GENOMIC TESTING


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A number of for-profit companies now provide personal genomic testing services to clients directly, without input from a physician or other health care provider, and the results of these tests include predictions about a broad spectrum of disease risks and traits. Validated clinical genetic testing and direct-to-consumer (DTC) genomic tests differ substantially in their reliability and usefulness, raising many clinical, ethical, and societal challenges, which are discussed in this Commentary. Of special concern is the problem of misattributed equivalence, which occurs when a patient or physician mistakenly views alternative methods of genetic evaluation as equivalent in their results and analytic rigor. Despite the many challenges raised by DTC genomic testing, we are reminded that commercial interests have sometimes acted as a disruptive force or technology that drives nonconventional approaches to difficult problems.

INTRODUCTION

The completion of the Human Genome Project and several subsequent studies of human genetic variation (such as the International HapMap Project) have heralded the start of a genomics-based revolution in health care in which it may soon be possible to tailor medical interventions to the specific needs and genetic constitutions of each patient. With the human genome in hand, and the vision of personalized medicine looking ever more achievable, health care professionals and patients should be ecstatic.

But, Mousie, thou art no thy lane,
In proving foresight may be vane;
The best-laid schemes o' mice an' men,
Gang aft agley.
An' lea' us nought but grief an' pain,
For promisèd joy!
—Robert Burns, 1785

As with other major advances in medicine and society, the path forward is unclear. In the wake of recent developments in genomics, several for-profit companies are offering direct-to-consumer (DTC) personal genomic testing to anyone interested and willing to pay. With the emergence of DTC genomic testing, Pandora’s box has been opened (1).

Patient access to personal genomic testing will present challenges (2), because limited data are available to guide physicians in interpreting personal genomic information (3). Enthusiasm for personalized medicine has prompted the release of commercial testing products before the creation of a robust genomic knowledge base to support their interpretation. Public interest in personalized health care appears strong enough to support DTC products over time, raising a difficult question: Is DTC genomic testing a development to be feared or celebrated?

INTERPRETIVE CHALLENGES RAISED BY DTC GENOMIC TESTING

Health care professionals might wonder why the knowledge required to interpret genomic data is inadequate, particularly because great advances in human genetics have been made over the past several decades. The answer is complex but critical for understanding the current limitations of DTC genomic testing (3, 4).

In contrast to relatively uncommon syndromes caused by mutations in single genes (Mendelian syndromes), the extent of heritability of most common diseases, such as congestive heart disease and diabetes, is unknown (5, 6). Before the completion of the Human Genome Project, about 5 to 10% of all human diseases were thought to be caused by high-penetrance mutations in Mendelian genes. An additional 10 to 15% of all diseases, observed to occur in some families more often than expected by chance, were attributed by many to low-penetration genetic factors but could also be caused by common environmental factors. The majority (≥75%) of diseases were believed to be sporadic.

Knowledge from the Human Genome Project facilitated systematic genome-wide investigation of genetic variation in populations. The observation of genome-wide variation suggested an alternative hypothesis: Common genetic variation might account for the majority of common diseases. To examine this idea, multiple genome-wide association studies (GWASs) of common complex diseases were conducted over the past decade. GWASs are large genetic studies in which samples from hundreds to thousands of individuals are used to search for common genomic variations that are statistically over- or underrepresented in disease cases in comparison to controls. The genomic variants typically examined in GWASs are single-nucleotide polymorphisms (SNPs), which may or may not have any known functional consequences.

The aim of a GWAS is to define an odds ratio or relative risk describing the likelihood that an individual with a particular genetic variant will have an associated disease. Unfortunately, this approach has not proven very fruitful. As of the end of 2008, just 7% of the >11,000 purported associations discovered among individual SNPs and specific diseases in GWASs have been replicated and validated (4). These findings have prompted many to declare that the “common variant–common disease” hypothesis has been refuted and that most common diseases are not caused by genetic variants.

Researchers, nonetheless, continue to identify potential genetic contributions to human diseases at a rapid pace. Many of these SNP/disease associations will fail to be replicated in future studies, but others will no doubt yield insights into the etiology of complex diseases. Several validated genetic associations have been reported between SNPs and such common diseases as breast cancer, colon cancer, prostate cancer, Crohn’s disease, type 1 and type 2 diabetes mellitus, and cardiovascular disease.

Taking into account only well-validated SNP/disease associations, typically 1 to 3% of disease cases are associated with SNPs
For example, validated breast cancer–associated SNPs account for ~2% of all breast cancers, whereas germline mutations in BRCA1 and BRCA2 (BRCA1/2), the two susceptibility genes for the “rare” Mendelian heritable cancer syndrome called hereditary breast-ovarian cancer syndrome (HBOC), account for 7% of all breast cancer cases. These data illustrate that although there are genetic contributions to many common diseases, these genetic factors generally account for a very small proportion of the overall disease burden in a population.

SNP/disease associations from GWASs are among the data that inform DTC genomic testing products. Typically, these products use such data to estimate a client’s personal risks of developing multiple disease conditions during his or her lifetime. Some products also examine a client’s likelihood of developing several rare Mendelian diseases [such as HBOC, Lynch syndrome (hereditary nonpolyposis colon cancer syndrome), type 1 neurofibromatosis, cystic fibrosis, and Tay-Sachs disease] by looking at limited numbers of SNPs in the disease-associated genes (without interpretation of these findings by a genetic specialist). In some cases, these products do not test for the most likely mutations in a given gene in a particular patient. In contrast, Mendelian gene testing, when initiated and interpreted by a trained genetics professional, carries high analytic validity, clinical validity and utility, and, most importantly, actionability.

Given the current state of knowledge, DTC genomic tests have serious clinical limitations. For example, DTC genome scan results provide a very limited picture of an individual’s overall disease risk, because the markers examined account for only a very small proportion (typically <3%) of all disease carriers. Importantly, the SNPs themselves are not validated well enough, especially from a clinical outcomes point of view, to provide good estimates of population risk, especially given that a SNP association in one racial or ethnic population may not be germane to others (3, 4).

**THE PROBLEM OF MISATTRIBUTED EQUIVALENCE**

The considerations above highlight a major challenge in integrating DTC genomic testing into clinical settings. That problem is how to distinguish DTC genomic test results from the types of information generated through clinical genetic tests, which might be appropriately ordered by a physician in response to a clear family history of disease or other red flags signaling disease heritability, such as a very young age at onset of an older-age disorder.

To illustrate this problem, consider an analogy. No responsible physician would be concerned to hear that a woman who believes that she might be pregnant has used an at-home pregnancy test. If the test were positive, then this woman would probably meet with her doctor, who might appropriately seek to confirm the at-home test result by ordering a pregnancy test run in a certified clinical laboratory. Indeed, as a practical matter, if every woman who believed she was pregnant scheduled an appointment with her obstetrician before confirming this result with an at-home test, then obstetricians would be overwhelmed with unnecessary office visits. In this regard, at-home pregnancy tests are useful, giving rise to more appropriate and productive office visits. One might view DTC genomic testing in much the same way. Like at-home pregnancy tests, DTC genomic testing could anchor specific discussions between doctors and their patients, in some cases serving as the impetus for additional medical exams and confirmatory diagnostic testing.

It would be a mistake to view these two cases as analogous, however, and their differences reveal important insights about the limitations of DTC genomic testing. Unlike at-home pregnancy testing, clinical genetic testing might not be an appropriate response to a patient’s interest in diagnostic results. Clinical genetic testing is offered by health care providers, who are frequently formally trained genetics professionals, to individuals who are at high risk for Mendelian genetic disorders. This model of validated testing focuses narrowly on the evaluation of one, or perhaps several, plausible genes that are known to be strongly associated with the disease of concern. The clinical genetics professional selects these genes to evaluate based on his/her expert assessment of the patient’s personal and family histories. Patient interest alone is an insufficient rationale for the pursuit of clinical genetic testing, particularly if there are no medical actions that would result, because genetic testing presents psychosocial risks to the individual evaluated.

DTC genomic testing is very different from at-home pregnancy testing in another important way. The results generated via a pregnancy test are very much the same whether that test is performed at home or ordered by a physician. In contrast, there are a number of substantial differences between DTC genomic tests and clinical genetic tests for inherited disease risks (Table 1).

These differences in test reliability and usefulness highlight what might be called the problem of misattributed equivalence. This problem is evident when a patient or physician mistakenly views alternative methods of genetic evaluation as equivalent in their results and analytic rigor. It would be a mistake, for example, to view a genetic

| Table 1. Differences between high-penetrance Mendelian gene mutations and SNPs analyzed by DTC genomic testing. RR, relative risk (relative risk of developing a disease in a given population); CLIA, Clinical Laboratory Improvement Act; CAP, College of American Pathologists. |
|---------------------------------|---------------------------------|
| High-penetrance mutations      | DTC trait-associated SNPs       |
| Proportion of disease due to mutations or variants | High (typically >70%) | Low (1 to 3%) |
| Attributable risks              | High (RR > 2, typically RR > 10) | Low (RR, 1.0 to 1.3) |
| Analytic validity               | Close to 100% (for laboratories with CLIA certification and CAP accreditation) | Variable |
| Clinical validity               | Found with high probability in individuals with disease; never or rarely found in normal individuals | Same SNPs found in individuals with disease or trait and in controls (but in different proportions) |
| Clinical utility                | Used as molecular diagnostic and as predictive test | Typically not clinically useful |
| Actionability                   | Often changes or informs medical management, such as indicating organ-specific surveillance | Not actionable; attributable risks are too low |
test that examines just a few common mutations in the BRCA1/2 genes, relevant only to a specific population (such as Ashkenazi Jews), as comparable in scope and clinical utility to a genetic analysis involving comprehensive DNA sequencing and deletion testing of these two genes. Similarly, a DTC genomic test that examines several pur- ported SNP associations with breast cancer should not be viewed as comparable in quality to a test that involves clinical genetic testing of known mutations based on expert assessment of a patient's family history.

Even among DTC genomic testing options, it would be incorrect to assume that SNP-based genomic risk assessments by dif-
ferent companies will yield similar results. Some companies examine certain diseases and disease traits that other companies do not (7–9). In addition, both the methods of data interpretation and the SNPs analyzed within and around a given gene may differ between companies, as illustrated by a recent report by Venter and colleagues. The authors submitted saliva specimens (from which genomic DNA is extracted) to two DTC personal genomics companies (10). For five individuals, SNP-based risk predictions for 13 disorders or traits reported by the two companies were systematically compared. Risk predictions differed for half of these disorders or traits. These disparate results are almost certainly a result of the use of different SNP/disease associations to estimate risks, and perhaps different statistical algorithms to calculate total risk burden at these DTC companies.

To return to our analogy, unlike an at-home pregnancy test, which DTC genomic test a client uses matters a great deal. The DTC products are often not testing for the same diseases. Even in cases where the same diseases are examined, the techniques may differ across DTC platforms, often yielding very different estimates of disease risks (3, 4, 10). In addition, with virtually every DTC testing option, the techniques used to estimate disease risks are not the same as those that would be used by a licensed genetics professional in a medical setting.

The problem of misattributed equivalence has a number of important practical and ethical implications. Many DTC testing com-
panies provide genetic results directly to the consumer, without input from a physician or other health care provider. As a result, it is possible that some patient-clients may fail to appreciate important differences between DTC genomic testing and clinical genetic testing. Thus, some patients might decline medically indicated genetic testing because they mistakenly believe that they have pre-
viously been evaluated for this risk through DTC testing (Table 2 and Fig. 1). Some patients might also seek out prophylactic treat-
ments based on DTC genomic testing, potentially burdening medical professionals and driving up health care costs (11).

RECOMMENDATIONS

Because of insufficient data about the clinical validity and utility of most SNP/disease associations, physicians should not recom-
 mend that patients elect personal genomic screening. Other validated risk assessment measures, such as blood chemistry profiles, health behaviors, and family history remain the gold standard for predicting disease. A recent large study analyzing a SNP strongly associated with cardiovascular disease (rs10757274 at 9p21.3) in white women demonstrated that this SNP did not add any helpful risk classification as compared to family history evaluation and blood levels of C-reactive protein (12). Another large pro-
spective study found that although analysis of 11 SNPs previously linked with a risk for type 2 diabetes very slightly improved the ability to predict disease development, clinical and family history risk factors were the predominant indicators of future disease (13). In a landmark study, Xu and col-
leagues analyzed the utility of the 14 SNPs associated with prostate cancer risk (14). By themselves, the SNPs were not particularly helpful for identifying men who would go on to develop prostate cancer. However, the SNPs had value in specific situations. For example, it is standard clinical practice to biopsy the prostate when blood levels of prostate-specific antigen (PSA) are >4 ng/ml, but there is no consensus about how to handle borderline PSA levels (2 to 3.9 ng/ml). Xu and colleagues examined the utility of these SNPs in such men, using the SNPs in conjunction with PSA levels to deliver a SNP-adjusted PSA score to help in the bi-
opsy decision. The researchers also exam-
inued the utility of combining SNP risks. In the absence of a family history of prostate cancer, they found that the presence of all 14 SNPs raised the risk of a white individual developing prostate cancer between the ages of 55 and 72 years from 13% (the general population risk among whites) to >20% (14). In the presence of a family history of prost-
tate cancer, however, having eight or more of these SNPs raised the risk of developing prostate cancer between the ages of 55 and
72 from 13 to 25%. In this scenario, having >8 SNPs delivered incremental risks beyond 25% and would be actionable, if these data can be replicated independently.

Arguably, the most promising application of GWAS research is its use with known clinical tools or in particular scenarios, as illustrated by Xu’s work. In this context, pharmacogenomics, the ability to predict an individual’s drug metabolism or response to specific pharmaceuticals (15), would be an extrapolation. As such, multidisciplinary research involving academia, pharmaceutical companies, and DTC genomic screening companies should focus on clinical outcomes and specific clinical applications in which genomic testing adds substantially to other information obtained by routine clinical testing. For example, it would be useful to explore whether any of the breast cancer risk SNPs can help determine whether to biopsy after a borderline mammographic abnormality is detected.

Participation in GWASs or studies that examine clinical outcomes from GWAS-generated data is quite different from seeking DTC genomic testing. Research involving multidisciplinary expertise and various stakeholders is encouraged by the 2008 Workshop on Personal Genomics led by the Centers for Disease Control and Prevention, National Institutes of Health, and Personalized Medicine Coalition (4). Those participating in research, however, should be aware that some DTC genomic testing companies are beginning to represent their products as research tools, although they lack many features typical of clinical research. By doing so, the companies may mislead patients, deflect foundational and philanthropic dollars away from legitimate biomedical research, and even turn research participants away from legitimate research. There is potential for misattributed equivalence here as well.

Because SNPs are heritable, and in isolation are inconsistent and confusing, clients who are thinking of using DTC services or who have already received DTC scanning results would benefit from genomic counseling. Currently, virtually no genetic counselors have been trained in genomic counseling (3), and to compound this, there are no data available currently on which to base evidence-based genomic counseling.

We also do not have quality data on the complex ethical and legal issues that surround DTC personal genomic screening, or on societal and health care provider needs. Research addressing these issues urgently needs to be performed. Both consumer and health care provider education in the 21st-century practice of Mendelian genetics and genomic medicine must be pursued quickly.

CONCLUSIONS

To the extent that the research that fuels DTC genomic testing is being produced in real time, validated clinical outcomes data are unlikely to be readily available to those physicians who would benefit most (4). The pessimists conclude that this problem provides good reason to shut Pandora’s box and place restrictions on DTC genomic testing (16). The optimists view this response as alarmist, suggesting that DTC genomic testing presents an opportunity to forge new collaborations among academic, industrial, and patient-driven organizations with a stake in the future of personalized health care (4).

A more objective appraisal of recent developments suggests a position somewhere between these two extremes, in which data regarding the effect of DTC genomic testing is collected routinely and used to inform regulatory policies and professional guide-
lines related to the use of DTC products (17). In particular, research studies that seek to (i) characterize both the medical and nonmedical benefits of DTC genomic testing, (ii) standardize the practice of genomic counseling (in contrast to genetic counseling), and (iii) address the bioethical issues of providing genomic data directly to patients and customers are needed.

Because knowledge from genetics research has increased exponentially in the past decade, most non-genetics health care professionals have not fully grasped the utility and power of validated genetics input in routine patient care. It is often said that a disruptive technology or force is required for a “sea change” in the current reactive practice of medicine. Beyond genetics, genomics will probably transform many aspects of medical care. The emergence of DTC genomic testing companies is one step in that direction, despite the many challenges that we have discussed. It is important to note, however, that commercial interests have sometimes driven innovation and encouraged non-conventional approaches to difficult problems such as the ones delineated here.

REFERENCES AND NOTES

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