INTERPRETING GENOMIC TESTING RESULTS GUIDE

This document has been created by Genetic Health Queensland **for Queensland Health clinicians** as a guide for **interpreting clinical diagnostic genomic testing results** for **patients with a suspected genetic condition**.

Test report

It is important to become familiar with the content of genomic test reports. Although reports may appear different between clinical laboratories, the reports will contain common essential information (see Appendix).

Demographics
- Patient identifiers
- Clinical information
- Samples details
- Requesting clinician
- Testing laboratory details

Test requested
- Genomic test type
- Gene panel(s) applied

Results
- Diagnosis (if made)
- Interpretation
- Recommendations

- Gene name
- Disease (MIM)
- Inheritance of condition
- Variant in HGVS nomenclature
- Genomic location
- Zygosity
- Parent of origin
- ACMG Classification

Variant description *(and evidence for classification)*
- Variant type and effect
- Zygosity
- Parent of origin
- Conservation of nucleotide/amino acid
- Location of variant (exon number, functional domain)
- Computational predictions
- Functional evidence
- Mechanism of disease
- Control databases
- Disease databases
- Relevant publications

Methodology
- Test capture method
- Reference Sequence
- Analysis method
- Gene panel(s) applied
- Variant classification method

Limitations

Outcomes

There are 3 possible outcomes of diagnostic genomic testing:

- Pathogenic / likely pathogenic variant
- No variants reported
- Variant of uncertain significance (VUS)

Each outcome requires clinical interpretation and may have clinical and/or familial implications.

Pathogenic or likely pathogenic variant

This outcome means a **genetic cause *may* have been identified** in the patient.

It is important to clarify the following points:

- Does the result explain the patient's full clinical phenotype? Could there be another diagnosis?
  - Complete match (explains all features)
  - Partial match (explains some but not all features: blended phenotype vs. phenotype extension)
  - Incidental/secondary finding (significant finding with clinical impact but unrelated to clinical presentation)
- Is the mode of inheritance (MOI) of the condition consistent with the variant(s) reported?
  - Do the number of variants identified in the gene match the MOI of the condition?
    - e.g. two pathogenic/likely pathogenic variants are required for autosomal recessive conditions
  - Do the location of variants identified in the gene match the MOI of the condition?
    - e.g. two pathogenic/likely pathogenic variants are required on separate copies of the gene (i.e. in *trans*) for autosomal recessive conditions
    - segregation studies by testing both parents can assist with this
- Consider the information above and decide if the result is diagnostic for your patient:
  - Consistent with MOI AND phenotype match = diagnostic
  - Consistent with MOI but NOT phenotype match = incidental finding
  - Inconsistent with MOI = carrier status
- What are the management implications for the patient?
- What are the implications for family members?

A referral to Genetic Health Queensland is recommended for detailed discussions of the implications of the result for the patient and their family.

No variants

This outcome means a **genetic cause *has not* been identified** in the patient, but is not excluded.

It is important to clarify if any of the following reasons may explain the negative test result:

- Patient factors
  - Atypical presentation of phenotype
  - Incomplete phenotype due to early presentation
  - Non-genetic/complex disease aetiology
- Test factors
  - Incorrect test type for disease aetiology, mechanism, and variant type
  - Incorrect/incomplete panel(s) selected for phenotype
  - Technical limitations of test
  - Limited evidence to interpret variants analysed
  - Variant in non-coding/regulatory regions which cannot be interpreted/detected
- Knowledge factors
  - Undiscovered disease aetiology, disease mechanism, and/or gene for condition

If there is a strong suspicion of a monogenic condition in the patient, consider further testing (if relevant) or reanalysis of the genomic test data in 2-3 years.

A referral to Genetic Health Queensland is recommended for advice, further assessments of differential diagnoses and alternate genetic testing methods.

Variant of uncertain significance (VUS)

This outcome means there is a variant in a relevant gene, however there is insufficient evidence to fully understand this at this time. The **result is *uninformative*** for the patient.

It is important to clarify the following points:

- Does the patient's clinical phenotype match the known information on the condition?
- Do the number of variants identified in the gene match the mode of inheritance of the condition?
  - i.e. two disease-causing variants are required for autosomal recessive conditions

Some VUS will be re-classified as benign or pathogenic in the future as further evidence is obtained, but this does not occur automatically.

If you are highly suspicious that a VUS may be the cause of the condition for a patient:

- Discuss with the testing laboratory if further clarification can be made by any of the following:
  - Review of the clinical phenotype
  - Family segregation studies
  - Functional studies of the variant
  - Discussions with disease experts
- Plan to request a re-review of the VUS with the testing laboratory in 2-3 years.

A VUS is uninformative and should not be used to:

- confirm a genetic diagnosis
- make clinical management decisions
- test unaffected family members at risk of the condition or for family planning / prenatal testing

A referral to Genetic Health Queensland is recommended for further assessments, interpretation, and discussion of the results.

Case discussion and support

You may wish to discuss with or seek support from Genetic Health Queensland.
For example: complex phenotype; interpretation of results; managing risk and/or a diagnosis; or complex social, family communication or ethical issues.

For case discussion, please contact the on-call team at Genetic Health Queensland on:
Phone: (07) 3646 1686
Email: GHQ@health.qld.gov.au

Appendix - Example genomic test report

Test Requested Genome 15
Reason for Referral Cystic kidneys
Gene list(s) applied *Renal Macrocystic Disease v0.19*

Results	**Genetic diagnosis of polycystic kidney disease 2.**

Interpretation

This individual is heterozygous for a **PATHOGENIC** variant in the *PKD2* gene. Pathogenic variants in this gene are associated with autosomal dominant polycystic kidney disease 2 (MIM#613095). Parental testing indicates that the variant in this individual is due to a *de novo* event.
Future re-analysis is available on request (additional charges may apply). Genetic counselling is recommended.

Findings related to phenotype

Gene	Genomic Location	Variant	Zygosity	Classification	Inheritance
PKD2	chr4:88046671	c.1349G>A; p.(Gly450Asp)	Heterozygous	Class 5	De novo

Variant Descriptions

NM_000297.3(PKD2):c.1349G>A; p.(Gly450Asp)

This variant is classified as Pathogenic.
Evidence in support of pathogenic classification:
- Variant is absent from gnomAD (both v2 and v3).
- This variant has limited previous evidence of pathogenicity in unrelated individuals. It has been reported as a VUS and as likely pathogenic in individuals with autosomal dominant polycystic kidney disease (ClinVar, PMID: 26150605).
- Variant shown to be *de novo* in proband (parental status not tested but assumed).

Additional information:
- Loss of function is a known mechanism of disease in this gene and is associated with polycystic kidney disease 2 (MIM#613095).
- This gene is associated with autosomal dominant disease.
- Variant is predicted to result in a missense amino acid change from glycine to aspartic acid.
- This variant is heterozygous.
- Missense variant with conflicting *in silico* predictions and uninformative conservation.
- Variant is located in the annotated PKD channel domain (NCBI, PDB, DECIPHER).
- No comparable missense variants have previous evidence for pathogenicity.
- No published segregation evidence has been identified for this variant.
- No published functional evidence has been identified for this variant.

Test capture
Panel applied
Diagnosis
Gene
Variant nomenclature
Variant classification
Zygosity
Parent of origin
Control databases
Literature
Variant effect
Computational predictions
Conservation data
Functional domain
Functional evidence