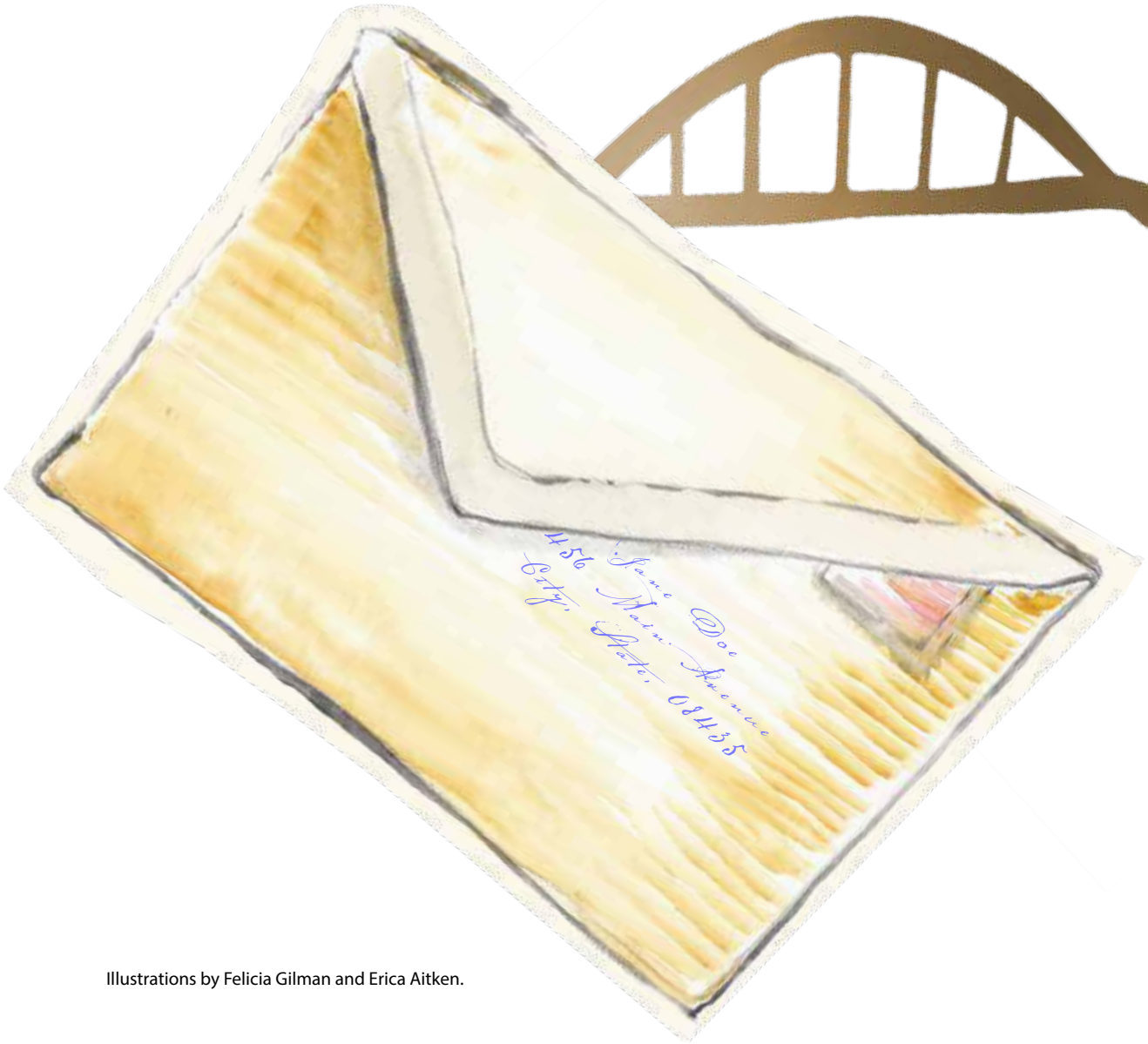
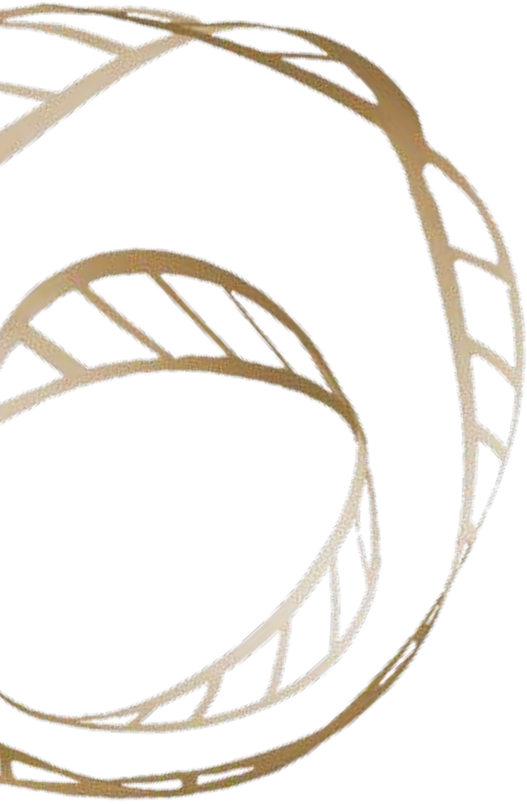
23andWe

How can doctors decode direct-to-consumer genetic testing?



Illustrations by Felicia Gilman and Erica Aitken.



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When I first heard the term "direct-to-consumer (DTC) genetic testing," I had two automatic responses. First, I immediately began to re-label the "consumers" as patients—after all, if someone is getting medical tests, it seems fair to consider him a patient. People seek genetic testing because they want information about their health—no one gets genetic testing instead of going to a concert or buying a television—and in my mind that makes them patients. My second reaction was to ask why the product is touted as direct-to-consumer. The term implies that someone or something is standing so obstructively between patients and their genetic information that the entire premise of the product is to bypass this unnamed roadblock. Of course, the roadblock is the same as that standing between a patient and any medical test—the patient's doctor. These implied issues of accessibility spurred the evolution of genetic testing.

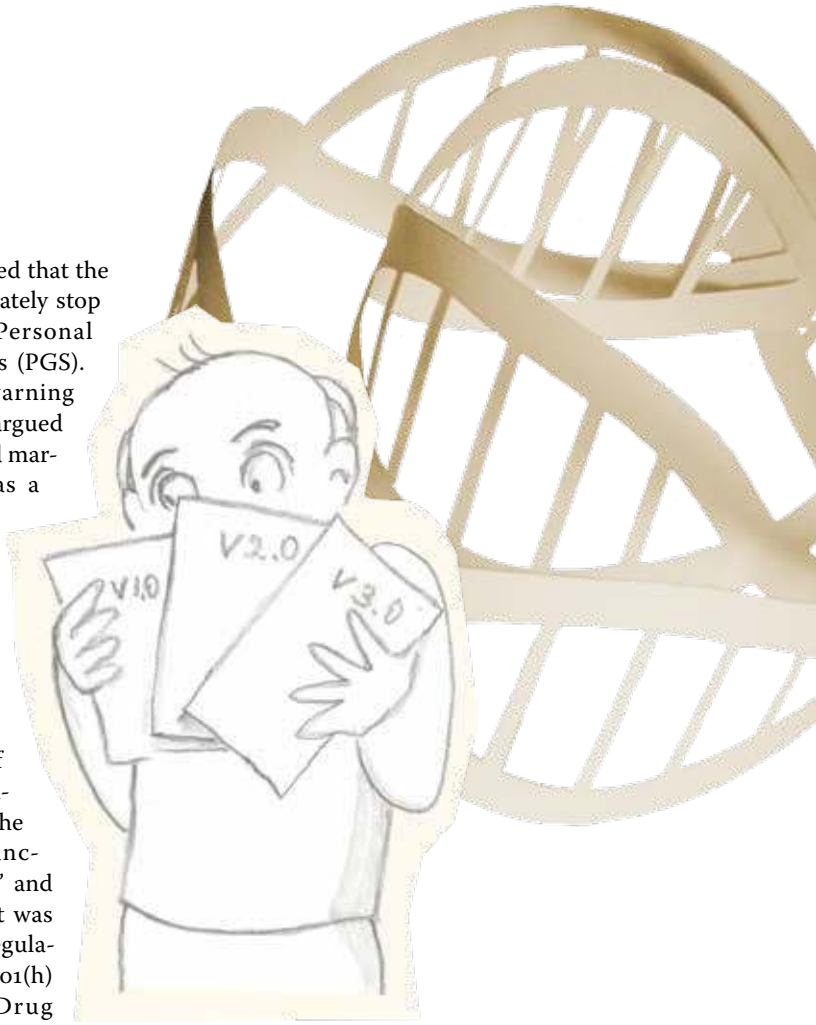
Genetic testing for years has been a rare but valuable tool for those at risk for specific conditions, or a novelty for the curious few willing to spend a significant amount of money for a look at their genetic code. But in recent months, rapidly changing policies, increased commercial availability, and evolving public opinion have made DTC genetic testing much more accessible, and much more popular. Now patients can—and will—order personalized genetic testing without any involvement from their physicians. This has its downsides: physicians cannot ensure that the information will be reliable, or that the provider will ensure that the results are fully understood. They also have no control over whether the consumer/patient's privacy will be protected. But these advances also provide physicians with a unique opportunity to help patients understand the genetic information given to them and—even more importantly—to further engage patients in their own health and health care.

A free-for-all of genetic testing

The technology to conduct genetic tests has been available for years, but in many ways the race toward widely available DTC genetic testing began on June 13, 2013, when the Supreme Court handed down a decision in *Association of Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*[1] This case not only brought up many of the most divisive issues surrounding genetic testing, the decision enabled companies to move forward with offering more tests. Following studies at the University of California, Berkeley, that demonstrated the association between BRCA genes and breast cancer, biotech company Myriad Genetics sequenced the BRCA1 and BRCA2 genes, enabling them to test for these genes for clinical purposes. It then patented the locations and sequences of these genes, and by virtue of that information, the ability to test for mutations. One patent in particular, 17Q-linked breast and ovarian cancer susceptibility gene (U.S. 5747282 A), filed in 1995, enumerates an (unsurprisingly) extensive list of the scientific and therapeutic items that the invention relates to, most relevant here being "the screening of the BRCA1 gene for mutations, which are useful for diagnosing the predisposition to breast and ovarian cancer."[2] This broad patent prevented others from conducting testing and research surrounding the BRCA genetic sequences, prompting the Association of Molecular Pathology to contest its validity.

The patent asserts that the regulatory sequences, promoter regions, coding regions, and specific mutations of chromosome 17 are Myriad's scientific creation. That position was negated in Justice Thomas's unanimous majority opinion, which elaborated on the statement that, "A naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated,"[1] and noted that Myriad did not seek to patent any sequencing method or machine to which a patent could have actually been applied. Justice Thomas made the point that the BRCA gene sequences have been isolated as a naturally occurring DNA sequence unlike, say, cDNA, which is created as a complementary sequence to the edited downstream messenger RNA sequence, and *is* patent eligible because it is an inherently man-made entity. The oral arguments of the case ranged far and wide, ultimately comparing the difference between patenting naturally occurring genes and modified, lab-created cDNA to the difference between patenting a tree and a wooden baseball bat.

The Supreme Court's invalidation of Myriad's patents eliminated the



company's monopoly on the genetic test for BRCA, which, given the prevalence of breast cancer in America, is a widely sought after metric. The service that Myriad had charged approximately $4,000 to provide was suddenly susceptible to competitive market rates, and was incorporated into existing DTC genetic testing kits. As the breadth of information available in these kits grew, the companies providing them found ways to make them more widely affordable as well.

No company achieved rapid name recognition, popularity, and affordability quite the way that 23andMe did. 23andMe was founded in 2006, and by 2008 its personalized genetic testing kit was *Time Magazine*'s "Invention of the Year."[3] At that time, 23andMe sold what *Time* dubbed the "Retail DNA Test" for $399—not prohibitive, but not quite an impulsive Christmas gift for the curious.

In the five years following that article, 23andMe incorporated a number of new tests—notably the BRCA tests, which were added in 2013. Even more importantly, the company received an influx of cash from venture capital (much came from Google,* an obvious choice when you consider that the company plans much of its further expansion through gathering and monetizing "personal information"[4]). This increase in funding allowed 23andMe to offer its kit at the ultimate bargain-basement price: $99. At that price, it's no surprise that as of November 2013, 23andMe had sequenced the genotypes of approximately 500,000 individuals, making it the most popular and visible provider of DTC genetic testing.[5]

But popularity doesn't mean invincibility, and by rising to the top of the food chain, 23andMe acquired a target on its back. The largest controversy so far erupted in November 2013, when the FDA demanded that the company immediately stop marketing its Personal Genomic Services (PGS). In a scathing warning letter, the FDA argued that 23andMe had marketed the PGS as a medical device, "intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease . . . or intended to affect the structure or function of the body" and that as a result, it was subject to the regulations of section 201(h) of the Food Drug & Cosmetics Act, 21 U.S.C. 321(h).[6] By ordering 23andMe to comply with these regulations, the FDA essentially required that the company demonstrate that its tests actually detect what they claim to detect. The warning letter cited as an example the potential consequences of false test results for the BRCA genes—either an unnecessary prophylactic procedure in the event of a false positive, or a lack of preventive screening or prophylaxis in the event of a false negative. The alternative response, which 23andMe has employed in the meantime, is to offer genomic sequencing for consumers with absolutely no interpretation of what the information might mean—in essence, eliminating the troubling marketing element and making it no longer a "medical device." Yet once 23andMe has provided the data and modifications required by the FDA, it is likely that they will be able to return to their original model of operation.

Concerns from all sides

The FDA's warning outlines what should be the medical profession's greatest concerns surrounding DTC genetic testing—how reliable is it? And can we make clinical decisions based on such tests? Of course, a demonstration of just how reliable 23andMe's services are is exactly what the company has been cited for not providing, so the jury is still out. In a public statement in reply to the FDA's warning, co-founder Anne Wojcicki insisted that, "We have worked extensively with our lab partner to make sure that the results we return are accurate. We stand behind the data that we return to customers—but we recognize that the FDA needs to be convinced of the quality of our data as well."[7]

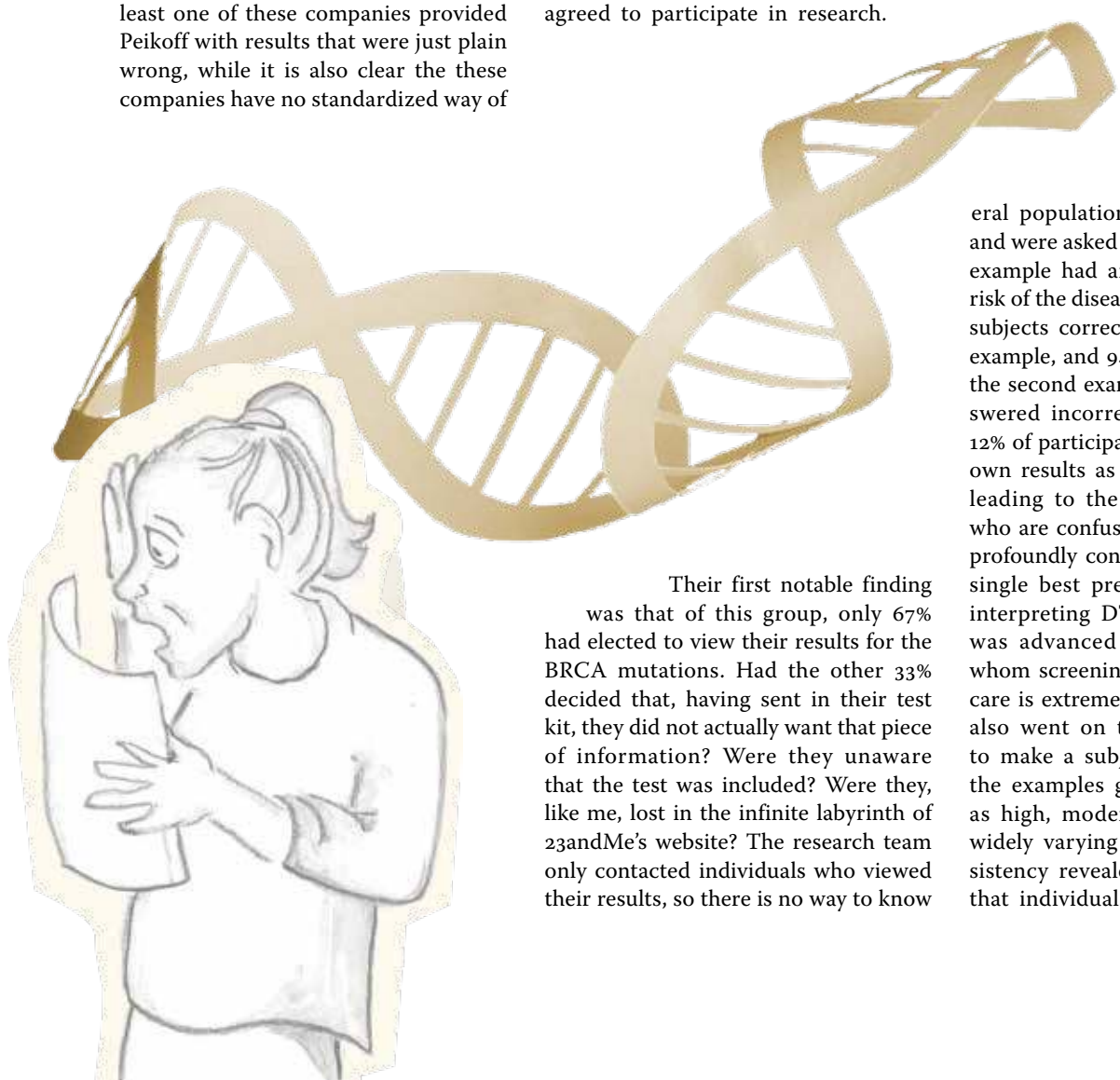
While providers clash with the FDA, the public discussion of the potential inaccuracy of these tests is getting louder. On December 30, 2013, the *New York Times* featured an article by Kira Peikoff, a bioethics student at Columbia, in which she underwent genetic testing provided by three different companies—23andMe, Genetic

* It is worth noting that 23andMe co-founder Anne Wojcicki and Google co-founder Sergey Brin are married, although now separated.

Testing Laboratories (GTL), and Pathways Genetics—and compared the results. The discrepancies were alarming. The results diverged on Peikoff's genetic risk for a number of conditions: for example, 23andMe's test estimated her lifetime risk of psoriasis as 20.2%, while GTL's test placed her risk at 2%. Even in cases in which they did agree on the numbers, the companies offered different interpretations of those numbers, categorizing identical results as "reduced risk" versus "medium risk," and giving significantly different impressions about what concurring results meant.[8] Both of these types of discrepancies are alarming—it is clear that at least one of these companies provided Peikoff with results that were just plain wrong, while it is also clear the these companies have no standardized way of interpreting results for patients, so that even if numerical accuracy is assured, consumers may not really understand what their results mean.

This issue of interpretation is more contentious—it is easy to agree that the results should be accurate, but it is unclear what the obligation a company has to explain results to a patient. Companies are eager to refute accusations that their consumers do not fully understand the results they are given, yet criticism persists that, as a result of poorly explained testing, patients are not making fully informed decisions, and that incomplete understanding of results leads to poorly informed health care decisions and significant anxiety.

23andMe's research division conducted its own evaluation of customers who were BRCA-positive and had agreed to participate in research.



Their first notable finding was that of this group, only 67% had elected to view their results for the BRCA mutations. Had the other 33% decided that, having sent in their test kit, they did not actually want that piece of information? Were they unaware that the test was included? Were they, like me, lost in the infinite labyrinth of 23andMe's website? The research team only contacted individuals who viewed their results, so there is no way to know why the others did not look at them. But of the BRCA carriers who did view their results, only 41% of them knew that the test was included when they purchased it. This begs the question—why did so many not know the full nature of the product they were ordering? Did 23andMe obtain the informed consent of these customers before viewing their test results? 23andMe does try to keep its customers from being unwittingly surprised by the result by adding the extra step of "unlocking" the result. Yet electing to undergo the testing and choosing to view the results are two separate steps, and the patient should be able to give informed consent at both stages.[9]

One study by Kaufman et al. examined the ability of a group of consumers to interpret the results of some basic sample test results. For the study, participants were given an example lifetime risk of a certain disease, in addition to the general population's risk of that disease, and were asked to interpret whether the example had an increased or reduced risk of the disease. Ninety percent of the subjects correctly interpreted the first example, and 94% correctly interpreted the second example. Yet those who answered incorrectly were likely in the 12% of participants who described their own results as difficult to understand, leading to the conclusion that those who are confused about the results are profoundly confused. Furthermore, the single best predictor of confusion in interpreting DTC genetic test results was advanced age, a population for whom screening and preventive health care is extremely important. The study also went on to ask the participants to make a subjective judgment about the examples given—classifying them as high, moderate, or low risk—with widely varying results. The only consistency revealed by this analysis was that individuals without postgraduate

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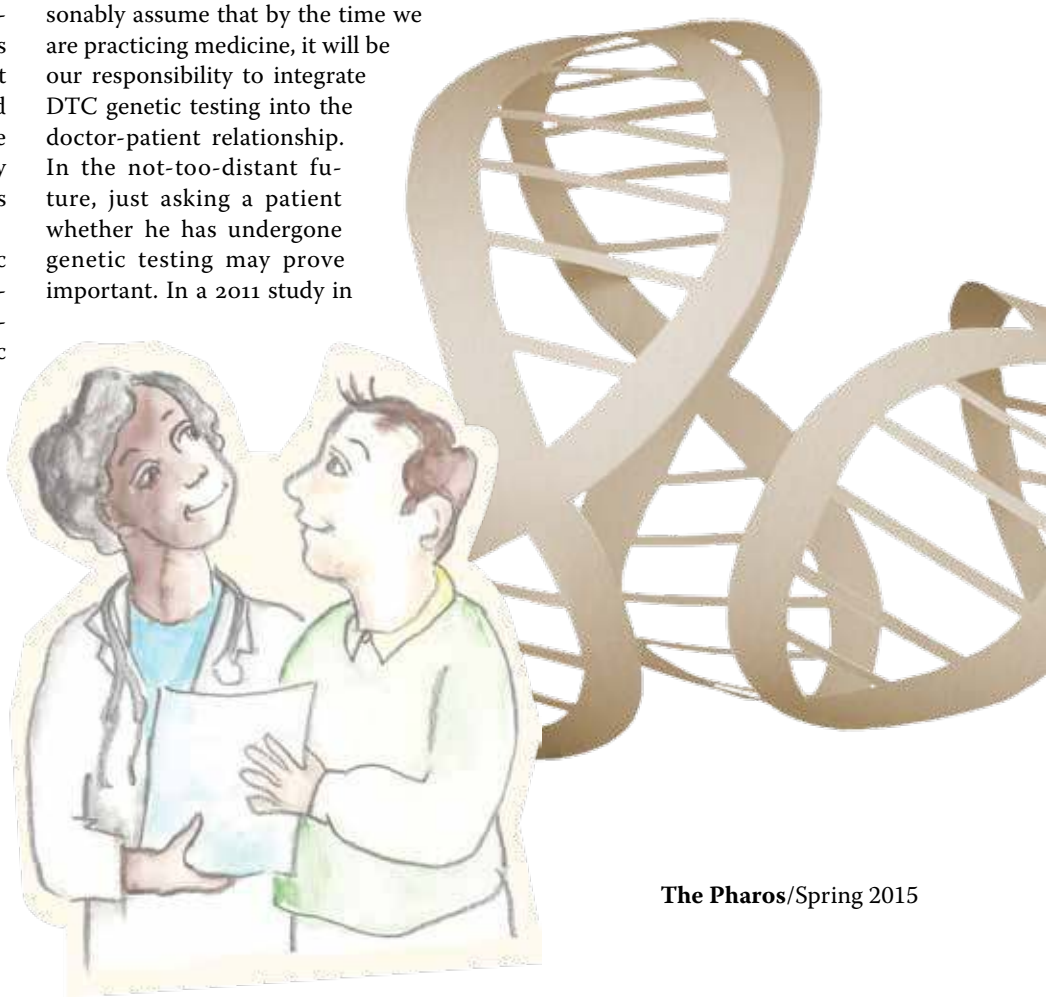
education were more likely to minimize the risk of an example with elevated risk of disease.[10] These results show that even in a clear-cut example of increased risk, understanding of the results was not perfect, and interpretation of the results varied considerably. This finding reinforces concerns that patients who have DTC genetic testing do not fully understand their test results and therefore are not benefiting from the information they are given. They may even be harmed by misunderstandings of their results.

Medical professionals and the public alike have also raised concerns regarding the privacy of patients' genetic information in the hands of DTC genetic testing providers. It is possible that individual genetic information could be abused, leaked, or stolen, and when the information is in the hands of a for-profit company—as opposed to a hospital dedicated to providing care—the possibility for misuse seems greater. 23andMe acknowledges that it is retaining its customers' de-identified information for the purposes of creating a dataset that will be marketed to industries like the pharmaceutical industry. While this has the potential to generate useful research on an unprecedented scale, many distrust the extent of the company's privacy protections. The possibility for misuse of data that combines genetic and personal information appalls conspiracy theorists wary of the partnership of 23andMe and Google. Yet these suspicions have little firm basis in fact, and the question of genetic privacy in DTC genetic testing is a better question for lawyers than for physicians. Regulations such as the Genetic Information Non-Discrimination Act of 2008 prevent health insurance providers and employers from discriminating on the basis of genetic information.[11] But as genetic testing continues to evolve, physicians can expect to be called upon to advise lawmakers about the best ways to protect patients in the fact of advancing technology.

The role of physicians in DTC genetic testing

As 23andMe and its competitors take off, today's medical students can reasonably assume that by the time we are practicing medicine, it will be our responsibility to integrate DTC genetic testing into the doctor-patient relationship. In the not-too-distant future, just asking a patient whether he has undergone genetic testing may prove important. In a 2011 study in the *New England Journal of Medicine*, Bloss and colleagues found only 26.5% of consumers shared their results with their physicians.[12] A follow-up study in 2013 by the same group found that 39.5% of their respondents had discussed their results with a physician.[13] These results suggest that although some 39.5% of DTC genetic testing patients may be receiving valuable information about their genetics from their doctors, 60% or more of patients are left to interpret their results on their own, meaning an increased potential for a consumer to forgo important screenings, to place less importance on certain lifestyle choices, or to simply feel anxious about elements of their results. All of these potential problems will decrease if more physicians ask their patients whether they have joined the growing ranks of the DTC-tested.

The 2011 Bloss study also presented a more heartening finding—those patients



who underwent genetic testing and *did* choose to discuss the results with their physician were significantly more likely to make lifestyle changes than those who did not. These patients both increased their physical activity and decreased their fat intake. Similarly, the Kaufman study observed that patients who discussed their results with a physician were significantly more likely to reduce their fat intake and undergo preventive screening tests. While the relationship might not be causal, and it seems likely that a self-selecting demographic elects to undergo genetic testing, the result is still encouraging. If a $99 test can help patients feel more engaged in their health care, and can create a personally applicable impetus for them to make healthier choices, physicians should consider this an opportunity. Patients are aware of the impact of lifestyle choices on health, but because these seem broad and unspecific, patients often struggle to apply this knowledge directly to their own lives. Using genetic testing to relate to patients their personal risk of diseases that are affected by how they behave could be the direct link between an individual's health and lifestyle that motivates him to make better choices.

Physicians can also view a patient's decision to undergo genetic testing as indicative that the patient is particularly receptive to discussing preventive health care. The physician should seize the opportunity to acknowledge that the patient has taken this step towards assessing his own health status and capitalize on the fact that he might want to do more. Even if an increased risk of a particular condition is not identified, the physician can still use this opportunity to engage the patient in discussing what preventive screenings or lifestyle choices are most important to him. The 2013 Bloss follow-up study found that patients who discussed their results were more engaged in their health care, undergoing significantly more screening procedures than those who did not discuss their results with their physician. In the event that a significant risk of a genetic condition is identified, this should be viewed as reason to investigate further. In light of the current doubts about the validity of DTC genetic testing, results that are strongly associated with serious conditions should be replicated before proceeding. Yet regardless of whether an individual result proves to be a true-positive or a false-positive, it remains likely that many patients will eventually learn of significant genetic risk for a serious illness that would otherwise have gone undetected. Therefore it makes sense that DTC genetic testing could serve as a first-line screening tool, despite its many shortcomings.

Physicians must navigate the complex arrival of genetic consumerism in the clinic both because of, and in spite of, the potential pitfalls. Physicians must be involved because the consumers of DTC genetic testing are patients—and the potential consequences of DTC genetic testing's problems are medical. Physicians are thus those who are best situated to ensure that patients are educated and protected when they use DTC genetic testing. Furthermore, physicians are those who can bring this method of testing to its full potential. The information gained is intended to inform a patient's medical decisions and lifestyle choices, and physicians are the most suited to help patients use this information in the best way possible. DTC genetic testing continues to advance, and as its reliability becomes established, so will its popularity. Therefore physicians must prepare to meet this new player in health care, and seize the opportunity to use it to its full potential.

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