KNOWING ME, KNOWING YOU

Patients are beginning to present with not only a web diagnosis but predictions of future disease.

Jeanne Lenzer and **Shannon Brownlee** examine the problems of the rise in commercial genetic testing

Do you want to Google your genes or peer into your future risks of heart disease or cancer? Now you can, according to direct to consumer testing companies. Gone are the days when genetic testing was limited to doctors ordering tests for rare, but prognostically potent, single gene disorders such as Huntington's disease, Duchenne's muscular dystrophy, or cystic fibrosis. Thanks to an explosion of newly discovered single nucleotide polymorphisms, or SNPs (pronounced snips), companies are marketing genetic tests for traits ranging from the mundane—eye colour and wet ear wax—to serious conditions such as Crohn's disease and Alzheimer's disease.

While the global market for these tests is growing rapidly—estimated at \$730m (£366m; €463m) last year and growing by 20% annually¹—evidence that they can provide patients with clinically useful information is lagging far behind. There is little regulatory oversight of the tests, and even less in the way of clinical data to help doctors guide patients who go to them carrying printouts of their genetic details. Genetic tests and “personalised medicine” are supposed to enable doctors to customise each patient's care, yet there is a paucity of studies on interventions for patients with genetic variants.

The promise being made to consumers is clear: forewarned is forearmed. The website

for deCODE genetics, based in Reykjavik, says its tests will “help to empower individuals and their doctors.” The Californian company 23andMe, which has backing from Google and the biotech company Genentech, provides an “odds calculator” that the company says will allow customers to see which “health concerns are most likely to affect a person with your genetic profile.” Navigenics, also based in California, claims its tests can provide a “roadmap to optimal health” that can enable customers to “take action before a disorder strikes to delay or even prevent the illness altogether.” And all for a fee ranging from \$1000 to \$2500.

A more likely scenario is that these tests will raise more questions than they answer. It is unclear what consumers think they are learning from their “genetic blueprints.”

“There are few hard numbers that can accurately predict the contribution of a particular polymorphism to an individual's phenotypic risk”

Some screening tests, though non-invasive and seemingly harmless, have been shown to trigger a cascade of further evaluations and interven-

tions that result in measurable harms while providing no benefit.²⁻⁵

Although widespread genetic testing might eventually lead to well defined risk profiles and the ability to tailor drugs to the individual, such results may not be available for many years. In the meantime, genetic testing poses important and largely unacknowledged risks. As well as clinical concerns, there are questions about the effect of the corporate

partnerships that link genomic data mining companies to electronic medical records, hospitals, and drug companies.

Genomics revolution

Direct to consumer genetic testing has its roots in the human genome project, which was launched in 1984 with the promise of opening frontiers in medicine. Novel, personalised treatments would flow from an understanding of genetic underpinnings of disease, and some experts predict that the genomics revolution is poised to deliver information that will allow people to make personalised lifestyle changes or decide whether to have a child, and allow doctors to prescribe correct drugs at correct doses.⁶ Linda Avey, cofounder of 23andMe, is an advocate of personalised medicine. “We're still using very antiquated systems for diagnosis and for prescribing therapies. Whenever you take a drug it's kind of a gamble whether your body will respond appropriately to it,” she said.

Thus far, however, only a handful of genetic tests can indicate how a patient will react to a drug, and even then, the test may lack clinical value. For example, a working group that reviewed studies of dosing of serotonin reuptake inhibitor drugs based on the CYP450 polymorphism concluded that there is no evidence that the test is “useful in medical, personal, or public health decision-making.”⁷ Even the discovery of the genes for many single gene conditions has failed to lead to the expected cures. For some diseases, like Huntington's disease and sickle cell anaemia, the prospects for treatment seem as remote as they were before the genes were discovered.

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Along with genetic information, some companies offer to calculate a customer's risk of developing conditions such as type 2 diabetes, cardiovascular disease, and prostate and breast cancer. 23andMe, for example, offers a scan of some 580000 SNPs and a report on roughly 14 conditions for which customers might be at risk. These risk calculations are exceedingly rough, however, as most SNPs have been only loosely connected to any particular disease, and there are few hard numbers that can accurately predict the contribution of a particular polymorphism to an individual's phenotypic risk.

A lack of data has not stopped genomics companies from capitalising on the appealing concept of personalised medicine, starting with their names, which include 23andMe (23 chromosomes), deCODEme, and Knome (pronounced know me). Knome is founded by George Church, professor of genetics at Harvard, who helped develop the first direct genomic sequencing method. For upwards of \$350000, Knome will sequence a customer's entire genome. 23andMe also provides genetic information for "entertainment" and "education" purposes, such as whether one has genetic markers for an enhanced ability to taste bitterness or for athleticism.

Companies are careful to acknowledge in the fine print the lack of meaningful data. In a special message "To the Medical Community," 23andMe acknowledges that the information it provides "is tailored to genotypes not to individuals"—an acknowledgment that belies the claim of personalised, clinically relevant health information. But 23andMe cofounder Anne Wojcicki argues that people

have a right to know their genetic information and says that the company is not providing "actionable" health information but information that is largely intended to educate and lead to better research.

But what is it that customers are being educated about? When asked if customers of 23andMe were under the impression that they could obtain health information that would be useful to them, Professor Church, who is an adviser

to 23andMe, responded, "I hope not." He added, "Education is useful, but distinct from clinically accepted diagnoses."

Estimating risk

Nevertheless, doctors are likely to be seeing more and more patients arriving at their doors, genomic results in hand, requesting treatment for diseases they do not yet have or more screening tests. Most doctors, according to a recent systematic review by RAND Health, are "woefully underprepared" to counsel patients about genetic tests.⁸ According to one study cited in the review, only 5% of doctors said they felt "confident in their ability to interpret test results."

Rather than improving health, widespread genetic testing is likely to result in widespread anxiety. In a commentary published in *JAMA*, Gilbert Welch and Wylie Burke caution that there is substantial confusion about estimates of genetic risk.⁹ Selection bias, they say, can lead to "overestimates of both risks and consequences of disease." For example, the oft cited 87% risk of cancer by the age of 70 years among women who test positive for the BRCA1 gene was derived from tests of exceptionally high risk women who had at least four family members with ovarian or breast cancer diagnosed before age 60 years. Far lower estimates were obtained when the inclusion criteria for testing were broadened.⁹ Another form of bias, surveillance bias, can lead to similar exaggeration of risk when people with a certain genetic trait choose to have more frequent testing. "The quickest way to develop breast cancer," said Dr Welch, "is to be tested for it."

Framing risk can have a powerful effect—an effect that genomics companies are putting to use when marketing their tests. The website of 23andMe warns of a "1 in 8" chance of developing breast cancer, a risk that can be expected to alarm many women. Yet a woman's risk is that high only once she reaches the age of 70. In the US, such risk estimates have led many women to overestimate their chances of dying of breast cancer, which accounts for only 3% of female deaths annually.¹⁰

Similarly, telling men (accurately) that more than half of them will have prostate cancer by the age of 60 years, and that men with certain genetic variants have a four times greater risk of developing prostate cancer than men with none of those variants (also accurate) could understandably persuade some men to have prostate specific antigen testing.¹⁰ But if the information is framed differently men might not be so enthusiastic. "Only 3% of men die of prostate cancer," Dr Welch says. Instead of telling men that they are at an 80% increased risk of developing prostate cancer, he says, doctors should tell men that their lifetime risk of dying from prostate cancer is 3%. "And an 80% increase of that risk doesn't even increase the risk to 6%."

Research benefits

The potential pay-off, for both patients and companies, lies with pharmacogenomics, the development of new, more personalised drugs. This requires access to huge numbers of research subjects, their genomes, and their phenotypic (clinical) records—an extraordinarily expensive undertaking. In a clever reversal, companies are getting research subjects to pay—rather than be paid—to become research subjects. Genetic testing companies' primary source of income is fees paid by customers. In future, they can expect to earn even more by selling the genomic information they gather to researchers and to biotechnology and drug companies. Customers of 23andMe sign a consent document indicating that the company may share their genomic data (anonymously) and that the company may sell the data to researchers. Customers of 23andMe are asked if they would like to make their health records available (free) to researchers to advance medical science.

Companies are planning ways to integrate

genomic data with phenotypic information from patients' electronic records. Google, which invested \$3.9m in 23andMe, is poised to launch its online personal health records. (The cofounder of Google, Sergey Brin, is married to Ann Wojcicki, cofounder of 23andMe.) Ms Avey says 23andMe plans to work with personal health record companies to enable data merger.

Although 23andMe insists it is in the business of advancing research, its commercial appeal to the public suggests a different interest. Dr Welch says that telling customers about their risk factors could result in surveillance bias. "They might be conducting research," he said, "but it won't be good research."

The potential gold mine in combining genomic and phenotypic information is evident from the fact that at least one company, the Coriell Institute for Medical Research in New Jersey, is offering genetic testing to 10000 people. The institute has partnered with several healthcare organisations, including Cooper University Hospital, which is offering Coriell's free genomic screening to the first 2000 of its 5500 employees who sign up. The response has been "overwhelmingly positive," according to a hospital spokeswoman. Cooper's chief medical officer, Simon Samaha, says that the hospital is planning training sessions for doctors, who expect an influx of patients after the screening.

While genomic databases may lead to better drugs, integrating genomic and phenotypic data has raised concerns about potential discrimination by insurance companies and employers. In the US, antidiscrimination laws vary from state to state, and there is little agreement among payers, physicians, researchers, and patients about whether insurance companies should have access to genomic information. Dr Samaha says that he's not sure that it's wrong for insurance companies to have access to such genomic data: "It raises a question about how open the economy should be."

Failed regulation

Concerned with the potential for harm, advisory bodies in the US and UK have recommended regulatory oversight of direct to consumer genetic testing—yet national agencies in both countries have failed to act. According to Public Citizen's Health Research Group, a public interest group

based in Washington, DC, the 2004 draft report by the US secretary's advisory committee on genetics, health and society was

"notable" for its "accurate diagnosis of the manifold problems in the oversight of genetic testing and . . . for its complete failure to identify an appropriate treatment for these problems."¹¹

Critics say that regulatory oversight is uneven to non-existent. There is little oversight of clinical validity (is the genetic variant reliably associated with the

phenotypic change observed?) and clinical utility (do enhanced surveillance, prophylactic treatment, or lifestyle changes improve outcome?).

Even accurate detection of genetic variants is not necessarily assured. In 1997 and 2001, US governmental groups and an earlier advisory panel recommended proficiency testing for all laboratories doing genetic tests—but those recommendations were simply ignored by federal agencies.¹² In an almost comical response, the Center for Medicare and Medicaid Services, the agency responsible for ensuring analytical validity under the Clinical Laboratory Improvement Amendments, argued that setting laboratory standards for genetic testing was too difficult. To prove its point, it cited the agency's previous difficulty in ensuring the accuracy of cervical smear testing, which took 17 years to complete. The reason the amendments were passed (and proficiency testing instituted) was because of massive malpractice suits resulting from the deaths of women whose cervical smears had been misread.¹²

Peter Lurie, deputy director of Public Citizen's Health Research Group, is disturbed by the lack of oversight of genetic testing. He worries that the public may "assume there is the same degree of oversight" for genetic tests as there is for tests such as a red blood cell count. "But," he said, "they are not even remotely the same." Similar problems plague the UK. Sir John Sulston, acting chair of the Human Genetics Commission, which lacks regulatory authority, says that nothing has changed since December 2007, when he wrote that direct to consumer genetic testing is "for now, largely in the hands of commercial test providers: the pharmaceutical companies, their marketing departments and PR agents."¹³

What all this means is that testing companies are operating in a regulatory vacuum.

The steps needed to protect the public have been clearly laid out by the various public interest groups and advisory panels. Until national agencies act, it will be up to doctors to handle the expected influx of questions and problems that arise from direct to consumer genetic testing. The first step towards reducing the chances of harm posed by widespread genetic testing is to educate doctors and patients about the limited value and potential harms of testing.¹¹⁻¹³

Perhaps the most powerful argument for regulation comes from a surprising source. Dietrich Stephan, cofounder and chief science officer of Navigenics, says that his company has had discussions with the Food and Drug Administration and determined that "right now we are exempt from FDA regulation." But he says his company would welcome FDA oversight because there are "a lot of charlatans and pseudoscience occupying this space and we are ready to be regulated."

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