

Rethinking health and disease in the era of personalized medicine

Alessandro Rosa^{*}

Abstract: Genome-based medicine, usually referred to personalized medicine, aims to provide tailored treatments for a single patient according to his/her genome. Thanks to correlations between genotype and phenotype, it is also able to assess the chances of developing a disease given to the presence of a specific genetic mutation. Within the aforementioned paradigm, the first challenge to address is to properly define what is usually meant by the expression ‘personalized medicine’, specifying the methodologies it uses and the premises it is based on. Then it appears fundamental to discuss whether and how such vision entails any change for our theoretical concepts of health and disease. I will argue that this is the case and, in particular, that being able to predict the probability of diseases’ occurrence can significantly affect our philosophical concepts of disease, illness and sickness in different ways.

Keywords: Personalized Medicine; Health; Disease; Genomic

1. Introduction

As the name suggests, personalized medicine is a medical paradigm that aims to get to the personal level, essentially by assessing diagnoses and providing therapies tailored for a single individual¹. To achieve such ambitious goal, personalized medicine relies on a growing corpus of knowledge regarding genotype-phenotype associations². At the most basic level possible, genes are what makes us as human beings: they encode for proteins that build our organisms, thus they are responsible for many bio-

^{*} University of Bologna
alessandro.rosa7@studio.unibo.it

¹ Cf. for instance M. Hamburg, F.S. Collins, *The Path to Personalized Medicine*, “New England Journal of Medicine”, CCCLXXXIV, 4, 2010, pp. 301-304.

² Cf. A. Gamma, *Personalized and precision medicine*, in M. Solomon *et al.* (eds.), *The Routledge Companion to Philosophy of Medicine*, Routledge, New York 2016, pp. 411-421.

logical mechanisms involved in human physiology. Most of the human genome is identical across different individuals, but about 1% of it diverges in each person. This 1% is responsible for many of the variations that we are familiar with: some of us have green eyes, some blue ones, some are taller than others, there are people with red hair and people with black hair. These little variations are usually called single-nucleotide polymorphisms (SNPs) and they are also the probabilistic causes of many diseases related to genetic dysfunctions.

Personalized medicine embeds a vision according to which it is possible to take into account the consequences of all these SNPs to assess a specific diagnosis according to the genetic variation that a single individual carries. The underlying assumption is that we do not differ only in our external features, but also (and arguably, more importantly) in the features that predispose us to different disorders. The ultimate goal of personalized medicine is to consider these differences to develop more effective and safer drugs, assess more accurate diagnoses and elaborate better prognoses and provide predictions regarding future state of health.

Thanks to the newest technological advances in the biomedical field³, the dream of tailored treatments promises to become true. However, personalized medicine poses many challenges to several theoretical concepts related to medicine, and it is going to have practical impact as well. The focus on genes is likely to change many aspects of current clinical practice, and to raise many issues that might lead for some reshaping of future healthcare. As I am going to argue, personalized medicine is going to increasingly force us to rethink our concepts of health and disease: a large literature of philosophy of medicine questioned for many decades now what health and disease are, and the time has come to address such question under the light of the personalized medicine paradigm⁴. Moreover, as it is often the case when we discuss philosophical concepts in medicine, many ethical questions arise, in particular regarding the justification of those preventive treatments and the way in which healthcare is going to provide access to such treatments to all the patients.

In the first section I will provide a brief sketch of what personalized medicine is. Currently in medical literature the proper definition of person-

³ Cf. Akram Alyass *et al.*, *From Big Data Analysis to Personalized Medicine for All: Challenges and Opportunities*, "BMC medical genomics", VIII, 2015, pp. 33.

⁴ There are many volumes that try to address the issue with a philosophical perspective. Among these, cf. for instance, M. Gadebusch Bondio *et al.* (eds.), *Medical Ethics, Prediction, and Prognosis: Interdisciplinary Perspectives*, Routledge, New York 2017; T. Fischer *et al.* (eds.), *Individualized Medicine: Ethical, Economical and Historical Perspectives*, Springer, Cham 2015.

alized medicine is not entirely clear, and many terms have actually been proposed (e.g. precision medicine, stratified medicine, individualized medicine). To develop a proper framework for our philosophical investigation, I will start by considering the definitions given by the scientific literature and disentangle their ambiguities, claiming that they embody different sides of a more general biomedical paradigm. Then I will discuss the concepts of health and disease under the light of personalized medicine. I will focus my investigation on the well-known distinction between three different aspects of malady⁵ namely the distinction between disease, illness and sickness. I will briefly present those concepts and analyse how they are affected by the personalized paradigm, claiming that if we consider individuals already ill before a malady is taking place, personalized medicine is going to make a sharp distinction between symptomatology and the actual pathological condition. I will argue that, by detaching the symptoms from the malady, a sort of ‘de-temporalization’ of health is taking place. I will suggest that further philosophical reflections should be pursued which should get deeper into the consequences that such biomedical paradigm is going to have on the understanding and use of the concepts of health and disease.

In the following discussion I will mainly refer to oncology as the primary field in which personalized medicine has been successfully applied, due to the fact that cancer is a disease with a strong genetic component. However, an individualized approach can also be applied to the case of rare diseases. Often referred to as “orphan diseases”, rare disorders are usually related to genetic variations and mainly single-gene mutations⁶. Thus, personalized medicine has the potential to mark significant progresses towards the development of specific drugs for treating rare diseases which currently have no proper pharmaceutical treatment.

2. *Medicine at the personal level*

Following some fundamental discoveries in biomedical field – such as, e.g., penicillin to defeat bacterial infections – medicine has often thought

⁵ This distinction was originally laid out by Andrew Twaddle, but more recently it has been developed by Bjørn Hofmann. Cf. B. Hofmann, *Complexity of The Concept of Disease as Shown Through Rival Theoretical Frameworks*, “Theoretical Medicine”, XXII, 2001, pp. 211-236; Id., *On the Triad Disease, Illness and Sickness*, “Journal of Medicine and Philosophy”, XXVII, 6, 2002, pp. 651-673.

⁶ Cf. R. Trevor et al., *Rare disease terminology and definitions—a systematic global review: report of the ISPOR rare disease special interest group*, “Value in Health”, XVIII, 6, 2015, pp. 906-914.

about treatments according to the paradigm of ‘one drug fits all’. Accordingly, research has largely strived to develop ‘magic bullets’, i.e. drugs fighting directly pathogenic agents, and mean to invariably destroy them. Only with the works of Archibald Edward Garrod⁷, mostly forgotten until the mid of XX century, it started to appear that such model was not applicable to all cases. Garrod himself claimed that the way in which drugs are metabolized, and thus their efficacy, varies from individual to individual. From this simple but fundamental intuition the field of pharmacogenomics originated, a new branch of pharmaceutical and biomedical sciences focusing on how the effects of drugs are influenced by the genetic profile of the single patient. Reactions to the drugs have to do with “how the organism handles the drug (absorption, distribution and elimination), or changes in the direct response of the organism to the drug”⁸.

Personalized medicine aims to take into serious account individual differences to assess the best possible therapy for the single patient under investigation. Here the basic proposal is that, instead of developing magic bullets to cure all the occurrences of a disease in the same way, it would be best to develop targeted bullets, i.e. drugs that interact only in specific occasions. One of the fields that most benefited from this methodology is oncology. Until the late 70s, chemotherapy was the only strategy for fighting cancer, but it was indeed a costly one: chemotherapeutic drugs are highly cytotoxic, meaning that they negatively affect cells in the whole organism, without distinguishing between healthy and tumoral ones. Targeted drugs, instead of a scorched-earth strategy, try to aim only for the cells that went out of control. One paradigmatic example is a drug called tamoxifen which, by inhibiting the estrogenic binding in ER-positive cells, is able to stop cells replication in tumoral cells only, leaving the healthy ones almost intact, thus avoiding many of the major side effects of regular chemotherapy⁹.

During the last decades, one of the major scopes of biomedical research has turned into seeking relationships between gene variation and pathological conditions in order to gain insights of the underlying mechanisms involved in the latter. Thanks to the newest genome sequencing

⁷ Cf. A. Garrod, *The Incidence of Alkaptonuria: A Study in Chemical Individuality*, “The Lancet”, CLX, 4137, 1902, pp. 1616-1620.

⁸ H.E.M. Zu Schwabedissen, *The Role of Pharmacogenomics in Individualized Medicine*, in T. Fischer *et al.* (eds.), *Individualized Medicine: Ethical, Economical and Historical Perspectives*, cit., p. 94.

⁹ Cf. V. Craig Jordan, *Tamoxifen: A Most Unlikely Pioneering Medicine*, “Nature reviews Drug discovery”, II, 3, 2003, pp. 205-213.

technology, reading the human genome has constantly become easier and cheaper. Following the conclusion of the Human Genome Project, which was completed in 2003, the cost for a single complete genome screening has plummeted and machine learning algorithms used in bioinformatics allow researchers to intertwine large amount of -omics data (genomics, epigenomics, lipidomics, transcriptomics). This was the main step that allowed scientists and researchers to search for a way to develop personalized treatments.

By posing such attention to genotype-phenotypes correlations, both biomedical research and clinical practice are going to undergo significant changes. On the one hand, drug design is rapidly evolving: by knowing the molecular targets involved in a pathological condition, it is now possible to develop drugs aimed at only one specific target. This means that drug discover may become more analytical, thus less useful or even harmful compounds might be completely avoided¹⁰. In turn, this will also affect the way in which clinical trials are designed and evaluated. If we know that every individual has his/her specific genetic features, it only sounds reasonable to subdivide them according to their genome. Indeed, stratification is one of the core features of personalized medicine: once we know the genetic features that can influence the course of the disease, it is possible to create different clusters of patients that react in different ways to the same treatment.

In the actual clinical practice, stratification is going to play a fundamental role. To begin with, physicians can take advantage of the information they have regarding the genetic pool of their patients to make more thoughtful decisions regarding which drug to prescribe and in which dose. Having the complete genomic information of their patients, physicians would be able to prescribe and administrate more effective and safer drugs, according to case-by-case necessities. One recent example is Abacavir, which is commonly employed for AIDS patients¹¹ and which shows different effects according to a specific genetic mutation.

Analysing the pathological mechanism at the genomic level also significantly enhances our chances of dealing with rare disorders¹². Rare disorders are strongly related to genetic variations, and most of them are relat-

¹⁰ Cf. G.S. Ginsburg, J.J. McCarthy, *Personalized Medicine: Revolutionizing Drug Discovery and Patient Care*, "TRENDS in Biotechnology", XIX, 12, 2001, pp. 491-496.

¹¹ Cf. R.R. Shah, D.R. Shah, *Personalized Medicine: Is It a Pharmacogenetic Mirage?*, "British journal of clinical pharmacology", LXXIV, 4, 2012, pp. 698-721.

¹² Cf. Francesc Palau, *Personalized medicine in rare diseases*, "Personalized medicine", XIX, 2, 2012, pp. 137-141.

ed to single-gene variations, making them heritable diseases which significantly affect all family members that share the same genome. Therapeutic options for rare diseases are usually scarce and this entails that there are millions of people nowadays lacking proper medical treatment (despite their rarity, there is a huge variety of rare disorders, and thus as whole they affect a high number of individuals). A personalized approach in drug development, for instance, could lead to major advances in the development of proper biomarker for rare diseases, consequently improving our understanding of the pathological mechanisms underlying the malady, and thus increasing the chances of developing appropriate pharmaceutical therapies.

The most important theoretical change (at least with respect to the reflections pursued here) is the fact that with such knowledge regarding genotype-phenotype associations it became theoretically possible to make assessments regarding individuals' future states of health. Since we get our genes before we are born, personalized medicine is not only able to cure according to genetic features, but also to evaluate the probability of the occurrence of future pathological conditions. Oncology, again, offers a paradigmatic example: BRCA-1/2, a gene whose mutations are correlated to a high incidence of breast cancer in women¹³. In this sense, it is usually said that BRCA-1/2 is a biomarker for breast cancer, meaning that its mutation indicates a serious predisposition for the disease. The main problem that I will try to address in the following pages is whether such predisposition can then be understood as the philosophical concept of disease, and in what relations the two stands. Before that, however, I am going to explore more in depth the definition of personalized medicine itself.

3. *Personalized medicine: Many names for the same thing?*

Most of the debate around personalized medicine has been focusing on the question 'hype or hope?', thus asking whether a complete personalization of treatments could become reality or it is only intended as an idealistic goal¹⁴. Less effort was spent to propose a clear definition of the

¹³ Cf. S.A. Narod, W.D. Foulkes, *Foulkes Brca1 And Brca2: 1994 And Beyond*, "Nature Reviews Cancer", IV, 9, 2004, pp. 665-676.

¹⁴ Cf. for instance F.S. Collins, H.A. Varmus, *New Initiative on Precision Medicine*, "New England Journal of Medicine", CCCLXXII, 9, 2015, pp. 793-795.

expression “personalized medicine”, for instance to understand whether it can be encompassed in a single definition or if it has to be conceived as an umbrella-term that includes heterogeneous aspects¹⁵. As a consequence, scholars and researchers tend to use different expressions when they refer to a personalized approach depending on the specific situation, leading to what I believe is semantical misunderstanding. Here I will analyse the different ways in which personalized medicine has been addressed by scholars and researchers (that are: precision medicine, stratified medicine and individualized medicine) and try to identify patterns of usage, in order to make some (hopefully) clear distinctions. My suggestion here is to identify the different expressions that have been adopted in the scientific literature as sorts of sub-parts of a more comprehensive sense of ‘personalized medicine’, which should be intended as a paradigm¹⁶ (in the Kuhnian sense of the term), or, as it has been argued, as “sociotechnical imaginary”¹⁷. I believe that by doing so we could have a better understanding of what kind of practice personalized medicine is, what are the methods on which it relies on and what are its theoretical implications, which are going to be explored in the next and final section.

First of all, much focus has been put on the different strategies to stratify population according to their genetic features. For this reason, ‘*stratified medicine*’ is a rather popular choice among expressions in medical literature¹⁸, as it clearly indicates the methodology that has been used. This approach aims to stratify the groups of patients at the finest possible level, i.e. to have small clusters of patients representing every single mutation that is relevant for a pathological condition. Ideally, these small groups could be so sophisticated to include only one single individual, but this is not strictly required. Instead of treating a group of patients (for instance, all of those who suffer from cardiovascular disease) with the same drug, it is possible to subdivide them according to different criteria (usually genetic ones) and administrate different drugs to

¹⁵ Cf. D.M. Roden, R.F. Tyndale, *Genomic Medicine, Precision Medicine, Personalized Medicine: What’s In A Name?*, “Clinical Pharmacology & Therapeutics”, XCIV, 2, 2013, pp. 169-172.

¹⁶ The debate whether personalized medicine is actually a complete new biomedical paradigm is still open. Cf. for instance M. Gadebusch Bondio, F. Spöring, *Personalized Medicine: Historical Roots of a Medical Model*, in G. Boniolo, M.J. Nathan (eds.), *Philosophy of Molecular Medicine*, Routledge, New York 2016, pp. 43-64.

¹⁷ H. Tarkkala et al., *From Health to Wealth: The Future of Personalized Medicine in the Making*, “Futures”, CIX, 2019, pp. 142-152.

¹⁸ Cf. A. Greystoke, A. Chaturvedi, *An Introduction to Stratified Medicine*, “Drug Discovery Today”, XX, 12, 2015, p. 1409.

each of them. From a methodological point of view, stratified medicine is the first step to reach an actual personalized medicine, as it allows both biomedical researchers and healthcare professionals to make more rational classifications of diseases according to their risk factors, thus providing a better understanding of biological mechanisms.

Secondly, the term '*precision medicine*' is often used as a synonym for personalized medicine. When biomedical researchers talk about precision, they mostly refer to the ability of looking at the molecular level to understand every single point of a biological mechanism¹⁹. The main advantage of this approach is that by targeting only the molecular points involved in the physiological dysfunction there is less risk of harming the organism of the patient and, at the same time, higher chances of actually fixing the broken biological pathway. Nevertheless, one should not forget that more precise does not automatically mean better. If taken by itself, precision medicine only requires operating at the molecular level to target only the essential points of the mechanisms involved in the disease and leave the rest untouched. But the incredible complexity of biological organisms cannot always be tackled according to such an approach: the development of pathological conditions cannot be reduced only to a form of genetic determinism, as there are many factors that can concur²⁰.

Thirdly, the differences between '*individualized medicine*' and 'personalized medicine' are often very slight. The semantic shift might also be due to different language origins; for instance, Tobias Fischer et al.²¹ argues that for German speakers 'individualized medicine' is often preferred to 'personalized medicine', which is more commonly used in Anglo Saxon areas. If stratification and precision are indispensable tools for a medicine able to develop tailored therapies, individualized medicine stresses out the importance of taking into account specific individual needs. Personalized medicine does not only aim to be a precise and targeted medicine, but most likely a form of medicine that takes into consideration *all* the relevant evidence. To achieve such goal it is fundamental to include "genetic background, age, gender, environmental risk factors, lifestyle, culture and beliefs as well as social status in the overall predisposi-

¹⁹ Cf. J.L. Jameson, D.L. Longo, *Precision Medicine: Personalized, Problematic, and Promising*, "Obstetrical & Gynecological Survey", LXX, 10, 2015, pp. 612-614.

²⁰ Cf. A. Gamma, *The Role of Genetic Information in Personalized Medicine*, "Perspectives in biology and medicine", LVI, 4, 2013, pp. 485-512.

²¹ Cf. T. Fischer et al. (eds.), *Individualized Medicine: Ethical, Economical and Historical Perspectives*, cit.

tion of individuals to specific diseases, the disease development, the natural course of disease and the response to therapeutic intervention”²².

In the end, I believe that most of the enthusiast scholars prefer to use ‘*personalized medicine*’ due to the fact that, from a semantic point of view, ‘personalized’ automatically implies the acknowledgement of a sort of primary importance of the patient as a person. If that is the case, it should be noted that the expression ‘personalized medicine’ could, however, be misleading: although a more person-centred medicine is indeed hopefully to be included in every aspect of clinical practice, the methodology that has been actually pursued in biomedical research under the label of ‘personalized medicine’ has little to do with that. Taken by itself, personalized medicine is simply the sum of stratification strategies and precision at the molecular level. This, of course, does not automatically imply that a person-centred approach is not compatible with the methods and goals of personalized medicine, but the discussion of this point goes well beyond our argumentation.

So, where do the differences actually lie? The different terms used to talk about personalized medicine are not merely different names for the same thing, but they indicate different aspects of this whole new approach in health care. I suggest personalized medicine should be conceived as a combination of:

- a) a stratification approach that plans to subdivide groups of patients affected by the same type of disease on the basis of
- b) a deep knowledge of the molecular features and potential differences among specific cases of the same disease to
- c) correctly assess the risks of undergoing a certain treatment and/or taking a certain drug
- d) in order to develop and administrate the most appropriate pharmacological therapy for each single patient.

To achieve all of these goals, personalized medicine relies on new information technologies and digital tools that gather huge amount of data regarding the single patient and integrate them with the data already gathered from other patients that share some characteristics with him/her.

Currently, those goals are far from being reached, and some scholars are starting to use the term “semi-personalized medicine”²³ to describe a

²² O. Golubnitschaja *et al.*, *Medicine in the Early Twenty-First Century: Paradigm and Anticipation-EPMA Position Paper 2016*, “EPMA Journal”, VII, 1, 2016, p. 2.

²³ Cf. N. Marino *et al.*, *Breast Cancer Metastasis: Issues for the Personalization of Its Prevention and Treatment*, “The American Journal of Pathology”, CLXXXIII, 4, 2013, pp. 1084-1095.

clinical practice in which stratification and molecular precision play a fundamental role. However, despite still in development, the premises of personalized medicine are already affecting our concepts of health and disease. Does personalized medicine provide a new biomedical paradigm to conceive health and disease? As Thomas Kuhn famously remarked,²⁴ one important feature of paradigm shifts is that they provide scientists with tools with which they can see reality in a new and different way. Admittedly, since the conclusion of the Human Genome Project, biomedical research has fundamentally changed its trajectory by giving ever more weight to genomic data. Therefore, we should now turn our attention to ways in which personalized medicine affects our theoretical concepts regarding medicine: to what extent are they affected, and how?

4. *Health, disease, illness and sickness*

As it was previously mentioned, Bjørn Hofmann has elaborated a useful framework to understand the debate around health and disease. Stressing that we should start off from the concept of disease he claims that a pathological condition can be a disease, an illness or a sickness depending on the level that we are interested in. It may be the case that, in a given situation it is all the three at the same time; this would make it the 'ideal' case and the less controversial one. There are, though also cases in which it is more difficult to assess in which sense an individual has a pathological condition (for instance in case of illness without disease).

The term 'disease' refers to the way in which scientists and healthcare professionals assess that a certain condition is pathological, which is usually made by performing measurements of specific biological parameters. It is strictly related to the way in biomedical knowledge that scientists have, for instance the fact that a high cholesterol level is associated with cardiovascular malfunctioning. This is intended to be as objective as possible: no personal or normative evaluations are included in such measurements, what is crucial is the data that are gathered.

The term 'illness', on the other hand, is related to how individuals feel: do they feel pain? What are their symptoms? Are they suffering from mental discomfort due to their condition? Do they consider themselves as patients in need for a treatment or not? The point is that there are some

²⁴ Cf. T. Kuhn, *The Structure of Scientific Revolutions* (1962), *La struttura delle rivoluzioni scientifiche*, tr. it. by Adriano Carugo, Einaudi, Torino 2009.

variables that cannot be just measured objectively by medical staff and that are related to the personal experience, i.e. how one lives her/his condition pathological condition. The domain of illness includes all the sensations (usually negative ones) that we feel as individuals, but there is a sense in which every one of us is part of a larger collective, hence there is a social sense of disease. We thus have ‘sickness’, i.e. the malady as it is perceived by ‘others’, by society in the broadest sense possible. This includes not only how sick individuals are seen by the people that surround them (relatives, friends, co-workers etc.), but in a broader sense by societal institutions (government, public health care, companies etc.). The concept of sickness is fundamental, as usually people are treated as patients only when social institutions recognise them as patients.

With the triad framework it is easy to understand the main disagreements between different accounts of health and disease. The most established account of naturalism in medicine is Christopher’s Boorse²⁵ biostatistical theory (BST from now on). According to Boorse, “health is the normal functioning, where the normality is statistical and the functions biological”²⁶, meaning that to define health we have to look at the way in which organisms function in their “natural” way. For instance, to be healthy one must have a normal heart, which is just a heart that fulfils its main purpose, which is pumping blood into circulation.

Describing ‘normal’ is far from being an easy task, but according to BST we can limit ourselves with the statistical meaning, i.e. considering normal what, from a biological point of view, appears to be the common with respect to a certain reference class (e.g. Caucasian men of age above 65). As for functions, they are intended as a form of contribution for a goal: the heart normally pumps blood because it contributes to the general goal of making the organism survive. Therefore, a particular condition is pathological only when there is a sort of malfunctioning in the physiology of the individual, as compared to the way in which it normally works. For instance, a certain level of cholesterol in the blood stream of an individual is currently referred to as hypercholesterolemia and it is treated as a disease (for example, with drugs able to lower the level of cholesterol).

It is clear that according to Boorse a pathological condition is equal to a disease, in the sense illustrated above. Does this mean that we should

²⁵ Cf. C. Boorse, *On the Distinction between Disease and Illness*, “Philosophy & public affairs”, V, 1, 1975, pp. 49-68; Id., *Health as a Theoretical Concept*, “Philosophy of Science”, XLIV, 4, 1977, pp. 542-573 and Id., *A Second Rebuttal on Health*, “Journal of Medicine and Philosophy”, XXXIX, 2014, pp. 683-724.

²⁶ C. Boorse, *Health as a Theoretical Concept*, cit., p. 542.

not care about the personal experience of the patient? This is not the case. In fact, Boorse specifically addressed the problem by claiming that personal experience of pathologies (e.g. the symptoms that the patient suffers) are not entirely denied by BST, but they are conceptually subordinate with respect to biological malfunctioning. Illnesses exist, but they “are merely a subclass of disease. Namely those disease that have certain normative features reflected in the institution of medical practice”²⁷. According to Boorse, there might be cases in which illness is present along with disease, whereas the opposite is not possible.

Anti-naturalism approaches oppose this overall framework by claiming that there is nothing ‘natural’ in the concepts of health and disease. One approach that denies naturalism is normativism. The key feature of normativism is that health cannot be entirely reduced to a natural concept, as the way in which we use health and disease terms are strictly dependent on the norms that we adopt. In other words, health is a state that has a positive value for us as a single individuals or as a social group, while disease is something that we regard as harmful for us. According to Rachel Cooper, “by disease we mean a condition that it is a bad thing to have, that is such that we consider the afflicted person to have been unlucky, and that can potentially be medically treated”²⁸. This, of course, does not mean that biology has nothing to do with health. What is stressed out by normativists is that we should firstly consider the meaning that health and disease have for us, i.e. our personal experience as patients and social conceptions. This entails, among others, that such concepts are subject to change due to shifts in the cultural context.

One famous example that might shed light on the issues involved in the naturalism/normativism debate is provided by the case of homosexuality, which was considered a disease by the first edition of the *Diagnostic and Statistical Manual of Mental Disorders* and was only removed in 1973 after a heated debate²⁹. Homosexuality was considered a disease for a lot of reasons that nowadays we would reckon as mere prejudices regarding homosexuals, and we will all currently neglect that it is a disease.

Differently from what naturalism holds, according to normativism illness and sickness are conceptually prior to disease, i.e. it is more important to consider how patients feel and how society consider them than to

²⁷ C. Boorse, *On the Distinction between Disease and Illness*, cit., p. 56.

²⁸ R. Cooper, *Disease*, “Studies in History and Philosophy of Biological and Biomedical Sciences”, XXXIII, 2002, p. 271.

²⁹ Cf. R.L. Spitzer, *The Diagnostic Status of Homosexuality in DSM-III: A Reformulation of the Issues*, “American Journal of Psychiatry”, CXXXVIII, 2, 1981, pp. 210-215.

count, e.g., how many blood cells he/she has in circulation. There are obviously many ways of identifying good and bad values and this is not the place to address them thoroughly, but basically a pathological condition is something that causes some kind of harm to the person, while health is something desirable. The focus is on the harm that the individual suffers and less on the biological dysfunction that is going on in his/her organism.

To conclude, according to naturalism a pathological condition is always a disease, which only in some cases can also be intended as an illness. For normativism, on the other hand, illness and sickness are primary concepts for understanding a pathology, as personal evaluations and social norms actually shape the way in which we intend pathological conditions³⁰. Given this traditional framework, let us now ask: in which ways does personalized medicine affect this debate? Does the focus on genomic data bring any consequences on the concepts of disease, illness and sickness? Does a predisposition for a disease count the same as a pathological condition? The next section will provide some tentative answers to these questions.

5. Health and disease in the era of personalized medicine

As recalled above, personalized medicine does not only want to achieve custom-made treatments, but also tailored predictions. According to this approach, people might receive relevant information on the basis of genetic tests before any sign of the disease has even occurred. For instance, it might be assessed that a particular woman has an 85% chance of developing breast cancer in her life due to the fact that she is a BRCA-1/2 carrier. To have predictive tools is indeed a great opportunity for medicine, and it comes without doubts that it might significantly enhance clinical practice; however it also has serious implications for our concepts of health and disease – as well as, it goes without saying, for the perception of one own's condition and for related personal decisions.

To begin with, one could argue that if personalized medicine heavily relies on genetic traits to predict the occurrence of a malady, it implies that pathological conditions are thereby conceived as biological dysfunc-

³⁰ The description of the debate depicted above is, of course, highly simplified. The contrast between naturalism and normativism can be analysed at many different levels and from many different points of view. For an overview, also cf. Elseltijn Kingma, *Naturalism about health and disease: adding nuance for progress*, "The Journal of Medicine and Philosophy", XXXIX, 6, 2014, pp. 590-608.

tions, in the sense that we have illustrated in the previous section. Let us wonder: is being predisposed for a particular condition the same as having a biological dysfunction? Is it a matter of fixing threshold, i.e. is there a certain value of risk above which it is possible to claim that a predisposition is already a disease? Is personalized medicine creating a new category of patients, people who are both healthy and ill at the same time just due to the fact that they carry a particular genetic mutation?

Genetic biomarkers, as it is the case of BRCA-1/2, are not intended to hint that a biological process is not working properly, but only that such event may occur in an unknown future, i.e. they indicate a predisposition for a pathological condition. Where does this sort of predisposition lie within the naturalists' approach? According to Boorse, this cannot just count as a disease. In order to be a disease, a condition has to be a "an impairment of normal functional ability"³¹, i.e. a biological *dysfunction*. Genetic mutations associated with risk do not always trigger and then lead to a disease, as they are not always a dysfunction *per se*. In this sense, a sort of 'detachment' of disease from its symptoms is in place. However, the issue here is not only the fact that there might be cases in which there is disease without symptoms (which is rather a common scenario in infective diseases, for instance), but whether it makes sense to claim that there can be situations in which there is not any biological dysfunction and still someone is considered as a patient and treated accordingly.

If we look at the molecular level, almost everyone has some kind of genetic glitch: SNPs are rather common and, in fact, they make us unique human beings. If we consider genetic mutations as biological dysfunctions, are we claiming that everyone is diseased? Accepting such conclusion would be undoubtedly too costly for naturalists, as it would imply that there is no one who is disease-free: were we to go that far, at the end of the day the very distinction between health and disease would turn out to be vacuous. According to Boorse's BST variation does not imply malfunctioning, so even if everyone has some genetic glitch this does not mean that he/she is diseased. Boorse might have not been thinking about genes in particular, but he includes both variation and dysfunction in his BST exactly to counter this kind of objection; for instance, since it does not entail any impairment, it is not true that people who have red hair are diseased even if such trait is not common among the human population.

³¹ C. Boorse, *Health as a Theoretical Concept*, cit., p. 8.

However, there is a sense in which biomarkers can be intended as dysfunctions in the context of personalized medicine. Consider the case of BRCA-1: as BRCA-1 is involved in DNA repairing, a variation in such gene could cause failures in DNA replication, which in turn could lead to breast cancer. In this case, the presence of the mutation tells us that a dysfunction is already going on, although it did not already lead to the exterior symptoms. Thus we could claim that the individual is diseased, although he/she does not suffer from the disease that the mutation is associated with (in this case, breast cancer). If that is the case, we should make a distinction between two possible scenarios: one in which there is an altered version of a gene, which can cause the breakdown of a biological mechanism and is already on going, and a second case in which the mutation is present, but it has not (yet) been involved in any pathogenic processes. It is clear that the second case cannot be addressed as a case of biological dysfunction, as there is not any mechanism that is not working as it is supposed to do. As for the first case, I believe that we should actually be talking of biological dysfunction, thus claiming that a form of disease is present, even though the pathology we are screening for is not there.

Of course, risk factors are not entirely born with the development of personalized medicine, nor with the current study of genomics. Health states like obesity can account as potential risk factors for cardiovascular diseases without being themselves diseases; also traditional cancer screening does not rely on genetic tests (consider for instance the first wave of mammographies that started in the 70s), and it can detect small tumoral masses that have not yet started to spread through the organism, which would lead to a proper biological dysfunction³². However, I believe that the case of personalized medicine is different, not only regarding its magnitude, but also conceptually.

In the aforementioned cases, it seems to me that the issue is a matter of threshold: small tumours are not (yet) diseases because they are *small* at a given time, but in the moment in which they expand they are probably going to be regarded as proper diseases. Obesity is not a malady per se, but it could lead in the future to cardiovascular diseases; however, those cardiovascular diseases are going to be caused by some biological dysfunctions that are already taking place in the patient. In contrast, personalized medicine claims that we could potentially talk of a state of dis-

³² P.H., Schwartz, *Small Tumors as Risk Factors not Disease*, "Philosophy of Science", LXXXI, 5, 2014, pp. 986-998.

ease even in case there is biological abnormality or dysfunction of any sort except for genetic mutations that have not already started to modify any biological mechanism in the organism³³.

As for the individual level, namely what concerns illness, the fundamental issue could be summarized in one simple, yet complicated to discuss, question: are people who carry malignant mutations already patients? In other words, is predisposition sufficient to label someone as ill and to treat her/him as such? Some distinctions need to be in place. According to normativist accounts, which are primarily interested in the concept of illness, in order to be considered as pathological, a condition needs to somehow be a burden for the individual (it has to be a 'bad thing to have', to use Cooper's words). This is often intended as 'it needs to cause symptoms on the individual e.g. to cause pain or lead to some sort of impairment.

As at the time of the screening, in the absence of symptoms, the individual is more likely to think of him or herself as healthy, considering him/her a patient at that point would go against his/her personal evaluation. Personalized medicine wants to gather more objective evidence regarding the status of the patient through the reading of -omics data, but normativism would reject such a view, arguing that there cannot be objective, value-free criteria for labelling a condition as pathological. If one does not suffer from any symptoms there is no illness. In this sense, the quest of personalized medicine to gain an objective knowledge of the health status of individuals would go against the individuals' norms and might thus be seen as a form of forced medicalization.

Nevertheless, if we consider the way in which such predictions can change the lives of those who undertake genetic tests, things may appear differently. For instance, consider the case of a woman who decides to undergo a genetic test for BRCA-1/2 mutations and that gets a positive result. These people live in a strange limbo: they are not diseased, as they have not got cancer, and yet they are not considered as healthy as the average population, and they have to be constantly monitored by the healthcare system. They also have to face some difficult ethical dilemmas³⁴ in order to decide whether they should take preventive measures

³³ However, I still agree with Schwartz conclusions: in the actual clinical practice, it does not matter that we could or could not claim that a condition is a disease to justify medical interventions, but we should more likely consider whether such interventions reduce the chances of morbidity and mortality.

³⁴ Cf. G. Boniolo, V. Sanchini (eds.), *Ethical Counselling and Medical Decision-Making in the Era of Personalised Medicine: A Practice-Oriented Guide*, Springer, EPub 2016.

(even drastic ones) or not. Some scholars refer to them also as “healthy ill”³⁵ or “healthy sick”³⁶, with an emphasis on the fact that they are at the same time healthy and characterised by a predisposition for a pathological condition.

A diagnosis of high-risk condition might be considered as a proper illness, insofar as the prediction itself can cause significant harm to the individual, e.g. in the form of anxiety and mental stress. From the moment in which they are identified as carriers for a mutation accountable for a pathological condition (e.g. breast cancer), their “illness identity” starts to develop³⁷: they are not patients for the disease they are being tested for, but for the experience that they are living as carriers. For instance, carriers of BRCA-1/2 mutations are not cancer patients, and yet they live in a very similar way: they tend to absorb the medical vocabulary, gather tons of information regarding cancer, start connecting with other people who have found out to be carriers or who are cancer patients. They are completely immersed in the biomedical context of their disease, the attitude of their beloved ones is likely to change as well. Apparently, there are two different forms of health: the present one, which might be disease-free, and the future one, which can be predicted with some sort of degree and, despite not being realized, still can still affect the individual.

It is hard to conceptually understand what it means to be healthy and ill at the same time, mainly because we are used to think of health as something that belongs to our current time. We are, at a given moment in time, healthy or ill depending on how we are feeling. Personalized medicine, however, manages to detach our personal perception of malady from the actual mechanisms of disease, so that what are we feeling now is no longer indicative of our health-status. If we start to think according to this framework, we can distinguish two different kinds of health: the present one, which is related to how the individual feel and to the current biological functioning of his/her organism; and the future one, which is related to how the genetic traits are going to shape, in probabilistically terms, his/her organism.

³⁵ Cf. J.-Ch. Pöder, H. Assel, *The Concept of Disease in the Era of Prediction*, in T. Fischer *et al.* (eds.), *Individualized Medicine: Ethical, Economical and Historical Perspectives*, cit., pp. 165-180.

³⁶ Cf. M. Langanke *et al.*, *Patients' Responsibility for Their Health*, in T. Schramme, S. Edwards (eds.), *Handbook of Philosophy of Medicine*, Springer, Heidelberg 2017, pp. 620-640.

³⁷ Cf. G.A. Sulik, *Managing Biomedical Uncertainty: the Technoscientific Illness Identity*, “Sociology of Health & Illness”, XXXI, 7, 2009, pp. 1059-1076.

Finally, let us turn ourselves to the concept of sickness, i.e. the malady as it is seen by society. The issues regarding society and health are very extensive and it would be impossible to fully address them here. Let me then just focus on a particular problem that, I believe, gives us precious insights on the matter, namely the relationship between personal health and responsibility under the light of personalized medicine³⁸. The problem, which exists even outside the realm of personalized medicine and genomics, is usually summarised as follows: are people responsible for their own health? Can they be blamed for not being healthy? If so, are healthcare systems allowed to make a sort of hierarchy of patients (e.g. dividing them on the basis of how much they take care of their health) and provide treatments and services accordingly?

Since its beginning, personalized medicine has been addressed as a form of empowerment for patients. The fact that people could be able to gather information regarding their own genome, i.e. the building ‘bricks’ that constitute their organisms, has been seen as a way to take more careful and well-planned decisions about their lifestyle. Francis Collins, in one of his famous books regarding genomic medicine, constantly invites the readers to “join the personalized medicine’s revolution”³⁹ and even provides steps to improve one’s health according to genetic tests. The presence of Direct-To-Consumer genetic tests on the market is another element of ‘democratization’ of health, as companies that provide those tests offer them at affordable price⁴⁰. Furthermore, the rise of wearable devices designed to monitor health information such as blood pressure, cardiac rhythm, sleep patterns, etc., has also provided a wide range of tools for individuals to keep track of their health status without getting directly in touch with healthcare professionals⁴¹.

The question here is to see how healthcare systems and social institutions would react to such empowerment of the patients due to personalized medicine’s paradigm. A vast amount of information regarding their own health could make individuals more aware of their conditions, but al-

³⁸ Cf. for instance M. Langanke *et al.*, *Patients’ Responsibility for Their Health*, in T. Schramme and S. Edwards (eds.) *Handbook of Philosophy of Medicine*, cit., pp. 620-640.

³⁹ Cf. F.S. Collins, *The Language of Life: DNA and the Revolution in Personalised Medicine*, Harper-Collins, Epub Edition, 2010.

⁴⁰ Cf. P. Borry *et al.*, *Where Are You Going, Where Have You Been: A Recent History of the Direct-To-Consumer Genetic Testing Market*, “Journal of Community Genetics” I, 3, 2010, pp. 101-106; E.M. Bunnik *et al.*, *Personal Genome Testing: Test Characteristics to Clarify the Discourse on Ethical, Legal and Societal Issues*, “BMC medical ethics”, XII, 1, 2011, pp. 11-24.

⁴¹ Cf. M. Ruckenstein, N. Dow Schüll, *The Datafication of Health*, “Annual Review of Anthropology”, XLVI, 2017, pp. 261-278.

so more exposed. As biomedical research develops, more and more genetic variations might be associated with pathological conditions, meaning that more people would be labelled as sick despite their personal evaluation. If this is the case, the aforementioned alleged empowerment should be rediscussed. On this regard, one of the major issues that social institutions need to further address in the near future is the way in which the genomic data taken from donors and/or consumers are gathered, managed and distributed⁴².

The important thing here is to understand whether interventions are justified or not, and if so, in which scale and to what extent. We might decide to consider people responsible for their health, especially in an era in which gathering health information is easy and affordable; it is theoretically possible (but still very debatable) to blame individuals for careless behaviours, such as smoking or ignoring healthcare advice; still, what would such an assessment of responsibility led to? In any case, “we cannot decide not to have the genetic mutation in our bodies”⁴³: genome medicine stresses out the fact that many of our ‘faults’ are ‘by design’ and they are only related to the genome we are born with. For clinical practice this is indeed a relevant message, as it encourages researchers to develop target treatments; for society it should be recalled that people with malignant mutations should not be disadvantaged in any respect.

Furthermore, it might be highlighted that ‘our’ genome is not only ours, but it is shared among a wide range of individuals, namely our relatives. Thus, predisposition for pathological conditions do not only concerns single individuals, but also their relatives⁴⁴. In fact, I believe that this is also another significant difference between standard risk addressing and personalized medicine. It is not entirely new for medicine to consider previous cases of pathological conditions in members of the same family, but with the pivotal role of genes in personalized medicine it is more likely that this side will be taken into more serious account. Guidelines related to genetic screening usually suggest making contact with your family’s members before and after genetic tests. It may be the case

⁴² Cf. for instance S. Leonelli, *Locating Ethics in Data Science: Responsibility and Accountability in Global and Distributed Knowledge Production Systems*, “Philosophical Transactions of the Royal Society”, CCCLXXIV, 2083, 2016, pp. 1-12.

⁴³ R. Campaner, M. Cerri, *Manipulative Evidence and Medical Interventions: Some Qualifications*, “History and philosophy of the life sciences”, XLII, 2, 2020, p. 11.

⁴⁴ Cf. J.N. Weitzel et al., *Genetics, Genomics, and Cancer Risk Assessment: State of the Art and Future Directions in the Era of Personalized Medicine*, “CA: a cancer journal for clinicians”, LXI, 5, 201, pp. 327-359.

that there is a family member who had developed a pathological condition which is known to be hereditary (as it is the case of BRCA-1/2). But it is also important to share the results of tests with relatives, as it can have important repercussion for their health. If that is the case, we might wonder whether healthcare system of the future will consider as sick not only individuals who carry predispositions for a disease, but also their families. This would change the way in which institutions consider sick people, and it may also further concerns over the actual rights and the privacy of those individuals.

As it is often the case when we inquire into medical matters, there are also many ethical issues that need to be addressed. When we talk about personalized therapies, similar to the case of rare diseases (which are, not by mere chance, often referred to as “orphan disease”) we face the problem of developing and administering drugs that are meant for a very small number of patients. It is true that by avoiding wrong pharmaceutical therapies some costs would be cut down, but it is also true that the costs for developing individualized therapies is going to skyrocket in the near future⁴⁵. Who is going to uphold such increased costs? Private pharmaceutical companies, public healthcare systems, or the patients themselves? If the problem is the allocation of resources, it makes only sense to ask whether every individual (or groups of individual) is going to benefit from personalized medicine or if it will provide more advantages for some particular cases. Oncology is probably the field that has gained more from this approach, but it is a very heterogeneous field, and it is not clear that every oncological patient is going to benefit in the same way. To decide who and in which extent is going to access such kind of therapies is going to be a complex task to address in the near future by healthcare policymakers.

6. Conclusions

At the moment, a universal definition of personalized medicine is not available yet and many scholars prefer to stress out some of its core features by using specific terms (e.g. precision medicine, stratified medicine, individualized medicine). Here I have suggested to use the expression ‘personalized medicine’ as an all-encompassing term that comprehends a

⁴⁵ Cf. Maks Takinikar, Petra Došenović Bonča, *Personalised Medicine in Public Healthcare Systems*, in N. Bodiroga-Vukobrat *et al.* (eds.), in *Personalized Medicine in Healthcare Systems: Legal, Medical and Economic Implications*, Springer, Cham 2019, pp. 269-281.

precision approach (i.e. it looks at the molecular level and at the role that genes play in pathological conditions), a stratification approach in which patients are subdivided according to molecular criteria (for instance, all the women that have a BRCA-1/2 mutation), and an individual approach, according to which clinical professionals should take into account all possible features of their patients, including but not limited to sex, age, life habits, genetic profile, diet, clinical history, etc. Moreover, it can be seen as an opportunity to tackle the issue of rare disorders, which are currently undertreated.

As we have seen, this new approach in medicine can potentially challenge most of our theoretical concepts regarding health and disease. By allowing physicians to draw predictions regarding future states of disease, health is somehow de-temporalized, insofar as that the disease is detached from its symptoms. Being able to calculate the chances of developing a disease based on a genetic test open many scenarios. For instance, people may be labelled as 'healthy-ill' i.e. individuals who are in a present state of health but are likely to be sick in the future. If that is true, then the concepts of health, disease, illness and sickness need to be tweaked accordingly. A disease, which is commonly intended as a biological dysfunction, might be equal to a genetical predisposition, but only if the biological dysfunction is already there. Healthy-ill individuals should not be patients, in the sense that they are not ill; however, the implications that a predisposition carries with it might as well count as an illness, as in the circumstances pointed out above. Finally, social institutions may decide to take into consideration genetic profiles to label a citizen as sick, thus providing or denying access to treatments.

The fact that health is going to be somehow detached from exterior symptoms is also quite important, because it leads us to a sort of 'de-temporalization' of health itself. We could distinguish between two different types of health: the present one and the future one. The latter is, by definition, not yet existent, but it might be inferred thanks to genetic tests. So some of the relevant questions to ask are: which health do we want to take care of? Which one is the most important for us, as individuals/patients, and which one should be taken into account by healthcare professionals? Arguably, one of the goals of medicine is not only to cure, but also to preserve health. However, in the context of personalized medicine it has yet to be precisely defined which health we really want to maintain.

To conclude, personalized medicine poses a whole range of new challenges for philosophy of medicine. It might also be asked whether all those risks we are able to predict can actually be managed by medicine,

and whether there is a threshold over which treatments are less effective or even completely ineffective⁴⁶. Is there any risk that, by focusing so much on the molecular level we are missing the bigger picture? These questions are relevant in general and they are even more important as the COVID-19 crisis is on is showing us there are cases in which the big picture might be at least as important as – and maybe more – what we see through a focus lens. There is little doubt that biomedical research is going to explore more in depth the human organism, and consequently many advances in the field are going to be made; at the same time, however, I believe that it is important to bear in mind that the molecular precision should only be a part of a more comprehensive idea of clinical medicine.

⁴⁶ Cf. J.W. Mold *et al.*, *The Law of Diminishing Returns in Clinical Medicine: How Much Risk Reduction is Enough?*, “The Journal of the American Board of Family Medicine”, XXIII, 3, 2010, pp. 371-375.