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Genomic test results

Most Canadian accredited laboratories have adopted the American College of Medical Genetics and Genomics (ACMG) five-tier system of genomic variant classification based on strength of supporting evidence.

This resource is intended to facilitate discussion between clinicians and patients about possible results of genomic testing.

This not specific to any one genomic test and can be applied to various technologies e.g. panel gene testing, whole exome sequencing, microarray.

Consider reaching out to a board-certified genetic counsellor at the laboratory where the genomic test is performed.

Pathogenic/Likely pathogenic

A *pathogenic* variant is well established to be causative of a hereditary condition. A variant is *likely pathogenic* when there is 90% or greater certainty to be causative for a hereditary condition.

In conjunction with clinical information, this result may confirm a diagnosis and can be used in medical decision-making.

Relatives can be offered testing for this familial variant.

Variant of uncertain significance (VUS)

There is insufficient evidence to classify this variant as either pathogenic or benign, or the evidence for benign and pathogenic is contradictory.

A VUS should not be used in clinical decision-making.

Relatives may be offered testing to see if the VUS is seen in other affected relatives.

Benign/Likely benign

If a variant is common, observed in more than 5% of a control/unaffected population, it is classified as *benign*.

Likely benign classification is used when there is 90% or greater certainty the variant is benign.

These variants are most often not reported.

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Ordering clinician's role:

- Provide complete and accurate clinical and family history information
- Coordinate follow up testing if indicated (e.g. parental testing)

Richards S, et al. Genet Med. 2015 PMID: 25741868

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Additional considerations

Setting expectations:

The best person in whom to begin genomic testing within a family is the person most likely to carry a pathogenic or likely pathogenic variant. Often, this is the youngest affected individual whose clinical presentation is most strongly associated with the diagnosis under investigation.

The implications of a positive result, where a pathogenic or likely pathogenic variant is identified, depend on the type of test. For example, predictive testing, pharmacogenomic testing, diagnostic testing, etc.

A true negative result is one where an individual is found not to carry a known familial pathogenic variant and so is not at risk for the familial condition. Their offspring would also not be at risk for the familial condition. This result is specific only to the familial condition tested.

A negative result, where no variants of clinical significance are found, can be reassuring depending on the diagnostic yield of the test ordered and the initial degree of clinical suspicion for a genomic etiology.

Variant of uncertain significance (VUS) is where a variant in a gene was identified, but its significance is not yet known. The laboratory cannot confidently determine if the gene variant identified is pathogenic or benign, as available evidence is insufficient or conflicting. Not used to change clinical management. Testing is not usually offered to relatives.

Secondary findings

Pathogenic and likely pathogenic variants may be identified in a gene unrelated to the clinical indication for testing.

Patients need to be aware that these results, which may have implications for relatives or future screening/surveillance, may be reported.

The ACMG has assembled a list of medically actionable genes for which disclosure is recommended. Some testing settings may have options for disclosure of additional genomic conditions.

Insurance

There is protection for Canadians under the Genetic Non-Discrimination Act (GNA).

GNA prohibits:

- Discrimination based on genomic characteristics
- Providers of goods and services (including insurance) from requesting or requiring a genomic test/disclosure of genomic test results either past or future
- Federally regulated employers from using genomic test results in decisions about hiring, firing, job assignments, or promotions

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