How genomics is changing clinical practice

Q&As from RACP webinar held 28 July 2021

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General genetics

Could you explain what "high frequency" vs "low penetrance" means?

Allelic frequency relates to the proportion of individuals in a population who have inherited a specific variant. **High frequency** in this context means there is a high proportion of individuals in a population who have inherited the specific variant.

Penetrance refers to the probability of detecting the presence or clinical expression of a gene or combination of genes. If the penetrance of a particular condition is less than 100%, not all individuals who carry a variant in the gene or genes responsible for the condition will develop symptoms of the condition it causes. Such a genetic condition is said to have low, reduced or incomplete penetrance.

Genomic testing

When it becomes more easily available, in what situations would you choose a whole genome over a whole exome study?

Whole genome sequencing (WGS) will eventually become the test of choice, as it can detect certain pathogenic variants that are not identified using whole exome sequencing (WES), including rearrangements, small duplications and deletions of genes (although these are somewhat covered by chromosome microarray [CMA] at present), microduplications and microdeletions within genes.

At present, WGS should be considered after discussion with a clinical geneticist, if WES if negative, there is a strong suspicion of a monogenic disorder and there is a reproductive question. WGS is likely to become the test of choice as the test cost reduces, as the yield is higher.

In single parent families, is duo testing (child and one parent) more helpful than singleton testing?

Duo testing is not always more helpful than a singleton test but in general it is beneficial to have the additional data.

If a specific exome panel (eg epilepsy) is negative, will the specimen be kept and re-tested automatically every few years or would clinicians have to request retesting?

The referring specialist can request the patient's WES or WGS be re-examined by the original pathology service as more information about gene variants becomes available in the future. This re-analysis does not happen automatically, so the referring clinician will need to request the re-analysis using Medicare item number 73360.

What is your take on the commercially available panels and single gene tests?

Most are well validated tests run in good laboratories. If ordering a commercially-available panel, ensuring informed consent is obtained is mandatory. Given laboratories have varying reporting practices, discussion with a clinical geneticist may be helpful before ordering the panel as your local Genetics Service often has lab-specific knowledge. Complex or ambiguous results may also be discussed with the local genetic service. Single gene tests are only done very rarely now.

Can everyone access trio exome testing?

Currently, trio exome testing is highly unlikely to produce a useful result if there is no clinical indication for testing (e.g suspicion of a single gene disorder). Testing of healthy individuals is likely to result in variants of uncertain significance, or an inconclusive result, creating uncertainty and anxiety. For this reason, exome testing is not available to everyone.

Can you direct us re testing public and private?

Clinical genomic testing should be performed in a National Association of Testing Authorities (NATA) accredited laboratory. A listing of Australian laboratories offering WES is available at the NATA directory of accredited laboratories. Search by your state with the keyword "exome" and contact the laboratory directly for more information.

Few genomic tests are publically funded. Are there commonly-used or sought tests for which there is strong economic evidence?

Many genomic tests have good economic evidence although the economic analysis is complex and needs to be far-reaching because the effects of non-diagnosis are difficult to quantitate. Further research would need to be conducted to identify specific tests for which strong evidence is available.

What advice do you have for clinicians who have to manage patients who come in with a genetic report from a commercial provider/DIY genetic testing kits?

This is something that will increasingly occur as these tests become more widely available. The panel recommends taking the direct to consumer (DTC) tests seriously, and looking for any results that may be of clinical significance and/or discussing the result with the clinical team. Often the findings of these tests are only very loosely associated with disease and not very useful from a clinical perspective, however they should not be dismissed.

To discuss the result with the patient, it is advisable not to overtly discredit the reliability of the DTC test but to explain the difference between the DTC test and a clinical test that is conducted in a NATA-accredited laboratory, and which has been ordered by a clinician or a doctor. It is helpful to describe the weight and evidence that goes into generating a clinical report compared with the analysis involved in a DTC test.

Sometimes I see a lab report that reports VOUS. However, googling the gene reveals associations with the relevant condition, eg autism. Can you please comment?

If a direct link with a condition such as autism is identified, it is worthwhile to have a conversation with a geneticist to discuss whether the identified link is robust. The medical literature needs to be interrogated, as one report is not sufficient to validate the initial diagnosis. Further, just because there is a change in a gene that can cause a condition does not necessarily mean the particular change identified is causing the condition.

What can microarray not detect?

Microarray testing cannot detect single gene mutations, cases of Fragile X syndrome or balanced rearrangements (translocations and inversions)

When will whole genome sequencing replace newborn blood spot screening?

This is unlikely in the near future. Most recent studies were unequivocal, with sequencing missing many cases that were detected by newborn screening

Paediatric intellectual disability/developmental delay/childhood syndromes

When contrasted with moderate intellectual handicap, what percentage of children with a mild intellectual handicap will have an abnormality on SNP or WES?

Currently there are no strong data to answer this question. In a study of 106 children with intellectual disability (ID) (Gieldon et al 2018), similar diagnostic yield was obtained with targeted WES for children with severe ID (36%) compared with children who had mild ID (44%). However, over 90% of children in the study were classified as being syndromic, defined as the presence of at least one additional symptom besides ID/developmental delay (e.g. minor facial anomalies, major anomalies or seizures).

In general, a specific genetic cause is more likely to be detected in severe and syndromic forms of ID than in mild and non-syndromic forms.

Of the children who have a genetic cause of their intellectual handicap identified, what percentage are due to a spontaneous mutation?

De novo (new) variants account for a majority of genetic diagnoses. In the largest study to date, 42% of children with neurodevelopmental disorders were found to have a causative de novo mutation (Deciphering Developmental Disorders Study 2017)

Can you update specifically about autism spectrum disorders (ASD) in children as well as global developmental delay?

Although there is considerable overlap between the genetic causes of autism and ID, most autism is thought to be caused by the interaction of large numbers of common genetic variants that are inherited from both parents. See Amor et al 2018 for more information.

Patient counselling/consent/ethical issues

How do you manage disclosure to other possible at risk relatives?

The Centre for Genetics Education (www.genetics.edu.au) has two resources of relevance to disclosure:

- A video for health professionals: Testing for Relatives, and
- A brochure for families: Talking to your family about a genetic diagnosis or test result

Further guidance can be found on page 2 of the NSW Health Genomic Testing Consent form (Release of Genetic Testing Results section): *Please note: Genetic information can be used and disclosed without consent in order to lessen or prevent a serious risk to the life, health or safety of a genetic relative no further removed than third degree; and, only where the disclosure is made in accordance with the guidelines issued by the Information and Privacy Commission NSW*

Families wonder who owns the genetic information and what will they do with it. How do you answer that question?

This is lab-dependent, but at present if testing occurs at a NATA accredited lab in Australia, clinical information and genetic data are stored on a secure database. Some laboratories share and store de-identified data and associated health information in order to help advance scientific knowledge. This information will be included on the consent form required by the laboratory used.

The Centre for Genetics Education has a set of resources (Genomic Testing Consent Resources for Medical Specialists) that can help with addressing some of these issues including a section (Family considerations) that specifically discusses the consent form.

What is the impact of genomic testing on the child or parent's ability to obtain personal insurance?

While it is impossible to predict what will happen in the future, there is a currently a Moratorium on Genetic Tests in Life Insurance, which continues until 2024. As a result of the Moratorium, insurance companies will not be able to use genetic test results as part of an insurance application up to the value of $500,000 (for death or total permanent disability), $200,000 for trauma and $4,000 a month for income protection.

At the moment, individuals are not required to have a genetic test as part of the risk assessment when applying for life insurance. If they have already had a genetic test, their life insurance company must not use their genetic test results (up to the financial limits set above) unless the individual chooses to declare them.

The Centre for Genetics Education has a number of resources that may help with conversations about insurances, including:

- A basic information brochure for families, About genomic testing, explaining genomic testing and its potential implications
- Videos and resources for medical specialists about consent for genomic testing
- Implications for life insurance resources
- Life insurance products and genetic testing in Australia fact sheet

If the WES is done as a triome, however the results show the father is not the biological one, is this relayed to us or are we kept in blissful ignorance?

Trio WES has the potential to identify unexpected family relationships, and if identified, may be included in the results report. It is important to discuss this possibility with families during the consent process.

The Centre for Genetics Education has resources that address the possibility of non-paternity, including a video for health professionals on Unexpected Family Relationships. This is also covered in the section on Family considerations.

With increasing use of donors for conception, do you see a future where these donors will be asked to contribute to the trio test? And its legal implications

As guidelines change to ensure transparency of health information to offspring from donor parents, it is possible in future that donors may be contacted and asked to contribute to this testing.

As a paediatrician, I am often asked by parents fearful about the ethical dilemma of testing

Whether to undergo genetic or genomic testing is a personal decision for each family but being informed about the possible outcomes and implications of genetic and genomic testing may help families weigh up this dilemma. The fact sheet Ethical Issues in Human Genetics and Genomics may help with discussions like these. The general fact sheet About Genomic Testing may also help inform families considering genomic testing for childhood syndromes/intellectual disability.

Is there utility of microarray if WES is being considered - meaning do we do SNP then WES as per the Medicare rules?

Micro-array must be performed and an undiagnostic result obtained prior to Medicare-rebatable WES. For more information, refer to the recent article on Medicare-rebateable WES (Sachdev et al 2021).

For a child with ASD level 2, and no associated ID, is doing only a CGH array (chromosome microarray [CMA]) appropriate? If no result is obtained, is this worth repeating later, if the parents have similar phenotypes?

ASD level 2 without co-morbidity has a low diagnostic yield, unless the patient has intellectual disability and dysmorphism, significant macrocephaly, and/or epilepsy.

However, Fragile X testing is still indicated for a child like this. Repeating the analysis in the future may be worthwhile after discussion with your local genetic service given evolving genetic discoveries.

In intellectually handicapped children who have a genetic diagnosis which is associated with disruptive and aggressive behaviours, in what percentage is a disturbed biochemical pathway established as the cause for this difficult behaviour?

Metabolic conditions underlie 0.8–1.8% of global developmental delay and intellectual disability, some of which are treatable. For more information see Silove et al 2013, Poplawski et al 2002, and Sempere et al 2010.

Isn't it inappropriate that NDIS checks results of gene testing. I can see them electing to deny funding if results are non-informative

Interpretation of complex results can be difficult. Supportive letters from the patient's managing paediatrician and geneticist may be more useful for NDIS

Specific medical conditions

How do you test for mitochondrial diseases?

Previously this was done by enzymology of tissue biopsies (liver, muscle, skin). Blood-based testing is becoming increasingly available to look for either mitochondrial or nuclear encoded variants.

Is consumption of alcohol, smoking or consumption of illicit drugs during pregnancy associated with increased incidence of genetic abnormality detected by WES or WGS?

No. These may have epigenetic effects but it is the effect of these substances on the developing brain that is the main issue, depending of course on the amount of substance consumed. Mothersafe NSW has excellent resources and experts in this area as well and are available as a direct patient contact service.

Any comments on reverse cascade screen as in Familial Hypercholesterolaemia?

When a person is identified as having Familial Hypercholesterolemia (FH), their first degree relatives (parents, children, brothers and sisters) all have a 1 in 2 (50%) chance of also having FH. Relatives may be screened by checking their cholesterol levels through their family doctor or genetic testing may be offered if the gene variant has been found in their family.

As of 1st May 2020, FH genetic testing may be ordered to test an 'index case' by a specialist (73352) or for (cascade) testing first or second degree relatives of a patient with an FH-causing variant by their GP or specialist (73353). The testing laboratory will need to know which specific gene variant causes FH in the family before they do cascade testing.

Would the presence of *BRCA2* or other potentially important genetic change, for instance, be included in the results?

Incidental findings (where a variant is identified in a gene that is not related to the condition for which the testing was done), are identified in less than 1% of tests performed in NSW. The laboratory are not actively looking for these variants, but if identified, will typically be included in the results if they can alter a family's future health management

Is there an age where a genetic cause is less likely, especially in cardiovascular disease (CVD)?

There is not a particular age, but certain diseases carry less of a risk of being due to monogenic causes. Examples include CVD and hypertension. There are many examples of genetic diseases that can present at any age.

At the 2018 RACP Congress we were told that everyone could benefit from having their genome assessed at age 70. What are said benefits?
Some benefits might be finding variants of relevance to other family members, pharmacogenomic results, and increased risk of malignancy.

I am 60 years of age. Can I have genomic testing to find out if I have a high risk of Parkinson's disease, dementia or aggressive prostate cancer?
Technically, testing is available for each of these. Practically though, testing for these indications is unlikely to be offered without a significant family history.

How common is Long QT syndrome is? Is it a contraindication for Methadone? Is it advisable to do ECG before starting any patient on Methadone or other medicine that may affect QT?
According to the GeneReviews article on Long QT syndrome (LQTS), the prevalence of LQTS has been estimated at 1:2,500.

The Australian Medicines e-Handbook (accessed via CIAP 4/8/21) states “Precaution: Risk factors for prolonged QT interval—in high doses, methadone may prolong the QT interval and increase risk of arrhythmia; avoid use if risk factors cannot be corrected."

Similarly, eMIMS (accessed via CIAP 4/8/21):"Methadone is contraindicated in individuals with existing QT prolongation, including those with congenital long QT syndrome."

Consultation with a cardiologist is recommended to answer the third part of the question.