection explains part of this stability at the level of evolution: variations that do not lead to a viable lineage are selected against. At the level of organisms, we assume that constraints collectively maintain each other, and we have developed a framework to analyze this situation that we called the closure of constraints (Montévil and Mossio 2015; Mossio et al. 2016). This framework reconnects with principled concepts in Bernard (2015), and the organicist tradition in theoretical biology (see Varela et al. 1974; Rosen 1991; Kauffman 1993) where the meaning of parts depends on their relationship with the whole.

Last but not least, cell theory remains fundamental in biology; however, it is insufficient to understand cellular behaviors. As a result, modelers choose hypotheses somewhat randomly (Montévil et al. 2016b). To overcome this situation, building on previous work (Sonnenschein and Soto 1999), we proposed to reuse a method of theorization existing in physics that starts by defining a "default state." For example, inertia describes what happens when nothing is done to an object in classical mechanics, and the departure from the state of inertia requires a cause by hypothesis; causes are forces in this context. Let us emphasize that, in this method, causation is defined by the departure from the default state. Similarly, the default state of cells is what they do spontaneously. We posited that the default state of cells is proliferation (with variation) and motility, in line with the theory of evolution (Soto et al. 2016a). Like in the case of inertia in physics, a departure from the default state requires causes. In our framework, these causes are constraints. In a developing organism, cells proliferate, mutually constrain each other, and generate other constraints acting on the default state. This perspective transforms the analysis of phenomena such as carcinogenesis or development because the study of constraints and their action on the default state becomes central (Montévil et al. 2016b; Sonnenschein and Soto 2016; Montévil and Pocheville 2017).

In this overall framework, we can specify the theoretical nature of the access to empirical objects, that is to say, the theoretical nature of measurement as commonly thematized in physics (Montévil 2019a). This theoretical question also illustrates the epistemological structure of the theory we are sketching. To fully understand the situation in biology, a critical comparison with physics is necessary due to the historical trickling down of physics views in biology without the corresponding theoretical backbone. In physics, measurement is mostly about getting the position of an object in a theoretically pre-defined space — position and momenta in classical physics. This view is justified by the hypothesis that underlying equations and the corresponding patterns are static. In biology, however, there are changes in constraints and novelties that generate new relevant quantities and relations. Consequently, measurement is firstly about the determination of the relevant constraints, defining an organization. These constraints are never all *explicitly* determined because biological organisms are too complex, and new constraints appear over time. That is to say; constraints are partially unknown both for epistemic and principled reasons. As a result, it is impossible to follow the physics view, which defines objects by static mathematical relations, and the corresponding

invariants. An accurate alternative is to refer to historical relationships, for example, defining groups by a common ancestor. We analyze that the practical way to define experimental organisms builds on their historicity, a rational that is theorized in systematics. The phylogenetic classification of living beings, for example, provide the names used ubiquitously in biology. In this method, groups are all the descent from a common ancestor. The same strategy is used to define laboratory strains of cells, animals, and plants, albeit, in some cases, the history of objects can be complex such as in the case of chimera. The growing weight of the microbiome in the analysis of metazoa also entails that we should consider that complex natural histories are the norm more than an exception.

Let us emphasize that historical definitions do not entail the same kind of practical definition of the object than the definitions of physics. In physics, objects with the same theoretical identity can be obtained de novo because it is sufficient for objects to follow the same invariants to be theoretically identical. By contrast, historical definitions require a material connection and a concrete object as reference for a class — all other objects of the group are connected genealogically to this reference specimen by definition.

Defining objects by their past leads to definitions that remain valid whatever variation occurs. At the same time, this kind of definition does not explicitly provide a control on the organization of objects, that is, the properties relevant for experimental biology and medicine. However, it does give a partial control on these properties, due to the limited pace at which novelties appear and the stabilizing processes mentioned above, that is, natural selection and organization *sensu* closure of constraints (Montévil and Mossio 2020). By definition, constraints have more or less intrinsic stability (Montévil and Mossio 2015), and the stabilizations discussed above are more or less intense, depending on the constraints considered. Moreover, the historical dimension of measurement is complemented by direct observation and control of a limited number of constraints, such as the criteria used in tests to enter a randomized trial. Contexts are also critical and can be controlled more or less strictly before and during an experiment. In the case of human experiments, this control is always limited for obvious ethical reasons, whereas experiments on other living beings can control context strictly for generations (Montévil 2019a).

In this framework, part of the theoretical concept of measurement is a procedure of symmetrization: organisms are considered as equivalent when they have a given shared past, a shared more or less controlled context and some similar constraints that may be directly observed. However, organisms are never genuinely equivalent because variations always occur according to the principle of variation. Depending on the cases, symmetrization can be sufficient to study the structure of one or several related constraints and the structure of the relationship of these constraints with organisms as a whole.

In this context, there are several measurement strategies. Some may aim to obtain organizations that are as close as possible to each other, for example, a population of inbred mice in controlled conditions. However, this somewhat standard strategy bears a cost: it studies a very specific organization which may be far from representative of the population of interest. By contrast, it is also

possible to embrace biological diversity in order to obtain results with some general validity. For example, instead of using a single inbred strain, biologists sometimes use several laboratory strains or even wild animals. The cost is a higher variability of the results, and sometimes uncertainty on the nature of what is measured since the underlying constraints may be diverse. It follows that empirical evidence in biology builds on a compromise between stronger symmetrizations that provide very specific results, and more generality that goes together with a more significant diversity of the objects measured. Building on this trade-off seems more accurate than the opposition between evidence-based medicine and personalized medicine.

To synthesize this theoretical view, we have introduced a framework that integrates the two kinds of epistemology required. Constraints correspond to the relational component of organisms' definition, and are epistemologically closer to physics. Constraints are not principled, theoretical invariants. However, they are valid for a time and a group of organisms, with possible variations requiring different definitions – a change of constraints. It follows that they can be investigated both empirically and by modelizations. In particular, disorganizations such as diseases do not involve a change of all constraints. For example, from the perspective of our framework, the heart model of Noble describes many constraints that are common to health and disease, and only some of them are altered in diseases, leading to irregular heartbeat or even a stroke – this is why this model can analyze several diseases at the organ level.

We also introduced a new symbol, χ, that represents the contextual and historical component of the theoretical and practical definition of organisms, in combination with constraints (Montévil and Mossio 2020). We contend that this kind of epistemological architecture is required for theoretical accuracy in biology. For example, observing only constraints is insufficient to define objects, and such observations also require historical and contextual specifications. It follows that precision medicine, understood as genomics-based medicine, is inaccurate: it accommodates DNA sequences, which acts as constraints on many processes but are a small part of the organization. However, it does not take into account a significant part of organizations. It does not acknowledge the historical component of biological definitions, for example, life history in the case of medicine. Last but not least, introducing, χ, that is to say, historical definitions, implies that we acknowledge the epistemological limitations of descriptions relying only on explicit constraints, including the ability of organisms to generate functional novelties.

Applications and Extensions to Medicine

Let us discuss the consequences of our framework for medical care. First, we examine these consequences at the strictly biological level, and, accordingly, this part of our discussion applies also to veterinary care. Then, we introduce concepts and questions proper to humans.

According to Leon (2012), the difference between evidence-based and personalized medicine is that the former assumes homogeneous populations, while the

latter does not. This author calls for a perspective that would integrate what these two approaches bring to the table, and we think that our framework meets this specification. On the one side, the constraints of interest may be common to a group of organisms, and their integration to the organism, that is to say, their function, may be generic to an extent. Then, we can justify the assumption that a population is homogeneous for these constraints, and thus support the use of randomized trials. On the other side, populations of organisms as such are ultimately heterogeneous, and this may have more or less impact on the constraints of interest — these constraints may change, or their integration with the rest of the organism may be different (Montévil 2019b; Montévil and Mossio 2020).

The analysis of regularities as constraints opens the possibility to integrate different levels and scales, a critical challenge for systems pharmacology and medicine (Sorger et al. 2011; Stéphanou et al. 2018). For example, DNA sequences are constraints on protein production, but the vascular system's geometry is also a constraint, which acts on blood flow. Using this language implies departing from the strictly molecular ontology inherited from the molecular biology revolution, without neglecting its results — the latter can be reinterpreted critically from the organicist perspective. Incidentally, our framework also enables biologists to reinterpret models based on the epistemology of physics. From our theoretical perspective, these models build on constraints and require an explicit articulation with the rest of the organism and the historical dimension of biology.

In our framework, organisms are not objects that follow generic rules. Some aspects of them, constraints, may have restricted genericity; however, the constraints we know at a given time do not entirely and accurately define organisms. It follows that biological norms are not generic; in particular, statistical norms should not be conflated with the organicist norm of a given patient — the norm defined by the analysis of its organization. This idea is emerging in personalized medicine, albeit mostly at the genomic level. When building on this level, norms are somewhat individualized, but they are static and defined at fecundation (except in the case of cancer interpreted with the somatic mutation theory). When faced with diseases or environmental challenges, organisms can generate new norms, at least to an extent. This normativity is central to the conceptualization of medicine by the philosopher and medical doctor Canguilhem (1972). It is also a question that biologists increasingly take into account (West-Eberhard 2003).

Last, current drug designs focus on pushing a target variable towards its statistical norm. If this variable plays the role of constraint, then this normalization can be useful to prevent the disorganization of constraints that depend on it — assuming that the statistical norm is appropriate for the organism of interest. This therapeutic strategy fits well with the kind of evidence promoted by evidence-based medicine. Theoretically, it matches the cybernetic paradigm where the existence of a target value is a critical assumption, and homeostasis for this value results from feedback mechanisms. However, we argue that this paradigm is insufficient because it does not accommodate the structure of biological variability (West 2006) and the articulation between such quantities and the organism (see Bich et al. 2020 for a detailed example and a discussion). As a result, normalizing the value of a quantity

tends to hinder more involved strategies where the interdependence between several aspects of the patient is critical, and analyses at different levels are necessary. Some such situations can be relatively generic; however, they may also be specific to an individual. Then, the practitioner aims to respond to the patient's normativity and accompany it instead of enforcing a statistical norm that is inadequate for the patient.

As mentioned, the discussion to this point is not specific to medicine as such; that is to say, the care of humans. Let us now analyze aspects proper to medicine. To address this question, we consider that a characteristic of humans, beyond the physiological and developmental specificities of *Homo sapiens*, is the massive plasticity that stems from the *noesis*, thinking, and the cultures that it generates. Noesis and culture are not just symbolic; they contribute to shaping human bodies, and the world humans live in. In particular, technics generate what can be analyzed as exosomatic organs, leading to a major transition in the process of evolution, that is to say, evolution by producing inorganic organs, typically artifacts (Lotka 1945). Similarly, culture shapes the non-human organisms living in human worlds, both by the extinction of large predators and the domestication of plants, animals, and even bacteria, for example, to produce fermented food. All the corresponding practices are shaped by knowledge in the broad sense instead of biological evolution alone.

What are the consequences of this theoretical framework on medicine? We discussed above the contextual nature of biological objects: in the absence of principled theoretical invariants, constraints of an organism depend on their past and present contexts. It follows that changes in technics, for example, typically can be associated with changes of organizations even at the strictly biological level. Let us unpack this idea.

A patient's conception shapes the biological level significantly. A patient anticipates her future, and these anticipations impact her medical decisions straightforwardly. In this sense, patient anticipations are a normative force on the biological level of description, via medicine.

Moreover, the way a patient conceptualizes her own body has a profound impact on diseases, as exemplified by the fact that some diseases are specific to a culture (Kuriyama 1997, 1999). Moreover, a patient's conception impacts her everyday life, and the latter profoundly influence health and disease, as illustrated by the current pandemic of non-communicable diseases (Moodie et al. 2013).

Technics and technologies shape more or less directly biological norms and diseases. Let us consider dyslexia. This condition only makes sense once writing appeared. To better understand this case, it is critical to recall that writing appeared relatively recently in human history and became a practice of general populations even more recently. As a result, the ability to perform these activities is not stabilized by evolution. Unlike spoken language; reading and writing require exaptations of several brain areas that are facilitated at each generation by pedagogic methods. Moreover, these exaptations differ depending on the writing system and the media — which explains why reading with digital media differs from reading on paper (Wolf and Stoodley 2008). In this case, technics, culture, and biology become intertwined to define health and disease, and it stands to reason that norms cannot stem only from the evolutionary past.

The case of dyslexia may be seen as somewhat specific since it corresponds to the mastery of a specific technic (reading and writing). However, we argue that the impact of technics on biological property is deeper. Protsiv et al. (2020) observe a decrease of body temperatures since the industrial revolution. Moreover, the pandemic of non-communicable diseases, such as diabetes and obesity, is a major illustration of the intrication between technics and somatic heath. This pandemic stems from the organization of production and the prescription of behaviors by mass media and advertisement. However, the relationship between technics and organic properties is far broader. As pointed out by Lotka (1945), technics are a fundamental part of the way humans evolve, i.e., change the way they live, in a process that he called exosomatization; that is to say, the functional use of non-somatic organs. However, this process destabilizes both somatic and social organizations, and, in the philosophy of Stiegler, care and knowledge are critical for social and biological reorganizations to incorporate new technics and technologies, mitigate their toxicity and reshape them to this end when needed (Stiegler 2016; Stiegler and Ross 2017). The pandemics of non-communicable diseases driven by industrial technologies strongly suggest that much work remains to be done to mitigate the negative impacts of current technologies on the biological level (Moodie et al. 2013). In this context, the theoretical analysis of how technics can disrupt biological organizations remains insufficient (Montévil 2021). Such disruption range from the chemical level, for example, in the case of endocrine disruptors, to the use of digital media by young children and their parents. Endocrine disruptors are chemicals or mixtures of chemicals that interfere with hormone action and disorganize the development and physiology of exposed organisms (Zoeller et al. 2012). Similarly, digital media, especially smartphones, tend to capture attention by design and disrupt the relationship between children and their parents and between children and their toys, leading to detrimental consequences (Brown et al. 2011).

Following the broader line of reasoning of Bernard Stiegler and the *Ars Industrialis* group (Stiegler and Kyrou 2015), we argue that future medical care requires developing popular knowledge. Groups typically generate such knowledge. Examples are groups of patients with a chronic disease, such as diabetes, or patients experiencing addiction such as alcoholism (Kelly et al. 2020). Such knowledge should be generated on the vectors of these non-communicable diseases, and, more generally, on the changes introduced by technics and technologies. Such knowledge should shape technology uses and technological developments towards less toxic paths. In other words, normativity should extend beyond the somatic body including for the health of the somatic body. For example, knowledge on food, from raw products to cooking has a direct impact on somatic health, including the microbiome and the immune system. Another direct example are prostheses from glasses to artificial limbs with digital technologies. However, the general idea that we defend is that there is no sharp line between prostheses and general technologies. For example, technologies are central to follow sugar levels in the case of diabetes. Knowledge is also relevant for the prevention concerning vectors of communicable diseases that are indirectly affected by technologies, like the tiger mosquito, which migrates in response to climate change. In this perspective, patients

and the general public are no longer considered as passive recipients of vulgarized medical knowledge, making informed decisions; instead, they become normative not only for themselves but for technologies as such. Moreover, this normativity does not stem from individuals. Instead, it is the result of collective work, and primarily group works.

This general reasoning also applies to medical care practitioners. Medical practitioners have to tame the technologies that they use to ensure the accuracy of their work. To this end, a critical assessment of the technologies pushed forward as precision or personalized medicine is mandatory. This assessment should include the theoretical points we have developed above; however, it should also include the consequences of these technologies for the practitioners. For example, relying on automated diagnosis means that knowledge is transferred from the practitioner to the technological apparatus. This transfer entails a loss of practitioner knowledge in a process called proletarianization. By contrast, computers can be used to increase clinicians' capabilities in the sense of Sen (1999). These capabilities should enable medical care practitioners to go beyond the application of standardized protocols and accompany patients' normativity better, both at the individual, biological level, and at the group, noetic level.

Let us wrap our discussion up. Accuracy in medicine requires a well-defined theoretical basis. We argue that this basis should analyze organizations as a whole and in their historicity. Historicity means that organizations are the result of history but also that they produce history by generating new constraints. It follows that statistical norms and biological norms cannot be conflated and that medical practitioners cannot always follow standardized protocols if they are to accompany this normativity. This normativity is not just strictly biological. Instead, patients' ability to generate knowledge is part of this normativity, and this work is typically performed in groups. Groups are then a fundamental level for health care. Let us emphasize that the current period is characterized by rapid changes in technologies or due to technologies, such as climate change. As a result, an accurate account of health care cannot ignore this group level normativity that impacts lifestyles, technics, and biological properties. Last, the same applies to the use of technologies by healthcare practitioners themselves, such as the ones advocated by evidenced-based or precision medicine. Technologies require specific knowledge to mitigate their negative consequences, and specifically, algorithmic methods tend to ignore normativity at all levels.

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Personalized Treatments: Where Patient's History and Biological Background Meet

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Basic Definitions

Personalized Medicine (PM) (Hamburg and Collins 2010) – "to match the right drugs to the right patients" – has become a widely used term in both the scientific community as well as in the public debate, its vagueness notwithstanding. Indeed, PM lacks a clear definition and is open to interpretation (Evers et al. 2012). In the early twentieth century, PM was referring to a number of integrated medical resources (not limited to drugs), set in place to address patient's needs in a "holistic" way. As such, a "personalized approach" is a common tenet of old western practitioners and physicians in the eastern World, the latter mostly relying

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Fig. 1 Personalized Medicine in Ngram and PubMed. Representation of "Personalized Medicine" as area of interest in both PubMed (Left) and Ngram Viewer (Right side). The diagram illustrates how interest as well as quoting of "Personalized Medicine" in both scientific and popular articles, is rapidly declining

for their treatments on "personalized", complex mixture of herbal compounds, assembled according to the specific traits of each individual (Leonti and Casu 2013). However, in the last 20 years, PM acquired a different meaning, indicating a target-based treatment for selected sub-groups of patients carrying the genetic/biochemical abnormalities considered the driver cause of the disease under scrutiny. Unfortunately, this definition involves a number of unresolved epistemological and theoretical issues that further complicate an already complex puzzle. Just to start with, several diseases – like cancer, cardiovascular diseases, and diabetes – cannot be ascribed to a unique, simple deregulated genomic pathway, while effective drug-based targeting of such processes is still far from being achieved with our current technologies. PM seeks to improve stratification and timing of health care by utilizing information primarily obtained from the lowest biological level, i.e., the genomic-proteomic level. Therefore, a major drawback of PM lies precisely on the fact that this approach disregards almost completely those factors acting at levels higher than the cellular one (microenvironment, tissue and physiological levels), whose contribution is anything but irrelevant in triggering the transition from healthy status to disease.

Therefore, it is not so surprising that experimental studies were finally unable to substantiate the very preliminary expectances of PM. In fact, sobering recent studies have generally shown that most patients with cancer, clustered according to sophisticated genomic testing, do not benefit from a "precision medicine" strategy (Fojo 2016; Letai 2017). This finding, altogether with the epistemological indeterminacy that wraps the concept of PM, can partly explain why in the last years PM has lost much of its charm, as evidenced by the decreased recording in both PubMed and Ngram Viewer (Fig. 1). It is quite disturbing that this happened the US federal government's 2016 Precision Medicine Initiative, as well as the Cancer Moonshot effort championed by former Vice-President Joe Biden, notwithstanding.

Therefore, some authors have tried to overcome such perceived failure by incorporating "extra-genomic" factors in the PM framework, thus implicitly recognizing the intrinsic inadequacy of preliminary approaches (Snyderman et al.

2016). However, "When evaluating any new intervention, we rightfully expect to see trial data that demonstrate improvement in a prospectively defined, clinically significant end point measured in a population of patients who receive the novel approach compared with those who are managed by current standards of care. Though precision medicine is a buzz-worthy catchphrase, it falls woefully short by these criteria" (West 2016a, b).

Promises and Premises of Personalized Medicine

As above sketched, advances in genomics has allowed to stratify patients into distinct groups, based on a few molecular differences, which are deemed to play a critical role in the pathogenesis process. Accordingly, disease individuation mostly relies on the gene-expression pattern associated in a specific patient, allowing depicting a one-to-one correspondence upon a hypothetical Cartesian space, between the "genomic signature" and the illness in each individual (Joyner and Prendergast 2014). This promethean dream comes true in 1999, when Francis Collins established in a seminal paper the ways the human genome would be used to predict, prevent, and treat disease in the next 10 years, so as a complete transformation in medical practice would be expected even before 2020 (Collins 1999). This is the (bewildering) promise. However, we are in 2020 and this astonishing revolution in medicine is not tacking off.

Clinical randomized trials have provided little if any evidence of benefits when patients with different disease have been treated with personalized-based treatments (Prasad et al. 2016; West 2016a, b), contributing eventually to the emergence of the so-called "reproducibility crisis" in biology and medicine (Ioannidis 2005; Bizzari 2019). Still worse, these disappointing results prompted to cast on doubt the foundational assumptions of precision medicine (Joyner and Paneth 2019).

Indeed, even "simple", monogenic diseases – in which a single point mutation is recognized as the "main" causative factor – are not "simple" in their pathogenesis, as a number of additional factors, distributed across different hierarchical levels of the living organisms (from the DNA to physiological apparatus), are ultimately responsible of the disease phenotype. A paradigmatic case is provided by sickle cell anemia, a classic monogenic disorder, in which the interplay among a number of context-dependent cues enacts the emergence of no less than six different pathological phenotypes (Kato et al. 2007). Some patients develop principally painful crises with or without bony infarcts; others are prone to hemolytic crises; some develop vaso-occlusive crises, including stroke; still others develop acute chest syndrome, while many are phenotypically normal, except for mild anemia. What matters here, is that the treatment – to be "precise" – must be tailored according the emerging clinical pathophenotype, and not based on the original point mutation. In this case, the PM could hardly fit the specific needs of each patient, given that the genotype cannot predict the phenotype (Loscalzo et al. 2007). Additionally, gene variants (including mutated genes), initially thought to play a "pathogenetic" role in several complex diseases have been "reclassified", given that their involvement

becomes "problematic" (Sorelle et al. 2019). Overall, only a small proportion in the frequency of different illness can be ascribed to gene variance, and in the majority of cases, genes involved do not seem to possess any hypothetic, biologically based link with the pathogenetic mechanism, nor they can offer any clinical utility for prognosis (McClellan and King 2010). As a fact, the relative risks for the vast majority of gene variants rarely exceed 1.5 (meaning that the increase in risk attributable to that genetic variant account for 0.5), and these variants have added little useful predictive power to traditional risk prediction algorithms. Even for diagnostic purposes, wide genome analysis often fail to equate the predictive power of classical medical parameters (anamnesis, neighborhood, socioeconomic status, dietary habits) and sophisticated assessment of gene expression patterns add little (if any) to conventional predictive models (Morris et al. 2016).

It has been argued that the discouraging results obtained by PM-based clinical trials should be attributed to selection bias and uncertainty in defining clear outcomes (Schwaederle et al. 2016), while developing more sophisticated approaches to identify specific patients subsets – using broad molecular testing and integrated genomic data from liquid biopsy samples (Lebofsky et al. 2015; Gyawali 2017) – would in principle help in overcoming such a failure. This is wrong, as although the number of patients eligible for genome-driven treatment has increased over time, these "tailored" drugs have helped only a minority of patients with advanced cancer (Marquart et al. 2018). Moreover, unambiguously statistical criteria for patient's selection and for outcome parametrization are still inadequate. A number of technical methodologies – including unsupervised, agnostic, discovery, and data mining – have been used without explicating clear hypotheses to justify the observed (statistical) correlations. Therefore, selection bias and factors that can distort exposure-outcome correlation are usually overlooked. However, population based studies of a disease require specific theoretical assumptions that inform data collection and allow to ascertain both exposures and outcomes in a standardized fashion (Joyner and Paneth 2015).

To address such issues, instead of reconsidering the biological assumptions on which the PM strategy has been developed, an increasing number of scientists preferred to bypass that hurdle by adopting a new statistical-biometric approach as such provided by the Big Data Theory. Yet, even this framework showed to be unsuccessful (Prasad 2016). Data handling does not produce any new information by itself, as correlation does not means "causation". Furthermore, few prognostic factors or systems are robustly validated, and still fewer have made a convincing difference in health outcomes or in prolonging life expectancy (Ioannidis 2009). For most diseases and outcomes, a considerable component of the prognostic variance remains unknown, for our understanding of the critical mechanisms on whom the disease process depends is still insufficient. Additionally, most correlations are spurious, i.e., very large databases have to contain arbitrary correlations (Calude and Longo 2017). Empowerment of statistical analysis and sophisticated modelling cannot compensate for the lack of theory into which information from experiments need to fit. Computationally intensive tools for the exploitation of huge data sets are still based on poorly designed model; presumptively, they can only help in

generating new hypothesis, but not true explanations. Consequently, applications of Big Data Theory have met with limited success in scientific domains, up to now (Karpatne et al. 2017). Therefore, a new theoretical framework is urgently warranted "as a guide to experimental design for maximal efficiency of data collection and to produce reliable predictive models and conceptual knowledge" (Coveney et al. 2016).

Limits of Personalized Medicine Unveil the Inadequacy of Pathogenesis Theories

Numerous members of the oncologist community have warmly embraced personalized Medicine – often called also "precision medicine" – as a way to find drugs that could selectively interfere with critical targets (Kaelin 2005). The theoretical framework on which such treatments rely has been borrowed from the Somatic Mutation Theory (SMT). According to SMT, cancer is a cell-based disease (Weinberg 2008), due to the accumulation of somatic mutations and/or chromosomal aberrations that alter the control of proliferation in a single cell that eventually will generate a neoplasia. This approach is essentially "reductionist" in essence, as it posits that the system – cells, tissues, cancer – can be explained by studying its parts in isolation, while the principal causative factor must be identified at the lowest level of organization (i.e., DNA, proteins and so forth). This model has been extensively criticized given that is unable to accommodate with an increasing number of controversial and paradoxical results (Bizzarri et al. 2008; Weinberg 2014; Apple 2016). For instance, accumulating evidence shows that genomic alterations, such as those in BRAF, RAS, EGFR, HER2, FGFR3, PIK3CA, TP53, CDKN2A, and NF1/2 – all of which are considered hallmark drivers of specific cancers – can also be identified in benign and premalignant conditions, occasionally at frequencies higher than in their malignant counterparts (Martincorena et al. 2015; Kato et al. 2016).

Furthermore, the search for critical genomic targets is seriously flawed from the outset by the unavoidable, intrinsic genomic heterogeneity of cancerous tissues (Kamb et al. 2007). Distinct coding region mutations can be present as high as 100 million even in a single tumor (Ling et al. 2016), while sequencing and genome analysis of multiple biopsies from different regions of the same tumor reveals the wide spreading of genomic heterogeneity (Gerlinger et al. 2014). Intratumor heterogeneity is present since the early steps of cancer development and, it is uncanny that chemotherapy can select further subclones, sharing increased aggressiveness and dedifferentiation, progressively becoming insensitive to any medical control (Bhang et al. 2015). Such heterogeneity, arising from a hierarchical pattern of stem-cell divisions, yields a mosaic of different cells and, ultimately, can hamper cancer treatment (Seoane 2017). This inescapable complexity contradicts the superficial textbook concept of clonal expansion of a dominant cell clone carrying the oncogenic mutation that "takes over" the entire tumor. In the real world each cell show a distinct set of mutations, while the subset of cells carrying

"driver" mutations are unable to canalize the overall population into an unique, homogenous gene-expression pattern. In fact, although some tumors harbor a dominant population emerging from clonal selection, genomic diversity is the rule than the exception (Navin et al. 2010). This process entails not only the topological distribution of cancer cells within the tumor, but also emerges at multiple time points during tumor progression, as demonstrated by liquid biopsies obtained from serial samples (Ma et al. 2015). These data indicate that distinct clusters from the same tumor may undergo independent progression pathways, which culminate into the simultaneous presence of different phenotypic populations, each one harboring different malignant traits. This bewildering variety in cancerous phenotypes cannot be ascribed to differences in genomes, but call into question the existence of epigenetic mechanisms and subtle modulation of the gene regulatory networks (Brock et al. 2009). This non-genetic heterogeneity of tumor cell states defies a "precise" genotype–phenotype causal relationship and allows them to adapt to both environmental perturbations (nutrients availability, cells crowding, and hypoxia) as well as treatments without enacting the appearance of additional mutations. Again, these findings confirm that there is no straightforward linear causal relationship between tumor genotype and phenotype (Huang and Brock 2017). Moreover, cancer cells within individual tumors often exist in distinct phenotypic states. Given certain conditions, any subpopulation of cells (i.e., with different phenotypes) will return to equilibrium phenotypic proportions over time, after experiencing a critical transition (Gupta et al. 2011), which enacted the disclosure of multiple, branching differentiating trajectories (Anderson et al. 2011). Notice that cancer stem-like cells arise de novo from non-stem-like cells, thus *regenerating* the malignant potentiality of the tumor. This is why seemingly identical cells respond differently to treatments, given that phenotypic and genotypic differences provide differentiated response by activating even opposite outcomes in cell behavior and ultimately escaping the drug-induced inhibition on specific targets (Li and Zeng 2009). Overall, these findings highlight how complex and unstable is the gene expression pattern of a tumor population, within each patient (Swanton 2019).

This body of evidence cannot easily accommodate with the prevailing carcinogenesis model. Instead, accumulated pitfalls contribute in laying bare the inadequacy of the SMT. To overcome these limitations, SMT became subject to a number of course-corrections, which strive to integrate new concept by recurring to twisted arguments (Wallace 2012). Latest versions of SMT include even the microenvironment – viewed as instrumental in promoting carcinogenesis – while trying to preserve the native mutation-based hypothesis (Bissell and Hines 2011). All in all, these attempts looks like the epicycle-based strategy used in ancient time to accommodate with the experimental facts that challenged the Ptolemaic system (Sonnenschein and Soto 2006). In alternative, in order to get rid of these conundrums, cancer has been proposed as an emergent phenomenon, due to a deregulated cross talk between cells and their microenvironment (Bussard et al. 2010). Carlos Sonnenschein and Ana Soto have conceptualized this new framework within the Tissue Organization Field Theory (TOFT) (Sonnenschein and Soto 1999; Bizzarri and Cucina 2016). TOFT is anchored at the tissue level of biological

organization and conceives the development of cancer as a relational problem, focusing not on a single cell type but, as in organogenesis, on the interactions among different cell types and their microenvironments. The alteration in the interplay among those components involves different levels of organization and a number of *secondary* changes, eventually including the emergence of disrupted gene-expression patterns. In agreement with TOFT, mutated genes are the result, and not the cause, of the disrupted normal tissue architecture that eventually ends up in fostering cancer onset (Sonnenschein and Soto 2020). Therefore, changes in genomic profiles or in biochemical pathways can only be *associated* rather than considered as *causative*. Admitting this bitter conclusion would deprive precision medicine in oncology of its rationale, given that PM relies on targeting a validated and genetically stable driver of disease. To date, proof-of-concept trials have not supported this premise (Bizzarri 2019; Bowen and Sasadevall 2015). Moreover, target-based treatments in oncology suffer from two major drawbacks: (1) currently available inhibitors of specific pathways provide only minimal or complete blockade of biochemical pathways, and are therefore inefficient or too toxic to be used (Greenwell et al. 2017). (2) Second, critical networks in cancer – as well as in living cells – show a bewildering plasticity and adaptability, even under harsh environmental conditions, thus allowing the system to escape from programmed cell death (Johnson et al. 2014). Overall, those considerations help in explaining the shift in interest from the cancer cell to the stroma (Tchou and Conejo-Garcia 2012), and substantiate the relevance of microenvironment-based studies in search of new treatment options, as advocated by TOFT (Bizzarri and Cucina 2014).

Furthermore, even attempts to "reconcile" the "causative" role of mutated gene with the microenvironment-based perspective – as that aptly argued and proposed by advocates of the so-called dynamic reciprocity model (Bissell and Hines 2011) – failed in demonstrating that mutations are mandatory to enact the cancerous phenotype. Indeed, experiments with chick embryos infected with the "oncogenic" Rous sarcoma virus (RSV) did not lead to malignant transformation, even though the proto-oncogene v-Src was expressed and active. However, cells explanted from these embryos rapidly became transformed in culture, when they are losing the tissue-based constraints (Dolberg and Bissell 1984). As recognized by the Authors, these experiments indicated that factors involved in wound repair and tissue remodeling exert a mandatory role in RSV-oncogenic transformation, "and that as long as tissue architecture was not disrupted, RSV-infected cells did not become malignant" (Kenny and Bissell 2003). Furthermore, mutated cells that, according to current dogmas, should lose control becoming invasive cancers, not seem to form as many cancers as would be expected from the number of harmful mutations (Bissell and Hynes 2011). Finally, when human breast cancer cells in three-dimensional laminin-rich gels were shown to *revert* to a near normal phenotype, the genome of the reverted cells was shown by comparative genomic hybridization to be no different than the mutated and malignant cells grown in two-dimensional cultures (Weaver et al. 1997). These experiments clearly demonstrated that a proper microenvironment can successfully neutralize the putative carcinogenetic effect of "oncogenic mutations" (Weaver et al. 1995).

Personalized treatments are unable to cope with such an overwhelming complexity (Scannell and Bosley 2016), and the small improvement in cancer survival recorded in the last years can only minimally be ascribed to target-based therapy (Hawkes 2011; Bizzarri 2017). Namely, randomized, large studies with different combination of target-based treatments in a number of cancer types, failed to demonstrate any significant encouraging efficacy in any of the treatment arms or patient subsets (Dingemans et al. 2013; Papadimitrakopoulou et al. 2016). A multicenter randomized trial of treatment based on tumor sequencing compared with conventional cancer treatment showed no advantage of sequencing (Le Tourneau et al. 2015), as did the NCI-MATCH (National Cancer Institute–Molecular Analysis), in which almost 6000 patients have been enrolled (Eckhardt and Lieu 2019). Similarly, a basket trial testing molecularly guided treatment approaches for multiple mutations in advanced non–small-cell lung cancer demonstrated to be unsuccessful (Lopez-Chavez et al. 2015). Expectancies from the recent introduced immunotherapy approaches have been disappointing as well. Immunotherapy had only limited effects on the drop in overall cancer mortality. The undisputed benefits for melanoma and for advanced and metastatic lung cancer are impressive, but so far affect relatively few people and are associated with life-threatening side effects (Kroschinsky et al. 2017). Overall, the weight of this evidence prompted to suggest, "our best weapons against cancer are not magic bullets" (Prasad 2020)· Therefore, precision medicine – especially in oncology – has lost most its fashion and raised embarrassing concerns. A sober view of the evidence derived from prospectively designed trials of personalized medicine, inevitably leads us to consider "that our current oncology community will be guilty of hubris and of overpromising what we can deliver in a realistic time line" (West 2016a, b).

Disease as a Controversial Concept

It is disheartening that the debate on PM has left aside a preliminary premise: what do we mean by "disease" (Hesslow 1993)? No doubts that a number of inconsistencies of our modern treatment strategies – including those claimed by PM – should be attributed the controversial concept of human disease. The debate on that subject mostly developed around two opposite positions represented by Constructivism and Naturalism. The former, essentially denies the naturalist thesis that disease necessarily encompasses bodily malfunction and claims for a general "reformation" of the concept of disease, conceived as a "societal", historical-based construct (Reznek 1987). On the contrary, according to the naturalistic perspective – by far the only to which the daily medical practice actually relies – a disease involves malfunction of organs/apparatus, which either can or cannot be perceived as such, i.e., by complaining symptoms (Kitcher 1997).

The latter model originates from Virchow's conclusion that all diseases result from cellular abnormalities (Porter 1997). Since the discovery of the double helix in the 50s, however, that framework was strongly superseded by an even more reductionist approach, as that provided by the New Genetics, which posits that every

disease can be traced back to the malfunctioning of a discrete number of genes (Stefl et al. 2013). Briefly, this reductionist model relies on the following three premises: (1) the disease recognizes a dominant (molecular) cause; (2) medical signs and symptoms – which all together constitute the disease phenotype (the "pathophenotype") – are linearly correlated with the molecular cause; (3) removal/correction of the underlying, putative "cause" will restore healthy conditions. Sad to say, that model still awaits to be vindicated beyond any reasonable doubt, especially for degenerative diseases or mental illness (Wade and Halligan 2004). Moreover, such framework becomes problematic when considering in the perspective of "preventive" medicine (Smith 2002). Are presumptive markers of a "future" disease condition reliable enough to ask for a "preventive cure"? Could a genomic profile allows drawing a reliable probabilistic ascertainment of a future disease? Thereby, could someone with a "genetic predisposition" – whatsoever this really means – be considered already sick?

Nevertheless, in the last 30 years diseases have been increasingly "equated" to the malfunctioning of a few, critical pathways or of their related driver-genes. Consequently, drug discovery has been dominated by reductionism, aiming to identify drugs that activate or inhibit specific molecular targets. Unfortunately, therapeutic approaches based on such a simplistic paradigm often showed either unforeseen toxicity or lack of efficacy when tested in clinical trials (Scannell et al. 2012).

Furthermore, the adoption of this reductionist-based approach progressively distorted and shaped medical practice – namely by radically modifying the diagnostic methodology and the doctor-patient relationship – leading towards a new "disease taxonomy" (Kola and Bell 2011). Consequently, we are witnessing a number of inadequacies in the current medical practice, which often reflect a lack of specificity (i.e., inability in defining a disease unequivocally), and a lack of sensitivity (i.e., incapacity in recognizing preclinical, true causative state of disease). Ultimately, this model proven to be confounding, as it often posits wrong correlations between the disease-associated biological parameters (usually identified only when illness reach a "stable-state") and the alleged causative processes, thereby prejudicing efficient treatment strategies.

Disease as a Historical Process

At a first glance, the starting premise of PM rely on the following, abridged statement: one genotype-one pathophenotype. This is wrong, even for simple monogenic diseases. The abovementioned example of sickle cell anemia highlighted a complex interplay of different causative factors – spanning from cell to higher levels of living system's organization – which ultimately fosters the emergence of no less than six different disease phenotypes. Similarly, EBV infection is recognized to promote mononucleosis or Burkitt's lymphoma. In both conditions, B cells are the primary targets of EBV infection (Thorley-Lawson 1998), and infection of B cells leads to the expression of a limited set of viral gene products, which drive

the cells into proliferation. In inhabitant of Western countries, proliferation of EBV-infected B cells is limited by CD8+ and CD4+ T cells, thus leading to the onset of infectious mononucleosis. On the contrary, in children living in a number of equatorial countries of World, EBV infection is more likely to induce a tumor of the lymphoreticular system (Wright 1978). It is now widely recognized that a critical issue that can switch the outcome from a mild form of influenza to an aggressive lymphoma is the host response to EBV infection. A factor that cannot be deduced from the genomic analysis either of the viral genome, nor the genome of the host. The difference lies on the previous medical history of the host and on the specific interactions that EBV triggers with the immune system of each individual (Giller and Grose 1989). In simple words, the specific disease arises from a dynamic process in which the primary causative factor (the virus) interacts in a non-linear fashion with complex apparatus of the host (not limited to the cellular compartment). Organs, cells and tissues are in turn "shaped" and "customized" by the previous medical history of the organism living in a very unique environment (Grömminger et al. 2012). As a result, EBV infection is currently known as the main "causative" factor of a number of disparate diseases, including pharyngeal carcinomas (Rezk et al. 2018), gastric cancer (Naseem et al. 2018), as well as non-malignant illness, such as the childhood disorders of Alice in Wonderland Syndrome (Mastria et al. 2016), systemic lupus erythematosus (Ascherio and Munger 2015), and acute cerebellar ataxia (Nussinovitch et al. 2003). This example epitomizes that a disease cannot be considered a "static" state, but should instead be considered a dynamic process, ruled by non-linear dynamical relationships, which can ultimately drive the system toward very different outcomes. Broadly speaking, "genetic defects" cannot predict the pathophenotype, which ultimately emerges from the complex interactions among different factors, distributed across several, hierarchically organized levels.

According to the PM premises, the causative factor(s) that are thought to contribute to the disease process, still should be "at work" at the time of treatment. However, as happen for several conditions, the mechanism/gene responsible for the onset of the illness might have exerted its action during early pathogenic steps and could no longer be active during the steady state of the disease, when diagnosis is usually reached. Some developmental-based diseases, like mental illness (Hirsh and Weinberger 1995) or cardiovascular diseases, falls within this category, as well as some cancers that "must" lose their mutated, "driver" oncogenes precisely when they metastasize and – paradoxically – become more aggressive (Plattner et al. 1996).

However, pathogenic interactions distributed across a space-temporal continuum, given that a number of genomic-related factors are likely to act only during some critical developmental phases (during the intra-uterine life, at the birth, in the neonatal and pre-pubertal period). This is why disease development is a time-dependent process, tightly linked to the patient's history (Fig. 2).

In the last resort, disease should be viewed as a manifestation of developmental plasticity, the phenomenon by which one genotype can give rise to a range of different physiological or morphological states in response to different

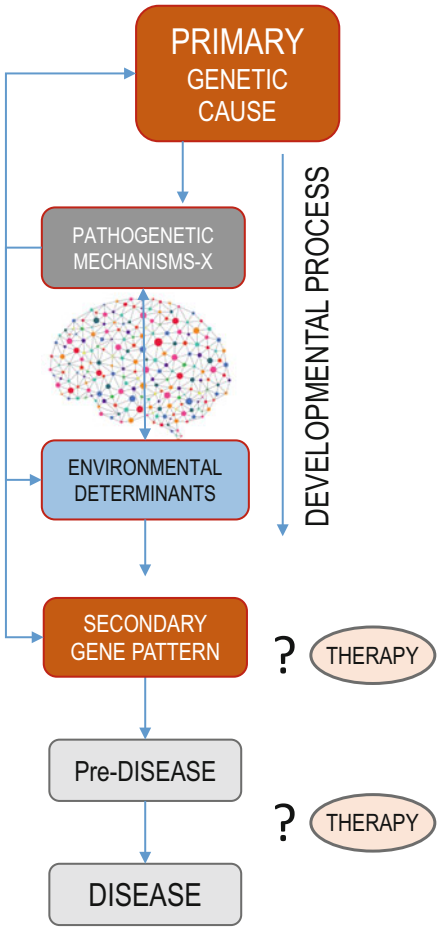

Fig. 2 Genetic predisposition + environmental cues + unknown triggering factors at the roots of Schizophrenia. Recent studies suggest schizophrenia is caused by a developmental deficit during the prenatal period or around birth. The cause of the deficit could be a range of factors such as viral infections in utero or hypoxia during birth that affect the normal developmental process. This means that the factors that caused the changed development may only have been present for, for example, 30 min around birth and then are gone forever and that the genetic environment only confers a susceptibility to the individual in terms of being extra sensitive towards these external manipulations at the time of the insult. The consequences are that a treatment does not have to be related to the factors that caused the disease initially or to the genetic predisposition. The disease process cannot be reversed in the adult because the brain cannot be rewired back to the connectivity it should have had if the developmental insult had not taken place

environmental conditions during development (Barker 2004). Therefore, numerous chronic diseases are currently supposed to arise from some "disturbances" acquired during critical developmental periods (Barker 1990). The capacity of genetically similar individuals to produce substantially different phenotypes depending upon

environmental conditions during early life or in some other critical periods (puberty, pregnancy, peri-menopause, etc.) is usually defined as *developmental plasticity*. Emergence of disease can *intersect* developmental plasticity by establishing complex links between critical life periods and adult health (Garland and Kelly 2006). A disease can assume different *shapes* and specific evolutionary traits according to the period at which the pathogenetic cues interact with the developmental processes. In other words, those environmental conditions that actively entail developmental processes can also modify in a significant way the "natural history" of the disease (Kuzawa and Quinn 2009).

Epigenetic and post-translational changes can efficiently begin as early as during pregnancy (still in womb), and may be affected by the paternal/and maternal environments, as well as by early life events (dietary habits, childhood diseases, premature exposure to environmental carcinogens and toxicants like endocrine disruptors) (Soto and Sonnenschein 2018). These modifications play a critical role in shaping cells and tissue sensitivity to carcinogens, ultimately favoring the emergence of cancer in the adult life (Speroni et al. 2017; Soto et al. 2013).

This premise carries additional consequences. Diseases – altogether with their "causative" targets – are usually recognized by late-appearing manifestations. However, disease development entails a number of time-distributed steps, and specific treatments should be put in place at each, distinct phase. Moreover, diagnostic parameters and putative causative factors are frequently associated with the steady state of the disease. This approach involves the obvious risk to consider a late emerging symptom/target as the driver-causative element of the pathogenic process, while discarding early, critical signs.

Definitely, current PM-based treatments are unable to cope with such an overwhelming complexity, and their acknowledged failure in curing cancer cannot be viewed as an unannounced surprise (Scannell and Bosley 2016; Bizzarri 2017). Consequently, "we overdiagnose, overtreat, and overpromise, with high costs and without clear benefits" (Hawkes 2011).

A Systems Biology Approach for Reframing the Concept of Human Disease

The reductionist model of disease usually overlook the relevance of multifactorial etiology of the disease and underestimates the robustness and resilience of the (pathologic) phenotype, especially when pharmacologically perturbed. For instance, single gene knockout or complete silencing, have shown little, contradictory or even null effect on the pathophenotype (Zambrowicz and Sands 2004). Inhibiting a selected pathway can be insufficient in controlling the "corresponding" biological function, as the network can switch toward alternative in response to changing requirements of the context in which the system belongs (Barabási and Oltva 2004; Wagner and Wright 2007). This switch occurs at specific bifurcation points – corresponding to regions of critical transition – allowing the system to access previously unexplored attractors, when perturbed. This property may explain why

cancer or bacterial infections usually develop drug resistance, as these populations – due to their intrinsic dynamics and genomic heterogeneity – can move from one attractor to a new one, often resilient to the original perturbation. At the bifurcation point, we may observe an increase in the fluctuation of several molecular factors. Fluctuations are critical for enzymes to work, for a receptor to switch between states, and for the chromatin to express the right protein at the right time (Rychkov et al. 2017). Overlooking these fluctuations will likely affect the identification of those states in which the system affords the choice in between different cell fate commitment (Mojtahedi et al. 2016).

The contribution of internal or environmental constraints in "driving" such transitions is mandatory, as they represent additional "causative factors" (Bizzarri et al. 2020a, b). The emergence of a specific network associated with the time-dependent state of the disease process can be properly ascertained only if the specific microenvironmental field is *concurrently* contemplated. Genetic regulatory networks and the context-dependent constraints are tightly intertwined and therefore a successful therapeutic strategy should embrace all of them if the aim is properly to cure the patients, and not only "to fix" a "singled out" pathway (Keith et al. 2005).

A comprehensive approach to this problem would enable in providing a complex network structure, constituted by modular sub-systems, whose (non-linear) interaction will drive the organism response toward emergent properties, i.e., disease or health. Therefore, human disease needs to be conceptualized as an "emergent property" of the human body (Csermely et al. 2013). Overall, these considerations ask for revisiting the concept of illness on which any personalized medicine could deal with. Systems biology may help in establishing a new model, able to integrating different "causative" factors, distributed across different scales (from molecules to organs) and times (from the early life to the present). Within this framework, response parameters should be provided by the overall system estimate, rather than on singled-out molecular target (Anderson et al. 2012). In other words, disease should be conceptualized as a non-linear dynamic process displaying classical features of complex systems, including resilience, sensitivity to initial conditions and multi-attractor accessibility. Transition from different states – healthy, high-risk conditions, pre-disease and disease states – has been documented and modeled in many instances (Tanaka et al. 2008; Venegas et al. 2005). Namely, the existence of "critical period" during the lifespan (especially during early life) have been highlighted by several studies that have identified a strongly link between those periods and the appearance of different diseases in the adult period (Eriksson et al. 2001; Lithell et al. 1996). During the development, organs and systems of the body go through "critical" periods, in which their sensitivity to internal and environmental perturbations is dramatically amplified (West-Eberhard 1989). While it is intuitive that such a plasticity – i.e., the capacity to dynamically respond to surrounding stresses by shaping morphology and functions – is an advantage from the evolutionary perspective, nonetheless such a capability exposes the organism to unwarranted risks. Indeed, when the system experiences important perturbations, even pathological states can arise and eventually maintained if they become reliable, adaptive issues.

Briefly, the physiological system can travel across that metaphorical landscape (remnant of the Waddington's approach) (Waddington 1942), accessing different attractors, depicted as different physiological/pathological states – a normal state, a pre-disease state, a disease state – in which the disease can alternatively move towards progression or healing. Identification of these bifurcation points could help in understanding the meaning of the overall process and in managing it toward beneficial outcomes (Liu et al. 2017). Finally, identification of biomarkers ("early-warning signals") indicating an imminent bifurcation or sudden deterioration before the critical transition occurs, can help in planning an appropriate management of the disease or the pre-disease state, thus providing the "preventive" strategy with a an entirely new meaning (Chen et al. 2012). This framework is remnant of those based on a systems biology approach (Hood and Friend 2011), while differing in that "classical" omics strategies focus (almost essentially) on gene regulatory networks (GRNs), often caught at the steady state of the disease. Instead, we should look to identify both molecular and non-molecular factors (biophysical constraints), acting across a space-temporal continuum, i.e., involving different levels of living organization at different times. Just to provide some examples, current approaches do not take into consideration the participation of (systemic as well as local) immunological factors in shaping the evolution of the cancerous disease, given that GNRs models do not entail such "external" cues. On the contrary, a "personalized" attempt would incorporate data coming from history of both the "disease" as well as those provided by the "patient", meaning the immune/nervous capability of the entire organism to cope with the pathogenetic insult. In this way, the Hippocratic tradition could be reconciled with modern high-throughput technologies. By no doubt, this scenario reveal that – *in potentia* – there is much more to personalized medicine than envisioned within the traditional concepts of molecular differentiation epitomized by pharmacogenomics (Weinshilboum and Wang 2017). In other words, PM could be "reframed" by encompassing a number of integrated data, which could enable in tracing back the landscape through which the organisms travelled prior to accessing the "disease attractor". This reconstruction would be instrumental in recognizing the "escapes" available for the system to revert into health, by acting on a few, critical targets (not limited to the molecular ones!) that can actually "displace" the system, driving it toward alternative "healing pathways".

Conclusions

For three main reasons a genetic approach is unlikely to be a solution to common diseases in the near future. The first is the great importance of environmental circumstances in determining health, the second reason is the great complexity of gene/gene, gene/environment interactions, and the third reason is the high individual variability (Baird 2001). Indeed, for most common diseases, hundreds of genetic risk variants with small effects have been identified, and it is hard to establish an unambiguous picture of who is really at "risk" and for "what". Conclusively "for

widespread diseases like diabetes, heart disease and most cancers, no clear genetic story has emerged for a vast majority of cases. Age, sex, body weight and a few simple blood tests are much better predictors of Type 2 diabetes, for example, than a genetic score based on how many snippets of "risky" DNA you have" (Joyner and Paneth, 2015). Additionally, misperception of PM may foster unsubstantiated expectations or anxious attitudes amidst patients. People believing not to be at risk after being reassured having performed a "genome-based test", will probably dismiss appropriate behaviors and health care precautions; on the contrary, people "informed" to be at high risk shall probably endorse a resigned attitude, therefore discarding medical controls and treatments (Schleidgen et al. 2013).

Despite PM missed its promises, we yet continue to overinvest our hope (and money) in genomic-based approaches. Yet, genetics cannot deliver unaffordable expectations – as recognized even by PM advocates during the recent Covid-19 pandemics (Parens 2020) – given that genes do not constitute that "privileged" level of causation the reductionist medicine was searching for establishing a deterministic biological model (Noble 2012). In simple words: we actually lack the minimal "facts needed to support the hope that genetics can be a key to realizing that vision" (Parens 2020).

A more prudent reappraisal of PM has evidenced the paradox behind this approach. In principle, PM-based treatment are themselves more precise than standard chemotherapeutic agents, although the clinical evidence supporting the benefits of these therapies is often considerably less precise and still awaits sound confirmation (Wheler et al. 2016). Paradoxically, clinical trials designed to assess PM efficiency demonstrated a lack of precision in respect to conventional trials (Moscow et al. 2018). Namely, these studies comprise several treatment arms in which far fewer patients than in conventional phase III investigations are generally enrolled. It is quite disturbing that these patients are usually not randomized owing to the difficulties in determining a sufficient number of eligible patients or in planning a proper control treatment. Furthermore, results are biased by the limited choice of end-points (usually confined to the overall response rate), thus undermining the trials validity, "most of which can only be viewed as multiple signal-finding studies organized into a parent study that then require confirmatory studies if preliminary evidence of drug activity is detected" (Moscow et al. 2018).

Secondly, to extract knowledge from a complex system, one must focus on the right level of description (Bizzarri et al. 2013). No doubts that the disease is an emergent phenomenon involving the organism and not limited to molecules or cells. Thereby, any attempt to establish a precision-based treatment should look at the "system", instead to focus on single molecules or pathways. To sum up, we should shift from targets to processes, and identify a poly-target array, which could entail different mechanisms of action, as suggested by the network polypharmacology approach (Csermelye et al. 2005). Modulation of processes implies we should be able to "redraw" the disease-related landscape, favoring the system displacement from pre-clinical state or true disease-states towards healing pathways. Disease could eventually be "reverted", involving also a "reprogramming" of the gene-regulatory network, as proposed in some carcinogenic models (Telerman and

Amson 2009; Livraghi et al. 2005; Bizzarri et al. 2020a, b). Indeed, as cancer can be successfully *reverted* through the modification of the dynamical cross talk with its microenvironment, cell-stroma interactive network must be recognized as a target for pharmacological intervention (Proietti et al. 2019; Bizzarri et al. 2014). How should we investigate the evolution of such a complex system over time? We are aware of the fact that distributed nonlinear network systems are hardly mathematically tractable when matched with simple feedback systems, usually described by means of control theory. Disease response is habitually simplified by describing changes in a single (or a few) parameter. Instead, we have to move from target-related parameters to system-parameters, which could capture those modifications that could likely impact on the whole systems dynamics. Nowadays, such needs can be satisfied by metabolomics studies, given that metabolites fluctuations usually amplify subtle modulation of the genome/proteome networks over time. Metabolomics is deemed to capture temporal changes in complex systems dynamics as well as the "adaptive", phenotypic response to a wide range of perturbations (Goodacre et al. 2004; Urbanczyk-Wochniak et al. 2003; Harrigan and Royston 2003).

Moreover, metabolomic-based studies offer the opportunity to follow the evolution of the disease in each individual, so that patients will not be compared with a vast control population anymore, but will become their *own* control (Nicholson and Lindon 2008). This approach will enable in assessing how the system changes by looking at those parameters that significantly change in travelling across different conditions (from healthy to overt disease states). Noticeably, metabolomics approaches – when adopting an unsupervised framework as such that provided by Principal Component Analysis – do not require strong a priori theoretical assumptions, and can generate in their own "driving hypothesis" by allowing the identification of critical (often-unexpected) critical targets (Giuliani 2017), as well as their response to treatments (Everett 2016). By this way, metabolomics can greatly help in establishing fruitful *historical* correlations between disease evolutivity, changes in physiological states and respective time-dependent patterns. Conclusively, the exciting new concept of longitudinal pharmaco-metabonomics involves the tracking of a patient's metabolic profile over time. Although the approach has not yet been validated in the clinic, the patient's metabolic trajectory will reflect both disease progression and the results of treatment, thus allowing patient stratification in terms of the prediction of outcome and the choice of optimal treatment (Nicholson et al. 2012).

In our opinion, interventions should aim in the future to find the way to modulate the metabolomic fingerprint of a disease in a "precise" and efficient fashion, instead of searching for hypothetical "causative target" and "magic bullets". Some pioneering approaches demonstrated that such an approach could successfully recognize subsets of patients within the same disease, characterized by different pathophenotypes and distinct activated pathways that can be successfully targeted with very different treatments (Gu et al. 2012). This selection is performed through a systems biology approach and do not relies on single targets as it focus on the overall behavior of the system under scrutiny.

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Personalised Prevention: Increasing or Decreasing Over-Medicalisation, Overdiagnosis and Overtreatment?

Julia Tinland

Introduction

Recurring Ethical Issues in Preventive Medicine

Three interconnected ethical issues have taken a centre-stage position when it comes to reflecting on the potentially problematic implications of preventive medicine: *over-medicalisation* (placing ever new circumstances under the purview of medical scrutiny); *overdiagnosis* (the process through which a disease is diagnosed which would never have been perceived during a patient's lifetime and which would not have changed this patient's quality of life or lifespan), and *overtreatment* (the over-utilisation of therapeutic interventions).

These are issues which are intrinsic to preventive actions in medicine. Trying to understand what elevates risks of developing an illness, be it a person's lifestyle, diet, hereditary traits, genome, etc. comes with the possibility of over-medicalisation because it may transform what used to be rightly considered benign or harmless features into (potentially) pathological ones. Trying to identify whose risk is elevated enough – including among persons who were previously seen as healthy – that their condition corresponds to diagnostic criteria comes with a possibility of overdiagnosis because people whose quality of life and lifespan would never have been negatively impacted by a newly-defined disease may now be diagnosed or identified as at-risk. Finally, one is usually attempting to take measures to reduce such risk, which comes with the possibility of overtreatment, because it may mean the prescription of medication or therapy to people who have no need for either.

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That the development of personalised medicine – and the perspective of personalised prevention it opened – led to an intensification of these concerns is not surprising, nor is it illegitimate. Indeed, while the processes of medicalisation, diagnosis and treatment are not necessarily worrisome in and of themselves, and may even benefit many people if done correctly, their overdevelopment may cause significant harm, especially if it means that people incur high costs – economic, healthwise, social, professional, etc. – for virtually no benefit. But before delving into the ways in which personalised prevention may increase or decrease problems of over-medicalisation, overdiagnosis and overtreatment, let's sum up briefly why interest in personalised approaches to prevention has skyrocketed in recent years.

Personalised Prevention

Preventive approaches more generally have started to be favoured over curative or palliative ones for several reasons, the first of which being that early detection and interventions are thought to prevent much pain and suffering caused by severe, or even fatal, illnesses. An ounce of prevention is worth a pound of cure, as the old adage says. As such, any progress in preventive medicine is seen as a way in which the costs of such illnesses might be lessened considerably, be it in terms of economic or health resources, or in terms of human lives and quality of life.

For a very long time, primary and secondary prevention have belonged to the realm of public health.[1] Population-wide measures, or screenings and interventions targeted towards higher risk groups based on age, sex, etc. are argued to have a potentially huge impact on people's overall health, and so with regards to many different diseases (diabetes, heart diseases, cancer, psychiatric disorders etc.). But recent advances in personalised medicine have challenged this heretofore almost undisputed reign of public health over the development of primary and secondary preventive measures, giving researchers and medical professionals a sliver of hope that prevention might transform from a one-size-fits-all approach to a more tailored venture. The promises of personalised prevention then rely on its potential to identify precursors to disease at an individual level, offering a more finely-grained understanding of risk than the broad strokes of population-based approaches. Quite importantly, then (and this is where the traditional concerns outlined above are promptly revived), personalised prevention is thought to enable the identification of markers of risk more precise than ever before. Seeking to incorporate the newest technological advances so as to create a "data ecosystem" (Jaffee et al. 2017) that can better identify and address an individual patient's course towards

[1] Primary prevention encompasses all interventions before health problems might even start to occur. Secondary prevention designates measures of early detection and interventions, in the very first stages of an illness and before the onset of severe signs and symptoms. Tertiary prevention, on the other hand, covers the management of illness post diagnosis in order to slow down or stop its progression, or potential complications – as such, it is integrated within medical care rather than public health.

disease, personalised medicine aims to integrate seamlessly clinical phenotypes and biological information, from imaging to laboratory tests (including -omics data) and health records (Ramaswami et al. 2018). Its rationale, then, is to develop a new taxonomy of human disease based in great part on molecular biology (Ramaswami et al. 2018). Risk and vulnerability, therefore, are not only individualised, they are also identified at a level that was inaccessible until recently, and might profoundly alter the ways in which diseases are understood and defined. For example, the genetic, epigenetic, and inflammatory pathways that may affect how and where tumours develop could perhaps be mapped, thus forming the basis of early detection and screening (Jaffee et al. 2017).

In this context, the personalisation of prevention is mostly seen as the integration of a great variety of biomarkers statistically correlated with the development of specific diseases (diagnostic biomarkers), with the adverse but natural evolution of a disease (prognostic biomarkers), with the evolution of a disease when treatment is received (predictive biomarkers), or even with (un)favourable responses to a particular kind of therapy (pharmacogenetic biomarkers) (Guchet 2014). When identified in an individual, these biomarkers are supposed to help medical professionals predict accurately how that person's state of health should evolve, and how best to prevent its deterioration.

Personalised prevention's characterising feature is thus twofold: if it does manage to fulfil its promises, it should enable the progressive individualisation of risk as well as the identification of multiscale risks.[2] And in this lies its potential either to increase considerably or possibly to decrease problems of over-medicalisation, overdiagnosis, and overtreatment.

Increasing or Decreasing Issues of Over-Medicalisation, Overdiagnosis and Overtreatment?

As mentioned earlier, that the development of personalised prevention might heighten concerns of over-medicalisation, overdiagnosis and overtreatment commonly associated with preventive medicine is neither surprising, nor is it unsubstantiated. Because prevention's core intent is to address health issues before they may become harmful to a person to the point of seeking medical help, it exceeds the bounds of prevalent curative or palliative care. It intrudes on parts of a person's life which had remained untouched by medical scrutiny. If, as some argue, personalised medicine is to expand and deepen preventive capacities greatly, it makes sense that ethical issues associated with them would also expand proportionally.

[2]Multiscale modeling of risks, here, refers to attempts (in systems medicine, for example) to predict the problematic behaviour of diverse biological and/or other systems through their interactions at multiple scales. It can therefore be used in attempts to solve problems which have important features at multiple scales of time and/or space (e.g., tissues and organs, as well as molecular biomarkers).

One of the main mechanisms through which processes of medicalisation, diagnosis and treatment can become problematic in preventive medicine is the identification of subclinical illness states which, when increasingly defined through abnormal biomarkers, also implicate many more asymptomatic people (Page and Etherton-Beer 2019). Diagnostic thresholds are significantly lowered, bringing more and more people into the ever-growing shadow cast by diagnostic categories. Even seemingly small changes in diagnostic thresholds can have significant ramifications on the number of people diagnosed with a condition (Page and Etherton-Beer 2019). Critically, what is now regarded as "disease", "early disease" or being "at-risk" extends the number of people considered to be in need of medical attention (Green and Vogt 2016). Nosologies themselves can be profoundly altered by personalised approaches to care and prevention: the description and classification of diseases are transformed by the advent of high speed technologies, which have divided them into subclasses characterised by newly discovered molecular mechanisms (Guchet 2014).

An important objection against the prospects of personalised prevention is that it might fundamentally misrepresent the nature of complex and/or common diseases, "because, unlike Mendelian disorders, common diseases clearly result from the interaction of many genetic and environmental influences, so that the correlation with any one factor is weak" (Wright and Hastie 2001). Complex diseases such as cancers or psychiatric disorders cannot be reduced to straightforward, monocausal mechanisms, and the identification of specific biomarkers might not account for the plurality of development courses that these diseases follow, thus being at best rather weak predictors.

Another key driver of over-medicalisation, overdiagnosis and overtreatment in personalised prevention would be technology itself: the technologies used in the detection of risk aim, and often manage, to detect ever smaller abnormalities (Green and Vogt 2016), therefore multiplying the number of markers that can serve as a basis in the definition of risk. Such detailed screenings might generate waste and harm more easily than broader approaches to prevention, as they can detect non-serious abnormalities that would not cause a problem during a person's lifetime, either because they disappear spontaneously, do not progress, or progress so slowly that people die from other causes (Vogt et al. 2019). Serious harm can be caused by identifying benign abnormalities as pathological, and this risk should not be downplayed: people in whom such abnormalities have been detected may be diagnosed with a disease and then treated for it. They could then have to deal with severe side-effects (for example, weight gain, impotence, incontinence, exhaustion, etc.), and many other burdens on their quality of life (for example, stress, discrimination, anxiety, financial strain, etc.), for little to no benefit.

Moreover, the situation of identified at-risk individuals fitting into newly defined pre-disease states is a peculiarly uncomfortable one. Trapped between a state of disease and health, feeling well yet expecting to become unwell, plagued by uncertainty and anxiety, the people concerned inhabit a fundamentally hazy place. If they are indeed on the verge of developing new health issues and benefit from demonstrably effective early interventions, then it is a price that they might be fully

ready to pay. But, as mentioned earlier, biomarkers are rarely so predictive that they can allow for a clear-cut demarcation between the presence and the absence of risk in complex diseases.[3] It might be said that people who would not have gone on to develop any problematic symptoms, whose quality of life or lifespan would not have been affected in any way, are actively harmed by their being labeled as "at-risk". Harm, here, refers to injury (adverse effects, financial toxicity, depression, etc.) that individuals-turned-patients incur from receiving treatments, active surveillance or interventions when they don't need them to preserve their health (Norton et al. 2019).

The purpose of this chapter is not to make light of such concerns, or simply to brush them aside. On the contrary, many of these concerns are incredibly serious and point to genuinely worrying trends in medicine today. None of them are to be alleviated or invalidated here, and it is not the goal of this chapter to do so. The aim here is rather to explore whether or not the contributions of a personalised approach to prevention might only lead to problematic practices in preventive medicine, or if it is also possible for it to be used more wisely, as a form of de-escalation.

In doing so, this chapter goes through a series of empirical arguments, drawing from a series of relevant examples ranging from oncology to psychiatry. Woven into its development is also a more theoretical line of reflection touching on the impact that personalisation can have on our conceptualisations of – and thus responses to – vulnerability.

It is indeed crucial to understand that the development of personalised prevention effectively promotes particular models of vulnerability: more or less complex, purely biological or multifaceted, more individual than universal, inherent or situational, etc. Not all models are equally compelling, and it would be a mistake not to go to the trouble of distinguishing and evaluating them. Even small variations in our conceptualisations of vulnerability can be substantial enough to bring about considerable reformulations of the ethical issues at play in the development of personalised prevention. The manner in which we define vulnerability is primordial, in the sense that it can inform, whether consciously or unconsciously, how we then evaluate the benefits and the risks of an activity, a process or a response. How can we have a deep enough understanding of the harms that can be caused to someone without having reflected on what that person risks losing and on what ought to be preserved? The risk of undergoing unnecessary treatments for a cancer that may have never progressed – and the harms that may result from it – will be interpreted differently if vulnerability is seen first and foremost as a deeply corporeal, inherent

[3] While the predictive validity of some markers has been established – for example, between 55 and 65% of women who present the BRCA1 genetic mutation will develop breast cancer by the age of 70 years, and 45% of women who inherit the BRCA2 mutation will develop breast cancer by 70 years (Ramaswami et al. 2018) – there are a great many cases where predictive validity remains much too low to be of clinical use – in psychiatry, for example, "so far no biomarkers [...] or other risk markers are available to create profiles to enhance prediction and therapeutic selection in psychiatry. Stratified or personalized interventions remain aspirational, yet potentially within reach" (McGorry et al. 2014).

condition (highlighting its inescapability, but also perhaps breeding apathy when harm could perhaps be prevented), as a situational socially-constructed predicament (highlighting the need to avoid overly-medicalised responses to risk), or if protective responses are favoured over those that sustain autonomy (if screening can help prevent serious diseases, it would then be, perhaps, a worthwhile endeavour).

The first step is to look at the wider context in which personalised prevention takes place. Indeed, it arrives at a point in time when prevention more generally has already changed the landscape of medical diagnosis and care extensively, meaning that personalised prevention might perhaps play a "corrective role" rather than simply an "incremental" one with regards to preventive measures already in place.

A Context of Pre-existing Over-Medicalisation, Overdiagnosis and Overtreatment

Enthusiasm towards preventive measures such as screenings or check-ups is not a novel thing. Prevention – and especially primary prevention – has been shown to be more effective and less costly than curative care in several instances, and the impact of public health measures regarding dietary and smoking habits, exercise, pollution, etc. is now widely recognised as positive. The widening availability and vast implementation of screenings and other secondary preventive measures also predate the development of personalised prevention, and will be the primary focus of this section. As time went on, the ethical issues these measures of secondary prevention sometimes posed were made apparent and have left the door open for personalisation to be presented as a potential corrective tool.

The Wide Net of Preventive Screening

Few areas of medicine have shown the potential for over-medicalisation, overdiagnosis and overtreatment inherent to preventive ventures than campaigns encouraging cancer screening. Past a certain age, people the world over become frequent visitors to their gynecologist's or proctologist's offices, and to a multitude of other screening facilities. This type of prevention casts a very wide and often imprecise net over large groups thus deemed "at-risk".

For the World Health Organisation (W.H.O.), where tests for cancer of specific sites are available and facilities are appropriate, screening of apparently healthy individuals can disclose cancer in early or precursor stages and thus lead to more effective treatment (W.H.O. 2002). The most common examples of wide-scale screening programmes adopted for routine use in Europe, for example, include breast cancer screening using mammography or clinical breast exam; cervical cancer screening using pap smears, human papillomavirus test or visual inspection; or colorectal cancer screening using stool tests, flexible sigmoidoscopy or colonoscopy (Ponti et al. 2020). In Europe, substantial improvement in screening implementation using population-based approaches was documented, and access

to screening increased from only 42.6% of the age-eligible populations in 2007 to 72.4% in 2016 (Basu et al. 2018). The populations who go through such screening are therefore larger now than they used to be, in part because access has been improved, but also because requirements have been widened. For example, the latest European Guidelines on breast cancer screening published by the European Commission Initiative on Breast Cancer (ECIBC) extended the age recommendation for mammography screening from 50–70 years to 45–74 years: "there is moderate certainty of the evidence that mammography screening at 45–49 and 70–74 years can reduce breast cancer mortality and the balance between benefits and harms favors mammography screening" (Ponti et al. 2020).

Population-based screening programmes, if made widely available and organised properly, are argued to be highly effective in reducing mortality from breast, cervical and colorectal cancers. These three types of cancer together were estimated to be responsible for 0.26 million deaths in Europe in 2012, and there is now established evidence that implementation of organised screening through a population-based programme can significantly reduce mortality from such cancers (Basu et al. 2018; Ponti et al. 2020).

Weighing the harms against the benefits of screening, the website of the W.H.O. regional office for Europe indicates that, based on the existing evidence, mass population screening can only be advocated for cervical, breast and colorectal cancer. On the other hand, systematic prostate cancer screening for all men above a certain age is not recommended, overdiagnosis being recognised as a substantial issue in this case (W.H.O. Regional Office for Europe). Some estimate that the risk that a cancer detected with prostate-specific antigen (PSA)[4] represents overdiagnosis is between 60 and 67% (Welch and Black 2010). Similarly, the pertinence of screening for lung cancer has also been subjected to doubts: the annual screening of heavy smokers aged 55–74 years might allow for a significant reduction in lung cancer mortality, but high rates of false-positive diagnoses are also reported, since a great majority of suspicious nodules in the lungs turn out to be benign lesions (Ponti et al. 2020).

These existing approaches to cancer prevention, screening, and early detection have therefore been quite generic, driven by sex or age categories; and assessments of risk have unfortunately remained quite imprecise (Jaffee et al. 2017). Even in the case of cancer screenings which have been demonstrated to help lower mortality significantly, rates of false positives – and thus of overdiagnosis – remain problematically high. It is because these programmes lead to more frequent diagnoses of early tumour states or precursor lesions that they inevitably result in overdiagnosis (Scharl et al. 2015).

In view of this, it can easily seem like the introduction of progressively more sensitive screening techniques is part of the problem, and certainly not part of the solution: increasing precision necessarily means increasing the number of benign markers of risk or abnormalities identified and treated that would never have been

[4]The PSA test is a blood test used primarily to screen for prostate cancer. The test measures the amount of prostate-specific antigen (PSA) in the blood.

detected before, and which would not have evolved in such a way as to cause any harm to a person – a potentially very strong point against personalised prevention.

Increasingly Sensitive Screening Techniques

Screening is "useful" in terms of public health if it is both necessary and efficient, meaning when it demonstrates a clear benefit in terms of mortality, morbidity and other possible health costs, as well as a favorable benefit-risk ratio (Delaloge et al. 2016). Have recent technological advances in screening entailed a drop in their accuracy, however? After all, new technologies are now available which increase considerably the precision and sensitivity of existing tools for prevention, screening and early detection (Jaffee et al. 2017). But it does not necessarily follow that the people in whom abnormalities are detected thanks to these are truly at risk. Ho et al. have fittingly described this as a "phenomenon that has been called an epidemic in diagnosis rather than an epidemic in disease" (Ho et al. 2015).

Thyroid cancer screening is one area in which this issue has been made particularly salient. Well-differentiated thyroid carcinoma has seen a tremendous rise in global incidence over the past three decades (Kovatch et al. 2018). This higher incidence of thyroid cancer has traditionally been assumed to be due to environmental exposure to atmospheric radiation and iodine insufficiency. However, recent research on other potential causes includes iatrogenic exposure to radiation, reproductive patterns in women, body mass index (BMI), but also – and increasingly so – improved pathology diagnosis and increasing detection by diagnostic imaging (Hall et al. 2014). Recent technological progress has indeed increased the sensitivity of this type of cancer screening: "The recent prevalence of ultrasound-guided fine-needle aspiration biopsy has resulted in a marked increase in the number of patients with papillary microcarcinoma [...] of the thyroid detected by this sophisticated tool" (Ito et al. 2003). But cancers demonstrate a diversity of behaviour, encompassing a spectrum of risk that "ranges from indolent tumors that cause no harm during a patient's lifetime to more aggressive subtypes that inflict considerable morbidity and death" (Ho et al. 2015). Papillary thyroid cancer is most often an indolent cancer type, and has escalated in incidence due to the wider use of advanced medical imaging. The advisability of treating persons thus diagnosed (usually with surgery), has been called into question by growing numbers of researchers and medical practitioners, and their doubts are seemingly justified. Studies have found, for example, that occult papillary thyroid carcinoma was present in about 36% of autopsy specimens, leading to the supposition that its prevalence was likely much higher, perhaps even existing as a "normal variant" and thus representing a silent and clinically insignificant disease reservoir (Kovatch et al. 2018). Additionally, when the widespread availability of sensitive forms of screening leads to the diagnosis of a very large number of milder cases for which outcomes are excellent, it might appear – deceptively so – as though outcomes are improving greatly (Ho et al. 2015). This can lead clinicians to overestimate the benefits of therapy in a cycle of escalating intervention (Ho et al. 2015). If most thyroid cancers now diagnosed

comprise small, low-risk cancers that are incidentally found and are unlikely to cause harm during a person's lifetime, many people who undergo preventive treatment would then be actively harmed by overly precise screening campaigns.

Prostate cancer similarly harbours a well-behaved subclinical reservoir, a long natural history, and superlative outcomes that have made active surveillance the *de facto* guideline recommendation for low-risk disease (Ho et al. 2019). Both prostate cancer and thyroid cancer therefore have to undergo "recalibrated, de-escalatory shifts to counter changing epidemiologic landscapes" (Ho et al. 2019).

Nevertheless, new screening techniques not only allow for a substantial gain in sensitivity, they also participate in the acquisition of new knowledge regarding risk factors in areas such as molecular epidemiology, genetics, environmental exposures, infectious diseases, and behavioural and lifestyle factors. In doing so, they form the basis of a redefinition of risk assessments and diagnostic testing for early cancer detection (Jaffee et al. 2017). Despite its potentially harmful impact, precision screening might perhaps also enable redefinitions of risk through stratification, participating in de-escalation efforts.

Personalisation and Risk Stratification

Identification of Low Risk Patients

The previous section has shown that wide-scale screening campaigns have been implemented for many years and that over-medicalisation, overdiagnosis and overtreatment are already embedded issues in preventive medicine. The path towards de-escalation might very well be the one which allows for a finer demarcation between truly high risk individuals and very low-risk ones – a path perhaps opened by personalised prevention.

De-escalation can take many forms. A useful mechanism through which the impact of over-medicalisation, overdiagnosis and overtreatment can be lessened is through the stratification of risk. If the only way to account for detected abnormalities is to label the people concerned as "at risk", it leaves few options for a more nuanced understanding of their vulnerability to disease, and will inevitably lead to a skewed view of its gravity. Risk stratification can maybe help alleviate at-risk individuals' anxiety and minimise pressure to overtreat (Ho et al. 2019). What is needed is better to identify patients whose prognosis is so good that certain therapies can be foregone and treatment is unnecessary (Scharl et al. 2015). This is how, in the case of prostate cancer, active surveillance has been established as a first-line treatment approach for properly stratified low-risk patients, while observational trials for thyroid cancer have also made strides in defining higher risk and eligibility for surgery (Ho et al. 2019).

What is most needed is a way to distinguish which types of cancer are likely to progress from those which are indolent; and a personalised approach to prevention might very well be the most likely candidate to fulfil such a need. Prognostic and predictive data obtained thanks to gene expression profiles should help make

significant progress in this area, which could be translated in routine clinical care in the near future (Delaloge et al. 2016). The limits of these promises must be acknowledged, however, considering the difficulties that have been encountered in the identification of sufficiently predictive and accurate biomarkers in personalised medicine (Hey and Barsanti-Inness 2016).

In the case of breast cancer screening, where the problem of overdiagnosis is acknowledged as very harmful (Jacklyn et al. 2018), personalisation might help decrease the number of women routinely screened or preemptively treated. Personalisation according to genetic risk (in connection with germinal mutations of the genes BRCA1/2, TP53, PALB2, etc.) can improve overall life expectancy in this subgroup (Delaloge et al. 2016). Studies have shown that among women who inherit the BRCA1 mutation, between 55 and 65% will develop breast cancer by the age of 70 years; 45% of women who inherit the BRCA2 mutation will develop breast cancer by 70 years, as compared with 12% of women in the general population (Ramaswami et al. 2018). Genetic profiling can be used to improve diagnosis among family members and therefore spare unaffected individuals from unnecessary routine surveillance or screening procedures that may be associated with harm (Ramaswami et al. 2018). It is now possible to use sequencing on another scale: for example, high-throughput sequencing techniques looking for tumor mutations, or gene panels to evaluate a possible predisposition to cancer via mutations (Delaloge et al. 2016). Although not available for clinical use yet, this type of personalisation could perhaps one day become a beneficial part of the future of prevention – a response to pre-existing problems of over-medicalisation, overdiagnosis and overtreatment – though only if it becomes sensitive, specific, available and affordable enough.

Similarly, understanding the low-risk behaviour of papillary thyroid microcarcinomas is also crucial, as it would support the reevaluation of certain surgical practices for small, localised, well-differentiated thyroid cancers (Ho et al. 2015). A movement strongly questioning whether all cases of thyroid cancer merit treatment emerged, pushing a trend towards "thoughtful, evidence-based treatment de-escalation paradigms", reflecting better risk stratification of thyroid cancers, and the recognition that not all detected disease poses a threat to health or survival (Kovatch et al. 2018). One of the biggest challenges is predicting which of these seemingly low-risk tumors may harbour the behaviour of a "bad actor" (Kovatch et al. 2018). Physicians have become more aware that indolent illnesses are being overtreated, and this has been reflected in updates to clinical practice guidelines over the past decade: professional guidelines proposed by many influential stakeholders address the "epidemic of papillary thyroid microcarcinoma" with a trend toward no treatment, meaning in this case that there is a decrease in patients receiving treatment (Kovatch et al. 2018). Recommendations are now more likely to recognise the role of active surveillance in low-risk diseases.

Overdiagnosis and overtreatment linked with Barrett's oesophagus have also been at the centre of de-escalation campaigns thanks to a precision-based approach to risk stratification (Jaffee et al. 2017): "Barrett's oesophagus predisposes to adeno-

carcinoma. However, most patients with Barrett's oesophagus will not progress and endoscopic surveillance is invasive, expensive, and fraught by issues of sampling bias and the subjective assessment of dysplasia" (Ross-Innes et al. 2017). The value of endoscopic surveillance in Barrett's esophagus is thus under debate (Sato et al. 2008). Ross-Innes et al. investigated whether a non-endoscopic device, the Cytosponge, could be coupled with clinical and molecular biomarkers to identify a group of patients with low risk of progression suitable for non-endoscopic follow-up (Ross-Innes et al. 2017): "Since most Barrett's oesophagus cases will not progress to cancer, strategies to risk-stratify patients and avoid overdiagnosis are also very important. Furthermore, given the heterogeneity in the molecular genetic patient profiles of those progressing to cancer, identification of very low-risk patients might be a more achievable biomarker strategy" (Ross-Innes et al. 2017). Their objective is to identify very low-risk patients, so that they can be reassured without having to undergo endoscopy (Ross-Innes et al. 2017). Heightening sensitivity for high-risk patients with Barrett's oesophagus is also crucial, and it is through the inclusion of additional molecular biomarkers combined with clinical factors that progress may be made (Ross-Innes et al. 2017).

Risk stratification based on the contributions of personalised prevention could therefore open new avenues for reduction of over-medicalisation, overdiagnosis and overtreatment by offering the possibility of detecting not simply the presence of risk, but also the level of risk, from very low to very high. As such, more adapted (and perhaps less medicalised) responses could be made available to people thus identified as more vulnerable.

The Example of Chronic Lymphocytic Leukemia (CLL)

Once knowledge is gained about a person's vulnerability in the face of specific events (in this case, in the face of illness), it demands a response – either individual or collective, or both. Vulnerability, in this sense, is a profoundly normative concept. If its presence is revealed, whatever answer is brought to it is moral in nature and reveals a lot about what is valued, what is deemed worthy of protection and what is not, what ought to be preserved in priority, etc. Because it is one of the areas of medicine directly confronted with identifying and responding to vulnerability, choices made in preventive medicine participate in shaping our relation to it, our understanding of it as a universal condition shared by all as living beings, but also as an acutely personal condition anchored in our singular bodies. This is also why issues of over-medicalisation, overdiagnosis and overtreatment are so central here: they reveal the tension that can exist between the will to control and protect from painful illness (better safe than sorry) and the preservation of life unconstrained by medical care and cautiousness (watch and wait).

In order to illustrate the role that risk stratification can play in terms of de-escalation in a way that highlights its impact on our understanding of risk and vulnerability, on nosology, and on what kind of response is provided, the case of Chronic Lymphocytic Leukemia offers a particularly compelling example.

The diagnosis of CLL is often made fortuitously, when a blood test that had been prescribed for something else yields abnormal results. This explains why around two thirds of CLL patients are asymptomatic at the time of diagnosis. The news that they have leukemia is an unexpected and frightening blow. Of the two thirds of newly diagnosed, asymptomatic patients, half of them will never develop a problematic form of the disease, and will therefore never receive treatment for it. Diseased but not ill,[5] unsure whether they will one day need to be treated, these patients often mention Damocles' sword to describe their predicament. Studies have indicated that, as for virtually all cancers, the diagnosis of CLL can precipitate substantial anxiety and adversely impact quality of life (Strati and Shanafelt 2015).

Two staging systems are used to diagnose CLL in the world: the Rai system is mostly used in North America, while the Binet system is used throughout Europe and elsewhere. Both systems describe three major prognostic subgroups, and they remain the backbone of any clinical decision-making process (Binet et al. 2006). The notion of indolent disease is quite familiar to hæmatologists dealing with CLL, and guidelines clearly indicate that therapy must only be initiated once it has been ascertained that one is dealing with an aggressive form of the disease (e.g., Binet stage B, Rai stages II-IV). Although a few clinical trials have been (and continue to be) led in order to determine if preemptive treatment might help prevent or delay the onset of a more severe form of the disease, results so far tend to support a "watch-and-wait" strategy rather than the alternative. Most asymptomatic patients thus newly diagnosed with CLL are monitored every few months, but go on without treatment until the disease has evolved to a later stage, since only patients with active[6] or symptomatic disease require therapy (Hallek 2019).

CLL is defined by the clonal proliferation and accumulation of mature, typically CD5-positive B-cells within the blood, bone marrow, lymph nodes and spleen (Hallek 2019). The diagnosis of CLL itself is established by the presence of more than 5000 B-lymphocytes per μL in the peripheral blood for the duration of at least 3 months.

A precursor state – monoclonal B-lymphocytosis (MBL) – is used for patients who don't (yet) fit into CLL criteria (absence of lymphadenopathy or organomegaly, cytopenias, or disease-related symptoms, and the presence of fewer than 5000 B-lymphocytes per μL blood) (Hallek 2019). Seemingly a condition that may occur at high prevalence in the general population (from about 3.5% to 12% in individuals older than 40 years, depending on technique sensitivity) (Strati and Shanafelt 2015), high-count monoclonal B-lymphocytosis seems to progress to frank CLL at a rate of 1% to 2% per year (Hallek 2019). Despite its high prevalence, though, MBL is not a physiological event that occurs in all individuals with increasing age but a specific condition affecting select patients in whom at least some predisposing risk factors have been identified (Strati and Shanafelt 2015).

[5]Referring to Boorse's distinction between disease, meaning the malfunctioning of biological systems, and illness, referring to the deterioration of one's well-being (Boorse 1975).

[6]Meaning that there is evidence of rapid progression.

What separates MBL from CLL is a thin line. It is even acknowledged outright by Strati and Shanafelt (2015): "The threshold selected to distinguish high-count MBL from CLL [...] was arbitrary"; by Oliveira et al. (2015): "The arbitrary threshold of 5 × 109/L chronic lymphocytic leukemia (CLL)-like lymphocytes differentiates monoclonal B lymphocytosis (MBL) from CLL", and even by Binet et al. (2006): "Classically an arbitrary threshold of 5000 lymphocytes/L has been considered as a prerequisite for diagnosis". In the 2000's, revisions redefined the threshold to diagnose CLL based on the absolute B-lymphocyte count (ALC) rather than the absolute lymphocyte count. Going from an ALC-based criteria to a B-cell count–based criterion reclassified many patients who would have previously been considered Rai stage 0 CLL into the high-count MBL category – meaning they went from being diagnosed with cancer to not being so:

> Many of the biological characteristics of high-count MBL are similar to Rai stage 0 CLL. These facts raised the question of whether high-count MBL should or should not remain an entity separate from Rai 0 CLL and, if a separate entity, what threshold should be used to segregate the 2 conditions. Because the designation of CLL and MBL are clinical diagnoses, a number of groups advocated that the distinction should be based on the clinical implications for patients, such as having an impact on survival (Strati and Shanafelt 2015).

In the end, a B-cell threshold was estimated to be the best predictor for survival, considering that higher B-cell counts seem to be associated with a shorter time to progression and a shorter time to first treatment. Current consensus is that low-count MBL signifies a lower risk of progression, has no clear clinical implications, and requires no specific clinical follow-up (Strati and Shanafelt 2015). The choice to distinguish between MBL and CLL based on precise markers, and therefore the recognition of a pre-disease category (or precursor state) like this one can help prevent over-medicalisation and overdiagnosis. The impact of risk stratification on nosologies is of particular interest here: indeed, the way in which patients are eventually monitored and treated depends in great part on how new discoveries are integrated – formally or informally – into a diagnostic category.

What of the many asymptomatic patients diagnosed with CLL who will never develop any symptoms or need to be treated? Here again, markers have been identified which could help distinguish between asymptomatic patients whose disease will start evolving from those whose disease is very likely to remain indolent, especially because (as mentioned earlier), risks of progression are linked to the characteristics of tumour cells themselves and not to age. Nevertheless, their diagnosis remains the same – Chronic Lymphocytic Leukemia – though the line that separates them from monoclonal B-lymphocytosis is quite thin. It has been recognised that the Rai or Binet clinical staging systems alone are not sufficient to estimate the individual prognosis reliably, particularly for patients with early-stage disease.[7] Therefore, additional parameters have been sought to assess more accurately the prognosis of patients with CLL, and this search has provided a steadily increasing number of laboratory tests able to predict the response to

[7] E.g., Binet stage A, Rai stages 0-II.

treatment, progression-free survival or overall survival of patients with CLL (Binet et al., 2006; Hallek 2019). A comprehensive, international prognostic score (CLL-IPI) integrates biological and clinical variables to identify distinct risk groups of CLL patients (Hallek 2019): this score integrates various markers which are thought to have good prognostic value.[8] While such scores are mostly used to identify very high risk patients in order to provide them with the best possible care, other markers have been determined to denote much lower risk; for example, an isolated del(13q14) is characterised by a benign course of the disease (Hallek 2019).

Active treatment, even for preemptive purposes, is not recommended for asymptomatic patients, and especially not for low-risk ones. But in studying their situation, one has to wonder: is there not a way in which the burden borne by these non-ill but diseased persons, whose quality of life and lifespan are unlikely to be affected at all despite the fact that they have been diagnosed with cancer, can be lessened? The act of diagnosing someone with cancer is not anodyne: it can have a profound psychological and financial impact on a person's life. Doing so when that person is unlikely to be adversely affected by the disease itself, even more so. Avenues of de-escalation can be explored here too, however. For example, in France, an extension of the "right to be forgotten" is under consideration for CLL patients whose condition is likely to remain indolent, despite its status as chronic illness (usually, this right to be forgotten allows patients who are several years into remission not to disclose their diagnosis to insurance companies or banks anymore).

The example of CLL illustrates how disease stratification based on personalised approaches to prevention might lead to a form of de-escalation of over-medicalisation, overdiagnosis and overtreatment. Risk stratification, however, might not be, on its own, the most effective form of de-escalation. Couldn't personalised prevention be used more convincingly if the radical impact it can have on diagnostic categories themselves is acknowledged and accepted?

Changing Nosologies: A Bridge Between Personalised Prevention and Public Health

Changing Perceptions and Labels

So far, this chapter has focused on risk stratification when used to lessen the burden of at-risk individuals once diagnosed – through reduction (less frequent and/or intense detection or interventions); replacement (substituting the existing practice with a different one); removal; or restriction (narrowing the target population or

[8]The CLL-IPI uses a weighted grading of five independent prognostic factors: TP53 deletion and/or mutation (collectively called TP53 dysfunction), immunoglobulin heavy chain variable (IGHV) mutational status, serum β2-microglobulin, clinical stage, and age (Hallek 2019): "One very important value of the CLL-IPI also lies in the fact that it identifies – more accurately than the clinical staging – CLL patients without need of therapy. Patients with a low risk CLL-IPI (0–1) and asymptomatic disease do not require treatment" (Ibid., 2019).

the setting of the intervention), to use the terminology proposed by Norton et al. (2019). However, while the discovery of markers of high or low risk can influence how people are treated, it might also change how they are diagnosed.

Ideally, the measures of de-escalation outlined in the previous subsection could help change our perception of cancer from a deadly disease to a condition affecting a very large number of people, sometimes unbeknownst to them. This could maybe help lessen the impact of its diagnosis and encourage de-escalation in many cases. It is likely that such a change in perception will not take place swiftly, however, and, in the meantime, the name "cancer" will continue to wreak havoc in the minds of those to whom it is associated and to encourage them and their caregivers to seek whatever measures could help fight it back.

In a debate published in early 2019, Laura Esserman and Murali Varma defended opposite responses to the question "Should we rename low risk cancers?"

Murali Varma outlined his reservations regarding this rather radical approach to de-escalation, highlighting the difficulties in determining with certainty the natural course of any low risk tumour, and arguing that alternative terminology may induce confusion and anxiety (Esserman and Varma 2019). Rather than focusing on semantics, a more effective method would be to educate everyone (from the public to healthcare professionals) about the meaning of a diagnosis of cancer.

Laura Esserman, on the other hand, defends an idea closer to the notion of "undiagnosing" used by Page and Etherton-Beer (2019). According to her, ethical concerns alone require that a very strict definition of cancer – a word to which universal fear is attached – be used, so as to avoid unnecessary harm to patients (psychological, physical and financial) from unnecessarily invasive investigations and treatments (Esserman and Varma 2019):

> The clinical definition of cancer describes a disease that, if untreated, will grow relentlessly and spread to other organs, killing the host. What we routinely refer to as cancer today is a disease marked by heterogeneity, varying in metastatic potential from ultralow (<5% chance of progression over two decades) to extremely high (>75% chance of progression over one to two years). Many thyroid, prostate, and breast cancers are ultralow risk lesions (Esserman and Varma 2019).

To her, then, a condition that is indolent or rarely metastasises does not fit the clinical definition of cancer, and she claims that it is essential to use genomic tests to inform our understanding of risk and vulnerability and to change how we define cancer. According to Esserman, there is an ethical imperative to "relabel lesions that are ultralow risk" so as to spare patients the unnecessary physical and psychological trauma of a cancer diagnosis, as well as the attendant fears of recurrence or side effects of treatment (Esserman and Varma 2019). Esserman also points out that de-escalation of treatment has proved to be extremely difficult in view of the fear of patients told to wait and watch once they have been told they have cancer (Esserman and Varma 2019). She argues that a change in nomenclature would lead to a change in what researchers investigate and what clinician investigators report, being, in that sense, one of the most effective forms of de-escalation of over-medicalisation, overdiagnosis and overtreatment.

Whether one is more convinced by Varma's or by Esserman's outlook on this question, their paper has the great merit of confronting an important question regarding the impact that personalisation can have on diagnosis. Our conceptualisations of vulnerability, and of the responses that ought to be brought to it, depend at least in part on such nosological choices. The way in which risk is integrated – or not – within specific diagnostic categories is of great consequence:

> One of the ways in which treating susceptibility is more complicated than treating disease is that disease is relatively well defined and susceptibility is not [...] Determining who is a suitable candidate for intervention entails narrowing down what constitutes compelling vulnerability (Corcoran et al. 2005).

Questions surrounding vulnerability, how it is defined and how we ought to respond to it as a society, or as medical professionals, are implicitly present throughout ethical debates regarding personalised prevention. Only rarely are they explicitly at the heart of these discussions, however.

Applying the insights of feminist philosophy and of the ethics of care about how universally interdependent and exposed to harm we are as living beings, Rogers, Mackenzie and Dodds (2012) introduce useful taxonomy of vulnerability which can help highlight what is at stake here.

According to them, sources of *inherent* vulnerabilities are ingrained in the human condition. They are those vulnerabilities that arise from our "corporeality, our neediness, our dependence on others, and our affective and social natures" (Rogerset al. 2012). This notion of inherent vulnerabilities is able to account for sometimes strong individual disparities in the level of risk faced by all humans. Corporeality, for example, while it does indeed define all living beings' relationships to the world and to others, remains at the same time a profoundly singular, embodied and finite experience which is dependent in great part on individual material and physical features. It cannot simply be a universally-shared condition; it must also be irreducibly individual. As such, early markers of risk can be understood as *inherent* vulnerabilities that personalisation is well-suited to identify and address.

On the other hand, *situational* vulnerabilities – by which are meant vulnerabilities that are context-specific – are generally caused, or exacerbated by "the personal, social, political, economic, or environmental situation of a person or social group" (Rogers et al. 2012). The distinction between *inherent* and *situational* sources of vulnerability can be pertinent on its own, but the possibility of pathways between both kinds of vulnerability is markedly more so: "biologically grounded vulnerabilities are intrinsically linked to and often exacerbated by vulnerabilities that arise from contextual factors, such as discrimination, poverty, and dependency" (Rogers, 2014). As will be seen in the next section, it is in disregarding such sources of vulnerability that personalised prevention sometimes becomes ethically problematic.

Some responses to the identification of vulnerabilities may indeed exacerbate them, or even generate new ones: these constitute *pathogenic* vulnerabilities. Rogers, Mackenzie and Dodds' work documents the harm that can be produced by such inadequate reactions to vulnerability. Pathogenic vulnerabilities might arise

from targeted responses to perceived vulnerabilities. Over-medicalisation, over-diagnosis and overtreatment are, in this case, pathogenic responses to exceedingly rigid, biologically-grounded and apprehensive conceptualisations of vulnerability. Varma and Esserman's debate about the re-naming of low-risk cancers shows how reflecting on such notions may lead one to question more radically how newly-identified vulnerabilities ought to be integrated (or not) into pre-existing diagnostic categories, or even transform them profoundly.

The field of pre-emptive psychiatry might be argued to be an area in which this kind of debate has occupied a much more preeminent place than in oncology, illustrating some of its most important ramifications in a way that ought to inform further reflections in other medical fields.

From Diagnostic Categories to Staging in Psychiatry

The case of pre-emptive psychiatry might provide an example of how nosologies themselves – and not just interventions – could be impacted by personalised approaches to prevention, opening a potentially more radical path towards de-escalation.

At least two diagnostic models have been suggested to account for a newfound capacity to identify individuals who are more at risk than others to develop serious mental health issues – especially psychotic disorders. Three different subgroups of people at risk for psychotic disorders have thus been identified: people suffering from attenuated positive symptoms[9]; those who have gone through brief intermittent psychotic states; and persons who have a genetic and familial risk for psychotic illnesses[10] coupled with a recent and dramatic decline in functioning (Addington and Heinssen 2012).

The first of the two models presented here, the Attenuated Psychosis Syndrome (APS), is a diagnostic category that was proposed for the publication of the *Diagnostic and Statistical Manual for mental disorder* (DSM-5) in 2013. As a diagnostic category, it attempts to capture the symptomatology of the prodromal phase[11] of psychotic disorders; however, the transition to full-threshold psychosis being

[9]Positive symptoms, in psychiatry, are understood as symptoms which bring about new phenomena, such as hallucinations, delusions, etc., while negative symptoms point to the loss of capacities, like apathy, speech difficulties or social and emotional withdrawal.

[10]The prevalence of schizophrenia, for example, is generally said to be around 1% in the general population; but "in early studies [...], the risk of developing a psychotic disorder increased from the expected rate of approximately 10% in family high-risk groups to approximately 30% to 50% in clinical high-risk samples followed for one to two years" (Addington and Heinssen 2012). Ethical debates surrounding the benefits/risks ratio of pre-emptive psychiatry have been fierce, balancing the possibility of over-medicalisation, overdiagnosis, overtreatment, stigmatisation, and injustice against that of being able to prevent the development of a particularly harmful disorder.

[11]The prodrome of a disease encompasses early signs or symptoms before more diagnostically specific signs and symptoms develop.

uncertain at best, it was decided that a label integrating the notion of "risk" was more anxiety-inducing than helpful. The APS, as such, is considered as a diagnostic category in its own right – and as a prime example of over-medicalisation and overdiagnosis for its detractors. Conversion to full-threshold psychosis is generally based on increasing symptom severity, which would result in the recognition and diagnosis – once such severity has reached a certain level – of actual psychosis (Carpenter 2009). Consequently, the Attenuated Psychosis Syndrome leaves open the possibility of conversion to full-threshold psychosis without explicitly giving the "at-risk" label to those diagnosed with it.

On the other hand, staging models inspired by what is done in fields like oncology – though not necessarily incompatible with attenuated syndromes like the APS – offer an alternative that profoundly transforms how psychiatric illnesses and vulnerabilities are conceptualised. Staging models account for the evolution of a disorder from an at-risk (but asymptomatic) state to the later phases of a chronic illness, while traditional, categorical approaches are more rigid. For that reason, they, too, are accused of widening considerably the scope of diagnosable conditions. Staging models in psychiatry originated from the idea that traditional diagnostic categories were failing, especially in terms of clinical utility. The primary goal of a diagnosis must be to assist clinicians in improving their selection or sequencing of treatments, and to enable them to make more accurate prognostic statements in keeping with newer concepts and knowledge (Hickie et al. 2013). Another criticism levelled at traditional diagnostic categories in psychiatry by proponents of staging models is their tendency to presuppose that independent causal pathways exist for each clinical phenotype – "an assumption that is not supported by contemporary family, genetic, neurobiological or risk factor research" (Hickie et al. 2013). It is considered more useful to examine "specific neurobiological domains that cut across diagnoses", focusing on "cross-cutting dimensions rather than categorical distinctions" (McGorry et al. 2014).

McGorry and colleagues proposed a staging model for major mental illnesses (including psychosis) that is, interestingly, nonspecific for the earlier stages. It starts with an "at-risk" but asymptomatic state (stage 0); evolving to an initial stage of undifferentiated general symptoms followed by a worsening of these existing symptoms and the acquisition of new ones, associated clinically with hints of greater syndromal specificity and with behavioural and functional decline (stage 1); then, further progression of illness may result in the occurrence of a first episode of a full-threshold syndrome(s) (stage 2), which may in turn be followed by the development of persistent symptoms, frequent relapses and ongoing impairment (stage 3), or even severe, unremitting illness (stage 4) (McGorry et al. 2014).

The idea underlying such staging models is embedded in the basis of pre-emptive psychiatry: remission and amelioration are possible at every stage, though it is less likely with each advancing stage (McGorry et al. 2014). It is indeed important to note that staging models are dynamic, not only in the sense that they account for the evolution of a disorder through distinct stages, but also in the sense that an individual's mental health can worsen or improve. Movement is possible across these stages in both directions, which is precisely why proponents of staging models

advocate for interventions adapted to each stage: their aim is not only to stop progression to a further stage but, conjointly, to facilitate regression to an earlier stage (McGorry 2007). There are many different possible development courses for an individual whose condition corresponds to the at-risk mental state, and specific and direct progression to a full threshold psychotic disorder is only one of them: "several different outcomes are possible in a population considered to be at risk, including conversion to psychosis, symptomatic recovery, and stable presentation of prodromal symptoms" (Addington and Heinssen 2012). As such, the confrontation of various diagnostic models (categorical vs. staged) in psychiatry illustrates how various conceptualisations of vulnerability may be produced within them.

Stratified or personalised interventions remain aspirational, yet potentially within reach in psychiatry, according to McGorry et al. (2014). In psychiatry, potential biomarkers – including markers of risk – are readily understood to go beyond genomics, and many of them are under study so as to further stratification: cognitive markers (mild significant premorbid neurocognitive and social cognitive deficits); brain structural markers (in gray matter volume, notably, though the role of antipsychotic medication in these progressive brain changes is also a potential key factor); mismatch negativity as a marker of brain function; sleep and chronobiological markers (disruption of sleep, often accompanied by specific shifts in the sleep-wake cycle); neuroendocrine markers (alteration of the hypothalamic-pituitary-adrenal axis and an impaired ability to cope with stress, both at the psychological and biological level); inflammatory and oxidative stress markers (infusion of pro-inflammatory cytokines and interferon) or fatty-acid markers (polyunsaturated fatty acids) (McGorry et al. 2014).

Stratifying risks for mental disorders can have a significant impact on the implementation of pre-emptive measures in psychiatry. Staging models require "an accurate understanding of the broad social, biological, and personal risk and protective factors that influence movement across stages" (McGorry 2007). The idea is to link psychopathology to the biological and psychological nature of disease processes (Müller-Spahn 2008):

> Further risk stratification is urgently needed to identify subgroups with specific needs and response patterns and thus improve the cost-benefit ratio of preventive interventions. Hence, it has been suggested to develop prediction models that integrate information from various assessment domains, including psychopathology, sociodemographic characteristics, neurocognition, blood parameters, neuroimaging, and neurophysiology (Studerus et al. 2016).

In this sense, public health measures could be led to play a crucial role in the implementation of preemptive interventions adapted to the earliest stages of psychiatric disorders: far removed from medical settings, they would be designed to address needs for public measures, from psychosocial to academic support.

From Personalised Prevention to Public Health

The example of pre-emptive psychiatry highlights an important tension in the development of personalised prevention: that which might pit personalisation and public health against one another. Psychiatry is a field in which the complexity and multiplicity of causal factors operating at different levels in the development of a disorder are readily acknowledged. In this field, the notion of personalisation has never been – and cannot be – reduced to genomics.

Public health commentators have been skeptical regarding the wisdom of prioritising individualised approaches that focus on at-risk individuals rather than on population-based preventive programs that consider the behavioural, environmental, and social determinants of health, much more consequential (Ramaswami et al. 2018; Phelan et al. 2010). In particular, concern has arisen that a too strong focus on genomics is misleading, given the relatively small impact of genomic factors on overall health in contrast to these other factors (Ramaswami et al. 2018).

The shift of focus from culturally or structurally related causes of diseases (socio-economic factors, pollution, urban planning, etc.) to individualised preventive strategies must indeed be backed up by evidence that this can improve health outcomes (Green and Vogt 2016). The role of factors such as social inequities, poverty and racism has been shown to have a profound impact on suffering and on life expectancy (Ramaswami et al. 2018). However, personalised prevention might also participate in reinforcing the claim that, in many cases, contextual factors do have a far-reaching impact regarding many chronic diseases, including and up to common cancers (Jaffee et al. 2017).

There is an expectation that "big data" technologies can account for an increasing number of such factors (including socio-economic and environmental ones) that influence health and disease (Green and Vogt 2016), deepening our understanding of complex diseases. The inclusion of environmental and social aspects in the development of personalised medicine may indeed be seen as an improvement, embracing human biocomplexity (though some apprehensions have been expressed about the extent to which newer areas of human life might come to be controlled by technoscientific concerns) (Green and Vogt 2016).

A symbiotic relationship between public health and personalised medicine may one day exist. More specifically, the relationship between personalised prevention and public health might encourage a form of "integration" between primary and secondary preventive strategies (Ponti et al. 2020). In principle, primary prevention can be offered either universally or, more selectively or indicatively,[12] to healthy individuals with known risk factors. However, many obstacles still face those who

[12]Prevention programmes, in principle, can follow three different approaches – universal, selective and/or indicated. Each reflects segments of the population as well as levels of risk. A universal prevention targets the general population unspecifically as a whole; a selective prevention approach aims at a segment of the population which is clinically healthy, but at a high risk for the disease (e.g., because of a genetic liability); indicated prevention targets persons who already show clinical signs and are possibly in a prodromal state.

would favour a universal approach to primary prevention: attempting to reduce risk on a universal scale would require immense politico-social will, means, and reach. Several goals would have to be pursued simultaneously, and the allocation of responsibilities for these ambitions (between healthcare professionals, social workers, policy-makers, politicians and others) is, in itself, an incredibly arduous and complex task – though still one worth pursuing.

Because personalised prevention targets more narrowly selected populations, it might help promote the implementation of selective or indicated primary preventive measures. The process of risk stratification ought to encourage the development of non-medicalised forms of primary prevention for many complex diseases, rather than be restricted to secondary or tertiary prevention. Translated to the case of pre-emptive psychiatry, for example, this could mean for identified at-risk individuals the encouragement of lifestyle changes (disruption of sleep is a ubiquitous characteristic of the onset period of most major psychiatric disorders (McGorry et al. 2014) and could be the focus of pre-emptive measures, for instance), a more accessible provision of psychosocial or academic support, or even the reimbursement of sporting activities (regular physical activity has been associated with a significantly decreased prevalence of depressive and anxiety disorders, and is sometimes used as a treatment option to alleviate early symptoms of psychosis (Goodwin 2003; Firth et al. 2018). "The public health approach relies on primary prevention, promoting individual responsibilities and resilience, while also sustaining existing services and tackling inequalities" (Bhui and Dinos 2011): with staging models, attention can be paid more openly to a vast array of risk factors that are known to increase vulnerabilities (both inherent and situational) from a very early age.

Personalised prevention should not be in competition with more traditional, public health-based approaches to prevention. On the contrary, one can hope that its development, enlightened by a deeper understanding of what might constitute pathogenic responses to vulnerability (to use Rogers, Mackenzie and Dodds' taxonomy of vulnerability outlined earlier), will highlight the crucial importance of the behavioural, environmental, and social determinants of health, and will encourage, through risk stratification and individualisation, the development of more widely-available, non-medicalised forms of primary prevention.

Conclusion

Serious concerns have been expressed regarding the tendency of personalised prevention to exacerbate issues of over-medicalisation, overdiagnosis and overtreatment. Indeed, it is said to lead to the discovery of a multitude of small abnormalities as well as of diagnostic, prognostic, predictive and pharmacogenetic biomarkers of low significance and low predictive validity (Esserman et al. 2014; Gyawali 2017). Several diseases are now detected in their earliest stages, many of which would never have developed in such a way that it would have negatively impacted a person's quality of life or lifespan. In such cases, the harm caused to these persons can be significant. Nevertheless, the aim of this chapter has been to explore

the mechanisms through which personalised prevention could reduce these risks, rather than exacerbate them. First, the development of personalised prevention takes place in a context where issues of over-medicalisation, overdiagnosis and overtreatment are already prevalent in prevention. Widespread screening and the growing precision of screening techniques have meant that small tumours and other abnormalities have been detected in larger numbers of people, highlighting the need for a way to distinguish between those who would go on to develop problematic forms of the disease from more indolent ones. Secondly, if the process of risk stratification encouraged by personalised approaches to prevention appears to fulfill this need, it is because it enables a more nuanced conceptualisation of risk, from very low to very high. A more nuanced understanding of risk would promote watch-and-wait strategies in place of active treatment and the restriction of screening programmes to those most likely to benefit. Lastly, the more radical impact that personalisation and risk stratification could have on nosologies and diagnostic categories themselves may help bridge the gap between public health and personalised prevention, encouraging the implementation of preventive measures that ensure that identified at-risk individuals have access to needed forms of public support. In analysing and evaluating the conceptualisations of vulnerability brought forward by the development of preventive strategies, one may hope to understand better why they can easily become ethically problematic (conceptualisations that are too simplistic and overly cautious), and how they could offer more nuanced and respectful responses in embracing complexity, and even the need for sometimes radical change.

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Making Feasible Personalized Nutrition: Between Science and Daily Habits

Laura Dugo, Andrea Pensotti, and Vincenzo Fogliano

Introduction

Nutrition and lifestyle are well recognized as contributors to health status and disease prevention. Common diseases such as stroke, type 2 diabetes, and cancer have been closely linked with dietary factors in terms of both preventive potential or aggravating risk cause (Micha et al. 2017; Ferlay et al. 2012; GBD 2015).

Unfortunately, the attempts to improve public health and wellbeing through nutritional intervention have had limited impact. We are continuously exposed to an unlimited food offer and pushed to eat a lot more than our actual energetic requirements ask for, leading to a physiologic increase of energy storage and body weight. Homo Sapiens biological roots do not help in this respect: human body is programmed to accumulate calories to survive the periods of scarcity; this genetic design led humans through terrible times of famine, and it is still securely held in our cells today (Qasim et al. 2018). A large part of global population today faces quite the opposite side of famine: food offer is at its highest in terms of quantity, although

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in some case reaching quite a low level in terms of quality of nutrient contents (Santeramo et al. 2018). All this happens while people still die of malnutrition somewhere in the world.

Having experienced the "dark side" of over nutrition, nowadays the awareness about food quality and is increasing both from the side of consumers and both from the side of producers. Interestingly we assist to a growing movement of people concerned for the fate of our planet and its environment, inevitably involving food production, availability and distribution. The recent EAT-Lancet commission paper reports interesting epidemiological data suggesting the "best diet for humans". A strict observation of such a diet would eliminate personal choices or preferences but will alleviate health care costs by ameliorating general health and will reduce environmental impact by increasing the consumption of eco-friendly foods (Willett et al. 2019).

If in the past an un-effective food chain prevented people from the opportunity to choose what to eat, the actual food chain efficiency lets emerge the opposite condition: people have too much opportunities to choose what to eat and they're not educated enough for choosing well.

It is in this framework that new technologies may help people to better orientate in their food choices. Forster et al. (2016) defined it as an approach to "assist individuals in achieving a lasting dietary behaviour change that is beneficial for health". But is there a standard dietary behavior? The growing knowledge given by the so called "omic science": nutrigenomic, metabolomic, proteomic and so on, along with a large amount of studies on nutrigenetic, opened the way for a new promising field of nutrition: personalized nutrition. The concept of "personalization" is finding interest also in marketing strategies: detailed labels, health claims, new foods design and intelligent packaging are only a few of several innovations investing the great organized distribution (Santeramo et al. 2018). For the more demanding, health-conscious, wellbeing-driven consumers, food is not only supposed to feed us, but eventually it is expected to prevent, or even cure, a variety of widely diffused diseases. This message is well vehiculated by major communication sources as well as social media.

The big issue now is how to manage this huge amount of information coming both from personal data and from a constantly growing data production by scientific research. The ambitious goal is to design a tailored diet aimed to preserve or increase health using an array of relevant information about individuals (Ordovas et al. 2018). Several smartphone applications have been developed and are today recording a massive amount of data from their user's lifestyle; also, wearable devices are now able to monitor blood pressure, heartbeat, sleep patterns and other biomarkers of body functionality. As a result, users can benefit of customized suggestions regarding their eating needs and behaviour.

We can therefore say that by merging science of personalized nutrition with digital health technologies people and health systems will benefit in terms of prevention and management of diseases.

Nevertheless, it's still not well clear what will be the real impact on people, both on scientific and technological side. Do people will accept to be driven by science

and technology on their food choices? Do such kind of personalized nutrition will affect the whole population or only the niches of people with metabolic disorders?

Personalized Nutrition: Definition, Opportunities and Limits

A clear definition of personalized nutrition is needed before analyzing its opportunities and limits. The pillars of nutrition recommendations are indeed very general and, although not very innovative, ever so valid for everybody: "eat plenty of fruit and vegetables, increase the amount of fiber, follow a varied diet". There are certain exceptions to this rule: scientific research proved specific nutrients, therefore specific foods, to be useful for subjects having a specific genetic profile or a peculiar microbiota composition (Corella et al. 2017; Kolodziejczyk et al. 2019). On the other hand, some people can benefit from a specific diet for medical reasons such as allergies or intolerances, adverse reaction (celiac disease), personal or ethical choice (vegetarian, vegan), or simply taste preferences. The personalized nutrition tool can be helpful in a variety of situations, to keep a diet which is restricted or limited in one or more nutrients and/or foods, within the borders of a balanced intake of nutrients.

Parallelly, the quest for a healthy aging is bringing people to look for healthy habits also when they are not coping with diseases such as allergies, metabolic disorder or intolerances. Marketing named this segment of consumers "active aging" meaning that they can sell products designed for helping people to age healthy and empower their current health.

The science of personalized nutrition, developed essentially for managing pathological conditions, offers nevertheless concrete answers also for this kind of new needs.

We can therefore identify two different needs and types of personalized nutrition: one for people with some physiological disorder and the other for healthy people.

Globally personalization can be based on a genotypic and/or phenotypic profile, associated with biological evidence of differential response to specific foods or nutrients. Moreover, a detailed analysis of current nutritional habits, tastes, preferences and dislikes can be carried out building a data set, which could be used to motivate and enable each one to make the appropriate changes to their eating pattern. Science tells us that different people or communities can respond differently to dietary components (Miller et al. 1988; Morris et al. 2013). Personalization could play a key role for specific age groups or stage of life, ethnicity or religious need to follow a specific diet. The recent scientific advance in genetic profiling has made it available and relatively affordable for the generic public. On this wave, nutrigenetic has risen as the discipline that studies the different phenotypic response to diet depending on the individual genotype, evolving to the point of using a whole genome approach studying interactions with different dietary patterns (Corella et al. 2017; Frazier-Wood 2015).

Genetic information still represents a key component of the diet personalization potential. The Academy of Nutrition and Dietetics confirms how diet and genotype

interaction can affect phenotype, although implementation of nutrigenetic testing to provide dietary advice is not ready for routine dietetics practice (Camp et al. 2014). A framework to validate scientific evidence for nutrigenetic tests has been released, aiming to properly regulate information delivered through the internet in order to develop scientifically appropriate advice for people that voluntarily apply for nutrigenetic test (Grimaldi et al. 2017).

Researchers and stakeholders have focused mostly on the genotypic and phenotyping profiling, simply assuming that personalization of diet will be most effective when based on the largest possible array of individual data measurable (Riedl et al. 2017). But sticking to a diet is not nearly as easy as sticking to a medical plan. Most people can easily follow a drug prescription, often for a very long period of time, but will find extremely difficult to implement a radical change of the way they eat. Dietary changes require a continuous and effective compliance at every meal of the day, resisting impulse eating and "forbidden" foods.

The Food4Me study is the largest randomised controlled trial to date to have investigated the efficacy of personalized nutrition. It was implemented as an internet-based intervention, designed on the like of commercial personalized nutrition services. It included more than 1600 adults over seven European countries and investigated new approaches of both collection and data analyses of biological samples. One limit of the study is a quite short 6 months endpoint; but researchers state a very clear answer: personalization of dietary advice motivated consumers to change their dietary and lifestyle habits toward healthier choices. The Healthy Eating Index was used as a general "healthiness" measure. Interestingly the adoption of sophisticated and expensive personalization tools such as genetic profiling, did not result in additional benefit. This study represents an important step in the validation of appropriate personalized nutrition systems, providing a model for the use of internet as a channel for the delivery of personalized nutritional intervention (Celis-Morales et al. 2015, 2017, 2018, 2019; Forster et al. 2016; Hollands et al. 2016; Guasch-Ferré et al. 2018).

Digital Health: Definition, Opportunities and Limits

Technology development opened the way to new opportunity in order to monitor and evaluate specific health conditions of each person. On one hand new wearable devices allow to measure several parameters such as heart rate, walking distances, glycemia, etc. on the other hand, artificial intelligence programs allow to manage these data in order to provide life-style programs, including personalized diets.

The ability to measure as much as we can has been implemented by fitness trackers and smartphone apps, although their utility is yet to be fully proven (Chiauzzi et al. 2015; Patel et al. 2014). A study from Lloyd-Price et al. (2017) involved 108 people, collecting personal data as well as whole genome sequences, blood tests, blood metabolome and proteome, fecal microbiome and lifestyle habits over a 9 months period. This massive amount of data was used to generate correlation networks potentially associating analytes with physiology or diseases. Genotype

and clinical markers data were also used to generate personalized coaching aimed to improving participants health status. Participants for the study were self-selected, this probably making the whole study far-fetched for its application to general population. However, the major findings of the study were the realization that highly motivated people are willing to collect personal data over a long period, and also that those highly motivated people could really benefit from personalized nutritional coaching in changing their eating behaviour.

In 2015, a study Zeevi et al. reported high interpersonal variability in post-meal glycemic index in an 800-person cohort; glucose levels were continuously monitored week-long, finding high variability in the response to identical meals, suggesting that universal dietary recommendations may have limited utility. Authors devised a machine-learning algorithm that integrates blood parameters, dietary habits, anthropometrics, physical activity, and gut microbiota measured in this cohort showing that it accurately predicted personalized postprandial glycemic response to real-life meals. This led to the conclusion that using personal and microbiome features enables accurate glucose response prediction and that short-term personalized dietary interventions successfully lower post-meal glucose (Zeevi et al. 2015).

More and more people are used to "be managed" by smart technologies, therefore it is likely to use these technologies in order to perform personalized nutrition program.

Nevertheless, a big gap is still present between possibility and reality, and it is mainly related to the free will of people regarding their daily food choices. Are we ready to be dictated what to put on our plate, regardless to what we feel like eating? Eating is such an intricate business. Despite our energetic needs, eating is far from a strictly "energy refuel affair". We eat as a result of habit, social life, emotional reward, irresistible temptation and, often last of the list, hunger.

We assist periodically to the publication of best-selling books reporting the best possible diet. Several doctors and nutritionists, based on the available scientific knowledge, have told us what, how and when is best to eat. The web is ever so full of rapidly accessible information on food and nutrition, so much so that general population is struck by its amount, unable to decipher it. Whether technology may manage this psychological variable is still an open question.

Among the open issues on the use of technology for personalized nutrition, we have to consider the one related to reliability of data. How many data are "self-produced" and how many are required to be provided by the user? The more is needed an active operation by the user, higher is risk of unreliable information. Another issue is related to the frequency of data picking and their correlation. It is still unknown how much deviation from the standards is allowed. The question that arise is: at which level of details we want to monitor the person? With what precision and at which time interval we want to monitor the data?

Conclusions: Looking for an Optimal Equilibrium

Personalized nutrition represents a promising concept, which needs to be approached scientifically to find the correct mode of implementing it for the general population. A simple Google search offers hundreds of choices in products and services related to personal nutrition, but are those really useful and, above all, effective? Technology and fancy devices can motivate healthy eating but ultimately the best motivation of all is the true realization that we could substantially affect our health by making sensible eating choices. Genetic tests and personalized recommendations could facilitate the transition, but more work should be done towards the development of behavioral approaches to motivate specific individuals or cultural groups (Macready et al. 2018; Horne et al. 2018).

To date, no personalized nutrition study has been carried out at a large scale, in an appropriate population group and over a sufficient amount of time. The design of a nutritional study of this sort is very complex, other than financially and logistically challenging. It must be said that potential market for personalized nutrition is huge and can target a vast number of consumers.

Moreover, it is important to define specific goals we want to reach with personalized nutrition. In the case of people with some disease, the goal should be to manage their health by an appropriate personalized nutrition plan. Condition such as diabetes, hypercholesterolemia, hypertension, irritable bowel, and so on could clearly benefit by the synergy of a pharmacological approach with a personalized nutrition plan. Technology can be very useful in order to collect the data of the patients and to suggest/remind them the best diet plan to follow. We can say that technology allows an active surveillance of the disease or pre-disease state and a personalized nutrition plan helps both in terms of prevention and disease management. For this group of patients, the motivation is supposed to be high and technology should constantly remind them their risk in order to prevent a fall of "alert state".

Differently in the case of healthy people, the outcomes are quite different. The goals are on one hand the prevention of diseases, on the other hand a good aging process, which mean a way to get older keeping their body active. In this second case is more difficult to plan clinical trial and collect data. It is also difficult to keep people motivated. Generally, only people who wants to age well, people who care for their wellbeing, have enough motivation to follow personalized diet plan and constantly use technology such as wearables and apps.

Another issue is related to the levels of details at which we collect data and how they are presented to the user. The meaning of data is a fundamental issue that should be better investigated, both scientifically and psychologically.

On one hand, we should better study the processes of metabolisms and nutrigenomics in order to have better predictive model. On the other hand, we should identify the key motivators that pushes people to follow a personalized diet plan. What is scientifically relevant is not necessarily relevant for the person, but the success of personalized nutrition strongly depends on the user motivation.

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Part II

Personalized Technology: From Epistemology to Data Management

The emergence of personalized medicine has been shaped by, and in turn shaped, technology. While this has been a fruitful interaction, there should be critical reflection on the challenges arising in interactions between the two, as well as theoretical presuppositions informing both. The reflections on personalized medicine collected in the previous section focused on bio-medical case studies. In this second thematic section, the interplay of personalized medicine and technologies is at stake, focusing in particular on their epistemological commitments. The papers contained in the second part of this volume thus approach some issues related to a non-trivial understanding of technology applied to personalized medicine. In this way, they also contribute to reading "personalized medicine" in the light of the complexity that characterizes the living organisms, the technological models based on them, and the derived health data. To begin with, epistemic uncertainties about patient-derived models, such as tumor organoids, are the focus of Sara Green, Mie S. Dam, and Mette N. Svendsen's paper (Patient-derived organoids in precision oncology – Towards a science *of* and *for* the individual?). One challenge in using tumor organoids is accounting for the complex relationship between in vitro technology and the patient it is supposed to represent. Balancing standardization and variation in personalized medicine is an open-ended issue: patient-derived models, Green and her colleagues argue, are not generating an actual "science of the individual". Rather, an examination of the use of patient-derived models highlights the relational structure of evidence in personalized medicine, where patients are linked in novel ways via genetic markers and biobanks.

An enhanced digital development is required when bio-medical challenges are at stake, as the current Covid-19 pandemic is demonstrating. Together with digital development goes the problem of data organization, and this applies to personalized medicine too. Issues of biomedical data's organization are raised in the last three papers of this section, showing that a non-trivial and relational understanding of data is necessary for personalized medicine. Francesco De Pretis, William Peden, Jürgen Landes, and Barbara Osimani (Pharmacovigilance as personalized evidence) discuss the "E-Synthesis" tool, developed in order to facilitate causal assessment in pharmacovigilance. They inquire into the theoretical and methodological rea-

sons why integrating pharmacovigilance and personalized medicine raises difficult problems. This concerns, among others, the need to make estimates regarding possible *causal* effects of a treatment, in diverse statistical populations (reference classes), e.g., through the identification of possible moderators, and the estimate that a given individual belongs to one rather than another of such reference classes. While this stands as an ideal goal in pharmacovigilance, it does not in personalized medicine, which rather focuses on predictive factors. The article ultimately offers a possible bridge between these two fields.

Data science, A.I., in silico medicine, and personalized medicine in their mutual interactions are the topics at core of the papers by Edwin Morley-Fletcher (New solutions to biomedical data sharing: secure computation and synthetic data) and Liesbet Geris (Realizing personalized medicine using in silico tools: A community effort). From the viewpoint of, respectively, an expert of ICT for health and of tissue engineering, both papers take concrete and up-to-date case-studies to approach the subject of the volume in the framework of recent European initiatives. Morley-Fletcher presents the outcomes of the European funded project "MyHelathMyData (MHMD)", facing the challenge of big data health sharing by especially applying synthetic data to bio-medical cases. Geris describes an initiative promoted with the support of the European Commission, named "Virtual Physiological Human (VPH)" and the related non-profit organization "Virtual Physiological Human Institute". The project focuses on the use of in silico modeling in healthcare, helping the pathway toward personalization of medical treatments.[1]

[1]The last two papers of this section somehow adopt a different style and narrative with respect to the previous contributions in the section, especially to the extent that they make use of some philosophical terms in a broad and non-technical meaning (e.g., "mechanistic" or "phenomenological" are used outside of a technical philosophical framework). Yet, both papers keep addressing relevant epistemological problems related to data production and organization, as connected to personalized medicine. All these problems and their elaborations by the authors of the two papers can be thus read against the background of the general "philosophical perspectives" dominating the volume.

Patient-Derived Organoids in Precision Oncology – Towards a Science *of* and *for* the Individual?

Sara Green, Mie S. Dam, and Mette N. Svendsen

Introduction

Personalized medicine raises interesting philosophical questions about what counts as good translational models and appropriate evidence in a context where disease categories become hyper-stratified. We focus here on precision oncology, a field which is promoted as the most advanced domain within personalized or precision medicine (Plutynski in this volume).[1] In this context, personalized models are currently developed as an attempt to account for the genetic heterogeneity of individual patient's tumors. This chapter focuses on so-called tumor organoids, i.e., 3D cultures developed from tumor samples of individual patients. We explore how the translational potential of organoids is viewed and negotiated in laboratory research and clinical practice, and discuss how epistemic uncertainties concerning

[1] We use the terms "precision medicine" and "personalized medicine" medicine interchangeably to refer to the attempt to stratify and individualize modeling and treatment recommendations to individuals or finer-grained disease groups though the use of new molecular and computational techniques (such as genomics).

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the representational status of organoids intersect with ethical considerations about patient care.

Organoids have a complex conceptual and experimental history (Drost and Clevers 2018; Simian and Bissell 2017). Developmental biologists have for decades emphasized the potentials of 3D cell cultures for capturing how spatial conditions influence cell differentiation and cell reprogramming, including tumor development (e.g., Bissell et al. 1987; Barcellos-Hoff et al. 1989). Research on organoids recently gained momentum with new approaches in stem cell research, exploring also the potential of organoids to develop lab-grown miniature versions of human organs such as guts and neural structures (Sato et al. 2009; Eiraku et al. 2011; Lancaster et al. 2013). In this chapter, we focus on organoids as models that aim to recapitulate *genetic heterogeneity* of patient tumors and hence to allow for *patient-specific drug screening* (Huang et al. 2015; Ooft et al. 2019; Sachs et al. 2018).

Patient-derived models potentially reshape how we think about science and medicine. The emphasis on patient variation in personalized medicine calls for reconsideration of the merits and necessity of the long-standing trust in numbers and standardization procedures in clinical trials (Lillie et al. 2011; Green et al. 2019). *Nature* recently endowed organoids as the "Method of the Year" (Nature Editorial 2018), and some have suggested that patient-derived models in personalized medicine will revolutionize the study of cancer and other diseases (e.g., Akkerman and Defize 2017). Organoids derived from patient tumors have been suggested to represent a kind of "disease in a dish", because one can directly intervene on malfunctioning tissues (Shen 2018). Philosopher Giovanni Boniolo even suggests that tumor organoids, qua their material embodiment of patient diversity, pave the way for a "science of the individual":

> Since the Aristotelian discussion of the architectonic of knowledge, it has been accepted almost as a platitude that there is no science of the individual. [...] Whenever you study the primary cancer cells of a given patient, you are also studying tumor heterogeneity, that is, something at the universal level. But you are also studying the particular disease of that particular patient, that is, you are also studying the individual. [...] Put in a different way, within the field of tumor heterogeneity we have the possibility of doing science of the individual, since the tumor cancer cell population actually is an individual (patient) *in vitro*. (Boniolo 2017, p. 29)[2]

Similarly, organoid biobanks refer to their resources as "a patient in the lab" (Hubrect Organoid Technology 2020), and organoids combined with patient-derived xenografts (PDX, or personalized mouse models) have been described as giving way for a "one-patient paradigm" in medicine (Malaney et al. 2014). Questions about the translational potential of patient-derived models are thus intimately connected

[2]It is beyond the scope of our paper to discuss the notion of a "science of the individual" in Aristotle's writings and later scholarly work (see e.g., Foucault 1973 [1963]). Similarly, we cannot go into the discussion whether medicine should be understood as a science or an art, and whether such a dichotomy is fruitful (see Solomon 2015). Or primary focus is to explore the implications of attempts to develop more "individualized" models to account for the shortcomings of standardized procedures.

to questions about how the "personal" gets constituted in personalized medicine. Important questions include whether it is possible and desirable for in vitro models to become "substitutes" for patients or patient types (cfr., Svendsen 2018).

Organoids are philosophically intriguing because they blur the boundaries between human patient and experimental model. The quote by Boniolo above seems to suggest that tumor organoids establish a relation of *metonymy*, i.e., a part-whole relation of sameness between a 3D culture and the tumor of a specific patient. Similar to how we often take a picture of a face to represent a whole person, organoids come close to the vision of experimenting directly on a part of the patient in the lab. However, the idea of patients in vitro is complicated by ontological and epistemic instability of cancer itself. Whereas representation of heterogeneity is highlighted as a virtue of organoids, it is unclear which level of variation is necessary or useful to represent in experimental models. Heterogeneity of tumors does not "bottom out" at the level of cancer subtypes or even at the level of individual patients. Rather, tumors of individual patients consist of *spatially* and *temporally* heterogeneous cell populations – what is often referred to as *intratumor heterogeneity* (Bertolaso 2016; Plutynski 2018). Intratumor heterogeneity is a major challenge in clinical practice, as there can be heterogeneity across metastases from the same primary tumor. This problem also challenges the stability of personalized models, as it is unclear to what extent tumor samples can account for biologically relevant features of whole patient tumors.

Moreover, the view of personalized medicine as a departure from procedures of standardization is complicated by its epistemic dependency on and contributions to population science (Hoeyer 2019). Organoids are clinically useful only insofar as they allow for inferences about features and drug targets concerning cancer subtypes that go beyond individual variation. Hence, organoid research presents insights into how material embodiment of patient variation also depends on and co-produces new relations of inference between patient-specific biology and shared molecular markers, i.e., between the individual patient and the collective (data populations of extant and future patients). The issue of interest is therefore not whether organoids adequately represent the patient tumor per se, but to explore what is considered the right level of abstraction of models for clinical purposes. We show how challenges of reaching a balance between variation and standardization are tied to social and ethical implications in translational contexts.

Our philosophical analysis is informed by a literature study of published scientific material on organoids as well as insights from ethnographic work. As part of a research project on personalized medicine in the Danish welfare state, we have followed the development of initiatives to implement personalized medicine in the Danish health care system. Through interactions with researchers and clinicians, we have explored how personalized medicine at the same time is shaped as a wide-ranging political priority (e.g., through the establishment of a National Genome Centre) and as a concrete practice that materializes in different laboratory and clinical settings. Specifically, we have followed a preclinical project where organoids are used to guide decisions on experimental cancer treatments in a phase I clinic, based on genetic and kinase profiling. In this context, we

(together and separately) have participated in daily clinical practice and tumor board meetings, and have conducted interviews with researchers, oncologists, and patients. Moreover, we have interviewed researchers in the US working on patient-derived organoids for research purposes.

Our analysis shows that although organoids and other patient-derived models are sometimes framed as a technique that allows for direct inferences of patient-specific drug response, their status as preclinical and research models is complicated by various uncertainties and practical challenges. At present, organoids can be interpreted as future-oriented epistemic objects (Rheinberger 1997). This implies that open-ended questions about their evidential status are intimately connected to uncertainties about the nature of cancer itself, and about how much variation models in personalized medicine can and should embody.

What's So Special About Organoids?

Anti-tumor drug screening on human cancer cells began in the 1970s. From the late 1980s, standardized cancer cell lines have been developed for 2D studies and testing in murine models, following guidelines of the US National Cancer Institute. While standardized cell cultures have the advantage of allowing for comparison of drug screening results, critics have pointed to the translational challenge that very few candidate drugs make it further than phase III Studies (Kamb 2005; Feng et al. 2013). The translational gap is often seen as resulting in part from the failure of cancer models to account for patient-specific variation, as well as from the limitations of especially 2D cultures (or 2D monolayers) to recapitulate structural context of tumors. Tumor organoids are hoped to account for both limitations by embedding tumor cells of individual patients in a 3D matrix that mimics microenvironmental features, such as the chemical and physical structure of the extracellular matrix (Xu et al. 2018; Shen 2018). Organoids also have the advantage of being less resource-demanding compared to murine in vivo models. Thus, they can be seen as a kind of intermediate model that in time may allow for faster and finer-grained drug screening (Yang et al. 2018).

Cancer has from the beginning been a major topic in organoid research, but the potential of organoids received renewed attention in recent years with the emphasis in personalized medicine to account for *genetic variation* as a predictor of drug response (Dancey et al. 2012; Kaushik et al. 2018). Meritxell Huch and colleagues demonstrated that organoids based on liver cancer tumors preserve tissue structure and gene expression patterns seen in patients, and that certain expression patterns correlate with poor prognosis (see also Vlachogiannis et al. 2018; Broutier et al. 2017). Several studies have documented the capacity of organoids to predict drug response in individual patients, which opens for the possibility of patient-specific drug screening (Huang et al. 2015; Ooft et al. 2019). In this context, a comparison of organoids grown from tumors and normal tissue can help establish which drugs primarily target cancer cells without harming normal cells.

Organoids raise intriguing questions about the implications of patient-derived models, and what evidence means in a context where each patient's cancer is considered unique. The ability of organoids to account for patient heterogeneity is typically seen as a positive feature. However, there are trade-offs between the variability of the experimental system and the reproducibility of experimental results, especially if cancer tumors are also *internally* heterogeneous (Huch et al. 2017). Moreover, organoids lack important elements of the natural environment of cancer tumors, such as blood vessels, immune cells, and other stromal components that are known to influence tumors beyond the tumor microenvironment (Laplane et al. 2019). It is therefore currently unclear to what extent organoids present an alternative to traditional cancer models, and what level of variation researchers should aim for, if the aim is to infer molecular action mechanisms or drug targets (Lang 2019). Developing models for personalized medicine is thus not about maximum fine-graining. Rather, it is about finding the right "resolution" or "level of variation" to provide meaningful evidence-based results for research and clinical practice (Reardon 2017).

In the following, we draw on insights from ethnographic studies to analyze how researchers and clinicians manage variation and uncertainty in two different contexts (a research laboratory and a phase I cancer clinic). We highlight that epistemic aspects concerning the evidential status of organoids are intimately related to social and ethical implications of the use of organoids in preclinical and clinical practice.

Organoids as Disease Models and Living Biobanks

Realization of the research potential of organoids requires infrastructures that facilitate sharing of knowledge (cancer genomics) and material resources (tissue samples). Initiatives are currently taken to establish so-called *living biobanks* consisting of cryopreserved organoids, i.e., frozen but viable tissue cultures that can be (re)used as a resource for research and drug screening. The aim of such biobanks is to provide viable specimens representing tumor heterogeneity for research and drug screening, as well as protocols for method development (Sachs et al. 2018). One prominent example is the Hubrecht Organoid Technology (HUB), established in 2013, but living biobanks are being established in many places throughout the world as way to establish closer collaborations between universities and cancer clinics.

One of the sites for our analysis is a US-based lab aiming to develop a living biobank, initially of breast cancer organoids, as a resource for translational preclinical studies. In this context, organoids are based on excess tissue material from breast cancer surgeries at a hospital they collaborate with. A goal stated in the institute's annual report, as well as in interviews with the researchers, is to develop organoids as intermediate models that display important model virtues of

both standardized cell lines and mouse models. The same institute also has mouse models, and the two experimental systems are perceived as having complementary benefits and limitations. Patient-derived xenografts are highlighted as providing an in vivo context for tumors, while organoids have other benefits in being less expensive and labor intensive to grow. Organoids also allow for dealing with obstacles resulting from the species barrier of mouse models. One example is estrogen receptor positive breast cancer, which requires estrogen supplement in mice. So far, the growth rate they have achieved with this cancer type in organoids is 80%, compared to only 10% in mice.

A key aspect of organoids emphasized in interviews is the aim of expressing the clinical heterogeneity of breast cancers. Because organoids embody the genetic and morphological heterogeneity of patient tumors, a panel of organoids is seen as an alternative to standardized (cell-line based) mouse models in clinical trials:

> Now in the lab, traditionally, what we'd do in a mouse experiment is to get 20 mice with the exact same tumor and then look to see if they respond or not. When, really, we should have mice of 20 different types of that tumor to really, really recapitulate what's happening in the clinical setting, right? With organoids you can look at these subgroups of disease and have a true representation of the heterogeneity and then ask questions about drug screening and about gene expression and response. (PI of an organoid research project)

Organoids are here seen as better translational models because they allow for testing on more subtypes of cancer. This has intriguing implications for how we think about evidence in personalized medicine. The researchers hope that the FDA and other drug regulatory agencies in the future will accept drug testing based on a different test design, where testing on a panel of organoids can supplement and partly replace standardized animal experiments.

Using organoids, however, does not mean that every possible aspect of the model is attempted to be "personalized". To grow organoids for biobanking, many labs follow a standardized protocol, such as one developed by Hans Clevers' group at the Hubrecht Institute, Utrecht, where organoids are grown in a standardized 3D-matrix. A basement membrane functions as a more biologically realistic scaffold in which also the biomechanical tension of cancer tissues is mimicked. The gel is generated from mice tumors and mimics the tumor microenvironment by having a similar chemical and physical structure of the extracellular matrix. However, patient variation concerning stiffness of the surrounding tissues is currently not accounted for via organoids. This may be seen as a limitation of organoids as personalized models, since tissue stiffness can vary between different cancer types and patients, and also influence cancer development, metastasis, and drug response (Green 2021). Yet, standardized protocols and procedures are required to minimize the complexity of the experimental tasks and to generate comparable results.[3] Hence, the most

[3]Our interviewees mentioned potentials for also personalizing biophysical cues in the future but highlighted that there at present are more serious uncertainties to address first, and that there is a limit to how many variables can be meaningfully handled at present.

useful "resolution of variation" is therefore not necessarily the one that maximally mimics all aspects of variation among patients.

Mäel Montévil (in this volume) contends that it is misleading to oppose evidence-based medicine and personalized medicine with reference to the often-mentioned dichotomy between a one-size-fits-all approach and one accounting for heterogeneous populations. Rather, he argues, the practices are better distinguished by different ways of addressing an inescapable compromise between specificity and generality as model virtues. This description fits well with what we see in the context of oncology, where tumor heterogeneity is often presented as both a virtue and a vice. The uniqueness of specific cancers is what motivates the field and continuously opens for new treatment options. Yet, as more genetic variants are uncovered in cancer genomics, the more researchers are confronted with additional layers of complexity, such as the vast heterogeneity of mutations between and *within* tumors (de Bruin et al. 2014; Kerr et al. 2019). The aim to embrace heterogeneity thus often results in the challenge of how to deal with the 'curse of dimensionality' resulting from the ever-expanding list of factors influencing tumor development and the associated expansion of treatment options (Plutynski in this volume).

As a researcher working with organoids in the lab noted, a patient-specific tumor is in itself thought of as a heterogenous group of cells rather than as a stable entity with clear boundaries. The spatial and temporal diversity of tumors not only has theoretical implications for the strength of inferences made but also comes with practical implications for model development. Because cancer tissue is a scarce resource, the development of organoids for living biobanks requires procedures for organoid expansion called in vitro passaging. Tumor cells are taken from patients (via biopsied or surgical material) and grown in 3D wells until they reach a certain density and size. Smaller clumps of the primary organoid are then taken out and grown in separate wells to expand the material and to get more test specimens. This procedure requires that the essential biological features of tumors remain stable through passaging. The researchers sometimes refer to the cell population dynamics in tumors as self-organizing "social capacities", which raises interesting questions about how far tumors can be fragmented and still retain their identity. The issue of tumor identity is not just a philosophical or theoretical problem, but also of practical concern in procedures of tumor fragmentation and passaging:

> When you have grown up organoids and you want to break them apart and plate them for an experiment, you don't digest them down to individual single cells. You should leave them as small clumps to then regrow and keep that heterogeneity. Right? But then when you see cells in multiple wells, you're getting different sized clumps in different wells. Your error bars are always pretty big. (PI of an organoid research project)

The quote illustrates how optimization of passaging procedures requires exploration of how far a tumor can be broken down before the cell population patterns seen in the original tumor are lost (or at least differentiated in the new organoids). Thus, the relation of metonymy between tumor and organoid cannot be grounded at the lowest scale of analysis (e.g., in genetic signatures of individual cells). The phenomenon of interest literally disappears at the lowest scale, because cancer is a cell population phenomenon. In this sense, the individual patient's tumor gets

destabilized through experimental procedures. A related concern is whether tumor biopsies can capture the relevant features of the whole tumor, as biopsy samples from different spatial sites in a tumor are likely to have different proportions of mutations. A researcher figuratively described a biopsy sample as a "look through the keyhole", where they only get to see and intervene on some aspects of the tumor. This presents a severe challenge for drug screening, as highlighted in the following quote:

> You know, let's say you get a biopsy and it looks HER2-negative, so you don't give the patient HER2-therapy. Yet actually, if you look to the whole tumor, maybe some of it or a lot of it would have been HER2 positive. (PI of an organoid research project)

A related challenge is that tumors display plastic behaviors that change over time, in patients as well as in the 3D matrices. For instance, a post.doc explained how fibroblast cells are present (and clearly visible) in the first organoid culture from patient tumors but disappear over time and through multiple passages.[4] This makes organoids a research resource that is available only within certain time windows. While cryopreservation is an efficient strategy to deal with the temporal challenge, the evolvability of organoids adds to the complexity of the model system (Green et al. 2021).

Researchers must balance tradeoffs between maximally accounting for patient-specific features and developing tractable methods that allow for comparison across cases. Similarly, they must balance the aims of ensuring model validity and that of developing material resources for biobanking. Tradeoffs between these arise when there is uncertainty about whether the cultures are "contaminated" with normal (non-cancer) cells and there is limited organoid material to perform a validation analysis. Cancer cells are typically conceptually distinguished from normal cells based on their tendency to grow more aggressively, e.g., by replicating infinitely and resisting apoptosis (Hanahan and Weinberg 2011). In the context of the lab, however, cancer cells often grow slowly, and studies of the histology of tumor tissue (microscopy) do not always give clear answers to whether the culture only contains cancer cells, or also normal cells. In such cases, genome sequencing to test for occurrence of cancer-related mutations may be needed to validate the model. But this procedure also faces practical constraints:

> With sequencing technologies and things like this we are able to [determine whether it is cancer], but this also takes a lot of resources. Organoids divide and proliferate and expand. But still, you start with a tiny bit of material, and even if you expand them tenfold, you still got a really small amount of material. And now you want to sequence it to characterize it, but the only value of characterizing it is if you're then going to use it for something else. So, then you sequence it, but then you also need enough to drug screen, and then if you publish it, someone else is going to want some. How we can manage this is challenging. (PI of an organoid research project)

[4] He clarified that this is probably due to the lack of growth factors for stromal components in the Matrigel, and that it is currently unclear what this means for the capacities to draw inferences from later passages to patients.

The quote illustrates that the need for validation analysis must be weighed against the importance of other epistemic aims. The ideal of organoids as living biobanks highlights the role of organoids as collaborative and commercial commodities for reuse across different institutions and borders. But since organoids have to be grown from patient tissue and may change over time, they present a resource that is limited and exhaustible.

The challenges brought up in this section highlight that organoids at present by no means constitute straightforward and stable representations or "substitutes" of individual patient tumors. As research tools with open-ended features and applications, organoids may be seen as what Rheinberger (1997) termed epistemic objects, i.e., as research entities with unstable features that productively generate new research questions alongside their role as models in knowledge production. Importantly, the instability of organoids in this context is tied to uncertainties about the nature and stability of cancer itself, and about how much variation models in personalized medicine can and should embody. The following section explores how these and related uncertainties play out, when organoids are used as preclinical models in a translational cancer project. In this context, organoids speed up the traditional translational process by making new or off-label treatments available to patients, but they also introduce new complexities in the cancer clinic.

Organoids for Patient-Specific Drug Screening

As mentioned in the introduction, organoids are currently promoted as translational models that enable patient-specific drug screening. Developing organoids for this purpose is the aim of a preclinical research program for cancer precision medicine in Denmark that we have followed. In this project, scientists in a biotech center at a university and clinical researchers in a phase 1 unit at one of the main hospitals collaborate closely to identify effective treatment options for metastatic cancer patients that have exhausted all standard treatment options. Organoids are hoped to provide patient-specific evidence on whether a potential targeted treatment[5] could be effective for incurable cancer patients.[6]

The ideal diagnostic pipeline in the preclinical project can be summarized as follows. When a patient has consented to take part in the project, biopsies of metastatic tissue will be scheduled and a lab team member collects the tissue samples at the hospital immediately after biopsies have been performed. The tissue samples are then analyzed and cultivated in several ways. Through a combination

[5]The majority of the drugs are targeted treatments approved for other cancer types (say, breast cancer), but here given "off-label" to patients with a different type of cancer (say, pancreatic cancer), because the molecular analysis and drug screen suggest a potential match and benefit.

[6]To be included in experimental treatment protocols, patients must have (i) exhausted treatment options (or are expected to exhaust standard treatment options shortly), (ii) a performance status of 0–1, (iii) a life expectancy of at least 3 months, (iv) normal organ function, (v) measurable disease, and (vi) metastatic tissue accessible for biopsy.

of kinase profiling and DNA and RNA sequencing, the researchers seek to identify potentially effective drugs (kinase inhibitors). This takes two tissue samples and the analyses take 4–6 weeks. In parallel, a third tissue sample is cultivated in vitro in a 3D organoid cell culture. If the organoids grow, they can serve as the basis for patient-specific drug screens, which is ideally established within about 5 weeks. In practice, however, the translational path is far bumpier.

Major translational bottlenecks are created by two serious issues also seen in the research context described in section "Organoids as disease models and living biobanks", namely limitations on the tissue material available and the slowness of cancer cell growth outside the human body. The challenge is here further complicated by the specific clinical context. Metastatic cancer tissue is often difficult to access and can only be collected through core needle biopsies. Common complications of the procedure are pain and discomfort, while rare but serious complications include infection, bleeding, and organ damage. When deciding whether or not to take additional biopsies, clinicians must therefore balance the risks of biopsy procedures against potential benefits of a drug screen that could open a door to a potentially beneficial treatment (see also, Kerr et al. 2019). Whether the patient will benefit from the procedures is, however, not clear due to uncertainty about the status of organoids as substitutes for patients in a clinical trial. As we shall see below, this creates new ethical dilemmas for clinicians.

For researchers working on culturing organoids in lab, the scarcity of tissue material (a few needle biopsies) makes it very challenging to grow the in vitro models within a clinically meaningful time-window.[7] Also in this context, researchers have to prioritize different epistemic and practical aims. The priorities are explicitly highlighted in team meetings through common procedures to follow during laboratory practices. The first priority is to grow and maintain organoids for patients that could potentially benefit from drug screens. If a cancer patient who has donated cancer tissue dies, the researchers will cryopreserve the organoids for later use and instead prioritize the lab resources to grow organoids for patients who could still benefit from a drug screen. Prioritization of laboratory resources is here particularly important to ensure that there is sufficient organoid material to run a drug screen of multiple treatment options. In this context, organoids take on a role as patient substitutes that undergo different parallel treatments. However, also in this context, the role of organoids as in vitro models of patient tumors gets de-stabilized through uncertainties about the relation between organoid and tumor.

Researchers (biomedical as well as clinical) in the translational project sometimes talk about the organoids as individual patients that recapitulate key features of patient tumors. For instance, a researcher in the lab explained that "there is a patient in each plate" (plates for culturing organoids), and metaphorically referred to the fridge-like incubators for organoids (37 °C) as a "hospital" hosting patients.

[7] Initially, the aim was to also grow tumors inside the body of a mouse (or a PDX) to also allow for in vivo drug validation. Because of practical difficulties, this part of the project was put on hold and we here focus primarily on the use of organoids.

But when asked about the identity and stability of the organoids, researchers often express uncertainties about how stable the organoids are, whether the biopsy samples only contain tumor cells or also normal cells, and whether biopsies taken several months ago are still representative of specific patient tumors, if the patient's tumor has since progressed and possibly developed new genetic alterations. Similar to what we described in section "Organoids as disease models and living biobanks", resources spent to ensure the validity of the model trade off with those needed for practical uses of organoids:

> It is a bit of a dilemma whether one should drug screen without knowing whether they are cancer cells or if you should do a DNA analysis, and then risk that there are not enough cells to do a drug screen. (Interview with a post.doc in the preclinical research project)

The challenge that tissue samples become exhausted in the analytical and diagnostic process is particularly hard in clinical contexts where the available material amounts to a few biopsies (see also, Kerr et al. 2019, p. 229). Moreover, procedures to ensure model stability and optimize testing cultures must be balanced against the time pressure to deliver test results to patients. Waiting longer to grow more organoid material for multiple drug screens must be balanced against the risk that the performance status of the patient declines, which can make the patient unable to receive the targeted treatments. Hence, even if "the right drug for the right patient" can be found, it may not be available "at the right time".[8]

As a result, the hopes and suffering of cancer patients move into preclinical research and manifest as a pressure to deliver reliable results within a clinically defined time frame. Researchers in this context become stretched between the practical challenges of growing organoids and the temporal constraints determined by the patients' progression status. This is illustrated in the following quote by a post.doc in the translational project, who has just been informed that a successful test result came too late for the patient to receive treatment:

> Oh. That is so sad! You see, it has been like that with a lot of [the organoids] I've had. When I've done the drug screen and sent it to the clinic, half of the patients [that I have made drug screens for] have died. Then I'm left thinking: could something have been done if I had been faster?

The researchers work hard to align the different temporalities of laboratory work and clinical practice, but keeping pace with the clinical needs is a constant struggle. This greatly contrasts with how organoids are often presented in literature as rapid models for real-time drug screening. It takes tremendous work and care to grow the fragile cancer cells to a size where they allow for drug screens. Organoids must have optimal growth conditions, which involves changing the nutrient media twice a week as well as strict hygiene requirements to avoid contamination of the cultures.

[8] See also Plutynski (in this volume) for a discussion of the commonly used slogan of precision oncology to provide "the right drug, at the right dose, for the right patient, at the right time".

To manage the practical challenges of personalized models, options for standardization and simplification of some procedures are often considered. For instance, the organoids are also in this context "housed" in a standardized medium:

> Right now, we use the same medium for all [cancers], no matter whether it is breast cancer or colon cancer or whatever, and that is maybe not optimal, but on the other hand we would like a system that is "one-size-fits-all", so that it – for those running the program – doesn't get too complicated. (Postdoctoral researcher in the preclinical project)

It is here striking that a practitioner within personalized medicine, a field explicitly defined as a departure from a "one size fits all" approach in medicine, stresses the need for standardized procedures to make laboratory work practically tractable. Another important aspect of standardization in this context is drug administration. To generate evidence for the protocolized treatment, drug doses and enrollment guidelines must be standardized. This raises important questions about how the personalization of some aspects of treatment often requires standardization of others. More generally, it also raises questions about what aspects of medicine are possible or most useful to "personalize", and for what purposes.

The instability of organoids has important implications for status of these as new "technologies of hope" (Koch and Høyer 2007), envisioned as translational models that provide a road to personalized medicine. Insights into challenges do, however, not automatically lead to revision of the near-future expectations to personalized medicine. As emphasized by Roger Strand (in this volume), challenges and knowledge claims are representations of present realities, whereas personalized medicine presents a vision or imaginary of desired futures that are hoped to revise existing states of knowledge. In the exploratory space where new medical technologies are developed and implemented, uncertainty has "generative potential" in mobilizing further investment in and expansion of research domains (Timmermans et al. 2017). This is for instance highlighted in a publication in the journal *Cell*, emphasizing the genetic basic for cancer treatment decisions:

> Although the challenges of integrating genomic testing into cancer treatment decision making are wide-ranging and complex, there is a scientific and ethical imperative to realize the benefits of personalized cancer medicine, given the overwhelming burden of cancer and the unprecedented opportunities for advancements in outcomes for patients. (Dancey et al. 2012, p. 409)

Anticipation of future scientific advancements is not only an epistemic orientation toward the future, but is also an *ethical imperative* to inhabit states of uncertainty so as to improve future conditions for research and clinical practice (cf. Adams et al. 2009). In other words, evidence must be co-produced with procedures for implementation. In this sense, the ethical imperative to improve existing practices also comes with concerns about how to manage the current gap between the persistent uncertainties of and high expectations to the new technologies in contexts where patient care is the central concern (Kerr et al. 2019).

From interviews and interactions with patients and oncologists we have learned that organoids generate new hope for incurable cancer patients. The translational project on organoids open for new treatment options that could potentially prolong

their life, and organoids present an intuitive and more "personalized" form of evidence. For oncologists, however, the possibility to attain new forms of evidence also entails a confrontation with new types of uncertainties – as well as new ethical responsibilities to inform patients about these to recalibrate their expectations. As expressed by an oncologist in the phase I unit:

> [The patients] sometimes ask, "How are the organoids doing? Does something happen?" Sometimes things do happen and we conduct a drug screen, but it can also be that we get more confused about the result. Sometimes we get data that we don't really know what to do with. If we do not get any effect on the drug screen, then it is clear that we cannot use it. We can maybe use it when we get a signal, but it is perhaps not quite clear, and then the question is whether we should give a treatment, that may have side effects, and that blocks the patient from receiving another treatment. So again, it generates a lot of dilemmas. (Oncologist in phase I unit)

A "signal" in this context means cell death, growth, or growth inhibition, but a decrease in organoid growth cannot straightforwardly be interpreted as treatment efficacy. There can be multiple reasons for why organoids grow slowly or die, and the strength of the signal can vary. Also the clinicians are therefore stretched between the patients' hopes and epistemic uncertainty. In the interview, the oncologist further emphasized that he views organoids as being quite low on the evidence scale, in part because the lab results often are uncertain, and in part because they cannot rely on statistical results from many patients receiving specific genetically targeted drugs or off-label treatments. Such reflections also destabilize the idea of organoids as an alternative to standardized forms of evidence. At present, organoids are primarily seen as an additional tool that in a few cases may provide new treatment possibilities, and where the potential is still uncertain and future-oriented:

> I tell my patients that they should not expect to benefit from this. It is a method under development, and it is only something that can give a piece to the puzzle. It is not something that can stand alone. It cannot. So they have to see it as a bonus, and as a way to help research further. In 5 years, things probably look differently. So in this way it is really interesting from a scientific point of view. In the clinic it is not that interesting yet. But it will be, we think. And that is probably the expectation you have to have, so we don't talk up the method to patients either. (Oncologist in the phase I clinic)

The quote exemplifies how appeals to existing uncertainties are used to moderate patient expectations, while at the same time motivating the production of evidence for future needs (see also, Kerr et al. 2019).

Organoids at present fulfill purposes of cancer research and clinical practice in different ways. There are more immediate benefits of the results for research, as organoids are already helping researchers identify new genetic variants and pathways that can guide the understanding of cancer and suggest potential drug targets (Broutier et al. 2017).[9] Clinical benefits at present comprise only a few

[9]In the context of the specific translational project, though, the need to prioritize laboratory resources for clinical purposes makes it difficult to develop publishable results. In an interview, the

cases, where patients respond well to new targeted treatments. The main clinical benefits are therefore envisioned to be realized in the future. Hence, the oncologist is concerned about the risk of installing unrealistic expectations in the hopeful cancer patients. This concern is not only relevant in the context of the phase I unit, but also for discussions about who will contribute to and benefit from personalized medicine more generally (Plutynski in this volume). To clarify this point further, the following section examines how personalized medicine not only focuses renewed attention to individual differences but also form new epistemic and ethical collectives.

Personalized Medicine from a Population Perspective

The emphasis on individual variation may give the impression that personalized medicine marks a departure from population science. However, realizing the potential of the new technologies requires heavy investments in population-based databases to integrate genomic data with other health data (Hoeyer 2019). Organoids may seem like the exception, since they physically represent individual tumor samples. Upon closer inspection, however, the use of organoids relies on results from population-based efforts and, as we shall show, also mobilize new collectives through data collection and biobanking.

The current use of organoids in research and clinical practice is highly focused on the identification of genetic biomarkers, e.g., of mutations or overexpressed genes, which may be suggestive of a cellular pathway to explore in research or a potential targeted drug for cancer therapy. These markers are established on the basis of a comparison of the individual's profiles to data on thousands of other individuals. The identification of molecular features or "biomarkers" characterizing the individual patient's tumor presupposes comparisons to reference classes and, hence, relationships of similarity in terms of shared biology. In the context of the translational project, clinicians rely on a bioinformatics analysis of the sequenced genome. Software filters based on compiled cases help to identify potential clinically relevant targets. Yet, as we and others have observed during tumor board meetings, the actionability of identified genetic variants is often uncertain and depends on many factors such as the availability of open treatment protocols, the frequency of the variants, other test results, previously received treatments, and patient status, as well as the often changing evidence status of specific genetic variants (see also, Hey et al. 2019; Kerr et al. 2019). The evidence status of markers can change over time with the inclusion of more cases in the database, further exemplifying the relational characteristics of biomarkers (Timmermans et al. 2017).

PI commented on how many researchers are not interested in doing translational research, because it involves many uncertainties and practical challenges. But she also highlighted that alignment of project goals is central for closing the translational gap between biomedical research and clinical practice.

Hence, variation in personalized medicine is always relative to a specific scale of analysis, and defined in relation to specific epistemic purposes.

Practitioners must in this context navigate in a space where reliance on statistic evidence is very limited, and where treatment options are only open for patients fulfilling certain requirements (biomarkers and disease status, see note 7). The results from genetic testing and organoid drug screens for individual patients must be evaluated against highly limited knowledge about the efficacy of the drugs, which again must be contextualized according to the specific patient's situation. At the same time, current implementations are also conducted in order to develop better diagnostics and treatments for similar (future) patients:

> On the one hand we consider the utility value for the individual patient, but there is also the consideration that patients – who are in treatment either on the basis of drug screen or phase I trials – deliver utility for the general good. You also have to take this into consideration, and we also present the considerations to the patient. We have some that we treat "beyond progression", meaning that they still get drug in the phase I trial even if the disease is progressing – you can do that in some protocols. If it is written that this is acceptable, we have a conversation with the patient where we say "the cancer is progressing but you can be allowed to continue in the protocol, knowing that [the drugs] probably do not work so well on your illness, how do you feel about that?". And some say that "I really want that, because I keep delivering data for the experiment, and it gives meaning to my disease. [. . .] For some, it makes sense to be able to deliver something to future patients". (Oncologist in phase I unit)

Notably, this way of ethically justifying a practice that may be of limited benefit of current patients *epistemically* presupposes that targeted treatments are not specific for individual patients, as results must be comparable to broader population types. The expectation of benefits for future patients is based on the hope that personalized medicine – with time – can compile enough cases for databases and biobanks to ease the translational paths for future patients with similar tumor characteristics.

Recategorization of cancer into finer-grained subtypes co-produces new epistemic relations of (molecular) identity or similarity, and may also give rise to what Gibbon and Novas (2007) term *biosociality*. The term points to how the collective of data populations also have social and ethical implications. The willingness of oncologists and patients to contribute to the development of personalized medicine shows how personalized medicine does not represent an individualizing departure from reliance on the collective, epistemically as well as ethically.[10] Although much focus in personalized medicine is on the development of more individualized models, the vision for future living biobanks presupposes a coarse-grained mapping of variation that does not drill down the heterogeneity to the uniqueness of individual patients.

[10] Similar wishes to contribute to the development of cancer research for future patients with similar diseases is seen in a recent pilot project on patient-derived xenografts, where a patient says the following: "I understand there is no gain to me directly. But in a small way, maybe I can help grow our understanding of what makes triple-negative breast cancer what it is." (Wanner and Haskell 2014).

Precision oncology develops around the negotiation of the trade-off between emphasis on tumor heterogeneity of individuals and genetic similarity of coarser grained (although stratified) patient groups. But while not departing from statistical methods altogether, precision oncology does potentially change the nature of relations that connect different patients. As Montévil (in this volume) highlights, measurement in medicine is conditioned upon procedures of symmetrization by which organisms are considered equivalent with respect to some specific selected features, while being non-equivalent with respect to others. In this context, traditional criteria of diagnosis and case comparison – such as cite of tumor origin, histology and stage of tumor – are being reframed in light of genetic technologies that categorize cancers and cancer patients in new ways. This can not only change how we conceptualize disease but also how health systems and clinical trials are organized (Green et al. 2019; Plutynski in this volume).

Large-scale cryopreservation of patient-derived models, biobanking, and sharing of data and research results exemplify how the contributions of individual patients can become scientific and social commodities of benefits to the collective of future patients. At the same time, national initiatives for collection of population-wide genomics data and integration of health records exemplify how the collective of large data populations is envisioned as a requirement for realizing personalized medicine for the individual patients. One example is the National Genome Centre in Denmark that has recently been launched to integrate genomic data and health data on the whole population. Within this context, establishment of personalized medicine is seen as something that requires the participation of the whole population. Initially, data will be stored from selected patient groups, and cancer patients are among the candidates to make up (some of) the 60.000 already financed whole genome sequences. The database is expected to create an invaluable source for research and personalized medicine in the future. At the same time, the envisioned implementation also raises concerns about how new procedures for genome sequencing of cancer patients will affect the patients' expectations:

> If it's just about putting data in the bank and looking at it later, then that's fine. But many will have the expectation that they upfront must have an in-depth explanation of exactly their gene profile and why they should have the standard treatment. Many will say: "I don't want the standard treatment, I need something that is special for me". Many have the expectation that if there is a skilled doctor who has looked at a genome profile, something that is better than standard treatment can be offered. But the vast majority should still get the standard treatment. (Oncologist in phase I unit)

The quote highlights the difficult challenge of communicating to cancer patients that the benefits of personalized medicine is at present only for a relatively small patient group with rare variants and poor response to standard treatment (see also, Prasad 2016; Marquart et al. 2018). The reality in clinical practice is thus often very different from the picture painted of personalized medicine in politically authorized reports and communication material, where a vision of tailor-made solutions to all patients are promoted while the effects of standardized treatments are downgraded (Hoeyer 2019). Hope based on unfounded hype can create unrealistic expectations among patients and can negatively affect science and medicine when promises are

not realized. Pioneers in organoid research have similarly expressed concerns about overpromising in their field and have emphasized the need for a slower pace to realize the potential of organoids (Huch et al. 2017). These worries add to concerns about the consequences of fast tracking of drug approval for targeted cancer therapies, including waste of resources and potential harm to patients (Plutynski in this volume).

Aside from the issue of pace of implementation and realization, the quote above raises an important question about whether "personalization" is a useful regulatory ideal for medicine or cancer treatment in general. As highlighted by Anya Plutynski (in this volume), precision oncology has so far primarily been successful in cases where the cancers are relatively simple (from a molecular perspective), and it is unclear whether "low-hanging fruits" can also be found among more complex cases. While tumor heterogeneity is what motivated precision oncology in the first place, the realization of precision medicine through organoid biobanking is conditioned upon the potential to reduce the dimensionality of variation to a manageable number of genetic variations with associated treatment options. Ultimately, creating substitutes for patients and patient types hinges upon the ability to *control variation*, i.e., to represent the clinically relevant kind and level of heterogeneity in models for drug testing.

Concluding Remarks

Patient variation at the same time motivates and challenges precision oncology. Tumor organoids exemplify the aim to recapitulate the heterogeneity of tumors through personalized models developed from individual patients. As a kind of material substitute for patients, organoids call for rethinking models and evidence standards in translational medicine, as well as the relation between experimental model and human target. But whereas precision oncology is often presented as the very anti-thesis of a one-size-fits-all approach, it may not be productive to view the field as developing towards a science *of* and *for* the individual. Despite being directly derived from the patient's tumor, our cases show how organoids by no means straightforwardly represent the individual patient's tumor, and how that is also not always intended as the aim of patient-derived models.

Organoid research illustrates the difficult challenge of managing and representing variation at different levels: between cancer types, between patients with different tumors, and even within the individual patient's tumor. Hence, patient-derived models, perhaps surprisingly, destabilizes the very notion of individual patients and patient tumors as unique and homogenous entities with clear boundaries. Important epistemic uncertainties include the extent to which biopsies only present a "look through the keyhole" of a spatially diverse tumor with different cell populations. Similarly, the experimental task to find the optimal size and density of tumor fragments for in vitro passaging raises intriguing questions about the extent to which the self-organizing capacities and ontological identity of tumors can be recapitulated in growing tumor fragments. Moreover, whereas organoids are often considered

as "personalized models", the anticipation of future benefits via biobanking is epistemically dependent on the ability to connect test results of extant patients to future patients with similar molecular profiles. Thus, patient-derived models representing the individual patient also rely on and co-produce a vision of biosocial relations among larger collectives.

As a result, the most useful resolution of variation is not necessarily the one that maximally mimics the heterogeneity of the individual patient or patient tumor. Our analysis shows that the challenge of balancing standardization and variation still remains in personalized medicine. We see this epistemically in the ways in which the use of patient-derived models and biomarker analysis is dependent on standardized procedures and population science. And we see this ethically in how experimental treatment of individual patients are expected to primarily benefit future patients when enough cases have been collected to allow for inference of evidence of treatment effects. The latter also shows that realization of personalized medicine for the individual relies on the establishment of new collectives based on shared molecular characteristics. The individual *me* of patients and patient-derived organoids is dependent on the collective *we* of data and tissue donors. At the same time, the collective *we* of future patients are dependent on present procedures to develop models for patient-specific drug screening.

New sources of evidence in personalized medicine come with new uncertainties and ethical responsibilities to inform patients about these. Developing patient-specific organoids can potentially open a translational path for new treatments for incurable cancer patients, but the approach also involves risks associated with biopsy procedures and uncertainties about test results and treatment benefits. Moreover, time constraints for growing organoids present severe challenges for the aim to deliver the right drug for the right patient *at the right time*. Facilitation of medical innovation alongside considerations about patient care can be challenging to achieve in practice. Researchers and clinicians are therefore often stretched between epistemic uncertainties and patient expectations, and between the potential benefits for the individual and future patients.

In summary, tumor organoids do not straightforwardly represent a shift from the collective to the individual. They can be seen as new technology-mediated ways of "inscribing the population in the individual and of letting individuals contribute in new ways to the population" (Hoeyer 2019). Organoids represent both these aspects. They are experimental models that embody important features characteristic of specific patients' cancers, but they do so through reliance on population sciences. At the same time, patient-derived organoids are at present not only developed for the sake of extant patients. Tumor organoids exemplify how individual cancer patients contribute to future populations through relations of biosociality, i.e., by generating "living biobanks" as forward-looking resources for precision oncology.

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Pharmacovigilance as Personalized Evidence

Francesco De Pretis, William Peden, Jürgen Landes, and Barbara Osimani

Introduction

Pharmacovigilance (or pharmacosurveillance) has gradually emerged during the last century, in the aftermath of notorious disasters related to pharmaceutical products. The most notorious was the Thalidomide case, but others include the DES case, Croniassal case, and more recently the Vioxx case.[1] The establishment of the institute of pharmacosurveillance emerged in the course of time out of

[1] For an historical overview of the role and drug agencies in the postmarketing phase and the related regulation see Osimani (2008); for an overview of the complex ecosystem of epistemic, regulators,

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the increased awareness that pharmaceutical products (like other chemicals) are associated with unknown risks, which may go unnoticed during the studies for approval, because they might be related to long-term use, drug-drug interaction, or particular physiological co-factors. Drug monitoring thus registers suspected case of adverse events, collects them, analyses them and constantly evaluates their import in relation to the drug risk-benefit profile.

Like personalized medicine, pharmacovigilance is a fast-growing part of modern medicine. Both fields face many of the same methodological challenges, and developments in each one of them will impact the other; however, their interrelations and potential for integration are under-investigated, especially by philosophers. Both personalized medicine and pharmacovigilance aim to accurately predict what would happen to a given individual, were he to receive a given treatment X. This sort of promise relies on two ingredients: (1) causal knowledge about the possible effects of X *in a given statistical population*; (2) assignment of the given individual to a suitable reference class. These two inferential problems have been extensively analysed in the philosophical and methodological literature (Reichenbach 1951; Pollock 1990; Hájek 2007; Pearl and Bareinboim 2014; Luo et al. 2019; Stoffi and Gnecco 2018; Xie 2013; Nilsson et al. 2019; Pearl 2012; Osimani 2020). We discuss here how they are related and present a methodological tool, *E-Synthesis*, that is able to exploit the evidence for either inferential targets, based both on statistical knowledge about relevant subgroups of users and causal knowledge about the drug-effect relationship. This tool was originally developed for assessing causality in pharmacovigilance; we examine here the prospects for applying it to questions in personalized medicine.

E-Synthesis is a Bayesian approach to aggregating heterogenous evidence for the purpose of assessing causal relationship between pharmaceuticals and adverse reactions in probabilistic terms. The Bayesian element in *E-Synthesis* consists in its use of Bayesian learning methods, which are explained below. Bayesian reasoning is very popular in contemporary philosophy of science, but the application of Bayesian ideas to complex methodological issues in sciences like medicine is still a work in progress. *E-Synthesis* contributes to the cutting-edge research in applied Bayesian philosophy of science. Landes et al. (2018), De Pretis and Osimani (2019), De Pretis et al. (2019), and Abdin et al. (2019) illustrate this new framework for evidence synthesis focusing on various components of the system. We continue here to develop this methodology to questions concerning the estimation of single patient's adverse drug reactions (ADRs).

Before going on, we warn the reader about our goals and scope. We do not intend here to offer an instrument for causal search (testing hypotheses about causal models against data) or causal inference from data. Neither do we intend to provide instructions on choosing the right kinds of statistical models. Instead, we provide an instrument that uses probabilistic knowledge about such models in order to output a

ethical and financial constraints informing the process of evidence collection, evaluation and use for decisions in the medical and pharmaceutical domain see Osimani (2020).

probabilistic estimate that a given individual might be affected by a given ADR. In order to do this, we adopt a Bayesian model averaging approach, that allows us to contemplate diverse causal models as possible generators of the observed data and to compute the individual estimate, on the basis of their plausibility and their relevance to the specific features of the considered individual. We also trace and explicate the epistemic steps that may guide the inference from available causal models plausibly linking the drug to the ADR, to the prediction that an individual may be affected by that ADR upon taking the drug.

We proceed as follows: in the section "Personalized Medicine and Pharmacovigilance" we discuss the similarities and differences between pharmacovigilance and personalized medicine at a broad level. In the section "*E-Synthesis*", we introduce *E-Synthesis*. In the section "Pharmacovigilance as Personalized Evidence", we provide an example application of this approach to determining the probability of an ADR in a single patient. The idealizations and limiting assumptions that we make are indicative of future directions for research and development for attaining this goal in real-world medical decisions. Finally, in the section "Discussion", we close with a general discussion.

Personalized Medicine and Pharmacovigilance

In this chapter, we understand the term "personalized medicine" as referring to the targeting of interventions, drugs, and other parts of medicine to particular patients, based upon their membership of multiple populations for which we have at least some relevant statistical data. In an ideal world for medical research, we would know exactly what effect a given treatment would cause in every given patient. In a less ideal world, we would have some probabilistic knowledge about that patient's probability of suffering an adverse effect, given that they have taken a drug. Our world is even less ideal: we typically lack even such probabilistic information, especially regarding ADRs. Personalized medicine uses statistics from various covariates (genotype, clinical biomarkers, age etc.), identified by stratifying patients according to physiological and other characteristics, in order to identify the most adequate reference class for a given individual with respect to a specific effect.[2] Improvements in personalized medicine hold the promise of the systematic and precise application of medicines to patients, rather than a "casual hit and miss" approach (Wertheimer 2016).

Since every patient is a member of many reference classes and we often have conflicting data for these various categories, personalized medicine must deal with the problem of combining and interpreting the diverse data. The Problem of the Reference Class is one of the greatest problems in the philosophy of statistics; it

[2] A reference class is a group of objects or events that we describe using a statement of probability. For example, the reference class in "The probability of $1 coins landing heads is approximately 50%" is the class of $1 coins.

is thereby relevant to all sciences (Venn 2013, p. 194; Hempel 1962, p. 374).[3] In essence, this problem is simple: everything we consider in science (patients, chemical samples, thermometer readings etc.) is a member of many reference classes, and we will often have statistical data for these reference classes that point in different directions with respect to the hypothesis that we are considering. For example, imagine that we know the frequency of a drug's effectiveness among women and patients over 65, but not the intersection of these reference classes (i.e., women aged over 65). Suppose that the data suggests a high degree of effectiveness in women, but a very low effectiveness in patients over 65. Given a female patient, aged over 65, which reference class should we use for estimating whether the drug will be effective in treating her? There is a massive literature on this topic in general philosophy of science and philosophy of medicine, including personalized medicine (Kent et al. 2018) and in philosophies of other disciplines (Franklin 2011; Strevens 2016).

The reference class problem affects the estimation of beneficial and harmful effects of treatments, which is often the cornerstone for risk policy. For example, suppose that policymakers discover that a drug D has a favourable safety profile for its average user, but it has an unfavourable safety profile for a particular subgroup S. The policymakers might decide that D should not be withdrawn from the market, but instead to circumscribe its use to those groups of consumers for which its benefit-risk profile is favourable. This decision-making might seem trivial, but it requires identifying the relevant subgroups in a rational way. Furthermore, both before and after drug approval, evidence of harms is sparse and noisy. Because of the awareness of such latent risk enduring also after approval, and of the epistemic and methodological difficulties surrounding risk assessment, drug monitoring has been institutionalised (both through the development of a sophisticated set of norms in soft and hard law, as well as through the establishment of national and supranational agencies for drug approval and monitoring), with the purpose of updating the drug safety profile in an ongoing manner and make timely decisions on this basis.[4]

If we know the exact causal relations for a particular patient, then we evade the Problem of the Reference Class. For instance, if matters were as simple as "A patient with Gene X will have adverse reaction Y" and we can easily test each patient for Gene X, then we do not have to consider the patient's class memberships. However, in practice, things are rarely so simple. The relevant causal mechanisms in a patient can be impossible to identify. The causal mechanism might not be a closed system. Gene X might be part of a wider causal mechanism, including the patient's social environment, lifestyle choices, other medications, and so on. (For discussions

[3] In this chapter, we consider only the epistemic version of the Problem of the Reference Class; there is also a metaphysical version concerning the "true" physical probability of some particular event (Hájek 2007, pp. 565–566).

[4] For philosophical discussions on the underpinnings, rationales and issues concerning pharmaceutical regulation see (Teira and Reiss 2013; Teira 2013; Andreoletti and Teira 2019; Osimani 2013, 2007).

and examples, see the contributions by Xavier Guchet, Maël Montévil, and Anya Plutynski in this volume). Thus, in practice, personalized medicine must make use of statistical data about the reference classes to which a patient belongs.

Pharmacovigilance also faces challenges of synthesising and interpreting heterogeneous data. The term 'pharmacovigilance' covers both the empirical study of harms caused by drugs (i.e., ADRs) and the regulation of drugs given these harms. ADRs are a broad category covering a large spectrum of effects. ADRs happen within the so called "therapeutic range". According to the traditional WHO (World Health Organization) definition, ADRs are: "A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" (WHO, 1972) The classical Rawlins and Thompsons categorization of ADRs subdivides them in: (1) Type A: dose-dependent effects, predictable from the drug pharmacology; (2) Type B: effects independent from dosage, unavoidable reactions with no predictable connection with the drug known mechanism (off-target effects); these are generally characterized by high severity and irreversible damage (e.g., anaphylactic shock); (3) Type C: chronic reactions; (4) Type D: delayed reactions (e.g., adenocarcinoma in women exposed in utero to diethylstilbestrol); (5) Type E: withdrawal reactions (as a consequence of addiction: e.g., benzodiazepines); (6) Type F: failure of therapy (lack of efficacy). Determinants of individual susceptibility to this range of reactions can be practically anything, including age, sex, genetic make-up, physiological changes, exogenous factors (drug-drug or food-drug interference), and disease-drug interaction; additionally, ethnicity is a carrier of factors (environment, genetics, lifestyle) determining higher or lower susceptibility to drug efficacy and ADRs (Aronson and Ferner 2003).

Mechanisms leading to ADRs may be the same that produce the intended therapeutic effect (e.g., non-steroidal anti-inflammatory drugs' inhibition of prostaglandins production causing both anti-inflammatory effects and gastritis), or may be related to the drug binding to the intended receptors (for the intended pharmacological reaction) at different sites other than the target organ, or else it can be the result of an integrated response of separate levels in the organ system (interaction of different organ levels). ADRs may be collateral effects, that is, effects which are merely distinct from the intended therapeutic goal. However, they can also be paradoxical, i.e., consisting of exactly the opposite effect of the one which the drug was intended to produce, or bidirectional effects in which the same drug produces opposite effects in the same individual at the same time (Smith et al. 2012).

Unlike personalized medicine, the focus in pharmacovigilance is to identify possible causal relations between drugs and adverse effects in the first place, rather than merely identifying statistical relations between drugs and memberships of particular reference classes. The two inferential targets, however, may work together, as we will see in the following.

Interpreting and combining heterogeneous evidence of different sorts of ADRs is fraught with methodological challenges, included the Problem of the Reference Class: drug testing provides data in favour of many statistical hypotheses about

many reference classes, our target population will generally be a member of multiple reference classes, and often the statistical evidence will point in different directions regarding likely ADRs in the target population. More often, evidence will be very "local", e.g., individual case reports, which point to very specific subsets of features, any of which may have been relevant for the occurrence of the ADR.

Fortunately, shared problems often have shared solutions. Firstly, advances in statistical methods, medical epistemology, and improved experimental practices in pharmacovigilance can assist with personalized medicine, and vice versa. For example, techniques for synthesising heterogeneous evidence in pharmacovigilance might also be adaptable to applications in personalized medicine. Similarly, answering the Reference Class Problem in personalized medicine, at least partially, would also help address it in pharmacovigilance. Secondly, solving problems in one field might ipso facto alleviate problems in the other, at least in some cases. For instance, we sometimes have excellent data of the effects of particular medicines on specific genotypes, and sometimes even causal knowledge of various kinds, such as knowing the interactions that occur with the drug and specific enzymes expressed by people who possess a particular genotype (Wertheimer 2016). Genotyping may also assist the pursuit of external validity in pharmacovigilance, because it would help us identify target groups that may suffer from specific ADRs in view of their genetic make up. Group-specific effects also generate practical issues in drug labelling, which are shared by personalized medicine as well (Fang et al. 2016).

There has not yet been much research on the relationship between personalized medicine and pharmacovigilance. However, the personalized medicine emphasis on targeting treatments to patients with a high probability of a positive response has inspired some research in pharmacovigilance, in proposals for targeted research by pharmaceutical companies (Enjo and Aisabokhae 2018).[5]

From the other side, researchers in personalized medicine have noted the importance of better pharmacovigilance data for personalized medicine (Ennezat et al. 2017; Masimirembwa et al. 2016). At the applied level, pharmacogeneticists are seeking methods that will concurrently improve the two research areas (La Russa et al. 2017). Given the great importance of pharmacovigilance and personalized

[5]Some philosophers have emphasized the privileged role of "dispositionalist" views on causation as more adequate approaches to causal inference in pharmacovigilance (Anjum and Rocca 2019; Rocca et al. 2020, 2019). In this paradigm, causation cannot be established without a thorough knowledge of the context in which the particular causal event happens: understanding the dispositions at place in one single patient (especially in cases of unexpected effects of a drug) can potentially help improve the knowledge about the intrinsic properties of the drugs, and the way such properties might interact. While the dispositionalist approach to causation promises to be very fruitful in the biological sciences and pharmacology particularly, we emphasise here that *E-Synthesis* does not commit to any specific ontological view on causation and is intentionally flexible as to the metaphysical stance that one assumes with regard to causality.

medicine for the health and wealth of nations, the integration of insights and methods across these areas is a burning issue for the philosophy of medicine.

We present here an approach to the reference class problem which draws on knowledge about the causal structure about the data generating process. We thereby emphasize a division of labour between the phase of hypothesis generation regarding such causal structures, and that of hypothesis confirmation through probabilistic evidence. Furthermore, since in the field of pharmacovigilance we are mainly dealing with "little" rather than "big data", and we may lack the required resources to test causal models with several variables involved, we propose here a method for hypothesis confirmation that makes the most out of all the available evidence, of whatever quality and relevance it is. This holds a promise for personalized medicine in that, especially in the early phase of risk detection, the availability of big data is not the common scenario, while tools for the optimization of the available evidence can serve the purpose of approaching an accurate individual estimate of the individual risk associated with drug intake, based on the current state of the art.

E-Synthesis

E-Synthesis has been developed to aggregate evidence in the process of pharmacosurveillance and make timely decisions in view of incoming "safety signals" (Landes et al. 2018; Abdin et al. 2019; De Pretis and Osimani 2019; De Pretis et al. 2019). In the preceding papers, we have presented its theoretical foundations (Landes et al. 2018), how information about evidence quality may be incorporated in the risk estimation (De Pretis et al. 2019), and how evidence of biological mechanisms or dose-response contributes to the confirmation of causal hypotheses (De Pretis and Osimani 2019; Abdin et al. 2019). In the present paper, we illustrate how issues related to the specification of the causal claims between drug and ADRs with respect to the subgroups to which they relate may be efficiently addressed by our framework. This will help the prediction of drug effects on individuals, based on available knowledge, both derived from established theory and from learning techniques (e.g., machine learning, statistics, artificial intelligence).

Motivation

From its conception, throughout the development phase, and continuing in the post-marketing phase, each drug risk-benefit profile is assessed and continuously updated. If the utility from the expected benefits outweighs the expected disutilities from harms (and possibly monetary costs), then the assessment is favourable and development and/or circulation of the drug in the market are advisable. Instead, if the negatives outweigh the positives, then there might be a decrease in research effort or a (partial) withdrawal from the market, depending on the development stage. Hypotheses of causal associations between drugs and harms consolidate only gradually on the basis of heterogeneous evidence. However, these causal

associations should be anticipated as much as possible in order to minimize harm to exposed subjects. Hence, decisions concerning a drug (e.g., approval, suspension, withdrawal, administration) should be based on all the available evidence at any point in time. This can imply that one may need to base such decisions on evidence that is normally perceived as weak, based on current evidence standards, such as basic science studies.

A sophisticated set of tools for meta-analyses and systematic reviews has been developed for the purpose of evaluating the intended therapeutic effects of interventions, but the adaptation of these instruments with the aim of evaluating the safety of health technologies encounters various problems. These are mainly due to the sparsity, heterogeneity, and "fragility" of data concerning unintended effects of medical treatments: (1) evidence about unknown risks emerges gradually from spontaneous reports or other kinds of sporadic data: especially in the earlier phases of risk detection, these data can be at the same time very noisy and rare; (2) furthermore, the data may come from heterogeneous sources (such as clinical case series, animal studies, or molecular studies, etc.); and (3) it can be unreliable, because of noise and/or confounding. As a matter of fact, evidence for harm emerges unsystematically and unpredictably. The evidence demands evaluation (and decision) even when it cannot deliver perfect information about the state of nature.

Aims and Scope

The need to provide an instrument for synthesizing the evidential support of heterogeneous sources for assessing hypotheses of causal association between drugs and harms at any point in time and on the basis of any kind of available evidence led us to develop *E-Synthesis* (Landes et al. 2018; Abdin et al. 2019; De Pretis and Osimani 2019; De Pretis et al. 2019). This framework provides a theoretical basis for justifying the probabilistic confirmation of causal hypotheses, on the basis of all the available evidence. It puts forward a Bayesian epistemic network incorporating indicators of causality derived from Bradford-Hill "guidelines" for inferring causation (Hill 1965) and indicators of evidence quality. The result of the assessment is a probabilistic estimation of the causal hypotheses of interest, which reflects the degree of support provided by the available evidence (Hawthorne 2005). We formalise our hypothesis of causation as follows: "Cause D causes effect E in a given population p and a given causal model M".[6]

However, we have not yet illustrated how updating the causal hypothesis itself may work by taking into account incoming information about the causal structure

[6]By "causal model" we mean an ordered set of variables and a description of their interrelationships in terms of varying strengths and functional forms (Cartwright and Stegenga 2011), as exemplified by Structural Equation Models and Directed Acyclic Graphs (Cowell et al. 2006; Dawid 2010; Pearl 2009). See also subsequent sections.

generating the data and/or evidence about subgroup effects. That is, we aim to determine probabilities over the causal models in which the drug does cause the particular ADR we consider. The causal models allow for predictions which take into account characteristic properties of individual patients and may thus in turn better predict the outcome of individual patients than the generic causal hypothesis © (D causes E *in a population*). With these probabilities over the causal models in hand, we hence aim to defeasibly determine the probability that a particular patient will (not) suffer the ADR after the administration of the drug D.

Background

A Very Short Introduction to Bayesian Epistemology

E-Synthesis puts forward an epistemic network drawing on Bayesian updating as the main computational tool. For those unfamiliar with the topic, we briefly introduce it here and give the rationales of this inferential tool.

Bayesian epistemology is a philosophical account of rational beliefs in hypotheses that comes in degrees.[7] Bayesianism represents uncertainties by modelling them as probability functions.[8] To determine the conditional posterior probability P of the hypothesis being true—in our case this hypothesis is that of the drug causing an ADR (denoted by ©)—given the available evidence, $\mathcal{E}$, one applies Bayes' Theorem:

$$P(©|\mathcal{E}) = \frac{P(©) \cdot P(\mathcal{E}|©)}{P(©) \cdot P(\mathcal{E}|©) + \sum_{i=2}^{N} P(H_i) \cdot P(\mathcal{E}|H_i)},$$

where the hypotheses H_i together with $© = H_1$ form a mutually inconsistent and exhaustive partition.[9]

With this mathematical formula, the posterior probability of the hypothesis given the evidence, $P(©|\mathcal{E})$, only depends on prior probabilities $P(H_i)$, and likelihoods $P(\mathcal{E}|H_i)$. Bayesian epistemology allows one to conditionalise on any proposition (or event) whereas in Bayesian statistics one conditionalises on statistical models.[10]

[7] In the philosophy of science, there are controversies regarding the extent to which Bayesianism's subjectivity is a problem (Gelman and Hennig 2017; Sprenger 2018). We assume here that the possible drawbacks related to such issues are compensated by its flexibility in interpolating and extrapolating data when these are fragmentary and heterogeneous. In pharmacovigilance, our data often has these characteristics.

[8] Philosophy of science also draws on the formal tools developed within Bayesian epistemology in order to investigate scientific inference (Bovens and Stephan 2003; Talbott 2011; Howson and Urbach 2006).

[9] We abuse notation in the usual way by using the same symbol denoting a variable and the variable being true.

[10] These likelihoods are relatively easy to determine, since they provide probabilities on the assumption that a certain hypothesis is true and thereby considerably shrink the set of possible worlds. For example, determining the likelihood for a statistical hypothesis H_i is merely an

The probabilities in Bayesian epistemology are interpreted more widely as one's uncertainties about general propositions or as degrees of support for the hypotheses of interest.

Bayesian Networks

Bayesian networks are a convenient tool to graphically display and reason with probability functions. They allow us to specify and read-off conditional independencies from a graph. Formally, a Bayesian network is built up on a number of pairwise different propositional variables which form the nodes of a graph. The graph topology on these nodes forms a Directed Acyclic Graph (DAG). This means that edges are directed and that there is no directed cycle in the graph, i.e., there is no path of directed edges which leads back to its starting point.

Finally, one needs to specify the (conditional) probabilities of all variables. For a variable Y one first determines the set of parent variables: a variable X is a parent of Y if and only if a directed arrow originates at X and ends at Y. Denoting the parents of Y by $X_1, \ldots, X_n$ one specifies

$$P(Y = y | X_1 = x_1, \ldots, X_n = x_n) \in [0, 1]$$

for all possible values $y, x_1, \ldots, x_n$ under the condition that

$$\sum_x P(Y = y | X_1 = x_1, \ldots, X_n = x_n) = 1.$$

This condition ensures that one defines a probability function. Conditional and unconditional probabilities of arbitrary events are calculated by (repeated) application of the so-called "chain rule". For more background on Bayesian networks, see (Darwiche 2009; Neapolitan 2004).[11,12]

General Approach

While Bayes' theorem is essential in Bayesian epistemology, it is by no means clear how to determine the likelihoods $P(\mathcal{E}|H_i)$ in our concrete application where $\mathcal{E}$ is all the available information that might (dis)confirm that a given drug D causes adverse effect E.

exercise of probability calculations. It would be much harder to specify probabilities on all states generated by the variables of interest. We demonstrate below that although the task to determine the likelihoods is relatively easy, it is by no means a trivial task.

[11] Every Bayesian network uniquely specifies a probability function. However, typically a probability function is representable by multiple Bayesian networks.

[12] Conditional independencies are given by the d-separation criterion (Geiger et al. 1990).

To facilitate this task, we introduce abstract indicators of causality. We distilled six indicators by applying a philosophical analysis of current theories of causation to the Bradford Hill Guidelines (Landes et al. 2018). Our indicators of causality are: (1) difference making, (2) probabilistic dependence, (3) dose-response relationship, (4) rate of growth, (5) temporal precedence and (6) mechanistic knowledge.[13] Conceptually, our indicators are testable (probabilistic) consequences of the hypothesis of interest. As such, experiments and observations can, by providing evidence against or in favour of the indicators, thereby probabilistically (dis)confirm the causal hypothesis of interest. The common definition of an "indicator" implies that it is more likely to be true, if the inferential target is also true, than if the latter is false.[14] Hence, in our case:

$$P(Ind|©) > P(Ind|\overline{©})$$

Each experimental study, observational study, case series, case report or basic science finding is then associated with a set of causal indicators which it is informative about (Landes et al. 2018; De Pretis et al. 2019). This procedure routes the inference from medical data to a theoretical entity (causation) via abstract intermediaries (causal indicators). Such an approach recalls Bogen and Woodward's distinction between data and phenomena (Bogen and Woodward 1988): *E-Synthesis* breaks down the inferential process from the raw data to the hypothesis that a causal link holds between Drug and ADR into two steps: (1) from data (study reports) to causal indicators; (2) from causal indicators to causality.

Items of evidence (dis)confirm indicators of causation to different degrees. The degree to which indicators of causation are (dis)confirmed is made partly explicit by spelling out evidential modulators, which signals the quality of evidence as a function of various choices in study design and data analysis (blinding, randomisation, sample size, study duration, stratification), see Fig. 1.

[13] By proposing his guidelines, Bradford Hill meant to offer an alternative method for causal inference in the face of hazard, in a context dominated by hypothesis testing. While he obviously did not exclude experimental sources of evidence as a basis for causal inference, he emphasised that non-experimental evidence may also contribute to assessing the causal import of a specific chemical/molecule. Some paradigmatic examples are when many items replicate the same results, converge towards the same hypothesis, or cohere with available theoretical and/or empirical knowledge. *E-Synthesis* pays homage to such "higher order" considerations too, in that it allows diverse items of evidence to jointly contribute to the probabilistic (dis)confirmation of the hypothesis under investigation, and therefore, to exploit their (lack of) coherence.

[14] With this, *E-Synthesis* relaxes standard necessary and sufficient conditions for causation developed in the philosophical literature on causation (Landes et al. 2018).

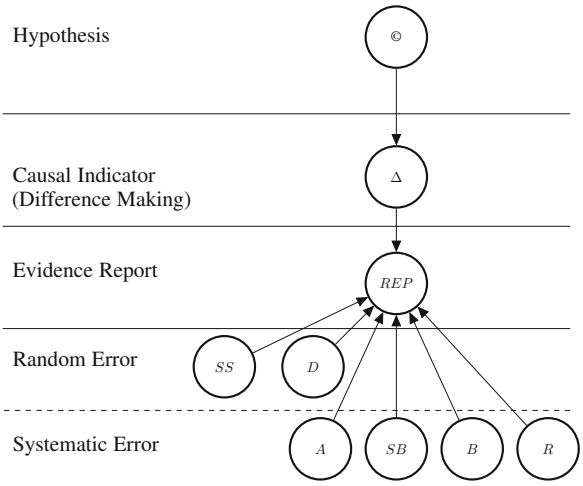

Fig. 1 Graph structure of the Bayesian network for one randomized controlled trial (RCT) which informs us about difference making (Δ) which in turn informs us about the causal hypothesis. The information provided by the reported study is modulated by how well the particular RCT guards against random and systematic error. The evidential modulators for an evidence report are SS = Sample Size; D = Study Duration; A = Adjustment for covariates or subgroup analyses and the like; SB = Sponsorship Bias; B = Blinding; R = Randomisation (De Pretis et al. 2019)

Pharmacovigilance as Personalized Evidence

We now discuss how to expand *E-Synthesis* for personalized medicine. We investigate how a framework developed for inferring causation in a population can be adapted to inferring the probability of an ADR occurring in a particular patient, and which philosophical problems require to be addressed during this development. As a preliminary step to such a form of "extrapolation", one would normally need to identify the closest "reference class" instantiated by the individual at stake on the basis of available knowledge. We adopt a "structural" approach to this problem, in that we derive the probability P of a particular drug consumer being affected by a given side effect not only by assigning him to a given reference class, but also by drawing our inference on a weighted estimate of different causal models being at play, based on the available evidence and theoretical knowledge. We will not be able to determine for certain which causal model is correct, if any. Instead, we can use the models as tools for assessing the likelihood of a causal connection in the case of a particular patient, by considering their predictions, weighted according to each model's probability given our evidence. As a preliminary step to this we need to update probabilities over plausible causal models, conditional on incoming evidence of various kinds.

We show how this can be done in principle by *E-Synthesis*, by drawing on the distinctive components of *E-Synthesis's* inferential structure. A hypothesis about a causal relationship between the drug and the side effect is represented by the

variable ©. In turn, this is a disjunction of mutually exclusive and jointly exhaustive causal models: $\mathcal{M} = \{\mathcal{M}_1, \ldots, \mathcal{M}_n\}$ partitioning ©. Every model $\mathcal{M}_i$ consists of a set of functions mapping a set of variables (relevant causal factors for developing a given side effect) to the set of possible values measuring the strength of the effect: thus a model $\mathcal{M}_i$ consists of a set of equations of the form $Y^k = F^k(X)$, where the F^k are functions relating random variable(s) X to random variable(s) Y, representing causal relationships.

The causal models relate the drug dosage D and the ADR E by embedding them in a causal structure. Each model delivers an expectation about the intensity of a given side effect E, given a certain dosage, and other constraints (co-factors contributing to the side effect, such as mediators, moderators, interactive causes etc.). For instance, a model $\mathcal{M}_i$ could read as follows:

$$E = \alpha + \beta_1 D + \beta_2 D^2 + \epsilon_1$$
$$D = \gamma + \beta_3 C + \epsilon_2$$
$$C = \lambda + \beta_4 F^2 + \epsilon_3$$

where, for example, α is the base rate of the adverse effect in the population and the epsilons are error/noise terms. Structural coefficients, such as β_1, represent the strength of the causal relationship between independent and dependent variable. This may due to the intrinsic intensity of such relationship, but also other, possibly unknown, moderating factors (such as age, sex, co-morbidities, etc.). We assume that at each stage, the available domain knowledge (knowledge about biological processes, physiology, the pharmacodynamics and pharmacokinetics of the drug, epidemiological and clinical data, etc.) delivers an exhaustive set of mutually exclusive causal models with respect to the current state of the art. Although, the availability of an *exhaustive* set of mutually exclusive causal models underpinning the data is not a realistic assumption, we make it here for the sake of simplifying the representation of the essential components of our inferential machinery, cf. 6 in the discussion.

A probability distribution P over the set of causal models $\mathcal{M}$ measures the support these enjoy from the theory and the data, and gets updated upon new evidence. The probability that a *specific individual* may get a side effect is calculated on the basis of P over $\mathcal{M}$. It is then updated on the basis of new evidence, as we explain in the section "From Models to Individual Patients".

The absence of any causal connection, e.g., between E and D may be formalised by having coefficients for D set to zero. We subsume such models under $\overline{©}$ which refers to the state of affairs where there is no causal connection between D and E. For obvious reasons, even in the absence any causal link between D and E, there might still be a non-zero base-rate of people who suffer the adverse event E for causes other than D.[15]

[15]In a real-world structural equation model, we would more richly describe the interrelations between D and other variables in the model, e.g., our variables for age, sex, and blood cholesterol. In our examples, we will only consider simple single equation models.

Generating Causal Models/Hypotheses Using *E-Synthesis*

Data and Theory

The system starts with model hypotheses of causation, which do not specify its functional form, nor its parameters; (Fig. 2) for instance $\mathcal{M}_i : E = f_i(D)$, where D stands for the drug (dosage) and E stands for the strength of the adverse effect. $\mathcal{M}_i$ represents the assumption that there might be a causal effect from the drug

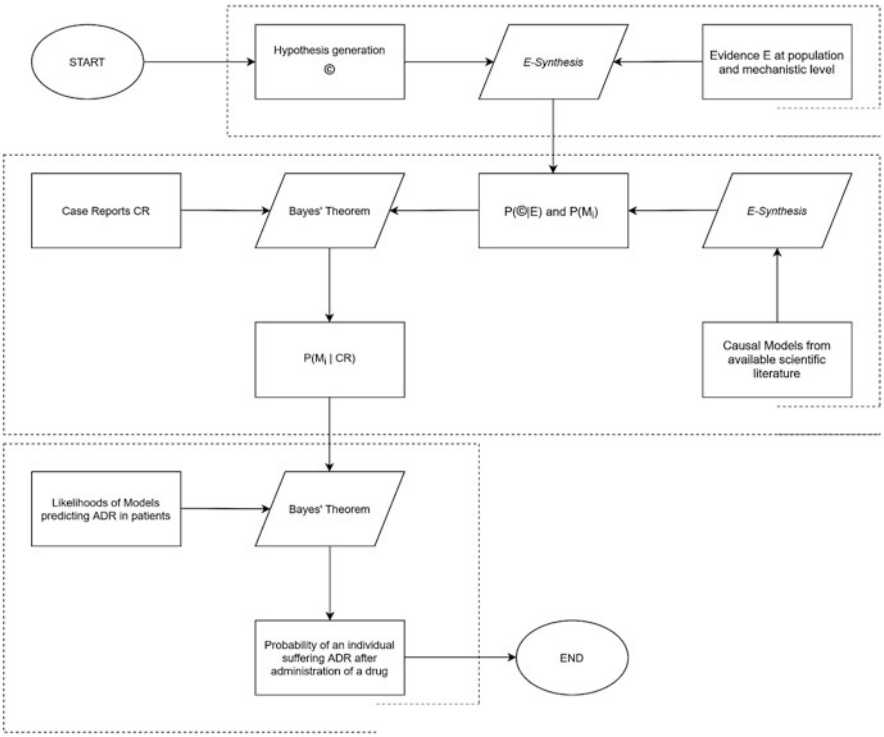

Fig. 2 Flowchart representing the structure of our reasoning process. Parallelograms represent processes; rectangles represent inputs or outputs of such processes; dashed rectangles represent sections. Upper dashed rectangle, section "Generating Causal Models/Hypotheses Using E-Synthesis": The overall process starts with the generation of a hypothesis of adverse drug reaction (ADR) on the basis of spontaneous reports or other signals from nature: ©; this is the first input to E-Synthesis, which then incorporates any other incoming evidence (at population, clinical and mechanistic level), by letting the data feed into the Bayesian network. Central dashed rectangle, section "Testing Causal Models/Hypotheses": Update of the causal hypothesis is mediated by averaging over available causal models, which the scientific literature puts at disposal. In our example, we then show how the observation of a series of clinical cases (Case Reports, CR) updates the probability distribution over the available causal models. Lower dashed rectangle, section "From Models to Individual Patients": Once data about the individual patient are taken into account, his individual probability of being affected by the ADR can be then calculated through Bayes Theorem. Further details are explained in the text

to E without specifying its functional form, possible mediators, interactive factors and the strength of such relationship. Incoming evidence from, say, observational studies, might reveal subgroup effects for specific users or specific dose-response curves. In the following, we will outline an example to illustrate, step-by-step, the inferential procedures we are considering.

Example: First we will give a simple example of a causal model which relate the effect E (a change in body temperature in degrees Celsius) and the dosage of the drug D. Every model depends on the characteristics of a patient. This set of characteristics can be formalised by some tuple $\vec{t}$, say $\vec{t} = \langle \text{age, genetic makeup, diet} \rangle$. Every model then maps every such tuple $\vec{t}$ to a real number. Let us call this mapping β. For instance, it may turn out that women taking a drug are more intensively affected by the side effect than men; also having a specific genetic makeup and age may interact with the effect of the drug, while smoking habits may constitute a reason for suffering from the side effect independently of drug consumption. We would put the interacting factors in the coefficient β, smoking in the intercept α, and leave an error term ϵ for other yet unidentified "disturbances". So now our causal model would look like:

$$E = \alpha + \beta D + \epsilon \ .$$

We may also consider non-linear models. For example, a set of causal models could just be:

$$\begin{aligned} \mathcal{M}_1 : &\quad E = \alpha + \beta_1 D + \epsilon_1 \\ \mathcal{M}_2 : &\quad E = \alpha + \beta_2 D^2 + \epsilon_2 \\ \mathcal{M}_3 : &\quad E = \alpha + \beta_3 D + \beta_4 D^2 + \epsilon_3 \ . \end{aligned}$$

The base rate α of the effect in the population (distribution of fevers in the population) is for ease of exposition assumed to be independent of a particular model and thus it is the same in all models. The different models have, in general, different functional forms, different error terms and a different number of contributing terms.

Testing Causal Models/Hypotheses

Confirming Models

In order to test the models, we will use the information we have to discern among the models in the available case reports to learn which model is most likely.

At this stage of the inquiry, we have applied *E-Synthesis* to determine a probability of the drug causing an adverse reaction *in the general population* (©) and a "prior" probability distribution over the possible models $\mathcal{M}_i$, $P(\mathcal{M}_i)$. In order to update the probability distribution over the $\mathcal{M}_i$ on the available case reports we apply Bayes' Theorem.

Denoting the set of available case reports by CR, applying it here this theorem tells us that:

$$\begin{aligned} P(\mathcal{M}_i|CR \wedge ©) &= \frac{P(\mathcal{M}_i \wedge CR \wedge ©)}{P(CR \wedge ©)} = \frac{P(\mathcal{M}_i \wedge CR)}{P(CR \wedge ©)} \\ &= P(\mathcal{M}_i) \cdot \frac{P(CR|\mathcal{M}_i)}{P(CR \wedge ©)} = P(\mathcal{M}_i) \cdot \frac{P(CR|\mathcal{M}_i)}{\sum_l P(CR \wedge \mathcal{M}_l)} \\ &= P(\mathcal{M}_i) \cdot \frac{P(CR|\mathcal{M}_i)}{\sum_l P(\mathcal{M}_l) P(CR|\mathcal{M}_l)} \\ &= P(\mathcal{M}_i|©) P(©) \cdot \frac{P(CR|\mathcal{M}_i)}{\sum_l P(\mathcal{M}_l|©) P(©) P(CR|\mathcal{M}_l)} \\ &= \frac{P(\mathcal{M}_i|©) \cdot P(CR|\mathcal{M}_i)}{\sum_l P(\mathcal{M}_l|©) P(CR|\mathcal{M}_l)}. \end{aligned} \tag{1}$$

The updated probability of a model can thus be calculated from prior probabilities of models ($P(\mathcal{M}_l|©)$) and likelihoods of observations ($P(CR|\mathcal{M}_l)$). The likelihoods are specified by the probabilistic models (see section "Likelihoods of Case Series").

How have the posterior probabilities changed? The greater the likelihood of the observations given a model, the more of boost the model will obtain from the observations, *ceteris paribus*. Therefore, while there are many factors involved in confirming models in Bayesianism, the key issue for a model's evidential support by the observations is simply the likelihood of those observations given that model.

Example: Suppose we have $P(©) = 20\%$. The probability of the different models (being mutually exclusive and exhaustive) have to add up to 20%. So, let us suppose that the conditional probabilities of the models—given that © is true—are 25%, 25%, 50% for $\mathcal{M}_1$, $\mathcal{M}_2$, and $\mathcal{M}_3$ respectively. Now, suppose the likelihoods of the case reports for the three models are $P(CR|\mathcal{M}_1) = 0.05\%$, $P(CR|\mathcal{M}_2) = 0.1\%$ and $P(CR|\mathcal{M}_3) = 0.025\%$. We obtain a posterior probability of the models:

$$\begin{aligned} P(\mathcal{M}_1|CR \wedge ©) &= \frac{25\% \cdot 0.1\%}{25\% \cdot 0.05\% + 25\% \cdot 0.1\% + 50\% \cdot 0.025\%} \\ &= \frac{0.00025}{0.001} = 25\% \\ P(\mathcal{M}_2|CR \wedge ©) &= \frac{25\% \cdot 0.2\%}{25\% \cdot 0.05\% + 25\% \cdot 0.1\% + 50\% \cdot 0.025\%} \\ &= \frac{0.0005}{0.001} = 50\% \\ P(\mathcal{M}_3|CR \wedge ©) &= \frac{50\% \cdot 0.05\%}{25\% \cdot 0.05\% + 25\% \cdot 0.1\% + 50\% \cdot 0.025\%} \\ &= \frac{0.00025}{0.001} = 25\%. \end{aligned}$$

We can now see that given CR, the probability of $\mathcal{M}_2$ conditional on © being true has doubled and it is now the most probable model, whereas the previously most probable model $\mathcal{M}_3$ is now equiprobable with the least likely model $\mathcal{M}_1$. This is intuitively plausible, e.g., CR is most probable if $\mathcal{M}_2$ is true, so learning CR gives the probability of $\mathcal{M}_2$ a relatively large boost. Therefore, while the relative probabilities of the models are initially determined by their priors, updating with some evidence such as case reports can change the ordering of their probability, depending on their respective likelihoods for that evidence.

Likelihoods of Case Series

In order to determine the value of probability $P(\mathcal{M}_i|CR \wedge ©)$, it insufficient to specify the conditional probability of the models given observations and ©. We also require the likelihood of the case series. The likelihood of the case series, provided that the observations are independent, is simply the product of the likelihoods of the individual patients suffering the adverse event within the case series, assuming that all sub-groups of patients have an equal probability of having their adverse effect reported. In case this last assumption is not appropriate, it is possible to use weighting factors to balance over/under-reporting of subgroups.

Example: Returning to our example, suppose that the case reports CR consist of only five reports for five patients: Rep_1, Rep_2, Rep_3, Rep_4, and Rep_5. Given our assumptions so far, their likelihoods given a model and © may take a number of values; for illustrative purposes, we assume:

$$
\begin{array}{lll}
P(Rep_1|\mathcal{M}_1) = 5\% & P(Rep_1|\mathcal{M}_2) = 75\% & P(Rep_1|\mathcal{M}_3) = 50\% \\
P(Rep_2|\mathcal{M}_1) = 50\% & P(Rep_2|\mathcal{M}_2) = 20\% & P(Rep_2|\mathcal{M}_3) = 25\% \\
P(Rep_3|\mathcal{M}_1) = 20\% & P(Rep_3|\mathcal{M}_2) = 25\% & P(Rep_3|\mathcal{M}_3) = 8\% \\
P(Rep_4|\mathcal{M}_1) = 40\% & P(Rep_4|\mathcal{M}_2) = 33.\dot{3}\% & P(Rep_4|\mathcal{M}_3) = 10\% \\
\underbrace{P(Rep_5|\mathcal{M}_1) = 25\%}_{P(CR|\mathcal{M}_1)=0.05\%} & \underbrace{P(Rep_5|\mathcal{M}_2) = 80\%}_{P(CR|\mathcal{M}_2)=0.1\%} & \underbrace{P(Rep_5|\mathcal{M}_3) = 25\%}_{P(CR|\mathcal{M}_3)=0.025\%} .
\end{array}
$$

We show in the next section how to calculate the likelihood of a particular patient suffering an ADR according to some causal model $\mathcal{M}_i$ given the patient characteristics.

From Models to Individual Patients

We have performed the necessary steps to finally give a probability that the patient in front of us taking a certain dosage of the drug will suffer an adverse drug effect. As a simplifying measure, we focus on the case of uniform probability distributions for the conditional probabilities that a particular patient has an ADR given a set various characteristics.

If one of our causal models is indeed the one true model, then the model will predict how strong the side effect is going to be for this particular patient. The prediction consists of a probability density function assigning probabilities to effects given the dosage. The probability of an ADR, that is, an adverse event that is attributed to the drug's causal effects, is the probability of an adverse event occurring after taking the drug (whatever its cause), minus the base rate (the probability of such event occurring independently of drug intake).

Of course, we are unsure about which of our models represents the actual world, the predictions made by the models are thus weighted by their respective probabilities.

As for the problem of the reference class, our approach inherits the strengths and weaknesses of the standard Bayesian approach to this issue (Hájek 2007). On the one hand, given a suitably rich probability distribution, determining whether a patient known to possess various characteristics (a particular age group, having/not having a relevant gene etc.) will experience an ADR is just a matter of mathematical calculation. On the other hand, the question of how these priors might be determined rationally (if at all) is a heated question in the philosophy of statistics (the infamous "problem of the priors").

Example: Denoting by P' the probability of taking all but the case series into account, we now calculate the probability that an individual patient k will suffer the adverse event of strength E

$$\begin{aligned} P'(E_k|D) &= P'(\overline{\copyright}) \underbrace{P'(E_k|\overline{\copyright})}_{\text{baserate}} + P'(\copyright) \cdot \sum_i P'(\mathcal{M}_i|\copyright, CR) P'(E_k|D, \mathcal{M}_i) \\ &= P'(\overline{\copyright})\alpha + P'(\copyright) \cdot \sum_i P'(\mathcal{M}_i|\copyright) \cdot [\alpha + \beta_i D^{\delta_i} + \epsilon_i] \ , \end{aligned}$$

where δ_i is the exponent of D in model $\mathcal{M}_i$, and *individual* is the hypothesis that the given patient suffers the side effect. The probability of suffering the adverse event *caused* by the administration of the drug is obtained by subtracting the base rate.

According to Bayes' Theorem (1) only prior probabilities and likelihoods are required to compute posterior probabilities. In particular, there is no need to determine which model/s is/are most relevant to a particular patient.

To determine the probability of a particular patient aged 65 years, who possesses a particular gene, has a daily salt intake of 5 g per day and takes a daily dosage of 100 mg of drug D for some model $\mathcal{M}_j$ with $\alpha = 1\%$,[16] a single coefficient on D, $\beta_j = 0.1(\text{age} - 60) + \text{gene} + 0.4 \cdot (\text{saltintake} - 3)$, $\delta_j = 1$ (linearity) and a normally distributed error term ϵ_j with mean $\mu_j = 0$. So, this patient has a β_j value of $0.5 + 1 + 0.4 \cdot 2 = 2.3$. The mean expected increase of temperature of the adverse effect under model $\mathcal{M}_j$ is thus 2.3 degrees Celsius, the probability density function

[16] Strictly speaking, α should be a probability density function specifying how likely a fever of a particular temperature is.

of the strength of the adverse effect is a normal distribution with mean 2.3 and a variance given by the error term ϵ. To determine the probability of this particular patient suffering an adverse effect, one needs to determine such likelihoods for all models, weigh them according to their probabilities and the probability of ©, and add the probability of suffering the adverse effect without the drug D causing it (which is just the base rate α).

Discussion

Personalized medicine promises to accurately predict what would happen to a given individual, instantiating a given set of relevant characteristics, were he to receive a given treatment X. This promise relies on two points: (1) causal knowledge about the possible effects of X *in a given statistical population*; (2) assignment of the given individual to a suitable reference class. Regarding point 1, standard approaches to causal inference are generally considered to be characterized by a trade-off between how confidently one can establish causality in any given study (internal validity), and extrapolating such knowledge to specific target groups (external validity). Regarding point 2, it is irreducibly uncertain which reference class leads to the most reliable inferences (Reichenbach 1951; Salmon 1977). Furthermore, the reference class problem threatens all approaches to causal inference alike. Even if methods for dealing with population heterogeneity have been developed to differing degrees of sophistication (Reichenbach 1951; Pollock 1990; Hájek 2007; Pearl and Bareinboim 2014; Dahabreh et al. 2016; Yeh et al. 2018), the problem of identifying proper subgroups explaining variance in the causal effect is of a different nature to that of assigning a given individual to such subgroups.

By its very nature, pharmacovigilance is focused on both elements of the individual prediction at the same time, that is, the establishment of the possible causal link between a given drug and an observed adverse event, and the identification of possible subgroups, where such links may arise. This happens for several reasons: first of all, ADRs are by definition unintended effects that should occur in a minority of users, and it is important that such users are characterized as detailed as possible, in order to minimize the risk of future events in the population of consumers; secondly, risk signals from spontaneous reports, which are the first source of evidence for ADRs in the postmarketing phase, are primarily based on establishing whether the observed adverse event may be causally attributed to the drug or not (Karch and Lasagna 1977; Naranjo et al. 1981); thirdly, in the postmarketing phase it is of utmost importance to carefully weigh the drug benefits against its risks in specific subgroups of patients, so as to exclude from consumption only those groups for which the benefit-risk balance is unfavourable (Osimani and Mignini 2015).

We developed an epistemic framework that exploits the joint contribution of different dimensions of evidence, and, specifically for the present discussion, evidence about the causal link between drug and adverse event on one side, and evidence about contextual information related to the determinants of the effect variance in specific subpopulations on the other side. At the same time, this

framework keeps the individual inputs of such sources of evidence conceptually and computationally distinct: this allows us to deal with the reference class problem not only by relying on statistical data about covariances, but also by drawing on causal knowledge. That is, the probability that a given individual will face a given side effect, will probabilistically depend on his features (e.g., age, genetic make-up, smoking, blood cholesterol etc.) *and* the plausible causal models in which such features become relevant. The evaluation of the causal models is grounded on the available evidence and theory.

We now briefly enumerate our major limiting assumptions and discuss their impact.

1. There are the limitations our analysis inherited from *E-Synthesis* such as the choice of indicators of causation, the Bayesian tenets and limitations of the Bayesian machinery. These limitations have been discussed in previous work (Abdin et al. 2019; Landes et al. 2018; De Pretis et al. 2019; De Pretis and Osimani 2019).
2. We only use case series to inform the updating of the beliefs in the models in section "Testing Causal Models/Hypotheses". It is desirable—even normatively required (Carnap 1947, § 3)—to use all the available evidence to inform rational beliefs and make decisions. We must leave it to future work to also use multimodal evidence.
3. The current state of the art of *E-Synthesis* still uses a binary variable © to reason about causation in the general population. Incorporating strength of causation would be desirable, in particular in light of the result of our approach here which produces a probability density function capturing the intensity of causation (β).
4. We employ some notion of causation which is expressible in terms of (structural) equations. While this view is virtually unchallenged in the social sciences, it is not without critics in philosophy. For example, causal pluralists (Reiss 2009) might deny that all of the concepts of causation in medicine can be formalised by structural equations. Furthermore, we can't know a priori which models—or which parameters—have to be considered into our ensemble of structural equations. However, we resort here to a Bayesian approach, allowing a certain grade of uncertainty attaching to choices of parameters/models.
5. We limited ourselves to causal models $\mathcal{M}_i$ which are mutually exclusive to make use of the standard Bayesian machinery. In practice, one may want to consider models which are not mutually exclusive, because different models specify the causal connection in different levels of detail, e.g., model $\mathcal{M}_1$ might have a wider error distribution rather than $\mathcal{M}_2$ due to the latter being able to explain more variance. For non-exclusive models one cannot apply Bayesian updating. In that case, one can use comparative measures of evidence, such as Bayes factors, to inform beliefs about which of the models (best) describes the actual world.
6. We assumed that the different causal models are jointly exhaustive, which was not realistic. The problem of Bayesian learning in the absence of a fully-specified partition of possible alternative hypotheses is a major issue in Bayesian philosophy of science. One option is to define a "catch-all" hypothesis, to

assign it non-zero probability, and to allocate probability from the "catch-all" to alternative hypotheses as they are conceived (Shimony 1970; Wenmackers and Romeijn 2016). There are alternative approaches to this issue in Bayesianism (Salmon 1990).

There are a number of possible directions for future research. One is relating our discussion more closely to evidence assessment in medical practice and the many disagreements among practitioners (Stegenga 2014b). We shall now discuss the conception and formulation of these new causal models. In pharmacovigilance, hypotheses about side-effects may be (jointly) generated by various sources: asymmetries in databases of spontaneous case reports, clinical case studies, basic science, animal studies etc. (De Pretis and Osimani 2019). At the time of its generation the hypothesis about drug-induced side-effects is relatively unspecific, while it progressively becomes more articulated as new evidence of various sources comes in. The incoming evidence may be informative about particular subgroups showing specific patterns of reactions to a range of drug dosage. These diverse types of information allows one to progressively refine the entertained causal models by pointing to relevant factors, their interactions and their importance (Stegenga 2014a; Reiss 2015). For instance, observations relating drug dosage and strength of effect made in populations or basic science can be informative about the functional form of the relationship between drug and effect, regardless of whether the relationship is causal or not. Furthermore, the formulation of more specific models makes variables salient, which were previously incorporated in the error term. By having such variables being represented explicitly in the model equations, the random error/noise in the model is reduced.

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New Solutions to Biomedical Data Sharing: Secure Computation and Synthetic Data

Edwin Morley-Fletcher

Introduction: Expectations of Stochastic and Algorithmic Production of Knowledge Based on Big Data

The stochastic and algorithmic production of knowledge is increasingly affecting even far-reaching scientific hypotheses, and this process, which is more and more being currently conducted on Artificial Intelligence (AI) and Machine Learning (ML), hugely augments the capacity to investigate the ever-growing complexity of the information structure of life.

Among other very important implications, this is a situation based on the fundamental innovation that, "for the first time in our development, we have technologies that can regularly and normally act as autonomous users of other technologies" (Floridi 2010, p. 36), taking stock of the "digital uniformity between data and programs", which "was one of Turing's most consequential intuitions" (Floridi 2019, p. 45), with the effect of partially reducing the role of human judgment in producing usable knowledge.

An essential pre-condition is, however, the availability of Big Data, given the fact that it is "starting from a large and varied amount of data, [that] artificial intelligence algorithms are able to identify complex patterns of relationships that can escape (human) researchers" (AGCM 2020).

In the new data driven analytical paradigm, big data contribute, in fact, "not only to verify theoretical hypotheses with statistical techniques, but also to explore new scenarios and derive new theories, as well as, more generally, to discover new knowledge through artificial intelligence algorithms. From a methodological point of view, this is a completely innovative approach to the acquisition of information

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and the generation of knowledge, assigning a guiding role to data and algorithms for finding models that the traditional methodology could perhaps only hardly identify (and would still need to subsequently validate). The innovative scope is such that some scholars speak of a real scientific revolution compared to the classic 'hypothesis, model, experiment' approach" (AGCM 2020).

"Algorithm machines" (Gillespie et al. 2014) enable to automatically perform millions of operations per second, minimising human error and hugely reducing costs, once a rigorous logical definition of what is the problem at stake has been attained, straddling the competing demands of formal abstraction and empirical contingency, and eventually allowing to break the task down into a precise set of instructions.

On this basis, it has been possible to build predictive models, either by assuming a mechanistic cause-effect relationship, or by developing predictors, ascertained within phenomenological models, which stem out of a large body of empirical observations without making any causal assumption.

Both mechanistic and phenomenological approaches can be combined together to determine the optimal computer modelling and simulation strategy, taking into account (and even augmenting) quality and quantity of data required to build, run, and validate each predictive model, and being cautious, especially in deep learning (DL) applications, of explicability issues and changes in unforeseen ways of statistical properties of the target variable over time (implying the risk of concept drift).

The process of algorithmic production of knowledge is quite often "unpredictable by design", being normally based on big data analytics testing large numbers of algorithms on the data, in view of discovering meaningful correlations, on which ML causality or DL infer. Furthermore, DL implies feeding vast quantities of data through non-linear neural networks, which classify the data based on hierarchical outputs from each successive layer, and the complexity of this self-modelling is, as yet, inherently not-easily self-explicative.

A consequence of such a state of the art is that this may lead to a black-box effect, with the risk of rendering automated decision-making inscrutable, or prone to hidden biases, though apparently functioning. Hence the request for algorithms that respect the FAT principles (Fairness, Accountability, and Transparency) and the whole ongoing debate on AI Ethics (European Commission 2018, 2020a; Kearns and Roth 2019; Coeckelbergh 2020), which unrolls in parallel with the European Union's ambition of becoming a world leader in trustworthy AI.

Of course, these issues become particularly crucial when the data they refer to are personal data and the sector in which AI is employed is the biomedical one.

A Europe Fit for the Digital Age?

Even before the dramatic increase in the need of enhanced digital development brought forward by the COVID-19 pandemic, the EU had set far-reaching objectives, such as tripling by 2025 the share of companies using AI and big data,

ensuring "gigabit internet connectivity with equally fast upload and download speeds for all main socio-economic drivers, such as schools, hospitals, businesses" and achieving "an internet where citizens are in control of their data, and their online identity [...] with the clear understanding of [...] how their data is protected". However, the very same document remarked that "many of the opportunities of digitalisation are still ahead and are complex to unlock. A greater willingness to share data will help address important social challenges. Europe must seize the vast potential of the exponentially growing amounts of data, particularly in areas where it is strong [...] and to maintain leadership in key sectors, such as health [...]" (European Commission 2020b).

Notwithstanding the pressing demand for data driven by AI and big data, the inconvenient truth is that the ambitious goals set by the European Commission will be at risk so long as data sharing in healthcare remains rare, characterised by high transaction costs and happening mostly under private agreements typically enacted by large corporations. Indeed, "although available data is continuously expanding, it largely sits idle" (Finck 2019), i.e. fragmented in siloes carefully guarded by data controllers to reduce legal exposure. The advent of truly open and competitive big data and AI environments is still delayed in Europe, with not only economic consequences, but personal and societal ones as well, like in the case of rare diseases which altogether affect 30 million people in Europe, for which research data are still dramatically scarce.

"Big health data" is the immense data generated from patient health records, diagnosis, treatments, genomic sequencing, medical research, smart devices, wearables, and various other sources. These data are available in high volume, can be transferred at high velocity, and are highly variable (being generated from multiple sources). As big health data grow larger, advanced data analytics and cognitive computational methods have emerged as promising tools to harness the power to convert heterogeneous data sets into clinically useful information, integrating digital health and personalised medicine.

Although this data-driven approach may seem to challenge the conventional approach of hypothesis-driven medicine, its real promise lies in synergy rather than in replacement. Both these approaches can be combined to improve clinical practice, and by using advanced analytical tools to look across huge numbers of patients, patterns may emerge allowing to identify subpopulations that respond to treatments differentially, providing a pathway toward optimisation of personalised treatment protocols and toward more targeted drug development.

In any case, the impact of data quality and quantity on modelling for diagnostic, predictive, and prescriptive analytics is critical, both whether working with traditional statistics or when having recourse to ML or DL AI developments. There is therefore the need to set a strategic focus on technologies that can allow to effectively scale up a compliant data ecosystem for the biomedical sciences.

GDPR and the Health Data Sharing Challenge

The General Data Protection Regulation (GDPR) (European Parliament 2016) draws a dividing line between personal data and non-personal data, which is paramount to determine the scope of application of the European data protection law, given that personal data are subject to the Regulation, and non-personal data are not. In particular, anonymous data, i.e. "personal data rendered anonymous in such a manner that the data subject is not or no longer identifiable" (European Parliament 2016, recital 26), fall outside of the scope of the GDPR.

In fact, applying this distinction to health data, anonymisation is defined as the process by which the data are irreversibly altered in such a way that a data subject can no longer be identified (by "all the means reasonably likely to be used"), directly or indirectly, neither by the data controller alone, nor in collaboration with any other party, and by any malicious third party.

This non-re-identifiability requirement can, however, reduce information in the data to the point of making them unusable for scientific discovery or realistic AI-systems training. Being a subtractive technique, based on stripping away direct and indirect identifiers, anonymisation has the flaw of "incurring not only poor privacy results, but also lackluster utility" (Bellovin et al. 2019; Ohm 2010; Narayanan and Felton 2014). Whereas anonymisation based on k-anonymity, i.e. the methodology, originally devised at the Harvard Privacy Lab (Samarati and Sweeney 1998; Sweeney 2002), by which the information for each person contained in the release cannot be distinguished from at least k – 1 individuals whose information also appear in the release, has shown for instance to work on constrained data uses, while losing reliability as the number of aggregated records increases (Aggarwal 2005).

At the same time, the issue is further complicated by the emergence of AI-based tools for re-identification (McPherson et al. 2016), which push even further the amount of information that needs to be removed from a given data set to make it actually anonymous.

Pseudonymisation, which is the other method of protecting privacy introduced by the GDPR, relates to the processing of health data in ways by which they can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that data are not attributed to an identified or identifiable natural person. As re-identifiable, even encrypted data are pseudonymous. Given their re-identifiability, and therefore qualifying as personal data, all pseudonymous data require on principle a specific legal ground, such as an explicit personal consent, for being shared with third parties. Pseudonymisation requires in fact defining, among all actors involved, formal relationships under which data can be de-crypted.

Because of these specificities, both anonymous and pseudonymous health data end up by being either inherently inadequate or extremely hard to scale up to an aggregation level of bigdata sets that can allow an efficient development of robust AI

solutions. Neither of these approaches is technically and economically sustainable to boost data-driven research and development at industrial scales.

Compliance risks act also as a constraint in the development of a thriving data economy driven by direct incentives. It is evident that supply/demand dynamics will be key in the growth of the European Digital Single Market as they are doing in other, more permissive, jurisdictions.

In the ideal scenario, data controllers and individuals should be able to share the largest possible data sets within the broadest possible community, while effectively protecting the identities of individual subjects and, in turn, be able to re-capture value from data transactions, fostering network effects to progressively increase the total volume of available data.

Alternative Modes for Dealing with the Issue of Sharing Health Data

Recent outcomes of a Horizon 2020 EU-funded project, MyHealthMyData (MHMD)[1], have highlighted two alternative ways of facing the challenge of big data health sharing.

One is the so-called "visiting" mode, in which data are not physically accessed by third parties, but "algorithms are brought to the data" and only the outcomes of secure computations are released. This approach is consistent with a growing concern to preserve the privacy of sensitive health information, while promoting the development of personalised medicine, by increasing the usage of cryptographic techniques suitable for addressing privacy-related issues in data-driven models[2].

The "visiting" mode was exemplified in MHMD through mechanisms like homomorphic encryption, secure multi-party computation, and federated learning with untrusted black-box. These solutions were realised in conjunction with a permissioned blockchain system for recording transactions, an off-chain storage of health data, a metadata catalogue to view and request available data assets, and smart contracts for automatically handling individual consent and institutional permissions.

Homomorphism is the property of an encryption scheme that allows to perform operations on encrypted data. Once the results are available, they are sent back and decrypted at the source. The computing service has access only to the encrypted data, and since the decryption key is not available to the service, no personal or useful information can be extracted. This approach represents a superior alternative to anonymisation, given the typical trade-off between confidentiality and utility

[1] www.myhealthmydata.eu.

[2] Parallel approaches, building privacy-preserving solutions based on moving vetted algorithms to the data, have been pursued by the MIT Media Lab with the OPAL project (Alsalamah and Pentland 2018) and, more recently, by Qualcomm AI Research and the University of Amsterdam. (Delcker 2020).

of the latter, while, specifically in the case of genomic data, DL operating on homomorphic encryption can gain valuable information and insight from the encrypted data.

The solution enacted by the Transylvania University of Brasov within MHMD is based on Fully Homomorphic Encryption (FHE) making use of MORE (Matrix Operation for Randomization or Encryption) as encryption scheme, enabling the computations within a neural network model to be directly performed at a relatively small computational overhead (Vizitiu et al. 2019a, b, 2020)[3].

Secure Multi-Party Computation (SMPC) is a cryptography modality aiming to create methods for parties to jointly compute a function over their inputs, keeping these inputs private. SMPC allows a set of distrustful parties to perform the computations in a distributed manner, while each of them alone remains oblivious to the input data and the intermediate results. The computation is considered secure if, at the end, no party knows anything except its own input and the results.

Federated learning (Bonawitz et al. 2019) with untrusted black-box has been jointly developed, within MHMD, by Siemens Healthineers and Athena Research Centre, using SMPC and Differential Privacy (DP). A federated learning platform allows training of complex deep-learning models without ever centralizing or exposing the underlying raw data, while providing formal privacy guarantees through DP mechanisms and SMPC cryptographic techniques.

The "black-box" ML modules can be provided by third parties and executed locally at the data providers to support model training. As such, this solution can be an important building block of a privacy-by-design data sharing system for healthcare research.

As yet, however, SMPC still implies a large communication overhead which makes it hard to use where very large amounts of data are required, since communication and computation costs can be greatly affected by the increase of the number of involved parties or of the model's complexity.

Therefore, notwithstanding the promise implied in further developing the "visiting mode", a complementary biomedical data sharing approach has also been explored within MHMD and deemed to be deserving a particular attention: the generation of synthetic data.

Synthetic Data

The use of synthetic data is attracting growing attention as a practical solution to the quandary of maintaining privacy in big data ecosystems. The UK Government Statistical Service has defined it "an unprecedented opportunity to innovate with data, while safeguarding privacy and fostering public trust" (Quality Centre 2018)

[3]This homomorphic encryption solution, developed by the Transylvania University of Brasov (Romania) within the MyHealthMyData project, was awarded the E.U. Innovation Radar Prize 2019 in the category Industrial & Enabling Tech.

and even the Financial Times has remarked that "improvements in machine learning and computing power make it a technology to watch" (Ahuja 2020).

Public Health England's National Cancer Registration and Analysis Service (which collects data on all cancers diagnosed in England) has been running a synthetic database called "Simulacrum" since November 2018[4].

The Stanford Technology Law Review has stated that "synthetic data is a viable, next-step solution to the database-privacy problem", which allows "to step away from the deidentification–reidentification arms race and focus on what really matters: useful data [. . .] combined with differential privacy to achieve a best-of-both-worlds scenario" (Bellovin et al. 2019).

Synthetic data are created from real data, by machine-learning generative model to "produce realistic, yet artificial data that nevertheless has the same statistical properties [. . .] to create an as-realistic-as-possible dataset, one that not only maintains the nuances of the original data, but does so without endangering important pieces of personal information" (Bellovin et al. 2019).

The difference between traditionally anonymised data and synthetic datasets is that "these datasets protect privacy through the addition of statistically similar information, rather than through the stripping away of unique identifiers" (Bellovin et al. 2019).

Statistical characteristics of the real population are "learned" during synthetisation, from the original data, while the synthesis process uncouples sensitive information from the data information content, attaining anonymity though still preserving information richness. This directly responds to the GDPR specification of "personal data rendered anonymous in such a manner that the data subject is not or no longer identifiable" (European Parliament 2016), while the overarching objective is to create "high-quality synthetic data that closely resemble the real data and are a suitable substitute for processing and analysis" (ONS 2019).

Recent literature has highlighted differential privacy as an additional privacy protecting measure to further enhance synthetic data (Page et al. 2018). Information leakage from each query can, in fact, be minimal on synthetic data, but is, by definition, never zero. Overtime, with each database query, the amount of leaked information grows.

The U.S. National Institute of Standards and Technology has launched a Differential Privacy Synthetic Data Challenge in 2019, showing a keen focus on developing "a mathematical theory, and set of computational techniques, that

[4]Simulacrum, developed by Health Data Insight in partnership with AstraZeneca and IQVIA, and launched in November 2018, is a synthetic database which does not reveal sensitive information, but maintains most of the properties of the original data. Because the data model (but not the data) is the same as the real model in the Cancer Analysis System, researchers can use Simulacrum to plan and test their hypotheses before making a formal request to Public Health England to analyse the real data.

provide a method of de-identifying data sets—under the restriction of a quantifiable level of privacy loss"[5].

The developments and potentialities of data synthetisation and augmentation are also becoming part of a broader field of investigation. For instance, in "radiomics", new AI-based image reconstruction tools are applied at the stage of raw data decoding and transforming, with the effect of hugely accelerating image acquisition processes with minimal compromise on final image quality, despite what would traditionally be considered as data "under-sampling" and patient "under-exposing" (Rizzo et al. 2018).

A Novel Anonymisation Paradigm

Synthetic data were introduced in 1993 (Rubin 1993; Little 1993) as a way to replicate the statistical properties of a database without exposing identifiable information, acting therefore as a statistical disclosure control (SDC) method or as an alternative to SDC (Elliot and Domingo-Ferrer 2018).

Methods to produce them vary (Reiter and Raghunathan 2007; Drechsler and Reiter 2011; Surendra and Mohan 2017; Hu et al. 2018; Abay et al. 2018), but the underlying principle is that values in the original data are algorithmically substituted with others taken from statistically equivalent distributions and structures, to create entirely new records, with as little traceable relation to the originals as possible.

In MHMD synthetic data have been successfully used[6] to publish clinical data and MRI cardiovascular images, to train machine learning tools, and to validate clinical decision support applications. A growing body of international research is showing evidence that they can yield equivalent analytical results as original data sets (Patki et al. 2016; Aviñó et al. 2018; Brown 2020). While their adoption is suffering from lack of standards and best practices, their use in specialised sectors of biomedical research (e.g. in-silico clinical trials) is growing, especially under the auspices of the US FDA.

The value of synthetic data resides in a series of key characteristics:

1. They are used in the same way original data sets are and therefore with the same storage, maintenance and analytical infrastructures.
2. They maintain statistical characteristics of the original data, but can be expanded for imputating (replacing missing values with substitutes) and augmenting real

[5]NIST, Differential Privacy Synthetic Data Challenge: Propose an algorithm to develop differentially private synthetic datasets to enable the protection of personally identifiable information (PII) while maintaining a dataset's utility for analysis, Submission Start: October 31st 2018 - Submission End: May 20th 2019.

[6]Thanks initially to the ground-breaking contribution of one of MHMD clinical partners, namely the Queen Mary University of London team, composed by S. Petersen, A. Lee, and M. Jennings (acknowledging also support from the "SmartHeart" EPSRC programme grant - www.nihr.ac.uk EP/P001009/1).

data. They can thus fill gaps, correct skewed value distributions, or remove spurious values in the original data, addressing collection, formatting or normalization issues, which are pervasive in clinical data sets, and thus producing data that are actually more informative and realistic than the original ones (Nowok et al. 2017; Brown 2020; El Emam et al. 2020).
3. They can be produced at low costs, for a variety of uses and in very large volumes to jump-start AI-development in areas where data are scarce or too expensive, such as the biomedical sector which, as discussed above, suffers in this regard from both economic and legal limitations.
4. The actual risk or re-identification can be effectively quantified in relation to the original ones with differential privacy and modulated, in the generative process, based on the intended use and distribution.
5. Being fully artificial, they are non-personal data, and are therefore freely exchangeable, falling outside of the GDPR scope.

The Technology

Synthetic data can be generated by a diverse range of systems (Park and Ghosh 2014; Ping et al. 2017; McLachlan 2016; Syahaneim et al. 2016; Walonoski et al. 2018; Chen et al. 2019; El Emam et al. 2020), including naive Bayes models (Multani et al. 2018) or statistical shape analysis (Bruse et al. 2017; Biffi et al. 2017) (for imaging data), according to user/customer requirements and intended dimensionality in the resulting set.

In particular, Generative Adversarial Networks (GANs) (Goodfellow et al. 2014) brought renewed attention to this application, having achieved remarkable results in generating data "without the need for vast troves of painstakingly-labeled training data [. . .], [being hailed] as one of the most important innovations in deep learning" (Bowles et al. 2019).

A Generative Adversarial Network uses two models playing against each other. The Generator learns to capture and recreate the data distribution while the Discriminator estimates the probability that a generated sample belongs to the original data distribution or rather has been created by the Generator; in other words, it decides whether the data is fake or not.

GANs can discover structures in the data well beyond what other techniques can do, but other unsupervised statistical techniques can be utilized, such as Monte Carlo simulations, which have been shown to reduce leakage (the accidental insertion of a priori knowledge in the synthetic set) and to perform well in reproducing statistical multi-dimensionality, especially when compared to supervised methods.

Interpretability

Statistical realism is of course key to valid inferences on synthetic data and discriminators are not surprisingly a crucial area of research and innovation.

Commonly used systems in this space, based on Random Forest or MMD statistics, do assess the overall statistical resemblance of two sets, but in case of discrepancies they cannot identify the underlying reasons.

While these types of discriminators remain useful as a first line of evaluation, new methods now allow to weight each original variable in the generation process, thus supporting detailed diagnostics and direct, ongoing improvements to the generative pipeline. These new approaches to algorithmic transparency, i.e. the ability for a human operator to trace the weight of original variables in the synthetic set, reduce the risk of "mode collapse", the tendency to learn from and thus replicate only the most prevalent features in the original data. Such systems now allow to continuously optimise the data creation process and systematically address biases.

Among other approaches, these tools leverage iterative L1-regularised parametric models using the interpretable components as inputs (Van Belle and Lisboa 2014), which identify the relative weight of each original variable in the generation of the synthetic replica and therefore allow targeted adjustments of the generative process. This direct feedback loop design has shown to drastically improve efficiency of and control over the generation process (Choi et al. 2017; Jordon et al. 2018; Hui 2018; El Emam et al. 2020).

3D and 4D Synthetic Images and Genetic Synthetic Data

New methodologies for artificial surfaces models have been developed to support the creation of 3D and 4D images, i.e., including haemodynamic data. Vascular structures or solid organs are first initialised from original radiology images and corresponding geometric information is then reproduced to replicate vessel radius, degree of tapering, branch length, among other things. Finally, pathological aspects are modeled. Synthetic images have an additional and substantial advantage in medical-AI applications: time consuming and costly manual annotations, to train algorithms on clinically relevant features, can be inserted automatically in the synthetisation process by the generative pipeline reducing the overall cost of AI-systems development (Guibas et al. 2017; Yi et al. 2019).

These approaches can be applied to replicate synthetic distributions of gene expression too, including single nucleotide polymorphism, copy number variation or protein-protein/gene-gene interactions. Deep learning approaches (especially GAN and InfoGAN) have demonstrated both scalability and statistical robustness in this area while ongoing work, targeting the oncology drug development sector, is showing promising results in the generation of both SNP-chip like genotypes (containing only common genetic variants), and sequencing data (Azencott 2018; Ellis 2019).

Synthetic Data and Differential Privacy

As defined in the seminal work of Cynthia Dwork and Aaron Roth in 2014 (Dwork and Roth 2014), differential privacy provides a mathematical foundation to substantiate privacy assessment and its legal definition.

The idea of adding differential privacy to neural networks drew interest as early as 2016 (Abadi et al. 2016); however, it was not until 2017–18 that researchers realized the potential implications and advantages of applying the technique to GANs (Lu and Chia-Mu 2017; Xie et al. 2018), by implementing noise, i.e., applying filters and weights, into the training data.

A recent literature has articulated the key role of differential privacy in combination with synthetic data (Langarizadeh et al. 2018; Rocher et al. 2019; Jordon et al. 2019), as being the only solution to sufficiently protect privacy while maintaining utility. Differential privacy's and its robust guarantees do not only mitigate the risk information leakage, but also the risks of adversarial machine learning.

Although the technique is relatively new (and the optimal means of applying differential privacy to synthetic data is not yet settled), differential privacy nonetheless provides a better way of assuring privacy given chance identification. Significant further advances are also to be found in recent work on building DP Bayes Nets (Zhang et al. 2017).

Caveats

Some careful analysis needs to be further developed with regard to possible limitations of the synthetic data solution. Researchers from one of MHMD partners, SBA, have in particular, highlighted some potential attribute disclosure risks, though globally validating synthetic data robustness in terms of identity protection (Hittmeir et al. 2019a, b, c; Taub et al. 2018). Whereas, other approaches state that "attribute and inferential disclosure are both forms of statistical analysis, and therefore we would not want synthesis to protect against these" (El Emam et al. 2020).

Synthetic Data and AI Biases

As AI capabilities are boosted by innovation in algorithm design, the old saying that "lots of data beat algorithms and good data beat lots of data" remains globally true.

Yet, the quality of biomedical data sets is traditionally poor, due to the complexities and cost of measuring biological and clinical parameters. This leads to two sets of issues: AI systems trained on poor-quality data struggle to achieve sufficient accuracy, and even when they reach it, they carry the risk of incorporating systemic biases that skew their behavior in detrimental or unethical ways.

Recent cases have brought to the public's attention worrisome examples of AI biased in important social functions. The issue affects well curated data too. In medicine, for instance, rare diseases or uncommon presentation of more frequent ones offer unique challenges in terms of data availability. Their low prevalence leads to systematic understudy. A diagnostic algorithm trained on commonly available data will tend to underdiagnose them, compounding the underestimation of their actual incidence.

Synthetic data in such a case can be used to extend underrepresented populations and rebalance outputs. They can also be used to influence AI behavior in ways that even the most exhaustive training data set cannot, as in the case of social inequalities which are indeed factual and thus expressed in even the most accurate snapshots of general population and, if not corrected, are simply perpetrated by AI-systems.

When direct data manipulation, such as down-weighting or rebalancing key variables with ethical dimensions (e.g., race), is not feasible or cost-effective, synthetic data represent a low-cost solution to correct algorithms' behaviors toward socially responsible decisions, and the current debate on the "Ethics for Trustworthy AI" (Bellovin et al. 2019) should usefully take into account that ethically desirable scenarios can in fact be deterministically implemented by having appropriate recourse to synthetic data. Artificial intelligence is then trained on enriched, real-life information reflecting a consciously chosen digital structure in which "data is still king but ruling as benevolent monarch rather than prejudiced patriarch" (Bellovin et al. 2019).

Concluding Remarks: A Rich Health AI Ecosystem to Complement the GDPR

Synthetic data show a promising path toward a secure and scalable biomedical data economy, which deserves to be fostered and framed in depth, if it is to grow.

This solution stands to become a highly valuable currency in the healthcare and pharmaceutical, artificial intelligence ecosystem. This will be especially true if such an ecosystem develops the ways by which to allow an increasing number of individuals (and/or clinical institutions) to safely provide their data with the aim of letting specialised and trusted processors generate high quality synthetic versions of them, with absolutely negligible risks of eventual re-identification and the full freedom of lawfully extracting value by sharing the resulting synthetic data.

Non-European institutions, such as the US NIST, have taken actions to foster this technology in main-stream industrial applications and research, but a scientific and strategic direction is still missing in terms of technological best practices, legal interpretations and market organisation, aiming at empowering plural approaches in feeding big data AI developments.

Technology advancements have opened the way to real-world generation and scaling up of synthetic data, but in absence of validated frameworks for their creation, validation and use, commercial and institutional players are not likely to adopt them in time for placing Europe at the fore front of this innovation (Avicenna

Alliance 2020; BDVA 2020). Standards and user workflows for the selection and management of most appropriate data generators, and for their configuration, would allow unskilled data analysts to confidently assemble generative pipelines to serve their organisations' R&D goals. Similarly, robust proof of statistical reliability will foster their adoption by key decision makers.

The time is therefore ripe for an initiative by the European Commission, that addresses the absence of adequate legal and technical definitions, as well as of policy, and promotes the experimentation of such innovative solutions to the current difficulties with health data sharing, while fully implementing both the spirit and the letter of the GDPR.

New calls for EU-funded projects bringing together leading private and institutional subjects around the potential of synthetic data and of secure computation, would help to develop the needed framework and to test the concrete use-cases for a main-stream implementation and market adoption. Funding research and innovation actions in these areas can prove to be a crucial stepping stone to enhance the EU competitiveness and activate a thriving Digital Single Market for the biomedical sciences.

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Realizing Personalized Medicine Using In Silico Tools: A Community Effort

Liesbet Geris

Introduction

The strict bio-medical domain and the societal one, cannot be treated separate from each other. Addressing both levels in an integrated way means taking into account the complexity of the biological processes that underlie diseases as well as the lifestyle choices and environment of the patient that impact these biological processes (cfr., Bertolaso and Beneduce in this volume, Introduction). One possible way to endeavor to bring both levels together is through the use of computer modeling and simulation as an integrative technology so as to implement personalized medicine.

Virtual Physiological Human, virtual human, digital human, digital twin, digital patient, virtual patient, patient avatar etc. These terms might all have slightly different meanings depending on the context they are used in or the person who uses them. However, the one common denominator in all these terms is the concept of using computer modeling and simulation in healthcare applications, from prevention over diagnosis to treatment selection and patient follow-up. This field is also indicated with the name "in silico medicine" with the term "in silico" referring to the main component of computer chips, silicon, chosen in analogy to the other two main categories of experiments in biomedical sciences: "in vitro" (bench tests) and "in vivo" (in living beings). The aforementioned nuances in meaning to given

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terminology often depend on the community or field the term originated. The clearest example is that of the "digital twin", a concept from industry 4.0 and used much wider than only in the biomedical context. A digital twin is a virtual representation of a physical object or process that is in direct real-time connection with its physical counterpart, reading in data from sensors and evolving with it. Digital twins are used to understand, inspect and optimize the physical objects or processes they are linked to. When applying this concept to biomedical and healthcare processes, the real-time connection is often not the main purpose of the digital twin. It rather seeks to take historic and actual patient information (images or other medical data) into account and provide a personalized prediction of disease progression or impact of treatment. The term digital twin in healthcare is therefore mostly synonymous to a computational model built with patient data.

Examples of success stories of the in silico medicine field for various organ systems can be found in a recently published special issue of the journal *Morphologie*, addressing the impact in silico medicine has on the clinical practice (Van Sint Jan and Geris 2019; Vardakis et al. 2019; Thomas 2019; Kaul 2019; Viceconti 2019; Astudillo et al. 2019; Lyon et al. 2019; Tawhai et al. 2019; Hester et al. 2019). Figure 1 shows examples of the use of such personalized in silico models starting from the patient's physiology to explain the impact of ventilation on lung function and associated risk of right heart-failure in patient suffering from acute pulmonary embolism (Burrowes et al. 2011).

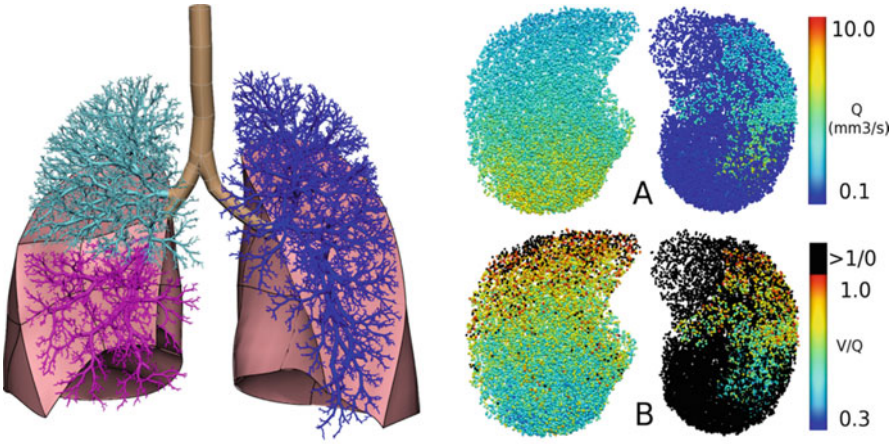

Fig. 1 Physiology-based patient-specific model of the lung (left). Right: a comparison between modeled output parameters for healthy patients (left side) and patients (right side) suffering from occlusion due to the presence of emboli in the left part of the lung. The resulting values are plotted on a representation of the alveoli. (**a**) shows the perfusion rate and (**b**) the ventilation to perfusion ratio (V/Q). A high V/Q ratio means a higher steady-state rate of gas transfer, and therefore higher end-capillary partial oxygen pressure due to low osygen uptake by the blood. (Adapted from (Tawhai et al. 2019) with permission)

Systems Biology and Physiology-Based Modeling

The field of in silico medicine is far from being a homogeneous block, owing to the variety of in silico technologies that can be used. Bioinformatics, artificial intelligence, computational biology, systems biology, systems medicine, mathematical biology, theoretical biology, biomedical modeling and physiology-based modeling are variations on the in silico medicine theme, working with different types of input data, different scales, different modeling and solution strategies and with different end objectives. An interesting case is that of the relation between the systems biology/medicine community and the physiology-based modeling community. Both communities are active contributors in the personalization of medicine. The systems biology community studies biological and biomedical questions from a systems perspective, often focusing on the intracellular regulatory networks as can be inferred for instance from the patient's genome, defining emerging behavior on a systems level. The physiology-based modeling community studies these same biological and biomedical questions, starting from a representation of the patient's morphology and a (multiscale) description of the processes under study. In the past, both communities had relatively few interactions and mostly emphasized their differences. Interestingly, they both consider Dr. D. Noble as one of the pioneers of their community. It is perhaps not unsurprising that Dr. Noble himself considers the cell as fundamental unit, as the correct level of abstraction (Noble 2008). The level of the cell is where the intracellular models (system biology) and physiology-based models meet and exchange information, facilitating both upward and downward causation. This exchange of information is increasingly also taking place between the communities where systems biology is increasingly embracing the physiological envelop of the tissues and organs, and the physiology-based modeling community is integrating intracellular mechanisms, providing an additional level of control for the models.

Artificial Intelligence and Mechanistic Modeling

Another place where clinical reality begs previously separate worlds to meet, is in the specific in silico technology used to build the models and the role experimental data is playing in that process. On one end of the "in silico spectrum", there are the "data-driven technologies" such as biostatistics, bioinformatics, machine learning and artificial intelligence. These technologies rely on the data, without including previously established mechanistic information about the process and the resulting phenomenological models are also referred to as "black box models". On the other end of the in silico spectrum, there are models that start from previously identified mechanisms (that, of course, were often established based on experimental data). Models relying mostly on first principles and cause-effect relationships are also referred to as "white box models". When modeling (patho)physiological processes, full white box models are unachievable. "Mechanistic models" focusing on a

particular time and length scale (cell, tissue, etc.) and even multi-scale models, make abstraction of the scales below (e.g., transcription & translation in most multi-scale models) and above (e.g., the impact of the other organ systems & the environment in many models). This abstraction takes the form of boundary conditions and phenomenological model parameters. So models of the cellular level make abstraction of the entire body surrounding the cell and models focusing on an organ or organ group might homogenize the heterogeneity of the multiscale nature of the tissues and embedded cells.

Conversely, in certain areas of medicine, insufficient data is available from clinical studies and clinical practice to build data-driven models. Take the example of clinical trials in regenerative medicine where data sets are very limited, owing to the intrinsic limited size of patient populations combined with the highly personalized treatment strategies (if using autologous cells). Using these data sets to build a predictive model of clinical trials by means of artificial intelligence techniques is not feasible and researchers are including previously established causal relationships within the biological process, to feed and enhance the model. These models that combine data-driven and mechanistic approaches are also referred to by the name of "grey box models". Figure 2 provides a schematic overview of the complementarity of the white box (deductive) and black box (inductive) approaches.

In an increasing amount of in silico models in the biomedical field, combinations are made of data-driven and mechanistic approaches. Mechanistic models can

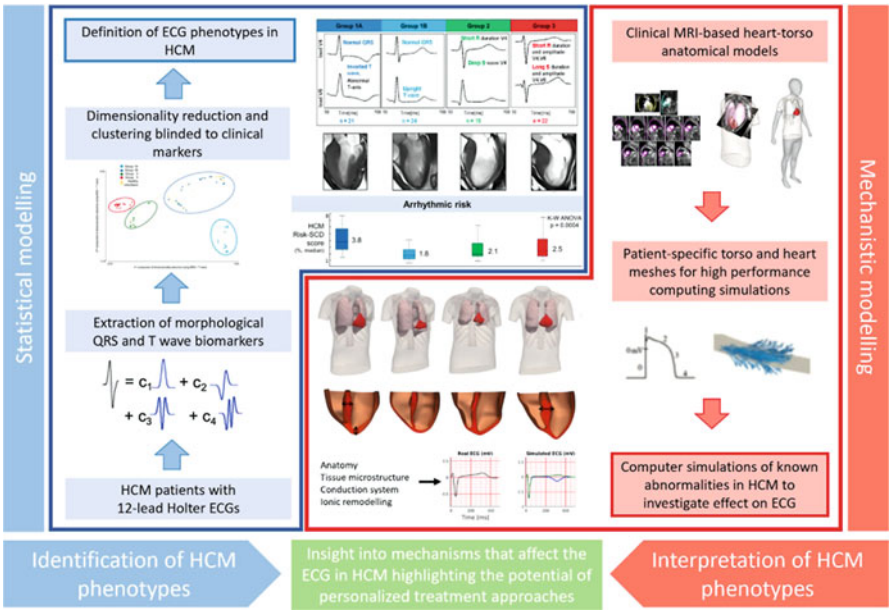

Fig. 2 Schematic overview of the complementarity and applications of data-driven and mechanistic approaches in the field of precision cardiology. (Corral-Acero et al. 2020)

provide digitally generated data to train data-driven models or provide a benchmark against which the accuracy of artificial intelligence algorithms can be tested. Data-driven technologies are used to provide phenomenological descriptions of those biological or physical elements that are not explicitly included in mechanistic model such as the aforementioned description of biological material properties that do not capture all details of its multiscale nature. Data-driven modeling techniques are also increasingly used to perform uncertainty quantification of mechanistic models or to develop (phenomenological) "surrogates" to replace (parts of) mechanistic models that would otherwise take too long to compute to meet is clinical purpose. An example of such a combined approach can be found in Fig. 3, showing how machine learning applied to a data set of electrocardiograms of patients suffering from hypertrophic cardiomyopathy (HCM) can be used to identify various HCM phenotypes (answer the "who" question) whereas physiology-based mechanistic models can provide the interpretation of these different phenotypes (answer the "why" question).

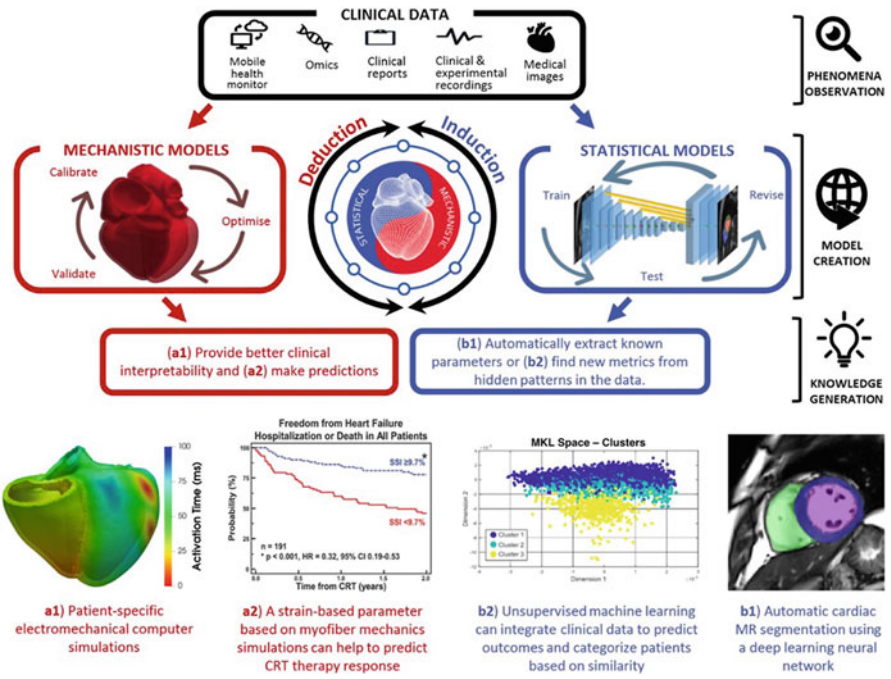

Fig. 3 Synergy between machine learning and mechanistic modeling to provide inside in the various phenotypes and related mechanisms within the patient population suffering from hypertrophic cardiomyopathy. From (Corral-Acero et al. 2020)

Building an In Silico Medicine Community

With in silico medicine on the rise, there is a need for the community to come together in an effort to increase the quality, robustness and repeatability of the developed technologies and to bring the technologies to the patient in order to realize the potential of personalized medicine. In the remainder of this chapter, we will use the "Virtual Physiological Human (institute)" as a case study to highlight how the in silico medicine has evolved over the last three decades, the current community and its activities as well as the future challenges.

The mother of the Virtual Physiological Human (or in silico medicine in general) is the "Physiome project". The Physiome project was first presented at the World Conference of the International Union of Physiological Sciences (IUPS) in 1993. Its aim was to provide quantitative description of the physiological dynamics and functional behavior of the intact organism (IUPS 2000; Hunter and Borg 2003). Rather than taking a reductionist approach to biology and physiology as was standard practice in (experimental) biology and physiology, the Phyiome project wanted to piece everything together again by using computational models. Instead of studying each and every component of the body individually, they should be studied as part of an integrated whole. Pioneering work, exemplifying the Physiome concept, was performed by Peter Hunter at the Auckland Institute of Bioengineering, studying the heart. Models focusing on the electromechanical functioning of the heart integrated models of ion channels, myofilament mechanics and signal transduction pathways at the subcellular level with models of tissue mechanics, wave-front propagation and blood flow in the coronary arteries (Hunter et al. 2003). To this day, the cardiovascular field is one of the leading physiome systems, despite (or perhaps thanks to) its intricate multiscale and multiphysics properties.

The Virtual Physiological Human

After several years, a European Physiome initiative was launched by the European Commission, entitled the Virtual Physiological Human (VPH). The aim of the VPH initiative was very ambitious: "The VPH has to tackle all areas of the human anatomy, integrate data from all levels, provide predictive simulations with almost infinite resolution to let scientists and medical practitioners know as much as possible about the Real Physiological Human" (VPH Institute 2005). The implementation of this ambition started with the development of a roadmap to paint the way ahead for the EuroPhysiome (STEP consortium 2007) in the European multi-annual financial framework program 6 (FP6). This was followed with a dedicated funding stream in the following program, FP7, funding over 20 EU consortium projects focusing on a variety of diseases, each combining the use of personalized imaging with the development of physiology-based computational models. Since those early projects, over 100 projects have been funded by the Commission related to VPH technology. Significant scientific progress was made in terms of modeling biological systems and solving these models. Owing to the

very interdisciplinary nature of the VPH, many conceptual and technical challenges had to be overcome on a wide variety of fronts, including the biological, clinical, modeling, computational and regulatory ones. Every step forward was accompanied with the discovery of a new series of questions and challenges that needed to be addressed. Progress was hard won, but it was real as can be appreciated from the examples shown in Figs. 1 and 3.

In the projects, the concept of VPH was not only elaborated from the point of view of a specific disease or organ system, but also from the point of the view of the end user. For the individual patient, personal health forecasting tools are important in prevention and disease progress prediction. Clinical end users will use the digital patient as a clinical decision support system to compare treatment strategies for a given patient, determine optimal timing for intervention etc. The possibilities and challenges of the digital patient were elaborated in the Discipulus roadmap (Díaz et al. 2013). Most recently, the impact of the use of computer modeling and simulation in the context of clinical trials was elaborated in the Avicenna roadmap (Viceconti et al. 2016).

The Virtual Physiological Human Institute

As many of the challenges encountered in various projects and elaborated in various roadmaps are agnostic to the biological application that models are focusing on – definitely the modeling and computational ones but also the biological and clinical ones – a need was felt to bring a community together to tackle these challenges together. This resulted in the establishment of the Virtual Physiological Human Institute (VPHi), as a non-profit organization in 2011. The vision of the institute is to ensure that the Virtual Physiological Human is fully realized, universally adopted and effectively used both in research and in clinics (VPH Institute 2020). In order to realize this vision, the VPHi takes on a hybrid role of scientific community and trade organization. It works to bring the scientific community together in a variety of activities and events, ensuring that state-of-the-art knowledge, technologies and best practices can be exchanged and disseminated effectively. Beyond the activities of a typical scientific society, the VPHi also puts the scientific community in contact with a variety of different stakeholders in order to maximize the benefit of VPH approaches for the healthcare industry and for the public good. These stakeholders include patients, policy makers, science funding bodies, regulatory agencies, payers, clinical organizations and industry. Strategic partnerships are formed with third parties to further specific parts of the mission such as with the Center for Alternatives to Animal testing (CAAT) for advancing the use of computer modeling and simulation as key factor in realizing the "3Rs (refinement, reduction & replacement of animal testing)". Figure 4 gives an overview of a number of key activities leading up to the establishment of the VPHi, and organized by VPHi since its incorporation.

Momentum has been steadily increasing for in silico medicine in general and, as part of the outcomes of the Avicenna road mapping, the alliance between VPHi and

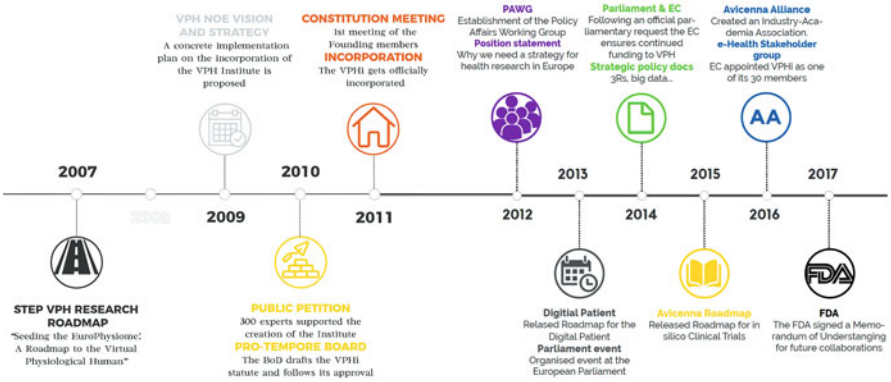

Fig. 4 Timeline of key events in the VPH community and institute

industry was formalized in the Avicenna Alliance (Avicenna Alliance 2020). This created a scale increase and allowed to increase the pace and scope of the policy and regulatory work.

In Silico Medicine Community: Where Are we Now?

After decades of work within the in silico community, the technology has now evolved to the point where the advantages of computational modeling in healthcare are undeniable. Besides the continued development of the technology, the community has also started to focus on tackling the possible roadblocks encountered on the path from the screen to the (individual) patient. Policies need to be altered to explicitly allow for the use of in silico tools, and regulatory agencies need to develop guidelines to appropriately deal with evidence generated by in silico tools.

Regulation

On the regulatory side, pharmaceutical dossiers have since long included in silico elements such as pharmacokinetic/pharmacodynamics (PK/PD) models to investigate dosing and time course response. However, recently the biggest advances have been realized in the devices field with the Food and Drug Administration of the United States of America (USA-FDA) leading the way for the inclusion of in silico tools in its regulatory processes. A series of guidance documents and standards (co-)developed by the FDA indicate how in silico evidence should be presented in regulatory submissions (FDA 2017) as well as how much verification and validation is required for a specific context of use. The latter is described in the V&V40 standard that was developed in a community effort between industry and FDA by the American Society for Mechanical Engineers (ASME 2018). The

momentum created by this effort has resulted in increased submissions of regulatory dossiers where in silico models are playing a key role – to the point of having in silico clinical trials replacing actual premarketing clinical trials on patients in selected cases (Faris and Shuren 2017). Despite the V&V40 being written in a very generic in silico technology-agnostic fashion, certain technologies require a dedicated approach. Adaptable AI algorithms that can learn from real-world data can evolve after regulatory approval has been granted. A specific strategy is therefore required to ensure the validity of these AI models, which is currently under discussion at FDA (FDA 2019). Driven by the progress on the devices side, regulators of pharmaceutical dossiers are extending the scope of the in silico tools in their regulatory process. In Europe, the VPHi is actively working with the European Medicines Agency to co-develop guidelines for the validation of in silico tools in the drug development pipeline (Musuamba et al. 2020). A good overview of in silico-related regulatory documents in EU and USA can be found in (Viceconti et al. 2020).

Policy

On the policy side in Europe, the targeted efforts of the in silico medicine community have resulted in the inclusion of in silico tools within the new Medical Device Regulation, as well as in the legal framework of the European Medicine Agency and the EU eHealth Action Plan. Rather than having one dedicated policy for in silico medicine, in silico medicine should be included in all policies related to, or having an impact on, health. In the USA and other countries, policy makers and legislators launched calls to action in the in silico and personalized medicine area. The advantage of the relative novelty of policies and regulations related to in silico medicine is that it could facilitate harmonization of (to be) adopted regulations and standards across the globe from their inception. Full convergence is likely to be unfeasible, due to the embedded nature of in silico tools in the various healthcare policy and regulatory systems. Clarification of the policy and regulatory landscape will have a snowball effect on the uptake of in silico tools in industry. Since the publication of its guidelines and standards work, FDA has seen a strong increase in the pre-submission inquiries involving computational modeling (Morrison et al. 2018).

In Silico Personalized Medicine: Current Challenges

There is a growing consensus across the healthcare sector that big data and digitalisation, including computer modelling and simulation, will allow to transform the healthcare of the future by providing tools to understand complexity of health and disease both on an individual and a population basis. The development, implementation and uptake of in silico models will facilitate an innovative, sustainable and high-quality healthcare, it will allow citizens to remain healthy for longer by allowing “personal health forecasting” and it will provide tools to tackle diseases

and reduce its burden for individual patients and society as a whole. To give a few examples related to upcoming revisions of EU regulations: with computer modelling and simulation in pediatrics, we can move to confirmatory clinical trials rather than exploratory – raising the bar for safety in trials with children. In orphan medicinal products, in silico models can vastly expand the potential trial candidates and improve understanding of rare diseases by running virtual trials as a support (augmentation) for traditional trials. In the field of ageing – a core priority for many nations worldwide – in silico models can help to better understand polypharmacy and make sure that we are preserving not just life but livelihood by better understanding the interaction of treatments and multi-morbidities. To fully exploit the potential of these new technologies in the area of personalized medicine, and despite the progress reported in the previous section, there are still many challenges to be tackled including challenges related to the technology and the community.

Current Challenges for In Silico Medicine

A number of these technology challenges are related to the data required to build the in silico models: FAIRification (making data Findable, Accessible, Interoperable and Reusable), data storage, data protection, ethics. Any model can only be as good as the data or mechanisms it is based on. Generation and curation of high-quality data as well as access to data that is collected in large repositories and databases is a necessary step to the successful implementation of in silico models. This data is not limited to electronic health records of individual patients but also pertains to data and tissues collected in biobanks and other collections. In order to maximize the use of these precious sources, actions are required to tackle the legal, economical and technologies barriers making it difficult to use and share them today. When (patient) data cannot be accessed directly or is insufficient to work with, "synthetic data" approaches could be used to recreate or enhance existing data, adding the advantage that anonymization can be built in into the data in a mathematical way.

Further development of the digital technologies themselves is essential including interoperability of the developed solutions, integration across scales and inclusion of the environmental influences (toxicology). The latter is particularly relevant in the scope of personalized medicine as it allows combine the societal dimension with the biomedical one (cfr., Bertolaso and Beneduce, Introduction in this volume). Most (bio)medical questions will require a range of digital technologies to be used to provide appropriate answers for patients and professionals, combining tools that start from data (AI, machine learning) with mechanistic tools that start from the insights in biomedical processes that were obtained by years of biomedical research. These hybrid approaches require further elaboration (and regulation), allowing for the direct crosstalk between known disease mechanisms with real world data.

Growing the Community

Additional challenges are related to the organization of the community producing the in silico tools, as well as to the uptake of these tools by healthcare professionals, patients, regulators and authorities. The definition of "Good Simulation Practice" (GSP), in analogy to "Good Clinical Practice" (GCP) or "Good Manufacturing Practice" (GMP), will provide a general guideline ensuring the generated in silico tools are reproducible, high-quality as well as appropriately verified and validated. The GSP not only for the industrial actors in in silico medicine, it will also benefit the scientific community. A full implementation of GSP, similar to a full regulatory approval, is not always necessary for academic settings, especially for the conception and elaboration of novel models and technologies. However, for more applied situations, implementation of certain elements of the GSP, similar to the creation of GMP-like testing conditions implemented at the end of the research phase in an experimental biomedical research lab, could elevate the quality of the field and increase the likelihood of clinical/industrial uptake of its tools.

Integration of in silico tools in clinical workflows is a very big challenge. Clinical workflows are well elaborated and therefore inclusion of additional elements will need to have a clear added value over and above the current state of the art, in terms of patient outcome, clinical ease of use and time spent on reaching clinical decisions. In the current high-pressure time-restricted clinical climate, inclusion of a new tool means that the tool needs to be adapted to the existing workflow or offered as a service that can be ordered in the same way a medical exam or a blood test can be ordered. In order to reach this uptake, the in silico medicine community needs to engage with its clinical stakeholders similar to how it is engaging with regulators and industrial partners. An additional element that is important in this context is the reimbursement of in silico services, requiring health economics arguments to show sustainability and engagement with payers and health technology assessment agencies. Last, but not least, patient acceptance of the use of in silico technologies can provide a strong drive to accelerate its uptake. Information and education tailored to the public at large, patients and citizens in general, needs to be provided.

Conclusion

In silico medicine has a definite role to play in tackling a number of challenges related to how biomedical research and healthcare are currently organized, including (but not limited to) the use of laboratory animals, multimorbidities, personalization of medical treatment and the increasing costs. In silico models allow to combine a variety of patient-specific information, both on the (internal) biological processes and the life style choices and exposure, with state-of-the-art medical knowledge on disease mechanisms and their trigger, in an integrative framework that will ultimately provide a holistic and personalized view of the patient. To reach its full potential – and hence contribute to the realization of personalized medicine

as a whole – in silico medicine requires the contribution of a wide variety of stakeholders amongst which academia, industry, patients, healthcare professionals, payers, regulators and policy makers. Organizations like the VPHi and the Avicenna Alliance play a key role in bridging the gaps between different in silico (technology) communities and between the in silico communities and their stakeholders. By bringing all the actors together in one big community, the field of in silico medicine as a whole can continue to grow and actively contribute to realizing the potential of personalized medicine.

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Part III

Personalized Healthcare: From Ethics to Policies

The last section of this volume is based on a wide-ranging groups of topics related to personalized medicine and healthcare issues and strategies, addressed by different perspectives: history of science and epidemiology, law, economics and ethics. The first two papers deal with some social and political factors that should be taken into consideration when addressing personalized medicine. More precisely, they highlight how those social and political concerns should substantiate the theoretical background for any improved discussion about "personalized medicine". The contribution by Xavier Guchet (Exposomics in the era of personalized medicine: A critical analysis) identifies one of the major problems with personalized medicine in its controversial capacity of taking into account epidemiology and public health concerns. Guchet points out a gap between ecogenetics and exposomics (the study of how genetic makeup affects the way organisms respond to environmental substances, and the study of how environmental exposure affects health outcomes). Issues of bioethics and biopolitics raising from personalized epigenetics are addressed by Silvia Caianiello's paper (Personalized epigenetics: Prospects and challenges). Reshaping personalized epigenetics in synergy with personomics (the incorporation of individual's preferences, values, goals, health beliefs, social support network, and unique life circumstances into diagnostic and treatment assessments) is the strategy proposed by Caianiello towards more comprehensive healthcare approaches. Concepts such as "exposomics" and "personomics", installed in the current limits of scientific knowledge and counting with a great projection, profit from a relational approach focused on contextual factors. Healthcare policies and strategies related to personalized medicine should be indeed also substantiated by strong ethical and bioethical reflections. Antonella Ficorilli's paper (Personalized medicine and research biobanking: From traditional to new informed consent generating a need for participatory governance) and Maria Rosaria Brizi's paper (Biobank research and data protection issues under the GDPR) address the topic of biobank research, which production is constitutively linked to personalized medicine. By interlacing ethics and law, the two papers deal with the latent conflict between the public interest in biobanking and the research subjects' interests. Accordingly, the two papers respectively reflect upon possible new models

of informed consent related to biobanks (broad consent and dynamic consent) and on the safeguards available to the donors of biological samples, in the light of the informational value that the samples do vest and of the subsequent risks that the donors may face in case of manipulation or abuse of their genetic profile. Yet, the use and interpretation of bio-medical data in a critical way is not only a matter of bio-ethics and law. From the viewpoint of an economist, Maria Sophia Aguirre's paper (Shedding light on the application of pharmacogenomics to the United States opioid crises: A relational approach) inquires on the use of opioids in the United States by applying a critical understanding of social dynamics. In the opioid epidemic, channels of relations can design effective prevention strategies and treatments. This shows again that an integral and relational understanding of the human being is essential to any successful attempt of fulfilling the aims of personalized medicine. As Aguirre shows, reductionist paradigms are not able to face complex healthcare scenarios. Personalized medicine is an imaginary, an expression of desire running counter to knowledge, exactly to the extent that it depends on reductionist assumptions. This ideal of personalized medicine dates back already to the Cartesian idea that "we might free ourselves from countless of diseases [...], if we knew enough about their causes [...]"[1]. Roger Strand points out so in the last paper of this volume (The impact of a fantasy). He stresses that citizens can improve practices of healthcare by destabilizing reductionist imaginaries. "New" conceptions of medicine, he adds, should take into account human vulnerability, often forgotten in modern civilizations. That relational view of "person" by which implementing *personalized* bio-medicine, technologies, and healthcare strategies, we thus argue, must acknowledge human vulnerability. Rather than deny this intrinsic condition of human being, personalized medicine will be most successful when it embraces our vulnerability. This embrace of human vulnerability exemplifies the relational perspective, insofar as it acknowledges the ways in which disease and illness is always shaped by a person's relationships to their environment, their social circumstance, biomedical and historical context.

[1] For reference to this quotation, see Strand in this volume.

Exposomics in the Era of Personalized Medicine: A Critical Analysis

Xavier Guchet

Introduction

In its current although restricted meaning, personalized medicine is mainly defined as the tailoring of diagnosis, prognosis and therapeutic choices to each individual patient, with regard to her/his unique biological (and mainly genetic) profile. To be sure, the individualization of diagnosis and therapies with respect to the genetic profile of a single patient is not new (Calabrese 1996); however, intensive technological developments boosted by the Human Genome Project in the 1990s (high-throughput DNA sequencing; high-density microarrays for gene expression analysis; bioinformatics) led us to hope that in a not too distant future, physicians would be more and more capable of prescribing "the right drug to the right patient at the right time".

Quite paradoxically however, the better biologists and physicians became equipped to carry out in-depth exploration of the human body (with increased capacity to highlight the molecular mechanisms of biological processes), the less they could undervalue the strong relationships between intracellular processes and the "environment" within which they occur – be it the close environment of the cell or the broad physical and social environment where the individual lives (Niewöhner 2011). Alongside the development of the so-called "-omics" technologies for mapping and studying the whole set of molecular interactions within the organism, at various levels of complexity (transcriptomics for RNA, proteomics for proteins, metabolomics for metabolic pathways), the urgent need for high-throughput molecular technologies to address the relationships between the individual and her/his environment became more and more obvious throughout the

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2000s. The term "exoposome" can be considered to be an answer to this challenge. The term itself was first coined in 2005 by cancer epidemiologist C.P. Wild (2005), who defined it as all that is not genetic, i.e., all that is "environmental". Exposomics is supposed to be the new science devoted to the study of the exposome. The term itself echoes the term genomics, defined as the extended structural and functional study of the human genome that the availability of the "-omics" technologies, as well as the development of bioinformatics, made possible. In his seminal paper, Wild lamented technological and financial over-investments in genomics – a situation that resulted, according to him, in an insufficient assessment of the non-genetic, environmental factors of diseases. Rappaport and his colleagues (2010) as well as Jones (2016), among others, made the same diagnosis: long after the completion of the Human Genome Project, funding has continued to be oriented towards genomics in order to improve the human genome map and to correct errors. It is time, these authors claimed, to shift the priority from genomics programs to extended studies of molecules other than DNA. In particular, metabolites directly unveil how environmental factors impact cellular functions and should prompt particular attention. Undoubtedly, exposomics is strongly related to "-omics" technologies, and current research projects mainly aim at combining these technologies with other ones (such as satellite data or geo-tracking) to better identify and characterize environmental factors at molecular level (Wild 2005, 2012; Rappaport and Smith 2010; Espín-Pérez et al. 2014). "In contrast to high-tech GWAS[1], searches for causal exposures have been limited to only a few hundred chemicals or mixtures and have relied upon low-tech methods, primarily questionnaires" (Dagnino and Macherone 2019). From now on, Exposome (or Environment)-Wide Association Studies (EWAS[2]) can take advantage of technologies which examine a significantly wider range of environmental factors.

The terms exposome and exposomics received little attention at first, but they have been prompting increasing interest since the end of the 2000s. A growing number of publications started to deal with the exposome, research projects were and still are generously funded (see for instance the European projects EXPOsOMICS, HEALS or HELIX), the European Commission even launched a "Human Exposome Project" within the European research and innovation program H2020.

At first glance, personalized medicine and exposomics apparently pursue opposite goals: while the former aims at making genomics pervade clinical settings, the second rather conveys the idea that non-genomic factors of diseases deserve careful attention. Wild's 2005 paper is unambiguous: far from being committed to a more individualized and personalized medicine, exposomics primarily aims at reinforcing

[1]Genome-Wide Association Studies aim at evidencing correlations between specific molecular patterns and disease phenotypes, by means of extended genome analysis that high-throughput technologies and bioinformatics have made accessible.

[2]In a nutshell, EWAS extend GWAS approaches to non-genetic factors. The aim of EWAS is to provide extended analysis on molecular networks linking environmental factors to intra-cellular signaling pathways.

public healthcare actions over the whole population. In this respect, exposomics is supposed to be nothing but the continuation of molecular epidemiology in the era of "-omics" technologies. However, things changed a few years after the publication of Wild's paper and, as Rappaport and his colleagues argued in 2010, "exposome technologies [will] provide feedback for therapeutic interventions and personalized medicine". The EXPOsOMICS project exemplifies this convergence insofar as the project explicitly refers to personalized medicine (Vineis et al. 2017): it proposes to combine data related to external pollutants (basically in air and water), data related to internal molecular pathways (obtained by means of "-omics" technologies) and data related to individual behaviors, with the aim of validating a more individualized approach to "exposure assessment". And as the Welcome Letter of the HEALS project claims, "HEALS proposes the functional integration of -omics derived data and biochemical biomonitoring to create the internal exposome at the individual level". Undoubtedly, the combination of epidemiology and individualized patient care is nothing new; however, exposomics recently gave extended significance and technological possibilities to this crossing.

Why did this convergence between personalized medicine and exposomics occur? A possible answer is that exposomics was welcomed to provide the promoters of personalized medicine with relevant arguments for countering some serious criticism which they had faced in the mid-2000s. In other words, exposomics was supposed to help those who champion personalized medicine to extend its "moral economy", and to make it assimilate perspectives that were considered missing by critics.

This article proposes an analysis of this convergence between personalized medicine and exposomics, of its main significance and of its limits.

Personalized Medicine and Its Moral Economy

Unsurprisingly, the expression "personalized medicine" was not in use before the end of the 1990s. As a molecular technology-based medicine, it was first coined in a 1999 paper published in the *Wall Street Journal*, then republished in *The Oncologist* a few months later (Landgreth and Waldholz 1999). Admittedly, a previous occurrence can be found in a 1971 paper written by a physician who worried about the vanishing of the traditional doctor-patient relationship: personalized medicine, he foretold, was threatened by the rise of a more a more technoscientific and overspecialized medicine, leaving less and less room for listening and dialogue in the doctor's office (Gibson 1971). Thus this physician lamented that personalized medicine was doomed to be replaced by a more impersonal, technology-based medicine. At the end of the 1990s, the expression "personalized medicine" increasingly connoted (conveyed?) ideas such as "revolution", "paradigm shift", "big data" – in a nutshell, it was considered the medicine of the future, not of the past.

The 1999 paper was about the creation and the functioning of a consortium that gathered around ten of the most important pharmaceutical companies, IBM,

Motorola, five academic research centers and the British Wellcome Trust. The main goal of this consortium was to map the single nucleotid polymorphisms (SNPs) that could be found in the genome of most people, and to identify those which impacted drug response. In the early 2000s, more than 1.5 million common SNPs were identified. As a matter of fact, the existence of correlations between genetic variants and drug response gained evidence long before the Human Genome Project, in the 1950s (Motulsky 1957). The term "pharmacogenetics" was coined in the early 1960s by a German geneticist, F. Vogel, to label this new research field (Kalow 1962). The sequencing of the human genome in the 1990s and the development of high-throughput technologies for molecular analysis gave a new momentum to this research area, and brought it to more extended studies of gene-drug correlations, giving rise to "pharmacogenomics". In the mid-2000s, GWAS gave hope that soon, patients would be cured more and more accurately thanks to an increasing capacity to screen and analyze their whole genetic profile. Admittedly, "personalizing" medicine did not mean to design a specific drug for each single patient; it rather meant that from then onwards, patients could be classified according to their genetic features, dividing them into three categories, namely good, non- and bad responders to existing drugs. In this respect, the expression "stratified medicine" has been considered more suitable than "personalized medicine" to label the promise for more refined drug prescriptions.

This promise relied on several claims that fed the booming of personalized medicine, shaping its "moral economy". In the mid-1990s, science historian Lorraine Daston coined the term "moral economy" to highlight the close intertwining between science and values (Daston 1995). Daston defined it as a web of values and affects that explains "how scientists at a given time and place dignify some objects of study at the expense of a great many others, trust some kinds of evidence and reject other sorts, and cultivate certain mental habits, methods of investigation, and even characters of a distinctive stamp".

The moral economy of scientists refers neither to their individual motivations, nor to ideologies that pervade society. Claiming that either motivations or ideologies impact science, Daston argued, does not really challenge the clear-cut divide between scientific work on the one hand, and values and affects on the other. The permeability of the former with regard to the latter remains superficial, and the focus on both motivations and ideologies does not stand in contradiction to the traditional definition of science as a value-free activity. On the contrary, the concept of "moral economy" implies that the epistemological framing of a scientific field always as a moral significance per se.

Although personalized medicine gathers numerous scientific communities that relate to different moral economies (biologists, geneticists, biocomputer scientists, statisticians, clinicians, etc.), there is some evidence that a few general claims, pervading the whole range of scientific approaches to personalized medicine, can serve to identify a moral economy of personalized medicine as such. Two major elements should be mentioned here.

First, the widespread idea that both medical epistemology and patient healthcare organization are facing a major paradigm change, namely a shift from the so-

called organ medicine to a molecular medicine. Each sick individual is supposedly characterized by a very specific molecular signature, whatever the organ within which his/her disease is located. From now on, lung cancer for instance is divided up into more than ten diseases: each of them evidences a specific molecular signature that makes it a very different disease than another lung cancer with a different signature. Conversely, two types of cancer that are located in different organs (for instance, lung and colorectal cancers) may evidence very similar molecular signatures, leading to the same patient healthcare strategy: providing that a targeted therapy is available, this therapy should be efficient for treating both types of cancer. Thus, bringing the fallouts of "-omics" technologies and bioinformatics into care settings is expected to prompt deep reconfigurations within nosology (i.e., disease classification and description) as well as within patient care.

Secondly, the main objective of personalized medicine appears to be the identification of "actionable" targets, i.e., molecular alterations for which a drug already exists. Some scholars claim that this search for "actionability" has become a priority (Nelson et al. 2013), overriding more classical approaches to diseases focusing on risk factor and risk assessment, and also overriding the efforts to identify and explain the pathophysiological mechanisms that are involved in diseases. For instance, sociologist Pascale Bourret and her colleagues (Bourret et al. 2013) highlighted the shift from risk factor approaches to "actionability" ones in a paper that examines how studies devoted to BRCA-1 and BRCA-2 (two genes for which several mutations had been identified to predispose women to develop breast cancer with very high probability) have changed their priority in the 2000s. In the previous decade, investigators intended to identify mutations on both genes that placed women at very high risk of developing breast cancer. In the following decade, the priority became to identify "actionable" mutations, i.e., molecular anomaly on BRCA-1 or BRCA-2 for which a drug existed.

On the basis of these two doctrinal pillars that shape its general moral economy, personalized medicine provoked severe criticism in the mid-2000s. Two main arguments have been put forward.

First, personalized medicine was accused of demonstrating duplicity. Indeed, how can a medicine that primarily aims at bringing the fallouts of high-throughput technologies for molecular analysis and bioinformatics into care settings be really considered a "personalized" medicine? There is strong evidence that this kind of technoscientific medicine, rather than being centered on the "person", increasingly disregards the patient as a whole subject, silencing her/him when he/she claims what her/his own preferences and values are. Far from being more "personalized", personalized medicine was accused of accentuating the objectifying and molecular turn of Western medicine, threatening the uniqueness of the patient-doctor relationship (Cornetta and Brown 2013). As a matter of fact, a rival term has gained increasing attention in past years: precision medicine. This alternative expression was probably motivated by the will to overcome the ambiguity of personalized medicine with regard to the term "personalization".

Secondly, insofar as personalized medicine primarily focused on "actionability" i.e., "druggability", it was accused of being above all at the service of Big Pharma

companies. It has been considered an invention of the pharmaceutical sector, allowing it to overcome the thorny pitfalls it had to face, and in particular a very high rate of failures in clinical trials (in the 2000s, around 95% of tested molecules failed to reach the market). Two other pitfalls have been pointed out: the inefficiency of existing drugs, reaching the astonishing rate of 75% for certain diseases (Paci 2013), and the existence of damaging adverse effects caused by a significant number of drugs. Some considered personalized medicine nothing more than a strategy to help pharmaceutical companies to solve these problems, and to develop new and very profitable markets. Roche is sometimes credited with having invented the concept of personalized medicine as such, insofar as in 1998 the company brought to the market an anti-breast cancer drug with pharmacogenetics indications (Herceptin®). This drug is usually considered the first targeted therapy. In this respect, the concept of personalized medicine is often accused of above all serving the interests of Big Pharma companies, instead of serving the general interest of the overall population. Indeed, targeted therapies are very expensive and it is widely admitted that public health insurance systems will fail to support their costs. Moreover, health inequality issues have been highlighted: will these innovative therapies be accessible to the largest number? These issues have been put at the forefront of controversial debates in the past years, and have gained strong ethical significance (Fleck 2014).

Furthermore, both aforementioned pillars of personalized medicine (namely the dismissal of organ location approaches and the "actionability" paradigm) faced limits and difficulties.

First, the shift from an organ-centered medicine to approaches based on molecular signaling pathways is far from being achieved. To date, the former is still relevant and even irreplaceable. In the past decade, innovative cancer trials were launched worldwide, precisely with the aim of validating molecular signature approaches versus organ-centered approaches to patient care. The results of these trials are rather disappointing: no real benefit to patients has been demonstrated (Tannock and Hickman 2019; Jordan 2019). Furthermore, it was found that using the same targeted therapy (namely an anti-EGFR monoclonal antibody) to treat metastatic colorectal cancers with different locations in the colon, led to uneven results (Moretto et al. 2016[3]). The efficiency of the drug may strongly vary according to the organic location of the tumor and as a consequence, the latter remains an impacting characteristic that has to be taken into account.

Secondly, it has been acknowledged that "actionability" approaches could not replace mechanistic approaches. Indeed, according to the so-called "Russo-Williamson" thesis, there is rather a strong need for better combining both correlation-based and mechanistic investigations into diseases (Russo and Williamson 2012; Clarke et al. 2014). The search for "actionable" targets, through the identification of statistically significant correlations, does not suffice to improve patient care: significant advancements in biomedical knowledge about diseases are required.

[3]The paper highlights "the potential role for primary tumor location in driving treatment choices".

Exposomics to the Rescue of Personalized Medicine

In this context, strong interest and great enthusiasm were aroused concerning two new concepts in the 2010s: epigenome and exposome. The concept of epigenome refers to the whole set of mechanisms that regulate and modify gene expression without altering the DNA structure (such as DNA methylation or histones modification). The concept of exposome is usually defined as "the measure of all the exposures of an individual in a lifetime and how those exposures relate to health. An individual's exposure begins before birth and includes insults from environmental and occupational sources. Understanding how exposures from our environment, diet, lifestyle, etc. interact with our own unique characteristics such as genetics, physiology, and epigenetics impact our health is how the exposome will be articulated" (Centers for Disease Control and Prevention 2014). A popular expression summarizes this ambition to exhaustively measure the exposures that affect an individual throughout her/his lifetime: individuals have to be scrutinized "from the womb to the tomb". Admittedly, the exposome covers a wider range of phenomena than the epigenome, but in both cases, the environment is similarly highlighted as a very influential factor, having a strong impact on human health at the molecular level.

The success that these two concepts encountered can be explained by the quite modest – not to say disappointing – results of Genome-Wide Association Studies. Due to intensive developments in molecular technologies (high-throughput DNA sequencing, high-density microarrays) and bioinformatics since the mid-1990s, the study of how genetic alterations and induced gene expression modifications impact diseases had gained extended accuracy and exhaustiveness. However, despite the considerable investments and efforts that have been granted to pangenomic studies, to date very few correlations of statistical importance between genes and genetic expression on the one hand, and pathological phenotypes on the other, have been evidenced. In this context, it has become more and more obvious that genes and gene expression explain a very low percentage of pathological phenotypes: non-genetic factors had to be identified in order to explain diseases. "Results from roughly 2000 GWAS have found only modest effects of common genetic variants. [...] Thus, it is reasonable to infer that exposures and gene–exposure interactions are the major causes of cancer and other chronic diseases" (Dagnino and Mecherone 2019). As Ken Olden, who was director of the *National Institute of Environmental Health Sciences* in the 1990s, metaphorically claimed, "genes load the guns, the environment pulls the trigger".

Undoubtedly, the critical role of environment in the etiology of diseases had been highlighted for a long time, but dramatic improvements in molecular technologies, allowing researchers to analyze small molecules (such as proteins and metabolites), deeply reconfigured the field of environmental sciences from the 1990s, and brought them to refocus their research programs towards the study of molecular mechanisms that link environmental factors to intracellular processes (Shostak 2013). Environmental factors that have still to be determined modulate gene expression as well as

transcriptional, translational and post-translational mechanisms, leading to dramatic changes in enzyme and protein activity. Complex diseases result from these changes. Furthermore, it is now widely acknowledged that both genetic and environmental factors do not act separately: diseases emerge from their close intertwining. Nature and nurture cannot be considered as separate any more (Miller and Jones 2014). As a consequence, the term "environment" has no clear delineated perimeter: it covers a wide range of factors, such as intra-organic processes (in particular those related to the microbiota); pollutants in air, water or food; lifestyles; exposure to noise as well as to magnetic fields, and also to phenomena that prove hard to quantify, such as psychosocial stress or even the quality of social interactions.

As noted above, despite the fact that exposomics and personalized medicine seem to have taken two opposite ways, both converged in the early 2010s. A possible hypothesis would be that this coming together of personalized medicine and exposomics proved to be strategic for the former. Indeed, exposomics was welcomed to provide it with relevant arguments for both countering the aforementioned criticism, and overcoming the limits personalized medicine faced.

While personalized medicine was accused of being an invention of industrialists in search of new markets and huge profits, its extension towards exposomics is supposed to invalidate this diagnosis: personalized medicine above all feeds the ambition to apprehend the whole range of factors that may affect the health condition of each individual, with the aim of identifying what can be done at a political level to protect each of us against these deleterious factors. Far from being a mere servant of Big Pharma companies, personalized medicine is pervaded with strong public healthcare concerns. Indeed, the goal of exposomics is not to favor the individual level of analysis, to the detriment of epidemiological studies at the population level: it rather aims at combining both an individual approach to diseases, leading to risk assessment and personal monitoring, and investigations into the population's health. In this respect, exposomics is "about how exposures in the natural, built, social, and policy environments get under the skin to affect personal health outcomes and contribute to population-level health disparities" (Dagnino and Macherone 2019). In 2016, the French National Assembly approved a law to modernize the national healthcare system. The legislator considered that healthcare policy was above all about improving the monitoring of the population's health and the identification of its major determining factors, and to this end, the concept of exposome – the legislator claimed – could be a guiding one. Thus, connecting personalized medicine to exposomics could appear to be a strategy for bringing public healthcare concerns within the perimeter of the former. Far from dismissing the social determinants of health at the population level – as it was accused of doing–, personalized medicine focuses on the whole set of relationships that link the individual to his/her environment, with the aim of highlighting the mechanisms that explain how these complex relationships may impact individual health. The final purpose of personalized medicine is not to boost Big Pharmas, but to improve policy makers' capacity to intervene on the determining factors of individual health and that of the population as a whole.

Furthermore, connecting personalized medicine to exposomics could also provide arguments to counter the accusation of objectification and reductionism. Indeed, while personalized medicine has been accused of molecular reductionism and geno-centrism, the holistic ambition of exposomics provides it with a counter-argument. Holism seems to be the new motto of those who champion personalized medicine. In this respect, the spectrum of factors that exposomics is supposed to cover is constantly expanding. A new concept, the "environtome", has been coined by V. Özdemir, chief editor of *OMICS: Journal of Integrative Biology*. The environtome seems to have a wider perimeter than the exposome as it is currently defined, even though both terms refer to the same reality (Özdemir et al. 2017). Indeed, as Özdemir claims:

> we define "environtome" as the entire complement of elements external to the human host, from microbiome, ambient temperature and weather conditions to government innovation policies, stock market dynamics, human values, political power and social norms that collectively shape the human host spatially and temporally.

When personalized medicine becomes connected to exposomics, it can display some evidence that it does not reduce human beings to their molecules any more. On the contrary, it claims to grasp them in their entirety, including the whole spectrum of social norms and values that shape their individual existence. The thorny issue of this ambition is to find a way for articulating all these heterogeneous data in a unique and robust explanatory model – a problem that remains to be solved. "How to assess and quantify these exposures in epidemiological studies to allow for more comprehensive understanding of a person's environmental exposure remains [in 2019] a significant challenge" (Dagnino and Macherone 2019).

To conclude, exposomics seems to be expected to help personalized medicine overcome the disappointing results of GWAS: focusing on environmental factors, as well as on the molecular mechanisms that relate them to disease, is supposed to result in better understanding the pathophysiology and in more efficient therapies.

Rival Approaches to Exposomics

It is however possible that this strategic alliance between personalized medicine and exposomics may lead to some ambiguity and misunderstanding. Actually, those who promote the development of exposomics do not share the same definition of the exposome; yet these conflicting views about the exposome are not only of epistemological, but also political significance.

In 2012, Wild made a clear-cut distinction between:

> three broad categories of non-genetic exposures: internal, specific external and general external [...] First, the exposome comprises processes internal to the body such as metabolism, endogenous circulating hormones, body morphology, physical activity, gut microflora, inflammation, lipid peroxidation, oxidative stress and ageing. These internal conditions will all impinge on the cellular environment and have been variously described as host or endogenous factors. Secondly, there is the extensive range of specific external

> exposures which include radiation, infectious agents, chemical contaminants and environmental pollutants, diet, lifestyle factors (e.g., tobacco, alcohol), occupation and medical interventions. In the past, these have been the main focus of epidemiological studies seeking to link environmental risk factors with cancer. Thirdly, the exposome includes the wider social, economic and psychological influences on the individual, for example: social capital, education, financial status, psychological and mental stress, urban–rural environment and climate. (Wild 2012)

As a matter of fact, Wild's distinction between internal, specific external and general external exposures is not consensual. Contrary to Wild, Rappaport and his colleagues rather propose a rival conception of the exposome. According to them, external factors (be they specific or general) deserve attention only if they have a strong repercussion within the organism. The exposome should not be defined extensively as everything we are exposed to, but in a more specific way as everything we are exposed to and that affects our health. These effects on health find evidence in metabolic changes and consequently, the exposomics should be understood as the comprehensive study of these changes. Rappaport and his colleagues define the exposome as the response of the organism to environmental exposures (Rappaport and Smith 2010; Rappaport 2011).

Two rival approaches to the exposome take shape here: a bottom up approach, focusing on the measurement of all exposure factors (be they internal, specific external or general external) with the aim of evidencing how they relate to intracellular metabolic pathways (Wild); a top-down approach of which the aim is to measure all the chemical substances that can be found in the blood, and that are supposed to reflect how the organism responded to exposures (Rappaport). In the latter approach, attention is paid to biomarkers that evidence this response: "intermediate biomarkers directly or indirectly represent events on the continuum between exposure and disease. Intermediate biomarkers can provide important mechanistic insight into the pathogenesis of environmental diseases" (Vineis et al. 2009). To be sure, this perspective gives rise to a thorny difficulty: some exposure factors, such as stress, noise or magnetic fields for instance, cannot be easily matched with specific molecular biomarkers within the organism (Peters et al. 2012).

It is worth noting that neither bottom-up nor top-down approaches to the exposomics raise epistemological or methodological issues only, but that they also give rise to rival political stances. On the one hand, the distinction between internal, specific external and general external exposures may seemingly lead to taking into account public health policy concerns, insofar as it focuses on exposure factors (in occupational settings or in the whole society) that are subject to political intervention with the aim of protecting people; on the other hand, top-down approaches possibly lead to a purely technical significance of epidemiology, focusing on the quantification of data at the individual level.

As a matter of fact, this situation looks a little bit paradoxical with regard to French philosopher George Canguilhem's analysis of the concept of "milieu" (Canguilhem 2008). Indeed, Canguilhem strongly emphasized the political significance of the divide between two rival understandings of the term "milieu": the milieu can

be defined in a purely mechanistic way; in this respect, it conveys an understanding of the living organism that is deprived of any biological significance: the living being proves to be the focal point of factors that affect it through cascades of physicochemical interactions. This mechanistic understanding requires technical interventions on the milieu with no consideration at all for what Canguilhem called the "vital values" of the living being. Conversely, the milieu can be defined as everything that has biological significance for the living being – for instance, as von Uexküll pointed out, the milieu of the tick is limited to three signals that command its vital behaviors (von Uexküll 2010). As Canguilhem noted, considering that hedgehogs should not cross the road if they do not want to be run over by cars is misleading: actually, the road has no biological significance for hedgehogs, it does not exist in their milieu. Canguilhem concludes that hedgehogs do not cross the road: it is better to say that the road crosses the milieu of hedgehogs. The living being behaves with regard to vital values and any human intervention on the environment has to be assessed with regard to how, and to what extent, it impacts the milieu of a given living species. As a matter of fact, the Wild-Rappaport debate related to exposomics seems to turn Canguilhem's analysis: on the one hand, the divide between the internal and the external may lead to a mechanistic account of the environment, insofar as it invites us to pay attention to the continuum of events that link the external to the internal. In any case, Wild's approach remains focused on epidemiological and public health policy concerns and in this respect, it preserves the possibility of supporting a critical perspective on how social and political choices, resulting in individual exposures to damaging factors, may affect human health. On the other hand, Rappaport and his colleagues defend a biological approach to the organism, insofar as they focus on how the latter shapes a global response to environmental exposures. However, the top-down approach is in danger of prompting a depoliticized intervention strategy: the target of interventions are not exposure factors as such, but their corresponding molecular effects within the cellular processes.

To summarize, it is far from evident that exposomics can provide personalized medicine with the relevant arguments that would allow it to counter the criticism it has to face. Indeed, exposomics itself refers to a couple of rival models of what studies on genes-environment interactions should be: a public healthcare model and a biomedical one. Most of all, exposomics aims to hang these two models together, and to put the technological capacity to acquire and process data of all kinds, in particular molecular data, at the service of public health policy. "The exposome is perhaps the biggest of the big data entities, whose characterization will require advanced computation, bioinformatics, and statistics. And finally, as combined GWAS/EWAS lead to discoveries of causal exposures and gene–exposure interactions, public health professionals will be able to develop interventions for reducing disease risks" (Dagnino and Macherone 2019).

Two Models for Exposomics as an Environmental Health Science

It is worth noting that exposomics, combining "-omics" technologies, biomarker research and exposure science (Canali 2020), has inherited some of the tension that has underlain the whole history of environmental health sciences (EHS) for the past decades. As sociologist Sara Shostak (2013) pointed out, the two main disciplines of EHS, namely epidemiology and toxicology, respectively come from two very different approaches to how environmental factors impact human health. First, the "sanitary engineering" approach, which is field-based, collects data in situ and aims to reconfigure built environments in order to make them less harmful for human health. This approach led to epidemiology. Second, the "industrial hygiene" approach, which is laboratory-based and aims to evidence, by means of in vitro studies or studies using animals, the mechanisms that link chemical exposures to pathophysiology. This approach led to toxicology. The institutionalization of EHS in the United States at the end of the 1960s (creation of the National Institute of Environmental Health Sciences, NIEHS, in 1969; creation of the Environmental Protection Agency, EPA, in 1970) was primarily oriented towards public health concerns, focusing on population-level rather than individual-level interventions. At that time, studies on how genes and environment interact took two different directions, but both addressed public and not individual health issues.

The first one focused on the variability of individual responses to environmental exposures. In the beginning of the 1970s, it was admitted that this variability should be explained, at least partly, by genetic differences. This approach was labeled "ecogenetics". This term was first coined by geneticist R. Brewer who claimed in a short text (Brewer 1971) that a given environment has no unique effect on those who are exposed to it: some people will develop pathological phenotypes, other will not. It was well known at that time that these differences in individual responses were partly due to distinctive genetic characteristics. The correspondence between genetic profile and responses to environmental factors was evidenced in the 1950s for drugs (which are a particular class of environmental factors). When Brewer coined the term ecogenetics, he undoubtedly had the model of pharmacogenetics in mind: as he explained in his 1971 paper, ecogenetics is nothing but the extension of pharmacogenetics to factors other than drugs. Although it focused on individual genetic differences, ecogenetics was above all commanded by a public health perspective. As Shostak claimed, "Ecogenetic researchers thus expanded the focus of research on genetic control of the metabolism of chemicals beyond the clinic, to the factory and the community, domains under the jurisdiction of public health research, practice, and policy making" (Shostak 2013, p. 80).

The second approach to studying gene-environment interactions focuses on DNA mutations caused by exposures to radiations, but also to chemical compounds that can be found in the environment. Sociologist Scott Frickel (2004) demonstrated that a new discipline – namely "genetic toxicology" – which appeared at the end of the 1960s, favored a complete redefinition of the concept of "chemical mutagens", on both epistemological and political levels. Since the 1940s, chemical mutagens

were used as laboratory tools for studying DNA and genetic heredity. In the 1960s, they were progressively reconsidered as environmental risk factors, capable of causing heritable damage to DNA structure. As Frickel convincingly argued, genetic toxicology was related to the environmental movement which gained political significance in this period. It did not focus on individual and clinical issues, but on population health concerns.

It is worth noting that none of these developments in the study of gene-environment interactions (ecogenetics and genetic toxicology) led to the "geneticization" of the EHS, i.e., to the idea that issues related to environmental exposures could be considered in purely genetic terms, leading to biomedical interventions on diseased individuals. The biomedical shift of the EHS occurred later, in the 1980s and especially in the 1990s. Shostak explained why this shift happened. At the end of the 1990s, it was widely admitted that many diseases were genetic phenomena. In this respect, it was expected that science would provide an accurate account of molecular mechanisms linking exposures to genes. Yet, the EHS traditionally focus on environmental determinants of diseases, outside the body. They were not equipped for scrutinizing the underlying molecular mechanisms of diseases, inside the body. As a consequence, they were considered of lesser importance than other disciplines. The shift of the EHS towards molecular biology and related technologies was supposed to help them enhance their credibility, and better fit the "molecular turn" of biomedicine. While the EHS were traditionally oriented towards public health, they undertook a significant shift towards a more biomedical model, turning their attention to intra-bodily molecular processes.

The *Environmental Genome Project* (EGP), which was launched in the 1990s, illustrates the biomedical shift of the EHS. In a paper dealing with the ELSI (Ethical, Legal, Social Impacts) issues of this project, R. R. Sharp and J. C. Barrett, from NIEHS (Sharp and Barrett 2000), highlighted common bioethical concerns such as the protection of research participants, informed consent, discriminatory use of genetic information, difficulties in adopting a recommended lifestyle, gene modification for better responding to environmental risk factors. A short paragraph at the end of the text underlined the risk of reducing social issues to biological ones, but inequalities with respect to environmental exposures (which more strongly impact the minorities than the upper classes) were not even mentioned. Environmental justice was apparently not the priority of the EGP.

The shift of the EHS from a public health model towards a more biomedical model prompted much criticism in the 2000s. Some observers lamented that genomics was used much more with the aim of identifying individuals at risk (and also to help Big Pharmas develop new markets), than with the aim of reducing health inequalities and helping to solve environmental justice issues (Olden and White 2005). Shostak was told by an epidemiologist she interviewed: "if you have an individual who is in the workplace and is exposed to an agent in the workplace that could be very toxic, if it's metabolized and converted to a more toxic metabolite, then you might intervene with another agent that would inhibit that enzyme. That's frequently done in clinical medicine" (Shostak 2013, p. 119). According to environmental justice activists, the molecular shift of the EHS may

result in a significant loss: making social determinants of health inequalities less visible and, as a consequence, turning policy makers away from interventions on deleterious aspects of the social environment, in favor of biomedical interventions on "actionable" molecular targets inside the body.

It is worth noting however that it was less a question of the EHS abandoning the public health model, than intending to combine biomedical and public health models (Omenn 2000). As a matter of fact, exposomics has been influenced by this attempt to better articulate both perspectives.

The public health perspective can be illustrated by two research projects that were both led in the last decade, namely LIFEPATH and IBISS.

The LIFEPATH project (2015–2019) aimed to take advantage of "-omics" technologies to "improve the understanding of the mechanisms through which healthy ageing pathways diverge by socio-economic status" (SES). In other words, the goal of the project was to accurately evidence the molecular mechanisms underlying the correlation between inequalities in SES and diverging individual health-trajectories.

The IBISS project (2013–2016) seemingly aimed to take advantage of molecular technologies (a) to evidence how early psychosocial exposures modify biological processes and lead to diseases; (b) to identify which mechanisms are at stake here; (c) and finally to demonstrate that differences in exposure can explain social inequalities in health.

As a matter of fact, molecular technologies and bioinformatics may be put at the service of a critical epidemiology, made capable of providing policy makers with strong mechanistic arguments that some exposures are deleterious to human health. "External exposure assessment provides the possibility to precisely pinpoint the environmental sources of disease-causing exposures, which is vital for effective public health intervention and prevention strategies" (Dagnino and Macherone 2019, p. 257). Thus, exposomics "may help to inform researchers and policy makers of the cumulative risk in [ethnic minorities and low-income communities] and could be used to monitor the impact of interventions aimed at mitigating inequities in exposure to environmental stressors" (Dagnino and Macherone 2019, p. 5). Exposomics provides tools for identifying the mechanisms that lead to health inequalities with great accuracy: "more importantly perhaps, exposomics could provide clues as to the mechanisms behind these adverse interactions allowing for effective interventions" (Dagnino and Macherone 2019, p. 5). In this respect, Juarez and his colleagues (2014) proposed an approach labelled Public Health Exposome, of which the goal was to measure the impacts of environmental exposures on individual health, on population health as well as on health inequalities.

The biomedical perspective can be illustrated by the evolution of ecogenetics from Brewer's 1971 paper to date. In 2006, Costa and Eaton edited a voluminous collective book that claimed to cover all the aspects and issues related to the intertwining of gene expression and environment (Costa and Eaton 2006). The term "exposomics" is not mentioned, it probably still lacked widespread recognition at that time. The rival term that the authors put forward was "ecogenetics", which is considered to be nothing but the extension of pharmacogenetics (in the same

way as Brewer considered it). "The extrapolation that genetic variations would be expected to affect responses to any kind of environmental and xenobiotic agent, not just drugs, led to ecogenetics". There is however a major difference between Brewer's paper and the 2006 collective book positioning. In the latter, ecogenetics is presented in a close relationship to a particular class of genetic variants, namely single nucleotid polymorphisms (SNPs). SNPs are mutations on a single nucleotid, resulting in the change of a unique base. In the 1990s, SNPs were identified as mutations of particular interest, due to the impact that some of them were supposed to have on drug metabolism and efficiency. In this context, pharmacogenetics research programs focused on the correlations between response to drugs and SNPs (more precisely common SNPs). In the 2006 book, ecogenetics is presented as a way to give more extension to this approach by means of new technological methods, in particular "-omics" methods, for evidencing actionable correlations between exposures, SNPs and individual phenotypes. In line with this perspective, exposomics aims to enrich the spectrum of the various methods that would allow these correlations to be identified. Thus, a sort of continuum seems to link pharmacogenetics, ecogenetics and exposomics, suggesting that exposomics continues the critical questioning of Brewer's paper and brings it into personalized medicine.

Unfortunately, this is far from being the case. Indeed, despite the fact that Brewer also focused on genetic variants and correlations between those variants and the effects of environmental exposures on individuals, just as the contributors to the 2006 book do, his general philosophy was very different from that of Costa and Eaton. Brewer asked: "are human geneticists seriously neglecting an area of involvement in which all scientists have a responsibility and in which human geneticists should have some expertise, that is, the interaction of man and his environment?" He continued: "many people, including many scientists, believe that we are facing an environmental crisis of such proportions that our very existence is threatened" (Brewer 1971). Ecogenetics is understood here as the contribution of human geneticists to the collective effort to solve the environmental crisis industrial societies were facing, and still face. Ecogeneticists are dedicated scientists, they worry about the future of the planet. They are committed to providing citizens and policy makers with accurate knowledge on how industrialization and related social and political choices dramatically affect our health. Ecogeneticists are less interested in the relationships between *genes* and environment, than in the relationships between *humans* and their environment. According to Brewer, humans shape their environment by means of technology and in the industrial context, their technological activity resulted in the proliferation of pollutants and other damaging factors that affect human health. Beyond human life, what is at stake today is the existence of life as such on earth.

It is worth noting that Brewer's conception of the environment is not very different than that of Canguilhem: for both, humans shape their environment according to values that are embedded within technology, and that may conflict with vital values, threatening the very existence of humans as living beings (and also the existence of other living beings). Thus, for Brewer ecogenetics should provide

informed arguments for questioning our social and political choices at a global scale. It is worth noting that environmental justice activists assign the same meaning and goal to EHS: "questions about how we organize ourselves as a society, questions about corporate accountability, social and environmental justice, questions about who bears the burden of industrial society? [. . .] Questions about what is progress, what is technology and when do we stop? When is it enough?" (Shostak 2013, p. 192).

Costa and Eaton's 2006 book gives the impression of abandoning this critical perspective. From now on, the approach seems to be considered as purely technical, focusing on relevant and actionable biomarkers for individual monitoring. As early as the 1980s, environmental health scientists lamented that ecogenetics had become primarily devoted to "[examining] the relation between genetic markers and disease without regard to environmental determinants" (Khoury et al. 1988). In the same vein, Exposomics can prove to be annexed to industrial interests and achievements, and in this case any kind of critical perspective would be removed from it. To some extent, pharmacogenetics took this direction: in the first place, it served to define personalized medicine and was undoubtedly supported by Big Pharma companies. As a matter of fact, pharmacogenetics gave the latter new opportunities for increasing their profits. The question of how environmental exposures impact our health, leading to political action to change the environment, may prove to have less priority than the identification of actionable, i.e., "druggable", molecular targets.

Conclusion

From the mid-2000s onward, conflicting debates around personalized medicine have mainly focused on the questionable capacity of this supposedly new medicine to better consider the uniqueness of each patient. To be more precise, it was widely admitted that increased capacity to evidence and study specific molecular patterns that make each disease unique would lead to more individualized healthcare pathways. It was not so obvious however that assigning a very specific molecular signature to each disease sufficed to support the claim that medicine was becoming more and more personalized. Indeed, opponents to personalized medicine claimed, an individual cannot be reduced to her/his molecules. A truly personalized medicine should rather aim at better taking into account the patient as a subject in a whole care setting.

My intention through this paper has been to shed a different light on personalized medicine. It seems that the major problem of personalized medicine is not related to its person-centeredness ambition, but rather to its controversial capacity to really take into account epidemiological and public health concerns, and to provide policy makers with improved knowledge of how social determinants mechanistically impact individual health. The coming closer of personalized medicine and exposomics precisely puts this challenge in the foreground, and makes the personal-impersonal issue less relevant.

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Personalized Epigenetics: Prospects and Challenges

Silvia Caianiello

Introduction

Personalized medicine, in the widest sense of the translational program of tailoring prediction, preventative and therapeutic intervention on the individual patient, has been "first coined in the context of genetics" (Zhang et al. 2015) and has initially relied mostly on the detection of genetic variants.[1] Shared genomic signatures proved more reliable and mechanistic than former epidemiological criteria for stratifying populations in cohorts according to distinct disease risk profiles and drug-response, and made pharmacogenomic profiling possible (Evans and Relling 2004). Actually, personalization is first and foremost an outcome of big data science (Green et al. in this volume), of large-scale genome-wide screening programs aimed at detecting associations between DNA variants and disease phenotypes at the population level (GWAS, or Genome-Wide Association Studies; Feinberg 2018). Particularly polygenic risk score estimates (PRS), established by GWAS like the 1000 Genome Project launched in 2007, promised to be good predictors for complex disease phenotypes (Cichon et al. 2009; Visscher et al. 2012, 2017).

However, it was soon clear that even accounting for lower effect variants at multiple loci did not significantly reduce the amount of "missing heritability"

[1] On the different definitions of *precision*, *personalized*, *individualized* and *stratified* medicine, see Pokorska-Bocci et al. (2014).

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(MacArthur 2008; Kilpinen and Barrett 2013; Carlberg and Molnár 2019). The predicted increase in accuracy expected from the development of cost-effective whole-genome sequencing techniques, as well as from third-generation sequencing progress in longer and more significant reads (Schadt et al. 2010; Marx 2013), is expected to raise the score of genetic heritability of disease risk from the actual 20% to no more than 1/3 (Visscher et al. 2017). Moreover, the vast majority of candidate genomic variants identified are in noncoding regions, and thus affect "transcriptional regulation rather than translation" (Carlberg and Molnár 2019; Verma 2016; Gagliano 2017; Nicolae et al. 2010; Cortessis et al. 2012). The interpretation of genetic variants in noncoding regions is often challenging (Chuan 2019); for example, it is not straightforward to establish whether genetic variants of disease risk identified in GWAS reflect the effect of modifiable risk factors rather than truly genetic effects, short whether it might be the case that the well-known equivalence or interchangeability of genetic and environmental effects could induce in mistaking phenocopies for genocopies (Gage et al. 2016; see Zuckerkandl and Villet 1988; Hamet 2016).

Indeed, the integration of multi-omics data has been the goal of the Systems, 4P Medicine project since its earliest proposal (Hood et al. 2004). The envisioned radical shift from a "reactive", post-symptomatic, data-poor evidence-based medicine to a "proactive", data-rich, preventive, predictive, personalized and participatory paradigm was based on the new enabling technologies of functional genomics, especially next (by now second) generation sequencing (Hood and Flores 2012; Kilpinen and Barrett 2013). Since then, programs like ENCODE (Encyclopedia of DNA elements), Roadmap Epigenomics, IHEC (International Huamn Epigenome Consortium), TCGA (The Cancer Genome Atlas Program), Fantom5 (Functional Annotation of the Mammalian Genome), GTEx (Genotype Tissue Expression) and lately EWAS (Epigenome-Wide Association Studies) Atlas (2019) and EWAS Data Hub (2020) have been gathering large-scale high-throughput screening data of common cell-type and tissue-specific epigenetic variants associated to reference and pathological phenotypes. The epigenetic molecular biomarkers detected by EWAS are the major tools of epigenetic epidemiology (Cortessis et al. 2012), which in the last decade has grown up to the task "to incorporate genetic variation with environmental exposure in explaining common diseases mediated by the epigenome" (Feinberg 2018; Jablonka 2004; Rakyan et al. 2011).

Increasing evidence of multi- and transgenerational epigenetic inheritance, and its potential for explaining at least part of the "missing heritability" conundrum (Cortessis et al. 2012; Visscher et al. 2017) appears to have finally succeeded in superseding former, slow to die, computational metaphors of genetic blueprint and programs. The once heterodox concept of the genome as a developmental "resource" (Oyama et al. 2001) has gained mainstream currency (Pearson 2003), and has triggered a quite remarkable mediatic hype (Mill and Heijmans 2013; Prainsack 2017). Unsurprisingly, it has also prompted new computational metaphors, such as that of DNA as "hard drive of genetic information that requires the "software" package of epigenetic control to determine its full transcriptional output" (Azad et al. 2013). Thus, adding the molecular informational layer of the epigenome might

be seen as the seamless achievement of an "integrated functional genomics" (Mill and Heijmans 2013). Enriching GWAS with EWAS, integrating the two layers of information – the ancestral identity encoded in the DNA sequence and the cell-specific identity derived from epigenetic processes (Szyf 2012) – fosters a more holistic view of the interplay between the genome and an active epigenome in complex diseases (K. C. Wang and Chang 2018; Hood and Flores 2012). It allows evaluating the functional consequences of genetic susceptibility loci on a range of epigenetic states, related to disease or to the action of environmental influences.

However, even the coupling of these two layers does not make the whole of biological information integrated into the individual organism. Personalized Medicine must take into account also the other major source of biologically relevant information, "the environmental signals brought from outside the genome" (Hood 2013; Hood and Flores 2012). As Hamet has stressed, "precision medicine can perhaps do without environment, but personalized medicine without consideration of environment, a person's exposure to it or adapting to it, cannot function" (Hamet 2016). In its actual extension, heralded by President Obama in 2015, it must encompass "individual differences in people's genes, environment and lifestyle" (Prainsack 2017).

As a matter of fact, in its epidemiological application, epigenetics appears to have shifted from "largely self-contained developmental processes" to "environmental influences on phenotypic readout of genotypes" (Cortessis et al. 2012). Thus, even if epigenetic changes may be issued by stochastic processes, such as epigenetic drift in aging, what personalized epigenetics is mostly about is how far this "software" is actionable by the environment, and how much of this action can be transmitted long after the environmental finger has triggered the switch.

Epigenetic Biomarkers and the 4 Ps of Personalized Medicine

Epigenetic changes are chemical marks affecting gene regulation – either chemical modification of DNA or modification of the associated proteins – that do not involve changes in the underlying DNA sequence. Changes in DNA methylation, histone posttranslational modification, chromatin remodeling, noncoding RNAs transcripts, may be induced by the environment and inherited, escaping the two waves of epigenetic erasure in the germline and in pre-implantation embryo development.

Epigenetic memory, or the heritable change in gene expression or behavior, varies according to the environment of reference and the time scale of its persistence. Three major kinds of epigenetic memory may be distinguished: 1. cellular memory, in which developmental signals induce changes in gene expression and chromatin structure that define and maintain cell identity; 2. short-term environmental transcriptional memory, mitotically transmitted, when environmental stimuli alter the responsiveness of the organism in its life span; 3. trans- and even multigenerational memory, when meiotically heritable changes in the gene expression and physiology of organisms are induced by environmental stimuli affecting the previous generations (D'Urso and Brickner 2014; Gilbert and Epel 2015).

Epigenetic marks are established early in development, are cell-type and tissue-specific and may change along the life span either stochastically or in the plastic response to environmental exposure. The complete collection of the epigenetic marks which specifically characterize each cell and tissue defines the epigenome of the organism at a given point in time (Rakyan et al. 2011). Thus, in contrast to the genome, a large part of the epigenome is highly dynamic, consistently with its role in fine-tuning key biological processes to changing internal and external conditions. Furthermore, although there is a general consistency in the overall epigenome patterns of all humans, "individuals vary far more on the level of their epigenomes than on the level of their genomes" (Carlberg and Molnár 2019, p. 10; Tollefsbol 2015; Mill and Heijmans 2013). Thus, profiling the unique characteristics of the individual epigenome in time allows to fine-tune population stratification on a more individualized scale (Dirks et al. 2016).

The disease-related molecular epigenetic biomarkers, that is the aberrant epigenetic changes associated to pathological states, discovered through large-scale EWAS, may be exploited both as diagnostic tools and therapeutic targets (Verma 2016b). Their impact on the three "medical" Ps of personalized medicine is profound (as well as on the fourth – the participatory one – however for different reasons I will discuss later). In fact, they may function both as diagnostic tools and actionable therapeutic targets *even regardless* of the actual direction of causality, the otherwise crucial issue whether epigenetic changes are causal factors or mere consequences of pathological states (Carter et al. 2017).

As in the vast majority of complex diseases, epigenetic signatures are more informative than genetic ones, their detection is relevant for *prediction* and *prevention*. The discovery of epigenetic biomarkers is becoming increasingly important for research on cancer, where "aberrant epigenetic changes occur more frequently than gene mutations" (Yan et al. 2016; Verma 2016) but also for metabolic diseases, infertility, pregnancy complications, allergy and respiratory diseases, autoimmune diseases, neurodegenerative disorders, aging and age-related diseases (García-Giménez et al. 2017).

Epigenetic marks may allow early detection of cancer risk (Mulero-Navarro and Esteller 2008). The identification of epigenetic biomarkers for neurodevelopmental and neurodegenerative diseases, where tissue analysis is possible only postmortem, would represent a huge advance for early diagnostic (Landecker and Panofsky 2013), and there is some indication that this might be the case of schizophrenia (Akbarian and Huang 2009; Wockner et al. 2014). Furthermore, epigenetic marks may reveal disease susceptibility related to lifestyle factors on which a timely intervention can avoid the pathological outcome. A major example is nutrition, where the detection of epigenetic marks associated to obesity may elicit a change in nutritional habits and prevent the outbreak of related disorders such as type 2 diabetes, cardiovascular disease, and metabolic syndrome. These issues are being addressed by the emerging field of nutriepigenomics, which may integrate nutrigenomics and push the personalization of nutrition to the individual epigenetic profile (Landecker 2011; Lindroth et al. 2015; cfr., Dugo et al. in this volume).

Equally important is the *prognostic* function of epigenetic biomarkers. Longitudinal studies before and after therapy may highlight changes in epigenetic marks and allow prognostics of disease evolution. DNA methylation changes have proved to be informative for the prognosis of tumor recurrence and overall survival, as well as predictive of the response to chemotherapeutic treatment. For instance, demethylation of the DNA repair gene *MGMT* in glioblastoma has been found to counteract the alkylating agents employed in chemotherapy (Dirks et al. 2016). EWAS on a mixed population of more than 700 women could distinguish different epigenetic profiles of never smokers and former smokers and assess their differential risk of lung cancer, identifying for the first time a set of aberrant epigenetic alterations which persisted for 35 years after stopping smoking (Feinberg 2018).

Last but not least, the dynamic and reversible nature of epigenetic signatures makes of them possible actionable targets for *therapeutic* interventions with enzyme inhibitors. Some DNA methyltransferases and histone deacetylase inhibitors have already been tested in the clinic. One of the best-tested case is the reactivation by hypermethylation of *MGMT* which sensitizes gliomas to alkylating agents and increases the efficacy of chemotherapy (Majchrzak-Celińska and Baer-Dubowska 2017). In the Angelman syndrome, a severe developmental disorder caused by the epigenetic silencing of an allele, the functional protein has been restored by means of a topoisomerase inhibitor (Huang et al. 2012). The development of epidrugs is the goal of the burgeoning research field of pharmacoepigenetics (Majchrzak-Celińska and Baer-Dubowska 2017; Yan et al. 2016). To date, despite some success in hematological cancers, epidrugs still lack sufficient selectivity and give often rise to off target effects (Mack 2010). However, the therapeutic potential of targeting single epigenetic signatures may also be hampered by the fact that the epigenetic response tends to be system-wide (Szyf 2012). As different epigenetic processes may synergistically or epistatically determine gene expression, it may be often difficult to unravel the distinct causal contribution of different epigenetic marks. Significant progress in unveiling their distinct causal roles is expected from epigenome editing tools, such as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) system, that allow targeting and experimental manipulation of single epigenetic marks (Holtzman and Gersbach 2018).

The causal complexity of epigenetic regulation is not the only hindrance to the success of personalized epigenetics. The requirements of epigenetic epidemiological screening are in principle different from GWAS, where the same genomic information is collected from any peripheral tissue. Actually, one of the reasons why most epigenetic research relies upon DNA methylation marks, besides their stability and cost-effective detection techniques (García-Giménez et al. 2017), is that they can be searched in the existing large genomic DNA sample archives collected by GWAS (Mill and Heijmans 2013). This first step is however far from capturing the whole richness of epigenomic signatures that ongoing research is bringing to light (Chan and Baylin 2012; García-Giménez et al. 2017; K. C. Wang and Chang 2018). For instance, it has been shown that whole-genome bisulfite sequencing, a powerful next-generation sequencing technique employed for genome-wide methylation analysis, cannot distinguish between DNA methylation

and hydroxymethylation, an epigenetic process which is involved in the regulation of enhancer activity and may play an opposite role (Song et al. 2011; Mill and Heijmans 2013). Leroy Hood's "holy trinity" recipe – "biology drives technology drives computation" (Hood 2013) – has driven progress in the accurate detection of the different epigenetic marks (see Petrov and Riddle 2016); however, the underlying problem of biological sampling in EWAS is far from solved. It goes under the name of "tissue issue" (Bakulski et al. 2016; Hannon et al. 2015).

The tissue issue revolves around the informative value of easily accessible peripheral tissues for epigenetic screening, where inter-individual epigenomic variation should be studied in primary disease- or exposure-relevant target tissues or cells, which are often inaccessible. Furthermore, even target cell and tissue samples may exhibit a wide variability, due to the high heterogeneity of cell types within a given tissue, as well as to the variability of the epigenome even within the same cell type, a problem which is currently being addressed by means of single-cell epigenomic sequencing methods (Clark et al. 2016; Carlberg and Molnár 2019). Nonetheless, there is consistent hope that peripheral tissues may be equally informative, consistently with the assumption that epigenetic response to environmental stressors involves multiple systems at once (Szyf 2012). Epigenetic biomarkers have a high stability in biofluids as well as primary types of tissue preparations (García-Giménez et al. 2017; Zhang et al. 2015), so that the actual practice is to search them in body fluids (blood, saliva, urine, plasma, sputum, semen, and others) which are easily collected in a noninvasive and cost-effective way, as well as biobanked (Rakyan et al. 2011; Peiró-Chova et al. 2016). Blood, which comes in contact with all organs, may play the role of "information highway in the body" because it contains "organ-specific biomarkers whose changes therefore most likely reflect changes in the selected organ itself" (K. Wang et al. 2010). However, the "tissue issue" can be solved only if all organ-specific biomarkers are firstly identified in target tissues and their presence in biofluids is fully assessed. A major goal of the phase II of the TaRGET (Toxicant Exposures and Responses by Genomic and Epigenomic Regulators of Transcription) environmental epigenomics program of NIEHS (National Institute for Environmental Health Sciences) is exactly to assess "the utility and admissibility of surrogate tissues as representative of changes in target tissues" (T. Wang et al. 2018).[2]

[2]The NIEHS TaRGET program is one of the few EWAS devoted to the systematic study of "how epigenetic patterns are perturbed by environmental exposures and, in turn, influence susceptibility to environmental diseases" (T. Wang et al. 2018); cfr., Silver et al. 2015. The first phase, started in 2012, conducted longitudinal studies on mice exposed to toxicants, and the current second phase is mostly devoted to test the validity of surrogate tissues and liquid biopsy, before launching the next phases of exposure-related EWAS on human populations (T. Wang et al. 2018; B. P. U. Perera et al. 2020).

The 4th P

These and other challenges make still uncertain how much of the potential of personalized epigenetics will be realized (Heijmans and Mill 2012; Hussey et al. 2017; Birney et al. 2016). Yet, whatever the vagaries of success and failure, epigenetic personalized medicine is already impacting on the 4th P, the "participatory" one, as the demands it places on the participant citizens are quite high. The involved citizens are asked a lifelong commitment, even more stringent than in longitudinal GWAS design. In fact, not only sampling must take place multiple times during the lifetime, it must start before the individual is in the condition to give her consent, from the very prenatal period, "from prewomb to tomb" (Topol 2014). Of course, this longitudinal design applies as well to patients, as in the case of the multiple epigenetic screenings for prognostic aims after treatment as well as healing, or to cohorts already selected by genomic screening for disease risk, as to healthy volunteers for establishing a "normal" reference epigenome (Peedicayil 2015; Carlberg and Molnár 2019; Carter et al. 2017). Further, epigenetic marks must be coupled with data about the concomitant environmental exposure, which means enriching them with a wealth of contextual information on people's lives and experience that borders on total visibility.

Specific cohorts are particularly informative for epigenetic epidemiology: longitudinal studies of disease-discordant monozygotic twins; family-based (parent-offspring pairs or trios) cohorts studies, prenatal cohorts (Mill and Heijmans 2013), all enriched with the detailed history of the individual's specific environmental exposure. Actually, epigenetic screening introduces a new anamnestic temporality, which must encompass more generations in order to track the nonmendelian transgenerational transmission of epigenetic marks (Chiapperino et al. 2017; Rakyan et al. 2011b).

Thus, even if the "tissue issue" should be positively resolved in favor of noninvasive sampling, its impact on the 4th, the participatory P, in personalized epigenetics may be no less burdensome if seen in terms of intrusiveness and potential control. Actually, epigenetic screening is poised to become a continuous process, driven by data from wearable digital monitoring devices, constantly updating the "somatographic" record of a population of "dynamic corporealities" (Beck and Niewöhner 2006).[3]

There are therefore several reasons why it is legitimate to think, unlike Chadwick and O'Connor (2013), that in many respects large-scale epigenetic profiling does pose brand new, and not simply "more complicated" ethical issues than those "discussed in relation to genetics". To be seen genetically is not the same as being seen "epigenetically", if only because while genetics can easily stand for just biology, epigenetics is about the inextricable intertwining of biology and

[3]Cfr., Hood 2013: "In 10 years, we may have a little hand-held device that will prick your finger, make 2500 blood measurements, and will longitudinally follow the organ-specific proteins for 50 different organs".

biography (Chiapperino and Testa 2016; Chiapperino 2018), the multiple influences and dimensions that interact in the unique individual pathway to personhood.

Many of these new ethical issues are actually under scrutiny. Studies are being conducted on how to reframe informed consent (Jallo et al. 2013; cfr., Ficorilli in this volume) to tackle the specific requirements of epigenetic screening. Other issues are related to privacy, and express concerns about how far anonymization may be effective in presence of the wealth of data required to make sense of epigenetic marks, from the in-depth recording of the life history and circumstances to the profilation of biological, mental and even cognitive characteristics of the involved subjects (Diemer and Woghiren 2015). Actually, there is no clear dividing line between medical and nonmedical data relevant for epigenetic studies, so that norms for ruling the "data use" to avoid that nonmedical data are exploited for other research or control aims are particularly critical. Prainsack aptly underlines the importance of the principle of solidarity, which however requires the possibility of restricting the use of such data to public rather than corporate interest (Prainsack 2017). A new normative framework is needed to eschew new forms of "epigenetic discrimination" (Dupras et al. 2018). This rich debate underscores the fact that, while the realization of personalized epigenetics may be a matter of the "next 50 years" (B. P. U. Perera et al. 2020), such issues are a concern of the present, and in no way "futuristic" (Chiapperino and Testa 2016), as large-scale EWAS are already underway and are poised to increase exponentially (Gagliano 2017; T. Wang et al. 2018).

In what follows, I will focus on the new dimensions of responsibility that personalized epigenetics brings to light. In fact, what EWAS add to the picture of extant longitudinal studies in GWAS and otherwise is not simply a trifling detail: it is the causal relationship between epigenetic marks and different kinds of environmental exposure, from those dictated by socio-economic circumstances to those concerning lifestyle habits. Thus, from the ethical perspective, the dividing line between genomic- and epigenomic-oriented 4P medicine is responsibility, a responsibility which is crucially related to exposure.

Exposure and Responsibility

Linking the genome to the epigenome, the integration of GWAS and EWAS information, as in general the integration of genomic variants with further layers of -omic information may appear as the seamless consequence of the evolution of functional genomics, driven by the aforementioned "holy trinity" recipe. Nonetheless, the major novelty of epigenetic epidemiology and epigenome-wide studies for personalized medicine is bringing into the picture "the patient's existing environmental load" (Feinberg 2018), the association of disease risk with her own or even her ascendancy's environmental exposure.

The perspective of a "personalized" environmental epigenetics (Tollefsbol 2015) is grounded in the remarkable advances in the last decade in the understanding of the molecular mechanisms of environmentally induced phenotypic response

together with the increasing evidence of trans- and multi-generational epigenetic inheritance. Driven by the original emphasis of evolutionary developmental biology on phenotypic plasticity, a new conceptual framework, lately synthesized by eco-evo-devo,[4] has highlighted the different pathways by which contextual environmental signals are elaborated by molecular and cellular mechanism of environmental perception. The exposure to abiotic and biotic environmental signals in the prenatal and perinatal period elicits a "predictive adaptive response" which instructs the formation of the phenotype, whereby the "mismatch" between the predicted and the actually encountered environment may result in maladaptive, potentially pathological phenotypes, which may be transmitted for one or several generations through epigenetic inheritance. The emerging field of "developmental origin of health and disease" (DOHaD) has already contributed significant insights into the origin of several pathologies, from metabolic diseases related to maternal nutrition (the thrifty phenotype hypothesis, Hales and Barker 2001; Waterland and Jirtle 2003), to neurodevelopmental disorders related to low maternal care (Weaver et al. 2005), to the long-term pathogenic consequences of the exposure in utero to environmental stressors like endocrine disruptors (Gilbert and Epel 2015; Gluckman and Hanson 2006; Kubota 2018; Rosenfeld 2016; B. P. U. Perera et al. 2020).

However, EWAS intent of associating aberrant epigenetic changes related to different pathological outcomes with different environmental stimuli requires both a precise measure of quantity and timing (critical windows) of exposure and a dissection of the "exposome" itself according to the different nature and action of the environmental factors involved (Faulk and Dolinoy 2011; cfr., Guchet in this volume). Associating the exposome with epigenetic marks can help to disentangle the direction of causality, and help improving diagnostics and therapeutic decisions. More importantly, some epigenetic marks may work as a proxy for environmental exposure, and even provide information about the time of its action. For instance, epigenetic variation that is present prior to overt signs of disease in all tissues included the germline may be amenable to transgenerational epigenetic inheritance, while if it is limited to one or a few tissues or only soma-wide it may hint at changes induced by environmental factors in the lifetime of the individual, such as diet and smoking (Rakyan et al. 2011). Some toxins such as arsenic and lead can leave unique signatures on the epigenome which may help to diagnose the source of toxicity (Yosim et al. 2015).

[4]The new synthetic proposal of eco-evo-devo is not only more encompassing, but also more radical than environmental or social epigenetics, especially in so far as it incorporates all epigenetic inheritance systems, from the strictly "vertical" one to niche ecological inheritance, and puts them on an equal footing (Gilbert and Epel 2015). From the biomedical point of view, one of the advantages of this approach is that it allows including also the case of the "horizontal epigenetic inheritance" involved for instance in the developmental symbiosis between mammal gut and microbiome. This stance is the more sensible as the jury is still our as how far epigenetic marks are stably transmitted through cell divisions or are reestablished from other information after mitosis (Cortessis et al. 2012; Nicol-Benoît et al. 2012).

But, however relevant this dissection may be for personalized prevention and treatment, what the biomedical gaze unveils will also have extremely important implications for the different dimensions of political, social and individual responsibility that the exposome brings into play (cfr., Guchet in this volume).

I will try to characterize three major dimensions of responsibility, which the analysis of the exposome may bring to light, and call attention to some of their wider societal and cultural repercussions. To this aim, I will rework with some liberty the classification of discourses about responsibility in obesity proposed by Swierstra (2011), that Chadwick and O'Connor (2013) have already extended to personalized epigenetics in general: the *environment* discourse, which politicizes without individualizing; the *body* discourse, which individualizes but does not moralize; and the *behavior* discourse, which both individualizes and moralizes. It is important to stress that all of these dimensions of responsibility stem from what Jasanoff (2004) has aptly called the co-production of science and society. The contribution of epigenetics to the environment discourse, which is currently displaying its transformative potential in society and politics, is an example of this co-production. However, the two "individualizing" dimensions that concern more directly personalized epigenetics are still in the making. As they have the potential of establishing a novel biopolitics of the body (Prainsack 2017), a timely reflection on their possible impact may help to shape personalized epigenetics toward the more comprehensive approach to health care that Ziegelstein has labeled "personomics" (Ziegelstein 2015).

The Environment Discourse: Anthropogenically Altered Environments

Several anthropogenic chemicals, which affect indiscriminately all human and nonhuman organisms, do not alter the DNA sequence but the epigenome.

For instance, exposure to endocrine disruptors in the critical window of fetal and early postnatal period alters the germ cell epigenome, causing health effects which emerge only much later in the offspring life. Xenoestrogens interfere in a competitive or antagonistic way with the action of hormones, such as aromatase, which are essential to the growth and functional differentiation of the gonads but also of the bones, brain, and organs of the cardiovascular system.

The effects of the massive introduction of xenoestrogens into the environment, especially after World War II, were firstly denounced by Rachel Carson in 1962 (Carson 1962). The ensuing history of the environmental movement ever since Rachel Carson's *Silent Spring* to the as of yet uneven adhesion to the precautionary principle by many major States[5] is a news story of the day (Khondker 2015; Guillette and Iguchi 2012; Gilbert and Epel 2015).

[5]For instance, Bisphenol A, an endocrine disruptor that is used to harden plastic, has been banned by European Union only in 2017, while in America it is still allowed with some restrictions.

However, the molecular understanding of their mode of action began only in the early 1990s (Colborn et al. 1993), and has paved the way to the establishment of environmental epigenetics as an independent research field (Skinner 2015). These studies were substantial in demonstrating the toxicity of endocrine disruptors, which had long been obscured by their delayed effects. Furthermore, they showed that, unlike classical teratogens, they are effective only at very low dosages, exactly those long permitted by law. There is increasing evidence that the epigenetic modifications they induce may be transmissible by epigenetic inheritance, in some cases also to the third generation (Schug et al. 2016). Endocrine disruptors are currently considered among the possible causes of large-scale epidemiological phenomena in human populations, such as the anticipation of the onset of female puberty, the decrease of male fertility, and the increase in reproductive organ cancers, besides the endangering of wildlife reproduction already highlighted by Carson.

The dimension of responsibility is here clear-cut: it is political and socially distributed. This kind of distributed responsibility may, therefore, fall into the *environment* discourse, which politicizes but does not individualize. The contribution of science in the making of this political discourse has been and will continue to be crucial. From the body of evidence provided by molecular epigenetic research to the potential diagnostic application of epigenetic biomarkers, the blurring of the border between biology proper and socio-cultural and political dimensions (the "environtome", cfr., Guchet in this volume) is nowhere seen better than in the engagement of environmental epigenetics at the forefront, spurring collective awareness and action, demanding appropriate institutional response at the national and international political levels (Gilbert and Epel 2015).

Involuntary Exposure: The Developmental Origin of Health Inequalities

The exposure to the social environment and social interactions in early childhood can be deemed as passive, in contrast to adult voluntary lifestyle choices. New molecular evidence has provided support to the so-called social or critical epidemiology approach (Krieger 2001), which highlighted the differential susceptibility to both physical and mental disorders, as well as the differential life expectancy, related to social hardship and low socio-economic status (SES) and occupational workload (Loi et al. 2013). Social epigenetics may be considered an application of DOHaD to the specific case of the "socially-shaped gene expression" (Landecker and Panofsky 2013), which may, with the tools of epigenetic epidemiology, associate socio-economic stressors and impairing social interactions with specific epigenetic markers (McGuinness et al. 2012; McGowan et al. 2009; Szyf 2012).

As suggested by Chadwick and O'Connor (2013), personalized epigenetics may contribute to the political ethics of the capability approach, according to which it should be the government's responsibility to address by affirmative action "any harm that potentially limits a person's innate capabilities" (Khan 2010). In particular, social epigenetics may bring to light how these differences are not

"innate", but co-constructed by the interaction between developing organisms and the social environment. The realization of how epigenetic marks are shaped by social conditions may provide new insights into the very process by which the differential "capabilities" are established and thus on the deeper-lying causes of social inequalities (Sen 1992). Thus, epigenetic biomarkers may provide new, molecular visibility to the otherwise immaterial "unequal obstacles" disadvantaged groups face in "the enjoyment of their basic constitutional entitlements" (Nussbaum 2007).

Epigenetic stratification according to social risk factors is radically different from the genome-based one. It bridges the nature-nurture divide, and, by taking into full account the causal circularity between the shaping of the body social and its societal effects, it may place on a new footing the interaction between biology and social sciences (Landecker and Panofsky 2013).

However, the "translational" impact of the socio-economic stratification of epigenetic risk factors on societal dynamics is not actually predictable and demands caution. The very materiality of molecular markers may play different roles, both as an opportunity and as a potential danger.

For instance, methylation patterns in rRNA genes have allowed discriminating suicides victims which experienced child abuse from those that did not (McGowan et al. 2008). The possibility to capture the "quality of life" (Nussbaum and Sen 1993) of an individual at a very early time – in this case, a child that is still unable to speak for herself – through such material, biological measure may facilitate the timely adoption of precautionary intervention and mitigate the risk of pathological outcomes.

On the other side, the dangers may arise at least in two forms, both related to the risk of a renaturalization of social evils. The first is that the fine-grained "molecular" profilation of individuals, reaching as well the socio-economic as the psychological and even cognitive sphere, may endorse discriminatory uses of such embodied measures. The second, highlighted by Guchet (in this volume), is to divert attention from the primary social causes, and focus corrective action on the biological effects, whereby science may end up playing a conservative role in the societal arena, instead of the proactive one it displays in the environment discourse.

Compared to the environment discourse, involuntary exposure is an individualizing discourse. It demarcates a socially-shaped environment, segregated from the collectively shared environment by social forces and circumstances, as in the case of occupational exposure to toxicant such as asbestos (Ziech et al. 2010), or of the spread of asthma among children of low-income racial minorities ghettoized in New York highly polluted city neighborhood and prenatally exposed to high rates of hydrocarbons (F. Perera et al. 2009).

Involuntary exposure to social stressors calls – or should call – for a collective and political dimension of responsibility, which however differs from the former "environmental" one. It does individualize, bringing to light the socially-shaped body, but, like the *body* discourse, it does not moralize, as the causal factors lay beyond the individual's control.

Voluntary Exposure: The Individual Burden?

"The silver lining is that the epigenetic profile is not fixed in stone; you may improve your epigenome by changes in diet, exercise, or other modifications" (Carter et al. 2017). Improving the epigenome is the crowning of the empowerment tale of personalized medicine, whose major topos is the "proactive" patient. Here, the willingness to provide data-hungry 4P medicine with constantly updated records of one's own physical parameters is rewarded by becoming a "vital new stakeholder" of a new democratic health care system, in which the patient actively demands personalized care and prevention rather than being a "passive recipient of expert advice" (Hood and Flores 2012).

Personalized epigenetics conveys a new "economy of promises" (Bensaude Vincent 2015), an enlarged transformative power on one's own life which has no counterpart in the former, "naturalizing" genomic biological discourse (Chiapperino and Testa 2016; Feiler et al. 2017; Prainsack 2017; Strand in this volume). However, this empowerment comes at the cost of charging the individual with an unprecedented burden in terms of responsibility (Chadwick and O'Connor 2013; Hedlund 2012). The individual dimension of responsibility disclosed by epigenetics concerns all kinds of exposures that are the result of *choices*: exercise, alcohol assumption, smoke, diet and so on. The dilemmas of an ethics of responsibility, extended to the well-being of future generations, impinge on the individual, whose management of her own body comes under the spotlight of the public health sphere. DOHaD literature presents us with armies of smoking mothers affecting the prospective health of their children (Richmond et al. 2015), although recent research is contributing the cold comfort of enlarging the blame to paternal misconduct (Hughes 2014).Therefore, with voluntary exposure we touch the third, *behavioral* discourse: the one that individualizes and moralizes.

Under the behavioral paradigm, the task of the ethical discourse revolves around issues of transgenerational justice, the search of a balance between the individual's right to self-determination and the rights of future generations (Chadwick and O'Connor 2013). However, this view of individual responsibility may not be exhaustive of the actual complexity of the biopolitical dimension of the body, and even contrast starkly with what epigenetics has taught us about what counts as an individual.

Conclusion: From Personalized Epigenetics to Personomics

Many observers have called attention on the danger of the "sociotechnical imagery" underpinned by a neoliberal interpretation of individual empowerment. In the light of a substantial ambiguity between health care idealism and commercial interest, the catchword personalization may end up supporting the global trend to devolve

responsibility and costs of public health to the citizen/consumer up to the point of disintermediation (Chiapperino and Testa 2016; Prainsack 2017).[6]

Besides these wide-ranging political implications, there is the irony that nothing could be further from the lesson of epigenetics than the neoliberal imagery of individuality as self-contained, captured in isolation from constitutive environmental and social influences, abstracted from the history of all the interactions that make up her unique epigenetic configuration in time (Landecker 2011; Beck and Niewöhner 2006). This is best exemplified by the challenge eco-evo-devo has lately thrown down to former, strictly Darwinian notions of biological individuality equally suspected to perpetuate, under the banner of science, the political imagery of the self-interest-driven *homo oeconomicus*. Constitutive developmental symbiosis, such as the one between mammal gut and microbiome, and epigenetic transgenerational inheritance of environmentally induced variations challenge traditional notion of self-contained biological individuality, based on genetic uniqueness and homogeneity and solely genetic heredity (Gilbert et al. 2012). Rather, they strongly encourage an alternative view of organisms as "relational processes in time" (Gilbert and Epel 2015, cap. 10), whose individuality is the emerging output of the dynamic interactions of the genome with multiple biotic and abiotic environmental factors at different space and time scales at once (Gilbert et al. 2012).

It may be equally difficult, in dealing with lifestyle choices, to determine the actual borders of individual responsibility. As centuries of philosophical, anthropological, sociological and not least psychological thinking have highlighted, to think of individuals as "fully independent entities" is misguiding (Prainsack 2014). Indeed**,** to the several internal and external dimensions of biosociality which eco-evo-devo recognizes within the individual organism, the biomedical gaze of personalized epigenetics adds the bond of a new temporality, which extends the anamnesis beyond the limits of a single lifetime (Chiapperino et al. 2017). The blurring of the borders between past, present and future bodies challenges the very notion of selfhood (Beck and Niewöhner 2006), and calls for a new intergenerationally distributed notion of responsibility across human generations.

The pragmatic consequence of this extended view of individuality is that, in order to elicit a transformative response in terms of lifestyle and self-care, the patient must be framed in the wider context of the multiple environmental, social, psychological and cultural present and past influences which shape and constrain her horizon of expectation and the efficacy of her own action. The transformative process may need to involve not only supporting institutional actors, but the whole network of significant interactions the "relational personhood" is embedded into (Prainsack 2014; Douglas and Ney 1998). In this perspective, tailoring the therapeutic intervention on the patient is likely to prove ineffective if it is limited

[6]Cfr., Hood 2013: "Individuals will be their own control in establishing a wellness baseline, monitoring the progression to disease state, and monitoring treatments that will perturb the systems back to a healthy state".

to demanding of her the solitary promethean act to get rid of the multiple bonds that substantiate her history and identity.

On the other side, the libertarian-democratic imagery of the new participatory digital medicine is in no better shape than naïve political imageries of e-democracy, harshly belied by recent developments (Caianiello 2019). "Participation is not always synonymous with increasing deliberation, diversity, and democracy" (Prainsack 2017, p. 194). Even the prophets of this new health care system resort to correctives such as science education for increasing the medical competency of patients and prevent awkward situations in which "patients come to their physicians with incorrect information that has been obtained from the Internet". Even in this "distributed" health care system, the clinician plays the pivotal role of the ultimate interpreter of the output of the long chain of big data processing (Hood and Auffray 2013).[7]

A crucial question is what patients actually ask in exchange of their burdensome "patient work" (Prainsack 2017), and of the hypervisibility necessarily entailed in the practice of personalized epigenetics. In a recent study, Wöhlke et al. (2013) have highlighted a remarkable misunderstanding in the respective expectations of patients and healthcare professionals toward personalized medicine, which diverges remarkably from the "proactive" imagery. The frustration of patients in front of the complexity of the medical explanation does not lead to a demand for more information. It would be simplistic to understand the lack of interest in informed consent, which patients were found to sign often without reading, as passivity or failing "biological citizenship" (Rose and Novas 2008; Caianiello 2019). It appears, from Wöhlke's study, that the patient rather asks to be seen in her entirety as a *person*, much in the way old bedside medicine has always understood personalization (Prainsack 2017).

Personalized epigenetics appears to call for a renewed medical gaze and a new alliance and trust between patient and physician. The opportunity for this alliance may rely on the new possibility of looking at the patient's biology and biography at once, even in absence of the lifelong relationship of a primary medical care doctor, by interpreting the "somatography" of her epigenetic traces. That is, by conceiving of her in a *concrete* way – by considering her actions and actual state in the context of the full temporal thickness of her life course and experiences –, rather than in an *abstract* way – that is extrapolating the time section of a single state or choice from that course (Hegel 1977).

Ziegelstein has dubbed personomics a dimension of care that takes into account the whole "concrete" dimension of the patient in the tailoring of her treatment: life experiences, socio-economic status, social capital (Ziegelstein 2015; cfr., Guchet in this volume). Turning into personomics, personalized epigenetics may have

[7] Hood and Auffray 2013: "it is clear that if the information from patient data clouds is to be used effectively to optimize their wellness and minimize disease, there needs to be a trusted interpreter of these data clouds for each patient".

the potential to deal also with individual responsibility in terms of "capabilities", blurring the thin line between the body and the behavior discourse.

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Personalized Medicine and Research Biobanking: From Traditional to New Informed Consent Generating a Need for Participatory Governance

Antonella Ficorilli

Introduction

Research biobanking is the collection and storage of human biological samples[1] and associated data[2] in a structured and large-scale manner by institutions specifically created for this purpose (i.e., research biobanks), and the distribution and sharing of these materials and data to/with local, national and international groups of research for current and future research purposes (Parodi 2015). Biospecimens and associated data can be stored, shared and used in an identifiable form, directly or through one or more codes, and in an unidentifiable form, i.e., completely anonymised (Council of Europe 2016).

Research biobanks, which belong to large public research centres, hospitals, or to pharmaceutical and biotechnology companies, and which also act as national large-scale *repositories*, were set up during the 1990s[3] due to the scientific need to collect and store for future use a large quantity of biological samples and

[1] Blood, tissues, cells, nucleic acids, proteins, etc.

[2] Personal, genealogical, clinical, life style.

[3] The word "biobank" was used for the first time in literature by Loft-Pulsen, *Cancer risk and oxidative DNA damage in man*, in the "Journal of Molecular Medicine", 1996, 74, 297 ss. to indicate the storage and conservation of biological material carried out in hospitals and in public and private structures. In 1994, the Council of Europe had used the expression human tissue banks in Recommendation N. R(94)1 of the Committee of Ministers to member states on human tissue banks, 14 march 1994, where the human tissue bank is defined as a "non-profit" organization that must guarantee the treatment, conservation and distribution of biological materials.

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associated data. This need has emerged following the introduction of biomedical research innovations concerning genetic, genomic and post-genomic investigation methodologies, and innovative ways of organizing biomedical research projects thanks to the ability to develop large electronic databases that can store large quantities of information.[4] Therefore, in the face of such a change of scenario, the small and mostly non-homogeneous collections, with which the researchers had been accustomed to using, are no longer adequate because it is not possible to find sufficient and high quality material to conduct research projects and obtain valid scientific statistics.

Biobank-centred research is crucial in order to foster the development of personalized medicine in the era of genomic research (European Science Foundation 2011). Indeed, emerging personalized medicine necessitates the collection, storage and processing of an increasing number and type of human biological samples and associated data within research biobanks throughout the world, materials and data which will be used in future large-scale health-related studies. "Without data, there will be no personalised medicine. Existing systems for data collection and storage, particularly biobanks, must therefore be consolidated and agreements reached on how to ensure future harmonisation of data collection and handling throughout Europe" (European Science Foundation 2012). Furthermore, because the scientific value of such collections increases with their size, large-scale biobanks have been widely developed, making samples and data available for different studies.

With large-scale research biobanks, ethical concerns regarding the use of human biological samples and personal data for future research purposes have increased. Particularly in matters pertaining to appropriate procedure for asking informed consent; privacy protection and identifiable data and samples; commercialization of research results and issues such as who benefits from economical profits; ownership of samples and data; benefit sharing in connection with asymmetry between samples and data as donation and new products protected by intellectual property (Budimir et al. 2011).[5] In the present paper, I will focus on the evolution of the debate or whether or not maintaining the informed consent model used in traditional health research sufficiently guarantees the dignity and rights of subjects, while at the same time serving as a good tool to obtain an appropriate balance between the research subjects' interests and public interest (Kegley 2004). At this regard, the central issue concerns the difficulty in providing complete information to participants at the moment biospecimens and associated data are collected regarding the objectives, risks and benefits implicated in the future research projects in which these materials will be used, given that such projects have yet to be designed or even foreseen. The dilemma involves two apparently contradictory requirements: to respect ethical

[4] About origins and developments of biobanks see Fantini and Rufo (2017); Coppola et al. (2019).

[5] It is worth highlighting that research biobanking involves industrial and commercial interests that should be carefully weighed against the interests of individual donors and society at large. This regards a huge issue that it is essential to take into account in the ethical map of research biobanking, as Karlsen and Strand have pointed out (Karlsen and Strand 2009).

standards on the one hand, and to encourage twenty-first century scientific practices on the other.

The paper aims to illustrate the evolutionary path of ethical reflection concerning this issue related to the use of research biobanking to foster personalised medicine (Salari and Larijani 2017). The debate has focused on identifying new models of informed consent, such as broad consent, dynamic consent, and meta consent. At the same time, this path generates the need for new types of governance that take into account the necessity of involving subjects in the decision-making process, especially in light of advancements in data mining and big data technologies.[6]

Information and Informed Consent: Which Model to Adopt?

Requiring informed consent from people who participate in scientific projects is one of the fundamental conditions for a research protocol to be considered ethically and legally valid. This instrument of subject protection in research projects emerged in the second half of the twentieth century in the field of biomedical research and in medical treatments in a clinical context in order to protect the integrity of the body, individual autonomy and decision-making of each individual involved in a clinical trial or medical treatment. In particular, in biomedical research, informed consent was considered an essential tool for the protection of human subjects and the promotion of personal autonomy, and criteria were established in the Nuremberg Code (1947) and the subsequent Helsinki Declaration (1964), which were later consolidated extensively in literature and other international documents (Council of Europe 1997, 2005).

In order to exert their freedom of choice, people must be informed about the purposes of a project and the possible risks and benefits involved. Therefore, information is a key element in the process of requesting and collecting informed consent. In addition, the information that the individual receives must be complete and clearly understandable (Beachamp and Childress 2009).

Ethical and legal requests to obtain informed consent was also extended to scientific research on identifiable human biological samples and associated data, especially starting from the 2000 revision of the Helsinki Declaration in which for the first time research involving identifiable human biological samples and data is considered equal to that carried out on humans.[7] Initially, traditional approaches towards requests for informed consent were used. That is, obtaining permission for the collection and storage of biological samples and data to be

[6]Note that the need for new types of governance in the direction of forms of participatory governance is also linked to the broader ethical issues listed above, especially when questions are at stake such as scientific advances are for the benefit of what, for whom, for which interests.

[7]In the 2000 modification of the Helsinki Declaration of the World Medical Association, art. 1 states: "The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data".

used in a specific and current research project for which detailed information concerning the protocol, objectives that will be pursued, and possible risks and benefits involved can be provided for participants, so that consent is effectively informed. This procedure has been found to be no longer adequate, or in any case has led to difficulties, when the methods of research on biological samples and data profoundly changed in the light of the innovations of the post-genomic revolution. The need has, therefore, emerged for specific places, that is research biobanks, where large quantities of biological samples and associated data can be collected and stored, so making it possible to carry out large-scale genomic projects, which would be otherwise extremely difficult and expensive to achieve quickly when a specific project is defined. Therefore, it is a matter of implementing a further method of collecting biological samples and associated data that arises outside specific research projects. That is to say, asking people to confer biological samples and data to be stored in a biobank to be possibly used in future projects for which you are provided with no detailed information and whose purposes are not yet known. Indeed, in a situation of progressive and rapid evolution of scientific knowledge, methodologies and possibilities of biomedical research in the field of "omics", current research purposes might quickly be replaced with innovative purposes that are not foreseeable at the time of collection of biospecimens and data. Furthermore, the materials and data stored in a biobank might be used in various research fields, such as oncology, cardiology, autoimmunity, etc. As a result, clinicians and researchers find themselves in situations where it is difficult to provide detailed information at the present moment x about what research projects will be pursued in future moments y. This difficulty in providing exhaustive information poses a problem when one considers the traditional model of informed consent where people must be able to exert their right to self-determine on the basis of complete information and consequently choose in an informed way whether or not to participate in a research study.

The shift from the use of human biospecimens and data in current research projects to their use in future research projects undermines the ethical requirement to provide research subjects with complete information on what will be done. Hence, we have the emergence on the one hand of the practical difficulty of obtaining valid informed consent, while, on the other, we have the problem of the ethical issue regarding whether the informed consent given on the basis of incomplete information can still be considered an expression of the person's self-determination principle. If you remain within the traditional ethical framework, the procedure that research biobanks should follow is to request a first informed consent at the time of collection to keep biological samples and data in the biobank. Then, a second informed consent should be obtained each time a specific research project is outlined in the future to use the samples and data previously collected and stored in that project. However, this procedure is problematic for various reasons. A first reason is connected to the large number of people to be contacted which makes it a costly procedure, both economically and as regards the time required to perform it, and which implies having to maintain constant communication with all participants. A second reason is related to the long-term storage of samples and data, which implies

having to contact the participants many years after the collection of the samples and data. During this long period, it may happen that it is no longer possible to contact many participants because, for example, they do not answer the phone, or have changed their address and have not informed the biobank, or have died. Any situations that increase the difficulty in contacting people in future moments will reduce the scientific value of the samples and data stored in a biobank. A third reason regards the psychological stress that such an approach can entail for participants who might consider being contacted every time a new project is outlined as an excessively burdensome and intrusive procedure (Elger and Caplan 2006). Hence, an ethical debate has arisen to identify an ethically acceptable and practically feasible alternative to the traditional procedure for requesting informed consent in order to overcome the difficulty of obtaining a new consent for each future use.

Alternatives to Traditional Informed Consent

In 1999, the United States National Bioethics Advisory Commission (NBAC 1999) addressed the practical and ethical challenge we are examining by suggesting a layered informed consent model that offers the participant the opportunity to choose various option. This model, which is entitled in literature *multi-layered consent*, aims to help research participants to clearly understand the nature of the decision they are making precisely through reflecting on a whole range of options that can be followed and which allows participants to exert their autonomy by choosing which option they prefer. Indeed, as can be seen from the list of options that the Commission suggests, and which we report below, the choice ranges from refusal to make their materials available for scientific research to a growing possibility of use when deciding to participate in research with your biological samples.

(a) Refusing use of their biological materials in research,
(b) Permitting only unidentified or unlinked use of their biological materials in research,
(c) Permitting coded or identified use of their biological materials for one particular study only, with no further contact permitted to ask for permission to do further studies,
(d) Permitting coded or identified use of their biological materials for one particular study only, with further contact permitted to ask for permission to do further studies,
(e) Permitting coded or identified use of their biological materials for any study relating to the condition for which the sample was originally collected, with further contact allowed to seek permission for other types of studies, or
(f) Permitting coded use of their biological materials for any kind of future study (NBAC 1999, p. v).

Note that when human biological materials are collected for biomedical research uses and stored and used irreversibly anonymously (i.e., unidentified or unlinked/no

coded), no particular ethical issues arise. However, the researcher is required to comply with the ethical duty to obtain informed consent to collect, store and use these materials in an anonymous way, based on respect of the principle of self-determination of each individual regarding the choices about their body and parts of it, and to apply both security measures and personal behaviours to maintain anonymity. In this form of procedure, no particular ethical issues arise because the information that will be extracted from samples cannot be easily traced back to the person from whom the material originally came.[8] Indeed, the crucial and controversial ethical aspects which could arise in this research field include possible breaches of information confidentiality and participant's privacy, compliance with the ethical duty to communicate the research and individual results, and the emergence of possible risks of discrimination, stigmatization and psychological stress. All these aspects are strictly connected to the possibility of linking biospecimens and data to the person from whom they came. The lack of these crucial ethical aspects has been considered a sufficient ethical justification for only one option (*b*) that is provided for the participant, without the need to go into further details as happens when the samples are not anonymous (options *c*, *d*, *e*, *f*). Furthermore, this justification has also been advanced by those who accept that in the presence of collections of biological samples that had already been set up in years where there were still no biobanking activities and the request for informed consent for using biospecimens for future research uses was not a regular practice, it is ethically justified to use these samples under specific conditions. More precisely, there are three conditions: making the biological samples irreversibly anonymous when it is no longer possible to contact the person in question to ask for their consent; having a scientifically relevant research project approved by an ethics committee; and having no evidence that the person concerned is against such research use.

The scenario instead changes when the biological material is identifiable, that is, directly associated with the identifying information of the person from whom it comes, or coded, that is, indirectly associated with the identifying information through one or more codes. In this case, the material detached from the body is or can be traced back to the person from whom it originates. Therefore, the information that is extracted from it could cause damage to participants and also their families if disclosed to third parties and not used appropriately. Hence, the relevance of putting each individual in the condition of being able to choose how to consent to the future use of their identified or coded samples (options *c*, *d*, *e*, *f*), considering that at the time of collection, researchers cannot provide complete information on the objectives, risks and benefits of future research projects. The consent mode options

[8]It must be stated that, although this is the current position of the European legal framework (Council of Europe 2016), it is however controversial. Biological material, containing DNA, inevitably uniquely identifies people on a biological level and this identifying element cannot be deleted even if the material is not associated with name and surname. Furthermore, the acquisition of an ever more sophisticated genomic investigation capability and the growing possibility of linking different databases makes it more and more feasible to be able to trace the name and surname of those who gave samples and data in the presence of unidentified materials.

c), d), e), f) that the US Commission suggests encompassing the models of *specific content* (*c*), *partial restricted consent* or *broad consent* (*e*), *blanket consent*[9] (*f*) on which the debate has focused in the first two decades of the twenty-first century, and which have been used in national and international documents of ethical and legal relevance.

The blanket consent allows the use of biological samples and associated data for future purposes of all kinds, at any time and with no limitations (Wendler 2013). The partial restricted consent allows the use of biological samples and associated data for a specific and current research study and for future purposes that are directly or indirectly associated with the original research, while for further purposes it is necessary to request a new consent (Salvaterra et al. 2008). The broad consent allows the use of biological samples and associated data for a range of biomedical research areas subject to specific conditions, such as the ethical approval from an ethics committee for each future research project and the participant's right to withdraw consent for future use. For further research not included in the areas indicated, a new consent must be requested (Wendler 2013). The specific consent allows the use of biological samples and associated data only in a specific research study and forbids their use in any future studies except with the acquisition of a new consent.

The specific consent has been evaluated by most scholars and researchers to be unfeasible based on the reasons illustrated above when we focused on the modality of a double informed consent. The first regards the collection and storage of samples and data in a research biobank, while the second, which will be given at future times, refers to permission to use in each future research project those samples and data previously collected. Based on the difficulties identified, it was considered ethically acceptable to move away from this traditional method of informed consent, considering that scientific research using biological materials of human origin and associated data stored in biobanks is now a fundamental element for the developments that may occur in the field of prevention and treatment of diseases. Therefore, the achievement of these important benefits justifies not providing complete information to research participants. Furthermore, it was argued that the risks involved in biomedical research on human biological material and associated data are minimal risks compared to those implicated in traditional clinical trials on human subjects because they do not involve a physical risk and do not have a direct impact on the health of the individual. In addition, sociological surveys show that public opinion favours new forms of consent. At the same time, strong opposition has been raised against this position. T. Caulfied (2007), for example, recalls that informed consent is a fundamental pillar in research involving human subjects, in conjunction with the recognition of the ethical criterion of placing participants' interests before the general public interest in matters pertaining to developments in scientific knowledge. The need to identify ethical standards in biomedical research has stemmed from the discovery of experiments in which participants' informed consent had not been requested, starting from the Nuremberg trial and then from other cases such as the Tuskegee case. Therefore, to argue

[9] In literature, it is also indicated with the expression *narrow consent*.

that the goal of achieving community benefit through progress in research is a justification for reducing ethical standards is not ethically acceptable. Moreover, the author claims that there is an inability to provide data concerning public perception based on sociological surveys in support of a paradigm shift in the informed consent procedure. The surveys are partial in that they report the public perception of only one or more population groups. This partiality arises strongly when surveys show conflicting data, as in the case of preferences for blanket or broad consent for research biobanking.

Providing blanket consent to any future use without any limitations has been deemed to be ethically inappropriate as the concept of informed consent itself is deprived of meaning. Indeed, this concept implies that people can choose whether to consent or not, an aspect that is covered by the blanket consent since people are asked to consent. Yet, the concept of informed consent also implies making an informed choice, an aspect that is not present in this type of consent since nothing is said about the multiple research scenarios that may open up in the future. In addition, two further arguments have been advanced against blanket consent. The first refers to the social importance that biobank-centred biomedical research has and which could be undermined by this method of consent. Hansson et al. highlighted that "blanket consent could lead to the consumption of important samples, potentially allowing commercial, purely technical or political applications (e.g., development of new methods for criminal investigations, for refinement of paternity tests, or for helping immigrant authorities to identify the ethnic origin of immigrants). Although some donors might be willing to accept such use of their samples, it might substantially jeopardise public trust in biomedical research" (Hansson et al. 2006, p. 268). The second argument refers to the possibility that the fundamental values of the subjects who provide biological samples and data are not respected, thereby causing them damage in terms of non-health interests. For example, participants may prefer that the samples and data that they confer are not used in projects that conflict with their own values, such as for example a project on cloning (Wendler 2013).

Partial restricted consent restricts the consent to a specific biomedical research field (e.g., cancer research) starting from the request for samples and data for a specific research project and to the use of possible residuals of these samples, together with associated data, in future projects that fall within the field of the original project for which consent was obtained. Therefore, this model provides detailed information on one specific project and on the research field in which it falls. In addition, information is provided on further aspects relevant to participants, which will be the same for each research project that will be conducted in that field. This information includes for example the security measures that will be implemented for the protection of samples and data and the participant's right to withdraw consent at any time for future use of samples and data provided. The information includes conditions that biobank and researchers must comply with for the long term-management and use of samples and data in future projects.

Broad consent means giving permission for future research uses that are more restricted than the blanket consent and wider than partial restricted consent. People are asked to consent to a range of research fields subject to specific conditions.

Therefore, on the one hand, it is a collection and future use of biospecimens and data which is subject to restrictions, unlike the blanket consent approach while on the other hand, multiple fields of research and not just one are taken into account and regardless of a specific and current project, unlike the partial restricted consent approach. Again, certain conditions are central regarding how samples and data will be managed and used for future use. Indeed, which type of governance will be implemented is precisely the main element that justifies the adoption of the broad consent model (Petrini 2010). Information is considered appropriate and ethically valid precisely because it informs people about the ethical, research and governance framework within which samples and data will be kept and used (Steinsbekk et al. 2013).

Partially restricted and broad consent procedures have been evaluated to be ethically acceptable on the basis of three aspects deemed to be relevant. Firstly, the type of information is considered appropriate so that individuals can make an informed choice. Secondly, there are some limitations in the collection and use of samples and data for future projects. Thirdly, there is the trust that participants give to institutions and professionals involved in biobanking, including ethics committees that will oversee future projects, delegating much of the control over their samples and data to such bodies. Consequently, there is the trustworthiness that institutions and professionals are required to show by adopting adequate institutional policy and conduct codes. I will focus on these aspects in more detail below.

To identify what information is relevant to enable participants to choose in an informed way, it is important to bear in mind the specific benefits and risks involved in research biobanking, where genetic and genomic investigations are central. Possible benefits are mostly indirect benefits. This is because investigations of biospecimens and data mainly produce basic results, which over time perhaps will produce results that are applicable in the clinic and health prevention. In addition, individual results, where there are any, may not have clinical relevance and raise psychological stress (e.g., when genetic susceptibility to a disease is found). Possible risks mainly concern, on the one hand, any breaches of information confidentiality and measures of privacy protection at all stages of biobanking, from the collection and storage of samples and data, to their sharing and use, and to the dissemination of results. Such breaches could lead third parties to discover sensitive data and to use it in ways that may conflict with participants' interests, for example not to hire them. On the other hand, there could be a risk that research projects are carried out whose purposes could contrast with the participant's values. Therefore, since the first debates took place regarding the setting up of large DNA databases, information that has been identified as relevant for participants includes the following.

- What is the scope of research in which human biological samples and data will be used;
- How human biological samples and data will be stored: anonymised (irreversibly anonymous), coded or identified form;

- What security measures will be taken to protect information confidentiality and privacy of participants;
- Who will use the biological samples and data (e.g., public or even private, national or even international research groups), and in what form (anonymised, coded or identified);
- How the dissemination of research results could impact participants and members of their family, clearly explaining the possibility of discrimination, stigmatization and psychological stress (e.g., the possibility that sensitive biological information, such as non paternity, might be obtained from investigations, which could have harmful effects, if disclosed; as well as the possibility of obtaining information concerning the fact that a participant or member of the family may have a genetic susceptibility to developing a disease);
- Possible development of commercial products;
- If and how results will be returned, both research and individual results including incidental findings;
- What benefits could be achieved, being very clear in communicating that in this research area direct benefits for participants are difficult to achieve (Reilly et al. 1997)

Compared to the traditional consent model, there is a shift regarding what information is relevant. It involves passing from detailed information on the objectives, possible risks and benefits of a specific and immediate project to providing information, with as much detail as possible, regarding the ethical, research and governance framework of the biobank. From this approach, if such information is provided, people can voluntarily and with an adequate level of information decide whether or not to contribute to the possible benefits that could be obtained from future research projects and to expose themselves to possible risks that could arise. In addition, they are aware that they have the right to withdraw (Beskow et al. 2010).

Coming to the second aspect relating to limitations on future uses, considering that these two models of informed consent reduce the control that individuals have on their samples and data, it was deemed appropriate to introduce conditions that guarantee participants that the samples and data they provided will be stored, shared and used in accordance with their interests (Hansson et al. 2006). At the same time, this introduction is considered to be essential to foster participants' trust towards biobanks and researchers. The conditions identified can be summarized in the following list.

- Biological samples and associated data must be stored, shared and used by adopting high standards of security and protection of participants' privacy (e.g., using sophisticated coding systems for their distribution to research groups);
- Participants must be able to withdraw consent at any future time, even after many years;
- Any future research project must receive ethical approval in order to guarantee the scientific relevance of the investigations that will be carried out and to protect the interests of people whose samples and data are used in such studies, including

care not to use these samples and data in projects that could conflict with the participants' values;
– Involve participants through continuous information on biobank activities and research studies, for example through a website.

Finally, trust is an important factor when choosing the broad consent model in such research contexts. This is particularly true considering the reduction both in the direct contact between researchers and research subjects and in the direct control that the subjects can have on their own samples and data. In addition, participants are asked to delegate the control of their own samples and data for future research purposes to biobanks, researchers and ethics committees. It is useful to specify that trust refers to trustworthiness, which is an essential characteristic that the subjects involved in research biobanking must actively show. Hence, it is important to establish the type of governance that biobanks adopt and a form of transparent communication of this governance for participants through the process of informed consent and continuous communication over time. It is also important that biobanks disclose the criteria of access to the samples and data they keep to researchers who want to use them in research projects, and that they implement documents such as *Material Transfer Agreement* and *Data Transfer Agreement* in line with the governance adopted.

Dynamic Consent and the Beginning of an Active Participation

Based on developments in information technology and the widespread diffusion of Internet in recent years, the main practical difficulty in contacting large numbers of people in the future to seek new informed consent has been significantly reduced, at least in western societies. Indeed, the development of interactive digital platforms makes it possible to reach and keep a communication channel with a large number of people open, so reducing time and costs. As a result, the main objection to the traditional informed consent has lost some of its strength.

In the light of these advancements the further alternative of dynamic consent has been proposed (Budin-Ljøsne et al. 2017; Kaye et al. 2012, 2015). It aims to give the possibility to participants to consent in real time to future projects in which their samples and data will be used through an interactive digital platform. They receive constant information on projects and can express their consent or dissent case by case thanks to this digital interaction. With dynamic consent, the procedure to request informed consent does not take place in a single moment in which a decision is taken on everything that is yet to take place. Rather, it is a process where participants are in constant dialogue over time with biobanks and researchers. This way of proceeding, unlike the non-dynamic model, places participants in an active role, changing the nature of participation in biobank-centred biomedical research.

Therefore, the dynamic consent aims to achieve several objectives, which include respecting participants' autonomy by allowing them to express their will for each new research project; redefining the relationship between research participants

and researchers towards an active involvement of people, both by giving them back the control on their own samples and data for each future use and through a constant dialogue between participants, researchers and biobanks; encouraging the improvement of participants' knowledge on how genomic research works (participants' empowerment) through continuous access to information on research projects; and fostering and maintaining public trust by greater transparency and active involvement.

Those who advocate this model deem it to be more appropriate than the other alternatives proposed not only because they believe it is an ethically valid and practically feasible approach to overcome the difficulties that have arisen with large-scale research biobanking this regard, but also for two other reasons. Firstly, the dynamic approach, they argue, promotes people's trust in biobank-centred biomedical research, which is increasingly involving whole genome investigations, data sharing, use of publicly available databases and big data. All these are aspects that make it difficult to guarantee the participants' rights, such as maintaining the anonymity of previously de-identified samples and data over time and fulfilling requests to destroy their samples and data after having withdrawn consent (Kaye 2015). Secondly, it encourages democratic participation in scientific research towards an increasing democratization of science since "research participants are located at the centre of decision making as equal partners in the research process" (Kaye et al. 2012).

At the same time, some difficulties have been recognized in adopting this approach. Dynamic consent requires a cultural change in the way researchers consider research subjects and in the way participants themselves consider their role. It takes time and is costly to implement the necessary technology and keep the communication process active. It could exclude some populations, considering that not everyone has access to Internet, or because it is their choice or because they live in social and political conditions that do not allow it (the so-called digital divide problem).

Some scholars have raised criticisms of dynamic consent, comparing it with broad consent (Steinsbekk et al. 2013). The difficulty in distinguishing between relevant and irrelevant information when a large amount of information is received. Furthermore, there is a risk of fuelling the *therapeutic misconception* problem through greater involvement of participants, which may lead them to erroneously think that the research objective is a direct benefit for them. There is also a problem regarding the burdensome commitment that is required of participants given the complexity of current biomedical research and the many times that in the future they will be asked to agree, a commitment which many people will not necessarily want to take on. The digital divide problem which inevitably excludes parts of populations. Finally, there is a problem in considering the participant as a subject on par with the researcher since participation is inside an already established biobank-focused research framework. "[A] true democratic and participatory model of medical research in general would be a model where citizens were allowed to impact on what kind of research initiatives they thought would have the biggest effect on promoting health and reducing the burdens of disease in a society. In such

a model, they would have power by being able to say yes or no to, for instance, large-scale biobank initiatives in a society. However, such a model is far from the model described in relation to dynamic consent" (Steinsbekk et al. 2013, p. 900).

It is worth highlighting the difficulty concerning this burdensome commitment. In fact, with dynamic consent, new practical difficulties emerge. Among these, the main one regards the fact that the participant receives a large number of requests for consent whereby it is necessary to read and understand a large amount of information. Although with digital interaction, you can reach a large number of people quickly and at low cost, it does not reduce the time and effort necessary both for researchers to provide appropriate information and participants to understand it, even more so since it regards complex information such as that linked to genomic research. There is a big difference in the commitment and time required compared to the traditional context of clinical studies.

Indeed, scientific research that uses resources stored in large-scale biobanks introduces the innovative element of using the same resources (samples and data given by an individual at a time x to a biobank) in multiple research projects over time, including very long periods. This is different to what happens in traditional clinical research in which a research subject is involved just in one or some research projects throughout her life. This innovative aspect implies that not only must there be a reconsideration of the informed consent process but also of the type of commitment that is required from participants and researchers themselves.

Note that what is being stated does not mean claiming that people are unable to read and understand a multiplicity of information on research projects if they receive adequate information and really want to understand. Yet, raising attention to the new type of commitment that is required both of the researcher, if he/she wants to inform people effectively and be ethically approvable, and of the participant, if he/she wants to provide a well-pondered consent. This attention leads us to the informed consent model of the meta consent, in which the participants themselves decide which level of commitment is the most appropriate for them.

Meta Consent and the Beginning of a Bottom-Up Approach

The nature of research biobanking (Hofmann 2009) and the type of commitment required from participants, as highlighted above, has led to belief regarding the inadequacy of the one-size informed consent model – a fixed model – for the use of biospecimens and data for future uses of research, be it a specific, broad or dynamic consent model.[10] A strong component of uncertainty about what will happen in the future in conjunction with the extent of the commitment over time that participants are asked for requires a reconsideration of the type of choices that participants should make, including the choice of which model of informed consent they prefer.

[10]The idea that one-size consent for everything does not fit every scenario had already been put forward in the following paper Hofmann et al. (2009).

Hence, some authors have offered the meta consent model, a flexible method of consent as an alternative to the one-size model (Ploug and Holm 2015a, b, 2016).

Meta consent gives people the chance to choose between the four informed consent options provided (dynamic consent, broad consent, blanket consent, blanket refusal) based on what they consider is the most appropriate for themselves. This choice will depend on their own preferences with reference both to the type of research context (private or public; commercial or non-commercial; national or international) and to the type of data that will be involved (electronic medical records; tissues or genomic data; health data; non-health data).[11] For instance, participants might choose broad consent for national research with public funding on non-genomic data; specific consent for each future project for national research with public funding of genomic data; and not permit the use of their biospecimens and data for international research or for commercial purposes. Once these choices have been made, it is possible to change them over time. Meta consent, as well as dynamic consent, also needs an interactive digital platform in order to be implemented.

The authors argue that there are good reasons to support this kind of approach. On the one hand, empirical data shows a diversity among people regarding which model of informed consent they prefer. On the other hand, theoretical considerations that regard respecting the participants' autonomy in the research show that this respect also implies respecting their will on which informed consent procedure they prefer for the use of their samples and data in future research projects.

This is precisely the main ethical point. The differences in people's preferences as to when and how they should be contacted to obtain their consent for the future use of their samples and data reflect differences in values, emotions and levels of trust that each individual feels towards the purposes of research and conditions under which it is carried out. Therefore, if you want to give people the opportunity to make an autonomous choice based on their values and preferences, you must give them the opportunity to choose which consent procedure they prefer. For instance, people might give a different value to research aimed at the development of commercial products compared to research that does not have such an objective. They might have different emotional reactions when they find out that others will have access to their personal information or that their data may be lost or stolen. They also might have a different level of trust towards researchers and research bodies depending on their past experiences, which strengthened or reduced their past sense of trust.

Another aspect that the authors' position advances in favour of the meta consent is linked to the problem concerning the high number of requests that participants might receive over the course of a year regarding their consent or dissent to specific

[11] It should be noted that meta consent does not take account the distinction between identifiable and non-identifiable data. Indeed it is no longer relevant in a research and social context in which it is now increasingly difficult to guarantee that non-identifiable data will remain so over time even though European legislation continues to maintain this distinction as an essential element for requesting consent or not.

projects. This regards an issue that arises in the approach of specific consent that includes both traditional consent and dynamic consent. Such a high number of requests, it is argued, is very likely to lead people to respond mechanically, routinely, without actually reading the information received and without reflecting on the choice to be made, which in all probability will simply repeat the choice made previously. The meta consent approach can reduce the threat of such routine by encouraging participants to reflect on when they want to receive detailed information and provide consent for future projects by choosing among different options. For example, if people choose one of the blanket, broad consent or refusal of consent modalities for the public research context and the dynamic consent modality for the private research context, they will reduce future informed consent requests compared to the approach in which specific consent is the only option provided. It is very likely that they will choose to be contacted and receive information for a new consent regarding research projects that interest them or that for some reason worry them. Therefore, they will pay attention to the information they receive on those projects before expressing their consent or dissent. In other words, this mode provides participants with a balance between "the threats of the consent being uninformed and unreflected as a result of being based on too little specific information and the threat of consent being uninformed and unreflected as a result of too much information through too many repeated consent requests, leading to the routinization of consent" (Ploug and Holm 2016, p. 730).

Four main objections have been raised against this approach (Manson 2019; Sheehan et al. 2019). The high costs that its implementation requires. Not providing adequate protection of the interests of participants by also including also the broad and blanket consent options. To take into consideration an unnecessary aspect of promoting personal autonomy. Finally, not taking into consideration the authority that researchers and research institutions have in the context of research biobanking.

It is worth concluding this paragraph by dwelling on the second objection. From this position, it can be argued that the blanket and broad models of consent do not adequately protect individuals because they do not provide sufficient information to make informed choices and expose the participants to the risk of being part of future projects in which they would not have wanted to take part if they had known about them. The authors advocate the meta consent by leveraging the shift that this model poses from considering only researchers as competent to establish what information and protection is adequate to recognising participants as competent in identifying which information they prefer to receive. "Broad and blanket consent limit the number of requests to the individual, and by incorporating these in the model of meta consent, we leave it to the individual to balance the interest in specific information about research projects against trust in researchers and the interest in not being overloaded by consent requests and other related interests and preferences" (Ploug and Holm 2016, p. 732).

Note how in the broad and dynamic consent models, we remain within a top-down decision-making approach, as the participants are faced with one or more choice options already established by others and only have to decide whether to join or not. The meta consent model, on the other hand, is closer to a bottom-up

model of decision-making process, although the participants are still required to choose from a series of options already defined, they are however much wider than the options provided by the one-size consent models. Indeed, it is a model that leaves participants with the freedom to control also part of the decision-making by choosing which informed consent they prefer to receive and by incorporating into the decision-making process personal values, emotional reactions and level of trust that the participants have towards the different purposes and contexts of research.

Conclusions: Towards Models of Participatory Governance

Although a consensus has yet to be reached among the ethicist community regarding which alternative model can fulfil the ethical requirements for informed consent, it seems plausible to conclude that the evolution of the ethical debate described highlights the increasing need of respecting participants' rights through an extension of their involvement in the decision-making process.

It is also worth highlighting that the idea, central in the broad consent, that citizens delegate much of the decisions on their samples and data to biobanks and researchers belongs to a paternalistic model of relationship between science and society. However, this model is no longer adequate to account for the current process of democratization of the science decision-making in which all of stakeholders involved should voice their opinion. In other words, we are moving from a top-down model of knowledge to a form of public debate and co-production model in which lay people intervene in the process of knowledge creation (Rufo and Ficorilli 2019). The innovations introduced by dynamic consent and meta consent reveal the need to take account of this profound change in the relationship between science and society which inevitably also concern biobank-focused research field.

Indeed, the adoption of models of informed consent increasingly inclusive of participants' active role fosters the cultural change needed regarding the role of research participants so that they can effectively become an active actor. Moreover, it encourages the promotion of a further change which is needed to take into consideration the active role not only as a simple choice over time within the rules already given, as Steinsbekk et al. (2013) have highlighted, but also as a role on par with the researcher. Therefore, this means playing an active part in data governance and in general in controlling the research agenda.

However, at this point, it is no longer just a matter of reconsidering which model of informed consent is appropriate, but it is also and above all a question of rethinking which model of governance of research biobanks is appropriate. The direction is to take into consideration the involvement of participants in all the decision-making process, including the outlining of research policies and objectives, towards forms of participatory governance (Biggeri and Tallacchini 2018; Buyx et al. 2017; O'Doherty et al. 2011; Tallacchini and Ficorilli 2019). This need increasingly begins to be felt especially in the light of the rising level of sophistication of technologies adopted to extract genetic and genomic data

from biological samples, such as genome-wide association studies (Kaye et al. 2010) and for the analysis and management of big data related to health. These are developments that considerably weaken one of the main guarantees for the protection of research participants' privacy, namely de-identification processes of samples and data such as anonymisation, coding and pseudoanonymisation (Vayena and Blasimme 2017).

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Biobank Research and Data Protection Issues Under the GDPR

Maria Rosaria Brizi

Introduction

Biobanks, typically understood as the collection of biological samples and associated information, which are stored for current and future research purposes, are an important component of personalized medicine. While contributing to the advance of scientific research, biobanks nonetheless feature as storehouses of personal information, some of them particularly sensitive, such as genetic and health data. Such data pertain to a particularly intimate domain, the exposure of which can be particularly harmful. Hence, those who participate in biobank research by providing bio-samples and associated information need being shielded against any possible discrimination or harassment that may result from their genetic and health profile being disclosed. This inevitably gives rise to data protection issues and calls for the implementation of adequate safeguards.

Over the past two decades, a relevant literature, while investigating the many questions that biobank research raises at the interplay between law and ethics, has

This article is based on my contribution in the Experts Meeting "Personalized medicine: A multidisciplinary approach to complexity", which took place at Campus Bio-Medico University of Rome on February 4th, 2020. That contribution and its rielaboration in the present version are meant to comment upon and elaborate further on Antonella Ficorilli's chapter in this volume, "Personalized medicine and research biobanking: From traditional to new informed consent generating a need for participatory governance". My angle has been that of law and politics as to highlight the concerns – in terms of protection of individual rights – that are still far from being solved, notwithstanding the regulatory advances in the domains of biobanks.

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thoroughly debated the importance of striking a balance between scientific research purposes and the protection of the providers of human biological materials.[1] The key-question is about identifying what rights the participant to a biobank research gives to the biobank and what rights, on the contrary, the participant maintains.

Over time, the relationship between the provider of the bio-sample and the bio-sample itself has been framed either in terms of individual proprietary rights, or in terms of the right to privacy, understood as individual autonomy. Nevertheless, both approaches, the former mainly pursued in the US and the latter in Europe, have been questioned. Allocating proprietary rights in one owner seems to imply that the human biological material, *per se*, has no distinct value, either individual or collective. On the other hand, framing it in terms of privacy, therefore individual autonomy, may also prove misleading, because it ends up disregarding the public feature of the values at stake (Tallacchini 2015).

The public dimension is undeniable when considering data protection issues in biobank research. Article 8 of the Charter of the Fundamental Rights of the European Union (Official Journal of the European Union 2012) states that "everyone has the right to the protection of personal data concerning him or her",[2] while the European General Data Protection Regulation (GDPR)[3] clearly states that "the processing of personal data should be designed to serve mankind. The right to the protection of personal data is not an absolute right; it must be considered in relation to its function in society and be balanced against other fundamental rights, in accordance with the principle of proportionality" (Official Journal of the European Union 2016, Recital 4). Therefore, data protection, though acknowledged as a right, is not unlimited, precisely because of its collective dimension.

Within the European Union, it is thus unquestionable that everybody, including those who provide biobanks with human biological materials, have the right to the protection of personal data, while mankind as a whole has an interest in scientific advances, including whatever valuable treatment, in terms of therapy or prevention, may result from biobank research. The question, then, is how to strike a balance between scientific advance and the necessity of data protection.[4]

[1] For a very comprehensive review and in-depth debate, already more than a decade ago, see Solbakk et al. 2009. More recently, Mascalzoni 2015.

[2] Article 8 of the Charter of the Fundamental Rights of the European Union reads as follows: "1. Everyone has the right to the protection of personal data concerning him or her. 2. Such data must be processed fairly for specific purposes and on the basis of the consent of the person concerned or some other legitimate basis laid down by law. Everyone has the right of access to data which has been collected concerning him or her, and the right to have it rectified. 3. Compliance with these rules shall be subject to control by an independent authority".

[3] The European General Data Protection Regulation entered into force on May 24, 2016. It became binding and directly applicable in all member states from May 25, 2018.

[4] Whatever balancing act amongst conflicting values implies a choice, which is not in the least trivial. Nonetheless, in principle, fundamental rights including the right to data protection should not be traded against any other values. The inherent, underlying theoretical question is particularly complex and far from being solved. Alas, it is well beyond the scope of this article to investigate its many facets and to constructively discuss it. For the purpose of this article, may suffice it to

This article, drawing from the reflection of several scholars, will briefly review the main concerns pertaining to the protection of personal information with regard to research biobanks and then consider what safeguards the GDPR establishes, while prohibiting the processing of sensitive personal data on the one side and allowing for a number of exemptions on the other. In particular, it will highlight the favour for scientific research, including cross-border studies, which seems very encouraging a feature for the furtherance of biobank research.

Protecting Personal Information

Personal information is costantly being threatened by the way the Internet allows to collect, store and exchange data. Therefore, protecting those facts that one deems particularly private and witholding them or restricting their disclosure are matters of primary concern. When we complain about private facts being disclosed and fear losing control over them, we raise privacy issues.[5] By and large, our interest in protecting and shielding those facts is what privacy mainly relates to (Monti and Wacks 2019).

Those facts are the information that can be extracted from an array of different sources, including human biological materials. Quite obviously, this is a key-issue in biobank research. What the participants to a biobank research contribute is not only a biological sample to be analysed. They also contribute the information that each and every sample carries.

The use of human biological materials for research purposes reaches beyond their mere corporeality, while their informational content is the main focus of attention (Lattanzi 2016). Thus, the human body is perceived as de-materialised, since it is mainly prized for the information that it carries. Accordingly, the informational value overshadows the inherent value of the means that carry it. Hence, the

highlight that the public interest in scientific research – which, according to art. 13 of the Charter of the Fundamental Rights of the European Union, "shall be free of constraint" – and the contribution of scientific research to the societal good make limits to the fundamental right to data protection justifiable, provided the said limits are necessary and proportional to the purpose and provided the essence of the said right is respected. Obviously, drawing the line between what is necessary and what is merely useful or desirable is a question of great complexity that adds to the inherent difficulty of any act of balancing. Balancing can as well be read as a consequence of proportionality, which allows for limitation of fundamental rights in the European Union only "if they are necessary and genuinely meet objectives of general interest recognised by the Union or the need to protect the rights and freedoms of others" (Charter of the Fundamental Rights of the European Union, art. 52). On the proportionality test and the technique of balancing, see Scaccia 2019. Furthermore, focusing on the case law of European Courts, see Lind and Strand 2011.

[5]Whether data protection is broader or narrower in scope than the concept of privacy is questionable. By and large, privacy encompasses data protection, but also pertains to private and family life and respect for the confidentiality of their correspondence and communications. In this respect, see Focarelli 2015; Rodotà 2014; Davis and Patterson 2012.

information ends up living a life of its own, given the scientific, economic and even judicial value that it embodies (Tallacchini 2015).

When the information coming from the bio-samples is linked or can be linked to the identity of an individual, then, it becomes personal information. Thus, while the materiality of the sample is separated from the individual, the information is still to be referred to him or her.

The disclosure of genetic profiles, including disease status, disease likelihood or relatedness status, can spur different types of manipulation and discrimination.[6] Besides, not only can it expose the individual the human biological material is gathered from, but also his or her next-of-kins, on account of genetic connection. Alas, genetics can be intrusive and the intrusion may prove far-reaching.

The GDPR defines genetic data as "personal data related to the inherited or acquired genetic characteristics of a natural person which give unique information about the physiology or the health of that natural person and which result, in particular, from an analysis of a biological sample from the natural person in question" (art.4). The said identified or identifiable natural person, according to the GDPR, is the "data subject".[7]

Data protection is pretty much a matter of confidentiality, thus entailing the possibility of sharing private information with someone without it being passed on (Ursin 2008). Therefore, in biobank research, the protection of the data subject, meaning the individual that has provided human biological material, is about protecting personal sensitive information by avoiding disclosure or uses that identify that individual, or make him or her identifiable. Any such aim is generally addressed by using anonymisation and pseudo-anonymisation procedures,[8] which certainly discourage identification, though not totally preventing it from happening. This is a matter of long-lasting concern. According to the findings of the first permanent ethics committee in the United States, back at the end of the 1990s, the samples that were identified at the moment they were taken, even if subsequently coded or anonymised, still inevitably maintained a certain level of re-identifiability (Tallacchini 2015).

Ever since, anonymization and pseudo-anonymization techniques have made great headways. Technology nowadays allows for a number of different options, such as encryption or restriction of access to raw data. Obviously, if the data can be rendered totally anonymous and unidentifiable, there is no further concern.

[6] E.g., by employers or insurance companies, just to name the most obvious.

[7] Interestingly, while providing a EU-wide legal framework for the protection of personal data, the GDPR altogether omits the term privacy.

[8] Truly anonymized data cannot be linked back to an individual, whereas pseudo-anonymized data have identifiers removed and replaced by a key-code that can be used to trace back an individual. Pseudo-anonymization is defined in the GDPR, sec. 4.5., as the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Nonetheless, total confidentiality is still hard to achieve and the risk of identification may linger under the surface, especially when biological samples are compared to a database.[9] The higher the number of databases and the links amongst them, the more critical the risk of identification.

This is all the more evident when considering secondary research, which draws upon existing information. Those information are increasingly shared in the unlimited arena of cross-border scientific networks. Quite obviously, the wider the scale of the data sharing, the more challenging the data protection issue. This implies that the current key-issue is no longer whether data should be shared, rather how to share data, provided the sharing is a fact that cannot be avoided (Kaye 2015). Quite the opposite, rather.

In this respect, the GDPR is pretty adamant: albeit protecting the right of natural persons to the protection of personal data, "the free movement of personal data within the Union shall be neither restricted nor prohibited for reasons connected with the protection of natural persons with regard to the processing of personal data" (art.1). Therefore, under the GDPR, the rationale is quite clear: data protection, albeit a matter of utter concern, cannot supersede other values and goals such as the free flow of data.

Personal Information and Informed Consent

Since the early international instruments, some basic safeguards regarding personal data were established: data relating to an identifiable individual should not be collected in the absence of a legitimate rationale and the consent of the individual concerned. The current research governance system generally requires consent to be given before the beginning of a research and that an individual always has a right to withdrawal.

By giving consent, the participant to biobank research waives part of the control on something that is utterly private, such as the bio-sample in itself, plus the associated information and the possible uses thereof. There is an underlying issue of control, which inevitably stems from the fact that data are extracted from biological materials and that is all that matters in biobank research. When science becomes mainly a matter of quantitative data, control is *in re ipsa* and features as a trait of modern science (Ghilardi 2018).

It is for the individual who participates in biobank research to consent to the gathering and further use of the information that pertains to him or her. Before giving consent, the participant to a biobank research should be well aware of what his or

[9]Whether data can be considered anonymous or not is a matter of risk assessment depending on a number of factors such as the technology available at the time of processing, the costs and the amount of time required for identification. Therefore anonymity is not a static concept, rather one that changes depending on specific, objective circumstances.

her participation in the biobank entails. He needs being informed, so that he can decide whether to take part to the research or not.

Informed consent has been the gold standard since the Nuremberg code, whose principles were nonetheless conceived in a totally different scenario, with a view to shield research participants from physical harm, rather than informational wounds.

According to the Nuremberg principles, research subjects should know the nature, duration and purpose of the experiment they would get involved in, as well as the inherent method and means. Research subjects should know all possible inconveniences and hazards that can be reasonably expected. Moreover, research participants always have the right to withdrawal as the Declaration of Helsinki,[10] which has furthered the Nuremberg principles, sets out.

Nevertheless, while the said requirements can be reasonably met in clinical settings, this does not seem quite the case in biobank research. The typical pillars of medical research governance such as informed consent and withdrawal do not seem to fit the specificity of biobank research, which features wide-scale data and samples sharing (Kaye 2015).

Biobank research is typically open-ended and future-oriented, therefore there is no such thing as an informed consent that is truly and fully informed. Biobanks are not a single research project, they rather consists of a resource for research (Widdows and Cordell 2011).

Therefore, consent given when providing a biological sample inevitably lacks in specificity, which certainly raises concerns as to how fully informed participants actually are and whether they are really in a position to evaluate the privacy risks of their participation in biobank research (Kaye 2015). At the time of consent, information in full not being available, a tension can be envisaged between the right to freely decide if to take part to a biobank research and the need for that kind of social solidarity that ensures wide engagement of participants in a research programme (Penasa 2018).

With regard to research projects based either on stored materials or on previous studies that have already drawn upon stored materials, seeking consent is particularly hard, costly and time-consuming, if not outright impossible, given the difficulty in re-contacting people in great number, as time goes by.

A further complication pertains to those individuals who are genetically connected to the providers of biological samples. In no way they have consented to their genetic profile being disclosed and yet, by means of genetic connections, they end up being exposed. This is a fact that the informed consent paradygm can in no way bypass.

To fit the specificity of biobank research, alternative forms of consent have been suggested, such as broad consent, which entails permission to do whatever the recipient biobank sees fit with biospecimens and associated data, once collected. From the standpoint of the researcher, the benefit of broad consent is quite evident: it

[10]The Declaration of Helsinki further requires that research subjects should also know the sources of funding, possible conflict of interest, prospective benefits and any other relevant aspect.

allows for the re-use of research materials in future projects, after long-term storage and even in the light of protocols which are not yet known at the time the individual consent is obtained.

Broad consent is widely relied upon in genomic research and enjoys noteworthy recognition in law and practise in Europe (Hallinan 2020). Nevertheless, broad consent alone is not much of a solution, since the participants from whom the samples are taken end up being informed of little more than the fact that they have renounced to know about the biological samples' future usage (Widdows and Cordell 2011). Moreover, in no way broad consent protects genetically connected individuals.

Thus, the paradygm of informed consent does not entirely fit the specificity of biobank research nor it provides a totally effective safeguards in terms of protection of the providers of bio-samples. The right to withdrawal is not much of a safeguard either. The latter, though allowing for the possibility of discontinuing participation in a research at any time, does not guarantee that the participants who withdraw may regain full control of the information that pertain to them. Probably, their records will somehow stay in the biobanks and the distributed sample remnants will hardly be traced and destroyed.

Not to mention the fact that in no way the withdrawal can hinder further studies based on previous research or allow for the re-capturing of the information that have already circulated. In the era of network and infrastructure research, total withdrawal is probably impossible (Kaye 2015). Alas, in biobank research, what is realistically possible is also limited.

Informed Consent and Transparency under the GDPR

Under the GDPR, the key-tenet is that personal data need be processed "lawfully, fairly and in a transparent manner in relation to the data subject" and that "personal data shall be collected for specified, explicit and legitimate purposes and not further processed in a manner that is incompatible with those purposes" (art.5).

The use-limitation and purpose-specification principles, together with the principle that personal data need being collected by lawful and fair means, provide a framework for safeguarding the use, disclosure, and fair collection of sensitive personal data in biobank research, albeit the GDPR establishes that processing of sensitive personal data is prohibited (art.9). Nonetheless, it also sets out exemptions.

Consent is one way to meet the GDPR requirements. If the data subject has given consent to the processing of personal data, any such processing is legitimate, provided certain conditions are met. According to the GDPR, consent of the data subject is "any freely given, specific, informed and unambiguous indication of the data subject's wishes that he or she, by a statement or a clear affirmative action, signifies agreement to the processing of personal data relating to him or her" (art.4).

Therefore, by means of consent, data subjects freely decide if, when, where and by whom their personal data can be processed. A consent freely given must be genuinely voluntary (Eaton 2010).

Consent must as well be informed. Under the GDPR, data subjects are granted a right to information, amongst several other rights.[11] Accordingly, data controllers and processors[12] have a number of obligations: they have to establish clear and transparent procedures for data protection, security and confidentiality, as well as accountability and demonstration of compliance.

By and large, informed consent is a matter of transparency, which is one of the core principles in the GDPR, albeit not defined herein. Nevertheless, Article 29 Data Protection Working Party, in its Guidelines on Transparency,[13] has emphasised that "transparency is a long established feature of the law of the EU. It is about engendering trust in the process which affect the citizens by enabling them to understand, and, if necessary, challenge those processes. It is also an expression of the principle of fairness in relation to the processing of personal data expressed in Article 8 of the Charter of the Fundamental Rights of the European Union".

On the whole, transparency is about fairness and fairness entails empowering data subjects to hold data controllers and data processors accountable for compliance with their obligations under the GDPR. Accordingly, data subjects must be informed about whether, how and by whom data relating to them is processed. They also have a right to obtain confirmation and communication of personal data concerning them, which are being processed, taking into account the specific circumstances and context in which the personal data are processed.

Namely, recital 39 of the GDPR sets out that "it should be transparent to natural persons that personal data concerning them are collected, used, consulted or otherwise processed and to what extent the personal data are or will be processed. The principle of transparency requires that any information and communication relating to the processing of those personal data be easily accessible and easy to understand, and that clear and plain language be used. That principle concerns, in particular, information to the data subjects on the identity of the controller and the purpose of the processing and further information to ensure fair and transparent processing in respect of the natural persons concerned [*omissis*]".

Additionally, recital 60 sets out that "the principles of fair and transparent processing require that the data subject be informed of the existence of the

[11] Including the right to access, to rectification, to erasure, to restrict processing, to data portability and to object.

[12] According to the GDPR, "controller" means the natural or legal person, agency or other body which determines the purposes and means of the processing of personal data, whereas "processor" means a natural or legal person, public authority, agency or other body which process personal data on behalf of the controller (Official Journal of the European Union 2016, art.4).

[13] The Art.29 Working Party was the body entrusted with the task of providing EU level interpretation of data protection law under Directive 95/46, subsequently replaced by the Data Protection Board when the GDPR entered into force. It consisted of representatives of data protection authorities, in charge of the task to interpret and enforce data protection law in EU member states. The Art. 29 Data Protection Working Party adopted Guidelines on Transparency under Regulation 2016/679, which set out general principles in relation to the exercise of data subjects' rights under the GDPR. Albeit not binding, these Guidelines are particularly authoritative and influential.

processing operation and its purposes. The controller should provide the data subject with any further information necessary to ensure fair and transparent processing taking into account the specific circumstances and context in which the personal data are processed. Furthermore, the data subject should be informed of the existence of profiling and the consequences of such profiling. [*omissis*]".

Information must meet certain requirements. According to the GDPR, data subjects are entitled to receive information that need be "concise, transparent, intelligible and easily accessible", while clear and plain language must be used (art.12). Thus, information has to be provided in a way that enables all data subjects to fully grasp the scope and consequences of the processing of personal data pertaining to them.

Different obligations relate to information to be given to data subjects, depending on whether data is collected from the data subject (art. 13) themselves or from third parties (art. 14). The obligations also vary depending on whether the data subjects themselves invoke their right to access (art.15).

As far as biobanks are concerned, if data are collected from the data subjects, biobanks must provide their participants with information pertaining to the identity and contact details of the controller, the purposes of the processing for which the personal data are intended and the legal basis for any such processing, the length of time for which the personal data will be stored, or, if that is not possible, the criteria used to determine that period.

Moreover, they have to provide information about the existence of the right to request from the controller access to and rectification or erasure of personal data or restriction of processing concerning the data subject, or to object to the processing as well as the right to data portability.

Besides, where biobanks process personal information on the basis of consent, they have to inform the data subjects of the existence of the right to withdraw consent at any time, without affecting the lawfulness of processing based on consent before its withdrawal. Information on any processing that personal data for a purpose other than that for which the personal data were collected also has to be provided.

If data are not collected from the data subject, as specified in art. 14, biobanks must provide their participants, along with the identity and contact details of the controller, the purposes of the processing as well as its legal basis, the recipients of personal data, if any and, where applicable, the fact that the controller intends to transfer personal data to a third country or international organisation. Biobanks also need informing about the length of time for which the personal data will be stored and the existence of the right to request from the controller access to and rectification or erasure of personal data, as well as restriction of processing or to object to processing.

Furthermore, where biobanks process personal information on the basis of consent, biobanks have to provide information regarding the existence of the right to withdraw consent at any time. Additionally, if data are collected through third parties, biobanks also have to inform about the source from which the data originate.

As specified in art. 15, when data subjects invoke their right to access their data, biobanks must provide participants confirmation as to whether or not personal data concerning him or her are being processed and further inform about the purposes of the processing, the categories of personal data concerned, the recipients to whom the personal data have been or will be disclosed, in particular recipients in third countries or international organisations.

Besides, if possible, biobanks have to provide information regarding the envisaged period for which the personal data will be stored or, if not possible, the criteria used to determine that period.

The existence of the right to request from the controller rectification or erasure of personal data or restriction of processing of personal data concerning to the data subjects or to object to that processing as well as the right to lodge a complaint with a supervisory authority are also information that need being provided.

Therefore, under the GDPR, biobanks collecting personal data about their participants must provide them with wide-ranging information about how and what data is processed, by whom and to what end. Nevertheless, the obligation to provide information may not apply in certain cases, such as when the participant already has the information, or where the recording or disclosure of the personal data is established by law. The same applies if the personal data have been obtained by a third party or in any case where the provision of information to the data subject proves to be impossible or would require disproportionate effort.

The Research Exemption Under the GDPR

To the aim of biobank research, meeting the GDPR requirements implies, in the first instance, acquiring informed consent from the individuals whose data are processed. Nevertheless, the general prohibition of processing personal data does not apply not only in the case of informed consent, but also when the processing is necessary for scientific research purposes.

Thus, biobanks can be exempted from a number of GDPR's general principles, obligations and data subject rights, if and when they collect and process personal data for the purpose of scientific research goals. In any such case, though, the GDPR requires it to be proportionate to the aim pursued, respect the essence of the right to data protection and provide for suitable and specific measures to safeguard the fundamental rights and the interests of the data subject (art.9).

All exemptions are however subject to the implementation of appropriate organisational and technical safeguards. This is obviously a way to strike a balance between the goal of not hindering scientific research on account of data protection issues and yet granting protection of personal data.

Safeguards that are particularly relevant in biobank research are the principles of data minimisation and storage limitation. In particular, the respect of data minimisation principle, as mentioned in article 89, is a basic requirement.

The principle of data minimisation implies that data have to be de-identified to the extent that research objectives can be achieved. Future research goals and

the need of protecting individuals participating in the research should always be taken into account. The data minimization principle may as well include pseudoanonymization, as the GDPR also applies to pseudo-anonymized data, in contrast to anonymous or anonymized data.

According to Recital 26, pseudo-anonymized data must be considered to be information on identifiable natural person. In the case of pseudo-anonymization, data subjects are obviously more vulnerable than in the situation of truly anonymized data: for instance, in the case the key-code is hacked, then all the data can be traced back to an individual (Rumbold and Pierscionek 2017).

If data are collected and processed solely for research purposes, the data storage limitation principle can also be modified and personal data can be stored for longer periods, pursuant to art. 89 and subject to the implementation of technical and organisational measures that the GDPR requires.

The GDPR also retains the presumption of compatibility of use for research purposes. It actually allows for further data processing for scientific research purposes, regarding data which were originally processed for a different purpose, provided that there is a valid legal ground for the initial processing in EU or there is a law in Member States that so establishes (art.5).

Furthermore, the GDPR allows for exemptions to various data subjects' rights,[14] whenever the exercise of these rights is likely to make impossible or seriously impair the achievement of the research and such derogations are deemed necessary to the fulfilment of the research purposes (art.89).

The exemption from the obligation to provide information whenever compliance may render impossible or seriously hinder the achievements of the research objectives is particularly relevant in biobank research. Providing information may prove extremely difficult, expensive and time-consuming, especially in the case of large-scale, cross-border studies.

Additionally, the GDPR acknowledges that the purpose of scientific research cannot always be specified at the time of the initial data collection. This is very significant when it comes to biobank research, which is open-ended in nature. Recital 33 allows for data subjects to "consent to certain areas of scientific research when in keeping with recognized ethical standards for scientific research. Data subjects should have the opportunity to give their consent only to certain areas of research or parts of research projects to the extent allowed by the intended purpose".

Overall, the research exemption to the general prohibition of sensitive personal data processing is very far-reaching and may end up relieving both data controllers and data processors from the requirement of obtaining consent from the data subject.

The acknowledgment of the utmost importance of scientific research by the GDPR can therefore entail several undesirable consequences for the data subject. Depending on how Member States make use of the discretion afforded to them by the GDPR, this might generate an unbalance between the interests of data subjects

[14] Such as the right to access, the right to rectification, the right to restriction of processing, the right to object.

and those of data controllers and processors, very much in the favour of the latter (Pormeister 2017).

The way Member States make use of any such discretion may also induce forum-shopping, where data processors are encouraged to operate in those states where the unbalance in their favour is particularly relevant. This obviously undermines any goal of uniformity within the European Union, where safe havens for data processors may occur where data subjects be substantially, if not formally, deprived of many of the guarantees that the data protection set-up was originally meant for (Pormeister 2017).

Conclusion

Bio-bank research vests a significant collective interest for its potential in the development of personalized medicine. Furthering biobank research is therefore a goal to be pursued, albeit it requires balancing the freedom of research with other very relevant targets, such as the protection of sensitive information pertaining to those who provide biobanks with human biological materials.

Alas, an effective sensitive personal data protection, including genetic and health data, is not easy to achieve. Nevertheless, the GDPR, which entered into force in 2018, certainly entails a huge step forward, at least in terms of legal certainty, since it provides a comprehensive framework for the protection of personal data within the European Union.

This is particularly relevant when it comes to biobank research, where researchers and biobank management may find it difficult to understand what the legal requirements are and certainly benefit from legal certainty and uniformity, also as a way to prevent administrative inconveniences, extra costs and unfair competition.

Nevertheless, though providing for rights and safeguards on behalf of data subjects and obligations for data controllers and processors, the GDPR states that the free flow of personal data within the European Union can neither be restricted or prohibited for reasons connected with the protection of natural persons with regard to the processing of personal data. This is critical in biobank research, which is typically cross-border and large-scale in nature. Yet, the flow of data raises further questions, especially regarding the future use thereof.

As time goes by, the set-up devised by the GDPR is translated into practice and its effectiveness in all possible fields, including biobank research, gets tested. Nevertheless, only time will tell to what extent such set-up truly works when it comes to data extracted from human biological materials.

Effectiveness in data protection is pivotal for biobank research to thrive and for participants to genuinely trust the researchers' purposes and methodology. Thus, in order to foster adequate commitment and engagement of the wider public to biobanking, it is necessary to guarantee that participating in biobank research is not going to allow for the misuse and abuse of the genetic and health information that the bio-samples carry. Should the participants withdraw because they do not

trust the research community and the effectiveness of the data protection set-up, biobanking is bound to fail.

As far as the goal of furthering scientific research is concerned, the GDPR is however very attentive. Though prohibiting the use of personal sensitive data in principle, it allows for exemptions. In particular, when it comes to the research exemption, the GDPR allows for a number of derogations to the data subjects' rights that member states can enact. Accordingly, once genetic data have been gathered from the data subject, they can further be processed for research purposes that were not in the least envisaged at the time of the collection.

Therefore, the key-question remains the identifiability of the data subject. Outright avoiding identification would be the key-answer. Should non-identifiability becomes ordinary ritual, an acceptable balance between conflicting values, the furtherance of biobank research on the one side, full protection of personal sensitive data on the other, would be eventually reached.

Hence, further investments, both theoretical and practical, are needed to pursue non-identifiability as the future, regular feature of biobank research. Alas, although great headways have been made in this respect, the issue is not yet solved. Pseudo-anonymization, for instance, is definitely not enough of a guarantee and the risk of manipulation of genetic profiles inevitably lingers under the surface.

As for today, the possible "leakage" of sensitive information extracted from human biological materials and the misuse that may subsequently result, feature as some kind of externality that the participants to biobank research face for the greater good of science. An externality that the GDPR, albeit providing for a number of safeguards, cannot completely overcome.

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Shedding Light on the Application of Pharmacogenomics to the United States Opioid Crises: A Relational Approach

Maria Sophia Aguirre

Introduction

In the past decade, the United States has experienced a surge of drug overdose and suicide, both linked to the use of opioids. Personalized medicine or precision medicine aims to overcome many treatment concerns, by utilizing information about a person's own genes or proteins to prevent, diagnose, or treat disease. In recent year, precision medicine in the form of pharmacogenomics, i.e., the study of genetic variants that impact drug effects through changes in a drug's pharmacokinetics and pharmacodynamics have been applied to opioid addictions. More specifically, efforts have been made to integrate pharmacogenomics into clinical pain management practice. Underlying this integration, is the assumption that individual genes can be predictive of how a patient may respond to a drug treatment. Therefore, authors claim, it could facilitate pain management by providing personalized medical care tailored to each patient based on their gene variants. In the context of the opioid crisis, it is believed that pharmacogenomics can potentially identifying opioid-vulnerable patients. Thus, from a personalized medicine perspective, the integration of pharmacogenomics into clinical practice creates better and safer healthcare practices for patients, which in turn can lead to a reduction of opioid addictions.[1] However, literature on the subject of opioid addictions also suggests other than genetic causes at the root of this addiction.

[1] Blum et al. 2017, Ruaño and Kost 2018, are examples of the mentioned approach.

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Several causes have been identified in the literature as responsible to what is typically labelled as the opioid epidemic. The crisis originated within the healthcare system and have been influenced by several socioeconomic factors. Among the causes mentioned in the literature regarding the healthcare system and pharmaceuticals' involvement, are excessive prescriptions for opioids to improve pain management; an aggressive – and at times, fraudulent – marketing effort by pharmaceutical companies combined with a large-scale production and distribution of pure, potent, orally effective and addictive opioids[2]; a medical system that incentivizes physicians to increase the number of patients to be treated with pain medications rather than a more hands-on approach such as physical therapy; the enforcement of Value-Based Purchasing (VBP), which until 2017, could lead to a reduced hospital reimbursement by Medicare if poor patient satisfaction with pain care was reported (ONDCP 2017); and inadequate oversight by the Food and Drug Administration (FDA) (Van Zee 2009). Easy access to inexpensive and illicit heroin, the influx of fentanyl/fentanyl analogs, the production of illicit opioid pills containing deadly levels of fentanyl made by authentic pill presses accelerated the transition from prescription opioid misuse to heroin and fentanyl addictions. In addition, lack of health care access, unemployment, as well as some cultural and socio-economic trends have contributed to what is now a full-blown crisis.[3] Relational factors, however, have not received due attention in previous analyses. By engaging an integral economic methodology to impact evaluation, this paper seeks to shed some light on the root causes of the opioid crises. In doing so, it hopes to assist in the efforts of public health authorities and healthcare practitioners to manage and prevent the epidemic of opioid addiction. It also hopes to provide evidence as to why a reductionist approach, often inherited by many contemporary trends in personalized medicine, falls short as a tool of prediction, diagnoses or treatment of opioid addictions.

A person's behavior, defined as actions, investments or consumption choices towards his or her health, shape the production of a person's health, and can either increase or decrease one's mortality risk.[4] Health behavior takes different forms and include negative habits, such as the opioid use, or positive actions such as eating healthy foods. Research in the area of economics and human capital in their multiple dimensions, has underscored the importance of family interactions, the most basic social structure, in the decision process, including health behaviors. Information flow, education, interpersonal relations, and the creation of habits and norms are some of the channels through which family members influence

[2]De Weerdt (2019) reports that Purdue Pharma claimed that OxyContin was less addictive than other opioid painkillers, yet this was proved to be untrue. In 2007, the company admitted that it knew it was addictive during a lawsuit that resulted in a US$635 million fine for the company.

[3]For a more detailed analysis of the mentioned root causes see among others Scherbaum and Specka (2008), Han et al. (2017), Hedegaard et al. (2017), Hser et al. (2015), GAO (2003), Van Zee A. (2009), Cicero et al. (2011), Aguirre and Zuniga (2020), Dart et al. (2015), De Weerdt (2019), Eisenstein (2019) and ONDCP (2017).

[4]For further discussion on these subjects see Cicero et al. (2014) and Cutler et al. (2009).

decisions and behavior.[5] To address effective solutions to the opioid crisis, it is important to identify which of these family-related factors lead to addiction, and what factors assist in preventing it, focusing on pharmacogenomics is not enough. However, identifying causal interpersonal relations on family members' behavior in general and on health behavior in particular, can be challenging. This is because of unobservable correlations across and within generations of the family. In the last decade, however, several authors have contributed to overcoming this challenge by employing behavioral economics and experimental techniques.[6] In this paper, we study the impact of interpersonal family relations on opioid addiction and other substance abuse. We do so by instrumentalizing both separation/divorce and the quality of family relations as reported by adolescents, parents and/or spouses. The estimation strategy relies on the timing of the shock, in this case the occurrence of the adolescents' parents' separation/divorce, constructing counterfactuals. Thus, the experiment can be understood as the introduction of a "negative treatment" that could potentially increase the risk of opioid addiction. A similar technique is used for the study of the impact of deterioration in interpersonal relations within the family, on opioid addiction, as well as of the experience of physical or sexual abuse or neglect in childhood.

The analysis employs an integral economics methodology as proposed by Aguirre (2011, 2013, 2018, 2019). At the core of this methodology is the recognition of the social nature and temporality of economic agents and therefore, the acknowledgment that, in making economic decisions, they maximize both as social persons and intertemporally – i.e., taking into account how current decisions are affected by factors and options that have occurred/made in the past and that will become available in the future. The methodology accounts for the interpersonal-relational dimensions of human actions, as the way persons interact can either help or jeopardize sustainable development. To do so, the methodology focuses on the direct beneficiaries of interventions in the targeted communities. The analysis incorporates not only immediate outcomes, but also includes interpersonal-relational factors to identify the effective channels of these relationships that ensure successful interventions and that help render them sustainable. It also identifies relationships that can undermine outcomes. Rather than embracing a reductionist understanding of reality, as often personalized medicine does, the integral methodology proposes an integrated view, thus it incorporates in the analysis relational factors.

With the assistance of experimental and behavioral economics within an integral methodology to impact evaluation, we leverage data on family and relational factors provided by the *National Longitudinal Study of Adolescent to Adult Health* (Add-Health), waves I (1994–1995), III (2001–2002) and IV (2008), to analyze

[5] See for example Waldorf (1983), Neighbors et al. (1992), Fadlon and Nielsen (2019), Aguirre et al. (2015), Meylet et al. (2007) and Skolnick (2017).

[6] Some of these efforts include Cerdá (2015), Cutler et al. (2009), Cutler and Glaser (2010), Fletcher and Markesteiner (2017), Cawley et al. (2017), and more recently Fadlon and Nielsen (2019), Aguirre and Cruz Zuniga (2018, 2020).

the impact of relational factors on opioid addiction and other substance abuse. These longitudinal surveys are of special interest, as data collected on adolescents overlap with the development of the opioid crisis, and it follows them over the course of 13 years. Adolescents are one of the groups identified in the literature as an at-risk group.[7] The sample includes 4105 participants. Of these 1017 were adolescents in the first wave of Add Health. The sample contains other household members including parents, spouses, and siblings who reported the quality of their relationship with the adolescents in the context of the home. Approximately 6% and 23% of the adolescents reported parents not living together in waves III and IV respectively. Sixteen percent of these adolescents also reported suffering opioid addictions in 2008.

Outcomes suggest that interpersonal factors within the most fundamental societal structure, the family, are key determinants in opioid addiction, thus focusing exclusively on pharmacogenomics is not sufficient as it does not properly address the causes of opioid addictions. Specifically, adolescents who experienced their parents' separation/divorce, have a 58% higher probability of opioid addiction 13 years later compared to adolescents whose parents remained together. Similarly, poor relations with family members also increase the provability of opioid addiction, albeit with a smaller impact. Having suffered sexual or physical abuse as well as neglect at an early age, also increase the probability of opioid addiction.

The paper is organized as follows: section "Background information of the opioid epidemic" presents background information and past literature findings to provide context; section "Research design" presents the research design; section "Findings" reports the impact of the deterioration of interpersonal family relations on opioid addiction; and concludes with the discussion and implications of the findings.

Background Information of the Opioid Epidemic

De Weerdt (2019) provides a short history of the US opioid crisis, which is helpful in framing this study. The author tracks the seed of the crisis to the 1980s when a stream of legislation was approved, which protected physicians from lawsuits when they prescribe controlled substances for their patients to manage their pain. About a decade later, in the mid-1990s, pharmaceutical companies introduced new opioid-based products, mainly OxyContin, produced by Purdue Pharma. A combination of lobbying efforts, continual medical-education courses, pharmaceutical representatives' visits to doctors' offices, and marketing efforts in white suburban and rural communities, accompanied the introduction of the new products and encouraged their widespread use. Predominantly white suburban and rural areas were of interest to pharmaceuticals because the risk of drug addiction was perceived to be lower there than in inner cities. At the time, the latter were mainly populated by low-income, African Americans and Hispanics, among whom the

[7] See Cutler and Gleaser (2010) and ONDCP (2017).

incidence of drug addiction was higher. In 2017, the Office of National Drug Control Policy (ONDCP) identified low-income areas in West Virginia, Ohio, Kentucky and New Hampshire as states highly impacted by the crisis that, as previously mentioned, were the original focus areas. Today, abuse of prescription opioids has affected people of different ages, races, socioeconomic strata, and urban and rural residents. Furthermore, because of the unexpected surge in opioid addictions, treatment services are insufficient to meet demands and provide medication-assisted treatment (MAT) (ONDCP 2017).

Three phases in the development of the epidemic have been acknowledged by the literature. "The first was dominated by prescription opioids, the second by heroin, and the third by cheaper – but more potent – synthetic opioids such as fentanyl" (De Weerdt 2019, p. 15). Han et al. (2017) found that 12.2% of adults with prescription opioid use, reported misusing the prescription. The most common reason for misuse is the release of physical pain (63.6%). They also reported that the profile of the majority of addicts included unemployed adults, low income, or persons with behavioral health problems. Among adults who are addicted to opioids, 62.2% reported using it without a prescription, while 40.6% obtained prescription opioids for free from friends or relatives.

Once the prescription opioid problem was acknowledged in the first phase, measures to decrease its consumption were put in place. This included new physicians' organizations guidelines, "U.S. state and federal agencies clamped down on the availability of such drugs, and Purdue Pharma reformulated OxyContin to make it more difficult to crush and inhale" (De Weerdt 2019, p. 16). The combined efforts reduced prescription abuse, but users substituted its consumption with heroin in the second phase. The last shift took place around 2013, when heroin dealers introduced fentanyl/fentanyl analogs. As the latter is stronger than heroin, it has generated a raise in the number of deaths of those consuming it.[8] Because the data included in this study stops in 2008, this analysis does not capture the third shift.

The literature also has recognized medical and other spillover effects attached to the opioid crisis. In addition to increasing the probability of other forms of substance abuse, it also negatively affects people's brains, bodies, and behaviors, increasing suicide, and elevating other mortality causes.[9] ONDCP (2017, p. 40) reports that "addiction is the most prevalent and costliest of neuropsychiatric disorders and the leading cause of premature, preventable deaths and disability in the United States". To provide for the medical needs of patients with this profile is very costly. In addition to the burden generated in the healthcare system, drug consumption negatively impacts the life of entire families and communities, their educational environment, labor productivity, traffic safety, and the criminal justice system, among others.

[8] Hedegaard et al. (2017) report that between 2013 and 2016, overdose deaths from fentanyl and similar molecules increased by 88% per year.

[9] De Weerdt (2019), reports that deaths due to opioid overdoses increased by a factor of six between 1999 and 2017.

Yet among the vast number of studies in recent years addressing the opioid crises, few of them incorporate relational factors. Even fewer incorporate interpersonal family aspects when analyzing relevant factors leading to opioid addiction. For the most part, if these factors are mentioned in the studies, they are typically addressed within the context of recovery efforts. For example, Waldorf (1983), Scherbaum and Specka (2008) and Hser (2015) find that family, social support, and employment are associated with improved recovery rates, while a history of sexual or physical abuse and some mental disorders are correlated with opioid use. One of the few exceptions is the 2017 National Survey of Substance Abuse Treatment Services, which identifies parental attitudes as critical in determining youth drug use. Measures utilized in the survey focus on externalization of disapproval, education and awareness, as well as monitoring. The assumption is that these attitudes can support prevention programs efforts. However, measures of interpersonal relations such as family dynamics, its stability, friendship between parents and children, or the quality of the existing relations are typically not factored in the analysis of the opioid crises. The omission could be damaging, as are precisely these very important relationships in the life of children, adolescents and adults, that help them or jeopardize the development of a balance personality and of an overall healthy life.[10] Therefore, they can also be important in considering prevention as well as recovery efforts.

Research Design

The purpose of the study is to identify the dynamic causal effect of the breakdown of interpersonal family relations on opioid addiction. In an ideal setting, the implementation of a randomized controlled trial (RCT) experiment would be the appropriate tool to engage. Such setting would allow for the comparison between ex post opioid addictions to a counterfactual behavior of ex ante similar unaffected subjects. As this is not possible, we frame the analysis as a quasi-experiment where we exploit the potential randomness of the adolescents' timing of a parents' separation/divorce, as well as the deterioration of interpersonal family relations within a course of 13 years.[11] Counterfactuals in this analysis were constructed by means of instrumentalizing the two aforementioned variables (Table 1).

All adolescents who reported having parents married and living together in Add Health Wave I (1994–1995), were included in the sample. Data provided by Add Health Wave I was utilized as the baseline. Data for corresponding parent, spouse

[10] See among others Aguirre (2006, 2018), Aguirre et al. (2015), Akerlof and Yellen (1994), Amato (2005), DeRose and Wilcox (2017), Poponoe (1996) and Richaud et al. (2013).

[11] Considering the timing of parent's divorce to be random, differs from considering divorce to be random. Literature on the latter suggests that past experiences can increase but not necessarily determine, a person's probability of divorce. These experiences include, among others, parents having divorced, having experienced abuse, etc. See previous footnote for references in the literature. We address this issue under the research design.

Table 1 Treatment effects, principal findings

	Opioid		Other drugs		Opioid		Other drugs		Opioid		Other drugs	
Variable of interest:	Coefficient	Std. Error	Coefficient	Std. Error	Coefficient	Std. Error	Coefficient	Std. Error	Coefficient	Std. Error	Coefficient	Std. Error
Treatment: parents divorces/ sepratation (treatment = 0, Contol = 1)	−0.58[a]	0.09	−0.09[a]	0.03								
Treatment: qQuality biological family relations (1 = poor or very poor relations, 0 = otherwise)					0.90	0.83	0.17	0.34				
Treatment: quality step parents' relations (1 = poor or very poor relations, 0 = other-wise))					2.53[b]	1.28	0.08	0.22				

(continued)

Table 1 (continued)

	Opioid		Other drugs		Opioid		Other drugs		Opioid		Other drugs	
Variable of interest:	Coefficient	Std. Error	Coefficient	Std. Error	Coefficient	Std. Error	Coefficient	Std. Error	Coefficient	Std. Error	Coefficient	Std. Error
Treatment: suffered sexual or physical abuse or neglect when young									−0.32	0.42	0.90[b]	0.42
Adolescent's use of prescribed pain reduction medicine	0.07	0.12			0.08[b]	0.04			0.03	0.02		
Adolescent's opioid consumption – baseline	−1.15[b]	0.56			−1.5[b]	0.69			−1.31[b]	0.59		
Adolescent's addiction as of 2001			0.03	0.03			0.06	0.14			0.32[b]	0.17
Adolescent has no health insurance – as of 2008 (Wade IV)	0.20	0.51	0.26	0.22	0.47	0.70	0.27	0.24	0.16	0.53	0.28	0.24
Adolescent unemployed – as of 2008 (Wave IV)	1.26[b]	0.58	0.63	0.66	1.90	1.31	0.68	0.67	1.08[c]	0.61	0.46	0.55

Household's holding of assets – baseline	−0.51[b]	0.24	0.15[c]	0.08	−0.36	0.23	0.18[a]	0.05	−0.46[b]	0.23	0.13	0.08
Live in rural areas	0.92[c]	0.56	−0.34	0.23	1.13[c]	0.59	−0.19	0.27	0.94[a]	0.51	−0.20	0.31
Observations (treatment only)	870		870		570		570		762		456	
Mean of dependent variable (control)	5.57[a]		−1.99[b]		3.81		−1.95[c]		6.14[a]		−2.38[b]	
p-value (test:Divorce/separation = still live together)	0[a]		0.0119[a]									
p-value (test:quality biological family relations (poor or very poor) = quality of relation (good or very good)					0.2796		0.6076					
p-value (test:quality step parents' relations (poor or very poor) = quality of relation (good or very good)					0.0498[b]		0.7119					

(continued)

Table 1 (continued)

	Opioid		Other drugs		Opioid		Other drugs		Opioid		Other drugs	
Variable of interest:	Coefficient	Std. Error	Coefficient	Std. Error	Coefficient	Std. Error	Coefficient	Std. Error	Coefficient	Std. Error	Coefficient	Std. Error
p-value (test:suffered sexual or physical abuse or neglet when young = did not suffer sexual or physical or neglect when young)									0.4421		0.0357[b]	
p-value (test:adolescent's use of prescribe pain reduction medicine = no use)	0.2626				0.0321[b]				0.2376			
p-value (adolescent opioid consumption – baseline = no consuption – baseline)	0.0536[b]				0.0321[b]				0.0262[b]			

p-value (test:adolescence addiction as of 2001 = no addiction in 2001)			0.5593				0.6471				0.0584[b]	
p-value (test:adolescent has no health insurance – as of 2008 = he/she has health insurance in 2008)	0.7108		0.2395		0.5047		0.2493		0.7676		0.2475	
p-value (test:adolescent unemployed in 2008 = employed in 2008)	0.0401[b]		0.3386		0.1494		0.3074		0.0747[c]		0.4004	
p-value (test:household's holding of assets – baseline = household's holding of assest makes no difference – baseline)	0.0428[b]		0.076[c]		0.1151		0.0014[a]		0.0458[b]		0.1133	
p-value (test:live in rural areas = live in urban areas)	0.1038[c]		0.144		0.0568[b]		0.476		0.0658[c]		0.5263	

Note: ANCOVA estimations with individual state fixed effects
[a]significant 1%, [b]Significant 5%, [c]significant 10%

or partner of responding parent, and siblings no participating in Add-Health were mapped. If a parent was reported dead by the time of Wave II, the corresponding adolescent was not included in the sample.[12] Subsequently, those reporting parents separated/divorced by the time of Add-Health Wave II or Wave III, were assigned to the treatment group T (negative treatment or shock), while those reporting that their parents were still married and living together through Wave III, were assigned to the control group. The specific variable utilized to determine treatment and control groups from Waves III and IV Parents Codebooks reads: "Now we need to update our records. When we interviewed you in [Survey Month] of 1995, the records show that you were married or living with a partner. Was that person [name of spouse or partner]? [Or if no name ask, Are you with the same person now?]" The identifying assumption is that other things being equal, if there is not separation/divorce of parents, or if family relations do not deteriorate, there will be no difference between the opioid consumption of treatment and control groups.

To measure the quality of family members' interpersonal relations, two indices were created by means of principal component analysis.[13] The first index measures the quality of the relations with biological parents and siblings as reported by adolescents first in 1994–1995 and then in the consecutive two waves. It includes nine variables measuring how much adolescents enjoyed living with their parents, whether they had a warm and loving relationship with them, and whether or not they feel close to their biological mother and father as well as to their siblings. Variables are measured in a 1 to 5 scale or 1 to 4 scale, one being "completely agree" or "frequently", and 5 or 4 indicating "strongly disagree" or "never." Table 2 in the Appendix, reports all variables included in the index. In all cases, the bigger the number, the worse is the relationship with their family members. Similarly, the bigger the number, the more the adolescent experienced abuse as a child. Based on these index values, the treatment variable was assigned the number of 1, if the index value indicated poor or very poor relations and 0 otherwise. In the case of abuse, the treatment variable was assigned a 1 if the index reflected subjects having suffered abuse or neglect and 0 if they did not.

Two measures are utilized as variables of interest to measure addiction. The first variable reports opioid addiction, and the second one is an index constructed based on other reported substance used by adolescents such as marijuana, cocaine, and crystal methamphetamine. The specific formulation for the first variable reads:

[12]The literature provides evidence indicating that the natural death of a parent does not have the same effect on children than separation or divorce, see Popenoe (1996), Orr and Roth ((2000)) and Neighbors et al. (1992). Consequently, and in an effort to reduce unnecessary noise in the sample, those cases were not included in the sample.

[13]Principal components analysis (PCA) calculates certain values – called "eigenvectors" –based on correlations between the variables. These eigenvectors are used as weights for each variable in the index so as to give prominence to the variables which held the strongest influence over the direction of the index. We did not drop any variables, as is often the result of PCA, because we wanted to capture as much of the reality as possible.

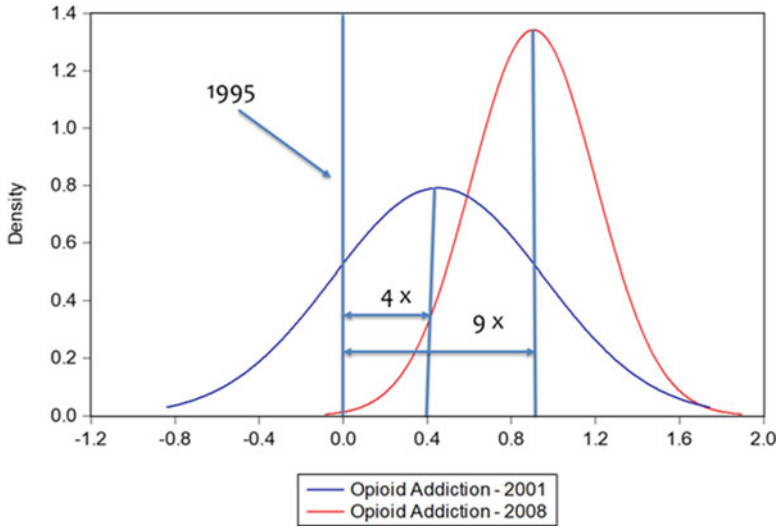

Fig. 1 Opioid use among adolescents, 1995–2008. (Source: Add Health Wave I (1994–1995) to Wave IV (2008))

> Which of the following types of prescription drugs have you taken that were not prescribed for you, taken in larger amounts than prescribed, more often than prescribed, for longer periods than prescribed, or that you took only for the feeling or experience they caused? – Pain killers or opioids, such as Vicodin, OxyContin, Percocet, Demerol, Percodan, or Tylenol with codeine.

Yes = 1 and No = 0. The second indexed variable includes the following substance in response to the same question:

> Marijuana (hash, bhang, ganja), cocaine (crack, coca leaves), crystal methamphetamine (ice), and other types of illegal drugs, such as Lysergic acid diethylamide (LSD), phenylcylcidine (PCP) or angel dust, ecstasy, heroin, or mushrooms; or inhalants.

Figure 1 presents the normal probability distribution functions of opioid use for 2001 and 2008, respectively. Between 1995 (base year) and 2001, there was, on average, a fourfold increase in opioid use. By 2008, on average, opioid use was 9 times higher.

Balance's test outcomes, for treatment and control groups in 1995–1996 (or baseline), are reported in Table 3 of the Appendix. Overall, both groups are statistically comparable at baseline. Both variables of interest and demographic characteristics are comparable with only few exceptions. These include adolescents' age, number of people living in the house, and parent's age. Thus, the sample meets the requirement of a balanced sample at baseline.

On average, adolescents in the sample are single, white, high school students, aged 15–16 years in 1995–1996, U.S. born, Christians, who have an average of two siblings, and had one job while studying. The average household income ranged

between $30,000 and $35,000, and were not part of a food stamp program. Parents in this study were mainly college-educated, white, and mainly reported that their children did not have an opioid addiction or other substance abuse at baseline. Treatment parents were younger than the control parents (42 years old vs 46 years old respectively). We control in the analysis for encountered baseline differences.

As previously mentioned, identifying causal interpersonal relations on family members' behavior can be challenging because of unobservable correlations across and within generations. In this case, one of these unobservable correlations could be the existence of preexisting conditions in the life of the parents that could increase the probability of parents divorcing. One of these conditions that was measured in Wave I and that the literature has identified is the experience, at an early age, of violence. Thus, to test for the presence of preexisting conditions, that could bias outcomes, we carried out a balance test on the experience of violence at an early age as reported by parents. The exact formulation of the question responded by the parent of the adolescents is: "As a child, were you ever badly beaten up by your parents or the people who raised you?" We found no statistical significance difference between parents in treatment and control group.

The Analysis of Covariance Model (ANCOVA), was utilized for the treatment effect analysis. ANCOVA is often engaged to measure treatment effects while controlling for baseline values of the same indicator.[14] Its estimates are preferred over difference-in-differences (DiD) estimates in scenarios in which the autocorrelation of outcomes is low over time as it provides a more efficient estimation of the effect (McKenzie 2012). Autocorrelation tests on residuals for the main outcomes reject the hypothesis of autocorrelation; thus, supporting the application of ANCOVA to this analysis (Table 4 reports autocorrelation results). Equation (1) presents the model estimated:

$$Y_{it} = \beta_0 + \beta_1 T_{it} + \beta_2 Y_{i0} + \phi X_{it} + \varphi C_{it} + \nu_{it} + \epsilon_{it} \quad (1)$$

Where Y_{it} is the outcome variable or variable of interest as specified above, opioid used and other substances used. T_{it} is a binary variable indicating if the adolescent received or did not receive the treatment, i.e., whether his or her parents separated or divorced by the time Waves III and IV of Add Health were collected. The variable takes the value of 0 if parents divorced/separated, and 1 if they remained married. Y is its baseline value. X is the vector of explanatory variables that are relevant to the analysis. C is the vector of control variables including demographics. ν is the individuals state fixed effect and ϵ is the error term. Heteroscedasticity, when present, was corrected by means of White's method of computing heteroscedasticity-consistent standard errors for panel data. Finally, Add Health weights were incorporated in the analysis.

[14] See for example Valli et al. (2019) and Sedlmayr et al. (2019).

The explanatory variables included capture relevant factors mentioned in the literature as important determinants of opioid addiction. These comprise having suffered some type of chronic pain and having been prescribed opioid-based medicines by a physician to manage pain at baseline, living in rural areas, being unemployed in the past year, level of wealth, and not having access to health insurance in the past 12 months.

As past studies also reported a higher prevalence of opioid addiction among whites at the beginning of the crises, we controlled for race. Due to a high correlation found between Black or African Americans and White adolescents as well as between both of these groups and adolescents from Hispanic origin, we were unable to desegregate the race impact by specific races. However, as Whites are coded as 1 and Blacks or African American are coded as 2, clear inference can be derived from the estimations, regarding the influence of race in opioid addictions. Age of adolescent at baseline, whether they are U.S. citizens or not, years of education completed since baseline, sex, number of siblings at baseline, number of jobs held at baseline, religion, whether they practice their faith or not, and marital status in 2001 (III Wave) were also included. Finally, we controlled for parent's race, education, household income at baseline.

One thousand forty-seven adolescents reported living with their parents at baseline. In 2001 (Wave III) the number of adolescents remaining in the control group decreased to 988, which constituted an 8% increase in the treatment group. By 2008, however, the control group (or those subjects whose parents remained married) had been reduced by 49% or 534 adolescents. Thus, in 2008, the treatment group included 513 subjects while the control group included 534. In addition, 180 adolescents reported opioid addiction and 219 reported addiction to other drugs. Seventeen adolescents reported having a poor relationship with their biological parents and 34 reported the same type of relation with their step-parents. Finally, 492 reported having been subjects of abuse or neglect.

Findings

In this section we analyze the treatment effects on adolescents' behavioral health changes. Specifically, we measure the behavioral health change in terms of an increase of substance abuse: for opioids and other drugs. Table 1 reports principal estimations' outcomes for the different definition of treatments previously discussed. Complete outcomes are presented in Tables 5, 6 and 7 in the Appendix.

We first address the treatment effect of parents' divorce/separation on opioid and drug addictions. Findings indicate that divorce/separation increases the probability of both opioid and other drugs addictions among young adults (by 2008 the Add Health adolescents were on average 28–29 years old).

The treatment effect is statistically significant and it is higher for the case of opioids than for addictions to other drugs, 58% and 9% higher probability, respectively. We also find statistically significant findings for the main causes of opioid abuse previously mentioned in the literature with one exception. Specifically, this

study found that the probability of opioid abuse was 92% higher for rural residents compared to urban residents, 51% higher for adolescents living in households with scarce resources, and 26% higher for participants who are unemployed in 2008 (Wave IV). This study, however, did not find that access to healthcare insurance to be a determinant factor on opioid consumption. Finally, having been prescribed pain medicine at baseline does not necessarily increase opioid addiction, but if the adolescent reports not being addicted at baseline, the probability of consuming opioid as a young adult is 15% higher compared with their control group. Family disruptions, unemployment, or rurality, not opioid-based prescriptions resulted in new cases.

Other relevant factors influencing opioid consumption include years of education completed since 1995 (16% higher probability by year) and being White or African American (32% higher probability than among other ethnic groups). Being U.S. citizens by birth, subjects' sex, the number of jobs held at baseline, marital status in 2001 (Wave III), as well as their parents' race, education, and income at baseline are found to not be statistically significant in influencing the young adults' health behavioral change regarding opioids. (Table 5).

Regarding consumption and addictions of other substances among young adults, in addition to the impact of parent's separation/divorce, living in wealthier households (0.15 more substances the higher the income), being a U.S. citizen by birth (on average they consume close to 1 more substance −0.79-, than those who are not), and remaining single in 2001 (on average increases consumption by close to 1 more substance −0.69-) are found to be positive and statistically significant. Substance addiction also increases among young adults who are non-Christians - i.e., other than Catholics or Protestants- (0.30 higher number of substance), and if they do not practice the faith they profess (0.12 higher number of substances). Participants' age, years of education completed since 1995, race, sex, and number of jobs while attending high school, parents' race, parents' household income, lack of access to health care, and unemployment are not statistically significant (Table 5).

Overall, outcomes suggest that opioid addiction, as of 2008, cannot be solely attributed to prescription opioid use among participants who have experienced the divorce/separation of their parents. It also suggests that the youths who abuse substances other than opioids differ in their profile from those affected by opioid misuse. They do, however, have two things in common: U.S. citizenship status and initiation of substance use when they experienced their parents' separation/divorce during their teenage years. Their socioeconomic conditions varied. While opioid addiction is prevalent among disadvantaged young adults, both white and Black, addictions to other types of substance, on average, are more prevalent among young adults with wealthier backgrounds, independently of their race or sex. Therefore, when considering prevention, treatment and policy design, it is important to consider the impact of the breakdown of the family in drug addiction. We will return to this point later in the analysis.

We next examined the impact of interpersonal family dynamics on opioid and other drug addictions. Table 1 report relevant estimates. We find no statistical evi-

dence that deterioration of interpersonal relations with biological relatives (parents and siblings) led to opioid addictions, which is not surprising given the small number of adolescents reporting poor relations. However, statistically significant evidence was found of poor relationships with step-parents, where the probability of opioid addiction increased by a factor of 2.53. The presence of a step-parent often is conflicted so it is not surprising that opioid addictions are higher when step-parents are present and there is a bad relationship.[15]

Consistent with previous findings in the literature, we find that White and Blacks participants who live in rural areas have a higher probability of being addicted to opioids, 27% and 1.13 times respectively. However, contrary to previous studies' findings, we find a higher probability of opioid addiction among adolescents not prescribed opioid-based medication to manage pain between 1995 and 2001 (1.5 times higher). The latter is consistent with the treatment effect findings of divorce/separation.

Other relevant factors leading to opioid addictions in the presence of family conflict include sex (59% higher probability if the subject is male), immigrant status (1.68 times higher probability), and being married by 2001 and have wealthier backgrounds (8% higher probability of being addicted) (Table 6 in Appendix).

No statistically significant treatment effect was found for addiction to other substances. Consistent with the previous estimation for the same variable of interest, adolescents living in wealthier households consumed more types of drugs. In addition, statistically significant outcomes were found indicating that having married at Wave III, being Christian (Catholic or Protestant), and practicing their faith, are mitigating factors in drug addiction (Table 6 in Appendix). Finally, consistent with findings mentioned above, subjects from wealthier households consumed more drugs (0.15 more drugs per wealth level bracket).

As it was the case for the treatment effect analysis of divorce/separation on drug addiction, these outcomes also suggest a different subject profile between those addicted to opioid compared with other drug addictions. The latter increase with wealth and is more common among non-Christian participants or individuals lapsed in their faith, while the former is prevalent among poorer households.

Finally, we address the impact of sexual and physical abuse as well as neglect in opioid and drug addictions. No statistically significant treatment effect was found for opioid consumption but it is positive and statistically significant for the use of other drugs (the types of drugs consumed increased by almost 1).

Consistent with previous findings in the literature having been prescribed pain killers, being unemployed as well as living in rural areas increase the probability of opioid addictions if participants suffered abuse. Level of education, being White or Black, and number of siblings also influence outcomes (Table 7 in Appendix).

[15] See Popenoe (1996) and Amato (2005). Findings suggest that more often than not, the presence of step parents in a household follow a divorce/separation rather than the death of a parent. Thus, the presence of conflicts between step parents and children, only escalates the experience of family instability for the children.

Findings are consistent with what has been reported by previous studies on the opioid crises with the exception of lack of access to healthcare insurance. As all subjects have as a default medical coverage, Medicaid, findings are not surprising. Abuse of opioid-based medications is not covered by any insurance. At the same time, findings highlight family instability such as parents' divorce/separation, poor relationships with parents and/or step-parents, and experience of abuse increase the risk of adolescents than adolescents who have stable families.

Discussion and Conclusion

In an effort to understand the root causes of the opioid epidemic in the U.S., studies have identified opioid-based prescriptions, unemployment, lack of healthcare access, and poverty. Relational factors have not received due attention in previous analyses. By means of a randomized controlled trial (RCT) designed within an integral economic methodology, this paper sheds some light in the understanding of the opioid crises' root causes. Three relational instruments were utilized to capture the effect of disruptions of family relations on the use of opioids: parents' divorce/separation, poor relations with parents or step-parents, and the suffering of abuse.

We find evidence of relational factors having a statistically significant effect on opioid consumption. The relevance of findings is manifold. First, they highlight the importance of healthy interpersonal relations within the family in the prevention of addictions, thereby, identifying at-risk populations while generating important information for the design of preventions. The role of parents and siblings in helping with the prevention of drug addiction requires more than simply manifesting disapproval of drug consumption or policing their children. Second, it showcases the fundamental role the family can play in both treatment and prognosis in adolescents' drug addiction. Healing broken relations is important as they play a significant role. Finally, in the context of personalized medicine, outcomes suggest that, in trying to conceptualize opioid addiction, a reductionist model of understanding this medical phenomenon and of the person's health behavior, necessary falls short as the basis to provide effective personal care. This is so because interpersonal relations also influence health behavior and choice as the data clearly reflects. Interpersonal relations need to be factored in to provide an effective whole-person, integrated care for individuals with opioid addiction.

Appendix

Table 2 Definition of indices

Quality of interpersonal relations – biological relatives	
Variables included – biological mother/father	**Scale**
You enjoy doing things with your mother	1 = strongly agree, 5 strongly desagree
Most of the time, she is warm and loving toward you	1 = strongly agree, 5 strongly desagree
How close do you feel to your biological mother?	1 = strongly agree, 5 strongly desagree
You enjoy doing things with your father	1 = strongly agree, 5 strongly desagree
Most of the time, he is warm and loving toward you	1 = strongly agree, 5 strongly desagree
How close do you feel to your biological father?	1 = strongly agree, 5 strongly desagree
Variables included – for up to three sibling	**Scale**
How close do you feel tohe/her?	1 = very close, 4 = not at all close[a]
How often do you tu rn to {HIM/HER} for help wh en you have personal problems, or problems at school or work?	1 = very often, 4 = never[a]
How often do you and {HE/SHE} quarrel or fight?	1 = never, 4 = very often
Quality of interpersonal relations – step father or mother (included only up to two)	
You enjoy doing things with your step mother	1 = strongly agree, 5 strongly desagree
Most of the time, she is warm and loving toward you	1 = strongly agree, 5 strongly desagree
How close do you feel to your step mother?	1 = strongly agree, 5 strongly desagree
You enjoy doing things with your step father	1 = strongly agree, 5 strongly desagree
Most of the time, he is warm and loving toward you	1 = strongly agree, 5 strongly desagree
How close do you feel to your step father?	1 = strongly agree, 5 strongly desagree
You enjoy doing things with your step mother (previous one)	1 = strongly agree, 5 strongly desagree
Most of the time, she is warm and loving toward you (previous one)	1 = strongly agree, 5 strongly desagree
(previous one) how close do you feel to your step mother?	1 = strongly agree, 5 strongly desagree
You enjoy doing things with your step father (previous one)	1 = strongly agree, 5 strongly desagree

(continued)

Table 2 (continued)

Most of the time, he is warm and loving toward you (previous one)	1 = strongly agree, 5 strongly desagree
How close do you feel to your step father? (previous one)	1 = strongly agree, 5 strongly desagree
Physical and sexual abuse and neglect	
By the time you started sixth grade, how often had your parents or other adult care-giv ers left y ou home alone when an adult should have been with you?	1 = one, time 5 = more than 10 times
How often had your parents or other adult care-givers not taken care of your basic needs, such as keeping you clean or providing food or clothing	1 = one, time 5 = more than 10 times
How often had your parents or other adult care-givers slapped, hit, or kicked you?	1 = one, time 5 = more than 10 times
How often had one of your parents or other adult care-givers touched you in a sexual way, forced you to touch him or her in a sexual way, or forced you to have sexual relations?	1 = one, time 5 = more than 10 times

Notes; Al questions can be found in public in home questionnaire code book I, III, and IV
[a]Scale assigned in original survey was reversed or modified to be consistent with other variables included in the index

Table 3 Balance test at baseline (1995–1996)

	Treatment group	**Control group**	**Balance test difference of two means**
Demographic characteristcis			
Age of adolescent included in add-health/siblings included in sample	15	16	Significant
US citizen by birth	YES	YES	Not significant
Highest education level achieved by adolescent	Attending high school	Attending high school	Not significant
Race adolescent	White	White	Not significant
Race of parent with whom h/shee lived	White	White	Not significant
Religion	Christian	Christian	Not significant
Sex of adolescent	Female	Female	Not significant
Number of siblings	2	2	Not significant
Number of people living in the house	3	2	Significant
Marital status of adolescent	Single, never married	Single, never married	Not significant
Number of jobs	1	1	Not significant
Family received foodstampoodstamp	NO	NO	Not significant
Houehold income	$30,000–$35,000	$30,000–$35,000	Not significant
Highest level of education achieved by parent	Bachelor's	Bachelor's	Not significant
Parent race	White	White	Not significant
Parent's age	42	46	Significant

(continued)

Table 3 (continued)

	Treatment group	Control group	Balance test difference of two means
Demographic characteristcis			
Parents: Enployed	YES	YES	Not significangt
Parent: As a child badly treated	NO	NO	Not significant
Index of personal ills	2.52	2.72	Not significant
Variables of interest			
Quality of interpersonal relations – biological parents and siblings	0.10	0.10	Not significant
Quality of interpersonal relations – step parents	6.72	7.00	Not significant
Opioid use	Definitively has not used it	Definitively has not used it	Not significant
Other drugs used	Definitively has not used it	Definitively has not used it	Not significant

Note: Control and Treatment groups are defined by parents reporting living together in 1995 and continue doing so at the time of Wave III and IV (control) or not contiue living together at the time of Wave III and IV (Treatment)

Table 4 Test for autocorrelation of residuals (1995–1996 to 2008)

Divorced/Saparation – opioid						
Autocorrelation	Partial correlation		AC	PAC	Q-stat	Prob
.|. |	.|. |	1	0.006	0.006	0.0054	0.942
.|. |	.|. |	2	0.035	0.035	0.1762	0.916
.|. |	.|. |	3	0.051	0.051	0.5401	0.91
Divorced/separtion – other drugs						
.|. |	.|. |	1	−0.013	−0.013	0.0716	0.789
.|. |	.|. |	2	0.025	0.024	0.3203	0.852
.|. |	.|. |	3	0.034	0.034	0.7833	0.853
Interpersonal relations – opioid						
. |. |	. |. |	1	−0.002	−0.002	0.0003	0.986
. |. |	. |. |	2	0.015	0.015	0.0216	0.989
. |. |	. |. |	3	0.042	0.042	0.1974	0.978
Interpersonal relations – other drugs						
Autocorrelation	Partial correlation		AC	PAC	Q-stat	Prob
.|. |	.|. |	1	−0.005	−0.005	0.0035	0.953
.|. |	.|. |	2	0.001	0.001	0.0037	0.998
.|. |	.|. |	3	0.037	0.037	0.2136	0.975
Sample (adjusted): 13892						
Autocorrlation (AC) and Partila Autocorrlation (PAC) functions and tests						
Null hypothesis = autocolleration present						
Ljung-box Q-statistics and their p-values						

Table 5 Impact of parent's divorce/separation on opioid and other drugs' addiction

Variable of Interest: *opioid addiction as of Ad-Health Wave IV (2008) (0 = No, 1 = Yes), other drugs = consumption of marijuana, cocaine, and crystal myth as of Ah-Health Wave IV (2008) (Number of drugs consumed)*	Opioid		Other Drugs	
	Coefficient	Std. error	Coefficient	Std. error
Control and explanatory variables				
Intercept	5.57[a]	2.01	−1.99[b]	1.03
Tretament (0, Contol = 1)	−0.58[a]	0.09	−0.09[a]	0.03
Age adolescent – baseline	0.12	0.10	0.03	0.05
US citicen by birth (1 = YES, 0 = NO)	−0.44	0.40	0.79[a]	0.26
Years of education completed since 1995	0.16[a]	0.07	−0.06	0.05
Adolescent's race (1 = white, 2 = black, 3 = American Indian, 4 = Asian or Pacifc islander, 5 = Hispanic)	−0.32[a]	0.11	0.12	0.06
Parent's race (1 = white, 2 = black, 3 = American Indian, 4 = Asian or Pacifc islander, 5 = Hispanic)	0.00	0.01	0.01	0.00
Adolescent's sex (0 = male, 1 = female)	−0.12	0.11	0.04	0.05
Number of siblings – baseline	0.39[b]	0.17	0.02	0.07
Paent's education – baseline (1 = eighth grade or less, 13 = completed post baccalaureate professional education (e.g., law school, med school, nurse)	0.11	0.16	0.01	0.06
Household income – baseline (1 = < $5000, 12 = $150,000 or more)	0.00	0.01	0.000	0.003
Number of jobs Adolescnet- baseline	−0.004	0.005	0.002	0.002
Adolescent's religion- Christian – baseline	−0.22	0.47	−0.30[c]	0.16
Practice his/her faith – baseline	0.09	0.13	−0.12[a]	0.05
Marital status adolescent (marriage = 1, 0 otherwise) 2001 (Wade III)	−0.40	0.70	−0.69[a]	0.27
Adolescent'suUse of prescribe pain reduction medicine	0.07	0.12		
Adolescent opiod consumption – baseline	−1.15[b]	0.56		
Adolescence adiction as of 2001			0.03	0.03
Alolescent has no health insurance – as of 2008 (Wade IV)	0.20	0.51	0.26	0.22
Adolescent unemployed – as of 2008 (wave IV)	1.26[b]	0.58	0.63	0.66
Household holding of assets – baseline	−0.51[b]	0.24	0.15[c]	0.08
Household holding of assets X married 2001- (wave III)	0.63	0.39	0.04	0.15
Live in rural areas	0.92[c]	0.56		
R2/N	40	887	21	990

Note: ANCOVA estimations with individual state fixed effects
[a]significant 1%, [b]Significant 5%, [c]significant 10%

Table 6 Impact of quality of inter-personal family dynamics on opioid and other drugs addiction

Variable of interest: *opioid addiction as of Ad-health Wave IV (2008) (0 = No, 1 = Yes), other drugs = consumption of marijuana, cocaine, and crystal myth as of Ah-Health Wave IV (2008) (Number of drugs consumed)*	Opioid		Other drugs	
	Coefficient	Std. error	Coefficient	Std. error
Control and explanatory variables				
Intercept	5.86[b]	2.95	−1.91[c]	1.14
Quality biological family relations (1 = poor or very poor relations, 0 = otherwise)	0.90	0.83	0.15	0.28
Quality step parents' relations (1 = poor or very poor relations, 0 = otherwise)	2.53[b]	1.28	0.08	0.22
Adolescent sex[a] quality of step parents' relations	−0.97	0.78		
Age adolescent – baseline	0.22	0.16	0.04	0.05
US citizen by birth (0 = NO, 1 = YES)	−1.68[b]	0.77	1.01[a]	0.24
Years of education completed since 1995	0.09	0.14	−0.06	0.05
Adolescent's race (1 = white, 2 = black, 3 = American Indian, 4 = Asian or Pacific islander, 5 = Hispanic)	−0.27[a]	0.10	0.09	0.06
Parent's race (1 = white, 2 = black, 3 = American Indian, 4 = Asian or Pacific islander, 5 = Hispanic)	−0.01	0.01	0.01[c]	0.00
Adolescent's sex (0 = male, 1 = female)	−0.59[a]	0.14	0.03	0.05
Number of siblings	−0.05	0.23	0.02	0.07
Parent's education – baseline (1 = eighth grade or less, 13 = completed post baccalaureate professional education (e.g., law school, med school, nurse)	−0.003	0.01	0.001	0.003
Household income – baseline (1 = < $5000, 12 = $150,000 or more)	−0.01	0.01	0.002	0.002
Number of jobs adolescent- baseline	−0.04	0.62	−0.27	0.17
Adolescent religion- Christian – baseline	0.09	0.20	0.27	0.24
Practice his/her faith – baseline	−1.26	1.10	−0.14[a]	0.05
Marital status adolescent (marriage = 1, 0 otherwise) 2001 (Wade III)	0.08[b]	0.04	−0.50[b]	0.26
Adolescent's use of prescribe pain reduction medicine	−1.5[b]	0.69		
Adolescent opioid consumption – baseline	0.06	0.32		
Adolescence addiction as of 2001	0.47	0.70	0.06	0.14
Adolescent has no health insurance – as of 2008 (Wade IV)	1.90	1.31	0.27	0.24
Adolescent unemployed – as of 2008 (wave IV)	−0.36	0.23	0.68	0.67
Household holding of assets – baseline	0.78	0.49	0.18[a]	0.05

(continued)

Table 6 (continued)

Variable of interest: *opioid addiction as of Ad-health Wave IV (2008) (0 = No, 1 = Yes), other drugs = consumption of marijuana, cocaine, and crystal myth as of Ah-Health Wave IV (2008) (Number of drugs consumed)*	Opioid		Other drugs	
	Coefficient	Std. error	Coefficient	Std. error
Control and explanatory variables				
Household holding of assets [a] married 2001-(wave III)	0.78	0.49		
Live in rural areas	1.13[b]	0.59	−0.19	0.27
R2/N	41	570	18	570

Note: ANCOVA estimations with individual state fixed effects
[a]significant 1%, [b]Significant 5%, [c]significant 10%

Table 7 Impact of Abuse on Opioid and Other Drugs Addiction

Variable of interest: *opioid addiction as of Ad-health Wave IV (2008) (0 = No, 1 = Yes), other drugs = consumption of marijuana, cocaine, and crystal myth as of Ah-Health Wave IV (2008) (Number of drugs consumed)*	Opioid		Other drugs	
	Coefficient	Std. error	Coefficient	Std. error
Control and explanatory variables				
Intercept	6.14[a]	2.12	−2.38[b]	1.09
Suffered sexual or physical abuse or neglect when young (1 = yes, 0 = no)	−0.32	0.42	0.90[b]	0.42
Age adolescent – baseline	0.10	0.11	0.01	0.05
US citizen by birth (0 = NO, 1 = YES)	−0.37	0.37	0.90[a]	0.20
Years of education completed since 1995	0.16[a]	0.07	−0.06	0.05
Adolescent's race (1 = white, 2 = black, 3 = American Indian, 4 = Asian or Pacific islander, 5 = Hispanic)	−0.32[a]	0.11	0.08	0.05
Parent's race (1 = white, 2 = black, 3 = American Indian, 4 = Asian or Pacific islander, 5 = Hispanic)	−0.001	0.006	0.01[b]	0.00
Adolescent's sex (0 = male, 1 = female)	−0.14	0.12	0.02	0.04
Number of siblings	0.44[a]	0.18	0.04	0.07
Parent's education – baseline (1 = eighth grade or less, 13 = completed post baccalaureate professional education (e.g., law school, med school, nurse)	0.17	0.16	0.02	0.06
Household income – baseline (1 = < $5000, 12 = $150,000 or more)	0.00	0.01	0.00	0.00

(continued)

Table 7 (continued)

Variable of interest: *opioid addiction as of Ad-health Wave IV (2008) (0 = No, 1 = Yes), other drugs = consumption of marijuana, cocaine, and crystal myth as of Ah-Health Wave IV (2008) (Number of drugs consumed)*	Opioid		Other drugs	
	Coefficient	Std. error	Coefficient	Std. error
Control and explanatory variables				
Number of jobs adolescent- baseline	−0.01	0.01	0.00	0.00
Adolescent religion- Christian – baseline	−0.17	0.49	−0.35[b]	0.16
Practice his/her faith – baseline	0.05	0.13	−0.09[c]	0.05
Marital status adolescent (marriage = 1, 0 otherwise) 2001 (Wade III)	0.11	0.20	−0.45	0.29
Adolescent's use of prescribe pain reduction medicine	0.09[a]	0.04		
Adolescent opioid consumption – baseline	−1.31[b]	0.59		
Adolescence addiction as of 2001			0.32[b]	0.17
Adolescent has no health insurance – as of 2008 (Wade IV)	0.16	0.53	0.28	0.24
Adolescent unemployed – as of 2008 (wave IV)	1.08[c]	0.61	0.46	0.55
Household holding of assets – baseline	−0.46[b]	0.23	0.13	0.08
Household holding of assets[a] married 2001- (wave III)	0.50	0.33	0.10	0.15
Live in rural areas	0.94[a]	0.51	−0.20	0.31
R2/N	26	762	25	456

Note: ANCOVA estimations with individual state fixed effects
[a]significant 1%, [b]Significant 5%, [c]significant 10%

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The Impact of a Fantasy

Roger Strand

Introduction: Personalized and Precision Medicine as a Sociotechnical Imaginary[1]

In their much-cited research paper, Jasanoff and Kim (2009) set out to improve the theoretical framework for studying and analysing how states come to delineate the objectives of publicly funded research. To that aim they introduced the concept of *sociotechnical imaginaries*. Their initial case study was a comparison between US and South Korean post-WW II nuclear power policies, and they defined national sociotechnical imaginaries as "collectively imagined forms of social life and social order reflected in the design and fulfilment of nation-specific scientific and/or technological projects" (Jasanoff and Kim 2009, p. 120). In looser and more colloquial terms, sociotechnical imaginaries can be defined as collective visions of good and attainable future science, technology & society.

Jasanoff's and Kim's concept of sociotechnical imaginaries is firmly rooted in Jasanoff's general analytical perspective of co-production. One may think of this perspective as an analytical lens of describing and interpreting the developmental trajectories of modern science, technology and society, respectively, as mutually entangled with dependencies in all directions, causally as well as with regard

[1]The opening paragraphs of this section closely follow the exposition in my report "Sociotechnical Imaginaries: Research and Innovation Policy as Creative Politics", produced for internal use at the EC-Joint Research Centre at Ispra (Italy) and hitherto not published for a wider audience.

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to the production of sense and meaning. From the co-production perspective, it makes little sense to study the development of science and technology without a simultaneous study of the development of society, and vice versa. For instance, the development of the life sciences and biomedicine in the late twentieth and early twenty-first century would not be adequately described and understood without taking into account the political investment in the hope in science-driven innovation as a locomotive force for prosperity and economic growth in the same period. One would also need to know about the developments in public and political expectations for public health. Conversely, the political visions for prosperity and health in the emerging bioeconomy of this period would not be adequately interpreted without an understanding of the advances of molecular biology, genetics and biotechnology, to mention a few rapidly evolving fields.

Alessandro Blasimme and Effy Vayena have previously elaborated how precision medicine may be described and interpreted as a sociotechnical imaginary *sensu* Jasanoff and Kim (Blasimme and Vayena 2016, 2017; Blasimme 2017); even originating as a *national* sociotechnical imaginary in the US and as part of Obama's political platform before it was adopted on a global scale, that is, within countries and economies aspiring to the ambitions of the bioeconomy (see also Tarkkala et al. 2019 for a recent analysis).

"Sociotechnical imaginary" is a critical concept in the sense that it is intended to be helpful in order to gain critical distance to actors' self-understandings and other commonsensical or naïve understandings. As such it is no different from any other concept of social science. It is important to recall, however, that the word "imaginary" is not meant to have a derogatory connotation, neither in Jasanoff's sense nor in previous usages (such as with Benedict Anderson or Charles Taylor). The choice of the term "imaginary" does not imply a dismissive value judgement upon validity claims as being unrealistic or lost in fantasy and illusion. Rather, from this perspective, imagination is considered to be a normal and legitimate component of the creation (or rather co-production) of research policies, research trajectories and (other) political decisions. The reason is that there is a difference, if not in essence at least in degree, between decisions on, say, research trajectories, and many other public issues: research is expected to and indeed intends to produce something unforeseen and unforeseeable, namely new knowledge that opens up for new applications. Regular cost-benefit analyses or similar formal decision-making strategies are ill-suited to choose between surprises; indeed, in order for cost-benefit analysis to be legitimate, the outcome space must be known and well-characterized in terms of probabilities or likelihoods. Research policy-making is less a matter of choosing between well-characterised outcomes and more a matter of envisioning potential outcomes and choosing the potentially desirable ones, thereby creating political and scientific momentum to gather resources to try to realize those visions. In the words of Jasanoff and Kim (2009, p. 122):

> The concept of sociotechnical imaginaries builds in part on the growing recognition that the capacity to imagine futures is a crucial constitutive element in social and political life. Imagination is no longer seen as mere fantasy or illusion, but as an important cultural resource that enables new forms of life by projecting positive goals and seeking to attain

> them. Nor is imagination understood as simply residing in individual minds in the form of aesthetic considerations. Rather, imagination helps produce systems of meaning that enable collective interpretations of social reality; it forms the basis for a shared sense of belonging and attachment to a political community [. . .]. In short, imagination, viewed as "an organized field of social practices", serves as a key ingredient in making social order.[2]

While Jasanoff's analytical perspective may have run counter to certain well-established research traditions in social science (such as rational choice theory), it seems to resonate well with the practitioners' self-understanding that it set out to be critical of. Indeed, the title of an ambitious policy document by ASCO, the American Society of Clinical Oncology, was "Shaping the Future of Oncology: Envisioning Cancer Care in 2030", in which they stated already in their foreword: "By anticipating the future, we can shape it." (ASCO 2012, p. 2).

The exact content of the imaginaries of personalized medicine/precision medicine varies across nations, disciplines, policy arenas et cetera. There is "P4 medicine", in which "participation", construed as an opportunity and a right for the scientific citizen-patient, is a central part of the imaginary. Blasimme (2017) argued that this ingredient played an important role in the quest for political legitimacy of personalized medicine in the US. There are also more modest visions of personalized medicine that focus on opportunities of incremental progress by means of a somewhat higher degree of tailoring of treatment according to patient characteristics. In this chapter I shall focus on the absolutely not modest version that strongly resonates with the more recent concept of *precision medicine*. The core of the imaginary to be analysed in this chapter is the idea that healthcare may and will be improved by the application of molecular life sciences combined with big data approaches in order to tailor medical treatments: "the right drug to the right patient, at the right moment and in the right dose" (see, Plutynski in this volume). The idea is that poor response or harmful side effects of treatment, in particular drug treatment, is due to differences between the biological constitution of the individual patient and the average or general type that previous medical knowledge had as its reference. By knowing all relevant biological parameters of the individual patient, one is then supposed to eliminate uncertainty and obtain precise control over the disease on a par with exact sciences and the (imagined) state of art in physical engineering (see Fig. 1).

Sociotechnical imagination departs from mere wishful thinking, however, in its efforts to specify the concomitant developments in scientific, technological, and societal infrastructures and institutions that would be needed to produce the overall desired future. For instance, the mentioned vision exercise of ASCO (2012) goes far to delineate a new healthcare system in which the health data of all cancer patients are part of one universal research project, and there is a complete, seamless merger of cancer care and cancer research (Fig. 1). This vision is not only a matter of change in institutional and professional practice but also profound change in the sick role:

[2]The many in-line references of the original have been omitted for readability.

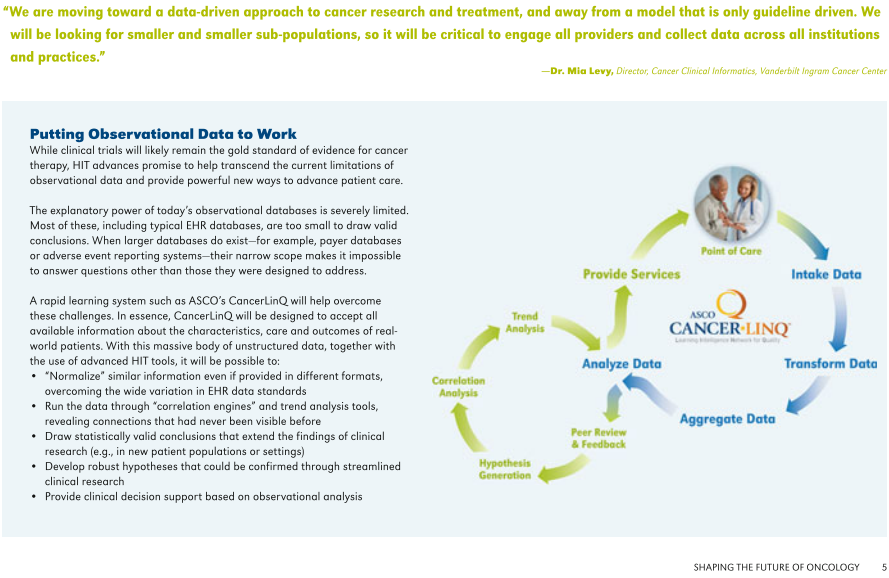

Fig. 1 Facsimile from ASCO's vision document for the oncology of the future (2012, p. 5)

> Patients as full partners. Through personalized, patient-friendly HIT tools, patients will have a much greater opportunity to serve as well-informed advocates for their own care. While not every patient will take advantage of these possibilities, most will. By 2030, the results will include a significant shift in the doctor-patient relationship. By the time patients arrive for consultation with an oncologist, most will already know a great deal about their cancer, thanks to personalized information from patient portals in CancerLinQ or other systems. They will expect to contribute to all important decisions about their care, while looking to their physician to suggest alternatives (ASCO 2012, p. 6).

Again, this should not be read as imagination and anticipation and not as prediction – who can predict events in 2030 in a world that seems to produce surprises ever more rapidly? In ASCO's own words, their use of language is to be seen as speech acts and not truth claims: "By anticipating the future, we can shape it."

The Imaginary of Precision Medicine Runs Counter to Knowledge

While molecular genetics did not emerge until the latter part of the twentieth century, the hope of curing and eliminating disease and suffering is not new. Already René Descartes postulated that "we might free ourselves from countless diseases of body and of mind, and perhaps even from the infirmity of old age, if we knew enough about their causes and about all the remedies that nature has provided for us." (Descartes 1637, p. 25).

For philosophers of science it is quite evident that the imaginaries of personalized medicine and precision medicine depend upon, and are built upon, a set of reductionist assumptions. The composition of this set of assumptions will of course depend on the exact content of the imaginary in question. While a given policy report or scientific publication may not adhere to all of the following, and while the list is not likely to be exhaustive, I present below a set of six such assumptions that I personally have encountered during my 25 years of taking part in debates within and around medical and health-related research and policy making (see also Strand 2000; Schei and Strand 2015):

1. In general, illness is reduced to disease. More precisely, there is little or no distinction between the (phenomenological) experience of illness/poor health and the (biological) existence of biological disease in humans; or if the distinction is made, it is assumed that the illness is caused by a corresponding disease and that the illness can be and should be treated, that is, cured or cared for, by curing or otherwise addressing the disease.
2. In general, it is assumed that states of disease are distinct and sharply demarcated states in the sense that they are descriptively identifiable, recognizable, and quantifiable. There are clear demarcations between the normal and the pathological.
3. In general, it is assumed that patients with diseases should be treated by medically correcting pathological biological states, e.g., by fully or partially restoring biological normality.
4. Most often, it is assumed that the relevant entity of disease is confined to the body of the individual patient, and that treatment is and should be an intervention on that body. While the slogan often reads "the right drug at the right dose", proponents of these imaginaries do not necessary exclude interventions addressing diet or exercise. However, the focus is often on drugs – what the nineteenth century champion of physiology Claude Bernard called "toxic substances" given to correct physiological imbalances and restore normality.
5. In general, it is assumed that there is a "right" way to give medical treatment to persons with disease, and that this right way is preferable to no medical treatment, or treatments that are not directed towards correcting the pathology. A special case of this assumption is the one holding that disease simply is an imbalance of some sort, and the right treatment is that which restores balance.
6. In general, it is assumed that health is such an important value that other personal or societal costs, e.g., of changing norms, expectations and thresholds for taking on a sick role, the role of what it is to be a patient or an individual at risk, are small in comparison. In slightly more involved terms, it is not necessary to pay attention to the hazards of medicalization, or the risk that the costs of medicalization outweigh the health benefits of personalized/precision medicine.

I do not claim that this set of assumptions is the only reasonable formulation. Undoubtedly it would be possible to identify more such assumptions, or slightly different ones, or find specific examples of imaginaries where not all these claims are being made (neither explicitly nor implicitly).

I claimed above that these assumptions are reductionist. By that I have allowed myself to use a broad concept of reductionism: illness is being reduced to disease; disease is being reduced to identifiable pathologies in the individual body; wise governance of life with disease is reduced to medical intervention; the good life is reduced to health. We may add that there sometimes are flavours also of genetic reductionism and upward causation (from molecules to cells; from cells to tissues) in these imaginaries.

We might wish to enter detailed discussions about each of such assumptions. We may entertain detailed, sophisticated conversations with medical scientists and practitioners about biological complexity, epigenetics, upward and downward causation et cetera, going into cutting-edge details from life science research. In this book chapter, however, I wish to do something else: simply state that there is *established knowledge* in the thought collectives of health science, psychology, philosophy of science, philosophy of medicine, complexity theory, philosophical anthropology and, I expect, other fields that I do not know well, that undermine the set of assumptions 1-6 above. Just to give some examples, Mervyn Susser (1973) introduced the distinction between illness, sickness and disease almost 50 years ago, and there is a huge body of research that shows that these categories are distinct and cannot be reduced to each other (Hofmann 2002). Georges Canguilhem (1966) provided his profound analysis of the non-triviality of the distinction between the normal and the pathological much before. Well-established critiques of medicalization and healthism have been around for decades (Ilich 1975; Skrabanek 1994). For those of us who are familiar with this type of knowledge, we know that there can be disease without illness, illness without suffering, suffering without illness or disease; other values in the good life than health; different concepts of health; ways to live and die with illness and disease that sometimes are better than undergoing treatment, and so on and so forth. If we choose to converse with scientists trained only in the natural sciences or in biologically oriented medicine, or with medical practitioners from conventional medical schools, it may be that our interlocutors are unfamiliar with these sources of knowledge. It may also be that they have little interest in or respect for these bodies of knowledge, which invariably have less in common with the ideals of exact physical science than at least they believe medical science to have. And so we may find it worthwhile to translate our insights into their vocabularies, conceptual schemes and paradigms. Accordingly, we talk and write about epigenetics, complex adaptive systems, mirror neurons et cetera when we could have expressed the same points better in our own thought collectives that allow the vocabularies of the humanities and social sciences. Rather than epigenetics, we could have talked about how the life of a human is imbued with meaning and sense and entangled into the lives of other humans and non-humans, and how each of us meets the existential challenges of defining our sense and purpose, and of coming to terms with and ascribing meaning to our own mortality and vulnerability. For some individuals, as their (our!) minds and bodies become old and weary, perhaps with metastases, or with onset neurodegenerative disease, or simply with our vitality ebbing out, it may or may not be that biological disease interventions could improve quality of life or the capacity to live a good

life; it may equally well be that such interventions are irrelevant to the existential challenges of living and dying. The assumptions A-F might have worked if humans were Cartesian machines, but we are not. Even by the Cartesian scheme, we are absolutely not mere machines or mere animals. Already Descartes recognised this in a way so different from the cardboard figure that sometimes is taught in poor classes of philosophy:

> So instead of finding ways to preserve life, I have found another much easier and surer way to deal with death, which is not to fear it. But this doesn't depress me, as it commonly depresses people whose wisdom is drawn entirely from the teaching of others, and rests on foundations that depend only on human prudence and authority (Descartes 1646, p. 183).

To sum up, as activists and citizens, in our mission to improve the world and specifically the institutions and practices of healthcare, we may find it important to translate anti-reductionist insights in order to dissent, challenge and destabilize reductionist imaginaries. When we meet between ourselves, however, as well-read philosophers, this *knowledge question* is perhaps not so pressing. We know that these assumptions do not hold in the general case.

"We Have Never Been Modern": On Fantasies and Futures

Let us dwell for a moment, however, on our experiences with engaging with the knowledge question in debates and conversations with the proponents of these reductionist imaginaries. Were they easily impressed? I would be interested to know if they were; in my experience the immediate response varies from rejection to intellectual curiosity while the long-term response, in terms of change in imaginaries, plans and policies, is meagre or absent. In this sense, we may criticize them for promoting *fantasies*, that is, imaginaries that are irresponsible in their representations of reality as we know it.

Such criticism tends – again, in my experience – not to make a great impression, either. I think there are a number of relatively independent reasons for that. First, there are of course situations in which the conversation does not take place in mutual good faith and in which the interlocutors do not wish to respect the norm of intellectual truthfulness when the outcome of the conversation may be detrimental to their own interests, which could be prospects of profit, power, status or also an identity project or otherwise a psychological or existential matter. There is marketing, hypocrisy and illusion. I am mentioning this not because it is my main experience, but to acknowledge that lack of good faith also is a real phenomenon in this world.

There are more interesting explanations, however, than those ascribing behaviour to interests. One explanation is that of a particular brand of *scientism* that comes together with reductionism and which creates tensions with intersubjective mutuality and communicative action, to borrow two terms from Habermas. It is the position that validity claims from holders of knowledge that is non-scientific or belonging to other academic fields than those endorsed as appropriately reductionist, in principle

are inferior. Accordingly, to the extent that they contradict reductionist positions, truth claims or beliefs, they do not deserve to be taken into serious consideration. More than incommensurability this is perhaps to be likened with sectarianism. This type of attitude is rarely stated in writing. A prominent exception is the introduction to Francis Crick's (1994) *The Astonishing Hypothesis.* The hypothesis that Crick finds so bold, astonishing and credible is that humans have no free will; he takes the exact sciences to prove this claim. In the introduction, he reveals that he is aware of the long debates around free will in philosophy and psychology, but simply dismisses them as play with words: "You do not win battles by debating exactly what is meant by the word battle." (Crick 1994, p. xi). While Crick might be in for surprises if he got to discuss with military strategists, the point of the metaphor is not only clear but revealing: knowledge and power come to the same thing, as Francis Bacon wrote more than 300 years earlier.

Another explanation belongs more to psychology: knowledge is not necessarily the crucial element when people make up their minds on political issues. This is well known with respect to elections and the general electorate. There is little reason to believe that the scientists, policy-makers, entrepreneurs and other stakeholders who take part in the creation, shaping and promotion of sociotechnical imaginaries are different. The reason that some might express, is some kind of modernist belief in the superior rationality of the scientific and political elites of the modern society; that they indeed are the philosopher-kings, as it were. This belief is in no way confirmed by empirical studies of science in practice, ever since Kuhn. More fundamentally, such modernist beliefs tend themselves to make assumptions about the clean separation between facts and values, and reason and passion, that contemporary philosophy thought collectives to a large degree abandoned with the critiques of positivism. Reductionist types of biomedical science and non-reductionist types of health science are value-laden each in their own way, and when knowledge claims clash, it is by no means certain that it is a case of clean, value-free commensurability and theory choice.

More importantly, there is the sociological explanation that was provided by Steve Rayner (2012) with his concept of socially constructed ignorance. The abstract of his paper begins as follows:

> To make sense of the complexity of the world so that they can act, individuals and institutions need to develop simplified, self-consistent versions of that world. The process of doing so means that much of what is known about the world needs to be excluded from those versions, and in particular that knowledge which is in tension or outright contradiction with those versions must be expunged. This is *uncomfortable knowledge*. The paper describes four implicit strategies which institutions use to keep uncomfortable knowledge at bay: denial, dismissal, diversion and displacement. (Rayner 2012, p. 107).

That is, the institutional situation, and indeed the individuals' own work, becomes impossible or unbearable if one allows oneself to be confronted by uncomfortable knowledge and acknowledges it. Anti-reductionist insights are instances of uncomfortable knowledge in institutions of health practice and policy that build upon and embody reductionist assumptions.

Finally, and most profoundly, it is important to realize that imaginaries and knowledge claims are different in that imaginaries are descriptions of *desired future states* while knowledge claims are representations of *present reality.* Knowledge claims, especially those analogous to impossibility claims – "it is not possible to cure cancer; it is not possible to make people happy just by giving them a pill" – are subject to the counter-argument that it is not thought to be possible yet, but that in the future, we will have advanced our knowledge and in the course of that process have falsified and rejected our impossibility beliefs. Who would have thought that phenomena such as radioactivity, black holes, moon travel, and the internet were possible? The idea of "the science of the future" implies the idea that some of our present claims to knowledge may turn out to be false and that we should be cautious with giving current knowledge too much weight, especially in decisions in which conservatism might impede progress. If our knowledge is poor (in this sense), it may even be rational under certain circumstances to ignore it and place more emphasis on imaginaries and their corresponding action plans to improve the state of knowledge. Bruno Latour (1993) made the case that "we have never been modern" in this sense; that the development of modernity with its idea of scientific and political progress, indeed rested on the ideologies of scientific objectivity, of the dichotomies between science and politics; facts and values; nature and culture; and reason and passion, while the practices of modernity never assumed or upheld these dichotomies. Although Latour to my knowledge never used the term himself, the ideological work in modern society, what he called the work of purification, was a matter of ideology in the classic sense: of false consciousness.

This explanation does not render the knowledge question irrelevant. The fact that we know now – at least those who have made themselves familiar with it – the importance of the distinction between illness and disease, is not rendered irrelevant by the logical possibility of creating a future where such a distinction does not hold or has no relevance anymore. Likewise, today it is a fact that humans hold dear to them many other values than that of good health. It may be logically possible to create a future in which humans by far value health over any other aspect of life. What is at stake, however, is not just the epistemic question of what is the case and what might become the case, but also the normative question of what is desirable. The philosopher of biology and medicine Wim van der Steen (1995) was always careful to point out that the counterpart to value-laden facts are fact-laden values. The normative questions about what kind of future may be desirable, can be reasonably informed by facts about the present and facts about reasons for valuing aspects of the present. It means, however, that if we wish to engage in conversations about the knowledge question as we called it above in order to engage in the coproduction of imaginaries and the shaping of the future, we are well-advised to acknowledge that it is a normative question as much as a descriptive one.

What Is a Stake? The Possible Impacts of a Fantasy

If we pursue the line of argument that I have sketched above, the pertinent question becomes: *what is at stake?*

There can be no unique answer to that question and no monopoly on answering it. The formulations of the sociotechnical imaginaries of personalized/precision medicine have their own (explicit and implicit) answers to it: diseases cause tremendous illness and suffering, and by pushing for further advances in biomedicine, the suffering may be reduced.

In the existing, rather shallow political debates on the development of biomedicine, risks to privacy and the spiralling costs are among the foreseen side effects of the merger of biomedicine and big data.

Given the enormous scope and size of the health sector in modern societies, however, there is almost no end to the list of what issues may be at stake. On a level higher than individual economic interest, personal as well as corporate, there is no doubt that the governments in industrialized countries invest hope in personalized/precision medicine as part of the envisioned emergence of a bioeconomy that will replace old, fossil-fuelled industries and take especially Northern and Western countries out of chronic economic stagnation. As an instance of imaginaries of technoscience, personalized/precision medicine both reinforces and borrows credibility from sustained visions of capitalist societies with wealthy and healthy consumers. It is part of what Foucault called biopolitics. This is why the issues of growth, de-growth and post-growth also are at stake. Be it politically incorrect, the question is what effect increased longevity and an increased health sector will have on mankind's huge challenges of sustainability. How many of us are going to live for very long and how much are we supposed to consume during these lives? I will leave this as an open question.

At the individual level, for those who are facing grave illness and disease in the present, hope and despair are what may be at stake. While there is little reason to believe that the prospect of lethal disease and painful death was less terrifying and appalling to the human beings of the past, the difference now is that the metaphysical catastrophe of the suffering individual, through social media and mass media, may mobilize political power. Brekke and Sirnes (2011) coined the term "the hypersomatic individual" to describe how the fatally ill of our time and culture may succeed in mobilizing so much political attention that even governments may be pressured to increase budgets, change health priorities and even change laws. The hypersomatic individuals approaching their catastrophe, cry out that Science could and should save them, had it not been for political shortcomings (lack of funding, strict regulation of biotechnology, ethics that slows down research):

> There are no inherent obstacles or pitfalls of science that could stop the realization of revolutionary cures. Therefore, this is not about science; it is all about politics (p. 356) [. . .] individuals caught in a somatic reality with a shrinking space for action and coping, and the future is seen as determined by medical diagnostics and prognoses. In this general biosocial condition of being "locked in," there is an urgent need for emergency exits that manifests itself in a fundamental desire to escape the limitations of scientific uncertainties

> and rational calculations of risk. The main escape route is constructed by conflating time and institutional fields: the future is swallowed by the present, and the scientific by the political. The morally correct political actions will produce fundamental scientific breakthroughs in the present, and thereby create medical alternatives for the paralyzed biocitizens who otherwise have no alternatives (Brekke and Sirnes 2011, pp. 357–358).

The result is that the value of justice as fairness suffers as experiments to treat high-status diseases such as cancer gain resources at the expense of a number of other health problems and social causes.

Brekke's and Sirnes' (2011) analysis focused on political power. At the same time, it seems reasonable to speculate what the developments – real as imaginary – have of impacts on cultural understandings of the good life and the good or bad death (Engen 2017). In this sense, in terms of what is at stake for the human condition, it seems pertinent to invoke the insights from 40 years of discussion of medicalization, since Ilich. Vetlesen (2009) has warned against a medicalized culture that contributes to individual and collective avoidance and denial of the basic conditions of human life such as that we humans are vulnerable and mortal and that we depend on each other and the potentially fragile relationships between us. We may recall the exemplary future patient imagined by ASCO, who should and will devote considerable attention to the scientific understanding and management of her or his disease, even when ill. How will one's salutogenic potential, that is, one's bodily and mental resources and potentials to support own health and well-being, change if personalized medicine becomes a reality, or alternatively, the imaginary becomes absorbed into culture and self-understanding? How much attention will be left to create a sense of meaning of one's condition together with family and friends, to create, develop and experience love in the midst of suffering or as life ebbs out? What role will spirituality be allowed to play in such a culture? How might the conditions change for learning to let go of this life? By stating this multitude of open questions, I do not pretend to know that the impacts will all be negative. Rather, the impacts are in principle uncertain and the attempt to realize such imaginaries is an open-ended social if not civilizational experiment, both what concerns their intended, unintended and unimagined consequences. It is fully imaginable and, I would argue, plausible from a non-reductionist position that the full impacts might become quite undesirable even if some of the reductionist dreams come true.

The New That Cannot Be Born

Antonio Gramsci (1947) famously wrote: "The crisis consists precisely in the fact that the old is dying and the new cannot be born; in this interregnum a great variety of morbid symptoms appear." What he had in mind was the socioeconomic and political order; the main morbid symptom was fascism.

Together with my colleagues, Anne Bremer (née Blanchard) and Caroline Engen, I have wondered if not Gramsci's quote also might provide a lens for interpreting the emergence of a "war on cancer" in the 1970s and the imaginaries of personalized/precision medicine of the 2000s (Blanchard et al. 2017). If these

imaginaries are seen as a morbid symptom, what is the old that is dying and the new that cannot be born?

We have argued that the old that is dying may be the Cartesian dream of freeing ourselves "from countless diseases of body and of mind, and perhaps even from the infirmity of old age" (Descartes 1637, p. 25). Above I noted how Descartes himself appeared to be able to distinguish fantasy from reality and wake up from this dream (see also Schei and Strand 2015). The dream lived on, however, as a programme for the abolishment of suffering, death and, more fundamentally, uncertainty. Claude Bernard wrote the following, 200 years after Descartes:

> Absolute determinism exists indeed in every vital phenomenon; hence biological science exists also; and consequently the studies to which we are devoting ourselves will not all be useless. General physiology is the basic biological science toward which all others converge. [...] By normal activity of its organic units, life exhibits a state of health; by abnormal manifestation of the same units, diseases are characterised; and finally through the organic environment modified by means of certain toxic or medicinal substances, therapeutics enables us to act on the organic units (Bernard 1859, p. 65).

Indeed, it is instructive to read Bernard's accusations against epidemiology and clinical science for not being truly scientific because they deal with variation and not determinism. While it would require a more detailed analysis than presented in this paper, it should be possible to show not only the reductionism but also the implicit and latent determinism within the imaginaries in particular of precision medicine.

The "old", then, can be understood as this dream and programme of denial, rejection and declaration of war on suffering and death by means of the weapons of medicine. Its form of dying, of degeneration into morbid symptoms, is the practical *reductio ad absurdum* when the weapons are turning against the human condition itself, creating threats to our cultural and existential resources and practices for creating good and meaningful lives, as well as absorbing and consuming ever more economic resources to the point where no government or insurance can pay anymore, and social and individual life becomes fully absorbed in a war against death that we are bound to lose.

What is the new that cannot be born yet? It seems to be very simple: The new is to come to peace with our own mortality and vulnerability as a fundamental condition not only for life, but for the good life. It is new, but at the same time, very old, not only the wisdom of Descartes after he woke up from the Cartesian dream; it is of course as old as all written sources, going back to the Old Testament, to the Greek philosophers, to the Daoists; to all traditions that regarded humans as having not only a physical body and an intellectual mind but also something more, sometimes called a soul and sometimes a spiritual life. In this sense it *is* born, it has always been there, and it still is. Unfortunately, however, the ideological work of purification in modern civilizations demanded that we pretend as if it does not exist. This is the paradox, then, of modern medicine, brought to its climax with precision medicine: It insists on the disenchantment of the world in order to make us believe and opt into a fantasy.

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