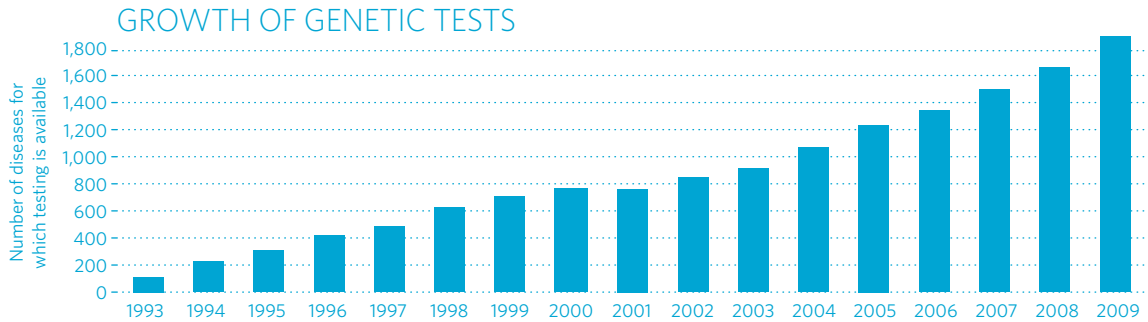
OPINION

Which way for genetic-test regulation?

Although largely unregulated, genetic tests are increasingly used to diagnose conditions, map ancestry or predict disease risk. In the first of two related pieces, **Arthur L. Beaudet** advocates the US Food and Drug Administration banning direct-to-consumer medical tests but leaving the analysis of clinical diagnostics to specialists. In the second, **Gail Javitt** argues that the agency should implement a regulatory framework for all health-related tests.



SOURCE: REF. 3

Leave test interpretation to specialists

Several regulatory agencies are gearing up to control at least some aspects of genetic testing. In the United States, the Food and Drug Administration (FDA) held meetings in June and July on how and what to regulate[1,2]. In Europe, regulatory authorities and industry lobbyists are pushing to remove an exemption from the European Union directive on *in vitro* diagnostic medical devices. This currently allows institutions to design, produce and validate the performance of their own tests.

Some regulation is essential. Yet implementing appropriate constraints is a formidable challenge given the complexity of the biology and the speed at which the technology and knowledge are evolving. If the FDA follows through on the approach that it seems to be pursuing — and regulates the interpretation of genetic tests in impractical detail — at best, a huge amount of government time and money will be wasted. At worst, genetic diagnostics will grind to a halt. To ensure that patients are not deprived of real and potential benefits of medical advances, the agency should instead apply stringent regulation to the performance of the tests themselves and allow the interpretation of the results to be carried out by board-certified practitioners.

Genetic-testing services are proliferating fast. In 1993, tests were available for about 100 diseases. By 2009, the number was almost 1,900 (see 'Growth of genetic tests')[3]. Some forms of testing are major advances in the diagnosis of certain conditions, such as Rett syndrome and types of brittle bone disease. The clinical utility of others — such as the high-throughput genotyping that is widely offered by companies that sell tests directly to consumers — is debatable.

Less than 1% of genetic testing is currently overseen by regulatory agencies, such as the the FDA and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom. Increasingly, such agencies are responding to calls to exert greater control — from politicians, health-care administrators and government advisory committees, as well as from geneticists and the public.

Academic organizations in Europe and the United States are right to have recommended a ban on 'direct-to-consumer' medical genetic testing[4,5]. Direct-to-consumer tests, by definition, mean that individuals are given their results without the involvement of a health-care provider. In the future, this method of delivering results could be approved for testing ancestry or determining the sex of an unborn baby. But the interpretation of findings that might warrant medical intervention requires a level of expertise that is currently beyond the capacity of even most physicians.

In the clinic

Turning to the kind of testing used in clinical diagnostics, recent FDA announcements[1,2] and recommendations from a US government advisory committee on genetics, health and society[6] suggest that the FDA is pursuing an ill-considered approach. Some statements[6] imply that genetic tests should meet certain requirements for clinical sensitivity (the proportion of patients for whom the test correctly identifies or predicts a disorder), clinical specificity (the proportion of patients for whom the test correctly detects or predicts the absence of a disorder) and clinical utility (the balance between the health-related benefits and the harm, either psychological or medical, that might result from a test).

Homing in on this level of detail has been appropriate in more straightforward scenarios, such as the regulation of HIV testing. But making a clinical diagnosis based on genetic testing often means assessing tens of thousands or even hundreds of thousands of variations in the genome — as well as complex interactions between genetic variants and the environment. Also, one of the novelties of the genetic data currently being generated is that we know that we will be able to interpret them more accurately in one, five or ten years from now.

Some genetic tests are fairly straightforward. For example, in Marfan syndrome and neurofibromatosis, a relatively simple relationship exists between each disease and a single mutation — although even for these conditions, the importance of several other disease-associated mutations is uncertain. In other cases, the significance of observed genetic variation is unclear. Laboratories carrying out tests to detect the number of copies of specific DNA sequences in the genome routinely report findings of uncertain significance, with the expectation that their clinical relevance will become clear in the next few years.

If regulatory agencies block testing until the clinical sensitivity, specificity and utility of all

the genetic markers involved in any one diagnosis have been assessed and approved, the use of genetic diagnostics will come to a standstill. In such a situation, almost all complex forms of genetic testing would become outmoded before they could be approved.

To allow the science and medical practice of genetic testing to flourish, regulatory agencies should ensure that all genetic tests provide accurate and reliable genotype, sequence and copy-number data. They should also ensure that complete and detailed data sets are stored electronically in a way that guarantees the privacy of individuals — for example, as part of, or linked to, medical records. By contrast, the agencies need to understand that data interpretation must remain an integral part of the decision-making 'art' of medical practice and be held in check only by the mechanisms normally used to oversee the practice of medicine — primarily board certification.

This dual pathway would be similar to the regulatory framework used in radiology, say. For magnetic resonance imaging of a patient's brain, for example, agencies such as the MHRA and FDA regulate the equipment used (whether the software and magnets are appropriate, for instance). The interpretation of the scans is overseen through the training programmes, examinations and licensing procedures for radiologists.

Currently, the results of genetic tests are interpreted by molecular geneticists, cytogeneticists and molecular pathologists. As more is discovered, perhaps more specialist 'genomicists' will be needed. These people would be trained specifically in disease pathogenesis, genetics, genomics and bioinformatics.

Ultimately, separating test performance from test interpretation will make the tasks of regulatory agencies far more achievable and keep them within the purview of their public mandate. ■

Arthur L. Beaudet is in the Department of Molecular and Human Genetics at Baylor College of Medicine, Houston, Texas 77030, USA.
e-mail: abeaudet@bcm.edu.

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The author declares competing interests: details accompany the article at go.nature.com/RVnqJ8.

Assign regulation appropriate to the level of risk

This summer, the US Food and Drug Administration (FDA) sent letters to several companies that offer health-related genetic testing directly to customers. These missives informed the companies that the tests are medical devices requiring FDA authorization. The agency has stopped short of threatening to block sales, but the implication is clear: the FDA believes the current marketing of these tests to be unlawful.

Opponents of direct-to-consumer (DTC) testing, who worry that consumers could make harmful decisions after receiving incorrect or inadequate information about test results[1], may be relieved by the FDA's actions. Proponents of such testing may question whether the FDA can justify acting as gatekeeper to people's genomes. Either way, the FDA's letters are a stopgap measure that fails to ensure genetic testing quality in general or to position DTC tests appropriately within an overarching regulatory scheme.

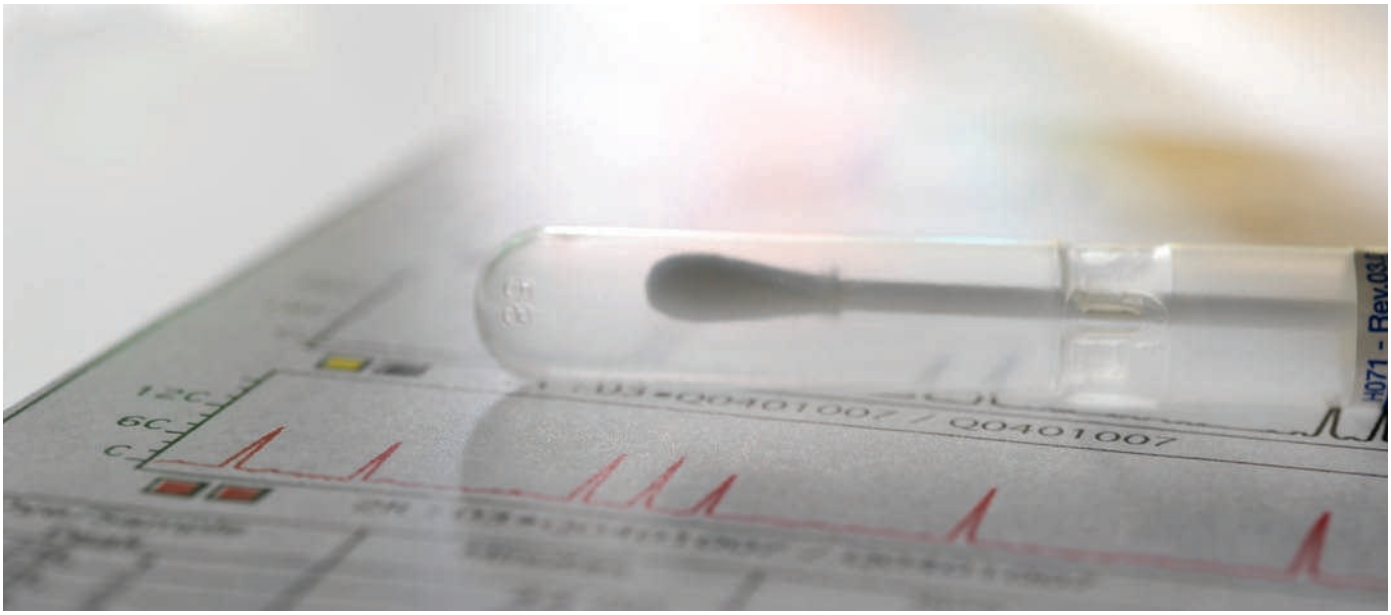
'Direct to consumer' is simply a delivery method that in itself provides no information about the quality of the test offered. Instead of treating DTC genetic testing as a special case, the FDA and other agencies around the world should implement a regulatory framework that ensures the quality of all health-related genetic tests and imposes requirements commensurate with each test's level of risk. Within this framework, regulators should define the contexts under which direct consumer access to health-related genetic tests is appropriate. They should also put in place requirements to ensure that customers receive adequate explanation of test results.

About 30 companies worldwide now offer more than 400 tests directly to consumers. These range from the 'recreational', such as

GENETIC TESTS OFFERED BY DIRECT-TO-CONSUMER COMPANIES

Type of health-related condition or trait assessed	Examples	Number of companies
Chromosomal aberrations	Recurrent pregnancy loss, deletion of a piece of chromosome 22q (DiGeorge syndrome)	2
Single-gene diseases	Cystic fibrosis, haemochromatosis	7
Susceptibility to cancer	High risk: variants of tumour-suppressor genes *BRCA1*, *BRCA2*, *PTEN*	3
	Low risk: variants of genes associated with lung cancer or prostate cancer	7
Susceptibility to non-cancerous common complex diseases	Cardiovascular: thrombosis	15
	Digestive : Crohn's disease, gall-bladder disease	8
	Endocrine: obesity, type 2 diabetes	6
	Immune: allergies, lupus	6
	Nervous: amyotrophic lateral sclerosis, epilepsy	10
	Reproductive: endometriosis, infertility	4
	Respiratory: asthma, emphysema	4
	Skeletal: arthritis, back pain	9
	Skin: psoriasis	3
	Urinary: kidney stones	2
Susceptibility to psychiatric conditions	Depression, schizophrenia	4
Risk due to oxidative stress	Coenzyme Q10 efficiency	3
Metabolism of, or response to, pharmaceuticals or other substances	Caffeine metabolism, β-blocker response	13
Substance dependence	Nicotine dependence, heroin addiction	4
Risk or progression of infectious disease	Norovirus resistance, HIV infection progression	3
Non-disease-related health profiles	Fatigue, body composition	9

SOURCE: REF. 5



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those for earwax type, to the serious, for the risk of developing diabetes or heart disease (see 'Genetic tests offered by direct-to-consumer companies'). In most cases, the results of tests are provided with little if any involvement of a health-care practitioner. Recent analyses have found that many of the companies' claims relating to the significance of genetic markers are overblown[2,3] — suggesting that at least some businesses will not be able to validate their tests to the FDA's satisfaction. Yet if the agency's endgame is to block DTC testing in the long term — as recent statements by some FDA officials imply — it will have to come up with a rationale beyond whether the tests are adequately validated.

Some in the genetics community would like to draw a line between 'legitimate' tests offered by clinical laboratories and DTC genetic tests. But such a distinction is likely to prove illusory. Any test performed on a blood or saliva specimen could, in theory, be offered directly to consumers, and many such tests have already been well validated, including those for diagnosing classical Mendelian disorders such as sickle-cell anaemia and cystic fibrosis. For some of the emerging predictive genetic markers, validation data are likely to surface after further research.

"A categorical ban on direct-to-consumer testing using validated tests would be difficult for the FDA to justify."

A categorical ban on DTC testing using validated tests would be difficult for the FDA to justify. Certainly, in the past decade, the agency's ability to prevent the public from gaining access to truthful, non-misleading information about prescription drugs and dietary supplements has been sharply curtailed by the judiciary[4].

In reality, the problems popularly associated with genetic tests go beyond DTC testing. Insufficient oversight is in place to ensure the clinical validity of at least some of the newer, more complex tests offered by both DTC companies and clinical laboratories. Also, for many genetic tests, neither health-care providers nor the public has access to enough information to properly interpret test results.

Prior knowledge

US regulatory agencies have many tools already at hand to ensure that all genetic testing is valid and safe, regardless of how test results are delivered. They should draw on their considerable experience in dealing with other regulated products, such as pharmaceuticals.

A first step should be for regulators — in particular, the US Federal Trade Commission, which protects consumers against fraud — to enforce existing laws against companies making false or misleading claims about their tests. Some of the more outrageous claims (for instance, accurately predicting the sex of a child five weeks into a pregnancy, which is not supported by scientific evidence) have come from DTC testing companies, so in this regard the DTC testing industry does need particular attention.

Agencies should next assign regulation to each test according to its level of risk. It would be a waste of resources for the FDA to require laboratories to submit clinical validation data for certain tests. Those recommended by professional medical societies for prenatal or newborn screening, for example, are already well validated and are now part of standard medical practice. However, the FDA should ensure that tests based on novel methods, or used to make therapeutic decisions with significant clinical impact, are properly validated before they are introduced into health care.

Whether a test can be delivered directly to consumers should depend on its level of risk — as is the case for other FDA-regulated products. Some genetic tests are likely to be comparable to pregnancy tests and could be sold over the counter. Others may be similar to HIV test kits. In this case, sample collection kits may lawfully be sold directly to customers but need to be sent to a laboratory for processing. Manufacturers of such tests are required by the FDA to ensure that counselling is provided. Still other tests should be treated in the same way as diagnostic tests for cancer, which currently can be obtained only through a health-care practitioner.

A particular challenge for the regulators of genetic testing, both in the United States and elsewhere, is that geneticists' understanding of the clinical significance of markers is evolving rapidly. Again, the FDA can draw on past experience to deal with this. Existing regulatory tools — such as those used for prescription drugs — allow companies to make certain changes to their products, without prior FDA approval, in the light of new information. They also allow products to be marketed on the condition that more data will be collected.

In such a fast-changing landscape, striking the right balance between protecting the public and promoting innovation is crucial. To get it right, agencies must proceed in small steps, articulate clear goals and rationales for their proposed actions, and consider input from all those affected. ■

Gail Javitt is a research scholar at the Berman Institute of Bioethics, Johns Hopkins University and counsel at Sidley Austin.
e-mail: gjavitt1@jhu.edu

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