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Direct-to-consumer DNA genetic testing and the GP

Background

From early 2000 a new form of DNA genetic testing became available commercially. It bypasses the medical practitioner and can be ordered directly by the individual.

Objective

To understand direct-to-consumer (DTC) DNA genetic testing and be able to respond appropriately if asked to be involved by a patient.

Discussion

Presently, all but one or two DTC DNA genetic testing laboratories are located outside Australia. The industry promotes itself as a means to better health through giving individuals complete control over their results. When communicating with patients about DTC DNA genetic testing, general practitioners will need to make a determination about the clinical utility of the test and the laboratory validity, both of which can be difficult in the current environment. Assistance may be available through public hospital clinical genetics services, although waiting times can be long. There is likely to be tighter regulation of these types of testing in the future, which may include involvement of medical practitioners.

Keywords

genetic testing; human



Direct-to-consumer (DTC) DNA genetic testing for medical purposes involves the sale of these tests to the public without the involvement of a medical practitioner. It provides an internet-based model for delivering genetic medicine and is feasible because DNA can be transported by post. Presently, all but one or two DTC DNA genetic testing laboratories are located outside Australia, predominantly in the USA. In these circumstances Australian consumer protection laws do not apply and court proceedings, should problems arise, would be based overseas. There are advocates for this type of service delivery but the industry has also been criticised because there is little scientific evidence that the product sold (medical DNA genetic tests covering a range of medical disorders to normal traits) can deliver on the many broad promises for better health (Table 1). Nevertheless, this model is unlikely to go away and the general practitioner (GP) might, at some time, have a patient requesting this service or presenting with results from DTC DNA genetic testing. For the purpose of this article, DNA genetic testing does not include genealogy testing or genetic tests that influence diet and nutrition (nutrigenetics).

The road to DTC DNA genetic testing

DNA genetic testing has been available since the mid-1970s and medical practitioners can order these tests for different clinical purposes including:

- confirming a diagnosis
- screening family members at risk for a genetic disorder
- predicting that someone will develop a genetic disorder in the future
- prenatal genetic diagnosis.

Most of these tests are not funded by Medicare and so are provided predominantly through public hospital laboratories in Australia.

From early 2000 a new form of DNA genetic testing became available commercially. It bypasses the medical practitioner and can



be ordered directly by individuals.¹ The industry promotes itself as a means to better health through giving individuals complete control over their results. While the marketing makes these tests sound good, it does not present the complete picture (*Table 1*).

The DTC DNA genetic testing industry has been subject to oversight from various bodies. One of two critical reports from the US Government Accountability Office stated '10 of the 15 companies we investigated engaged in some form of fraudulent, deceptive or otherwise questionable marketing practices'.² There was further adverse publicity in 2010 when the US-based company 23andMe had to apologise for 96 incorrect results because DNA samples had been inserted in the wrong orientation when tested. This incident also showed that 23andMe was not actually doing the test but referring DNA samples to another laboratory.

Examples of some tests offered DTC and comments on how useful these might or might not be in clinical practice are shown in *Table 2*. The DTC DNA testing industry has tried to avoid the regulatory barriers by claiming its product is information rather than a test for medical decision-making. Nevertheless, this disclaimer tends to be lost in the glossy advertising material presented on many of the companies' websites.

About 12 months ago 23andMe was offering a wide range of DNA genetic tests covering around 116 medical conditions and traits including type 2 diabetes (T2D), arthritis, cancer (breast, prostate and colon), heart and bone diseases, Parkinson's disease, Crohn's and coeliac diseases and restless leg syndrome – all for a special price of \$99 (USD). Currently it is selling only genealogy DNA genetic tests until

it has responded to a number of concerns from the US Food and Drug Administration (FDA).³

Variations on the theme

The DTC DNA genetic testing industry has evolved rapidly in the past decade with a recent change being the re-establishment of links with the medical profession by:

- Asking customers to get their medical practitioners to order the tests. One Australian company (now defunct) would provide customers with the name of their closest GP who could order their tests if the customer did not have a GP or the customer's GP was unwilling to order the test. In this circumstance tests are no longer DTC, although advertising through an unregulated internet remains DTC.
- Forming partnerships with DTC genetics counselling services accessible by phone or through the internet, in response to criticism that consumers have no support or counselling. These services are located overseas so there are difficulties with quality assurance and access to legal redress should problems arise.

Industry oversight

The health regulators have been slow to act, so it was with some surprise that late in 2013 the FDA closed down the medical DTC DNA genetic testing service for 23andMe until it could be assured its concerns were addressed.⁴ Other companies soon received 'please-explain' letters from the FDA requesting more information about their 'products' and their relevance to health. The Australian regulator, the

Table 1. Some advantages and disadvantages of DTC DNA genetic testing¹¹

Advantages	Author's comments
Empowers people and gives them greater control in improving the quality of their lives.	Important goals that are relevant to all aspects of medicine – genetics is no different.
Allows: <ul style="list-style-type: none"> • rapid diagnosis of disorders when public or other private healthcare resources are in short supply • earlier intervention. Alerts relatives to important genetic conditions of which they may be aware.	Correct but only if it can be proven that the results from these DTC DNA genetic tests are clinically meaningful and so lead to appropriate interventions.
Disadvantages	Author's comments
Customers' lack of preparation for results and what to do about them without individualised medical supervision and genetics counselling.	Some companies are attempting to bypass this criticism by offering DTC genetic counselling services, most of which are located offshore, as with the laboratory component of the DNA test.
Access to tests requires pre-payment, which might result in social inequity. Scarce public health resources may be used in unnecessary follow up.	
Relatives may find themselves alerted to health risks of which they would have preferred to have no knowledge.	
The information itself may be of little real use or induce anxiety. Alternatively, the results may give the customer a false sense of security.	



Therapeutic Goods Administration (TGA) has a new set of regulations for medical DNA genetic testing but it remains unclear how these might impact on DTC testing conducted in Australia.⁵ Similarly, Australia's National Pathology Accreditation Advisory Committee (NPAAC) has published guiding principles on how DTC DNA testing companies in Australia should operate but these principles cannot be enforced onto overseas-based laboratories.⁶

Presently, the medical DTC DNA testing industry is at a crossroads, depending on how it deals with the FDA. Whatever the outcome, additional information sought by the FDA, particularly that related to clinical utility of tests being sold, will improve transparency. If the

FDA is not satisfied, the companies may move to involve medical practitioners. This is likely to be a positive outcome, but only if the practitioners are sufficiently qualified to manage the nuances of DNA genetic testing and, in particular, interpretation of the results.

How might DTC DNA genetic testing impact on the GP?

There are two likely scenarios in which a GP would need to engage on the topic of DTC DNA genetic testing.

1. Patients may enquire about DTC DNA testing or request a test because of feedback from a family member and/or information

Table 2. Examples of DTC DNA genetic testing

Testing for	Comment
Sickle cell defect (HbS)	DNA genetic test that detects one mutation so the reporting format is straightforward and easy to understand.
Breast cancer gene test	Gene testing of the <i>BRCA1</i> and <i>BRCA2</i> genes is used to assess risk by looking for mutations in these genes. Unlike the HbS test, there are hundreds of different mutations that might influence risk. Therefore, understanding and interpreting a result from this type of genetic testing needs considerable expertise and the reporting format is correspondingly more complex.
Type 2 diabetes (T2D)	This test relies on DNA genetic markers called polymorphisms (single nucleotide polymorphism or SNPs). It does not look for gene mutations but measures risk (relative or absolute risk) that is derived from population research studies comparing the frequency of a SNP between normal and T2D populations. The SNP DNA markers used are not the causative genes for T2D and do not take into consideration the environmental factors in the causation of T2D. Although a risk can be measured, it has limited meaning to the individual.
Pharmacogenetic test	The purpose of these tests is to guide medical interventions such as selecting a particular drug or tailoring the dose to the individual's genetic ability to metabolise or activate the drug. Two challenges in pharmacogenetics DNA testing are: <ul style="list-style-type: none"> • Does the test alter decision-making? Two recent large clinical trials assessing pharmacogenetics testing prior to warfarin treatment gave the exact opposite conclusions.^{12,13} Despite this, DTC DNA testing companies provide warfarin genetic testing. • How can the DNA genetic test result be translated into an actual clinical decision for drug selection or dosing? As yet there are few examples of software programs that can help here although there is progress with warfarin but even this is work in progress.¹⁴

Table 3. Ways in which DNA genetic test results are provided

Some changes in the DNA nucleotide sequence will lead to gene dysfunction. These are now called pathogenic variants but historically are known as mutations. Interpreting a DNA genetic test result that looks for a mutation is relatively easy (ie. it is either there or not). An example of this is HbS (sickle cell defect). One mutation causes HbS and it can be detected by blood analysis or a DNA test. Complexity in the interpretation of DNA genetic test results starts to emerge when different mutations, or even mutations in different genes, can produce the same clinical problem (phenotype). For example, there are >1,000 mutations in the *CFTR* gene that cause cystic fibrosis. So finding a known mutation is helpful but not finding a mutation might exclude cystic fibrosis or it might mean the patient has another rare and as yet undescribed mutation.

The next level of complexity involves mutation detection for the complex genetic disorders such as sporadic cancers, common forms of diabetes or dementia. In these cases there are no single or even combinations of mutations known to cause these disorders. In terms of genetic DNA testing all that can be done is to use DNA markers called polymorphisms to measure risk – either absolute or relative risk. Determining this type of risk is possible mathematically but as risks have been derived from population studies, the relevance of a risk to the individual is unknown. In addition, the complex genetic disorders have various environmental contributors to pathogenesis and these are not considered in the DNA genetic test. So a DTC DNA genetic test might show a relative risk of 1.5 with a corresponding absolute risk of 15%.¹⁵ These risks might have some value in a population research study but will have very little clinical meaning for an individual's health. The conventional medical DNA testing laboratory does not provide a service for detection of complex genetic disorders because of the uncertainty of the results as described above.



obtained from the internet or via the media. This is a demanding consultation because the GP will need to know about the clinical value of the test (ie. what is its clinical utility?). Additionally, a decision will need to be made about the accreditation status of the testing laboratory, which most likely will be located overseas (ie. is the laboratory any good at doing the test (laboratory validity) or getting the correct result for what is being claimed (clinical validity)?) Neither of these two questions will be easy to answer. In Australia, there is no mechanism available for medical practitioners to log into a central repository to check if a DNA test has been shown to have clinical utility. The only exception is the dozen or so tests that are funded through Medicare but this leaves about 500 other DNA tests yet to get this tick of approval. Assessing the accreditation status of a DNA testing laboratory located outside Australia is complex as each jurisdiction has its own way to assess and define competency.

2. Patients may present to the GP with results they have already obtained by DTC DNA testing and request an interpretation. As the GP did not order the test, it is likely the results, particularly the way they are presented, will be difficult to understand (*Table 3*).

What can the GP do?

Referral to a specialist is available through clinical genetics services, most of which are located in public hospitals.⁷ In Australia there are very few private clinical genetics services, so the waiting time in the hospital system can be long. It is interesting to note that in a recent survey of Australian genetics specialists, including genetics counsellors, only about 7% said they would be confident to interpret and explain these types of tests.⁸ The National Health and Medical Research Council (NHMRC) has published two brief but helpful pamphlets (one for patients and the other for medical practitioners). It would be useful to have printed copies available if needed.^{9,10} The Royal Australian College of General Practitioners could also provide some guidance, for example, through their educational resources.

If the regulatory environment continues to toughen, the move to include medical practitioners in the loop will increase. In this way, companies can continue to advertise DTC and make profits while the responsibility for ordering and interpreting reports shifts to the medical practitioner. It would be important, if this were to occur, for the relevant colleges or medical associations to develop policies on this new model of care.

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References

1. Genetics and Public Policy Center. GPCC releases updated list of DTC genetic testing companies. Available at www.dnapolicy.org/news.release.php?action=detail&pressrelease_id=145 [Accessed 26 May 2014].

2. United States Government Accountability Office. Direct-to-consumer genetic tests. 2010. Available at www.gao.gov/new.items/d10847t.pdf [Accessed 26 May 2014].
3. 23andMe. Find out what DNA says about you and your family. Available at www.23andme.com/ [Accessed 26 May 2014].
4. US Food and Drug Administration. Inspections, Compliance, Enforcement, and Criminal Investigations: 23andMe, Inc. 11/22/13. Available at www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm376296.htm [Accessed 26 May 2014].
5. MacKee N. Clampdown on DIY genetic tests. MJA InSight 2014. Available at www.mja.com.au/insight/2014/6/clampdown-diy-genetic-tests?0=ip_login_no_cache%3D1cdfb2a3ec059890b33054a59bd28ffc [Accessed 26 May 2014].
6. National Pathology Accreditation Advisory Council. The provision of direct-to-consumer genetic tests: guiding principles for providers 2014. Canberra: Commonwealth of Australia. Available at [www.health.gov.au/internet/main/publishing.nsf/Content/93C565034C1ABF5ECA257C8C001A56D3/\\$File/Final%20NPAAC%20Genetic%20DTC%20Guiding%20Principles%20-for%20printing-Feb%202014.pdf](http://www.health.gov.au/internet/main/publishing.nsf/Content/93C565034C1ABF5ECA257C8C001A56D3/$File/Final%20NPAAC%20Genetic%20DTC%20Guiding%20Principles%20-for%20printing-Feb%202014.pdf) [Accessed 26 May 2014].
7. NSW Government Health Centre for Genetics Education. Genetic Services. Available at www.genetics.edu.au/Genetics-Services [Accessed 26 May 2014].
8. Brett GR, Metcalfe SA, Amor DJ, Halliday J. An exploration of genetic health professionals' experience with direct-to-consumer genetic testing in their clinical practice. *Eur J Hum Genet* 2012;20:825–30.
9. National Health and Medical Research Council. Direct-to-consumer DNA genetic testing: an information resource for consumers. Available at www.nhmrc.gov.au/_files_nhmrc/publications/attachments/ps0004_dna_direct_to_consumer.pdf [Accessed 26 May 2014].
10. National Health and Medical Research Council. Direct-to-Consumer DNA Genetic Testing. Discussing direct-to-consumer genetic testing with patients – a short guide for health professionals. Canberra: Commonwealth of Australia; 2013. Available at www.nhmrc.gov.au/_files_nhmrc/publications/attachments/g7_direct_to_consumer_dna_testing_health_pro_140108.pdf [Accessed 26 May 2014].
11. European Academies Science Advisory Council. Direct-to-consumer genetic testing. Federation of European Academies of Medicine 2012. Available at www.easac.eu/fileadmin/PDF_s/reports_statements/Easac_12_DTCGT-Lay_Web.pdf [Accessed 26 May 2014].
12. Kimmel SE, French B, Kasner SE, et al. A pharmacogenetic versus a clinical algorithm for warfarin dosing. *N Engl J Med* 2013;369:2283–93.
13. Pirmohamad M, Burnside G, Eriksson N, et al. A randomized trial of genotype-guided dosing of warfarin. *N Engl J Med* 2013;369:2294–303.
14. WarfarinDosing. Available at www.warfarindosing.org/Source/Home.aspx [Accessed 26 May 2014].
15. Ng PC, Murray SS, Levy S, Venter JC. An agenda for personalized medicine. *Nature* 2009;461:724–26.