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Federal Neglect: Regulation of Genetic Testing

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Federal Regulation of Genetic Testing Neglect

Government needs to ensure that genetic tests provide useful medical information and that the test results are reliable.

U.S. consumers generally take for granted that the government assesses the safety and effectiveness of drugs and other medical products before they are made available commercially. But for genetic tests, this generally is not the case. At the same time, the number and type of genetic tests continue to increase, and tests for more than 900 genetic diseases are now available clinically. Genetic testing is playing a growing role in health care delivery and is providing information that can be the basis for profound life decisions, such as whether to undergo prophylactic mastectomy, terminate a pregnancy, or take a particular drug or dosage of a drug. Current gaps in the oversight of genetic tests, and of the laboratories that offer them, thus represent a real threat to public health.

Currently, the government exercises only limited oversight of the analytic validity of genetic tests (whether they accurately identify a particular mutation) and virtually no oversight of the clinical validity of genetic tests (whether they provide information relevant to health and disease in a patient). To the extent that oversight exists, it is distributed among several agencies, with little interagency coordination. As a result, no clear regulatory mechanism exists to guide the transition of tests from research to clinical practice, or to ensure that tests offered to patients are analytically or clinically valid. In order to protect consumers, and to help advance the potential benefits offered by genetic testing, government action is urgently needed.

Lingering problems

Most genetic tests are not sold as stand-alone products but as services by clinical laboratories. Clinical laboratories are regulated under the Clinical Laboratory Improvement Act (CLIA), as amended in 1988. CLIA was enacted to strengthen federal oversight of clinical laboratories and to ensure accurate and reliable test results after Congress found widespread poor quality of laboratory services.

CLIA, which is administered by the Centers for Medicare & Medicaid Services (CMS), imposes basic requirements that address personnel qualifications, quality-control standards, and documentation and validation of tests and procedures. For most "high-complexity" tests, meaning those that require a high degree of skill to perform or interpret, CLIA requires periodic "proficiency testing," in which the laboratory must demonstrate its ability to accurately perform the test and interpret the results. Genetic tests are high-complexity tests, but CMS has not created a genetic testing "specialty" for molecular and biological tests, and therefore specific proficiency

DENNIS ASHBAUGH, *Grape-Pumpkins*, Mixed media on canvas, 50 x 55 inches, 2002.

testing for these genetics tests is not mandated under CLIA. This means that laboratories must determine their proficiency for themselves. Some labs do so by using proficiency-testing programs established by professional organizations; however, the use of these programs is not required under CLIA, and these organizations provide proficiency-testing programs for only a small subset of genetic tests.

As early as 1995, the National Institutes of Health (NIH) and the Department of Energy jointly convened a government task force to review genetic testing in the United States and make recommendations to ensure the development of safe and effective genetic tests. Since that time, government advisory bodies have urged CMS to strengthen CLIA oversight for genetic tests by, among other things, establishing a specialty area for genetic testing. However, although the government announced in 2000 that it would establish a genetics specialty area, no standards have yet been issued.

Test kits and home brews

A genetic test can be performed using either a "test kit" or a "home brew." Test kits, as their name implies, contain the reagents needed to perform the test, instructions on test performance, and information regarding what mutations are detected. Kit manufacturers sell these tests to laboratories, which use them to perform the tests. "Home brews" are assembled in house by the laboratory and are used by the laboratory to analyze patient samples and provide results to health care providers and patients.

Laboratories that use home-brew tests currently are subject to only minimal CLIA oversight. CLIA does not explicitly authorize CMS to evaluate how accurate home-brew tests have to be in predicting a particular clinical outcome (clinical validity) or the likelihood that the use of a test will lead to an improved health outcome (clinical utility). Moreover, CLIA does not permit CMS to be a "gatekeeper" for home-brew tests, in that it authorizes neither prospective review nor pre- or postmarket approval of new tests by CMS. The decision to offer a new genetic test is within the sole discretion of each clinical laboratory director. Nor can CMS restrict when and for whom a test may be performed, meaning that it is up to the provider to determine whether a particular test is appropriate for a particular patient, without the help of specified indications for use (such as those provided for drugs and medical devices).

The Food and Drug Administration (FDA) customarily regulates most medical products, but its jurisdiction over home-brew tests is unclear, and the agency at various times has taken different positions on the issue. Recently, the agency has stated publicly that it lacks the statutory authority to regulate home-brew tests.

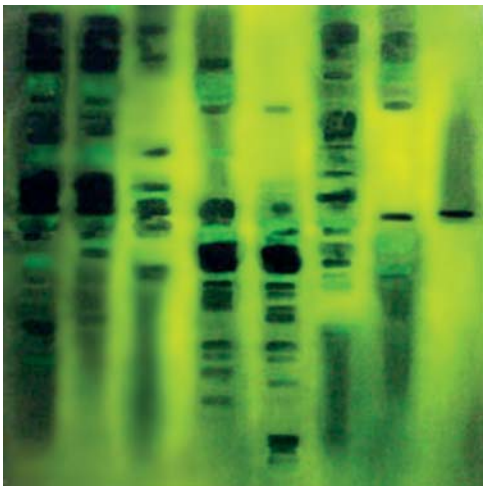
Test kits, however, are regulated by the FDA as medical devices. Before they can be marketed, the manufacturer must submit data to the FDA demonstrating that the test accurately identifies a mutation of interest and that the mutation correlates with present or future health status. However, of the more than 900 diseases for which genetic tests are currently available clinically, the FDA has approved only four test kits to detect mutations in human DNA: for factor II and factor V Leiden, which affect blood clotting; cytochrome P450 genotyping, which affects the rate at which drugs are metabolized and thus can help in determining dosage; and cystic fibrosis. The manufacturer or laboratory, and not the FDA, makes the decision whether to develop a particular genetic test as a test kit or a home brew and, therefore, whether submission to FDA is required. The tiny number of FDA-approved test kits makes it clear that manufacturers prefer the less-regulated status and that the regulatory regime allows them to avoid stringent FDA oversight.

The FDA also regulates as medical devices certain components, known as "analyte-specific reagents" (ASRs), of home-brew tests. ASRs are small molecules that serve as the active ingredients of home-brew tests, and they can be manufactured for sale or made in house by the laboratory. The FDA's oversight of ASRs is fairly narrow; ASRs that are manufactured must be sold only to laboratories certified to perform high-complexity tests and must be labeled in accordance with FDA requirements. Also, FDA regulations state

Dennis Ashbaugh

Contemporary painters often work within a tradition of ideas about the function of painting—a community-specific dialogue that can seem obscure to the uninitiated. Although New York artist Dennis Ashbaugh's use of color and light in his large-scale paintings is similar to that of the early colorists, he has broken free of self-referential formalist conventions by utilizing genetic imagery in his work. Ashbaugh began thinking about making DNA paintings in 1987 and was among the first artists to experiment with autoradiograph marking. Autoradiographs provide a means for visualizing the invisible. By incorporating this imagery into his paintings, Ashbaugh challenges his own profession to, in the words art historian and theorist Suzanne Anker, "reveal the inner code beneath appearances."

Paintings by Dennis Ashbaugh will be on view at the National Academy of Sciences, November 10, 2006–April 1, 2007. For information on programming and events associated with the exhibition, visit www.nationalacademies.org/arts. Ashbaugh's work is represented in Washington, D.C., by The Ralls Collection (www.rallscollection.com).



DENNIS ASHBAUGH, *#6*, Mixed media on canvas, 8 x 8 inches, 2002.

that home-brew tests that are developed using commercially distributed ASRs must be ordered by a health professional or "other persons authorized by state law." The FDA interprets this regulation to require that an ASR-based home-brew test be ordered only by a health care provider, but the agency does not appear to have ever enforced this provision. Additionally, the regulation does not distinguish between a patient's personal physician and a physician-employee of the testing laboratory. Nor does the FDA regulate the claims that laboratories make about tests developed using ASRs.

In the absence of a coherent system of oversight, it is difficult for providers or patients to have confidence in the claims made by those selling genetic tests or in the competence of the laboratories performing them. The absence of a regulatory system that requires a premarket demonstration of validity, moreover, has created an environment ripe for entry into the marketplace of tests of unproven medical value that are targeted directly to consumers.

Targeting consumers

The phrase "direct to consumer" is best known in the context of pharmaceutical advertising, where it is used to refer to advertisements that inform patients of the availability of a particular medication to treat a specific condition, such as depression or erectile dysfunction, and encourage them to ask their doctor about the drug. These ads have generated controversy, with some observers arguing that the ads induce demand inappropriately and fail to inform patients adequately regarding the risks of the drugs being promoted. Nevertheless, for prescription drugs, these ads can increase demand only indirectly: The physician serves as a gatekeeper, ensuring that only those medications appropriate for a patient are prescribed. Additionally, the safety and effectiveness of the drugs have already been assessed by the FDA.

Direct-to-consumer (DTC) genetic testing, in contrast, encompasses three different scenarios: the advertising of a genetic test that is available only upon a health care provider's order; the advertising and sale of genetic testing directly to consumers, without the involvement of any health care provider; and the advertising and sale of testing services directly to consumers, with some involvement by a health care provider employed by the tester (for example, the laboratory). Today, several genetic tests are being advertised and sold directly to the public, both through Internet Web sites and retail stores.

Most laboratories do not currently offer genetic testing directly to the public. In fact, only about eight companies promote DTC testing through Internet Web sites for health-related conditions (excluding, for example, genetic tests such as those for paternity and ancestry). However, the growth of DTC testing is likely to continue, given the low barrier to market entry, particularly via the Internet; the rapid pace of genetic research; and the interest of consumers in self-care.

Tests offered over the Internet include some that are conducted routinely as part of clinical practice, such as tests for mutations causing cystic fibrosis, hemochromatosis, and fragile X (an abnormality of the X chromosome leading to mental impairment and other conditions). For these types of tests, the most readily apparent differences between DTC testing and provider-based testing are who collects the sample, to whom test results are communicated, and who interprets test results. Some laboratories require a patient to provide the name of a physician and will send results only to that provider, whereas other laboratories send results directly to patients and do not request the name of a provider. Some laboratories have genetic counselors on staff to take medical and family history information and be available for questions about test results; others do not.

Internet-based DTC testing also includes another category of tests: those for conditions lacking adequate evidence of predictive value for a disease or condition in the scientific literature. Examples in these categories include "genetic profiling" to guide the selection of nutritional supplements, testing to determine propensity to depression, and testing to select an appropriate skin care regimen (also sold by the testing company). One company advertises its

tests for obesity and osteoporosis susceptibility and for "oxidative stress" to the nutraceutical, personal and skin care, and weight-loss industries, which, presumably, would offer them directly to consumers.

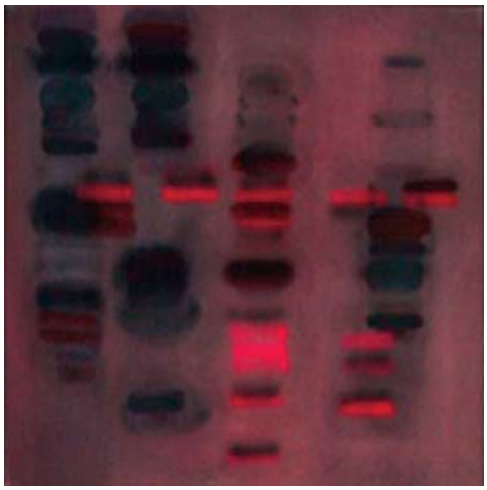
DTC tests also now include so-called "pharmacogenetic" tests: those used to determine whether a particular medication or dosage of medication is therapeutically appropriate. Although pharmacogenetics holds the promise of improved drug efficacy and reduced adverse reactions, the endeavor is predicated on the availability of accurate and reliable genetic tests. The current lack of coherent oversight threatens to derail this promising new field. Manufacturers and laboratories can simply claim that the tests are home brews in order to avoid rigorous FDA review of their quality.

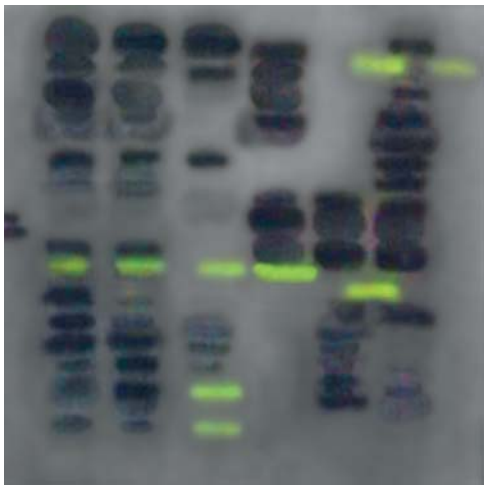
Avoiding harm

The initial criticism of DTC genetic testing highlighted harms from both advertising of tests and access to tests in the absence of a health care provider intermediary. The underlying theme of these criticisms has been that consumers are vulnerable to being misled by advertisements and lack the requisite knowledge to make appropriate decisions about whether to get tested or how to interpret test results. It has been argued that consumer-directed advertisements underemphasize the uncertainty of genetic testing results, and overemphasize testing's benefits to a public that is not sophisticated enough to understand genetics. Critics argue that genetic test results are complicated because they may provide only a probability of disease occurring, and that a health care provider is needed to put the test result in context and explain its subtleties. Further, it is asserted that ads may exaggerate the risk and severity of a disease for which testing is available. Thus, DTC advertising and unmediated access will have the negative effects of increasing consumer anxiety and generating demand for unnecessary testing.

In order to avoid the harms of DTC genetic testing, some observers have proposed restricting access to tests or advertising of tests. Regulating access would involve limiting those authorized to order the tests and receive the results. Regulating advertising would involve limiting the claims that test providers could make about their tests and, potentially, limiting the media through which claims could be made.

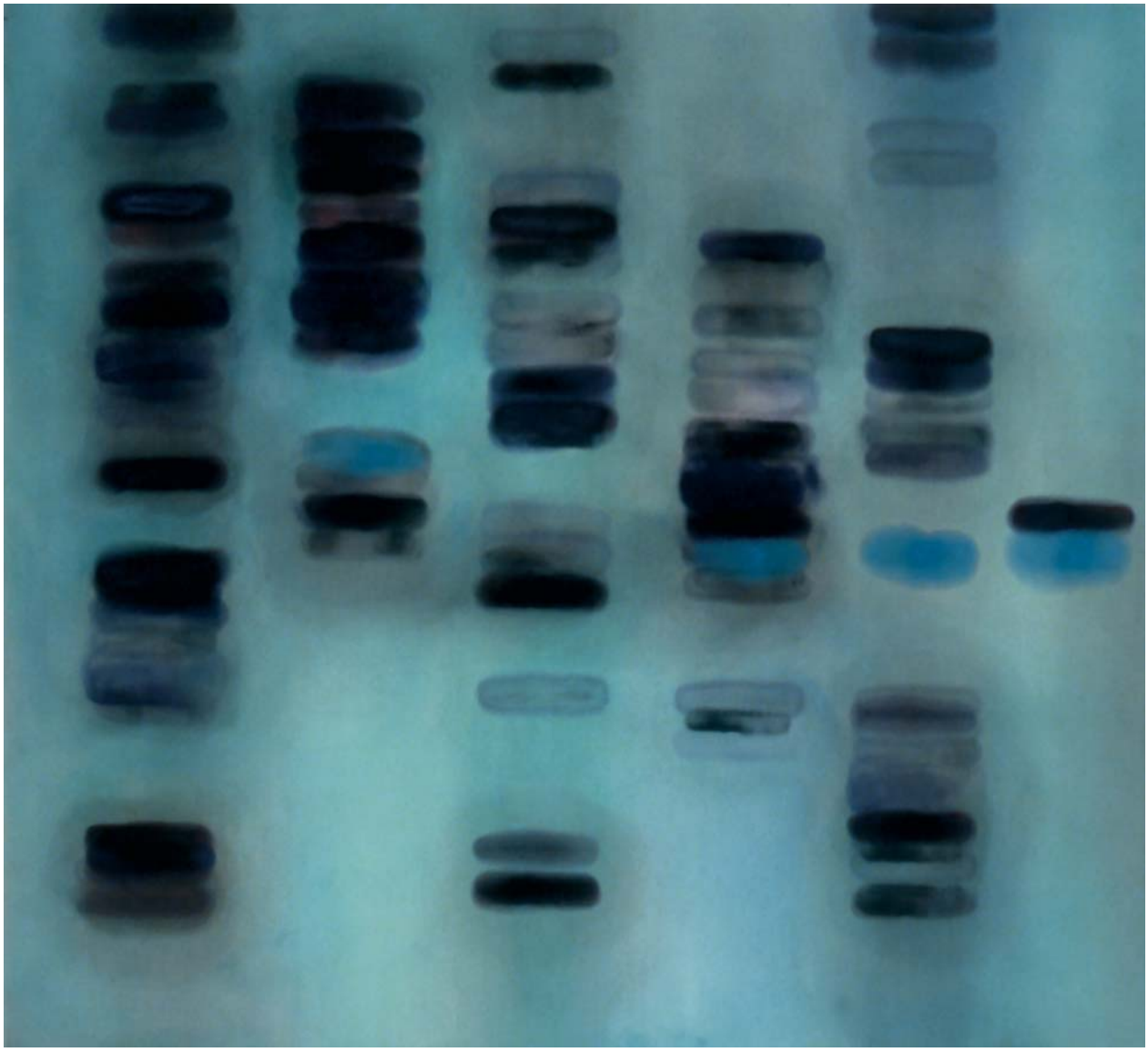
Regulating access. Whether health care provider authorization is required in order to obtain a genetic test, or any laboratory test, is the province of state law. Some states explicitly authorize patients to order specified laboratory tests (such as cholesterol or pregnancy tests) without a prescription from a health care provider. Other states categorically prohibit all DTC testing. And still other states are silent on





Above top:
DENNIS ASHBAUGH, *AKA/AKC Cicero*, Mixed media on canvas, 18 x 18 inches, 2002.

Above:
DENNIS ASHBAUGH, *AKA/AKC Snowball*, Mixed media on canvas, 19.75 x 19.75 inches, 2002.



DENNIS ASHBAUGH, *Son of Sam (#29)*, Mixed media on canvas, 74 x 84 inches, 2002.

the issue, meaning that individual laboratories decide whether to offer DTC testing. As of 2001, more than half of the states permitted DTC testing for at least some types of tests, whereas 18 prohibited it. Even where a provider's order is required, it may not be the case that the patient's interest is the provider's only interest; sometimes a physician employed by the laboratory is empowered to authorize testing on behalf of a patient.

Federal or state law could prohibit direct patient access to genetic tests by requiring a health care provider to order the test and receive the results. However, relying on state law would probably lead to a patchwork of non-uniform requirements; and Internet-based genetic testing, which may operate outside the reach of any one state, may make enforcement of such laws more difficult. In addition, federal or state restrictions on access would be predicated on the assumption that health care providers, unlike patients, are adequately prepared to appropriately order and interpret tests, but stud-

ies have shown that providers often have inadequate knowledge and training to provide quality genetic services.

Regulating advertising. Federal law protects consumers against unfair, deceptive, or fraudulent trade practices, including false or misleading advertising claims. Ads violate the law if they make false statements about a product or service, fail to disclose material information, or lack adequate substantiation. The Federal Trade Commission (FTC) has enforced the law against manufacturers of a variety of purported health products available without a prescription, such as companies that claim that their products promote hair regrowth, cure cancer, or cause weight loss. The FTC also regulates Internet-based advertising of products, including those making health claims, and the agency has conducted periodic sweeps of the Internet and sent notices warning companies of violations of the law.

The FTC has asserted its jurisdiction to take action against genetic test advertising that is false or misleading, and the agency has announced a joint effort with the FDA and NIH to identify appropriate targets for legal action. Nevertheless, the FTC's limited resources have hampered the agency in pursuing these claims, and this limitation leads the agency to focus on claims with a high likelihood of causing serious harm to many people. Perhaps as a result of its resource shortages, the FTC appears to have taken no action against any genetic test advertisements, even those that would appear clearly false and misleading on their face.

To the extent that advertising is neither false nor misleading and the product or service advertised is legal, the government's ability to regulate it is highly constrained. The First Amendment provides broad protection for so-called "commercial speech," and the government bears a high burden of proving that speech is harmful and that restrictions are needed to mitigate or prevent such harms.

Some observers have proposed intervention by the FDA to limit advertising claims about genetic tests. However, the FDA's jurisdiction to regulate claims made about a product is predicated on the agency's authority to regulate the product itself. For regulated products, the FDA's authority extends to claims about these products made in their labeling (and, in the case of prescription drugs, in their advertising as well). The FDA can both mandate the disclosure of risks and warnings and prohibit claims that it believes are inadequately supported by scientific evidence.

The fact that the FDA currently does not regulate most genetic tests precludes review of claims made about those tests. The FDA's lack of involvement also can affect the FTC's response, because the FTC, in enforcing its laws against false and misleading advertising, often looks to the FDA's labeling requirements for guidance regarding appropriate claim parameters. Thus, the absence of a designated oversight body for most genetic tests also means that there is no expert agency with clear authority to assess whether advertisements appropriately disclose all pertinent information to consumers.

GIVEN THE HIGH STAKES INVOLVED, THE GOVERNMENT NEEDS TO CORRECT THE SYSTEMIC GAPS IN OVERSIGHT THAT RENDER VULNERABLE THE QUALITY OF ALL GENETIC TESTS AND THE SAFETY OF CONSUMERS.

Laws also could be enacted to prohibit advertising of genetic testing to reduce opportunities for patients to be confused or misled or to make inappropriate decisions based on testing. Such laws, in addition to being subject to criticism as unduly paternalistic, also could be subject to challenge on First Amendment grounds to the extent that they prohibit advertising claims that are not clearly false or misleading. Furthermore, although the FTC is currently empowered to prohibit advertising claims that are clearly false and misleading, the agency is not enforcing these laws against the purveyors of any genetic tests.

Crafting a holistic approach

Aside from such practical challenges, restricting access and advertising would not address fundamental concerns regarding the analytic and clinical validity of all genetic tests. Although it certainly is important that patients be adequately informed about the benefits and limitations of genetic tests, test quality is a threshold, and therefore more fundamental, concern. Suppressing advertising about the tests would, to be sure, limit the number of consumers who find out about the tests, and limiting direct consumer access would decrease the number of consumers who could obtain them. But nei-

ther of these potential fixes would address whether the tests are performed correctly or are supported by clinical evidence demonstrating that they correlate with current or future health status. Yet these tests can have profound consequences. A predictive genetic test—for example, one that indicates a heightened risk of hereditary breast cancer—may lead a woman to choose prophylactic mastectomy. A diagnostic genetic test—say, for prenatal diagnosis—may lead to termination of pregnancy in the absence of any corroborating medical evidence from other laboratory tests or physical examination. A pharmacogenetic test to predict drug response may lead to prescribing a particular drug at a particular dosage or, alternatively, foregoing a particular therapy.

Given the high stakes involved, the government needs to correct the systemic gaps in oversight that render vulnerable the quality of all genetic tests and the safety of consumers. The current system is fragmented and riddled with gaps. CLIA in theory requires laboratories to demonstrate the analytic validity of all tests performed, but regulations that would better ensure analytic validity for most genetic tests have yet to be implemented. CLIA has the legislative authority to establish a genetic testing specialty, but it has chosen not to do so. The FDA has the expertise to evaluate home-brew genetic tests, just as it does genetic test kits and many other diagnostic tests, but the agency lacks a clear mandate to review most genetic tests. The FDA might have the legal authority to act, but new legislation that clarifies the agency's authority would eliminate the uncertainty and give the FDA a clear mandate to act.

These hurdles could be overcome through more effective leadership at the federal level, predicated on awareness that ensuring analytic and clinical validity is essential if genetic medicine is to achieve its promise of improving health. Regulating test quality would involve establishing and enforcing standards to ensure the analytic and clinical validity of tests before they are made available to the public and to ensure that laboratories are competent to perform them and report results appropriately. Thus, the best approach to alleviating concerns would be a system of oversight to ensure that all genetic tests, whether DTC or physician-based, home brew or test kit, are analytically and clinically valid.

Although DTC testing has been a vivid and headline-grabbing development in genetics, it would be a mistake, and ultimately an unsuccessful endeavor, to focus efforts on remedying the potential harms from DTC tests without considering the entire regulatory context. Without a system in which an upfront expert evaluation can be made with respect to the analytic and clinical validity of genetic tests, it will be difficult if not impossible to make rational decisions about who can and should order the test and receive the results and what claims are appropriate in advertising.

The time has come to shift the focus to ensuring the quality of all genetic tests. Focusing on quality would address many of the concerns raised about access and advertising and would also help to ensure the quality of all genetic tests, not just those provided directly to consumers. Although there are limits on how much the government can or should do to protect consumers, there are clear opportunities for it to provide patients and providers with greater assurance that genetic tests are accurate and reliable and to provide information that is relevant to health care decisionmaking.

Recommended reading

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