Genomics What it means for patients and GPs

LISA EWANS MB BS, BSc, FRACP MARY-ANNE YOUNG GradDipSocSci(FamTherapy), MHSc

Genomics is an important emerging field in medicine that will have increasing relevance in general practice. This article outlines the current utility of genomics and provides information to enable discussion about the application of genomics.

he Human Genome Project, completed in 2003, was a combined global effort to map the human genome as a reference source.¹ Tools developed during this project provided the catalyst for the subsequent significant advances in genomic technology to enable rapid and cheaper genome sequencing and improved interpretation of genomic data. The technology is often referred to as next generation sequencing (NGS) or massively parallel sequencing (MPS) and the term genomics refers to the use of this technology to sequence either the entire genome – whole genome sequencing (WGS) – or all the genes in the genome – whole exome sequencing (WES).

The advantage of genomic technologies over more traditional genetic testing modalities is that WES and WGS allow for a broader diagnostic search for the underlying genetic cause in an individual suspected or known to have a genetic disease. Over the past decade, genomic sequencing has gone from being a research-based tool to a testing option that is being used widely in clinical practice.²

MedicineToday 2018; 19(8): 26-32

Dr Ewans is a Clinical Geneticist at Royal Prince Alfred Hospital, Sydney; a Genome Analyst at Genome.One, Sydney; and a PhD student at UNSW Sydney and the Garvan Institute of Medical Research, Sydney.

Ms Young is the Head of Clinical Service Development at Genome.One, Sydney, NSW; and has more than 30 years clinical experience encompassing nursing, family therapy and genetic counselling. She is the immediate past President of the Human Genetics Society of Australasia.



Types of testing

Many different genetic tests are available and used in patient care for purposes ranging from diagnosis of rare genetic conditions to preconception carrier screening. Although Medicare rebates are available for some genetic tests (such as those for haemochromatosis and Fragile X syndrome), there is currently no Medicare rebate for many others, including genomic testing. The cost of the tests varies depending on which laboratory is offering the test and is largely determined by the technology used, the number of genes covered, the speed of the result and the country in which the laboratory is based. Patients seen through public clinical genetics services when offered testing usually have no out-of-pocket costs, which is an important consideration as some genetic test costs are high.

Single-gene and multi-gene panel tests

There is a wide range of genetic tests available, including single gene tests for conditions that have a single gene basis such as cystic fibrosis and tests for panels (groups) of genes known to be associated with specific genetic diseases or organ pathology that are genetically heterogeneous (i.e. could be caused by one of many genes). Laboratories are increasingly moving to gene panel testing via NGS to increase the number of genes tested and reduce costs. Gene panels commonly used include those for cardiac diseases such as cardiomyopathy, ocular disorders such as retinitis pigmentosa and neurological disorders such as epilepsy.

Whole exome and whole genome sequencing

The major difference between WES and WGS is that WES is designed to capture only the exome, the protein-coding portion



of the gene, and WGS produces data across the entire genome. Although the exome comprises less than 1.5% of the total genome, it carries most of the genetic variation known to cause disease (pathogenic variant).³ WGS produces data on noncoding regions that have recently been shown to have important roles such as gene expression;⁴ however, variation in these regions remains difficult to interpret for clinical use. Although a specific set of genes can be analysed from WES or WGS, often these technologies are used for a broad analysis of all known human disease genes and variation in these are linked to the patient's clinical features.

Although WGS is a more expensive test than WES, it provides higher diagnostic return than WES. This is partly because of more consistent sequencing coverage of genes, improved detection of copy number variation (where sections of the genome are duplicated or deleted)⁵ and sequencing of the mitochondrial genome.

Testing practicalities

GPs generally counsel patients and order some genetic tests such as for haemochromatosis. They may be increasingly involved in preconception carrier screening for couples planning a pregnancy with or without a known personal or family history of genetic disease.

However, patients with complex or rare

KEY POINTS

- Over the past decade genomic testing has become more accessible and affordable with results available much sooner.
- Genomic tests, particularly whole exome and whole genome sequencing, are now increasingly used to diagnose patients with Mendelian genetic diseases including syndromal intellectual disability, cardiac disease and cancer.
- Genomic tests are more recently being used in preventive health. This includes pharmacogenomics testing and testing of healthy individuals for genes that are rare but significantly increase disease risk.
- Patients' genomic data will become more accessible in the future and is set to play an increasing role in guiding patient care.

conditions who may benefit from genomic testing are usually referred to a specialist genetics clinic or a relevant specialist for further assessment. The typical process of genomic testing is outlined in the Figure and how to interpret the results is listed in Table 1.

Applications of genomics

Genomic testing is routinely used to aid the diagnosis of complex, rare and suspected genetic diseases. Its greatest use to date has been in patients in whom it has not been possible to make a diagnosis based on their clinical presentation or when there are several genes that could be causative.⁶ The key to making a diagnosis is to be able to make the link between the patient's clinical features, their phenotype, and the genetic variation, genotype. This clinical interpretation of genomic data is challenging and requires unique skill sets to link the patient phenotype to the correct gene variant(s) responsible for disease in that patient from a large list of possible variants.



Figure. Typical genomic testing process.

	TABLE 1. WH	ABLE 1. WHAT DO GENOMIC TEST RESULTS MEAN?	
	Result	Interpretation	
	Positive	A genetic variant has been found that is known or likely to be the cause of a genetic condition	
	Negative	No genetic variants have been found that are considered to be the cause of a genetic condition	
	Variant of uncertain significance (VUS)	A genetic variant has been found but it is not clear whether it is disease-causing or not; in some cases, further testing of family members may clarify the disease-causing status of the variant	
	Incidental (or additional) finding	A genetic variant has been found in a gene not relevant to the patient's clinical presentation; the variant is clinically significant and indicates that the patient has an undiagnosed genetic disease or is at increased risk of developing disease in the future; the variant is clinically significant and indicates the individual carries a recessive disorder and could be at risk of having a child with a genetic disease	

Australian research suggests that children who are likely to have a rare undiagnosed condition should be referred early to clinical genetic specialists for WES, because it has been shown to be a costeffective option compared with traditional diagnostic pathways.⁷⁸

Pharmacogenomic testing examines common genetic variation that influences an individual's drug metabolism and is increasingly being utilised. An individual who metabolises a particular drug rapidly may clear the drug too quickly, rendering it ineffective. Conversely, those who metabolise the drug too slowly may

2. CASE SCENARIO: FINDING A SUITABLE KIDNEY DONOR

Diane, 53 years, had autosomal dominant polycystic kidney disease (ADPKD) and end-stage renal disease. She required a kidney transplant and her son Robert, 25 years, was keen to donate a kidney. However, Diane's doctor was concerned that Robert may have inherited the genetic variant causing ADPKD from his mother, although as yet he had not shown any signs of the disease.

Diane underwent genetic testing for the *PKD1* and *PKD2* genes by whole genome sequencing and a pathogenic variant in the *PKD1* gene was identified. Robert's GP referred him for genetic counselling to discuss the pros and cons of genetic testing given that Robert did not have any features of ADPKD.

After consideration of the implications (including life insurance), Robert underwent predictive testing for the *PKD1* pathogenic variant. His test showed that he had not inherited ADPKD, and he was able to successfully donate a kidney to his mother. The family GP provided support for both Diane and Robert throughout this process.

1. CASE SCENARIO: DIAGNOSING A COMPLEX CONDITION

Jacob, 4 years, had a diagnosis of moderate developmental delay and was the only child to an unrelated couple. His parents wished to have more children but were concerned that they would have another child with high needs and would not be able to cope.

Jacob was referred to a clinical genetics service and whole exome sequencing was ordered to assess for a genetic cause of his developmental delay. The results identified two separate pathogenic variants in the *MED23* gene giving a diagnosis of autosomal recessive intellectual disability.

The parents sought a referral to a fertility specialist to pursue in vitro fertilisation and preimplantation genetic diagnosis. They had a successful pregnancy and went to their GP for shared care with the local hospital.

experience toxic effects. Prescribed drugs that are often included in pharmacogenomics testing include analgesics, antidepressants, anticoagulants and statins. If pharmacogenomic test results are readily accessible as part of a patient's electronic health record, they will prove a useful tool to guide prescribing decisions and reduce adverse events.⁹

One of the newest applications of genomic testing is for healthy individuals to have their genome sequenced and analysed to assess if their risk of developing certain genetic diseases is increased. It is possible to assess whether an individual carries a gene variant that can predispose them to rare heritable genetic disorders such as cardiomyopathy or a familial cancer syndrome (e.g. *BRCA1* or *BRCA2*). Interpreting such a variant without a corresponding disease or family history can be challenging so a high level of

3. CASE SCENARIO: MANAGING FAMILIAL HYPERCHOLESTEROLAEMIA

Malcolm, 49 years, underwent personalised health genomic testing to explore possible health risks due to genetic disorders and provide a record for his children. The whole genome sequencing analysis revealed that Malcolm had a pathogenic *LDLR* variant that causes familial hypercholesterolaemia (FH).

FH is an autosomal dominant condition that affects one in 250 people, but it is under-recognised as high cholesterol levels are relatively common in the general population. Untreated, it results in premature coronary artery disease, bringing forward the onset of cardiovascular disease by one to four decades.¹²

In addition, Malcolm had pharmacogenomic testing that revealed he had a major drug-gene interaction with certain statins. Malcolm's GP sought advice from a specialist FH service that helped guide the use of suitable cholesterol-lowering medication based on his pharmacogenomic results. As his adolescent children had a 50% chance of having inherited FH and may require medical therapy, the GP arranged fasting cholesterol studies and referral for consideration of genetic testing to determine if they had or had not inherited the pathogenic *LDLR* variant.

4. CASE SCENARIO: AN ANAESTHETIC WARNING

Linda, 49 years, had genomic sequencing to investigate for a genetic cause of her retinitis pigmentosa and she was interested in looking for incidental findings as part of the testing. The test result was negative, but an incidental finding was reported regarding a pathogenic variant in the *RYR1* gene known to be associated with malignant hyperthermia, a life-threatening condition that can be triggered in susceptible patients by certain volatile anaesthetic gases or muscle relaxants (succinylcholine) that can be used in general anaesthesia.

Linda's GP entered an alert on her electronic health record, noting that this pathogenic variant could also be present in her children. So when her son, 10 years, needed to undergo a routine procedure, Linda's GP ensured that the anaesthetist was made aware of this possibility and they were able to consider alternative anaesthetic agents for the surgery. Following this, the GP referred Linda's children to a local clinical genetics service for discussion about predictive genetic testing.

5. CASE SCENARIO: HERITABLE CANCER RISK

Gary, 52 years, had developed a right-sided colorectal cancer at the age of 42 years. Recently, he had a gene-panel test and was found to have a pathogenic variant associated with Lynch syndrome.

Gary had three children aged 27, 25 and 22 years. He wanted to talk with his children about the genetic findings. He understood that genetic testing was an option for his children and that if they had inherited the pathogenic variant, regular colonoscopic surveillance, aspirin and healthy lifestyle choices could reduce their risk of cancer. The GP was able to provide him with additional information and talked him through the process of referral to a family cancer service.

6. CASE SCENARIO: PRECONCEPTION CARRIER SCREENING

Jing and Chuan, a healthy unrelated young couple, attended their GP as they were planning their first pregnancy. They knew that there was a risk of them carrying a genetic condition and wanted to know more about this. The GP was aware of preconception carrier screening for common genetic conditions such as spinal muscular atrophy, cystic fibrosis and Fragile X syndrome, and referred the couple to have their blood taken for this testing.

The results were returned and no pathogenic variants were identified and the couple feel reassured. The GP was careful to point out that this test was only looking at a small number of common genetic conditions and that there were private companies offering more comprehensive genetic testing for rarer genetic conditions.

The couple decided not to have further testing because they had no family history of inherited disease.

The RACGP recommends that all women or couples planning a pregnancy should have a comprehensive family history recorded, and those who have a relevant family history should be made aware of the availability of preconception carrier screening and offered referral to specialist services such as genetic clinics.¹¹

confidence that the variant is disease-causing is needed for reporting. Although the proportion of individuals with a positive finding from this type of personal genomic testing is relatively low, knowing such information can enable them to manage the increased risk, including undertaking more regular screening or riskreduction strategies such as medication or lifestyle changes.¹⁰

The RACGP recently released guidelines on the use of personal genomic testing that stated the clinical utility of such testing was variable.¹¹ It recommended that patients who wish to pursue personal genomic testing should opt for a full-service provider that includes the need for referral by a GP, test interpretation and genetic counselling support.

Implications of genomics in primary practice

When a patient discovers through a genomic test that they or a family member has a genetic condition, this can lead to a number of outcomes. They may require additional screening for particular conditions for which they are at increased risk, or they may have a new understanding of inheritance patterns that has implications for family planning and other family members. GPs have an important role in assisting patients with medical and psychosocial support and providing referrals to appropriate specialists.

The case scenarios in Boxes 1 to 6 highlight different ways in which genomics can impact primary care practice.^{11,12} Some GP resources are provided in Box 7.

Genetic counselling and patient considerations

There are several factors that patients should consider before having a genomic test. Genetic counselling should be an integral part of the testing process and can be provided by a genetic counsellor, clinical geneticist or experienced medical specialist (Box 8). The role of genetic counselling involves ensuring the patient understands the test they are having and what information it can and cannot provide, as well as explaining the practical information about the testing process.

Genetic counselling can be provided face-to-face or through telehealth (telephone or online counselling). The aim is to help patients to consider what their motivation is for having the test, what they are hoping the test will achieve, and how they will adapt to the results, whether they are positive, negative or inconclusive. Patients also need to be aware that their test findings may have implications for their family members, including their siblings and children.

If patients are undergoing WES or WGS, there is a small possibility the testing will reveal incidental findings – a genetic variant found in a gene not relevant to the patient's clinical presentation. It is important that this possibility is discussed as part of the testing consent process and that the patient is clear about what information they want returned.

Although genetic results do not affect private health insurance premiums, they can have implications for risk-rated insurance policies

7. GP RESOURCES

- RACGP Genomics in General Practice¹¹ www.racgp.org.au/download/Documents/Guidelines/ Genomics-in-general-practice.pdf
- NSW Health Centre for Genetic Education www.genetics.edu.au

such as life insurance, disability insurance and income protection insurance (Box 9).¹³ Genomic data are a lifetime resource that will likely form an integral part of patients' medical records in the future. Given the value of this data, it is also important that patients and their clinicians consider factors such as whether the testing laboratory is clinically accredited and what policies it has regarding data security, privacy and access and any possible future uses of their data.

How will genomics change the way doctors practise in the future?

One of the first areas where GPs are likely to feel the impact of a shift towards greater clinical use of genomic data is in the area of

8. KEY PATIENT CONSIDERATIONS

- Purpose of the test, including the range of possible findings and limitations
- The consent process, including what information the patient wants returned
- · How patients will adapt to any diagnoses or findings
- Implications for family members
- Potential implications for insurance premiums
- · The security and future use of patients' genomic data
- Future access to patients' genomic data

reproductive carrier screening. In this year's Federal Budget, the Government announced a \$500 million, 10-year Australian Genomics Health Futures Mission,¹⁴ which will begin with a \$20 million preconception screening trial for birth disorders including spinal muscular atrophy, Fragile X syndrome and cystic fibrosis.

Genomic sequencing, unlike traditional pathology tests, can provide ongoing personal health utility. This can be accessed through reanalysis of the data in response to a new health issue

9. INSURANCE IMPLICATIONS OF GENETIC TESTING

Receiving a positive result from genetic testing can impact an individual's ability to obtain life insurance or other risk-rated insurance policies and the premiums on such insurance.

Patients may be required to disclose any personal or medical genetic test information when applying for such insurance policies, so it is important they consider insurance implications before having their blood collected. A positive result is unlikely to affect an individual who already has a clinical diagnosis that the genetic test is confirming.

An Australian Parliamentary Joint Committee into the life insurance industry recently released its recommendations.¹³ These included a recommendation for the assessment of the introduction of a moratorium on life insurers using predictive genetic information, as is in place in several other countries. If adopted, this change would mean genetic results would not adversely affect individuals' life insurance access or premiums.

or to search again for a genetic disease cause from a previously negative test result with the emergence of new genetic knowledge. In the future, if these data can be fully integrated into our healthcare systems and become available at the point of care, it will enable precision medicine with GPs and other clinicians able to personalise healthcare for individual patients.

Conclusion

Genomic testing is increasingly being used in patient care to diagnose, screen for and assess risk of inherited conditions and diseases. GPs will increasingly have access to patients' genomic data to help guide their clinical decision-making.

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Dr Ewans and Ms Young both work for Genome.One, a commercial genomics company that performs whole genome sequencing and other genomic testing.



Genomics

What it means for patients and GPs

LISA EWANS MB BS, BSc, FRACP; MARY-ANNE YOUNG GradDipSocSci(FamTherapy), MHSc

References

 National Human Genome Research Institute (NHGRI). All about the human genome project (HGP). Bethesda, MA: NHGRI; 2015. Available online at: www.genome. gov/10001772/all-about-the--human-genome-project-hgp (accessed July 2018).
Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. N Engl J Med 2014; 371: 1170.

3. Gilissen C, Hoischen A, Brunner HG, Veltman JA. Disease gene identification strategies for exome sequencing. Eur J Hum Genet 2012; 20: 490-497.

 Mattick JS, Dinger M, Schonrock N, Cowley M. Whole genome sequencing provides better diagnostic yield and future value than whole exome sequencing. Med J Aust 2018; epub ahead of print (doi: 10.5694/mja17.01176).

5. Noll AC, Miller NA, Smith LD, et al. Clinical detection of deletion structural variants in whole-genome sequences. NPJ Genom Med 2016; 1: 16026.

 Boycott KM, Vanstone MR, Bulman DE, MacKenzie AE. Rare-disease genetics in the era of next-generation sequencing: discovery to translation. Nat Rev Genet 2013; 14: 681-691.

7. Tan TY, Dillon OJ, Stark Z, et al. Diagnostic impact and cost-effectiveness of wholeexome sequencing for ambulant children with suspected monogenic conditions. JAMA Pediatr 2017; 171: 855-862.

8. Ewans LJ, Schofield D, Shrestha R, et al. Whole-exome sequencing reanalysis at 12 months boosts diagnosis and is cost-effective when applied early in Mendelian disorders. Genet Med 2018; epub ahead of print (doi: 10.1038/gim.2018.39).

9. Verbelen M, Weale ME, Lewis CM. Cost-effectiveness of pharmacogenetic-guided treatment: are we there yet? Pharmacogenomics J 2017; 17: 395-402.

 Linderman MD, Nielsen DE, Green RC. Personal genome sequencing in ostensibly healthy individuals and the PeopleSeq Consortium. J Pers Med 2016; 6(2). pii: E14.
RACGP. Genomics in general practice. East Melbourne, Vic: RACGP; 2018.
Available online at: www.racgp.org.au/download/Documents/Guidelines/Genomics-ingeneral-practice.pdf (accessed July 2018).

12. Hamilton-Craig IR, Watts GF. Familial hypercholesterolaemia in Australia: new insights and developments. Med J Aust 2013; 198: 72-73.

13. Parliamentary Joint Committee on Corporations and Financial Services. Life insurance industry. Canberra: Commonwealth of Australia; 2017. Available online at: www.aph.gov.au/Parliamentary_Business/Committees/Joint/Corporations_and_ Financial_Services/LifeInsurance/Report (accessed July 2018).

14. The Hon Greg Hunt MP, Minister for Health. Guaranteeing essential services – record investment in health. Media release; 8 May 2018. Available online at: www.health.gov.au/internet/ministers/publishing.nsf/Content/health-mediarelyr2018-hunt052.htm (accessed July 2018).