

What price personal genome exploration?

Companies offering direct-to-consumer genomic information face tough questions about who regulates them, where they fit in health care and how to value their services. What will it take to move them from niche services to a broader customer base? Jeffrey Fox reports.

In August, two Silicon Valley direct-to-consumer (DTC) genome information marketers, Navigenics and 23andMe, won an important round with regulators when officials in California granted them licenses. Earlier, each had received cease-and-desist letters from officials in Sacramento, along with similar orders from regulatory officials in New York. Yet, even as these companies and others offering similar services are poised to overcome such regulatory stumbling blocks, they face numerous other business challenges, from quality assurance in testing to the validity of medical correlations with genomic data, the willingness of medical professionals and insurers to accept such tests, and regulatory oversight at all levels. More to the point from a business perspective, can they win broader consumer acceptance and build sustainable businesses that cater beyond the well-heeled and well-informed? Certainly, at least one of these companies is looking to widen its appeal: just three weeks

ago, 23andMe slashed the price for its services from \$999 to \$399.

Whence personal genomics?

Soon after the first high-quality human genome sequence was completed in 2003, federal officials began investing in programs aimed at linking genetic variants with risks for specific diseases, at a cost of as much as \$6 million per disease. More than a few genomics-minded entrepreneurs recognized that these programs provide entry points to potentially lucrative health-care applications, including the development of disease prediction testing services, which channel results to consumers through clinical laboratories that run tests ordered by physicians. Typically, such testing is for one or a few specific, inherited diseases, such as cystic fibrosis or Tay-Sachs. In most cases, the doctor is the main point of contact for the patient regarding test results and interpretation.

Amid those conventional developments, a different cadre of company has emerged with the express aim of personalizing genomic information and purveying it through DTC genetic analyses to individuals or families—geared mainly, but not exclusively, to describing a client's risk for slates of disorders and other physical traits. Although specific practices vary, companies now offer to analyze DNA from mailed-in tissue or saliva samples and then provide clients with reports outlining the likelihood of displaying a trait, on the basis of correlations with single nucleotide polymorphisms (SNPs), along with some form of genetic consultation.

So far, the major corporate players providing DTC haploid genome-wide SNP analysis include 23andMe, a privately held start-up based in Mountain View, California (founded by Anne Wojcicki, the wife of Google cofounder Sergey Brin, who supplied some of the initial start-up funds); deCODEme, a spin-off from the Reykjavik, Iceland-based deCODE; and Navigenics, a privately held start-up based in Redwood Shores, California (which, interestingly, also got a cash injection from Google).

Meanwhile, another privately held company, Knome in Cambridge, Massachusetts, takes the DTC model for vending personal genomics data further: it is offering its elite clients their full diploid genome sequence.

What's on offer?

23andMe offers its clients a 'whole' haploid genome SNP analysis (Table 1), providing information on more than 80 diseases, conditions and traits. DNA analysis is outsourced to San Diego-based Illumina, which has customized its HumanHap550+ BeadChip (550,000 SNPs) with 30,000 additional SNPs selected by 23andMe. The service is intended to provide a user with information on both health-related and nonmedical traits, such as earwax consistency or the likelihood of developing back pain or male baldness. Another important component of the service is how genome information can inform customers about their ancestry and family history. The site (<http://www.23andme.com>) offers users the opportunity to share their genome information with, and ask questions of, other 23andMe customers. "Part of our service is intended to be fun," says company spokesperson Rachel Cohen. In September, 23andMe announced a partnership with Ancestry.com, which will give Ancestry's customers genetic information from 23andMe that will better enable them to trace their roots, according to Cohen.

23andMe also hopes to leverage customer SNP information in research studies, provided customers have opted in and given the necessary consent. For example, it is in the early stage



A business worth spit? Last month, 23andMe held a 'spit party' in New York to attract rich and famous clientele. Left to right: Rupert Murdoch, Barry Diller, Anne Wojcicki, Diane von Furstenberg, Sergey Brin (Google CEO), Wendi Deng, Linda Avey (23andMe CEO) and Harvey Weinstein.

Table 1 Direct-to-consumer marketers of genetic information

Company	Technology	Cost
23andMe	Illumina HumanHap550+ BeadChip, oligonucleotide bead arrays in microwells on bundled optical fibers for detecting 550,000 SNPs plus 30,000 additional SNPs selected by 23andMe	\$399
deCODEme	Illumina Human1M BeadChip, for detecting >1 million SNPs	\$985 introductory price
Knome	Illumina genome sequencing platform	\$350,000
Life Code	Undisclosed SNP genotyping arrays	€1,200 to €2,400
Navigenics	Affymetrix Genome-Wide Human SNP Array 6.0, a photolithographically synthesized oligonucleotide chip for detecting 600,000 SNPs	\$2,500 plus \$250 per year "for continuous service"

of a partnership with the Parkinson's Institute and Clinical Center of Sunnyvale, California, with support from the Michael J. Fox Foundation for Parkinson's Research in New York to develop "advanced methods for clinical and epidemiologic research" on Parkinson's disease. According to Cohen, the company contemplates taking a similar approach for other diseases.

Navigenics, which also contracts out its DNA testing, is focusing more narrowly on variants that address "health conditions" (no earwax). Its Health Compass provides in its first wave of analyses information about 21 medically related conditions, according to Amy DuRoss, vice president for policy and business affairs. Currently, the company uses the Genome-Wide Human SNP Array 6.0 from Affymetrix of Santa Clara, California, to test for over 900,000 SNPs. But DuRoss is quick to point out that "we're technology agnostic, and poised to incorporate sequencing when it's cost-effective and warranted." As part of its service (<https://www.navigenics.com/>), Navigenics provides its customers with 24/7 access to genetic counselors who help explain to users what the genetic analyses mean and advise on the best course of action to take with the information in hand.

The company is working with medical centers to determine how likely individuals are to change behaviors as they respond to genetic information about their risk of developing particular diseases. If individual clients want to consult with health-care providers, she adds, the company "provides a channel for that." The company also provides a voluntary means for clients to release anonymized data for use in public health studies.

Last November, established biotech company deCODE, which develops drugs and diagnostics on the basis of a gene and tissue bank of the Icelandic population, launched deCODEme (<http://www.decodeme.com>) as its DTC arm. According to CEO Kari Stefansson, the new company is initially offering clients SNP-based genomic testing for 29 diseases and traits. Similar services will

be available in the UK through a partnership with Lab21 of Cambridge, UK, although not as a DTC service.

Unlike Navigenics or 23andMe—both of which Stefansson calls mere "dot-coms, portals that receive orders and dispatch results"—deCODEme is an arm of the larger biotech entity that is already doing its own genetic analyses and discovery while developing technologies and both diagnostic and therapeutic products. "We're a comprehensive genetics, not just a consumer-service, company," he says. However, he is keen to point out that there is no blurring of the boundary between providing users with genome data and leveraging those data for discovery: "In no way are we using the data from that service for our research."

The Illumina chip now being used for its DTC clientele is "designed to find common variants and can't be used for rare SNPs," he says. However, as a recent paper attests¹, Stefansson believes that certain variations that confer disease risk are under negative selection because of reduced fecundity. And by looking for variations in gain or loss of rare, large chunks of DNA (copy-number variations) in the genomes of parents and their unaffected offspring, it is possible to identify new variants that can then be tested for association with disease. Thus, over the coming years, deCODE and others are likely to be generating more of the rare variants that may prove more informative in terms of disease risk.

Such developments make these "exciting times," Stefansson says. "We focus on common diseases, and our goal is not to be exhaustive but to put together meaningful numerical values for [estimating] the risk of having those diseases."

LifeCode, a DTC portal of a German sequencing service provider GATC Biotech (Konstanz, Germany) is promising to offer a suite of genetic analyses of various cancers, with other common disease genes to follow. The service, which employs one of the SNP chips, is tiered from €1,200 to €2,400, depending

on the level of counseling and whether the information will be updated.

The last genome information provider that has been making the headlines is Knome. For its first round of 20 clients, each is flown to Boston (or a team is sent to visit clients where they reside) for individual tutorial sessions and to provide extensive information on genomics in general. Once a client signs up for the service, the company uses Illumina genome sequencing platform to sequence a client's diploid genome. This sequence is then provided to the client to keep on a shiny 8-GB drive.

Each client is given control of his or her own fully encrypted data set after it is generated. "We have to ask them each time for any particular request to participate in a research project, and they then can provide access to us through their passkey," says CEO Jorge Conde. Because the data are not centralized, there are fewer security risks that personal information will be inadvertently released or misused.

Looking for clients

Surveys indicate that consumers are lukewarm when it comes to personal genomics and genetic testing. According to a recent survey by the investment bank Burrill & Company², only 5% of consumers said they were "very likely" to take a disease-specific genetic test in the next few years, and 35% said they would not submit to genetic testing at all. Indeed, the companies themselves are not talking about their client base.

23andMe has run perhaps the most glitzy media campaign to publicize its service, aiming primarily for cachet; thus far, the company has been actively recruiting the rich and famous, as well as prominent intellectuals, as first adopters. Last month, for example, New York society was abuzz about what was termed a 'spit party', in which members of the social set in New York got together and provided saliva samples that 23andMe would analyze. According to Cohen, there are no "concerted" marketing efforts except through the company's web site. "We provide no information on the number of our customers, but it's growing all the time, and we're encouraged by the interest so far."

She adds, however, "Price is an issue, and we would like more diversity"—which may explain why the company dropped its prices last month. At present, Cohen says the company is operating in the US, Canada and Europe, but not in Asia, South America or Africa.

According to Navigenics' DuRoss, for now, most of the company's clientele is drawn from North America, but there is "quite a bit of interest overseas." Navigenics not only charges users \$2,500 for the initial screen, but also \$250 a

year “for continuous service” and to keep their subscription active.

At deCODEme, Stefansson says that it is in its early days, but in the next few years, he expects “college-educated people will want genomic analyses.” Thus, he anticipates “tremendous demand as we transition from R&D to marketing products to physicians and consumers. We’re building our sales force.”

If the clientele of the above companies is rather select, Knome is aiming for an entirely different stratosphere—the super-rich. According to CEO Conde, the business model that Knome is following is all about anticipating technical and intellectual developments, while depending for now on clients with deep pockets and an eagerness to be ahead of the pack. Thus, the company is going after a “rarefied segment of the market,” says Conde. The company knows, and those clients surely realize, that “those costs will come down drastically.” This model is “not unique to genomics,” he adds. “You see it in other arenas with early adopters who pay higher prices for cell phones or, the more current example, for personal space travel. The early adopters market is attractive for developing services that are highly personal and [in which] clients participate.”

To avoid disappointing clients, Conde notes, “We spend a lot of time before we sign our contracts making sure they understand what we can and cannot provide, and we go through a selection process.” The client group is “very international, predominantly men, and Europe and Asia are well represented,” he says, noting that the recent weakness in the dollar helps to explain some of the non-US tilt for the initial clientele. “There’s a certain similarity we see in that they are highly engaged, call with questions and forward information to us. Almost to a ‘T’ they’re entrepreneurial, very well-informed and highly intrigued by genomics or health care generally. And that’s part of the learning process for how we can serve this market.”

“But it won’t be long before the cost is tens of thousands of dollars lower,” he continues. “In the future, as costs come down and there is new information [to use in interpreting the data], we will reach an intersection in which this service will be more broadly accessible. That’s what we’re looking for. The other companies that are offering [SNP-based] services for about \$1,000 will upgrade later, whereas ours is designed to work with self-selected individuals. We can deploy more widely when the product becomes less expensive.”

What does it all mean?

Published findings that are used to correlate individual SNP patterns with specific disease risks are widely recognized as subject to

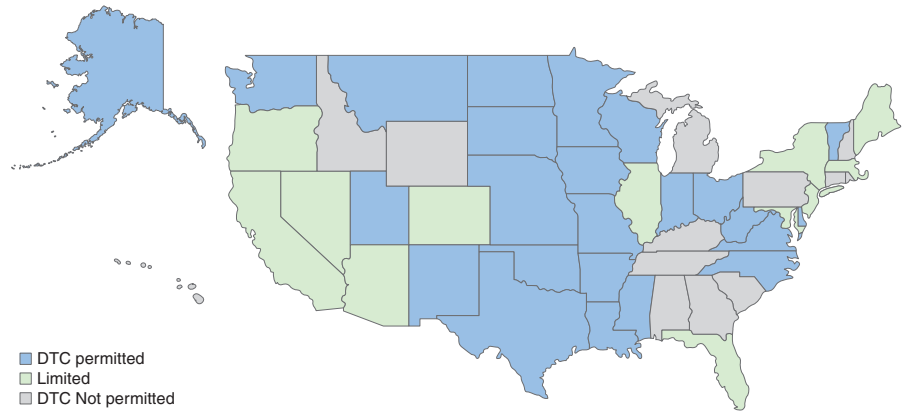


Figure 1 DTC genomics companies have to navigate a patchwork of regulations at the state level. Source: Genetics and Public Policy Center, Washington, DC.

inconsistencies and need to be reexamined and revised periodically to reach a fresh consensus. To that end, officials at the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, launched a program in 2004 called Evaluation of Genomic Applications in Practice and Prevention (EGAPP). It is systematically evaluating genetic tests that emerge from genomic technology and other developments and assessing how they apply to clinical and public health practices.

Several recently completed EGAPP reviews overseen by the CDC are having an important clinical impact in terms of how, for example, breast and colon cancer patients are tested and treated, according to Kathy Hudson, director of the Johns Hopkins Genetics and Public Policy Center in Washington, DC. In the absence of these reviews, there is a tendency to hear “breathless enthusiasm for new tests,” she says. With those reviews at hand, “we can use them to do comparisons with what people are saying about tests.” For instance, a forthcoming review evaluating “sets of variants for cardiac disease risk is directly relevant to 23andMe and Navigenics,” she says.

The interface by which 23andMe users view the results of their genome-wide marker analysis classifies disease-related traits into ‘established’ and ‘preliminary’ categories, with disease ‘propensities’ reported to clients as risk against the population. Navigenics also provides risk in the context of the population, although it is more conservative in terms of the diseases for which it provides risk estimates.

DTC genome information of this sort “has the whole worldwide genetic community worried,” says geneticist Roderick McInnes, scientific director of the Canadian Institute of Health Research in Toronto. Describing these companies as part of a “free-for-all,” he points

out that the risk factors they cite address health risks in terms of the population at large, but “are kind of meaningless for individuals,” particularly when the specific disease risk is “low in the population.”

Another problem is that such information, no matter what counseling is provided, sometimes leaves individuals with a “misguided sense of genetic determinism,” he adds. In those cases where individuals, on the basis of a genome profile, discard advice that could improve their health, such testing “could have a malign influence.” For example, a patient with a genome profile indicating a low risk for cholesterol might pay less attention to their diet than they would have otherwise. Alternatively, individuals with a poor folate metabolizer profile might misguidedly binge on folate supplements that in turn increase their risk for certain cancers.

If anything, the DTC situation could be worse than misleading, according to Walter Bodmer at the University of Oxford. “In my view, an individual’s medical risk at the genomic level has little to do with most polymorphism studies,” he says. “The effects of any partial variant are too small. The only way to look is to sequence [the genes] of individual patient groups to check variants. In my view, that’s the way to go for multifactorial diseases. Companies like 23andMe have some understanding of this, but their [results] on the risks of disease are very limited and hard to make use of, and they can create a lot of anxiety that’s not necessary”³.

Bodmer argues, as does deCODE’s Stefansson, that rare variants, rather than the common ones that are being picked up through current SNP analyses, may hold more relevant information for predicting health outcomes for individuals. In the case of breast cancer, there

is a large number of variants with unknown significance, according to Bodmer. “We argue most of those variants probably have functional consequence at low level of penetrance,” he says. “We’re not yet sure what to do about it, but it’s a different way of thinking that’s only beginning to be appreciated.”

Regulatory ambiguities abound

Although the companies differ in their approaches and attitudes, they all applaud enactment in the US last April of the Genetic Information Nondiscrimination Act (GINA). This new federal law, which took many years and iterations before being passed, prohibits health insurers and employers from discriminating against individuals on a genetic basis, removing a major barrier for many kinds of research and making it a good deal less worrisome for individuals to seek genetic information about themselves and their families.

Passage of GINA early this year widened opportunities for these three DTC genomic analysis companies (and others doing genetic testing), but they face plenty of regulatory ambiguity at both the state and federal levels. Currently, 24 states prohibit or limit DTC testing without the involvement of a medical professional. Some states, such as Maryland, insist that genetic tests be done only if physicians request them (Fig. 1).

More worrisome, however, is a series of cease-and-desist letters that these three and other genetic companies received from state public health officials—earlier, from New York and, more recently, from California. Despite the difficulties dealing with a wide variety of state laws, vastly different approaches to enforcing them and outright confusion over what these new companies are doing, some of the problems are being sorted out, according to Navigenics’ DuRoss. California, for example, recently characterized Navigenics as being a ‘dry lab’, thus recognizing that its DNA analysis is done elsewhere but still seeking to regulate its handling of data under the guise of a laboratory. “This is such a new hybrid field that it’s hard to anticipate [these regulatory] issues,” she says.

Of course, one way to trump disparate state-level rules is to seek uniformity from

the federal level. But the only explicitly relevant framework at the national level is through the Clinical Laboratory Improvement Amendments, which mainly address quality control issues in laboratory settings. Another potential federal regulatory home for DTC testing is the US Food and Drug Administration (FDA), which regulates other types of genetic testing. The Advisory Committee on Genetics, Health and Society of the Department of Health and Human Services, which houses the FDA, has issued several series of recommendations and continues to examine policy options that could lead to new means of regulating DTC genetic tests.

One other federal body, the Federal Trade Commission (FTC), could regulate DTC testing, drawing from statutory authority that requires commercial enterprises to provide customers with truthful information. Currently, the commission is investigating two genetic testing entities but has not revealed what is at stake.

Professional geneticists are also scrutinizing DTC testing. “We want to make sure that anybody who goes to DTC companies understands the claims being made,” says Joann Bougham, executive vice president of the American Society of Human Genetics (ASHG) in Bethesda, Maryland. “ASHG also recognizes that DTC testing is building awareness of genetics and may help people make wise choices.” Meanwhile, a sister organization, the American College of Medical Genetics in Bethesda, takes a tougher stance, laying out a series of stringent “minimum requirements” for DTC companies to meet.

The path ahead

From a technological perspective, the entire DTC sector is likely to be transformed by the new sequencing technologies that are just beginning to come online. As current Affymetrix and Illumina chip technology used to analyze genetic variation can only capture a tiny fraction of genetic risk for common disease, companies providing individuals with their full diploid genome sequence will be able to pinpoint not only common variants, but also rare variants and large structural information (copy-number variants), which

constitute a much larger fraction of genetic risk for disease. What’s more, once an individual has their whole genome sequence in hand, it will never become obsolete—only refined, for example, in highly repetitive regions of the human genome that are refractive to current platforms. In a sense, a genome sequence can only be sold once, but there’s no reason companies would not build on it, selling individual transcriptomes, for example.

Although sequencing technology remains in flux, companies providing DTC genome information so far remain targeted to a relatively elite clientele and face an uphill struggle to broaden their customer base. There is considerable skepticism aimed at DTC services, not only in the medical community but also among consumers. Navigenics founder David Agus has been quoted as saying, “Going to the individual is how we’re going to change doctors, and that’s how we’re going to change medicine and health-care costs.” But according to the Burrill survey² and several others, US consumers are “wary” of these products, the benefits they offer and the personal risks that users may encounter. Although consumers are “warming” to such tests, “they still need to be convinced of the value of the information these new tools provide.” And as long as the information DTC services provide is of questionable utility, the public’s concerns over genetic discrimination by employers, health insurers or even life insurers is unlikely to be easily assuaged, even with the passage of GINA.

But Raju Kucherlapati, director of the Partners Healthcare Center for Genetics and Genomics at Harvard Medical School in Boston, is more upbeat: “DTC companies are changing that,” he says. “People go because they’re curious, and that’s wonderful. GINA and DTC are driving things, and that fear is receding.”

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1. Stefansson, H. *et al.* *Nature* **455**, 232–236 (2008).
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3. Bodmer, W. & Bonilla, C. *Nat. Genet.* **40**, 695–701 (2008).