PREGEN

ANTENATAL GENOMICS
& NEWBORN CARE

Prenatal Diagnostic Genomic Testing – Clinical Referrals

Availability:

NSW Health Pathology Randwick, VCGS and SA Pathology. Prenatal trio WES is currently available with WGS to become available in the future. Please check with laboratories for details on the most appropriate test for your patients (trio, singleton, gene panel).

Please direct testing inquiries to your local Genomic Laboratory:

- **NSW Health Pathology - E:** NSWPATH-RandwickGenomics@health.nsw.gov.au or **P:** +61 2 9382 9169 or +61 2 9382 9114
- **VCGS – E:** VCGSgenomics@vcgs.org.au or **P:** 1300 118 247
- **SA Pathology – E:** Prenatal Coordinator wendy.waters@sa.gov.au or **P:** 08 8222 3000

Prenatal Diagnostic Genomic Testing may be suitable if:

- Fetal imaging anomalies consistent with a clinically significant disorder.
- The underlying condition is likely to have a monogenic or copy number variant basis.
- Perinatal management may be improved if a genetic condition is identified.

Consenting Families for Prenatal Diagnostic Genomic Testing

- Maternal Fetal Medicine and Clinical Genetics teams provide pre-test counselling.
- Locally approved consent forms may be used for consent for prenatal genomic testing.

Sample Requirements

- **If CVS/Amnio had already been completed,** send information on what prior testing was undertaken (chromosome microarray, karyotype), whether amniotic/chorionic sample used, date of sample and laboratory where sample was analysed.
- **If CVS/Amnio had not been completed,** send 2 x 20ml of amniotic samples to NSWHP Randwick, VCGS or SA Pathology. A chromosome microarray will generally be run in advance of the WES/WGS, however in some circumstances running a concurrent array is acceptable and can be discussed with the PreGen team.
- **5-10ml EDTA** blood for DNA from both parents (trios) for extraction and storage
- Maternal EDTA blood is required for maternal cell contamination studies (all studies).
- If insufficient DNA is available, DNA cell culture or a new amniocentesis will be required.

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Prenatal Diagnostic Genomic Testing Documentation Requirements

For requests to NSWHP Genomic Laboratory Randwick:

- Send test request form to: NSWPATH-RandwickGenomics@health.nsw.gov.au
- Please note where consent is stored.
- Please provide a gene list or contact the laboratory for gene choice for gene panels.

For requests to VCGS:

- Test request form (https://vcgs.link/genomics-request) with a clinical summary
- Signed informed consent form (https://vcgs.link/genomics-consent)
- Payment authorisation
- Select targeted gene panels for (PanelApp Australia (umccr.org))

For more information you may contact the laboratory on **P:** 1300118247 or **E:** vcgs@vcgs.org.au

For requests to SA Pathology:

- For any sample queries, please contact Genome Analyst, Lucas DeJong, at SA Pathology on (08) 8222 3438 or Lucas.Dejong@sa.gov.au or Health.SAPathologyGenomicsUnitFRM@sa.gov.au
- Please provide a clinical summary to accompany the test request.
- SA Pathology request forms and genomic test consents are available on request.

Results and turn-around times (TAT) for prenatal genomic testing

- TAT is usually within 4 weeks of sample receipt. TAT may be longer if cells need to be cultured to ensure sufficient DNA is available.

Variant Reporting

- Variants are reported if pathogenic/likely pathogenic with a clear relationship to a disorder.
- **Variants of unknown significance (VOUS) will not be reported** unless:
  (1) in an autosomal recessive condition where there is a likely pathogenic or pathogenic variant *in trans* with a VOUS or
  (2) additional clinical information changes the prior assessment of a variant as a VOUS to pathogenic or likely pathogenic.
- Variants associated with an untreatable adult-onset condition in the fetus and/or a parent **will not be reported**.
- Variants associated with a treatable adult-onset condition in a parent **will be discussed with the referring clinician** prior to reporting.
- **Carrier status for autosomal recessive conditions** outside the clinical phenotype are generally not reported.

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Billing and Charges

- The institution from which the referral is made is responsible for covering the cost of the prenatal genomic diagnostic testing, unless written payment authorisation is received for a different funding source or the patient provides written payment authorisation for patient-funded genomic testing.

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PreGen Antenatal Genomics and Newborn Care Study

What is PreGen?

PreGen will provide funded genomic testing via exome and genome trios in 3 national diagnostic genomic laboratories (NSW Health Pathology Randwick, VCGS, SA Pathology) for families who have ultrasound abnormalities identified in pregnancy.

To qualify for a PreGen funded prenatal exome or genome, families will need to consent to be part of the research study after they have received information about PreGen. The study involves undertaking two psychosocial questionnaires with the PreGen Genetic Counsellor and allowing the study to access their MBS and PBS data for the length of the project.

If a microarray is uninformative or likely to be uninformative due to the phenotype, genomic testing may progress.

How are families enrolled in PreGen?

Clinical teams will discuss and consent the family for clinical prenatal genomic testing using their usual counselling and consent processes. Prenatal diagnostic testing will be requested from genomic laboratories based on clinical criteria prior to involving families in PreGen study discussions.

After amniocentesis or CVS and parental blood samples have been collected for clinical prenatal genomic testing, families may be considered for enrolment in PreGen by the clinical genetic and maternal fetal medicine teams from major national hospitals where:

- The PreGen clinical criteria (see below) are met.
- The parents wish to discuss the study with a PreGen Genetic Counsellor.

There will be no obligation on parents to enrol in the PreGen study or undertake the questionnaires when contacted by the PreGen genetic counsellor. Diagnostic genomic testing will be available to the parents as previously planned by the clinical team if they choose not to be part of the study when they are contacted by the PreGen team.

What testing is available via PreGen?

Trio WES testing is currently available in PreGen. Trio WGS will be available soon. The total number of trios funded nationally will be no more than 400.

- Anticipated finish date of PreGen project: 30/06/2024

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What does PreGen research study involve for families?

Information collected during PreGen will help to understand the best way to care for families who have genomic testing in pregnancy and to assess the need for and future use of a Medicare item number for prenatal genomic testing.

Parents will be asked to complete two questionnaires, one within 4 weeks of study enrolment (before genomic results are returned) and the other within 6 months post genomic results. De-identified information provided in the questionnaires will determine understanding and expectations for prenatal genomic testing.

Permission will be sought to access MBS and PBS data for the length of the study to assess the health economic benefits of antenatal diagnosis.

The PreGen genetic counsellor will consult with referring clinicians prior to contacting families to ensure whether it is an appropriate time.

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PreGen Inclusion Guide

PreGen is limited to those families who will undergo genomic diagnostic testing as a family trio or where both the mother/egg donor and father/sperm donor are available for testing. Single parent families or those requiring a gene panel or singleton test may access prenatal genomic testing but cannot be included in the translational PreGen project.

PreGen will also accept:

- Families considering the option of termination if they fulfill other inclusion criteria
- Families who have decided to have a termination where the process of termination has not begun, if they fulfill other inclusion criteria
- Referrals from private practitioners if the patient/ family meets the inclusion criteria and a clinical geneticist or clinical genetic counsellor is involved in their care.
- Public referrals when alternatives for funded genomic testing (e.g., a clinically appropriate genomic panel) are available as a local alternative test.

Eligible participants must also be able to:

- Provide informed consent.
- Be Medicare eligible.

Testing in PreGen is limited to:

Families where the fetus is believed to be alive at the time of enrolment (preterminal imaging findings are exclusion criteria). Families must have seen a Genetics service for clinical testing consent to be included in the PreGen study.

Clinical Inclusion

A fetus with a structural anomaly likely to have a single gene germline aetiology including:

- A significant/ severe brain abnormality
- Bilateral ventriculomegaly over 12 mm
- A significant cardiac abnormality
- Renal anomalies with a likely Mendelian basis
- A phenotype consistent with skeletal dysplasia
- Evidence of multi-joint arthrogryposis
- Non-immune fetal hydrops
- Isolated NT of over 5mm
- Isolated agenesis of the corpus callosum or a significant abnormality of the corpus callosum

Significant isolated malformations (i.e., bilateral talipes, cleft lip/palate, or others) that usually occur in isolation but which have an early onset, are severe and/or combined with other ultrasound abnormalities.

Significantly abnormal biometry:

- Growth restriction (<3rd centile) without placental insufficiency

Exclusion Criteria

- The family do not wish to take part in PreGen.
- The process of termination of pregnancy has begun.
- Likely non-genetic or undiscoverable aetiologies including teratogenesis, viral infections, and poorly controlled maternal diabetes.
- Recognised syndromes/ malformation complexes with no known gene associations (Pentalogy of Cantrell/ limb body wall complex/ cloacal anomalies/ field defects)

Anomalies with a low diagnostic yield including:

- Apparently isolated anatomical cardiovascular defect with minimal implications for postnatal clinical care (such as ASD, VSD, PDA)
- Isolated mild unilateral or bilateral ventriculomegaly

A chromosome microarray will generally have been run in advance of the WES/WGS, however in some circumstances, running a concurrent array is acceptable and can be discussed with the PreGen team.

Inclusion criteria for specific families will be discussed in a PreGen subcommittee if their acceptability into the project is unclear.

The team will also contact clinicians asking the purpose of their referral and whether a diagnosis is required or needing to be excluded.

Additional non-PreGen funded clinical diagnostic testing may be requested by the treating clinician outside of these criteria after discussion with the testing laboratory.

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Contact Information for the PreGen team

PreGen Website: https://pregen.neura.edu.au

- Referral and consent forms and laboratory information are available here.
- For further information and referrals, please contact your local PreGen team.

PreGen Genetic Counselling Team (central contacts)

- **P:** +61 2 9399 1817; pregen@neura.edu.au

These contact details should be used for all urgent inquiries as it is monitored by a PreGen Genetic Counsellor who can direct your inquiry to the most appropriate contact.

Primary PreGen Contacts (Sydney)

- Tony Roscioli – Genomic specialist & Chief Investigator **P:** +61 2 9382 9169
- Alyssa Wilson – PreGen Program Manager **P:** +61 400 422 639

Primary PreGen contacts (Melbourne)

- George McGillivray – Geneticist & Lead Investigator **P:** +61 3 8341 6366 (VCGS switchboard)

PreGen Genetic Counsellors

- Rebecca Vink – **P:** +61 2 9399 1817; r.vink@neura.edu.au
- Kate Ross - **P:** +61 8 8161 7375 / +61 0403 217 360; kate.ross@sa.gov.au
- Sarah Long – **P:** +61 404 475 632; pregen@neura.edu.au

Local Genomic Laboratory Contact Details

NSW Health Pathology
E: NSWPATH-RandwickGenomics@health.nsw.gov.au
P: +61 2 9382 9169 or +61 2 9382 9114

VCGS
E: VCGSgenomics@vcgs.org.au or **P:** 1300 118 247

SA Pathology
Contact: Genome Analyst, Lucas DeJong lucas.dejong@sa.gov.au or
E: Health.SAPathologyGenomicsUnitFRM@sa.gov.au **P:** 08 8222 3438