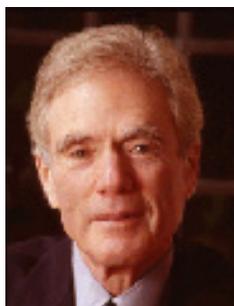




Prospective care: a personalized, preventative approach to medicine



Ralph Snyderman^{1†} &
Ziggy Yoediono²

[†]Author for correspondence

¹Duke University,
Duke University Medical
Center, Box 3059, Durham,
NC 27710, USA

E-mail: snyde001@
mc.duke.edu

²Duke University,
Center for Research on
Prospective Health Care,
Durham, NC 27710, USA

“We now have emerging capabilities to understand each individual's risk of developing disease, for tracking this risk over time, and for recommending appropriate therapeutics”

Need for transformation to a prospective healthcare system

The concept of prospective healthcare began evolving over a decade ago, when it became increasingly apparent that the US healthcare system's focus on treating late-stage disease rather than preventing it was a major impediment to its effectiveness. As a consequence, almost 75% of the money spent on healthcare in the USA is on late-stage chronic disease. It was also becoming obvious that amongst the most important consequences of the genomic revolution was the increasing capability to predict health risks, to track the evolution of disease from a state of health and to intervene early. Despite the profound impact that these new capabilities could have on the practice of medicine, neither leaders of medical education nor healthcare providers were positioning themselves to utilize them to improve care. Simplified, neither the healthcare system at Duke University (NC, USA), nor other institutions throughout the USA, were positioned to take advantage of the emerging capabilities that, for the first time in history, were permitting personalized, preventative approaches to care.

As a leader of one of the nation's major academic health systems, I felt obligated to deliver the message and facilitate change. Indeed, the transformation of medicine by science a century ago was led by the development of the modern day academic medical center structure, which has been the main vector through which progress, as well as the current disease-oriented practice of medicine, has come about. It is naturally the responsibility of academic medicine to support and develop the changes whereby medical education and care can now be based on the emerging capabilities to practice prospectively,

based on determining each individual's health risks and developing plans to mitigate them – ‘prospective care’ [1].

Our opportunities for productive change are strikingly reminiscent of medicine roughly a century ago, when scientific discoveries were first developing powerful applications to the practice of medicine; for example, microbiology, roentgenology and biochemistry. However, initially the profession did not welcome these advances, and indeed resisted them. It was not until many decades after fundamental discoveries, showing the power of science to understand disease, that they were incorporated into the training of physicians and the practice of medicine. Similarly, today we have emerging capabilities to understand each individual's risk of developing disease, for tracking this risk over time, and for recommending appropriate therapeutics. Nonetheless, the healthcare system is not yet poised or positioning itself to change its orientation from a disease-based to a prospective personalized approach.

Disease concept evolution from reductionism to emergence

Current approaches to healthcare are largely reductionist, based on the concept that a disease is due to a pathologic event initiated by a specific initiating factor, and that if the defect is found, it can be reversed and fixed. This concept of ‘find it and fix it’ is a natural consequence of the application of reductionist science into the practice of medicine approximately a century ago. The major transformation of medicine from one of mythology and anecdotal observation to scientific experimentation was driven by discoveries by greats such as Koch, Lister and Pasteur, who founded the concept of ‘germ theory,’ which explained many of the major diseases of that era. This indicated that single initiating agents could lead to major and, at times, catastrophic host responses. The reductionist approach has been a powerful tool in facilitating the broad range of scientific disciplines supporting medicine. This approach has enabled medicine to reverse some diseases, prolong life and, at times, effect wondrous cures. However, the reductionist approach to medicine is limited in that the evolution of virtually all diseases is more

complicated (Figure 1). Disease development, including infectious disease, is based on an individual's inborn baseline susceptibilities, followed by environmental exposures that convert these potential susceptibilities into the development of disease under certain conditions. By focusing primarily on the reductionist model of disease development, the US healthcare system has, unfortunately, not effectively dealt with complex chronic diseases. At present, individuals with five or more chronic conditions account for roughly two-thirds of all healthcare expenses. A more rational approach to healthcare would be personalized prevention and, when necessary, intervention at the earliest possible stage before irreversible pathology sets in (Figure 2).

“A key feature of prospective care
is strategic personalized
health planning.”

Incorporating genomic medicine into personalized health planning

A key feature of prospective care is strategic personalized health planning. This requires a health risk assessment, including determining an individual's baseline susceptibility to disease, their current health status and current risks for major, chronic or uniquely inherited diseases. To effect rational care, the individual and their provider should develop a strategic health plan to mitigate risk and track health status in order to determine if any particular diseases are developing [2–4].

Many of the technologies that enable prospective care – risk assessment, disease tracking and personalized therapy – are now evolving, and were not even available ten years ago. The capabilities for this evolution will stem, in part, from genomics, proteomics, metabolomics, advanced medical technologies, and the ability to store and analyze large amounts of data to be used to predict susceptibility and risk (Figure 3).

Identifying predictive biomarkers requires predictive models, which are statistical representations of measured outcomes of multiple past events. These models, which utilize mathematical equations, distributions or rules, have enabled the forecasting of many nonhealthcare events, such as stock market trends and satellite orbit paths. For biomarker identification, the predictive models consist of risk predictor variables mined from particular clinical cohorts, to which myriad procedures for establishing models can be applied. Such technology, along with the incorporation of emerging biomarker analysis, will enable medicine to utilize causative predictive data in a prospective manner.

Research is already identifying how biologic components, including genes, act as networks to regulate various metabolic processes, including the development of those that are pathogenic. The measurement of components of the network in health and disease will provide a rich source of predictive biomarkers.

Genomic medicine will thus be a catalyst enabling strategic personalized health planning. Due to the success of the Human Genome Project and the advancement of high-throughput ‘omics’

Figure 1. Concepts of disease.

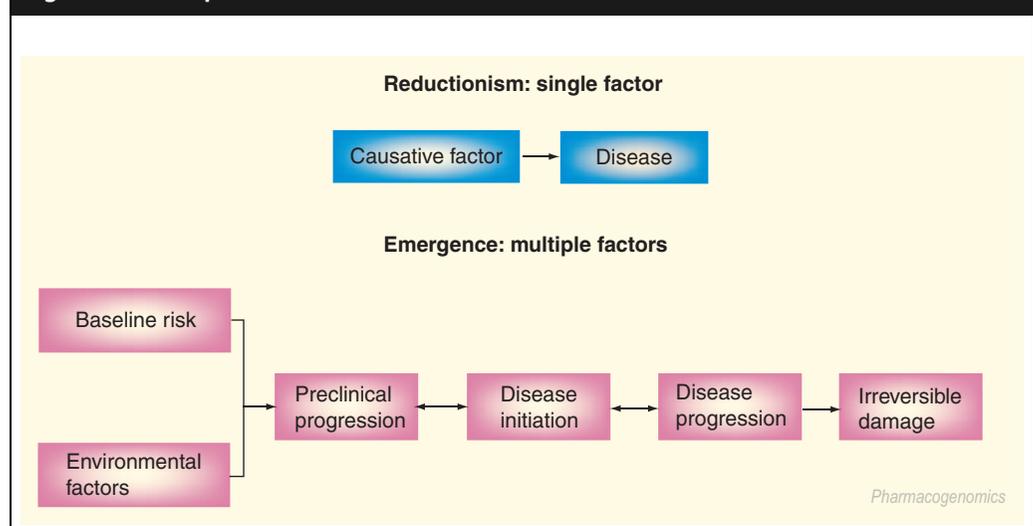
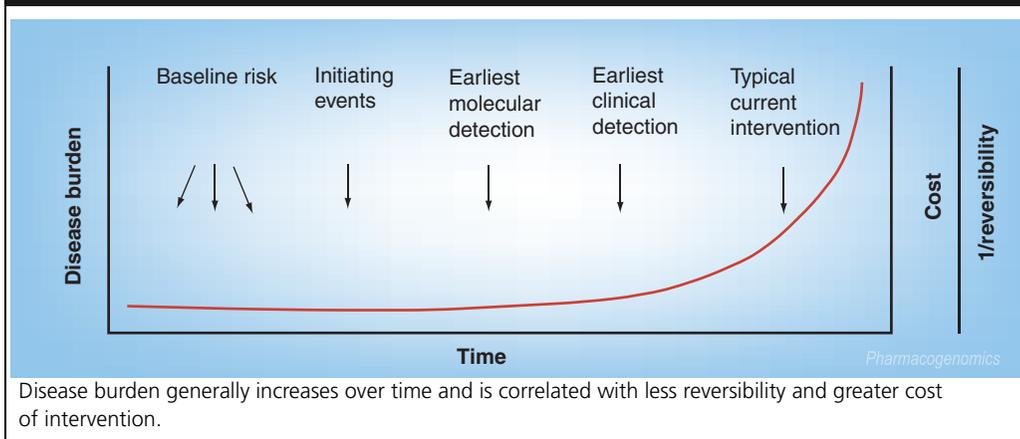


Figure 2. The development of chronic disease and opportunities for intervention.



technology, the elucidation of disease pathogenesis at the molecular level has made enormous strides. Such understanding facilitates a domino effect of improvement: identification of new biomarkers, which improves the sorting of myriad biological data, which then allows the production of a best fit model for quantifying disease evolution and event prediction. The overall effect is the increasingly more sophisticated and accurate incorporation of genomic data as a risk predictive and tracking tool.

“Genomic medicine will provide a rich source of predictive biomarkers and will thus be a catalyst enabling strategic personalized health planning.”

Currently, clinical data, family history, clinical laboratories, and genetic pedigree are the main types of data utilized for baseline risk assessment.

Unfortunately, the accuracy of such traditional methods is generally limited to ‘you are at an increased risk for disease/event X,’ with no quantitative time or probability parameters provided.

The prospective strategic personalized health plan would increase the predictive accuracy and validity of baseline risk by incorporating more causal biomarkers, including inherited genomics and dynamic factors, such as gene expression, proteomics, and so on. Single nucleotide polymorphisms (SNPs), haplotype mapping, and gene sequencing for abnormal alleles are already providing good baseline risk data in selective areas. As an example, SNPs are the main type of clinically usable biomarker data, for example, for the diagnosis of Mendelian diseases such as long QT syndrome and cystic fibrosis [5].

The translation of genomic medicine into a prospective strategic personalized health plan requires decision-support tools. Quantitative assessment by such tools would likely encompass three disease progression phases and an intervention phase: baseline risk, preclinical

Figure 3. Risk assessment process.

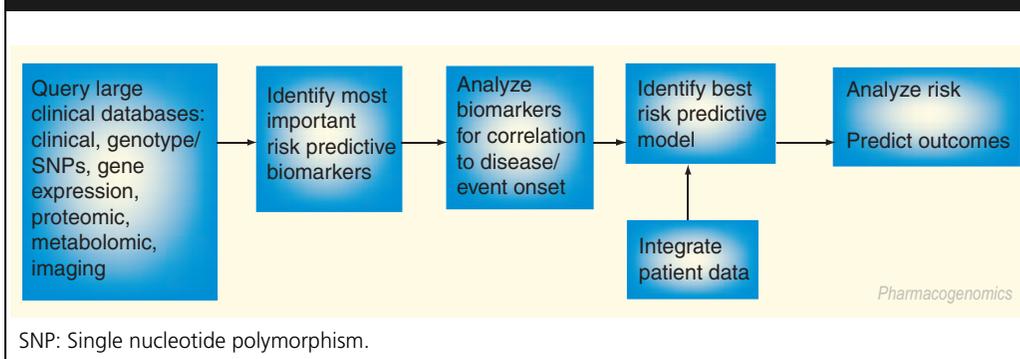
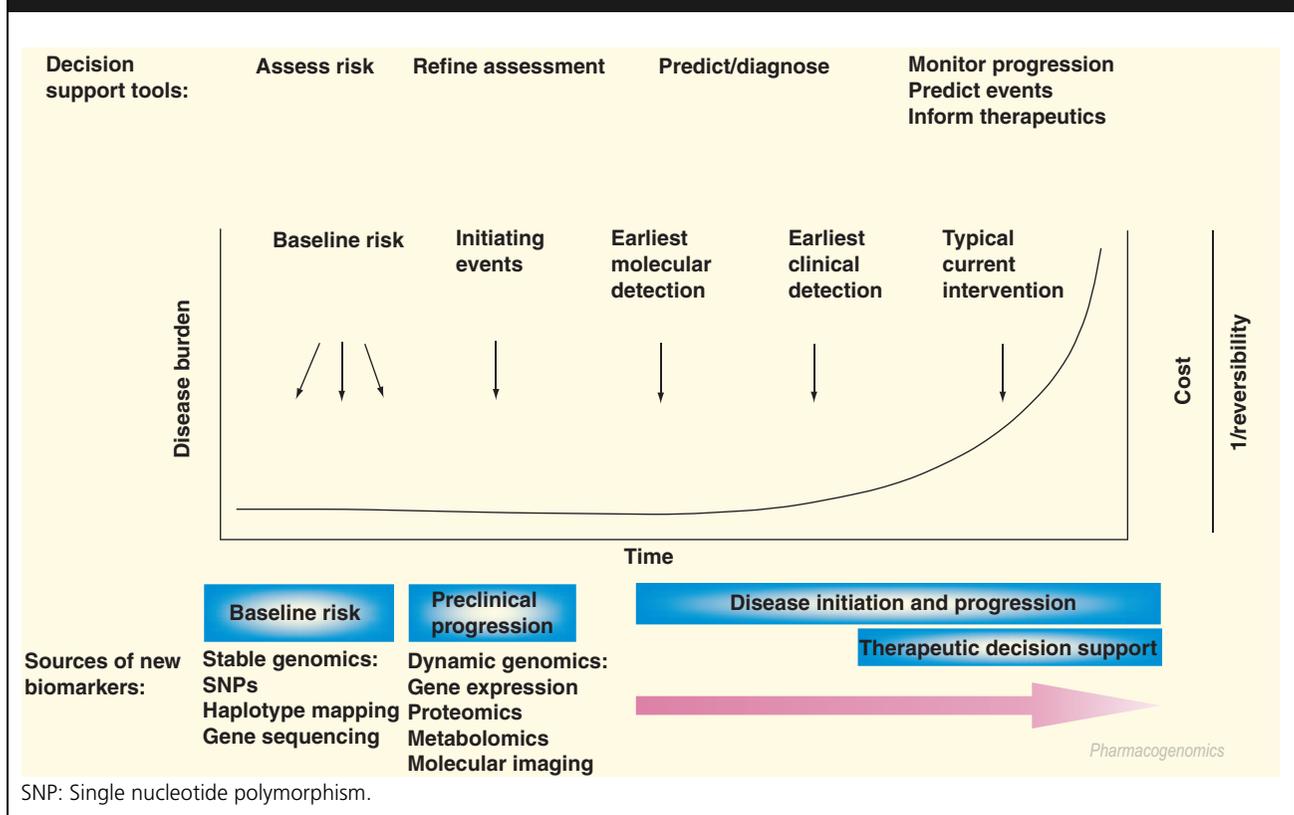


Figure 4. Tools required for prediction and personalized care.



progression, disease initiation/progression, and therapeutic decision support (Figure 4).

“The translation of genomic medicine into a prospective strategic personalized health plan requires decision-support tools.”

Baseline risk can lead to preclinical progression as a consequence of initiating events taking effect. Traditional clinical medicine has only recently begun to formally assess this stage in selective areas, predominantly for cardiovascular and selective cancer risk. A prospective strategic personalized health plan will broaden such capabilities and formalize the concept by incorporating dynamic genomics: gene expression, proteomics, metabolomics, and molecular imaging. Obviously, these fields are still in their infancy with regard to predictive value, but it can be assumed that progress will be rapid and facilitated by technologic advances. Subsets of genomic medicine are actually in current use, especially in cardiology for applications such as the development of atherosclerosis [6].

Although SNPs are mainly utilized, gene expression patterns are often used in oncology to distinguish between tumors that appear histologically

similar. Oncogenomics has witnessed the emergence of numerous technologies. For example, diagnostic tools have been developed to quantitatively predict disease recurrence among breast cancer patients and assess the likelihood of beneficial response from certain chemotherapies. Gene expression has also been adapted to predict the likelihood of heart transplant rejection [7].

Two technologies have facilitated the utilization of proteomics. The first is 2-D gels, which identify proteins correlated with particular diseases. Second is mass spectroscopy, which today enables the sifting of myriad peptide and protein structures from biologic fluids and disease tissues. As a result, proteomics has already found a clinical utilization in the risk stratification of individuals with acute coronary syndromes [8–10].

Nuclear magnetic resonance and mass spectroscopy have enabled the quantitative analysis of various types of metabolites and even metabolite patterns, which are required for disease risk prediction/tracking. Metabolomics has been utilized to risk stratify those with coronary artery disease [11,12].

From preclinical progression, the disease burden may advance to actual disease initiation/progression. Typical medical intervention

usually occurs during the latter stages of disease progression, when disease burden is well advanced and less amenable to intervention. Clinical features, histopathology and diagnostic imaging are currently the main tools utilized at this stage, and would continue to be an integral part of the prospective strategic personalized health plan. However, they will be markedly improved by algorithmic disease tracking tools measuring causative biomarkers.

Pharmacogenomics is an integral area concerned with therapeutic decision support, and such genomic data should be utilized in several ways. The first way is to utilize genetic markers to predict individuals who will or will not respond beneficially to the drug. For example, recent data have shown that genetic variations influence factors such as cholesterol production, lipoprotein catabolism, and intestinal cholesterol absorption, which in turn influence statin responsiveness and drug metabolism. The second way is to use such data to decrease drug toxicity by identifying groups of patients who are most vulnerable to complications, thereby precluding a scenario of minimal benefit but significant adverse reactions [13,14]. The third way is to analyze gene expression in diseased or

surrogate tissues to inform the aggressiveness of the disease (for example, cancer), as well as the most appropriate therapeutic regimen.

Individual responsibility

Prospective care requires not only a major change in the healthcare delivery system (as well as reimbursement and many legal protections), but also provides a major opportunity and responsibility on the part of the individual. A major responsibility for mitigating risk will rest on the individual who will clearly need the support of an appropriate healthcare system. Much of this will be in education, in addition to mentoring when necessary. Full implementation of this approach, including an improved understanding of inherited susceptibilities, measures of disease progression and therapeutic decision support, will take many years to be implemented. Nonetheless, the emerging capabilities resulting from genomic research are providing some useful tools now, and will progressively move healthcare from a reactive disease-oriented model to a more strategic, prospective approach.

Disclosures

Ralph Snyderman, MD, is the Chairman and Founder of Proventys, Inc, and sits on the Board of Directors of XDX, Inc.

Bibliography

- Snyderman R, Williams RS: Prospective medicine: the next health care transformation. *Acad. Med.* 78(11), 1079–1084 (2003).
- Williams RS, Willard HF, Snyderman R: Personalized health planning. *Science* 300 (5619), 549 (2003).
- Langheier JM, Snyderman R: Prospective medicine: the role for genomics in personalized health planning. *Pharmacogenomics* 5(1), 1–8 (2004).
- Snyderman R: AAP Presidential Address: The AAP and the Transformation of Medicine. *J. Clin. Invest.* 114, 1169–1173 (2004).
- Lai E: Application of SNP technologies in medicine: lessons learned and future challenges. *Genome Res.* 11(6), 927–929 (2001).
- Lopes N, Vasudevan SS, Alvarez RJ, Binkley PF, Goldschmidt PJ: Pathophysiology of plaque instability: insights at the genomic level. *Prog. Cardiovasc. Dis.* 44(5), 323–338 (2002).
- Shulzhenko N, Morgun A, Rampim GF: Monitoring of intragraft and peripheral blood TIRC7 expression as a diagnostic tool for acute cardiac rejection in humans. *Hum. Immunol.* 62(4), 342–347 (2001).
- Seo D, Ginsburg GS: Genomic medicine: bringing biomarkers to clinical medicine. *Curr. Opin. Chem. Biol.* 9(4), 381–386 (2005).
- Aebersold R, Mann M: Mass spectrometry-based proteomics. *Nature* 422(6928), 198–207 (2003).
- de Lemos JA, Morrow DA: Combining natriuretic peptides and necrosis markers in the assessment of acute coronary syndromes. *Rev. Cardiovasc. Med.* 4(Suppl. 4), S37–S46 (2003).
- Seo D, Ginsburg GS: Genomic medicine: bringing biomarkers to clinical medicine. *Curr. Opin. Chem. Biol.* 9(4), 381–386 (2005).
- Brindle JT, Antti H, Holmes E *et al.*: Rapid and noninvasive diagnosis of the presence and severity of coronary heart disease using 1H-NMR-based metabolomics. *Nature Med.* 8(12), 1439–1444 (2002).
- Bell J: Predicting disease using genomics. *Nature* 429, 453–456 (2004).
- Kajinami K, Okabayashi M, Sato R, Polisecki E, Schaefer EJ: Statin pharmacogenomics: what have we learned and what remains unanswered? *Curr. Opin. Lipidol.* 16(6), 606–613 (2005).