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Direct-to-Consumer Genetic Testing: Reliable or Risky?

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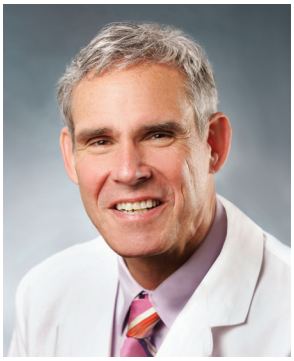
In recent years there has been a dramatic increase in the discovery of information related to the genetic risk of disease, as well as in the technical ability to accurately measure an individual's genotype. These advances underlie the promise of personalized medicine, in which a patient's genotype informs the medical care they receive. Private companies are attempting to capitalize on these advances by providing direct-to-consumer (DTC)[6] genetic testing that estimates the risk of disease for a customer, given their genotype. Because these tests make claims about medical conditions, they have come under scrutiny by regulatory agencies. We ask experts in the field to comment on several issues relevant to DTC genetic testing.

DTC genetic testing is based primarily on associations between common genetic variants and disease. Do we have enough evidence about these associations to use them as genetic tests?



Eric Topol: Yes, without question, in *select* circumstances. For several pharmacogenomic interactions, the information can be especially valuable for an individual to avoid a major adverse side effect (as with carbamazepine) or to ensure efficacy (clopidogrel). Also, when there is clear evidence of heightened risk (e.g., 2-fold or greater) for a common disease, such as diabetes, heart attack, colon, melanoma, or other cancers, there can be actionable information to get appropriate screening (e.g., colonoscopy) or potential preventive steps (e.g., protection from the sun). As we move toward sequencing and identification of rare or low-frequency variants that have high penetrance, it is unlikely that the heightened risk from the previously identified common variants will go away.

James Evans: We clearly do not. This is best demonstrated by several straightforward studies in which the same sample was sent to leading DTC companies for analysis. The results included wildly divergent risk estimates, with companies reporting "above average," "below average," and "average" risks for the same condition in the same individual. This demonstrates that our present knowledge of genetic risk factors is insufficient to aggregate single-nucleotide polymorphism (SNP) genotypes into reliable estimates for disease risk. Even when (or if) we gain sufficient knowledge to make accurate inferences about common disease risk from genetic analysis, it is highly doubtful that such information will be clinically useful in the majority of cases, because most diseases are multifactorial in nature and genetics is only one (usually rather small) component of risk.

Robert Green: Yes. The sensible application of even modest probabilistic risk factors to influence individual human behavior or medical intervention is the basis for considerable progress in modern public health. Thus, if handled responsibly, the more robust associations between ge-

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[6] Nonstandard abbreviations: DTC, direct-to-consumer; SNP, single-nucleotide polymorphism; FDA, U.S. Food and Drug Administration.

netic variants and disease that have been replicated in large samples and across many human populations have the potential to be meaningful and moderately useful, whether in a medical setting or through DTC services. There are concerns, but very little evidence, that misunderstanding could dwarf such utility if genetic risk factors are overvalued and the additional influence of family history and environmental factors are ignored. However, health professionals are still the licensed gatekeepers for diagnostic procedures and prescription pharmaceuticals, and as professionals and consumers become better educated about the limitations of genetic-risk information, the potential for misunderstanding will diminish.

Zivana Tezak and Elizabeth Mansfield: Genetic tests providing medical information that may be used to diagnose, prevent, or treat disease are considered medical devices under the Federal Food Drug and Cosmetic Act and are regulated by the U.S. Food and Drug Administration (FDA). Some tests offered by DTC genetic-testing companies include genetic markers of diseases with a known genetic cause. Others include susceptibility markers for common diseases that estimate disease risk by using associations between common genetic variants and disease that are derived from genome-wide association studies. The recently held FDA Advisory Panel expressed concerns that current scientific knowledge may not warrant the risk-assessment claims made by DTC companies.

The analytical validity across multiple genetic-testing companies has been demonstrated in several published studies. However, there have been reports that different DTC genetic-testing companies provided conflicting disease risks for the same person. What do you think is the cause for these discrepancies?

Eric Topol: The genotyping accuracy of Navigenics, 23andMe, deCODE genetics, and Pathway Genomics is exceptionally good. The problem that has driven inconsistency is what studies are picked by each company to use in their reporting of disease susceptibility. That has varied considerably between companies and largely accounts for the disparate risks reported. The FDA has asked the companies to develop uniform standards for reporting out risks, and this is necessary to develop consensus on what constitutes appropriate evidence.

James Evans: Part of the answer lies in the fact that each company uses different panels of risk SNPs to arrive at an aggregate risk estimate. The very fact that different companies use different data reveals that no one really knows what the correct panel should be. Standards could be developed to harmonize the use of risk SNPs so that most laboratories use the same panel, but we do not understand the complexities of risk estimation sufficiently to make this more than just an arbitrary exercise. A more fundamental problem, though, is that the genesis of most disease is multifactorial and other factors (e.g., our environment) are highly relevant to our risk of disease. Until we are able to synthesize environmental risk and genetic risk, it is unlikely that we will be able to provide reliable, robust, and—most importantly—useful estimates of risk for common disease.

Robert Green: The most likely cause for these discrepancies is that different companies have chosen different SNPs to include in their estimates, as well as different combinatorial algorithms. This points to the lack of standards for genetic-risk paradigms and is a sign that the DTC industry, and indeed the entire field of genetic risk assessment, is young and evolving. But this does not mean, as some have implied, that risk estimation is fundamentally flawed—just that it is at an early stage. It is worth noting that physicians talk to their patients every day about genetic and nongenetic risks in ways that are not always consistent and may even be contradictory.

Zivana Tezak and Elizabeth Mansfield: Several published studies compared the overall concordance between analytical outputs for SNPs between microarray platforms used by several DTC companies. For example, in a recently published study, the concordance between platforms was very high, but there were between 300 and 3700 SNP calls that were not concordant between array platforms. If these results were used clinically, the question would be whether nonconcordant SNPs are used to calculate results for medical claims. In addition, because the methods used for calculating risk estimates by different DTC companies may differ, different values can be obtained even when using the same set of published papers.

There has been a lot of discussion recently about the regulation of DTC genetic testing. Most DTC genetic-testing companies perform testing in a CLIA-certified laboratory. Is this sufficient? Are there other regulations that should be in place?

Eric Topol: It depends on the company and the product. There is an incredibly wide range of consumer genomics offerings from nutrigenomics, ancestry, and many outside of the 4 companies cited above, so CLIA may not be sufficient across the board. Some of the companies in this space are clearly predatory and not

evidence based; they unfortunately give the ones trying to provide an important service a bad name.

James Evans: Requiring CLIA certification is a good first step. I feel that the major thrust of regulations should be focused on making sure that existing companies follow truth-in-advertising rules, something that is clearly not being done at present. Implicit and explicit claims that DTC genetic testing represents "a guide to your medical care" are simply false, and the laboratories that claim (or imply) that they are offering tests that are medically useful should be called out and prevented from doing so. I have no objection to consumers seeking their genetic information, but I don't think they should be lied to about its usefulness.

Robert Green: CLIA certification is an important quality standard that should be in place for all genetic testing; however, it is not sufficient. CLIA certification is designed to ensure quality laboratory testing, but not that tests are clinically useful. This could be addressed by establishing a national genetic test registry and soliciting consensus recommendations from professional organizations about the use of specific tests. Furthermore, professional organizations and/or regulatory bodies could evaluate individual components of multivariate genetic tests to decide which targets are valid for making inferences about genetic risk. One way to make sure that leading DTC companies provide appropriate products and services is for clinicians and scientists to engage with them as advisors and collaborators. Beyond this, companies that engage in fraud and deliberate false advertising (such as those linking genetics to dating, nutrition, or cosmetics) should not be tolerated.

Zivana Tezak and Elizabeth Mansfield: The FDA has stated publicly that DTC genetic testing should be regulated by the agency. Several companies have decided to come to the FDA with premarket submissions, and these are in the process of working with the FDA to come into compliance. In March 2011, a Molecular and Clinical Genetics Advisory Panel meeting was held in part to try to help the FDA navigate through some of the questions the FDA is deliberating.

Do you think the genetic testing offered by DTC companies should require direct physician involvement? What about genetic counseling by certified counselors?

Eric Topol: I believe that consumers have the right to the data without necessarily requiring a physician to order the test, or obligatory genetic counseling. It is the consumer's DNA and his/her right to acquire the data and decide if consultation with a physician or genetic counselor is appropriate.

James Evans: For genetic testing that is of primarily entertainment value (such as risk SNP analysis for common diseases), I don't see the need for a medical professional to be involved—as long as the patient is given an accurate assessment of how little value such tests have for any kind of medical purpose. For those genetic tests that offer real medical information (e.g., those tests that identify highly penetrant mutations for serious disease), I feel it is best for a medical professional (e.g., a genetic counselor) to be involved.

Robert Green: Genetic information that is delivered by a knowledgeable professional and contextualized by a patient's family history, medical course, and psychological state is generally accepted as the most appropriate mechanism for disclosing genetic risk. However, some individuals prefer learning about such risks outside of the medical system, and in an era where consumers seek and obtain medical information from many varied sources, it seems anachronistic and unrealistic to require involvement by a medical professional to obtain genetic-risk information. While there are legitimate concerns about individuals misunderstanding genetic-risk information, there is as yet no compelling evidence of harm that would support requiring the involvement of a physician or counselor.

Zivana Tezak and Elizabeth Mansfield: One of the questions the FDA asked its advisory panel was related to the risks and benefits of making clinical genetic tests available without the involvement of a physician. The panel generally agreed that several categories or specific genetic tests should be offered solely upon prescription, including presymptomatic tests that are highly predictive of an individual developing a condition with potentially severe consequences. Some other test categories were assessed as potentially lower risk and, with appropriate caveats, potentially not as problematic to offer directly to consumers. There was general agreement that certified genetic professional(s) may need to be involved in interpreting or delivering the results of DTC tests. The FDA is currently considering all these discussions and recommendations, including public comments that were received from various stakeholders on the meeting docket, and trying to decide the best path forward.

DTC genetic-testing companies have capitalized on low-cost genotyping technologies. In the near future, inexpensive sequencing technologies will likely make it possible to provide consumers with their entire genome sequence for a cost that is similar to current

DTC genetic tests. How do you think this will affect DTC genetic testing in the future?

Eric Topol: This field will continue to grow, and eventually on a logarithmic basis, once whole-genome sequence data are available with the requisite rich information that is needed to make this worthwhile. We are at least a few years away from that point, and the bottleneck is no longer being able to rapidly and inexpensively obtain sequence data; it is our inadequate capability of interpreting such data and generating valuable information and knowledge for an individual. Eventually we will get there.

James Evans: It will make the subject only more complex. The medical utility of current DTC genetic testing is rather trivial, but this will change dramatically with the advent of whole-genome sequencing. While most individuals who undergo such sequencing will learn little of importance, it is inevitable that some will learn information that could be both highly medically relevant and highly problematic. For example, whole-genome sequencing for some individuals will identify mutations in very high–penetrance genes that promise the development of devastating diseases for which there are no effective interventions. Given the serious medical and other implications of this type of information, it seems logical that it be subjected to reasonable regulation and oversight to ensure that we can derive its benefits without causing harm.

Robert Green: DTC companies will certainly progress from genotyping to sequencing and will provide consumers with their genome sequence and interpretation, but hopefully so will the medical establishment. While sequence information will be immediately valuable in some instances, particularly around cancer, pharmacogenomics, and preconception planning, its limitations will rapidly become apparent to both medical practitioners and consumers. Within a few years, risk-assessment paradigms will become more sophisticated, blending sequence information with other clinical data in an integrated and evolving fashion. Ultimately, all of these developments will further the goal of broadly shared access to personalized, predictive, and preventive medicine for the betterment of human health.

Zivana Tezak and Elizabeth Mansfield: The effect of genome sequencing on DTC genetic testing remains to be seen. Rapidly evolving genomic-sequencing technologies are extensively used in research and are entering clinical diagnostic use; they are expected to bring transformative public health applications. As a part of broader efforts that are ongoing with other government partners as well as a wide range of stakeholders, on June 23, 2011, the FDA hosted a public meeting entitled "Ultra High Throughput Sequencing for Clinical Diagnostic Applications – Approaches to Assess Analytical Validity." The purpose of this initial public meeting was to discuss challenges in assessing analytical performance for ultrahigh-throughput genomic sequencing–based clinical applications.

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