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What happened to personalized medicine?

Personalized medicine falls a long way short of the predictive and preventative healthcare paradigm it once promised.

In some respects, 2011 was a banner year for personalized medicine. Academic medical centers began to demonstrate the feasibility of routine clinical genotyping as a means of guiding treatment selection in oncology. The US Food and Drug Administration released its companion diagnostics draft guidance. Sanofi, Pfizer and AstraZeneca signed deals with Medco and WellPoint for access to their large databases of patient data. Cancer Research UK's Stratified Medicine Programme was launched to demonstrate how genetic tests can be used to match National Health Service cancer patients to treatments. And two new targeted oncology therapies, Roche/Genentech's Zelboraf and Pfizer's Xalkori, were approved in conjunction with companion diagnostics for *BRAFV600E* and structural variants of anaplastic lymphoma kinase (*ALK*), respectively.

All are no doubt important steps, but illustrative of a rather pedestrian form of progress in personalized care rather than a march to the future.

Back in the late nineties, following the approvals of Gleevec and Herceptin, it all seemed so different. Personalized medicine was the powerful idea that would drive rational use of pharmaceutical products. Healthcare would shift from treatments of last resort to a system that emphasized disease risk prediction, prevention and early therapeutic intervention. Single complex, heterogeneous conditions, such as hypertension, would be profiled and end up as many molecularly defined subtypes, each with its own tailored, highly efficacious therapy. Genotyping would enable the surveillance of mutations in cancers and infectious agents associated with the emergence of drug resistance. Molecular profiling would be used to resurrect drugs that had been shelved because of a poor therapeutic index. Genetic polymorphisms linked to variability in patient responses would allow drug dosage to be tailored accordingly. The right drug for the right patient at the right time.

Bur perhaps the past decade was not exactly the right time for such a model, given the paltry number of examples in clinical practice.

One reason for slow progress is simple economics. Until recently, big pharma's model was based on selling as much medicine to as many people as possible. Thus, personalized medicine, which involves the increased cost of prospective trials involving biomarkers and the decreased margins of segmented markets, never exactly caught on. What's more, as it is big pharma's agenda that determines which biomedical innovations get funded, very little funding for personalized approaches has flowed into the biotech sector. Thus, even though an estimated 90% of drugs currently on the market work in only ~40% of individuals—translating annually into $350 billion worth of ineffective prescriptions—pharma has had little incentive to adopt personalized business models.

In addition, there is a technology lag. On the one hand, enormous progress has been made in next-generation sequencing platforms, social networks to link patients with one another, the adoption of electronic health records and the miniaturization of existing devices and electronic data capture. But integrated and foolproof microfluidic point-of-care devices that provide unequivocal readouts to clinicians (or patients) remain some way off. Technology enables research, but not clinical practice.

Which brings us to perhaps the key impediment—biology. One reason why pharmaceutical R&D is so inefficient is that all the new shiny technologies from biotech companies have generated more data but ultimately made very little impact on predicting whether an experimental drug works in humans. We now appreciate, of course, that gene mutations do not perfectly predict outcomes. Many conditions come about through a combination of numerous variants of low penetrance, some of which may lie outside coding regions, and genetics is only part of the story. Epigenetic changes, modifications at the protein and metabolite level as well as xenobiotics all contribute to disease over a lifetime. Work on the microbiome is also adding to this complexity—up to 20% of the small molecules in the circulation are microbially derived.

Given that most disease is currently only diagnosed in its terminal and symptomatic stages, when multiple parts of a biological system are dysfunctional, it's little wonder that most of the molecularly targeted therapies have a limited influence on the course of disease.

So how can we get closer to the goal of prevention and prediction?

The first task is to broaden the concept of personalized medicine from the genetically reductionist version to one that includes other types of markers. Funding bodies and insurance companies will need to launch more long-term studies, such as the Framingham Heart Study, the US National Children's Study or TwinsUK, linking specimens, sequence and other biomarker information to clinical outcomes.

Second, physicians need to be educated about the new diagnostics and how to integrate them with existing clinical information. This will require better genetics education in medical schools, the development of robust point-of-care devices and data-sharing technology and the establishment of trusted sources (e.g., medical association position statements on tests or the National Institutes of Health's genetic testing registry).

Third, patients—and ultimately all individuals—will need to be educated about the benefits of a healthy lifestyle and wellness and disease prevention. Government plans, like the US Surgeon General's National Prevention Strategy, will help, but new technologies should be made available that help patients monitor their health, share their medical data and seek attention when needed. Insurance premium incentives could encourage individuals to make positive lifestyle choices.

Most importantly, payors should identify areas where early, targeted interventions would reduce disease burden and cost. They should also clearly communicate to drug companies their willingness to pay for targeted therapies in these areas.

This last point is critical. The current reimbursement environment is all about limiting which treatments are paid for. But if payors gave drugmakers incentives to shift from last-ditch treatment to targeted therapies and diagnostics, it would be in their best interests. It would lessen the reimbursement headaches for drug companies. And most important of all, it would better serve patients.

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