PERSPECTIVES

Personalized Medicine: Understanding Probabilities and Managing Expectations

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Personalized medicine promises to represent a transformation in clinical care that will be ushered in by the unprecedented growth and development in the field of human genetics. Further examination of the scientific foundations of this new hope reveals a great number of challenges that lie ahead. While basic science research feverishly races to produce solutions, we continue to wait for the translation of deliverables. Products that have and will come to market may leave our clinical communities and systems exposed and unprepared. At each step, from basic science research to infrastructure development, a great deal of creativity and investment are required before the arsenal of more personalized tools can be assimilated into our current models of health care. This commentary seeks to share perspectives on the current status of personalized medicine from the vantage point of several potential investors, and integrate them into a common set of goals and understanding. We conclude that the stylized model of personalized medicine is more akin to a marketing tool than a literal prediction of the future.

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In recent years the public has been offered a new vision for health care. The terms "individualized medicine" and "personalized medicine" have crept into common language. They signal a transformation of clinical care from a paradigm where diagnostic labels and treatment benefits and risks are determined for populations of patients, to one where each individual patient will have care tailored to him or her. The scientific foundation for personalized medicine will be derived from a more complete understanding of the most basic and fundamental information about individuals, namely their genes. The promise that care will be improved from a systematic understanding of genetic biology is tantalizing to say the least. In this commentary we discuss the complexities that will be involved in translating a platform of basic science knowledge into clinical care. We conclude that the term "personalized medicine" is best thought of as a marketing tool rather than a literal prediction of the future.

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GENETIC AND MOLECULAR MEDICINE: PERSONALIZED INFORMATION OR PERSONALIZED COMPLEXITY?

A highlight of genetic biology has been the human genome project which for the first time mapped human beings' entire genetic information. While initially it was believed that only 2% of the genome was involved in transcription and translation, the findings of the ENCODE consortium have revealed a language of non-coding regions or non-gene regulatory processes that have yet to be translated. It has since been estimated that over 80% of disease associated genetic variants fall outside protein coding regions.[1] Furthermore, it is now widely understood that genes are in fact not static but rather are intimately involved in their own translation in a time and environment-dependent manner.[2]

Combining DNA microarray platforms with the information generated by the International HapMap project has allowed researchers to undertake genome wide association studies (GWAS) in the search for variants of specific genes, or narrow genomic regions associated with human disease. Commercial gene chips have progressively increased the number of genetic variants investigated in a single study from several thousand to more than a million single nucleotide polymorphisms (SNPs) in thousands of individuals, and have begun to incorporate structural variants, and copy number variants as well.[3] However, genes identified to date only account for a minor portion of the overall genetic contribution to disease, and so far, for common diseases, the risk imparted by each is modest, with odds ratios in the range of 1.1 to 1.4.[4] This leaves researchers with the challenge of accounting for the missing heritability, or the "dark matter" of GWAS[1]. Currently there is no clear focus or direction to future research strategies designed to tackle the building number of hypotheses and still a great deal of work to be done to determine the functional basis for associations already identified.[5]

The next steps in the model involve understanding how RNA transcripts inform functional proteins which signal cell behavior. RNA transcriptional identification and quantification has equally benefited from the rapid development of microarray technology; however, it paints an incomplete picture as mRNA expression correlates poorly with specific functional proteins manifesting disease.[6] Functional proteomics is then charged

with mapping the extensive network of signaling pathways that encompass an estimated one million proteins that make up the human proteome. Over the past 40 years the model of protein based biomarkers employing immunoassays has been used to help clinicians make decisions about diagnosis and treatment. There is a hope that proteomics will be used in a similar fashion to inform clinical care; however, there is a clear need to validate findings across these new fields as well as to creatively translate true positives into clinical applications.[7]

DIAGNOSTIC AND DRUG RESEARCH

While personalized medicine has the potential to have an impact on every aspect of health care, the greatest expectations are within the realm of pharmaceuticals. The current model of drug discovery and translation into commercially available products has used profits as the incentive to search for "blockbusters": drugs that will have worldwide sales that exceed one billion dollars per year. The early success stories of personalized medicine, however, like Gleevac (imatinib mesilate) or Herceptin (trastuzumab), have not provided replicable platforms for the discovery of other drug entities or commercial products.[8] One of the hopes for pharmacogenetics and pharmacogenomics, two terms that are aimed at describing the impact of personalized medicine on drug development, lies in the potential to improve productivity by discovering molecular biomarkers that identify patients as potential responders or those that are higher risk for suffering adverse events. This will require the development of a new business model that will integrate lab services with drug delivery.

There are two basic strategies in current use. The first is to target therapies that are currently licensed for sale to improve the efficiency of their use. Perhaps the best described example of this phenomenon is testing for genetic variance in CYP2C9 and VKORC1 which have been shown to alter patients' response to Coumadin, a medication that is used by millions of people in the United States and is associated with a significant risk of bleeding.[9] An initial report by AEI-Brooking Joint Centre for Regulatory Studies suggested that testing for polymorphisms in these genes would decrease health care spending in the United States by up to two billion dollars annually.[10] This report, which was published before any clinical study had empirically demonstrated improved patient outcomes, has been subsequently followed by several studies that are more discouraging. Of note, one randomized control trial showed no difference in "out of range" INRs using a genotype guided therapy strategy,[11] while a second was able to predict out of range INRs, with differences being only shades of probability (e.g., 49.4% vs. 33.3% or 24.8% vs. 7.2%), and in those cases, only in patients requiring very high or very low doses.[12] Despite these uncertainties the FDA added pharmacogenomic information to the warfarin label in 2007.

A recent analysis of warfarin pharmacogenomic testing concluded that although some clinical benefit may be expected, there remains great uncertainty to the cost, and therefore, the economic value.[13] While the debate continues, the fruit of this labor may lie solely in the process as newer anticoagulants like dabigatran etexilate, apixaban, and rivaroxaban hit the markets with the potential to replace coumadin.[14]

The second strategy involves the use of molecular diagnostic tests in tandem with drug development. Small diagnostic companies are teaming up with large scale pharmaceutical companies to achieve this goal. For example, Monogram Biosciences Profile test, which determines the chemokine receptor (CCR6 or CXCR4) utilized by a patient's human immunodeficiency virus (HIV) population to enter their cell, has been used by Pfizer in phase 2 and phase 3 trials. Pfizer has taken advantage of the information added from the test results to produce samples of patients where the effect size of new interventions, namely chemokine receptor antagonists, can be maximized.[15] A more recent publication demonstrated that a newly enhanced tropism assay would be a better screening tool for eligibility of the antagonist by identifying genetic variants below the detection limit of the original assay.[16] This example demonstrates the moving target of accuracy in this rapidly evolving field.

Ultimately, the value of these partnerships is difficult to measure up to the present time and investors have clustered primarily around proven success stories. The term 'theranostics', which implies the marriage of diagnostic tests with therapies, has arisen to characterize this phenomenon. Since its introduction, new challenges have arisen. For example, toxicities of drugs developed to target specific personalized genetic defects that vary across individuals with a single disease (e.g., Duchenne's muscular dystrophy) may be species specific, calling into question the value of animal testing, and raising the ethical dilemma of determining toxicity based on solely patient exposure.[17] The many limitations to the predictive capability of genetic testing, as well as the potential problems related to compliance, side effects, and treatment failure, make it difficult to foresee the day when theranostics, an attractive theoretical concept, becomes standard of "care".

PERSONALIZED MEDICINE AND HEALTH CARE SYSTEMS

Mercifully, genomic based medicine has not flooded into our health care system, for if it did we would certainly not be ready for it. Exceptional breakthroughs that have come to market like HER2 testing to target trastuzumab treatment for patients with breast cancer have highlighted the problem of translating basic science into clinical practice. Approximately 20% of the HER testing has been reported to be inaccurate posing a significant risk of cardiotoxicity to those without potential benefit and significant costs to the health care system from this one drug alone.[18] An increasing proportion of novel therapeutic interventions rely on genetic testing to determine clinical utility or guide therapy. Many of these tests have not been independently reviewed for accuracy and reliability by the FDA.[19] Before genetic testing hits its primetime, it will need to meet current and established standards in order to determine their clinical utility. In some cases this will require databases linking test results to treatment outcomes for populations of patients and involve post-marketing genetic surveillance in order to maximize the potential benefit of this approach. These variables may also require repeated measurements if they demonstrate variability over the clinical course, or if as previously highlighted, newer, and more sensitive tests are developed.

The personalized medicine movement may be a boon to biostatisticians and those who design clinical trials and research studies of other design in that there will surely be novel methodological issues. It will be particularly important to perform hypothesis testing studies (i.e., those which are an empirical test of a previously derived model) rather than rely on the current association-driven results which are merely hypothesis generating. This same issue was crucial in the development of clinical algorithms beginning 30 years ago. The huge number of genes available for demonstrated associations and the wealth of information being churned out at an increasing pace leave some with the feeling that we are producing more data than we can analyze or understand.[7]

The personalized medicine vision of the future will most likely not simplify clinical decision making but rather make it more complex and will be unable to fulfill the promise of informing patients with certainties. Just as clinical algorithms either increased or decreased patients' probabilities of developing disease or responding to therapy, the personalized medicine platform will mostly likely do the same. Patients, providers, and payors will instead be provided with a spreadsheet of personalized probabilities. This in fact will not be much different than the way that clinical medicine is practiced now.

CONCLUSION

Fundamental scientific discovery has on occasion provided spectacular success stories with significant improvements in the health of populations and individuals. The most obvious recent example was the story of the diagnosis and treatment of a new disease, human immunodeficiency virus. In less than 20 years clinicians and scientists together discovered the cause of a new disease, how to diagnose it, and developed effective therapeutic strategies that converted an almost uniformly fatal illness into one where life expectancy and quality of life are almost at the same level of the non-infected population. The marriage of basic scientists with the profit driven pharmaceutical industry clearly worked here. The hope is that the same stimuli that provided the success story in HIV will produce similar results using the platform of the model of personalized medicine. However, when one steps back to reflect on how improvements in health care have developed over the last two centuries, one realizes that it will never be quite that simple.

The stylized model of personalized medicine is currently being used as a marketing tool to give the public hope for the future and to encourage the flow of funds into medical research. Stylized models and catch phrases can indeed be very useful motivators of public will and response. President Nixon's "War on Cancer" was a useful motivator for expansion of NIH funding. However, even the most optimistic scientist with a full understanding of the personalized medicine model knows that it is simply that, a target, a strategic objective, and not likely to be a fully accurate description of the future. While we would never want to dampen the enthusiasm for funding research, we think it is important that everyone understands this at this time.

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