On the valuation of genetic tests

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Continuing progress in the field of human genetics may lead to more widespread use of genetic screening in medicine. While hundreds of publications have so far reported the identification of novel genetic disease risk factors and genetic mediators of treatment response, only a few FDA-approved genetic tests are presently available. Nevertheless, in an era where healthcare costs continue to rise, the possibility that genetic testing may prove a cost-effective means to optimize therapy seems worth pursuing. As stakeholders engaged in basic research, business development, regulatory affairs and clinical practice work toward an era of personalized medicine, it is increasingly possible to view the field from afar as a whole.

One concept that underlies the entire process by which data from basic population genetic studies are converted into FDA-approved, commercially viable genetic tests is that of 'valuation'. In a general sense, it is often useful to be able to compute the expected value of a future benefit in order to know how much to invest in research and development. In the case of genetic tests, where the stakeholders consist of scientists, early-stage venture financiers, large pharmaceutical firms, third party payer organizations, clinical practitioners and regulatory officials, many divergent and field-specific factors can contribute to an overall sense of the value of a particular genetic test. For example, treatment with trastuzumab (Herceptin®) is enhanced by genetic prescreening for expression of HER-2/NEU, the receptor to which the drug binds. From the population geneticist, the clinician and, most importantly, the patient's point of view, the ultimate value of such a genetic test may lie in its ability to predict treatment outcome (survival). From the third party payer's point of view, the value of the test may be impacted by the overall cost savings per quality-adjusted life year (QALY). From the regulatory official's point of view, the value may have more to do with minimizing the potential downside risk of false positives. Finally, business development teams may focus strictly on the present value of expected cash flows from sales of genetic tests. While these perspectives differ greatly there may be several points of overlap shared across these disciplines. These underlying factors may provide common ground to construct more detailed valuation models for the purposes of development.

Variability in the human genome forms a fundamental basis for personalized medicine. Differences in genome sequence (some 4.5 million at the latest count [1]) are an historical record of some of the mutational events that have accumulated over the course of human evolution. As such, these single sites can vary dramatically in frequency within and across populations. Mutational events that occurred early in human evolution may be present at moderate frequencies in all human populations, whereas events that occurred after humans migrated into Europe, Asia and the Americas may be found at high frequencies in some populations and low frequencies in others. Indeed, 'one-size-fits-all' therapy stands in stark contrast to the rich variability of the human genome, which has been subject to thousands of generations of mutation, recombination migration, and, at times, Darwinian selection. Patterns of human genetic variability have been well cataloged and analyzed. In the case of the genetic test for thiopurine methyltransferase (TPMT), about 1 in 300 Caucasian, African and Asian individuals are homozygous for TPMT deficiency. When homozygous patients are treated with mercaptopurine-based chemotherapy, a severe form of bone marrow suppression can occur. There are 1 in 10,000 individuals homozygous for a mutation in dihydropyrimidine dehydrogenase (DPD) that leads to an adverse drug reaction (ADR) to fluorouracil chemotherapy. Additionally, while many thousands of polymorphisms have been identified, very few have been functionally characterized. Confidence in statistical links between a genetic change and treatment response can be greatly enhanced in the context of a known biochemical pathway or mechanism. Presently, the effects of only a few genetic polymorphisms, such as those coding for the binding site of the epidermal growth factor receptor (EGFR), are supported by knowledge

of a biochemical mechanism. This genetic information can be used to guide treatment with gefitinib (Iressa®), which was approved by the FDA last year. The functional effect of a single polymorphism can also vary greatly. In the case of TPMT deficiency, the concordance between genotype and a deleterious, and even fatal, mercaptopurine dose response is > 95%. In the case of EGFR polymorphisms, the response to treatment is significantly different, but with a lower concordance rate. The predictive ability of the TPMT genetic test is based on an understanding of the molecular mechanism of prodrug metabolism, while tumor response to EGFR binding involves more complex biochemical pathways.

While the HER-2/NEU, TPMT, DPD and EGFR genetic tests are different, a few basic issues, such as the population frequency, understanding of mechanism and the concordance between genotype and treatment response form essential underlying components of a valuation equation. These issues are of concern to all stakeholders who can then form reasonable expectations about the demand and efficacy of the genetic test. In the coming years, as more population genetic data are acquired, new polymorphisms will emerge with the possibility of clinical benefits. Improvements in technology, such as microarray-, microfluidic- and/or mass-spectroscopic-based genotyping, may dramatically reduce the cost of genetic data collection. Consolidation among molecular diagnostic platforms, witnessed by the recent joint venture between IBM and the Mayo Clinic and the merger of Amersham with General Electric, will also lower barriers to pharmacogenetic data analysis. While these changes in the clinical and business landscape will alter business models and the valuation equations they are based on, a basic understanding of the genetic history and biochemical mechanism of each candidate polymorphism will remain fundamentally important.

Website

1. http://www.ncbi.nlm.nih.gov/SNP/snp_summary.cgi
NCBI's dbSNP summary.