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POLICY FORUM

Direct-to-Consumer Personal Genome Services: Need for More Oversight

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Genetic tests have been developed for approximately 1,500 diseases. Most of these tests have not yet been incorporated into standard primary care due to limited evidence regarding their clinical validity and utility; the complex and not well-understood role that genes play in the development of many common diseases; physicians' limited knowledge of genetics; and public fear of genetic discrimination [1]. Despite these concerns, genetic tests are increasingly being sold direct-to-consumer (DTC)—predominantly over the Internet and with minimal or, in many cases, no involvement of health care professionals. The American public generally assumes that the government has assessed the safety and efficacy of all consumer (including medical) products. But there are significant gaps in the regulation of genetic testing that pose threats to consumer health and safety. Despite rapid scientific developments made during the last decade, the regulatory environment has changed very little [2].

While individual genetic tests have been available DTC for some time, within the last few years several companies have started to offer personal genome services, which scan a person's genome at hundreds to thousands of sites and provide risk information for a variety of health and nonhealth-related traits. About nine companies including 23andMe, deCODEme, DNA Direct, and Navigenics currently offer personal genome services [3-6]. (The precise number is difficult to determine and is constantly changing. DTC genetic testing is likely to grow rapidly given the easy market entry, especially for Internet-based sales, high consumer interest, and the rapid pace of genetic research [7].) Tests are purchased and results delivered via the Internet. Prices vary, and companies test for somewhat different diseases, but for anywhere between $200 and $2,500, customers can mail in a saliva sample or cheek swab and receive a personalized report within a matter of months. Depending on the company, risk can be assessed for type 2 diabetes, venous thromboembolism, various cancers (including breast, lung, skin, and stomach), obesity, male infertility, hemochromatosis, Parkinson's disease, Alzheimer's disease, bipolar disorder, schizophrenia, and back pain, in addition to many other diseases and traits. Individual data are compared to the results of genome-wide association studies (GWAS), which look for statistically significant correlations between genomic variations at specific locations on a given chromosome (single-nucleotide polymorphisms, or SNPs) and increased susceptibility to disease. Most SNPs discovered in GWAS are associated with very small increases in risk (odds ratios of 1.5 or less), calling into question the usefulness of this information for clinical decision making [8].

Genetic testing provides information that can be the basis for many important health care decisions—attempting to quit smoking, losing weight, having children, terminating a pregnancy, or starting on a drug regimen. How much information consumers have prior to the decision to purchase DTC personal genome services and their experience receiving and interpreting test results significantly influences their health-related behavior, future health care decisions, and overall trust in the application of genetics and genomics in medicine. Because of these significant public health implications, it is critical that appropriate protections are in place so that consumers are only offered tests that are accurate, reliable, and meaningful. To this end, it is important to understand three criteria used to evaluate diagnostic tests:

1. Analytic validity—in the case of genetic tests this is the ability of a test to accurately and reliably identify and measure the genotype of interest. There is not much concern about the analytic validity for most genetic tests sold DTC, although small sampling errors or poor quality control could affect test performance [8].
2. Clinical validity—the ability of the test to detect or predict the associated disorder. The clinical validity of any diagnostic test includes considerations of sensitivity, specificity, and positive and negative predictive value. There is much skepticism regarding the clinical validity of genetic tests based on GWAS. First, much of the data used to determine associations between SNPs and disease susceptibility is preliminary. Studies could benefit from larger and more representative sample sizes. Second, most of the diseases screened for by companies offering personal genome services are complex diseases known to be caused by multiple gene variants, interactions between gene variants, or interactions between gene variants and environmental factors; therefore, identification of the genotype associated with increased risk is only part of the overall risk profile [8, 9].
3. Clinical utility—the likelihood that the test will lead to an improved health outcome [10]. Currently, almost no data are available regarding the effects of DTC testing on health behavior and outcomes. It is likely that systematic study will determine that some tests have good clinical utility while others do not [11].

There are several challenges to oversight of the marketing and sales of DTC genetic tests. Regulations for the testing of human biological materials in general are vague and were not developed with the DTC context in mind. There is also lack of agreement about the type of oversight that is appropriate for DTC tests and the level of consumer protection that is needed. Regulation is complicated by the range and heterogeneity of genetic tests, the laboratories that perform them, and the modes of testing, delivery of results, and advertising. Several regulatory entities are involved, all of which are understaffed [1, 2].

Regulation of Laboratories that Perform Genetic Tests

Laboratories that perform tests on human biological materials are certified by the Center for Medicare and Medicaid Services (CMS) under the Clinical Laboratory

Improvement Amendments (CLIA) [12]. CMS has the authority to assess laboratory personnel, quality control, and proficiency. CLIA regulates laboratories' operations but does not assess the analytic validity, clinical validity, or clinical utility of specific genetic tests performed by labs (although CMS does assess such factors in other types of laboratories and tests) [13]. While there are specialty areas for cytology and other complex testing services, there are no laboratory quality or proficiency standards specific to genetic testing. Laboratories can choose to be accredited by a private accrediting body with higher standards, however, such as the College of American Pathologists [2]. Several groups have lobbied for a genetics laboratory specialty, but CMS has repeatedly denied requests, citing costs [13]. CMS has no adequate mechanism for publicly sharing information regarding the CLIA-certification status of individual labs.

Those states that have chosen to adopt standards that are stricter than CLIA's require authorization by a professional to obtain a laboratory test. Based on current information, 13 states (including New York and California) prohibit consumers from ordering tests (i.e., a physician or other authorized health care professional must order and receive test results). Another 12 states prohibit consumers from ordering certain kinds of tests but do not name genetic tests specifically in this category. Twenty-five states and the District of Columbia allow consumers to order genetic and other tests without restrictions [9]. But state regulations that essentially prohibit DTC testing are difficult to enforce when tests are bought and sold via the Internet, and companies have tried to skirt professional-authorization requirements by employing physicians who then order all tests. These physicians never come in direct contact with consumers who buy the tests, although some companies offer physician counseling to assist with interpretation of test results for an additional fee. To address this practice of skirting state regulations, the California and New York State Departments of Public Health sent "cease and desist" letters to several companies in 2008, ordering them to either submit a plan to become compliant or face sanctions [14].

Regulation of Genetic Tests

Oversight of the tests themselves falls under broad Food and Drug Administration (FDA) statutes regulating "in vitro diagnostic devices" (IVDs) [15]. Premarket review requirements for IVDs are not nearly as burdensome as regulations for pharmaceutical products, and, to date, genetic tests have been subject to far less regulation than other medical devices. As explained below, many genetic tests are not regulated at all. There are three types of genetic tests:

1. **Test kits**, in which components are bundled together, labeled for a particular use, and sold to laboratories as a unit. Of the hundreds of genetic tests currently available DTC, only about a dozen are sold as test kits. Test kits must undergo premarket review by the FDA to establish safety, effectiveness, and clinical validity prior to commercial distribution, but the amount and type of evidence required depends on the specific claims of the manufacturer.
2. **Laboratory-developed tests** (LDTs), sometimes referred to as "home brews," are developed in-house by laboratories and do not become part of a

test kit. Most genetic tests sold DTC are of this type. The FDA has the jurisdiction over all LDTs as medical devices but thus far has decided not to regulate them.

3. LDTs that include **analyte-specific reagents** (ASRs), the active ingredients in a test that can be manufactured for sale or made in-house by a laboratory. The FDA has some oversight of ASRs, specifically regarding to whom they can be sold and how they must be labeled. FDA regulations require LDTs developed using commercially distributed ASRs to be ordered by a physician or other person as authorized by state law, but the extent to which this is actually enforced is unclear [16].

Because the vast majority of genetic tests sold DTC are laboratory developed and therefore *not* reviewed by the FDA, consumers have no way of determining whether there is adequate scientific evidence to support the claims of the company selling the test—i.e., if a test will be accurate in diagnosing or predicting disease. The Centers for Disease Control and Prevention (CDC) sponsors the Evaluation of Genomic Applications in Practice and Prevention (EGAPP), which aims to establish a systematic, evidence-based process for assessing the validity and utility of genetic tests [17]. It is unlikely, however, that individual consumers will gain access to EGAPP information.

Regulation of Advertising Claims

There is concern that advertising for DTC genetic tests provides insufficient information for consumer decision making, leaving great potential for consumer misunderstanding of results or overestimation of clinical value [1]. Studies assessing the marketing practices of companies that offer genetic testing services online consistently find a genetically reductionist view of health; inconsistent, unreliable, and incomplete information (as well as overwhelming amounts of information); and limited provisions for physician involvement and genetic counseling [18]. FDA premarket review of test kits includes assessment of advertising claims, but since laboratory-developed tests (the majority of tests sold DTC) are not reviewed by the FDA, consumers are vulnerable to false or misleading advertising claims [2].

The Federal Trade Commission (FTC) Act [19] prohibits false advertising (including omission of facts as well as false representation) to induce the purchase of medical devices. The FTC has the authority to take action against false advertising claims, but it does not have adequate staff to monitor the genetic-testing industry and therefore can only respond to complaints filed against specific companies. They have not done so thus far, despite having received complaints [2], but the FTC did issue a general consumer warning against at-home genetics tests in July 2006 [20].

Congress also has the authority to investigate companies it suspects to be making false advertising claims. In 2006, the General Accounting Office (GAO) issued testimony to the Senate Special Committee on Aging entitled, "Nutrigenetic Testing, Tests Purchased from Four Web Sites Mislead Consumers," which found that tests purchased from four unnamed companies "mislead consumers by making predictions

that are medically unproven and so ambiguous that they do not provide meaningful information to consumers" [21].

Proposed Legislation and Other Recommendations

In 2007, two bills were introduced in Congress to strengthen oversight of genetic tests in general and DTC genetics tests in particular. The Laboratory Test Improvement Act (introduced by Senators Kennedy and Smith) would have granted the FDA the explicit authority to regulate LDTs as medical devices, meaning that LDTs sold directly to consumers would have to undergo FDA review before entering the market. The Genomics and Personalized Medicine Act of 2007 (introduced by Senators Obama and Burr) would have mandated the Department of Health and Human Services (DHHS) to improve the safety and effectiveness of genetic tests; specifically, the DHHS would be required to commission an Institute of Medicine (IOM) study to make recommendations regarding which genetic tests should be regulated and how, and the CDC would be mandated to study consumer impact of DTC testing [2]. Neither bill passed.

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) advises the Secretary of the DHHS on health and societal issues raised by the development, use, and potential misuse of genetic technologies. In April 2008, SACGHS issued the report, "U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services," which recommended actions to close critical gaps in the regulation of genetic tests and the laboratories that conduct them. The report recommended specific mechanisms to address the clinical validity and utility of the tests as well as the educational needs of health professionals and consumers [22]. In an April 2009 letter to the DHHS Secretary Kathleen Sebelius, a coalition of diverse organizations—including genetic testing laboratories, patient advocacy groups, and health policy researchers—called for a more "reasonable and responsible regulatory framework" for genetic tests and recommended (1) FDA oversight of all LDTs (not just test kits); (2) development of a publicly accessible registry that includes information on laboratories that perform genetic tests and companies that develop tests as well as information to support claims about how useful tests are in improving clinical care; and (3) strengthening CMS oversight of laboratories [23].

In accord with many other professional organizations, the 2008 American Medical Association (AMA) Board of Trustees report, "Direct-to-Consumer Advertising and Provision of Genetic Testing," discourages DTC genetic testing [10]. Based on this report, AMA Directive D-480.987 [24] was modified to recommend that genetic testing be made available only under the supervision of a qualified health care professional, that physicians be educated about DTC testing, and that the FTC enhance its regulation of the marketing of DTC genetic tests.

Conclusion

There is a wide range of possible policy options to fill existing gaps in the oversight of DTC genetic testing. While a total ban on all DTC testing and advertising or a free

market with absolutely no restrictions are both unrealistic, the kinds of tests sold DTC can be restricted (e.g., to those that are identified as appropriate without medical referral), the kinds of entities that can sell genetic tests DTC can be limited (e.g., to those that meet specific licensure or quality control requirements), and the conditions under which genetic tests are sold DTC can be limited (e.g., to those tests that undergo premarket review and meet certain standards for clinical validity and utility). Advertising can also be limited to certain media or types of tests, and specific disclosures can be required [2]. Perhaps the most critical concern is that there currently is no single agency that assesses whether genetic tests provide information to physicians and consumers that is clinically useful [17]. DTC sale of worthless genetic tests has the potential to undermine public trust in personalized medicine—a development widely touted as the future of American health care and largely built on the science of the Human Genome Project. Genetic tests are not all the same, and therefore they should not all be regulated in the same way.

Physicians now face the possibility of being asked by patients to interpret the results of genetic tests the patients purchased over the Internet. In the case of personal genome services, even a physician with advanced understanding of genetics is challenged to provide a meaningful explanation of test results to a patient who may have just spent a significant amount of money on this test, perhaps with the expectation that his or her physician would know how to make sense of the results and act accordingly. Given the current regulatory context in which tests of questionable validity and clinical utility are commercially available, physicians would be well-advised to caution patients who are interested in personal genome services about the serious limitations of commercially available tests [8].

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