Genetic tests: between risks and opportunities

The case of neurodegenerative diseases

Donato Ramani & Chiara Saviane

In the age of the Internet, a wealth of information lies at your fingertips—even your genetic ancestry and your fate in terms of health and sickness. A Google search for ‘genetic testing’ immediately comes up with a list of companies offering quick, direct-to-consumer genetic tests (DCGT) for relatively little money. “Claim your kit, spit into the tube and send it to the lab,” states the website of 23andMe—the company whose Personal Genome Service was named the ‘2008 Invention of the Year’ by *Time* magazine. Six to eight weeks after sending in a sample, customers can log on to the company website and learn about their genetic origins and ancestry if they opted for the ‘Fill in Your Family Tree’ option, or can explore their genetic profile under the “Health Edition” and what it says about personal disease risks and drug responses.

The availability of next-generation high-throughput DNA sequencers has enabled companies to sequence the genes of a large number of customers at a low costs and with few personnel

23andMe is one of several companies that offer predictive genetic tests covering a range of multifactorial and monogenic disorders (STOA, 2008). This is clearly a revolutionary approach to personalized medicine; it not only allows individuals to learn about genetic risk factors for a variety of diseases, but also does so outside the established medical system. Before the advent of DCGTs, genetic tests were only carried out at specialized medical institutions

under controlled conditions, and only on referral from a physician. The decreasing price of DNA sequencing, new technologies for high-throughput sequencing and the growth of the Internet have all helped to reduce the technical, financial and access barriers to genetic testing. It is therefore not surprising that private enterprises moved into this fast-developing market.

The availability of next-generation high-throughput DNA sequencers enables companies to sequence the genes of a large number of customers at a low cost and with few personnel. They can therefore offer this service at attractive prices, in the range of a few hundred dollars. The Internet conversely enables accessibility: a few mouse clicks are enough, while completely bypassing the usual checks and balances of organized healthcare. This means that expert advice is often lacking for patients about results that predict inherited risks for diabetes, cancer, neurological disorders and drug response (STOA, 2008).

The simple, affordable and rapid service offered by these companies raises concerns about the clinical validity and utility of the tests, as well as the information and support that they offer to properly interpret the results. In June this year, the US Food and Drug Administration (FDA) contacted five companies that sell genetic tests directly to consumers and asked them to prove the validity of their products (Pollack, 2010). The FDA argues that genetic tests are diagnostic tools that must obtain regulatory approval before they can be marketed, but it did not order the companies to stop selling their tests. 23andMe—one of the five companies that

were contacted—replied: “We are sensitive to the FDA’s concerns, but we believe that people have the right to know as much about their genes and their bodies as they choose” (Pollack, 2010). Last year, researchers from the J. Craig Venter Institute (San Diego, CA, USA) and the Scripps Translational Science Institute (La Jolla, CA, USA) reported inconsistencies between results obtained from two DCGT companies in an opinion article in *Nature* and made recommendations for improving predictions (Ng *et al.*, 2009).

A balance must be struck between consumer choice, consumer benefit and consumer protection. On one side is the individual’s right to have access to information about his or her health condition and health risks, so as to be able to take preventive measures. On the other side, serious questions have emerged about the lack of proper counselling in a professional setting. Are customers able to correctly understand, interpret and manage the information gained from a genetic test? Are they prepared to deal with the health risk information such a test provides? Are the scientific community and society as a whole ready to change the focus in medicine from morphological and physiological factors to molecular and genetic information?

A balance must be struck between consumer choice, benefit and protection

These concerns become more complicated when companies offer genetic tests for neurodegenerative disorders for which there are no preventive measures or treatments, such as Alzheimer, Parkinson or Huntington

diseases. Most of these diseases are severe, debilitating and can lead to stigmatization and possible discrimination for patients. Brain disorders that cause progressive mental decline affect not only the health of the individual, but also their identity, self-consciousness and role within the family and society. As Judit Sándor, Director of the Centre for Ethics and Law in Biomedicine at the Central European University (Budapest, Hungary) put it: “The stigmatization of hereditary diseases in society may lead to ethical and legal consequences that are difficult to grasp. The stigma associated with neurodegenerative diseases would be even harder to bear if the disease is proven to be hereditary by some form of genetic testing.”

In this context, 60 experts from a range of disciplines—scientists, clinicians, philosophers, sociologists, jurists, journalists and patients—from Europe, Canada and the USA met at the 2010 workshop ‘Brains In Dialogue On Genetic Testing’ in Trieste, Italy. The meeting was organized by the International School for Advanced Studies, as part of the European project ‘Brains in Dialogue’, which aims to foster dialogue among key stakeholders in neuroscience (www.neuromedia.eu). The use of predictive genetic testing for neurodegenerative diseases was the main focus of the meeting

and represents an interesting model for discussing the risks and benefits of DCGTs.

Very few neurodegenerative disorders have a typical Mendelian inheritance. The most (in)famous is Huntington disease, which typically becomes noticeable in middle age. Symptoms include progressive choreiform movements, cognitive impairment, mood disorders and behavioural changes. Huntington disease is caused by an increase in the number of CAG repeats in the gene *Huntingtin*, which can be tested for easily and reliably (Myers, 2004) in order to confirm a diagnosis or predict the disease, in at-risk groups or prenatally. The results have psychological and ethical implications that affect individuals and their families. According to the STOA report on DCGTs, only one company offers a test for Huntington disease.

Most neurodegenerative disorders have a more complex set of genetic and environmental risk factors that make it difficult—if not impossible—to predict the risk of disease at a certain age. A small percentage of cases of Alzheimer and Parkinson diseases—usually early-onset—carry specific mutations with a Mendelian inheritance, but genetic factors are also involved in the most common late-onset forms of

these diseases (Avramopoulos, 2009; Klein & Schlossmacher, 2006). Nicholas Wood of University College London, UK, commented that: “[t]here has been a revolution in our molecular genetic understanding of Parkinson’s disease. Twenty years ago Parkinson’s disease perhaps was considered the archetype of non-genetic disease. It is now clear that a growing list of genes is primarily responsible for Mendelian forms of Parkinson’s disease. It is also clear from recent studies that, due to reduced penetrance, some of these ‘Mendelian genes’ play a role in the so-called sporadic disease.” Nevertheless, a genetic test based on susceptibility genes would not enable a clear diagnosis—as in the case of Huntington disease—but only an estimate of the individual’s risk of developing the disease later in life, with varying reliability.

For Alzheimer disease, genetic testing is usually only recommended for individuals with a family history of early-onset or with immediate relatives who already have the disease. The most common form of late-onset Alzheimer disease has a complex inheritance pattern. The medical establishment does not therefore recommend genetic testing for it, although a polymorphism in the Apolipoprotein E (*APOE*) gene has been unequivocally associated with Alzheimer

disease (Avramopoulos, 2009). The identification of such risk factors through epidemiological studies provides valuable information about the molecular basis of the disease, but the management of this information at the individual level seems difficult for clinicians and patients. Agnes Allansdottir of the University of Siena, Italy, explained these difficulties stating that “research on decision-making processes demonstrates that we humans have severe problems dealing with probabilities.”

Sándor expressed concerns that these difficulties could lead to additional discrimination. “Most people know what to do if they have high blood pressure, for instance. However, information coming from a genetic test is much more complex—their reading and interpretation require special expertise,” she said. She pointed out that some groups might be unable to access that expertise, while others might be unable to understand the information. “As a consequence, they will suffer an additional form of discrimination that is the ‘discrimination in the accessibility’ of sensitive and complex medical data, and that affects [...] the right to privacy, as well.”

...“research on decision-making processes demonstrates that we humans have severe problems dealing with probabilities”

It is certainly possible that individuals who do not understand what probabilistic estimates of risk mean will be upset to find out they have a higher risk of developing a certain disorder, even though in absolute terms this risk is marginal. Avoiding this situation is what genetic counselling tries to achieve: to inform patients and help them to interpret the results of genetic tests. For the same reason, genetic testing for most common forms of late-onset Alzheimer or Parkinson disease—both of which are multifactorial—is not recommended, precisely because of the limited predictive value of these tests and the lack of proven preventive measures. However, various companies including deCODEme offer to identify your *APOE* variant and calculate “your risk of developing late-onset Alzheimer’s Disease” as part of their service.

Research has demonstrated that genetic testing may be a useful coping strategy for some at-risk individuals (Gooding *et al*,

2006), a conclusion that was also reached by the Risk Evaluation and Education for Alzheimer’s Disease (REVEAL) study (Green *et al*, 2009). Some results showed that knowledge of their *APOE* genotype and numerical lifetime risk influenced the health-related behaviour of asymptomatic adult children of Alzheimer disease patients. The discovery of increased risk of disease through an education-and-disclosure protocol was associated with a stronger motivation to engage in behaviours that reduce risk, such as changes in medications or vitamin intake, even if their effectiveness is still unclear (Chao *et al*, 2008). Genotype disclosure did not result in short-term psychological problems, despite the frightening nature of the disease and the lack of therapies for it (Green *et al*, 2009). These studies highlight the importance of education and counselling in understanding risk and evaluating the means of counteracting it.

Yet the ease with which DCGT companies offer tests over the Internet creates a new kind of autonomy for patients. “Genetic information serves often as a key to future decisions. Based on the information, they may rearrange the priorities in their life or change their lifestyle in order to fight against the manifestation of the disease, to decrease its symptoms or simply delay its progress,” Sándor said. “For many people, nothing else is worse than the lack of certainty and thus knowledge, in itself, can be a value.”

To know or not to know: that is the question—particularly for neurodegenerative diseases. In addition to the opinions of the experts at the meeting, the public round table, ‘Health and DNA: my life, my genes’, showed that the choice whether to take a test should be a personal decision; certainly nobody should be forced in one direction or another. During the discussion, different opinions and experiences regarding the use of genetic testing were presented by members of the panel and the public. Verena Schmocker, a Swiss woman affected by Parkinson disease, explained why she refused to be tested, despite a strong family history of early-onset Parkinson disease. “I knew already that the disease was in my family, but I didn’t want to take any genetic test. I chose to live my life day by day and live what is there for me to live.” Another woman in the audience explained that she wanted to know her destiny: “[w]hen 15 years ago I was diagnosed with Huntington’s disease I woke

up from a nightmare of doubts. I started organizing my life, I got married and got prepared for the future.”

In many ways, Huntington disease is an unrepresentative example—not only because it is an untreatable, debilitating Mendelian disease, but also because patients typically receive mandatory and sophisticated patient counselling. Most importantly, as Marina Frontali from the National Research Council (Rome, Italy) highlighted, counselling should enable and respect autonomous decisions by the person at risk, even in light of third-party pressure to take the test, not just by employers or insurance companies, but also by family members. The counselling service for Huntington disease—through a tight collaboration between laypeople and professionals—is a valuable example of the management of genetic testing.

...the ease with which DCGT companies offer tests over the Internet creates a new kind of autonomy for patients

The Eurobarometer 2005 survey showed that EU citizens are generally supportive of the use of genetic data for diagnosis and research, and 64% of the respondents said that they would take a genetic test to detect potential diseases (EC, 2006). In reality, however, attitudes vary between countries: in most cases, people would be willing to take a test only in exceptional circumstances or only if it was highly regulated and controlled. Interestingly, those countries in which people expressed more concern and negative attitudes towards testing were those with higher levels of education and scientific literacy, where the mass media is more attentive to science and technology and where the public and political debate is more advanced. It shows, again, that increasing scientific literacy is not enough to overcome people’s fears and objections to genetic testing; the more they understand the issues, the less likely people are to be enthusiastic about new technologies.

These concerns notwithstanding, the number of tests that are available is growing, and genetic testing—whether as part of the healthcare system or through DCGT companies—is becoming a model for preventive medicine and discussions about the impact of genetics on public health (Brand *et al*, 2008). The advances

brought about by genomics will lead to more targeted health promotion messages and disease prevention programmes specifically directed at susceptible individuals and families, or at subgroups of the population, based on their genomic risk profile.

The controversial nature of the political discourse concerning science and health often raises controversy, and the integration of genomics into public healthcare, research and policy might therefore be challenging. According to Brand *et al* (2008), the question is not whether the use of genomics in public health is dangerous, but whether excluding genomic information from public health interventions and withholding the potential of evidence-based prevention might do more harm. The next decade will provide a window of opportunity in which to prepare and educate clinicians, public health professionals, policy-makers and the public for the integration of genomics into healthcare. Brand *et al* (2008) argue that there is an ethical obligation to meet this challenge and make the best use of the opportunities provided by scientific progress.

This, inevitably, requires a legal and regulatory framework to ensure that the benefits are made widely available to the population and, in particular, to protect consumers—today, DCGT by private companies remains a largely unregulated market. In 2008, the Committee of Ministers of the 47 Member States of the Council of Europe adopted the first international legally binding document concerning genetic testing for health purposes (Lwoff, 2009). The Additional Protocol to The Convention on Human Rights and Biomedicine about Genetic Testing for Health Purposes addresses some of the issues raised by genetic testing, from quality and clinical utility, to public information and genetic screening programmes for health purposes (Council of Europe, 2008). According to the Protocol, a health-screening programme that uses genetic tests can only be implemented if approved by the competent body, after independent evaluation of its ethical acceptability and fulfilment of specific conditions. These include the health relevance, scientific validity and effectiveness, availability of appropriate preventive or treatment measures, equitable access to the programme and availability of adequate measures to inform the population about the existence, purpose and accessibility of the screening programme, as well as the voluntary nature of participation in it.

Two particular issues were discussed during the development of the Protocol: direct access to tests by individuals; and information and genetic counselling (Lwoff, 2009). The Protocol includes some debated restrictions to DCGT (Borry, 2008), to guarantee the proper interpretation of predictive test results and appropriate counselling to understand their implications. According to Article 7, with few exceptions “[a] genetic test for health purposes may only be performed under individualized medical supervision.” In order to assure quality of information and support for the patient, Article 8 states that “the person concerned shall be provided with prior appropriate information in particular on the purpose and the nature of the test, as well as the implications of its results.” Moreover, for tests for monogenic diseases, tests that aim to detect a genetic predisposition or genetic susceptibility to a disease, or tests to identify the subject as a healthy carrier of a gene responsible for a disease, appropriate genetic counselling should be available. It states that “the form and extent of this genetic counselling shall be defined according to the implications of the results of the test and their significance for the person or the members of his or her family, including possible implications concerning procreation choices.” According to this document, genetic counselling could thus go from being a “very heavy and long” procedure to a “lighter” one, but should be guaranteed in any case. The Protocol has already influenced legislation, but it will apply only in countries that have ratified it, which, so far, is only Slovenia.

Companies that offer DCGTs are harbingers of change for personalized medicine. Their increasing popularity—owing not least to the ease with which their services can be obtained over the Internet—shows that the public is willing to pay for this kind of personal information. Nevertheless, healthcare systems and regulators must ensure that developments in this area benefit patients. Experience from genetic testing for neurological diseases—given their particularly severe impact on patients and their families—highlights both the current lack of proper regulation and oversight, as well as the potential health benefits that can be reaped from genetic tests.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

- Avramopoulos D (2009) Genetics of Alzheimer's disease: recent advances. *Genome Med* **1**: 34
- Borry P (2008) Europe to ban direct-to-consumer genetic tests? *Nat Biotechnol* **26**: 736
- Brand A, Brand H, Schulte in den Bäumen T (2008) The impact of genetics and genomics on public health. *Eur J Hum Genet* **16**: 5–13
- Chao S, Roberts JS, Marteau TM, Silliman R, Cupples LA, Green RC (2008) Health behavior changes after genetic risk assessment for Alzheimer disease: The REVEAL Study. *Alzheimer Dis Assoc Disord* **22**: 94–97
- Council of Europe (2008) *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes*. Strasbourg, France: Council of Europe. <http://conventions.coe.int/treaty/EN/Treaties/Html/203.htm>
- EC (2006) *Europeans and Biotechnology in 2005: Patterns and Trends*. Brussels, Belgium: European Commission. http://ec.europa.eu/public_opinion/archives/ebs/ebs_244b_en.pdf
- Gooding HC, Linnenbringer EL, Burack J, Roberts JS, Green RC, Biesecker BB (2006) Genetic susceptibility testing for Alzheimer disease: motivation to obtain information and control as precursors to coping with increased risk. *Patient Educ Couns* **64**: 259–267
- Green RC *et al* (2009) Disclosure of APOE genotype for risk of Alzheimer's disease. *N Engl J Med* **361**: 245–254
- Klein C, Schlossmacher MG (2006) The genetics of Parkinson disease: implications for neurological care. *Nat Clin Pract Neurol* **2**: 136–146
- Lwoff L (2009) Council of Europe adopts protocol on genetic testing for health purposes. *Eur J Hum Genet* **17**: 1374–1377
- Myers RH (2004) Huntington's disease genetics. *NeuroRx* **1**: 255–262
- Ng PC, Murray SS, Levy S, Venter JC (2009) An agenda for personalized medicine. *Nature* **461**: 724–726
- Pollack A (2010) FDA Faults Companies on Unapproved Genetic Tests. *The New York Times*, June 11
- STOA (2008) *Science and Technology Options Assessment: Direct to Consumer Genetic Testing*. Brussels, Belgium: European Parliament

Donato Ramani [left] and Chiara Saviane are at the Interdisciplinary Laboratory for Advanced Studies, SISSA, Via Bonomea 265, 34136 Trieste, Italy.

E-mails: ramani@sissa.it; saviane@sissa.it

Received 30 June 2010; accepted 18 October 2010; published online 19 November 2010

EMBO reports (2010) **11**, 910–913.
doi:10.1038/embo.2010.177