REQUESTING DIAGNOSTIC GENOMIC TESTING GUIDE

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

Introduction

Genomic testing includes the following test types:

- Targeted gene panel sequencing
- Whole exome sequencing (WES)
- Whole genome sequencing (WGS)

It is applicable to monogenic (single gene) conditions which are genetically heterogeneous.

The guide does **not** describe the processes for requesting:

- Other diagnostic genetic tests
  - Testing for conditions caused by different aetiologies (e.g. chromosomal, mitochondrial, imprinting, or polygenic).
  - Contact Genetic Health Queensland for advice regarding choosing the best test type for a patient.
- Predictive, carrier, or cascade genetic testing
  - Testing for a known familial causative gene variant in either affected family members (i.e. confirmatory diagnostic testing) or asymptomatic family members (i.e. predictive or carrier testing).
  - These individuals should be referred to Genetic Health Queensland for formal genetic counselling.
- Research genetic or genomic testing

Pre-test requirements

Prior genetic testing

Review prior genetic testing to avoid duplicate and unnecessary testing:

- Clarify if genetic testing has been done or is pending in patient
  - Review Auslab/Auscare for any previous or concurrent genetic testing
  - Review all patient URNs
  - Genetic testing is most easily identified when “View Type” is set to “Requests”
- Clarify if genetic testing has been done in family members with same phenotype/condition
  - If a familial disease-causing variant is known
    - Targeted confirmatory testing in patient is more appropriate
  - If no variant(s) identified on recent testing
    - Limited benefit in genetic testing in patient and may not be required

Clinical indication

Determine the clinical justification for diagnostic genetic testing in the patient:

- Diagnostic uncertainty
  - To refine a diagnosis for conditions with genetic/phenotypic heterogeneity
- Management planning
  - To enable new/ongoing targeted treatment/surveillance
- Genetic counselling
  - To clarify risk for family members and/or provide information for reproductive decisions

Clinical phenotyping

Genetic testing performs best when there is a genetic hypothesis and phenotype-driven analysis is possible.

Collect detailed phenotype information as this is crucial for:

- Formulating a list of differential diagnoses
- Clarifying the prior probability of a genetic condition
- Determining the mostly likely disease aetiology and mechanism
- Selecting the correct genetic test/gene panel(s)
- Analysing the genetic test
- Interpreting genetic test results

Clinical phenotype includes:

- History and examination findings
- Relevant family history
- Diagnostic features from non-genetic investigations
  - May require other investigations (e.g. haematology, biochemistry, histopathology, and radiology)
- Information from cross-speciality MDT discussions (especially if seen by multiple teams)

Be aware of:

- Atypical presentations and phenotypic variability
- Incomplete phenotypes due to early presentation
- Potential for multiple genetic or non-genetic diagnoses in one individual
- Confounding environmental, prenatal, or non-genetic factors

Genetic hypothesis

Performance of genetic testing depends on the genetic hypothesis and pre-test probability.

- Is a genetic condition *strongly suspected* over other non-genetic causes? or
- Are you seeking to *exclude* a genetic cause for an undifferentiated condition in which non-genetic causes are still being considered? Genetic testing cannot exclude a genetic condition.

Consider further clinical phenotyping to exclude non-genetic causes.

Determine the mostly likely disease aetiology and variant types (there may be multiple possibilities):

- Chromosome
  - Numerical
  - Structural (deletion, duplication, ring, inversion, translocation)
- Single gene
  - Single nucleotide variant
  - Insertion/deletion
  - Nucleotide repeat
  - Copy number variant (e.g. exon(s) deletion/duplication)
- Mitochondrial
  - Single nucleotide variant (in mitochondrial DNA or nuclear gene(s))
  - Copy number variant (i.e. mitochondrial DNA deletion or depletion)
- Epigenetic
  - Single nucleotide variant (in imprinting centre or imprinted gene(s))
  - Copy number variant (i.e. deletion/duplication of imprinting centre or imprinted genes)
  - Uniparental disomy
  - Methylation anomalies (epimutation)

Test type

Determine the test(s) most likely to target the disease aetiology and variant types (there may be multiple possibilities):

- Chromosome
  - Conventional (G-banded) karyotype
  - Fluorescence *in situ* hybridization (FISH)
  - Microarray
- Single gene
  - Sanger sequencing
  - Southern blotting / Triplet primed PCR
  - Multiplex ligation-dependent probe amplification (MLPA)
  - Genomic testing (targeted gene panel, whole exome, whole genome)
- Mitochondrial
  - Sanger sequencing
  - Mitochondrial genomic sequencing
- Epigenetic
  - Microarray
  - Methylation-specific MLPA
  - Sanger sequencing

Test tissue

Determine the tissue most likely to have the highest diagnostic yield, based on disease aetiology:

- Blood for most germline genetic conditions
- Other affected tissue (e.g. skin, tumour) for suspected somatic/mosaic genetic conditions

Clinical urgency

The turnaround time of genomic testing will vary between laboratories, and some options may not be available in each laboratory.

Determine the desired turnaround time of the test based on clinical urgency for the patient and clinical teams:

- Ultra-rapid = <5 days
- Rapid/semi-urgent = 2-3 weeks
- Routine = 2-6 months

Genomic test selection

The availability of genomic testing will vary between laboratories, and some genomic test types may not be available in each laboratory.

Determine the genomic test that best addresses the variant type(s) in your suspected disease(s) and/or gene(s) of interest (e.g. targeted gene panels and WES require additional testing methods to address copy number variants - MLPA). This may require a literature review to clarify the proportion of variant types in a specific disease.

Test selection may be determined by:

- Patient phenotype
- Size of panel (i.e. number of genes)
- Clinical urgency
- Test cost
- Availability of testing laboratory

Panel (gene list) selection

Genomic testing includes the following test types:

- Targeted gene panel sequencing
- Whole exome sequencing with virtual gene panel analysis
- Whole genome sequencing with virtual gene panel analysis

Selecting the correct targeted or virtual panel(s) is very important and should be clarified prior to requesting genomic testing. Failure to include this information in the request will result in delays. Detailed phenotyping will inform selection of the correct relevant panel(s) and genes.

Panels may be selected from:

- Predefined commercial laboratory gene lists
  - There may be discrepancies between and inaccuracies in commercial laboratory gene panels
  - These can sometimes be modified with the addition and/or removal of genes
- PanelApp Australia (https://panelapp.agha.umccr.org/)
  - These are consensus panels utilised by most Australian diagnostic laboratories
  - The genes/panels are updated and reviewed regularly by an expert panel of clinicians and scientists, with evidence for gene-disease associations
- Custom gene list(s)
  - These can be created/designed for a specific phenotype and/or diseases of interest
  - Ensure all genes selected have clear evidence for gene-disease association

Important points to review during panel selection include:

- Number of panels
  - One panel for a highly defined patient phenotype
  - Multiple virtual panels in one test (WES/WGS) for patients with complex phenotypes
- Size of panel
  - Small panels may miss relevant gene(s) for patients with complex phenotypes
  - Large panels will be more complex to analyse and interpret, as there may be many 'variants of uncertain significance' (VUS) identified, and there is an increased chance of an incidental or secondary finding.
- Genes in panel
  - Should include genes with clear evidence for gene-disease association and with both clinical validity and clinical utility
  - Should exclude (or include with caution) genes with limited/disputed evidence for gene-disease association (gene of uncertain significance; GUS) and/or unrelated to phenotype

Test cost and funding

The cost of genomic testing will vary between laboratories, and will depend on:

- Genomic test type (i.e. targeted panel vs exome vs genome)
- Size and number of panels (i.e. number of genes analysed)
- Turnaround time requested
- Singleton (patient only) vs trio (patient and both parents)

In addition to the laboratory cost of testing, a DNA extraction and send away cost may be incurred for testing performed at an interstate or international laboratory.

Determine the method of test funding:

- Public (speciality service) - ensure there is approval from relevant consultant and/or clinical director
- Medicare - ensure you review eligibility criteria for testing (www.mbsonline.gov.au)
- Private (patient self-funded)

Laboratory selection

Determine which accredited clinical laboratory (local, interstate, or international) can perform the desired genomic test, within the desired turnaround time that applies to the clinical urgency, and within the available funding for testing.

Commonly used laboratories include:

- VCGS
  https://www.vcgs.org.au/tests/genomics
- Westmead
  https://www.schn.health.nsw.gov.au/find-a-service/laboratory-services/sydney-genome-diagnostics/molecular-genetics
- PathWest
  https://pathwest.health.wa.gov.au/Our-Services/Clinical-Services/Diagnostic-Genomics
- Fulgent
  https://www.fulgentgenetics.com/
- BluePrint
  https://blueprintgenetics.com/
- PeterMac
  https://www.petermac.org/
- SA Pathology
  https://www.sapathology.sa.gov.au

Test requirements

Patient consent

Pre-test written patient consent is an essential process for requesting diagnostic genomic testing and constitutes standard practice.

Most accredited clinical testing laboratories will request a copy of the signed consent form. Australian Genomics have developed national clinical genomic testing consent forms, which have been adapted by Pathology Queensland. These are available at:
https://qheps.health.qld.gov.au/pathology-queensland/testing/specialty-testing/genetic-testing

Consent discussions must cover all points on the consent form and include:

- Type of genomic test (e.g. panel, exome, or genome)
- Type of analysis (i.e. genes/diseases associated with the phenotype)
- Possible outcomes (e.g. positive, negative, variant(s) of uncertain significance)
- Limitations of test
- Chance of incidental findings (including incidental diagnosis, unexpected family relationships)
- Potential alternatives to testing
- Implications for future insurance
- Implications of and access to results for family members
- Expected timeframe for results
- Method of returning results
- Data and sample sharing and storage

Provide the patient with a genomic testing fact sheet (available online at above address).

A patient may decide not to proceed with diagnostic genomic testing or may wish to have more time to consider the above issues.

Ensure a copy of the signed patient consent form is saved in the patient's medical records (e.g. ieMR).

Pathology request form

Public services requesting genetic testing in Queensland should use Pathology Queensland request forms. These are available at:
https://qheps.health.qld.gov.au/pathology-queensland/testing/specialty-testing/genetic-testing

Complete the relevant pathology request form based on test funding:

- Public request form (red colour) for testing funded by a speciality service
- Private request form (cyan colour) for testing funded by Medicare

For accurate test processing and billing, clearly document the following on the form (see Appendix):

- Clinical phenotype information
- Relevant family history
- Name of testing laboratory (if not performed at Pathology Queensland)
- Type of genomic test
- Name of gene panel(s) requested
- Primary consultant's name, contact details, and department
- Billing institution (i.e. speciality service, Medicare, or patient)

Test requisition form

Some accredited clinical testing laboratories will request a completed test requisition form, which can be completed on a paper form or through an online portal with clinician specific log in details.

For accurate test processing and billing, clearly document the following on the form:

- Clinical phenotype information
- Relevant family history
- Type of genomic test
- Name of gene panel(s) requested
- Primary consultant's name, contact details, and department
- Billing institution (i.e. speciality service, Medicare, or patient)

Interstate/international laboratories

Samples sent for genomic testing performed at interstate or international laboratories are processed through Pathology Queensland.

For accurate test processing and billing, email the 'Genetic-Referrals' department (Genetic-Referrals@health.qld.gov.au) in Pathology Queensland with the following details:

- Demographic details of patient (i.e. name and date of birth)
- Name of testing laboratory
- Type of genomic test/name of gene panel(s) requested
- Test requisition form (if paper)
- Consent form

Post-test requirements

Ensure you are confident in interpreting the outcomes of genomic testing and the relevant implications.

Result disclosure remains the responsibility of the requesting clinician/consultant, so ensure you have agreed a plan for results disclosure with the patient. You may wish to discuss with or seek additional support from Genetic Health Queensland.

Referrals for patients to Genetic Health Queensland to discuss and/or interpret their genomic test results will be subject to standard clinical prioritisation criteria and triaging. Please consider timing of a referral to Genetic Health Queensland when arranging a genomic test.

Case discussion and support

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

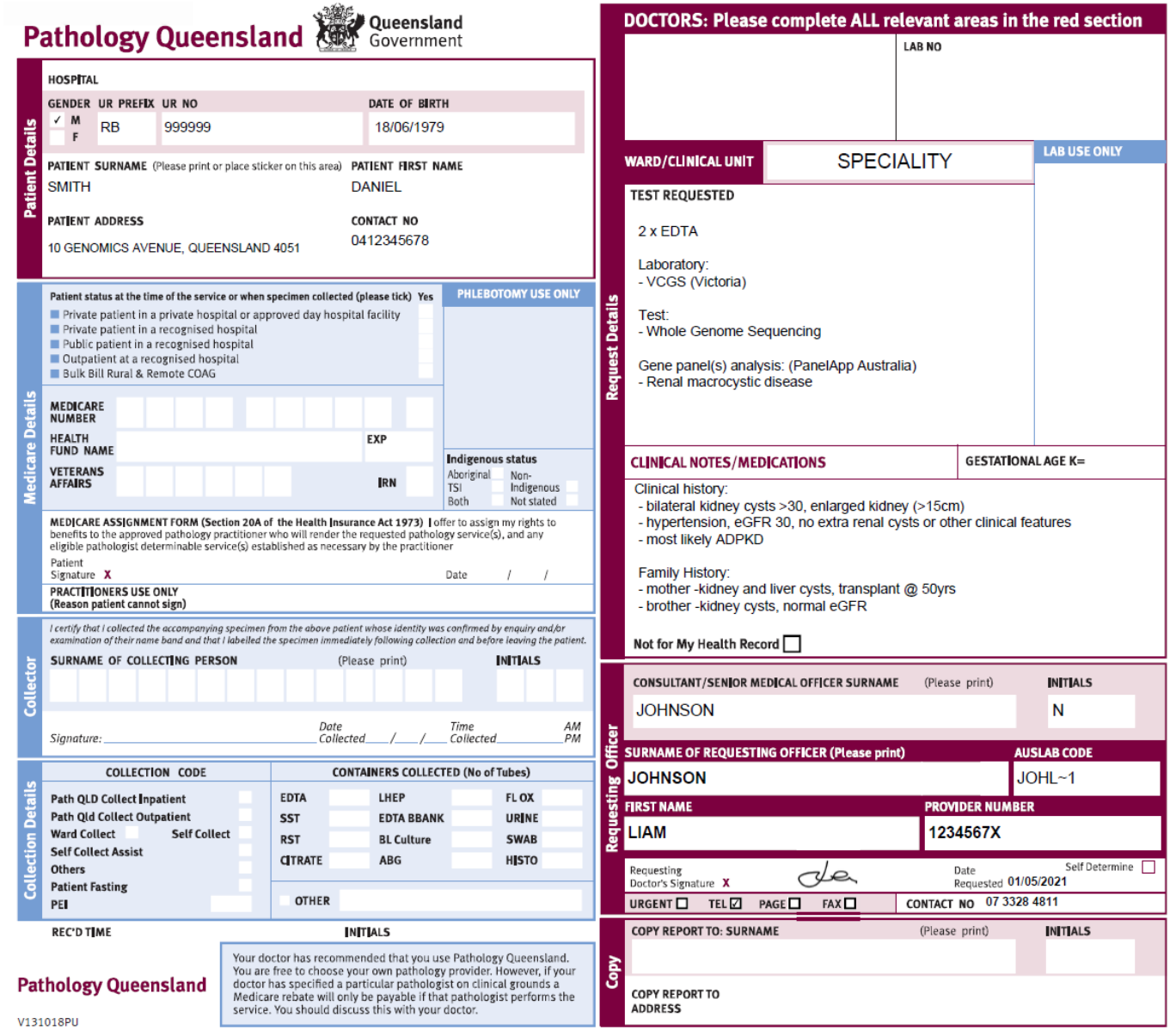
For case discussion, please contact the on-call team at Genetic Health Queensland on:
Phone: (07) 3646 1686
Email: GHQ@health.qld.gov.au

Resources

Further educational resources can be found at:

- Queensland Health
  - Genomics Foundations online modules
    https://central.csds.qld.edu.au/central/courses/466
- The Royal Australasian College of Physicians
  - College Learning Series
    https://elearning.racp.edu.au/course/view.php?id=94
  - Clinical Genomics for Physicians
    https://elearning.racp.edu.au/course/view.php?id=147
- The Centre for Genetics Education - Genomic testing
  https://www.genetics.edu.au/health-professionals/genomics-1/genomics
- Melbourne Genomics Health Alliance - Genetic and genomic testing guide
  http://learn-genomics.org.au
- Health Education England Genomics Education Programme
  www.genomicseducation.hee.nhs.uk
- National Human Genome Research Institute Genomics Education Websites
  www.genome.gov/about-genomics/teaching-tools/Genomics-Education-Websites

Appendix - Example pathology request form



Pathology Queensland — Queensland Government

Patient Details

HOSPITAL

GENDER	UR PREFIX	UR NO	DATE OF BIRTH
✓ M / F	RB	999999	18/06/1979

PATIENT SURNAME (Please print or place sticker on this area): SMITH

PATIENT FIRST NAME: DANIEL

PATIENT ADDRESS: 10 GENOMICS AVENUE, QUEENSLAND 4051

CONTACT NO: 0412345678

Medicare Details

Patient status at the time of the service or when specimen collected (please tick) — Yes

- Private patient in a private hospital or approved day hospital facility
- Private patient in a recognised hospital
- Public patient in a recognised hospital
- Outpatient at a recognised hospital
- Bulk Bill Rural & Remote COAG

PHLEBOTOMY USE ONLY

MEDICARE NUMBER

HEALTH FUND NAME — EXP

VETERANS AFFAIRS — IRN

Indigenous status: Aboriginal / TSI / Both / Non-Indigenous / Not stated

MEDICARE ASSIGNMENT FORM (Section 20A of the Health Insurance Act 1973) I offer to assign my rights to benefits to the approved pathology practitioner who will render the requested pathology service(s), and any eligible pathologist determinable service(s) established as necessary by the practitioner

Patient Signature X — Date / /

PRACTITIONERS USE ONLY (Reason patient cannot sign)

Collector

I certify that I collected the accompanying specimen from the above patient whose identity was confirmed by enquiry and/or examination of their name band and that I labelled the specimen immediately following collection and before leaving the patient.

SURNAME OF COLLECTING PERSON (Please print) — INITIALS

Signature: _____ *Date Collected* __/__/__ *Time Collected* _____ AM PM

Collection Details

COLLECTION CODE		CONTAINERS COLLECTED (No of Tubes)			
Path QLD Collect Inpatient		EDTA		LHEP		FL OX	
Path Qld Collect Outpatient		SST		EDTA BBANK		URINE	
Ward Collect / Self Collect		RST		BL Culture		SWAB	
Self Collect Assist		CITRATE		ABG		HISTO	
Others							
Patient Fasting		OTHER					
PEI							

REC'D TIME — INITIALS

Pathology Queensland

V131018PU

Your doctor has recommended that you use Pathology Queensland. You are free to choose your own pathology provider. However, if your doctor has specified a particular pathologist on clinical grounds a Medicare rebate will only be payable if that pathologist performs the service. You should discuss this with your doctor.

DOCTORS: Please complete ALL relevant areas in the red section

LAB NO

WARD/CLINICAL UNIT: SPECIALITY

LAB USE ONLY

Request Details

TEST REQUESTED

2 x EDTA

Laboratory:
- VCGS (Victoria)

Test:
- Whole Genome Sequencing

Gene panel(s) analysis: (PanelApp Australia)
- Renal macrocystic disease

CLINICAL NOTES/MEDICATIONS — GESTATIONAL AGE K=

Clinical history:
- bilateral kidney cysts >30, enlarged kidney (>15cm)
- hypertension, eGFR 30, no extra renal cysts or other clinical features
- most likely ADPKD

Family History:
- mother -kidney and liver cysts, transplant @ 50yrs
- brother -kidney cysts, normal eGFR

Not for My Health Record ☐

Requesting Officer

CONSULTANT/SENIOR MEDICAL OFFICER SURNAME (Please print): JOHNSON — INITIALS: N

SURNAME OF REQUESTING OFFICER (Please print): JOHNSON — AUSLAB CODE: JOHL~1

FIRST NAME: LIAM — PROVIDER NUMBER: 1234567X

Requesting Doctor's Signature X — Date Requested 01/05/2021 — Self Determine ☐

URGENT ☐ TEL ☑ PAGE ☐ FAX ☐ — CONTACT NO 07 3328 4811

Copy

COPY REPORT TO: SURNAME (Please print) — INITIALS

COPY REPORT TO ADDRESS