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# PRECISION MEDICINE IN SOCIETY: PROMISES, EXPECTATIONS AND CONCERNS AROUND SOCIAL AND HEALTH EQUITY

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**List of abbreviations:**

100KGP: 100,000 Genomes Project

CDC: Center for Disease Control and Prevention

HPO: Healthcare Provider Organization

DV: Direct Volunteer

EHR: Electronic Health Records

ELSI: Ethical, Legal, Social Implications

EMBL-EBI: European Bioinformatics Institute

EU: European Union

FDA: Food and Drug Administration

FOLSATEC: Foundations Of The Life Sciences and Their Ethical Consequences

GMC: Genomic Medicine Centres

HeLEX: Centre for Health, Law and Emerging Technologies

IEO: Istituto Europeo di Oncologia

IG: Ilaria Galasso

MEGA: Million European Genomes Alliance

NCI: National Cancer Institute

NEJM: New England Journal of Medicine

NHS: National Health Service

NIH: National Institute of Health

ONC: Office of the National Coordinator for Health Information Technology

PMI: Precision Medicine Initiative

PPI: Participant Provided Information

PPH: Precision Public Health

R: Respondent

RFI: Request For Information

SEMM: Scuola Europea di Medicina Molecolare

SDOH: Social Determinants Of Health

SOTU: State of the Union Address

STS: Science and Technology Studies

UK: United Kingdom

US: United States

WHO: World Health Organization

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**Thesis abstract**

This thesis analyzes precision medicine from an ethical and political perspective, especially in terms of distributive justice: it is aimed at investigating the kinds of benefits that can be produced after precision medicine, and the possible distributions of those benefits, by considering the consequent impact of precision medicine on social and health equity.

Precision medicine is considered as a social construct subjected to different interpretations, and it is analyzed by mainly referring to two major case studies: the Precision Medicine Initiative in the US, and the 100,000 Genomes Project in the UK. The analysis focuses on the promises of precision medicine, as expressed in the discourses of the two projects, compared with the expectations and the concerns, as expressed in published comments and in fieldwork interviews with relevant stakeholders. The analysis investigated the scope of precision medicine with respect to public health, the inclusiveness of precision medicine, and the democratizing capacities.

It emerged that there are different versions of precision medicine, which encompass different scopes and possibly produce different kinds of benefits. In particular, one version, by also including in its scope the social determinants of health, is argued to have the 'societal potential' to inform socio-political interventions to promote social equity and, in return, health equity. It is argued that, although the benefits directly deriving from precision medicine - tailored biomedical treatments and information supposed to empower individuals - risk to totally exclude socio-economically disadvantaged groups, thus preventing any solidarity-based participation, on the other hand, the implementation of the 'social potential' would foster the public good and a solidarity-based medicine, to the advantage of everybody.

Some challenges for the actualization of this 'societal potential' are identified and discussed. The aim of this thesis is to contribute to overcoming those challenges by promoting the dialogue and the alignment between medical innovation and socio-political reforms.

*"Con la diagnosi in faccia e per tutti era uguale:*

*ammalato di fame, incapace a pagare"*

(Fabrizio De André, Un Medico, *Non al denaro non all'amore né al cielo*)

**PREFACE**

**Precision medicine from an ethical and political perspective**

This thesis is the product of four years of doctoral research on precision medicine from an ethical and political perspective.

Precision medicine is the medical approach generally defined as prevention and treatment strategies that take individual variability into account (Collins and Varmus 2015). The quote at the beginning of this thesis recalls a scenario possibly very far from this framework: this thesis opens with a quote by Fabrizio De André, not only in homage to the excellent songwriter my hometown is very proud of, but also because that quote is a perfect provocative summary of the societal issues affecting health and healthcare, which are questioned as the limits of precision medicine in terms of distributive justice. De André, while revisiting Edgar Lee Masters' *Spoon River Anthology*, describes the patients of the idealist doctor as "con la diagnosi in faccia e per tutti era uguale: ammalato di fame, incapace a pagare" ('having the diagnosis written on their faces, the same for everyone: sick of hunger, unable to pay', English translation by myself). This couple of verses includes the main criticism that have been addressed to precision medicine from different fronts, and that are analyzed in this thesis:

'The diagnosis written on their faces, the same for everyone': the superfluity of precision medicine for all the problems connected to social inequalities, as they often are already well known, and it is often already evident what is needed.

'Sick of hunger': the societal causes of disease, which rather than a high tech medical advancement would require a redistribution of resources.

'Unable to pay': the inaccessibility of healthcare costs, which risks excluding low socio-economic groups even when their societal problems translate into medical problems.

Precision medicine is questioned as useless and even detrimental for the people like the patients of De André's doctor: it is accused to have a totally bio-molecular focus that leaves their problems aside, and that even 'distracts' from them, in so far as they are related to societal conditions (Bayer and Galea 2015). Moreover, when these societal problems

translate into biomedical problems, they fail again to be alleviated by precision medicine: other societal problems, like poverty and low education, are questioned to prevent the access to precision medicine benefits (Rothstein 2017).

These concerns could be extended to medicine in general. However they are all the more relevant to precision medicine as far as it is perceived as an advancement of solely the biomedical techniques, to provide advanced diagnoses that the people 'sick of hunger, unable to pay' do not need, and specialized treatments they cannot afford, while not including a corresponding advancement of socio-environmental awareness which is proper of other medical approaches such as public health: a further emphasis on the micro at the expenses of the macro. On the other hand, opposite to this perspective, precision medicine is hyped as the opportunity for 'all of us' to 'remake our destiny', by promising an unprecedented inclusivity (Obama 2015a and Obama 2015b, allofus.nih.gov).

Against this background, this doctoral research collected data and perceptions about the reach of precision medicine regarding people the most exposed to societal disadvantages, by considering on one side the concerns about the exclusion of these groups and their needs, and the consequent exacerbation of existing inequalities, on the other side, the promise of unprecedented inclusion and consequent promotion of equity.

Several ethical, legal and social implications (ELSI) of many different kinds have been identified around precision medicine and its analogous (personalized medicine and, according to some interpretations, genomic medicine). Some of the scholars who analyzed precision medicine (or its analogous) within the domain of the social sciences, had a remarkable inspiring influence on the development of this research, and will be recurring references throughout the thesis. Among them (from the oldest to the most recent): Philip Kitcher (*The Lives to Come*, 1996) analyzed the risks of genetic knowledge as related to genetic determinism and new forms of discriminations; Adam Hedgecoe (*The Politics of Personalised Medicine*, 2004) considered the practical limits of pharmacogenomics and personalized medicine by analyzing the hype around the medical revolution in a framework

of sociology of the expectations; Nikolas Rose (*The Politics of Life Itself*, 2007) analyzed the emphasis on genetic risk within the framework of personalized medicine and of genomic medicine, as a form of bio-politics grounded on new forms of individual responsibilization, and demanding a range of individual actions; Steven Epstein (*Inclusion*, 2007) analyzed what he calls the "inclusion-and-difference paradigm" of contemporary medical research, aimed at including representatives of every groups to mine the differences, and contested this paradigm as a risk for justifying disparities, and as insufficient to address inequalities if it is not corresponded by a fair distribution of societal and healthcare resources; Richard Tutton (*Genomics and the Reimaging of Personalized Medicine*, 2014) analyzed the 'imaginaries' of personalized medicine with their practical limits, by underlining the risk of fostering individual responsibilization without genetic information really providing corresponding adequate and equally distributed forms of empowerment; Sarah Shostak (*Exposed Science*, 2013) analyzed the risk that the overemphasis on genomics could deemphasize the role of the environment, and undermine initiatives for environmental justice; Donna Dickenson (*Me Medicine vs. We Medicine*, 2013) analyzed personalized medicine as the epitome of a medical and political attitude fostering individualism to the detriment of the public good; Barbara Prainsack (*Personalized Medicine*, 2017) analyzed the limits of the forms of participation and of empowerment underpinned by the framework personalized medicine, while advocating a model of empowerment that, rather than leaving individuals alone with their (presumed) responsibilities, engage them in decision making, and universal and affordable healthcare system that promote a solidarity-based participatory model; Kadija Ferryman and Mikaela Pitcan (*Fairness in Precision Medicine*, 2018) analyzed the bias compromising the fair applicability of precision medicine, such as lack of demographic diversity in the research dataset, and overemphasis on individual responsibility by leaving out structural factors.

Among the many various ELSI of precision medicine, this thesis focuses on those related to social and health equity. Precision medicine is mostly implemented around the

construction of large volunteer cohorts, by grounding on public participation and data sharing. As such, precision medicine is largely exposed to the three of the "basic ethical principles" established by the *Belmont Report* (1979) for research involving human subjects: respect for the person, beneficence, and justice. Although the implications of precision medicine in relation to the three of them are highly debatable and actually debated, the present thesis is primarily focused on the third, justice, rather than on the first two principles.

This research focuses on the ethical and political assumptions and implications of precision medicine in terms of distributive justice: by considering the official promises, as well as the expectations and the concerns of different stakeholders, it is aimed to analyze what kind of benefits are promised and expected to be produced by precision medicine, and how they are promised and expected to be distributed. In particular, by taking into a full account the literature evidencing a correlation between social and health inequalities, this thesis explores the connections of precision medicine with equity, both in terms of socio-political and of health needs. Three main issues, which will be illustrated one by one in section 1.3, are analyzed as especially relevant to the connection between precision medicine and social and health equity: implementation of public health policies, inclusivity and accessibility of precision medicine, and democratization of medicine. For the three of these issues, the promises have been analyzed against the concerns, and the opportunities against the risks, with the final aim to individuate strategies to harness them and to promote the equitable implementation of precision medicine.

The main object of analysis of this thesis are the *discourses*, as expressed in precision medicine initiatives' official releases, and the *commentaries of discourse*, as expressed in published comments or in face-to-face interviews. Both discourses, and commentary of discourses, are here understood and examined in alignment with Foucault's analysis (1969 and 1981): discourses are defined as "practices that systematically form the objects of which they speak" (Foucault 1969, 54), by producing epistemic realities and forms of power and control, and commentaries are defined as "new speech acts which take them [discourses] up,

transform them or speak of them" (Foucault 1981, 57). Discourses are analyzed, in alignment with Foucault, as producing versions of an object, and those versions as constituting the object itself, which in return produces and justifies practices of power. Within this framework, precision medicine is here understood as a social construct and as a matter of interpretation, rather than as an object in itself: it is analyzed as the concretization of the versions emerged out of the discourses and of the commentaries. Within this framework, this thesis, rather than precision medicine in itself, analyzes the discourses on precision medicine, and the commentaries of discourses, and the versions of precision medicine produced by these discourses and commentaries.

**How it all began: precision medicine, STS and I**

On January 20, 2015, at the State Of The Union Address (SOTU), the then President of the United States, Barack Obama, launched "a new Initiative on Precision Medicine". It was the beginning of renewed popularity, expectations and concerns around precision medicine. And it was the beginning of my doctoral research.

In November 2014, I was enrolled in a highly interdisciplinary PhD program at the *European School of Molecular Medicine* (SEMM), based at the Research Campus of the *European Institute of Oncology* (IEO). The IEO Campus is a research facility at the forefront of molecular medicine, where causes, progressions and possible therapies of several kinds of cancers and of other diseases are analyzed in depth, *in vitro* and *in vivo*, in their molecular features, through complex experiments carried out in laboratories, through data combinations, analyses and interpretations by bioinformaticians and statisticians, by timely experimenting and applying innovative techniques and technologies. In this facility, PhD students are educated and trained in the different and often combined fields and disciplines at the forefront of medical research and innovation. The PhD program hosted at the Campus, is in *System Medicine*, and it welcomes several kinds of scientists, such as biologists, medical

doctors, computer scientists, physicists and mathematicians. And also philosophers, psychologists and social scientists.

This openness to human sciences explains my presence in this research facility. As a matter of fact, my background is in philosophy, and in particular in ethical-political philosophy (bachelor degree and ongoing interest) and philosophy of science (Master degree in *Logic, Philosophy and History of Science*). The SEMM PhD Program in *System Medicine*, in addition to the curricula in the subjects most evidently related to the advancement of the molecular life sciences, such as Molecular Oncology, Human Genetics, Computational Biology and Medical Nanotechnology, also includes a curriculum in Human Sciences. At the time of my enrollment, it was called *Foundations Of Life Sciences and Their Ethical Consequences* (FOLSATEC). Nowadays, the SEMM curriculum in Human Sciences is called *Foundations of the Life Sciences, Bioethics and Cognitive Sciences*, it is mainly focused on the wellbeing and on the empowerment of the patient, and most of the PhD students have a background in psychology. The former FOLSATEC, in which I was enrolled, and within which I developed my doctoral research, was organized across three research units: one aimed at investigating and scrutinizing the foundations and the consistency of the life sciences and of medical research in a framework of philosophy of science; one aimed at investigating the ethical consequences of the life sciences and of medical research and practice in a framework of bioethics; and one, coordinated by Giuseppe Testa, aimed at exploring the relationship between biomedicine and society in a framework of *Science and Technology Studies* (STS).

STS was a new subject for me at the time of my enrolment, I had never worked in this field before. However, my background and my interests in ethical-political philosophy and in philosophy of science, were perfectly appropriate to be developed in the framework of STS. In a sense, I had the impression that STS combined the two objects of my interest, by having as object of study the ethical and political assumptions and implications of scientific epistemology and innovation. If my interest on the one side is ethics and politics, and on the

other side it is science, then STS is a perfect marriage, as it analyzes the ethics and the politics of science. But STS is much more than a mere combination of what I was doing before, STS is a different subject with its own specific theoretical grounding and analytical tools, from which the development of my research, although still anchored to philosophical reasoning and problematization, benefitted and took its fundamental perspective and its originality.

STS is an interdisciplinary field (Jasanoff et al. 1995, Hackett et al. 2005). Starting "from the assumption that science and technology are thoroughly social activities" (Sismondo 2010, 10), it aims at "investigating the place of science and technology in society" (Jasanoff 2004, 2). In other words, STS seeks to analyze the impact that societal and political contexts have on scientific and technological innovations and, vice-versa, the impact that scientific and technological innovations have on their socio-political contexts. Sheila Jasanoff has framed this relationships through the "idiom of co-production", according to which the epistemic and the social order are reciprocally shaped (ibidem), as well as the epistemic and the normative order (Pickersgill 2012 and 2013): knowledge-making is incorporated into practices of governance and into ethical issues and prescriptions, and, in reverse, practices of governance and ethical issues and prescriptions influence the making and use of knowledge.

In January 2015, I had been enrolled in the FOLSATEC PhD program for three months. I was studying the bases of molecular biology, to integrate myself in the research context of my laboratory and of my institution, and I was familiarizing (as I am still to some extent familiarizing today) with the STS theoretical grounding and methodology. I still had to find my place in that framework, the directions I wanted to take with my research were quite clear in my mind, but at that time I still had only vague ideas about a topic in step with the times I could focus on to analyze the relationship between politics and science. It was at that point that Barack Obama, one of the most influent political figures in the world, talked next to a model of a DNA double-helix about the societal promise of a new medical initiative. And it was at that point that I got my research project.

My research project started with the launch of this huge and very ambitious initiative on precision medicine. That *Precision Medicine Initiative* (PMI) in particular, and the precision medicine approach in general, with the hype, the hopes and the concerns around them, are the object of my doctoral research. In particular, by mainly following an STS approach, my research was aimed at analyzing the social, political and ethical assumptions and the implications of precision medicine.

**Thesis structure**

This thesis is structured by following the guidelines provided by my institution in conformity with the general international model for PhD theses, which includes four sections: introduction, materials and methods, results, and discussion. However, the compliance to this partition is not completely straightforward for my research. As said, precision medicine is here analyzed especially as a social construct and as a matter of interpretation, and it is mainly followed a hermeneutic and interpretivist approach in line with Foucauldian discourse analysis: as *the interpretations are interpreted*, the background, the data, the results, and the research strategies, tend to merge by mutually shaping and reshaping each other in a *hermeneutic circle* (as described in Gadamer 1989), in line with grounded theory.

Grounded theory is a major approach for sociological research that, in different ways and by following different strategies (Bryman 2012), builds on the data to frame the research questions and the research methods, and the research is then developed in an iterative and recursive way: the research questions and the areas of investigation lead to the emerging of some data, the analysis of these data leads to reframing the research questions and the areas of investigation, which in turn lead to the emerging of other data, which lead again to new research questions and areas of investigation, and so on, so that "data collection and analysis proceed in tandem, repeatedly referring back to each other." (ibidem, 287). By following this kind of approach, it happens that some of the results become the background for the final frame of the research, by also reframing the methodological strategies, and part of the

background is revisited and acquires different meanings and relevance after the analysis, to the extent to be possibly considered in terms of results.

I did my best to fit this thesis in the requested model, while keeping the intrinsic dynamicity of this research. According with the institutional guidelines, this thesis is organized in the scheme: introduction, materials and methods, results, and discussion. Each of these sections corresponds to one chapter of this thesis, which consequently consists of four chapters, each of them organized in sections and subsections.

Chapter 1 operates as the introduction, it contextualizes the research, provides the background, introduces the research questions. In particular, the first section (1.1) introduces and contextualizes the object of the analyses: precision medicine. Section 1.2 describes the two precision medicine projects analyzed as case studies: the American All of Us Research Program, and the British 100,000 Genomes Project. Section 1.3 maps the debate my research is situated in, by presenting three pairs of expectations and concerns related to precision medicine with respect to distributive justice.

Chapter 2 describes the materials and the methods of the research. The first section is dedicated to justifying the choice of qualitative methodology and grounded theory to analyze precision medicine as a matter of interpretation by focusing on the discourses, and to illustrating how the implementations of the precision medicine projects under analysis have been followed, and how relevant documents and comments have been accessed. Section 2.2 is focused on the fieldwork interviews: it explains how the interviewees have been chosen and reached, how the interviews have been outlined, and how the data have been analyzed. Section 2.3 focuses on the analytical tools for examining the effectiveness of the democratic participation in the two projects: it describes the direct experience of the participatory practices made available by the All of Us Research Program, and the theoretical references to measure the effectiveness of the participatory models. Section 2.4 illustrates the

organization of a workshop aimed to collect and compare experts' opinions and points of view on precision medicine and equity, specifically in the Italian context.

Chapters 3 illustrates the results of the research. Section 3.1 observes how precision medicine is interpreted differently in different contexts, the meaningfulness of different names to denote the same kind of medical approach, and the different interpretations these names have in practice. Section 3.2 explores the relationship between precision medicine and public health, by comparing different positions. Section 3.3 collects the results related to the issue of inclusivity: it examines the engagements strategies and the motivations proposed to participants, as well as the challenges and the efforts for achieving diverse and inclusive participation, both upstream in the research cohort, and downstream in the distribution of benefits. Section 3.4 compares the participatory models of the initiatives by grounding on theoretical references to measure their democratic capacities. Section 3.5 considers the expectations for the future of precision medicine in relation to the impact of major political reconfigurations. Section 3.6 focuses on what emerged by situating the issue of equitable precision medicine in the Italian context. Section 3.7 concludes by focusing on the interpretations over the scope and the outreach of precision medicine, which are proposed as the critical dimensions in terms of distributive justice.

Chapter 4 is dedicated to the discussion of the results of the analyses, and to drawing the conclusions. Section 4.1 is dedicated to discussing the scope of precision medicine as it emerged according to various interpretation, by discussing the differences captured by the use of different names, and the differences that move beyond that, and it concludes by proposing a distinction between three version of precision medicine. Section 4.2 is dedicated to discussing the outreach of precision medicine: the detrimental imbalance between upstream and downstream strategies, and the incompleteness of the proposed democratic models. Section 4.3 considers the connections between the scope and the outreach of precision medicine: the failure of downstream outreach is discussed as detrimental for the scope as well. Conversely, the inclusivity of the scope of certain versions of precision

medicine is discussed as triggering a ‘virtuous circle’ also benefitting the outreach. Section 4.4 considers the limits of the argument of the virtuous circle, and the challenges to actualize it. Section 4.5 is dedicated to drawing the conclusions of my research in relation to the wider STS analyses. Finally, section 4.6 is dedicated to discussing the future: the future of precision medicine as well as the future of my research.

# 1. INTRODUCTION

## 1.1 Precision medicine

### 1.1.1 "A new Initiative on Precision Medicine"

At the 2015 SOTU, the then president of the US, announced "a new Initiative on Precision Medicine" (Obama, 2015a). The launch of the American PMI was charged, since the very beginning, with political values. At the SOTU, it was introduced from a patriotic perspective, by referring to the key role that the US has had in the advancement of progress, and that it is expected to keep on having. In their article entitled "The Precision Medicine Nation", Maya Sabatello and Paul Appelbaum (2017) interpret this nationalistic appeal as one of the strategies to overcome skepticism by building a collective identity as a PMI nation, by recalling Benedict Anderson's concept of "imagined community" (1991). The very first motivation provided for the implementation of the initiative was indeed a sort of nationalist pride:

> "Twenty-first century businesses will rely on American science and technology, research and development. I want the country that eliminated polio and mapped the human genome to lead a new era of medicine -- one that delivers the right treatment at the right time." (Obama 2015a).

This is the very first introduction of the American PMI. Remarkably, it was introduced as the entrance in "a new era", stressing with this the idea of precision medicine as a new and revolutionary approach. In these first words of introduction, also the core idea of precision medicine is mentioned: getting the knowledge to "deliver the right treatment at the right time". The speech by Obama continued with the official launch, by stressing the opportunities in terms of medicaments and in terms of empowerment:

> "In some patients with cystic fibrosis, this approach has reversed a disease once thought unstoppable. So tonight, I'm launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes, and to give all of us access to the personalized information we need to keep ourselves and our families healthier. We can do this." (ibidem).

Remarkably, he immediately stressed that the opportunity is for "all of us", by emphasizing the inclusive aspiration of the initiative, to the extent that "All of Us" later will be chosen as the name of the research cohort program of the PMI.

The SOTU is an annual and relatively short speech expected to cover, among other things, a report of the condition of the nation, the legislative agenda and the national priorities on all fronts. There was consequently no space but for a short introduction of the PMI. But even this short introduction emphasized several core discourses around precision medicine, especially interesting from an STS perspective.

To wrap up: the nationalistic pride ("I want the country that eliminated polio and mapped the human genome to lead…"), the novelty and the revolutionary nature ("a new era of medicine"), the tailored approach and the precision ("the right treatment at the right time"), the therapeutic opportunities ("curing diseases like cancer and diabetes"), empowerment through access to information ("access to the personalized information we need to keep ourselves and our families healthier"), and inclusivity ("…to give all of us…").

However, after this first, though already dense of essential information, glimpse, more detailed remarks followed. Ten days after the SOTU, on January 30, 2015, Obama held another speech, entirely focused on the PMI. At the *Remarks by the President on Precision Medicine*, Obama talked next to a 3D model of a double helix DNA, and in the presence of several members of Congress and of several people "who are doing outstanding work to keep Americans healthy" (Obama 2015b), among whom Francis Collins, director of the National Institute of Health (NIH), and Harold Varmus, then director of the National Cancer

Institute (NCI). Two guests (Elana Simon and Bill Elder), were there especially for their experience as patients: they are severe illness survivors, recovered from cancer and from cystic fibrosis, respectively, who got cured thanks to special molecular features detected in their diseases, which it was possible to target through specific therapies. The conference started with Elana Simon, young woman and promising scientist, introducing the President by talking about her positive recovery experience, and it ended with the President introducing Bill Elder, likewise young and promising: two tangible examples of the life-changing benefits of precision medicine, "living proof that the dawn of a new era has arrived" (ibidem).

In the *Remarks*, Obama expanded and explained what he started introducing at the SOTU, with the same nationalistic charge: "we're here to harness what is most special about America, and that is our spirit of innovation; our ability to dream and take risks, and tinker and try new things". In particular, he explained the core principle of precision medicine as new therapeutic and prevention opportunities on the basis of a better understanding of the specificity of diseases:

> "something called precision medicine -- in some cases, people call it personalized medicine -- gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen. Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type. That was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature? And that's the promise of precision medicine -- delivering the right treatments, at the right time, every time to the right person." (ibidem).

He argued that “the time is right to unleash a new wave of advances in this area, in precision medicine, just like we did with genetics 25 years ago”, thanks to the unprecedented advances in technology and costs reductions in terms of data collections and analyses, such as genome sequencing, wearable electronics and electronic medical records. Then he explained the initiative he was about launching: a $215 million investment from the 2016 President budget (Whitehouse Fact Sheet), to be distributed among the NCI “to find the genetic factors that can lead to cancer”, the Food and Drug Administration (FDA) “to develop new approaches for evaluating next-generation genetic tests” and to the Office of the National Coordinator for Health Information Technology (ONC) to address privacy issues. However, the biggest part of this budget ($160 millions), was assigned to the NIH “to create a research group of one million volunteers”, a research cohort as the ultimate data mine for the PMI research to underpin precision medicine.

In this speech of *Remarks*, the PMI and the precision medicine approach in general are described in very promissory terms as an opportunity not only to overcome illness, but also to improve health, by focusing on “prevention and keeping healthy, not just on curing diseases after they happen” and “to create a genuine health care system as opposed to just a disease care system”, with a very central discourse of empowerment through information: “to allow each of us to have sufficient information about our particular quirks that we can make better life decisions”. In fact, the reach of the PMI was promised as expanding far beyond the medical domain, far beyond curing diseases, far beyond improving health. The PMI was presented as an opportunity for the US and for everyone in that country to “remake that world”:

> “that most extraordinary gift anybody can imagine, and that is not just a chance to live a long, and happy, and healthy life in this greatest country on Earth, but also the chance to remake that world continuously, in ways that provide great promise for future generations.” (ibidem.)

And it was even described as the unique opportunity to "remake our destiny":

> "We want to have a nation in which the accidents and circumstances of our birth aren't determining our fate, and therefore born with a particular disease or a particular genetic makeup that makes us more vulnerable to something; that that's not our destiny, that's not our fate -- that we can remake it."

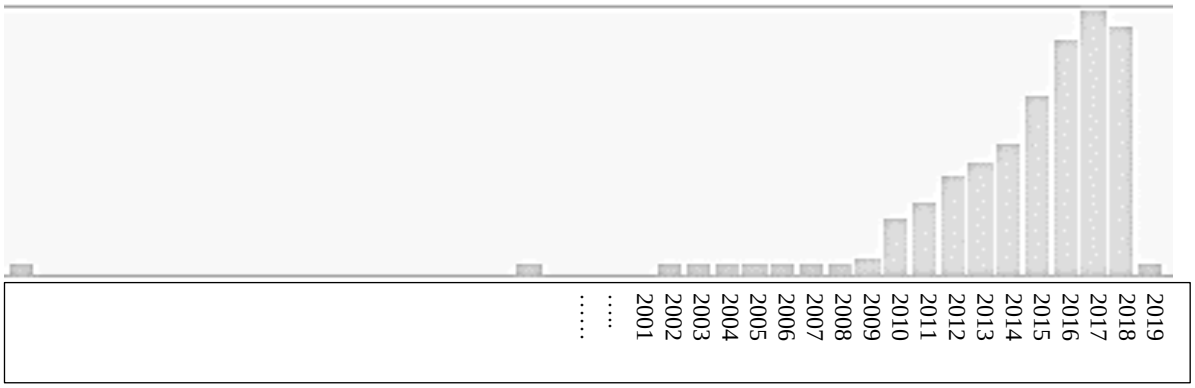
### 1.1.2 Novelty and popularity of precision medicine

The term "precision medicine" was not new at the time of the launch of the PMI, it was already used at least since 2010 (742 results on *PubMed*, All fields). Then, in 2011, a first proposal was made by the *National Research Council of the National Academies* in the US to the underpinning of precision medicine (National Research Council 2011), which to some extents was then implemented with the launch of the PMI in 2015. It was a report by a special Committee in charge "to explore the feasibility and need for 'a New Taxonomy of human disease based on molecular biology" and to develop a potential framework for creating one." (ibidem, 1). The Committee indicated that "major beneficiary of the proposed Knowledge Network of Disease and New Taxonomy would be what has been termed "precision medicine."" (ibidem, 7). The Committee's recommendations to foster precision medicine included "widespread data sharing" to link molecular and phenotypic data of individual patients, and large scale observational studies. Among the examples of pilot study in this direction, one proposal was the "Million American Genomes Initiative", which is from many points of view mirrored by the proposal of the PMI research cohort that, four years later, complied with these recommendations.

Starting from 2010-2011, the number of the search results for "precision medicine" on *PubMed* (All Fields) has been growing continuously and vertiginously year on year (Figure

1): 954 in 2011; 1,322 in 2012; 1,480 in 2013; 1,789 in 2014; 2,398 in 2015; 3,172 in 2016; 3,587 in 2017; 3.333 in 2018.

**Figure 1**: search results by year for "precision medicine" on *PubMed* (All Fields). Readapted from: https://www.ncbi.nlm.nih.gov/pubmed/?term=%22precision+medicine%22%5BAll+Fields%5D



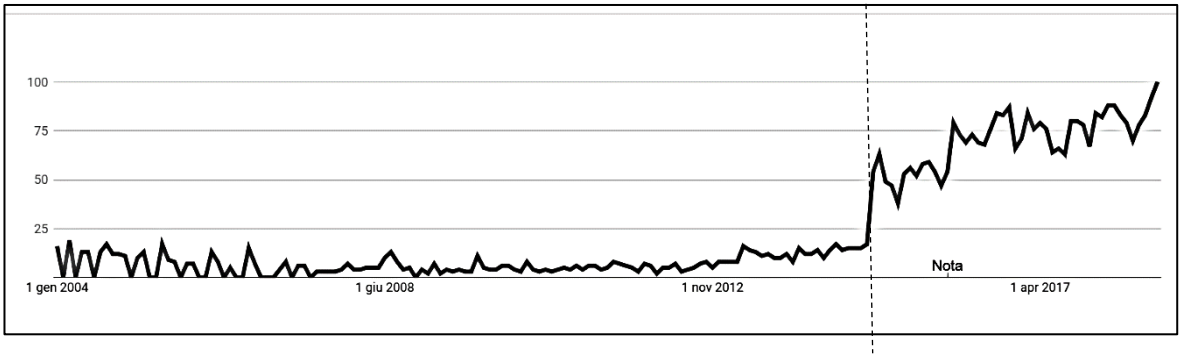

The increasing popularity of precision medicine can also be distinctly visualized on *Google Trends*. *Google Trends* is a web facility showing with which frequency a given term has been entered into Google's search engine over time. Unlike *PubMed*, *Google Trends* does not provide absolute numbers, *Google Trends* does not show how many times the search has been entered in absolute. However, it shows, as an order statistic, the comparative frequency of a search, so that it is very useful to monitor the increasing or the decreasing popularity of an item among Google users. The highest peak over a given period of time is fictitiously posed as 100, and the "interest", or the search frequency over time, is quantified in relation to this peak. In the case of precision medicine, by looking at the frequency of the search all over the world between January 2004 and July 2018, the highest peak is in January 2018 (Figure 2). However, the maximum is nearly reached several times between 2016 and 2018.

The most evident trait of the *Google Trends'* graph, is a huge hike corresponding to January 2015. Before that hike, from January 2004 to December 2014, the "interest over time" is never higher than 17 (by referring to 100), and it always lies well below the first quartile. In December 2014 the frequency of the search of "precision medicine" is 20/100, in January 2015 it rises to 56/100, and with this it exceeds at once, both for the first time in ten years, the first quartile and the first half. Then, with ups and down, the "interest" for precision medicine keeps on rising steadily, to the point that after January 2015 it hardly drops below the upper half, and after January 2016 it hardly drops below the upper quartile. In summary, if we look at the "interest over time" as shown by the graph on *Google Trends*, we see the frequency of the search lying below the first quartile until January 2015, then sharply rising to the upper half and finally to the upper quartile. These data validate the hypothesis that, even if the term "precision medicine" has existed and has been used and searched on Google at least since 2004, the launch of the American PMI in 2015 significantly contributed to the rising of the public interest towards it.

**Figure 2**: interest over time for 'precision medicine' on *Google Trends*, worldwide, from 2004 to present.

Readapted from:

https://trends.google.it/trends/explore?date=all&q=precision%20medicine



*Google Trends* also offers the opportunity for another very interesting insight about the novelty of precision medicine. In fact, on *Google Trends* it is also possible to compare the "interest over time" about two or more terms. Muin Khoury, Director of the Office of Public Health Genomics at the Centers for Disease Control and Prevention (CDC), and key figure in the debate around the opportunities and the challenges about precision medicine and public health, in its "Genomics and Health Impact Blog" suggested to compare the "interest over time" on *Google Trends* for 'precision medicine' and for 'personalized medicine' (Khoury 2016). It is actually from this blog and in particular from this post that I took the idea to use *Google Trends* as a tool of analysis to look at the novelty and at the popularity of precision medicine.

The relevance of personalized medicine in the context of precision medicine is given by the fact that these two terms are often considered as synonymous. Many experts, including Khoury in the blog at issue, argue that precision medicine is the evolution of personalized medicine, or even a pure "rebranding" of it. Under this hypothesis, the popularity of personalized medicine is very relevant to the popularity of precision medicine, or even equivalent. Even if we do not accept the argument of the "rebranding", and the complete synonymy of the two terms, the connection and the at least partial overlapping of the two concepts cannot be denied. Obama, when introducing precision medicine as it is framed by the PMI, remarked that "in some cases, people call it personalized medicine" (Obama 2015b). Also in the *Report of the National Research Council* (2011), in the glossary, the items 'precision medicine' and 'personalized medicine' refer one to the other, and the definitions provided are identical. Given this, it is obviously quite important, when considering the novelty and the popularity of precision medicine, to also focus on personalized medicine.

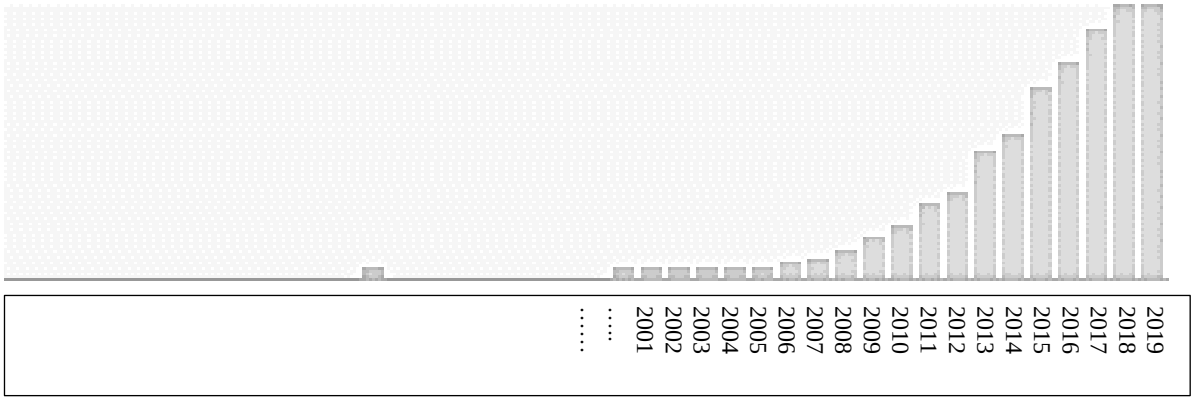
By looking at the results on *PubMed*, it is evident that also the number of publications mentioning at some point to 'personalized medicine' (or 'personalised medicine') have been rising steadily in the last years (Figure 3). However, the rising of the number of publications

referring to ‘personalized medicine’ as reflected by *PubMed*, is much more gradual, and less vertiginous than the references to ‘precision medicine’. The highest number of results per year is 2,133 in 2018 (All Fields), while ‘precision medicine’ surpassed it in 2015 with 2.398 results (All Fields), and reached 3,587 results in 2017 (Figure 1).

**Figure 3**: search results by year for “precision medicine” on *PubMed* (All Fields).

Readapted from:

https://www.ncbi.nlm.nih.gov/pubmed/?term=%22personalized+medicine%22+or+%22personalised+medicine%22

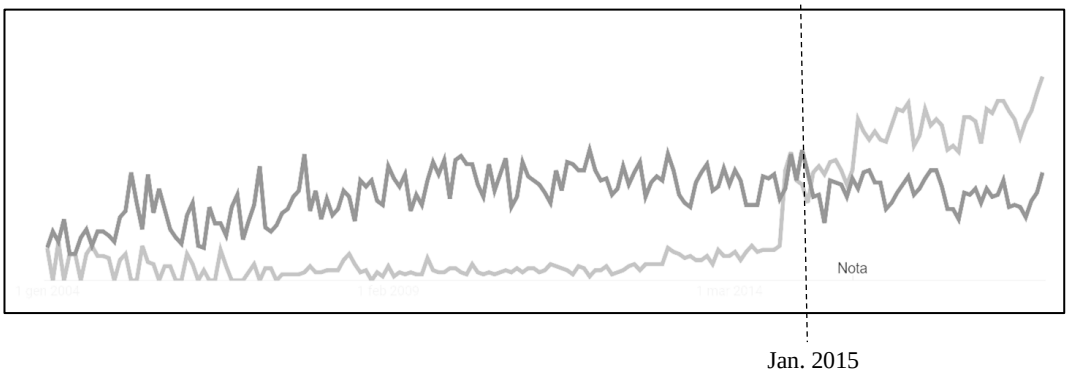



It is also evident by looking at *Google Trends* that both the “interest” towards precision medicine and towards personalized medicine have been growing steadily in the last decade (Figure 4). However, something happened at the beginning of 2015, coincidently with the launch of the PMI: the “interest” towards precision medicine sharply rose, surpassed the “interest” towards personalized medicine, and since then it has always been much higher.

**Figure 4**: comparative interest over time for 'precision medicine' and "personalized medicine" on *Google Trends*, worldwide, from 2004 to present.

Readapted from:

https://trends.google.it/trends/explore?date=all&q=precision%20medicine,personalized%20medicine




Jan. 2015

The argument by Khoury in this respect, is that the launch of the PMI triggered a "shift" from 'personalized medicine' to 'precision medicine'. This interpretation is questionable, and it will be questioned in the thesis. What these data show is that the concept of precision medicine and personalized medicine were not new at the time of the launch of the PMI, but that this launch coincided with an increase in the popularity of precision medicine and in the use of this term.

As a matter of fact, many events and scholarships have been dedicated to the development and/or the analysis of precision medicine since the launch of the PMI, and precision medicine has become one of the most widespread and discussed topics in the medical field. Also, a lot of renewed hype has risen in relation to precision medicine, and with this new and renewed hopes and concerns, not only related to the medical field but also to societal issues. It is for this reason, for the renewed interests that it seems to have catalyzed around precision medicine and its socio-political implication, that this STS analysis on precision medicine mainly focuses on the PMI and its impact.

### 1.1.3 Defining precision medicine

In the *Remarks* by Obama, a definition of precision medicine is not really provided. It is described as the medicine that "delivers the right treatment, at the right time, every time to the right person". This is one of the most quoted slogans about precision medicine, and it condenses the core idea of precision medicine in all its understandings. The aim of precision medicine is to acquire the knowledge to deliver the treatment (in certain framings 'treatment' is to be interpreted in a very broad sense, also including preventive strategies) that turns out to be the most effective for the specific conditions of the person at issue ("the right treatment to the right person"), by also taking into account the temporal dimension, the continuous evolution of diseases and of people's conditions ("at the right time"). Some argue that this has always been supposed to be the mission of medicine: delivering the most effective treatment possible. This concern will be taken into a full account in the analysis of the novelty of precision medicine that will follow. Anyway, precision medicine is proposed to focus on one specific aspect of what could be argued it has always been good medical practice: the differences between people and between diseases that make treatments differently effective in situations apparently similar, as opposed to a (hypothetical) "one size fits all" approach.

It is important to remark that precision medicine is not aimed at treating every individual specifically, but rather at classifying individuals into subpopulations (National Research Council 2011), in connection with the features that make them differently susceptible to certain diseases, and/or differently responsive to certain treatments. One of the reasons often advanced to justify the shift from 'personalized medicine' to 'precision medicine' is exactly the need to avoid the misinterpretations the term 'personalized medicine' could be subjected to, as treatments are supposed to be tailored to subpopulations rather than to persons (ibidem). Personalized treatments in the literal sense of treatments tailored to each specific person, nowadays are only the autologous cancer immunotherapies, involving the withdrawal, the engineering and the reinfusion of the very cells of the patient, like in the

case of CAR-T cell therapy. In CAR-T, the T cells of the patient are engineered by adding to them the gene for a Chimeric Antigen Receptor (CAR) that bind with specific antigen on the acute lymphoblastic leukemia or lymphoma tumor cells. These kinds of therapies are tailored to the specific individual in the sense that, as the treatment coincides with the reinjection of the (modified) cells of that very patient, then it can be effective only for that patient from whom the cells have been extracted in the first place. However, precision medicine, at least in the formulation embodied by the PMI, is not (only) about that. It is mainly about identifying those specific features of the disease, or of the person, or of the surrounding environment, which situate cases differently, by requiring different kinds of interventions.

A typical example of precision medicine in practice, also mentioned by Obama in the *Remarks*, is blood transfusion. Patients in the need of a blood transfusion can have very similar symptoms. However, in relation to their individual variability, they may need to be treated differently: the blood type infused must be compatible with the specific blood group of each patient. Other examples where precision medicine can be applied by efficaciously matching different treatments to different conditions, are all those cases in which a specific genetic mutation can be targeted by a specific therapy. In these cases, distinguishing patients with or without the mutation is vital and lifesaving, as it allows to deliver the treatment that is efficacious in each specific case.

Significant examples of diseases successfully treated by detecting and targeting a specific mutation were mentioned by Obama at the very first launch of the PMI at the SOTU: cancer and cystic fibrosis. A very famous case in cancer is Trastuzumab and HER2 positive breast cancer: Trastuzumab (sold as Herceptin), is a monoclonal antibody targeting human epidermal growth factor receptor 2 (HER2). Several studies and happy-ending stories show that if and only if a breast cancer patient is found out overexpressing HER2, she can be efficaciously treated with Trastuzumab.

The mission of precision medicine research is to find out other cases, other matches between specific traits and specific treatments. This ambition requires a deep longitudinal analysis of the specific features of the person and of the disease to be treated. The timeliness of the PMI is given, as remarked by Obama, by the fact that these analyses are nowadays made possible by cutting-edge technologies in terms of genome sequencing, electronic health records and wearable monitoring devices. Precision medicine research, at least in the version of the PMI, is expected to take advantage from the unprecedented technological opportunities in terms of data collection and analysis to mine individual variability.

The individual differences relevant to the delivery of efficacious treatments can be at many different levels. In this respect, it is important to remark that precision medicine, at least in the PMI version, is not only about curing diseases, but it is supposed to also have a strong commitment in the preventive dimension. Given this, even if the slogan is "the right *treatment* to the right person", it is not only about delivering "treatments" in the narrowest sense, as medical therapies. 'Treatment', at least in certain interpretations of precision medicine, especially when the preventive dimension is fully embraced, has to be understood in a broader sense: it might include, for example, behavioral and dietary changes, or limitation of certain environmental exposures.

Right after the *Remarks* by Obama, Francis Collins and Harold Varmus who, as the director of the NIH and the then director of the NCI, were invested with key roles in the implementation of the PMI, published a perspective article (2015) on the *New England Journal of Medicine* (NEJM) that has been a core reference for the whole literature on precision medicine since then. In that seminal article, Collins and Varmus define precision medicine as "prevention and treatment strategies that take individual variability into account" (ibidem, 793). Often, the individual variability mined by precision medicine is assumed to be *genetic* variability, or more in general molecular variability. However, it is not necessarily the case. In the definition by Collins and Varmus, for example, it is not specified what kind of variability it is to be taken into account. This is instead specified in

the White House *Fact Sheet* delivered jointly with the *Remarks*. In the *Fact Sheet*, precision medicine is defined as "an innovative approach to disease prevention and treatment that takes into account individual differences in people's genes, environments, and lifestyles". Similarly, in the latest version of the website of the PMI research program, precision medicine is defined as "a revolutionary approach for disease prevention and treatment that takes into account individual differences in lifestyle, environment, and biology" (allofus.nih.gov). In this framing, the individual differences considered relevant to tailoring efficacious treatments and preventive strategies, are not only related to genetic mutations or more in general to biological conditions. A much wider range of differences are considered relevant to the implementation of precision medicine, as differently affecting susceptibility and responsiveness. These remarkably include differences in lifestyle and in environmental exposures. In this thesis the scope of precision medicine in this respect is a major object of analysis, as it will be argued that the kind of individual differences that are included as layers of analysis in precision medicine research, are the crucial element to delineate different models of precision medicine with different societal potentials.

As it is generally defined and understood, clinical precision medicine is about: looking at the relevant data (that, as seen, can be of various nature) of the person (who is not necessarily a patient, as precision medicine may also be about prevention), figuratively situating the person in a subpopulation according to the relevant specific traits, and treating them consistently with what it is most beneficial for that particular subpopulation. In the case of blood transfusion, for example, the blood of the person is analyzed, the blood type is identified, and the person is treated as part of the subpopulation having this specific blood type, by receiving blood that is compatible with that subpopulation. In the case of breast cancer, among other things, the expression of HER2 is analyzed, and patients are situated and treated accordingly. On the other side, precision medicine research is committed to detect relevant differences of this (or other) kind, by finding out correlations between individual traits and conditions, and specific health and diseases predispositions and onsets,

as well as different reactions to treatments, with the final aim to underpin timely interventions on the individual conditions affecting disease susceptibility, and appropriate treatments for the best response under specific conditions.

Precision medicine research is often arranged around longitudinal cohort studies, as it is also the case for the PMI research. Data of cohort volunteers are collected and in some cases monitored over time, and put in relation with the different evolutions of health and disease conditions, with the final aim to detect the significant trait(s) or exposure(s) that make the difference. These cohorts are as large as possible, as a larger sample has higher statistical power and it grants higher opportunity to correctly detect the significant difference(s).

The core premise of these precision medicine research cohorts is what David Shaywitz on *Forbes* (critically and provocatively) calls "the central dogma of precision medicine" (2015): the assumption that, collecting and comparing several kinds of data from large amounts of people, "will enable sophisticated patients segmentation, revealing biologically distinct subgroups and pointing the way to precisely targeted treatments" (ibidem). The very radical objection argued by Shaywitz is that the subpopulations that are supposed to emerge, might not exist at all. Among all the criticisms around precision medicine, several of which will be examined in this thesis, this is the most destructive, as it questions the essential premise of precision medicine research.

However, it is important to remark that these hypothetical subpopulations that are expected to emerge, are not "universal". The population is not supposed to be "segmented" permanently. Like in set theory, the allocation in the subgroups will follow a specific criterion: when the criterion of categorization is different, also the allocation into subpopulations will be different. The same population would be segmented in one way if the classification criterion is predisposition to cardiovascular diseases, in a totally different way with respect to predisposition to cancer, in another way with respect to responsiveness to antibiotics, with respect to blood groups, and so on. It has already been demonstrated it is possible to identify medically relevant subpopulations on the basis of certain classification

criteria (for example the blood groups). The bet of precision medicine is to find out other medically relevant and consistent classification criteria to accordingly enable the delivery of timely and appropriate interventions. Combining data from large cohorts of people is the strategy generally adopted by precision medicine research to the pursuit of this goal.

Remarkably, this kind of precision medicine research grounds on data collection and public participation. People and their data are the primary and irreplaceable resources, and this is one of the features that make precision medicine research especially exposed to ethical, legal and social controversies, some of which are the object of this thesis. The management of data collection and of people engagement, are primarily socio-political issues. The configuration of different research settings in this respect, and their implementations, are especially relevant within an STS framework, as they have profound implications both in terms of robustness and applicability of the research, and in terms of democratization and distributive justice in society.

### 1.1.4 Precision medicine research projects

The PMI is not the first precision medicine initiative in the world. Actually, this assertion requires some specifications. As it will be argued in the thesis, there are different definitions and different understandings of precision medicine and of precision medicine projects. As it will be discussed in the next chapters, under certain points of view, it can be even argued, and it has indeed been argued, that the PMI itself, in spite of the name, is *not* a precision medicine initiative. In the same way, it could be argued, and in some cases it has indeed been argued, that projects totally different from the PMI for their design and their mission, have nonetheless to be considered as precision medicine projects. Then it is questionable to argue both that the PMI is the first precision medicine project, and that it is not the first precision medicine project, as the very idea of what can be considered a precision medicine project is questionable.

This thesis will discuss the variety and, in some cases, the inconsistency of the research programs considered as precision medicine projects, as well as the discrepancies in the understandings of precision medicine. It will problematize how the very same project could be considered a precision medicine effort according to certain definitions, but not under others, and vice versa. At this stage, rather than to proceed by choosing a specific definition of precision medicine, I propose to provisionally consider in this analysis all and only the projects that have been explicitly and with justification referred to as precision or personalized medicine, either by the proponents of the projects themselves, and/or by commentators. Under this specification, we can safely say that the PMI is *not* the first precision medicine project as far as it is *not* the first project to be defined as precision medicine.

The oldest large-scale research program that has been put in relation with precision or personalized medicine is probably *deCODE genetics*, founded in 1996. *deCODE genetics* is an Icelandic biopharmaceutical company that, in its gene discovery work, collected and compared genetic data and medical conditions from more than 160,000 Icelanders volunteers (more than a half of the adult population of Iceland), for studying genetic risk factors for common diseases (www.decode.com). Another very famous and large-scale study related to personalized medicine prior to the PMI, is the UK *100,000 Genomes Project* (100KGP), launched in 2012, combing genome sequencing data with medical records. This project will be described more in depth in the next section, as it is one of the two major case studies of the thesis. To make another example, another important research project to the underpinning of precision or personalized medicine is the *Qatar Biobank*, launched in 2010 and correlating lifestyle and health conditions of Qataris (www.qatarbiobank.org.qa); since 2015, it also includes a whole genome sequencing project called *Qatar Genome Program* (qatargenome.org.qa). Then several precision medicine research projects were launched explicitly on the wake of the PMI, by specifically following its model. Even if the ideas proposed by the PMI were not new, the hype around its launch has been an unprecedented

catalyst for the development of similar efforts in other parts of the world. Among the most ambitious and large-scale initiatives explicitly inspired by the launch of the PMI, are the *Chinese Precision Medicine Initiative*, and *Genomic Medicine 2025*, both of them governmental national initiatives, respectively in China and France, both of them focused on massive whole genome sequencing. Also the Italian government approved a national precision medicine project on the wake of the PMI, it was called the *Italian Genomes Project*. The *Legge di Stabilità 2016* (Articolo 1, Commi 580-581, available from gazzettaufficiale.it) established the allocation of five million euros per year for three years to the implementation of the project, and the foundation of a specific Commission for the management of the program. Also in this case, on the model of the 100KGP and of the PMI, the quintessence of the project was massive whole genome sequencing. However, the Italian project was abandoned due to lack of co-financings (www.cattaneoinsenato.it).

The precision medicine projects listed so far, including the PMI itself, including those ongoing, those aborted and those only planned, are all national projects, in the sense that they are developed on a national scale. However, also some cross-national initiatives have been recently announced. One of them is the *Nordic Society of Precision Medicine*, a common genome sequencing program involving Denmark, Iceland, Estonia, Norway, Finland and Sweden (nordicprecisionmedicine.org). Another European example is the *Million European Genomes Alliance* (MEGA), subscribed by thirteen EU countries (ec.europa.eu). Aimed at sequencing one million genomes across EU, MEGA has been considered the European "response to Obama's Precision Medicine Initiative" (Petrone 2016). A similar effort is GenomeAsia100K, a consortium to sequence 100,000 individual genomes across at least 12 South Asian countries, and 7 North and East Asian countries (genomeasia100k.com).

### 1.2 The case studies: design, mission and scope of All of Us and the 100KGP

In the panoply of precision medicine initiatives around the world, this thesis is mainly focused on the US PMI. In some contexts, it is considered the precision medicine initiative *par excellence*, as it appears as a unique catalyst for the popularity of the precision medicine approach itself, and for the implementation of other precision medicine research initiatives. The ambitious scale of the project, and the hype around its potentialities, significantly impacted on the affirmation and on the development of the precision medicine approach, to the extent that the PMI is the explicit or implicit source of inspiration and the reference for many of the other initiatives. Also, the hype around the PMI generated, as it will be discussed in the next section, unprecedented expectations and concerns around the implications of precision medicine in society. Given its apparently far-reaching transformative role, the PMI is an essential case study in this thesis that aims at scrutinizing the societal implications of the affirmation of precision medicine.

In addition to the PMI, another precision medicine project is examined in depth in this thesis, with the aim to achieve a better understanding of the societal meaning of precision medicine through a comparative analysis. As anticipated, the second case study is the UK 100KGP. When this doctoral research started, apart from the PMI, the 100KGP was the largest scale whole genome sequencing project in the world, either under implementation or in program. In particular, it was chosen as the comparative case study because in many discussions, analyses and comments on precision medicine, the 100KGP has been mentioned together with the PMI as the paradigmatic precision medicine project. Then this thesis analyzes and compares what the public opinion apparently considers the two leading precision medicine projects. However, even if they are very often matched, these two projects are very different from one another in terms of design, mission and scope.

### 1.2.1 The 100,000 Genomes Project

The 100KGP was launched in December 2012 by the then UK Prime Minister David Cameron, who appealed to a sort of nationalistic pride, similarly to Obama when launching the PMI. Like Obama did three years later, Cameron ahead of the announcement of the 100KGP referred to the leading role historically covered by his country in medical innovation, and to the necessity to harness the opportunity to keep that role:

> "Britain has often led the world in scientific breakthroughs and medical innovations, from the first CT scan and test-tube baby through to decoding DNA. It is crucial that we continue to push the boundaries and this new plan will mean we are the first country in the world to use DNA codes in the mainstream of the health service" (www.gov.uk).

The UK government earmarked £ 100 million to underpin the whole sequencing of 100,000 genomes from cancer and rare disease patients within the National Health Service (NHS). To deliver this 100KGP, in July 2013, the then Secretary of State for Health, Jeremy Hunt, set up *Genomics England*, an organization wholly owned and funded by the Department of Health. Then 13 *Genomic Medicine Centres* (GMC) were set up across England, as the centers where participants' samples are collected and processed.

The aim of the 100KGP is to provide a better understanding of genetic diseases, of their specificity and of their proximate causes, with the goal to deliver new or more precise diagnoses, and possibly to develop new and more effective treatments (www.genomicsengland.co.uk). The diseases studied by the 100KGP are rare diseases (from a specific list available from the Genomics England website, which in its latest updating of November 2017, included 216 rare diseases) and cancer (according to very specific eligibility criteria, also well specified in the website).

The ancient Greek historian Polybius, in the *Histories*, famously analyzed the concept of "cause" by distinguishing between the *aitia*, the real, upstream cause of an event, and the *arche*, the immediate downstream spark that starts the event. Individuating the "real cause" of cancer, in the sense of the *aitia* in Polybius' *Histories*, is one of the most studied and debated issues of our time. The controversy about the link between cancer and mobile phones (Grimes 2018) is an epitome of the urgency and of the uncertainty of the questions about the *aitia* of cancer, as well as the studies on the risks related to the consumption of red and processed meat (Bouvard et al. 2015), while on the other side the "bad luck theory" has been causing sensation by arguing that the majority of cancer risk is due to the random mutations regularly arising during DNA replication without lifestyle and environment playing significant role in this (Tomasetti and Vogelstein 2015). Quite significantly, Schoenfeld and Ioannidis provocatively observed how almost everything we eat has been object of studies putting it in relation with cancer. Their literature review shows that 40 in 50 common ingredients from random recipes in a cookbook have articles reporting on their cancer risk, which often contradict to one another (2013). The 100KGP is not dealing with this sort of enquiry, the aim is not to investigate the cause of cancer (or of rare diseases) in the sense of the *aitia*, but the cause in the sense of Polybius' *arche*, the beginning. In other words, 100KGP is not directly concerned with the primary distal causes, but the ultimate, proximate, triggering event, the genetic mutation(s) with which the disease begins.

The rare diseases and cancer patients participating in the 100KGP are requested to provide samples for whole genome sequencing, which are put in relation with their historical medical records. To facilitate the detection of the genetic mutations relevant to the disease among the three billion nucleotides composing the human genome and the variations related to the individual variability, the genomes are compared with the most similar healthy genomes available: the genome of a normal cell from the same person in the case of cancer patients, and the genomes of close relatives in the case of rare disease patients. By only focusing on the genetic differences between a tumor cell and a normal cell in the same

person, or a sick person and a healthy person from the same close family, it is possible to appropriately restrict the search for the genetic variations relevant to the onset of the disease. Participants affected by rare diseases and their close relatives are requested to donate blood samples, or saliva in case blood cannot be taken. Participants affected by solid tumors are requested to donate a sample of blood (or saliva if blood cannot be taken), and a piece of their tumor. Participants affected by blood cancer donate a sample of blood and a sample of saliva. All these samples are processed, and whole genome sequencing is performed. It is worth remarking that, consequently to its research design based on the comparison of healthy and affected genomes, the 100KGP does not plan to sequence 100,000 people: it really plans to sequence 100,000 *genomes*, which will be from much less than 100,000 people, considered that every cancer patient will have *two* genomes sequenced. On December 5, 2018 (one year later than the first self-imposed deadline), it was announced that the project has reached the goal of sequencing 100,000 genomes (genomicsengland.co.uk).

The participants in the 100KGP have access to the main findings from the genomic analyses about themselves, which are returned to them by the clinical teams. If participants consent, also secondary findings are returned: they are communicated to the participants' physician, who is expected to discuss their meaning with the person concerned. All the data are accessible to healthcare professionals in GMC. Researchers from outside the GMC can also access to the de-identified genomic and health data of the 100KGP dataset, but only under the approval of an application form including a detailed research plan that should be proved to be aligned with the aims and with the ethical principles of the 100KGP (genomicsengland.co.uk).

The 100KGP, like most of the precision medicine projects listed in the previous section, is mainly about whole genome sequencing and genetic analysis of diseases, to the extent that these projects could be also considered as genomic medicine projects. The kind of precision medicine they are expected to underpin is mainly a sort of genomic medicine. Even if some of these genomic medicine projects have been explicitly inspired by and modeled after the

PMI, it is worth remarking that the PMI is not (only) a genomic medicine project. As a matter of fact, even if the 100KGP and the PMI are often described as homologous projects, they are very different from many points of view. They both perform whole genome sequencings, they both build on large national cohorts. But this is actually all they do have in common.

### 1.2.2 The All of Us Research Program

As mentioned in the previous sections, the PMI is a US national effort earmarking funding to the NIH, the NCI, the FDA and the ONC to support the development of the expertise, of the infrastructures and of the regulatory framework to underpin precision medicine. A major piece of this national effort is the NIH *Precision Medicine Cohort Program*, which since October 2016 was renamed the *All of Us Research Program* (nih.gov.org). All of Us is expected to produce and furnish the unprecedented rich and diverse dataset on which the new understanding of the relevance of human variability and of contextual situations, with respect to health and disease conditions, will be based upon. It is around All of Us that most of the hype, of the expectations and the concerns related to precision medicine and to the PMI are concentrated. Consistently, All of Us is the main focus of this analysis and of this thesis.

All of Us is a longitudinal research cohort study, aimed at enrolling at least one million volunteers. In contrast to the 100KGP, All of Us is not focused on any specific disease, but is instead aimed at exploring how individual differences can influence health and disease overall. The eligibility criteria are consequently far more inclusive than for the 100KGP. While in the 100KGP only NHS patients affected by very clearly specified genetic diseases are eligible to take part, everyone residing in the US can participate in All of Us, whatever their medical conditions are. The only individuals excluded from participation are, at the initial launch: children under the age of 18, adults unable to consent, and prisoners. However, strategies are under evaluation to also open enrollment to these populations at a later stage (All of Us Operational Protocol, 2018). Healthy volunteers are welcome, as also the remote,

upstream, distal causes affecting diseases onsets and predispositions are examined. The *aitia*, not only the *arche*, is the object of the study.

Given the very different mission and the different scope, a much broader range of data is analyzed by All of Us than by the 100KGP. The 100KGP, aimed at exploring the genetic causations, only matches genetic variation with electronic health records. All of Us is aimed at exploring all the possible factors affecting health. These factors, the individual variations considered relevant to health and disease onsets, are considered as embedded into three macro categories: biology, lifestyle and environment. The research of All of Us focuses on the intersection of these three factors, and any kind of personal data relevant to them is collected by the study.

As seen, the 100KGP is essentially a genomic medicine study. At the beginning, when the PMI was launched, whole genome sequencing was presented as a quintessential part of the project. However, with the development and the implementation of All of Us, the centrality of genomic data was largely downsized to the advantage of other research directions, up to the extent that sharing genetic data is only optional for the All of Us participants. It is not possible to participate in the 100KGP without having the genome sequenced, because to participate means to have the genome sequenced and to share the data. Conversely, it is optional for All of Us participants to undertake sequencing of any sort and to share their genetic data.

Participating in All of Us, implies to share information about the lifestyle and the medical history via questionnaires and surveys (Participant Provided Information, PPI). Any other kind of data sharing is optional (All of Us Sample Consent Form, 2018). All participants are also asked to share their Electronic Health Records (EHR), like in the 100KGP - but differently from the 100KGP, acceptance is not compulsory for participating in All of Us, and is consented for on a separate form (All of Us Sample EHR Consent Form, 2018). Additionally, participants may also be asked to contribute by providing physical measurements and biospecimens; in this case, they are classified as “core participants”. They

can also contribute by providing digital health data using sensor modules or wearables. Still, they can always decline without compromising their role as participants.

To sum up, the data collected by All of Us include all or some of the following: PPI about lifestyle and medical history, electronic health records, physical measurements, biospecimens (including blood or saliva for genetic assays), and passive mobile and digital health data (All of Us Operational Protocol, 2018). The goal is to combine data in order to have access to the most complete possible picture of biological, environmental and lifestyle factors for every participant, for better understanding the differences in terms of disease and health from the very upstream.

The results of the analyses will be available to the participants. This has actually been one of the core discourses of the project since the very beginning: empowering participants with information about themselves and their own health. Consistently with this framework of empowerment, participants will have direct access both to their personal data and to their personal results (the interpretations of the data), through an online Participant Portal for which the participants will have a personal account. The *Operational Protocol* notes that healthcare providers should *not* be used as intermediaries for communicating the data or the results. The declared rationale for this is that not all participants will have a healthcare provider, and that this is also a way to guarantee participants "the freedom to make the decision of if, when, and how to communicate individual-level results information to their healthcare provider" (ibidem, 51). To facilitate understanding without intermediation, the intention is to develop "easy-to-read templates" (ibidem). Moreover, the *Protocol* states that a hard copy of the physical measurements be also provided, and trained program staff is required to call the participant's attention on any blood pressure or heart rate measurements considered emergent or urgent against the standard range assumed by All of Us. Participants may also choose not to receive results: a specific consent form is dedicated to the access to the results. A separate procedure and consent process is planned for returning genetic/genomic results, which is currently in development (ibidem, 24 and 59).

The aim of All of Us is to create a "resource for research" (ibidem, 9). In this respect, the study is primarily designed to produce a dataset for enabling scientific research to the underpinning of precision medicine. This dataset is planned to be organized into a *Cured Data Repository*, where all the data will be encrypted and personal identifiable information will be removed, which will be publicly accessible through a Research Portal (ibidem, 59). The first version of the All of Us dataset is expected to be available in 2019. Anyone will be able to apply for having access to the data: researchers from academic, commercial, public, or private institutions, and also "citizen scientists" (researchallofus.org).

Voluntary enrollment in All of Us started on May 6, 2018. The latest update I received via the All of Us newsletter reported that, in the week of August 13, 100,000 participants were registered and 50,000 were fully enrolled, 360,000 vials of blood were collected, and 200,000 online surveys. This information is probably publicly available on the website joinallofus.org, but I do not have access to it as it is not accessible from outside the US.

Both All of Us and the 100KGP are cohort studies. Apart from this, what they have in common, as noted above, is the large scale of the cohorts, the performing of whole genome sequencing, and the aim to build a dataset as a research resource. However, they follow two very different models, by encompassing very different scopes. To recap: the 100KGP is focused on the study of very well specified genetic diseases; All of Us is not focused on any specific disease, but on any kind of health and disease condition. Only genetic diseases patients are eligible for 100KGP; eligibility for All of Us is not related to health and disease conditions. The 100KGP is aimed at uncovering solely the genetic *arche* of the diseases; All of Us any possible *aitia* or influence of any kind. The 100KGP is entirely developed around whole genome sequencing; in All of Us, genomic data is only (an optional) one of the many kinds of data collected.

Even if they are generally matched as the two leading precision medicine projects, as two paradigmatic versions of the same approach, actually only the general idea is similar, while

implementation and scope are totally different. As a matter of fact, All of Us has been designed by taking as a reference another UK project: not the 100KGP, but *UK Biobank*.

### 1.2.3 UK Biobank

UK Biobank was established in 2003 by the medical charity the Wellcome Trust, the Medical Research Council, the Department of Health, the Scottish Government and the Northwest Regional Development Agency. Its founding aims were to improve the prevention, diagnosis and treatment of a wide range of illnesses.

UK Biobank is very rarely enumerated as a precision medicine project, and actually it was not founded as a precision medicine project. However, it is a very large scale observational cohort study, and it is very similar in structure, design and scope to All of Us. Like All of Us, UK Biobank is focused on the study on how genes, environment and lifestyle increase the risk for different diseases. Like All of Us, UK Biobank enrolled its participants independently from their initial health conditions, and it is following their medical records over time by keeping them linked to the information they shared. UK Biobank recruited 500,000 people aged between 40-69 years in 2006-2010. All of them have undergone measures, provided blood, urine and saliva samples for future analysis, detailed information about themselves, and agreed to have their health followed (www.ukbiobank.ac.uk). These are all the very same data asked to be shared by All of Us, even if many of them are optional for All of Us participants. In addition to this, genotyping has been undertaken on all the UK Biobank participants, and 100,000 of them have been monitored by a wearable activity monitor for one week. Like in the case of All of Us, the primary aim of UK Biobank is to produce a dataset as a research resource to be accessible "to all bona fide health researchers" (ibidem). The Data Showcase is publicly accessible on the UK Biobank website, and it provides summary information about all the data collected through the initiative. To gain access to the detailed information necessary to conduct a

study, researchers need to apply, to have their research approved, and to pay a fee (the amount varies according to the kind, the amount and the format of the data requested).

Differently from All of Us, UK Biobank is not doing whole genome sequencing, and there are currently no plans for whole genome sequencing on UK Biobank participants. Another fundamental difference is that, opposite to the very flagship idea of All of Us, UK Biobank does not return data nor results to participants, except for some measurements during the visit (*UK Biobank Consent Form*). Apart from this, the structure, the design, the mission, the scale and the scope of UK Biobank and All of Us are very similar. This is probably not by chance, as All of Us has been explicitly referring to UK Biobank as a model (as remarked for example in the video 'The Dish: Standing on the Shoulders of Giants', allofus.nih.gov), to the extent that Rory Collins, Principal Investigator and Chief Executive of the UK Biobank, has been included since the very beginning in the Advisory Panel of All of Us (allofus.nih.gov). Consequently, although the PMI is commonly matched to the 100KGP, which is considered as the other leading precision medicine program, it rather mirrors, by construction, a research cohort which is not generally assumed as directly related to precision medicine: UK Biobank.

### 1.3 Social promises and concerns around precision medicine

The PMI is an especially interesting case study for STS analysis. As seen, its launch immediately preceded, and probably catalyzed, the rise of the popularity of precision medicine: an unprecedented bloom of scholarships on precision medicine, events on precision medicine, analyses, researches and google searches on precision medicine, as well as a proliferation of precision medicine projects around the world. But that is not all. The hype around the PMI also triggered expectations and concerns around socio-political matters, and the ELSI of precision medicine and of the PMI have already drawn the attention of many social sciences analysts (among others: Hedgecoe 2004, Rabinow and Rose 2006, Rose 2007 and 2013, Novas and Rose 2010, Tutton 2014, Dickenson 2014, Prainsack 2014, 2017, 2018, Blasimme and Vayena 2016, Sankar and Parker 2017, Ferryman and Pitcan 2018). Among the ELSI of precision medicine, this thesis is focused on those promises and those concerns related to distributive justice.

A major concern for precision medicine in the socio-political domain is obviously privacy and data security and regulation. It is not (directly) related to distributive justice, and as a consequence, this thesis will only slightly deal with that. However, it is not possible, in this analysis on the socio-political concerns around precision medicine, not to mention what many scholars consider as the major challenge for this approach. As seen, participation in All of Us, as well as in other large-scale precision medicine cohort studies, primarily involves sharing personal data. In some cases, they are very sensitive data. Indeed, some data contain information about the participants that is unknown to the participant themselves; e.g., any kind of genetic data. Moreover, these data contain information not only about the participants, but often also about their relatives (i.e., again, genetic data). Who has access to these data, and how these data can be used, are major concerns about precision medicine cohort studies. The ghost of Foucault's surveillance (1977), with its consequences in terms of political intromission and control over "life itself" (Rose 2007, Rabinow and Rose 2006)

is resumed and reconsidered at a renewed and much deeper level, to the extent that the term 'endopticon' has been proposed in the place of Foucault's *panopticon*, to stress the intimate nature of the data that are under surveillance in this modern medical model, which requires to share, among others, data about physiological states and molecular individualities (Maturo 2015).

Apart from concerns about political surveillance, this level of personal and biological data sharing also relates to very serious problems of data use and misuse, from commercialization to new forms of discriminations. Serious concerns have been advanced in terms of "genetic discrimination" in case genetic information could be accessible to insurance companies or to employers (Billings et al. 1992, Kitcher 1996, Clayton 2003, Wolf 2005, Epstein 2007). In "the age of big data" (Lohr 2012), data protection is one of the most pressing issues of our times. Precision medicine research grounds on personal data sharing, and it is especially exposed to these concerns (Prainsack 2015).

However, rather than on issues related to the possible harms and injustices deriving from participating in precision medicine research, this thesis is focused on the issues related to the possible harms and injustices deriving from *not* participating in precision medicine research, in alignment with the seminal article by Jonas Lerman "Big Data and Its Exclusion" (2013). My doctoral research is mostly devoted to analyzing the promises, the opportunities, the challenges and the risk of precision medicine in terms of the distribution of the (possibly) deriving benefits, from a perspective of social and health equity.

The concept of equity, as well as its connection with the concept of equality, is far from being univocal. Different principles of distributive justice attach different weight and different meaning to dimensions such as luck, responsibility and desert, and propose different distribution criteria to be considered as fair (Lamont and Favor 2017). These different principles are all the more relevant in the context of *health* equity, where the roles played by luck, by personal responsibility and by societal determinants are highly controversially intertwined (Eyal et al. 2013, Sreenivasan 2018).

This thesis, while taking into account and sometimes referring directly to the different principles of distributive justice, especially as far as responsibility is concerned, is developed under the general definition shared by the World Organization (WHO) of inequity as avoidable and unfair inequality (www.who.int/healthsystems, PAHOWHO 1999): equity is referred to "differences which are unnecessary and avoidable, but, in addition, are also considered unfair and unjust", as it is famously expressed by Margaret Whitehead (1992, 5).

The reason why health equity and social equity are mentioned together, here as well as in the title of the thesis, is that a huge amount of literature, which has been increasing for more than one century, evidences a significant correlation between them (Sreenivasan 2018, Commission on Social Determinants of Health 2008, CDC 2013, Department of Health and Social Security 1980). Central to this correlation is the effect of the so called *social determinants of health* (SDOH), defined by the WHO as "the conditions in which people are born, grow, live, work and age. These circumstances are shaped by the distribution of money, power and resources at global, national and local levels. The social determinants of health are mostly responsible for health inequities - the unfair and avoidable differences in health status seen within and between countries" (www.who.int/social_determinants). In other words, the SDOH are all those social conditions affecting health conditions, and in particular the social inequalities generating also health inequalities.

Concern about the detrimental health effects of certain social realities dates back to at least the middle of the nineteenth century, when Friedrich Engels, in his book *The Condition of the Working Class in England* (1845), reported a much higher mortality rate among industrial workers in Manchester than in the countryside and denounced deprived social conditions as the cause of that. In the same historical period, in 1848, Rudolf Virchow reported the causes of a typhus epidemic to be associated with hunger and war, then the epidemic being due to social and ultimately political conditions. Consequently, he developed principles that today are still known as 'Virkowian' and continue to be considered as an

essential basis for public health: “Medicine is a social science, and politics nothing but medicine at a larger scale’” (see Mackenbach 2008).

In recent years, the concept of SDOH has been more precisely and systematically defined and denounced by the works of Michael Marmot and his colleagues (e.g. Marmot et al. 1978, Marmot et al. 19997, Marmot and Wilkinson 1999, Marmot 2001, Marmot 2004, Marmot 2017). Starting with the famous *Whitehall Study*, a perspective cohort of British Civil Servants, where a correlation was observed between life expectancy and occupational rank, Marmot advanced the idea of a social *gradient* in health. Generally speaking, the social gradient in health means that the lower is the socio-economic status, the shorter is the life expectancy and the higher the likelihood to develop poor health conditions. Level of income, of education, and social rank, are usually the factors with which health conditions are evidenced to correlate mostly. This co-variance is mostly explained by referring to two pathways (not necessarily mutually exclusive): material and psychosocial (Sreenivasan 2018). The material pathways associate poor health outcomes with all the unhealthy behaviors and environmental exposures related to a low socio-economic status: poor socio-economic conditions often imply poor housing or poor neighborhoods, overexposed to harmful environmental factors; and also imply very often lack of resources and/or of education for leading what it is considered a ‘healthy lifestyle’. The psychosocial pathways relate poor health outcomes to the detrimental long terms effects of stress, derived from living in a condition of poverty, of social segregation, of exploitation, of discrimination, or of unsafety. In addition to these material and psychosocial pathways, another connection between socio-economic conditions and health outcomes is related to different level of access to healthcare (Daniels 2017), an issue that will have some space in this thesis as far as access to precision medicine treatments is concerned.

Given all these links between social and health conditions, this thesis explores the connections of precision medicine with both social and health equity, by taking into a full account their correlations. As anticipated in the preface, the analysis is mainly articulated

across three relevant strands: (1) the effects of precision medicine for the implementation of public health policies, (2) inclusivity and accessibility of precision medicine benefits, (3) the role of precision medicine for underpinning democratization of medicine.

### 1.3.1 Precision medicine and public health policies

When Obama introduced the PMI in the first place, he remarked it as an opportunity to "remake our destiny". However, "destiny", even just in terms of health, is related to a multitude of determinants, of multifactorial nature, intersecting biological, environmental, social, psychological factors. An anticipatory reply to Obama's promise to "remake our destiny" came from Philip Kitcher's book *The Lives to Come* (1996), which critically analyzes the dichotomy between devastating health impairments due to genetic aberration or to social deprivation and violence, by arguing on the moral duty to intervene on both these categories of causes:

> "our lives are the products of many lotteries, and only one of them shuffles and distributes pieces of DNA…if we are prepared to reallocate assets to combat the effects of disabling alleles, then, by analogy, we should also be ready to undertake similar schemes to prevent the damage done by brutalizing environments".
>
> (Ibidem, 312-313)

Against this background, a very important direction of analysis about the equitable capacity of precision medicine concerns its scope with respect to the social inequalities affecting health.

The SDOH are generally considered in the domain of public health, "the art and science of preventing disease, prolonging life and promoting health through the organized efforts of society" (Acheson, 1988; WHO), and especially of the "Virchowian" versions of public health, which include an active political engagement. The relationship between

precision medicine and public health has been problematic since the inception of the former, by possibly expanding a centuries old debate about the roles of medicine for the health of population, and the societal duties of medicine (Pearce 1996, Rothman et al. 1998, McMichael 1999). A case in point Geoffrey Rose's seminal article *Sick individuals and sick populations* (Rose 1985), in which he distinguishes between strategies focusing on the vulnerabilities of individuals and strategies focusing on the external general causes of disease for the whole population. A similar distinction has been proposed much more recently, in 2016, by Ron Zimmern, exactly in relation to precision medicine.

Soon after the launch of the PMI, first Michael Joyner, and then Ronald Bayer and Sandro Galea, took similar position by questioning the usefulness of precision medicine for the health of the population, as precision medicine might be at the cost of leaving more urgent and effective public health strategies aside.

Immediately after the SOTU and the announcement of the PMI, Mayo Clinic medical physiologist Michael Joyner expressed his concerns in *The New York Times* ("'Moonshot' Medicine Will Let Us Down", 2015), then in *The Lancet* (Coote and Joyner 2015, "Is Precision Medicine The Route To A Healthy World?"), and subsequently in several other publications (Joyner and Paneth 2015, Joyner 2016, Joyner 2017). His concerns are especially related to the limits of precision medicine, which is questioned to have poor predictive power, and to consequently lead to overdiagnosis and unnecessary medicalization, while more appropriate and efficient interventions would focus on the social and behavioural determinants of health.

The argument by Ronald Bayer, political scientist co-director of the *Centre for the History and Ethics of Public Health* at the Mailman School of Public Health of Columbia University, and by Sandro Galea, physician and epidemiologist, dean of the Boston University School of Public Health, is slightly different, but the conclusions are similar. Their concerns about precision medicine were first expressed in a perspective article on the

NEJM (Bayer and Galea 2015, "Public Health in the Precision-Medicine Era"), then more extensively on the *Annual Review of Public Health* (Ramaswami, Bayer and Galea 2018, "Precision Medicine from a Public Health Perspective"). They do not express special concern about the validity and the helpfulness of precision medicine in itself, but rather express unease about the *prioritization* of precision medicine efforts over public health strategies targeting social and environmental determinants of health. They draw on the data mentioned at the beginning of this section about the health relevance of social inequalities, and on their major impact despite biomedical innovations (Institute of Medicine 2013), to argue that the most urgent and effective interventions need to target social inequalities rather than further improve the biomedical system. Hence, they assert that public health interventions need to be prioritized over innovation in precision medicine.

I propose to refer to the kind of criticism proposed by Bayer and Galea, and by Joyner, as to the *distraction argument* (Galasso and Testa 2017b). This is because, in both cases, the main point is that precision medicine is detrimental as long as it is "a distraction" from the most urgent public health interventions on social, environmental and behavioral determinants of health, in the sense that it diverts resources and attentions from them, as it is also worried by Sarah Shostak (2013). The term 'distraction' is indeed recurrently used in this context.

In the analyses by Joyner, it is argued that:

> "it [precision medicine] could be a *distraction* from low cost and effective population-wide interventions and policies."
> (Coote and Joyner 2015, 1617, emphasis added).

And, as a consequence, that:

> "Open discussion and debate related to precision medicine are urgently needed to avoid misapplication of resources, hype, iatrogenic interventions, and *distraction* from established approaches with ongoing utility."
> (Joyner 2016, 651, emphasis added).

Similar to this, are the concerns expressed by Bayer, Galea and colleagues:

> "We worry that an unstinting focus on precision medicine by trusted spokespeople for health is a mistake — and a *distraction* from the goal of producing a healthier population."
> (Bayer and Galea 2015, 501, emphasis added).

As they reiterate in the conclusion of their more recent and longer article:

> "The core public health concern is whether the new enthusiasm for targeted clinical intervention represents a profound *distraction* from population-level challenges that demand resources and sustained scientific attention."
> (Ramaswami, Bayer and Galea 2018, 164, emphasis added).

While on the one hand the 'distraction argument' is advanced to frame an antagonistic relationship between precision medicine and public health, on the other hand commentators have engineered a rapprochement between these frameworks through introducing the notion of 'precision public health'. The general idea of precision public health is that precision medicine could serve as a tool to public health, by translating its insights from individuals to populations. In the words of Muin Khoury:

> "If precision medicine is about providing the right treatment to the right patient at the right time, precision public health can be simply viewed as providing the right intervention to the right population at the right time."
> (Khoury et al. 2016, 398).

More broadly, precision public health envisions to guide public health interventions with the use of data (Dowell et al. 2016). This vision has been primarily and most intensively developed by Muin Khoury, founding director of the CDC's *Office of Public Health Genomics* (Khoury et al. 2016; Khoury et al. 2018), and by Sue Desmond-Hellman, Chief Executive Officer of *the Bill & Melinda Gates Foundation*, and also member of the PMI Working Group (Desmond-Hellman 2016; Dowell, Blazes and Desmond-Hellman 2016).

In some senses, the position of the 'distraction argument' and of precision public health are in opposition: the first considers precision medicine as to the detriment of public health, whereas the second regards it as a unique opportunity for the advancement of public health. Nevertheless, it would be misleading to consider the debate in terms of opposite factions. The proponents of the 'distraction argument' are not blind to the potential of precision public health, and the proponents of precision public health are totally aware of the risk of undermining policies and initiatives aimed at intervening in relevant social and behavioral determinants of health. Both sides, actually, consider both the risks and the opportunities of precision medicine with respect to public health, even while they attach different weights to them.

The dialogue between the approaches is epitomized by an article co-authored by the leading proponents of the two positions, Galea and Khoury (2016, "Will Precision Medicine Improve Population Health?"), in which they systematically discuss the reasons why precision medicine can or cannot improve population health. In addition to this, the "distraction argument group", recently published another perspective article on the NEJM specifically to discuss the framework of precision public health (Chowkwanyun, Bayer and

Galea 2018, ""Precision" Public Health – Between Novelty and Hype"): although they ferociously criticize precision public health as "a quixotic search for magic bullets that undermines belief in broader social determinants as foundational — an abandonment of public health's longstanding mission", Chowkwanyun, Bayer and Galea also acknowledged that "If the PPH [precision public health] concept aids integration of technological developments into work that responds to social concerns and helps produce demonstrable results, it may be a welcome development." (ibidem, 3).

It is, then, possibly correct to consider in principle two key and ostensibly distinct positions in the debate about the relationship between precision medicine and public health, but it is not correct to consider these as necessarily directly opposite factions. In any case, the debate over the role of precision medicine with respect to public health and public health policies is open, and all the more relevant to the analysis over the effects of precision medicine for health equity, in so far as it is tightly connected to social equity.

### 1.3.2 The inclusivity of precision medicine

Another issue catalyzing both promises and concerns about precision medicine capacities in terms of equity relates to the accessibility of the deriving benefits. On the one hand, All of Us makes of inclusion one of its core principles, by totally embracing Epstein's "inclusion-and-difference-paradigm" (Epstein 2007), the research ideology promoting "the inclusion of members of various groups generally considered to have been underrepresented previously as subjects in clinical studies; and the measurement, within those studies, of differences across groups with regard to treatment effects, disease progression, or biological processes" (ibidem, 6) . The name "All of Us" itself was explicitly chosen to emphasize the inclusivity of the program, and the openness of participation to all (www.nih.gov). In particular, one of the primary missions of the project is to ensure diversity of representation. Special emphasis is put on the opportunity to gather an unprecedented diverse research cohort, and major efforts are invested for including those minorities that have been historically

underrepresented in medical research, with the aim to "allow robust inferences on these groups" (Precision Medicine Initiative Working Group Report 2015, 26).

The rationale for this emphasis on ensuring diversity is related to the increased concerns about medical research being biased by only relying on the data of certain demographic groups. Spratt and colleagues (2015), for instance, denounce the disproportionally white composition of *The Cancer Genome Atlas*, a huge genomic dataset of cancer patients in the US. In 5,729 participants, 5,145 self-declared their race; among those, 4,389 declared themselves as white. Thus, more than 85% of the participants who accepted to declare a race, and more than 77% of the total participants, are self-declaredly white. Ongoing concern is related to this disproportional representation, as medical research results are mostly grounded on data from some demographic groups: it is seen as jeopardizing the robustness and the extensive and effective applicability of results, to the detriment both of scientific advancement and of societal equitable benefit (Mersha and Abebe 2015; Cohn, Henderson and Appelbaum 2017).

In some senses, the concerns over disproportional representations in medical research could be considered as a sort of starting point, and as the central intuition of precision medicine: that individual differences matter, and that they need to be taken into account for delivering appropriate health interventions. The problem of disproportional representation in medical research is indeed all the more relevant in the framework of precision medicine, defined as the medical approach which mines differences. As the very concept of precision medicine is based on taking into account individual specificities, if certain populations are not included in the research, and their specificities are not taken into account, then, by definition, precision medicine cannot be applied to them. Against this background, All of Us describes itself as the long-awaited solution to the problem of underrepresentation, and as a unique and unprecedented opportunity to reach and benefit all the diverse populations in the US by representing all of them (allofus.nih.org).

On the other hand, in contrast to the inclusive promises of All of Us, there is the widespread concern that precision medicine will exacerbate existing health disparities by only benefitting certain segments of the population. These concerns have been expressed, among others, in very ferocious and clear terms by Mark Rothstein, Founding Director of the *Institute for Bioethics, Health Policy and Law* at the University of Louisville School of Medicine (Rothstein 2016 and 2017):

> "precision medicine seems to be proceeding with *a monolithic vision of the patients* who will benefit from this developing approach to medicine. They are patients who are uncommonly *tech savvy*, highly *health literate*, *self-directed*, *information seeking*, *English fluent, health focused*, and *well insured*"
> (Rothstein 2017, 6, emphasis added).

With this, Rothstein highlights the main barriers to have access to the benefits of precision medicine, which possibly frustrate the promises about inclusion.

To analyze the obstacles that might prevent access to the deliveries of precision medicine, and the strategies implemented to overcome them, I propose to consider separately the problem of exclusivity *upstream* and *downstream*. This distinction is similar to, but not overlapping nor connected with, the distinction between bias in datasets and bias in outcome proposed by Ferryman and Pitcan in their *Fairness in Precision Medicine* project (2018).

By *upstream exclusivity*, in this thesis, it is meant all the factors possibly preventing the enrollment in the precision medicine research cohorts, and consequently determining even the *a priori* inapplicability of precision medicine to certain groups. The upstream barriers are then in turn distinguished between *objective* and *subjective* obstacles. In some senses, this distinction could be understood in terms of the two concepts of liberty theorized by Isaiah Berlin (1969): the objective obstacles as relevant to negative liberty, meaning the absence of obstacles external to the agent; the subjective obstacles as relevant to positive

liberty, as intrinsic control of the agents over themselves. More specifically, by *objective obstacles* it is here meant all the conditions preventing *de facto* participation in precision medicine cohorts, in the sense of the practical impediments compromising the possibility to participate. Some examples of objective obstacles might be unfamiliarity with information technology if enrollment or participation are mainly online; poor scientific education if the language is technical; inadequate English fluency if the material and the requests are in English. Conversely, the *subjective obstacles* are all those factors preventing some people from participating even if they have all the tools, the facilities and the abilities to participate. The typical example of subjective obstacle is mistrust. Mistrust is a widespread issue, especially in the case of precision medicine projects grounded on data collection, as there are many concerns about privacy and data misuse (Cohn et al. 2015). In addition to these general concerns, mistrust is especially relevant as far as ethnic minorities are concerned (Jacewicz 2016): studies show that members of some ethnic groups are discouraged from participating as research subjects by the fact that medical research is mainly conducted by white experts, and that the 'wounds' of historical injustices against people of color in medical research, like the notorious episode of Henrietta Lacks (Nisbet and Fahy 2013; Shiber and Foxwell 2013) and of the Tuskegee Studies (Alsan and Wakamaker 2016), still have to be "healed", and the memory of them is still a major cause of distrust (Cohn et al. 2015).

In addition to all these objective and subjective upstream obstacles, another issue is related to *downstream exclusivity*. Downstream exclusivity refers to the possibility to have access to the benefits deriving from precision medicine, either therapies or other kinds of health interventions. The main obstacles in this respect are: the possible unavailability of treatments in certain areas and, most importantly, the costs of the treatments.

The debate about the effect of precision medicine on healthcare costs is an open one. On the one hand there is hope that, as tailored treatment will maximize effectiveness and reduce wastes, the healthcare market will be more cost effective, and the prices of healthcare will decrease. On the other hand, since precision medicine treatments are tailored to specific

groups, they will have smaller markets; moreover, they will be developed by applying expensive technologies. Hence, there are worries that prices might increase.

I leave it to economists to make predictions about the effects of precision medicine on healthcare costs. What it is relevant to the scope of this thesis is that people who cannot afford even basic healthcare treatments will no doubt be similarly unable to afford precision medicine treatments, whatever the prices will be. Then, if having limited access to healthcare is a health and social disadvantage (Daniels 2017), and if precision medicine is, as the promise is, an improvement over 'regular medicine', then existing health disparities will be exacerbated. People who already have good access to healthcare will experience greater benefit from precision medicine by accessing to (possibly) even more beneficial healthcare, while people with poor healthcare access will have no additional benefit. It means that, with respect to the current situation, people who are already advantaged in terms of healthcare opportunities will have a further advancement, while people already disadvantaged will not advance. This would widen the gap between them. Although some distributive justice principles would approve this distribution, such as Utilitarianism and the Pareto Principle, as far as some gain without anybody losing, and the overall population would have a gain, Egalitarian principles cannot accept it as it would exacerbate inequalities.

The problem of inaccessible costs, around precision medicine as well as around healthcare in general, is very relevant to issues of health equity. The US has a private healthcare system: people have healthcare costs covered by their healthcare insurances (up to a certain extent, according to the kind of insurance). It has been reported that in 2017, 8.8 percent of American people, which is 28.5 million, did not have health insurance at any point during the year (www.census.gov). However, exclusive healthcare is not an issue only in the US, or in other private systems. A general privatization of resources has raised concerns in public healthcare systems as well. The NHS in the UK is a public system, yet a recent article on *The Lancet* questioned the appropriateness of investing in the 100KGP and in genomic medicine, since, "as the NHS increasingly struggles to deliver basic services, now may not

be the time for the NHS to lead this change" (Mody 2017). To keep the recurring metaphor of precision medicine as 'a moonshot', used both in a positive (cancer.gov) and in a negative sense (Joyner 2015), the problem can be summarized with the words by the racial justice activist Patricia Benn, as reported by Ruha Benjamin:

> "Before we start designing ways to get to the moon, can we just make sure everybody on my block can actually get to work?"
> (Benjamin 2013, 12).

### 1.3.3 Democratizing capacities of precision medicine

One final relevant issue to scrutinize the potential effects of precision medicine in terms of equity, concerns the declared democratizing turn. Both All of Us and the 100KGP have relied on 'the rhetoric of citizen science' to incentivize participation (Woolley et al. 2016). Treating "participants as partners" is one of the major and most recurring slogans of All of Us (allofus.nih.gov), and involvement and engagement are encouraged at many levels, including in the governance. By referring to the three different although overlapping concepts of participation (participation, engagement and involvement) proposed by Woolley and colleagues (2016), precision medicine cohort participants are invited not only to take part as human subjects, but also to be *engaged* in the research, in the sense of understanding the background, the purposes and the utility of the research itself and of their own role, and even to be *involved* in the sense of involvement as it is defined by Woolley and colleagues: the possibility for the public to "have an active role in in the planning and conduct of the research itself, even to the level of choosing the scientific questions to be addressed" (ibidem, 2). This concept of participation is here understood as reaching the level of *coordination* as expressed in Prainsack's (2014) analysis: "agenda setting, determining the terms of the execution of the idea/procedural aspects, deciding what results are (and what 'good' results are), deciding what will be done with results, deciding on intellectual property

questions" (ibidem, 7). The framework of participants involvement "as partners" at the coordination level is relevant to the analysis of the equitable capacities of precision medicine inasmuch it mirrors a democratic model, and democracy is often conceived as a guarantee for the pursuit of the public interest, by producing equitable outcomes as a corollary (Pateman 1970).

Barbara Prainsack (2017, 11) in her book *Personalized Medicine* observes that it is probably "not a coincidence that we see a renewed emphasis on patient participation at a time when medicine is particularly hungry for data and other contributions from us all". As discussed above, precision medicine itself grounds on public participation and data sharing. Consequently, "Without patients contributing data, time, effort and self-care, current vision of personalized medicine cannot be realized" (ibidem). Given the centrality and the necessity of the active collaboration of participants, the extension of their role from mere research subjects to "partners" might be seen as a sort of acknowledgement -either real or specious- of their important contribution, and as a way to incentivize long term participation. Moreover, public involvement at the coordination level could also provide a sort of justification and shared responsibility for the choices in terms of setting and directions for the project (Flear and Pickersgill 2013).

The promise of precision medicine in terms of democratizing capacities is related to the emphasis that the discourses put in this respect, and to the procedures actually implemented to involve participants at many levels (e.g., different kinds of online forms, surveys and participants panels). More specifically, involvement at the coordination level is offered by the 100KGP through the *Disease Nomination Forms*, online forms to nominate a new rare disease to be included in the research, or new cancer eligibility criteria. Apart from that, participants and their relatives or carers can be involved in the governance of the project by taking part in the Participant Panel. This acts as an advisory body across the committees and boards of Genomics England (genomicsengland.co.uk.

As far as the PMI is concerned, several channels have been opened over time for collecting public feedback: the NIH divulgated several *Requests For Information* (RFI), online forms to share comments on specific issues; and a 'feedback site' was opened at some point with a similar format. More recently, suggestions for 'research priorities' have been collected through *Ideascale* (allofusresearchpriorities.ideascale.com), a sort of online forum where it is possible to share "ideas" and to vote for the ideas of others. Then also in the plans of All of Us there will be a Participant Panel, and some participant representatives are also planned to be members of the committees (Allofus Operational Protocol).

For the other issues described in this section, the opportunities were described against the opposite risks. On the one side there were the promises that precision medicine could facilitate the implementation of public health strategies, on the other side the concerns that it could subtract resources and attentions from public health urgencies. On the one side there were the promises of precision medicine fostering the inclusivity of healthcare, on the other side the concerns that it could exacerbate exclusivity. Concerning the issue of democratizing capacities, the situation is slightly different. On the one hand, also in this case, it is envisioned the opportunity that precision medicine could facilitate the democratization of medical research and care. But, on the other hand, there is no specific concern that precision medicine could in itself damage the democratization of medicine. Rather, the risk envisioned is that the precision medicine *promise* of democratization could damage actual democratization, if it remains unfulfilled. In other words, the concern, not specifically about democratic participation in precision medicine, but about democratic participation in general, is related to *tokenism,* and in particular to the risk that an illusory involvement at decisional level, with no real executive capacities, could give the false impression that the interests of everybody are taken into account, while obscuring the evidence that only certain interests are actually pursued. As expressed by Sharry Arnstein in her seminal article "A ladder of citizen participation" (1969):

“participation without redistribution of power is an empty and frustrating process for the powerless. It allows the powerholders to claim that all sides were considered, but makes it possible for only some of those sides to benefit.”

(ibidem, 216)

## 2. MATERIALS AND METHODS

## 2.1 A qualitative hermeneutical research: discourse analysis and interpretation of interpretations

My research is aimed to analyze the connections between precision medicine and social and health equity, by investigating the kinds of benefits that are supposed to be produced, and their possible distributions.

By considering the long-term and future-oriented nature of medical research (Hedgecoe 2004, Fortun 2008), rather than by trying to quantitatively measure the (hypothetical) direct effects of precision medicine on social and health inequalities, these issues are investigated by mainly comparing the promises of the proponents in the discourses, with the expectations and the concerns of the stakeholders about the implementations. This research is mainly epistemologically oriented as interpretivist, and ontologically oriented as constructivist. The constitutive role of discourses, understood in the sense of Foucault (1969), and the performative role of interpretations, promises, and expectations for influencing the scientific and social order (Brown and Michael 2003, Hedgecoe 2004, and Borup at al. 2006) are the core assumption for this analysis.

Rather than an object in itself, precision medicine is here analyzed as a social construction: its features, its scope, and its import in terms of social and health equity are mainly considered as depending on interpretations, which are analyzed as produced by discourses and commentary of discourses (Foucault 1969 and 1981). Interpretations, in turn, are considered as performative for shaping the scientific and the social order, which are understood in a co-productionist framework (Jasanoff 2004).

Against this background, my analysis is developed as a qualitative, hermeneutical research, aimed at *interpreting the interpretations*, in a sort of Gadamerian hermeneutic circle (Gadamer 1989). In particular, it drew on the principles of grounded theory, in its general definition as "theory that was derived from data, systematically gathered and analyzed through the research process. In this method, data collection, analysis, and eventual

theory stand in close relationship to one another" (Strauss and Corbin 1998, 12). In other words, my research is grounded on data in the sense that the research questions, the directions of the research and the arguments, are framed according to what emerged from data analysis; *vice versa*, data are mined in relation to the emerged research questions, directions, and arguments, and so on, in a recursive way. Accordingly, the research questions and the arguments have been reshaped and reframed several times during the advancement of the research, and data collection redirected (Bryman, 2012).

As anticipated, the data my research grounds on, are especially discourses and commentary of discourse, by focusing on those promises, expectations and concerns around precision medicine, which are relevant to social and health equity. These are essentially qualitative data, which have been extrapolated through document analysis and in-person qualitative interviews. These data mostly come from the observation and the analysis of two major case studies: All of Us and the 100KGP. The promises have been analyzed as related to the discourses, by following the implementations of the two projects and by studying their official releases. The expectations and the concerns have been analyzed as related to commentary of discourses, by following the published comments, by attending relevant conferences, and by interviewing relevant stakeholders.

The implementation of the two case studies has been followed since their very first announcement until the most recent progress and releases. They have been analyzed as follows: by mining all the information available in the different sections of the official websites (respectively: *allofus.nih.gov*, and *www.genomicsengland.co.uk*), which have been checked regularly over time in order to track the updating; by following the news around them, mostly reported in the websites themselves, and by receiving updates via email as I subscribed to the e-newsletters of both projects; by examining the official documents such as the research protocols (at different stages, in the case of All of Us), the consent forms, the information sheets, the withdraw forms; by referring to the informative or communicative videos and materials dedicated to the (potential) participants that are available on the

websites; by following, any time that the reports and/or the videocasts were available and accessible, the official events such as seminars, webinars, workshops and advisory panels meetings. In this way, I tried not to miss any important official information or release from and about the two projects under analysis. The only official information I am aware that I totally missed is the material provided on the website *joinallofus.org*, the internet page specifically dedicated to participants enrollment for All of Us, as the page is not accessible from outside the US, and it was not active yet when I was located in the US for my research fieldwork.

It is important to remark an essential difference in my analyses of the two projects: when I started my doctoral research, the 100KGP was already ongoing and everything was already set: no major changes occurred in the design of the project during my analyses. For All of Us it was exactly the opposite: when I started my research, nothing was established or set, and I have been following the arrangement and the development of every specific part of the project in real time.

Specific analyses were dedicated to the discourse on the public involvement practices of the projects, which will be discussed separately in section 2.3.

To analyze the discourse against the implementation, in addition to following the official releases and documents, I also dedicated major attention to expectations and concerns as expressed in external comments and criticisms about precision medicine, such as the concerns introduced in the first chapter. In particular, special attention was dedicated to the comments on precision medicine that are relevant to socio-political issues, published on scientific journals or online blogs. Moreover, I attended to - and in some cases participated in - various events dedicated to the analysis of precision medicine, such as conference panels or whole congresses or series of seminars. Among them, the most remarkable ones for setting the background, formulating the research questions, and suggesting directions for this thesis, are: the seminars series on precision medicine organized in 2015 by Carlo Alberto Redi at Collegio Ghislieri in Pavia (collegio.ghislieri.it), where I first presented my research, then at

a very preliminary stage; the Inaugural Columbia Precision Medicine Initiative conference "Advances in Precision Medicine: Genetics" on April 28, 2017 at Columbia University (precisionmedicine.columbia.edu); the 4th ELSI Congress "Genomics and Society: Expanding the ELSI University" on June 5-7, 2017 in Farminghton, Connecticut (braingenethics.cumc.columbia.edu), especially relevant as the major focus was the ELSI of precision medicine and of All of Us, and I had the opportunity to meet in person many of the key stakeholders, and to present my research to them; the panel track "Precision Medicine at the Crossroads" convened by my colleague Nadav Even Chorev and myself at the 2018 EASST Conference in Lancaster on July 27, 2018 (nomadit.co.uk), collecting papers on precision medicine from an STS perspective; and finally the workshop "Precision medicine for a changing population" (www.testalab.eu), organized by myself and my research unit with the aim to situate the issues of my research in the Italian social context, which will be discussed in depth in section 2.4. Also, I took any opportunity to present my research in STS conferences and to get feedback from the STS research environment.

### 2.2 Fieldwork interviews

In addition to observing official documents and to following comments and declarations, the originality of my research is mostly grounded on the research fieldwork: 43 semi-structured qualitative interviews to key actors in the debate over precision medicine and equity, 16 in the UK, 27 in the US.

The interviews were conducted, transcribed and analyzed by myself. Most of the interviews was in person (in 43 interviews, 37 were in person and 6 via telephone), and this also gave me the opportunity to visit and spend some time in relevant departments.

During my fieldwork in the UK, I was hosted from January 14 to February 2, 2017, by Professor Jane Kaye, at the *Centre for Health, Law and Emerging Technologies* (HeLEX), at the *Nuffield Department of Population Health* at the University of Oxford. Jane Kaye and her colleagues at HeLEX are brilliant analysts working on issues very much related to my research, and the time I spent with them, by getting feedback, references and inputs, was significantly helpful to strengthen and enrich my analysis.

For my fieldwork in the US, I was hosted from March 30, to June 9, 2017, by Professor Ronald Bayer at the *Center for the History and Ethics of Public Health*, at the *Mailman School of Public Health* at Columbia University, in New York City. My host, Ronald Bayer, is one of the main protagonists of the international debate over precision medicine and public health, and one of the leading proponents of the 'distraction argument'. During my visit, I had many precious opportunities of exchange with him, to learn more about his positions, and to discuss the premises and implications of the argument directly with the main author. Many of Bayer's colleagues at the *Center for the History and Ethics of Public Health*, with their expertise in socio-political analyses in the field of public health, also provided me with invaluable feedback and insights. Moreover, Columbia University is one of the pivotal centers of the PMI, at that time a place of fervent activity to the underpinning of the national effort, and it is also the basis of the program *Precision Medicine and Society*, specifically

aimed at addressing the societal issues related to the PMI (precisionmedicine.columbia.edu/content/precision-medicine-and-society). By staying at Columbia University, I was offered many opportunities of in-person exchanges with major stakeholders in precision medicine, as well as in the ELSI of precision medicine. During my fieldwork in the US, I also had the chance to visit other American research centers: in particular the NIH, and the headquarters of All of Us, in Bethesda, Maryland, the physical places where the program is practically organized.

### 2.2.1 Research ethics

The research protocol for the semi-structured interviews was approved by the Ethical Committee of the University of Milan. The research participants were contacted directly via email by myself, using my IEO email address. In the invitation emails I attached a 'Participant Information Document', which included the essential information about the project, its funding and the projected outcomes. A couple of days before the interview, the participants were also provided with the consent form. In the consent form, by checking a series of boxes, the participants confirmed to have read and understood the Participant Information document; to have understood that participation is entirely voluntary and that they are free to withdraw at any time without giving a reason; and to have understood to be free to refuse to answer any question during the interview. Also, they gave consent for the interview to be recorded and later transcribed, and for taking part in the study. Finally, they had the opportunity to request that publications resulting from the interview are delivered to them, and for the anonymization of their responses.

All the interviewees consented for the interviews being recorded and transcribed, then I recorded and later fully transcribed all the interviews I conducted, and the analyses were mainly performed on the transcripts.

Among the 43 participants, 34 requested for the anonymization of their responses. However, there are reasons to think that there are some bias in the expression of this request.

The first bias is that the opportunity to request anonymization was given prior to the interview, before the participants knew the specific questions and the responses they were going to give, then it is possible that, at least in some cases, the request for anonymization was mainly precautionary. Another bias is related to the fact that the box to be checked to request for anonymization was in columns together with the boxes for confirming to have understood the study and for consenting to participate. Then it is possible that, once they made sure that there were no risks related to participation, some of the interviewees, just to be as collaborative as possible, simply checked all the boxes with the idea to express consent to everything asked, without really noting that they were also requesting anonymization. Anyway, whatever the real interest for anonymization of the responses is, the request, whenever expressed, has been fully respected. Accordingly, most of the comments reported in this thesis are anonymous. The identities of the interviewees are here protected by using pseudonyms: the acronym UK or US to signify the country of reference, and numbers. In some cases, when the responses included especially sensitive material, such as political opinions or personal choices, as a further precaution to minimize the risk of reidentification, also the pseudonyms have been removed. Moreover, the comments that, by directly referring to the specific role of the person, would allow unequivocal reidentification of the author, have been omitted.

### 2.2.2 The interviewees

The original idea for the fieldwork interviews, against the background of the debate about precision medicine and public health, was to compare the perspectives of precision medicine supporters and of public health supporters. Like for the whole doctoral research, the case studies for the research fieldwork were the 100KGP and the PMI. The first idea then was to interview precision medicine supporters working in the organization of the 100KGP and of the PMI, respectively, to be compared with public health supporters respectively based in the UK and in the US. The original working plan consisted in a sort of fourfold comparison

among: precision medicine in the UK, public health in the UK, precision medicine in the US, and public health in the US.

Since the very first interview, it was clear that this plan was impractical. My very first finding from the interviews, as it will be described in the chapter of the Results, was actually that there is no clear boundary between precision medicine and public health. Accordingly, a dichotomic comparison was destined to fail. My second hypothesis was a sort of a gradient between precision medicine and public health, across which the interviewees could be situated. However, this plan was not practical either: some of the interviewees were very deeply engaged *both* with precision medicine *and* with public health, and it was incorrect to situate them 'in between'. Moreover, in many cases, different participants understood precision medicine and public health in diverse ways, to the extent that, by assuming different definitions, the same person or the same project could be situated totally differently across this hypothetical gradient between precision medicine and public health.

More space will be given to the issues above in the Results chapter. In this section, what is important to mark is that, given the emerged ambiguity of the relationship between precision medicine and public health, the interviewees have not been categorized in this respect. The only categorization is between interviewees based in the UK and based in the US. Apart from that, although at the beginning they were chosen as relevant actors in the field of precision medicine or in the field of public health, ultimately, the criterion to involve them was that they have to be: (1) experts working in the organization of All of Us or of the 100KGP; *and/or* (2) experts in public health, or health equity, or social determinants of health, operating in the same contexts of the 100KGP or of All of Us. It is important to specify 'and/or', because several interviewees were indeed involved in the organization of the precision medicine projects *precisely as* experts in public health, or in health equity. That was especially the case for advisory committees. Moreover, several interviewees have been invited as public health practitioners interested in genomics and precision medicine, or, *vice versa*, as geneticists or precision medicine proponents interested in public health issues.

The people to be invited for the interview were chosen: primarily from the boards and the advisory committees of the 100KGP and of the PMI; among the experts who took part in the debate about precision medicine and public health; then among the public health and health equity advocates conveniently located with respect to the departments I was visiting; finally, some people were contacted after their involvement was suggested by other participants. As a result, I interviewed 16 experts based in the UK (seven of which were directly involved in the 100KGP), and 27 experts based in the US (13 of which directly involved in All of Us). They included experts from the initiatives boards, from the executive staff, from the advisory panels, coordinators of regional centers, lead researchers; coordinators of organizations for the health promotion of vulnerable communities, and scholars researching in the field of public health, health disparities, social medicine, environmental health, ethics of genomic medicine.

Here below it is provided very basic information for each interviewee, the minimum to contextualize their comments while respecting anonymity whenever it has been requested:

- UK01: Jeb Rashbass: National Director for Disease Registration and Cancer Analysis at Public Health England
- UK02: field of public health and epidemiology, involved in the UK Biobank and in other projects labeled as precision medicine.
- UK03: field of genomic medicine, involved in the 100KGP
- UK04: field of genomic medicine, involved in the 100KGP
- UK05: both field of genomic medicine and of public health
- UK06: both field of genomic medicine and of public health, involved in the 100KGP
- UK07: scientific field, involved in the 100KGP
- UK08: field of health equity
- UK09: field of bioethics and public health, involved in the 100KGP

- UK10: Eric Brunner: Professor of Social and Biological Epidemiology at UCL, Principal Investigator in the Whitehall II Study
- UK11: Rolf Apweiler: Co-Director of EBI
- UK12: Ewan Birney: Co-Director of EBI and Board member in Genomics England
- UK13: field of bioethics and public health
- UK14: field of public health
- UK15: field of genomic medicine, involved in 100KGP
- UK16: field of public health and epidemiology

- US01: field of ELSI of medicine, involved in the PMI
- US02: David Goldstein: Director of the Institute for Genomic Medicine at Columbia University, in the Leadership of Columbia Precision Medicine.
- US03: Gwynne Jenkins: All of Us Chief of Staff and former Executive Secretary of the PMI, NIH.
- US04: field of genomic medicine and of health equity
- US05: field of genomic medicine and f health equity
- US06: field of ethics of genomic medicine
- US07: field of ELSI of genomic medicine, involved in the PMI
- US08: field of ethics of public health
- US09: Ronald Bayer: Co-Director, Center for the History and Ethics of Public Health, Columbia University (co-author of the 'distraction argument')
- US10: field of ethics of public health
- US11: field of ELSI of genomic medicine
- US12: field of molecular medicine, involved in the PMI
- US13: field of public health and health equity, involved in the PMI
- US14: field of genomic medicine, involved in the PMI

- US15: field of genomic medicine, involved in the PMI
- US16: field of medicine and ELSI of medical research
- US17: field of public health and epidemiology
- US18: field of clinical medicine and epidemiology, involved in the PMI
- US19: field of epidemiology and public health
- US20: field of ELSI of genomic medicine, involved in the PMI
- US21: Andrea Baccarelli: Environmental Health Sciences Department Chair and the Director of the Laboratory of Precision Environmental Biosciences, Columbia University
- US22: Linda Fried: Dean of Mailman School of Public Health, Columbia University, in the Leadership of Columbia Precision Medicine
- US23: field of public health and health equity
- US24: field of molecular epidemiology
- US25: field of molecular epidemiology
- US26: field of health equity
- US27: field of health equity and ELSI of precision medicine

### 2.2.3 The interviews outline

The interviews were semi-structured: the discussions were open, and the questions were adjusted according to the expertise, the interests, the role, and the contextual country of each interviewee. However, in order to preserve comparative analytical capacities, the same outline was followed with all the interviewees, and a specific set of topics was proposed to be discussed with everyone. The interview outline was mainly prepared by referring to Spradley (1979) and to Bryman (2012).

All the interviews started with a sort of 'introductory section', in which the interviewees were asked to situate themselves and their work between precision medicine and public

health: a sort of strategy to overcome the problem of ambiguous definition and blurred classifications, and also to start getting some ideas on how the interviewees conceptualized precision medicine, public health, and their relationship. More precisely, they were asked to briefly introduce their work and their field of expertise, and then to evaluate to what extent they perceived their work as related to precision medicine, and then to public health.

After that, it followed a sort of 'conceptual section', aimed at clarifying the concept and the scope of precision medicine in the perspective of the interviewees. Regarding the concept of precision medicine, the interviewees were asked to provide a definition for precision medicine, to comment upon the differences between precision medicine and personalized medicine (if any), and to provide some examples of precision medicine projects. In relation to the scope of precision medicine with respect to public health, participants were asked to focus on what they perceived as the most urgent public health matters in their countries, to comment upon the possible solutions, and then upon the possible contribution of precision medicine in that respect.

Next, a 'socio-political section' was included, to discuss the effects of precision medicine on societal issues and, conversely, the effects of the socio-political arrangements and rearrangements on the implementation of precision medicine. The major focus, given the intent of the research, was on equity, mostly in terms of distribution of benefits and of implementation of social policies. The participants were asked to express their opinions about which social groups stand to benefit most from precision medicine, about what impact precision medicine could have on health disparities, about the extent the molecular focus of precision medicine could be perceived as a risk to leave other factors aside, and about how precision medicine knowledge could contribute to the implementation of social policies.

Finally, in order to gather data about the relevance of the political context for the framing of precision medicine, participants were asked about their expectations and concerns for the future of precision medicine in relation to the political rearrangements in their countries. Both the US and the UK had some significant administrative rearrangements in the months

immediately preceding the fieldwork, with new political administrations not in continuity with the ones that launched the initiatives in the first place. In the case of the UK, Prime Minister Theresa May replaced David Cameron, and importantly the approval for the exit from the EU ('Brexit') was obtained following a citizen referendum. In the US, the Republican administration fronted by Donald Trump replaced, in a surprise to many, the Democratic administration led by Barack Obama. Specific reference to these political changes was included in all the interviews. Participants were asked to envision the future of precision medicine in the light of these political rearrangements.

From my perspective, this was the most difficult question of the interview. Answering to this question did not necessarily imply to disclose political opinions, however, in some cases, the respondents did. In other cases, they manifested discomfort and were elusive or reticent. Anyway, in most cases, by explicitly shifting the conversation from the scientific or at most societal domain, to the real political domain, this question generated more passionate reactions than any other question. In particular, in the UK this question was mostly accepted and welcomed by the respondents as an opportunity to clarify their position with respect to 'Brexit', and the conversation was accordingly and positively shifted to a more confidential level. In the US, conversely, this question mainly generated negative reactions and manifestations of discomfort, and in some cases refusal to answer. After the first few interviews in which these negative reactions were generated, I rephrased the question by asking more in general to make predictions about the continuation of the interest in precision medicine as a general attitude, by only slightly mentioning the political rearrangement, in such a way that that part of the question could be ignored if cause of discomfort. Anyway, given the particular sensitivity of this question, all the responses were totally anonymized by also removing the pseudonyms, as a further precaution to prevent reidentification.

At the end of the questions, all the participants were given the opportunity to add anything they wanted to say for the interview. Moreover, a very final question was proposed only to the participants based in the US, and only in the last eight interviews, as it was only around

the end of my research fieldwork that I got this insight. Although I was very interested, for the intent of my research, in understanding the perceptions of potential participants about All of Us, I did not have the approval to interview lay citizens. However, as anyone in the US is eligible to participate in the All of Us cohort, my approved interviewees were potential cohort participants as well. Hence, I asked my last eight interviewees whether they were considering participating in All of Us as research subjects, and their motivations to take part or not by sharing personal data. Also in this case, as the responses included very sensitive data such as personal choices, they are presented in a completely anonymized way.

### 2.2.4 Data analysis

The data analysis was performed on the transcripts of the interviews. In line with grounded theory, the first step for data analysis was *coding* (Bryman 2012). In the transcript of each interview, several themes were individuated, and the relevant lines were highlighted with different colors consistently with the theme. Then all the lines from all the interviews relevant to one theme were copied and pasted together, by only keeping separated the lines from interviews in the UK and in the US, as they were analyzed separately. Then two files were created for each theme: one gathering the relevant lines from the interviews in the UK, and one from the interviews in the US. The data were interpreted by comparing all the affirmations relevant to each specific theme, as they were released in the UK, and in the US.

The themes that emerged out of the analysis somewhat mirror the questions proposed in the interview outline. This is not, of course, a coincidence: the interview schedule was repeatedly revisited as themes became apparent during data collection, in a recursive way. In other words, the emergence of certain themes derived from a certain formulation of the interview, but in turn, that formulation of the interview derived from the directions indicated by the emergent themes.

Specifically, out of the final analysis, the following themes emerged, some of them thicker and some thinner than others: expertise and role of the interviewee; definition-description of precision medicine; mission and scopes of the initiatives; terminology (precision medicine or personalized medicine); the novelty of precision medicine; public health needs; the relationship between precision medicine and public health; precision public health; challenges and concerns about precision medicine (not included in other categories); precision medicine to promote behavioral changes; precision medicine as a distraction; precision medicine and equity; participation and engagement; democratization of science; international comparisons; overhype/overpromise; future and Brexit/Trump effects; personal motivation for (not) taking part (US only).

It is mainly from the analysis of these themes that the results of the research were elaborated. In the next chapter, by referring to the thematic analyses, it will be illustrated how different interpretations, expectations and concerns about precision medicine with respect to social and health equity, were distributed among the interviewees.

### 2.3 Experiencing the participatory process

A specific analysis was dedicated to the practices to involve participants at the level that in Prainsack's analysis is defined as coordination (2014). All the different participatory practices proposed by the two projects have been examined in depth, by paying a special attention to the requirements for participating in each of them, and to their effectiveness for translating deliberation into action.

To get a closer look, I participated myself in the process whenever relevant and possible according to the eligibility criteria; namely, in the requests for public feedback proposed by All of Us: the first two RFI divulgated by the NIH (one on the "NIH Precision Medicine Cohort", the other on the "Strategies to Address Community Engagement and Health Disparities"), the request for comments in the feedback site, and the request for idea sharing about research priorities on *Ideascale*. By participating with my comments, I had the double opportunity to actually give voice to the concerns and the potentials emerging out of my analysis, and to get a deeper insight into the participatory process by experiencing it on myself.

To evaluate the effectiveness of participation against tokenism, I mainly referred to the theoretical model proposed by the sociologists Cristopher Kelty and Aaron Panofsky (Kelty and Panofsky 2014; and Kelty, Panofsky et al. 2015), who propose the consideration of seven dimensions for distinguishing proper democratic participation from tokenism or even exploitation. These are: (1) Educative dividend: the possibility to learn something valuable from participating; (2) Goals and tasks: the possibility to participate in goal-setting and decision-making; (3) Resource control: the possibility to have control over the resources produced from participating; (4) Exit: the possibility to withdraw without detrimental effects; (5) Voice: the possibility to express feedback, comments, or complaints; (6) Visible metrics: the possibility to measure the effects of the participatory activity; (7) communicative capacities: the possibility to communicate with other participants.

This research attempts to recognize these seven dimensions in the participatory practices of All of Us and of the 100KGP, by comparing the democratic effectiveness of their models on the basis of the respective fulfillment of these dimensions. In the next chapter, the compliance of the two projects with these seven dimensions will be discussed one by one, by referring to the regulation of participation in the research as stated in the official documents, as well as to my own experience as a participant in the requests for feedback and for proposals.

### 2.4 Workshop on the Italian context

As my research and my life are situated in Italy, a special focus is dedicated to the Italian context, and to the relevance and the applicability of the research results in my homeland. In order to explore the issues of social and health disparities in Italy in relation to precision medicine, as well as the relevance of my results in that context, I participated in the organization of a workshop on that specific topics. The workshop, by engaging scholars from different disciplines, was expected to provide multidisciplinary insights into the advancement of precision medicine in Italy as well as on the societal opportunities and challenges for social and health equity in the specific context of the Italian changing population.

The workshop was organized together with the other members of the STS unit at the IEO: my supervisor Giuseppe Testa, and my two post-doc colleagues Nadav Even Chorev and Luca Marelli, and it was managed with the help of Sabrina Frata, SEMM event coordinator. The workshop received funding from the European Association for the Study of Science and Technology (EASST) 2018 Fund, and it was supported by the Italian Association for Social Studies of Science and Technology (STS Italia). It was hosted in the research campus of my institution, the conference room of Campus IFOM-IEO.

The workshop was aimed to uncover the major opportunities and challenges for the equitable implementation of precision medicine in the context of the ongoing societal and demographic transformations of the Italian population. To this aim, Italian stakeholders with different expertise as well as analysts from different fields were invited to take part in the workshop and to be engaged in an interdisciplinary dialogue. In the workshop program, major attention was dedicated to the social integration and to the medical research inclusion of migrants, and of so called ‘new Italians’.

In the context of our workshop, we considered different situations of migration, by working under the broadest definition of the term ‘migrant’ as “any person who lives

temporarily or permanently in a country where he or she was not born, and has acquired some significant social ties to this country" (unesco.org). As for 'new Italians', we referred to people born abroad, or born in Italy from foreign parents, who acquired Italian citizenship. The rationale for the special focus on these particular social groups in the context of precision medicine and health disparities in Italy was related to their increasing number in the Italian demography (istat.it), and to the related new challenges both from a societal and from a healthcare point of view.

Against this background, we aimed to consider the relevance in Italy of the issues faced by All of Us about the diversity of the US population. In particular, we considered migrants and new Italians as groups especially and distinctively vulnerable to the social determinants of health. The disadvantageous initial conditions as the latest arrivals in a new country often condemn these populations to poverty, low education levels, and segregation. Moreover, migration is a distinctive condition with respect to other groups of low socio-economic status: unlikely other disadvantaged groups, migrants experienced movement, which is often traumatic in itself, environmental change, and they are different from the majority of population, from a cultural, sometimes linguistic, sometimes even phenotypical point of view, and these differences might compromise their social integration while exposing them to discrimination. This is especially relevant inasmuch as racism and racial discrimination have been found to be correlated with poor health outcomes, independently from the other determinants of health related to low socio-economic status (Priest and Williams 2018, Williams and Mohammed 2009).

In addition to their distinctive vulnerability to social determinants of health, the focus on migrants and new Italians is also relevant to the analysis on precision medicine with respect to health disparities in so far as, like in the case of All of Us in the US, their inclusion in the research programs is vital to ensure the broad applicability of precision medicine. In this respect the concern is that precision medicine, in Italy as everywhere else, could be only suitable for the demographic groups that are included in the research, and if some groups,

like migrants and new Italians, are underrepresented, this reiterates the widespread problem of disproportional demographic representation in biomedical research (Spratt et al. 2016). As seen, if the specificities of certain groups are not taken into account, by definition, precision medicine and its benefits are not applicable to them. If migrants and new Italians are not fully integrated in the precision medicine agenda, then their specificities, not (necessarily) from a biological point of view, but certainly from the point of view of their societal distinctiveness, cannot be taken into a full account, and precision medicine could not be delivered equitably.

Focusing on migrants and new Italians in terms of equity was also especially relevant to the contextual political climate in Italy. Reiterated denunciations of widespread criminal episodes from immigrants on the one side (ilgiornale.it), and on the other side denunciations of rampant increase of aggressions, both verbal and physical, including shooting, and in some cases even homicidal, having immigrants or people of color as target, and no other demonstrated motivation than racism (www.google.com/maps), make the social situation highly unstable, and the integration of these populations quite problematic, by providing a very challenging scenario also for the equitable and inclusive implementation of precision medicine. The Italian changing population with intrinsic social tensions and renewed need, was the background of the workshop.

The workshop was open to the public, with no attendance fee, in order to be as inclusive as possible. It was advertised by the organizing committee through the networks of the IEO, of the University of Milan, of EASST, of STS Italia, and also via social networks and through word of mouth among friends and acquaintances interested in issues of integration and equity. We did our best to spread the invitation not only to the academic community, but to the general public, as we considered the issues we proposed to discuss as of potential interest for any citizen. The workshop was entirely in English, with the aim to facilitate the attendance and the participation of the foreign students and researchers at the IEO Campus.

The format of our workshop included an introduction to provide the background and the rationale both to the audience and to the speakers, then the speakers were asked to give short presentations, and then large space was let to the discussion both among the speakers and between the speakers and the audience. More in details, we proposed two panels: the first panel was mainly focused on health disparities in Italy and on the conditions of migrants and new Italians; the second panel was more specifically focused on precision medicine and on what precision medicine can do and cannot do for health equity. Four speakers - three external speakers and myself - participated in the first panel. Five speakers, including my supervisor Prof. Giuseppe Testa and my colleague Dr. Nadav Even Chorev, who were also part with me of the organizing committee, together with three invited speakers, participated in the second panel. Each of the speakers was asked to give a 20 minutes presentation. At the end, a roundtable discussion was arranged, during which the moderator first encouraged the speakers to comment upon the other presentations. After this second round among the speakers, the floor was then let to the public, and people from the audience were encouraged to ask questions and to give their comments.

The invited speakers were prominent Italian experts from different disciplines, including molecular medicine, political philosophy, medical anthropology and STS. They were chosen in relation to their previous works about precision medicine (being them to support, to underpin, to problematize or to criticize it), or about the social determinants of health, or for their engagement with the health and/or the rights of migrants. The aim was to provide the most complete possible picture of the issue, by including multiple expertise and multiple points of view. Unfortunately, the unavailability of several female scholars invited in the first place, generated a gender imbalance among the panelists. However, the speakers who participated composed a very complete range of the perspectives we were interested in putting together.

Martino Ardigò, researcher at the University of Bologna and at the Center for International Health, and Visiting Professor at the Universidade Federal de Mato Grosso do

Sul, was invited as especially engaged with the social determinants of health and health equity. Valeria Ottonelli, Associate Professor of Political Philosophy at the University of Genova, was invited for her theoretical expertise in distributive justice, and for her research on the rights of migration, to also provide a normative point. Emilio Di Maria, Assistant Professor of Medical Genetics at the University of Genova; Consultant Clinical Geneticist, Coordinator of *Gruppo Ligure Immigrazione e Salute, Società Italiana Medicina delle Migrazioni*, was invited for his expertise and his engagement both in genomic medicine and in health equity, and especially in the health of migrants. Pier Giusppe Pelicci, Director of Research and Chairman of the Department of Experimental Oncology at the IEO, and Full Professor of Pathology at the University of Milan, was invited for his expertise in precision medicine, and for his engagement in underpinning precision oncology through the program *Alleanza Contro il Cancro*. Giuseppe Remuzzi, Director of *Istituto Ricerche Farmacologiche Mario Negr*i and Full Professor of Nephrology at the University of Milan, was invited for his medical expertise and for his critical vision of precision medicine. Stefano Crabu, Assistant Professor at the Polytechnic University of Milan, was invited for his STS perspective on biomedical innovation. In addition, my colleague Nadav Even Chorev and my supervisor Giuseppe Testa, and myself, contributed with our own critical analyses on precision medicine in relation to the theme of the workshop.

The workshop was not only aimed to frame the debate in the Italian context, but also to actually individuate possible strategies to harness the opportunities and challenges for the equitable implementation of Italian precision medicine. As a first practical step to this aim, my colleague Luca Marelli, also part of the organizing committee, was in charge to take notes during the discussions, and to draw the conclusion at the end of the event on the basis of the major issues emerged during the workshop. The conclusive session was supposed to be not only a summary of the main points and links emerged, but also the very first attempt to channel them into a roadmap for Italian precision medicine, by laying the floor for further concrete developments.

The next chapter is dedicated to the systematic report of the results emerged out of my research through the documents analysis and the fieldwork interviews. At the end of the chapter, the main points raised in the Italian workshop will be presented in relation to the results in the international arena. In the Discussion chapter, the synergistic effect of the workshop among experts in different disciplines, will be presented as the first step for engaging stakeholders to concretely apply the findings of this research within a specific context.

# 3. RESULTS

This chapter is dedicated to illustrating the findings emerged out of the interviews and of the document analyses, on which the arguments of this thesis, drawn in the next chapter, are grounded. In particular, this chapter illustrates the emerged data regarding the three issues presented in the Introduction chapter as relevant to the connection between precision medicine social and health equity: the scope of precision medicine in relation to public health, the inclusiveness of precision medicine benefits, and the effectiveness of the democratizing capacities. The first two sections are respectively dedicated to illustrating the interpretations of the concept of precision medicine and of its scope as expressed by the interviewees, and the incompatibilities and the convergences between precision medicine and public health as different respondents expected and concerned. Section 3.3 is dedicated to revisiting the issues of upstream and downstream exclusivity in the light of the analysis on the strategies implemented by the two projects to overcome them, and of the perceptions of the interviewed stakeholders. Section 3.4 analyzes the participatory models of the two projects by considering the seven dimensions by Kelty and Panofsky in the light of the analyzed material and information. After that, section 3.5 deals with the expectations and the concerns related to the influence of the political order. Finally, section 3.6 reports the main points emerged in the Italian workshop, by putting them in relation with the findings in the international analysis. Each section is concluded by a short summary. Section 3.7 provides a sort of conclusion for this chapter, and a link to the next one.

## 3.1 Different understandings of precision medicine

As anticipated in the previous chapter when describing the organization for the fieldwork interviews, the very first (and maybe most important) finding was that different people have different concepts of precision medicine, which are different especially in their connections with public health. By looking at how the term 'precision medicine' and its analogous 'personalized medicine' are used in the literature in general, and by looking more systematically at how they are used and defined by the experts in the medical field involved in the fieldwork interviews, and at how the projects labeled with these terms are framed, a lack of agreement emerged about the ultimate meaning and scope of precision and of personalized medicine, and about the synonymy of these two terms.

### 3.1.1 "Different words for the same thing"?

As discussed in the first chapter, the terms 'precision medicine' and 'personalized medicine' are often used interchangeably. However, there are apparently different positions about the actual complete interchangeability of the two terms, and about the epistemic and socio-political significance of their difference. Some of my interviewees commented upon the issue of different terminologies spontaneously. All the interviewees were anyway asked to comment upon the sense of having (at least) two different terms, and upon the (possible) differences.

The wittiest, and in the same time most comprehensive and meaningful answer that I received in this respect, was from Rolf Apweiler, co-director of the European Bioinformatic Institute (EMBL-EBI), one of the four interviewees in the UK, and nine in total, who can be mentioned by his own name, as he did not request anonymization:

> IG*: Do you think there is any difference between personalized, precision and stratified medicine?*

The intent of the answer framed in this way is clearly humorous, yet it perfectly summarizes the issue: i.e., the ambiguity of having different words that denote the same kind of thing, but that still are different at least inasmuch they are different words.

Overall in the fieldwork interviews, with respect to the use of different terms, I noticed the US participants definitely preferred the term 'precision medicine', as it was the only term they used in that context, while in the UK it was alternated with 'personalized medicine'. Both in the UK and in the US, the prevalent opinion among the interviewees was that the two terms are interchangeable, and that precision medicine emerged over personalized in order to represent the novelty with a new term. In both countries, the interviewees who claimed that there is a conceptual difference, mainly envisioned personalized medicine as broader than precision medicine, by considering personalized medicine as supposed to encompass, besides the medical dimension, also a comprehensive attention for the patient as a person.

More in details: when asking questions during the interviews, as well as when inviting the participants in the first place, I always used the term 'precision medicine' rather than 'personalized medicine'. Nonetheless, in the UK, even if always asked about 'precision medicine', most of the interviewees in the discussion talked about 'personalized medicine'. Eleven of the 16 interviewees based in the UK mentioned 'personalized medicine' on their own initiative in the first place. One interviewee declared that he preferred the term 'genomic medicine' (UK12). Only four of the 16 interviewees accepted talking about 'precision medicine' without introducing any other terms in its place, at least until explicitly asked to comment upon terminology (UK08, 09, 10, 15). In some cases, the interviewees made explicit their choice of using another term than precision medicine, sometimes even by providing justifications for that choice on their own initiative. In other cases, they just changed term without providing any remark. In many cases, as the questions continued to

be referred to ‘precision medicine’, the respondents during the discussion switched randomly from ‘personalized medicine’ to ‘precision medicine’, and in some cases the two terms were used together (“personalized or precision medicine”). Some interviewees also mentioned the term ‘stratified medicine’ when remarking about the terminology: three participants introduced the term ‘stratified medicine’ as another saying to be compared to ‘precision’ and to ‘personalized medicine’ as a synonym (UK01, 04, 11); two participants declared ‘stratified medicine’ as their preferred term, as it is the most suitable to represent the framing of the medical approach at issue (UK06, UK13). One of them (UK06), added that even if ‘stratified medicine’ would be the most correct term from a scientific point of view, it cannot be used due to socio-political reasons: the idea of stratification and of segmentation, especially in the US, recalls the idea of social segregation and discrimination:

> “*The best term for that is stratification, or segmentation. But the Americans don’t like these words. Because to the Americans, stratification, has a social overturn of separating Blacks and Whites*” (UK06)

When explicitly asked to comment the relation between the term ‘precision’ and ‘personalized medicine’, nine of the 16 interviewees in the UK argued, with different emphasis and with different interest, that there is no conceptual difference between the two terms (UK01, 02, 04, 05, 06, 10, 11, 12, 14). The existence of two (or more) names denoting the same thing was explained as a local difference between UK and US: “*what we call personalized medicine here, they call pm in the US*” (UK05). Or as a ‘rebranding’ to give the idea of novelty and to get funding:

> “*I think the phrases are used interchangeably, it just depends on the politics of the time as to whether one word is considered more or less political acceptable, or more*

*or less scientifically effective in raising funding, I am not convinced they are particularly different in the way they have been used*" (UK02);

"*The fickleness of human nature is that we need something that is new, to present it as new, new things are the only things that get funded*" (UK04).

The other seven interviewees argued for a conceptual difference: mostly (UK03, 07, 08, 09, 13, 14), they claimed that 'personalized medicine' is a broader concept, as it also encompasses a personal dimension that goes beyond the medical techniques. In the words of UK09:

**"***personalized basically I think that implies some value judgements, which are not only coming from health services but also from the patient. So personalized means partly about drug treatments, partly means that decisions are appropriate to that person. It is broader concept. Precision has the implication that it is about accuracy and the quality of targeting and decision making in scientific and chemical terms. It is much more about getting the right medication, while personalized medicine is more about, it must be partly about, what is the right thing for this person.*"

Only one interviewee, exceptionally, argued the opposite: that 'precision medicine' is a broader concept than 'personalized medicine' (UK16).

Some respondents (UK02, 04, 08, 16) stressed, as an important difference, that 'personalized medicine' is a more promissory term as it gives the misleading idea of specific treatments for each person, while actually it is about groups. Another recurring remark (UK03, 07, 11) was that the preference for the term 'precision medicine' for denoting a new approach, is a way to acknowledge that physicians have always been doing personalized medicine:

*"I think precision medicine is kind of actually the same thing. I think there has been a move away. If think that's partly because doctors argue that personalized medicine is what they have always done" (UK07);*

*"At the beginning everyone used the term personalized medicine. Until some medical doctors said our medicine is always personalized, the person is in the middle! And then precision and stratified were used*." (UK11)

If in the UK the term 'personalized medicine' in the place of, or together with the term 'precision medicine', was introduced spontaneously by the vast majority of the interviewees, in the US it was quite the opposite. In 23 of the 27 interviews no other term than 'precision medicine' was ever spontaneously used by the participants to denote the medical approach at issue. Only four people out of 27 mentioned the term 'personalized medicine' on their own initiative (US06, 09, 12, 18). Mostly, they referred to personalized medicine when introducing precision medicine from a historical point of view, by describing precision medicine as the evolution of, or the new brand for, personalized medicine. The term 'stratified medicine' or 'stratification' was never used or mentioned by any interviewee in the US.

In the US, the vast majority of the interviewees, when asked, argued that there is no difference between 'precision' and 'personalized medicine' or that, if there is any difference, they are not aware of it, or they cannot appreciate it. In the words of US07: "*I don't pretend to appreciate or understand the difference!...Maybe there is no difference!*"; as US10 put it: "*I would use these two terms interchangeably, if the two terms mean something different, I don't know".*

Only five of 27 interviewees argued for a conceptual difference. In most of these cases (US04, 19, 20), like in the UK, the argument was that precision medicine is more focused on genetics while personalized medicine is broader:

"*Personalized was primarily to look into the patients as they are. It also had very strong interpersonal component, that's why it was personalized medicine, because it meant the physicians taking care of the specific patients as individuals, really interacting with them to better understand them. I think that is what every physician should be doing. Precision medicine is a slightly different approach. It is supposed to be very individualized, because it is supposed to be depending on your genetic makeup, but we have to think about where is the interpersonal interaction and interpersonal relationship that comes into place it, and I don't know whether they are still there.*" (US20)

The term 'precision medicine' was often seen as the evolution of the term 'personalized medicine', and in particular (US02, 06, 13, 21) as a 'rebranding' to give the idea of novelty and to get funding:

"*The real history is that everything to do with genomics and genomic medicine is associated with hype. So one term comes along and then we need to get ready because is getting a little bit tiring! So personalized medicine was the term for a while, precision medicine is the new term. Surely we have stories about what it means…but I think the real reason is that the community was entering into a new era and wanted to sort of create some distance to the old era."* (US02)

Another recurring argument (US02, 03, 05, 08, 18, 20, 27), which had emerged in the UK as well, was that the choice of a different name other than 'personalized medicine' is a way to acknowledge that physicians have always done, or should always do, personalized medicine. This was expressed in various ways:

"*The idea there is that medicine has always been personalized. So precision is meant to indicate something more than that"* (US02);

"*one of the reasons why precision medicine was selected as a term was that many clinicians, people who are there treating people every day, feel that they offer personalized medicine, they offer what is good for you based on what your experience is*" (US03);

"*when people use the term personalized medicine a lot of physicians don't like, because they felt medicine was always practiced at individual level*" (US05).

In this respect, a different term is presented as essential to stress that the approach the government is investing in is something different from what has always been done, or should always be done (the normative dimension was often called into question in this context). Only one interviewee, who referred to his own experience as a clinician, pointed out that physicians are supposed to practice both in a personalized and in a precise way, and that, as a consequence, in this respect the term 'precision medicine' is not better than 'personalized medicine' for acknowledging the efforts and the duties physicians have always had:

"*I am not a fan of either terms, because it implies what we were doing before wasn't a same attempt with the previous capabilities. As a cardiologist I always tried to personalize every decision I made. Every time I had a patient in front of me I wanted to be as precise as I can, and I wanted to personalize whatever recommendation as best as I can*" (US18).

The idea of precision medicine as a ‘rebranding’ to give the idea of novelty and to acknowledge the personalized approach already followed by physicians, were confirmed by two interviewees who had firsthand information about the choice of the term ‘precision medicine’ for the launch of the major US initiative to underpin this medical framework.

Overall, the exclusive preference in the US for the term ‘precision medicine’, while in the UK the general preference was for ‘personalized medicine’, supports the hypothesis that ‘precision medicine’ and ‘personalized medicine’ are mainly local differences for referring to the same thing, and that the name chosen for the PMI influenced the terminological shift in the US. Conceptually, the US terminological shift is explained in two major, opposite but not contrasting, ways: on the one side it is to dismiss the idea of treatments tailored to any single person, as this is supposedly out of the reach; on the other side, it is to dismiss the idea of caring about the patient as a person, as this is supposedly already reached. In addition to this, importantly, the new term implies an idea of novelty that can have a performative effect.

To conclude, although the terminological differences are significant for specifying the focus of precision medicine in terms of groups rather than persons, and that personalized care is not a primary goal for precision medicine as it is assumed to have already been achieved, the differences implied by different terms are not exhaustive to account for the different interpretations around precision medicine and its import regarding social and health equity.

### 3.1.2 Different things for the same word?

The different conceptual perspectives around precision medicine are not only related to the meanings of the different terms. By looking at the different framings of projects labelled as precision medicine, as well as by discussing with different stakeholders, it is evident that also the same word is interpreted and implemented in different ways. The different interpretations of precision medicine are sometimes so diverse from one another that, to

paraphrase the comment by Rolf Apweiler about precision medicine and personalized medicine possibly being "different words for the same things", it seems reasonable to question whether there might also be 'different things for the same word'.

As observed in the Introduction chapter, All of Us and the 100KGP are often considered as the two epitomes of precision medicine projects. However, as remarked, they are very different from one another, at many levels. In particular, the 100KGP is entirely focused on genetics (genetic diseases, genetic analyses, genetic causes, genetic medicine), while All of Us is expected to have a much broader scope (any kind of health condition, several kinds of analysis, any kind of causes, several kinds of health interventions). Against this diversity between precision medicine projects, I explored the scope that my interviewees attribute to precision medicine as a concept. Their understanding of precision medicine was investigated both by asking directly how they define precision medicine, and indirectly, by asking to comment upon the connection of their own work with precision medicine, and to provide some examples of precision medicine projects.

**"*It depends on your definition of precision medicine*"**

Several of the interviewees, both in the UK and the US, were actually fully aware of the multiple and sometimes diverging understandings of precision medicine, as illustrated by the following comments:

> "*people define it [precision medicine] depending on what they have and want to use it*" (UK04);
>
> "*I think everyone you ask will give you different answers*" (UK11);
>
> "*precision medicine is a term that is so general that you can put everything under this umbrella*" (US21).

Significantly, in some cases, when I asked the participants to situate themselves and their works with respect to precision medicine, they answered that it totally "depends on" the definition of precision medicine we assume:

"*it depends on the definition of precision medicine*" (UK02);

"*It depends on what you mean by precision medicine*" (US08);

"*it depends on how you want to call precision medicine*" (US15);

"*it depends on your definition of precision medicine*" (US24).

Overall, both in the UK and the US, the focus of precision medicine on the individual was very often primarily emphasized in the definition (UK01, 02, 03, 04, 06, 09, 10, 11; US02, 04, 07, 09, 10, 11, 13, 15, 16, 19, 20, 22, 23, 25, 26, 27). In the UK, the definitions mostly referred to the medical dimension, in terms of diagnosis and treatment, while in the US the preventive dimension was also often emphasized. As US03 described: *"I think precision medicine is kind of broader than just medicine in kind of the classic sense of the term, treatments, it's very much about what we can do preventively.*".

In the UK, 11 of the 16 interviewees defined precision medicine by referring to cancer. In the US, although cancer was sometimes mentioned as an area in which precision medicine can be especially advantageous (US09, 11, 15, 16, 19, 22), most of the participants connected precision medicine more broadly to health in general.

When asked to provide some examples of precision medicine projects, the UK respondents almost always indicated the 100KGP, also when they have no personal connection with it. UK Biobank was also often mentioned (UK02, 04, 09, 16), even if it was

not assumed to be a precision medicine project in the same straightforward sense as the 100KGP. This is apparent in the following comments:

> "*UK Biobank is built as a resource for scientists across the world to use, to study lots and lots potential determinants of disease, for lots and lots of diseases. So in a sense I think it is a precision medicine initiative*" (UK02);

> "*The 100KGP. Absolutely. You can think of the UK Biobank, but it is for healthy people. May lead to precision medicine, but it's not. This program is not just a research program, is an enabling program.*" (UK07).

However, it was sometimes specified that, rather than actual precision medicine projects, all these have to be more properly considered as projects *facilitating* the underpinning of precision medicine. Take, for instance, the following exchange:

> IG: "*Which are in your opinion the main precision medicine programs in the UK*?"
> UK11: "*I am not aware of any*."
> IG: "*Do you think the 100KGP could be considered as a precision medicine program?*"
> UK11: "*No. This is a program that will underpin precision medicine, but is not a precision medicine program*".

In one case, the whole UK healthcare system was indicated as the UK precision medicine project:

"*Every time a patient is seen, every time a decision is made, it becomes ultimately part of a kind of learning in the NHS. What that means is that the NHS itself is a precision medicine project, is going to be a precision medicine project!"* (UK09)

In general, the 100KGP was indicated as *the* precision medicine project in the UK, while the UK Biobank was described as a promising large-scale epidemiological study, yet it was indicated as the parallel study to All of Us. This parallelism, in one case, was extended to the affirmation that, like UK Biobank, also the PMI is a population health study rather than a precision medicine project, in spite of the name, by even arguing that *the Precision Medicine Initiative is not a precision medicine initiative*:

"*It [the Precision Medicine Initiative] is a name for a perspective cohort. I guess it's not a worst name than UK Biobank: it is neither a bank nor for UK. They are just names. In fact they changed the name into All of Us. It is a classic epidemiological project, excepting it's very much larger, and from a population health science perspective it's really different, it's the first time we are starting to see perspective cohorts that are big enough to identify reliably the alternative different conditions. So I wouldn't say it [the PMI] is being precision medicine, I'd say it is being population health science*." (UK02)

In the US, All of Us was always the reference for talking about precision medicine, to the extent that talks about precision medicine as an approach, and talks about All of Us, tended to mix and to overlap. UK Biobank was sometimes mentioned as the European counterpart and the model for All of Us (US03, 15, 16, 18). The 100KGP was never mentioned.

***"The magic triangle"***

Precision medicine, especially in the UK, was often defined by referring to genetics or more generally to the molecular dimension (UK03, UK10, UK13, UK14). The molecular understanding of precision medicine appeared very widespread among the UK interviewees, but it was also embraced by some participants in the US, who defined precision medicine as entirely focused on the genetic component of diseases and on genetic targets (US05, US06, US08, US09, US10, US11, US12, US17).

Despite this widespread interpretation in terms of genomic medicine, as seen, in the All of Us website precision medicine is defined as: "a revolutionary approach for disease prevention and treatment that takes into account individual differences in lifestyle, environment, and biology" (allofus.nih.org). In other words, in this understanding, genetics, and even more broadly biology, is considered only one of the three dimensions across which precision medicine is developed.

These three dimensions (biology, lifestyle, environment) actually also recurred in the talks around precision medicine by some of the interviewees: not only in the US, where the reference is All of Us, but also in the UK. Rolf Apweiler referred to these three recurring dimensions as to the 'magic triangle'**:**

> **"***the magic triangle between the genotypic situation, direct stimuli which are through direct environment and stimuli from wider environment… It is this triangle between direct genotype, direct environment and the wide environment. The direct environment is whether you exercise a lot, what you eat, what you drink. The wider environment is whether you live in a very health clean environment, or whether you live in a polluted environment. One thing is the environment you, yourself influence. You choose how much you move. You can't choose how clean is the air around you*."

In some senses, this 'magic triangle' might be seen as embracing all the determinants of health: the genetic and biological ones, the external exposures depending on the actions of the individual (lifestyle, or the 'direct environment'), and the external exposures independent from the actions of the individual (the 'wider' environment). This 'triad' was mentioned in other interviews than the one with Apweiler, as an alternative and broader framing for defining precision medicine than only in genetics terms. This understanding of precision that encompasses the three sides of the 'magic triangle' was suggested a couple of times in the UK (UK11, UK16), and more often in the US (US03, US04, US20, US27), especially by people somehow directly involved in All of Us.

***"It looks like a discrepancy"***

If the rhetoric of All of Us, also reiterated by some respondents, envisions precision medicine as having a totally inclusive scope, on the other way, several interviewees in the US expressed their concern that the embracement of other determinants of health than genetics is only in the discourse, while the implementation of precision medicine is totally focused at molecular level. Andrea Baccarelli, Environmental Health Sciences Department Chair and Director of the Laboratory of Precision Environmental Biosciences at Mailman School of Public Health, Columbia University, is one of the five interviewees based in the US who did not request for anonymization. He talked about an 'official version' and an 'unofficial version' of precision medicine, and about 'a discrepancy' between them:

> "*I think there is an official version of precision medicine, which is the attempt to create prevention and treatment for patients that are precise, using a wealth of information that is now available from every level of information…The unofficial version which is not what is in the Whitehouse website, is using genomics to do the same, so the same but the data is genomics. And I think if I look at the official definition of precision medicine it is very inclusive, but if I look at people who*

*actually designate themselves as people who are doing precision medicine, they are mostly people who work on genetics. It looks like a discrepancy. And also the promoters of the PMI are mostly geneticists, people who are working on genetics.*".

This 'discrepancy' was also argued by other interviewees in the US, who worried that, despite the discourse about studying environment and lifestyle as contributors to disease, the implantation is actually mainly focused on genetics (US01, US19, US25). There is however one interesting exception among the interviewees: US17 claimed exactly the opposite. He claimed that, despite All of Us was initially entirely focused on genetics, it then opened to include the other dimensions:

"*I think the PMI was* not *initially giving any space for anything other than genetic molecular targeting that will develop novel cures. I think it has, in response to critics, it has broadened its remit considerably, at least in what it says. I think that now there is a broader access for the idea that we need to take a more holistic approach to things.***"**

Apart from this exception arguing that All of Us has been reframed to possibly deliver more than it initially promised, both in the US and in the UK, 'overhype' and 'overpromise' were very often indicated as major concerns around precision medicine, which is worried to generate false hopes and unmet expectations, with all the related detrimental effects (Brown 2003). In the UK, the main concern around overhype was that precision medicine is sold as a sort of "wonder thing" (UK03) that will "solve all our problems" (UK09, UK13), by diminishing the importance of personal enterprise in terms of behavioral changes. In the US, All of Us is questioned as unable to actualize the expectations, as the claim is that *"the original plan underestimated the complexity of every part of the initiative"* (US01), and "*a lot of promises were made that were not based on a full understanding on the complexity*

*and difficulty of practicing precision medicine*" (US12). Moreover, it is questioned as having been sold as a new immediate medical opportunity, while "*it is a* research *agenda, and people think it is already medicine."* (US26), and anyway "*It is not going to be something that transforms medicine overnight, it's gonna take long, long time*" (US06).

***"Precision medicine has been going on forever…but now has been labelled and branded"***

Another argument frequently exposed both in the UK and in the US around the definition of precision medicine, still somehow related to the issue of overhype, concerns novelty. Both in the UK and US, the novelty of precision medicine was often questioned as a pretext, with the claim that 'precision medicine' is just a "rebranding", as it was often called, for something already existing. In both countries, if any novelty was acknowledged, it was in the new tools in terms of data collection and analysis that allow better (more precise) results, rather than in the framing of the approach.

In the UK it was often claimed (UK04, UK05, UK09, UK12) that precision medicine is nothing more than regular medicine or of good clinical practice. As expressed by UK04:

> "*In some ways it [precision medicine] is just contemporary medicine! Precision medicine is just a new term for good practice!...It's contemporary medicine, precision medicine is a new word that says we are going to do better quality medicine for the individual.*"

In the US, the opinion was often expressed (US15, US18, US19, US20, US21, US24) that what it is called precision medicine is actually classical epidemiology, or even public health or population health. As noted by US24:

> "*epidemiology has always been from the beginning focused on subgroups, the groups that can be affected by something and the group that are not. So to that extent there*

*is nothing new here…Epidemiology has always appreciated that there is heterogeneity and subgroups of people where the exposures and the treatments work differently*."

US15 expressed concern about the confusion created by 'rebranding' public health in terms of precision medicine:

*"I think what happens in terms of public health still remains public health, and I don't think framing and calling it precision medicine to be honest is really helpful."*.

Others, on the opposite, acknowledged some performativity in this 'rebranding', especially for getting renewed attentions and resources in line with the theory of performative nominalism (Pickersgill 2018) and more in general with sociology of expectations (Brown 2003, Brown and Michael 2003, Borup et al. 2006).
As expressed in the UK by UK05:

"*It is not necessarily defined any differently from proper medicine, but I think when we talk about personalized medicine, what happens is that other things start to happen*."

And in the US by US19:

"*I think it has been going on forever, but now has been labelled and branded, so that there is more attention and focus and money going into those kinds of projects*."

**Summary**

To recap, overall the interviewees did not agree upon a univocal definition of precision medicine, by validating the hypothesis of precision medicine as a social construct rather than an independent object, and by consequently justifying an interpretivist analytical approach. These differences cannot be explained in local terms, as different interpretations and awareness of ambiguity were present both in the UK and in the US. In particular, the different interpretations that are most relevant to this research are connected to the scope of precision medicine in terms of the dimensions of what has been referred to as the 'magic triangle': biology, lifestyle and environment. In particular, one interpretation configured precision medicine as solely in terms of genetics, in line with the 100KGP, while another one, in line with the discourse of All of Us, configured precision medicine as embracing all the determinants of health. However, a 'discrepancy' between discourse and implementation was lamented, by claiming on the one side that the interpretation which extends the scope of precision medicine beyond genetics, does not exist other than in the discourse; on the other side that precision medicine is something that has always existed that has been 'relabeled' as a new thing.

### 3.2 Precision medicine and public health

As anticipated, the interviews were designed not only to frame the different interpretations of precision medicine, which have been summarized in the previous section. In addition to this, the discussions with the interviewees were also aimed to understand the opinions of insiders and of relevant stakeholders about the appropriateness of precision medicine with respect to societal needs.

In their already mentioned editorial on the NEJM, cornerstone for my research questions, Bayer and Galea (2015) critically commented the affirmation by Collins and Varmus in their article introducing the PMI: "What is needed now is a broad research program to build the evidence base needed to guide clinical practice." (Collins and Varmus 2015, 793). Bayer and Galea emphasized the expression 'what is needed now' used by Collins and Varmus, to argue that, opposite to the conclusion by the authors, 'what is needed now' is not precision medicine but committed attentions and actions over the social inequalities majorly affecting health. With this criticism in mind, among other things, the interviews were aimed at exploring the opinions and perceptions of the participants about 'what is needed now', about how these needs could be met, and about what is and what can be the role of precision medicine in this respect.

#### 3.2.1 "What is needed now"

After talking about precision medicine, in all the interviews, the conversation was then shifted to public health: the interviewees were invited to list what they consider as the most pressing public health matters in the countries they are based in, and to suggest some strategies to overcome them. In the UK, the public health issues indicated were mostly actual health issues, while in the US societal issues were most frequently mentioned.

More specifically, in the UK, obesity and obesity related diseases were indicated as major public health issues by the vast majority (UK05, UK06, UK08, UK12, UK13, UK14, UK15,

UK16), mostly put in relation with unhealthy lifestyle and with poverty. Also smoking was often mentioned as a major public health problem (UK01, UK06, UK11, UK16).

In the US, most of the interviewees, rather than health conditions such as the obesity related diseases mentioned in the UK, indicated social conditions as major public health issues: in particular, socio-economic inequalities and access to healthcare (US01, US04, US06, US08, US09, US10, US11, US12, US13, US15, US16, US17, US19, US20, US26, US27). Sometimes they also mentioned health conditions and factors directly affecting health: the most recurring were obesity and obesity related diseases (US01, US03, US05, US06, US09, US15, US23), mental health (US01, US02, US07, US20, US25), opioids dependence (US03, US06, US16) violence (US05, US11, US16), and sometimes smoking (US07, US09, US24). Structural conditions, rather than unhealthy behaviors were the main object of discussion. When unhealthy behaviors were mentioned, they were mostly considered as the results of detrimental structural conditions. Significantly in this respect, US23, by referring to the public health problems affecting the vulnerable community she is engaged with, mostly stressed the societal conditions preventing healthy lifestyle, in contrast with the analysis by Apweiler who framed lifestyle as the dimension of the 'magic triangle' that can be influenced by the individual. In the words of US23:

> "*chronic disease is huge, and it's strongly related to lifestyle issues: unhealthy food, lack of exercise…all directly connected to poverty, inability to being able to afford high quality food, to access to safe places to exercise or to gyms, or they don't even have the time, or the energy, they have got multiple jobs, or they don't live in an environment where it is safe to go running, sometimes not even during the day*".

In both countries, the interventions indicated as possible solutions to alleviate the public health problems previously mentioned, were not in terms of precision medicine or medicine, but in terms of improving lifestyles and social conditions.

The needed interventions suggested in the UK were mostly related to promoting behavioral changes (UK01, UK05, UK11, UK13, UK15). In some cases, social reformations to reduce poverty and inequalities were rather recommended, especially by the interviewees more directly involved in public health or health equity studies (UK01, UK08, UK14). In any case, the proposed solutions were in terms of political or behavioral prevention, rather than in terms of medical interventions on the diseases. In the words of UK11:

> "*there is lot that can be done, investing in helping people to quit smoking, would be a huge improvement for life expectancy, the same is true for encouraging less car usage, and bike usage would reduce obesity and related diseases like diabetes or arteriosclerosis, much more than drugs*".

In terms of behavioral changes, both public policies and counseling were proposed. In this respect UK06, who is expert and active both in the field of public health and of genomic medicine, relevantly proposed distinguishing three historical phases, corresponding to three framings, of public health: classical public health (intervening on the external environment, typical of the XIX century), health promotion (intervening on human behaviors by disincentivizing the habits generally defined as unhealthy, typical of the XX century), and information engineering public health (intervening on human behaviors by providing tailored advice to the individual, typical of the XXI century). Among other things, UK06 stressed the 'ethical' difference in terms of individual liberty, between intervening through policies or through tailored advice:

> "*There is a difference to say to food manufactories to put less salt in the food because this is good for the population as a whole, and say to you, you must eat less salt…And this comes back to an old sort of ethical issue about to what extent is the State's role to change human behavior. Very happy for the State doing things to the water, the*

*air, to the housing. I am very happy for the State to give me information that I might need to change my behavior. I am* not *so very happy for the State to attempt to change my behavior*".

The needed interventions indicated in the US were mostly related to what US10 longs for as "*a complete transformation of our political culture*". In other words, the possible solutions considered are in the socio-political domain, and include drastic social reformations addressing inequalities, exposures in poor neighborhoods, access to medical care and education.

### 3.2.2 The role of precision medicine

In all the interviews, after discussing pressing public health needs and the possible strategies to alleviate them, the conversation was then shifted again on precision medicine, and the participants were invited to reconsider precision medicine, its role, and its scope, by directly referring to the public health context. They were asked to comment upon the contribution that precision medicine could bring to the health problems previously discussed as the most urgent: the contribution of precision medicine to 'what is needed now'. This part of the interviews explored how the participants, who importantly are all actively involved in the field of precision medicine, or in the field of public health, or in both, envisioned the relationship between precision medicine and public health.

Both in the UK and in the US, disagreement and different positions emerged, by somehow mirroring the debate described in the Introduction. It is not possible however to categorize the interviewees according to the position they support, as many of them are in between, or are open to consider different possible scenarios, and acknowledged both risks and opportunities. In any case, the different positions can roughly be reconducted to three general lines: negative, neutral, and positive. Which is: (1) precision medicine to the detriment of public health; (2) precision medicine and public health as not affecting each other; (3)

precision medicine as a contributor to public health, or even 'precision medicine' as a "rebranding" for contemporary public health.

***"At the expenses of the population"***

Both in the UK and in the US several respondents worried that precision medicine could undermine public health. Generally speaking, in the UK the concern was prevalently expressed in terms of a methodological bias: the limiting effects of focusing on individuals rather than on populations. In the US, the concern was mostly expressed in terms of resource allocation.

In the UK, when a contrast was argued between precision medicine and public health, it was mainly in terms of the target: precision medicine was interpreted as "opposite" (UK02) and "reverse" (UK13) to public health, inasmuch as the first focus on individuals, the second on populations (UK02, UK13, UK14). In the words of UK13:

> "*What you want to see with a public health intervention, is at a population level, the overall health of the public is the reason. That's sort of reverse of precision…interventions of precision medicine are directed to individuals, while interventions of public health are directed to populations. That's the fundamental pulling apart*."

In this respect, precision medicine could be questioned as "at the expenses of the population" inasmuch as it is conceived as "*a strategy where you have a very very specific treatment for a small number of individuals, they would do a little bit better than they would do otherwise, but you do that at the expenses of the vast majority of population.*" (UK02).

This idea of precision medicine and public health as opposite and incompatible approaches, inasmuch as the first is focused on the individual and the second on the population, was marked in the US interviews as well. As expressed, among others, by US25:

"*I think it [precision medicine] is a shift in thinking from a more social orientation to a much more individual orientation. That seems to be the goal of precision medicine, not to initiate things that are going to address the population as a whole but rather address the individual people*."

This perspective was literally painted by Ronald Bayer, one of the main proponents of the 'distraction argument', who kindly accepted to be interviewed without requesting for anonymization. He suggested a very helpful visualization of the contrast between precision medicine and public health, by referring to the former logo of the PMI (Figure 5):

"*The cover of the first presidential report on precision medicine had a sort of a map of the US and all these different people, short, tall, fat, skinny, obviously African American, obviously Latinos, the universe of people, and then one person is stepping forward, and that was the promotion: we identify the individual. From a public health point of view, it's just the opposite: it's all those people in the background that should be the concern."*

**Figure 5**: the former logo of the Precision Medicine Initiative Cohort Program, readapted from the *Precision Medicine Initiative Working Group Final Report.* Available from: https://allofus.nih.gov/about/all-us-research-program-protocol

In the US, when precision medicine and public health were interpreted as diverging, the main worries were in terms of resource allocation, political priorities and public awareness, by explicitly or implicitly reiterating the 'distraction argument' (US01, US09, US10, US11, US12, US16, US17, US21, US22, US25). In terms of resources, by grounding on the awareness that *"there is a finite number of dollars for doing research*" (US16), several respondents worried that "*when you decide resources into one particular direction, it is likely to impact negatively in other directions*" (US12), and that the PMI "*is gonna consume a lot of resources that otherwise would be available for programs of broader impact*." (US01), so that "*money that could be spent on other public health initiatives is going to be diverted into these high-tech analyses using genomics that really won't be helpful to people*" (US25).

However, this diversion, or 'distraction', was not expressed only in terms of money, but also, importantly, in terms of public awareness, as the talk was often about diverging "resources and attention" (US10, US11). In this respect, US17 worried that the PMI is a way to circumvent all the societal problems affecting health, by replacing the required societal reforms with the delivery of "a pill":

> "*I think the PMI frankly is a* distraction *from efforts on social policies. By saying we are going to have a pill for everything, you don't need social policies, this pill is going to make you better…If you believe that taking everybody a pill is going to make them better, then you don't have to worry about addressing income education, you don't have to worry about addressing early childhood education, you don't have to worry about make sure that people have affordable housing, make sure that have reasonable wages, make sure that people have low calorie nutrient food, it doesn't matter if people get sick, if they get sick they will give them a pill and then they will get better. I think if you believe that, you can* pill your way *out of all health problems,*

*then it distracts you from having to tackle the harder foundational issues. That's what I mean by distraction*."

**"*It's both/and rather than either/or*"**

Despite the concern expressed in both countries as illustrated above, several interviewees, both in the UK and in the US, resolved the worries of the 'distraction argument' by considering that "*it's not either/or, it's and/both*" (UK06, UK09, UK11, UK14, US08, US09, US11, US17, US22). Under this perspective, precision medicine and public health, although still seen as different and maybe opposite approaches, can be accepted as compatible with one another: rather than in competition, they can be considered as just parallel, or even complementary frameworks. As expressed by the interviewees:

"*these two ways of dealing with prevention are complementary. They are not in tension with each other. The two sides don't have to fight*." (UK06)

"*they are two different streams which need to inform each other and need to go on both…I think integration is the wrong word…I don't see need of integration but awareness of complementarity*." (UK11)

As anticipated, the respondents cannot be classified accordingly to their positions about the relationship between precision medicine and public health, because in most cases these positions were not rigid. Conversely, several interviewees were open to consider different scenarios. In some cases, the very same interviewees expressing major concern in terms of 'distraction', were also totally open to consider the two approaches as parallel and not interfering with one another. In particular, Ronald Bayer and US17 expressed openness to the "and/both" perspective:

"*They might say: 'going after the social causes is someone else's job, I am a laboratory scientist, and I have always recognized that what I do is only a contribution, there is a big thing out there, but that's what how do'.*" (Ronald Bayer).

"*This is not an* or *argument, it is an* and *argument*". (US17)

***"There are lots of way the two areas can work together"***

Several interviewees went one step further to this sort of 'neutral' position with respect to the positive coexistence of precision medicine and public health: they argued that precision medicine could offer new and improved tools to public health strategies. However, the benefits the interviewees expected from precision medicine for public health and for public health needs, were of different kinds.

Almost all the interviewees agreed that precision medicine will bring some medical benefits. A remarkable exception is UK02, who worried that:

"*Personalized medicine may be precise, but it may actually not be right. If one looks back there are many examples of that…So those individuals failed to get treatments that would have benefit them, based on personalized medicine that was incorrect…So personalized medicine has been to the detriment of many people, despite being rich, despite getting so called best medical care*"

With the exception of this very important concern, in general, even when precision medicine is questioned as to detriment of the actual priorities, the attitude towards the medical benefits brought by this approach is positive; e.g., in the words of US19: "*at the end of the day I think precision medicine is a wonderful thing if I were sick*". In this light, an obvious contribution from precision medicine to public health, which was often mentioned both in the UK and in the US, even by the most skeptical participants, is that, by alleviating at least the genetic

diseases, or at least the 'genetic component' of diseases, it ameliorates the health conditions of the population as a whole (UK08, UK11, UK12, UK14, UK15, UK16; US02, US04, US11, US16). UK08 described this as follows:

> "*if I am saying that 40 to 50, 40 to 60 % is social and environment, there is another 40% that is maybe a kind of biological and genetic that needs health service delivery as well*."

Another public health advantage possibly deriving from precision medicine, mentioned both in the UK and in the US, is the possibility to implement tailored screening programs in consideration of the genetic risk (UK04, UK05, UK06; US07, US21, US24),

***"Tailor the messaging to the individual"***

A much more controversial precision medicine benefit in public health terms was envisioned, both in the UK and in the US, in tailored behavioral advice (UK01, UK03, UK06; US07, US11, US21): the public health dimension that UK06 referred to as 'information engineering public health'. Andrea Baccarelli was especially positive about the benefits deriving from "tailor the messaging to the individuals", which he described as a possible solution to facilitate compliance against the current excessive number of recommendations which is unsustainable both for doctors and patients:

> "*if you look at the recommendations by the CDC, the number of recommendations of preventive actions is 6,000. Imagine a doctor who has to ask a patient about 6,000 items. We can use genetics or genomics to help doctors with priorities for that patient, or tell that patient 'your top priority is eating less, your top priority is exercising'…we know that we need to exercise, not to smoke….how much health advice we get everyday? Prevention is like flat, is so generic and in the end becomes*

*ineffective. If we had a tool that is well calibrated that tells the person we start with your genome, your morbidity data, your patterns of interaction over social media, your number one action for you is to increase the number of steps you do everyday, forget all the rest, just start with this*."

Others were similarly positive by suggesting that the awareness of genetic risk could incentivize healthy behavioral changes:

"*if you are a smoker and you don't know how to quit, and you know you have that gene, and you have 6 years old kids, maybe you are going to try harder*" (US07).

However, most respondents were aware of the complexity of the issue, and in several cases the very same person suggesting the possibility of "tailored messaging", also expressed skepticism about that:

"*It could help with obesity, helping to target people and engaging preventive behaviors, although not confident about that one*" (US06);

"*It is maybe naïve to think that, nothing gets people stop smoking, it's very very difficult, so to think that knowing your genotype is going to be the thing that puts you over the edge, is probably very naïve*" (US07).

Two major concerns were expressed about the actual benefits deriving from 'tailored messaging'. The first one questions the 'content' of the 'tailored messaging', by claiming that, whatever the genetic outfit is, "*the advice is still the same*" (UK05). In other words, precision medicine is questioned as not adding anything to what it is already well known in terms of behavioral advice. As expressed by US20:

"Y*ou don't need precision medicine to know that smoking is not great for you. We don't need precision medicine to know that eating McDonald every day is unhealthy for you*"

The second major concern is related to the 'effectiveness' of 'tailored messaging'. Several respondents suggested to perform studies on the effectiveness of genetic information for behavioral changes (UK12, US06, US07), as they noted that there is not enough evidence to count on an effective 'translational step' from awareness of genetic risk into actual behavioral changes. As expressed by US06:

"*I worry a little bit about that step, where you find there is a link between a genotype and a phenotype, and the phenotype suggests you should behave in some sort of preventative behavior. And getting people actually taking that behavior. I worry about that translational step. I think eventually people would be better. But we can't do people stop smoking and do exercise. Why do we think them stop smoking or start exercising because they got some genetic findings that suggest them more susceptible for cancer or heart disease? This gonna be a great challenge*"

***"That kind of research which is on the one hand a tool to support precision medicine, can also be a tool for social thinking"***

Another argument of discussion under the stimuli of my questions, was the possibility of precision medicine to have a positive impact on public health by providing better knowledge on the socio-environmental determinants of health. After my inputs, this perspective was embraced by many interviewees both in the UK and in the US (UK02, UK04, UK09, UK16; US03, US04, US05, US11, US18, US24, US26).

Among others, this point of view was supported by Gwynne Jenkins, the Chief of Staff of All of Us and former Executive Secretary for the PMI Working Group, one of the five American interviewees who did not request for anonymization:

> "*I think it [All of Us] will very much enhance what we can and do understand about social determinants of health, our ability to understand the ZNA factor, like how your zip code, where you live, is a proxy for what diseases are going to affect you, your mortality, if we are successful we are getting deep and really wide sets of data including environmental data*".

In general, both in the UK and in the US, they were the people who, like Gwynne Jenkins, are the most directly engaged with cohort studies, who were especially positive on the possibilities of better understanding the social determinants of health through precision medicine studies (UK02, UK09, UK16; US05, US14, US23). They noted, somehow in line with the idea discussed in the previous section of precision medicine as a 'rebranding' for large scale epidemiology, that precision medicine cohort studies offer a unique opportunity of combining several kinds of observations on large populations, thence to draw inferences at many level, to the extent that, as expressed by UK09:

> "*That kind of research which is on the one hand a tool to support precision medicine, can also be a tool for social thinking.*"

Sometimes however, it emerged concern about the possibility of actually translating the knowledge achieved through precision medicine studies into public health policies. In many cases the concerns were expressed by the very same persons who were positive about achieving a better understanding on the social determinants of health. Although there was a quite shared positivity about precision medicine producing valuable knowledge about the

social determinants of health, there was not as much positivity about the possibility to actually translate this knowledge into policies. The concerns expressed are similar to those about 'tailored messaging'. Also in this case, it was questioned that, as a matter of fact, much is already known without proper interventions are implemented. As expressed by UK02: "*The biggest failure in public health is to implement what we know"*. Or in the words of US20: "*we already know lot of things that have not been implemented… we don't need precision medicine in order to do all these public health initiatives*".

Moreover, also in this case, it was often doubted the real possibility of the "translational step" from knowledge to public interventions. In this case, the translational difficulty is not depending on the individual at issue as in the case of behavioral changes, but on the political order. In fact, translating knowledge into policies requires a shift from the medical to the political domain. As Gwynne Jenkins put it:

> "*Remember I am coming from the NIH, and what we support is basic biomedical research, we are not legislators, we are not policy makers*".

Also other interviewees, especially in the US, when asked, stressed this limit: that the precision medicine projects are *scientific* projects, and the *societal* reforms discussed are anyway out of the reach for the medical system. In the words of the respondents:

> "*those kinds of things need to be addressed by other parts of government, primarily in terms of looking at poverty, that's not something the NIH is equipped to do*." (US11)

> "*the government agency I work for at the NIH doesn't make public health polices, so that would not be a thing that we have in the program do, we are building a resource that scientists will use to develop knowledge, and ultimately we hope that policy*

*makers will learn from that, and ultimately the science and the evidence will inform public policies, but that's not our preview*" (US14)

"*They [the NIH] cannot change the government. I am not referring to this government, but in general, that's not in their power. They cannot change the system in which they work, which is a privatized health system*." (US20)

***"This idea of precision public health"***

In the context of the discussion on precision medicine to inform public health, participants in the US also discussed the related framework of 'precision public health'. Two of the five participants in the US that I am allowed to quote by name were particularly relevant to the analysis of this topic: Linda Fried, Dean of the Columbia University Mailman School of Public Health, and Andrea Baccarelli, both of whom are engaged with precision public health, even if with different ideas.

For Linda Fried, precision public health is:

"*the opportunity to actually utilize cutting-edge technologies combined with population health knowledge, to more effectively understand what drives health or the risk of disease in different subpopulations because of exposures, combined with their inherent characteristics that might put that at risk, and be able to tailor preventive approaches to match those issues in subpopulation*".

Andrea Baccarelli was less enthusiastic about the opportunities related to precision public health, as he argued it is just a 'rebranding' for something that has been existing since ever:

"*Something that has been around for 200 years, we have always called it surveillance, now we call it precision public health…Precision public health is a nice*

*name to call in a new way something that was already there. There is also a lot of rebranding in order to make what you do look more modern and more interesting, but many of us are doing exactly the same things we were doing for years*."

A similar perception of precision public health as adding nothing at all to 'regular' public health, was expressed by Ronald Bayer during his interview:

"*I have never heard anything as a description of precision public health as different from what public health has always tried to do, which is target vulnerable populations***.**"

US17 was even more critical with respect to precision public health, by arguing that not only it does not add anything to regular public health, but also it 'corrupts the public health community', in the sense that it is a sort of a sop, to make people concerned with public health positive about precision medicine:

"*I am not sure it [precision public health] is particularly different from public and from how data inform population health science, but it has been a convenient term…I think precision public health has been a useful term, that has corrupted the public health community. So that the public health community does not push against the raise and hegemonic influence of precision medicine. I think the proponents of precision medicine have done a nice job with this idea of precision public health. At the practical level, I am not sure precision public health influence what we do.*"

**Summary**

To recap, both in the UK and in the US, three main imaginaries emerged about the relationship between precision medicine and public health, not necessarily corresponding to different factions, as in many case the same person considered different scenarios as different possible outputs depending on the implementations. The three possible scenarios envisioned are: (1) precision medicine to the detriment of public health by focusing on the individual rather than on the population, and by diverting attention and resources from societal problems; (2) precision medicine and public health as operating in parallel in different domains in a non-conflicting way; (3) precision medicine to the advantage of public health by alleviating those part of the population health problems related to genetics, by providing 'tailored behavioral messaging', by providing information for social policies. However, the contribution from precision medicine to public health both in terms of 'tailored messaging' and of informing policies, was criticized as useless: in terms of content, as the behavioral and political changes to the improvement of health are in large part already known; as well as in terms of effectiveness, as in both cases several challenges are noted for the actual 'translational step' from knowledge to practice.

### 3.3 Inclusivity

As anticipated in the Introduction, after considered the kind of benefits that are produced, which has been in part the object of the previous section, a very relevant issue for analyzing precision medicine in terms of distributive justice relates to *how* the produced benefits are distributed. In other words, a special attention is dedicated to exploring which social groups are included in the precision medicine agenda as recipients and how. In this respect, as anticipated, inclusivity upstream and downstream are analyzed as two separated issues, although intertwined.

In this section it is investigated the equitable accessibility of precision medicine by considering, on the one side, the strategies implemented by the projects under analysis to overcome the obstacles to inclusive participation, as described in the official documents; and on the other side, the perceptions of relevant experts as expressed in my fieldwork interviews.

#### 3.3.1 Upstream inclusivity

In the *All of Us Operational Protocol*, several precautions are established to overcome the practical, objective obstacles for upstream participation in the cohort. In this respect, Rothstein (2017), in his analysis, pointed out as major obstacles those related to education, technological literacy, informatics skills, language fluency, by describing the beneficiary of precision medicine as "uncommonly tech savvy, highly health literate, self-directed, information seeking, English fluent, health focused, and well insured" (ibidem, 6).

To overcome the language barriers, the *All of Us Operational Protocol* establishes that "Educational content and consent materials will be available in English and Spanish at the national launch…in the future we will release materials translated in other languages reflective of the broader United States population" (ibidem, 12), and also the Support Center,

instituted to provide assistance to participants, will be equipped to assist both in English and in Spanish.

To overcome the barriers related to information technology literacy and access, the Support Center will be available to provide assistance also via telephone, not only via email and chat. With the same principle, the "electronic informed consent process will be adapted to meet the presentation needs of variable learning styles and health literacy levels. These plans include a video-only consent, a paper-based consent process, and the incorporation of kinetic elements into the consent process to aid comprehension and support autonomous decision. These procedures will serve those with low technology proficiency and/or without access to an online infrastructure and/or other preference or challenge that prohibits enrollment via the electronic process" (ibidem, 22-23).

To overcome mobility barriers, such as those related to disabilities or to living in poorly connected areas, home visits are arranged to reach potential participants challenged to physically reach an HPO (Healthcare Provider Organization) or DV (Direct Volunteer) site for the initial visit and for the collection of biospecimen: "In some circumstances, a home visit may be necessary (e.g., individuals who report limited mobility, whose health prevents commuting, and those who live in an area where there is no DV partner site within a reasonable distance)" (ibidem, 31).

Various strategies are also implemented to overcome the subjective, socio-cultural obstacles: a 'Mobile Engagement Asset' has been developed to physically reach the awareness of people in remote areas and to build direct contacts with communities (ibidem, 18). The problem of distrust is addressed by conducting focus groups within the most vulnerable communities (Cohn et al. 2015) and by providing dedicated informative material prepared in collaboration with members of those very communities, such as a series of videos produced by Elizabeth Cohn, director of the Center for Health Innovation at Adelphi University, in collaboration with focus groups participants from the community of Harlem (Cohn 2015). In those videos, the PMI is discussed from the perspective of a Harlem family,

which is shown to comment upon the government announcements by expressing questions and doubts of any sort, to which the videos provide dedicated responses (precision-medicine.us). Specific commitment is put in admitting the past misconducts of medical research like the case of the Tuskegee Studies and of Henrietta Lacks, and in stressing the dissociation with them. Among other things, as an act of special public impact and visibility, the All of Us engagement officers set a panel of discussion together with three members of Henrietta Lacks' family (today.uic.edu).

In my interviews, I did not have a specific question about upstream inclusivity. However, problems related to participants outreach and engagement emerged sometimes in the discussion, especially when the interviewees were asked in general about the challenges and concerns they have about the projects.

In the US, concerns about upstream participation and diverse representation emerged much more often than in the UK, where the problem of upstream inclusivity was mentioned only a few times. In particular, it was mentioned the problem of long standing follow-up (UK02), the difficulty to recruit people from rural areas (UK03, UK05), and the problem of stigma anxiety as far as consanguineous families are at issues (UK09).

In the US, challenges for the recruitment of minorities were discussed in most of the interviews, and several kinds of problems were indicated. In particular: mistrust (US03), fear (US07), suspicion towards the government (US13, US20, US27) and the medical establishment (US01, US20, US27), especially concerning privacy and usage of data. In the words of US07:

> "*We have increased concern about surveillance and people knowing more than me what I know about myself…There is this concern of someone being able seeing a big picture about me, that I can't see, not sharing that with me, and possibly using that against me*".

Other respondents remarked the challenges related to geographical barriers (US07, US15, US26), lack of education to understand the program (US01, US16, US27), and lack of time consequently to difficult societal conditions, as noticed by US15:

> "*for some of those people it is more complicated: their time may be more precious, in the sense that if you are working two jobs, or if you are taking care of your kid and working a job as a single parent, you may not have the time to be able to sign up with this. These are just realities.*"

US23 pointed out, as a further obstacle, the more urgent needs that remain unmet for the most disadvantaged groups:

> "*most people that are dealing with their health issues, they are so basic that something like precision medicine may seem completely out of their range of preference. They are struggling to dealing with basic chronic health issues like hypertension or diabetes, also many of them are not insured or are underinsured, they don't even have a primary care physician…it's very difficult for them*".

On the other hand, in some cases, despite the concerns, the efforts implemented by All of Us to overcome these barriers were fully acknowledged. As US20:

> "*I think the people who are working in the precision medicine are really dedicated, I think they are very very serious about how to maximize stakeholders' collaboration partnership, how to make sure that people who will be recruited will be part of that picture. They are really working hard, they are really dedicated, they really believe in that*."

A very interesting point of view in this respect was expressed by US13, who works on health initiatives at community level and is also engaged with All of Us. US13 proposed distinguishing between 'intention' and 'commitment' in reaching communities, by stressing the importance for the intention to be corresponded by appropriate commitment:

> "*I am sure they are interested in reaching Hispanics in an appropriate way. I think the intention is there. There is a difference between intention and commitment…it seems to me that the intention is there, and the commitment is there, and we'll see what happens*".

Intention and commitment as discussed by US13 are two notions that in the Discussion chapter will be recalled more than once to analyze the emerged 'discrepancies' between discourse and implementation or, with respect to other emerged issues, between potential and actualization.

### 3.3.2 "Why should I join?"

Apart from the removal of objective and subjective obstacles, inclusive participants outreach is also related to the possible motivations to participate. For dealing with motivations, this research grounds on the analysis proposed by Richard Tutton and Barbara Prainsack in their joint article "Enterprising or altruistic selves? Making up research subjects in genetics research" (2011). The authors consider the medical research participant to be addressed via two main strategies (that can also be combined): as an 'altruistic self' or as an 'enterprising self', defined as follows:

> "the 'altruistic self' who is addressed through a discourse of communitarianism, and who enrols in the biobank, freely giving of themselves with no expectation of anything in return";

and

> "the 'enterprising self' who is addressed through a discourse of democratisation and empowerment, and who has the right to information as a value in itself.…Rather than being an altruistic 'gift giver', this participant is engaged in a consumer transaction by which she both purchases and provides information about herself." (ibidem 1090).

The motivations for participating suggested in the dedicated sections in the websites of the 100KGP and of All of Us, respectively under the heading "Why do people take part?" (genomicsengland.co.uk) and "Why should I join?" (allofus.nih.gov), are almost specular:

> 100KGP: "Some people taking part will get a diagnosis for their condition for the first time, but many will not. For some patients, a particular treatment may be suggested based on their results. In most cases this won't happen. The main benefits are likely to be for other patients in the future"

> All of US: "To develop tailored treatments and prevention strategies, researchers need more data about the individual differences that make each of us unique. By enrolling in the *All of Us* Research Program and sharing information, you can help ensure that your community is included in the studies that lead to improved health for future generations.
>
> In addition, *All of Us* will also share data and information we collect about you, as well as certain study results, to help you know more about yourself."

We can observe that both studies mention both the benefits (possibly) resulting for the participants themselves as 'enterprising selves' in the sense of Tutton and Prainsack (2011), and the benefits that will (possibly) derive to others, in the future, by spurring the participants as 'altruistic selves' (ibidem).

As anticipated, my research did not collect data from (potential) participants about their motivations for participating and for not participating. However, I could get this kind of information from the experts I interviewed in the US, as anyone residing in the US is actually a potential participant.

While the other questions in the interviews were about providing comments about general concepts and situations, in some senses, this specific question about their own willingness to participate might be considered more 'personal': the interviewees were in this case addressed as persons rather than as experts, and they were asked to share their own personal choices. Given the particularly personal nature of this issue, in this section, as a further precaution to preserve confidentiality, I will report the responses as totally anonymous, by even removing the pseudonyms used until now (UKn, USn). As the only reference, I can specify that none of the eight interviewees to whom this question has been asked is directly engaged with the PMI; yet all of them have had some kinds of relations with it.

Of the eight interviewees who were asked about their intention to participate, only one appeared well convinced about enrolling: "*I will totally participate*".

One was positively oriented but seemed not to be really informed about the participatory process and even the eligibility criteria:

> R: "*If I were asked I would. Hopefully not, since they are recruiting from hospitals, I don't intend to be a patient*."
>
> IG: "*They are also recruiting healthy volunteers*."
>
> R: "*Are they? I didn't know that. So I would, I would have no problems*."

The other six respondents declared to be undecided or negatively oriented. When I asked: "*Are you going to participate in the PMI cohort?"*

I received the following replies:

- "*No. Unlikely*."
- "*No. I don't think so, I'm pretty sure that I won't…I don't know, I have never really thought about that, but I have absolutely clear that I don't want to participate*."
- "*I am undecided*."
- "*I haven't really thought about this… I don't really feel that strongly connected to a desire to be involved*."
- "*Probably not. I don't know. I have to see what it is. I mean, maybe, but probably not*."
- *"I honestly confess that I haven't thought about that, I don't know"*.

In summary, of eight experts working in the contexts of the PMI, only one appeared ready to enroll, while the other seven were undecided, or negative, or were lacking the basic information. Three of them declared that they had never thought about that before. Two complained that the people involved in organization and recruitment are not even considering participating themselves:

> "*I have never really heard people at Columbia talking about their own engagement in precision medicine… it's really about thinking including other people into this program"*;
>
> "*They asked to the investigators and almost everyone said not.*".

Some of the reluctant interviewees also provided an explanation for their unwillingness to participate, or for their doubts. In this respect, one referred to an objective barrier: lack of time. Others, to a subjective barrier: unpleasant feelings about being studied:

"*I don't want to have my genome sequenced...I think I'm too closed for the research community, I don't want to be a subject*";

"*I don't know we should know everything about our genetics, I am not in favor of knowing everything. I don't think we know enough at this point, how every genetic predisposition will translate into certain conditions, and I don't know that is necessary. Of course the PMI does not require you to know, you can choose whether you want to know or not, but once you are part of that I think it's different a little bit*".

Apart from that, in some cases the problem indicated was, rather than an obstacle, the actual lack of a motivation. In two cases, the lacking motivation they were referring to, was an 'enterprising' one:

"*I am very healthy, I don't really use any pharmaceutical drugs that is right now kind of the primary area for the focus of precision medicine, I do have some risk factors in my family, so I would be very interested in lifestyle modifications…but largely I am doing a lot of things that are very healthy and that would lead to better outcomes anyway*";

"*I am a pretty healthy person, I don't have too many worries about my future disease risk.*".

In one case, the point was the lack of an 'altruistic' motivation:

"*I don't need to provide any assistance. I would have loved to think, in other circumstances, in a national healthcare system, where everyone has access to*

*services, that's a very different scenario for me. Because it's all for one and one for all. But when it's only one for all, not even that, when it's only very specific stakeholder that will benefit from that, I don't think there is more question for me*".

To recap, even if the discourse of both the projects is frames as to construct both 'altruistic selves' and 'enterprising selves', the construction of the 'altruistic self' seems to have failed, at least in my very small (and as such, I have to admit, poorly generalizable) sample of potential participants. Seven of eight were not convinced or not well informed about participating. The motivations, when provided, were in a totally 'entrepreneurial' framework, 'altruistic' motivations were not even considered. In one case, on the opposite, the refusal to participate was motivated by the argued failure of the altruistic model.

### 3.3.3 Downstream exclusivity

Downstream inclusion, in the framing of this thesis, is related to the access to the benefits deriving from precision medicine. This issue was addressed in the interviews with specific questions: all the interviewees were asked who they think stand to benefit most from precision medicine, and which they think will be the impact of precision medicine on health disparities.

In general, in the UK the prevalent opinion was that precision medicine will worsen existing health disparities by mainly benefitting rich and educated people. This exacerbation would only be avoided in case it turns out that precision medicine is not so beneficial, as some respondents suggested. For instance, when I asked: "*What kind of people stand to benefit most from precision medicine*?", UK02 responded: "*The rich. But they may not. Personalized medicine may be precise, but it may actually not be right.*". UK13 described how the "*effects will be disproportionally to those people who can afford, so to that extent it is likely to make worse, but I am skeptical about how big the improvement is going to be overall.*"

Some of the worries about poorer and less educated people being left behind were related to the fact that precision medicine treatments will not be available in every hospital and in every area, and these groups might not even learn about these possibilities. As expressed by UK05:

> "*Well [to benefit most] I think it's obvious it's going to be the richer people, the people with more education, the people that are able to work this out themselves, people that can go to the doctor and demand an appointment, or to be referred to a specialist. Poor people and the less educated people, will not think about potentially in the same sort of way, they will not be as proactive, even if they do manage to get their local doctor, if the doctor say I shouldn't really worry about that, they are more likely to just agree and say no I read about this I need to go to the hospital. People that will fall behind will be poor people with less education and less resources. The poorer people with less education are less able to decide on anything in their life…When we develop things within the health service that are using these fantastic new technologies, we have to be very conscious of the fact that they get provided in Cambridge, Oxford, London, big medical centers, but 50 miles away people are much less likely to get access. Partly because there are not research programs going on they can be recruited into, they are not asking the right questions, the development is really inequitable".* (UK05)

Other worries about unequal access between groups were related to the costs of the treatments, which the NHS might not be able to afford:

> "*I think mainly costs actually. Some of these initiatives will be something that the State cannot afford to buy for everybody*" (UK06);

"*The worry of course is that in the short term some of these things are going to be too expensive, for something like the NHS to use, people who have got the money to spend privately will be able to spend*" (UK09);

"*The ways in which technology are developed, personalized, developed cost and glamourous, will only be affordable by people who can afford them. Will be unable to be afforded by certain groups of people*." (UK13).

In this respect, respondents complained about a general 'privatization of medicine' (UK08). Moreover, it was also argued that, even if the NHS will guarantee equal access, rich people will still have better opportunities; for instance: "*In the UK we have a free system. But still, people who are richer generally have access to better hospitals*" (UK08). Other interviewees, however, maintained that precision medicine will have no effect on health disparities, as all the social groups will have equal access (UK11, UK12, UK13).

In the US, the prevalent position was that access to precision medicine benefits will be very limited, by exacerbating health inequalities. In particular, it was very often expressed concern about the costs, and the access to precision medicine treatments for uninsured and underinsured people (US01, US02, US04, US06, US07, US09, uS10, US19, US22, US23, US24). The key message emerged out of the concerns of many, is that precision is expected to improve medical care, then the people who have access to high quality healthcare will benefit from it, while people with poor healthcare access will have no benefits from the advancement of something they cannot have anyway.

As summarized by US06:

*"If you are outside the system, the fact that the system is getting more efficient and has new tools is not that help you that much*"

Opposite to this position, Gwynne Jenkins, in line with the rhetoric of All of Us, argued very positively about everyone accessing to the benefits of precision medicine, and even about precision medicine likely to reduce health disparities, as far as the greatest benefit is expected to be for the segments of the population historically underrepresented:

> "*In as much as segments of the populations that have been historically underrepresented in biomedical research have by fact of that not been served by medicine because it is unclear what would work for them and what would not, then I think if we are able to bring in sufficient numbers of people, and if research comes and helps to get this population in the study in a way that we can figure out what can work best, I think that is going to be a huge benefit. That's one segment of the population that will benefit*".

In some cases, as well as in the UK, it was argued that there will be probably no impact on health equity as everyone will benefit in the same way, then the gap is expected to be shifted but by keeping the same opening. In the words of US11:

> "*It probably means everybody will improve a little bit. But I am not sure it will eliminate health disparities, people who are already well off will be even better off after precision medicine, people who are not as well off, will also be better off, but will the gap close? I am not sure, probably not.*"

Several interviewees considered both the risks and the opportunities of precision medicine around health disparities, in relation to the effect on the healthcare costs and their management, and stressed the need of human awareness and action to take the fair direction (US05, US06, US07, US08, US10 ,US13):

"*it can go either way. It could make things worse by creating new benefits only accessible to people with means. Or it could make things better by lowering the costs of treatments such that the government is more willing to provide universal coverage.*" (US06)

"*the door is open to increase disparities, wide open. And it will take human effort to push in the other directions*." (US07)

"*If it is carried out in the way that is intended, it should be relevant to diverse populations who are not the ones who always benefit the most from medical discoveries. It is my hope, my expectation. That's the promise*." (US08).

In line with what emerged in the previous section about the different possible contributions of precision medicine to public health, when discussing the distribution of precision medicine benefits, other benefits than solely healthcare treatments were considered, such as information and societal understanding. In particular, US14 insisted on the benefits deriving from the information returned to All of Us participants, by remarking that participating in the program in itself does not provide healthcare benefits at all, but benefits related to information:

"*we were careful to make this distinction, research is not healthcare, and if you join our program there is no promise of any medical benefit to you, we have to be careful to distinguish to our people that research is not medical …But we do think that people will always benefit, form being part of our study, we are going to be returning information to people, so if we learn something about an individual we will return that to them*."

US24, on the other hand, considered the benefits possibly deriving from social policies, which would be applied to everybody:

> "*If you work on the air pollution, regulation will then be applied to all. It depends on what intervention is. There is no one answer. Even smoking, even the evidence for that, much of our susceptibility to lung cancer is really determined by gene-environment interaction. Most people who smoke don't get lung cancer, they get heart disease. The policy for understanding that which essentially is a precision medicine question, got applied to everybody, into state and federal laws about smoking in buildings*."

Similarly, US27 considered the possibility to better understand societal issues as a benefit:

> "*There will be some benefits because we'll be able to study as we weren't before, but whether if your genes are the same but your phenotype is different, it would be very interesting to understand other public health issues, like racism. If you had people who are relatively the same genetically, but they self-identify as different from one another, then we could understand more about society*."

Opposite to these positions that consider the benefits related to the act of participating in itself, US20 marked the limits of considering participation alone as a benefit, if it is not corresponded by the access to the concrete emerging benefits:

> "*I think that what the PMI is offering to pretty much anyone across socio-economic status including people without health insurance, is the opportunity to join, to enroll in the PMI. I find it more problematic because from my perspective just participating in the cohort is not a sufficient opportunity. Opportunity for me is not just to* play *full*

*citizen, or* play *an active member of a cohort or to be involved in the discussions. You actually have to be also helped to get the benefits coming out of that.*"

**Summary**

To recap, the problem of upstream inclusivity is perceived as much more pressing for All of Us rather than for the 100KGP. Consequently, the All of Us agenda established a set of strategies to overcome the obstacles challenging participation. Nonetheless, many interviewees, although acknowledging the efforts by All of Us to be inclusive, expressed concern that several barriers are still preventing the participation of the most disadvantaged groups. Moreover, even if all the obstacles could be removed, people need strong motivation to participate. The two projects propose to construct motivations both in term of 'enterprise' and of 'altruisms', but the few responses collected in this respect from the US interviews suggested some limits in the discourse over altruism.

On the other hand, both in the UK and in the US, downstream exclusivity is perceived as a major problem, likely to exacerbate existing inequalities. In both countries, some respondents argued that precision medicine is not expected to produce significant healthcare improvements, so that no one will really benefit. Others argued that the healthcare benefits will be equally distributed, so that everyone will benefit in the same way. In these cases, either if nobody benefits, or if everybody benefits in the same way, the health gap is supposed to remain unvaried. However, most of the respondents, both in UK and US, worried that precision medicine will exacerbate existing health inequalities by producing healthcare benefits that, due to the exclusive costs, will be accessible only to wealthier people. On the other hand, in line with the discussions on public health benefits deriving from precision medicine, some respondents argued that precision medicine will produce other benefits than those in the healthcare domain, for example by providing information, and consequently that in this respect participation could be considered as a benefit in itself.

### 3.4 Effectiveness of democratic practices

Another important promise of the precision medicine approach is the discourse about involving "participants as partners". The public involvement at the coordination level (Woolley et al. 2016, Prainsack 2014) is relevant to the analysis of precision medicine in terms of equity inasmuch as a democratic approach could be considered as a guarantee for the pursuit of the public interest (Pateman 1970). My analysis on the democratic capacities of the two projects (Galasso and Testa 2017a), on one side, considered who can access to the democratizing practices, by looking at the requirements specified for each procedure, and on the other side considered the effectiveness of participation, by grounding on the model of the seven dimensions by Kelty and Panofsky (2014 and 2015).

#### 3.4.1 Which participants can be partners?

Concerning the accessibility of the involvement practices made available by the 100KGP, as specified when proceeding in the dedicated area of the website, the 'Nomination Forms' are to be submitted specifically by "clinicians and healthcare professionals, NHS Genomic Medicine Centres, GeCIP partners and industry partners" (genomicsengland.co.uk). As for the Participant Panel, "Anyone who has taken part in the 100,000 Genomes Project can be on the Participant Panel. Carers of people who have taken part are also welcome" (ibidem). However, the capacity of the Panel is limited to 30 members.

Concerning some of the involvement practices offered by All of Us, the general rhetoric is that they are open to 'you', whoever you are: "All of Us wants *your* ideas"; "We need *your* help!"; "we are asking to *you* to submit *your* ideas" (allofus.nih.gov, emphasis added). Anyone could participate in the RFI, in the feedback site, and in the 'ideas sharing' via *Ideascale*. It was not even required to be a cohort participant, unlike for the 100KGP Participant Panel. It was not even required to be based in the US, anyone from everywhere in the world could participate.

These procedures are inclusive to the extent that, as anticipated, I myself did participate, and no requirement at all was indeed requested to me for having access to these practices. Except that, of course, for participating I needed to be able to read and to write in English, I needed to connect to the Internet and, in the case of *Ideascale*, I had to register by providing my email address. As a matter of fact, in practice, I, like anyone else interested in participating by sharing comments, needed to be English proficient, to have access to a device connecting to the Internet, to actually have an Internet access, and in the case of *Ideascale* to have an email address.

In any case, other involvement practices planned by All of Us, such as the All of Us Participant Panel, as well as the representations of participants in the working groups, similarly to the 100KGP Participant Panel, are expected to be open only to cohort participants, and to have a maximum capacity.

### 3.4.2 The seven dimensions of participation in precision medicine

To compare the completeness of the democratic models respectively offered by the two projects, the participatory practices have been observed by referring to the seven dimensions identified by Kelty and Panofsky (2014 and 2015) as distinctive of proper democratic participation:

1) The first dimension is education, the possibility to learn something valuable from participating. This seems to be entirely fulfilled by both the projects, as both are catalyzed around the promise to provide participants with information about themselves and about their own health.
2) Goals and tasks: the possibility to participate in goal-setting and decision-making. The practices mentioned above, such as the Participant Panels, the 'Nomination Forms', the RFI and the other strategies for collecting public ideas, are implemented exactly to give the possibility to the public to provide their point of view on research priorities and goal-setting. The availability of these practices allows to consider, at

least in theory, this dimension as fulfilled. However, some differences need to be acknowledged between the practices offered by the two projects. The first relevant difference concerns the eligibility criteria to participate in the practices, as remarked at the beginning of this section. In addition to this, it is worth noting that, while the 'Nomination Forms' made available for the 100KGP can be submitted at any time, the practices made available for All of Us, such as the RFI, the feedback site, the ideas sharing via *Ideascale*, were open to collect proposal only for a specified limited timeframe, outside of which there is no way to submit ideas or proposals about goals and tasks.

3) Resource control: the possibility to have control over the resources produced from participating. This dimension is especially controversial as far as medical research is concerned. The health strategies developed after a study do not belong to the subjects who make the achievements possible by participating or by sharing their data or their samples, and they do not have any control above the delivery of those strategies. This is an issue in the programs under analysis as well as in any medical research program: this is actually one of the core points of the informed consent. However, even if, as themselves consented, participants cannot claim ownership nor control over the resources they contribute to producing by participating, they might at least be guaranteed to have access to these resources, and to have the possibility to benefit from them. However, as seen in the previous section, there are concerns about the accessibility of precision medicine strategies, and at the moment the research participants are not supposed to have any preferential facilitation in this respect. Then they are not going to have resources control and not even resources access.
4) Exit: the possibility to withdraw without detrimental effects. Both the projects, like any kind of medical research involving human subject after the *Nuremberg Code* (art. 9), allow the possibility to research participants to quit the program at any time without providing any reason and without penalty. In order to withdraw from the

100KGP, as established by the *Research Protocol* (87-90), and remarked in the Consent Form, participants, or those who give consent on their behalf, have to fill in a dedicated form available via the participant's clinical team or on the Genomics England website, and to return it to the clinical team. Two levels of withdrawal are possible: partial withdrawal 'no further contact', and total withdrawal 'no further use'. In case of total withdrawal, all the samples provided are destroyed, and the information about the participant cannot be accessed any more. However, in line with common practice, it is well specified that it is not possible to totally cancel every connection with the project. In particular, it is clearly stated that data and samples cannot be removed from underway or already done researches, and an audit record is maintained to keep track of the enrollment of the former participant. For withdrawing from All of Us, as established in the *Operational Protocol* (46-48), participants can just edit their status on the Participant Portal. Similar to the two levels of withdrawing from the 100KGP, All of Us participants can consider both 'un-enroll' (stopping or pausing being contacted and providing information), and real withdrawal. In the case of withdrawal, like for the 100KGP, no further research is authorized to use the data of the person, and the samples collected are destroyed. However, also in this case, data and biospecimens already used for research cannot be destroyed or recalled, and audit record of the enrolment is kept.

5) Voice: the possibility to express feedback, comments, or complaints. As seen, both the projects make some procedures available to express personal points of view. However, as already emphasized, in the case of the 100KGP they are always open but are accessible only to certain categories of people; while on the opposite, in the case of All of Us they are (theoretically) accessible to anyone but are available only during specific limited time frames.
6) Visible metrics: the possibility to measure the effects of the contributions provided. Concerning the effects of the contribution to medical research, as the data provided

are treated in an aggregated form, participants cannot track the effects of their own contribution in the research. Concerning the effects of the contributions in terms of comments, proposals and suggestions for the research setting and priorities, the different practices need to be considered differently. As far as the 'Nomination Forms' for the 100KGP are concerned, in case of acceptance, the nominator is contacted, and it is then possible to know whether the proposal has been accepted or not. In the case of the Participant Panels, both for 100KGP and for All of US, as they are involved in in-person meetings, it is reasonable to suppose that the comments provided receive immediate feedback. The most problematic cases are the procedures made available by All of Us and open to all, such as the RFI, the feedback site, and *Ideascale*, the three of them I experienced on myself. The three of these procedures, in different ways, offered some feedback. In the case of the RFI, the *PMI Working Group of the Advisory Committee to the NIH Director*, dedicated specific sessions in public workshop to summarize the emerged points of view (videocast and summaries available at nih.gov). In the case of the feedback site, as long as it was open, participants had the possibility to comment upon other participants' comments. For the 'ideas' on *Ideascale*, reciprocal feedback was more structured, as the registered users had the opportunity to vote for the 'ideas' they liked, and participants did even receive a score in relation to the collected numbers of votes. I submitted two 'ideas', which received respectively 2 and 4 votes, corresponding to a total of 89 points. The highest ranked participant got 2,427 points, the highest ranked 'idea' got 238 votes. However, it is important to notice a sort of bias in the ranking and in the voting procedure: voting was open only as long as the submission was open (which was for about 2 months). The coincidence of the timelines implies that, the earlier an idea is submitted, the longer it is there to be read and voted, proportionally. The 'ideas' that were submitted first, were being visible to be read and to get votes for up to two months, while the 'ideas' that were submitted later had progressively less time to be

read and voted as the deadline was approaching, and the very last 'ideas' that were submitted ended up having only a few hours or even a few minutes to get votes. In this light, it is reasonable to think that the votes and the ranking do not (necessarily) mirror the real public support of the 'ideas'. A similar bias concerns the comments on the feedback site: the viewpoints that were submitted later, often simply did not have the time to be commented by others. And moreover, while on *Ideascale* the submitted 'ideas' have remained visible even after submission and voting closed; on the opposite, the feedback site, with the collected comments, was no more accessible at all after the submission deadline. In any case, regardless of the summaries at the public workshops, regardless of the comments and the votes by other participants, there is no way to actually measure how and whether the provided comments are taken into account for the implementation of All of Us.

7) Communicative capacities: the possibility to communicate with other participants. Neither of the projects really offer chances of contact among participants, as privacy issues are also involved. The *Genomics England* website refer to other websites, such as *rareconnect.org* and *mygene2.org*, to be used by participants affected by rare diseases in order to connect with people in similar conditions. As far as All of Us is concerned, the only opportunities of contacts offered were the comments on the feedback site and on *Ideascale*, as long as they had been open.

**Summary**

By mining the participatory models implemented by the two projects to involve participants at the coordination level, it emerged that the democratizing practices made available by All of Us are supposed to be much more inclusive than those made available by the 100KGP, inasmuch as they are theoretically accessible to everyone. Nonetheless, some practical obstacles remain. Moreover, by considering the fulfilment of the seven dimensions identified by Kelty and Panofsky, the participatory model proposed by the 100KGP appears more

complete than All of Us, especially as far as the dimension of ‘Resource control’ and of ‘Visible metrics’ are considered.

### 3.5 Impact of the rearrangement of the political orders

As seen, both the 100KGP and All of Us are governmental initiatives. In both countries, the governmental assessments changed after the launch of the projects. As no changes have been officially announced in the implementation of the precision medicine initiative under analysis as connected with the new political orders, the entity and the directions of the impacts of the rearranged political orders, if any, are not easily measurable, especially in the short term. However, expectations about the future of precision medicine have been collected from the fieldwork interviewees, by specifically referring to the rearrangements related to 'Brexit' as for the UK interviews, and to Donald Trump government as for the US interviews. As the responses to this question often include political opinions, which might be considered as especially sensitive data, in this section it is adopted the further precaution of not mentioning even the pseudonyms of the interviewees, in order to minimize the risk of reidentification.

In the UK, most of the interviewees expressed concern that 'Brexit' could negatively affect precision medicine (and medicine in general) as a result of expected economic constraints. The general idea is that precision medicine will proceed, but there will be some challenges in terms of funding and of international collaborations. Among other things, it was expressed concern that the limitations in European collaboration would be to the detriment of genetic research, for which the size and the diversity of the sample is especially meaningful:

> "*in genetic research if you want to make any sense out of data, you need thousands of thousands of patients, and now the doors are closing, because why would European other countries want to collaborate with a country that is no longer benefitting from EU funding…particularly in this area it will be a disaster."*

IG: "*Do you think Brexit will have an impact*?"

R: "*Yes. Huge. In particular in rare diseases, the whole direction of flow for them is international collaboration"*

Moreover, it was in several cases mentioned a sort of "NHS crisis", and a sort of crisis of the public sector in general, to which it corresponds a general privatization that 'Brexit', by limiting international collaborations and funding, is expected to increase. In the words of the respondents:

*"the NHS is already in a really bad set at the moment and I can see that getting worse if the whole economy gets worse."*

"*If the UK will suffer the economic hit which the economists predict, then the NHS will continue to be starved of revenue."*

"*I suspect that the conservative party will sort of weaken the social nature of the NHS. What has already begun, a way of unpacking, making the NHS more marketized, making more elements of it open to the market. And I think that will continue."*

*"We have a government that has an ideology that is very much aligned with marketization of healthcare, and privatization healthcare"*

In other cases, on the opposite, some respondents argued that the projects are unlikely to be majorly affected by the political order. In few cases, it was denied any connection between the political situation and precision medicine or medicine in general:

"*I don't think it will have anything to do with it. I don't think the new Prime Minister even thought about it, or have anything to do with it. What is true is that the 100KGP was initiated by our former minister, and so 'the champion is gone' and so it may pull it back a little bit.*"

Others, minimized the impact of 'Brexit' by noting that precision medicine funding are mainly national, rather than European:

IG: "*Do you think Brexit is going to have an impact?"*
R: "*Yes, inevitably it will. But actually I don't know to what extent. If you look at UK Biobank it is entirely UK funded…We have a lot of collaborations with Germany, Finland, Sweden. I think these collaborations will continue, but maybe there will be some negative impact on the funding*."

"*I don't think it will have a big impact, because healthcare is a national thing and not a European thing. So I don't think there will be a big difference*."

In one case, the claim was that both the 100KGP and All of Us will proceed without being affected by the political rearrangements, by advancing in the very opposite directions to the recently established political mentalities:

"*We are building resources that are the opposite, if you like, of sort of Brexit mentality or of the Trump's mentality of closing borders. We are building resources without borders. Without them being only for the British or only for the Americans. These are resources that are being made available for all researchers around the world….So I think that the trend is going in the opposite direction of the Brexit or the US borders type of things."*

In one isolated case, 'Brexit', although declared as unwanted by the interviewee, was seen as an opportunity for the advancement precision medicine:

> "*I confess I am completely against Brexit…I do think potentially in this area, probably there will be a growth in precision medicine, if the UK is going to have to rethink the way it does its economy because of not being part of the EU, it is going to have to identify successful areas. Seems like there will be more precision, more emphasis placed on medical research. And to be successfully it has to be done closely to the NHS. My guess is that the UK will take quite a few advances in this area and try to be a leader in this space. Which will be good for patients. Possibly, despite me don't wanting the Brexit, it is possibly one area where you may actually see some benefits*".

In the US, the general feeling was that precision medicine and the PMI will proceed, but many concerns were expressed about All of Us being implemented as initially prospected. Several interviewees refused to answer to the question at all. It was often expressed a general feeling of uncertainty especially in terms of governmental priorities and resource allocations. Some interviewees were totally negative about funding for healthcare in general, including for the continuation of the PMI:

> *"I think everyone is going to have a cut. I think the PMI, I think it will be shut down, but I think all the old science here is under threat."*

> *"There is going to be very large cuts in the NIH funding, my guess is that significant budget cuts start to occur, precision medicine will probably be one of the first things*

*to go, because it is earliest, most speculative, and so there is real chance that it may not go forth."*

Most interviewees expressed the opinion that the PMI could be slowed down or downsized but not stopped: despite the general shortcut of funding in the field of healthcare, the PMI will be confirmed, at least because it could count on the support of the Congress.:

"*there is still a lot of governmental support for research in Congress, and I don't think research is going to come to an alt, I think this is an area of broad interest, it maybe be slow down, but I don't think it will stop*."

"*I know that there are some concerns that the funding might be cut… I don't think precision medicine will be affected as much as other fields… I've gone through different administration, I just say I didn't notice the difference in terms of NIH funding and NIH direction. Of course we can notice the difference when president Clinton doubled the NIH budget, that really make the difference, but this is only one president in 60 years, the others kept the budget flat, including president Obama. I don't know, my hope is that there will be no changes.*"

Other respondents declared themselves as totally clueless, by lamenting the unpredictability of the Trump administration as fostering a deep uncertainty:

"*the new presidential administration is just completely unpredictable, because it is so profoundly irrational, and completely disconnected to any sort of empirical reality. The administration in general is giving the impression, the president and all of his top advisors seem to have complete contemptuously idea of science, the budget had huge huge cuts for the NIH... Who knows! I don't think we have any basis for*

*predicting the actions of this administration given the temperament of the president and his mental state*."

*"budget was approved last week, the NIH did the need of funding for pm, and that was positive. But with the president changing views quite often, that could potentially quickly change. When you have an administration such as the one that we currently have, that can have a negative impact on many efforts that were undertaken such as precision medicine."*

"*I don't really know. The administration is so chaotic and so, really hard to know."*

Some interviewees, more than about the advancement of precision medicine and of medicine in general, expressed concern that the political rearrangement could negatively impact on the equitable distribution of healthcare:

"*I think it's pretty obvious that the new administration is not that interested in health disparities, given the way they have responded to modifying Obamacare, and so many millions of people are now going to be uninsured."*

*"It's a disaster! They are already trying to dismantle the major health advantage that we had during the Obama administration. There is already discussion about how many people will lose their insurance benefits, and that's really a disaster. I don't see that as long as we have the government in place that is in place now, things are going to moving forward."*

In alignment with this position questioning the equitable and societal commitment of the government, one interviewee was quite convinced that precision medicine, as far as it

bypasses societal problems with a generalized medicalization, is the approach the most likely to be supported by the new administration:

> "*I think if there is anything in biomedicine is going ahead within this administration, it is precision medicine*."

**Summary**

Both in the UK and in the US, although a full range of different opinions was displayed, the prevalently expressed feeling about the future of the initiatives in relation to the governmental rearrangements, was uncertainty. In the UK, main concerns were related to 'Brexit' as worsening the "crisis of the NHS" by fostering privatization, to 'Brexit' as negatively impacting on the economy by reducing funding for medical research, and to 'Brexit' as undermining international collaborations, all the more important for the robustness of genetic studies. However, some respondents were quite confident that 'Brexit' is not going to affect precision medicine, as it is mainly developed at a national level. In the US, the expressed concerns were especially in terms of priorities and resource allocations. The prevalent opinion was that the PMI will proceed but maybe slowed down, by being affected by the funding shortcut. Others commented that the PMI will continue to be developed, but the efforts for facilitating the equitable distribution of healthcare will be negatively affected. In both countries, the concerns and the uncertainty expressed by the respondents in connection to the political reassessments, in addition to confirming the tight bond between the political priorities and the directions of the scientific progress, enforced the idea that the current political leanings are directed to fostering neoliberal privatization, at the expenses of the welfare state, and that this 'privatizing turn' is also likely to affect medical research and implementation.

### 3.6 The Italian context

As anticipated in the Materials and Methods chapter, a special attention was dedicated to situating the results emerged out of my research in the Italian context. To this aim, a dedicated workshop was organized together with my research team, with the aim to investigate the pertinence and the translatability of the issues around the societal capacities of precision medicine in the Italian context.

The workshop turned out as an unprecedented opportunity to engage experts from different disciplines all together in a dialogue about the medical needs of the Italian evolving demography. Interestingly, three of the five external invited speakers started their talk by questioning to have been maybe invited by mistake, as they did not feel themselves experts in the general theme of the event. Of course, no invitation was sent by mistake: the speakers were accurately and relevantly chosen from different fields, with the aim to have the most complete possible range of relevant perspectives on an interdisciplinary and transdisciplinary problem. And indeed, each intervention fitted perfectly in the overall picture that was formed, by relevantly completing it, and all the speakers participated actively in the discussion, by also expressing interest for following up. The doubt of unsuitableness initially expressed by some of them, can be assumed as the confirmation that this kind of transdisciplinary dialogue on this specific theme was unprecedented, and that our workshop was an opportunity for experts in different disciplines to reason on that topic for the first time.

Presentations and discussions dealt with tensions and convergences between precision medicine and public health, the distinctiveness of the needs of the migrants, the supposed dichotomy between nature and nurture, reassessment of healthcare priorities, the need of political engagement of scientists, and fairness. Similar to the international debate around my two case studies, the medical promises and opportunities provided by precision medicine were examined in contraposition with the limits preventing to appropriately and fairly meet

the expectations (Di Maria, Pelicci, Remuzzi, Crabu, Even Chorev); it was reasoned about the unbridgeable gap between the frontiers of high-tech biomedical innovation and the societal emergencies faced by the most vulnerable segments of the populations, such as migrants (Ardigò, Di Maria, Galasso, Remuzzi); it was urged a new and appropriately informed political engagement (Ottonelli, Galasso, Remuzzi, Testa); and all these reasonings intertwined all together in a comprehensive multi-perspective discussion.

In summary, this workshop was very helpful to trace in the Italian context the same challenges and opportunities that emerged in my international analysis, by contextualizing them in the current stage of the societal integration of migrants and new citizens in my country. Notwithstanding the peculiarity of the contextual situation, which requires to be addressed into a full account of its social and political specificity, it emerged the same pressing need to include all the populations in the precision medicine agenda, the same urgency to prioritize basic care needs and societal deprivations, and especially the same need to align medical and political reasoning and interventions.

In this respect, the significant outcome of the workshop was not the promulgation or even the identification of specific strategies to harness opportunities and challenges of precision medicine in relation to Italian equity, which would be a very valuable but premature outcome. Rather, the most important outcome of the workshop was the launch of a dialogue for *getting awareness* of the opportunities and of the challenges for precision medicine in terms of equity, and of the possibility to harness them. The value of the workshop was its synergistic capacity, as it put together people unused to work together to the extent they though they have been "invited by mistake", by providing the opportunity to physicians and to molecular biologists of engaging with issues of societal integration, to social scientists and political philosopher of engaging with issue of medical advancement, and to all together for considering fostering a dialogue between the scientific and the political domain to the alignment of medical advancement and societal integration.

### 3.7. Conclusion: focusing on the scope and the outreach as matters of interpretation

This chapter illustrated the main outcomes of my research, which have been elaborated to draw my arguments, as they will be exposed in the next chapter. In particular, this chapter considered the findings on the definitions and conceptualizations of precision medicine, and on the expectations as related to the scopes; on the different interpretations of the relation between precision medicine and public health, from mutual exclusion, to contrast, to neutrality, to convergence, to overlapping; on the inclusivity of precision medicine research upstream, with the overcoming of objective and subjective obstacles and with the fostering of entrepreneurial and altruistic motivations; on the accessibility to precision medicine benefits downstream; on the effectiveness of the participatory model; on the perceptions over the impact of the reconfiguration of the political order; on the stage of the discussion over a coordination between scientific and political order with respect to precision medicine in the Italian context.

To sum up, the variety of interpretations emerged out of the material observed and of the opinions considered, suggested that precision medicine, rather than as an object in itself, should be considered as a social construct: the concept of precision medicine appeared as mainly a matter of interpretation, which, as such, was required to be framed into a hermeneutical analysis. This is the main reason why my research advanced recursively by following grounded theory: precision medicine was studied through the interpretations by different social actors in relation to different discourses. It was examined as the product of those discourses, and in particular of the interpretations of those discourses. It was analyzed as an interpretative construct that, in returns, produces other interpretations that are themselves performative in constructing ideas of precision medicine, and in influencing other interpretations.

In my analysis of precision medicine in terms of equity and distributive justice, the most relevant aspects of the discourse and of the interpretations, are those related to the *scope* of

precision medicine: the kind of analyses precision medicine is declared and interpreted to encompass and, consequently, the kind of benefits precision medicine possibly produces.

The counterpart of the scope of precision medicine, in my analysis, is the *outreach* of precision medicine: how, to which groups, and according to which strategies and principles, the benefits deriving from precision medicine are distributed. The outreach of precision medicine is analyzed by considering how different discourses and interpretations of precision medicine foster the participation of different social groups in the research, in the coordination, and in the benefits.

In the next chapter, the scopes of different interpretations of precision medicine, the outreaches, and the reciprocal influences between scope and outreach, are discussed in relation to their limits and their potentials for social and health equity.

# 4. DISCUSSION

In this chapter I discuss the data emerged out of my analyses on the discourses of the two projects, and on the expectations and concerns of the stakeholders, which are illustrated in the previous chapter, and I draw my arguments by referring to them.

The first section is dedicated to discussing the scope of precision medicine. The collected definitions, explicitly expressed or implicitly embraced, are considered as a basis to understand the different interpretations of precision medicine: first, as they are captured by the use of different names, then, as their differences are extended beyond the terminological domain. Next, an interpretation of the interpretations is proposed, by distinguishing three versions of precision medicine on the basis of the determinants of health that are included in the analysis, and to which different possible outcoming benefits correspond.

Section 4.2 is dedicated to discussing the outreach of precision medicine: it is argued that the disequilibrium in the efforts for fostering inclusivity upstream and downstream jeopardizes the participation of the most socio-economically disadvantaged groups. In addition, the participatory models offered are questioned as incomplete, and as such unsuitable to guarantee the inclusion of the interests of everybody.

Section 4.3 considers the connections between the scope and the outreach of precision medicine: it is argued that a broader scope possibly produces different categories of benefits, some of which could trigger a 'virtuous circle' of solidarity to the advantage of the socio-economically disadvantaged groups and of their participation. Section 4.4 considers the limits of the argument and the challenges to actualize it.

Section 4.5 is dedicated to drawing the conclusions of my research, and to putting them in relation to the wider STS framework. Finally, section 4.6 is dedicated to the future: to the future in the sense of the expected evolution of precision medicine by considering the political trends in different countries, but also to the future in the sense of considering the possible implication of my research, and also in the sense of future plans in terms of further research questions to be addressed, and of further analysis to be developed.

## 4.1 Precision medicine and its scope

The data displayed in the previous chapter suggest that, as precision medicine emerged as a concept constructed by different interpretations, its scope primarily depends on the interpretations considered. By looking at the differences among the projects labelled as precision medicine, by considering the differences in the definitions provided or implicitly embraced by relevant authors as well as by the interviewees in my research, it can be argued that the concept of precision medicine is understood and implemented in different ways, only partially overlapping, and that the concept of precision medicine is mainly a matter of interpretation. In particular, disagreement emerged on two directions: one is related to the different concepts denoted by different names, the other to the different concepts denoted by the same name.

### 4.1.1 The difference that words make: shades between precision, personalized, and stratified medicine

In the chapter of the Results, it has been observed that many stakeholders consider different terms as denoting the very same thing. However, the observations of the use of different terms, and the justifications for the preferences for one term or another, suggest that different names are chosen to emphasize different aspects.

Several analysts engaged with the profound meaning of the plurality of names that are referred to the approach here addressed as precision medicine (among others: Katsnelson 2013, Roden and Tyndale 2013, Pokorska-Bocci et al. 2014, Day et al. 2016, Juengst et al. 2016, Khoury 2016, Chan and Erikainen 2018). Most of them argued that choosing different words does make a difference, as in general, also in particular in the context of precision medicine, by noticing that "words matter" (Khoury 2016), or by reiterating the never answered Shakespearean question "what's in a name?" (Roden and Tyndale 2013, Pokorska-Bocci et al. 2014; Chan and Erikainen 2018). These analyses consider the differences that

different names make or imply, by analyzing the use of different terms possibly synonymous: precision medicine, personalized medicine, stratified medicine, individualized medicine, P4 medicine, system medicine.

My research only included analyses of the different use of the terms ‘precision medicine’ and ‘personalized medicine’, and tangentially ‘stratified medicine’, because these were the terms recurring in the material that I considered in relation to my case studies. My research, like the analyses above, included observations of how the different terms are used in the literature, and like the analysis by Day and colleagues (2016) and by Juengst and colleagues (2016), also observations and investigations of their use in interviews with insiders and stakeholders.

The terminological uses observed in my interviews, as well as the justifications provided by my respondents for preferring one term or another, mostly confirmed the conclusions drawn by the other analysists, and also added some further insights, which I set out below. In line with the conclusions by Pokorska-Bocci and colleagues (2014) after their literature review (conducted in 2012, before the launch of the 2015 PMI, but after the 2011 Report), the analysis of the comments released in my interviews uncovered some inconsistencies in the use of the different terms, and evidenced that when any difference is admitted, ‘personalized medicine’ is often considered as the broadest term. In line with Katsnelson (2013), with Khoury (2016), and Juengst and colleagues (2016), out of my analyses it emerged that ‘precision medicine’ is expected to overcome the over-expectations and also the limits of having the individual person as the fundamental focus. Again in line with Juengst and colleagues (2016), and also with Chan and Erikainen (2018), my data suggest that the saying ‘precision medicine’ has been established as the major term in the US after the launch of the PMI, and that it has been deliberately chosen as the most suitable term to build trust in the American context, as it avoids both the overpromise of personalization of treatments, and the negative associations with the idea of stratification.

In particular, in my interviews, the exclusive use of the term ‘precision medicine’ among my respondents based in the US, while my the respondents in the UK tended to use ‘personalized medicine’, or to interpose the two terms, validated the intuition, also proposed by some interviewees themselves, that ‘personalized medicine’ is the preferred term in the UK, while ‘precision medicine’ is the preferred term in the US. These data, against the historical timeline for the affirmation of the two terms as described in the Introduction, suggest that, at some point, the term ‘personalized medicine’ has been substituted in the US with the term ‘precision medicine’, which became the prevalent one, while in Europe ‘personalized medicine’ remained quite widespread.

The American popularity of the term ‘precision medicine’ coincides in time with the popularity of the PMI, which in the US is really the epitome of precision medicine itself, to the extent that, in the interviews in the US, talks about precision medicine and about the PMI overlapped. Some analysts (Juengst et al. 2016, Khoury 2016, Chan and Erikainen 2018) suggest that the establishment of the term ‘precision medicine’ over the others is, in large part, due to the popularity of the American initiative labelled with this name. I have no elements from my research to argue whether the American preferred term is ‘precision medicine’ because of the name of the PMI, or if conversely the PMI was named so because ‘precision medicine’ was the American preferred term. However, whatever came first, it is very probable that there is a connection between the name of the PMI and the almost exclusive use of this term in the US.

As confirmed by the two interviewees in my research who were involved in the choice, the term ‘precision medicine’ rather than ‘personalized medicine’ or other terms has been chosen carefully by the promoters of the 2011 report first, and of the PMI then, and this choice, from many points of view, can be interestingly situated in the framework of sociology of expectations (Brown and Michael 2003, Hedgecoe 2004, and Borup at al. 2006). In particular, it is interesting to remark, as also noticed by Juengst and colleagues (2016), that the term ‘precision medicine’ is often declared to be preferred to the analogous

‘personalized medicine’ because it departs from it in two opposite, although not conflicting, directions: precision medicine is envisioned to simultaneously take one step forward and one step back with respect to personalized medicine.

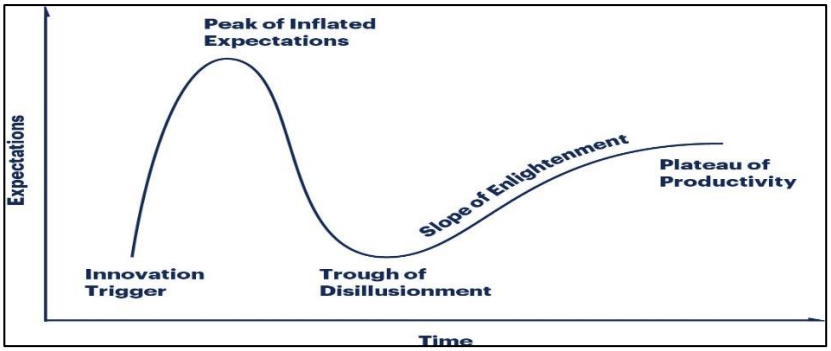
On the one side, as seen, precision medicine takes a step back by disowning the promise, misleadingly suggested by ‘personalized medicine’, of treatments tailored to every single person, thence preventing the negative effects of unmet expectations and disillusionment (Brown 2003).

On the other side, precision medicine diverges from personalized medicine in the context of ‘personalization’ in the sense of ‘personalized care’ (Cornetta and Brown 2013), interpreted as the attention to the patient as a person, with specific narratives, preferences, relations and values (Horwitz et al. 2013, Tutton 2014, Prainsack 2014, and Prainsack 2018). In this respect, personalized medicine is often, in the literature as well as in my interviews, considered as a broader approach, by also encompassing the personal dimension in this holistic and narrative sense. In this perspective, many of my interviewees declared to prefer the term ‘precision medicine’ because, rather than promising this kind of personalization as something that needs to be achieved, it acknowledges that medicine has always been personalized. According to this point of view, personalized medicine is aimed to achieve personalization by implicitly assuming that it still needs to be reached, while precision medicine implicitly assumes that personalization is already reached, and it is aimed to go further with more precise techniques. In this sense precision medicine is envisioned as a step forward with respect of personalized medicine.

In addition to the shades of meaning that make precision medicine promising a bit less (as it gives up about tailoring treatments to every individual), and a bit more (as it assumes personalization is already reached, and promises to fine-tune it with more precise techniques) than personalized medicine, the choice of a ‘rebrand’, as it is often called, or in other words the choice to propose a different term than the one that had been widespread for years, can be understood in terms of hype and in the logics of sociology of expectations. We can

consider in this respect the graph of the 'hype cycle' developed by Gartner (gartner.com): it famously represents a peak in expectations corresponding to the triggering of a new technology, followed by a nosedive, and finally by a compromise of more realistic and modest expectations (Figure 6). Even if this model has been criticized as too generalized and simplistic (Borup et al. 2006), here it is helpful to visualize the intuition that personalized medicine, after several years on the stage, has probably nowadays exhausted the initial charge of high expectations that correlates with novelty. Conversely, a new name can be presented as a new thing, and trigger the 'hype cycle' again, by bringing back the expectations to the phase of the initial peak, which is the most important phase in relation to get funding and support (Brown 2003). In this respect, the concept of 'performative nominalism' (Pickersgill 2018), again in the framework of sociology of the expectations, is very helpful: the name 'precision medicine' is not (only) used to *describe* a new concept, but also to contribute to building the concept itself, and the whole framework around it - as well as to catalyze expectations and, with them, public support.

**Figure 6**: representation of the 'hype cycle' as developed by Gartner. Readapted from: https://www.gartner.com/en/research/methodologies/gartner-hype-cycle



### 4.1.2 Precision medicine within the 'magic triangle' between biology, environment and lifestyle

The different shades related to different terms are not exhaustive of all the different understandings around precision medicine. As already observed many times during this thesis, projects similarly labelled as 'precision medicine' actually differ from one another at multiple levels, as well as the definitions explicitly provided, or implicitly assumed in the literature and in my fieldwork interviews. Precision or personalized medicine corresponds to different 'imaginaries' (Tutton 2014, Waldby 2000), from pharmacogenomics, to empowerment for informed behavioral changes, to patients involved in the decision making 'as partners', to holistic representation of the personal narratives. Among these different imaginaries, this thesis focuses on the different interpretations that are the most directly relevant to the research questions on social and health equity: the different interpretations of the scope of precision medicine, by considering which layers of analyses are encompassed, or, in other words, which determinants of health are taken into account and addressed.

As seen, one interpretation of precision medicine, relates to the 'imaginary' of genomic medicine. It is the version embedded by the 100KGP. The 100KGP, the reference for many interviewees in the UK when talking about precision medicine, is instituted to collect and analyze genomic data, with the aim to understand the genetic cause of genetic diseases, and to provide therapies into a full account of the genetic mutations at issue. The focus and the target are solely the genome and the genetic variations and mutations of the individual.

On the other hand, the White House, and the website of All of Us define precision medicine as taking into account "individual differences in lifestyle, environment, and biology" (allofus.nih.gov). These are the three dimensions also recurring in my research interviews, and which in particular have been described by Rolf Apweiler as 'the magic triangle', by implicitly assuming that the triangulation of these three categories of factors encompasses all the determinants of health: those related to congenital features, those related to behaviors, those related to external exposures, and those at the intersections of the

different categories. A precision medicine approach that, such as All of Us, is focused on the three of the sides and on the whole area of the 'magic triangle', embodies a different interpretation of precision medicine from the genomic medicine version of the 100KGP.

However, as seen, a recurring concern in the interviews questioned the inclusive approach of All of Us as one of the many instances of the overhype and overpromise lamented about the project. According to some perspectives, there is a 'discrepancy' between discourse and implementation in the PMI, and it is claimed that, despite the 'official version', in practice the project seems to be mainly if not exclusively related to genomic studies. In any case, even by giving credit to the 'unofficial version' of the PMI as actually a genomic study, it cannot be considered as a genomic medicine project in the same sense of the 100KGP, given the differences in the vey design. As reiterated several times, the 100KGP deals exclusively with genetic *diseases*, and uses the particular technique of comparative genomic analyses to individuate the specific variation(s) involved in the disease. Participants in All of Us, conversely, are not (only) genetic diseases patients, but volunteers in any kind of health and disease conditions, then there is no specific genetic variation to isolate. In this framework, the genomic analyses performed within All of Us, rather than with genetic diseases, are more appropriately considered as dealing with all the genetic variations epidemiologically correlated with phenotypical features, or in other words, dealing with genetic *risk.*

The causative genetic mutations for the 100KGP genetic disease patients, are the proximate *arche* (in the sense of Polybius' *Histories*) of a specific disease, and at that point other determinants of health are not considered as the priority. Conversely, the genetic risks for the All of Us volunteers, likewise for the volunteers of other similar programs involving genome sequencing without being focused on any particular disease, are often distal determinants of health, and the actualization of the risk often depends on the interplay of several factors within the 'magic triangle'. In particular, the rhetoric of empowerment of the PMI, is catalyzed around the idea of well-informed individuals improving their own health outcomes by themselves, by being provided with the tools to properly intervene on the

determinants of health they can have an influence on: the ‘direct environment’ in the ‘magic triangle’ described by Apweiler, or the lifestyle in the triangle graphically represented in the All of Us website.

Given the definitions and the expectations collected, I propose distinguishing at least three different versions of precision medicine, in consideration of their scope with respect of ‘the magic triangle’:

1) **One-sided precision medicine**

   Precision medicine as genomic medicine, then solely focused on the bio-molecular or biological dimension: it is the version embodied by the 100KGP, which is aimed to explore the genetic causes of genetic diseases, and to deliver therapies accordingly tailored. It is concentrated on a very specific target, on a single kind and on a single aspect of disease, on a single point: one vertex of the ‘magic triangle’.

2) **Two-sided precision medicine**

   Precision medicine as the analysis of genetic risk framed in the ‘direct environment’, focused on biology and on lifestyle: it is the version embodied by ‘the unofficial version’ of the PMI. It is cast across two components of health and illness, by covering the length of one side of the ‘magic triangle’.

3) **Three-sided precision medicine**

   Precision medicine as the study at the intersection of biology, lifestyle and environment: it is the version embodied by ‘the official version’ of the PMI. It is supposed to cover all the dimensions of health and disease, and the whole area of the ‘magic triangle’.

It is important to mark that, even if the first version of this classification is really focused on *genomics*, it is here described more broadly in terms of *biology*. This choice is related to the intent to emphasize the minimum common denominator of different precision medicine

approaches: according to the observation of my case studies, despite the recurring talk about precision medicine in terms of genomic medicine, the common denominator cannot actually be genomic analysis. As a matter of fact, genome sequencing is only one *optional* part of the PMI (*All of Us Operational Protocol*), and the PMI still remains generally considered as a precision medicine project (or even as *the* precision medicine project), even if deprived of the genomic part. Moreover, if we accept that the PMI is a precision medicine project, and that it is modeled after UK Biobank, we may infer, by analogy, that also UK Biobank is a precision medicine project, as it is indeed sometimes claimed. And, as seen, UK Biobank does not perform genome sequencing at all (ukbiobank.ac.uk). Of course, it is also possible to argue that neither the PMI nor UK Biobank are actually precision medicine projects (UK02). Alternatively, in order to include the PMI under the definition of precision medicine project, as it is generally accepted, the minimum common denominator, rather than genomic analyses, must be biological analyses in general.

Interestingly, if we accept defining precision medicine projects by giving up the requirement of performing genome sequencing, and by only requiring the inclusion of biological analyses (possibly but not necessarily integrated with other analyses involving data on the lifestyle and/or the environment), which is the only way to define the PMI as a precision medicine project, then also some projects that are not generally considered as related to precision medicine are included in the definition. One example is of course UK Biobank. However, another example, which might be quite counterintuitive, are the *Whitehall Studies*. As mentioned in the Introduction, the *Whitehall Studies*, founded by Michael Marmot and coordinated by his group, are considered as the cornerstone for the modern conceptualization of the social determinants of health. In *Whitehall II*, participants share several biological information (in some cases, even including DNA samples), which are analyzed in correlation with information about the lifestyle and about a specific kind of environmental exposures (the working social environment) (ucl.ac.uk).

By looking at their design, quite interestingly, and opposite to the intuition of the 'distraction argument' of precision medicine 'distracting' from the social determinants of health, the PMI, epitome of the precision medicine initiatives, and *Whitehall II*, epitome of the studies on the social determinants of health, are quite similar. To the extent that, by defining precision medicine on the basis of the individual data that are collected, analyzed and taken into account, either both projects should be considered as precision medicine, or neither. This argument is particularly impressive and relevant to this thesis as far as the Whitehall Studies are involved, given their immediate reminding to the efforts around the social determinants of health. However, the very same argument could be extended to almost any epidemiological study. The difficulty in finding a demarcation criterion between the PMI and any classical epidemiological study, including Whitehall II validates either the position, expressed by several interviewees, that precision medicine is just a 'rebranding' for classical epidemiology, or the position according to which the PMI is *not* a precision medicine study. What it is anyway clear is that the PMI cannot be considered a precision medicine project in the same sense of the 100KGP or other genomic medicine studies.

The precision medicine models of my categorization grounded on the sides of the 'magic triangle' that they encompass, accordingly, also have different potential outputs:

1) The potential outputs of one-sided precision medicine are, mainly, tailored biomedical treatments;
2) For two-sided precision medicine, which focuses on genetic risk in the frame of lifestyle, potential outputs are both tailored biomedical treatments, and information to empower behavioral changes;
3) For three-sided precision medicine, as the study at the intersection between biology, lifestyle, and environment, the potential outputs are tailored biomedical treatments, information to empower behavioral changes, and also information to foster appropriate social policies.

These expected outputs might bring different kinds of contributions to public health issues, as summarized in Table1. In this respect, we can consider the possible contributions from precision medicine to public health mentioned by the interviewees and reported in the Results: if one-sided precision medicine, solely focused on biology, can only contribute to public health by alleviating that part of the population who is affected by genetic diseases, or by diseases with a genetic component, to this, two-sided precision medicine, focused on biological predispositions and lifestyle, can also add 'tailored messaging'; while the broadest three-sided model of precision medicine, which encompasses biology, lifestyle and environment, could also contribute to implementing public health policies.

**Table 1**: three versions of precision medicines as related to different scopes and different potential outputs

| **Precision medicine version** | **Scope** (determinants of health encompassed) | **Example** | **Potential outputs** |
|---|---|---|---|
| One-sided precision medicine | • Biology | The 100KGP | • Tailored biomedical treatments |
| Two-sided precision medicine | • Biology<br>• Lifestyle | The 'unofficial version' of the PMI | • Tailored biomedical treatments<br>• Information to empower behavioral changes |
| Three-sided precision medicine | • Biology<br>• Lifestyle<br>• Environment | The 'official version' of the PMI | • Tailored biomedical treatments<br>• Information to empower behavioral changes<br>• Information to foster social policies |

### 4.1.3 The 'societal potential' of precision medicine

From the point of view of the research questions of this thesis, the three-sided version of precision medicine is especially relevant. As described in the Introduction, the social determinants of health play an especially significant role in health equity, which is the object of investigation of this thesis: societal inequalities are demonstrated by several studies to have a significant impact on health, and in causing health inequalities. The precision medicine version which scope encompasses the environmental component of health, especially if 'environment' is understood in the broadest sense, by also including the *social* exposures, or in other terms the social determinants of health, could be a unique opportunity to better understand the societal inequalities affecting health, and to possibly intervene on them.

This is what I call the '*societal potential*' of precision medicine (Galasso and Testa 2017b): by including in its agenda the investigation of the social factors affecting health, three-sided precision medicine could provide better knowledge, and catalyze renewed attention around the social inequalities impacting on health inequalities. This potential would be analogous to the studies on the social determinants of health, which as seen are so similar in the design, but the PMI would take advantage of a much larger scale. The potential further step to these improved and renewed understanding and attention could be intervention: the 'societal potential' of precision medicine is the possibility to foster public socio-political interventions to *improve health equity by improving social equity*.

#### The societal potential of precision medicine between the 'distraction argument' and precision public health

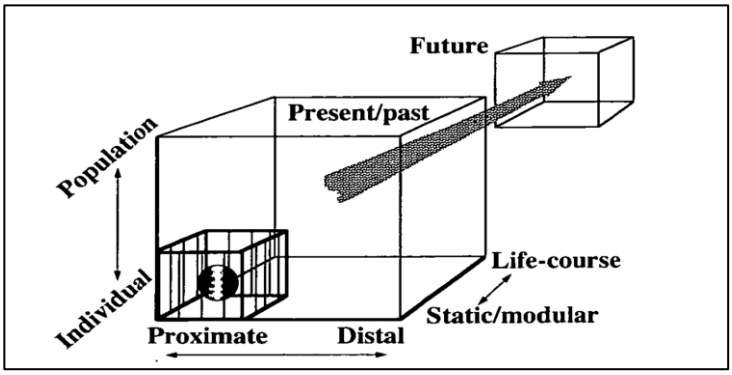
My argument on the 'societal potential' of precision medicine is the complete opposite of the 'distraction argument': the 'distraction argument' worries that precision medicine could *undermine* interventions on the social determinants of health, by diverting resources and

attentions from them; on the opposite, the argument of the 'social potential' considers that precision medicine could *foster* interventions on the social determinants of health, by providing new knowledge and attention. However, these two arguments are not necessarily incompatible: as several of my interviewees did, as well as some authors, it is possible to acknowledge different extremes as two sides of the same coin, by considering one as the opportunity, the other as the risk. My argument on the 'societal potential' is not expected to reject the 'distraction argument'. It all depends on the version of precision medicine considered, and on how it is interpreted and implemented.

For example, by considering the PMI, the three-sided 'official version' can be perceived as promising in terms of 'societal potential'. In parallel, the 'unofficial version', as it is understood as a two-sided precision medicine approach, by only focusing on biology and lifestyle, and entirely excluding the social determinants of health, can reasonably be perceived as a risk to 'distract' from them.

In responding to the 'distraction argument', the argument of the 'societal potential' is situated on a different plane from the framework of precision public health, the typical proposal to reconcile precision medicine and public health. To visualize this idea of the relationship between precision medicine and public health as cast across different planes, it is helpful to recall the analysis by the epidemiologist Anthony McMichael in the already mentioned article *Prisoners of the Proximate* (McMichael 1999), and situated in the debate over the socio-political role of epidemiology. In his article, McMichael visualizes epidemiology as constrained along four different axes, represented as geometrical dimensions (Figure 7), and advocates a shift across all of them: from proximate to distal risk factors; from individual-level to population-level focus; from modular to continuous risk acquisition; from a static to a changing global environment. Each of these shifts is imagined as collocated on a different plane.

**Figure 7**: schematic representation of the four different axes along each of which, according to McMichael, epidemiology is constrained and needs to move. Readapted from: McMichael 1999, 890.




With this image of different axes situated on different planes, we can observe that precision public health mainly proposes to shift precision medicine from an individual-level focus, to a population-level focus, by translating the tailored biomedical benefits (both in terms of treatments and of preventive screening) that are expected to be achieved for the *individual*, into tailored biomedical benefits for *populations*, but still remaining within the medical domain. To recall the already quoted words by Khoury and colleagues in the article "Precision Public Health for the Era of Precision Medicine", which is one of the major references for the framing of precision public health:

> "If precision medicine is about providing the right treatment to the right patient at the right time, precision public health can be simply viewed as providing the right intervention to the right population at the right time." (Khoury et al. 2016, 398).

The 'distraction argument', on the other hand, mainly advocates a shift from the *biomedical* to the *socio-political* domain. As expressed in the article by Bayer and Galea on the NEJM:

> "the challenge we face to improve population health does not involve the frontiers of science and molecular biology. It entails development of the vision and willingness to address certain persistent social realities." (Bayer and Galea 2015, 501).

It is exactly on this axis, from the biomedical to the socio-political domain, rather than from individual to population focus, that the 'societal potential' suggests moving along (Galasso and Testa 2017b).

## 4.2 The outreach of precision medicine

Another important dimension to consider in order to scrutinize precision medicine in terms of equity, in addition to the scope, is the outreach. The *scope* is here understood as the determinants of health and the kinds of interventions that are included in the agenda, and it is connected with *the kinds of benefits that can be possibly produced*. The *outreach* is here understood in relation to the segments of the population which can benefit from precision medicine, and it is connected with *the distribution of the produced benefits*. In the next section, it will be argued that scope and outreach are importantly related with one another. In this section, it is discussed the outreach in consideration of the strategies to facilitate inclusive participation and accessibility, of the motivations for enrolling, and of the efficiency of the democratizing practices.

### 4.2.1 Detrimentally unbalanced efforts for inclusion

This thesis proposed to analyze separately the challenges related to upstream participation in the research cohort, and to downstream accessibility of the benefits. However, some connections exist between these two levels, and it will be argued that incomplete inclusiveness at one level also affects the other level. In one direction, this is quite straightforward, as already mentioned in the previous chapters: if one segment of the population is not included upstream, the specific features and needs of that segment will not be taken into account for providing tailored interventions. As *by construction* precision medicine provides interventions that are tailored on the basis of the individual specificities that are taken into account upstream, as a consequence, it is unlikely that the groups, the specificities of whom are not taken into account, could benefit downstream. In this subsection, it is argued that also the other direction is as much problematic: that if one segment is not included in the downstream benefits, it is unlikely that segment participates upstream.

As seen, for the US initiative the problem of inclusive recruitment is perceived as much more challenging than for the 100KGP: in the 100KGP, all the potential participants are already reached as patients, while All of Us, which is not bound to any particular condition for recruitment, in many cases has to start reaching people from zero. Moreover, eligible participants for 100KGP are likely to be directly interested in the study, given that the project is aimed at studying exactly the diseases by which they are affected, while the eligible participants for All of Us, given the much broader scale and scope of the project, are less likely to be directly interested.

In the Results, it was reported the "recruitmentology" (Epstein 2007) effort - embodied in many strategies, some already implemented, some anyway in the plans (All of Us Operational Protocols) - to overcome both the objective and the subjective obstacles preventing participation in All of Us. By recalling the analysis by Rothstein (2017), who denounced that precision medicine stands to only benefit people "uncommonly tech savvy, highly health literate, self-directed, information seeking, English fluent, health focused, and well insured" (ibidem, 6), we can observe that All of Us planned strategies to overcome all the identified exclusivities. Except one: "well insured".

As a matter of fact, if on the one hand all the upstream obstacles have been addressed, on the other hand, the problem of the likely exclusive costs of the treatments remains unsolved. The exclusivity of the costs risks making treatments inaccessible to the most disadvantaged segments of the population: the very same segments to which the upstream efforts are dedicated. Among the experts I interviewed in the US and in the UK, there is a very widespread concern that the benefits of precision medicine will be accessible only to the better-off - with the exception of some positive perspectives expecting precision medicine facilitating in the long run the reduction of the cost of medical care. To my knowledge, no direct effort has been officially under scrutiny to guarantee or to facilitate the access of cohort participants to the expected healthcare benefits. In this respect, an *inconsistent*

*imbalance* can be appreciated between the efforts to reduce exclusivity upstream and downstream.

This imbalance is all the more inconsistent as far as probably they are in large part the very same groups that are at risk of exclusion both upstream and downstream. I could not find a clear statement about which populations are exactly meant by the very recurring saying in the discourse of All of Us "the historically underrepresented populations". Which populations this saying is referred to, is not specified in the *Operational Protocol*, nor in the *Working Group Report*, nor in the Executive Summary of the PMI workshop on *Participants engagement and health equity*. However, that kind of discourse is often framed by references to racial and ethnical minorities. Moreover, as seen, the strategies implemented to facilitate inclusive engagement often deal with material dedicated to undereducated people, to non-English speakers, and to specific ethnical communities. Remarkably, some of those categories to which the upstream efforts are dedicated, are especially likely to be affected by poverty, which is the main obstacle to access to precision medicine downstream benefits. Data evidence a correlation gradient between educational level and income (statista.com), and the majority of the uninsured Americans are from racial minorities (www.kff.org). These data suggest that, often, the very same categories in the need for facilitations to participate upstream, also need facilitations to benefit downstream. But while lot of discourse focuses on the inclusion upstream, as well as strategies concretely implemented or planned, no discourse and no strategy address inclusion downstream.

This imbalance could result in a scenario in which diverse representation makes medical research robust and widely *applicable*, but not widely *applied*. Some people risk being prevented to benefit from the resources they fundamentally contributed to develop by sharing their time and especially their data, in a sort of renewed 'Marxian alienation' (Kelty, Panofsky et al. 2015).

However, this likely unequal distribution of precision medicine benefits actually concerns *one kind* of precision medicine benefits: tailored biomedical treatments. As discussed in the

section dedicated to the scope of precision medicine, especially as far as broader interpretations are concerned, tailored biomedical treatments are not necessarily *the only* precision medicine benefits. In particular, some of the interviews respondents, as well as the very discourse of All of Us and of precision medicine in general, remarked that the expected benefits from the PMI are not only biomedical therapies, but first of all *information* to empower participants. Information, unlike medical treatments, is provided *for free* to participants. There is no risk of unequal distribution of information as related to socio-economic condition. But what are the benefits related to receiving information, and how are they accessible?

The reliability, the significance and the actionability of genetic information is often criticized in the light of the countless variables in the game (Buchanan et al. 2006, Millikan 2006, Prainsack et al. 2008, Rose 2013, Remuzzi 2014, Tutton 2014, Prainsack 2017). Anyway, if this information is anyhow valuable or empowering, also in this case it is possible to appreciate some constraints related to the socio-economic status that possibly prevent benefitting from that. The empowerment deriving from the health information delivered to the individuals who participate in precision medicine research is related to the informed decisions the participant is enabled to take, mainly in terms of healthcare therapies, preventive screenings, and lifestyle choices. However, if this information could empower participants to *make informed choices*, information is not enough to empower them to *implement those choices*.

The choices about undertaking healthcare interventions or preventive screening, are, like in the case of the biomedical benefits, constrained by the costs of medical care. The choices related to lifestyle changes are not less problematic. Leaving aside that the effectiveness of information for changing behavioral choices is very controversial (Marteau and Lerman 2001, Holland et al. 2016), the issue is all the more complicated as some structural factors can in some cases prevent any behavioral 'choice' at all. As emphasized by one of my interviewees who works with underserved communities, lifestyle is not always entirely a

matter of ‘choice’: many structural factors also play a role in terms of unaffordability, lack of time, of energy, or lack of safe environments to comply with ‘healthy lifestyles’ (US23). This perspective is actually confirmed by a huge amount of literature, in many cases related to the literature on the social determinants of health: studies on the so called ‘social determinants of behavior’ (Chin et al. 2000, Prättälä and Puska 2012), and on the costs of healthy lifestyle (Jones et al. 2014) evidence that behaving healthy is not only a matter of education or even of tailored information.

In many cases underserved people, even if well informed about the behavioral changes needed for sake of their own health, and even if totally keen to undertake those changes, will have no means to do so, and do receive no practical benefits from being informed. At least for those social groups, real empowerment would require, further to individual information, also structural reformations or some forms of social support (Egger and Swinburn1997, Chiapperino and Testa 2016, Prainsack 2017). It is then likely that the same people excluded from the therapeutic benefits of precision medicine because of economic reasons, cannot benefit from empowerment for the very same reasons.

People like the patients of De André’s doctor in the quotation at the beginning of the thesis, “sick of hungry, unable to pay”, seem to be inescapably excluded from the benefits of precision medicine: as ‘unable to pay’, they cannot cure their sickness by accessing to the healthcare deliveries; nor information would stop them being hungry.

The concerns expressed by Epstein (2007) seem to become reality in the implementation of the PMI: embracing the ‘inclusion-and-difference paradigm’ is just “one link in the chain”, which, in itself, does not foster health equity if not corresponded by a “serious commitment to addressing the power differentials and access to social resources and rewards that actually give many of those “differences” their social meaning” (ibidem, 301).

### 4.2.2 Obstacles removed. Then what? Looking for a motivation

The exclusion of some social groups from the downstream advantages deriving from precision medicine is, first of all, a huge and very serious matter of fairness. The distribution of benefits is not equitable and excludes the socio-economically disadvantaged groups that, according to the literature on the social determinants of health, are already especially exposed to social factors detrimentally affecting health: existing health inequalities risk to be exacerbated by the unequal distribution of precision medicine benefits, to the detriment of health equity. However, even if extremely serious, fairness is not the only problem. In this section it is argued that downstream exclusivity can be also detrimental for upstream inclusivity, by frustrating the efforts for facilitating enrollment.

As seen, All of Us has put a lot of effort in removing or reducing all the objective and subjective barriers for participating in the research cohort. Admitted this intent can be fulfilled, and that all the barriers can be removed and are actually removed, other challenges remain. In particular, the only absence of obstacles is not in itself a motivation to participate. If *motivations not to participate* can be removed, *motivations to participate* are still wanting, and they are poorly addressed.

As seen, both the 100KGP and All of Us, when answering the question 'why should people join?', refer to motivations that address, on the one side, 'enterprising selves', and on the other side, in the same time, 'altruistic selves', as they are defined in the analysis by Tutton and Prainsack (2011). However, as discussed above, some social groups cannot afford to be 'enterprising'. A possibility is to incentivize them with *extrinsic motivations*, that is motivations connected to explicit rewards, like gifts or payment (All of Us Operational Protocol). Paying participants was actually proposed as a solution to motivate diverse participation (Plunkett et al. 2015), but such a strategy is not immune to serious ethical concerns: payment could transform participation in medical research into 'clinical labor' (Cooper and Waldby 2014), with the risk to make it coercive and to threat personal

autonomy. Anyway, this proposal has been discarded, and participants in All of Us are only offered 25 $ as a sort of fixed refunding towards travel costs to the site for the initial visit.

As for altruism, my very small sample of interviewees who were asked about motivations, was not focused at all on it, quite the opposite: as seen, two of them answered that they are not going to participate because they are already healthy and informed, then they do not need precision medicine for themselves, without even considering the discourse that their participation could help other people who do need precision medicine. On the other hand, very interestingly, another interviewee, as a motivation for not participating, provided the reason that the PMI is *not altruistic*. The problem with altruism is that, even if in theory it could motivate to participate, in practice, the fact that the most vulnerable populations are probably anyway out of reach, represents a limit.

A motivation for participating in medical research connected (even if not overlapping) with altruism, which has been majorly analyzed by Barbara Prainsack together with Alena Buyx, and that it is worthy to consider, is *solidarity* (Prainsack and Buyx 2011, 2012, 2017). Solidarity can in some ways be aligned with altruism, but it is distinguished by the requirement that it is directed to others with whom a relevant similarity is recognized. In Prainsack and Buyx's definition: "Solidarity is an enacted commitment to carry 'costs' (financial, social, emotional or otherwise) to assist others with whom a person or persons recognise similarity in a relevant respect" (Prainsack and Buyx 2017, 52). In their analyses, Prainsack and Buyx consider the relevance of solidarity for participating in medical research: it is argued solidarity is one of the most powerful and functional motivators, also specifically in the context of precision or personalized medicine (Prainsack 2017, and 2018).

It is actually to this kind of motivation that All of Us appeals, rather than pure-altruism, by stressing the benefits participants can bring to their own community, that is, to people with whom they recognize a relevant similarity: "By enrolling in the *All of Us* Research Program and sharing information, you can help ensure that *your community* is included in

the studies that lead to improved health for future generations." (allofus.nih.gov, emphasis added).

According to this ideology, the 'upstream exclusion' problem itself could be the motivation for vulnerable minorities to participate: by participating they would guarantee proper representation to their communities, and would contribute to the larger scientific significance and applicability of the research. Some scholars, on the basis of this reasoning, argued for a "duty to participate" in medical research (Petersen and Lupton 1996, Chadwick and Berg 2001, Schaefer et al. 2009, Rhodes 2005, 2008 and 2017), which would be all the more imperative for the groups mostly affected by social injustices and health disparities. As expressed by Rosamond Rhodes in her article "In defense of the duty to participate in medical research":

> "existing injustices can only be exacerbated by members of those groups refusing to participate in research. If your group is not studied, it is less likely that advances to benefit people with your disease or with your genetic susceptibilities will be developed. And if your group does not participate in studies that assess health disparities, no one will know that health disparities of the sort that negatively affect you exist, and corrective measures will not be taken"
> (Rhodes 2008, 38; see also the analysis by Juengst et al. 2016).

In line with this reasoning, and opposite to the argument I propose in this subsection by claiming that, in addition to removing the reasons not to participate, reasons to participate need to be provided, Schaefer and colleagues (2009) argue that, as participation in medical research produces "a public good", the absence of reasons not to participate, should be considered in itself a reason to participate:

> "The current social norm is that individuals participate only if they have a good reason to do so. The public goods argument implies that individuals should participate unless they have a good reason not to" (ibidem, 67).

My reply to Schaefer and colleagues' statement on the duty to participate in medical research on the basis of the 'public good argument', as well as to the other scholars embracing similar positions, is that, by leaving aside the issues related to autonomy and voluntariness, 'the public good argument' on which this position relies, is invalid. As discussed above, the good produced by medical research, is not always public. In these conditions, as argued by Dickenson (2013), the premise itself of solidarity collapses, and medicine is inescapably individualistic and entrepreneurial.

As noticed, among others, by Rhodes, inclusive participation in medical research is especially valuable in order to guarantee the applicability of the research findings to the whole population. However, as discussed in this section, larger *applicability* does not mean larger *application*: the theoretical possibility to extend benefits to the most vulnerable populations, without any possible actual practical benefit, makes any sort of altruism totally pointless. As a consequence, an exclusive model prevents a solidaristic arrangement. The very same people lacking an 'enterprising' motivation, who do not benefit from precision medicine due to their socio-economic status, have little reason to participate for solidaristic reasons as well: *their communities*, the people with whom they recognize relevant similarities, are likely not to benefit as well, if they are in similar socio-economic conditions. in order to be applicable in medical research and in particular in precision medicine research, solidarity requires inclusive access to the benefits: universal access to healthcare is envisioned as the most appropriate solidaristic arrangement to underpin solidarity-based precision medicine programs (Prainsack 2017 and Prainsack and Buyx 2017).

If no downstream benefit is expected for low socio-economic groups, even if all the obstacles are removed, they still lack a motivation to participate, as neither 'enterprise' nor

solidarity are applicable to them, and the 'public good argument' is not applicable unless the good is actually public. In the end, it seems that *the main and most challenging problem for 'upstream exclusivity', is probably 'downstream exclusivity'*.

People like the patients of De André's doctor in the song are totally excluded from any possibly deriving benefit, then would have no reason to participate, and it is reasonable to think that they would probably exclude themselves upstream. Remarkably, their exclusion upstream would not worsen their conditions, as they would be excluded from the downstream benefits in any case: they had no advantage from participating, thence they do not lose anything by not participating. On the opposite, people who can afford access to the benefits downstream lose something if the poor do not participate upstream, and do not share their data for the research. As noticed by Foucault in his essay *The Birth of the Clinic* (1963):

> "in accordance with a structure of reciprocity, there emerges for the rich man the utility of offering help to the hospitalized poor: by paying for them to be treated, he is, by the same token, making possible a greater knowledge of the illnesses with which he himself may be affected; what is benevolence towards the poor is transformed into knowledge that is applicable to the rich." (ibidem, 84).

For the moment anyway, results seem not to validate the concern of downstream exclusivity reflecting on upstream exclusivity. As anticipated, volunteer enrolment for All of Us opened in May 2018. On September 13, 2018, only four months after the enrolment opening, in the videos regularly posted on the websites in which Eric Dishman, director of All of Us, presents the updates, it was celebrated 100,000 volunteers joining the program. Importantly, Dishman in the video declares that 75% of them come from groups that are underrepresented in medical research (allofus.nih.gov/news-events-and-media/videos/dish-celebrating-100000-participants-and-new-program-features).

However, also in this case, it is not specified which are the groups they refer to when talking about underrepresented populations. The demographic data of the volunteers are not available (unless they are available on webpages only accessible from the US), then actually, the numbers provided by Dishman are not sufficient to validate nor to discredit the argument of *downstream exclusion being an unremoved upstream obstacle*. The fact remains that the motivations reiterated in terms of empowerment and altruism, are not applicable to certain groups: those who cannot afford access to tailored biomedical therapies, nor lifestyle choices.

### 4.2.3 Incomplete democracy

In addition to the challenges related to the *inclusiveness* of participation, as discussed above, my analyses also underlined some challenges for the *effectiveness* of participation (Galasso and Testa 2017a). By referring to the seven dimensions theorized by Kelty and Panofsky (Kelty and Panofsky 2014, Kelty, Panofsky et al. 2015), it emerged that some of the requirements distinctive of authentically democratic participation are not fulfilled. Among the seven dimensions considered (1. Education; 2. Goals and Tasks; 3. Resource control; 4. Exit; 5. Voice; 6. Visible metrics; 7. Communicative capacities), the most problematic are the third and the sixth.

#### Resource control: a matter of exploitation

As discussed above, there are serious concerns about resource control, especially in the US, due to the costs of the expected deliveries, which risk being inaccessible to some participants. This dimension, in the analysis by Kelty and Panofsky, is considered as especially important to distinguish proper participation from exploitation. In this light, opening and facilitating enrolment to people who are prevented to benefit from the resources they contribute to producing, can be read as even more ethically reprehensible than excluding them at all. To exclude some groups from the delivery of precision medicine

benefits is a matter of inequality. To make those people contributing with their data to the developments of those very resources before systematically excluding them from benefitting, is a matter of inequality *and* of exploitation. As seen, given the high healthcare costs and the general privatization of medicine, this is a problem both in the UK and in the US, probably as well as in any other healthcare system. As a matter of fact, downstream exclusivity due to costs was lamented as a problem both by the interviewees in the UK and in the US, as well as in some published analyses (Modi 2007). However, in the US, the problem of costs and of inaccessibility is even more pressing since healthcare is mainly private.

**Visible metrics: a matter of tokenism**

The other especially problematic dimension is "visible metrics". As seen, there is an important difference in terms of inclusivity between the practices for involvement at the 'coordination' level that are made available by the 100KGP and by the PMI. In the case of the UK project, practices are very exclusive, as they are open only to very specific categories and groups of people (clinicians and healthcare professionals, NHS Genomic Medicine Centres, GeCIP partners and industry partners for the 'Nominations Forms', and a limited number of research participants for the Participant Panel). On the opposite, some of the practices proposed by the US initiative are totally inclusive, by (theoretically) consenting to everyone in the world to participate, with no limits. However, the proponents of the 'Nomination Forms' for the 100KGP are informed about their proposals being accepted or not, and the 100KGP Participant Panel meets the boards in person, and this facilitate receiving immediate feedback. On the opposite, the participants in the PMI requests for proposals have no feedback about their contributions.

The dimension of measurable metrics, fulfilled by the 100KGP but not by the PMI, is especially relevant in the analysis by Kelty and Panofsky as it is connected to tokenism: representative participation with the only effect to give the impression that the public interest

is taken into account and followed, while concealing that only the interests of some specific stakeholders are actually followed (Arnstein 1969).

Under a certain perspective, it is possible to analyze the democratic models proposed by the 100KGP and by the PMI as examples of representative and direct democracies, respectively, with all the limits proper of the one and the other. However, it is important to remark that the PMI is also planning the institution of a Participant Panel similar to the one of the 100KGP, by also integrating a representative democracy organ in its implementation. This Participant Panel is expected to have all the very same limits and advantages proper of the 100KGP Participant Panel, and of representative democracy in general: restricted but (measurably) effective participation.

### 4.3 The interdependence of scope and outreach

In the first section of this chapter, I discussed the limits and the potentials of the *scope* of precision medicine. In the second section, I discussed the limits and the potentials of the *outreach* of precision medicine. In this third section, I will discuss how the scope and the outreach of precision medicine are intertwined, and how their limits and their potentials are reciprocally related.

#### 4.3.1 The impasse: downstream exclusion

Concerning the scope, by looking at different projects and understandings of precision medicine, I argued that there are at least three versions, encompassing different scopes: one-sided precision medicine, analyzing the connections between genes (or more in general, biology) and health and disease outcomes; two-sided precision medicine, analyzing the connections between biology, lifestyle and health and disease outcomes; three-sided precision medicine, analyzing the connections between biology, lifestyle, environment and health and disease outcomes. The three of them, in order to uncover significant correlations, need to ground on the analyses of a large and diverse sample. One-sided precision medicine needs a genetically, or biologically diverse sample. Two-sided precision medicine, to this, needs to add the analysis of different kinds of lifestyles. Three-sided precision medicine, in addition, needs a sample exposed to a variety of environmental factors.

Concerning the outreach, which is directly related to the sample the different scopes could build on, I argued that, given the exclusivity of the costs downstream, people of low socio-economic status risk electing not to participate at all, as there would be no benefit neither for themselves nor for their communities. The exclusion of the low socio-economic groups from the research cohort is a matter of fairness in itself, but it also has an impact on the diversity of sample the scope could be developed on, and this impacts on the three of the considered precision medicine versions.

As for one-sided precision medicine, the effect might not be immediately evident. Even if in the groups that excluded because of socio-economic reasons there was a prevalence of some racial or ethnical groups, it could not be straightforwardly argued that their exclusion would affect the underrepresentation of some genetic or biological traits proper of those groups. Although many expectations about pharmacogenomics and precision medicine are related to mining health relevant racial differences (Kalow 2001, Satel 2002, Tate and Goldstein 2004, Cohn et al. 2016), the genetic and the biological distinctiveness of human races is very controversial, such as the very concept of human races, and several studies evidenced more genetic and biological differences within than across so called races (Lewontin 1972, Barbujani 2006, Mersha and Abebe 2015). By appreciating the complexity of the issue as emphasized by these studies, I am not going to deal here with the issue whether the exclusion of low socio-economic groups impacts on the scope of one-sided precision medicine by subtracting any distinctive genetic traits. However, I consider the argument that their exclusion could subtract some *epigenetic* traits.

Epigenetics has emerged in the last decades as a sort of meeting point between the biological and the social: some environmental exposures are evidenced to have an impact on genes expression, and socio-environmental factors are thus somehow translated into a *biological* component of heath and disease (Loi et al. 2013, Pickersgill et al. 2013, Meloni and Testa 2014, Meloni 2015). The underrepresentation of low socio-economic groups could affect the capacities of one-sided precision medicine in terms of the epigenetic components of health and disease: this would be all the more detrimental for the research if there was any association between the socio-economic status and epigenetic differences, as suggested in the study by McGuinness and colleagues, who reported different levels of global methylation as correlating to the socio-economic and health gradient of their cohort (McGuinness et al. 2012).

In addition to this (possible) epigenetic loss, two-sided precision medicine would have limited capacities by missing the habits related to disadvantaged socio-economic conditions

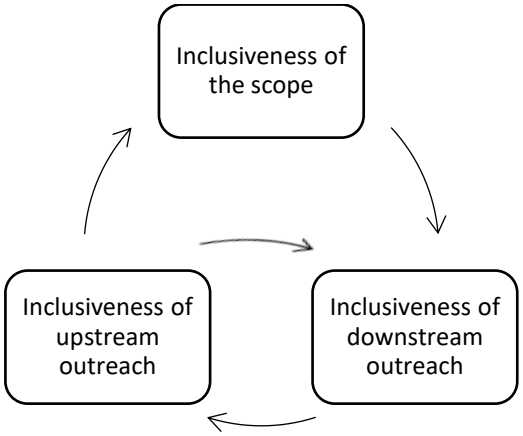
in the analysis of the connections between lifestyle and health. Three-sided precision medicine would additionally miss all the social and environmental exposures related to conditions of poverty and deprivation, by losing analytic capacities with respect to the social determinants of health: this would compromise the completeness of the analyses, and especially the 'societal potential'.

Precision medicine, its scope, its upstream outreach, and its downstream outreach, could be represented as a diagram (Diagram 1) in which each component influences the others, and the capacities of precision medicine in terms of social and health equity are related to the intertwinement of all the elements.

It has been discussed that:

- *Upstream outreach impacts on downstream outreach*, as the very premise of precision medicine is that it is possible to deliver effective interventions downstream by taking into account individual differences upstream.
- Conversely, *downstream outreach impacts on upstream outreach*, as the exclusion of certain communities from benefitting would undermine for them any 'enterprising' or solidaristic motivation to join upstream.
- *Upstream outreach impacts on the scope*, as the scope builds on the data provided by the cohort, and a less diverse cohort produces less diverse data.
- *The scope impacts on downstream outreach*, as different scopes are expected to produce different outputs and to provide different kinds of benefits.

D**iagram 1**: schematic representation of the interdependences between the inclusiveness of the scope, of upstream outreach and of downstream outreach in precision medicine research




Given this sequence of interdependences, one only flaw in the inclusiveness of any of the involved elements could compromise the entire mechanism, to the detriment of social and health equity. It has been observed that the *scope*, in itself, especially in the three-sided precision medicine version embodied by 'the official version' of the PMI, is remarkably *inclusive*, by theoretically encompassing all the possible determinants of health. It has been observed that *upstream outreach*, in itself, especially in the framework of the facilitating strategies implemented by All of Us, is remarkably *inclusive* as well, as the participation of all social groups is facilitated. On the other hand, it has been observed that *downstream outreach*, due to the costs of biomedical therapies and of lifestyle changes, is very *exclusive*.

The exclusivity of downstream outreach is the flaw that makes collapsing all the equitable capacities of precision medicine, by frustrating the efforts for an inclusive scope and for an inclusive upstream outreach. The preclusion of downstream benefits for certain groups undermines the participation of those groups upstream, despite all the efforts to reduce all the obstacles. The upstream exclusion of these groups limits the scope and the applicability of the research, by in return limiting even in principle the outreach of the expected benefits.

### 4.3.2 The 'societal potential' to overcome the impasse and trigger a solidarity-based virtuous circle

In the previous subsection, I argued that the exclusivity of the benefits expected downstream creates an impasse for the actualization of all the equitable precision medicine efforts both in terms of outreach and of scope. According to my analysis, downstream exclusivity is the crucial point of collapse. As a consequence, the solution to the general impasse needs to be searched by addressing the downstream exclusivity of the expected benefits.

The most straightforward solution to the 'downstream exclusivity' problem would be universal access to precision medicine care. Moreover, since, as seen, it would be very difficult to draw a clear line between precision medicine care and general medical care, universal healthcare coverage would be required, as it is also advocated, among others, in the conclusions by Epstein (2007), by Prainsack (2017) and by Prainsack and Buyx (2017). However, as far as private healthcare systems are concerned, universal access would require a radical societal and political reconsideration and reorganization, which are definitely out of the reach of my research, and also out of the reach of any precision medicine initiative and of the NIH itself. Thence, even if this would probably be the most resolutive solution to this problem in terms of societal and health equity (Daniels 2017), I will not discuss it here.

Another possible solution could be to guarantee free medical access to all and only the research participants, in order to overcome the 'Marxian alienation' problem of people excluded from the benefits they contribute to producing. This would also provide a strong (extrinsic) motivation to participate, because free medical assistance for participants would be a very attractive reward, especially for the uninsured and the poor. Yet it would be extremely problematic from the point of view of ethics and of autonomy: offering medical care in return for participation would be even more coercive than offering payment for that, because it could come up to literally be 'a matter of life and death', and freedom of choice could be seriously questioned by such an offering (Hunt 2001).

Apparently, there is no way to eliminate 'downstream exclusivity' in a private healthcare system without either implementing a radical socio-political reorganization or creating serious ethical challenges.

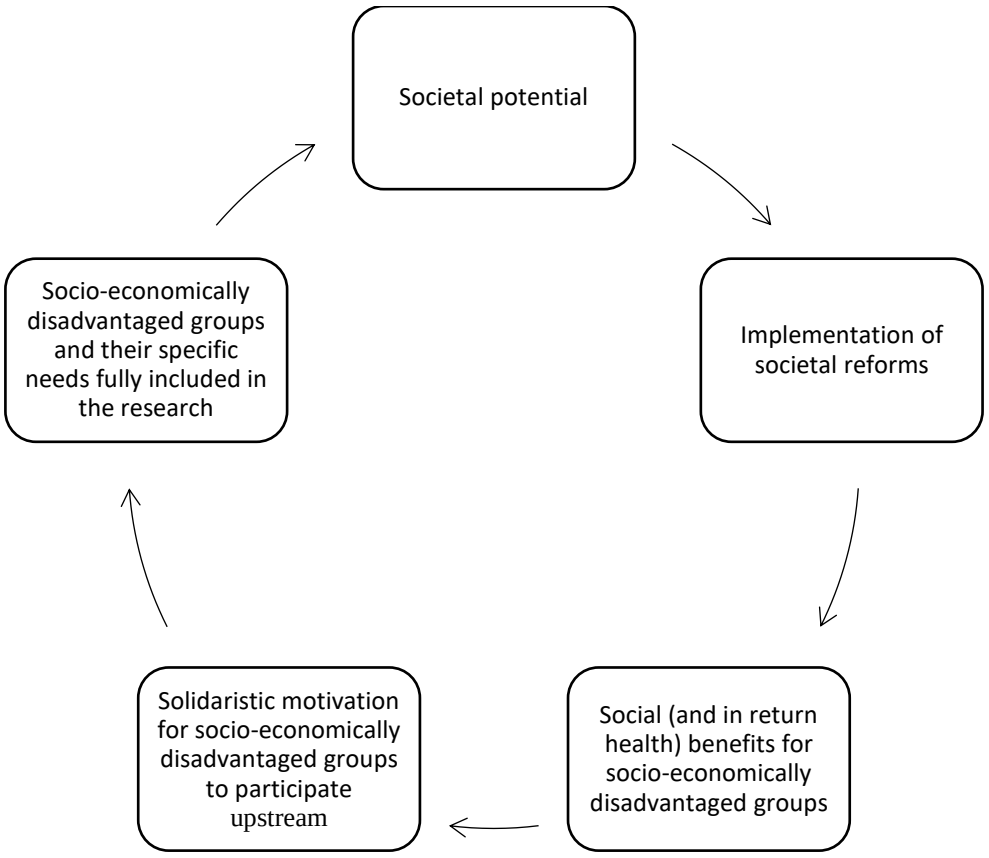
A possible way out is the intuition according to which healthcare benefits might not be the only benefits deriving from precision medicine. As a matter of fact, for example, as seen, empowering information is hyped as a major benefit deriving from participating in precision medicine research. However, as discussed above, also empowerment risks being for wealthy people only. Anyway, another potential output has been discussed earlier in this chapter, which could derive from one specific version of precision medicine to the benefit of all the social groups, and especially of those excluded from the healthcare and the empowerment benefits for socio-economic reasons. I am referring to the socio-political reforms possibly deriving from the actualization of what I called the 'societal potential' of three-sided precision medicine. In this perspective, even if some segments of the population are indeed likely to be excluded from the healthcare benefits deriving from precision medicine, they might still take advantages from it via the possible societal benefits produced.

In other words: as discussed at the beginning of this chapter, some versions of precision medicine, by including the social determinants of health in the research, have the '*potential*' to catalyze knowledge and attention to inform and incentivize socio-political reforms and interventions to reduce social inequalities. The result of the actualization of this 'societal potential' would be improved *social* conditions, and in return, in line with the studies on the social determinants of health, improved *health* conditions. This improvement would be especially to the advantage of the people who are excluded from the healthcare benefits due to socio-economic reasons, as the data on the social gradient in health evidence that the most socio-economically disadvantaged groups are the most affected by the social determinants of health. The societal and in return health benefits deriving from the actualization of the 'societal potential' could provide the most socio-economically disadvantaged groups with a motivation for participating in the research upstream. Given the long-term effectiveness of

public health and social reforming, solidaristic motivations are expected in this case to work better, as they would be more realistic than ‘enterprising’ motivations.

People “sick of hunger, unable to pay”, like in De André’s song, by participating, would inform the institution of their hunger, and of the detrimental health effects of their hunger. Maybe they will not be cured, but the information about them and their hunger could promote a societal plan for providing their community with some essential supports, which could prevent other people like them to become hungry and to become sick. This could actually be a motivation for participating on solidarity bases: he social benefits expected for their communities could provide the motivation to facilitate and incentivize socio-economically disadvantaged groups to participate upstream, to the advantage of a diverse research sample. A socio-economically diverse research sample would improve the robustness of the research scope, and in particular the ‘social potential’, which in return would increase the benefit and the solidaristic motivation to take part for socio-economically disadvantaged groups, and so on. The actualization of the ‘societal potential’ could overcome the impasse and trigger a ‘virtuous circle’ to the benefit of the most disadvantaged socio-economic groups, and of social and health equity, as represented below (Diagram 2).

**Diagram 2**: schematic representation of the actualization of the 'societal potential' in precision medicine as triggering a virtuous circle, alimented by solidarity, to the benefit of the socio-economically disadvantaged groups:



### 4.4 Challenges and open questions

This research examined the promises in the official releases, as well as the expectations and the concerns of insiders and stakeholders, as expressed in published documents or in face-to-face interviews, to analyze the epistemic and socio-political limits and potentials in the scope, as well as in the upstream and downstream outreach of precision medicine. After analyzing, on the basis of theoretical reasoning on the material examined, the interdependence between outreach and scope of precision medicine, the conclusion of my research envisions the actualization of what has been called the 'societal potential' of precision medicine as the key for the promotion of social and health equity. However, two levels of challenges undermine the scenario and the virtuous circle discussed above: those related to the presence of the conditions to *catalyze* the 'societal potential', and those related to the conditions to *actualize* it.

#### 4.4.1 Discourse VS implementation: the fleetingness of a 'societal potential' in precision medicine

As discussed in the first section of this chapter, the 'societal potential' occurs in the interpretations of precision medicine that fully encompass in their analyses the social determinants of health. An example of this version of precision medicine, as seen, is the PMI, as it proposes to consider all the determinants of health, including the socio-environmental determinants of health. However, as described in the chapter of the Results, two kinds of relevant concerns are connected to All of Us and to three-sided precision medicine in general. The first is that three-sided precision medicine does not exist but in the discourse. The second is that, if three-sided precision medicine exists, it is not three-sided precision medicine, and it is not precision medicine at all; rather, it is classical public health.

Regarding the first concern, in the US interviews my respondents often suggested a 'discrepancy' between discourse and implementation: they lamented a general overhyping

of precision medicine, and the discourse of including the social determinants of health would be part of that. It is questioned as one of the PMI unmet promises, which were sometimes interpreted in terms of *naivety*, sometimes in terms of *fraud*. Most of the interviewees who lamented overpromising were keen to explain it as a matter of naivety. In this respect, the distinction proposed by US013 between *intention* and *commitment* is helpful.

Many interviewees agreed that the *intention* to include the social determinants of health in the analyses was real. Some of them also acknowledged a corresponding *commitment*, and related the expected unfulfillment of the promise to the underestimation of the complexity of the project. Others, questioned the intention as not being corresponded by an appropriate commitment, as a matter of *akrasia* (in the sense of action not aligned with will). On the other hand, some interviewees also questioned the genuineness of the intention, by considering overpromises to be fraudulent and aimed to gather consensus by deliberately taking advantage from the expectations to get support and funding, or even to "corrupt the public health community" (US17).

The same kind of reasoning is applied to other kinds of promises by the PMI, such as overrepresentation of the minorities, which is the context within which US13 originally proposed the distinction between intention and commitment. Also in this context, the three of the perspectives were proposed to justify the expected unfulfillment: intention and commitment but underestimation of structural obstacles, intention but not appropriate commitment in a sort of *akrasia*, fraudulent overpromising to get consent with no intention and no commitment.

Anyway, whatever the real intention and real commitment are in this respect, since the implementation of All of Us is in a very preliminary stage, there is currently no evidence whether the PMI is going to actually encompass the social determinants of health or not.

The second kind of concern about three-sided precision medicine as catalyzing a 'societal potential' is related to the claim that that version of precision medicine should not be considered as precision medicine at all. As seen, this kind of concern even questions the PMI

as not being a precision medicine initiative (UK02). This position acknowledges the possibility of medicine catalyzing a 'societal potential', but not of precision medicine. The medical approaches fostering public policies should be considered as pure public health approaches, with no need to 'rebranded' them as precision medicine or as precision public health (Chowkwanyun, Bayer and Galea 2018).

According to this perspective, three-sided precision medicine is nothing but rebranded public health. Then precision medicine has no 'societal potential'. It is public health, whatever it is called, that has a 'societal potential': it is the potential that public health has always been supposed to have, at least since the times of Virchow.

This perspective, generally questions the 'rebranding' of public health as precision medicine or as precision public health to be useless (Chowkwanyun et al. 2018), or even unhelpful (US15). However, as suggested at the beginning of this chapter when discussing the shift from personalized to precision medicine, it is possible to read this 'rebranding' through the lens of sociology of the expectations. In this framework, even if three-sided precision medicine is nothing but classical public health, this 'rebranding' is not necessarily to be read as useless or unhelpful. On the contrary, also in this case, the use of a different name could be performative (Pickersgilll 2018) for generating the idea of novelty, and revitalizing expectations and support (Hedgecoe 2004, Brown and Michael 2003, Brown 2003, and Borup at al. 2006).

Under this perspective, precision medicine would not in itself provide the potential for informed socio-political intervention. However, as a 'performative brand', it would catalyze renewed attention and support around the social role of public health. The very same consideration could be applied to precision public health: if, as claimed by Chowkwanyun and colleagues, precision public health is nothing but public health with the word 'precision' added, this addition is not necessarily useless. Also in this case, even if precision public health does not embody the *substantial* improvement envisioned by *The Lancet* editor

Richard Horton (2018), it could embody an idea of novelty that, by catalyzing this sort of expectations, can attract new attention on old public health problems.

### 4.4.2 Potential outputs VS actual deliveries: advice in the place of reforms and individual 'over-responsibilization'

Apart from considering whether the 'societal potential' in precision medicine exists other than in the discourse, and whether in this case it is still licit to talk about precision medicine, a further issue concerns the *actualization* of this hypothetical potential. Even if precision medicine could provide the knowledge and the understanding for informed socio-political interventions, a translational step would be required to actualize the potential by implementing those interventions.

At the beginning of the chapters, I discussed the three versions of precision medicine together with their respective potential outputs. Then a big part of the chapter focused on 'three-sided precision medicine', the expected output of which, in addition to tailored biomedical treatments and information to empower behavioral changes, is also information to foster social policies. However, this kind of output is never considered in the frame of the PMI, not even in the discourse.

As observed many times throughout the thesis, many promises are associated with precision medicine in general and with the PMI in particular. The PMI advances with the promises to include all the segments of the populations in the research, to provide a 360-degree understanding of health and illness by investigating all kinds of exposures, to involve participants as partners, to put the person at the center, and to empower participants. As seen, all these promises are sometimes questioned as over-promises. Sometimes they are questioned as a matter of fraud, sometimes of *akrasia*, sometimes of underestimation, according to the different weights that are acknowledged to intention and commitment. However, no promise at all is officially made about ameliorating the society by informing political interventions. No over-promises, no false promises, no unengaged promises, no

promises of any kind in that respect. Not even the *intention*, pretended or real, to lay the ground for setting the socio-environmental conditions needed for improving health expectancy, or for actualizing the supposed empowerment, is expressed. If anything in this respect emerged in the interviews, it was only under my direct input. Apart from that, nothing in this respect is ever mentioned in the PMI agenda, as if the need to intervene on the socio-environmental context is not conceived as a need at all.

Apparently, the knowledge achieved through the study, is assumed as sufficient in itself to empower citizens to shape their own destiny by controlling their own health, and scientists to prevent and cure diseases. The need of an *external* reassessment to facilitate good health outcomes and healthy lifestyle is not even mentioned, as if there is nothing that the individuals cannot reach by themselves in whatever conditions, as true 'self-made-individuals'. The information provided to them as they participate in All of Us, together with the healthcare solutions developed through the PMI, are all the elements individuals are supposed to need to have the power to be healthy.

A possible explanation for this rhetoric is related to the fact that, actually, information and healthcare strategies are the only deliveries that the PMI can produce in itself. As observed by several interviewees, socio-political interventions are beyond the jurisdiction of the PMI: consequently, no promises can be made in this respect. At most, the PMI could promise to provide the *knowledge* to implement these socio-political interventions: but using this knowledge to actually implement interventions is in the jurisdiction of political authorities. Making promises in this respect would mean making promises on behalf of someone else. The information provided to participants is a totally different issue, because the promises are made to participants, it is up to them to translate that information into lifestyle changes and to fulfill the promise. Promises about socio-political interventions, conversely, would involve a third party. It might be helpful to recall the 'magic triangle' described by Apweiler and graphically represented in the webpage of All of Us: the determinants of health composing the triangle are those related to biology, those related to

the range of actions of the individual, and those beyond the range of actions of the individual. The "contracting parties" of the promises of the PMI are: the PMI itself and the individual. As a consequence, promises can be reasonably related solely to what is in the range of actions of the PMI or of individuals. As a consequence, the PMI can promise to address the determinants of health related to biology, by underpinning tailored healthcare strategies to be at the disposal of the individual (who can afford them). The PMI can promise to address the determinants of health related to the range of actions of the individual, by providing, as a tool, tailored information for empowering healthy individual choices (when it is possible to choose). But the PMI cannot promise, even in theory, to address the determinants of health beyond the range of actions of the individual, and beyond the biomedical domain, as they would require the action of a party which is not engaged in the promise. As a consequence, those determinants of health are left out of the promise.

In this context, as everything beyond the reach of the individuals is completely left out of the PMI discourse, individuals are implicitly assumed to have the whole power. And in parallel, individuals are assumed to have the whole responsibility. By not considering the influence and the constraints of all the elements that are out of the reach of the individual, it is implicitly assumed that everything is within the reach of the individual. However, as evidenced by several studies on the social determinants of health, as well as on the social determinants of behavior, and as discussed throughout the thesis, there is much beyond the reach of the individual. It is a sort of logical inference based on false premises: by considering individuals as entirely determining their own behaviors and their own healthcare choices, and by considering behaviors and healthcare choices as entirely determining health conditions, the logical consequence is to consider individuals as entirely determining their own health conditions. However, it has been argued that both the premises are questionable. The data on the social determinants and constraints for behaviors show that there are other factors than individual education and commitment that prevent a so called 'healthy lifestyle'. The data on the social determinants of health show that other factors than lifestyle and

healthcare impact on health outcomes. By not acknowledging the relevance of the socio-environmental context for health conditions and for behavioral 'choices', rather than empowered, individuals are 'over-responsibilized' (Rabinow and Rose 2006, Rose 2007 and 2013, Novas and Rose 2000, Nuffield Council of Bioethics 2010, Tutton 2014, Prainsack 2017, Ferryman and Pitcan 2018). The emphasis on the individual responsibility on health, as it derives from this implementation of precision medicine, is especially relevant in connection with distributive justice, insofar as, some principles of distributive justice, like *luck egalitarianism*, do not consider the inequalities depending on the responsibility of the individual as unfair, and deny the moral duty to intervene on them.

According to the analyses by Rose (2007 and 2013), by Rabinow and Rose (2006), and by Novas and Rose (2000), the responsibilization deriving from precision medicine, and more in general from the harnessing of genetic risks, would constitute a new form of power, by renewing Foucault's idea of *biopower* (Foucault 1978). In other words, according to this perspective, the opportunities hyped around precision medicine, would translate into duties. To recall the promise by Obama (2015b), the possibility to 'remake our destiny' would be translated into the *duty* to remake our destiny, and to remake it according to very specific rules: within this framework, the very promising affirmation "we can remake it" (ibidem), would be automatically reinterpreted as a threating 'we *must* remake it'.

The responsibilization of individuals, however, is not necessarily entirely negative: it has been observed that, if individuals only rely on the State by being dismissed from responsibilities over their own health, as it could be the extreme consequence of the welfare state, this could bring undesirable economic and ethical consequences (Rose 2013). Even if actions beyond their range are also required, it is still crucial that individuals do their part as far as their range of actions is concerned. Moreover, socio-political reforms require time, and the effects are generally only perceived in the long-run, then it is positive that in the meantime individuals are informed and encouraged, even if not really empowered, to do everything in their power for good health. However, if the socio-environmental conditions

are not duly acknowledged and addressed, the risk is not only that existing social inequalities will be left unaddressed. In addition to this, by entirely focusing on the individual capacities to shape health, the risk is that the social-political counterpart is forgot and that all the responsibilities are ascribed to the individuals by relieving the State from any duty to guarantee for the health of the population.

The original 'distraction argument' by Bayer and Galea (2015) claims that the emphasis on the biomedical advancement to give improved health opportunities to the population can 'distract' from the need of a socio-political advancement for pursuing the very same goal. In alignment with this argument, the exclusive focus on individual empowerment suggests the risk of an analogous 'distraction' from the social conditions needed to implement that empowerment, and from the political duty to facilitate those conditions.

If, as it seems by looking at the design of the project, the PMI is going to gather more precise knowledge and understanding, among other things, on the social determinants of health, it then has the potential, in the same way as it proposes to inform individual choices, to also inform political reforms. However, if this potential is there, no declared commitment is there, or even intention to actualize it. Despite the name of the cohort program being 'All of Us', which by including the plural pronoun 'Us' explicitly rejects the 'epistemic narcissism' (Twenge and Campbell 2009) of the singular person, the PMI seems to confirm the idea of precision medicine as 'Me Medicine', entirely focused on individual enterprise in a framework of neoliberalism, and opposite to 'We Medicine', focused on the public good in a framework of communitarism (Dickenson 2013).

### 4.5 Conclusion: aligning the medical and the social in a co-producing dialogue

My argument about the positive impact of precision medicine on social and health equity is aligned with those analyses that envision solidarity (Dickenson 2013, Rose 2013, Prainsack 2017, Prainsack and Buyx 2017, Prainsack 2018) as the ideal grounding for sustainable and equitable medical research. However, solidarity can only work when medical research is oriented to the production of the public good. As seen, several communities, in particular the most socio-economically vulnerable, are excluded from the benefits of precision medicine, and this prevent any solidaristic practice around them. Moreover, in general, despite the rhetoric embedded in the name 'All of Us', precision medicine does not seem oriented to the production of the public good. Rather, by limiting the promise of benefits to individual empowerment, it underpins an individualistic mentality, in which the individuals are overloaded with responsibilities about their own health. As emphasized by Chiapperino and Testa (2016) and by Prainsack (2017), empowerment needs to be corresponded by *structural conditions* allowing the pursuit of the individual informed choices, otherwise it is only a way to neglect that other responsibilities exist beyond the range of actions of the individuals, and to leave individuals alone. This is the risk for the empowerment fostered by precision medicine. It is the product of a neoliberal ideology in which individuals are and must be self-sufficient, and as such are left alone with their responsibilities. And in returns it produces a neoliberal ideology in which individuals are and must be self-sufficient, and as such are left alone with their responsibilities (Jasanoff 2004).

As a way out from the co-production of precision medicine and individualistic neoliberalism, I proposed to emphasize an aspect of precision medicine that is possibly related to the production of the common good and to a communitarian ideology. I identified this factor in the 'societal potential' of certain versions of precision medicine. If the 'societal potential' of precision medicine is developed and actualized, a totally different kind of co-

production could be possibly triggered: the co-production of precision medicine and of solidaristic communitarism.

This thesis examined the approach of precision medicine, and in particular the American PMI, in a perspective of distributive justice, by specifically focusing on the kinds of benefits that can be possibly achieved, and on their possible distributions. The scope, the outreach and the intertwinement of scope and outreach of precision medicine research programs, have been analyzed as the critical factors from a point of view of social and health equity. I argued that the outreach is limited by an inconsistent imbalance between upstream and downstream practices of inclusion, and by a participatory model that, under certain perspectives, recalls cases of exploitation and tokenism, rather than democracy. I argued that a broader scope could amplify the range of benefits to be produced by precision medicine, some of them pertaining to the socio-political, rather than to the biomedical domain, and to the benefit of everyone, especially of those excluded by the current outreach. I argued that such a version of precision medicine, by fostering the public good, would promote a solidaristic arrangement to the benefit of the outreach, by triggering a virtuous circle. However, the implementation of socio-political interventions after precision medicine, has been remarked to be undermined by some challenges at the interplay between intention and commitment, both for granting the premises for this 'societal potential', and for its possible actualization. Despite the official discourses promising the premises for this potential, no promise at all is made about the potential itself, least of all about the actualization. Maybe it is out of the interest, or maybe it is out of the reach (or both).

As emphasized by some of the US interviewees, the translational step from the epistemic to the social domain is out of the reach for the PMI itself: it is a medical research program, while social reforms would require *political* action. As suggested in the context of the Italian workshop about the impact of precision medicine for the most pressing health and social needs, it all depends on the construction of a constant and engaged dialogue between the scientific community and the political administration. My hope is that my research - by

highlighting the limits and the potential of precision medicine for social and health equity, and by indicating the solution to harness both of them in the synergistic collaboration of politics and science – could contribute to promoting this inter-domain dialogue, and the alignment of biomedical innovations and socio-political reforms.

## 4.6 The future: where it all will go

In the preface of this thesis, under the heading "How it all began", I described the beginning of the PMI and of the renewed popularity of precision medicine, but in particular the beginning of my involvement and of my interest in this subject. Symmetrically, this section deals with speculations about the future of precision medicine, but mainly with the future plans for my research.

### 4.6.1 The future of precision medicine

Concerning the future of precision medicine, for making predictions, it would be first needed to understand at least the *present* of precision medicine. As seen, precision medicine is mainly understandable as a social construction, which is subjected to very different interpretations. As discussed, for many stakeholders, precision medicine is nothing but a 'label' for something that has been going on forever, and that probably will go on forever. In relation to this interpretation, for example, the question about the future of precision medicine should specify if it is about the future of the 'label', or the future of the approach currently labelled as precision medicine. The future of the label 'precision medicine' is totally uncertain. As many of my interviewees suggested, in alignment with sociology of expectations, it is well possible that at some point, when 'precision medicine' loses its 'taste of novelty', it will be substitute with another new name, just to trigger a new 'hype cycle'.

As for the future of the medical approach identified by that name, the question is: which one? As discussed, there are at least three versions. Actually, none of the three is really new: all of them are focused on dimensions that affected health and disease since ever. One-sided precision medicine is the evolution of medicine solely focused on biology. Two-sided precision medicine is the evolution of medicine focused on biology and lifestyle. Three-sided precision medicine is the evolution of medicine focused on biology, lifestyle, and environmental exposures. Altogether, the three versions of precision medicine, generally

speaking encompass the directions of any possible medical approach. Within this framework, precision medicine, at least one interpretation of it, will proceed in so far as medicine will proceed. The reasonable question is: which version will prevail?

By considering the analysis above on the current co-production between two-sided precision medicine and individualistic neoliberalism, as well as the current political inclinations in the Western world, it seems reasonable to conclude that it is two-sided precision medicine that has the highest probability to prevail. This was also the opinion of several interviewees when asked about the future of precision medicine in connection to the political rearrangements. Accordingly, the individualistic ideology of two-sided precision medicine could, in return, furtherly foster the neoliberal mentality, and so on. However, it is also possible that, in line with the idiom of co-production, the political order change by following the affirmation of another version of precision medicine. The affirmation of three-sided precision medicine could impact on the political ideology, and influence a political inversion towards communitarism. Maybe, my research, among others, could somehow contribute to this change of direction. Anyway, this is my aim.

### 4.6.2 The future of my research

My research, since the very beginning, had a very strong normative commitment. What my research highlighted, in a nutshell, is: given the limits of healthcare accessibility and of empowerment, the functional and equitable implementation of precision medicine depends on the engaged addressing of the *social* inequalities affecting health, and on precision medicine actually *potentially* offering the tools to address them. The critical point is that precision medicine could even provide the tools, but it is in the jurisdiction of the political authorities to use them, as the required interventions in terms of social inequalities are in the socio-political, rather than in the biomedical domain. What it is required then, is a dialogue between the scientific and the political authorities. It is mainly at that level that I hope my research could have an impact. I aim to disseminate my research and specially to reach

scientists from different fields, and possibly politicians, by pressing them with the urgency of constructing a collaborative dialogue. As a first step, I aim to build collaborations among scholars to raise awareness for this need of medical engagement of politicians, as well as of political engagement of medical scientists, to the advantage both of social justice and of medical advancement. I consider the workshop that I organized together with my colleagues as the very first step in this direction, and I think it was quite successful in building a first synergistic collaboration within a multidisciplinary group, which I hope could go ahead and expand.

### 4.6.3 My future: next research questions

In this thesis, I left aside any attempt to solve the impasse in the distributions of benefits of precision medicine but with the 'societal potential'. However, the implementation of the 'societal potential' is one possible solution, but it is not the only one. It is the only solution that allows to directly address social inequalities, and as such it is important to pursuit it anyway. However, concerning the distribution of precision medicine healthcare benefits, there are some possible strategies to consider before just renouncing to them, but they are beyond the scope of my thesis. However, in my future researches, I plan to address part of them.

In particular, I plan to consider the role of democratization of science and of participants engagement and involvement for the fair distribution of healthcare benefits (Geiger and Gross 2018). In this thesis, among other things, I analyzed the practices for patients and citizens involvement made available by the precision medicine projects, by considering the democratization of medicine as a possible route to equity. However, I concluded that the available democratic models are incomplete, and I did not go further by reasoning whether, if these models were complete, they could contribute to foster the equitable distribution of healthcare benefits. This is the research question that I want to address in my next future.

In my next future, in addition to continuing reasoning on the arguments developed in this thesis, I also plan to consider different models of patients and citizens engagements in medical research, by observing the outcoming distributions of healthcare benefits in relation to principles of justice and equity. In particular, by building on the analyses I performed on the practices of All of Us and of the 100KGP, I plan to compare: ‘direct democracy’ and ‘representative democracy’ participatory models, online and offline practices, spontaneous movements and institutionalized engagement. I aim to uncover which of these models, if any, is the most effective for promoting equitable access to healthcare in alignment with egalitarian principles.

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