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Paving the Way to Personalized Genomic Medicine: Steps to Successful Implementation

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Abstract

Over the last decade there has been vast interest in and focus on the implementation of personalized genomic medicine. Although there is general agreement that personalized genomic medicine involves utilizing genome technology to assess individual risk and ensure the delivery of the "right treatment, for the right patient, at the right time," different categories of stakeholders focus on different aspects of personalized genomic medicine and operationalize it in diverse ways. In order to move toward a clearer, more holistic understanding of the concept, this article begins by identifying and defining three major elements of personalized genomic medicine commonly discussed by stakeholders: molecular medicine, pharmacogenomics, and health information technology. The integration of these three elements has the potential to improve health and reduce health care costs, but it also raises many challenges. This article endeavors to address these challenges by identifying five strategic areas that will require significant investment for the successful integration of personalized genomics into clinical care: (1) health technology assessment; (2) health outcomes research; (3) education (of both health professionals and the public); (4) communication among stakeholders; and (5) the development of best practices and guidelines. While different countries and global regions display marked heterogeneity in funding of health care in the form of public, private, or blended payor systems, previous analyses of personalized genomic medicine and attendant technological innovations have been performed without due attention to this complexity. Hence, this article focuses on personalized genomic medicine in the United States as a model case study wherein a significant portion of health care payors represent private, nongovernment resources. Lessons learned from the present analysis of personalized genomic medicine could usefully inform health care systems in other global regions where payment for personalized genomic medicine will be enabled through private or hybrid public-private funding systems.

Keywords

Personalized Genomic Medicine; Personalized Medicine; Ethics; Genomics; Policy

> "In the not-so-distant future, we can expect to walk into a physician's office for an annual physical and walk out with a blueprint of our genetic inheritance - and with the knowledge of the most likely cause of our own death." [1]

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DUALITY/CONFLICT OF INTERESTS

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1. INTRODUCTION

"Personalized medicine" is not a new concept. However, over the last decade it has increasingly become a policy priority and has attracted substantial professional and public attention [2-4]. The term personalized medicine can be used generally to refer to a more holistic vision of individualized or humanistic patient care. However, this article focuses on "personalized genomic medicine" (PGM), which is the utilization of genome technology to assess individual risk and ensure the delivery of the "right treatment for the right patient at the right time." Although there is general agreement about this overarching definition of PGM, different categories of stakeholders focus on different aspects of PGM and operationalize it in diverse ways. These stakeholders include health care professionals, patients, national organizations, research and treatment institutions, and a variety of industries, such as pharmaceutical corporations, technology firms and direct-to-consumer genomics companies.

This article identifies three core elements of PGM that are highlighted by these stakeholders: (1) molecular medicine; (2) pharmacogenomics; and (3) health information technology. The integration of these three elements has the potential to improve health and reduce health care costs, but it also raises many challenges. In order to address these challenges and ensure the successful implementation of PGM in the United States, significant investment will be required in the areas of health technology assessment, health outcomes research, education (both professional and public), communication among stakeholders, and the development of best practices and guidelines.

Some critics question the utility of PGM, arguing that it will not reduce costs and may only increase disparities in health care [5-7]. We are sympathetic to these concerns and believe they should be taken seriously. However, as long as PGM remains a policy priority [2,8], physicians, researchers, and others in the medical profession should work to ensure that it is responsibly and ethically implemented. By clearly identifying the most important components of PGM and the most prominent challenges to be addressed, and by recommending ways to combat these challenges, we hope to stimulate thought and discussion on these issues so that the road to PGM is more brightly illuminated and decidedly easier to navigate.

While different countries and global regions display marked heterogeneity in health care funding in the form of public, private or blended payor systems, previous analyses of PGM and attendant innovations have been performed without due attention to this complexity. Hence, this article focuses on PGM in the United States as a model case study wherein a significant portion of health care payors are private, nongovernment resources. Other countries are also grappling with the implementation and widespread adoption of PGM, but many of them - such as Canada, the United Kingdom, and France - are facing these issues within the context of a government-paid health care program. These programs are vastly different from the health care system in the United States, leading to radically different challenges and issues that demand different solutions. However, lessons learned from the present analysis of PGM could usefully inform health care systems in other global regions where payment for PGM will be enabled through private or hybrid public-private funding systems.

2. COMPONENTS OF PGM

The terms "personalized medicine," "personalized health care," and "personalized genomic medicine" are often used interchangeably. In a broad sense, medicine has always been "personalized." For instance, doctors have long considered the patient's environment, medical history and family medical history as they work to make treatment decisions for individuals. The significance of the "person" in personalized medicine should never be undervalued. Individualized and humanistic patient care is essential to good clinical practice. However, the politics and academic discourse related to "personalized medicine" has focused more on the

technical than the personal. For example, in 2002, Jain et al. argued that personalized medicine is comprised of just two components: molecular medicine (genotyping, haplotyping, proteomics and molecular diagnostics) and bioinformatics [9]. In November 2008, the Department of Health and Human Services (DHHS) expanded the definition of personalized medicine in a report entitled "Personalized Health Care: Pioneers, Partnership, Progress." This document aimed to "illustrate how personalized health care is coming to be defined, designed and delivered" by highlighting the various activities underway in both the public and private sectors that are attempting to integrate personalized health care into clinical practice [3]. The report identified several components of personalized medicine, including genomics and other molecular level techniques and the use of health information technology, but also included the integration of clinical care and research and the reorientation of various organizations toward a more patient-centric approach [3]. Finally, one of the more comprehensive discussions of personalized medicine came from the American Association for Cancer Research in 2008. They identified seven principal areas of personalized medicine: (1) whole genome sequencing, (2) diagnostic and prognostic testing, (3) molecular imaging, (4) information technology, (5) drug development, (6) gene based clinical trial matching, and (7) the development of partnerships [10]. Although these documents purport to define a broader notion of personalized medicine, their focus on genomics and innovative imaging and information technology suggests a narrower concept, which we refer to as PGM.

This article focuses on three core elements of PGM: (1) molecular medicine; (2) pharmacogenomics; and (3) health information technology. While these are not the only components of PGM that deserve attention, they are the focus of this article because they are the three areas consistently highlighted by stakeholders and they have become central to many PGM initiatives in the United States. Although these core elements are discussed separately in the discussion that follows, it is important to note that it is the combination of these three and their successful integration into clinical care that has the potential to bring about a new era of PGM.

2.1 Molecular Medicine

Molecular medicine includes a variety of scientific approaches including genetic and genomic sequencing, metabolomics, and proteomics.

Genome sequencing technologies have advanced significantly in the past five years. The Human Genome Project took 13 years (1990-2003) and $2.7 billion to complete [11,12]. By 2007, it was possible to sequence an entire individual human genome in four months and for less than $1.5 million [13]. The latest whole human genome sequences cost less than $500,000 each [14,15]. Within 5-10 years scientists hope to be able to sequence the genome for $1000, making whole genome sequencing broadly available to physicians and their patients. In an effort to accomplish this goal, the National Institutes of Health (NIH) has funded projects to advance sequencing technologies, and the X Prize Foundation has sponsored a $10 million prize for the first group to sequence 100 genomes in 10 days for less than $1 million [16]. These efforts and the technological advances that they produce will enable broad access to whole genome information. In fact, several companies (such as 23andMe and Navigenics) have already begun to offer genome-wide tests (sequencing of single nucleotide polymorphisms (SNPs) at more than 500,000 locations across the genome), and some companies that offer direct-to-consumer personal genome scans have recently partnered with physician groups to make their services available to patients and their health care providers [17]. However, the ability of this technology to achieve the promises of PGM and to be successfully integrated into routine clinical care is constrained by our limited understanding of the functional significance of human genetic variation [18,19].

In order to better understand human variation we have begun to see the integration of genome science and molecular biology. This has resulted in the emergence of many new areas of scientific inquiry, including proteomics and metabolomics. Proteomics is the large-scale study of proteins, particularly their structures and functions in each cell [20,21]. Metabolomics, on the other hand, is "the systematic study of the unique chemical fingerprints that specific cellular processes leave behind" [22]. Clinical metabolomics seeks to evaluate and predict individual health and disease risk by "investigating metabolic signatures in body fluids or tissues, which are influenced by genetics, epigenetics, environmental exposures, diet, and behavior" [23]. Both metabolomics and proteomics aim to advance research and lead to the development of new therapies that will result in more targeted treatment of patients using molecular medicine.

Some worry that the wide-spread implementation of molecular medicine, particularly genetic and genomic sequencing, will lead to a great deal of unintelligible data with the potential to confuse and worry patients, frustrate busy physicians who may become overwhelmed by anxious patients, and potentially even lead to the unjustified use of health care resources in an effort to follow-up on genomic data of unproven clinical utility [19]. This is a serious concern that can only begin to be addressed through the implementation of health information technology that allows for the more effective management and interpretation of the vast amount of data generated by molecular medicine.

2.2 Pharmacogenomics (PGx)

Although molecular medicine using whole genome sequencing is only beginning to be integrated into clinical care, recent advances in pharmacogenomics, or "the study of how individual genetic differences affect drug response" [24], have generated much excitement about the promises of PGM.

While only limited research exists regarding the uptake and feasibility of pharmacogenomics, a handful of noteworthy studies have indicated that the future of pharmacogenomics is bright. For instance, pharmacogenomic studies of tamoxifen - used to treat breast cancer - have shown that women with the *CYP2D6* genotype tend to have a higher risk of disease relapse, a lower incidence of hot flashes and generally poorer clinical outcomes because of the gene's impact on metabolism [25,26]. Similarly, research on warfarin - an anticoagulant - has shown that two genes (*CYP2C9* and *VKORC1*) impact the optimal dosing of warfarin [27-29]. These genetic factors account for 30-35% of the variability in warfarin dosing, while clinical factors are responsible for only 17-21% of the variability [30].

Despite these findings, pharmacogenomic testing has not yet been integrated into standard clinical practice [31,32]. However, there has been extensive regulatory evolution at the Food and Drug Administration (FDA) [33,34]. For instance, the FDA recently approved updated labeling for both tamoxifen and warfarin. The new labeling requirements are intended to highlight the importance of pharmacogenomic testing in making prescription and dosing decisions. The FDA approved the first genetic test for warfarin sensitivity [35], and now requires some form of genetic testing for at least four drugs, recommends it for another six, and tests are available for at least six others [36]. Additionally, the FDA's Voluntary Genomic Submission program has gathered genetic information on approximately 50 drugs [37].

Many research institutions have invested significant resources in pharmacogenomics research. It is also widely supported by pharmaceutical companies because they believe that personalized medicine generally, and pharmacogenomics specifically, will have many benefits, including the ability to resurrect drugs that were initially rejected, the ability to avoid investing in unfavorable products at earlier stages of development, the ability to design higher quality and more effective clinical trials, shorter drug development cycle times, decreased research and

development costs, decreased overall risks in drug development, and - ultimately - a favorable impact on profit [38-40].

One prominent example is Eli Lilly, a large pharmaceutical company that has invested significant amounts of time and money into the advancement of PGM. For instance, the company has embraced a tailored therapy strategy in an attempt to provide more predictable, personalized patient outcomes and the company is relying more heavily on access to genetic data in its clinical trial research [40]. Lilly has also signed a three-year collaborative research agreement with GE Global Research, the centralized research and development organization at General Electric Company. The partners hope to carry out research that will ultimately help predict cancer treatment response to targeted therapies [41]. Furthermore, Lilly is specifically working on tailoring two of its medications -- Xigris and Strattera -- in ways that may contribute to personalized medicine [39].

Although these initiatives may lead to the development of more pharmacogenomic tests and individualized therapies, it is not likely that they will be widely adopted by physicians or routinely reimbursed by insurers until outcomes research can show clear clinical benefit and cost effectiveness.

2.3 Health Information Technology (HIT; also known as Health Informatics)

A third component of PGM highlighted by stakeholders - health information technology (HIT) or health informatics - arose in response to the tremendous amount of data generated by molecular medicine and pharmacogenomics. These scientific advances created enormous volumes of data, but it will only be through the technological advances of HIT that these data can be interpreted and reconciled with respect to their biological significance and downstream impact on medical research and clinical practice. In addition to simplifying the organizational management of high dimensional genomics data, HIT will potentially allow for molecular data to be linked to other health information, primarily by way of Electronic Medical Records (EMRs) that include both physician and patient input.

Health informatics is defined as “the intersection of information science, computer science, and health care. It deals with the resources, devices, and methods required to optimize the acquisition, storage, retrieval, and use of information in health and biomedicine” [42]. It includes both bioinformatics - to meet the IT needs that arose due to proliferation of genomic information - and the introduction of EMRs to electronically manage all different types of -omics biomarker data and phenotypic characterization of research study participants.

Components of HIT include, but are not limited to, electronic medical records and other health information systems used for billing, scheduling and research; decision support systems in healthcare; standards and integration profiles to facilitate the exchange of information between healthcare information systems; controlled medical vocabularies used to allow a standard, accurate exchange of data content between systems and providers; hand-held or portable devices to assist providers with data entry and retrieval or medical decision-making.

This HIT component of PGM is the primary focus of many leading technology firms as well as some research institutions. For example, in 2003 Hewlett-Packard formed a partnership with Partners Health Care in an effort to accelerate clinical genomics and advance the concept of “individualized medicine” [43] by integrating genetic knowledge into the healthcare system [44]. HP argues that the right IT infrastructure will improve the quality and efficiency of both research and clinical operations, integrate genetic test results into electronic medical record systems, ensure the data integrity of the personalized medicine information flow, and manage costs [45]. The core of this IT infrastructure, and one of the first tangible outcomes of the HP/Partners partnership, is a software package named Gateway for Integrated Genomics-

Proteomics Applications and Data (GIGPAD). GIGPAD is described by HP as a "platform for consistently managing the process of creating, organizing and accessing genetic, genomic and proteomic data. It processes, stores and shares research results, manages workflows from individual or multiple laboratories and seamlessly integrates with laboratory information management systems.... [to enable] a wide variety of genetic/genomic research, so research findings can be rapidly transformed into clinical tests that physicians can use to better manage a patient's disease or predisposition" [45].

In similar fashion, Microsoft has partnered with over 35 other organizations and institutions to form the BioIT Alliance, a group with members from multiple industries that is working to advance translational and personalized medicine by better integrating science and technology into healthcare [46]. Microsoft has also developed a software platform that will help advance personalized medicine. Microsoft's Amalga (formerly known as Azyxxi) can "be used to assimilate large quantities of diverse data, including electrocardiograms, magnetic resonance imaging scans, dynamic angiograms, ultrasound images and, ultimately, genomic information, providing a visual gateway for instant access to the information, and allowing researchers to make and prove their hypotheses within minutes instead of months." Microsoft argues that "[Amalga] will help in the mining of data that allows [healthcare professionals] to make appropriate clinical and scientific discoveries, setting the stage for relating genetic information to clinical practice" [47].

3. CONCLUSIONS AND THE WAY FORWARD

Many believe that the implementation of PGM -- or the integration of molecular medicine, pharmacogenomics, and HIT -- will benefit patient health and the health care system in several concrete ways [48]. First, it is presumed that the new genome sequencing technologies will improve individual risk assessment, which will lead to disease prevention or at least early diagnosis and more tailored treatments for patients. Arguably, this could ultimately elevate the overall quality and effectiveness of health care and improve health outcomes [8]. Second, a major goal of PGM generally, and pharmacogenomics specifically, is to improve drug safety by reducing adverse reactions to pharmacotherapy and improving overall rational prescription and dosing capabilities [24]. Finally, many believe that personalized medicine also has the potential to decrease the costs associated with health care, which are arguably spiraling out of control in the United States [8,48].

Notably, this anticipated reduction in health care costs is attributed to two major changes. First, PGM will allow health care professionals to provide more effective treatments, thus reducing the number of unnecessary treatments. Second, PGM is expected to improve pharmaceutical research and development (R&D) so significantly that it will drive down the costs associated with R&D. At present it takes up to 15 years to develop a single medication (from discovery to treatment availability), and the average cost to research and develop each successful new drug is between $800 million and $1 billion because of the vast number of drugs that fail (approximately 7,500 compounds fail for every one that receives approval) [49]. Thus, any reduction in drug R&D costs could be considerably significant in decreasing the overall cost of health care in the United States.

If PGM translates into improved health outcomes and drug safety while decreasing health care costs, it will certainly be worth its investment and will transform the delivery of health care around the globe. However, whether pharmacogenomics - and PGM more generally - will actually improve health quality and decrease health care costs is an ongoing debate [50,51]. In fact, there is little empirical research to support the enthusiastic claims made by the proponents of PGM and many worry that such promises are little more than "hype". Critics point out that the implementation of PGM will require formidable resources in terms of both time and money,

and express concerns that the investments made in PGM will not ultimately pay off, arguing that it may in fact increase health care costs and will certainly exacerbate the problem of health disparities [5-7]. Even some proponents of PGM note that many challenges lie ahead [8,24, 52].

Evidence regarding the validity and clinical utility of new genomic technologies and personalized medical interventions is needed to overcome these obstacles. Building this evidence base will require significant investment in the areas of health technology assessment (HTA) and health outcomes research. HTA is a form of policy research that identifies both the policy issues and social consequences of the application or use of technology [53,54]. Generally, HTA considers the effectiveness, appropriateness and cost of technologies by asking four fundamental questions: does the technology work, for whom, at what cost, and how does it compare with alternatives? [55]. HTA studies to date have found that nurses can provide better quality care by using electronic medical records [56], electronic simulations improve the performance of caregivers [57], electronic prescribing systems reduce prescription errors [58], and a multitude of other results pertinent for medical research and clinical practice [59-61]. Adoption of genomic tests in clinical medicine must await similar appropriately designed studies with robust statistical power, and performed in settings relevant for clinical practice [62]. Yet, there is presently little relative investment in HTA among health care organizations [19,63,64]. This shortcoming must be addressed if PGM is to be fully implemented and adopted. As new technologies arise and are implemented into the clinical setting, assessment of their performance, resource requirements, and utility will be crucial. Such prospective and real-time assessment of new technologies and innovations can markedly facilitate the transfer of knowledge from the genomics laboratory to the clinic, as well as uptake by user groups in society.

In conjunction with adequately assessing PGM technologies, proponents of this approach must also invest significantly in conducting health outcomes research to examine the efficacy and effectiveness of personalized PGM-based treatments and interventions. To this end, health outcomes research has gained increasing attention in recent years, beginning largely with pharmacogenomics studies. For instance, the Medco-Mayo study of warfarin not only attempted to determine if pharmacogenetics testing for patients initiating warfarin therapy resulted in a significant reduction in hospitalizations for adverse reactions, but also sought to determine the time required to stabilize the dosing of warfarin, the costs associated with pharmacogenetic testing, and the total resources necessary to perform such predictive tests [65,66]. The NIH has created funding resources in their new transformative R01 program that specifically focus on providing an evidence-base for pharmacogenomics [67]. Additional research on health outcomes remains a critical step in the successful implementation of PGM.

This research will likely be heavily contingent on the adaptation of the regulatory environment, which is another immense challenge facing PGM [24,38,68]. Currently, there is little regulatory oversight of genetic tests, and the FDA does not provide sufficient guidance in this area. Both the DHHS and the Personalized Medicine Coalition (PMC) are working to help develop common policies [69,70], but many have called for increased regulation to ensure the safety and efficacy of new genomic technologies and other elements of PGM [71]. It will also require a sea of change in the reimbursement landscape if PGM is to be integrated into standard care [24,38,68,72]. However, this is unlikely to occur until there is more clear evidence of the validity and utility of personalized medical diagnostics, treatment and preventive care in the form of outcomes research, as mentioned above. Importantly, the adaptation of the regulatory and payment environment may be one of the most daunting and intractable challenges ahead on the road to personalized medicine.

If these challenges can be overcome, then the success of personalized medicine will depend on the development of widespread educational efforts, both for health care professionals as well as health care consumers. Research indicates that general practitioners do not feel competent to counsel patients about genetic tests for even single-gene disorders [73,74]. The vast amount of complex risk information that will be provided with whole genome sequencing will most certainly exacerbate the problem. Physician training should be a priority [75], particularly with regard to genetic-based probability and risk assessment [76]. Such a monumental task will not be met easily and will likely require a transformation in medical education and physician training. However, it should be noted that this challenge may become surmountable as HIT is implemented and health care becomes increasingly automated.

Patients are also generally inadequately informed about genetic risk and the meaning and utility of genomic information, so their understanding of genetic information is often inaccurate and/or incomplete [77,78]. This is due in large part to the fact that the information is complex and few people have a solid understanding of statistics and probability, which are critical to fully discerning the attendant genetic risks. Additionally, critics worry that the largest barrier to widespread patient and public understanding of genetics is the tendency to fall prey to genetic determinism, which is heavily influenced by the media [79].

In addition to educational reform, clinical practice guidelines need to be developed to help determine when and how to utilize PGM and the best way to interpret results and findings. There are not enough trained genetic counselors available to meet the growing demands of personalized medicine. It will therefore eventually become the responsibility of primary care physicians (including pediatricians and obstetricians) to insure that information gleaned through the use of PGM technologies is interpreted and utilized appropriately. Reliable, up-to-date information and clinical guidelines must be developed and made easily accessible to help guide decision making about diagnostic testing and follow-up clinical care.

As we prepare for this new era in PGM-guided health care, it is increasingly important that stakeholders work together to integrate the various components of PGM and develop a comprehensive understanding of its goals and a clear vision of its future. Some stakeholders have already realized the importance of fostering communication and exploring PGM with diverse groups of stakeholders [3,80,81,82]. However, these efforts only scratch the surface of what must be done to ensure the successful implementation and widespread adoption of PGM. The widespread utilization of health technology assessment, a focus on health outcomes research, professional and public educational efforts and campaigns, communication among the pertinent groups of stakeholders, and ultimately the development of best practices and guidelines are all critical next steps in paving the way toward the successful implementation of PGM. Additionally, since stakeholders often have a plurality of conflicting interests in PGM, mapping stakeholder interests and areas of synergy and/or competition may help forecast barriers to the uptake of PGM on its path from the bench to the bedside.

Still, the path ahead for PGM remains long and winding with many significant obstacles that must be navigated. This article focuses primarily on the scientific and technical challenges associated with realizing the promise of PGM. Yet, scientific and technical innovations like those that lie at the core of PGM (molecular medicine, pharmacogenomics, and HIT) transform the very roles of health professionals and health consumers. The transformation of these roles and the plethora of other human challenges in the areas of health policy, privacy protection, and patient autonomy are important and deserve attention in future research and commentary. Notably, it is also critical that scholars and stakeholders begin to explore the growing tension arising between public health initiatives, which seek to standardize care, and the personalized medicine movement.

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LIST OF ABBREVIATIONS

DHHS	Department of Health and Human Services
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GIGPAD	Gateway for Integrated Genomics-Proteomics Applications and Data
HIT	Health Information Technology
HTA	Health Technology Assessment
NIH	National Institute of Health
PGM	Personalized Genomic Medicine
PGx	Pharmacogenomics
PMC	Personalized Medicine Coalition
R&D	Research and Development
SNP	Single Nucleotide Polymorphisms

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