# Regulators weigh risks of consumer genetic tests



The onset of genetic testing as a widespread consumer commodity continues to gather pace. At least 27 web-based companies now offer genetic tests—once the exclusive domain of hospital clinics and academic laboratories—directly to consumers for costs ranging from roughly $100 for a simple gene scan to $350,000 for a personal genome sequence and related medical advice. The disconnect between the mushrooming number of tests on offer (*Nat. Biotechnol.* **24**, 888–890, 2006) and their quality has prompted the US Department of Health and Human Services (DHSS) to issue a report criticizing regulatory oversight as fragmented and poorly coordinated. A final version of the report is expected in April.

In 2006, the US General Accounting Office (GAO) investigated a random sample of consumer genetics companies and found that the information the firms provided (based on DNA-laden cheek swabs submitted by GAO employees) was "medically unproven" and "ambiguous." This set in motion a DHSS investigation—performed by the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS)—that in November confirmed these problems in a draft report. In the meantime, the Human Genetics Commission, a government advisory body in the United Kingdom, has also called for more pre-market evaluation of genetic tests.

Funded by infusions of venture capital, most consumer genetic testing companies reside in the US (**Table 1**), says Stuart Hogarth, a visiting research fellow at the Institute for Science and Society at the University of Nottingham. "These companies ride the back of new scientific findings emerging from genome-wide association studies, which have been publishing their results over the past year or so," he says.

The studies link particular genes with features such as disease, ancestry and even athletic prowess, making them appealing to the consumer. But research is revealing that the genome is vastly more complex than once assumed, and tests on the market might not fully reflect that complexity. The Reykjavik, Iceland–based company deCODE Genetics, for instance, offers a clinical diagnostic test that predicts type 2 diabetes on the basis of a single gene variation, even though at least ten other genes have also been implicated in the disease. (deCODE does make clear, however, that the condition is an interplay of several environmental and inherited risk factors). Similarly, Coral Springs, Florida–based CyGene Direct markets a test for glaucoma based on three variants of the myocilin gene, despite there being 80–100 myocilin changes associated with the disease.

Agendia

An Agendia laboratory technician places a MammaPrint micro array onto a micro array analysis unit, which contains patient samples.

Gail Javitt, a research scientist with the Genetics and Public Policy Center at Johns Hopkins University, says concerns over such tests' 'clinical validity' raise questions about their capacity to fulfill purported medical aims. A test might be analytically valid, meaning that it can reliably identify a target gene, but if that gene has little or nothing to do with the disease of interest, then the tests' clinical validity is negligible.

In the United States, oversight of genetic tests is the responsibility of the Food and Drug Administration (FDA; Rockville, Maryland). Yet in the case of most 'home-brew' genetic testing, which is carried out in specialist laboratories, FDA has chosen to overlook that responsibility by invoking a policy of 'enforcement discretion'—it has the jurisdiction to enforce, but simply has chosen not to. Steve Gutman, the FDA's director for *in vitro* diagnostics, says that's in part because of resource constraints at the FDA, and also because the agency is reluctant to impede the field's rapid development.

FDA does regulate the clinical validity of *in vitro* diagnostics (IVDs), which are tests that can be packaged and sold in drugstores as kits or medical devices. IVDs undergo an extensive pre-market review that few companies in consumer genetic testing are willing to endure. As a result, most companies choose the far less burdensome home-brew path to market, which is regulated by the Centers for Medicare & Medicaid Services (CMS) through what is known as the Clinical Laboratory Improvement Act (CLIA). Unlike IVDs, which can be commercially distributed, tests regulated under CLIA stay in the labs that created them. Consumers access these laboratory based tests by sending biological samples through the mail. The samples are screened for target genes, and results are posted, along with accompanying information, on secured links accessible on company websites. There are roughly 1,400 consumer genetic home brews on the market today, compared with a few dozen genetic IVDs at most, Gutman says.

The CMS's only responsibility under CLIA is to ensure that home brews are analytically valid. And that creates a loophole through which—facilitated by the FDA's enforcement discretion—clinically bogus tests can reach consumers, Javitt says. "Because regulation of clinical validity is poor, consumers may be getting test results that are at best non-informative and at worst misleading or false," she says. "Such results may lead to ill-informed healthcare choices or failure to take needed healthcare measures."

The SACGHS panel concurs with that view. But the panel admits that clinical validation is challenging for genetic testing: prospective data pertaining to a given gene

may not be available for years after a test is developed. The CMS, meanwhile, has no intention of imposing pre-market clinical validation on home-brew tests. "It's not like we're in some total dead end because CLIA is limited to analytic validity," one CMS official says. "Clinicians can rely on their own judgment and supplemental knowledge from colleagues and from the literature."

But the FDA isn't satisfied with that, and intends to regulate a subset of home brews, falling under the cumbersome term of '*in-vitro* diagnostic multivariate index assay' (IVD-MIA). To confuse matters further, IVD-MIAs are also considered to be home brews because they aren't commercially distributed. These particular tests quantify gene-specific risks for a given disease using data from the scientific literature. Algorithms are then used to calculate a consumer's overall risk, depending on his or her gene expression profile. Those algorithms are proprietary, however, which puts them beyond scientific scrutiny. And that makes regulators nervous. So far, just one IVD-MIA has undergone FDA's pre-market review: a diagnostic test for breast cancer recurrence, marketed by the Dutch company Agendia, which cleared the process in 2007. The FDA issued draft guidelines for IVD-MIA pre-market review last July. Gutman can't predict when the guidelines will be finalized. But he insists the agency won't impose pre-market review for home brews as a category. "The guidance covers a small niche of tests that are subject to error in design and error in performance," he says.

Changes also appear imminent with respect to proficiency testing for analytical validity under CLIA—the highest level of scrutiny for assessing laboratory competence. Under current CLIA regulations, this level of assessment need only be applied to 83 analytes, contained on a list that hasn't been updated since 1992. None of the analytes included on the list are genetic targets, however. Following the SACGHS's recommendation, the CMS now appears willing to add specific genetic targets to the list in "the reasonably near future," the CMS official says.

Trish Brown, vice president for clinical affairs with DNAdirect, says that adding genetic targets to the list is "a great idea." But she rejects calls for pre-market clinical validation of home brews. In reality, the whole system is self-correcting, she says. "The bad apples tend to get shut down quickly," Brown asserts. "My concern is that with more regulation, costs for genetic testing will rise, so patients will ultimately end up paying more for services that are already expensive on the basis of the technology alone."

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**Table 1 Select companies offering genetic testing**

| Company | Tests offered | Collection process and materials |
|---|---|---|
| 23andMe (Mountain View, California)[a] | Bitter taste perception, breast cancer, Crohn's disease, earwax type, myocardial infarction, lactose intolerance, multiple sclerosis, muscle fiber and sports, obesity, prostate cancer, restless legs syndrome, type 1 diabetes, type 2 diabetes, venous thromboembolism | Saliva collection using kit provided by company |
| Consumer Genetics (Sunnyvale, California) | Fetal gender (X/Y), caffeine metabolism (*CYP1A2*1A/1F*), alcohol metabolism (*ADH*), asthma drug response (*ADRB2*) | For fetal gender, blood spot obtained with a finger prick using materials provided by company<br>For other tests, cheek swab using materials provided by company |
| Cygene Direct (Coral Springs, Florida) | Osteoporosis (*PDE4D*, *BMP2*), athletic performance (*ACTN3*), glaucoma and macular degeneration (mycolin), thrombosis (factor II, factor V Leiden, *MTHFR*) | Cheek swab and specimen card using collection kit provided by company |
| DeCODE[b] | Disease risks for age-related macular degeneration, asthma, atrial fibrillation, breast cancer, celiac disease, colorectal cancer, exfoliation glaucoma XFG, inflammatory bowel disease, multiple sclerosis, myocardial infarction, obesity, prostate cancer, psoriasis, restless legs syndrome, rheumatoid arthritis, type 1 diabetes, type 2 diabetes | Cheek swab using materials provided by company |
| Genelex (Seattle) | Adverse drug reaction testing, diet and weight loss consultation, hemochromatosis, periodontal disease, celiac disease | Cheek swab using collection kit provided by company |
| Mygenome (Needham, Massachusetts) | Alzheimer's disease (*APOE*), drug sensitivities (*CYP2D6, CYP3A4*), cardiovascular disease, thrombosis, pregnancy risk, osteoporosis | Company asks potential customers to contact for more information |
| Navigenics (Redwood Shores, California) | No tests offered yet; reservations being accepted | No tests offered yet |

[a]For a list of relevant genes tested, go to: https://www.23andme.com/experts/letters/science/#table. [b]For information on variations tested, go to: http://www.decodediagnostics.com/physicians.php.

Source: Genetics and Public Policy Center; company websites.