Personalizing Medicine: Disease Prevention *in silico* and *in socio*

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ABSTRACT

Proponents of the emerging field of P4 medicine (defined as personalized, predictive, preventive and participatory) argue that computational integration and analysis of patient-specific "big data" will revolutionize our health care systems, in particular primary care-based disease prevention. While many ambitions remain visionary, steps to personalize medicine are already taken via personalized genomics, mobile health technologies and pilot projects. An important aim of P4 medicine is to enable disease prevention among *healthy persons* through detection of risk factors. In this paper, we examine the current status of P4 medicine in light of historical and current challenges to predictive and preventive medicine, including overdiagnosis and overtreatment. Moreover, we ask whether it is likely that *in silico* integration of patient-specific data will be able to better deal such challenges and to turn risk predictions into disease-preventive actions in a wider social context. Given the lack of evidence that P4 medicine can tip the balance between benefits and harms in preventive medicine, we raise concerns about the current promotion of P4 medicine as a solution to the current challenges in public health.

keywords: personalized medicine; systems medicine; primary care; systems biology; p4 medicine; medicalization; big data; disease prevention; overdiagnosis.

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1. Introduction

An important goal of *in silico* medicine is to improve biomedical research through computational integration of big data. This paper examines the challenges of implementing systems medicine (the medical application of systems biology) in primary health care. Specifically, we focus on the ramifications of strategies aiming to improve disease prediction and prevention through *personalization* of medicine, a concept promoted as P4 medicine that is *predictive*, *preventive, personalized* and *participatory* (Alyass et al., 2015; Benson, 2016; Duffy, 2015).

The goal of personalized medicine is as old as the profession, and can broadly be defined as the aim to account for those factors that make health and disease specific for each individual. What is new about P4 medicine is its emphasis on doing so "*in silico*" via data-integration, and "*in socio*" via *patient participation* in data collection and disease prevention. P4 medicine is based on the expectation that "big data" technologies can account for an increasing number of factors that influence health and disease, and that these data can be used to stratify the population and health problems according to various characteristics. Big data here refers to patient-specific data from various sources such as genomics, "phenomics" technologies that enable monitoring and self-monitoring of phenotypic biomarkers, health records, as well as "exposomics" that provide inputs on environmental exposure (Flores et al., 2013; Gjuvsland et al., 2013; Wild, 2012). The hope is that *in silico* computational integration of these data will generate a more complete understanding of each person´s health, better risk predicting algorithms and effective preventive strategies. *In socio*, its implementation in the context of each socially embedded person´s life requires a change in the current structure of health care towards increasing patient participation in data collection, self-management and prevention of future diseases. Through these strategies proponents expect that P4 medicine will increase the quality of care and lower the escalating costs of health systems (Bousquet et al., 2011; Flores et al., 2013; Kirschner et al., 2013; Diaz et al., 2013).

So far, important discussions about personalized medicine have considered ethical and legal issues such as informed consent, disclosure dilemmas, personal identity, data security, as well as the current discrepancy between marketing and the utility of genomic risk profiling (Bartol, 2013; Reydon et al., 2012, Rehman-Sutter & Müller, ed., 2009; Forgò et al., 2010; Juengst et

al., 2012). Our scope is wider in examining P4 medicine in general, and in discussing the overall clinical utility of the new preventive strategies for improving public health systems.

While P4 medicine also aims to target established disease with higher precision, we will focus on its primary strategy – to keep people healthy through individually targeted *predictive* and *preventive medicine*:

> Systems medicine aims at predicting the course of a disease in a given patient and how far it can be altered by available therapies. (...) The fundamental principle of systems medicine should thus be the prediction of benefit–risk for a single subject, a group, or a population" (Boissel et al., 2015, p. 138).

While P4 medicine aims to target the course of established disease with higher precision, P4 medicine also involves a stronger focus on healthy people through a more expansive and life-long detection of early disease and risk-factors using more data – literally "billions of data points" (Bousquet 2011, p. 7). In other words, P4 medicine constitutes a new form of continual *screening process*, which is unprecedented in intensity and scope (Vogt et al., 2016, Diamandis, 2015). For the balance of benefits vs. waste and harm to turn out positive, this radical expansion seems to presuppose very significant gains in the overall utility of preventive medicine. In this paper we examine challenges involved in achieving such a meaningful balance. Particularly, we critically examine an assumption that is often taken for granted, namely that large scale computational integration and analysis of "big" health data will lead to a preventive medicine with a more adequate utility (i.e. balance of benefits vs. harms and costs) (Flores et al., 2013; Kirschner et al., 2013; Topol, 2012).

The authors of this article bring together practice-oriented philosophy of science (SG) and philosophically oriented general practice (HV)[1] in an analysis of the clinical utility and societal implications of P4 medicine. In the context of the current paper, *clinical utility* is related to the concept of "actionability" used by proponents of P4 medicine (Hood et al., 2012). Utility and actionability presuppose not only that the early detection of disease and risk assessments have a high clinical validity (accuracy), predictive and prognostic power, but that they can be coupled to actions that show clinical efficacy and

[1] General practice (or family medicine) is the medical specialty that focuses on the whole patient, as opposed to subsystem-focused specialties. It is part of primary care, and often the point of access and "gate-keeper" to care. General practice is where most medical disease prevention takes place.

effectiveness as well as an adequate balance of benefits and harms in a wider clinical and societal context (Burke, 2014).

Thus, successful implementation of P4 medicine not only depends on its ability to accurately predict disease (detect very early signs of disease or risk factors), but also on its ability to translate these predictions into meaningful disease-preventive actions. The latter aspect requires that the strategies can work in clinical practice and people´s socially embedded lives. Historically, social aspects were at the center of personalized medicine as it was initially tied to a humanistic movement focusing not only on bodily fragments, but the uniqueness, experience and agency of the whole person over time (Cassell, 2010; Tutton, 2014). But whereas personalized medicine historically emphasized the person´s social context and the doctor-patient relationship, P4 medicine rearticulates the same goal via quantitative *in silico* models. This raises important questions about whether factors concerning social and human biocomplexity are sufficiently accounted for in strategies laid out to reach the ambitious goals of P4 medicine.

It may be objected to our analysis that these ambitious goals should not be taken seriously at this point. P4 medicine mostly exists as a set of promises about the future, and the published claims about the future of medicine may be seen merely as rhetorical strategies driving the competition for research funding. Admittedly, the above promises of P4 medicine are made with varying degrees of boldness, and current views on their soundness differ (Diamandis, 2015; Joyner & Paneth, 2015). However, they are published in scientific contexts, and accordingly may generate expectations and actions that influence choices concerning prioritization, funding and implementation of medical research and health strategies. Accordingly, we believe that researchers have a scientific responsibility to calibrate their promises to what can actually be expected of their methods and the consequences their claims may have (Forssén et al., 2011). We thus find it crucial to critically examine the promises, and the available evidence that may justify them. In the current paper we combine an analysis of P4 medicine´s science visions with historical insights into the challenges of disease prediction and prevention. Particularly, we highlight lessons from personalized genomic medicine and material summarizing the concrete results from a dedicated P4 medicine pilot project, the Seattle Institute for Systems Biology´s 'Hundred Person Wellness Project' (Hood et al., 2015a).

We begin by relating the promises of P4 medicine to the historical and current challenges in preventive medicine, particularly by examining the problems of producing findings of unknown significance, overdiagnosis, and overtreatment (Section 2). By examining the current status and future plans for P4 medicine, we then ask whether it is likely that *in silico* medicine will be able to better deal with such challenges by computational integration of patient-specific data. Section 3 examines the challenges faced for disease prediction, whereas Section 4 analyzes the challenges of turning risk predictions into disease-preventive actions in a wider social context. We point to the lack of evidence that P4 medicine can deal with the described challenges and raise concerns about the current promotion of P4 medicine.

2. Challenges of Waste and Harm: P4 Medicine in Light of the History of Preventive Medicine

2.1. A 'tipping point' in preventive medicine

As a form of individual-centric preventive medicine, P4 medicine establishes itself as the latest chapter in a longer story starting with the establishment of hypertension as a treatable risk factor for cardiovascular disease in the 1960s (Welch 2011, chapter 1; Getz 2006; Hamilton et al., 1964).

Individualized disease prevention has been associated with continued promises and high expectations (Yach and Calitz, 2014). It has certainly had its merits, but its success must be understood as relative to the problems it tries to solve, the expansiveness of its measures, costs and harms. Generally, preventive medicine has been most successful in cases where there is a relatively simple and strong relationship between risk factors and disease, e.g. patients with an established organ disease diagnosis or well people at very high risk (4S Study Group, 1994; Welch et al., 2011, chapter 1; Hamilton et al., 1964). However, preventive medicine has turned to more challenging problems, notably prediction and prevention of complex, non-infectious disease in a population of predominantly asymptomatic people at lower risk of disease. Compared to people at high risk, this demands more of the test´s capacity to predict disease and raise the probability high enough for action to be justified. In such cases, a higher number of patients must generally be treated in order to change one outcome ("number needed to treat"). In this

endeavor, preventive medicine has met with consecutive realizations that these problems are harder to tackle than expected.

Responding to these realizations preventive medicine has made its predictive and preventive efforts more expansive and complex, taking an increasing number of bodily factors and aspects of life into account. Critically, disease concepts have been widened by lowering diagnostic thresholds for what is regarded as "disease", "early disease" or "at risk" for each of these factors, thereby redefining an increasing number of people as in need of medical attention. An expanding number of risk factors in terms of biomarkers have been defined (Skolbekken, 1995; Getz, 2006, Petursson et al., 2009a, 2009b). As a corollary, clinical efforts have also expanded with more intervention strategies based on more measurements, including examinations of asymptomatic people to detect early disease or risk states (screening). As a result the scientific and clinical endeavor itself has been complexified, with more data to integrate and interpret, requiring more comprehensive and complex strategies.

P4 medicine may thus be seen as the culmination of a series of increasingly expansive efforts to improve predictive and preventive strategies to deal with the complexity of human biology and clinical practice. Today, we will argue, its advent coincides with a historical "*tipping point*" in the overall balance of benefits vs. harms and costs in preventive medicine (Starfield et al., 2008). On the whole, the strategies involved, such as implementation of preventive clinical guidelines, general health checks, screening and lifestyle counselling, seem not to work as effectively as expected in practice (Fretheim, 2007; Hetlevik, 1999; Krogsbøll et al., 2014; Jørgensen et al., 2012, Look Ahead Research Group, 2013). The reasons for this may be multi-layered. As one element, doctors may not follow guidelines (Ashenden et al., 1997; Hetlevik et al., 2008; Austad et al., 2015; Boyd et al., 2005). Another key problem is non-compliance of patients, particularly lack of response to risk assessments with sustained lifestyle changes (see Section 4). More fundamental, however, are concerns about negative effects of preventive strategies.

As a consequence, the last 20 years have seen an increasing concern in mainstream medicine about the overall utility, i.e. the balance of benefits and harms, of preventive medicine´s expanding efforts (Fisher & Welch, 1999; Sackett, 2002; Heath, 2013; BMJ; JAMA Internal Medicine). The waste and harm involved may be both *indirect* in terms of opportunity costs, where personnel and resources are diverted away from other issues, and *direct* in

terms of unnecessary side-effects and costs of diagnostics and treatments (Fisher & Welch, 1999; Welch et al., 2011; Heath, 2013; Moynihan et al., 2012; Hofmann, 2014). Although negative consequences are often not registered in trials (Heleno et al., 2013), and results are contradictory, diagnostic labelling and preventive measures have been associated with harm, e.g. distress and reduced quality of life (see e.g. Jørgensen et al., 2015; Haynes et al. 1978; Brodersen & Siersma, 2013). To understand the basis for the discussion of waste and harm, the following section will introduce key concepts denoting the important challenges of preventive medicine relevant for P4 medicine.

2.2. Key concepts in discussions on waste and harm

One way to conceptualize the expansion of preventive medicine described in Section 2.1. is as *medicalization* (Maturo, 2012). We will here define medicalization as the process by which aspects of life are defined in medical terms and underlain medical control (Vogt et al., 2016). Importantly, this definition does not imply that medicalizing an aspect of life is inherently negative. A main aim of medicine is *beneficent control*. However, any attempt to establish medical control comes with caveats of waste and harm (i.e. *overmedicalization*).

Perhaps the most banal problem involved in medical testing is what we can call *findings of unknown significance*. Any clinician, having for example used a biomarker to screen a patient, knows the feeling of getting test results back not knowing what to make of them, especially in light of uncertainties about the test's predictive power, the individual´s complex situation and the potential benefits and harms of further testing and treatment. Another, but related problem is *false positives*, i.e. tests that turn out positive when the person in fact *does not* have the disease (or risk factor). The opposite is the case for *false negative* results.

Overdiagnosis has been claimed to be "the biggest problem posed by modern medicine" (Welch et al., 2011, conclusion). It is defined as situations where an actual disease or risk factor is diagnosed in people who are mostly well, and where this condition will not actually come to influence future health, either because it disappears spontaneously without medical attention or remains asymptomatic until death from other causes. Overdiagnosis is hard to measure; it is not possible to know at the time of diagnosis exactly who will

suffer, but in theory those overdiagnosed can only be harmed (Brodersen et al., 2014, Hofmann, 2014). Overdiagnosis may also refer more generally to overmedicalization and processes leading to reclassification of asymptomatic or low risk individuals as in need of medical attention and subsequent overtreatment with a questionable balance of benefits and harms (Moynihan et al., 2012).

Whereas the optimism for improved health benefits of population screening was high in the 1990s and 2000s, recent meta-analyses show that intensified screening is strongly associated with higher rates of overdiagnosis and overtreatment (Moynihan et al., 2012). The difficulties of identifying the cases where risk factors or early signs of disease will pose future health problems is particularly telling if we consider screening programs for cancer. Despite strong associations between genetic risk factors and breast cancer, and despite 30 years of experience and development of advanced methods for early detection (mammography), the rate of overdiagnosis of breast cancer has turned out to be high (Løberg et al., 2015). It is estimated that 30%, or approximately 1,3 million women, diagnosed with breast cancer have been overdiagnosed because the tumors would not have developed into health problems (Jørgensen & Gøtzsche 2009; Bleyer & Welch, 2012). This raises important questions about the utility of population screening programs (Biller-Andorno & Diamandis 2015; Gøtzsche 2015; Biller-Andorno & Jüni, 2014; Gøtzsche & Jørgensen, 2013; see however Puliti et al., 2012 for a more positive view). Strikingly, the mortality rates not only for breast cancer but also for thyroid cancer, melanoma, kidney cancer, and prostate cancer have remained largely unchanged from 1975-2005, despite increasing rates of new diagnoses and treatment (Moynihan et al., 2012).

On a more general level, one key cause of waste and harm may be *fragmentation*. An editorial in the Annals of Family Medicine states:

> Underlying the current healthcare failings is a critical underappreciated problem: fragmentation – focusing and acting on the parts without adequately appreciating their relation to the evolving whole. This unbalance, this brokenness, is at the root of the more obvious healthcare crises of unsustainable cost increases, poor quality, and inequality. Fragmentation is at the heart of the ineffectiveness of our increasingly frantic efforts to nurture improvement" (Stange 2009, p. 100).

Human health problems have been categorized according to more minute bodily parts, and each factor is treated in separate "silos" of medicine (Parekh

& Barton, 2010). The sum of these parts, each with their diagnostics and treatments, adds up to "too much medicine", which may be wasteful, harmful and unmanageable in practice (Getz et al., 2005; Petursson, 2009b; Hetlevik et al., 2008).

One answer to the above challenges in preventive medicine is that science is simply not good enough in tackling the complexities and fragmentation involved, and that the solution lies in technoscientific breakthroughs. This is the position of P4 medicine (Vandamme et al., 2013). As proponents of P4 medicine also point out, current evidence-based prevention strategies are based on studies of large populations and therefore fail to capture patient-specific variation, thus potentially leading to poorer predictions and interventions, waste and harm (Topol, 2012).

However, what is at the same time often named as the foremost driver of increased medical costs and harm – notably also when it *does* have beneficial effects – is novel technology that enables more sensitive detection of disease and medical risk as well as attempts to improve prognosis (Bodenheimer, 2005; Callahan, 2008; Dybczak & Przywara, 2010; Moynihan et al., 2012; Hofmann, 2015). Yet, a solution based on more technology is precisely the promise of P4 medicine. This highlights the question whether P4 medicine can achieve a useful balance between benefits and harms.

3. The Utility of P4 Medicine: Disease Prediction in Clinical Practice

Based on the above discussion on the balance of waste and harm in screening and preventive medicine, we will now divide our further discussion of P4 medicine in three: In 3.1, we will discuss P4 medicine in light of lessons from *personalized genomics*, its immediate predecessor in preventive medicine. In Section 3.2, we will discuss early results from the first project that aims to pioneer *in silico* systems medicine. In 3.3, we look to the future and ask if we can expect more data and systems medicine to overcome tip the balance of utility in preventive medicine favorably. Our focus will mainly be on the diagnostic side and challenges of disease prediction, and less on the development of treatments for complex disease. However, we must underscore that this is an equally crucial step worthy of a publication of its own. If the prediction has no associated effective treatment, it is not actionable.

3.1. Genomic strategies and personalized genomics

The completion of the Human Genome Project was an important step in the development of biomedical, personalized medicine. Since the completion of the first human genome in 2003, the time and costs of sequencing of a human genome has decreased exponentially, enabling personalized genomics for large population groups. At the moment of writing, initial steps towards the development of personalized medicine are taken through the investment in large-scale projects such as the "Precision medicine initiative" (US) and the "100,000 genomes" (UK) project (Collins & Varmus, 2015; Marx, 2015). In addition to detailed whole genome sequencing, a prominent form of research underlying efforts in personalized genomics is genome-wide association studies (GWAS). The basic procedure of GWAS is to scan for genetic variants that are statistically significant when comparing two groups, typically a group with and without a specific disease. Risk alleles, or single nucleotide polymorphisms (SNPs), are said to be associated with a specific disease if its appearance among a group with a given disease is statistically significant compared to a group without the disease. GWAS have the dual aim of identifying new disease-related genetic variants for research purposes and to use the statistical estimates of disease risk for individualized disease prevention.

However, such GWAS-based efforts have already run into challenges of biocomplexity and prediction. To understand this we need a small historical detour. GWAS studies were originally designed to test the "common disease–common variant hypothesis", i.e., that common genetic variants could explain a large proportion of the variation in common diseases (McPherson & Tybjaerg-Hansen, 2016). Significantly, biologists warned from the beginning that:

> The common disease/common variant model is elegant, appealing and politically correct, but there are objections. The essential one is that it fundamentally misrepresents the nature of common disease. By definition, complex traits have (...) a low probability of carrying any particular susceptibility genotype given that the individual has a particular disease or trait phenotype. This is because, unlike Mendelian disorders, common diseases clearly result from the interaction of many genetic and environmental influences, so that the correlation with any one factor is weak" (Wright and Hastie 2001, p. 2).

The problem is here that each genetic biomarker has only a weak or modest association with a complex disease or *incomplete penetrance*.[2] In other words, a very large number of genes, each with small and context-dependent effects, are involved in determining disease and the exact causal relationship is complex and unknown (McPherson & Tybjaerg-Hansen, 2016). Researchers have major difficulties accounting for the heritability in terms of specific genetic variants even in cases where the heritability of a disease is high (Maher, 2008). This has created discussions about explanations for the "missing heritability". Some have suggested that the total heritability may be significantly inflated by gene-gene and gene-environment interactions, creating "phantom heritability" (Zuk et al., 2012). The importance of dynamic interactions means that the causal influence of any particular genetic risk factor is not stable and additive, but dependent on the biological and environmental context. This has discouraging implications of the predictive potential of gene tests (Wallace, 2012). While it was previously hoped that one could find variants that multiplied the risk 600%, the detection of variants rarely increase the probability of disease by more than 50% (Joyner &Paneth 2015; Kaiser 2012). This decreases the utility of such findings. While 50% may sound substantial, remember that when the probability of any given disease is initially low, which is often the case in well individuals, the test needs to raise the probability of disease substantially to add something useful to clinical judgement.

The aforementioned issues do not reject the potential for genomic strategies to play important roles as correlation-based research heuristics to identify candidate gene variants for further causal analysis. However, important concerns are raised in cases where SNP analyses are used as what Austin and colleagues (2013) call "shot-gun testing", i.e., simultaneous screening for multiple risk factors (e.g. in consumer genomics today). The (often unknown) causal complexity and incomplete penetrance between genetic variants and disease increases the challenges outlined in section Section 2, as we clarify below.

[2] Penetrance of a mutation is a statistical measure for the phenotypic impact of a genetic variant.

3.1.1. Personalized genomics: Variants of unknown significance

With new genomic strategies, the problem of findings of unknown significance has greatly increased in terms of so-called *variants of unknown significance (VUS)*. As one commentator working within genetics puts it, genome data today are "routinely failing to reveal useful insights about disease in general or a person's health in particular" (Cooper, 2015, p. 1423). In many cases, information about genetic associations is no more predictive of disease risk than factors such as family history, environmental risk, age, blood pressure etc. (Hall et al., 2010; Joyner &Paneth 2015). According to Cooper, "Such variants are trapped in the interpretive void between "benign" (i.e., definitively not relevant to disease) and "pathogenic" (i.e., definitively relevant to disease)" (Cooper 2015, p. 1423). What is deemed *significant* is also not only objective, but a culturally situated and value-laden act of interpretation: "Your VUS may be my diagnosis, depending on the manner in which we use the information and the weights that we place on the consequences of false positive and false negative conclusions" (Ibid., p. 1424).

3.1.2. Personalized genomics: False positives and false negatives

Uncertainties associated with genetic markers, the cumulative effects of these, and sampling procedures for GWA approaches also increase the problem of false positives and negatives (Ng et al., 2009; Tutton, 2014). On the basis of the expected high numbers of such results, critics of consumer genomics have stressed concerns about increased and unnecessary anxiety about future diseases and risk information, or a false sense of "genetic immunity" from these (e.g., Ransohoff & Khoury, 2010). Such concerns have not been sufficiently supported by empirical studies of self-reported reactions from early users of consumer genomics (Nordgren, 2014; O'Daniel et al., 2010). However, it can be questioned whether early users are representative of the general public, as admitted by the authors of one of these studies (MacGowan et al., 2010). This point is particularly important at the background of other studies documenting psychological distress associated with false positive results in the context of risk profiling for breast cancer (Brodersen & Siersma, 2013).

3.1.3. Personalized genomics: Overdiagnosis

The cancer researcher Gilbert Welch has stated that genetic testing should be considered the ultimate form of overdiagnosis, as virtually everyone will be diagnosed with risk factors (Welch et al., 2011). Many genotypes are weak predictors and, "Overdiagnosis and penetrance are inversely related. The less penetrant a gene is, the more overdiagnosis will occur, because most people with low-penetrance genes will not in fact go on to develop the disease" (Welch et al., 2011, chapter 9).

Generally, the benefits and harms of predictive and preventive interventions are not only influenced by the sensitivity of the testing procedures, i.e. their ability to detect disease, but also by factors associated with the absolute risk of a certain group. For instance, screening for different types of cancer is typically recommended only for particular age groups or for people with a higher expected risk due to their family history. Of particular relevance for further investigation is therefore whether personalized genomics can help identify the individuals for which further screening and monitoring is advisable. If so, personalized genomics could help health care providers tailor screening programs only to individuals that are most likely to benefit from these. Yet, we must in this context keep in mind the levels of uncertainty for shotgun tests for risk factors with low penetrance, compared to more traditional genetic tests for BRCA mutations and the concerns mentioned in Section 2 about overdiagnosis in screening programs.

3.2. Early evidence of P4 systems medicine in practice

With GWAS and personalized genomics, P4 medicine started out as a gene-centric project, focusing mostly on DNA. However, P4 medicine has increasingly seen the need to account for biological systems *as wholes*, whether in terms of whole pathways, whole cells, whole organs or even the whole human organism as *a system of systems* (Bjørnson et al., 2016; Flores et al.; 2013; Diaz et al., 2013). It is this development that is called *systems medicine*. So far, attempts to increase the predictive power of testing by using algorithms that combine several variables (e.g. smoking, cholesterol, blood pressure) have lead to misclassification and overclassification of risk status (Getz et al., 2005; Petursson et al., 2009b, 2012; Kolata 2010; van Staa et al., 2013). Although some significant progress has been made (Mega et al., 2015), the addition of

genetic information to such algorithms has generally also had limited success (McPherson & Tybjaerg-Hansen, 2016; Smith et al., 2015). This has strong relevance for P4 medicine, which acknowledges the weaknesses of previous tests, but promises to overcome the complexity involved by increasing the number of variables dramatically. As a tell-tale development, cardiovascular disease prevention, which started out 50 years ago with hypertension as a single biomarker, is now moving towards the use of high-throughput methodology and systems biology to improve prediction and prevention (McPherson & Tybjaerg-Hansen, 2016; Bjørnson et al., 2016). Thus, both the data and proposed algorithms involved in systems medicine are becoming even more complex. As preventive medicine stands at the tipping point described in Section 2, and the journal *JAMA Internal Medicine* (see reference list) as one example highlights "*less is more*", P4 medicine proposes to tip the balance of benefits and harm through *even more* medicine.

A project that may be seen as defining for the current status of P4 medicine is the Hundred Person Wellness Project (HPWP), performed in 2014 by the Institute for Systems Biology (ISB) in Seattle and prominently featured in *Nature* (Gibbs, 2014). This pilot study is important for our purposes, as it is the first real-world test of P4 medicine as conceptualized by the key visionary, biologist Leroy Hood.

The HPWP pioneers the most radical medicalization of human life in history. In total, 107 participants, mostly Caucasian, middle class and predominantly asymptomatic persons were included, each constituting a form of n-of-1 research project over 10 months. They were underlain a regime of fine-grained, multi-level and longitudinal monitoring aimed at the earliest possible detection of disease and risk factors, that is, a continual *screening process* of unprecedented scope. According to Hood et al. (2015a), patient-specific data were collected in "four main areas: 1) whole genome sequencing; 2) clinical and functional laboratory testing (every three months); 3) gut microbiome (every three months); and 4) quantified self and traits (physical activity, sleep, weight, blood pressure, personality and lifestyle factors, and so on)". These data were used as a basis for advice from health coaches (a novel primary care professional). In addition, a variety of proteomic and metabolomic markers were measured, creating individualized clouds of billions of data points for each individual to be computationally integrated and mined. The researchers aim to expand the HPWP to 100,000 participants in a "100 K Wellness project".

Little empirical evidence has been published about the clinical utility of P4 medicine or the HPWP. Recently, however, some early results from the HPWP and cases that are used as "proof of principle" narratives have been described. In our below discussion of these reports, the concept of actionability and "an actionable", which is frequently used by Hood and coworkers will be central. Hood & Price (2014, p. 22) have vaguely defined "an actionable possibility" as "a feature for an individual that, if corrected, could improve wellness or avoid disease".

3.2.1. Actionable gene variants: The case of vitamin D

Personalized genomics forms an integral basis of the HPWP and P4 medicine, and we will first examine this element in light of Sections 2 and 3.1. In their promotion, Hood and colleagues refer specifically to the concept of an "actionable gene variant", defined as a defective gene "that allows a physician to specify how a patient may improve his or her health" (Hood et al., 2012, p. 5). Furthermore, they claim that, "It is the continually increasing number of actionable gene variants that will be the major driver in having society accept whole genome sequences as an important part of each person's medical record" (Ibid, p. 5). Hood (2013, p. 9) claims that, "All individuals will benefit from sequencing their genome" due to the identification of such variants, and furthermore that "We have identified almost 300 highly penetrant variants that fall into the actionable gene variants category". Many of these "actionables" are supposedly linked to nutritional deficiencies (Hood & Price, 2014). In light of sections 2 and 3.1, this seems a high number, and we may ask: Why should these variants be regarded as "actionable"?

Hood and colleagues have in various publications exemplified what they mean by an "actionable gene variant" by describing the case of a man that is diagnosed with a gene that codes for a malfunctioning vitamin D transporter protein (Hood et al., 2012; Hood, 2013; Hood & Price, 2014). This variant is described as potentially leading to osteoporosis with early onset. The man is then described as being able to reverse this condition and prevent it from reoccurring by taking over time x20 the normal dose of vitamin D (or calcium according to Hood & Price, 2014).

Should this genetic variant actually be considered "actionable" in the sense Hood and colleagues define it above, and what does this mean for the status of the other 300 variants referred to? As Hood and colleagues do not refer to

clinical or other research on the 300 variants or the vitamin D case, which (as far as we can see) has not been described in a separate publication, this is unclear. However, from what is recounted the treatment in the case seems to be based solely on physiological reasoning about disease mechanisms. In general, this kind of reasoning has a problematic track record in medical decision-making (e.g., Echt et al., 1991). Additionally, Hood and colleagues do not mention eventual side effects of the x20 dose of calcium/vitamin-D. Taking vitamins (or calcium) may sound innocent, but side effects should always be taken into account. However, our main point here is that as an example of how "actionability" or "clinical utility" should be understood in P4 medicine, this case fails to give a clear and persuasive account.

3.2.2. Results and utility of the HPWP

Three publications and one plenary speech provide some preliminary results from the HPWP (Hood et al., 2015a; 2015b; Schmidt, 2014; Hood 2014):

- The project diagnosed "multiple 'actionable possibilities' for each participant" (Hood et al., 2015b).
- 57% were diagnosed with an actionable "cardiovascular pattern" (abnormal lipids, particle size or density), 53% with an "inflammation pattern" (elevated inflammatory markers) and 63% were diagnosed with an actionable "nutrient insufficient pattern" (defined as "decreased levels of key nutrients") (Hood, 2014). Regarding nutrition, the measurements had especially revealed vitamin D deficiency (Schmidt, 2014). Recommended actions against these "actionables" ranged from medication and supplements to dietary change, exercise, weight loss and stress management (Hood, 2014).
- 43 participants were diagnosed with *prediabetes*. 7 individuals were reported to have normalized and "many others had favorable improvements" in their prediabetes markers by the end of the study (Hood et al., 2015b).

Previous studies in Norway have shown that if one follows authoritative guidelines for disease prevention in a normal population, one would define a high proportion as "at risk" (Getz et al., 2005; Peturson, 2009). What is most striking about the above described results is that – at least as pioneered in the HPWP – the P4 medicine preventive strategy seems to define 100% of a

population of previously well as in need of medical attention. It is also striking that over half the population is diagnosed with a risk factor both with regard to CVD, nutritional status and inflammation. Of relevance, vitamin D deficiency and supplementation in asymptomatic people is a highly controversial issue in current debates on waste and harm, which is linked to poor clinical evidence as well as alternative medical practice (Welsh & Sattar, 2014). Also of relevance, prediabetes, an extension of the diabetes category with a lower diagnostic threshold, is a controversial case in ongoing debates on overdiagnosis as it may entail the downsides of being diagnosed with diabetes (costs and risk of treatment, challenges with insurance and employment, self-image) alongside questionable long-term benefit (Yudkin & Montori, 2012).

The above firstly raises important conceptual questions. Critically, it raises questions as to how the diagnostic thresholds have been defined. An "actionable" seems to be a rebranding of a finding that predicts disease, risk or at least something *suboptimal*. However, from the P4 medicine literature, there is conceptual unclarity as to what an "actionable gene variant" or "an actionable possibility" actually should correspond to in terms of utility and balance of benefits and harms. One may for example ask if detection of "actionables" points towards something more or different from what can be gathered from general, traditional health advice. Therefore, more conceptual work on what constitutes actionability and clinical utility in P4 medicine is needed.

Secondly, and most importantly, it raises questions about clinical utility. According to its lead scientists, many participants of the HPWP realized that with the information they could make decisions to improve their health and that "this can have enormous effects on reducing risk for downstream debilitating and expensive chronic and other diseases. This is central to reducing the cost of healthcare" (Hood et al., 2015b, p. 12). Without further documentation, Hood and colleagues insist that the benefits of their approach will "far outweigh any possible harms" (Hood et al., 2015a, p. 3). However, in light of our previous discussion on the history of preventive medicine, preventive genomics included and the enormous amounts of measurements and intensive management in previously well people in the HPWP, this is far from clear. The burden of proof should be regarded as heavy and entirely on the side of P4 medicine researchers.

Consider also *the law of diminishing returns*, which has been referred to since the beginning of discussions of waste and harm in mainstream medicine (Fisher & Welch, 1999). First described by economists this refers to the general trend that the first unit of input into a system (e.g. a unit of health care) will provide substantial benefit. However, for additional units (e.g. tests and treatments) the benefit decreases, and eventually, as each additional unit can offer comparatively little to previous units, the benefits of "more medicine" are eventually outweighed by the harms and costs.

At the time of writing, it is uncertain how much "actionable findings" add to current estimates of disease risk (or suboptimal health) in the individual. It is also unclear to what extent they can be coupled to interventions that have documented efficacy and effectiveness and can be predicted to change the prognosis in a real-life setting. The extent to which the massive number of "actionables" actually should be regarded as findings of unknown significance or overdiagnosis is thus unclear, but both must be regarded as potentially substantial. Screening for *risk factors* and an extreme focus on early detection of and intervention towards disease in asymptomatic people, as well as widening definitions of what is "actionable", increases the probability of overdiagnosis (Diamandis, 2015; Moynihan et al., 2012). The researchers themselves do acknowledge that, "It is inevitable that screening thousands of data points will generate false positives, as well as false negatives" (Hood et al., 2015a, p. 2).

More empirical evidence is thus needed to make a qualified evaluation of the HPWP. However, despite available guidelines for the assessment of evidence for and against the public health impact of personalized genomics, pilot studies such as the HPWP do not follow such guidelines, nor do they involve controls in order to evaluate interventions (cf., Diamandis, 2015; Hood et al., 2015a; Khoury et al., 2012).[3] Instead, the HPWP has a form of "*n-of-1*" research strategy of each individual that aims "to develop a series of stories about how actionable opportunities have changed the wellness of the participants – or made them aware of how they can avoid disease in the future" (Hood et al., 2015b). Although we will not dismiss such data-rich "bio-narratives" as informative, this makes it difficult to critically evaluate the results, and P4 medicine risks justifying the massive medicalization with

[3]For a reexamination of the Wilson-Jungner criteria for screening in the context of genomics and personalized medicine, see (Andermann et al., 2008; Diamandis, 2015).

anecdotal evidence. Additionally, the endpoints used in the HPWP seem mostly to be surrogate markers (e.g. blood sugar). However, continual correction of such markers is no guarantee that one can change the hard endpoints that actually matter (morbidity and mortality). Unless documentation is provided of what was actually done and achieved in the HPWP, the high profile project cannot be regarded as a credible scientific endeavor. Given its high profile in the promotion and promises of P4 medicine this is disconcerting.

3.3. Is more "big data" the solution for predictive and preventive medicine?

Having recounted the story of predictive and preventive medicine so far, including the HPWP, we now turn to its envisioned future. As mentioned in Section 2, what is exciting about P4 systems medicine is its promise to overcome fragmentation and "to provide the tools to take into account the complexity of the human body and disease in the everyday medical practice" (Vandamme, 2013, p.1-2; see also Mayer-Schönberger & Cukier, 2013). Ironically, however, what initially happens in P4 medicine is the most massive *fragmentation* in medical history through the gathering of fragmented big data.

The hope is that one can deal with multi-causality and overcome low predictability of complex diseases by accounting for an increasing number of risk factors. At least when considering the early results of the HPWP, each fragmented abnormal measurement seems to be taken as "an actionable", and when *interactions* between elements are taken into account, this is promised only to yield even more actionables (Hood et al. 2015b, p. 13). Risk profiling based on self-monitoring or gene testing results in an explosion of data points and factors of uncertainty – a challenge that physicians are not prepared for (Haga et al., 2012; Stanek et al., 2012). As Jameson and Longo (2015, p. 4) ask, "How can physicians adapt to this daunting explosion of information and the associated clinical guidelines?" The concern is that the sum of the fragmented measurements in P4 medicine adds up to an unmanageable amount of isolated diagnoses, treatments and considerations, each with a risk of waste and harm. A central premise for P4 medicine to work in practice thus seems to be that the vast amount of fragmented measurements can be *integrated* into models and algorithms so that *more* measurements can be translated into *less* waste and harm by registering only what is actually significant.

Proponents of P4 medicine expect that complex models can not only overcome many of the problems with traditional models, resulting from priorities on what to measure (cf., Kolodkin & Westerhoff, 2011), but also help identify the relevant variables as measures of health states and *stratify* the patient groups in need of particular treatments or health-optimizing actions (Hood and Flores, 2013). However, it should be noted that it is not always the case that more data will lead to better predictive models, while it is always the case that it comes with the caveats described in Section 2. Whereas the initial expectation that access to omics data would uncover underlying disease mechanisms via more complex models were high, it is becoming increasingly clear that there are serious practical and principal limitations to the idea of bridging the gap between genotypes and phenotypes via more datapoints (Noble, 2012; Wolkenhauer & Green, 2013). As proponents of systems medicine themselves admit: ″There is an urgent need to bridge the gap between advances in high-throughput technologies and our ability to manage, integrate, analyze, and interpret omics data″ (Alyass et al., 2015). One challenge is that the amount of noise inherent in the data increases as big data are collected, and handling and integrating large amounts of data pose a number of substantial challenges (Benson, 2016). These challenges include uncertainties about and differences among experimental methods and sampling procedures for statistical correlation studies, making data curation a much more complex matter than often assumed (cf. Mayer-Schönberger & Cukier, 2013; Leonelli, 2014).

Moreover, the hope of predicting and preemptively controlling disease raises fundamental questions about the general predictability and controllability of extremely complex systems (Cilliers, 2013). Such discussions are beyond the scope of this paper, but we wish to point to some lessons of systems thinking, and in particular challenges posed by the complexity of human biology and health, which is adapted to a complex social environment.

George Engel, founder of the widely recognized biopsychosocial medical model, formulated the challenge facing "personalized medicine" as the challenge of being *scientific in the human domain* (Engel, 1997). "*The human domain*" is here to be understood as *human biology* in the widest sense, as a complex, dynamic system. Health and disease emerges from an interaction between the biological, psychological and the social levels. As a modern recognition of these insights, scientists are now pointing out that a gene-

centric focus "will stymie progress" (Wild 2010, p. 1). For this reason, proponents of P4 medicine want to extend measurements to include "phenomics" (Gjuvsland, 2013) and "exposomics", the latter of which seeks to represent "every exposure to which an individual is subjected from conception to death" including the socioeconomic and "psychosocial" (Wild, 2010). But what are the reasons to believe that this will solve the problems involved in disease prediction and prevention?

Serious challenges are met in cases where there are complex feedback relations between molecular and social factors and adaptation to extremely complex social interactions. An increasingly rich biological literature from fields such as psychoneuroimmunology, epigenetics, psychosocial genomics and epidemiology documents how social and personal (psychological) experience of each individual affects the cellular and molecular levels (Marmot, 2005; Shonkoff et al., 2009; Holt-Lunstad et al., 2010; Danese & McEwen 2010; Eisenberger & Cole, 2012). Consider, as a striking example, how it is documented how neural circuits – notably the vagal nerve – relay signals from the socially situated brain to modulate the function of immune cells (Pavlov & Tracey, 2015). Such results empirically substantiate how the conceptual divides between nature and nurture, and mind and body, are untenable (Kendler 2005; Beauregard, 2007; Novack et al., 2007; Noble, 2012).

Our aim is not to reject that progress can be made, but to point out that the promises of P4 modeling strategies depends on the extent to which human biology, including the aspects we call "mental" or "psychosocial", are predictable and controllable at all (Strand et al., 2004; Vogt et a. 2014). Already in his book, *The Mirage of Health* from 1959, biologist René Dubos forcefully argued that, "exact science cannot encompass all the human factors involved in health and in disease" (p. 219). P4 medicine (still) cannot parameterize and measure this totality. Mapping the human genome has not changed the view that: "The complexity of control, overlaid by the unique experience of each individual, means that we must continue to treat every human as unique and special, and not imagine that we can predict the course of a human life other than in broad terms' (Sulston & Ferry, 2002, quoted in Noble, 2010). So far at least, we have no reason to assume that one can "measure everything" to faithfully or meaningfully capture the factors that influence human health and disease, with unknown, but potentially very significant consequences for disease prediction and prevention.

We do not deny that *some* or perhaps *many* significant predictions with time can be made via the P4 approach. Particularly, the clinical utility of genome sequencing is a moving target that may greatly increase with the development of reference-genomes made from deep sequencing of large populations. Our main issue is again with the discrepancy between the promises made on the hand, and the lack of evidence and theoretical justification that P4 strategies can deal with the complexity on the other. This has profound implications for the prospects of P4 medicine to improve public health practices.

4. "Participatory": Challenges and Implications of P4 Medicine in socio

In Sections 2 and 3 we have outlined some scientific challenges to predicting and preventing disease in complex human organisms through "personalized" *in silico* strategies. In this section, we widen our critique and the meaning of "human biocomplexity" by examining challenges and implications related to its implementation in a social context. Advocates of P4 medicine acknowledge that, "This societal challenge of deploying P4 healthcare is more daunting than the scientific and technological challenges facing P4 medicine" (Flores et al., 2013, p. 5). However, they mainly point to conservative viewpoints and methodologies of the medical establishment, regulation issues and reimbursement policies favoring "disease care" over prevention (Topol, 2012, Flores et al., 2013). Our focus will be on a different, and arguably more fundamental, challenge associated with the presupposed reactions to risk information. The issue concerns the extent to which the norms and goals of P4 medicine and the reality of patients are aligned.

4.1. Will P4 risk information be "actionable" for the general public?

Would P4 medicine be effective and useful, even if it had valid predictions and efficient treatments? An affirmative answer presupposes that individuals react to risk information by taking action to improve health outcomes via lifestyle changes or preventive treatments. Proponents of P4 medicine seem to assume that risk information consists of value-free facts that are directly translatable into risk-reducing actions. Moreover, they assume that the goals inherent in P4 medicine are perfectly aligned with other goals in personal life and society (e.g. Hood et al., 2012; Hood and Price, 2014).

A view from social science reveals that response to risk information is a much more complex issue (Lupton, 2012; Prainsack, 2014). As noted in Section 2, evidence from the history of preventive medicine suggests that so-called "compliance" issues are still immense hurdles for preventive strategies. Proponents of P4 medicine respond to such concerns by arguing that P4 medicine will provide a whole new level of motivation compared to previous population-based healthcare. It is argued that individualized risk information will be perceived as more relevant, and that the immediate feedback provided by continual testing, primary care-based health coaching and social networking between participants will create "relationship-based accountability" (Hood et al., 2015a, p. 4; Hood et al., 2015a, p. 11). Yet, empirical studies show little or no effect of risk information from personal genetic risk profiling, in particular on health-related actions (Hall et al., 2010; Heshka et al., 2008; Marteau et al., 2010; Nordgreen, 2012; Roberts & Ostergren, 2013, Grant, 2013). Moreover, a recent randomized controlled trial, which provided participants with common, chronic health conditions with an extensive self-monitoring system and follow-up over 6 months, showed no short-term effects on health care utilization or costs (Bloss et al., 2016).

In some cases, concerning serious hereditary diseases, attempted risk-reducing behavior is documented in response to individual genetic risk profiling and thereby taken as a "proof of principle" of the benefits of P4 medicine. For instance, a study of responses among women with a high risk of breast cancer considers prophylactic surgeries, screening, and encouragement to further testing of close relatives ″a model for high-risk actionable genetic tests of proven clinical utility" that provide "clear benefits to participants″ (Francke et al., 2013, p. 1; see also O'Daniel et al., 2010). However, as we emphasized in Sections 2 and 3, it cannot be assumed without further evidence that the genetic tests identify the persons for which further screening is advisable, or that more screening of asymptomatic individuals will result in health benefits and reduced medical costs (Hall et al., 2010; Biller-Andorno & Diamandis 2015; Gøtzsche 2015; Biller-Andorno & Jüni, 2014; Gøtzsche & Jørgensen, 2013). Furthermore, an important driver of cost escalation in health care is the introduction of medical technology itself, previously estimated by health care economists to be as high as 40-50% of the annual cost increases (Callahan, 2008).

These points are particularly relevant for the evaluation of the HPWP project. Its leading scientists recently claimed that their early results are proof of principle that actions of their participants are changing this picture since "most of them established a new and very personalized baseline for their own health and 70% of them acted on the coaching recommendations provided" (Hood et al., 2015b). However, as it is also the case for early users of consumer genomics, it seems highly unlikely that the selection of a population of largely middle class "health enthusiasts", a number of whom reportedly felt that pioneering the P4 project was " the experience of a lifetime" (Hood et al.., 2015b), is representative of the general population or those at highest risk. From a public health perspective, Burke and Trinidad (2011, p. 1) stress that "P4 medicine cannot solve the root problem: the need for political and public health action to improve the life chances of disadvantaged people. In this context, a realistic assessment of the prospects for systems biology is sorely needed". A related concern is the potential harmful effects of risk information (e.g. stress and anxiety), particularly when the information most likely involves high rates of false positives and overdiagnoses (e.g. Diamandis, 2015). P4 proponents have dismissed such concerns as a myth with reference to studies of early users of consumer genomics and highlight that health coaching is accompanied by information of uncertainties about test results (Hood et al., 2015a). But, again, evidence of negative psychological effects of false positives in population screening programs (e.g., Brodersen & Siersma, 2013) cannot be dismissed with reference to studies of health or technology enthusiasts that are not representative of the general public. Moreover, the implementation of testing programs with a doubtful or unknown balance between benefits and harms cannot be justified with reference to informed choice (Johansson & Brodersen, 2015). That is, information about uncertainties does not remove the burden of evidence for the benefits of the tests from companies, scientists or health authorities.

The idea that choices about testing can be left to individual patients is particularly concerning given that the majority of the general public seems to overestimate the benefits of screening (Gigerenzer, 2009). The cultural perception of screening is difficult to change, even if patients are given concise information about the risk of overdiagnosis (Henriksen et al., 2015). The cultural belief that more medicine is better, and the widespread faith in early detection and screening is currently considered some of the main drivers of overdiagnosis (Moynihan et al., 2012, Heath 2013, Hofmann 2014).

Moreover, a key driver of overdiagnosis is technology itself. The technologies of P4 medicine aim to detect ever smaller "abnormalities", thereby widening the scope of medicine through a re-articulation of healthy people into "risk individuals". The researchers involved in the HPWP reported that "Many individuals who report that they feel reasonable 'well', may, in fact, have multiple abnormalities in biochemical markers reflecting organ and system dysfunction, nutritional status or other health risk" (Hood et al, 2015a, p. 2, see also Hood et al., 2015b).

Labelling everyone as *not well enough* raises the possibility that it will be hard to feel completely healthy for people who enter such management (Vogt et al., 2016). In the HPWP, all healthy individuals are at the same time reclassified as in need of medical attention *and* as actors with the possibility (and responsibility!) to "take action" to optimize their health. Thus, the *degree of medicalization* amounts to what can rightfully be called a social transformation (Flores et al., 2013). As envisioned, P4 medicine is a system that expects the active participation of the whole of society far beyond the current health system, a *health society* with social ties based on the common quest for health in networks of wellness-seeking individuals.

4.2. P4 values vs. people values

As we have argued throughout the paper, and as the HPWP illustrates, P4 medicine entails a number of factors that have been associated with an increasingly precarious balance of waste and harm in medicine. Among these are the use of new technology that allows more and more sensitive measurements of bodily factors, and the widened scope of medicine through an increasing focus in healthy people and health consumerism (Moynihan et al., 2012; Heath 2013, Hofmann 2014; Fisher & Welch, 1999; Callahan, 2008;Welch et al., 2011; Brodersen, 2014). Moreover, the aforementioned assumption that more screening is safer is currently encouraged through the promotion of P4 medicine that is also intertwined with commercial and academic interests (see below).

We have argued that P4 medicine is the, to date, most radical attempt to medicalize all aspects of human life (see also Vogt et al., 2016). P4 medicine is promoted as "holistic" in the sense that it goes beyond gene centrism and focuses on individual biomarkers at all levels, from molecules to personal characteristics, to social networks over time. Yet, to extent that it is holistic, it

represents a *techno-scientific* holism that widens and redefines health and wellness in quantitative terms in order to reimagine human bodies as control systems "which comply with medicine's fantasies of perfect management" (Tutton, 2014 p. 10, quoting Waldby 2000). Thus, the intensified focus on disease prevention through genetic testing, extensive (self-)monitoring and self-regulation promotes a certain view of health as largely knowable through and determined by biomarkers, but controllable through informed actions of the individual patient and precise treatments. It is in this context that proponents of P4 medicine want to extend the scope of measurements to also include the total "*exposome*" (Benson, 2016), *"sociometrics"* (Flores, 2013) and *social biomarkers* like social networks, religious commitmens, and general social behavior in the algorithms (Prainsack, 2014).[4] Whereas the inclusion of social aspects on one hand may be seen as an improvement in embracing human biocomplexity, and to humanize medicine, it raises concerns about the totality of "surveillance medicine" (Armstrong, 1995) and its capacity to turn the acknowledgement of "the human domain" into *even more* technoscientific control (Tutton, 2014;Vogt, 2016).

These aspects should be seen in connection to commercial and professional vested interests in P4 medicine. P4 research and funding opportunities are crucially dependent on patient participation to deliver the raw material for analysis, namely patient-specific data. Although the new preventive strategies are marketed as an open choice, emphasizing the ideals of patient autonomy and empowerment (Topol, 2012; Hood et al., 2015a), the intensified focus on disease risk in P4 medicine comes with encouragements that imply particular social norms about responsible citizenship. In this context it is pertinent to note how a large group of P4 medicine advocates find it necessary to stray very near coercion and placing imperatives on people's lives in order to reach their own goals: "patients must understand that it is their societal responsibility to make their anonymized data available to appropriate scientists and physicians so that the latter can create the predictive medicine of the future that will transform the health of their children and grandchildren" (Bousquet et al., 2011, p. 3). Similarly, it is equally pertinent to ask whether patients would be held responsible if they refuse to react to information on risk factors (MacArthur et al., 2013 p. 918). In the context of preventive medicine, risk

[4] One example of the use of social biomarkers is a pilot study where patients with bipolar disorder were monitored via their cell phones (Doryab et al., 2015).

becomes a central organizing principle for responsible personhood and citizenship (see also Schwennesen et al., 2008). Yet, whether the right decision for the *individual* is to make life style changes, undergo preventive treatments etc. is also a matter of complex issues relating to personal and social values. Thus, whether risk information is "actionable", but also whether it *should be*, are important questions to address from the outset.

At the same time as P4 medicine is promoted as a participatory and "democratic" solution to the increasing costs of the medical system, it is also promised as a foundation for a "wellness industry" that will provide economic growth. Here, an expanded scope of medicine means expanded markets. Compared to the wide-ranging ambitions, proponents of P4 provide relatively few self-critical assessments and often promise a revolution in healthcare that is predicted not to happen now, but at a time-point that is conveniently beyond critical scrutiny, typically designated as "the near future" or "in 5, 10 or 20 years time" (Flores et al., 2013; Hood et al., 2015; Topol, 2012, Vandamme 2013). Lofty visions may be important to motivate scientific endeavors. However, pushing the envelope through rhetoric may also create unwarranted expectations and divert precious resources from other potentially productive activities. The shift of focus from culturally or structurally related causes of diseases (socio-economic factors, pollution, urban planning) to individualized preventive strategies must be backed up by evidence that this can improve health outcomes. Thus, the issue at stake is not only whether P4 strategies will give useful results, but also whether resources will be wasted that could be better spent elsewhere and whether *less medicine* in some contexts means *more health*.

5. Conclusion

We are currently witnessing visions of an unsurpassed expansion in medicalization with intensive monitoring of healthy people, creating huge datasets of enormous complexity. At the same time, we are witnessing an increasing realization that the social aspects of human life – or *the human domain* – is of crucial importance for discussions of the prospects of preventive medicine.

To what extent, and how, P4 medicine will impact society and the socially embedded clinic remains an open question. Our intention has not been to dismiss its potential for improving biomedical research and public health.

Nevertheless, we have identified and analyzed tensions between the promise of *in silico* modelling of patient data and clinical *in socio* reality and discussed a number of concerns relating to personalized genomics and pilot projects for P4 medicine. The general problems facing preventive medicine in combination with the lack of evidence for the benefits and harms of P4 strategies make its proponents' optimistic promises particularly suspicious. No *in silico* model to date, no professional, and certainly not people themselves are currently able to handle the data deluge. P4 medicine is thus currently starting to create a clinical situation that it cannot handle itself, but that it nonetheless promotes as a solution and introduces to the clinic and people´s lives.

Moreover, the challenges of making people and society *participate* the way that the preventive strategies require are, although perhaps more banal than the scientific, maybe the most daunting. The lack of evidence that people react to risk information in the way that P4 proponents presuppose highlights a possible conflict between the professional ideal of P4 medicine and the social realm of human beings: Is risk information as "actionable" as assumed? Is health just one among many priorities for individuals? Just how far are we willing to go to achieve the goals of an optimal health? In this question, the conflict between the public´s idea of the ″good life″ and science´s definition of health will come to an ultimate test in P4 medicine.

In summary, based on the historical and current challenges of preventive medicine, we find that the burden of proof for the benefits of P4 medicine should weigh heavily on those who make the promises. So far, such evidence is very limited compared to the indications that P4 medicine will increase the problems with traditional preventive medicine. Having examined early results from the HPWP, we may still conclude as Khoury et al. (2012, p. 642) that the "lack of information on the clinical utility for most proposed P4 applications produces an evidence dilemma and a conundrum for implementation into practice". The high risk of unintentional harm and wasted resources raises an important question about the price we are willing to pay to explore the path of P4 medicine. In our view, until stronger evidence exists for health benefits and wider social implications, there are reasons to be highly skeptical of the promises of P4 medicine to offer society an economic boon and enable individuals to prevent future diseases.

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