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After the revolution? Ethical and social challenges in 'personalized genomic medicine'

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Abstract

Personalized genomic medicine (PGM) is a goal that currently unites a wide array of biomedical initiatives, and is promoted as a 'new paradigm for healthcare' by its champions. Its promissory virtues include individualized diagnosis and risk prediction, more effective prevention and health promotion, and patient empowerment. Beyond overcoming scientific and technological hurdles to realizing PGM, proponents may interpret and rank these promises differently, which carries ethical and social implications for the realization of PGM as an approach to healthcare. We examine competing visions of PGM's virtues and the directions in which they could take the field, in order to anticipate policy choices that may lie ahead for researchers, healthcare providers and the public.

Keywords

empowerment; participatory; personalization; prediction; prevention; social worlds; stakeholders

With the completion of the Human Genome Project (HGP), a large volume of literature has emerged addressing the ethical, social and policy challenges that accompany the translation of genomic science into a 'personalized genomic medicine' (PGM). This literature has mostly framed these challenges in terms of external social barriers to progress. But it is not yet clear what PGM might look like in practice because different interpretations of its goals could take genomic research and healthcare in different directions. As many architects and stakeholders of PGM jostle for position in setting these directions, they will have to negotiate an important set of internal questions: how should the goals of PGM be interpreted in practice? How should their relative trade-offs be managed? How might different visions of PGM exacerbate larger social problems? This new round of internal questions is sure to

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pose new barriers unless they can be anticipated in advance. To begin that process, we examine competing visions of PGM's virtues, in order to identify their associated social risks and draw out the the research needs and policy choices that lie ahead for researchers, healthcare providers and the public as PGM matures.

PGM as a healthcare revolution

> "So you say you want a revolution? Well, you know, we all want to change the world … You say you've got a real solution? Well, you know, we'd all like to see the plan."
>
> – John Lennon

So goes the 1968 Beatles' song, which continues on to provide a cautionary perspective on the revolutionary rhetoric of that era about the reform of society and its institutions. Revolutionary movements often unite a broad array of stakeholders with different ultimate goals. Without anticipating these differences and where they might take a movement, it is hard to predict the outcome of a change in regime or to assess its real promise, and this is equally true of scientific and social revolutions.

The revolution associated with PGM is the 'paradigm shift' its promoters promise for healthcare. As Francis Collins, one of PGM's most vocal proponents writes:

> *"We are on the leading edge of a true revolution in medicine, one that promises to transform the traditional 'one-size-fits-all' approach into a much more powerful strategy that considers each individual as unique and as having special characteristics that should guide an approach to staying healthy"* [1].

Like many revolutionary movements, advocates of PGM believe that there is a critical problem with the existing regime – in this case, the 'traditional 'one-size-fits-all' approach' to healthcare – which can only be resolved through systemic, and perhaps even paradigmatic, change [1]. The Personalized Medicine Coalition, the movement's advocacy organization, writes "healthcare today is in crisis as it is expensive, reactive, inefficient and focused largely on one-size-fits-all treatments for events of late stage disease. An answer is personalized, predictive, preventive and participatory medicine" [101]. The 'more powerful strategy' that PGM represents is the translation of genomic research into molecular diagnostics and therapeutics that can help to predict and target a particular patient's health risks [1, 2].

Of course, it may well be that genomic tools will not spark a paradigm-shifting revolution for healthcare at all. The movement's focus on a one-size-fits-all approach as the source of the healthcare system's woes might be questioned by many traditional clinicians who pride themselves in already delivering individualized care. In addition, much translational genomic research (TGR) will be needed before it is clear how the theoretical benefits of PGM will be defined, realized and prioritized in practice.

In the interim, these ambiguities leave PGM open to subscription by a wide variety of adherents. The concepts behind PGM were initially articulated and defended by human geneticists, especially in developing a public justification for the scientific tool-building efforts of the HGP [3]. As genomic research moved from the completion of the HGP into its 'translational' phase, PGM and its cognates (e.g., individualized therapy and personalized healthcare) became a banner to unite many of biomedicine's leading research enterprises in their efforts to shape the future of medicine. Within the US federal government, former US Department of Health and Human Services Secretary Michael Leavitt produced reports promoting this vision [102, 103], former NIH Director Elias Zerhouni elaborated ambitious

'roadmap' initiatives to show biomedical researchers the way [4, 104], the CDC scrambled to find a place for PGM in public health [5] and the National Human Genome Research Institute reframed its mission to meet this vision's 'grand challenges' [6].

Leaders of academic and commercial biomedical research institutions followed suit, creating a national wave of new institutes, programs and companies [2], ultimately producing the Personalized Medicine Coalition, noted above, in 2004. In 2006, then-Senators Barack Obama and Edward Kennedy introduced federal legislation to help propel the movement [105]. Meanwhile, commercial consumer genomics companies bypassed the process of TGR altogether and began offering DNA-based health-risk assessments and personal genome-scanning services directly to the public [7–9]. Over the last decade, moreover, the personalized medicine movement attracted an array of subscribers that go well beyond profiling genomic risks and prescribing drugs. Today, the PGM label is used for activities as disparate as reproductive carrier screening, gastrointestinal bacterial profiling, behavioral modifications for health and wellness, nutritional supplement regimes, taking a family history and public health screening [5, 10–12, 106, 107].

Despite this enthusiasm, moving from the completion of the HGP to the realization of PGM has not been automatic or instantaneous. Much of the necessary science remains promissory, and current US remedies for protecting patients' privacy and the interests of human research subjects have been charged with slowing its progress [13–15]. Economic, regulatory and political barriers to progress have also slowed translation [15–17]. The USA lacks a system for ensuring the utility of new genetic tests before they are introduced [108], and it is not clear how 'individualized' their complementary therapies can become if they are to be commercially viable [18]. Despite the passage of federal legislation barring genetic discrimination in employment, there are persistent worries about the exclusionary use of genetic information in life and long-term care insurance [109].

These regulatory concerns were heightened when direct-to-consumer (DTC) genome services became available for purchase online in 2007. These consumer genomics companies are not required (and may have little incentive) to ensure that their services are accurate, clinically validated or reliable [8, 9], and skeptics have argued that clinicians are unprepared to counsel their patients on the implications of their DNA profiles [19, 20]. This has strengthened calls for regulation, regardless of how this might impact the pace of translation [21].

Issues related to regulation also provoke ethical concerns. If the costs of personalized genomic risk assessments and individually tailored therapies are high enough to limit PGM to 'concierge medicine' and other forms of elite healthcare [22], this will limit access and bring social justice challenges to PGM's priorities [23]. If PGM amounts to no more than patient-risk stratification along ethnic, racial or socioeconomic lines, this will exacerbate the social problems that already surround these categories [24–26]. If PGM's services are unreliable and clinicians are ill-equipped to interpret them, this will risk the best interests and welfare of patients and the public [27]. Finally, if enthusiasm for PGM threatens the protections that are now afforded to participants in biomedical research, this will provoke important questions of human rights and scientific integrity [28].

It is important to overcome these challenges if the clinical promises of PGM are to be fulfilled. But it is also important to anticipate the implications of the promises themselves. As the variety of stakeholders grows, so will negotiations over the ultimate complexion of PGM as a social practice. In pursuing their interests, proponents of PGM claim multiple virtues over the current healthcare paradigm, and different proponents understand and rank these virtues differently. Developing a responsible transition plan for PGM requires the

careful empirical mapping and analysis of these issues, as we describe below. Meanwhile, as Aristotle pointed out, manifesting virtue is often a matter of walking a fine line between too little and too much of a good thing [110]. Historical experiences help impart lessons about the potential correlative vices into which PGM could fall, especially when various interpretations of PGM's virtues are taken to extremes.

The virtues of PGM

Rhetorically, there is no mystery about the healthcare virtues promised by PGM. Every account repeats them as a mantra. While lists vary slightly, the canonical version can be distilled to four key points: first, because genomic profiles and other molecular markers can be associated with future health risks, including adverse reactions to drugs, PGM can enable healthcare to become more predictive. Second, this in turn should allow healthcare to shift from interventions that respond to fulminate disease to interventions that pre-empt illness through early detection and prevention. Third, because individuals' genomic profiles are unique at high levels of resolution, clinical medicine should be able to use this information to personalize its assessments and prescriptions to patients' genotypes. Finally, proponents assert that gaining such personalized information will enable patients to become more participatory in their healthcare and 'empowered' to take responsibility for their health. Some leading advocates even prefer to call PGM 'P4 medicine' in an effort to inscribe these central virtues in the movement's name [111].

None of these virtues are novel or unique to PGM. Individually, they each have long histories as directions for medical science and clinical practice. While their relative rank and interpretation in the context of PGM is still under negotiation, it is possible to sketch how their zealous pursuit has generated ethical and social issues in the past, and to forecast how they might distort the trajectory of PGM if they are neglected in the future.

Interpreting 'prediction'

PGM's promise to introduce an era of more predictive medicine stands out among its recognized virtues, but it is also the virtue most readily understood as double-edged. While genetic risk assessments can be useful to health planning in many contexts, they can also obscure more effective approaches to common complex disorders by eclipsing environmental and epigenetic factors that are actually more important than many genetic factors. Research also continues to document the ethical tensions that predictive genomic information can raise for clinicians, genetic researchers and consumers of commercial genetic services [29–31], as well as the complex implications of predictive genetic information for understanding of personal health, disease and identity [32].

Moreover, even where complementary interventions are available, the medicalization of probabilistic health risks can reify risk groups, stigmatize the vulnerable and foreclose treatment options. Since the diagnostic definition of these genomic risk categories often flows 'upstream' into genomic research from the clinical setting, healthcare providers who invent and use these foundational definitions are not just passive recipients at the end of the translational genomic pipeline. For clinicians, identifying risk susceptibilities and suggesting how to mitigate those risks is one way of legitimating early medical intervention. The medicalization of risk through increased clinical surveillance has a long history in medicine that would easily be continued into the era of PGM [33].

However, there may be psychosocial costs associated with justifying medical intervention by labeling people as unhealthy [34, 35]. To the extent that PGM is grounded in the identification of such health risks and frames them as personal flaws (e.g., poor drug

metabolism, low environmental threshold, mismatched mutation repair, weak toxin resistance), these issues will continue to demand the attention of its architects and users.

Interpreting 'prevention'

For many, the most attractive virtue of PGM is its promise to shift the focus of healthcare from disease treatment to disease prevention. For patient advocacy groups, prevention promises to spare families and communities the suffering that inspires their activism. For clinicians, healthcare institutions and commercial service providers, pre-emptive interventions promise better outcomes and the expansion of services to asymptomatic at-risk patients who seek 'health maintenance'. For health policy-makers and public health agencies, prevention promises lower healthcare costs and better population health measures. Philosophically, however, prevention in genetic medicine must always guard against two sets of moral mistakes: returning to a coercive ethos of reproductive control and subordinating therapeutic goals to the pursuit of socially valued 'enhancements' in human form and functioning.

At one extreme, studies of the appeal of prevention as a goal in reproductive and public health genetics show how easily the logic of prevention can lead to confusion between two different modes of preventive genetic risk testing: genetic testing as a technique for preventing the expression of a genetic disease in an individual ('phenotypic prevention'), or genetic testing as a technique for preventing the intergenerational transmission of disease genes ('genotypic prevention'). As the tools of personalized medicine become integrated into the shifting mix of existing population-based public health genetics programs, such as newborn and prenatal screening, they expose fundamental questions about the goals of the enterprise. What should genetic susceptibility screening strive to accomplish in the public health context and by what criteria should one measure success?

The pervasive answer in the public health literature is that the prevention of disease is a classic public health goal, one that is measured by a reduction over time in the morbidity and mortality caused by the target disease within the screened population. To flesh out the kinds of interventions that should be counted in those measures, most authors appeal to the public health field's scheme of primary, secondary and tertiary 'levels' of prevention. Most of the preventive interventions envisioned by PGM, such as avoiding predicted adverse drug responses or early intervention to forestall genetic risks, will be forms of secondary prevention: preventing the clinical sequelae of a genetic vulnerability without addressing its underlying causes. However, 'primary prevention' has always been the ultimate goal of public health interventions [36], and using this scheme provides a logic for shifting testing in that direction. As the US President's Council on Bioethics noted in discussing the expansion of the genetic testing panels used in newborn screening:

> *"Once personalized genomic medicine becomes standard medical practice for adults, the logic of providing physicians with this powerful tool earlier and earlier in the patient's life may prove to be inescapable. Even if cancers, for example, are relatively rare in children and adolescents, why wait until adulthood to uncover susceptibilities and vulnerabilities that could well be countered by changes in diet and life habits (to say nothing of prophylactic therapies) at an early age?"* [112].

Moreover, while newborn screening remains a form of phenotypic prevention, for genetics, primary prevention has traditionally been defined in terms of genotypic prevention: reproductive interventions that allow families and communities to avoid the birth of children with genetic diseases [37]. Genotypic prevention has long been an outcome of individual prenatal testing, but there are few examples of public health programs that mandate prenatal screening. One notable exception was the state-mandated, population-screening program for thalassemia in Cyprus in the 1970s and 1980s, which was defended as being a public health

intervention that was far from eugenic [38]. In the present day, the logic of prevention has already walked some expanded carrier-screening companies across the equivocal bridge between phenotypic and genotypic prevention, though these are still firmly in the realm of individual rather than public health interventions. It is therefore important to anticipate whether and how expanding applications of genotypic prevention in the context of reproduction might generate deeper questions of public authority, social justice and professional allegiance. These might invoke the shadow of eugenics and animate ethical concerns that PGM has avoided thus far, by focusing resolutely on phenotypic prevention. As reproductive genetic testing and population screening programs take up the mantle of PGM (so that, for example, *BRCA1* testing occurs in the context of preimplantation genetic diagnosis [39]), it will become important to test that resolve by examining the logic of prevention that PGM employs.

At the other extreme, the concept of prevention can also provide a useful cover for efforts to achieve forms of social advancement through biomedical manipulation. Research on a range of existing 'enhancement' practices (including cosmetic surgery, the use of performance-enhancing drugs in sport, biosynthetic growth hormone to increase stature, or psychopharmaceuticals to improve cognitive performance) underscores two important social planning problems regarding the use of genetic and genomic tools for enhancement. First, potential genetic enhancement interventions will be initially developed as therapies for diseases and then applied to healthy individuals for enhancement purposes once they are medically established. This creates regulatory and professional issues of 'off-label use' and shifts the focus of ethical responsibility for any potentially unjust uses of enhancement from the researchers who develop the interventions to the health professionals and users who would 'abuse' them. Second, the off-label use of these enhancing interventions can be medically justified as efforts to prevent the same diseases they were initially developed to treat.

Interpreting 'personalization'

Because the one-size-fits-all phrase is used by PGM's proponents to sum up the causes of current problems in healthcare, it is not surprising that personalization is a prominent virtue:

> *"Personalized medicine is often described as the right treatment for the right person at the right time. This emerging science has the potential to truly customize healthcare to the patient, enabling providers to match drugs to patients based on their genetic profiles, identify which health conditions an individual is susceptible to, and to determine how a given patient will respond to treatment"* [40].

PGM's claim to be able to 'individualize' medical interventions reflects an awareness and appreciation of human genetic diversity, which has medical, political and popular appeal. Ironically, however, this focus also brings the risk of depersonalizing medicine by reducing a patient's identity to her genes [41]. The simplistic appeal of this new type of genetic determinism is hard to resist and becomes easily transposed onto current types of genomic screening. For example, the reductionistic use of personalized medicine as a way of knowing oneself and one's identity is embedded in the rhetoric and names of the first wave of commercial DTC genome companies, which rely on first-person pronouns in their names – '23andMe' [114], 'deCODEme' [115], 'Knome' [116] and 'Mygenome' [117]. While Nordgren and Juengst have argued that the rhetoric of these commercial enterprises is more flamboyantly essentialist than that of other stakeholders in PGM, it nonetheless signals a broader concern about how to incorporate new genomic information into our sense of self without reducing ourselves to our genes [41]. Indeed, appeals to genetic essentialism – the view that our genomes do intrinsically define our personal identities as secular substitutes for the soul – do play at least an implicit role in many stakeholders' visions of PGM [41].

By suggesting that personal genomic information can help consumers understand socially potent aspects of their identities (such as their future potential, family membership or ancestral origins), these services naturalize identity categories that we usually embrace when they work in our favor socially but resist when they count against us [42]. By trading on the cachet of genomic science to legitimize these identities, consumer genomics can powerfully reinforce the importance of these socially ascribed identities for both the consumer's self-identification and identification by others. Far from providing startling insights that can liberate consumers from the constraints of old social labels, genomic testing may simply reinscribe those labels into their genes [43]. As commercial services become incorporated into more traditional healthcare, this risk will be propagated and perpetuated, underscoring the need to think clearly about the senses in which PGM is 'personalized'.

Anticipating the risks of essentialist and reductionist interpretations will also be particularly important for the parts of PGM that 'personalize' interventions by simply assigning individual patients to different population-based genetic risk groups [44]. Genomic risk profiles rarely, if ever, provide risk information at the individual level but are usually mapped onto group level experiences and measurements [44].

Because of its statistical foundation, genomic information can be used to illuminate the health risks of genetic 'super families', and the best PGM can do is classify individuals as members of those families. It will be a long time before individualized treatment is a routine part of disease management [45], though there are current applications of genomic information in oncology in which genomic profiling of tumors is used to predict responsiveness to specific drugs (i.e., trastuzamab and imatinib) and classify patients into groups to tailor their treatment. As a result, some argue that 'personalized medicine' should more accurately be described as 'stratified medicine' [46]. That is:

> *"The limitation in trying to reach the goal of having a unique medicine for every individual for every disease is that it is simply not practical. It is not practical from a research perspective nor is it practical from a pharmaceutical or diagnostic perspective … The first step to improving healthcare is to identify what those groups look like, how to cluster individuals within a group and then manage the behavior in terms of the clinical response of that group both for diagnosis and treatment. If we cannot treat patients in groups, then the hope of driving it even further into a personalized – completely personalized type of medication – is going to be well beyond our reach"* [113].

Of course, it would be a major rhetorical retreat for advocates of PGM to give up the idea of individualized assessments and tailored treatments in favor of stratifying patients into categories that are, ironically, not so far from a one-size-fits-all approach in the end. Most promoters of PGM therefore express hope that the present 'stop gap' state is temporary and that individualized assessments are a viable end goal:

> *"The goal for personalized medicine must be to move as swiftly as possible toward the identification of individual risk factors, be they environmental or genetic, that play a direct role in disease risk. Racial profiling in medicine, even if well intentioned right now, should recede into the past as a murky, inaccurate and potentially prejudicial surrogate for the real thing"* [1].

As the necessary tools are developed, it may well be that 'ancestry' will be replaced in an iterative fashion by the use of algorithms based on distinct genetic parameters that are more specific and informative (although perhaps still based in 'continental origin'). This hope for greater personalization has to be taken as an article of faith for promoters of PGM, in part because the general prospects of individual and community empowerment are intimately affected by population stratification. Against the backdrop of social and political

stratification, population classification schemes based on racial and ethnic categories can be actively depersonalizing for individuals, by encouraging potentially prejudicial associations between their group affiliation and health risks.

Nonetheless, despite the fact that community-based research has shown the disutility of social categories, such as race in segregating genetic risks [47], the power of these classification schemes nonetheless dominates biomedical thinking about human subpopulations. Indeed, large-scale efforts at mapping human genomic variation continue to be organized along traditional color lines (reframed as 'continental origins') [48] and, for a variety of moral, political and commercial reasons, those who develop and evaluate healthcare interventions also do so in racial terms [49]. To the extent that this scientific segregation continues to inform the clinical tools used in PGM, it is imperative to monitor the risk of conflating individual and group identities in essentialist ways.

Interpreting 'participatory'

The final virtue of PGM is the claim that it will 'empower patients' by increasing their personal control over their health and allowing them to participate more actively in healthcare decisions. This claim is pervasive in the marketing of consumer genomics companies [114, 117, 118], which capitalize on both the populist 'open source' ethos of the internet and the postmodern suspicion of authority and paternalistic expertise [41]. Personal genomic information as a 'locus of biosociality' that "forges social relationships based on beliefs of common genetic susceptibility that links risk, disease and group identity" [50]. These networks, in turn, can create powerful patient advocacy groups that can benefit families with rare diseases. Some have cautioned, however, that the mechanisms used by consumer genomics companies to promote biosociality provide little guidance as to how to make commonalities in genomic makeup meaningful for social identity or individual action [50]. In this way, the consumer genomics industry does not stray far from mainstream biomedical rhetoric about PGM. In fact, the rhetoric of patient empowerment seems equally popular at premier hospitals and research institutions [119, 120]. As other analysts of the movement note:

> *"The main characteristic of the evolving healthcare delivery model is that it is starting to become more collaborative; moving to a codiagnosis, cocare model between physicians, patients and other parties. The physician could start to be seen as a colleague and advisor, as one of many input sources in fashioning a care plan. The patient could become more of an informed participant, an active responsibility-taker, the owner, administrator and coordinator of his or her health program and health data"* [51].

In PGM, discussions of empowerment have often centered on early adopters of genomic risk assessment technology as 'lay experts' in a 'genetic citizenship' who may actually help construct and advance the technology [29]. However, it is short sighted to presume that genetic citizenship is the only logical end point for understanding identity in light of genetic information. Efforts to increase the patient's voice in clinical encounters have been the hallmark of medical ethics and the 'patients' rights' movement in law since the 1970s [52]. Students of that effort have shown that it is accompanied by its own risks – the relocation of responsibility for healthcare away from social and political reams and onto the shoulders of patients [53, 54]. As a result, they warn that:

> *"The emphasis on individual empowerment often disguises the fact that personal genomics is pushing the individualization of responsibility for health one step further. The quantity of information that individuals need to consider when making choices about their health is on the rise. Apart from increasing the burden of*

> *individual responsibility (and the blame for poor health), it is questionable how free and independent individual choices in this context are"* [55].

This shift should prompt significant concern within the PGM movement because it encourages a 'rights-based' demand for genomic information that is likely to bring confusion about both the risks being described and the responsibilities they entail [7, 56]. Even worse, those who are unable to use genomic information – due to insufficient will, low health literacy or poor health choices – are put at risk of being "marked out as irresponsible and hence unfit to be self-governing citizens" [57]. In these circumstances, patients may feel increased pressure to take control and manage their conditions, which seems just a small step away from demanding that patients have a moral responsibility to become well [58]. This responsibility is emphasized in the work of Collins, who closes his book with this plea:

> *"The success of personalized medicine will come about only when we each take responsibility for our health. Healthcare providers can help, but they cannot drive your bus … If you follow these recommendations, you will truly be on the leading edge of this new revolution. But the edge will keep moving, and so it will be essential to upgrade your own knowledge base periodically"* [1].

Of course, this moral imperative becomes increasingly complicated when the supposed source of the condition is thought to be genetic, as the avenues to manage one's health risks may not always be transparent or morally neutral.

The double-edged nature of patient empowerment means that we cannot take for granted that its promotion will always yield good outcomes. Part of the 'social impact assessment' of PGM therefore needs to be an effort to anticipate how the virtue of patient empowerment might go awry as PGM is realized. Because 'empowering patients' can also shift healthcare responsibilities in counterproductive ways for both clinicians and patients, it will be crucial for promoters of PGM to be clear about which of these functions their appeals to empowerment are meant to play, and for consumers of PGM to weigh the relative value of these functions to their own interests.

Convergence or chaos after the revolution?

As the preceding analysis suggests, one way to act in anticipation of virtues sliding into vices is to ask those involved in promoting PGM how they understand its goals, benefits and challenges, and where they expect this approach to take healthcare. The range of stakeholders in the PGM movement can be used to differentiate the full spectrum of agendas and aspirations that will shape the field. This diversity also creates the need for institutional and individual 'boundary work' within the PGM community to negotiate the use of the PGM label and their position and status with respect to it [59]. As subscribers to PGM move further away from its core practices, their attempts to adapt the model will force its reinterpretation and expose logical extensions of its precepts that can highlight the issues at stake, whether or not they are ultimately counted as legitimate.

Empirical research of this kind is needed to assess the myriad ways that stakeholders interpret the goals and the potential pitfalls of the realization of PGM, and to extrapolate an analytic map of the ethical and social challenges these interpretations might provoke in practice – which we are doing in a research project funded by the National Human Genome Research Institute. Our approach applies social worlds and arenas theory to the case of PGM, which suggests that what this approach to healthcare will look like will depend heavily on how the goals and methods of PGM are interpreted by its key stakeholders, especially those who dominate the movement [60–63]. Social worlds and arenas theory demands that we analyze a phenomenon in the social spaces it occupies, for it is only there that we can truly understand its functions. The 'coproduction' of social phenomena such as

PGM, then, is shaped by multiple agendas, cultures and values that vary in strength and type of influence.

We have identified ten social worlds that we believe will have a strong influence on the definition and ultimate direction of PGM, though there are surely others. As illustrated in Figure 1we group these ten worlds into four constellations according to their primary role in designing and implementing PGM:

- 'Promoters', who are its architects and builders, particularly in setting agendas and positing vision for the movement (e.g., researchers, commercial and nonprofit developers, sponsors of research and development, lobbyists and other advocates);
- 'Monitors', who are its gatekeepers as a professional movement, especially in setting standards, policing boundaries and defining its canon (e.g., editorial boards, regulatory bodies and curriculum committees);
- 'Providers', who operationalize it, particularly in delimiting its scope and content for healthcare institutions and professionals and in providing personalized genomic medical services in practice (e.g., clinicians and hospitals); and
- 'Users', for whom it is designed, who shape the public appeal and reception of the movement (e.g., patient-based organizations).

We are interested in identifying the special interests and perspectives that color how key actors in each of these constellations interpret their mission. As the dotted arrows in Figure 1 suggest, the social worlds of PGM do not act in isolation but interact, and in ways that reveal natural overlap – as well as synergy and conflict – among particular worlds. Most stakeholders, for example, will simultaneously be citizens of multiple social worlds, and many worlds are mutually interdependent.

In addition, the force lines in Figure 1 indicate that the social worlds that shape PGM also tether them in orbit around it. One measure of the importance of a social phenomenon like PGM is how far into social space its gravitational field extends. Clearly, some proponents would like PGM to dominate the biomedical sector by bringing the sector's many other defining features – such as the practice of medicine, concepts of health and disease, health policies and so on – and the social worlds involved in their coproduction into orbit around it. Whether this ambition will make PGM the lodestar of biomedicine – or its black hole – is the question that ultimately motivates our research.

If the translation of genomic research into health benefits is to succeed, it is imperative to map how the goals of PGM are interpreted by its stakeholders and forecast its implications. By emphasizing that important social practices, such as PGM are always coproduced by many social actors, and by opening up a range of stakeholder perspectives on what constitutes PGM, we will be able to isolate the most influential of its virtues described earlier and assess the potential for correlative vices to emerge.

Meanwhile, it is instructive to examine what we have learned in other contexts about the individual virtues that have been ascribed to PGM. These are summarized in Figure 2which illustrates the continua of virtues and vices through which PGM might swing in seeking a settled account of its promises for healthcare.

Thus, if in attempting to realize the clinical benefits of predictive genomic information, PGM slides into medicalizing more human traits as genomic health risk factors, it risks feeding the genetic determinism that encourages stigmatization. A natural response to these

risks is to emphasize PGM's preventive promise: if PGM can provide prescriptions for avoiding predicted health risks, it can undercut the fatalistic thinking that has accompanied genetic testing in the past. If, however, PGM is carried by the logic of prevention into pursuing genotypic preventive goals in reproductive and public health settings, it risks resurrecting coercive eugenic attitudes. To resist those inclinations, it will be natural to lean toward pharmacogenomics to underscore the prospect of personalizing therapeutic interventions to individual patients as its central promise. If this, in turn, reduces patients' personal identities to their molecular profiles – or to the statistical profiles of the populations to which they belong – this may exacerbate the individual and group forms of discrimination with which medicine is already too familiar. Finally, to counterbalance how molecular profiling might, ironically, depersonalize healthcare, it will be tempting to highlight how PGM can empower individual patients to be more participatory in their own healthcare. If, however, the rhetoric of empowerment and responsibility serves only to transfer public health responsibilities to at-risk individuals, this will only exacerbate healthcare injustices, not combat them.

Future perspective

Time will reveal whether the coming negotiations over PGM will follow this pattern. Like other early maps of unexplored frontiers, this chart only indicates some theoretical risks that pioneers may (or may never) encounter. But if the logic of these zigzag paths holds, it suggests a provocative conclusion. If PGM's stakeholders attempt to triangulate between these virtues and vices in setting their course, their dialog may boil down to a debate over how much to emphasize individual responsibility for health as a moral cornerstone of the movement. If, in fact, PGM is fundamentally about advancing individuals' interests in healthcare, its most important ethical challenge will be to ensure that individuals' healthcare interests are socially protected, rather than shifting those responsibilities to the individual. In countries where systemic health policy change will be required to realize that goal, the pursuit of PGM will involve fostering an even greater healthcare revolution than its promoters currently appreciate. The first steps in that direction will be to take care that PGM's promotional appeals to patient empowerment do not slide into simple consumerism, and to re-emphasize that the participation that will make PGM's other virtues possible must be public as well as personal.

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Executive summary

Personalized genomic medicine as a healthcare revolution

- Most of the discussion of the ethical and social challenges facing personalized genomic medicine (PGM) has focused on the external constraints that challenge the movement's success: provider education, test efficacy and social repercussions. However, even the internal virtues of PGM require careful contextual attention.

Interpreting 'prediction'

- If PGM slides into medicalizing risk factors, it risks feeding the determinism that encourages stigmatization.

Interpreting 'prevention'

- If PGM is carried by the logic of prevention into reproductive settings, it risks resurrecting coercive eugenic practices.

Interpreting 'personalization'

- If PGM is allowed to buttress reductionist thinking, it risks exacerbating individual and group forms of discrimination.

Interpreting 'participatory'

- If PGM serves only to transform social responsibilities for healthcare into individual responsibilities, it may exacerbate healthcare injustices rather than combat them.

Convergence or chaos after the revolution?

- Empirical research on key stakeholders involved in the translation of PGM from bench to bedside is needed to understand how well aligned their interests are in realizing the revolution.

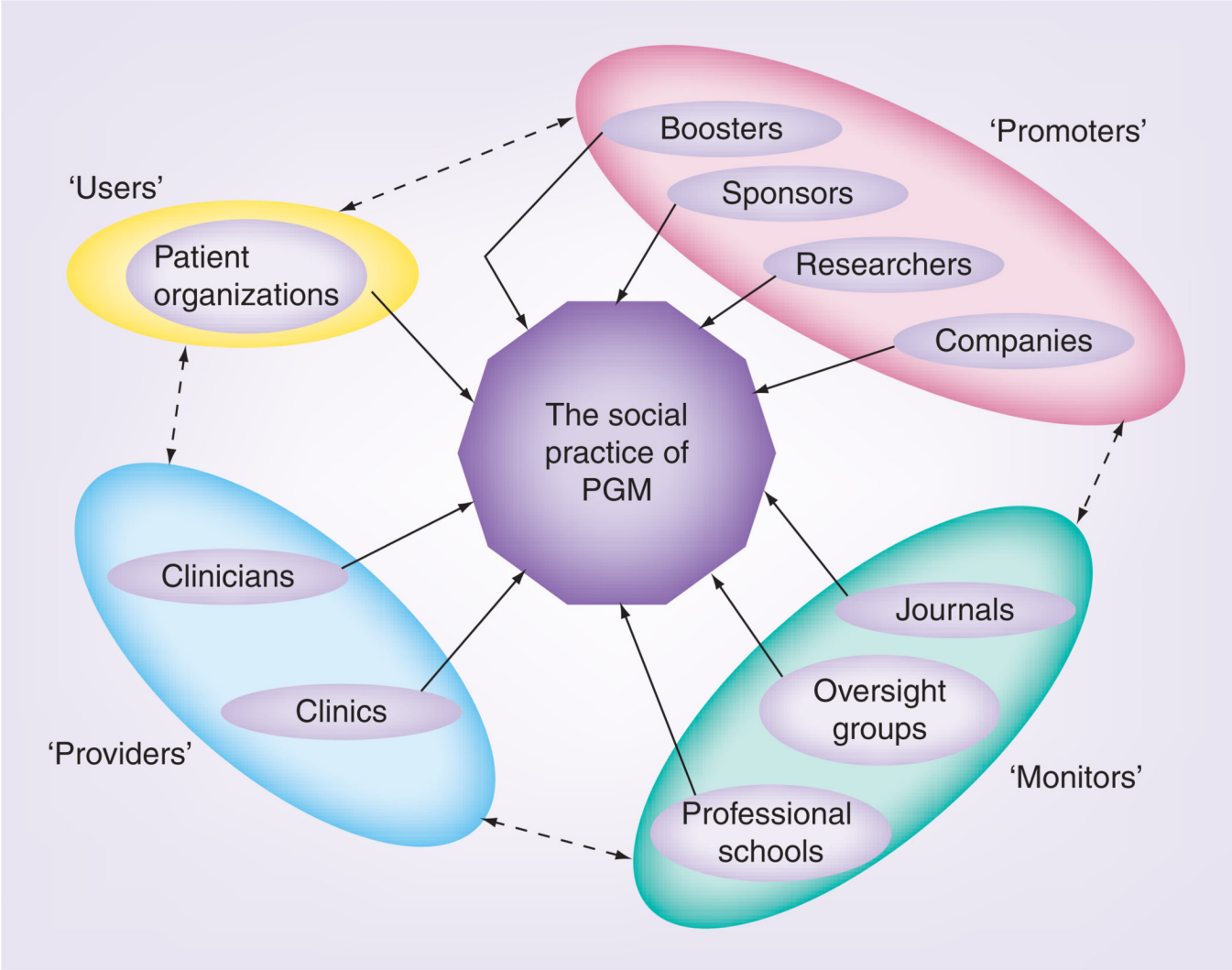

Figure 1.
Stakeholder coproduction of the social practice of personalized genomic medicine.
PGM: Personalized genomic medicine.

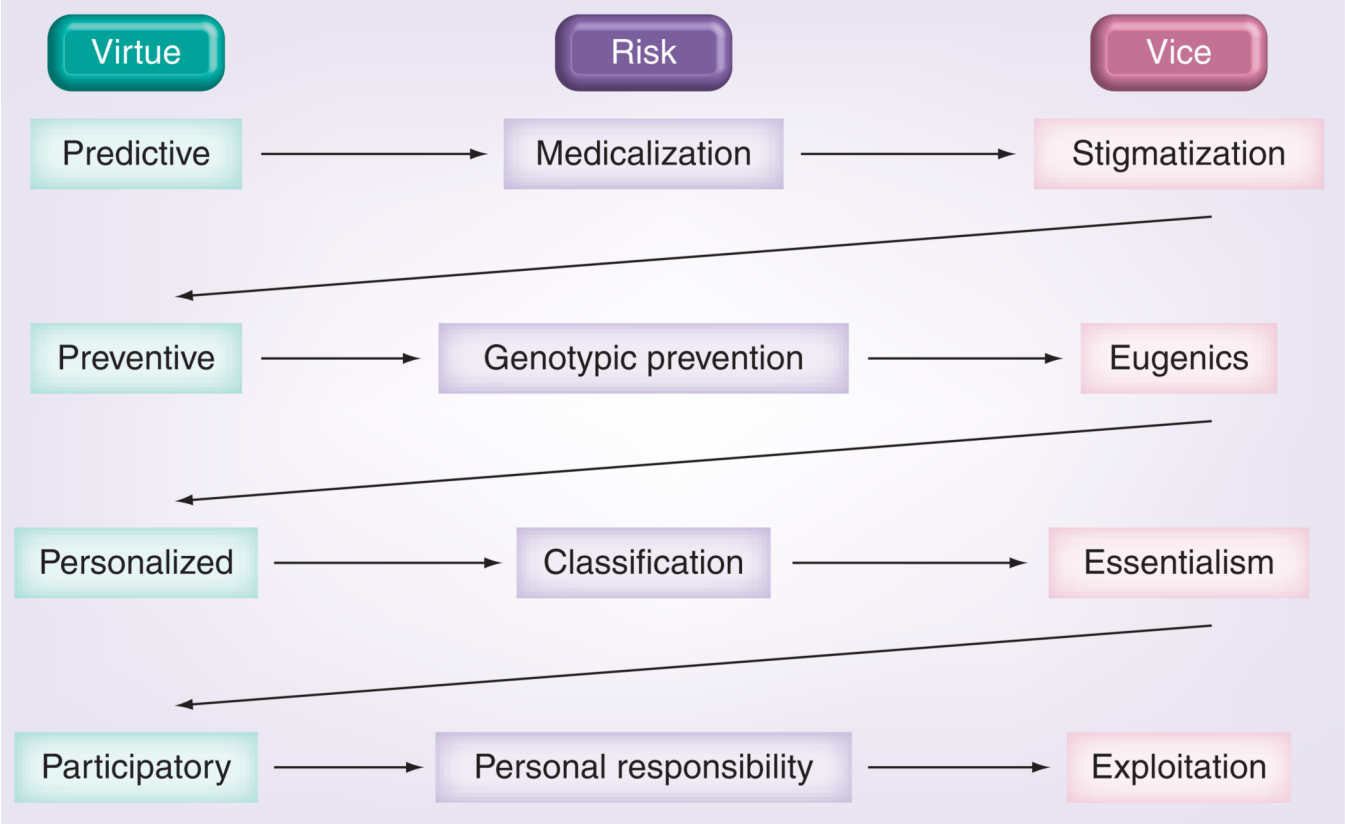

Figure 2.
The virtues and vices of personalized genomic medicine.