Personalized Medicine

Personalized medicine 2014: has healthcare been transformed?

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## Science & transformations in medicine

The complete sequencing of the human genome in 2003 was predicted to make medicine proactive and personalized. Since then, genomic technologies have made impressive technical advances, created important diagnostic tools, facilitated targeted therapies, and provided an understanding of the genetic complexity of common diseases. Nonetheless, the transformation of medical practice is just beginning to occur. Now a decade after the sequencing of the human genome, it's appropriate to look back and evaluate the impact genomics has played in enabling personalized health care and anticipate what we can expect going forward.

The role for a physician in society can be traced to earliest history, but it was not until the early 1900s that the sciences of pathology, physiology, chemistry, physics and microbiology enabled a major transformation in medicine from its basis on mysticism to a basis on science and the pathophysiology of disease. Since then, western medicine has become increasingly driven by scientific advances. The elucidation of the structure of DNA by Watson and Crick in 1953 provided the foundation for a broad understanding of life and disease [1]. Their discovery was followed by research providing ever more detailed comprehension of genetics at a mechanistic level. By the turn of the 21st century, scientific and technological advances made it clear that the human genome would soon be sequenced. This, along with the emergence of proteomics, metabolomics, advances in bioinformatics and so on, provided a new medical capability: prediction – the ability to quantify disease risks and to detect disease development before damage occurred. Thus, by the time of the complete sequencing of the human genome in 2003, a second transformation of healthcare was being anticipated. Rather than responding to disease events, care could be proactive, predictive and personalized. Indeed, in 2000, President Clinton predicted that decoding the human genome would lead to new ways to prevent, diagnose and cure disease [2]. In my Chairman's address to the Association of American Medical Colleges in 2002, I detailed the concept of 'prospective medicine', a new proactive, personalized model of healthcare delivery. I proposed that predictive technologies could help lead to the "next transformation in healthcare," from being reactive to disease to being proactive, personalized and preventative [3]. This transformation could have a profound impact on enhancing health and curtailing the epidemic of preventable chronic diseases [3,4]. Now, approximately 10 years after the complete sequencing of the human genome, it's appropriate to evaluate its impact on medicine [5].

Concept of personalized healthcare

The sequencing of the human genome stimulated a vision of care based on the principle that disease evolves as a consequence of the
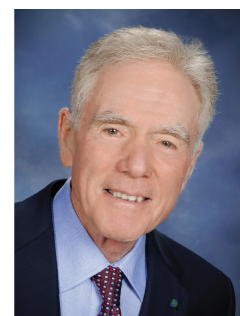
Ralph Snyderman

Duke Center for Research on Prospective Health Care, Department of Medicine, Duke University Medical Center, DUMC 3059; Durham, NC 27710, USA; Tel.: +44 919 684 2345; Fax: +1 919 681 9977; ralph.snyderman@duke.edu

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interplay of genetics and environment over time. With appropriate technologies, one could quantify an individual's disease risks, deploy preventative measures and track progression or regression over time. The adoption of this concept to a healthcare model required tools to quantify disease susceptibility, track its progress, define disease mechanisms and treat it specifically if it occurred [3,6–7]. Since prevention is a big factor, this model recognized the central role of the patient in their care. Genomic sciences could play an important role in providing the capability to define disease risks, understand disease mechanisms, determine disease activity and provide targets for therapeutic intervention. However, genetic medicine was only a part of a far broader approach that I termed prospective medicine or personalized healthcare (PHC) [8]. It was also referred to as P4 medicine; that is, personalized, predictive, preventative and participatory [9,10]. The terms personalized medicine, genomic medicine and precision medicine have also been used, often interchangeably, to describe the application of genomics and other technologies to the practice of medicine. Generally, these terms have been used to describe the use of personalized technologies to refine the treatment of disease. PHC utilizes all the capabilities of personalized medicine/genomic medicine/precision medicine to treat disease, but more broadly applies them to a personalized, proactive, preventative and patient-driven model of care delivery [11].

Impact of genomics on medicine since 2003

The practice of medicine has been greatly impacted by genomics and predictive technologies. Personalized medicine has emerged as over a US$40 billion industry devoted to diagnostics, therapeutics and medical devices and, with the inclusion of healthcare delivery, is estimated to increase to US$400 billion by 2015 [12]. The technology of genome sequencing has been revolutionized by next-generation sequencing (NGS), which has increased the speed of sequencing by many orders of magnitude and reduced its cost correspondingly. Illumina recently announced its HiSeq X Ten supercomputing machine capable of performing 20,000 whole human genome sequences per year for approximately US$1000 per genome rather than the initial cost in 2001 of greater than US$100 million [13]. As George Church indicated: "We are clearly ahead of even the most optimistic projections. For example, based on the aggressive Moore's law exponential curve, the US$1000 human genome should have arrived in 2060 not 2013" [CHURCH G, PERS. COMM.]. A value of genetic information gathered thus far has been the identification of approximately 500,000 to 1 million SNPs that account for the bulk of human genetic

variations, of which several thousand are known to be associated with diseases [14]. However, the contribution of a SNP to any common complex disease is generally only a small percentage and multiple SNPs, each contributing a small percentage, are associated with the chronic diseases studied thus far [15,16]. As Francis Collins indicated: "polygenic disease is really, really polygenic!" [COLLINS F, PERS. COMM.]. While the predictive value of genomic information for common disease is as of yet minimal, the information gathered through gene-wide association studies is providing information regarding genes and pathways involved in chronic disease development [14,15].

Genomic technologies have had their greatest impact on the field of oncology. The identification of genetic mutations predicting susceptibility to breast and ovarian cancer; for example, *BRCA-1* and *BRCA-2*, the definition of oncogenes driving tumor growth, the development of gene expression tests predicting a tumor's aggressiveness and the development of therapies directed to specific cancer targets have begun to personalize cancer care [16–18]. The targeting and inhibition of specific drivers of oncogenes have engendered miraculous remissions in some cancers. It is increasingly appropriate to sequence every cancer as part of the standard of care and use that information to individualize therapy [COLLINS F, PERS. COMM.]. Nonetheless, the subsequent development of resistance to targeted therapy has been the rule. Whole-genome or -exome sequencing of cancer tissues has revealed far greater genetic complexity than previously imagined with a single tumor often having dozens of mutations [18]. This observation likely explains the escape of cancers from singularly targeted therapies. Inhibition of a dominant cancer driver may initially create an apparent remission but allows breakthrough of mutants not inhibited by the targeted therapy. While the complexity of cancer genetics is currently confounding, future research will undoubtedly lead to more rationale therapeutic approaches.

Beyond oncology, multivariant genomic tests have been developed for defining cardiovascular disease risks, predicting transplantation rejection and providing risk assessment for metabolic diseases. Pharmacogenomics has enabled the identification of individuals with variations in drug metabolics and has been useful in predicting dosing levels for warfarin, adverse events to abacavir and efficiency of clopidogrel [16]. Genomics has been increasingly useful in identifying fetal abnormalities noninvasively through analysis of cell free DNA in maternal serum [19]. With NGS, cell-free DNA analysis will likely provide important surveillance and diagnostic tools for cancer, transplantation rejection, and immunologic and infectious

diseases. Direct-to-consumer testing has yet to have a major impact on healthcare because of the limitation of the tests' predictive value [20], but as progress is made in relating genetic variations to disease development and/or outcomes, this situation will change.

Conclusion & future expectations
My evaluation of the first decade of personalized medicine provides mixed grades. The advances in technologies, particularly in NGS, have exceeded my expectations. Nonetheless, the complexity of genetic factors that contribute to common disease have surprised most leaders of the field [COLLINS F, PERS. COMM.]. The impact of genomics on cancer has already been dramatic and engendered targeted therapies, one of the major accomplishments of personalized medicine thus far [WOODCOCK J, PERS. COMM.]. These capabilities will grow rapidly as genomics and other clinical data from individuals are wedded to their data collected from multiple sources and then tracked with clinical outcomes. The power of the capability to identify the causality of clinical outcomes using such strategies cannot be overstated [6].

What remains to be seen is when these emerging capabilities will actually 'flip' our care model from being reactive to disease to being proactive, preventative and personalized. Within a decade, I expect that a major focus in healthcare will be on enhancing health, longevity and minimizing disease as well as personalized care for established diseases. Changes in healthcare reimbursement to reward coordinated and continuous care, as well as good outcomes, are supporting changes in delivery paradigms that will encourage personalized healthcare. The importance of patients as key drivers of their care is now appreciated and models are being developed to increase their engagement. For example, the Veterans Health Administration has embraced personalized, proactive, patient-driven care as its underlying goal with personalized health planning as a core element.

In all, I'm encouraged by the accomplishments made during the first decade of personalized medicine and very optimistic about the acceleration of its application to clinical care. I expect that the next decade will experience the transformation of medicine to the personalized healthcare that I naively predicted over a decade ago.

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