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The PreGen Research Program: Implementing Prenatal Genomic Testing in Australia—A Commentary

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ABSTRACT

Prenatal genomic sequencing, which can provide a significantly increased diagnostic rate for fetal structural anomaly (FSA) compared with karyotype and microarray, is not available uniformly across Australia. PreGen, a 5-year translational research program, has identified significant barriers to implementation including access to funding, the availability of genomic testing, access to termination of pregnancy services and the availability of specialist genomic centres. A federal item number for prenatal genomic testing would increase equitable test availability and reduce delays to diagnoses by making them in pregnancy whilst removing the need for low-yield diagnostic interventions and enabling personalised patient management and family support.

1 | Introduction

The introduction of prenatal exome and genome sequencing (ES/GS) for fetal structural anomalies (FSA) has been shown to achieve a significantly increased diagnostic rate compared with karyotype and microarray [1]. Despite this, prenatal genomic testing is not available uniformly across Australia for families with high-risk pregnancies. Approximately 2%–5% of pregnancies will have an FSA detected on ultrasound [2], and more than 80% of these have a genetic aetiology [3]. The prenatal diagnostic rates for conventional testing (prior to next-generation sequencing) are 8%–10% for karyotype [2] and 6% for microarray [4]. The overall ES diagnostic rate for FSA has been estimated to be 31% [1].

Early diagnosis of a genetic disorder in pregnancy may benefit families by decreasing costly and time-consuming diagnostic odysseys [5] and enabling the development of tailored perinatal management plans and patient counselling [6]. Prenatal diagnoses can also facilitate reproductive modulation [6]. Even an uninformative result may be helpful in providing reassurance for families as the residual risk of a Mendelian disorder may be reduced.

PreGen (https://pregen.neura.edu.au/) is a 5-year translational research program that aims to implement prenatal genomic testing for FSA in the Australian population and to better understand how to care for patients and families undergoing genomic testing in pregnancy. As PreGen has progressed, we have identified significant barriers to the implementation of prenatal genomic testing in Australia. These include access to funding, the availability of genomic testing, access to termination of pregnancy services and the availability of specialist genomic centres and support services.

2 | Access to Funding

In Australia, prenatal ES trio testing costs approximately $3200. There is no uniformity of genomic testing budgets within the public hospital system. There are gaps in funding for some locations which may lead to referrals being made to laboratories with the lowest costs even if in a different state. ES trio costs are prohibitive for many patients to self-fund, further compounding the inequity of service provision. In the context of FSA, some maternity hospitals and genetic units without specific funding for ES trios may offer to fund less expensive alternatives with a lower diagnostic rate such as limited gene panels [7].

The PreGen program provides funding for prenatal genomic testing for families with an identified FSA who may then also take part in psychosocial and health economic assessments. The PreGen inclusion criteria are listed in Table 1. A requirement of referral to PreGen from a public hospital is that a funded genomic test would otherwise be available if the patient does not wish to take part in PreGen. This was an ethical consideration to reduce the risk of undue influence on patients invited to participate in the research program. This requirement for "safety net" funding has already highlighted that alternative funding options for prenatal genomic testing do not exist in some locations. Alternative funding pathways were required to be established by some referring hospitals to enable PreGen enrolment for their patients. The absence of uniform local funding could be resolved with a federal MBS item number for prenatal genomic testing.

3 | Availability of Testing

There are currently only three laboratories accredited for prenatal ES testing in Australia, meaning that patients from several states require samples to be transferred to interstate laboratories. This can increase the turn-around time for results as well as the chance of sample loss. The urgency of prenatal genomic samples also impacts every laboratory's resources to process local samples, both urgent and non-urgent. Ideally, each state should have an appropriately sized provider of prenatal genomic testing, which could be facilitated through a federal MBS item number.

In addition to sample processing arrangements, families who reside in areas that are distant from metropolitan hospitals may experience delays in diagnosis, as well as financial burden and logistical complexity. Rural and regional patients may be required to have multiple appointments in city hospitals or stays in a metropolitan area to access prenatal genomic testing. Some patients may need to rely on family members to look after other children while they attend multiple appointments. Other patients may not have this option, leading to additional logistical and financial burdens related to childcare arrangements. Each state also has different travel and accommodation benefits available for families. Unexpected costs and complex claims processes can impact patients financially at a time when they are under immense psychological pressure. The PreGen program is examining how the area of residence impacts families' experiences when accessing prenatal genomic testing with a view to improving the model of care and reducing inequity for rural and regional families.

4 | Access to Termination of Pregnancy Services

Access to termination of pregnancy after diagnosis of FSA varies across Australia. The termination of pregnancy laws also vary state by state (Table 2). In Australia, women routinely have a detailed morphology ultrasound examination at 18–20 weeks gestation. The earlier 11–14 week ultrasound scan confirms fetal number, gestation and viability and is used to screen for common forms of aneuploidy (trisomies 21, 18 and 13) [8], but most FSAs are currently detected later in gestation [9]. Given the restrictions placed on the termination of pregnancy in some states, families may have limited opportunity to decide on the outcome of a pregnancy if a genomic diagnosis occurs after 20 weeks gestation.

Faster and more accurate means of testing pregnancies for genetic conditions could facilitate broader choices regarding pregnancy management for families. A federal MBS item number for prenatal genomic testing could improve access, reduce turnaround times and promote discussion in legislative bodies regarding the discrepancies in termination of pregnancy laws around Australia. Examining some state-specific laws to harmonise the time required for families to access testing and facilitate reproductive decisions may be beneficial to improve equity of access to termination of pregnancy.

5 | Availability of Specialist Genomic and Support Services

While each state has maternal-fetal medicine teams, they are not all integrated with genetic services with ready access to clinical geneticists and genetic counsellors. Access to counsellors trained in providing prenatal genetic counselling is required for the best patient outcomes [10, 11] and patients also seek genetic counselling prior- and post-termination of pregnancy for FSA [12, 13]. Patients often want rapid answers following the termination of pregnancy to understand recurrence risk in future pregnancies [11]. Inadequately resourced genetics units have long wait times for appointments, limiting timely access to genomic testing for families planning future pregnancies.

Collaboration between maternal-fetal medicine teams and clinical genetics units is integral to the referral process and

TABLE 1 | PreGen inclusion and exclusion criteria.

Inclusion criteria

Guiding principles: Clinical genomic testing should be available to maximise diagnostic options for a pregnant woman and her partner. Inclusion in PreGen is limited to those families who have had 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 where a gene panel or singleton test on the fetus are most appropriate may access prenatal genomic testing as well, but cannot be included in the translational PreGen project to ensure standardisation of the analysis cohort.

Eligible participants must also be able to:

- Provide informed consent

Involvement in PreGen is appropriate when genomic testing has been performed already according to the following criteria:

- The underlying condition is highly likely to have a monogenic (single gene) basis
- The anomalies in the fetus are consistent with a clinically significant disease
- The underlying condition would be difficult to diagnose by traditional clinical non-genomic means
- Management, either during pregnancy or after birth, is likely to be better directed or altered if a gene change is identified

Testing is restricted to:

Families where the fetus is believed to be alive at the time of enrolment (fetuses with preterminal imaging findings should not be enrolled into PreGen)

A fetus with a structural anomaly likely to have a single gene germline aetiology. Some examples include (but are not limited to):

- 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 5 mm
- 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 may also be included if they 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 or the family have decided to have a termination of pregnancy no matter what is reported on genomic testing
- 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 defects with minimal implications for postnatal clinical care (such as ASD, VSD, PDA)
- Isolated mild unilateral or bilateral ventriculomegaly without other cerebral malformations

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

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

appropriate perinatal management [14, 15]. Patient services are maximised when teams work cohesively to counsel patients about ultrasound findings, arrange the most appropriate testing and provide genetic counselling in a timely manner [15, 16]. The extent to which collaborative management is achievable is often dependent on locality-specific resourcing which is not uniform across Australia. Local solutions are therefore required for best-practice patient management [17].

Multiple studies have highlighted the importance of support services being made available for families who have a diagnosis of an abnormality in pregnancy [18]. This can include social work support, experienced perinatal loss midwives and in-hospital psychology services [19]. Unfortunately, access to these services is not equal across Australia or even within states. Despite the existence of best-practice guidelines in perinatal loss, management pathways are heavily dependent on which facility identifies the FSA [20]. Some tertiary hospitals can provide access to all these support services however in other centres the perinatal loss midwife performs the role of social worker as well as mental health professional. Support services need to be available to all patients diagnosed with an FSA or experiencing pregnancy loss.

TABLE 2 | Abortion laws by the Australian State.

ACT	Termination of pregnancy is legal at all stages of pregnancy if performed by a qualified medical professional
NSW	Termination of pregnancy can be performed at up to week 22 of pregnancy. After that, two doctors must approve the procedure
NT	One doctor can approve and perform termination of pregnancy at up to week 24 of pregnancy. After this, at least two doctors must approve the procedure
QLD	Termination of pregnancy can be performed at up to week 22 of pregnancy. After this, two doctors must approve the procedure
SA	Termination of pregnancy can be performed at up to 22 weeks and 6 days of pregnancy. TOP performed after this time must be approved by two doctors and only if they agree that: • Your health or mental well-being is at risk, or • The procedure is needed to save another fetus (e.g. in a multiple pregnancy), or the fetus has a serious abnormality
TAS	Termination of pregnancy can be performed at up to week 16 of pregnancy. Between 16 and 20 weeks, two doctors must approve the procedure. After 20 weeks an abortion can only be performed for medical reasons, such as if the pregnancy is putting your life in danger
VIC	Termination of pregnancy can be performed at up to week 24 of pregnancy. After 24 weeks, two doctors must approve the procedure
WA	Until March 2024 termination of pregnancy could only be performed at up to week 20 of pregnancy. Termination of pregnancy after 20 weeks was very restricted and patients seeking termination of pregnancy had to apply through a ministerial panel which takes into account the severity of any fetal anomaly and the mother's circumstances. The law has now changed so abortion is permitted up to 23 + 6 weeks gestation and after that can proceed if two doctors agree

Note: Adapted from Health Direct, https://www.healthdirect.gov.au/abortion#:~:text=Abortion%20law%20in%20Australia%20varies%20across%20states%20and,of%20a%20clinic%20or%20service%20that%20provides%20abortions.

6 | Next Steps

There is a clear need for adequate public funding to be provided for pregnant women seeking prenatal genomic testing for FSA to achieve best practice and equitable care for all patients across Australia. The PreGen program's evaluation of the impact of prenatal genomic testing on decision making for patients and healthcare providers is providing valuable insights on how to address the current barriers to equitable access. PreGen has been well-received by families to date. Comprehensive data from the psychosocial sub-study will identify the psychological impact of PreGen, including perceived benefits and any associated challenges.

The results of PreGen will be used to design best-practice prenatal genomics management guidelines inclusive of psychosocial support and resourcing for required turn-around times for test reporting. The aim is to facilitate the provision of a federal item number for prenatal genomic testing to increase equitable test availability, promote the use of local resources and reduce delays to diagnoses by making them in pregnancy. The introduction of prenatal genomic testing will remove the need for low-yield diagnostic interventions while emphasising personalised patient management and family support.

Ethics Statement

The PreGen study has been approved by the Human Research Ethics Committee at The Royal Children's Hospital Melbourne (approval number: 74465).

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Conflicts of Interest

The authors declare no conflicts of interest.

References

1. R. Mellis, K. Oprych, E. Scotchman, M. Hill, and L. S. Chitty, "Diagnostic Yield of Exome Sequencing for Prenatal Diagnosis of Fetal Structural Anomalies: A Systematic Review and Meta-Analysis," *Prenatal Diagnosis* 42, no. 6 (2022): 662–685.

2. A. C. Jelin and N. Vora, "Whole Exome Sequencing: Applications in Prenatal Genetics," *Obstetrics and Gynecology Clinics of North America* 45, no. 1 (2018): 69–81.

3. F. Mone, C. O'Connor, S. Hamilton, et al., "Evolution of a Prenatal Genetic Clinic—A 10-Year Cohort Study," *Prenatal Diagnosis* 40, no. 5 (2020): 618–625.

4. R. J. Wapner, C. L. Martin, B. Levy, et al., "Chromosomal Microarray Versus Karyotyping for Prenatal Diagnosis," *New England Journal of Medicine* 367, no. 23 (2012): 2175–2184.

5. D. Incerti, X.-M. Xu, J. W. Chou, N. Gonzaludo, J. W. Belmont, and B. E. Schroeder, "Cost-Effectiveness of Genome Sequencing for Diagnosing Patients With Undiagnosed Rare Genetic Diseases," *Genetics in Medicine* 24, no. 1 (2022): 109–118.

6. D. Chitayat and R. Babul-Hirji, "Genetic Counselling in Prenatally Diagnosed Non-Chromosomal Fetal Abnormalities," *Current Opinion in Obstetrics and Gynecology* 12, no. 2 (2000): 77–80.

7. Y. Sun, C. A. Ruivenkamp, M. J. Hoffer, et al., "Next-Generation Diagnostics: Gene Panel, Exome, or Whole Genome?," *Human Mutation* 36, no. 6 (2015): 648–655.

8. International Society of Ultrasound in Obstetrics and Gynecology, C. M. Bilardo, R. Chaoui, et al., "ISUOG Practice Guidelines (Updated): Performance of 11-14-Week Ultrasound Scan," *Ultrasound in Obstetrics & Gynecology* 61, no. 1 (2023): 127–143, https://doi.org/10.1002/uog.26106.

9. A. Syngelaki, A. Hammami, S. Bower, V. Zidere, R. Akolekar, and K. H. Nicolaides, "Diagnosis of Fetal Non-Chromosomal Abnormalities

on Routine Ultrasound Examination at 11–13 Weeks' Gestation," *Ultrasound in Obstetrics & Gynecology* 54 (2019): 468–476.

10. C. L. Hennig, J. Childs, A. Aziz, and A. Quinton, "The Effect of Increased Maternal Body Habitus on Image Quality and Ability to Identify Fetal Anomalies at a Routine 18-20-Week Morphology Ultrasound Scan: A Narrative Review," *Sonography* 6, no. 4 (2019): 191–202.

11. B. A. Bernhardt, B. B. Biesecker, and C. L. Mastromarino, "Goals, Benefits, and Outcomes of Genetic Counseling: Client and Genetic Counselor Assessment," *American Journal of Medical Genetics* 94, no. 3 (2000): 189–197.

12. C. Smith, S. S. Hashmi, J. Czerwinski, et al., "The Impact of Genetic Counseling on Women's Grief and Coping Following Termination of Pregnancy for Fetal Anomaly," *Journal of Genetic Counseling* 30, no. 2 (2021): 522–532.

13. A. Ramdaney, S. S. Hashmi, M. Monga, R. Carter, and J. Czerwinski, "Support Desired by Women Following Termination of Pregnancy for a Fetal Anomaly," *Journal of Genetic Counseling* 24 (2015): 952–960.

14. S. Long, P. O'Leary, and J. E. Dickinson, "Women's Responses to Prenatal Genetic Diagnosis and Attitudes to Termination of Pregnancy After Non-Invasive Prenatal Testing: An Online Survey of Western Australian Women," *Australian and New Zealand Journal of Obstetrics and Gynaecology* 63, no. 2 (2023): 219–227.

15. A. Rogers, L. De Jong, W. Waters, et al., "Extending the New Era of Genomic Testing Into Pregnancy Management: A Proposed Model for Australian Prenatal Services," *Australian and New Zealand Journal of Obstetrics and Gynaecology* 64 (2024): 467–474, https://doi.org/10.1111/ajo.13814.

16. S. J. Ralston, S. R. Leuthner, Obstetricians ACo, Gynecologists CoE, and American Academy of Pediatrics CoB, *Maternal-Fetal Intervention and Fetal Care Centers* (American Academy of Pediatrics, 2011), e473–e478.

17. F. H. Dekkers, A. T. Go, L. Stapersma, A. J. Eggink, and E. M. Utens, "Termination of Pregnancy for Fetal Anomalies: Parents' Preferences for Psychosocial Care," *Prenatal Diagnosis* 39, no. 8 (2019): 575–587.

18. L. D. Pesacreta, K. E. Cilli, A. K. Lawrence, and D. I. Bulas, "The Key Role of the Pediatric Radiologist in Developing a Multidisciplinary Fetal Center," *Pediatric Radiology* 50 (2020): 1801–1809.

19. S. Heaney, M. Tomlinson, and Á. Aventin, "Termination of Pregnancy for Fetal Anomaly: A Systematic Review of the Healthcare Experiences and Needs of Parents," *BMC Pregnancy and Childbirth* 22, no. 1 (2022): 441.

20. J. Fisher and C. Lafarge, "Women's Experience of Care When Undergoing Termination of Pregnancy for Fetal Anomaly in England," *Journal of Reproductive and Infant Psychology* 33, no. 1 (2015): 69–87.