Clinical Exome Sequencing:

Medicare Item numbers 73358/73359

Tip sheet

This information is to help paediatricians complete the pre-approval form for Medicare funded clinical exome sequencing under item numbers 73358 and 73359.

Glossary:

Chromosome microarray (CMA or molecular karyotype): CMA has a Medicare item number for patients presenting with intellectual disability, developmental delay, autism, or at least two congenital anomalies. CMA is the recommended first line test in these cases as it can exclude a chromosome cause of disease which is unlikely to be detected by exome.

Gene panel is a set of genes that are known to be associated with a phenotype or disorder. They help narrow down the search for variants of interest to genes with evidence linking them to particular phenotypes

Human phenotype ontology (HPO) terms describe a phenotypic abnormality using a standard nomenclature. Ideally, all clinicians and scientists are using the same terms.

Mendeliome refers to the ~5,000 genes (out of about 20,000 protein coding genes) that are known to be associated with monogenic disease. As variants in new genes are identified with evidence linking them with human disease, they are added to the Mendeliome.

Monogenic conditions (as opposed to polygenic or multifactorial conditions) are caused by variants in a single gene. Variants may be inherited (dominant or recessive fashion), or may occur spontaneously (*de novo*) showing no family history.

Whole exome sequence – sequencing only the protein coding genes (exons). The exome is ~2% of the genome and contains ~85% of disease-causing gene variants.

Whole genome sequence – sequencing the entire genome (all genes, including coding and noncoding regions)

Singleton – Analysis of the child only.
Trio – analysis of the child and both biological parents.

Variant - A change in the DNA code that differs from a reference genome.

Eligibility criteria

Medicare criteria: Characterisation of germline variants known to cause monogenic disorders via whole exome or genome sequencing and analysis, as requested by a clinical geneticist or a consultant physician practising as a specialist paediatrician in consultation with a clinical geneticist in a patient aged ten years or younger with a strong suspicion of a monogenic condition based on the presence of any one of the two following clinical criteria:

1. dysmorphic facial appearance and one or more major structural congenital anomalies; or
2. intellectual disability or global developmental delay of at least moderate severity to be determined by a specialist paediatrician.

Performed only after non-informative microarray testing (item 73292) of the patient.

Need for phenotypic information

Detailed phenotype information (following HPO terms) ensures the right test is performed and also supports accurate interpretation of any variants found (and reduces the time taken to do so). Without detailed phenotype information, variant interpretation is difficult. This information also supports the selection of appropriate virtual gene panels for analysis. *The more specific phenotype information provided, the greater the chance your patient will receive a diagnosis.*

How much phenotype information is enough?

Here's an example of sufficient phenotype detail.

15 yr old male

Phenotype:
Moderate-severe global developmental delay; intellectual impairment; seizures; obesity.
No family history of note. Second child to non-consanguineous parents. Healthy older sister.

Previous normal investigations include: SNParray; VLCFA; Transferrin isoforms; Maternal UPD14 studies; PWS methylation studies; Urine organic acids; CSF amino acids, lactate/pyruvate; MRI brain.

Test Request: singleton exome with Intellectual disability gene list and Mendeliome.

Why do I need to select gene panels?

The selection of pre-curated phenotype specific gene panels from PanelApp Australia helps target the analysis of the exome data based upon your patient's clinical presentation.

NOTE: If initial analysis using these specific gene panels does not identify any variants of interest, analysis of the Mendeliome will automatically occur.

Why do I need to obtain informed consent?

It is standard medical practice to obtain written consent for genomic tests. This helps ensure patients and families are aware of the risks and benefits of testing as well as the possible outcomes. Important aspects to cover include the possibility of incidental findings, the identification of unexpected parental relationships, and the reporting of variants of uncertain significance (VUS). Consent discussions should also cover the storage of genomic data, possible use of data in future research and insurance implications.

NOTE: For trio analysis, consent is required from the child and both biological parents. Please refer to the patient information sheet and consent forms for information to help guide discussions.

Links to resources

Clinical exomes test page – including consent forms, test request forms