COMMENTARY: Personalized medicine—Bridging the gaps

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ORTLY AFTER THE LAUNCH OF the “largest human sequencing operation in the world,” an exploratory study in which 12 adults underwent whole-genome sequencing to detect clinically meaningful genetic variations was published. The results were sobering: incomplete coverage of inherited disease genes, low reproducibility of detection of clinically relevant genes and disagreement among experts about which findings were most significant. In short, for the most part, the findings were not actionable.

Therein lies the biggest conundrum facing the personalized medicine arena today—current and emerging technologies capable of providing persons-specific data far outpace the ability to effectively mine that data to draw clinical conclusions and develop clinically relevant products. The pressure to do so is growing, however. Consumer “wareables” that measure and record/report vital signs are spurring patients to try to control their own health and of the patient-doctor relationship. The advent of direct-to-consumer genetic testing, although somewhat curtailed by the U.S. Food and Drug Administration’s admonition to the genetic testing company 23andme, is further challenging physicians to treat their patients, quite literally, as individuals. High-profile stories of people such as Apple founder Steve Jobs, for whom an individualized treatment approach seems to have been life-extending, imbue the concept of personalized medicine with emotional fervor.

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The challenge, then, for the life-sciences sector is to bridge the gaps between technology innovation and clinical outcomes with appropriately targeted, cost-effective R&D. Personalized medicine is very much a work in progress because every individual, like every disease and treatment, is “complicated.” Specific tools are needed to deal with these specific challenges:

1. Disease heterogeneity: Most diseases are not singular entities; they vary wildly, and about half of the variability among individuals. For biopharmaceutical products to reliably deliver, researchers need a better understanding of disease biology, but also of molecular pathways, proteomics and the impact of epigenetics. Changes due to environmental factors rather than simple DNA sequence variants—each has a different error profile, some are better for resequencing while others are best for de novo sequencing—can hinder quality control efforts.

2. Data quality: Next-generation sequencing is a major driver of personalized medicine R&D. However, factors such as sequencing artifacts (e.g., low-quality reads, contaminants) can compromise data quality and analysis. Similarly, differences among the major sequencing platforms—each has a different error profile, some are better for resequencing while others are better for de novo sequencing—can hinder quality control efforts.

3. Data interpretation: Data from the GeneNet Epidemiology Research on Adult Health and Aging cohort, among the largest and most diverse genomic projects in the United States, were recently added to the U.S. National Institutes of Health’s online database of genotypes and phenotypes. The data transfer has the potential to yield new insights into a plethora of diseases, thereby informing drug discovery R&D; however, the data are meaningless without robust tools to accurately interpret and leverage the information to identify subpopulations of potential responders to new entities, as well as factors that contribute to resistance.

4. Data applicability: Largely because of disease heterogeneity, not all data are “actionable”; e.g., you know you have mutations in a particular gene that may confer greater risk for disease, but what can you do? DNA co-discoverer James Watson had his full genome sequenced in 2006; he would make the entire genome freely available, except for his APOE status; he did not want to know his status because an allele of the gene predisposes to Alzheimer’s disease, which his grandmother died from. That potentially frightening aspect of personalized medicine—the ability to identify risk factors, stop research and treat or prevent a disorder—remains today.

For certain types of breast and other cancer genes, a number of relatively effective treatments are available, genetic testing is appropriate, and targeting of treatments to individuals who are likely to respond. That won’t begin to happen for many other complex diseases until the field progresses, or at least the affected gene products, are identified. And identification means more than simply pinpointing genetic mutations in disease: some may be harmful, not drivers of disease. For researchers to know whether mutations they’ve found have already been unearthed by others, for example, using computational task involving reviewing and assessing the scientific literature and, from there, trying to determine whether existing treatments, or combinations thereof, might be helpful. Tools that can simplify the process, such as sophisticated data mining programs that can extract relevant information from the literature rapidly and accurately, are not yet in widespread use.

For the most part, identification of faulty proteins that are disease harbingers can, at best, lead to early detection. But many people will choose not to take advantage of this aspect of personalized medicine until we have treatments that act effectively with different subtypes and at different stages of disease.

5. Lack of standardization: Consistent standards for sample management, for example, if laboratory staff are not adequately trained for all technologies. At the discovery level, researchers need universally accepted standards for sample management, for example, since improper sample collection, storage and/or processing can make those samples useless for their intended purposes. At the publication level, including full methodologies in submitted papers can help readers better assess findings until the scientific community agrees upon universal standards. Once such standards are in place, clinicians are likely to have more confidence in findings that could influence practice.

6. Disruptive approaches: Novel methods for exploring the discovery of new drug candidates and identifying potentially responsive subgroups are promising, but have challenges associated with them. For example, using computational modeling/simulation techniques in the early R&D stages can save time and money, but only if the algorithms used in such efforts are reliable, available and reproducible—i.e., include error bounds so others can try to replicate findings and validate predictions, which often is not the case.

2. Collaborations: Information sharing within companies and among industry, academia and government is vital to realizing the full potential of personalized medicine. Some companies are taking a better stance than others (rather than outsource) such data across the sciences and ways to cross those barriers.

Industry/academia collaborations, in particular, such as the National Consortium for Data Science, which brings together universities, companies and government agencies, could help smooth the way by encouraging interaction among data experts from all sectors of the scientific community to deal with key challenges such as data sharing and privacy concerns.

Despite the challenges, personalized medicine is here to stay and will inevitably become simply the way medicine is practiced. Bottom-line concerns of big Pharma—such as that personalized medicine will segment markets and therefore mean lower profits—are dissipating. In 2012 alone, the U.S. government’s investment in human genome sequencing projects has generated, directly and indirectly, $6 billion in U.S. economic output and $31 billion toward the 2012 U.S. GDP, according to a recent report. Physicians cannot refuse to embrace new technologies or remain on the fringes of an early adopter of genetic risk profiling, but is likely to soften. Regulatory concerns exist but are being dealt with. Importantly, pressure from patients on one side and industry, academia and government on the other eventually will win out.

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