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Personal genomic testing

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Traditionally, genetic tests have been firmly placed within a clinical context — clinicians order tests to gather information to help or confirm diagnosis of a condition in a person who is showing symptoms, to predict whether a person with a family history will develop a late-onset condition when the test results can be accurately interpreted (e.g. Huntington disease), or to identify carriers of recessive conditions in a family (e.g. cystic fibrosis).

Gene testing is also used to screen populations where there is no known family history — for example, newborn screening for a few conditions to enable early identification and treatment, and carrier status for a limited number of recessive conditions to allow reproductive options in couples either planning a pregnancy or during pregnancy. These tests have focused on specific individual genes, and typically a restricted number of variants (or mutations) that are well known to be disease-causing (i.e. these are variants that have high 'penetrance', meaning that a person who has the variant/s has a very high chance of developing the disease).

Clinicians, often clinical geneticists or genetic counsellors, discuss the meaning of the results with the person to help them understand the clinical relevance and to support them in any decision making that might be required around treatment, management, or prevention, including reproductive choices.

What is personal genomics?

Increasingly, as genetic technologies have progressed, tests can now examine many thousands of variants (single nucleotide polymorphisms or SNPs) scattered across a person's complete set of genetic information (genome); this test is sometimes called a 'genome scan' or 'SNP genotyping'. More recently, tests are available that sequence a person's entire genome using next-generation sequencing technologies, which are now being introduced clinically, as described by Stark and North in this book (Chapter 9). 'Next generation genomics' has been described as one of the top 12 'disruptive technologies', together with the mobile internet and use of social media, that will 'transform life, business and the global economy' (Manyika et al., 2013).

A critical aspect of these new genomic technologies is that they have reduced the cost of testing dramatically and have provided the opportunity to challenge the traditional paradigm of genetic testing: healthy individuals can now access testing through the internet, either ordered directly by themselves (so-called 'direct-to-consumer' or 'at-home'), or else through a health practitioner, depending upon the type of test and the circumstances. Overall, this kind of testing is also referred to as 'personal genomics' (PG) or 'consumer genomics'. Private companies offering these tests advertise directly to the consumer via the internet; for example, the customer provides their saliva or cheek swab sample at their convenience and mails it back to the company, and costs of the test are borne by the customer. Results are provided by the company to the consumer with or without some form of interpretation as to the meaning of the results. Some companies require that the tests are ordered and/or the results are provided by a health practitioner, while others provide it to the consumer directly.

PG testing can provide information ranging from the quite banal (e.g. physical traits such as eye colour, the ability to taste bitter flavours, type of ear wax and alcohol flush reaction) to that which might be considered useful in ancestry tracking and genetic relationship testing, and even romantic compatibility with a partner, by supposedly matching people by analysing their DNA.

Some PG tests offer information that has health-related implications. These include tests that are conventionally offered in clinical settings, such as genetic variants that are strong predictors of risk for disease (highly penetrant, such as certain variants in the *BRCA1* gene involved in inherited breast cancers), others that have moderate risk prediction (such as the *APOE4* variant for Alzheimer disease, not typically used clinically without a strong family history), and carrier status for a wide range of recessive conditions, which may comprise additional variants that are increasingly being offered in clinical practice. Some tests are also available for variants that can inform response to drugs and medication (pharmacogenomics), although how many of these would actually alter drug prescribing is still being debated.

However, some PG testing companies include variants they claim provide other health-related information of a nature that is typically more uncertain and probabilistic, usually because the variants have low penetrance and the genetic contribution to the trait from each individual variant is quite small, the strength of evidence for association is less clear (and often contradictory) and environmental factors play a significant role. These tests might comprise: genetic variants that are much more weakly associated with susceptibility to disease (for so-called common complex conditions, e.g. type 2 diabetes and rheumatoid arthritis); information from genetic variants that are marketed to

predict sporting ability, including fitness and response to training regimens; genetic variants purported to provide information about response to diet, nutrition and weight loss, under the umbrella of nutritional genomics (e.g. the *MTHFR* gene, which encodes an enzyme involved in folate metabolism); and even variants that supposedly inform the person about how to manage their skin care, work out which career they should have and so on.

Estimates of risk for genetic predisposition to the characteristic or trait or disease being tested may be reported to the individual in different ways, often in terms of an odds ratio or a percentage, compared with the average risk in a reference population, or as lifetime risk. Notably, different companies may use different reference populations, research study findings and algorithms in their estimates of risk, such that a result from one company (even for the same DNA sample) may not be the same as that from another company (Kalf et al., 2014). The language used can be quite technical, although over the years more visual representations are being used to help a person to understand their risk level.

PG testing has been controversial among scientists and health professionals, bioethicists and governments, given the marketing rhetoric used and the variability in the range of claims and evidence used by the companies. This can make it very difficult for the consumer to decide on the true value and credibility of the tests. So, in the context of PG testing, should the 'buyer beware'?

Personal genomic testing: a shifting arena

Some companies began offering PG tests in the early to mid 2000s, and a few offering nutritional genetic testing for a limited number of genes came under the scrutiny of the US Government Accountability Office in 2005. The Office ordered

tests from websites from four companies by sending saliva samples taken from two independent people (male and female), but submitted these by creating 14 different fictitious people, answering lifestyle questionnaires and varying the gender, ages, weight and information on exercise, smoking, vitamin consumption, and intake of a variety of foods. The website questionnaires did not ask for information about medical conditions or prescribed medications being taken, and the websites stated they would not test for disease or predisposition to disease.

The report from the Office specified that the results came back with misleading recommendations of health-related predictions (for diseases such as type 2 diabetes, osteoporosis, heart disease and cancer) that were medically unproven and ambiguous in language (US Government Accountability Office, 2006). Two of the websites also recommended expensive 'personalised' dietary supplements they could sell to the (pretend) consumers. These products, from one company, were available to buy for US$1200 per year, and were essentially identical in ingredients, with multivitamins that could be store-bought for U$35 per year. Furthermore, these 'personalised' supplements were exactly the same for three fictitious consumers (from two different DNA donors with different lifestyle profiles), even though they were meant to be based on the unique genetic profile of each person. In fact, the recommendations from the different companies were more related to the fictitious lifestyles, based on 'common sense health and dietary guidance', rather than the DNA profiles.

Despite these concerns, it was around 2007 when three major companies launched their genetic testing services through their websites directly to the consumer that personal genomics really hit the global marketplace. Those three were

deCODEme (a subsidiary of deCODE genetics based in Iceland) and two US-based companies: Navigenics Inc and, probably the most well-known, 23andMe. Indeed, 23andMe's 'Retail DNA Test' was picked by *Time Magazine* as their top invention of the year in 2008. The rise of these companies, and others, was predicated on an increasing awareness of the internet by consumers and also on the notions of consumer autonomy and empowerment, allowing healthy individuals to have access to genetic testing beyond the clinic at 'affordable' prices.

Costs of the 'genome scan' tests varied at that time, with Navigenics charging US$2500 compared with just under US$1000 offered by deCODEme and 23andMe; tests also included information about health and could be ordered directly by the consumer without the involvement of a healthcare provider. Over time, the number of companies increased as did the number of traits and diseases being tested, while costs decreased substantially (e.g. in 2013, 23andMe were charging US$99 at their cheapest, and others ranged from this price to several hundred dollars, depending on the test), in keeping with the rapid advances of scientific knowledge and genetic technologies.

This burgeoning industry hit a partial roadblock in 2010 as a result of the US Food and Drug Administration (FDA) notifying companies that these direct-to-consumer health tests, if sold as kits, were considered 'medical devices' that required regulatory approval prior to marketing. This followed on from an announcement by Pathway Genomics stating that it had partnered with a US-based pharmacy chain to sell its kits through the pharmacies — which ultimately did not go ahead. Subsequently, some companies responded to FDA pressure and changed their practice to require a health practitioner to order the test, and also offered post-test genetic counselling (includ-

ing Navigenics and Pathway Genomics), while others, such as 23andMe, continued business as before.

Then, in November 2013, the FDA ordered 23andMe to stop marketing their health-related genetic tests because, without health professionals to help consumers understand their result, there were concerns that people might undertake unnecessary health procedures and the tests were deemed to require pre-market approval (Public Health Service Food and Drug Administration, 2013). The company continued to market their ancestry testing only, while some companies, often set up in different countries, were still advertising and selling their health-related tests directly to consumers. In 2014, 23andMe were able to market their ancestry and health-related tests in other countries (notably Canada and the United Kingdom) and more recently (April 2017), having worked closely with the FDA, are once again selling their health-related tests (albeit a more limited range) in the United States using a direct-to-consumer model.

In the meantime, the number of online websites and their suite of offerings is in a constant state of flux. Some companies, including Navigenics and deCODEme, were bought out by research and development/biotechnology companies and testing was discontinued; others simply disappeared, while yet others have evolved in terms of the types of tests on offer, with or without the involvement of a health practitioner. For example, in 2016, one company (Easy DNA) was advertising a DNA test for children that claimed to give parents information about their child's genetic predisposition to certain physical and behavioural traits, and cognitive skills to maximise 'parenting skills'. The following year, this test no longer appeared on their website. The rise and fall of companies and tests is fairly typical in this space, but whether this is because of financial

market fluctuations or the changing regulatory landscape is not clear.

Nutritional genomics is an area that straddles health and lifestyle and continues to be a major area in the online testing marketplace. In particular, in Australia, these tests are being advertised as 'genomic wellness' tests and are increasingly available through complementary and alternative health practitioners, including naturopaths and nutritionists; in some instances, these practitioners are required to undergo registration (and training) with the testing company to order the test and provide interpretation of the results.

We are seeing an ever-expanding level of global advertising for ancestry testing. This is linked, of course, to an interest in familial genealogy and, more broadly, in tracking one's roots ethnically and geographically. In Australia and elsewhere, ancestry DNA testing or genetic genealogy has been strongly promoted on television, often linked to documentaries or celebrity shows. Some services also match an individual consumer's DNA with DNA submitted by other consumers, to allow people to share their DNA information to find potential relatives.

Although PG tests may be marketed for one purpose, with interpretation of the SNP data for that purpose provided by the company to the consumer, the test may in fact include a larger number of SNPs/variants ('raw data') that are not interpreted by the company. Interestingly, in some circumstances consumers are able to download their 'raw data' from the company's website. For example, an 'ancestry' test might also include SNPs with health-related associations but interpretation of this information is not provided. A savvy consumer can now use online databases or software to do further analysis of the raw data, not only for more genealogical information but

also for health information. In this way, even though a test might be marketed just for ancestry, a consumer could find out additional information unrelated to the original purpose of the test. Furthermore, some genetic testing companies offer this interpretation as another fee-for-service, using an individual's raw data that was provided by a different company.

The debate around personal genomic testing

The potential benefits and harms from PG testing have raised concerns that underpin its controversy, particularly for direct-to-consumer health-related testing without the involvement of a health practitioner. Clearly, the credibility of some PG tests, in terms of the rhetoric used in promoting these compared with the limitations of a test's ability to predict outcomes (known as clinical validity when referring to disease outcomes), is disquieting. This criticism contributed to the push-back by the FDA and regulatory bodies in some other countries to require health practitioners be involved in the ordering and/or interpreting of these health-related tests.

Some companies may make recommendations to use specific practitioners who could order the test on behalf of the consumer, or themselves provide genetic counsellors who can discuss the results with the consumer. Increasingly, others state that the reports are provided for 'information or educational purposes only', with disclaimers that the consumer should discuss the results with a doctor or other health practitioner. However, practitioners themselves may have limited understanding of the nature of the test or its interpretation. Typically, these practitioners are general practitioners (GPs), perhaps other medical practitioners, or increasingly naturopaths and nutritionists, but less often genetic specialists, who themselves may be uncertain about the clinical validity of the results (Brett et al.,

2016). So, including health practitioners in the process, either ordering tests and/or interpreting, may be a two-edged sword, in that the consequences are a need for education to upskill practitioners around PG testing, and also the potential to overburden the healthcare system, which is particularly worrying when this is publically funded with limited resources (Goldsmith et al., 2017).

Those in favour of PG testing consider that knowledge gained from the information is empowering to the consumer who may then be able to act proactively to manage their health armed with that type of knowledge. A health test result that can be acted upon (in an informed way) is known as clinical utility. However, there have been concerns expressed that, given the poor clinical validity of many of the PG tests, some consumers may act inappropriately based on their genetic information. Some may place too much confidence in the meaning of the result and believe that their genetic make-up means they will either certainly develop or not develop a disease — a concept known as genetic determinism or fatalism. So, in some circumstances, people may believe it is not worth changing their lifestyle or not undergo relevant health screening, because they believe it won't make a difference — their genes are responsible and they can't be changed. Alternatively, others may undertake further testing or treatments that are not necessary (e.g. having unnecessary preventive surgery). Inappropriate action or inaction can be costly, not only to the individual's health but also add to the potential burden on the healthcare system.

The notion of making an 'informed decision' is at the crux of the ethical issues associated with PG testing. However, this could be addressed, although not necessarily fully resolved, in a number of ways: if clinical validity were to improve (through research to get a better understanding of the contributions of

genetic variants and environment to disease); if companies were held more accountable for their marketing hype and claims regarding their tests; and if consumers were to be better supported both before and after the test. Studies from a range of countries have shown that while the level of awareness of genetics and genetic testing in the public is generally high, how much people understand genetic terminology and testing procedures is often much lower, and it is a matter of debate how much people need to know and understand genetic information to be able to make an informed decision.

Other areas of concern relate to privacy and confidentiality of the information. There are clearly flow-on effects for other family members who may or may not want to know genetic information, and these can have serious implications. These can be relevant to ancestry testing, not just health-related information, since data from ancestry DNA testing can reveal issues of non-paternity or other genetic relationships unknown within families, that might have surprising and potentially negative consequences (Doe, 2014). On the other hand, there can be positive aspects for people who are adopted and seeking genetic relatives, and for families in general, when the outcomes are favourable for all parties.

There is also the potential that people might be tested without their consent. For example, a sample could be used for the predictive genetic testing of children that can reveal predisposition to ill health in the future, which is generally not recommended by genetic professional societies. Companies that perform relationship testing certainly practise in the direct-to-consumer space. Samples could be obtained without a person's consent for the purposes of paternity testing or even 'infidelity'/'discreet' testing (e.g. hair with roots, or semen stain on fabric), although the terms and conditions on these compa-

nies' websites will state that genetic results obtained in this way would not be admissible in a court of law without verification of the source of the material and the chain of custody.

The possibility of misuse of genetic information, with potential for discrimination, has been debated for many years. Concerns around negative impact on health and life insurance, or employment, have led to ways in which a variety of regulations have been established in different countries to manage, and ideally minimise, this. For example, the United Kingdom established a moratorium on the use of genetic test information by insurance companies in 2001, which is still in effect. In 2008, the *Genetic Information Non-discrimination Act* (GINA) was passed in the United States, which forbids the use of genetic information in health insurance and employment, but it can still be used in life and disability insurance. In Australia, health insurance is community rated and so is not influenced by family history or genetic test results. If a genetic test is taken after a life insurance policy is bought, the consumer does not need to disclose the information; however, results must be disclosed to life insurance companies if the test was performed prior to taking out or upgrading a policy. In this case, the *Disability Discrimination Act* is intended to ensure that premiums set by life insurance companies based on this information are reasonable and defensible, but this may be open to interpretation with potential for misuse.

The sharing of all types of personal information on the internet and especially on social media has been rapidly expanding, allowing intentional or unintentional access by others. PG testing companies may have terms and conditions that state how a consumer's genetic data are protected or how they might be shared with a third party — for example, for research, including for commercial purposes. If sharing with a third party

occurs, it is typically (although not always) done with specific consent, but not all websites display this information, while others have such lengthy terms and conditions that consumers may simply not read these. Furthermore, if a company changes ownership, then so do the data. Of course, consumers may choose to share their own genetic information or data themselves.

What are people doing with their genetic information?

Studies carried out so far indicate that, despite many of the concerns mentioned above, in fact there seem to be fewer harms than expected to people who have had PG tests. These studies were mostly from the United States, with early adopters of PG testing for health, including scientists, often taking the tests out of curiosity or because they may be more proactive in their health behaviours. While many people in these studies said they intended to change their lifestyle, overall fewer than 25% of people reported actually changing their health behaviours as a consequence; levels of worry and anxiety after receiving test results were generally low (Covolo et al., 2015). About a third of people shared their results with a health practitioner, which often did lead to health screening or follow-up tests, and in some cases this was useful and in others not. In another study, almost 40% said they had not thought about the possibility of receiving unwanted information.

Even though it would seem the clinical utility of the tests that people had was not high, the notion of personal utility seems more relevant for many people who undertake PG testing. Personal utility can be thought of as outcomes in terms of valuing increased knowledge about oneself (reflecting curiosity as a motivation for testing), increased knowledge about the trait or condition tested, anticipated coping, and altruism (e.g. helping research as a motivation for testing). Recreational tests

such as ancestry DNA testing could therefore have personal utility rather than clinical utility, and would be relevant to people undertaking ancestry DNA testing, especially in the genealogical world. Certainly, testimonials on PG testing websites suggest that many people are satisfied with their experiences, although this would be expected since these are promoted by the companies; conversely, there are anecdotes of both positive and negative experiences on social networks.

Many people who have had ancestry DNA testing have not only shared this information with their relatives, but also online with others through genealogical websites and social media. People who have participated in PG testing for a variety of purposes have also shared their information via crowdsourced online platforms that are not-for-profit, such as DNA.Land, OpenSNP and PatientsLikeMe. The data are used to help scientific research, and may or may not be anonymised; however, it should be noted that there are methods to re-identify supposedly de-identified information, and very little personal information is needed to link genomic data to specific individuals (Gymrek et al., 2013).

In Australia, there has only been a small amount of research around PG testing, since marketing has been fairly limited until recently. However, there has been increasing media awareness of PG testing, and advertising for ancestry DNA testing and 'genomic wellness' is growing. As part of a study known as GeNIOZ (Genomics: National Insights of Australians — www.genioz.net.au), Australians are being asked what they think about PG testing and whether they have had any experiences with this. This study is ongoing and the findings will help support the public to make informed decisions and inform policy makers, through identifying educational, communication and public engagement strategies.

Should the buyer beware?

As with any online shopping, consumers should be aware of exactly what they are buying, consider value for money, the terms and conditions listed on the website and their rights as consumers — and there should be no false advertising. Online PG testing is no different, but additionally there are implications that may be more far-reaching. Unlike buying a pair of shoes that don't fit and can be returned to the retailer, once genetic information is known, it cannot be unknown and simply returned to the company.

One thing is for sure, PG testing is here to stay. As of April 2017, 23andMe have more than 2 million paying genotyped customers, and AncestryDNA reached 4 million customers, with that number rising from 3 million in the previous three months. Potential consumers of PG testing should consider all aspects when they are thinking about having one of these tests. As with any shopping (online or otherwise), the old adage still applies — *caveat emptor* — let the buyer beware!

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