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The Current Landscape for Direct-to-Consumer Genetic Testing: Legal, Ethical, and Policy Issues

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Abstract

This review surveys the developing market for direct-to-consumer (DTC) genetic tests and examines the range of companies and tests available, the regulatory landscape, the concerns raised about DTC testing, and the calls for enhanced oversight. We provide a comparative overview of the situation, particularly in the United States and Europe, by exploring the regulatory frameworks for medical devices and clinical laboratories. We also discuss a variety of other mechanisms such as general controls on advertising and consumer law mechanisms.

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INTRODUCTION

DTC: direct to consumer

Direct-to-consumer (DTC) genetic testing is a growing phenomenon in the United States and (to a lesser extent) internationally. Harnessing the power of the Internet and the promise of the Human Genome Project, and fueled by the potential for profit and consumer interest in self-mediated healthcare, an increasing number of companies are starting to offer health-related genetic testing services directly to the public.

The advent of DTC genetic testing has sparked considerable alarm among geneticists, public health and consumer advocates, and governmental bodies (4, 36, 37, 46, 59, 77, 86, 90). Critics of DTC genetic testing have raised a number of concerns: the quality of the tests, the accuracy and adequacy of the information provided by companies, and the risk that consumers may be misled by false or misleading claims and may make harmful healthcare decisions on the basis of test results (36, 37, 48, 89). Some have asserted that genetic testing should take place only through a healthcare provider and with adequate counseling (4). Conversely, advocates of DTC testing—primarily representing purveyors of DTC tests—contend that a DTC approach enables greater consumer awareness of and access to tests. These tests can help them improve their health and make beneficial treatment and lifestyle decisions (10). These groups also claim that DTC testing provides a privacy advantage over testing through a healthcare provider (90). Little empirical evidence exists regarding the impact of DTC testing on the public.

Government oversight of DTC genetic testing—as with genetic testing generally—is quite limited. Most genetic tests are not subject to any type of government review before they are made available to the public. Federal requirements for genetic testing laboratories are general in nature and do not set specific standards for genetic tests. Thus, DTC companies face few barriers to market entry, and few governmental mechanisms exist to ensure that laboratories reliably obtain the correct result or that the tests they perform accurately predict phenotype.

The dynamic nature of the DTC marketplace makes it a somewhat difficult topic for a review article. Some DTC company websites that existed five years ago have disappeared, and those that are around today may not survive until this review's publication date. Despite the inherent fluidity of the marketplace, the commercial allure of DTC testing, coupled with the lack of regulatory barriers to market entry, has led to a steady stream of new entrants; currently more than two dozen DTC companies exist worldwide. Although some individual players may change, the phenomenon can be expected to grow in the absence of regulatory changes. Moreover, DTC offerings are expanding to include not only single-gene tests but also large-scale single-nucleotide polymorphism (SNP) profiling. Eventually, whole-genome sequencing may be offered affordably in a DTC fashion.

Given the expansive potential of DTC genetic testing, it is important to understand the regulatory framework in which DTC genetic tests are offered and the regulatory approaches that different countries have adopted. This review defines genetic testing, describes the types of genetic tests that are available, and explains the purposes for which they may be used. We then define DTC genetic testing, discuss the concerns that have been raised about specific tests (both tests currently offered and those expected to be offered in the future) discuss concerns about DTC marketing in general, and describe what is known empirically about consumer and provider awareness of DTC tests. Next, we summarize the regulation of DTC genetic testing in the United States and internationally, with particular focus on the European Union. We identify gaps in current regulations and their consequences, and discuss regulatory efforts that have been undertaken to address these gaps. Finally, we describe policy approaches that could be taken with respect to DTC testing and analyze the merits and drawbacks of such approaches.

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DEFINING GENETIC TESTING

DTC testing has emerged amid a period of rapid growth in the number of available genetic tests. Today, genetic tests for more than 1200 diseases are available in a clinical setting and several hundred more are available in a research setting (25).

There is no internationally agreed upon definition of the term 'genetic test.' The term has been defined in various ways in United States state laws, by United States and international advisory committees examining genetic testing oversight (11, 44, 49, 50, 53, 77, 78), and in recently enacted federal legislation to prohibit genetic discrimination (28). For the purposes of this review, genetic test refers to an analysis of human DNA, RNA, protein(s), or metabolite(s) to diagnose or predict a heritable human disease; to guide treatment decisions, such as drug prescribing or dosing on the basis of an individual's genetic makeup; or to predict disease recurrence on the basis of data about multiple genes or their encoded products (e.g., RNA or proteins).

Over the past decade, genetic testing has become integral to diagnosing, predicting, and preventing disease. Depending on the condition under consideration, genetic testing may be recommended throughout the life cycle. Preimplantation genetic diagnosis (PGD) following in vitro fertilization can identify embryos with specific disease-causing mutations, such as Fanconi anemia, or desired genetic characteristics, such as HLA type, prior to transfer into a woman's uterus (45). Prenatal testing is performed to detect genetic abnormalities, such as Down syndrome, in a developing fetus (26). Newborn screening is performed to diagnose certain metabolic disorders, such as phenylketonuria (PKU), for which early intervention can prevent adverse consequences (26). Genetic tests can be used to confirm the diagnosis of monogenic diseases, such as cystic fibrosis (26), or to determine the risk of developing a particular disease or condition, such as hereditary breast, ovarian, or colon cancer (26). More recently, interest has increased in using genetic tests to predict response to medication (76), such as Her2/neu testing prior to prescribing the breast cancer drug Herceptin.

With the exception of genetic tests performed on samples obtained through invasive medical procedures (e.g., amniocentesis), any genetic test could, in theory, be offered directly to consumers. Although a small fraction of tests, which are available for more than 1500 diseases, are offered in this manner today, there is no technological barrier to offering a wide range of DTC genetic tests, whether diagnostic, predictive, or preventive. Tests offered over the Internet include some that are conducted as part of routine clinical practice, such as those for mutations that cause cystic fibrosis, hemochromatosis, and Fragile X syndrome, as well as many tests that have not yet been accepted into routine clinical practice. This is particularly the case for tests that purport to predict susceptibility to common complex conditions, such as cancer and heart disease.

FDA: Food and Drug Administration

DEFINING DIRECT-TO-CONSUMER

The term 'direct-to-consumer' has been used variously to refer to both advertising and sale of genetic tests. In the first instance, the availability of a test is advertised to the public, but the test must be ordered by, and the results delivered to, a healthcare provider. This situation is similar to that seen for prescription drug advertisements in the United States, although unlike prescription drugs, the genetic tests being advertised are not generally subject to premarket review or approval by the Food and Drug Administration (FDA), as discussed below. Although much policy discussion has concentrated on advertising, many DTC companies appear to be focusing their marketing budgets on efforts to gain favorable media coverage.

In the second instance, genetic tests are not only advertised directly to consumers, but the purchase of genetic testing services also is initiated at the consumer's request, and the results

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are delivered directly to the consumer, without the involvement of the consumer's healthcare provider. In some cases, the test may be, as a formal matter, "ordered" by a healthcare provider employed by the company to comply with legal requirements, but the company-employed provider does not establish a doctor-patient relationship with the consumer. These two distinct DTC models have raised different concerns.

Direct-to-Consumer Genetic Test Advertising

Few genetic tests are advertised to consumers but made available only through healthcare providers. The best-known and most controversial example in the United States involves Myriad's advertising campaigns for its BRACAnalysis test, which predicts predisposition to hereditary breast and ovarian cancer. Myriad launched a pilot advertising campaign in two cities in 2002 (63, 74) using television, print, and radio to "alert women with a family history of cancer to recent advances in cancer prevention and early disease detection" (70). The advertising campaign encouraged consumers to consult their physician about the genetic test.

Several studies have evaluated the impact of Myriad's ad campaign on awareness and uptake of the test, as well as public reaction to the advertising. The resulting data indicate that the campaign led to increased awareness of testing among providers and patients, an increase in the referral rate for genetic counseling services among low-risk women (69), and an increase in the number of tests ordered (8). The data do not indicate any negative psychological impact on patients or primary care providers as a result of the ads (69).

In September 2007, Myriad again stirred controversy when it launched a larger-scale television, radio, and print advertising campaign for its BRACAnalysis test in New York, Connecticut, Rhode Island, and Massachusetts. The ads urged women to discuss their family history with a doctor or to call a toll-free number to find out if they are good candidates for the test. Some physicians supported the campaign as a means to educate women and primary care physicians (87). Critics of the campaign raised concerns that the ads may create unnecessary anxiety and lead to overuse of the test (88).

Direct-to-Consumer Genetic Tests: Models of Provision

The majority of tests advertised DTC also are sold directly to consumers. For example, although Myriad does not sell its BRACAnalysis test directly to consumers, the test can be ordered by consumers directly from a third party company, DNA Direct, which employs its own healthcare providers, who order the test from Myriad on behalf of consumers. DNA Direct then communicates the results directly to consumers. This marketing scenario demonstrates just how blurred the lines between DTC advertising and DTC sale can become. DTC testing has also brought about the rise of the third-party intermediary, a company interposed between the patient and the laboratory that makes claims about the test but does not perform the testing.

Similar arrangements have been seen in the United Kingdom; for example, the company MediChecks (65) offers a wide range of DTC tests via the Internet in collaboration with the private pathology laboratory TDL. Scienta Health Center (81), a Toronto-based company, offers a range of tests developed and performed by the Austrian company Genosense (31). Genosense has partners across the globe; for instance, their tests were recently made available in the United Kingdom by a company called Genetic Health (27).

Both the number of companies and the variety of tests offered have grown since DTC genetic testing first began. In 2003 Gollust and coworkers (36) identified seven websites offering health-related DTC genetic testing

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for seven conditions.[1] Of these seven, four are no longer in business or are no longer offering DTC testing. Today more than two dozen websites (including three of the original seven) offer more than 50 health-related tests to consumers.[2]

Recent entrants to the sector may augur a fundamental change in the size and nature of the DTC genetic testing market (**Table 1**). Fueled by the diminishing cost of performing DNA microarray analysis and the rapid pace of scientific discovery in genome-wide association studies, companies in the United States (1, 71) and Europe (12) are offering tests based on data from very broad panels of SNPs that provide information about a variety of common diseases. These companies, many of which have significant venture capital financing and collaborations with the leading manufacturers of the microarrays, seek to establish an ongoing relationship with customers by providing periodic updates on health risk based on new scientific findings. Some of these companies reportedly also are trying to develop large-scale biobanks for research purposes, and some people have questioned whether these companies are making their intentions explicit or appropriately obtaining informed consent from their customers for research use of their DNA (35).

Market for Direct-to-Consumer Testing

Little is known about consumer awareness and uptake of DTC genetic tests. Although DTC testing companies undoubtedly maintain information regarding the number of consumers using their services, such information is proprietary. Understanding the level of consumer awareness and interest would be useful in considering the need for and appropriate tailoring of policy responses.

A 2007 study by Goddard and coworkers (34) assessed consumer and physician awareness of nutrigenomic tests and consumer use of such tests via two national surveys. They found that 14% of consumers were aware of nutrigenomic tests and 0.6% had used these tests. Consumers who were aware of the tests tended to be young and educated with a high income. A greater percentage of physicians (44%) were aware of nutrigenomic tests compared with the average consumer, although 41% of these physicians had never had a patient ask about such tests, and a majority (74%) had never discussed the results of a nutrigenomic test with a patient.

WHAT IS THE HARM?

The debate about DTC genetic testing occurs within a broader social and historical context. Clinical genetics arose in the shadow of the eugenics movement during the first half of the twentieth century, a dark legacy that underpins many fears concerning the use and misuse of genetic information (72). In response, the clinical practice of genetics has come to place an immense value on informed consent, confidentiality, and nondirectional counseling. Additionally, clinical geneticists place special importance on the act of diagnosis, because many of the diseases they diagnose are not treatable and therefore require special sensitivity in communicating test results to patients.

As a consequence of this unique cultural and clinical context, clinical geneticists generally argue that the most appropriate means of accessing genetic tests is through a medical consultation in which patients receive appropriate counseling and advice about the suitability of the test and its potential implications, expert interpretation of the test results, and guidance about actions to take as a consequence (5, 49). DTC testing challenges this longstanding tenet

[1] Gollust and coworkers included an additional seven sites that either permitted consumers to order tests but required results to be received by physicians, or required consumers to inquire about ordering information. For the purposes of this review, neither of these scenarios is considered DTC testing. Of the seven sites that Gollust and coworkers identified in this category, only two remain active today.

[2] Tests for some conditions, such as cystic fibrosis, are offered on more than one website. However, because it is not possible to determine which mutations or SNPs an individual company is testing for, each test offered by each company was counted separately to arrive at the estimate of 50 tests total.

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Table 1 Direct-to-consumer (DTC) testing companies

Company	Tests offered	Delivery model
23andMe	Susceptibility testing for common diseases as well as ancestry testing	DTC via Internet
Acu-Gen Biolab, Inc.	Fetal DNA gender test	DTC via Internet
Consumer Genetics	Fetal gender; caffeine metabolism; alcohol metabolism; asthma drug response	DTC via Internet
Cygene Direct	Osteoporosis; athletic performance; glaucoma and macular degeneration; thrombosis	DTC via Internet
deCODE (Iceland)	Susceptibility testing for cancers, diabetes, heart disease, osteoporosis, and Parkinson's disease and others; also ancestry testing	DTC via Internet
Dermagenetics	Skin DNA profile; custom skin cream	DTC through spas and similar retailers
DNADirect (15)	α-1 antitrypsin deficiency; Ashkenazi Jewish carrier screening; blood clotting disorders; breast and ovarian cancer; colon cancer screening; cystic fibrosis; diabetes risk; drug response panel; hemochromatosis; infertility; recurrent pregnancy loss; tamoxifen	DTC via Internet; genetic counselors available by phone
G-Nostics (UK) (24)	Predisposition to nicotine addiction and response to nicotine replacement products	DTC via Internet and through pharmacies
Genelex	Pharmacogenetics testing; celiac disease; hemochromatosis; gum disease; nutritional genetic testing; DNA Diet™ consultation; weight loss system	DTC via Internet
Genetic Health (UK) (Tests are performed by Austrian test developer and laboratory Genosense)	For males: genetic predisposition to prostate cancer, thrombosis, osteoporosis, metabolic imbalances of detoxification, and chronic inflammation For females: genetic predisposition to breast cancer, bone metabolism (osteoporosis), thrombosis, cancer, and long-term exposure to estrogens Nutrigenetic test: test for range of genes that influence nutritional processes such as lipid and glucose metabolism Pharmacogenetic test: test for CYP450 genes, which influence how the liver metabolizes a large number of commonly prescribed drugs Premium Male Gene/Premium Female Gene: combine all the other tests except the nutrigenetic one	DTC via Internet; most services include a medical consultation
Geneticom (Netherlands)	Common disease risk	Not clear
Genosense (Austria)	Susceptibility tests	Do not offer DTC tests themselves but some of the institutions they partner with to order tests for consumers offer DTC testing (e.g., Genetic Health in United Kingdom)

(*Continued*)

Table 1 (*Continued*)

Company	Tests offered	Delivery model
Graceful Earth	Alzheimer (ApoE)	DTC via Internet
Health Tests Direct	More than 400 blood tests, including a few genetic tests (cystic fibrosis carrier screen, Factor V Leiden); others may also be available by calling	DTC via Internet
Health Check USA	A wide range of laboratory tests including the following genetic tests: celiac disease; factor V R2; factor V Leiden; hereditary hemochromatosis	DTC via Internet; as additional service, patient can request interpretation by board-certified physician; free genetic counseling offered by Kimball Genetics for physicians, patients, and families
Holistic Health	Nutrigenomic test: comprehensive methylation panel with methylation pathway analysis; company also sells a variety of nutritional supplements	Not described
Kimball	Wide range of well-established genetic tests	DTC via Internet but detailed telephone consultation with certified genetic counselor is mandatory; report is sent to physician and customer
MediChecks (UK)	Wide range of well-established genetic tests, from Factor V thrombosis risk to BRCA testing for breast cancer risk (most tests are performed by the private pathology laboratory TDL)	DTC via Internet but company recommends physician referral for high-impact tests such as BRCA
Medigenomix (Germany)	Thrombophilia and osteoporosis risk tests	DTC via Internet
Mygenome.com	Alzheimer's disease (genetic testing for common risk factors); drug sensitivities (genetic tests for genes that affect the safety and activity of many common prescription and over-the-counter drugs); cardiovascular disease (genetic tests differentiate treatable risk factors for heart disease and stroke); thrombosis (genetic tests identify risk factors for blood clots); pregnancy risk (genetic tests identify risk factors for complications of pregnancy); osteoporosis (genetic tests identify risk factors for osteoporosis and fractures)	Not clear
Navigenics	Risk analysis for more than 20 common diseases, such as prostate cancer and diabetes	DTC via Internet
Quixtar	Heart health; nutrigenic tests and supplements; also sells dietary supplement	DTC via Internet
Salugen	Nutrigenic tests and supplements	DTC sold through spas
Sciona	Heart health; bone health; insulin resistance; antioxidant/detoxification; inflammation	DTC via Internet
Smart Genetics	Prediction of HIV progression to AIDS	DTC via Internet; free counseling available
Suracell	DNA profile test that identifies inherited genetic aging profile, and a biomarker assessment test that measures DNA damage, oxidative stress, and free radical levels; personal genetic supplements for DNA repair and nutrition	DTC via Internet

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Clinical validity: the accuracy with which a test predicts a particular clinical outcome

of clinical genetics. Unsurprisingly, the growth of DTC genetic testing has thus provoked considerable concern about the quality of service that is provided to patients.

Critics of DTC testing, steeped in the clinical genetics tradition, argue that without medical context and qualified counseling, consumers are vulnerable to being misled and to making inappropriate healthcare decisions. For example, although mutations in the *BRCA1* and *BRCA2* genes are highly predictive of breast cancer in women with a strong family history of the disease, they do not signal increased risk in women with no family history of disease. Adequate counseling is needed to explain this context, yet the DTC mode of test delivery may make it difficult to communicate this nuance, particularly because companies have a commercial interest in selling tests to the broadest population possible. Inappropriate *BRCA*-gene testing may lead to needless anxiety or, more seriously, to women seeking unnecessary medical interventions.

However, the change in delivery model from clinical encounter to consumer transaction is not the only cause of concern. Some of the newer genetic tests being offered move beyond testing for traditional Mendelian disorders—where the presence of certain gene variants is highly correlated with the development of the condition—and into the arena of more common complex diseases, where the relationship between specific genetic variants and disease is less clear. An early example was Alzheimer disease, where certain variants in the *APOE* gene are associated with only a moderately heightened risk of contracting the disease. More recent examples include *CYP450* testing to guide selection of antidepressant (selective serotonin reuptake inhibitor) medication, notwithstanding expert reports that found a lack of evidence supporting the clinical validity or utility of such testing (17, 60). Other examples include genetic tests that purport to predict the risk of diabetes, obesity, and osteoporosis and then make diet and lifestyle recommendations on the basis of the results. Many dismiss these claims as premature and not useful to the public (6, 39, 54, 73). Thus, DTC testing raises concerns about the quality of the tests and the associated testing services.

The rise of DTC genetic testing raises concerns about both consumer harms and social costs. Potential consumer harms include discrimination and stigmatization if the privacy of results is not adequately maintained, increased anxiety and needless medical interventions based on erroneous or misinterpreted test results that indicate increased risk of disease, and failure to take preventive measures based on false reassurance that one is at low risk of disease. DTC testing could pose an additional social cost in wasted scarce health resources if it leads to unnecessary visits to healthcare providers and genetic counselors and unnecessary medical tests and procedures.

Proponents of DTC testing argue that it is a means to increase consumer access to genetic tests and to empower consumers to make independent medical decisions, as well as an opportunity to educate consumers about their own health risks and the steps they can take to mitigate those risks. There is also an argument that some genetic tests pose fewer risks than others and that it may be appropriate to offer some tests DTC but others not. Arguments against DTC must address the charge of genetic exceptionalism—i.e., the concern that genetic information should not be subject to special regulation that is more stringent than regulation that is required of other types of healthcare or health-related information (80). DTC proponents also argue that DTC tests are meeting unmet demand, that there is a public appetite for information about the fruits of the Human Genome Project, and that lack of clinical uptake of new tests can be addressed by DTC advertising and test provision. Furthermore, these proponents argue that it would be paternalistic to prevent individuals from accessing information about their genomes (49).

Although these are certainly potential benefits of the DTC model, their realization requires that DTC testing is offered to the appropriate population, performed accurately, interpreted correctly, accompanied by adequate

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counseling, and governed by appropriate safeguards to protect the privacy of the information. However, as discussed in the next section, the current lack of regulation at all stages of the genetic testing process precludes the ability to fully assure that DTC genetic testing will benefit, rather than harm, the public.

REGULATION OF DIRECT-TO-CONSUMER GENETIC TESTING

Regulation of What?

For genetic testing to benefit an individual patient or consumer, the laboratory performing the test must be able to get the right answer as to whether a specific genetic variant is present or absent—so-called analytic validity. The genetic variant being analyzed also must correlate with a specific disease or condition in the patient (i.e., a phenotype) or with heightened risk of disease. This is called clinical validity. Finally, the test must provide information that is helpful to the individual being tested (e.g., in diagnosing, treating, or preventing the disease or condition). The latter is termed clinical utility, and is a somewhat controversial subject among geneticists because determining whether information may be useful to an individual patient can include subjective considerations, such as whether knowing the genetic basis for a disease that cannot be treated or prevented may nevertheless provide peace of mind to the patient. Determinations of clinical utility tend to be made by payers, both public and private, in considering whether or not to reimburse for testing, rather than before a test is offered to the public. In the DTC context, the consumer ultimately makes the decision about whether taking the test will be useful, but such a determination may be flawed if the information provided by the DTC company is false or misleading or is not explained adequately to the consumer.

In the United States and other countries, different entities regulate—or foreseeably could regulate—the analytical and clinical validity of genetic tests as well as the claims made about those tests. To date, there is only one example of a regulatory regime specifically designed to deal with DTC genetic tests. The Advisory Committee on Genetic Testing (ACGT), a governmental body in the United Kingdom, was established in 1996 for the purpose of considering public health and consumer protection issues around genetic testing in both the public and private sectors (43). The ACGT developed a Code of Practice for genetic testing services supplied directly to the public that established requirements regarding informed consent, genetic counseling, and provision of information on the validity and utility of tests to patients in an easily understandable format (3). The Code also established a system of compliance and monitoring under which suppliers planning to offer a DTC genetic testing service (or proposing an amendment to an existing service) first would present their proposal to the ACGT. Although compliance with the Code was voluntary, companies that did not comply faced the threat of a statutory alternative.

The ACGT was disbanded in 1999, and its responsibilities were passed to the newly formed Human Genetics Commission (HGC), the United Kingdom government's strategic advisory body on developments in human genetics. However, after enforcing the Code once in the case of the nutrigenetics company Sciona, the HGC concluded its position as a regulator was incompatible with its primary mission to offer independent strategic policy guidance to the government; thus the Code is no longer enforced. In the absence of a system designed specifically to regulate DTC testing, regulation of these tests falls under the existing regulatory mechanisms that cover clinical laboratories, medical devices, and fair trade and advertising practices.

Regulation of Clinical Genetic Testing Laboratories

Laboratory oversight seeks to ensure the quality of the testing process by, for example, setting requirements for personnel training, specifying how and for what records must be maintained,

Analytic validity: the accuracy with which a given laboratory test identifies a particular genetic variant

Clinical utility: the likelihood that using the test result(s) will lead to a beneficial outcome

ACGT: Advisory Committee on Genetic Testing

HGC: Human Genetics Commission

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CMS: Centers for Medicare and Medicaid Services

CLIA: Clinical Laboratory Improvements Amendments

and assessing the analytical accuracy of tests performed by the laboratory. Laboratory oversight typically includes periodic inspection of the facility and its records and also may include other periodic assessments of quality, such as proficiency testing, which is a means to assess analytical accuracy. With few exceptions, the entities charged with regulating laboratories do not evaluate the clinical validity of the tests offered by the laboratories that they inspect.

United States Regulation

Federal regulation. The United States federal government exercises only limited oversight of laboratories that conduct genetic testing. The Centers for Medicare and Medicaid Services (CMS) implement and enforce the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (9). CLIA applies to all clinical laboratories that operate or provide testing services in the United States. The statute defines a clinical laboratory as a "facility for the . . . examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings [9, §263a(a)]. The statute prohibits the solicitation or acceptance of "materials derived from the human body for laboratory examination or other procedure" unless CMS or a CMS-authorized entity issues the laboratory a certificate [9, §263a(b)].

CMS issued final regulations that implemented CLIA in 1992 (64). These regulations created "specialty areas" for laboratories that perform high-complexity tests, which specified personnel, quality assurance, and proficiency testing requirements for tests such as toxicology and immunology. Genetic testing, which was in its infancy at the time, was not included in these specialty areas. As a result, proficiency testing was never mandated for genetic testing laboratories.

As awareness grew about the potential role of genetic testing in healthcare, several expert panels considered what regulatory changes would ensure the smooth transition of genetic testing from research to practice (53). Key among the recommendations of these groups was that CMS create standards that focused specifically on genetic tests (44, 78). Although CMS indicated for several years that it was developing new regulations for genetic testing laboratories (18), the agency abruptly changed its mind in September 2006 (19). Thereafter, several advocacy groups petitioned the agency to issue regulations (47), but CMS denied the petition, citing cost concerns (79).

Inadequate oversight of clinical laboratories under CLIA has harmful implications for DTC testing (57, 58). Analytical validity is essential for accurate test results. Yet the absence of a specialty area means that consumers cannot have full confidence in DTC tests. Although this is true for all genetic tests, not just those ordered DTC, the fact that the consumer's healthcare provider is not involved in test interpretation increases the likelihood that analytical errors in testing will not be detected.

Inadequate transparency by CMS also leaves consumers in the dark about whether the laboratory providing results is CLIA certified, has conducted proficiency testing, and/or has received any negative inspection reports; the statute states that proficiency testing results must be made publicly available, but CMS does not have a system for sharing such information. Although CMS does make public information about laboratories that have had their certificates suspended or revoked, the most current information is at least two years out of date.

However, even if CLIA was appropriately implemented, it would provide only limited assurance about the quality of genetic tests. Under CLIA, CMS certifies laboratories but does not evaluate the clinical validity of the tests those laboratories offer, instead leaving it up to the laboratory director's determination. Thus, although CLIA could, if appropriately implemented and enforced, ensure analytic validity of genetic tests (including those offered DTC), CLIA is insufficient to ensure their clinical validity, at least as currently interpreted by CMS. There also is some doubt about whether CLIA

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covers tests that fall somewhere on the boundary between clinical tests and so-called lifestyle tests.

State regulation. States may choose to follow the requirements of CLIA or to implement a system of laboratory oversight that is equally or more stringent. Only the states of New York and Washington have opted out of the CLIA program in favor of a state-supervised alternative. Therefore, laboratories that test samples from patients in New York must be certified and inspected by New York in addition to their inspection under CLIA. Laboratories also may choose to be accredited by a private accrediting body with higher standards than CLIA, such as the College of American Pathologists.

State law also dictates whether healthcare provider authorization is required to obtain a laboratory test, including a genetic test. Some states explicitly authorize laboratories to accept samples from and deliver test results for specific tests (such as cholesterol or pregnancy tests) directly to patients, without authorization from a healthcare provider. Even when states prohibit DTC testing they may face difficulties in prohibiting the sale of DTC tests to consumers in their state, particularly when such sales are mediated through the Internet. Other states, such as New York, categorically prohibit all DTC testing. Still other states are silent on the issue, which leaves it up to individual laboratories to decide whether to offer DTC testing. Currently, 25 states and the District of Columbia permit DTC laboratory testing without restriction, whereas 13 states categorically prohibit it (29). DTC testing for certain specified categories of tests is permitted in 12 states; these laws would likely not permit DTC genetic tests. Even when a healthcare provider's order is required, the provider may have a conflict of interest if he or she is employed by the laboratory that offers the testing.

European Union regulation. The regulation of clinical laboratories in Europe is similarly patchy. Although, as discussed below, there have been efforts to harmonize regulations governing in vitro diagnostic (IVD) devices, as yet no common European requirements for laboratory quality assurance exist. In part, this may be because laboratory testing often is carried out within national healthcare services, a sphere of activity that is seen as the responsibility of member states. A recent Europe-wide survey revealed that very few laboratories have formal accreditation; up to 50% of laboratories surveyed do not undergo any official inspection (52). A survey conducted in 1997 suggested that in European Union countries where clinical genetics is well established, often a legal framework governed the service (40). A more recent survey of European countries found that seven had legislation: Austria, Belgium, France, Norway, Sweden, Switzerland, and the Netherlands (33) (**Table 2**). This legislation often covers the licensing of laboratories but sometimes relates to the clinics within which genetics is practiced.

IVD: in vitro diagnostic

In the European Union, there have been considerable efforts to harmonize oversight of laboratory quality assurance systems through a number of national, regional, and international schemes, culminating in the European Molecular Genetics Quality Network. Participants in the Network include 34 European countries and laboratories from Australia and the United States. These quality assurance initiatives have led to a broader project, EuroGentest (16), an ambitious attempt to move beyond the previous focus on laboratory quality assurance to develop a series of discrete but linked programs that deal with all aspects of quality in genetic testing services, from evaluation of the clinical validity and utility of tests to genetic counseling.

In the United Kingdom (and the European Union generally), laboratory regulation is not dealt with by statute but through a voluntary system of accreditation. In the United Kingdom, this system is run by Clinical Pathology Accreditation UK Ltd. (CPA), a body set up by the four main United Kingdom organizations of laboratory professionals and the United Kingdom Accreditation Service (UKAS). Laboratories that participate in the CPA scheme are inspected every five years. Although the scheme

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Table 2 European legislation governing genetic testing

Country	Regulations
Austria	Gene Technology Act 1994 requires that labs that conduct predisposition and carrier status testing must be accredited; tests for diagnosis are exempt.
Belgium	1987 legislation stipulates that genetic diagnostic testing can be carried out only in the country's well-established genetics centers and with the provision of genetic counseling; state funding is provisional on the supply of detailed annual activity reports.
France	Legislation passed in 2000 states that testing can be done only by accredited personnel and labs and sets down guidelines that cover the reporting of results and confidentiality of records.
Norway	1994 act covers accreditation of institutions; it sets no restrictions on diagnostic testing but requires counseling for predictive, presymptomatic, and carrier-status testing and outlaws such testing on individuals 16 and under.
Netherlands	Legislation limits genetic testing to those institutions with a government license and places restrictions on commercial genetic testing.
Sweden	1988 act states that genetic testing can be carried out only with the permission of the National Board of Health and Welfare.

is voluntary, the majority of United Kingdom clinical laboratories participate. Within the National Health Service (NHS), all local pathology services are expected to be accredited by CPA or the equivalent, a requirement that includes NHS genetic laboratories (13). Membership in the recently established United Kingdom Genetic Testing Network also requires compliance with new European guidelines, evidence of internal quality control, and participation in external quality assessment.

With the exception of human immunodeficiency virus (HIV) testing, the United Kingdom has no restrictions on patients ordering DTC medical tests. The HIV Testing Kits and Services Regulations of 1992 made it an offense to sell, supply, or advertise for sale an HIV testing kit or a component part to a member of the public. In 2002, the Dutch government introduced regulations to restrict the availability of some tests so that they could be accessed only through doctors or pharmacists.

Regulation of Genetic Tests as Medical Devices

IVD genetic tests fall, at least in theory, under the broader statutory regimes for the regulation of medical devices. These regimes are far less onerous than those for pharmaceutical products, but they nevertheless share the goal of ensuring safety and effectiveness through a variety of regulatory mechanisms, including premarket review and regulation of labeling and promotional materials. Ensuring truth in labeling and truthful promotion—an honest account of the strengths and weakness of a test's performance—can be thought of as the fundamental function of premarket review. For high-risk tests the process may be more difficult. Regulators set out in some detail the types of clinical studies required to gain approval. Once a device is on the market, it is subject to postmarketing surveillance and to removal from the marketplace if it is found to be unsafe. However, as discussed below, although genetic tests are as a formal matter considered to be medical devices, for the most part they have been subject to far less regulation than other devices.

United States regulation. Currently, the FDA regulates test kits sold to clinical laboratories to perform testing pursuant to its authority to regulate IVD devices (55). Both genetic and nongenetic laboratory tests are considered to be IVDs if the components of the tests are bundled together, labeled for a particular use, and sold to a laboratory as a unit. Such kits must undergo successful premarket review before they may be commercially distributed. The amount and type of evidence that the FDA requires depend on the specific claims made by the test

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manufacturer. The FDA has to date reviewed approximately eight test kits that detect variants in human DNA or DNA expression products (55).

However, most genetic tests are developed in-house by clinical laboratories and do not use a test kit. These laboratory-developed tests (LDTs) use purchased individual components and/or components the laboratories make themselves. The FDA has historically exercised "enforcement discretion" with respect to LDTs. As a result, the FDA does not review the vast majority of genetic tests, and in particular does not assess clinical validity (55).

The FDA recently indicated its intention to require premarket review for a limited subset of LDTs known as in vitro diagnostic multivariate index assays (IVDMIAs) (22). IVDMIAs are LDTs that analyze laboratory data using an algorithm (an analytical tool) to generate a result for the purpose of diagnosing, treating, or preventing disease. The agency expressed heightened concern about these LDTs because they use proprietary methods to calculate a patient-specific result that cannot be independently derived, confirmed, or interpreted by a healthcare provider. The FDA cleared its first application for an IVDMIA in February 2007. The test analyzes gene expression products (mRNA) to determine the likelihood of breast cancer returning within five to ten years of a woman's initial cancer diagnosis (23).

Most genetic tests sold directly to consumers are LDTs and few, if any, would be considered IVDMIAs. Thus, most DTC genetic tests sold are not subject to any independent oversight to assure their clinical validity. Consumers offered these tests therefore have no means to distinguish those tests that have been shown to be useful in diagnosis or prediction of disease from those that lack adequate scientific support for the claims being made. Additionally, the FDA's ability to regulate claims about medical products is predicated on its regulation of the products themselves. When the FDA approves a test kit, it can also constrain the claims that can be made about a test's benefits and mandate the disclosure of information about a test's limitations or risks. In the absence of FDA oversight of LDTs, the agency has no mechanism to address false or misleading claims made by companies that sell DTC tests. As discussed below, a bill was introduced in the United States Congress in 2007 that would give the FDA explicit authority to regulate LDTs; however, as of the time of publication of this review the bill has not yet passed.

Laboratory-developed test (LDT): test developed for in-house use by a clinical laboratory

IVDMIA: in vitro diagnostic multivariate index assay

International Regulation

Other countries have taken varying approaches to LDT oversight. In the European Union, Sweden, and Australia, LDTs are included in device regulations (although there are exemptions in the European system for what are termed health institutions). In Canada, device regulators have sought legal opinion on whether they can regulate LDTs and have received a succession of conflicting opinions, the most recent of which suggests that such tests cannot be regulated as medical devices under current law.

Although Europe treats commercial LDTs as devices subject to the IVD Directive, it is not clear that this applies to LDTs performed by labs outside of Europe. For instance, the United States companies InterGenetics and Myriad have both made their tests available through third parties in the United Kingdom. These United Kingdom third parties collect the samples and return the results, but the test is performed in the United States. Both the United Kingdom regulator and the European Commission appear to consider such companies to be exempt from the IVD Directive. This is the opposite of the approach taken in the United States; a reference laboratory based in Europe would need FDA approval to market its test in the United States.

Although the European system treats LDTs as medical devices, most genetic tests nevertheless are not subject to independent premarket review in the European Union (42). This is because they are classified as low-risk and therefore exempt from review by an independent third party. In contrast, the United States,

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Table 3 Risk Classification

Country/region	Risk categories*	Genetic tests	Premarket review
United States	I–III	II or III	Yes
Canada	I–IV	III	Yes
Australia	I–IV	II or III	Yes (class III)
Europe	I–III	I	No

*I = low risk, II = moderate-low risk, III = moderate-high risk, IV = high risk.

Canada, and Australia classify genetic tests that fall within the medical device regulations as moderate- to high-risk, and therefore generally require premarket review (**Table 3**). Thus, although Europe does not suffer the confusion over the regulatory status of LDTs that prevails in the United States, it still does not review genetic tests, including those sold directly to consumers, before they are marketed.

Regulation of Claims

In addition to laws that regulate medical devices, laws that prohibit false or misleading advertising claims could ensure that consumers receive accurate information. In the United States, Europe, and elsewhere, general laws govern the misleading promotion of goods and services and can be enforced either through private complaints to the courts by individuals or through the actions of statutory bodies, such as the Federal Trade Commission in the United States and the Office of Fair Trading in the United Kingdom. However, these mechanisms by and large have not been used to prohibit false and misleading claims about DTC genetic tests.

United States

Federal Trade Commission. The Federal Trade Commission (FTC) Act declares unlawful "unfair or deceptive acts or practices in or affecting commerce" and directs the Commission to prevent such activities (21). The statute also specifically prohibits the dissemination of false advertising to induce the purchase of drugs, devices, food, or cosmetics and defines the phrase "false advertisement" as "misleading in a material respect." The statute directs the agency to take into account not only representations made for the product, but also omissions of facts that are material given such representations.

To the extent that companies offering DTC genetic tests make claims of clinical validity without adequate scientific evidence, the FTC has the legal authority to bring an enforcement action to prohibit such claims from being made. However, the FTC has not pursued enforcement action against companies that make false or misleading claims about genetic tests even when it has received complaints about a specific test. The agency did, however, issue a consumer alert warning the public to be wary of the claims made by some companies, and advising that some results have meaning only in the context of a full medical evaluation (20).

Congress. The United States Congress also has the power to conduct investigations and hearings to uncover unfair and deceptive trade practices. In 2006, the Senate Special Committee on Aging held a hearing (85) concerning a report by the Government Accountability Office (GAO) regarding companies that offer nutrigenetic tests over the Internet (86). The GAO investigated four such companies by submitting DNA samples along with fictitious consumer profiles and analyzing the reports provided by the companies. The GAO found that although all four companies stated their tests were not intended to diagnose disease or predisposition to disease, all sent back results warning that the fictitious customers were at risk for a range of medical conditions, including type 2 diabetes, osteoporosis, cancer, heart disease, and brain aging. These predictions appeared to be independent of which DNA sample was sent in and which gene variants were present in the

FTC: Federal Trade Commission

GAO: Government Accountability Office

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sample. The GAO also reported that several of the companies sent recommendations for "personalized" dietary supplements, which in reality contained ingredients similar to multivitamins that could be purchased in the drugstore, but that cost much more. Some of the claims for the supplements also were unproven, such as the claim that they could "promote DNA repair."

Following the Senate hearing, the FDA sent letters to several of the investigated companies expressing concern that their activities might be subject to FDA regulation, and requesting a meeting (38). It is unclear what subsequently transpired; however, these companies continue to offer their DTC tests.

States. State laws in the United States also prohibit unfair or deceptive trade practices within their borders, and these laws could be brought to bear on false or misleading claims about genetic tests. To date, these laws have not been used against any DTC test manufacturer. However, in the wake of Myriad's most recent campaign, the Connecticut attorney general issued a subpoena for information from the company on the basis of concern about the accuracy of some of the company's advertising claims (75).

Europe. The regulation of test claims in other countries varies, but instruments include voluntary advertising codes, statutes, and regulations. In the United Kingdom, the Medicines (Advertising) Regulations 1994 (SI 1932) appears to prohibit the advertising of DTC testing services (66, Regulation 9). However, the Medicines (Advertising) Amendment Regulations 2004 (SI 1480) amended the previous law and removed the prohibition on advertising over-the-counter medicinal products for the diagnosis of genetic disorders to the public (68). Still, the Advertising Standards Authority (ASA) (2) enforces a code of practice that requires that advertisements be "legal, decent, honest and truthful" and "capable of objective substantiation." Special rules apply to health products.

The ASA's powers were tested in 2003 when the HGC's Genetic Services subgroup complained about a product being sold by the Growth Hair Clinic (Genetic Hair). The ASA upheld the HGC's complaint that the advertisement implied that the product used genetic technology for hair restoration/grafting when in fact no such technology exists (43).

Although the ASA enforces a voluntary code of practice, promotional claims also are governed by statute, in particular the Trade Descriptions Act (84). Under the Act, it is an offense for a person to apply a false (to a material degree) or misleading trade description to goods or services. The Act was tested in 2004 when the nongovernmental organization GeneWatch UK complained about claims made by g-Nostics regarding the NicoTest. GeneWatch was told that the Act did apply, and the complaint was passed to the Trading Standards office in Oxford (local to g-Nostics). Shortly after GeneWatch filed its complaint, g-Nostics modified its website claims regarding NicoTest. Thus, GeneWatch did not pursue its complaint (Personal communication with Helen Wallace, Director, GeneWatch UK).

ASA: Advertising Standards Authority

Private Law Mechanisms

The judicial system also serves as a nonregulatory means to deter false or misleading claims that cause physical or financial harm to consumers. Whether in practice the threat of liability would deter false or misleading claims for DTC genetic tests is unclear. The consumer would first need to be aware that he or she was subject to false or misleading claims, and would have to demonstrate harm resulting from those claims. For example, the consumer would need to show that the test result led to some harmful action, and that the action was a foreseeable result of the misleading information. Emotional harm, such as added anxiety from being told one was at greater likelihood of developing a disease, would likely be an insufficient basis for receiving damages in the absence of more concrete injury. However, financial harm as a result of misstatements could be sufficient,

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and in fact is at the heart of the only lawsuit filed against a DTC test company so far. In February 2006, a class action lawsuit was filed against Massachusetts company Acu-Gen Biolabs for its Baby Gender Mentor test (56). The lawsuit, which was filed on behalf of women who had used the test and were dissatisfied with the incorrect results received, focused on the company's failure to honor its "200% money back guarantee" and its claim of "99.9% accuracy." In addition, the lawsuit claimed that the company provided incorrect medical advice to women about the health of their fetuses, which caused them emotional distress and led them to undergo unnecessary testing (5).

Private law mechanisms could—at least in theory—function in other countries as well. However, it is widely acknowledged that such consumer law mechanisms have significant limitations. In general, only a very small proportion of consumers with grievances pursue complaints against companies. The reasons for this include consumers' lack of appreciation of their legal rights, consumers' lack of resources (time, money, and the skills or experience to pursue legal claims), the limited number of legal firms practicing consumer law, and lack of access to experts able to provide evidence to support complaints (82).

PENDING LEGISLATION AND RECOMMENDATIONS

The year 2007 was marked both by a significant increase in the range of tests and test providers in the DTC testing market and by a renewal of the policy debate about the oversight of genetic tests in general and DTC genetic tests in particular. In the United States, two bills were introduced in Congress to strengthen government oversight over genetic tests, including those sold DTC. The Laboratory Test Improvement Act, introduced by Senator Edward Kennedy and Senator Gordon Smith, would grant explicit authority to the FDA to regulate LDTs as medical devices (62). DTC tests would have to undergo FDA review before being marketed. The Genomics and Personalized Medicine Act of 2007, introduced by Senator Barack Obama and Senator Richard Burr, would direct the Department of Health and Human Services (DHHS) Secretary to improve the safety and effectiveness of genetic tests (30). Under this bill, the Secretary would be required to commission a study from the Institute of Medicine that would make recommendations regarding the development of a "decision matrix" for use in determining which tests to regulate and how they should be regulated [30, §7(b)(3)]. The bill would direct the Centers for Disease Control to study the issue of DTC testing and its impact on consumers. The prospect for passage of either of these bills is uncertain.

In addition to these legislative efforts, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS), which advises the DHHS Secretary on genetics policy issues, was asked by Secretary Michael Leavitt to produce a report on the oversight of genetic tests as part of his Personalized Healthcare Initiative (14). A draft report was issued for public comment in November 2007, and the final report was issued in April 2008 (77) (**Table 1**).

In the United Kingdom, the HGC published in 2007 *More Genes Direct*, a report that revisits the recommendations the Commission made in 2003 about the regulation of DTC genetic tests (50). Whether or not the government will respond remains to be seen, but the HGC now intends to facilitate the development of a code of practice, and other actions may be taken at a European level. A revision of the IVD Directive is said to be imminent, and there is much expectation that it will become more prescriptive and plug some of the current regulatory gaps, in part to address concerns about genetic tests (7, 61). As part of the Global Harmonization Task Force (GHTF), European regulators have been involved in the development of a new model for risk classification and conformity assessment of IVDs, which, if adopted by Europe, would see many new genetic tests subject to independent premarket review (32).

Another European body, the Council of Europe, also is driving policy in this area. In

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2007, it published a draft Protocol on Genetic Testing that would require most genetic testing to be performed only "under individualized medical supervision." The impact of the Protocol will depend on how many states choose to formally ratify it and thereby accept it as a legally binding protocol.

Finally, in Australia the Therapeutic Goods Administration (TGA), the body responsible for licensing IVD devices, is revising its regulations, in part as a response to concerns expressed by successive Australian governments about the regulation of genetic tests. The TGA intends to implement regulatory mechanisms that will prohibit access to home use tests (self-testing) for serious disease markers, including genetic tests. As part of this process, the TGA has issued a guidance document about the regulation of nutrigenetic tests (83) (**See Supplemental Table 1**. Follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**).

POLICY APPROACHES

Since the early 1990s, numerous expert bodies have convened to consider the oversight of genetic testing generally and, in recent years, DTC genetic testing specifically. These groups, typically established by the government, have issued myriad reports and recommendations (**Table 1**). Notwithstanding these prodigious efforts, little has actually changed in the oversight of genetic testing, while the number and range of tests has risen dramatically.

There is a wide range of possible policy approaches to DTC genetic testing—from prohibiting the sale of all such tests to permitting them without limitation. Policymakers must decide if the risks posed by DTC genetic tests require a targeted approach, or whether existing regulatory frameworks are adequate and adequately enforced. Policymakers also must consider whether greater control over the DTC testing market would be best achieved through enhanced regulation of the quality of genetic tests more broadly, or whether there are additional risks raised by DTC genetic tests that require distinct regulatory approaches.

Between the two extremes of a total ban and an unfettered market lies the intermediate option of permitting certain tests to be sold DTC by certain entities under certain conditions. For example, in its *Genes Direct* report, the Human Genetics Commission laid out an approach that would limit the sale of DTC genetic tests to a subset of tests considered appropriate to be offered without medical referral. Other restrictions that could be put in place include demanding that entities offering DTC tests meet licensure and quality control requirements, and insisting on heightened scrutiny (e.g., premarket review) of tests marketed directly to consumers.

Limitations also could be placed on DTC advertising, such as prior review of advertisements to ensure accuracy, limitation of advertising to certain types of tests and certain types of media (e.g., print and Internet versus television and radio), and requiring the disclosure of certain information in advertisements. Any restrictions on advertising would need to be consistent with a particular country's legal protections of commercial speech.

Some of these policy options may be pursued by enhancing the enforcement or scope of existing regulatory instruments; others might require new mechanisms, such as the ACGT's Code of Practice. Such codes could be developed by a group of companies or a trade association and voluntarily adopted, or could be developed and enforced by a government agency. As in the case of the Code of Practice, the government also can threaten to impose mandatory requirements if companies do not adhere to a voluntary code (39, 40, 82).

CONCLUSION

DTC genetic tests continue to proliferate while policies to ensure their quality have lagged behind. Establishing a coherent oversight system is challenging because of the different entities involved in oversight, the lack of existing regulations tailored to the DTC testing context,

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and the lack of agreement about the need for and type of oversight appropriate for DTC tests (41). The heterogeneity of tests offered and the range of delivery and promotional models further complicate the development of oversight mechanisms. The challenge for policymakers is to create standards that adequately protect consumers from harms associated with unsafe tests, while ensuring access to tests that are analytically and clinically valid in a manner that provides appropriate context and counseling. Regulatory requirements must be proportionate to the risks posed by the tests, and must recognize that some tests carry greater risks than others.

It is unlikely that we will see the emergence of a common, harmonized approach to DTC testing. However, efforts to strengthen oversight of genetic testing generally, which are underway in many countries, will, it is hoped, improve the quality of DTC genetic tests.

SUMMARY POINTS

1. The range of companies and tests in the direct-to-consumer (DTC) market is growing and seems likely to continue to increase.
2. Clinicians, scientists, consumers, and patient groups have raised concerns about various aspects of the DTC testing market.
3. DTC genetic testing is subject to a complex overlapping series of regulations, but there are significant gaps in the existing regulatory systems in both Europe and the United States.
4. A succession of policy reports have called for enhanced oversight of genetic tests in general and DTC genetic tests in particular, but thus far there has been limited policy action.

FUTURE ISSUES

1. The recent high-profile launch of a number of new consumer genetics companies has heightened concerns, as have renewed efforts to advertise DTC tests.
2. These developments have been matched by a renewed interest in oversight among policymakers, but it remains to be seen what action will result.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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