Melbourne Genomics Health Alliance

# Genomic tests - Overview

| | Karyotype[1] FISH | Single gene test[2] | Chromosomal microarray (CMA)[3] | NGS Panel Sequencing | Whole Exome Sequencing (WES) | Whole Genome Sequencing (WGS) |
|---|---|---|---|---|---|---|
| **Aneuploidy** | + | -- | + | -- | -- | + |
| **Balanced chromosome rearrangements** | + | -- | -- | -- | -- | + |
| **Unbalanced chromosome rearrangements** | + | -- | + | -- | -- | + |
| **Copy number variants (CNV)**<br>-Large >5Mb<br>-Small: 0.1-1Mb | <br>+<br>-- | <br>--<br>-- | <br>+<br>+ | <br>--<br>+ | <br>--<br># | <br>+<br>+ |
| **Insertions/deletions (Indels) <100bp** | -- | + | -- | + | + | + |
| **Single nucleotide variants (SNV)** | -- | + | -- | + | + | + |
| **Trinucleotide repeat** | -- | + | -- | -- | -- | -- |
| **Mitochondrial DNA variants (mtDNA)** | -- | + | -- | + | -- | + |

[1] Karyotype now generally replaced by CMA. Fluorescence *in situ* hybridisation (FISH) detects range of chromosome variants and also single gene copy number and some small changes by using specific probes

[2] For simplicity, several tests have been condensed into this single gene test category; including Sanger sequencing; MLPA; PCR; Methylation studies; Repeat-primed PCR; Southern blot.

[3] SNP-array & CGH-array. SNP-array detects long contiguous sequences of homozygosity (LCSH), indicating consanguinity. CGH-array does not detect LCSH.

+ can be detected / -- not recommended

# can sometimes be detected, but this test not recommended for CNVs.

Exome sequencing is not an ideal test to identify CNVs. Therefore, CMA is often ordered prior to WES.

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| | Single Gene* (genetic test) | Chromosomal microarray (CMA) | NGS Panel (multigene panel) | Whole Exome Sequence (WES) | Whole Genome Sequence (WGS) |
|---|---|---|---|---|---|
| INDICATION | When you suspect condition caused by variants in one or a small number of genes,<br>e.g. Huntington disease. | Indicated for patients presenting with intellectual disability, developmental delay, multiple congenital anomalies, dysmorphic features. | When patient has a relatively well-defined phenotype and …<br>When you suspect a condition caused by a variant in one of several genes. | When you suspect a monogenic disorder caused by a variant in one of several genes.<br>Patients may show non-specific phenotype. | When you suspect monogenic disorder caused by a variant in one of several genes.<br>Patients may show non-specific phenotype. |
| BENEFITS | Very specific and accurate<br>Less chance of incidental or uncertain findings. | Medicare funding for certain indications.<br>Relatively cheap test compared to WES/WGS.<br>Can be performed using saliva, making it quick and easy. | Can provide better coverage of genes of interest compared to exome.<br>Less chance of incidental findings compared to exome/genome.<br>Often cheaper than exome. | Sequencing of the whole exome allows for future re-analysis of other genes as knowledge improves. | Covers non-coding regions; can identify variants not detected by exome, e.g. mtDNA, triplet repeats, deep intronic variants.<br>Costs are declining. New technology increasing speed & accessibility.<br>Can be reanalysed |
| LIMITATIONS | Limited utility for non-specific phenotype<br>Limited utility for conditions where multiple genes are associated. | Does not identify triplet repeats, balanced translocations, or point mutations. | Sequences only the genes covered on the panel.<br>No capture of other gene sequences so unable to re-analyse (i.e. analyse for other genes) later. | Incomplete coverage of exome - chance of false negatives.<br>Higher chance of incidental and secondary findings.<br>Time consuming variant interpretation. | Clinical use may be limited by cost/availability of services & expertise.<br>Incomplete coverage.<br>Some identified variants not readily interpreted. |

** This table has been simplified for teaching purposes. In particular, we have oversimplified the single gene category (methods including Sanger sequencing, Southern Blot, PCR, MLPA, methylation studies, repeat-primed PCR)*