VIEWPOINT

Seven Questions for Personalized Medicine

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Personalized or precision medicine maintains that medical care and public health will be radically transformed by prevention and treatment programs more closely targeted to the individual patient. These interventions will be developed by sequencing more genomes, creating bigger biobanks, and linking biological information to health data in electronic medical records (EMRs) or obtained by monitoring technologies. Yet the assumptions underpinning personalized medicine have largely escaped questioning. In this Viewpoint, we seek to stimulate a more balanced debate by posing 7 questions for the advocates of personalized medicine.

Does the Human Genome Contribute to Disease Risk Prediction?

Personalized medicine builds on the Human Genome Project, which was forecasted to revolutionize disease risk prediction, with projected relative risks as high as 6 for gene variants linked to specific diseases. However, the relative risks for the vast majority of gene variants rarely exceed 1.5, and these variants have added little useful predictive power to traditional risk prediction algorithms. Moreover, improved adherence with lifestyle interventions expected to result from the provision of genomic risk information to patients has not materialized.[1]

Will Gene-Based Drug Targeting and Development Fulfill Its Promise?

Personalized medicine predicts that therapies for cancer that target dysregulated "-omic" pathways will be transformative. Yet the benefit of such drugs on overall cancer survival has been limited, perhaps because of the adaptive nature of cancer. There is little evidence that targeted therapy will interrupt the cycle of expectation and disappointment that has typified many of the new approaches to cancer therapy. Most of the recent successes in cancer have resulted from the traditional public health measures of screening, early detection, and smoking reduction as well as some immunologic therapies.

For common disorders, the claim that genotype-based treatment schemes will be more effective with fewer adverse effects is not supported by negative findings for both tamoxifen[2] and warfarin.[3] Even though gene variant information can suggest new therapeutic targets, it will always have to be integrated into traditional drug discovery approaches.

Two much-publicized successes in disease gene identification were *BRCA1/2* for breast or ovarian cancer and mutations for cystic fibrosis (CF). Although finding a subgroup of the population that is at very high risk of cancer is important, no new therapy has resulted from discovery of the mutations. Instead, the 5% of patients with breast or ovarian cancer who are positive for *BRCA* are offered enhanced screening and preemptive surgery. In the 25 years since *BRCA1/2* was discovered, breast cancer mortality in the United States has declined by nearly one-third; however, little of this decline stems from the discovery of *BRCA1/2*. Moreover, *BRCA1/2* is a unique story because the gene variants account for such a substantial amount of the variance in outcome for a limited number of patients.

In CF, 2 drugs (ivacaftor and lumacaftor) have recently been developed based on the CF transmembrane conductance regulator gene (*CFTR*), but they are useful only in patients with specific *CFTR* mutations, in whom they increase, singly or in combination, maximum forced expiratory volume (FEV) by 5% to 10% and improve weight gain.[4] However, since the discovery of this gene in the 1980s, CF survival has improved substantially as a result of strict adherence to clinical management guidelines originating in pulmonary physiology and infectious diseases, but not genomics.

Although well-deserved recognition has accompanied these genetic discoveries, neither has been a significant factor in the substantial reduction in mortality from the 2 target diseases during the past 25 years. The commitment to screening technology and adherence to best practices has proven far more important to the lives of affected patients.

What Will EMRs Contribute?

The transition to EMRs has expanded the reach of medical record–based information, but has not markedly improved the quality of the data entered. Although examples of improved clinical practice driven by EMRs can be found, the quality and granularity of the data they record limit their use in research. The inherent variability of clinical data across institutions is magnified by institution-to-institution differences in EMR systems. A seamless, interoperable national EMR system is, at best, decades away for the United States and unlikely to include informative phenotypic data such as waist circumference, musculoskeletal fitness, and exercise capacity.

What Kinds of Studies Should Be Mounted in Personalized Medicine?

In recent years, terms such as *unsupervised*, *agnostic*, *discovery*, and *data mining* have been used to describe an approach to big data that proceeds without explicit hypotheses, with conclusions derived from the *P* values of discovered associations. Convenience samples are often used without an appreciation of how selection bias and other factors can distort exposure-outcome relationships. Much so-called discovery science presupposes that the individual is isolated from his or her social context and that cellular data are sufficient to predict disease. By contrast, successful population-based approaches to the study of disease, such as the

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Framingham Study, have specific hypotheses that inform data collection and carefully assess prespecified exposures and outcomes in a standardized fashion.

Genomically targeted drug therapies, like all other drugs, will need to be evaluated by rigorous clinical trials. But if the goal of personalized medicine is therapy targeted to the unique genome of an individual (or tumor), of what relevance is a clinical trial in individuals who do not share that genome? This perspective is supported by enthusiasm for N-of-1 trials, a sophisticated version of the trial-and-error approach of prescientific medicine. Other scientists recognize that the application of personalized medicine is not truly personal, but that genomic markers should be used to create smaller and more homogeneous subgroups of patients to treat with targeted therapy. Whether genomic markers will prove to be the best determinants of optimal treatment for cancer remains an open question. These concerns are amplified by the ongoing debate in the oncology community about appropriate outcomes for cancer trials and the predictive utility of surrogate end points. With increasing emphasis on the quality of well-being at the end of life, limited gains in overall mortality and disease-free survival may become less important.

How Should Institutional Conflicts of Interest Be Managed in Personalized Medicine?

Personalized medicine raises difficult conflict of interest issues beyond the level of the individual investigator to the level of the academic institution. The need for institutions to obtain more federal funding, philanthropic support, intellectual property, and industry partnerships have led to a rapid expansion of institutional personalized medicine initiatives. The widespread marketing of these initiatives based on optimistic projections of personalized medicine's potential requires safeguards to limit institutional conflicts.

How Will Personalized Medicine Affect the Costs of Medical Care?

Dzau et al[5] have suggested that medical care costs will be reduced if personalized medicine addresses prevention rather than therapy. However, the very nature of personalized medicine, which is targeted, specific, and personalized, must inevitably produce interventions that are much more expensive than historically successful preventive interventions that have been applied broadly to populations. Even though genomic risk markers do not seem to improve patient compliance with risk-avoiding behaviors, gene variant information has been shown to increase physician visits, laboratory tests, and patient anxiety.[6]

For drugs, costs depend on the size of the target population: the smaller the population, the costlier the drug. The target populations for personalized medicine drugs are by design small and selected. The average annual cost of new targeted cancer drugs frequently exceeds $100 000 per year. The authors of a recent trial of ivacaftor and lumacaftor for CF pointed out that these new medicines had effects on FEV in the first second of expiration "in the range of the magnitudes of change seen in studies of other cystic fibrosis therapeutics."[4] These include azithromycin, hypertonic saline, and ibuprofen.[7] Ivacaftor costs $300 000 per year, whereas a 1-year supply of ibuprofen costs approximately $30, and unlike ivacaftor, it can be used by all patients with CF.

Where Is the Public Health Benefit?

The most important question is the final one. Will personalized medicine reduce the major causes of morbidity and mortality? If not, why should the National Institutes of Health, and other federal agencies whose goals are improved health for the US population, invest so heavily in personalized medicine?

Historically, improvements in public health have come either from general improvement in socioeconomic conditions or from programs targeted broadly to entire populations, such as improved sanitation, mass immunization, and tobacco control. The human genome simply does not explain much of the variance of common human diseases, and the variance it explains is rarely susceptible to direct medical or public health action. Advocates of personalized medicine who disagree with this perspective should identify diseases for which they expect mortality rates to be improved and project the size of the effect for comparison with approaches that do not involve personalized medicine.

Conclusions

Even though personalized medicine will be useful to better understand rare diseases and identify novel therapeutic targets for some conditions, the promise of improved risk prediction, behavior change, lower costs, and gains in public health for common diseases seem unrealistic. Proponents of personalized medicine should consider tempering their narrative of transformative change and instead communicate a more realistic set of expectations to the public.

ARTICLE INFORMATION

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