"If it were not for the great variability among individuals, medicine might as well be a science, not an art."
Sir William Osler, 1892

Most experienced medical providers know this all too well. While the majority of patients respond to standard treatments, inevitably a patient will come along who breaks the mold. In the more than 100 years since Canadian biologist Osler made this observation, scientists have been trying to understand and categorize such variability among individuals in order to tailor medical treatments to each person’s unique genetic makeup?to turn medicine into a science,? to use Osler’s words. Personalized medicine has received a lot of attention in recent years, but as most physicians know, medicine remains an art. Will personalized medicine revolutionize healthcare? Is genetic testing the wave of the future? Should genetic tests be offered directly to consumers?

Two key technological advances have contributed to transforming personalized medicine from science fiction to medical possibility. In the 1970’s researchers discovered how to sequence DNA, the key to unraveling the genetic code, and scientists isolated restriction enzymes, special
chemicals found in bacteria which cut DNA at particular sequences. These two techniques enabled scientists to begin to isolate single genes, such as the cystic fibrosis gene, identified and sequenced in 1989, and the BRCA1 and 2 genes, implicated in breast cancer. A draft sequence of the human genome was published in 2000, and in subsequent years hundreds of genes associated with a variety of conditions have been identified and sequenced.

Each time a disease gene is identified, patient groups and researchers grow excited about the possibilities for improving diagnosis and developing new treatments. But turning information about the association between a disease and a particular region of the human genome into viable therapies requires additional technology and information.

In many cases, information about which human genes are involved in various diseases and conditions is used in the field of pharmacogenomics. Pharmacogenomics employs genetic tests in rational drug design: determining which drugs to use to treat a given medical condition, what dosages of those drugs to administer, and how best to reduce adverse effects, in light of underlying genetic differences in disease mechanism or drug metabolism. One of the most successful drugs produced this way, Herceptin® (trastuzumab), is a genetically engineered monoclonal antibody designed to bind to HER-2 (human epidermal growth factor receptor-2 protein), which is overexpressed in 25-30% of breast cancer cells. Herceptin is a multi-million dollar blockbuster drug. Pharmacogenomics also helped researchers learn that individuals vary in their ability to metabolize the anti-clotting drug Coumadin® (warfarin). In 2007, the FDA changed warfarin’s package insert to reflect data suggesting that people with certain gene variations need a lower dose.

Despite these significant and lifesaving advances, personalized medicine still faces significant challenges. Genome-wide association studies—the type of study most often used to find particular regions of DNA implicated in certain medical conditions—are limited in terms of the conclusions they can yield. These and other genetic studies are complicated by a factor geneticists call penetrance—the percentage of people with a given genetic variation who actually display the associated disease or condition. Penetrance is affected by environmental conditions and epigenetic factors, non-sequence based structural or chemical changes in the DNA that affect whether a given gene is active or silenced under various circumstances.

Further complicating things, translating information about what causes a disease into viable treatments can be even more technically difficult than identifying relevant genes. Gene therapy, which involves physically modifying genes, is not yet a safe and effective means of treating disease, and drug development is hampered by difficulties in delivering drugs to the appropriate target inside the body, as well as unintended side effects.

In addition to these technical challenges, the cost of both the genetic tests themselves and the associated interventions is prohibitive in many cases. And it is difficult to communicate complicated genetic information about disease risk to patients accurately, such that it actually alters patient behavior.

For these reasons, researchers and physicians have established three criteria for determining whether or not a genetic test is beneficial. First, a test must be analytically valid, meaning that test must accurately identify the presence or absence of a given genetic variation. Second, it must be clinically valid, meaning that the mutation or genetic variation must be associated with a
disease or medical condition. Finally, the test must be clinically useful, meaning that it must aid in the treatment or prevention of disease.

As it turns out, these criteria are difficult to meet.

In most cases genetic tests are ordered by a physician, and often the results are interpreted to patients with the help of a genetic counselor. However, because sequencing technology has become increasingly more cost effective, some companies have begun marketing genetic tests directly to consumers. Prior to 2006, most direct-to-consumer (DTC) genetic testing was conducted by companies advertising ?nutrigenetic profiles,? which marketed genetic testing toward the sale of nutritional supplements. From 2007 to 2008, new DTC companies emerged to market information about ancestry or paternity for ?informational? or ?entertainment? purposes, rather than ?clinical.? But after 2009 several companies, including 23andMe, Navigenics, deCode, Pathway, and Lumigenix, began marketing medical information as part of their genetic profiles.

23andMe, whose founder is married to one of the founders of Google, offers a ?Personal Genome Service? with the tagline ?Get to know your DNA. All it takes is a little bit of spit.? Included in this service is a ?health report? with information about 241 medical conditions, including carrier risk—the risk that the customer carries a gene for a medical condition they could pass on to their children—as well as disease risk—the risk that the customer will develop a certain disease or condition. The 241 conditions tested range from known single gene diseases such as cystic fibrosis to complex medical conditions such as back pain and asthma.

**Advantages and Pitfalls**

Looking at a common, complex condition such as Type II diabetes illustrates the advantages and pitfalls of this type of genetic testing. Among leading causes of morbidity and mortality in the U.S., Type II diabetes is particularly amenable to lifestyle interventions such as diet and exercise. Over 20 million Americans have diabetes, making the disease a major contributor to overall health costs. In 2005 researchers at the biotechnology company deCode found that 20% of people with Type II diabetes carry two copies of a high risk allele of the TCF7L2 gene. In fact, researchers found that even one copy of the allele confers significant risk above that of the average population.

So, is the TCF7L2 gene an ideal candidate for genetic testing? In 2007, the private company DNA Direct began to offer this genetic test directly to consumers. At first glance, the argument for offering the test this way is fairly straightforward. As Ryan Phelan, founder and CEO of DNA Direct, said, ?If [people] know they?re at an increased risk, they will be motivated toward stronger interventions, be it losing weight or quitting smoking.? But research shows that patient behavior is more complicated and unpredictable than this. Critics worry that patients who receive a negative result will develop a false sense of security and neglect lifestyle changes, such as exercise and losing weight. Other patients may succumb to genetic fatalism, giving up on lifestyle changes because they?re going to get the disease anyway. And many patients are simply resistant to change. Clinicians are all too familiar with the difficulty of getting patients to change behavior even in the face of known risk factors. How many physicians have warned their
patients to stop smoking or lose weight, only to have their advice fall on deaf ears?

In the case of Type II diabetes, it turns out that other factors, such as increased body mass index (BMI), increased blood pressure, and increased serum levels of triglycerides, apolipoprotein A-1, and liver enzymes, are better predictors of the onset of Type II diabetes than this genetic test, despite the apparent predictive power of the presence of the mutant allele. Genetic tests are expensive, and as Harvard researcher and diabetes physician David Altshuler points out, there is no evidence that this genetic test does result in an improved health outcome.[4]

Proprietary barriers further complicate the issue. Because the US Patent and Trademark Office offers patents not only on specific human genes, but also on specific variations of those genes, each genetic testing company offers unique genetic tests. For example, 23andMe offers a diabetes panel as part of its genetic profile, but it does not include TCF7L2 because deCode owns the patent on TCF7L2. This further hinders the patient’s ability to interpret a negative result.

So, are genetic tests offered directly to consumers medically beneficial? Maybe. But if as a patient you order a report from a DTC genetic testing company and see that you have a 30% increased risk of Type II diabetes, what does it really mean?

Interpreting the Data

Genetic data are complex and can be difficult to interpret and translate into meaningful information that will actually improve health outcomes. Interpreting odds ratios can be challenging for the average patient. Having your risk of a disease increase by 50% sounds ominous, but if it is a 50% increase over an already low risk (say 1% in the average population), then your increased risk is relatively minor. Making matters more complex, genetic markers vary widely in their specificity (the number of individuals correctly identified as low risk among those who will not get the disease) and sensitivity (the number correctly identified as high risk who will get the disease). Furthermore, because the odds ratios (or percentages) from genome-wide association studies are population averages, individual family history is often a better indicator of an individual’s risk.[5]

Ethical Concerns

In addition to these technical concerns, there are several ethical considerations which must be weighed as our society decides how to handle technological advances in genetic testing. Do people have a moral right to know the information in their own DNA? Should family members of individuals affected by relevant conditions be tested? Should genetic tests be performed for incurable, fatal illnesses? What do people DO with the information they receive? Can or should the government require medical oversight of genetic testing? How are gene patents helping or hurting patient interests? Should payers (insurance companies) reimburse for genetic tests? Under what circumstances?

Some of these questions are being addressed by professional associations, such as medical specialty societies. For instance, studies are currently underway to assess the value of including
testing for a heart disease-linked allele in standard risk assessment profiles for aggressive cholesterol intervention. And in 2011, the American College of Cardiology and the American Heart Association issued guidelines regarding hypertrophic cardiomyopathy (HCM), which can be caused by an autosomal dominant mutation. When patients are diagnosed with HCM, the guidelines recommend that family members be tested and appropriate interventions be applied. These guidelines, however, do not address the issue of over-the-counter availability of genetic testing.

The federal government has tasked several agencies with oversight of one aspect of genetic testing or another. As is often the case with emerging technologies, multiple agencies have dabbled in regulating the DTC genetic testing market, but the federal government has not yet developed a uniform approach to regulating the industry.

**Regulation of Genetic Testing**

Earlier this year, the National Institutes of Health launched a voluntary registry for genetic tests. The Food and Drug Administration (FDA) has the authority to regulate?through premarket submissions and postmarket controls?medical devices, a category defined broadly enough so as to include many genetic tests. According to the FDA, genetic tests directed toward ancestry, forensics, or other non-medical information do not qualify as medical devices subject to its oversight, but tests providing information on pharmacogenomic profiles, Mendelian (genetic) disease mutations, or risk assessments for medical conditions do qualify as such. Those genetic tests falling into this latter category, thus, are subject to FDA oversight. Since 2010, the FDA has been evaluating

(1) the risks and benefits of making clinical genetic tests available for direct access by a consumer without the involvement of a clinician, (2) the risks of and possible mitigations for incorrect, miscommunicated, or misunderstood test results for clinical genetic tests that might be beneficial if offered through direct access testing and (3) the level and type of scientific evidence appropriate for supporting direct-to-consumer genetic testing claims.[6]

The Federal Trade Commission (FTC) has the authority to regulate claims of false advertising. In 2006 the FTC released ?At-Home Genetic Tests: A Healthy Dose of Skepticism May Be the Best Prescription??a fact sheet for consumers, warning about the limitations of DTC genetic tests.[7] Although the FTC has been only minimally involved in DTC genetic testing regulation since then, some have proposed requiring companies that offer DTC genetic tests to register with the Genetic Testing Registry at the NIH, which might enable the FTC to better police spurious advertising claims.
The Center for Medicare and Medicaid Services (CMS) regulates medical laboratory testing through the Clinical Laboratories Improvement Amendments (CLIA). CLIA standards cover how tests are performed, the qualifications of laboratory personnel, and quality control and testing procedures for each laboratory. CLIA certification evaluates the analytic validity of genetic testing—that is whether or not the test accurately determines the presence or absence of a specific genetic variation. Not all DTC genetic testing companies are CLIA certified, and CLIA certification does not include standards specific to DNA-based genetic tests.

Between 2000 and 2004 the Centers for Disease Control and Prevention (CDC) piloted a project to provide a publicly available tool for evaluating scientific data on emerging genetic tests. In 2004 this was replaced by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP?) project, which provides objective, timely, and credible information that is clearly linked to available scientific evidence. This information will allow healthcare providers and payers, consumers, policymakers, and others to distinguish genetic tests that are safe and useful. To the extent that patients are aware of this tool, and to the extent that the project maintains enough funding to continue its work, the EGAPP table provides a useful place for consumers to check whether a given genetic test has the opportunity to provide any medical benefit.

In the absence of a federal response to the DTC genetic testing market, state governments have begun to take action. California and New York require companies to have state licenses and regulate DTC genetic testing companies as laboratories, and California prohibits companies from offering DTC genetic tests without a physician’s order.

In certain cases, personalized medicine has improved diagnosis, transformed certain procedures, and extended the length and quality of life for patients. As more professional associations make determinations about the best practices for the introduction of genetic testing into their specialties, these tests and treatments will benefit more and more people.

Nevertheless, though the individualism and autonomy so highly prized in our culture may incline us toward self-directed health care, consumers should recognize the inherent complexity of genetic information and discuss results ordered over the internet with their physicians. And at the cultural and governmental levels, we should continue to grapple with how to ensure that the vast and rapid availability of information, medical and otherwise, actually serves the common good.

References


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