SCIENCE AND REGULATION

Regulating Direct-to-Consumer Personal Genome Testing

International cooperation and postmarket regulation are needed for Internet-based direct-to-consumer genome tests.

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Direct-to-consumer (DTC) personal genome tests claim to provide consumers access to information about their genetic ancestry, susceptibility to traits such as excessive earwax, carrier status for diseases like cystic fibrosis, ability to metabolize drugs like statins, and likelihood of developing diseases such as cancer, Alzheimer's disease, and diabetes—all in one test, for a few hundred dollars, and without involvement of a health-care professional. Proponents of such tests tout the power of making such information easily available, while critics worry about consumer safety and harm that could result from unreliable tests, excessive claims about the meaning of tests or the benefits of being tested, and misinterpretation of test results (*1*, *2*). The U.S. Government Accountability Office (GAO) raised concerns (*3*, *4*), and the U.S. Federal Trade Commission (FTC) warned consumers to interpret at-home genetic tests with "a healthy dose of skepticism" (*5*). In 2009, the House Energy and Commerce Committee initiated an investigation into regulation of DTC testing (*6*).

Many problems of DTC tests reflect problems of genetic tests more generally. Well over 90% of genetic tests available in the United States do not receive data-driven review by an external regulator to confirm safety and effectiveness before moving into clinical use (*1*). There is broad consensus about the need for some form of regulatory review before allowing use of a genetic test (*7*), but there has been ongoing controversy about how to achieve this goal. Effective regulation will require cooperation from governmental agencies, and flexibility to accommodate the complexities of tests, like those offered by DTC companies, that provide genome-wide analysis producing results with variable and often uncertain validity and clinical utility.

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U.S. Federal Regulation

Laboratories that provide clinical testing services in the United States—such as diagnostic or genetic testing—are regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (*8*). The CLIA regulations address the quality of lab testing services, for example, by ensuring that laboratories are properly staffed and follow proper procedures. The genetic test kits that laboratories purchase from medical device manufacturers receive additional regulation by the U.S. Food and Drug Administration (FDA) as in vitro diagnostic devices (*9*). However, if a lab develops a test in-house [lab-developed test (LDT)], as opposed to purchasing the test from a device manufacturer, the test may escape FDA oversight. A lab cannot sell its LDTs for use by other laboratories but can use them itself to provide testing services to the public. Many LDTs arguably fall within the definition of a "device" that is subject to FDA regulation, but FDA, in an exercise of its enforcement discretion, has traditionally held back from regulating most LDTs (*10*, *11*).

This policy has a profound impact on the level of evidence required before a test can move to market. Lab-developed tests receive internal validation at the lab that developed them but do not generally receive data-driven review by a regulator to ensure their safety and effectiveness, nor are they subject to the postmarket vigilance and adverse event reporting that FDA regulations provide.

In contrast, FDA-regulated tests receive data-driven review. The precise data requirements depend on how the test is classified in terms of novelty and level of risk, based on factors such as the manufacturer's clinical claims (e.g., does the test predict cancer susceptibility or merely earwax type?) and the seriousness of interventions that might be taken in response to the test results (e.g., prophylactic mastectomy). Higher-risk genetic tests may be required to move through FDA's premarket approval (PMA) process, which requires at least some clinical trial evidence to show safety and effectiveness before introducing the product in the market. Moderate-risk tests would pass through the less-rigorous 510(k) clearance process. The 510(k) clearance process does not necessarily require clinical trials but does require premarket research to support the device's risk classification and to validate any analytical or clinical claims that the sponsor plans to make about the device. Either way, some data-driven external regulatory review is required before a test can be sold for commercial use.

Regulating DTC Tests

DTC genetic tests may escape premarket review by FDA under a business model in which consumers send their samples to a CLIA-certified lab that performs testing using its own LDTs. In response to this concern, FDA recently sent letters to multiple companies involved in DTC testing (*12*), signaling its intent to assert jurisdiction over DTC genetic tests. In July 2010, the FDA sponsored a public meeting to gather input on appropriate regulation of all LDTs, including DTC tests (*13*).

No one regulatory strategy will be suitable for all DTC tests.

There are two key barriers to FDA oversight of DTC tests: (i) there is a lack of data to support premarket clearance or approval, and (ii) even when data support the test's intended use, FDA cannot control off-label use (use in ways other than those intended by the manufacturer or reviewed by regulators). Although there has been speculation about the potential psychosocial harms of testing, such as an increase in anxiety or encouragement of fatalistic behavior, there are, to date, few studies addressing these concerns (*14*). The limited evidence tends to be reassuring, even for risk information associated with relatively serious ailments (*15*, *16*). However, iatrogenic harm (harm due to treatment) may be a more serious concern. In one study, 40% of participants with genetic test results indicating increased risk for Alzheimer's disease reported increasing their use of medications or vitamins, compared with 20% of those whose results did not indicate increased risk (*16*). Given that all medications carry the potential for adverse effects, the scope of

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potential harm from unnecessary or unproven treatment after genetic risk assessment is an important unstudied question.

There is a need for data, but there are genuine economic and feasibility issues in generating it before tests go on the market (*11*). Many personal genome tests provide predictive information, with the ultimate goal of long-term disease prevention. Thus, there may be decades of uncertainty before the risks and benefits are truly understood. Delaying consumer access to DTC tests until robust premarket data are available would inhibit product development and could effectively regulate DTC companies out of existence.

The solution lies in accepting that premarket studies cannot fully answer questions about the safety and effectiveness of genetic tests and focusing additional effort on postmarket surveillance and regulation. This mirrors the approach taken for drugs in the FDA Amendments Act of 2007 (FDAAA) (*17*), which expands FDA's authority to require ongoing studies after drugs are approved and calls for creation of a large data network to support outcomes-based observational studies (*11*). It would probably require new legislation to give FDA a complete set of FDAAA-like powers to regulate devices.

Moving Forward

No one regulatory strategy will be suitable for all DTC tests. Even within a single DTC test, multiple risk assessments are provided and each must be evaluated independently. We therefore support the recommendation for a risk-stratified approach (*1*). FDA premarket review would focus on higher-risk tests. Less-risky tests that receive lighter FDA premarket scrutiny would still be subject to other oversight mechanisms, such as a national registry or measures to disclose uncertainties and risks. Risk-stratification criteria have not yet been developed and remain an important policy priority.

All tests should be analytically valid (able to accurately and reliably measure what they say they are measuring), and any clinical claims made about the test must be accurate and substantiated. Safety and effectiveness data should be developed, but for many tests, this should be done through enhanced postmarket surveillance and clinical studies, rather than a more stringent premarket approval process. Premarket assessment would focus on identifying tests with potential for egregious harms (e.g., tests with uncertain validity or utility that could profoundly alter the course of medical treatment) and keeping those tests off the market until further studies show an acceptable risk-benefit ratio.

Finally, tests that fall within the highest risk classification should only be performed with pre- and/or post-test counseling by a licensed health care professional. There is general agreement among most professional organizations that genetic testing should only be offered under the supervision of a qualified health professional (*5*, *18*, *19*). However, mandatory physician involvement for all tests would limit access to tests that ultimately prove low risk and, without clear professional guidelines and education, could exacerbate the problem of unnecessary and potentially harmful and expensive follow-up based on test results of unproven clinical significance (*20*).

For clinicians—and anyone contemplating such testing—the key to responsible and safe use will be access to unbiased information. In the United States, both FDA and FTC could help ensure more accurate and scientifically informed testing claims and frank disclosure of what is still not known about a test. FTC and FDA share jurisdiction over regulating deceptive advertising, but FTC has responded to concerns primarily through public education, reserving its policing authority for cases of egregious abuse (*21*).

More informal policy action should also play a role. The proposed National Institutes of Health (NIH) Genetic Testing Registry (*22*) should be used to ensure more complete and systematic public disclosure of testing information by test developers. Publicly funded resources that provide authoritative information about clinical utility—such as GeneTests (*23*) and the Genomic Applications in Practice and Prevention (GAPP) Knowledge Base (*24*)—should be expanded.

Of course, the United States is not the only country to have considered the regulatory challenges associated with DTC genetic services (*25*). Germany, for example, has taken aggressive steps, banning public access to private tests (*26*). The response in the United Kingdom has primarily been through the production of policy reports (*27*). Given that this is largely an Internet-based industry, a comprehensive regulatory policy will need to consider international laws, local norms, and implications for stakeholders from diverse health systems. International cooperation will be required.

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