Expanding the Scope of Reproductive Genetic Carrier Screening

Towards a National Screening Program

Australian Genomics

June 2025

Australian Genomics

Acknowledgement of Country

In the spirit of reconciliation Australian Genomics acknowledges the Traditional Custodians of country throughout Australia and their connections to land, sea, and community.

We pay our respect to their elders past and present and extend that respect to all Aboriginal and Torres Strait Islander peoples today.

Artwork by Yorta Yorta artist, Alkina Edwards, for Australian Genomics.

Informing the Implementation of a National Reproductive Genetic Carrier Screening Program

Australian Genomics

Table of Contents

Author Acknowledgement

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To every individual, family, clinician, scientist, researcher, advocate and supporter who has lent their voice and expertise to this work, your collective efforts are laying the foundation for a more equitable and informed approach to reproductive healthcare in Australia. Together we are helping to make reproductive genetic carrier screening more accessible to families across the country empowering them with knowledge and choice for generations to come.

Executive Summary

Project Title
Expanding the Scope of Reproductive Genetic Carrier Screening: Towards a National Screening Program

Background
Reproductive genetic carrier screening (RGCS) identifies reproductive couples who have an increased chance of having children with serious childhood onset inherited conditions. While Medicare funding for carrier screening for cystic fibrosis, spinal muscular atrophy and fragile X syndrome commenced in 2023, larger gene panels remain user pays, creating inequitable access. The Mackenzie's Mission research project piloted large scale RGCS with over 9,000 couples, demonstrating that a couple based, digitally enabled screening model is feasible, acceptable, cost effective and ethically defensible, and underscoring the need for a nationally coordinated program.

Methods
This report draws on evidence and research outcomes from Mackenzie's Mission and three subsequent priority projects conducted by Australian Genomics, which modelled 2030 service volumes, evaluated access to downstream services and considered digital infrastructure requirements. Findings were refined through expert working groups covering laboratory, clinical, workforce, data and community engagement considerations.

Recommendations
This report outlines a comprehensive set of recommendations to guide the design and delivery of a National RGCS Program. It recommends adopting the Mackenzie's Mission RGCS model for delivery at population scale (i.e., available to all people considering reproduction), allowing self-referral and delivering combined couple results. A secure, centralised digital platform and national registry should manage enrolment, data, and result delivery. Timely access to genetic counselling, prenatal diagnosis and in vitro fertilisation with pre-implantation genetic testing must be nationally funded and delivered equitably, including in regional and remote areas. Strong data governance is essential, including protections for privacy and Indigenous data sovereignty. A national education strategy is needed to engage healthcare providers including general practitioners, obstetricians, midwives, nurse practitioners and fertility specialists.

Conclusion
Implementing these recommendations will enable an equitable, ethical, culturally safe National RGCS Program for all Australians of reproductive age. The foundations laid by Mackenzie's Mission and the priority projects show that national implementation is achievable, economically sound and capable of reducing the impact of serious childhood genetic conditions through informed reproductive choice. In moving forward, it is critical to ensure the program is guided by inclusive governance structures, continuous community engagement, and a commitment to responsiveness and adaptability as genomic knowledge evolves. These elements will help ensure that RGCS remains relevant, trusted and impactful as part of Australia's broader approach to preventive and reproductive healthcare.

List of Acronyms

AR	Autosomal recessive inheritance
CF	Cystic fibrosis
FXS	Fragile X syndrome
IVF	In vitro fertilisation
MBS	Medicare Benefits Schedule
MM	Mackenzie's Mission
MSAC	Medical Services Advisory Committee
NPAAC	National Pathology Accreditation Advisory Council
PGT-M	Pre-implantation genetic testing for monogenic conditions
RGCS	Reproductive genetic carrier screening
SMA	Spinal muscular atrophy
XL	X-linked recessive inheritance

Background

Reproductive genetic carrier screening (RGCS) is a genetic test offered to individuals or couples to understand their chance of having children with serious childhood onset autosomal recessive or X-linked conditions. These conditions account for a significant proportion of childhood disease, contributing to approximately 20% of infant mortality and 10% of paediatric hospitalisations in countries with advanced healthcare systems. Around 5,000 genes have been linked to recessive conditions, a number that continues to grow with ongoing discoveries. Recessive conditions are typically inherited, and many people unknowingly carry disease-causing variants, making carrier screening a valuable tool for reproductive decision-making.

RGCS began in the 1960s (Antonarakis, 2019), when testing was first offered based on biochemical assays such as hexosaminidase A measurement for Tay-Sachs disease or red blood cell indices for haemoglobinopathies. By the late 1980s, genetic testing became possible, initially focusing on specific variants in a limited number of genes and targeted towards people of particular ancestral origins, such as screening for cystic fibrosis in people of European ancestry or several conditions common to people of Ashkenazi Jewish ancestry.

Technological advances, particularly massively parallel sequencing, now allow for simultaneous analysis of thousands of genes at lower cost. As a result, RGCS can be offered for large numbers of genes pan-ethnically. This approach can identify couples who have an increased chance of having children with a condition screened. These couples may then consider reproductive options such as *in vitro* fertilisation (IVF) with preimplantation genetic testing (PGT-M), prenatal diagnosis or using the information to prepare for the birth of a child with the condition. In Australia, screening for haemoglobinopathies is publicly funded through Medicare and state or territory programs. Carrier screening for cystic fibrosis (CF), spinal muscular atrophy (SMA), and fragile X syndrome (FXS) became eligible for Medicare funding in November 2023. However, other forms of RGCS are offered on a user-pays basis by a range of local and international providers, with significant variability in the conditions screened and the types of variants reported (Wang et al., 2023). National guidelines currently recommend offering RGCS for at least CF, SMA, and FXS to all women or couples planning pregnancy or in early pregnancy, and providing information about RGCS for larger numbers of genes (Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2023). Despite this, there is wide variation in access to screening and most people remain unaware of their chance of having children with a serious childhood onset inherited condition.

To address inequity of access and explore the acceptability and feasibility of a national screening approach, *Mackenzie's Mission* (MM), a $20 million national research initiative, piloted the implementation of RGCS for a large number of genes at scale in Australia. Over 10,000 reproductive couples were offered screening (Archibald et al., 2022; Kirk et al., 2024), and 9,107 underwent couple-based testing for approximately 1,300 genes linked to ~750 serious childhood-onset conditions. Notably, **80% of couples who received an increased chance result were identified as carriers for conditions not included in the currently funded three-gene panel**, highlighting the limitations of restricted screening. Overall, 1.9% of reproductive couples (about 1 in 50) received a result indicating an increased chance of having children with one or more of the conditions screened, compared to only 0.4% detection using the CF, SMA, and FXS panel alone.

A key component of MM was the submission of Application 1637 to the Medical Services Advisory Committee (MSAC) in March 2020, seeking public funding for expanding the scope of RGCS. Application 1637 "Expanded reproductive carrier testing of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions" was submitted in March 2020, considered by the PICO Advisory Sub-Committee in August 2021, assessed at the Evaluation Sub-Committee meeting in June 2022, then considered by MSAC in July 2022. While MSAC did not recommend funding under the Medicare model, the Public Summary Document for 1637 recognised the significant unmet need and inequities in access. The Committee encouraged resubmission, addressing concerns posed in the public summary document, and recommended the Department of Health consider the most appropriate implementation methodology, noting the need for infrastructure and coordination more conventionally associated with formal population screening programs than Medicare-subsidised tests. The outcomes from MM also indicated the optimal model is a coordinated, national screening program using a simultaneous screening model with reproductive couple-based results. Such a program would require scaling the MM model and integrating additional foundational elements common to other national screening initiatives. This report responds to areas identified by the Australian Government Department of Health, Disability and Ageing as requiring further development to support the establishment of a national program.

These focus areas are being progressed through the National RGCS Priority Project, which comprises three sub-projects:

1. **Modelling Workforce and System Capacity**
2. **Evaluating Accessibility and Affordability of Flow-on Services**
3. **Digital Infrastructure**

This report outlines the objectives and outcomes of each sub-project and provides recommendations to inform the proposed model for a nationally coordinated RGCS program.

Current RGCS Utilisation

In developing a plan for a nationally coordinated RGCS program, it is essential to first understand the current landscape of RGCS utilisation in Australia. Examining how screening is presently offered, accessed and funded, provides important context for future implementation and highlights existing gaps in equity, awareness, and service delivery. At present, carrier screening for CF, FXS and SMA is publicly funded through Medicare Benefits Schedule (MBS) item numbers 73451 and 73452, introduced 1 November 2023. Broader panels, screening for hundreds to approximately 1,200 genes, are available on a user-pays basis through private pathology providers. These providers may conduct testing locally or through international laboratories via send-away services. To support decision-making around program implementation, data were collected and analysed on the current utilisation of both the three-condition MBS-funded RGCS and larger panel, privately funded RGCS.

Three Condition RGCS

To assess utilisation of three-condition RGCS, data from private pathology laboratories and the MBS were analysed. Three condition RGCS is typically offered via a sequential screening approach, where the partner of female sex is screened first for all three conditions. Screening of the partner of male sex is only conducted if the female partner is identified as a carrier of CF or SMA. MBS item 73451

covers carrier screening for CF, FXS and SMA in individuals who are pregnant or planning a pregnancy. Item 73452 applies to the reproductive partner of a person found to be a carrier of CF or SMA under item 73451.

Three Condition RGCS Prior to the Introduction of Medicare Funding

There is limited data on rates of RGCS prior to the introduction of MBS item numbers 73451 and 73452. However, Robson et al (2020) estimated an overall RGCS rate of 1.36% across Australia (except Victoria), noting a marked socioeconomic gradient, with the highest screening rates in the most advantaged deciles (Robson et al, 2020). Similar patterns were observed in Victoria, where an estimated 1.5% of women of reproductive age and 3% of pregnant women accessed RGCS during the time period studied (2013 – 2018). Screening rates were eight times higher in the most advantaged socioeconomic quintile compared to the least advantaged (Leibowitz et al, 2022). The concentration of screening in the more socioeconomically advantaged inner metropolitan Melbourne local government areas is illustrated in Figure 1.

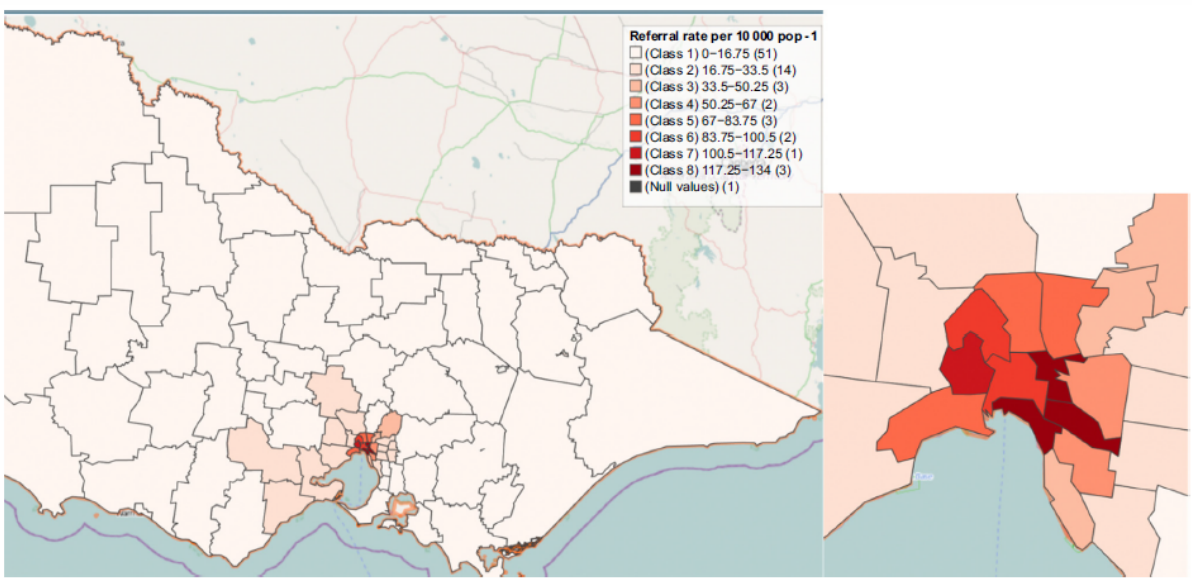


Figure 1: Screening rates per 10,000 population for each local government area in Victoria prior to the introduction of MBS item number 73451 (map on right is Metropolitan Melbourne area only) (Leibowitz et al, 2022).

To understand the impact of the introduction of MBS item numbers 73451 and 73452, testing data from two of the main RGCS pathology providers in Australia between November 2022 and November 2024 were requested and subsequently analysed. In the year prior to Medicare funding, the median number of tests per Local Government Area (LGA) was 1.9 (IQR 0.0 – 13.6). The number of tests per 100,000 in the female reproductive age population was highest in major cities compared to regional and remote areas (Figure 2A). The rate of tests was also highest in areas within the top SEIFA quintile (Figure 2B). A total of 139 LGAs had zero tests recorded and the distribution of LGAs with zero tests recorded differed significantly by remoteness area ($\chi^2(4) = 66.6$, $p < 0.001$) and SIEFA quintile ($\chi^2(4) = 39.2$, $p < 0.001$) (Figure 3). The spatial distribution of tests is presented in Figure 4A.

Collectively, published data and our analysis indicates that prior to the introduction of Medicare funding for three condition RGCS, screening rates were low and heavily skewed toward

socioeconomically advantaged and metropolitan areas, with substantial geographic and equity-related disparities across the country.

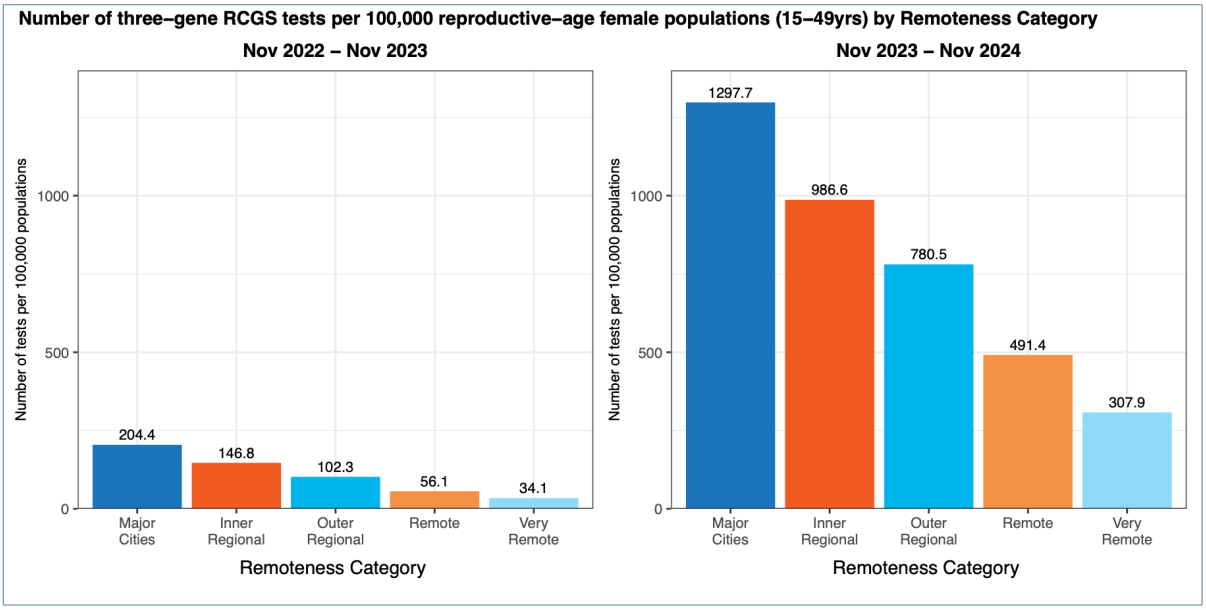
Impact of Medicare Funding for Three Condition RGCS

The impact of Medicare funding for three condition RGCS is evident from both MBS item number utilisation and laboratory testing data. In 2024, 112,644 tests were performed under MBS item number 73451 (Department of Health and Aged Care, 2025). This is approximately 41% of the estimated eligible population to whom RGCS would be directly relevant (i.e. planning a pregnancy or in early pregnancy). The most reliable benchmark for expected RGCS uptake is combined first trimester screening for common chromosome conditions such as Down syndrome. Although current delivery of chromosome screening is fragmented across multiple laboratories, historical data from a more centralised model at Victorian Clinical Genetics Services in 2014 showed that at least 77.5% of pregnant people accessed this screening. Similar levels of uptake would be anticipated for RGCS over time. Thus, three condition RGCS utilisation suggests that it has not yet reached anticipated population coverage.

Nonetheless, testing data from the two primary RGCS pathology providers show a 6.4 fold increase in sample volume within a year of Medicare funding, highlighting significant gains in access enabled by funded screening. These laboratories accounted for approximately 64.7% of tests billed under MBS item number 73451 for the same period. Across LGAs, the median number of tests was 14 (IQR 2.0 – 115.6). Test volumes were higher in major cities and in areas with greater socioeconomic advantage (Figure 2). Following the introduction of MBS funding, the number of LGAs with zero recorded tests decreased from 139 to 48, a reduction of 91 LGAs. However, the distribution of LGAs with no testing continues to vary significantly by remoteness area ($\chi^2(4) = 34.5$, $p < 0.001$) and SIEFA quintile ($\chi^2(4) = 42.2$, $p < 0.001$) (Figure 3). The spatial distribution of test volumes across Australia is shown in Figure 4B illustrating broader uptake.

Services Australia data support these findings, showing similar patterns of access by remoteness category and SEIFA quintile following implementation of MBS item 73451. However, the utility of this dataset is limited by suppression of some fields and a lack of granularity beyond broad demographic categories. For this reason, laboratory data have been presented as a more detailed and informative source. Services Australia records indicated that the highest screening rates occurred in the 30-34 age range (Figure 5) with the top three referring provider types being general practitioners, obstetricians and general practice trainees.

A)



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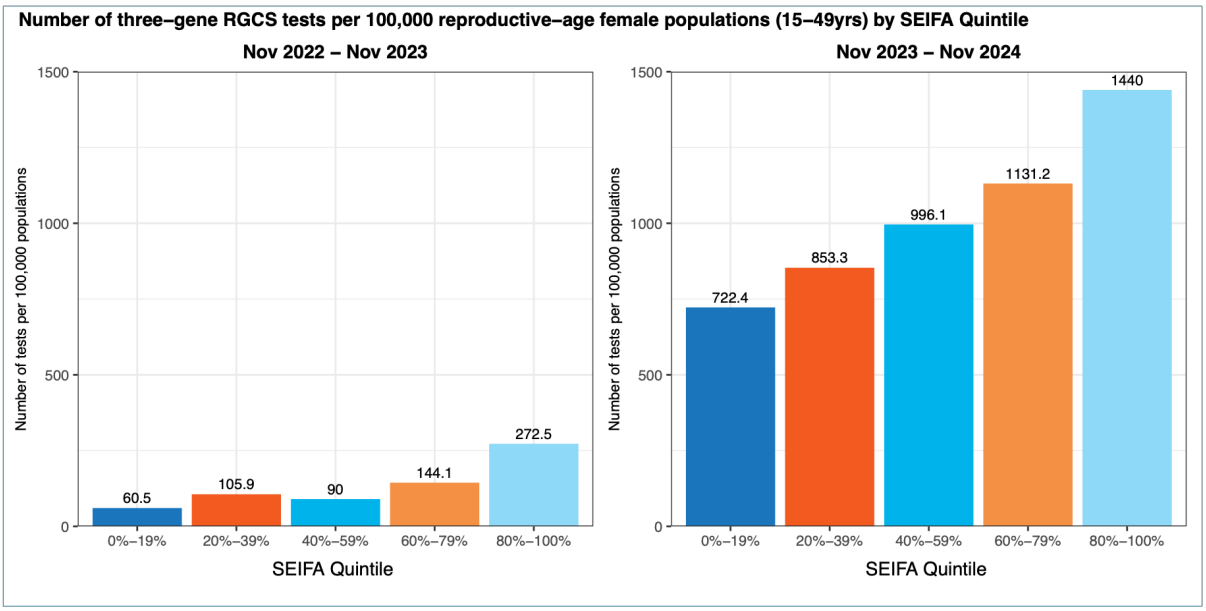

Figure 2: Rate of three-gene RGCS per 100,000 populations across A) Remoteness Category and B) SEIFA Quintile.

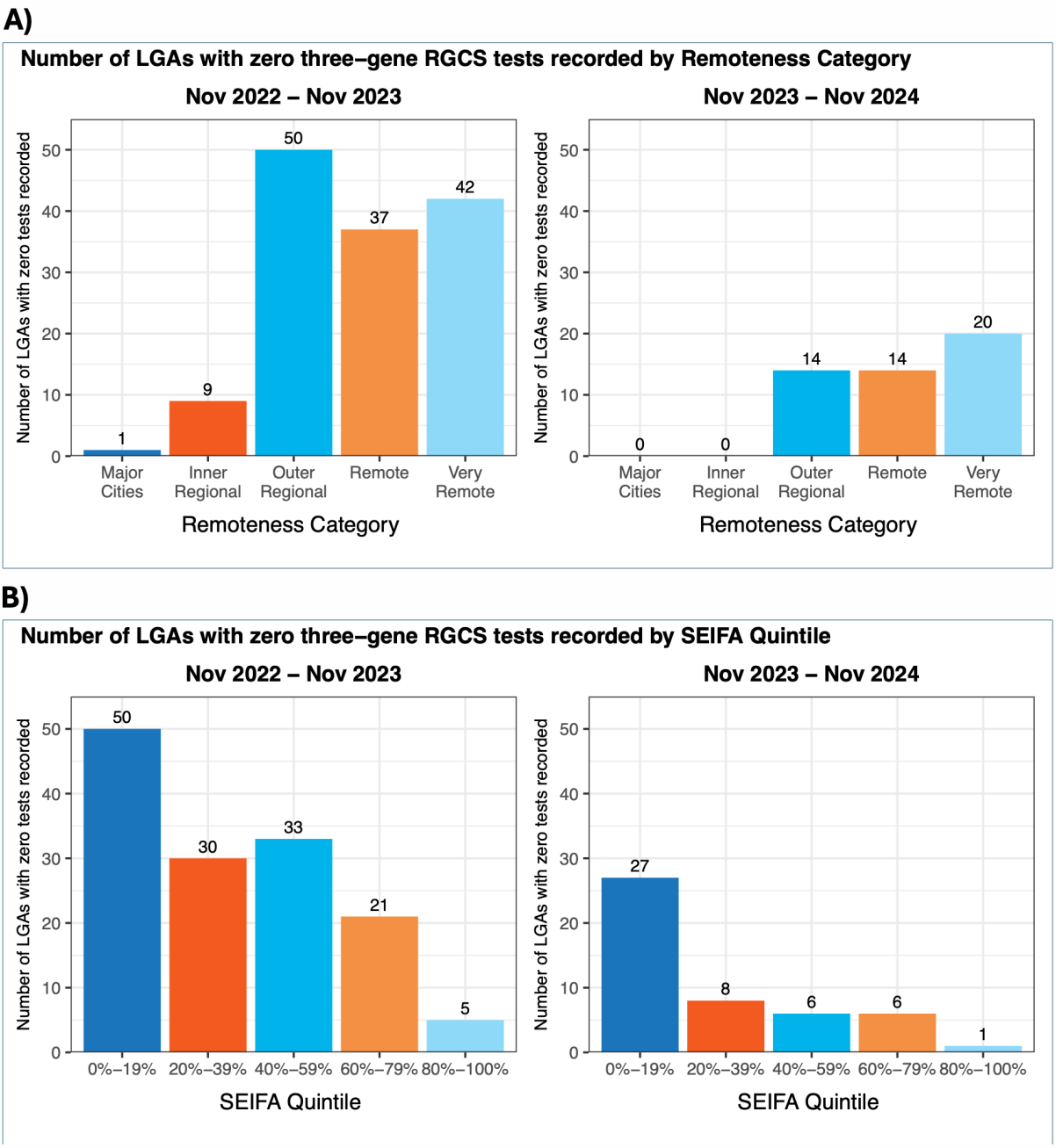

Figure 3: Number of LGAs with zero three-gene RGCS tests before and after the introduction of Medicare funding across A) Remoteness Category and B) SEIFA Quintile.

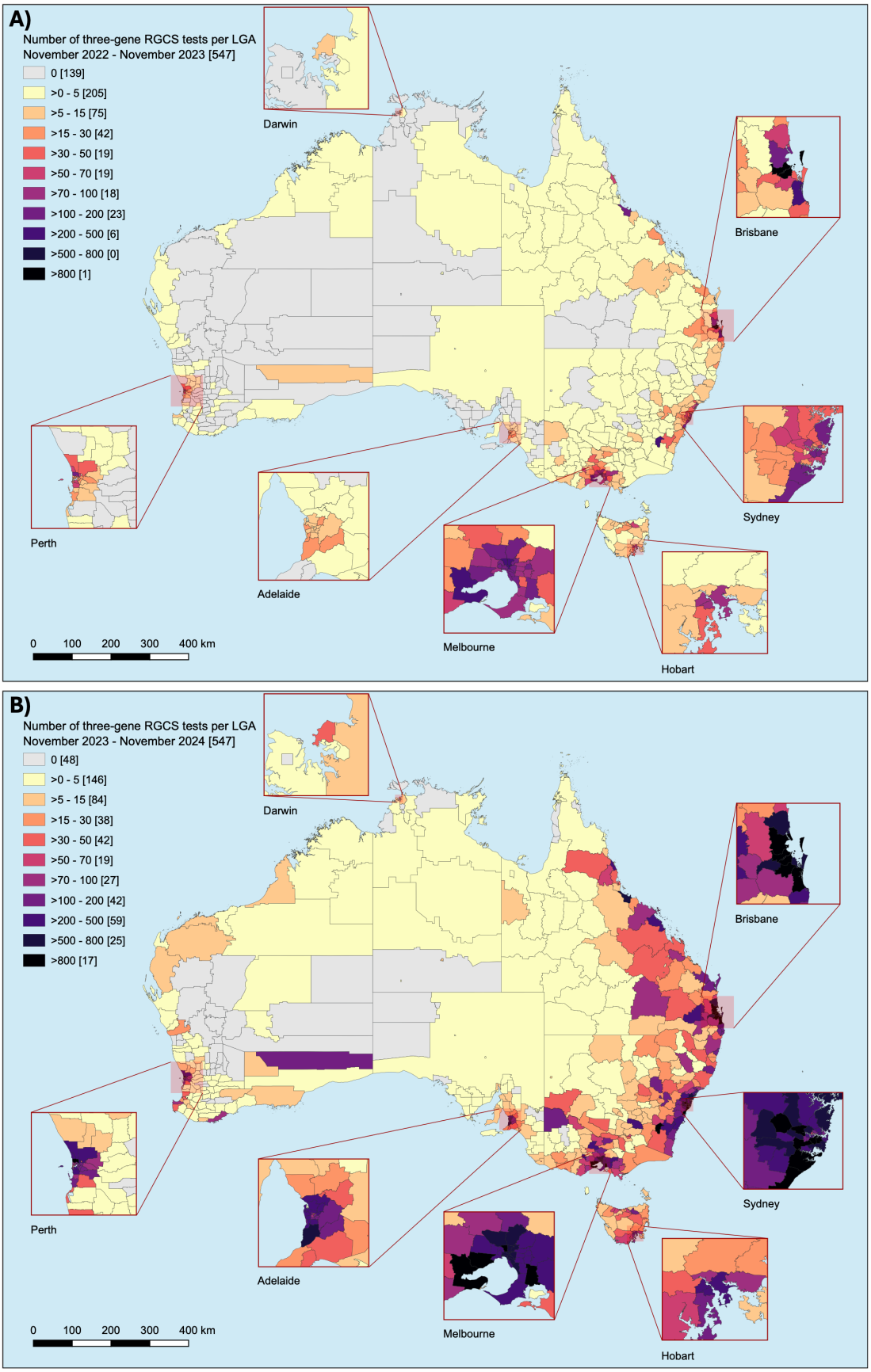

Figure 4: Geospatial distribution of three-condition RGCS A) before and B) after the introduction of MBS item number 73451

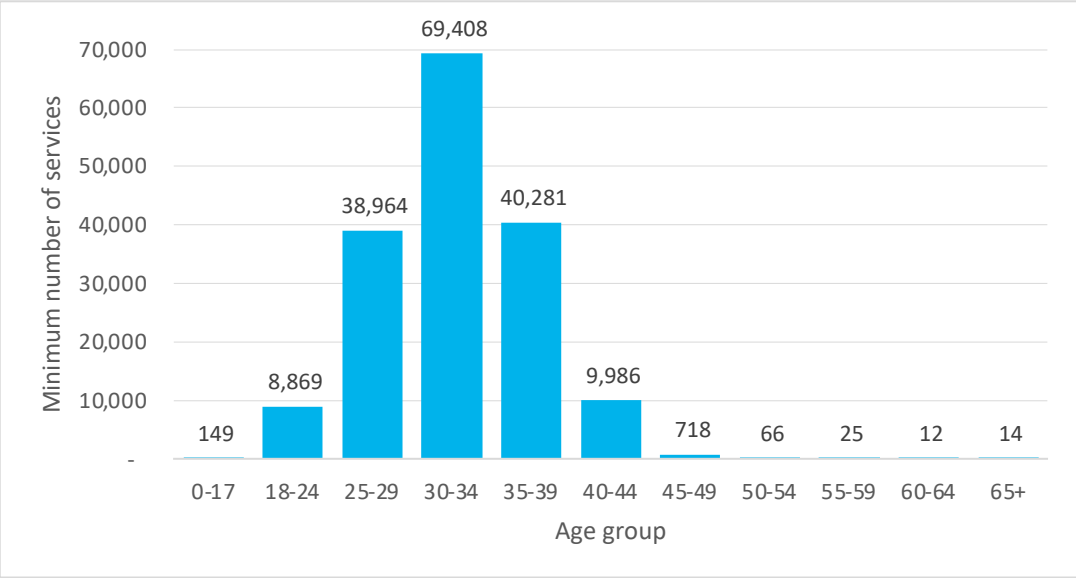

Figure 5: Minimum number of services recorded for Medicare Item Number 73451 and 73452 between November 2023 and April 2025 by age group.

In considering rates for testing for MBS item number 73452, in 2024 4,116 tests for partners of CF and SMA carriers were performed, representing 3.65% of tests performed under 73451. This is lower than expected, based on an estimated carrier rates for CF and SMA. A possible explanation for this is that the sequential testing model introduces additional barriers, as it requires the male partner to actively initiate testing following the female partner's carrier result.

In summary, there has been a substantial increase in the uptake of three-condition RGCS following the introduction of Medicare funding. General practitioners and obstetricians were the most common referrers, and while access has expanded nationally, disparities remain. People living in remote areas are still less likely to access screening than those in major cities, and individuals in higher SEIFA quintiles continue to have higher testing rates. Partner testing rates also remain lower than anticipated. Nonetheless, the removal of financial barriers through government funding has significantly improved access, particularly in lower socioeconomic regions. While there is still room for improvement, the data demonstrate a notable shift toward more equitable use of the three-disease screen across the Australian population.

Large-Panel RGCS

There is considerable variation in how large-panel RGCS is delivered across Australia, largely due to the lack of formal government oversight and consistent national guidance. In some settings, a sequential testing model is used, while in others, both reproductive partners are screened simultaneously. Sequential testing may be appropriate when screening for a small number of conditions; however, as the number of genes screened increases, so does the likelihood that an individual will be identified as a carrier. For example, in a sub-cohort of MM participants approximately 92% were carriers of a pathogenic variant in at least one of the genes screened (Kirk et al., 2024). In the context of large panels, often comprising hundreds or over 1,000 genes, simultaneous screening with a combined couple result becomes more efficient, and better oriented to program goals. It also minimises delays and optimises both laboratory and clinical resources. There is also significant variation in the lists of genes included across providers, which contributes to clinical complexity and challenges in interpretation and counselling. Approaches to result reporting also differ across providers. Some laboratories issue detailed individual reports listing carrier status for each gene, while others provide a combined couple-based report that focuses on reproductive risk indicating only whether the couple has an increased or low chance of having children with a serious childhood-onset inherited genetic condition, without disclosing individual carrier status for all genes screened. The simultaneous screening approach with couple-based reporting is more feasible, ethically defensible and acceptable to deliver at scale (Delatycki et al., 2020; Lewis et al., 2021; Newson et al., 2021).

Although the MBS item numbers 73451 and 73452 apply specifically to carrier screening for CF, FXS and SMA only, these conditions are included in all large-panel RGCS offerings. As a result, the Medicare rebate can be applied to reduce the out-of-pocket cost of large-panel screening. While it does not fully cover the cost, the rebate reduces fees, with large-panel tests typically ranging from approximately $600 to $1,500 (after the rebate), depending on the provider and panel size.

Analysing data collected from the two main pathology laboratories offering large-panel RGCS in the same timeframe (November 2022 – November 2024), large-panel screening did not show the same rate of increase as three-gene RGCS. In fact, large-panel screening rates declined in 175 LGAs, compared to only 15 LGAs that saw a decline in three-gene RGCS rates. This reduction primarily occurred in more remote areas and in regions with lower socioeconomic advantage (Figure 6). The median number of large-panel RGCS tests per LGA was 0.02 (IQR 0.0 – 4.2) before Medicare funding and 0.1 (IQR 0.0, 4.0) afterward, indicating minimal overall change in testing volume. The spatial distribution of large panel RGCS is presented in Figure 7.

In summary, despite the inclusion of CF, FXS, and SMA in large-panel RGCS and partial Medicare rebate availability, rates of large-panel screening have remained low and uneven, with minimal overall growth and notable declines in remote and socioeconomically disadvantaged areas. **These patterns highlight the need for greater national coordination and equity-focused strategies to support broader access to screening for serious childhood-onset inherited conditions.**

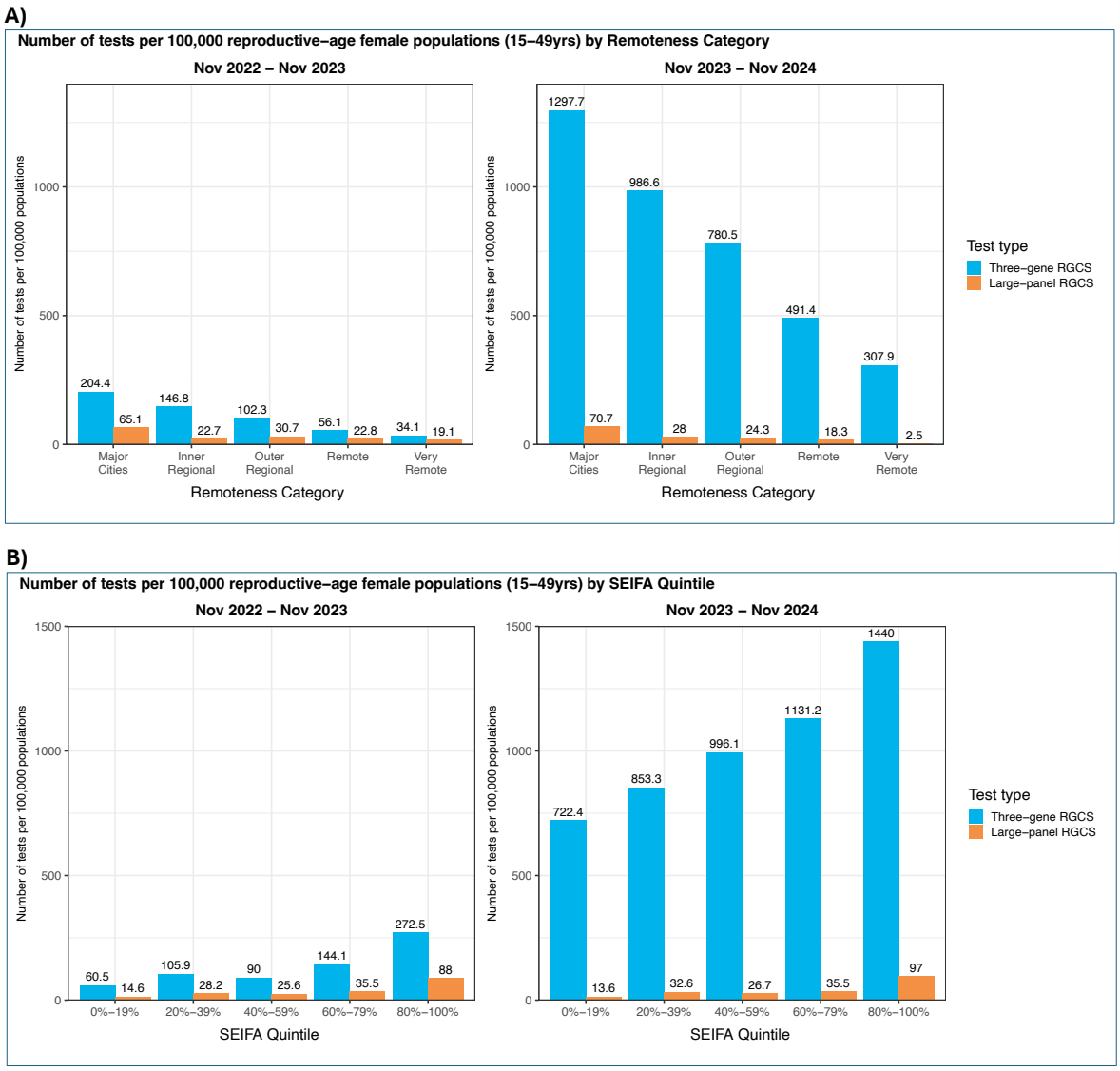

Figure 6: Comparison of rate of three-gene RGCS and large-panel RGCS before and after Medicare funding for item number 73451 across A) Remoteness Category and B) SEIFA Quintile.

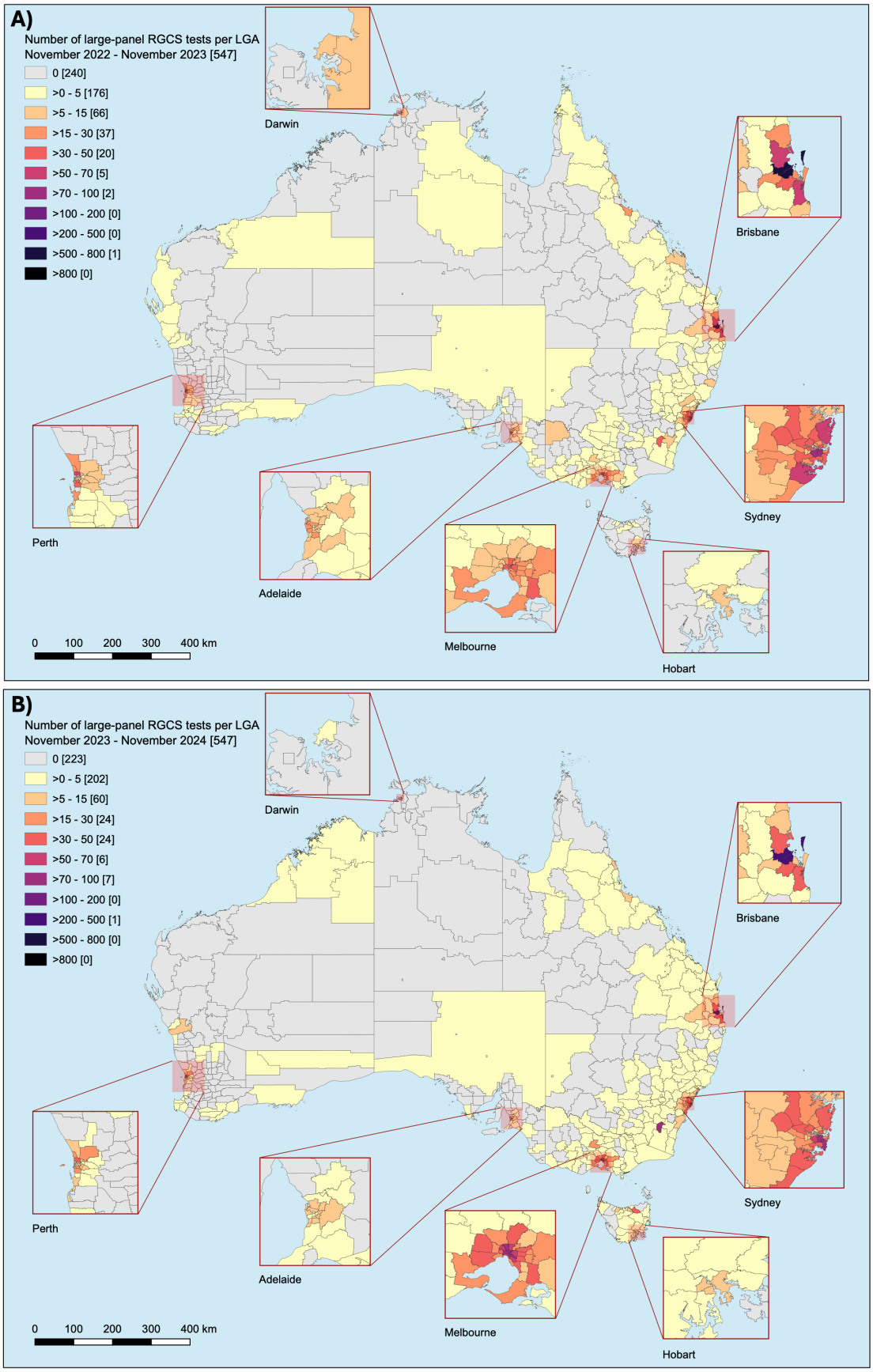

Figure 7: Geospatial distribution of large-panel RGCS A) before and B) after the introduction of MBS item number 73451

Healthcare Provider Perspectives

Research exploring the perspectives of healthcare providers can highlight factors impacting the incorporation of the offer of RGCS into routine care. Healthcare providers broadly support the concept of RGCS, recognising its potential to inform reproductive decision-making. Studies focused on Australian general practice show persistent barriers. Leibowitz et al. (2024) found that while general practitioners supported RGCS in principle, few offered it routinely. Barriers included limited time during consultations, competing clinical priorities, low awareness, and a lack of perceived patient demand for preconception care. Similarly, Valente et al. (2020) reported that GPs and other medical practitioners were more likely to offer cystic fibrosis carrier screening when they had prior experience or specific training, but many cited time constraints, limited knowledge, and a lack of confidence as key deterrents.

These findings are echoed in broader research examining healthcare professionals' views on RGCS implementation undertaken as part of MM. Best et al. (2021) identified common barriers across clinical contexts, including uncertainty about how and when to raise screening, and discomfort with discussing complex genetic information. Using behaviour change theory, Best et al. (2022, 2023) emphasised that successful implementation requires interventions that address not only knowledge and skills (capability), but also practical supports (opportunity) and professional motivation. Education alone is insufficient. Embedding RGCS into routine practice will require system-level change integrating screening into workflows, enabling efficient referrals, and providing digital tools and ongoing support. Collectively, these studies underscore that while healthcare providers support RGCS in theory, meaningful uptake depends on addressing entrenched structural and behavioural barriers.

Conclusion

An analysis of current RGCS utilisation in Australia highlights key patterns and disparities that are critical to informing the design of a nationally coordinated screening program. Since the introduction of Medicare funding for three-condition RGCS (CF, FXS, and SMA) via MBS item numbers 73451 and 73452, there has been a substantial increase in test uptake, particularly in urban and socioeconomically advantaged areas. Screening expanded to more local government areas and test volumes increased substantially, with general practitioners and obstetricians being the most common referrers. However, access remains uneven, with persistently lower screening rates in remote and socioeconomically disadvantaged regions. Large-panel RGCS which remains primarily out-of-pocket despite partial Medicare rebates (due to MBS item numbers 73451 and 73452) has shown minimal overall growth. Screening rates for large panels remain low, with a notable decline in many areas following the introduction of funded three-gene screening. These findings underscore both the positive impact of removing financial barriers and the need for national coordination, consistent clinical models, and targeted strategies to support equitable access to broader RGCS for serious childhood-onset genetic conditions across the Australian population. Research suggests that while healthcare providers are generally supportive of RGCS, practical barriers such as limited time, confidence, and system supports often prevent them from offering RGCS routinely highlighting the need for integrated implementation strategies.

Societal Perceptions of RGCS

A substantial body of Australian research has examined the perceived acceptability of RGCS, both for the three most common inherited conditions CF, FXS and SMA (Archibald et al., 2009, 2013, 2016; Ioannou et al., 2014a, 2014b, 2014c; Lawton et al., 2014) and for screening for larger numbers of genes (Ong et al. 2018; Thomas et al., 2020). These studies have all shown high rates of societal acceptability of RGCS. International studies have similarly shown that RGCS is widely perceived as acceptable (Aharoni et al., 2020; Birnie et al., 2021; Van Dijke et al., 2021; Van Steijvoort et al., 2022; Woodstra et al., 2022; Zhang et al., 2021)). However, the ultimate indicator of societal acceptance is test uptake, particularly in contexts where access barriers such as cost are removed. MM is by far the largest RGCS study offering screening for an extensive gene panel. It reported an estimated uptake of 45.9% (Kirk et al., 2024) despite being delivered in a research context with several participation barriers including completing questionnaires. In a clinical setting, where time and participation requirements would be significantly reduced, uptake is expected to be substantially higher.

Attitudes toward RGCS were further explored in MM through surveys and interviews, with 98.9% of participants viewing RGCS as acceptable (Tutty et al., in press) Notably, those who declined screening did so primarily due to constraints related to research participation or personal circumstances, rather than opposition to the notion of RGCS. Among participants who received an increased chance result in MM, the value of screening results in informing reproductive planning was emphasised and strong support was expressed for publicly funded RGCS (Tutty et al., in press). Australian research involving individuals who have a child diagnosed with a genetic condition demonstrated a clear preference for offering RGCS to prospective parents. These individuals emphasised, based on their lived experiences, the importance of ensuring that people planning a pregnancy or in early pregnancy are made aware of the opportunity to undertake carrier screening (Thomas et al., 2020).

While there is extensive data about research participants' perspectives on genomic interventions, there is little information about views of the general public who may not have interacted directly with genomic health care. To address this, Australian Genomics conducted a project to evaluate public acceptability of health genomics. This was conducted via a quantitative public survey of societal preferences and opinions about genomic health interventions, utilising a market research company to ensure a representative sample of participants. The project began in July 2024, with the public survey undertaken in February 2025. Responses were received from 1404 participants and covered topics such as the use of genomic technology in adult health risk screening, cancer treatment and reproductive carrier screening. A representative sample of the Australian population was reached in terms of age, metropolitan/regional location, and level of education. Four percent of respondents identified as being Aboriginal and/or Torres Strait Islander, and 24% of a culturally and linguistically diverse background.

Respondents were provided a scenario-based prompt (See APPENDIX II – Scenario-Based Prompt) describing RGCS, asking them to imagine they were of reproductive age and thinking about family planning. The survey asked about respondents' willingness to have the test, whether it should be broadly available, and the acceptability of RGCS, capturing both selections and optional free text responses.

The results suggest Australians have high levels of acceptability of RGCS, with 87% of respondents indicating they would or probably would have the test (

***Figure 8*Error! Reference source not found.**) and 79% believing it should be available to all Australians (Figure 9). Key themes from participant comments included gaining empowerment from knowledge, and the opportunity to plan for the future. For respondents who indicated they were unwilling to have RGCS, the predominant theme was around perceived anxiety caused by the results. The study found that 85% of respondents indicated RGCS was an acceptable intervention, with only 4.3% selecting unacceptable/completely unacceptable.

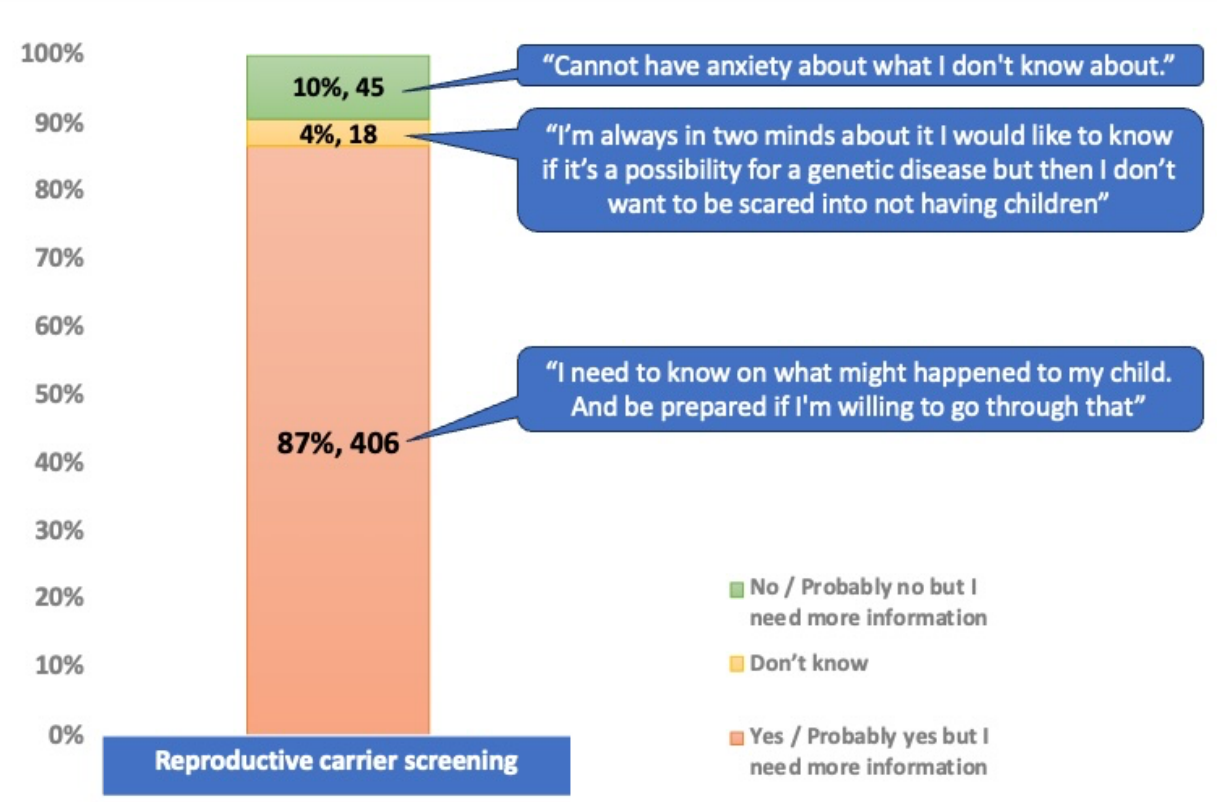

Figure 8: General Australian population willingness to have reproductive genetic carrier screening

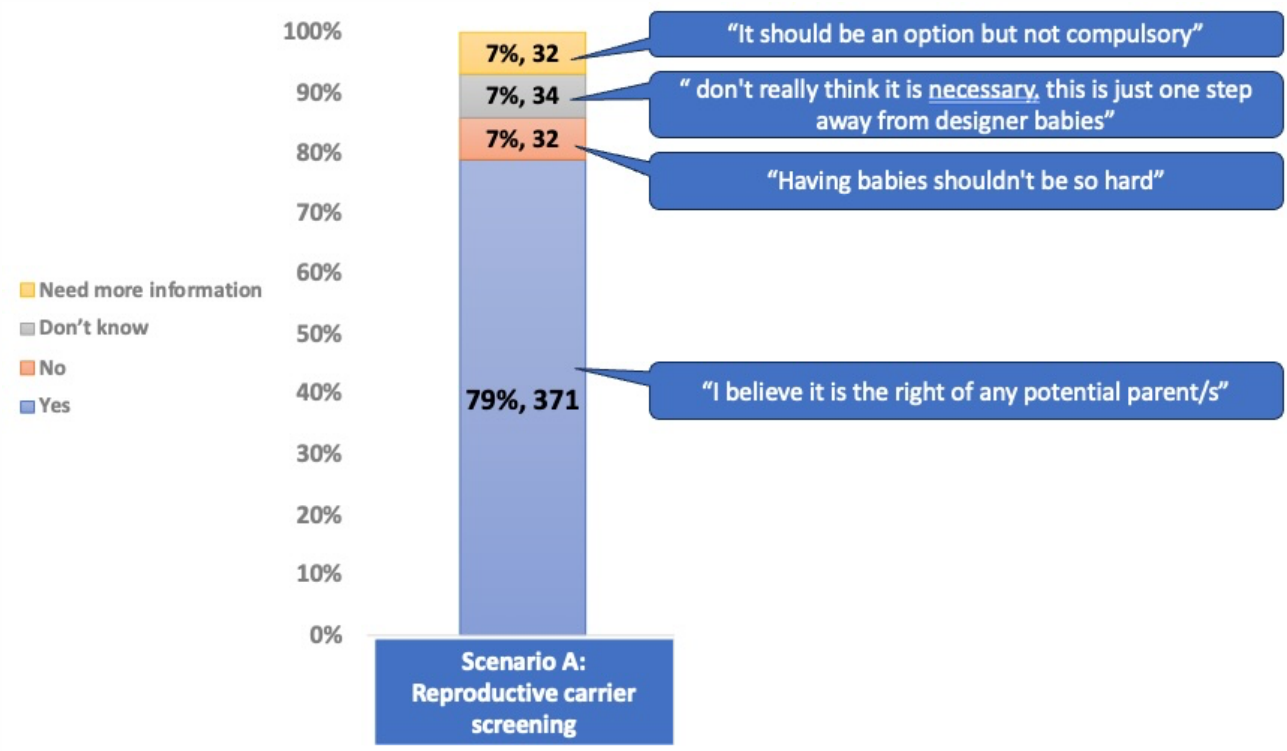

Figure 9: General Australian population views on whether reproductive genetic carrier screening should be available to all Australians of reproductive age

The Australian public have a strong interest in accessing RGCS, however the survey also indicated that this is highly dependent upon the cost of the test. When the survey presented the option of a Medicare-subsidised three condition screen, and an expanded screen for 700 conditions at an out-of-pocket cost of $1500, only 22% of respondents opted for the larger panel. When the survey indicated the expanded panel would be wholly publicly funded, 77% respondents then opted for the 700-condition screen.

Overall, there is strong evidence that RGCS is widely acceptable to both research participants and the Australian public. Studies, including MM, highlight support for screening for a larger number of genes using a simultaneous screening model with couple-based reporting, with acceptability driven by the value placed on informed reproductive planning. Public attitudes research further confirms that awareness, cost, and access are key factors that would influence test uptake. These findings reinforce the importance of ensuring RGCS is accessible, equitable, and supported by public funding.

Designing a National RGCS Program

Recognising the inequitable access to RGCS, the Australian Government announced *Mackenzie's Mission* in the May 2018 federal budget, a $20 million pilot project named in honour of Mackenzie Casella, who passed away from spinal muscular atrophy (SMA) in 2017 at just seven months of age. The aim of the project was to evaluate the feasibility and acceptability of a nationally coordinated approach to RGCS. A national pilot program was developed and implemented, offering screening for approximately 1,300 genes associated with serious autosomal and X-linked childhood-onset conditions (Archibald et al., 2022). The primary outcomes of MM, reported in 2024 (Kirk et al., 2024), demonstrated that the MM model successfully delivered screening to over 9,000

reproductive couples across Australia. These results confirmed the effectiveness and scalability of the model, providing a strong foundation for the development of a future National RGCS Program.

The Mackenzie's Mission Model

Mackenzie's Mission, also known as the Australian Reproductive Genetic Carrier Screening Project, piloted a national model for delivering RGCS in an accessible, equitable, and scalable manner. Through this model, screening for approximately 1,300 autosomal and X-linked genes with a combined couple-based result was offered to over 10,000 reproductive couples across the nation with 9,107 reproductive couples ultimately undergoing screening. The following key features of the model contributed to its success:

- **Effective Healthcare Provider Training and Engagement:**
  A comprehensive education strategy was implemented for healthcare providers involved in project recruitment, including general practitioners, midwives, obstetricians, genetic health professionals and fertility specialists. Interactive virtual sessions covered core concepts of RGCS, ethical considerations, and communication techniques, and further content was available via an online education platform. Supplementary materials and ongoing support networks were provided to enable confident and accurate counselling in clinical practice. Using an implementation science approach, a range of barriers experienced by healthcare providers when incorporating RGCS into practice were identified. A range of interventions were developed and trialled to improve engagement and program outcomes (Best et al., 2023).

- **Digital Enrolment and Education:**
  A standout feature of the MM model was its digital infrastructure. Almost all reproductive couples enrolled through an online portal, where they accessed educational materials and an optional decision-aid, provided consent, and completed research questionnaires. This streamlined, centralised approach made participation easy and consistent across the diverse range of participants. Participants were supported by high-quality, accessible educational materials tailored to a range of literacy levels and available in multiple formats. The online platform served as a central hub for information, while hard-copy materials and translations in languages other than English promoted inclusivity. Importantly, participants reported feeling well-informed, had high knowledge scores, were confident in their understanding of RGCS after engaging with these resources and had low decision-regret (Best et al., 2021; King et al., 2022; Kirk et al., 2024).

- **An Inclusive and Culturally Sensitive Approach:**

  There was a strong emphasis on inclusivity and the delivery of balanced, non-stigmatising information about RGCS. To ensure accessibility, complex genetic concepts, such as inheritance patterns, carrier status, and potential testing outcomes, were communicated in clear, comprehensible language. Balanced information was provided to support informed decision-making without invoking fear or stigma. Educational materials were culturally and linguistically appropriate, with translations provided in Arabic and Simplified Chinese, the two most common languages spoken other than English in Australia, and a researcher-assisted enrolment pathway supported by interpreter services. A tailored enrolment pathway was also provided for people conceiving via a donor(s) using sensitive and

appropriate language. Yet to be published evaluation data demonstrates these inclusive enrolment pathways were well received. Input was actively sought from the rare disease community to ensure that lived experience informed the design and delivery of information. Engagement with Aboriginal Medical Services in NSW and QLD played a valuable role in shaping culturally sensitive and respectful approaches to enrolment. However, earlier and broader engagement, including with more communities across the country, would have further strengthened the program's cultural responsiveness. This inclusive and collaborative approach was central to promoting equitable access to education and empowering participants to make choices aligned with their individual values, beliefs, and circumstances.

- **At-Home Sample Collection:**
  Saliva collection kits were mailed to participants, who returned their samples via post. This eliminated the need for in-person appointments and reduced barriers to participation, especially for people living in regional or remote areas.

- **Simultaneous Screening Model:**
  Reproductive couples were screened together with a combined result reported by the laboratory. A couple was considered at increased chance if both partners carried pathogenic or likely pathogenic variants in the same autosomal recessive gene, or if the female partner carried a pathogenic or likely pathogenic variant in an X-linked gene. In the absence of these findings, couples were informed they had a low chance of having children with one of the screened conditions. Carrier status for individual autosomal recessive genes was not reported, aligning with the principle that this information offers no clinical utility unless both partners are carriers of the same condition. This approach greatly reduced the laboratory and genetic counselling burden and other research has also demonstrated its acceptability (Plantinga et al., 2019; Schuurmans et al., 2019). Over 90% of individuals are carriers for at least one of the screened conditions (Kirk et al., 2024) but identifying and counselling every individual carrier would be impractical and inefficient. The MM model focused clinical attention only on couples with an increased reproductive chance for serious inherited conditions in their offspring.

- **Reproductive Utility of Results:**
  Results were focused on providing clear, actionable information with reproductive utility. The MM model focused on the identification and reporting of reproductive chance for severe childhood-onset genetic conditions, while aiming to minimise ambiguity and uncertainty. To support this, a national multidisciplinary Variant Review Committee was established to provide expert input into variant classification and to ensure consistency in the results returned to participants. This framework enabled responsible, clinically meaningful reporting and supported informed reproductive decision-making.

- **Embedded Genetic Counselling Support:**
  Genetic counselling was a critical component of the Mackenzie's Mission model and was available to all participants throughout the study. Genetic counsellors contributed to the development of educational materials and were accessible to individuals seeking support when considering screening. Couples who received an increased chance result were provided with timely, personalised counselling from genetic counsellors and clinical geneticists, helping them understand their genetic findings, inheritance patterns, and

reproductive options. This tailored support was essential for informed decision-making. In addition, referrals were provided to specialist physicians to further support understanding of the condition. Genetic counsellors also played a key role in educating healthcare providers involved in offering RGCS and acted as an important information resource for those managing patients with increased chance results, supporting both participant outcomes and workforce readiness (Best et al., 2023).

- **Reproductive Support Services:**
  Reproductive couples who received an increased chance result were offered genetic counselling and access to funded reproductive options. These included prenatal diagnosis for those already pregnant and one free cycle of IVF with PGT-M for those not pregnant. Approximately 76% of these couples undertook or intended to undertake a reproductive intervention to reduce the chance of having children with the identified condition (Kirk et al., 2024).

- **Ethical Considerations in Program Design:**
  Ethical concepts, values and principles were embedded throughout the design and delivery of the RGCS program to ensure it supported participant autonomy and promoted community trust. Recognising the ethical complexity of make a RGCS offer at a population level, the program incorporated structured bioethics input into gene list development and result reporting to inform decisions about clinical utility, condition severity, and public acceptability. Educational materials were carefully developed to present information in a balanced, non-directive manner, enabling people to make informed choices aligned with their values. Respectful, inclusive communication and consent processes were central to the program's approach, helping to avoid coercion or assumptions about what decisions should be made. Broader engagement with stakeholders, including patient support organisations, helped shape ethically robust implementation strategies sensitive to the social norms that inform reproductive choices and how these can shift in response to healthcare initiatives. Equitable access was prioritised to support fairness, reduce potential harms, and uphold the integrity of the program.

Using this model, recruitment for MM was successfully achieved across all Australian states and territories, with the geographic distribution of participants closely reflecting the national population, including representation from remote and very remote regions. Notably, 1.9% of couples were newly identified as having an increased chance of having children affected by a screened condition, substantially higher than the 0.4% detection rate seen with the currently funded three-condition panel for CF, SMA, and FXS. Importantly, 80% of these increased chance results involved conditions not included in the Medicare-funded panel, strongly reinforcing the clinical utility of expanding the scope of RGCS. The model's design, featuring online enrolment, postal sample collection, and simultaneous screening with a couple-based report, was key to enabling equitable access across diverse geographic and socio-demographic groups. While the participant cohort skewed toward higher socioeconomic and educational backgrounds, the successful engagement of individuals from all regions demonstrated the model's scalability and adaptability for broader implementation.

MM also provided strong economic justification for expanding the scope of RGCS and delivering it as a series of MBS-subsidised items with a health economic analysis estimating net savings of more than $400 million to Australian governments over five years, reflecting reduced costs associated

with managing serious childhood-onset genetic conditions (Scuffham and Downes, unpublished data).

As well as bioethics input into program design and delivery, an ethical analysis of RGCS was conducted as a distinct research arm within MM. This highlighted the importance of balancing the benefits of enabling informed reproductive decision-making with the need to address complex ethical concerns. While RGCS can offer additional reproductive choices, reduce uncertainty, and potentially ease future healthcare burdens, it also raises issues such as perceived pressure to test, lack of deliberation about the test, and implications for societal views on disability (Dive & Newson, 2021a). A key ethical challenge lies in determining which conditions to include, particularly given differing interpretations of "severity" and the risk of reinforcing stigma or shaping public perceptions about which lives are valued (Dive, Archibald & Newson, 2022; Dive, Archibald, Freeman & Newson, 2023). To avoid unintended harms, RGCS programs must be developed transparently, with interdisciplinary input, and in ways that respect disability perspectives (Freeman et al., 2025). Supporting reproductive autonomy requires respectful, values-based engagement with patients and inclusive consent processes that empower individuals rather than direct their choices (Dive & Newson, 2022). Broader concerns about eugenics or the commodification of reproduction can be mitigated through stakeholder engagement, equitable access, and careful program design (Dive & Newson, 2022). A couples-based, nationally implemented model offers a sustainable and ethically justifiable approach by reducing individual anxiety, focusing attention on screening outcomes that will have the greatest reproductive utility, and ensuring that autonomy and fairness remain central to service delivery.

Overall, the MM screening model demonstrated that the large-scale, equitable, ethically defensible, and efficient delivery of RGCS for a large panel of genes is achievable in the Australian context. By integrating digital infrastructure, couple-based result interpretation, accessible education, genetic counselling, and healthcare provider engagement, the project established a robust and evidence-based framework. This model lays a strong foundation for the future implementation of an organised, publicly funded RGCS program.

Recommendations for National Program Design and Delivery

As part of the National RGCS Priority Project, eight expert working groups were convened to support the achievement of the project's aims and objectives. The membership of each group is detailed in *APPENDIX I – Working Group M*. To comprehensively address the components of the Priority Project, it was necessary to develop a full model for a future National RGCS Program (see Figure 10). Building on the success of the MM model, the working groups examined key elements of program design and delivery at national scale and provided targeted recommendations. As there was strong alignment in perspectives across the groups, their collective recommendations are presented together.

Recommendation 1: Adapt the Mackenzie's Mission screening program design for national implementation. There was unanimous agreement across the working groups that the program design developed and successfully implemented in MM provides a strong foundation for a national reproductive genetic carrier screening program. As shown in Figure 10, this model includes online education, decision support and consent; sample collection via mail-out mouth swab kits; simultaneous screening with a combined result for the reproductive couple; and access to genetic counselling and reproductive options for couples receiving increased chance results.

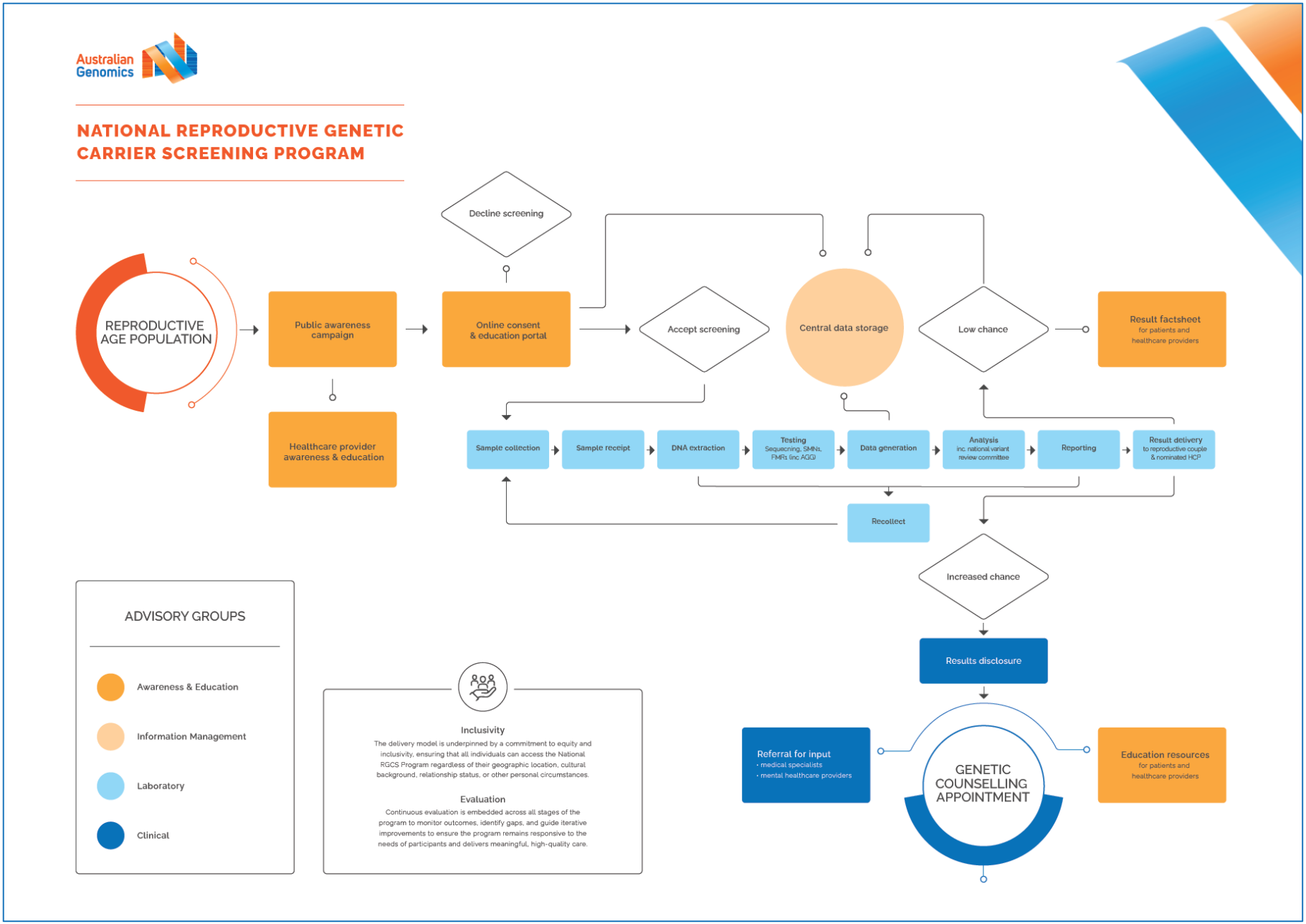

Figure 10: Proposed model for National RGCS Program

Planning and Engagement

Recommendation 2: Consult thoroughly with Aboriginal and Torres Strait Islander communities
Early, well-resourced engagement is critical. Consultation should commence as soon as funding is available to ensure the program is culturally safe, accessible, and equitable. To ensure equitable, culturally appropriate and effective delivery of RGCS to Aboriginal and Torres Strait Islander peoples, we recommend formation and funding of an Indigenous-led committee to: consult with communities to explore priorities, interests and considerations about accessing RGCS; assess the potential impact of RGCS on cultural norms, practices and traditional concepts; co-develop culturally appropriate resources with Communities to support Indigenous couples to access RGCS; develop strategies to ensure the incorporation of Indigenous data governance and custodianship as the foundations of a national RGCS screening program.

Recommendation 3: Develop and implement a national advertising and media campaign
A carefully designed national media campaign should be implemented to raise public awareness and acceptance of the RGCS program. Broad awareness is essential to support program uptake and engagement. Messaging must be clear, accessible, and easy to understand, with a strong emphasis on promoting informed choice. Such approaches increase awareness, particularly when grounded in transparency and cultural relevance. Given the complex and sensitive nature of reproductive genetic screening, a balanced approach is critical to avoid stigma and ensure respectful communication

Recommendation 4: Engage with diverse communities to develop multilingual, literacy-appropriate materials
Clear, inclusive content is essential for engaging culturally and linguistically diverse communities. Early and ongoing community engagement should begin as soon as funding is available. Partnerships with current relevant initiatives can support the co-design of tailored resources and help reach underrepresented groups effectively.

Recommendation 5: Engage and educate healthcare providers
Healthcare providers will be central to the implementation of the screening program. Engaging healthcare providers, particularly general practitioners and those working in reproductive healthcare including in public hospitals, in the design and development of the program will not only build awareness but also ensure educational and clinical materials are relevant, practical, and effectively tailored to the needs of both healthcare providers and their patients. A comprehensive education campaign should be delivered across relevant healthcare settings, including tertiary education and continuing professional development. Healthcare providers are trusted health advisors and must be equipped with the knowledge and confidence to accurately or appropriately discuss RGCS with patients. Integrating RGCS into undergraduate and postgraduate curricula and continuing professional development programs will support a sustained, informed, and engaged health workforce.

Digital Infrastructure and System Design

Recommendation 6: Develop a centralised integrated online platform for service delivery
A secure, user-friendly online platform should be designed to support the full RGCS pathway, including enrolment, education, decision support, consent, results delivery and initial clinical care. This platform must be mobile phone-friendly, available in multiple languages, and accessible to people with varying literacy levels, adhering to established digital accessibility standards. It should

incorporate a validated decision aid (King et al., 2022) to facilitate and encourage informed and values-based decision-making. Participants should be able to self-enrol, provide demographic and clinical information, nominate a healthcare provider to receive results, and provide consent independently. Integration with laboratories and the national RGCS registry (recommendation 8) will ensure seamless user experience, real-time data sharing, and efficient communication across the service pathway.

Recommendation 7: Build digital infrastructure that ensures equity in access and inclusion
Enrolment and engagement pathways must accommodate people without reliable internet access or digital literacy. Alternatives include paper-based options, program-assisted enrolment via phone, and support through local healthcare providers. The program must also accommodate diverse family structures and reproductive scenarios, including donor conception, re-partnering, and instances where one reproductive partner is unavailable. The infrastructure must be flexible and inclusive to ensure equitable access for all Australians of reproductive age.

Recommendation 8: Establish a national RGCS registry
A secure, centralised RGCS registry should be established to track participation, results, reproductive outcomes, and relevant clinical metadata. The registry must implement a standardised minimum dataset that captures essential demographic, clinical, and genetic data. It should also support real-time data analytics to inform public health planning, monitor program performance, and assess equity of access and outcomes. Integration with healthcare provider systems and My Health Record is essential for continuity of care and efficient service delivery.

Recommendation 9: Build scalable, interoperable, and future-ready infrastructure
The Australian Government should explore centralised genomic infrastructure models, similar to the NHS Genomic Medicine Service, where specimen reception and DNA-to-data processes are centralised and analysis and reporting are distributed. This would enable economies of scale, operational efficiency, and stronger negotiation power with laboratory suppliers. The digital infrastructure design could support future scalability, allowing for the integration of additional genomic screening programs and publicly funded diagnostics. Cloud-based infrastructure would ensure flexibility, adaptability, and long-term sustainability.

Recommendation 10: Secure and ethical genomic data storage and reuse
The RGCS program must establish robust policies for the retention and storage of genomic data, balancing clinical utility with storage costs and ethical considerations. Exome sequencing is recommended for its balance of comprehensiveness and cost efficiency. A tiered data retention strategy should be used, progressing from active cloud-based storage for short-term access to long-term cold storage of variant data.

Recommendation 11: Establish a reference database of Australian genomic variation
Anonymised variant data from population-scale RGCS should be retained and used to develop a national reference database of Australian genomic variation. This database would support diagnostic interpretation across the health system, improve equity in clinical genomics, and address current gaps in global reference datasets particularly for underrepresented populations, including Aboriginal and Torres Strait Islander peoples. Its design and implementation should align with existing clinical consent frameworks and draw on exemplars such as gnomAD and VariantArk, ensuring that only appropriately curated variant data is retained and shared.

Recommendation 12: Enable appropriate secondary use of genomic data
Genomic data generated through the National RGCS Program should be made available for ethically approved secondary use. Reanalysis of stored data must be clearly presented as point-in-time information, and reanalysis should only occur in response to participant-initiated requests, particularly in scenarios such as re-partnering or the diagnosis of a child with a genetic condition when individuals consent and when clinically appropriate. Secondary use must be governed by robust consent processes, privacy protections, and oversight mechanisms. To support this approach, clear and accessible educational content must be developed to ensure program users understand the purpose, scope, and considerations around reanalysis.

Recommendation 13: Embed strong governance, privacy, and indigenous data sovereignty

All digital systems supporting the RGCS program must be governed with transparency, privacy, and cultural safety. Data custodianship should rest with trusted national or public entities, as this aligns with public preferences for genomic data governance. Indigenous data governance must be embedded, including co-design with Aboriginal and Torres Strait Islander communities and establishment of Indigenous oversight mechanisms. These approaches are essential to build trust, enable equitable participation, and ensure long-term success of the digital infrastructure underpinning the program.

Program Enrolment

Recommendation 14: Enable self-referral to support equitable access
The screening program should allow self-referral for eligible individuals who are planning a pregnancy or in early pregnancy. Removing the requirement for a healthcare provider referral eliminates unnecessary barriers (such as practitioner gatekeeping and out-of-pocket costs for an appointment to obtain a referral) and supports broader access. Enabling self-referral promotes autonomy, reduces financial and structural barriers, and ensures more equitable participation in the program.

Recommendation 15: Enable access to RGCS for all Australians of reproductive age
The program should be available to all Australians of reproductive age; however, eligibility should focus on reproductive couples who are currently pregnant or actively planning to conceive. This approach ensures that the genomic analysis is clinically relevant and up to date at the time of use, while also minimising unnecessary testing in individuals who may delay pregnancy or experience changes in reproductive partnership. Clear eligibility criteria will help manage program resources, reduce the risk of outdated results, and ensure that RGCS delivers timely and meaningful clinical utility.

Recommendation 16: Enable healthcare provider involvement
Although participation in the program would occur by self-referral, there should be avenues for healthcare providers to be engaged and informed about screening, including the option to assist patients with enrolment if needed. Facilitating Healthcare provider involvement supports patient-centred care, enables shared decision-making, and ensures continuity of communication between patients and providers while maintaining flexibility and respect for individual choice.

Recommendation 17: Provide direct and responsive consumer support
People engaging with the program should have direct access to program staff through multiple communication channels, including phone, email, text, and a web-based chat function. Responsive,

personalised support is essential to promote informed choice, enhance user experience, and ensure equitable participation. A structured triage system should be implemented, where administrative staff handle general enquiries and refer complex or sensitive matters to an experienced genetic healthcare provider. This approach supports diverse communication needs, optimises resources, and ensures timely, accurate assistance for all participants.

Education, Consent and Decision-Support

Recommendation 18: Leverage Mackenzie's Mission education content to inform program materials

Education materials developed during MM were designed to support informed decision-making and were well received by participants. This approach provides a strong foundation for the National RGCS Program. Drawing on this work will support continuity, evidence-based design, and effective communication with participants.

Recommendation 19: Deliver information in multiple formats to support accessibility and understanding

To meet diverse learning styles and accessibility needs, education content should be presented in a variety of formats, including video, infographics, text, and images. Content development should be informed by experts in genomics, genetic counselling, bioethics and genomics education to ensure information is accurate, balanced, culturally appropriate, and sensitively communicated.

Recommendation 20: Provide access to genetic counselling for pre-test decision-making support

While a one-to-many education approach is effective in supporting informed decision-making for most participants, some individuals may have more complex questions or require additional support. Digital tools may assist in providing more detailed information and triaging enquiries. The program should offer access to genetic counsellors for those who need personalised guidance prior to testing, ensuring that all participants can make informed and confident decisions.

Laboratory testing

Recommendation 21: Centralise testing through a small number of laboratories using common methods

The preferred model for national implementation involves genomic testing being delivered by a small number of laboratories, ideally at least two, to ensure redundancy and no more than three to maintain efficiency. These laboratories should use common methods for data generation and analysis and establish processes for sharing data and variant curation. This approach promotes consistency, quality assurance, and resource efficiency across the program.

Recommendation 22: Offer convenient, mail-based sample collection to support equitable access

Following completion of consent and information requirements by both reproductive partners, sample collection kits should be mailed directly to participants, allowing at-home collection and return to the laboratory for testing, an approach successfully used in MM. While some participants may still access sample collection through pathology centres, offering mail-based kits is essential to ensure equitable access, particularly for individuals in rural and remote areas of Australia.

Recommendation 23: Adopt a nationally agreed gene list with a mechanism for regular review

The gene list developed and implemented in MM should serve as the foundation for the National RGCS Program, given it demonstrated clinical relevance and feasibility at scale. To ensure the

program remains responsive to emerging scientific evidence, a formal mechanism should be established for the regular review and update of the gene list. This process should be overseen by a multidisciplinary expert panel including people with lived experience of a genetic condition and include clear criteria for gene inclusion based on reproductive utility, severity, ethical considerations and age of onset. Adopting a nationally consistent gene list will reduce current variation between providers, minimise ambiguity in result interpretation, and decrease the burden on clinical services. Regular review will ensure the program remains current while maintaining clarity and consistency across Australia. Criteria for inclusion (or removal) of genes on the RGCS gene list should be clearly defined and publicly available.

Recommendation 24: Use exome sequencing as the preferred technology for program implementation

While genome sequencing offers greater sensitivity for detecting clinically relevant variants, exome sequencing is currently the preferred approach for a national screening program. ES provides a more cost-effective solution, requiring fewer sequencers, lower data storage capacity, and enabling the use of mouth swab samples, an option that is more acceptable and accessible than blood collection for many participants. However, this recommendation should be regularly reviewed, as advancements in sequencing technologies during the program's implementation timeframe may shift the balance of benefits and feasibility.

Recommendation 25: Provide simultaneous screening with a combined couple result

Simultaneous RGCS with combined couple-based reporting, as successfully implemented in MM, should be adopted as the standard approach. This model significantly reduces laboratory workload and the demand for genetic counselling by focusing clinical attention only on couples who receive an increased chance result. It promotes the focus of RGCS as informing reproductive decision-making. It also enhances efficiency and supports scalability, making it well-suited for national implementation at the population screening level.

Recommendation 26: Establish a national variant review committee

Establish a national multidisciplinary variant review committee within the National RGCS Program to ensure consistent, evidence-based decision-making for variant interpretation and reporting. Building on the successful model used in MM, this committee should comprise clinical, laboratory and bioethics experts who meet regularly to review potentially reportable variants and reach consensus on classification. The committee should incorporate clinical input from healthcare professionals to guide decisions on approaches to the communication of results.

Recommendation 27: Consider alignment of laboratory infrastructure with broader genomic initiatives

The implementation of a national carrier screening program may coincide with the rollout of other genomic screening initiatives, such as genomic newborn screening and population screening for adult-onset conditions (e.g. genetic predispositions to breast cancer). In designing laboratory services for carrier screening, it is important to consider laboratory capacity could be leveraged for other genomics applications.

Clinical Care

Recommendation 28: Provide access to pre-test decision-making support

In addition to online education and decision-support tools, the program must ensure access to

personalised clinical support for people with more complex needs. This includes those with a relevant family history of a genetic condition, consanguineous couples, people using donor gametes or embryos, and reproductive situations where only one partner is available or willing to undergo screening. In these scenarios, access to pre-test genetic counselling through the program is important to support informed decision-making, clarify limitations of screening, and ensure equitable care across diverse family structures.

Recommendation 29: Establish and resource a national clinical RGCS service
Develop a centralised national clinical team that delivers high-quality, equitable care across all jurisdictions. The team should include genetic counsellors, clinical geneticists, subspecialist physicians, clinical assistants and psychosocial care providers. This team would provide clinical support to those undergoing RGCS and receiving RGCS results with referral to local services for increased chance couples after the initial results consultation. This national model delivered via telehealth ensures consistent practice and supports geographic equity. Early investment is critical as no existing infrastructure currently meets these needs at scale. Workforce development must prioritise recruiting and training professionals with reproductive genomics expertise.

Recommendation 30: Embed comprehensive clinical support across the screening pathway
Design the clinical service to span pre-test triage and consent support through to post-result genetic counselling. Optimise the use of specialised expertise by reserving escalation to senior genetic counsellors and clinical geneticists for complex cases. Leverage automation tools and digital education resources to streamline common processes and enhance service efficiency. Establish clear pathways for referral for into local clinical services after initial management of increased chance results.

Recommendation 31: Ensure timely and sensitive disclosure of results
Results indicating increased reproductive chance must be disclosed in a value-neutral way and in a timely, compassionate and culturally appropriate manner. Providing prompt access to comprehensive genetic counselling consultations delivered by a genetic counsellor and clinical geneticist will support informed reproductive decision-making and address emotional and psychosocial needs.

Recommendation 32: Ensure access to the full range of reproductive options
Ensure equitable and timely funded access to all reproductive options including assisted reproductive technologies including IVF with PGT-M, prenatal diagnostic testing and using the information to plan and prepare for a child with a genetic condition. Geographic equity, especially for rural and regional populations, must be addressed in program planning and resourcing.

Recommendation 33: Integrate psychosocial care
Include a dedicated team of psychosocial care providers within the clinical program structure to offer short-term support. Provide referral pathways for participants experiencing emotional, relational, or psychological distress who require longer-term support.

Recommendation 34: Include subspecialist clinical input
Establish a national panel of condition-specific paediatric subspecialists (e.g., respiratory, neurology, metabolic) who are available to consult on increased chance results and provide timely, accurate, and balanced information to support reproductive decision-making.

Recommendation 35: Facilitate access to patient and peer support networks
Formally partner with condition-specific and broader patient support organisations to offer peer connection, lived experience insights, and emotional reassurance. These networks are vital in helping participants feel informed, supported, and empowered.

Recommendation 36: Provide inclusive clinical care for diverse family structures
Ensure the clinical care pathway for increased chance couples is designed to be inclusive of diverse family structures, including donor conception (known and clinic-recruited), surrogacy, re-partnering, and situations where only one reproductive partner is available for screening. Clinical systems and service models should support appropriate counselling, follow-up, and data linkage in these more complex family contexts to ensure equitable access to care.

RGCS priority projects

The recommendations outlined above provide a strong foundation for the design and delivery of a National RGCS Program. To support practical implementation, a series of RGCS priority projects were established to address key operational considerations. Activities included service mapping and program design, data collection and modelling, and the formation of expert working groups to advise on critical components in preparation for national rollout. These projects are essential to ensuring the program can be delivered effectively enabling equitable access to genomic testing while upholding high standards for data security, clinical accuracy, and utility.

Sub-project 1: Modelling workforce and system capacity

To understand workforce and system capacity and address the aims and objectives below, eight working groups were convened to consider the delivery of a national RGCS program. MM data were used to inform modelling and evaluate resourcing required. The working groups advised on core assumptions, delivery pathways and possible interventions to improve efficiencies.

Aim: Undertake an evaluation of the impact of an organised RGCS screening program on health system capacity

Objectives:

1.1 Elucidate core assumptions for a proposed model of delivery of a national RGCS program to inform modelling of system demands

1.2 Map potential delivery pathways and identify where alternative models/options should be explored.

- Include consideration of access to screening for individuals/couples using a sperm/ovum/embryo donor; with a partner/donor overseas (with or without DNA available); or individuals where the sperm/ovum/embryo donor or male contributor to a pregnancy is not available for couple screening.

1.3 Model projected national uptake of a screening program, informed by ADAR 1637, and increased chance couples identified. Based on these assumptions / modelling, project demand on associated services: laboratory services, clinical services, and reproductive services.

1.4 Evaluate current clinical / laboratory capacity, and project expansion in service resourcing required.

1.5 Identify possible efficiencies / interventions that could improve the efficiency and reduce the burden on health system capacity, including but not limited to centralised vs distributed service delivery, automation, digital resources, and program oversight.

Objective 1.1: Core Assumptions for Program Delivery

The proposed delivery model for a national RGCS program is built around several key assumptions that are critical for accurately modelling system demands, resource allocation, and workforce requirements.

Equity and Inclusivity

The delivery model is built on an assumption of equity and inclusivity, ensuring that all individuals can access the national program regardless of their circumstances. This includes:

- National reach, including rural and remote communities.
- Cultural and linguistic diversity, necessitating engagement strategies tailored for Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities.
- Diverse reproductive contexts (e.g., donor-conceived families and single parents), which may require adapted screening pathways.
- Accessibility for people with sensory or cognitive differences.

This assumption requires up-front investment in broad and inclusive engagement, co-design, outreach, and resource development.

Public Engagement and Education

The delivery model relies on the assumption that public awareness and understanding will be supported through:

- A targeted national communications campaign.
- Community engagement strategies co-designed with Indigenous leaders, culturally and linguistically diverse representatives, disability advocates, and advocacy groups.
- Clear, culturally appropriate messaging to ensure understanding of screening purpose, process, and options.

Centralised Online Portal

A national, centralised online portal is to be the primary mechanism for participant engagement, integrating education, consent, and return of low chance results. This approach assumes:

- Digital literacy and internet access among the reproductive-age population.
- Adequate IT infrastructure and administrative support to manage technical and general enquiries.
- That an online model will reduce burden on both genetic and non-genetic healthcare providers by shifting pre-test education and consent away from clinical encounters.
- Non-genetic healthcare providers will require awareness of the national RGCS program but are not expected to deliver in-depth pre-test counselling.

To ensure accessibility, the portal must be complemented by alternative pathways for those with limited internet access, low health literacy, sensory or cognitive disabilities, or who speak languages other than English.

Focus on Reproductive Utility

The test design is based on a model with high reproductive utility including:

- Simultaneous screening of the reproductive couple.
- Couple-based analysis with reporting restricted to “increased-chance” and “low-chance” outcomes only.
- No return of individual autosomal recessive carrier status unless both partners are carriers.
- No reporting of variants of uncertain significance.
- AGG interrupt testing for small FMR1 premutation results.

These assumptions are expected to: minimise anxiety and reduce demand on genetic counselling and laboratory resources, reduce clinical ambiguity and avoid unnecessary reproductive intervention. This necessitates robust infrastructure to manage conditional testing logic, data interpretation, and variant curation at scale.

Supportive Pathways for Reproductive Decision-Making

Increased chance couples will need to be provided with:

- Genetic counselling support.
- Referral pathways to condition-specific medical specialists to support informed reproductive choices.
- Access to publicly funded reproductive interventions (e.g., IVF with PGT-M, prenatal diagnosis, termination of pregnancy), irrespective of geography or personal circumstances.

Supportive care, management and access to treatment (if applicable) for reproductive couples proceeding with a pregnancy after an increased chance result/prenatal diagnosis.

Based on MM data, it is anticipated that ~76% of increased chance couples will pursue reproductive intervention (Kirk et al., 2024). This assumption underpins projections for service utilisation (e.g., IVF &PGT-M capacity, genetic counselling workforce).

Workforce Upskilling and Engagement

The program assumes that non-genetic healthcare providers (e.g., GPs, midwives, fertility specialists) will be key touchpoints for patients. Therefore:

- Education resources (e.g., webinars, conference presentations, videos) will need to be scalable and engaging.

These healthcare providers will not conduct detailed pre-test counselling but must understand the national program well enough to introduce and support the program.

Infrastructure and Data Management

To enable a sustainable program and future refinement, assumptions include:

- A national data registry.
- Integration with platforms like PanelApp Australia and Shariant.
- Long-term genomic data storage and governance structures to support both clinical and research use.

These core assumptions form the basis for projecting system capacity needs, identifying potential bottlenecks (e.g., IVF service availability, digital exclusion, workforce training), and designing implementation strategies that are equitable, scalable, and culturally safe.

Objective 1.2: Program Design Considerations

To equitably deliver a robust National RGCS Program that identifies and supports increased chance couples through the provision of information with reproductive utility, a strong governance structure is essential. As with other priority national initiatives, a coordinated framework of advisory groups should oversee the development, implementation, and ongoing management of the program. These groups would provide guidance across key domains, including community engagement, awareness and education, data infrastructure and management, laboratory processes, and clinical care.

Each advisory group would be supported by relevant sub-advisory groups to ensure diverse expertise and representation. For example, an Aboriginal and Torres Strait Islander Advisory Group could sit under the Community Engagement Advisory Group, while an IVF Advisory Group could operate under the Clinical Advisory Group. These groups would comprise subject-matter experts, key stakeholders, and members of the National RGCS Program operational team.

In exploring program delivery pathways, a range of considerations and models were examined. These are presented below in relation to engagement and consultation, program promotion and enrolment, as well as the laboratory and clinical components of service delivery.

Engagement and Consultation

A national RGCS program must be built on a foundation of deep, ongoing engagement with communities across Australia. From the outset, program design should be shaped through meaningful consultation processes that prioritise equity, cultural safety, and community partnership. Early engagement commencing as soon as funding becomes available is essential to build trust and ensure that the program reflects the values, needs, and preferences of all participants.

It is vital to engage Aboriginal and Torres Strait Islander communities through an Indigenous-led, well-resourced process. Establishing a dedicated Advisory Group to lead this work can support co-design of culturally appropriate pathways for screening, assess how RGCS aligns with cultural values and practices, and ensure Indigenous data governance and custodianship are embedded in the program's foundations. The NACCHO consultation model, used effectively in the National Lung Cancer Screening Program, provides a valuable framework for this work and could guide engagement strategy.

Equally important is the active involvement of culturally and linguistically diverse (CALD) communities. Engagement with CALD groups should inform the development of multilingual, literacy-appropriate materials that are accessible through a range of channels, including the online

platform. These materials must meet recognised accessibility standards and be co-developed with communities to ensure they are meaningful, respectful, and useful. Partnerships with organisations such as the OurDNA project (ourdna.org.au, 2025) can help extend the program's reach and relevance, particularly among communities historically underrepresented in genomic initiatives.

The rare disease community and those with personal experience of genetic conditions must also play a central role in shaping the national RGCS program. These individuals and advocacy groups bring essential insights into the realities of life with genetic conditions and the value of informed reproductive decision-making. Their perspectives are vital to ensuring that the program is inclusive, respectful, and responsive to the needs of families who are most directly impacted. Ongoing engagement with the rare disease community can also help inform communication strategies and ensure that screening is presented in a balanced way that respects the diversity of lived experiences.

This approach based on inclusion, consultation and responsiveness will support the creation of a program that is not only acceptable to communities but actively shaped by them. By embedding consultation and engagement as core, continuous elements of program delivery, RGCS can be made more equitable and accessible.

Program promotion and enrolment

The Awareness and Education Working Group considered aspects of the program design relating to activities needed to raise awareness and promote the program, eligibility, modes of enrolment and pre-test education and support.

Program promotion

A successful RGCS program will require sustained efforts to promote public awareness among people of reproductive age and healthcare providers. Public education strategies must be carefully designed to ensure they are balanced, culturally sensitive, and non-directive, supporting informed choice without creating stigma or pressure to participate. Messaging should clearly convey that RGCS is optional, not routine, and should focus on empowering people with information relevant to their reproductive planning. To achieve this, a comprehensive and accessible public awareness campaign will be essential, using diverse communication channels and tailored materials to reach a broad audience, including priority populations and communities with varying levels of health literacy. Healthcare providers will also require ongoing engagement to ensure they are well-informed and able to support individuals appropriately. This should include ongoing initiatives that deliver education to all healthcare providers delivering reproductive healthcare including general practitioners, obstetricians, midwives, nurse practitioners, and fertility specialists.

Eligibility

RGCS is relevant to all individuals of reproductive age. However, as outlined under Objective 1.1, the most resource-efficient model is to deliver screening at the reproductive couple level. Accordingly, RGCS is most effective when accessed by individuals who are nearing the time they intend to start a family. This timing maximises clinical utility and reduces unnecessary use of resources on relationships that may not continue. Although it is neither feasible nor appropriate to mandate the timing of screening, people should be supported to consider RGCS as an option when they are

actively planning for a family. This also ensures that variant interpretation and results are based on the most current scientific evidence.

While the preferred approach is to make RGCS accessible to all individuals of reproductive age living in Australia, the Clinical Working Group recommended that, in line with other national screening programs, access may be limited to those who are Medicare eligible. For individuals who are not Medicare eligible, alternative pathways such as private payment or private health insurance coverage should be made available. Importantly, because RGCS is delivered at the couple level, the program design must accommodate scenarios where only one member of the couple is Medicare eligible.

Enrolment

Discussion around barriers to engagement with RGCS led the Awareness and Education Working Group to recommend that people should have the option to self-refer into the program. Healthcare providers may lack a clear understanding of RGCS and, it is common for people to have been incorrectly advised that they were ineligible for screening based on the absence of a family history of genetic conditions, among other misconceptions. As a result, some people have been misinformed and did not access screening. Establishing a self-referral approach for the national program would empower people to engage directly and help mitigate the impact of such misinformation. It would also reduce the risk of incorrect gatekeeping by healthcare providers and ease the pressure on healthcare providers to be fully across the complexities of RGCS, as people could access screening without relying solely on healthcare provider initiation or knowledge.

While some healthcare providers may have limited awareness of RGCS due to, many will serve as important enablers. Although self-referral is the recommended primary access point for the program, it is essential to raise awareness amongst healthcare providers and provide them with appropriate education about RGCS and the national program. Healthcare providers should be supported by the program to engage proactively with their patients about RGCS. It was also recognised that some people may require assistance from their healthcare providers to enrol, and the online platform should include functionality for participants to nominate a healthcare professional to receive a copy of their results. This may also create an opportunity for “just-in-time” education that can build healthcare provider awareness and capability in real time.

To address inequities in access, resources should also be developed to support healthcare providers who wish to refer patients into the program. This dual approach could be modelled on the National Bowel Cancer Screening Program, which encourages self-referral but also enables healthcare providers to assist with education, consent, and sample collection. Such a model may be particularly valuable for people in regional and remote communities or those with accessibility challenges such as limited internet access or sensory impairments who may require additional support to participate effectively in the program.

Pre-test Education and Decision Support

In the context of genomics, it is essential that people can make an informed decision about testing. A responsible screening program must support informed decision-making, which includes ensuring that participants understand the purpose of screening, the potential outcomes, and the implications for reproductive choices. Providing comprehensive information and decision-making support is both

ethical and fundamental to high-quality program design. This is best achieved through a centralised online platform, which serves as a single, accessible repository of information about the program, the conditions screened, and the meaning of possible results.

An online platform allows people to access information at their own pace and in their own time. Incorporating a decision aid into the platform is particularly valuable. In MM, the use of a decision aid was high (83%) (Kirk et al., 2024) and was shown to be an effective tool in supporting both members of the reproductive couple to engage in decision-making (King et al., 2022). Importantly, it also helped involve male reproductive partners, who are often less engaged in these conversations in current care models.

This model was both convenient and acceptable to MM participants (Kirk et al., 2024). It contributed to strong knowledge outcomes and high rates of informed decision-making, demonstrating its effectiveness as a scalable approach for a national program.

Laboratory testing

The Laboratory Working Group considered the process of gene selection and review, overarching laboratory structure to most effectively deliver RGCS nationally, approaches to data analysis, key considerations relating to laboratory methods and the importance of a national variant review committee.

Process for Gene Review and Selection

Establishing a clear and robust process for gene selection and review is critical to ensuring the quality, consistency, and clinical relevance of a national RGCS program. The gene list forms the foundation of the RGCS delivered through the National Program and therefore must reflect current evidence, best practice in screening program delivery, and the needs and values of the community. To support this, a formal governance structure should be established, including a dedicated Gene Review Committee. This committee should comprise a diverse group of stakeholders, including clinical geneticists, genetic counsellors, laboratory scientists, bioethicists, experts in population screening, and patient/community advocates. Drawing on the process successfully implemented in MM (Kirk et al., 2021), this committee can guide the initial selection of genes and develop transparent criteria for inclusion.

The gene list should not be static; rather, it must be reviewed regularly to incorporate new evidence and evolving clinical standards. Clear mechanisms should be in place to support the timely addition of new genes when justified by strong evidence of reproductive utility, as well as the removal of genes that no longer meet established criteria. This dynamic and evidence-based approach to gene list curation ensures that the program remains scientifically rigorous, ethically sound, and responsive to advances in genomics and community expectations.

Overarching Laboratory Structure

The Laboratory Working Group considered several models for delivering testing services under a national RGCS program, including: a single centralised laboratory, a small number of laboratories using shared methods, and a distributed model involving state-based or contracted private providers (see Table 1 for a comparison of these models).

Preferred Model: Shared Central Laboratory Network

The recommended model involves two laboratories in different Australian states operating with shared testing protocols and common analysis software. Each site must be clinically accredited and led by specialised genetic pathology professionals. Given their limited availability, a centralised model reduces workforce pressure by requiring fewer such professionals than a distributed model. A minimum of two laboratories should be established in different states or territories to ensure redundancy and resilience in the face of potential disruptions (e.g., extreme weather or pandemics). The importance of such redundancy was demonstrated during the COVID-19 pandemic; at one point during the project, one of the participating laboratories had to temporarily cease testing due to disruption to staffing. Later, a different laboratory needed to send some testing interstate for several weeks, also due to staffing and other pandemic-related issues. If all testing were performed by a single laboratory, this would create the risk that a localised major event could shut down the program entirely for a period. Since a significant proportion of the testing will be performed during pregnancies, any substantial delay to testing is associated with unacceptable risks. While a third site may provide added flexibility, it would also introduce additional setup and operational costs due to required duplication of infrastructure and staffing.

Alternative Model: Distributed Laboratory Services

A distributed model involving state-based or mixed public-private services may reduce initial setup costs, as existing equipment could be repurposed. However, the long-term operating costs would be higher due to loss of scale efficiencies. While partial standardisation and data sharing may be possible, such a model would likely result in reduced consistency, equity concerns, and challenges in building and utilising a national variant frequency database.

Table 1: Comparison of centralised and distributed models for delivery of laboratory services in a National RGCS Program

Considerations	Centralised model	Distributed model
Set up costs	Higher	Lower
Operational costs	Lower	Higher
Workforce demands	Lower	Higher
Complexity of administration & governance	Lower	Higher
Consistency of service delivery	Yes	Unlikely
Centralised variant database allowing for improved screening and diagnostic testing	Yes	Unlikely

Genomic Data Analysis Approaches

In MM, reproductive couples were screened simultaneously, with joint analysis of their genomic data. This couple-based approach will be an essential component of the design of a national RGCS program. Under this model, results are reported as either “increased chance”, where both partners are carriers for the same autosomal recessive condition, or the female partner is a carrier for an X-linked condition; or “low chance”, where both reproductive partners are not identified as carriers for the same autosomal recessive condition and the female partner is not identified as a carrier for X linked conditions. Individual carrier status for autosomal recessive conditions is not reported, as it is not clinically actionable outside the reproductive context.

In the alternative model, sequential screening, the female partner is screened first, and the male partner is only screened if she is found to be a carrier for an autosomal recessive condition. However, the simultaneous couple-based model offers three major advantages:

- Simplified laboratory processes: By focusing only on variants that are relevant to the couple’s reproductive risk, the number of variants requiring review and classification is greatly reduced, markedly lowering laboratory costs.
- Significant reduction in genetic counselling demand: If individual carrier results are reported the vast majority of reproductive couples will require genetic counselling to discuss a carrier result. In the simultaneous approach less than 2% of reproductive couples will require genetic counselling, decreasing both program costs and the likelihood of causing unnecessary anxiety for carriers identified in isolation.
- Faster turnaround time: Screening both partners at once enables quicker result delivery, which is particularly critical in time-sensitive situations such as testing in pregnancy.

For these reasons, simultaneous couple-based screening and reporting is the preferred approach for a national RGCS program.

Laboratory methods

The Laboratory Working Group considered two well-established genomic sequencing approaches currently used in diagnostic settings in Australia: exome sequencing and genome sequencing (see Table 2 for a comparison of these approaches). Each has distinct characteristics relevant to the delivery of a large-scale RGCS program.

Exome Sequencing targets the protein-coding regions of the genome, representing approximately 1.5% of the total genome, along with small portions of intervening genetic sequences. While it requires greater read depth than genome sequencing, it involves substantially less total sequencing, resulting in lower overall costs and reduced equipment requirements. For instance, a single sequencing machine may process up to 150,000 exome sequences per year compared to around 10,000 genome sequences. Additionally, exome data requires significantly less storage, which further reduces ongoing infrastructure costs (see

Table 8). These advantages make exome sequencing highly suitable for programs involving sequencing DNA from hundreds of thousands of individuals annually.

Genome Sequencing reads nearly the entire human genome, offering higher sensitivity and the ability to detect structural variants and other types of genetic variation (e.g.: nucleotide repeat disorders) not captured by exome sequencing (Hughes et al., 2023). Although the current clinical yield is only modestly higher, ongoing improvements in genomic interpretation are expected to increase detection rate over time. Genome sequencing enables a more comprehensive analysis of genetic variation but comes with higher sequencing, storage, and infrastructure costs.

Table 2: Comparison of exome and genomic sequencing considerations in a National RGCS Program

Consideration	Exome sequencing	Genome sequencing
Cost of generating data	Baseline	More expensive
Cost of data storage	Baseline	More expensive
Ability to detect clinically relevant variants	Baseline	More sensitive
Sample types	Blood and mouth swab	Blood only (not mouth swab)

Sample Type Considerations

Sample type compatibility is a key differentiator. While blood is suitable for both sequencing methods, mouth swabs, which are far more acceptable to the public and facilitate mail-based collection, are well-suited to exome sequencing but less reliable for genome sequencing due to contamination risks. Given the high acceptability of swab-based testing, especially among individuals who are needle-averse, the choice of sequencing method may significantly influence program participation rates and equity of access, particularly for people in remote or underserved areas. Although in most cases the reproductive couple will be co-located, there will be situations where the reproductive partners are geographically separated for example, couples not living together, fly-in fly-out workers, situations where one partner is temporarily overseas, or if a partner is incarcerated. To ensure equitable access, the RGCS program must have mechanisms for delivering and receiving mouth swab kits across different locations, including assessing the feasibility of international shipping and returns.

Additional Testing Methods

Regardless of the sequencing approach chosen, additional specialised methods are required for certain conditions. Carrier screening for fragile X syndrome screening necessitates *FMR1* triplet repeat analysis, and spinal muscular atrophy screening requires specific detection of *SMN1* exon 7 deletions. Low-cost, high-throughput technologies for these tests are already in widespread use and used for the Medicare funded three condition RGCS. Confirmatory testing methods may also be required for a subset of other conditions depending on the primary sequencing approach used.

Preferred laboratory method: Based on considerations of cost, scalability, infrastructure requirements, sample type compatibility, and public acceptability, **exome sequencing** is the preferred sequencing method for a national RGCS program.

National Multidisciplinary Meeting for Variant Review

A key component of the variant interpretation framework used in MM was the establishment of a national Variant Review Committee. This committee met via teleconference and was attended by both clinical and laboratory staff as well as bioethicists and invited specialists as needed. It served as a forum for reaching consensus decisions on the suitability of variants for reporting. If consensus could not be reached, expert opinion was sought from physicians with specialist knowledge in the relevant condition. The committee met weekly and functioned as a central register for all reported variants, including those classified as clearly pathogenic. The committee also provided a mechanism for re-evaluating variants if new information emerged, such as family segregation data, that could alter the original classification. By bringing together a multidisciplinary team of experts, the committee ensured that variant reporting decisions were grounded in robust clinical and laboratory evidence. A similar model should be integrated into the National RGCS Program, involving clinical and laboratory representatives from within the program to maintain consistent evidence-based decision-making.

Supporting Autonomy in Reanalysis of RGCS Results

RGCS results are based on the best available genomic knowledge at the time of analysis. While this supports informed reproductive decision-making at that point in time, knowledge about the clinical significance of genomic information will continue to evolve. Unlike diagnostic genomics, where routine/automated reanalysis is more common, unsolicited updates on RGCS results may be confusing and/or distressing, especially if reproductive choices have already been made. It is also practically difficult to manage re-issuing results over time, as individuals may become lost to follow-up, creating a risk if an updated, actionable result cannot be communicated to the reproductive couple. To reflect this, a mechanism could be established that allows reproductive couples to recontact the program to request reanalysis of their data after a defined period if they are planning another pregnancy. A patient-led reanalysis approach promotes autonomy and ensures that updated information is accessed only when it is timely and meaningful. This option should be clearly communicated through educational materials to support informed engagement.

Clinical Care

The Clinical Working Group considered key clinical aspects of national RGCS program design necessary to deliver RGCS with optimum outcomes. There was strong support for leveraging the clinical care structure delivered in MM. This had been developed based on the clinical structure of the Genetic Counselling Screening Team at Victorian Clinical Genetics Services which has been delivering comprehensive clinical support alongside RGCS since its inception in 1997.

This involves the following elements:

Pre-test decision-making and consent support: People have varying informational and support needs when considering RGCS. While the majority are comfortable receiving information through an online platform with a decision-support tool, some require personalised discussion, particularly in the context of low literacy, complex scenarios such as family history of a genetic condition, consanguinity, use of donor gametes or when a reproductive partner does not consent to or is unavailable for screening. In MM approximately 3% of participants required pre-test consultation with a genetic counsellor (MM unpublished data). To ensure equitable access and appropriate care, the program must be resourced to provide pre-test support for those who need it.

- **Clinical input into variant interpretation and reporting:** clinical genomics healthcare providers including genetic counsellors and clinical geneticists play a critical role in multidisciplinary team meetings where potentially reportable variant combinations are reviewed. Their expert clinical input helps determine whether identified variants meet the criteria for reporting and, when reportable, guides decisions on the most appropriate and meaningful way to communicate those results to the screened individuals.
- **Prompt and sensitive disclosure of increased chance results:** Increased chance results contain sensitive and potentially distressing information, particularly for those who are already pregnant. Timely and compassionate disclosure is essential. These results are communicated by telephone by a member of the national program's genetic counselling team. The initial call includes a brief explanation of the result, followed by scheduling a more detailed consultation within a short timeframe to provide comprehensive counselling and support.
- **Comprehensive reproductive decision-making support:** a key component of RGCS service delivery is the post-result genetic counselling consultation. This session includes assessment of family history, explanation of the genetic condition and inheritance pattern, and discussion of available reproductive options. It is designed to support people in making informed decisions about their reproductive choices. Consultations are conducted by a genetic counsellor, with input from a clinical geneticist where needed. To further support decision-making, referrals may be provided to specialist physicians for detailed information about the condition as well as condition-specific patient support organisations.
- **Access to a full range of reproductive options:** to ensure that screening is delivered ethically and has clinical utility, the full range of reproductive options must be available to people who receive increased chance results. This includes timely access to assisted reproductive technologies such as IVF with PGT-M and conception using donor gametes or embryos; prenatal diagnostic testing, termination of pregnancy or postnatal testing. Ensuring equitable access across diverse populations, including those in rural and remote areas, is a critical component of an ethically robust program design.
- **Psychosocial support:** increased chance results can have profound emotional and psychological impact, given their implications for a couple's reproductive journey. Distress related to unexpected news during pregnancy can heighten relationship difficulties or confound prior trauma and mental health challenges. Care should be trauma-informed and holistic as prospective parents can experience levels of traumatic distress associated with post-traumatic stress disorder following a prenatal diagnosis. Access to psychosocial care should be available through mental health professionals withing the national program, ensuring timely and appropriate support and linkages to external, ongoing supports.

The Clinical Working Group emphasised the importance of comprehensive clinical care being an integral part of the National RGCS Program. The group recommended the program include a dedicated clinical team embedded within its structure. In current RGCS service models, results are typically issued to the referring healthcare provider, who is responsible for disclosing the result, with support from laboratory-based genetic counsellors as needed. However, this approach is problematic when the referring provider is not equipped to interpret or communicate the results effectively. As access to the National RGCS Program will occur via patient self-referral, the Clinical

Working Group advised that result disclosure should be handled directly by the program's Genetic Counselling team. This would ensure accurate, consistent, timely, and sensitive communication of results, along with appropriate follow-up and case management.

The Clinical Working Group discussed that the scope of the clinical care provided and funded as part of the National RGCS Program would include pre-test and decision support through to a comprehensive consultation regarding increased chance results and referral to relevant services for access to reproductive options/intervention (with publicly and privately funded options provided).

Clinical Considerations for Program Design

The Clinical Working Group discussed key clinical considerations for program design including the importance of having a process for managing family history information, re-partnering, accommodating diverse family circumstances, and eligibility situations.

Managing family history of genetic conditions

A small but not insignificant portion of reproductive couples undergoing RGCS have a family history of a condition, or conditions screened. In MM, 9.3% of those who underwent RGCS had a family history relevant to the genes screened. The National RGCS Program must have a robust process for assessing family history information to ensure that screening is appropriate for the specific family context and that any relevant testing limitations are clearly communicated. For example, some pathogenic variants are not identifiable by exome sequencing leading to potential false negative screening. From a risk management perspective, it is essential to evaluate family history data pre-test to confirm the suitability of RGCS and identify any aspects that may require further clinical attention. The process can be streamlined by incorporating targeted, well-designed family history questions into the online portal, enabling genetic counsellors to review responses efficiently and follow up with patients for clarification when needed. While this approach worked effectively in MM, it will require refinement to function at a population scale. Without clear processes, there is a risk that individuals may misinterpret what conditions are being screened, potentially leading to misunderstanding about the scope and limitations of the test.

Managing re-partnering

Whilst the reproductive couple-based screening model is the optimal approach for delivering RGCS offering a streamlined process that maximises both laboratory and clinical resources, it is estimated that approximately 18.25% of individuals who undergo RGCS will re-partner (Australian Bureau of Statistics *Marriages and Divorces Australia*, 2021). Therefore, the program must be designed to accommodate re-partnering scenarios, where one or both individuals in a new reproductive couple have previously accessed RGCS with a different partner. In such cases, stored genomic data (see sub-project 3) can be re-accessed, and a new RGCS result generated for the new reproductive couple. If one member of the new couple has not previously been screened, they can enrol in the program, provide a sample, and their sequencing data can be paired with the existing data from their partner. To support re-partnering scenarios, the program design should include mechanisms for ordering RGCS using existing data and for enrolling an individual who can be linked within the system to a partner with pre-existing genomic data. Re-partnering must be considered across all elements of program design, including the online platform, educational content, and laboratory and clinical workflows.

Accommodating diverse family circumstances

It is important to recognise that families come in all shapes and sizes and a National RGCS Program must be inclusive and accommodate the full range of family circumstances including: people conceiving with donor gametes or embryos, surrogacy, and circumstances where a reproductive partner is not available for screening.

RGCS in the context of donor conception

In Australia and New Zealand, approximately 4.5% of IVF cycles involve a donor (Newman et al., 2024). This may involve the use of donor gametes (egg or sperm) or donor embryos. Donors can be sourced either locally or from overseas. Locally sourced donors arranged by the individuals intending to conceive are referred to as "known donors," while those recruited through IVF services are referred to as "clinic-recruited donors." Currently, practices vary both nationally and internationally regarding whether IVF services routinely provide RGCS for donors. In clinics that do perform RGCS on donors, results are typically issued individually. Genetic counsellors or other clinical staff are then responsible for reviewing the donor and recipient results, interpreting them in combination, and providing an assessment of the reproductive couple's genetic chance of having children affected with any of the screened conditions.

RGCS in the donor context presents substantial complexity. Different IVF services may use different commercial RGCS providers, each with its own gene panels, variant classification methods, and reporting formats. This results in fragmented and inconsistent practices. The current model, which relies on manual comparison of individual reports, is resource-intensive and not sustainable for delivery at scale within a national RGCS program. Fortunately, there are emerging approaches that can streamline the RGCS process for individuals conceiving with a donor. For those using a known donor, the reproductive couple (defined here as the two individuals of female and male chromosomal sex who will be the biological parents of the current or planned pregnancy) would enrol in the National RGCS Program and access screening via the simultaneous screening model. This model would generate a couple-based report combining the known donor and the recipient's results. It is suitable for both known gamete and embryo donors. Clinic recruited embryo donors can also be included in this screening model, with each donor de-identified. To ensure inclusivity and informed decision-making, the RGCS consent process should be adapted to accommodate non-genetic parents who may be involved in reproductive decisions.

For clinic recruited gamete donors, we propose implementing a novel model recently developed and piloted at Victorian Clinical Genetics Services. This model, outlined in Figure 11, enables people conceiving with a clinic-recruited egg or sperm donor to access the simultaneous screening model with couple-based reporting. The process involves each IVF service partnering with the RGCS laboratory provider. Clinic recruited donors are consented for RGCS through their IVF clinic, and de-identified samples are collected and forwarded to the RGCS laboratory. The laboratory then processes the sample and generates genomic sequencing data, which is securely stored in a data bank until the donor is selected by a recipient. Once selected, the recipient (i.e., the person intending to conceive with the donor) is consented and their sample is submitted for screening. The donor and recipient data are then processed together through the RGCS bioinformatics pipeline, and a couple-based report is issued for the reproductive pair.

Individuals conceiving with internationally sourced donors present additional complexity in the RGCS context, mechanisms should be explored to receive DNA samples or genomic data from the overseas

donor to be paired with the local recipient for use for RGCS. If this is not possible, the recipient may be able to access RGCS via the individual pathways, outlined below.

RGCS where one reproductive partner is not available for screening

The program must accommodate circumstances where it is not possible to screen both gamete providers for a pregnancy. There may be situations where the female reproductive partner is pregnant, and the male reproductive partner is either unavailable for RGCS or does not consent to participate in RGCS. Scenarios include conception with an overseas sperm donor who has not undergone RGCS, unknown paternity (which occurs in approximately 3.9% of pregnancies (ABS *Births, Australia methodology*, 2022), loss of contact due to physical or emotional safety concerns, or if the male partner is deceased. The Clinical Working Group considered how the program should address these circumstances. While it is technically feasible to screen only the female partner and issue an individual RGCS result, this approach presents several challenges. The data analysis burden would be high due to the likelihood of identifying carrier status for multiple conditions, making interpretation time-consuming and resource intensive. Moreover, the clinical utility of such results is limited, as the absence of a male partner's sample prevents the generation of a combined couple-based result that reflects reproductive chance for the conditions screened. Individual carrier results could also cause unnecessary anxiety for the female reproductive partner. As a result, the Clinical Working Group did not recommend offering individual RGCS to the female reproductive partner.

The Clinical Working Group considered two alternative approaches when the male reproductive partner is unavailable for RGCS:

1. **Offer RGCS for XL and selected AR conditions** (CF and SMA for which individual carrier screening is already supported under MBS item 73451). If the female partner receives a carrier result, prenatal diagnostic testing for that condition could be offered.
2. **Offer prenatal diagnostic testing with RGCS performed via exome sequencing** on a CVS or amniocentesis sample, allowing for analysis of the full gene panel offered to other reproductive couples.

Option 1 provides a non-invasive approach with some clinical utility. XL conditions accounted for approximately 26% of increased chance couples in MM, and about 1 in 20 individuals are carriers of CF or SMA (Kirk et al., 2024). However, it would not allow access to screening the full number of genes on the RGCS panel. Option 2 allows for comprehensive analysis equivalent to that offered to other reproductive couples. However, it requires an invasive procedure, which carries a small risk of miscarriage and is more costly which means uptake is expected to be low. Additionally, operational integration into clinical care could be challenging as exome sequencing is currently reserved for cases with a high likelihood of a genetic condition. As part of preparations for a National RGCS Program, both approaches require further exploration of implementation and resourcing considerations. Regardless of the approach taken, situations where one partner is unavailable for screening should prompt referral to the Program's clinical team for individualised support.

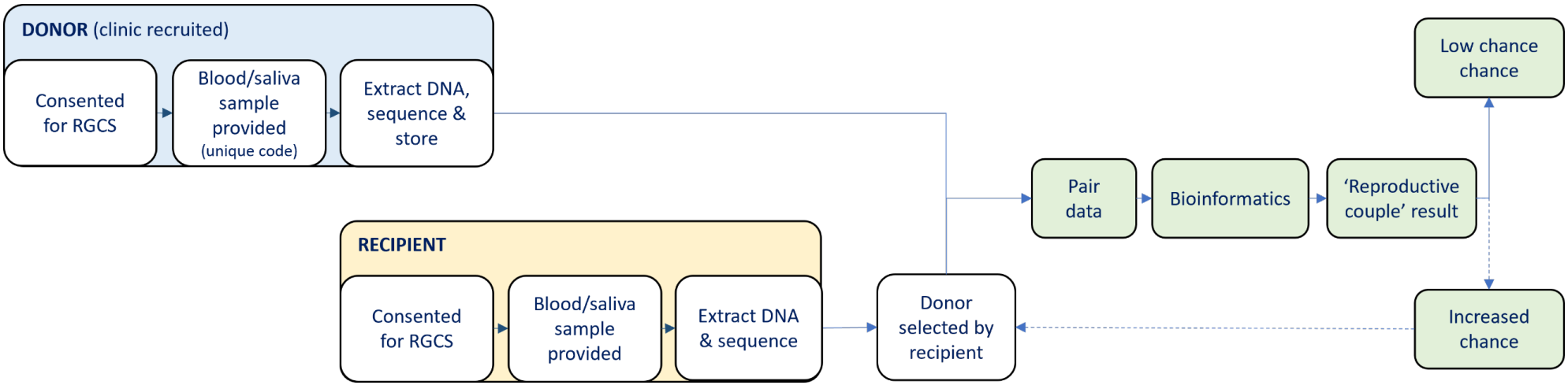

Figure 11: Proposed pathway for RGCS with a clinic recruited donor

The possibility that the female reproductive partner is not available for screening was also considered, although this is rare. One example includes conception by a male partner using an egg donor and a surrogate. In this scenario, the male reproductive partner could be offered carrier screening for common AR conditions (i.e. a variation of option 1) or option 2. However, the pre-test counselling must involve the gestational surrogate, as they must be willing to undergo prenatal diagnosis, and other antenatal interventions if there is an increased chance RGCS result.

In summary, when one reproductive partner is unavailable, the program should provide access to genetic counselling to support informed decision-making about tailored RGCS options.

Objective 1.3 Program Utilisation Modelling

To inform implementation planning for a National RGCS program, uptake was modelled using demographic projections from ADAR 1637 and assumptions about participation and increased chance rates. This modelling estimates the number of reproductive couples likely to undergo screening and, in turn, the number of increased chance couples expected to be identified each year. Based on these projections, demand on laboratory services, clinical care pathways and reproductive services was assessed. This analysis provides insight into the scale of service delivery required to support a national program.

Modelling of Projected Program Utilisation

The projected utilisation of a National RGCS Program is illustrated in Figure 12 and is based on modelling conducted by the MM Health Economics team. Modelling was based on the anticipated reproductive-age and Medicare-eligible population in 2030. The year 2030 was selected to represent a potential “steady state” of the program, recognising that in the initial years of implementation, uptake would be higher as all reproductive couples would be eligible for screening. In subsequent years, only those who have not previously accessed RGCS would be offered screening. While a higher proportion of reproductive couples will be eligible for RGCS in the early years of program delivery, actual uptake may build gradually as awareness increases. This trend was observed with prenatal screening for Down syndrome, where uptake in Victoria rose from 1.6% to 83% between 1996 and 2013 as community familiarity with the test grew (Hui, Muggli & Halliday., 2016)

RGCS uptake at steady state was estimated at 75%, which is higher than that observed in MM. This reflects the fact that although RGCS uptake in MM was 46%, it was delivered in a research context where additional consent processes and participation steps may have created barriers to access. In contrast, offering RGCS through a streamlined clinical service is expected to reduce these barriers and support broader participation. In a steady-state national program that has been established over several years, increased community awareness and understanding of RGCS would further contribute to higher uptake and align with levels similar to those seen for established prenatal screening for chromosomal conditions.

The number of reproductive couples undergoing RGCS is also influenced by re-partnering. According to the Australian Bureau of Statistics Marriages and Divorces data, 18% of couples re-partner (ABS *Marriages and Divorces Australia*, 2021). Individuals who have undergone RGCS and subsequently re-partner would be able to access the National RGCS Program, with their existing genomic data able to be paired with that of their new reproductive partner. As such, the modelling accounts for people accessing RGCS with a subsequent reproductive partner.

It was estimated that, at steady state, approximately 70% of reproductive couples undergoing RGCS will not be pregnant and 30% will be pregnant. Current data for three-condition RGCS suggest a roughly even split between pregnant and non-pregnant couples. However, with increased public awareness and education about the benefits of preconception screening as well as greater accessibility, it is anticipated that a National RGCS Program would shift screening earlier in the reproductive journey, resulting in a reduced proportion of pregnant participants by 2030.

To estimate the number of increased chance couples, a rate of approximately 1.5% was applied. While MM reported an increased chance rate of approximately 1.9%, this figure may be inflated due to higher recruitment through clinical genetics services, where participants were more likely to have a family history of a genetic condition. In contrast, the 1.5% rate observed among reproductive couples recruited through general practice settings is more representative of a true population-based screening approach and is therefore considered a more accurate figure for modelling purposes.

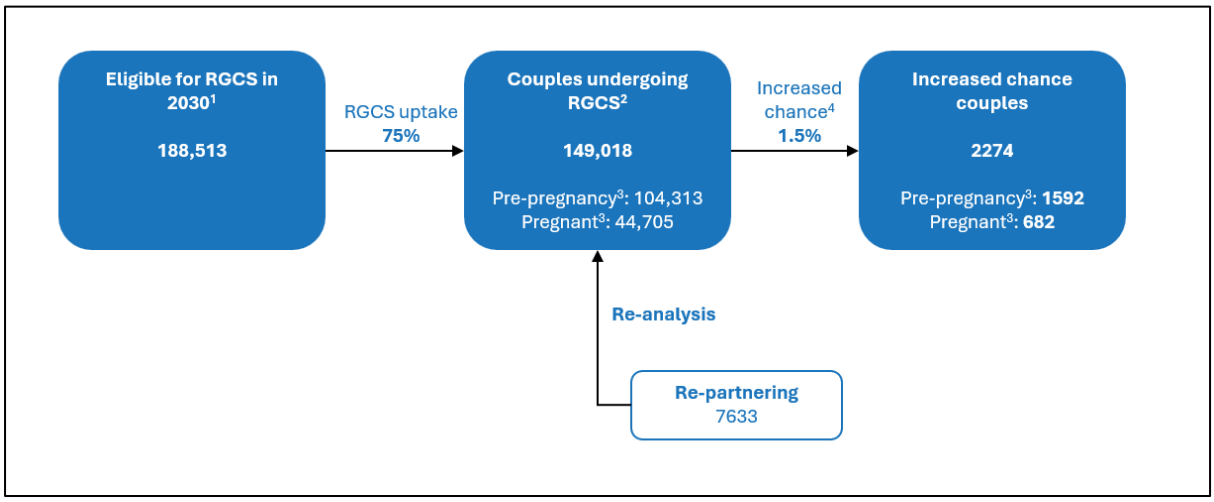

Figure 12: Projected utilisation of National RGCS Program

[1] Projected for 2030 based on population estimations and anticipating "steady state" for the program. Eligibility is based on Medicare eligible reproductive couples and first utilization of RGCS. Assumes a parity quotient of 1.5. [2] Based on estimated 75% uptake of RGCS, also includes couples screened previously through the program who have re-partnered. [3] Based on estimated 30% of couples pregnant and 70% non-pregnant when undergoing RGCS. [4] Based on 1.526% increased chance rate based on increased chance rate from MM participants recruited in primary healthcare settings.

Projected Demand on Services

Modelling indicates that education and awareness campaigns under a National RGCS Program would need to reach up to 400,000 reproductive-age individuals annually. Based on projected RGCS uptake, the program's online enrolment platform would need to accommodate and manage data for approximately 300,000 individuals per year. This would result in around 150,000 reproductive couple samples (i.e. 300,000 individual samples) being processed by the two laboratories servicing the national program. Based on the MM experience, laboratory teams would require administrative support to manage an estimated 5% of reproductive couples due to incomplete test request information or sample issues requiring recollection.

The clinical team embedded within the national program (see Objective 1.4) will require capacity to provide result disclosure and genetic counselling to approximately 2,300 increased chance couples annually. The key steps and associated time commitments for managing each increased chance

couple are outlined in Table 3. In addition, based on MM data and assuming recommended efficiencies are implemented, around 5% of the total cohort, equating to about 7,500 reproductive couples, are expected to require clinical support during enrolment or prior to results. This support may include assessing family histories for relevance to RGCS, navigating diverse family structures (e.g. donor conception) or managing situations where one reproductive partner is unavailable for screening. As outlined in Objective 1.4, these cases would be triaged by clinical assistants, with approximately 75% (5625) managed at that level and the remaining 25% (1875) managed by the genetic counselling team for higher-level clinical input.

Table 3: Key steps and estimated time involved in managing increased chance couple results

Responsibility	Team member	Duration per increased chance couple	Percentage of cases (approx. number of cases)
Administrative case management	Clinical Administrative Support Officer	30 mins	100% (2300)
Case review	Genetic Counsellor	30 mins	100% (2300)
	Clinical Geneticist	30 mins	80% (1840)
Result disclosure	Genetic Counsellor	30 mins	100% (2300)
Genetic counselling Appointment	Genetic Counsellor	60 mins	100% (2300)
	Clinical Geneticist	30 mins	80% (1840)
Clinical correspondence and record keeping	Genetic Counsellor	30 mins	100% (2300)
Specialist physician input/appointment[1]	Specialist in relevant condition	60 mins	70% (1610)
Psychosocial support	Mental health professional	60 mins	30% (690)

[1]Although specialist physicians could be involved in up to 70% of cases, some cases may require case-review input but not necessarily involvement in a clinical appointment.

Objective 1.4 Program Capacity and Resourcing Requirements

Establishing a National RGCS Program will require the development of a new, centralised service model capable of supporting large-scale screening and follow-up care. While this will involve building new clinical and operational teams, the program can leverage some existing laboratory infrastructure, RGCS protocols established via MM, and the specialised skill sets already present within the genomics and health workforce in Australia. This blended approach will support efficient implementation while maintaining high standards of service delivery.

Establishing Program Enablement Teams: Engagement, Education and Communication

The success of a National RGCS Program will depend not only on the quality of laboratory and clinical services but also on coordinated efforts to engage communities, educate participants and healthcare providers, and promote the program effectively across Australia. To support these functions, it is critical to establish dedicated Engagement, Education, and Communications and Service Promotion teams early in the program lifecycle.

Engagement Team

A dedicated Engagement Team should be established to ensure that the national RGCS program is developed and delivered in a way that is inclusive, culturally appropriate, and reflective of community values and needs. Embedding community voices in program design and implementation will be essential for building trust, addressing systemic barriers, and promoting equitable access.

Key responsibilities of the Engagement Team will include:

- Partnering with patient support organisations, especially those representing communities affected by the screened conditions. These organisations bring essential lived experience and can guide the development of relevant, empathic resources and communications.
- Engaging with Aboriginal and Torres Strait Islander communities to ensure the program respects and incorporates Indigenous knowledge systems and health priorities. This includes establishing an Aboriginal and Torres Strait Islander Advisory Group to provide ongoing, culturally informed guidance.
- Collaborating with broader community organisations, such as those supporting culturally and linguistically diverse communities, people with disabilities, and rural and remote populations. These partnerships will facilitate co-designed, locally appropriate service delivery approaches.

The Engagement Team will work closely with the Education and Communications teams to ensure that program strategies and content are inclusive, culturally responsive, and informed by community perspectives. In parallel, the team will coordinate with government stakeholders to ensure that engagement activities align with costed service plans, implementation timelines, and broader policy objectives.

Education Team

An Education Team, led by genomics education specialists will be responsible for developing accurate, accessible, and engaging educational resources for both the public and healthcare professionals. A Clinical Advisory Group including genetic counsellors, clinical geneticists, and specialist physicians will guide content development and provide expert review.

Education materials will be tailored to different audiences:

- Patients, via the online platform, covering topics such as inheritance, increased chance results, and reproductive options.
- Healthcare professionals, focusing on screening pathways, clinical relevance, and patient communication.

While much of the content development will occur during program establishment, ongoing resources and staffing must be allocated for continuous review, updates, and quality assurance. This is critical given the evolving nature of genomics and the need for materials to remain current and evidence based.

Communications and Service Promotion Team

The Communications and Service Promotion Team will lead the development and delivery of public-facing campaigns and messaging strategies to raise awareness of the national RGCS program and support informed participation. This team will be responsible for designing and implementing communication initiatives that are accessible, inclusive, and aligned with the program's core values.

Key responsibilities will include:

- Developing and managing social media, digital outreach, and print media campaigns to engage the public and increase program visibility.
- Creating targeted communication strategies for healthcare professionals to support their role in raising awareness and discussing RGCS with patients.
- Producing multilingual and culturally appropriate messaging that promotes informed choice, avoids stigma, and clearly communicates that screening is optional not routine.
- In collaboration with the Education team, developing and maintaining a program website that provides the community with key information about the National RGCS Program and serves as the entry-point for the online enrolment and participation platform.

The team will also ensure that content is accessible to individuals with varying levels of health literacy and familiarity with the healthcare system. In doing so, they will play a critical role in supporting equitable uptake and understanding of the program across diverse communities.

Building a National RGCS Laboratory System

The Laboratory Working Group considered the infrastructure, processes, and personnel needed to support the delivery of high-throughput, high-quality genetic testing within a National RGCS Program. The aim is to establish a centralised, scalable laboratory system across two geographically distinct laboratories, ensuring consistency, efficiency, and clinical reliability across all stages of testing and reporting. This dual-site model provides resilience, supports national coverage, and enables load sharing to maintain timely service delivery across the program. Although this approach involves higher initial investment, long-term efficiencies are expected through automation, bulk procurement, and streamlined operations. The centralised model also supports consistent quality standards, data management, and integration with clinical and digital systems.

Locating laboratories within existing NATA-accredited diagnostic or healthcare hubs will maximise infrastructure use and reduce costs. Co-location enables access to shared services and skilled personnel while supporting remote and centralised oversight. Automation will reduce manual processing and staff burden, particularly for wet lab workflows, sample tracking, and follow-up activities. To ensure national readiness, a staged implementation starting with a regional or state-based pilot is recommended prior to full-scale rollout.

Key Laboratory System Considerations

Choice of Sequencing Methodologies

Selection of sequencing technology must balance reliability, throughput, and cost. While Illumina remains the dominant provider, platform flexibility and procurement strategy will be key to ensuring long-term sustainability. Reagent supply chain management will also be critical to prevent service interruptions.

Laboratory Automation

To meet the high throughput demands of a National RGCS Program, the selection and implementation of automated systems for wet laboratory processes will be essential. Automation reduces manual error, enhances consistency, and enables efficient scaling with reduced staffing requirements. Equally important is the automation of administrative workflows, such as triggering follow-up communications for participants who partially complete the consent process or fail to return their sample kits within a specified timeframe. Investment in fit-for-purpose automation across both laboratory and operational processes will be a key driver of long-term efficiency and program sustainability.

Data Analysis and Reporting Systems

A range of tools are available to support data analysis, variant interpretation, and laboratory information management. However, to meet the specific needs of a National RGCS Program, these systems will likely require adaptation. Emphasis should be placed on automating routine reporting tasks such as the generation and delivery of low-chance results to improve efficiency and reduce turnaround times. Seamless integration between analysis platforms, laboratory information systems, and participant portals will be essential to support accurate, consistent, and timely communication of results at scale.

National RGCS Laboratory System Composition

Delivering high-quality and efficient testing as part of a National Program requires both scientific and operational expertise. This requires the following key roles and components necessary to deliver this service at scale:

- ***Laboratory Scientists***
  Scientists form the core of the laboratory workforce, responsible for sample processing, DNA extraction, sequencing, and quality control. Their expertise ensures the accuracy and reliability of results. As automation is introduced, scientists will increasingly focus on validating workflows, troubleshooting, and ensuring data integrity across high volumes. Ongoing training will be essential to maintain workforce capability and support technological adaptation.

- ***Bioinformaticians***
  A dedicated team of bioinformaticians will oversee data analysis, variant calling, and reporting processes. These professionals will also manage and refine laboratory information systems, ensuring interoperability with clinical systems and participant portals. Automation of routine analysis and reporting tasks will be critical to maintain scalability.

- ***Operational Support Staff***
  A skilled operational support team is essential to ensure the smooth running of logistical and administrative functions. Their responsibilities include receiving and logging samples,

coordinating mail-out and return of sample kits, managing follow-up with participants who do not complete consent or fail to return samples, and scheduling variant review meetings. Staff will also support the upload of low-chance results to participant portals and track sample reconciliation. Their work underpins the efficiency and user experience of the testing process.

- ***Quality, Accreditation, and Compliance Officers***
  As the laboratory must meet all relevant National Pathology Accreditation Advisory Council (NPAAC) and ISO standards, dedicated staff will be needed to manage compliance, lead validation processes, and oversee audits and accreditation activities. A quality assurance team will monitor ongoing performance, ensuring the program meets its clinical and operational benchmarks.

Establishing the National RGCS Laboratory Team

Given the centralised nature of the proposed model, a new national laboratory structure will need to be established. This team should draw from Australia's existing laboratory expertise in genomic testing while ensuring alignment with the specific requirements of a population-level RGCS program. Laboratory scientists and bioinformaticians should have experience in reproductive genomics and high-throughput sequencing. Operational and automation staff must be equipped to manage large-scale logistics and support continuous improvement through data-driven system optimisation.

A phased implementation will allow systems to be piloted and refined prior to national rollout. This should include live testing of automation tools, reporting workflows, and integration with clinical and participant-facing systems. As the program expands, flexible workforce models including cross-site collaboration and remote support can help maintain resilience and responsiveness.

Building a National RGCS Clinical Team

The Clinical Working Group considered models for clinical service deliver within the national RGCS program and discussed the composition of the clinical team that would support the program.

Proposed Clinical Service Delivery Model

A centralised clinical team should be established to ensure consistency, quality, and efficiency in service delivery across the National RGCS Program. Access to clinical support must be timely and flexible, with telehealth options available to overcome geographic and accessibility barriers and support equitable participation. A national team is preferred over individual state-based teams to allow for better alignment of systems, processes, and communication. Remote working arrangements can enable participation from clinical staff across Australia, supporting workforce flexibility and inclusivity. Genetic counsellors will be responsible for coordinating the day-to-day operations of the clinical service with the support of a clinical administration team. The genetic counsellor role includes managing pre-test enquiries, conducting result disclosure appointments, providing post-result counselling and support and liaising with local care teams to facilitate referral for reproductive intervention where requested. Clinical geneticists will provide overarching clinical oversight, contributing to the interpretation of complex cases and participating in increased chance consultations where their expertise is required. This model reflects the highly effective clinical structure delivered in many clinical genetics services and leverages the distinct and complementary skill sets of genetic counsellors and clinical geneticists to deliver high-quality, patient-centred care.

A team of specialist physicians is also required to service the program. During MM, timely access to subspecialist input was inconsistent, often limited by local service availability and clinician priorities. To address this, two models were considered: (1) appointing subspecialists in each capital city, or (2) establishing a national panel. The preferred approach is a national panel of at least two subspecialists per major condition group, available at short notice to consult with people who receive increased chance results.

Emerging long-term data from MM highlights the significant psychosocial impact of RGCS on some participants (Tutty et al., in press). We therefore recommend embedding more comprehensive psychological support within the program, with timely access to care and appropriate referral pathways for those needing ongoing support. A national team of multidisciplinary mental health professionals will be needed to support people who experience emotional or psychological distress regarding increased chance results. A national team structure is preferred to ensure consistent service delivery and to align with the centralised model for delivering clinical care.

National RGCS Program Clinical Team Composition

The Clinical Working Group recognised that delivering high-quality care as part of a National RGCS Program will require a specialised clinical genomics workforce comprised of genetic counsellors and clinical geneticists. It will also require specialist physicians and mental health professionals to provide condition-specific expertise and psychosocial support.

- **Genetic counsellors** are the cornerstone of the National RGCS Program clinical service. Their expertise spans genomic education, family history assessment, providing decision-making support, interpretation and disclosure of genomic results, and counselling around reproductive options. They also provide psychosocial support to people navigating the complexities of RGCS. For a national RGCS program to be effective, it must be capable of coordinating care across the pre-test and post-result stages. Genetic counsellors also play a key role in educating other healthcare professionals and engaging with patient support groups and broader healthcare services.
- **Clinical Geneticists** are equally critical, offering expert clinical oversight across the program. They contribute to family history assessment in complex cases, interpretation of genetic results, and provide clinical insight into the implications of conditions identified through screening for people who receive increased chance results.
- **Clinical Administration Assistants** will play a key enabling role in supporting the effective delivery of the clinical service. Their responsibilities will include co-ordinating appointments, managing documentation and data entry, triaging enquiries, facilitating communication between team members and participants, and ensuring smooth logistical workflows across the program. By managing these operational tasks, clinical administration assistants enable clinicians to focus on delivering specialised clinical care. Their contribution is essential to maintaining efficiency, minimising delays, and ensuring a seamless experience for participants.
- **Specialist physicians** will provide detailed clinical information to people who receive increased chance results, helping them understand how a condition might affect a future child. This includes discussion of prognosis, treatment options, and expected quality of life. Given the broad range of conditions screened, access to relevant specialists such as a

paediatric respiratory physician for cystic fibrosis or a paediatric neurologist for spinal muscular atrophy is essential to ensure condition-specific advice is available when needed.

- **Mental health professionals** play an important role in supporting people experiencing distress following an increased chance result. While genetic counsellors provide initial psychosocial support, some people may require more intensive support. Mental health professionals aligned with the National RGCS Program will be available to offer short-term interventions, particularly in situations involving decision-making, grief, anxiety, or relationship stress. Where appropriate, they can establish care pathways for longer-term psychological support. Working collaboratively with genetic counsellors, these professionals will contribute to a holistic model of care that recognises and addresses the emotional and mental health needs associated with RGCS.

The role of patient support organisations

To complement the clinical and psychosocial care provided by healthcare providers within the National RGCS Program, patient support organisations will also play a valuable and distinct role. Condition-specific organisations, traditionally focused on supporting individuals and families after diagnosis, are increasingly being approached by people who have received increased chance results through RGCS. These organisations can offer important insights into what a condition may mean in real life, helping individuals and couples understand the condition from a lived experience perspective. They also provide opportunities for increased chance couples to connect with families affected by the condition, which can aid in decision-making and emotional adjustment.

In addition to condition-specific support, there is a need to establish broader peer-based support mechanisms. While genetic counsellors, clinical geneticists, mental health professionals, and specialist physicians offer expert guidance, individuals may benefit from connecting with others navigating similar reproductive decisions. Peer support can reduce feelings of isolation, normalise emotional reactions, and provide practical advice based on shared experience. Connection is important for mental health and purposeful connection for increased chance families and will foster empowerment and confidence in reproductive decision-making. Patient support organisations are well placed to facilitate this, offering emotional reassurance and enhancing the overall care model by empowering individuals to make informed and supported reproductive choices. Specific resourcing should be provided for this function which could be integrated into existing patient support organisations or developed as a new service tailored specifically for those receiving increased chance results through the National RGCS Program.

Establishing the National RGCS Program clinical team

Given the preferred model of a national clinical team, no existing structure currently fulfils this function, and as such, it will need to be established. The genetic counsellors and clinical geneticists leading the team will have specific expertise in reproductive genomics and screening. Mental health professionals should similarly be experienced in reproductive healthcare and in providing crisis support when required.

The program will also require input from a wide range of specialist physicians to support the management of increased chance couples (see Table 4). However, the need for their involvement will be variable and often unpredictable, making it impractical to engage them on a full-time or part-time basis. Furthermore, many of these practitioners play essential roles in the broader public health

system. To ensure their availability and commitment, appropriate funding should be allocated to compensate subspecialists for their time on an as-needed basis. An expression of interest process should be undertaken prior to program commencement to identify suitable members for the specialist physician panel. Those selected should receive training in the reproductive and ethical considerations relevant to the program.

Table 4: Physician specialties required to provide input for increased chance couple results in Mackenzie's Mission

Physician specialty	Percentage of increased chance couples supported by physician specialty in MM[1]
Clinical genetics	29.5%
Metabolic medicine	14.5%
Neurology	13.3%
Respiratory medicine	11.6%
Ophthalmology	11%
Haematology	6.9%
Nephrology	5.8%
Immunology	2.9%
Dermatology	1.7%
Gastroenterology	1.1%
Cardiology	1.1%
Endocrinology	0.6%

[1] If, in the future, newer technologies are adopted for laboratory testing, there will likely be a significant increase in the number of reproductive couples identified have an increased chance for conditions such as congenital adrenal hyperplasia (endocrinology) and haemophilia (haematology). This is because the technology used in MM was unable to detect many of the common pathogenic variants associated with these conditions.

Objective 1.5 Efficiencies and Interventions

The relevant working groups discussed and identified possible interventions that could improve the efficiencies and reduce the burden on health system capacity.

Pre-test interventions to improve efficiencies

To improve the efficiency of clinical input required prior to testing, the following interventions could be implemented:

- *Broader awareness about preconception care:* Efforts to raise awareness of preconception care will improve the efficiency of a national RGCS program by enabling earlier identification of increased chance couples. Managing increased chance results preconception is significantly less resource-intensive than managing these during pregnancy.

- *Tiered and streamlined pre-test support:* a triage model is recommended in which trained clinical assistants manage routine or administrative enquiries, with more complex or sensitive cases escalated to a genetic counsellor. This approach reserves specialist expertise for individuals who require it most, optimising the use of limited genetic counselling resources. AI tools such as chatbots may assist in streamlining the management of basic enquiries directed to the clinical team.
- *Automation of family history review:* automating the review process for relevant family history information in people undergoing RGCS, particularly for standard or low-complexity scenarios, will reduce the need for direct clinical involvement and streamline pre-test workflows.

Together, these approaches will enhance the efficiency of pre-test support while maintaining appropriate clinical oversight and ensuring individuals receive the guidance they need.

Improving laboratory testing efficiencies

Improving laboratory testing efficiencies in a national RGCS program will rely heavily on the rapid development and use of shared data infrastructure. A centralised database of curated variants, along with a variant frequency database specific to the Australian population, will streamline variant interpretation and reporting. Evidence from the MM laboratory experience (manuscript in preparation) indicates that maintaining a database of previously curated variants significantly reduces the number of variants requiring manual review. At scale, this infrastructure is expected to enable automation of most reporting, with individual variant review needed only for a small proportion of reproductive couples.

Participating laboratories will also benefit from real-time data sharing, which will minimise duplicated efforts in interpreting recurrent variants and support the creation of a national variant frequency database using de-identified, summarised data. This shared resource will not only enhance the interpretation of RGCS results but also contribute to diagnostic genomics more broadly, particularly in addressing inequities caused by the underrepresentation of diverse ancestries in international databases. In addition, harmonised laboratory methods will generate further efficiencies through economies of scale, reducing the cost of sequencing reagents and consumables, and enabling reuse of existing data when individuals re-partner. Together, these strategies will improve both efficiency and equity within the program.

System-wide testing efficiencies

Screening for haemoglobinopathies

There may be opportunities to improve system-wide efficiency across existing genetic screening programs. For example, screening for haemoglobinopathies is currently delivered through state-based services by assessing blood parameters, with genetic testing offered only if results are suggestive of carrier status. Haemoglobinopathies, including alpha- and beta-thalassaemia, are among the most common inherited conditions, affecting approximately 1 in *X* individuals in Australia. While this haemoglobinopathy screening is partly Medicare funded and partly State funded, public and practitioner awareness varies, there is evidence of individuals being screened multiple times, national access is inconsistent, there are some clinical limitations on when screening

can be performed and the turnaround time for comprehensive results can be prolonged (Cousens, Gaff, Metcalfe & Delatycki, 2013).

In MM, screening for beta-thalassaemia through analysis of the *HBB* gene was included, but screening for alpha-thalassaemia via the *HBA1* and *HBA2* genes was not undertaken due to technical complexity and the existence of publicly funded testing. A national RGCS program presents an opportunity to review and integrate approaches to haemoglobinopathy screening. Centralising and streamlining the genetic testing component particularly by including *HBA1/2* screening may enhance efficiency, reduce duplication, and improve equity in access across jurisdictions.

FMR1 Carrier screening and AGG interrupt analysis
While carrier screening for fragile X syndrome (*FMR1* gene) is currently covered under Medicare item number 73451, clinical practice remains inconsistent with regard to whether AGG interrupt analysis is performed. AGG interrupt analysis is a specialised test that examines the pattern of AGG triplets within the CGG repeat region of the *FMR1* gene. These AGG interruptions help stabilise the gene and reduce the risk of repeat expansion, providing a more accurate estimate of the likelihood that a fragile X premutation will expand to a full mutation in future generations. AGG analysis is particularly important in carrier screening because a significant proportion of identified premutation carriers fall within the low premutation range, where most alleles are stable when passed to offspring. The AGG test is crucial in distinguishing which individuals have stable versus unstable premutation alleles, allowing for more accurate counselling and reducing unnecessary anxiety or intervention.

It is therefore critical that AGG interrupt analysis be included as a reflex or second-tier test following *FMR1* testing for fragile X carrier status. In Australia, some laboratories routinely include AGG analysis as part of their *FMR1* testing, while others do not, resulting in variability in the quality and clinical utility of results provided to patients. The ideal approach is that which was implemented in MM where small stable premutation alleles were reported as “low chance” for FXS. This reduces unnecessary anxiety, reproductive intervention and cascade testing in relatives. The current inconsistency in practice across laboratories is problematic, as it leads to inequities in care where individuals may receive different levels of information and follow-up depending on the laboratory performing the test. This is contributing to unnecessary downstream impacts on clinical genetics services, with follow-up testing frequently requested for children and other relatives of individuals identified with small premutation alleles, many of which would have been clarified as stable if AGG data were available. Incorporating AGG interrupt testing as a standard component of fragile X screening within a National RGCS Program would ensure consistent, high-quality delivery across the country, improving the accuracy of risk assessments, supporting reproductive decision-making, and reducing avoidable strain on genetic services.

Improving efficiencies in clinical care for increased chance couples

To improve the efficiency of managing increased chance RGCS results, several strategies can be implemented to better utilise limited genetic counselling resources while maintaining high-quality care:

- *Digital tools for preparatory education:* pre-recorded videos or podcasts can be developed to deliver standard information typically covered in increased chance consultations. These resources could explain specific genetic conditions, inheritance patterns, and available

reproductive options, allowing people to review key information prior to the consultation at their own pace. This preparatory support could enhance understanding and reduce time required in consultations.

- *Genetic counsellor-led consultations:* genetic counsellors should manage appointments with increased chance couples, with clinical geneticists consulted only for complex cases. This model helps preserve specialist resources while ensuring appropriate care.
- *Use of AI for clinical documentation:* Emerging AI technologies can assist with tasks such as generating patient summary letters and recording or structuring clinical notes. These tools can free up clinician time allowing more focus on direct patient care.

Collectively, these strategies would streamline service delivery while maintaining equitable and informed support for people receiving increased chance results.

Sub-project 2: Evaluating Accessibility and Affordability of Flow on Services

Sub-project 2 focused on the delivery of clinical services that follow an increased chance result from RGCS. It was informed by the Clinical Working Group and the IVF and PGT-M Working Group, which provided expert advice on downstream services including clinically viability, equitable access, and responsiveness to the diverse needs of the Australian population.

While Sub-Project 1 focused on the design of the national screening program itself, Sub-Project 2 concentrated on steps after an increased chance result including the clinical infrastructure, referral pathways, and support services required to enable informed reproductive decision-making. The Clinical Working Group brought together a diverse group of clinicians and health professionals from multiple jurisdictions and care settings, including experts in genetic counselling, clinical genetics, midwifery, obstetrics, and maternal fetal medicine (see ***APPENDIX I – Working Group M*** for full membership).

Discussions included the service pathways, costs, and care models following an increased chance result, including access to genetic counselling, prenatal diagnosis, IVF with PGT-M, and other reproductive interventions. Considerations included current system capacity, funding mechanisms, and the variations in access to services across geographic and health system boundaries. The cultural and linguistic acceptability of downstream care particularly for Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities is important and there is a need to identify and address structural and practical barriers that may impact equitable access.

This work informed recommendations on the delivery of downstream services that aligns with clinical realities, anticipates future demand, and supports people to make informed reproductive choices following RGCS.

Aim: Evaluate the flow-on services for couples identified as increased chance through RGCS, model the barriers to access and affordability and develop recommendations to ameliorate these barriers.

Objectives:

2.1 Elucidate the core assumptions for a proposed model of delivery of RGCS to inform the analyses of geographic distribution of clinical services downstream of RGCS

- Map potential delivery pathways and identify where alternative models/options should be explored

2.2 Perform a desktop review of costs of clinical services downstream of RGCS: MBS subsidised services, out of pocket costs, and evaluation of affordability of services against ABS / SES data

2.3 Consider the acceptability/support by these services for Indigenous and culturally and linguistically diverse people

2.4 Model the barriers and identify enablers to equitable access to services that flow-on from an organised RGCS program nationally.

Objective 2.1: Core Assumptions for Access to Reproductive Options Following RGCS

Several core assumptions underpin the assessment and planning of clinical services required downstream of a National RGCS Program. These assumptions inform system modelling, guide equity-focused access planning, and shape the design of referral pathways and support mechanisms.

Equitable Access to Reproductive Options

The model assumes that all who receive an increased chance result will have access to the full range of reproductive options regardless of geography, socioeconomic status, cultural background, or other circumstances. This includes:

- **Funded access to reproductive interventions** including: CVS and amniocentesis for prenatal diagnosis, termination of pregnancy, and assisted reproductive services including IVF with PGT-M and use of donor gametes or embryos.
- **Geographic equity** including: Provision for regional, rural, and remote patients to access reproductive services at major centres (if not available locally), with funding support for travel and accommodation where needed. Collaboration with state and territory health systems to ensure reproductive services are consistently accessible across jurisdictions.
- **Culturally safe care** including: Access to culturally safe, trauma-informed, and community-led care models for Aboriginal and Torres Strait Islander people and people of culturally and linguistically diverse backgrounds including interpreter services, multilingual educational resources, and cultural liaison roles.

These assumptions require coordination across federal, state and territory systems to align funding, service delivery, and referral models.

Supported Reproductive Decision-Making

Modelling assumes that increased chance couples will have access to:

- Genetic counselling and condition-specific medical information to support decision-making.
- Timely reproductive planning support, noting the time sensitivity of many interventions (e.g., prenatal testing options in a pregnant woman and availability of timely pregnancy termination if requested).
- Psychosocial support services embedded in care pathways.

These services are assumed to be delivered via a mix of local and centralised resources, supported by telehealth and digital infrastructure.

Assumed Utilisation Patterns
Drawing from MM data, it is assumed that approximately 76% of increased chance couples will pursue reproductive interventions (Kirk et al. 2024). This informs the modelling of service demand across:

- Public IVF services with PGT-M capability.
- Prenatal diagnostic procedures and associated obstetric care.
- Pregnancy termination services with appropriate counselling and clinical oversight.

Integration of Monitoring and Evaluation Mechanisms
The delivery model assumes the establishment of national mechanisms to monitor access, equity, quality, and outcomes of reproductive interventions post-RGCS. This includes:

- A national data registry linking RGCS results to downstream service utilisation.
- Equity indicators stratified by geography, cultural identity, and socioeconomic status.
- Mechanisms for patient-reported outcomes and experiences.
- Regular evaluation cycles to inform service planning, system responsiveness, and continuous quality improvement.

These assumptions support modelling of service needs and help ensure that reproductive options following RGCS are delivered equitably, responsively, and in alignment with the values and needs of all communities across Australia. To achieve this, the National RGCS Program must collaborate closely with fertility clinics, obstetric services, and genetics units across jurisdictions to establish clear referral pathways and reduce geographic, financial, and systemic barriers to access.

Objective 2.2: Clinical Pathways Downstream of RGCS

The ethical delivery of a National RGCS Program depends not only on effective screening but also on equitable access to the full range of reproductive options for people who receive increased chance results. This section outlines potential clinical service pathways downstream of RGCS such as access to genetic counselling, prenatal diagnosis, termination of pregnancy, and IVF with PGT-M. Ensuring timely, culturally safe, and geographically accessible care will be critical to supporting informed reproductive decision-making across diverse populations.

Reproductive options after increased chance results

Figure 13 outlines the clinical pathways available to people who receive increased chance results following RGCS. As part of the National RGCS Program design, a dedicated genetic counselling team will receive and disclose increased chance results and provide initial genetic counselling support. This may occur over one or more sessions, depending on individual needs, and will include discussion of the relevant condition(s), inheritance patterns, clinical features, available reproductive options, and strategies for communicating genetic information to family members. Where appropriate, genetic counselling may also address the potential need for diagnostic testing in one or both reproductive partners, existing children or other relatives. This may require referral to appropriate local clinical genetics services.

This phase of clinical care will provide tailored support to help people make informed decisions about their reproductive options. Once a decision has been made, the couple will be referred to appropriate local services to access their chosen pathway. Where required services are not available locally, referral will be made to the nearest major centre, with support provided for travel and accommodation to ensure equitable access to care. If patients later decide to explore a different reproductive option, they can recontact the National RGCS Program genetic counselling team for further decision-making support and updated referrals as appropriate

Reproductive Options for Increased Chance Results Received Preconception

For reproductive couples who receive an increased chance result prior to pregnancy, there are a range of reproductive options available to support informed decision-making. Following the result and initial genetic counselling provided by the National RGCS Program, reproductive couples may consider assisted reproductive technologies, opt to pursue prenatal diagnostic testing once pregnant, or choose to continue family planning without reproductive intervention.

One key option is IVF with PGT-M, which allows embryos to be tested for the condition before embryo transfer to the uterus. This option may be preferred by those seeking to avoid the potential challenges associated with prenatal diagnosis and possible pregnancy termination. Alternatively, some may choose to use donor gametes or embryos (from a screened donor/s) to minimise the chance of passing on the condition.

Another important option is prenatal diagnostic testing after natural conception. This involves procedures such as CVS or amniocentesis to test for the specific condition during pregnancy. This provides people with early and accurate information to guide decision-making during pregnancy. For many, prenatal diagnosis offers the opportunity for reassurance or preparation, while for others, it enables the consideration of pregnancy termination. Access to timely and sensitive counselling is essential to support individuals through this process.

Some people may decide not to pursue further children or may proceed without additional genetic testing or intervention. Adoption or foster care may also be considered as pathways to parenthood. In all cases, the reproductive pathway chosen should be supported by a tailored care plan, often involving referral to local fertility services, and guided by the individual values, circumstances, and preferences of the patient/s. Early access to genetic counselling and reproductive advice ensures that people are equipped to make choices that are right for them before pregnancy occurs.

Reproductive Options for Increased Chance Results Received in Pregnancy

Ideally, RGCS is undertaken preconception, as it allows access to the widest range of reproductive options. However, we estimate that approximately 30% of reproductive couples will access RGCS during pregnancy. It is essential that these individuals have access to appropriate reproductive options through the timely offer of prenatal diagnostic testing, and, where requested, pregnancy termination. Managing increased chance results during pregnancy can be complex, particularly when results become available later in gestation, which may limit available choices and increase emotional distress. Therefore, efforts should be made to promote the program and offer screening as early in pregnancy as possible to support informed decision-making.

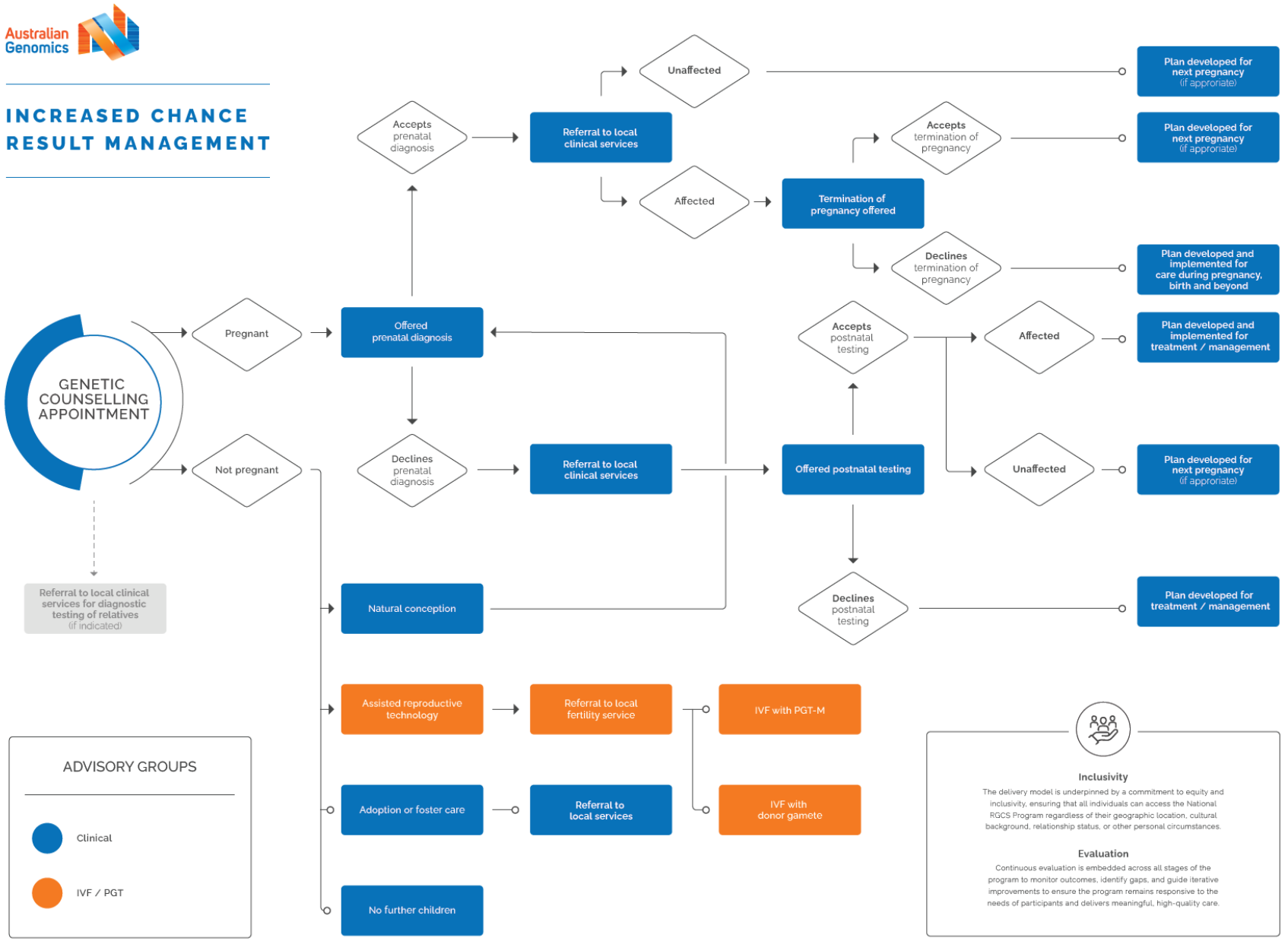

Figure 13: Pathways for reproductive choices for people receiving increased chance results

For those who are already pregnant at the time they receive an increased chance RGCS result, reproductive decision-making may involve consideration of prenatal diagnostic testing. Two primary diagnostic procedures are available: CVS and amniocentesis. CVS is typically performed earlier in pregnancy usually between 11 and 13 weeks and allows for direct testing of DNA in placental tissue, making it the preferred diagnostic approach for single-gene conditions due to the shorter turnaround time and earlier results. Amniocentesis, conducted later typically from 15 weeks onward, may require culturing of the amniotic fluid cells before testing, which can delay results. While both procedures are clinically acceptable, access to CVS is particularly valuable for timely decision-making. However, availability of both procedures varies significantly across Australia, particularly outside major centres, making improved and more consistent access to CVS an important consideration in the design and implementation of a National RGCS Program.

In some cases, RGCS may identify information relevant not only to the developing baby but also to the health of the pregnant person. For example, for carriers of an XL condition there may be implications for patient health and/or pregnancy management such as certain bleeding disorders or neuromuscular conditions and tailored clinical care may be required. Examples include but are not limited to Ornithine Transcarbamylase Deficiency (OTC), Duchenne Muscular Dystrophy (DMD), Haemophilia A and B (Factor VII/IX Deficiency), and Fabry Disease. In these instances, close coordination with the local maternal fetal medicine team and relevant specialty services is essential to ensure that appropriate investigations, monitoring, and management plans are in place. Clear referral pathways and timely communication of results to treating clinicians will be critical to ensuring safe and responsive pregnancy care.

Ongoing Care and Coordination for Future Pregnancies

When reproductive couples who have received an increased chance result through the National RGCS Program are planning a subsequent pregnancy, they should be linked in with their local clinical genetics service for preconception review and care planning. These services are best placed to provide ongoing support, revisit reproductive options as needed, and ensure timely coordination of diagnostic testing or assisted reproductive technologies. To meet this need, local clinical genetics services will require appropriate resourcing to manage the clinical workload generated by referrals from the National RGCS Program beyond their existing case volumes. However, this increase in caseload will be offset by a reduction in demand elsewhere in the healthcare system as the program will lead to fewer births of children with serious inherited genetic conditions. Strong communication and referral pathways between the national program's clinical team and local genetics units will be essential. This includes mechanisms to share results and clinical correspondence in both directions to support continuity of care and ensure that couples receive coordinated, informed, and context-specific support.

For some couples, the process of RGCS and receiving an increased chance result may trigger broader psychosocial health impacts. The experience of navigating complex reproductive decisions often within a time-limited and emotionally charged context can carry a significant psychological and emotional burden. For this reason, it would be prudent for couples undertaking reproductive interventions, such as IVF with PGT-M or prenatal diagnosis, to be offered ongoing psychosocial support. This could include access to mental health professionals through Medicare-subsidised mental health care plans, with referrals facilitated by the clinical team and/or a local GP to ensure timely and appropriate support.

Familial Implications and Downstream Diagnoses

RGCS generates information that is inherently familial, meaning its relevance often extends beyond the reproductive couple. In some cases, results may prompt the diagnosis of previously unrecognised conditions in existing children or other relatives. For example, an existing child of the reproductive couple may be found to have the condition identified through RGCS, or extended family members may benefit from cascade carrier testing to inform reproductive planning. As such, the implementation of a National RGCS Program will result in an increase in diagnoses of genetic conditions and an increase in known carrier status outside the original reproductive context. Clinical services will require appropriate resourcing to manage this downstream impact including genetic counselling, diagnostic testing, and long-term clinical management. Importantly, this represents a benefit of the program, as identifying affected family members can shorten or avoid lengthy diagnostic odysseys and enable earlier access to appropriate care and support. Recognising and planning for these broader familial effects is essential to ensure responsive, coordinated care and to maximise the health benefits of early detection.

Objective 2.3: Predicted Demand and Use of Flow on Services

Assessing the impact of a National RGCS Program on downstream clinical services requires analysis of each step in the care pathway. This includes examining how service utilisation may change and how existing funding mechanisms may be affected. Key areas of focus include forecasting demand for prenatal genetic counselling, prenatal diagnostic procedures, IVF with PGT-M, and other reproductive interventions following increased chance results. These projections inform the anticipated impact on clinical services and help identify where additional resourcing or structural adjustments will be required to ensure equitable access and financial sustainability under a national program model.

Our projections, outlined in Figure 14, are based on modelling undertaken by the MM Health Economics team. These estimates use predicted program volumes for 2030 and assume the program has reached a “steady state” following full national implementation, providing a forward-looking view of clinical service demand. Although long-term follow-up data from MM participants is still being collected and is expected to be finalised by mid-2026, interim reproductive outcome data has been used to estimate likely reproductive choices and service utilisation patterns (see Figure 14). To accurately assess the full impact on reproductive services, modelling also accounts for increased chance couples identified in years prior to 2030 who may access services in subsequent pregnancies.

Overall, the modelling suggests that of the approximately 4500 increased chance couples offered reproductive options after RGCS, approximately one third would request referral for IVF and PGT-M, another third would access prenatal diagnostic services, and the remaining third will include reproductive couples who decline reproductive options or pursue alternative reproductive pathways such as donor conception, adoption, foster care or choosing not to have (more) children.

Those who choose IVF with PGT-M will be referred by the National RGCS Program Clinical Team directly to their local fertility service. Those who are already pregnant at the time of receiving their increased chance result will be referred to their local prenatal clinical genetics service for coordination of diagnostic testing. Approximately half of those choosing prenatal diagnosis will not yet be pregnant when making that decision and will instead receive a referral and instructions for contacting their local genetics service upon future pregnancy. Emerging data from MM data on

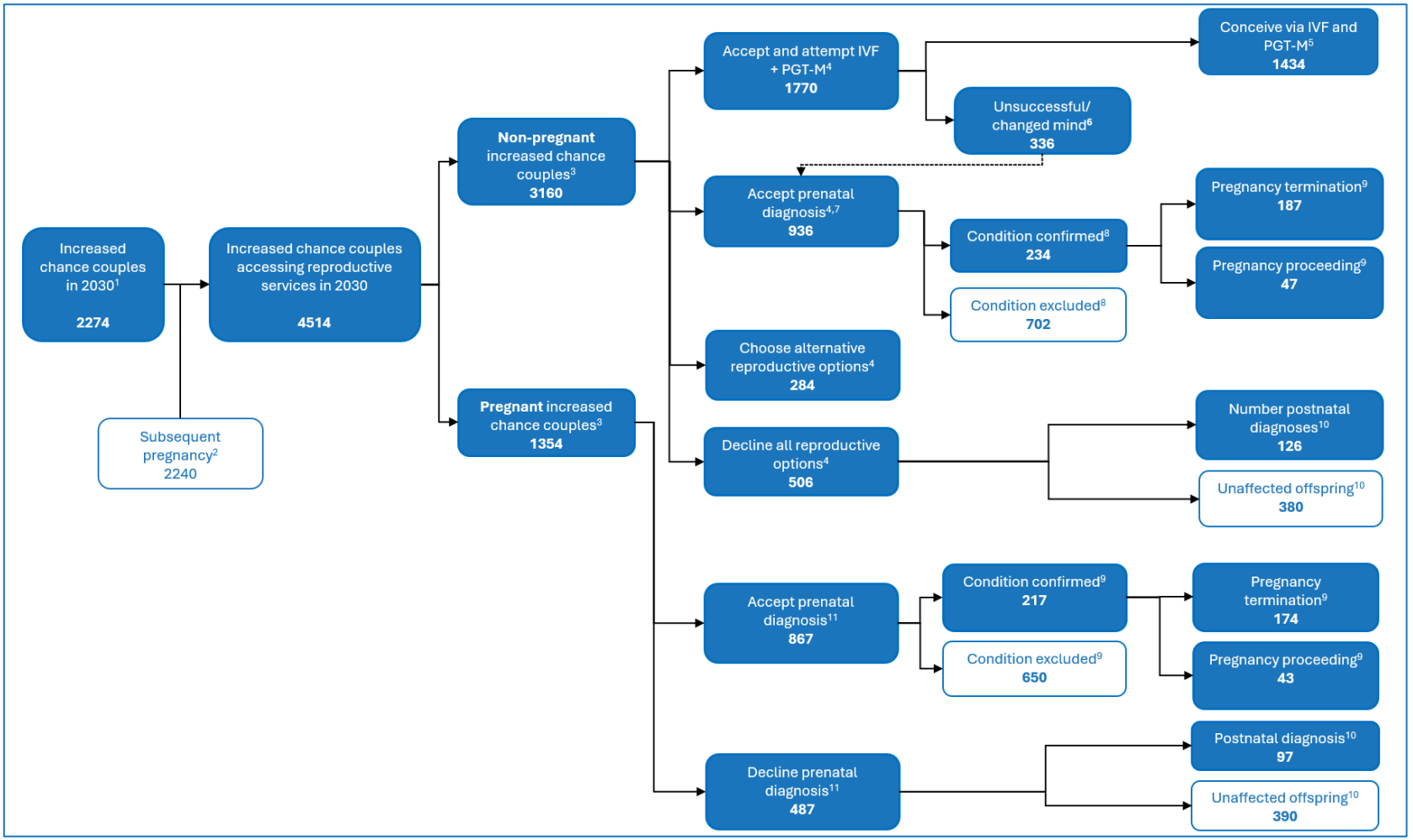

Figure 14: Predicted reproductive choices for increased chance couples in 2030

[1] Projected for 2030 anticipating "steady state" for the program and assuming a parity quotient of 1.5. Eligibility is based on a) Medicare eligible couples, b) first utilization of RGCS. [2] Based on estimated 75% uptake of RGCS, also includes couples screened previously through the program who have re-partnered (re-partnering rate: 18.25% (ABS Marriages and Divorces Australia, 2021)). [3] Based on 1.526% increased chance rate which is from MM recruitment in primary healthcare settings. [4] Based on estimated 30% of couples pregnant and 70% non-pregnant. [5] Based on MM outcome data: 56% accepted and attempted IVF + PGT-M; 19% accepted prenatal diagnosis after conception; 9% chose alternative reproductive options (donor conception, adoption & foster care, not having more children); 16% declined all reproductive options. Reproductive option choice calculations are based on choices made in the first pregnancy after RGCS (as the cost of IVF + PGT-M was not a barrier). [6] Based on MM outcome data: 81% conceived after IVF + PGT-M however, it is not clear how many cycles it took to achieve these pregnancies, and a full set of birth outcome data is not available for these pregnancies. [7] Based on MM outcome data: 19% of couples did not proceed with IVF + PGT-M and instead opted for PND after conception, this included 8% of couples where IVF and PGT-M did not result in a pregnancy that went to term and 11% who changed their mind and decided not to pursue IVF + PGT-M. [8] Based on MM data: Combines the number who accepted PND initially and those that opted for PND after IVF+PGT-M was unsuccessful. [9] Based on 25% affected pregnancy rate. [10] Based on MM data: 80% uptake of termination of pregnancy. [11] Based on 25% affected offspring. [12] Based on MM data: 64% acceptors, 36% decliners.

longer-term reproductive outcomes suggests that some reproductive couples may reconsider their initial decisions and pursue alternative reproductive options. It is therefore essential to establish a mechanism that enables people with increased chance results to re-contact the National RGCS Program Clinical Team for updated referrals and support.

Predicted Demand and Use of Fertility Services

IVF with PGT-M is a key reproductive option. Currently there are significant out of pocket expenses for IVF with PGT-M meaning this option is not equitably available to all individuals/couples. However, the proposal for the National RGCS Program includes funded IVF with PGT-M. Modelling based on MM reproductive outcomes data indicates it will be taken up by around one third of increased chance couples if this is funded through the National RGCS Program.

The IVF/PGT-M subcommittee considered what is required to be in place to manage increased chance couples identified by a national screening program. It examined the expected number of couples who will request this service if IVF/PGT is free of charge and the approximate number of cycles of IVF, the number of embryos requiring biopsy and testing and the number of embryos transferred. The committee then estimated the staffing required and other costs for providing this service.

The calculated number of eligible couples for RGCS when the program reaches a steady state is approximately 188,000 per year. If 75% utilise RGCS and approximately 1.5% have an increased chance result, this equates to 2274 couples per year. With an estimate that 70% of couples utilising screening will not be pregnant (1592 couples) and, based on data from MM, 56% will choose to utilise IVF and PGT,[1] we estimate 892 newly identified couples will require PGT-M test development and 878 couples will utilise IVF and PGT for a second child. This is a total of 1770 couples utilising PGT-M per year. This represents a 1.5 fold increase in the number of IVF with PGT-M test designs and a 3 fold increased in the number of embryos tested via IVF with PGT-M.

All 892 newly identified couples who choose to utilise IVF with PGT-M will require development of an appropriate test for PGT-M, incorporating linkage testing (karyomapping), direct detection of the variant, or a combination of the two. Karyomapping is a process where genes are followed through families which is generally more accurate than testing for the gene fault directly on DNA from the few cells removed from an embryo. Development of the karyomapping test requires DNA from the reproductive couple and other family members. The method of embryo testing is dependent on the variant(s) found and the availability of other family members to develop karyomapping tests.

Data from Mackenzies Mission identified that women over 35 years of age achieved a mean of 1.5 embryos per cycle that were suitable for transfer and women under 35 achieved a mean of 2.2 embryos suitable for transfer per cycle, following PGT testing (Sharyn Stock-Myer, personal communication). Women over 35 required a mean of 2.7 stimulated IVF cycles per delivery and women under 35 required a mean of 1.5 stimulated IVF cycles per delivery. Around 73% of women having babies in Australia are under 35 and 27% are 35 and over (https://www.aihw.gov.au/reports/mothers-babies/australias-mothers-babies/contents/overview-and-demographics/maternal-age). Therefore, there will be around 1292 women under 35 requiring 1.5 cycles per delivery which is 1938 cycles per year and 478 women over 35 requiring 2.7 cycles per delivery which is 1291 cycles per year. This is a total of 3229 cycles per year. Based on these data we estimate around 12,916 embryos will require testing and 3934 embryos will be transferred.

The committee recommend that funding to couples undertaking treatment under the program would not be extended following the birth of two babies (although if couples have surplus embryos in cryostorage after having two healthy children, they should be allowed to have these transferred if they wish). Table 5 provides estimated annual costs of providing funded IVF with PGT-M for increased chance couples identified through the National RGCS Program.

Table 5: Annual costs of providing IVF with PGT-M for increased chance couples identified through the National RGCS Program

Item	Unit Cost	Annual Cost	Notes
Test Design	$2500	$2,230,000	892 couples all expected to require one test design per high risk ECS result
Embryo Test	$1000	$12,916,000	12,916 embryos tested per year.
IVF Cycle	$12,500	$40,362,500	3,229 cycles per year. Includes cost for IVF specialists, embryologists and nursing associated with stimulated IVF cycle management
Frozen Embryo Transfer	$4,000	$15,736,000	3,934 embryos transferred per year from stimulated IVF cycles
Clinical Geneticists	$600,000	$4,000,000	6.0 FTE clinical geneticists to provide initial counselling and oversee clinical operation of program based on average cost + additional expenses/super
Genetic Counsellors	$120,000	$2,000,000	12 FTE genetic counsellors to provide ongoing support to patients and interaction with laboratory staff
Total annual cost		$77,244,500	

Predicted Demand and Use of Prenatal Services

Impact on Prenatal Genetics Services

Modelling (Figure 14) indicates that approximately 1800 reproductive couples will access prenatal diagnosis due to their increased chance of having children with an inherited genetic condition. A further approximately 750 reproductive couples will have declined reproductive options including prenatal testing but will require referral to clinical genetics services for assessment as to whether there are pregnancy management implications associated with their RGCS results and to develop a plan for testing and/or clinical assessment and management postnatally. To support planning for a

National RGCS Program, the workflows for prenatal genetics services were mapped to understand processes for managing pregnant increased chance couples. This mapping drew on reproductive outcome data from MM, combined with the expertise of the Clinical Working Group members, who represent a range of healthcare settings across public and private sectors. The resulting workflows depicted in Figure 15 illustrate the typical steps, timelines, and service touchpoints involved in the management of increased chance results by prenatal genetics services, helping to inform future service planning, resource allocation, and system readiness.

Impact on Prenatal Diagnostic Services

Approximately 1,800 pregnant people are expected to accept prenatal diagnosis annually as a result of learning through the National RGCS Program that they have an increased chance for an inherited genetic condition. Extrapolating Victorian prenatal diagnosis rates to a national scale indicates that demand from increased-chance couples will raise the total number of prenatal diagnostic procedures in Australia by about 33%. Projected annual numbers of additional prenatal diagnostic procedures by jurisdiction are presented in Table 6. Although approximately 75% of Australians receive maternity care in the public system and 25% in the private sector, a greater proportion of pregnant increased chance couples identified via the National RGCS Program may access prenatal diagnosis through the public hospital system as there is limited availability of private genetic counselling services to support these couples through the prenatal testing process. As an additional ~1,800 couples per year are projected to use IVF with PGT-M and national data show that ~8 % of pregnancies conceived after PGT-M opt for confirmatory prenatal diagnosis (Poulton, Menezes, Hardy, Lewis & Hui, 2025), this may further elevate requests for prenatal diagnosis. These projections help quantify the extra capacity needed in public genetics services, maternity units, and private ultrasound providers once the National RGCS Program reaches steady-state operation.

A projected 33% increase in prenatal diagnostic procedures across Australia will have significant implications for clinical resourcing and workforce capacity. This increase in demand will place additional pressure on already stretched prenatal genetics services, particularly in public hospital settings where the majority of procedures occur. To meet this increased volume, resourcing will be required to expand service capacity, including the recruitment and training of additional clinical geneticists, genetic counsellors, sonographers, and maternal fetal medicine specialists. Targeted workforce development initiatives, such as specialised training and upskilling opportunities, will be essential to ensure that services can continue to deliver timely, high-quality care. In parallel, infrastructure and administrative support must also be scaled to accommodate increased referral volumes and coordination of care, with a particular focus on ensuring equitable access for rural and regional populations.

Increased access to prenatal diagnostic services will also mean there will be approximately 360 additional pregnancy terminations per year. This increase has important implications for healthcare service planning, particularly in ensuring that termination of pregnancy services are available, accessible, and delivered in a compassionate and timely manner. Public hospitals, where the majority of such procedures are performed, may require additional clinical staff, counselling services, and procedural capacity to meet this demand. There will also be a need to provide specialised training for healthcare professionals in supporting patients through the complex emotional aspects of these decisions.

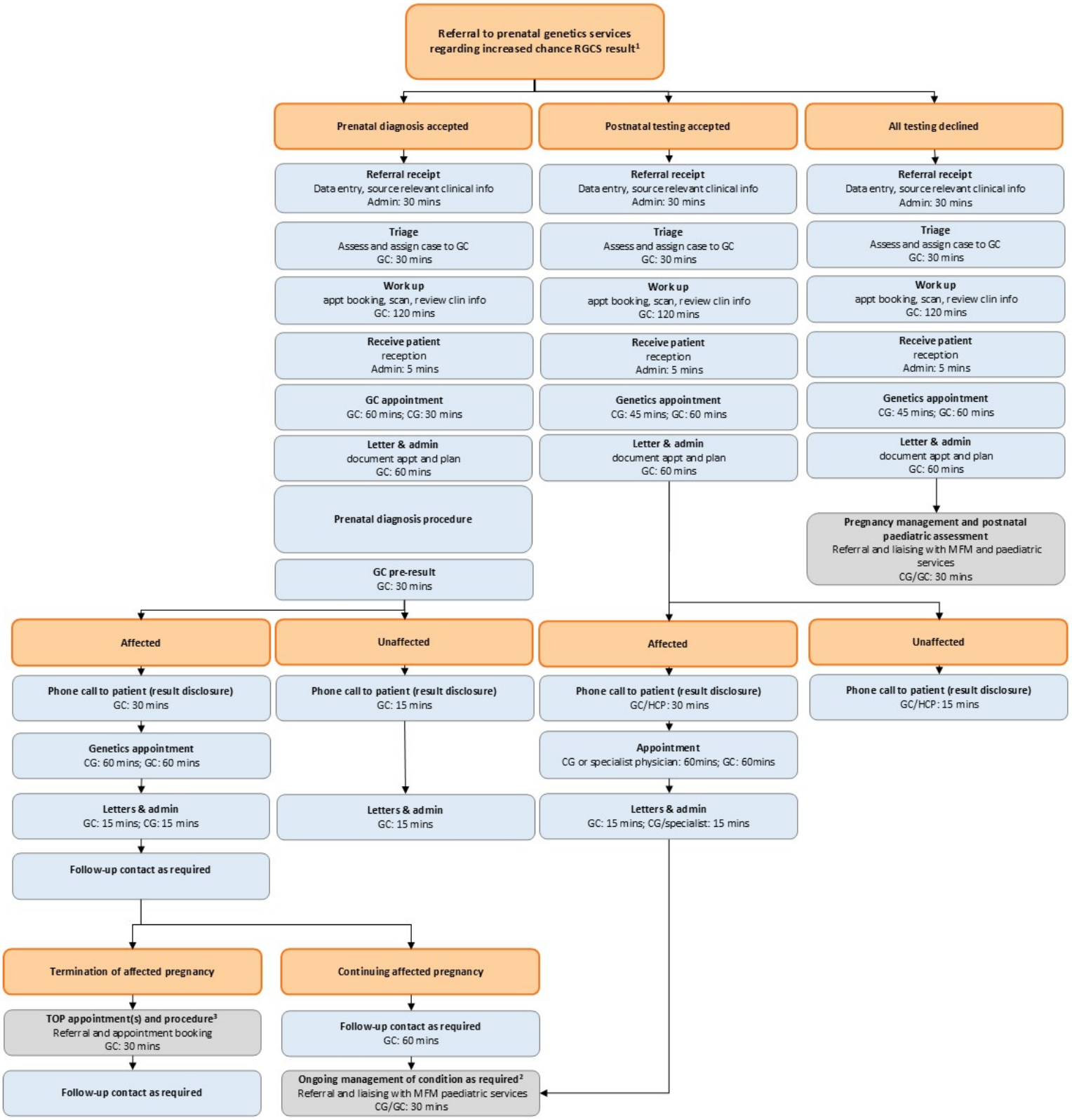

Figure 15: Clinical genetics workflow following increased chance results

Grey boxes represent services not provided directly by clinical genetics services and are thus not captured in this figure. [1] *Reproductive couples requesting IVF with PGT-M would be referred directly to a local fertility service by the National RGCS Program clinical team.* [2] *Managed external to clinical genetics service via maternal fetal medicine/paediatrics teams.* [3] *Managed external to clinical genetics services, services vary by jurisdiction.*

Furthermore, co-ordinated referral pathways, psychosocial support, and clear information for patients will be essential to ensure equitable and respectful care. In regional and rural areas, where access to termination services is often limited, targeted strategies may be required to address disparities and reduce delays in care.

Further work is needed to comprehensively map the downstream impacts of this projected increase in prenatal diagnosis and pregnancy termination volumes. This includes better understanding of regional variations in service capacity, workforce gaps, and the broader system-level implications for diagnostic testing, pregnancy termination services, maternity care, and psychosocial support pathways.

Table 6: Estimated additional annual prenatal diagnostic procedures for each state and territory after introduction of a National RGCS Program

State/territory	Percentage of births by jurisdiction[1]	Estimated annual number of additional prenatal diagnostic procedures
Australian Capital Territory	2%	36
New South Wales	31%	559
Northern Territory	1%	18
Queensland	21%	379
South Australia	7%	126
Tasmania	2%	36
Victoria	25%	451
Western Australia	11%	198

[1] Australian Institute of Health and Welfare, Australia's Mothers and Babies web report. May 2025.

Objective 2.4: Access and Equity of downstream services

For a sustainable and inclusive National RGCS Program, it is critical that downstream clinical services such as genetic counselling and access to reproductive interventions are culturally safe, linguistically appropriate, and equitably delivered for all Australians. This is especially important for Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities, who have and continue experience structural inequities in healthcare access, quality, and outcomes (Khatri & Assefa, 2022; Mengesha, Dune & Perz, 2016).

RGCS results often have implications not just for individuals but for their families and communities. For some, these results will trigger complex reproductive decisions; for others, they may reveal health information relevant to their own care or that of existing children and relatives. Navigating these pathways requires services that go beyond clinical competence and must be built on trust, respect, and cultural responsiveness. Acceptability of services cannot be assumed; it must be earned through long-term, community-led engagement, the allocation of appropriate resources, and a commitment to genuine partnership.

A central principle drawn from the work of the National Centre for Indigenous Genomics is the importance of cultural authority ensuring that Aboriginal and Torres Strait Islander people have control over how genomic information is discussed, shared, and applied in ways that align with community values (National Centre for Indigenous Genomics, 2025). This approach provides an example of how community partnership can inform key priorities by recognising the deep connection between health, family, Country, and community. Making downstream services accessible should involve working in partnership with community leaders and organisations such as the National Centre for Indigenous Genomics and Australian Alliance for Indigenous Genomics, to ensure culturally appropriate information, counselling approaches, and care pathways are embedded throughout.

This philosophy should extend to all downstream services, respecting the diversity within and across communities and avoiding one-size-fits-all approaches. Services can acknowledge the role of family and community in reproductive decisions, particularly in communities where a collectivist approach to health and wellbeing is the norm. The National Centre for Indigenous Genomics' work to develop culturally appropriate genomic resources (NCIG, 2025) illustrates the value of community-designed materials that reflect lived experiences and worldviews.

Structural barriers also persist for many people born overseas, who face challenges including lower health system literacy, limited access to timely care, and reduced autonomy in healthcare decisions. In the context of prenatal and reproductive services, this can manifest as unclear or culturally inappropriate information, and limited support following an increased chance result. These barriers are often compounded by language access issues as 22.8% of Australians speak a language other than English at home and 3.4% do not speak English at all (Australian Institute of Health and Welfare, 2022). Downstream services must therefore be resourced and structured to offer interpreting, translated materials, and culturally adapted counselling services.

People living in regional and remote areas face additional challenges, including geographic isolation, and limited access to specialised reproductive services such as prenatal diagnostics and IVF with PGT-M. Addressing these disparities requires targeted investment in service delivery models such as outreach clinics, telehealth, and mobile health services, as well as incentives and support for clinicians to work in underserved areas. Transport and accommodation support schemes may also be necessary to enable timely access to care, particularly for services that cannot be decentralised.

Lastly, the implementation of downstream services must be accountable to the communities they serve. This includes embedding systems for community-led monitoring, evaluation, and feedback, and drawing on frameworks such as the Victorian Health Cultural Responsiveness Framework to guide continuous improvement.

Sub-project 3: Digital Infrastructure Considerations

The Medical Services Advisory Committee and the Department of Health, Disability and Ageing identified several key data infrastructure elements that must be implemented to support an organised RGCS program:

- **Registry:** A registry to track test results and reproductive outcomes, ensuring comprehensive long-term data collection and evaluation.

- **Genomic Data Storage and Sharing:** Systems for long-term storage and secure data sharing across laboratories to support reanalysis and data reuse, particularly with respect to re-partnering scenarios.
- **Interoperability & Data Transfer Processes:** Facilitating secure and efficient data transfer of genomic data.

Designing a data infrastructure for a population-based RGCS program requires a robust, scalable, and secure system that integrates multiple stakeholders—laboratories, healthcare providers, participants, and public health authorities. This infrastructure must facilitate couple-based screening to ensure comprehensive genetic risk assessment and counselling. Addressing the challenge of data management for a genomic intervention at population scale is critical to ensuring the program can be implemented effectively, providing equitable access to genomic testing while maintaining high standards for data security, accuracy, and clinical utility. This section addresses the aim and objectives of sub-project 3.

Aim: Develop recommendations as to the establishment and management of digital infrastructure in support of RGCS; how to manage a national register of RGCS participation and outcomes; the process of recontacting couples in the case of variant reclassification, if appropriate; and management (and secondary clinical usefulness) of genomic data generated.

Objectives:

3.1 Elucidate the core assumptions for a proposed mode of delivery of the program to inform modelling data infrastructure requirements

3.2 Map potential delivery pathways and identify where alternative models/options should be explored

3.3 Identify minimum dataset for an RGCS register

3.4 Model data storage and retention requirements

3.5 Explore utility, feasibility and risks associated with recontact of couples as new knowledge comes available

3.6 Evaluate feasibility and utility of secondary clinical (and research?) use of datasets

3.7 Consider public acceptability / preferences regarding database structure / custodianship (e.g., government asset v industry management) noting the intersection with the *genomic acceptability - societal preferences, public opinion and analysis* project

Objectives 3.1 & 3.2: Data Infrastructure Requirements

This section addresses objectives 3.1 – 3.2 by presenting considerations for the establishment and management of the digital and data infrastructure required to support a national RGCS program. In the proposed RGCS program, there are a number of key points for data capture and retention which are summarised below:

1. **Program enrolment and test request**: When reproductive couples self-nominate to participate in the program, they generate a login for the online portal. Enrolment is undertaken separately as individuals nominating their current reproductive partner for data

linkage. Participants then provide demographic and clinical data, access information materials and decision support tools, and provide consent. This generates a 'test request' which is communicated to the laboratory team.

2. **Specimen tracking and logistics**: The process of requesting, dispatching and receiving self-collection specimen kits is recorded at a granular level. The accredited laboratory requires integrated Laboratory Information Systems to facilitate specimen kit send-out, tracking and receipt of samples, with time stamps captured in the centralised logistics infrastructure. This sample tracking follows the entire testing process from kit dispatch through to sample/data archiving, informing process improvement and supporting risk mitigation.
3. **Genomic analysis**: After sample receipt, the Laboratory Information Systems will record each step of sample processing through specimen reception, DNA extraction, genomic sequencing, variant curation and interpretation and result reporting. As noted in for sub-project 1, laboratories will analyse an agreed gene list, which is reviewed periodically and will be publicly available via PanelAPP Australia (https://panelapp-aus.org). Variant curation is supported by a shared digital infrastructure (akin to an expanded functionality to Shariant (https://shariant.org.au/) to improve curation efficiency and standardisation of results.
4. **Data Storage**: The secure retention of genomic data for a population-scale screening program is required not only to meet the retention requirements (Australian Commission on Safety and Quality in Health Care, 2022) of the NPAAC but also consider the re-analysis of data should a tested individual re-partner and require RGCS with that new partner. This data storage span will therefore need to extend to the reproductive lifespan (25 years).
5. **Result Submission**: Results will be electronically submitted to a centralised database and made accessible to both healthcare providers and participants through the secure online portal. Low chance reproductive couples and their nominated healthcare providers will be notified of their result via the online portal and results will also be uploaded to each individuals' My Health Record. Increased chance couple results will be transferred to the program genetic counselling team for clinical management. These couples will be contacted by a member of the program genetic counselling team. Results will be available on the online portal and uploaded to My Health Record after the initial genetic counselling appointment.
6. **Reanalysis**: As stored genomic data has utility beyond RGCS, e.g. for reanalysis for other clinical indications, such as other genetic predispositions to disease; pharmacogenomics; or on a targeted basis when clinical symptoms present, mechanisms will be established for secondary use of genomic data. The research potential for a population scale genomic data asset is also considerable, with appropriate permissions of data donors.

Objective 3.3: Establishing a National RGCS Data Registry

To address objective 3.3, this section defines the framework for a centralised system to track program participation, capture essential data elements, and facilitate data reanalysis (if necessary). To consider capabilities, functionalities and requirements of a national RGCS data registry, we evaluated examples of registries currently supporting healthcare delivery. The preeminent example we identified for this purpose is the **National Cancer Screening Register** (***APPENDIX III – Case Study***

– The National Cancer Screening Register) which was established to unify and streamline cancer screening programs across Australia by consolidating state and territory-based registers for cervical and bowel cancer into a single digital system. Announced in the 2015–16 Budget with an initial allocation of $148 million—later increasing to $236 million—the project was contracted to Telstra Health and officially launched in December 2017. The National Cancer Screening Register enhances screening efficiency by integrating with healthcare providers, pathology services, and My Health Record, enabling automated result submissions, standardised reporting, and real-time access to screening histories. Its **Healthcare Provider Portal** (Healthcare Provider Portal | National Cancer Screening Register) launched in 2020, allows clinicians to enrol patients, access screening records, request results, and manage follow-ups, while the **Participant Portal (**Participant Portal | National Cancer Screening Register) empowers individuals to track their screening history, update personal details, and manage participation preferences. The register also facilitates automated reminders, supports timely interventions for actionable results, and provides a centralised dataset for public health insights.

The National Cancer Screening Register serves as a strong model for an RGCS registry, as it demonstrates how a national digital system can efficiently manage participation, track outcomes, and support clinical decision-making. Like cancer screening, RGCS requires long-term data retention, secure information-sharing across laboratories, and mechanisms for recontacting individuals when new findings emerge. By leveraging lessons from the National Cancer Screening Register, an RGCS registry could use similar digital infrastructure.

Proposed Registry Dataset

The registry dataset should contain the following at a minimum:

- **Structure**: A secure, centralised database designed to store genetic screening events, results, demographics and metadata for individuals screened. This database will contain both participants' personal information, clinical and family history, and couple-based RGCS result.
- **Data Types**:
  - **Personal Identifiers**: Each partner's name, date of birth, contact details, Medicare details etc.
  - **Couple linker/couple record:** To allow for couples to be linked and unlinked as required
  - **Health Care Team:** Details of nominated health care professional
  - **Genetic Analysis Results**: Couple-based RGCS results
  - **Clinical Data**: Clinical and family history, consanguinity
  - **Demographics**: Data to support public health analyses, geographic, ethnic, and socio-economic information, if available
  - **Secondary results**: Reports of secondary analyses, if applicable.
- **Access Control**: Role-based access should be implemented for different stakeholders (laboratories, clinicians, public health officials) with stringent privacy controls to ensure compliance with regulatory standards. These include:
  - Australian Privacy Act 1988 (particularly the Australian Privacy Principles)
  - My Health Records Act 2021
  - Healthcare Identifiers Act 2010

Registry Integration

Laboratory Integration: Laboratories delivering RGCS must be capable of electronically submitting genetic results to a centralised database. Standardised data formats (e.g., HL7 or FHIR) are needed to ensure consistent and interoperable data sharing across laboratories.
Electronic Health Record (EHR) Integration: The system must integrate with existing electronic health records used by health providers, enabling clinicians to access real-time screening results and relevant patient information.
Electronic health record integration should also support clinical decision-making tools to assist in understanding screening results and implications for couples.
Patient Portal Integration: As noted in recommendations section, participants should have access to a secure portal to view information and decision-support materials, results and receive notifications. The registry will need to be connected (e.g. via an application programming interface (API) or fully integrated) with this portal to facilitate recording of data entered by couples, and potentially monitor user-interaction with the portal to evaluate engagement, optimise user experience and monitor long-term interaction with results.
Data Analytics: Data will need to be captured and managed in a way that it can be easily analysed to track participation rates, identify high-risk groups, capture downstream decision-making and health resource utilisation, and monitor the population-level impact of the program.

Objective 3.4: Genomic Data Storage

Australia's digital capacity and infrastructure lags behind most nations who have integrated genomic testing into healthcare (Australian Genomics, 2020). Digital infrastructure to support organised RGCS program will require significant investment but has the opportunity to progress national genomic information management capacity in Australian, not only for genomic healthcare, but also to enrich research. It will also be important to consider the Australian Government Digital Health Blueprint and proposed Digital Health Ecosystem and how capacity for genomic data storage at population scale can be incorporated. This can be informed by the National Approach to Genomic Information Management and Associated Implementation Recommendations which are proposed to be progressed under the refreshed National Health Genomics Policy Framework, due to be published towards the end of 2025.

RGCS genomic data management assumptions

The scale and cost of genomic data storage for an organised RGCS program were modelled for exome sequencing and genome sequencing at a read depth suitable for the RGCS assay (100X for exome sequencing, 30X for genome sequencing). Modelling reflected the estimated service utilisation of the program, as is consistent throughout this report (i.e., 149,018 couples receiving testing per annum by 2030). The National Pathology Accreditation Advisory Council has minimum retention requirements for laboratory records and data for accredited laboratories: 10 years for Variant Call Format (VCF) files and 4 years for raw genomic data (FASTQ or aligned BAM files) from the date of issue of test report. It should be noted that this is a minimum requirement only, and many accredited laboratories store genomic data files substantially longer, though the cost of protracted data storage at population scale will dwarf the volume managed by current diagnostic laboratories in Australia. We have proposed retention of the aligned reads (BAM files) rather than

FASTQ despite the slightly higher storage cost, as realignment to generate BAM involves significant computational demand. The Services Australia data regarding utilisation of three condition RGCS (item 73451) indicates 95% women are between the age of 25 – 44. We have therefore calculated for a 25-year retention of VCF data for reanalysis, should a couple re-partner. Consideration has also been given to minimising data retention costs through data compression, and archiving, and it has been assumed that cloud storage will be used for active storage (when RGCS laboratories might need to share / access data readily) and on-prem for cold/archive storage.

The proposed RGCS genomic data retention time and type is therefore:

- 3 months (to T+ 3mth): full genomic dataset (FASTQ/BAM/VCF) active storage, cloud.
- 3 months (to T+ 6mth): full genomic dataset (FASTQ/BAM/VCF) compressed, cloud.
- 3.5 years (to T+ 4 years): BAM, compressed, cloud.
- 24.5 years (to T+ 25 years): compressed, archived VCF, 21 years on-prem.

A detailed summary of data modelling inputs is provided in *APPENDIX IV – Input Data for Genomic Data Management Modelling for an Organised RGCS Program*.

Genomic data management costing

Applying these retention times and file types assumptions, the relative cost of WGS and WES data storage per couple can be estimated, as provided in Table 7 below:

Table 7: Estimated data storage costs per couple

Cloud storage per couple x NPAAC guidelines	Genome sequencing	Exome sequencing
3-month full dataset active storage[1]	$ 40.73	$2.95
3-month full dataset active compressed	$20.36	$1.47
3.5-year compressed BAM[2]	$157.50	$12.60
24.5-year archive compressed VCF[3]	$1.47	$0.15
TOTAL DATA STORAGE PER COUPLE	**$220.06**	**$17.17**
Average per annum storage – year 0 – 5	$43.72	$3.40
Per annum long-term storage – year 5 – 25	$0.07	$0.01

[1]Assume retention 3-month active full dataset AWS; 3-month compressed full dataset AWS; 3.5Y compressed BAM AWS; 24.5Y cold storage compressed VCF on prem. [2]Assume BAM not FASTQ - realignment compute costs outweigh reduced storage costs for FASTQ. [3]Assume 21Y VCF storage on prem compressed, cold storage.

An individual's genome is about 13 times more data intensive than an exome, which is reflected in the net storage costs per couple. When extrapolated to the storage requirements at population scale delivery of RGCS (Table 8)**, this results in a significant cost impact of WGS over WES. The steady state cost of data storage is reached at ~year 25, when VCFs are deleted of couples receiving screening at program commencement. WGS data storage is 8.75X the cost of WES data retention at steady state, at $47.5Mpa WGS vs $5.4Mpa WES.**

Table 8: Total data storage costs for National RGCS Program

Year	Genome sequencing	Exome sequencing
Year 1[1]	$ 6,514,676.17	$ 507,293.11
Year 2	$ 13,029,352.34	$ 1,014,586.21
Year 3	$ 19,544,028.50	$ 1,521,879.32
Year 4	$ 26,058,704.67	$ 2,029,172.42
Year 5	$ 32,573,380.84	$ 2,536,465.53
Year 6	$ 39,088,057.01	$ 3,043,758.63
Year 7	$ 45,602,733.18	$ 3,551,051.74
Year 8[2]	$ 45,613,685.97	$ 3,562,004.53
Year 9	$ 45,635,591.55	$ 3,583,910.12
Year 10	$ 45,668,449.93	$ 3,616,768.49
Year 11	$ 45,712,261.10	$ 3,660,579.66
Year 12	$ 45,767,025.06	$ 3,715,343.62
Year 13	$ 45,832,741.81	$ 3,781,060.38
Year 14	$ 45,909,411.36	$ 3,857,729.92
Year 15	$ 45,997,033.70	$ 3,945,352.26
Year 16	$ 46,095,608.83	$ 4,043,927.39
Year 17	$ 46,205,136.75	$ 4,153,455.32
Year 18	$ 46,325,617.47	$ 4,273,936.03
Year 19	$ 46,457,050.98	$ 4,406,369.54
Year 20	$ 46,599,437.28	$ 4,547,755.84
Year 21	$ 46,752,776.37	$ 4,701,094.93
Year 22	$ 46,917,068.25	$ 4,865,386.82
Year 23	$ 47,092,312.93	$ 5,040,631.50
Year 24	$ 47,278,510.40	$ 5,226,828.96
Year 25	$ 47,475,660.66	$ 5,423,979.23
Year 26[3]	$ 47,475,660.66	$ 5,423,979.23

[1]Simplified to average per annum storage costs for projected couples. [2]First tranche (year 1) couples transitioned to long term storage.
[3]Plateau storage costs - first tranche (year 1) couples' VCFs deleted.

Retention of the VCF for the purposes of reanalysis is still more cost effective than re-sequencing, however, with average per annum storage from WES at $0.69 for 25 years. The cost-effectiveness of genomic data storage will be enhanced if the data is available for other clinical purposes, and potentially research use, as discussed further in Section 3.6 below. The data storage estimates therefore support the recommendation for the use of exome sequencing as the preferred technology for program implementation.

Consent for Long-term RGCS Data Storage

There are several approaches to consent for storing genomic data from RGCS, each with pros and cons. Automatic storage of genomic data (beyond the obligatory NPAAC requirements of accredited laboratories) could be justified on the grounds of both individual and public health benefit, but risks include undermining public trust in national health initiatives. A more permissive option, opt-out consent, would involve automatic storage with the option for individuals to decline or withdraw consent later. The most restrictive, explicit (opt-in) consent requires individuals to provide clear consent before data is stored, but may reduce participation rates and limit the broader public health benefits. The type of consent chosen will impact both the ethical and practical aspects of secondary use of RGCS data.

Objective 3.5: Considerations around Managing Advances in Genomic Information

Explore utility, feasibility and risks associated with recontact of couples as new knowledge comes available

When the Australian Government Department of Health, Disability and Ageing identified digital infrastructure considerations to support the establishment of a national program, there was specific reference to considering the management of advances in genomic information, and the utility, feasibility and risks associated with recontact of couples as new knowledge comes available.

Recontact of previously screened couples when genes / variant classification changes is not recommended in the context of an organised national screening program.

In a diagnostic setting, where patients present for genomic testing to resolve the genetic basis for a clinically manifested condition, many practitioners are strong proponents for systematic – and even automated – reanalysis to ensure new genomic knowledge can be applied in a timely manner to inform patient care (Best et al., 2024).

However, in RGCS, asymptomatic couples are being genetically tested to identify whether they have an increased chance of having children with serious, childhood onset genetic conditions . In this scenario, reanalysis and recontact poses ethical, psychological and medico-legal, risks, as couples may have made reproductive decisions based on current information at the time of screening (e.g., termination of pregnancy).

RGCS reports reflect genomic knowledge at the time of reporting, and must be considered ‘point in time’ information. As new knowledge comes available over time, this will of course inform gene list selection and variant interpretation, but must not be applied retrospectively to previously-screened couples – *unless* a request for reanalysis is made based upon clinical circumstances such as significant time since RGCS or the birth of an affected child after undergoing RGCS.

Objective 3.6: Secondary Use of RGCS Data

Genomic data is a valuable health resource that can be re-analysed for purposes secondary to the purpose it was initially generated. The utility of retention and reanalysis of data generated though an organised RGCS program applies both to the individual screened (for secondary clinical diagnostic testing, risk prediction, pharmacogenomics) and to benefit Australian diagnostic practice and research.

The secondary use of genomic data involves re-analysing previously collected genomic information to identify additional clinically relevant genetic variations beyond the original testing purpose. While RGCS primarily informs reproductive decisions, given the proposed long-term retention of this genomic dataset (as outlined above) the sequential interrogation of the data could offer ongoing clinical and societal value. While the secondary use of RGCS offers significant efficiencies in public health delivery, the technical, ethical, and logistical challenges should not be overlooked. Ethical concerns regarding consent, data security, and the potential implications of new findings on family members must also be addressed.

A Reference Database of Australian Genomic Variation

Genomic analysis for diagnostic and screening purposes involves the interrogation of genomic data of an individual compared to a reference genome (currently GRCh38), and the identification of genetic variations. Understanding what variations are benign, and what changes might be associated with a condition, relies on understanding how common that variant is seen in a given population (allele frequency or AF). Therefore, reference population databases are a critical tool for the clinical interpretation of genomic data: allele frequency data from the general population can enable the removal of thousands of variants from consideration in genomic analysis if the AF are commonly seen in a given population sample. The Genome Aggregation Database (gnomAD) is the largest population frequency database, and is the most accessed resource by clinicians and diagnosticians globally: currently (V4, 2025) includes aggregated data from over 800,000 exomes and genomes, presenting over 910M variants. Despite the immense value of gnomAD as a genomic resource, it contains an overrepresentation of data from individuals of European descent. As a consequence, an individual from an underrepresented population will receive significantly more inconclusive results from genetic testing, be excluded from clinical trials, and receive less effective targeted therapies.

It is important to note that current laboratory consent forms, including those developed by Australian Genomics in 2024 which are used in 6 jurisdictions, do not require explicit consent for anonymised information to be shared with genomic databases that are used for patient care, so RGCS contribution to a Reference Database of Australian Genomic Variation would not be precluded under current consent guidelines.

Similar databases in other nations, such as VariantArk UK restricts retention of variant information only at variant AF<5% to minimise data processing / querying costs. It will be important to engage with such exemplars to inform the design and implementation of and Australian population reference database.

Retention of anonymised, aggregate genomic data from population scale RGCS would therefore have immense diagnostic and clinical value for the diverse Australian population, and be of transformative potential for populations not currently represented in global reference databases – including Aboriginal and Torres Strait Islander peoples.

Initiation of Reanalysis of Stored Data

Several key factors can prompt the reanalysis of stored genomic data from RGCS. One approach is individual-led requests, where individuals choose to make their genomic data available for reanalysis if they face a health issue or medical need in the future. Alternatively, more benefit may be found through a health systems-driven reanalysis which could involve offering reanalysis at specific time points or in response to certain events, such as when an individual develops an illness or reaches a certain age where screening for diseases like cancer is appropriate.

This opportunity to re-use genomic information must be offset with data storage costs (both financial and environmental) which are significant as noted above. However, if retention of RGCS data to support the analysis of individuals who have re-coupled is found to be justified over resequencing, there is a potential to apply this data to other health interventions, which could be offered to individuals screened through RGCS, for example: adult onset hereditary conditions such as hereditary breast and ovarian cancer, colon cancer, familial hypercholesterolaemia or pharmacogenomic testing. Integrating these approaches into clinical practice could enhance the secondary use of RGCS data and promote proactive approaches to improving health and wellbeing. However, such an approach may also lead to inequitable provision of such information and would need a separate analysis and comparison with alternatives such as a separate formal population screening program.

Secondary Use Case Study 1 - Adult Risk Screening

Preventative genomic screening of the adult population for common, highly penetrant cancers and cardiovascular disease has significant potential to prevent disease.

The MRFF-funded DNA Screen study (**DNA Screen – Secure DNA testing for your future health**) evaluated the feasibility, utility and cost effectiveness of screening for hereditary breast and ovarian cancer, lynch syndrome and familial hypocholesterolaemia. The study screened identified an increased risk in 2% of participants, which has enabled at-risk individuals to initiate preventative strategies to avoid the diseases later in life. Cost effectiveness analysis by the study (Zhang et al., 2019) found that population screening for these conditions would reduce variant-attributable cancers by **28.8% and cancer deaths by 31.2% compared with current targeted testing, and at $400 a test was highly cost-effective (reaching cost neutrality at $1200 a test).**

Such adult risk screening for cancers and cardiovascular disease is ideally offered to young adults (18 – 40) to identify at-risk individuals before the onset of disease. As this aligns with the age range of RGCS, it is a clear opportunity to leverage data generated from RGCS for secondary genetic risk analysis.

The temporal separation of offering adult risk screening by reanalysis of RGCS data would need to consider the reproductive stage and decisions of the couples, and potential psychosocial

implications, however both MM and DNA Screen found those screened were grateful for the information.

As we've explored in this report, evaluating the implications of re-analysis of RGCS data for cancers and cardiovascular risk would need to consider the accessibility, ethical acceptability and affordability of downstream clinical services, and health system capacity impacts.

Secondary use case study 2 – Pharmacogenomics

Medications don't always have the same effect: a person's genes influence the safety and efficacy of a medication, so different people can experience highly variable responses to the same drug and dose. This can have significant implications for patients and the Australian healthcare system. Pharmacogenomics is a field of precision medicine that applies knowledge of human genetic variation to individualise drug prescribing. It aims to prevent adverse drug reactions and improve drug effectiveness.

The Royal College of Pathologists of Australasia have developed National Clinical Indications for Pharmacogenomic Testing (Royal College of Pathologists of Australasia, 2025), The Co-Chairs of the RCPA Pharmacogenomics Working Group were consulted as to the opportunity to leverage RGCS - derived data for the purposes of population-scale pharmacogenomics testing. While they agree that the possibility of secondary analysis of the data with relevance to pharmacogenomics would be interesting, they consider it would be premature to undertake population-scale pharmacogenomic testing in the short-term, on the basis of a range of technical and implementation barriers:

- The challenge of accurately calling diplotypes from WES data
- The need to support adequate informed consent
- The need to provide a fully interpreted pharmacogenomic report that links diplotypes to prescribing guidance according to national and international knowledgebases and recommendations
- Longitudinal data and clinical information availability to ensure reinterpretation is possible as evidence develops and the patient's medications change
- The need to ensure pharmacogenomic test panel and associated information is updated, and
- The need for providing access to expert pharmacologist and counselling support.

While pharmacogenomic testing at population scale is not currently feasible as part of an organised national RGCS program, there may be potential to explore the utility of reanalysis of data for pharmacogenomic testing in a targeted fashion, when clinically indicated (Samuel et al., 2025)

Value of Long-Term Retention of Data

A key practical objection to retention of genomic data generated from RGCS for re-use is the possibility that sequencing technologies will improve over time, necessitating resequencing regardless of stored data. Current sequencing techniques, such as short-read sequencing, may not capture all regions of the genome or detect certain structural variants, while future advancements may offer greater clinical utility. Generating, processing and storing genomic data also has

environmental impact, and the sustainability implications of health care are increasingly being recognised (Samuel et al., 2025).

Another consideration is the potential cost-effectiveness of resequencing versus storing and reanalysing genomic data. While sequencing costs have decreased significantly, storage costs have also dropped. If the cost of storage continues to decline, secondary use of genomic data may become more cost-effective than resequencing, particularly if the data is used multiple times over an individual's lifetime. Additionally, reanalysing stored RGCS data avoids logistical challenges associated with sequencing on demand, such as the need for in-person medical appointments. Therefore, the cost-effectiveness of storing genomic data and reanalysing it over time are likely to change over time, making it an important consideration for future healthcare systems.

Despite the challenges, both the long-term utility and cost-effectiveness of storing and reanalysing genomic data, as compared to resequencing, should be evaluated as technologies continue to evolve. Policymakers must carefully weigh the costs and benefits, considering investments in infrastructure, data-sharing standards, and ethical frameworks to responsibly manage genomic data for RGCS.

Objective 3.7: Public Acceptability and Preferences for Data Custodianship and Governance

Consider public acceptability / preferences regarding database structure / custodianship (e.g., government asset v industry management) noting the intersection with the genomic acceptability - societal preferences, public opinion and analysis project

Australian Genomics' project to evaluate public acceptability of health genomics via a market research firm was described in the section 'Societal Perceptions of RGCS' (Page 19).

In addition to assessing public perspectives of the acceptability of different genomic interventions, including RGCS, all respondents to the survey (N = 1404) were asked a series of questions about their genetic data (full questions provided in ***APPENDIX V – Genomics Acceptability: Public Perspectives***). Overall, there was high acceptability of the use of deidentified genomic data for secondary purposes, including for the purposes of supporting the care of other patients; sharing with medical services to improve genetic testing; and for research, with ≥76% respondents considering this acceptable, or completely acceptable (see Figure 16).

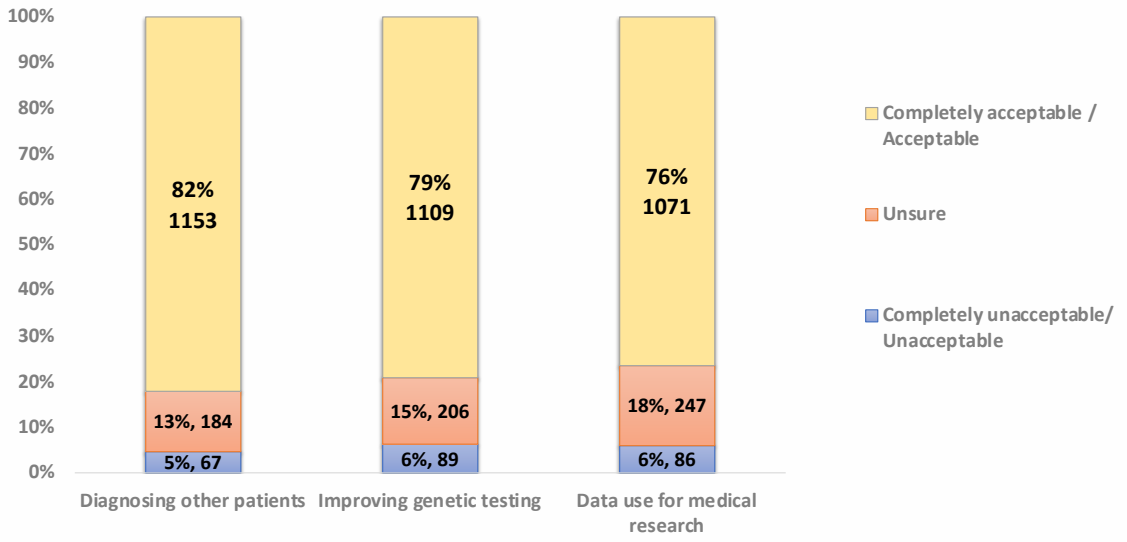

Figure 16: Societal acceptability of secondary use of genomic data from clinical testing

The survey also asked respondents to consider their preferences around data storage and management. It noted that longer-term data storage could support the secondary use of that data for healthcare and research, and asked the acceptability of different organisations/agencies as data custodians. A government-funded national agency had the highest acceptability for genomic data management and governance (77%) followed by state/territory public laboratory (72%) and federal government (61%). Only 41% respondents thought a private pathology provider would be an acceptable custodian for long-term management of genomic data (see Figure 17).

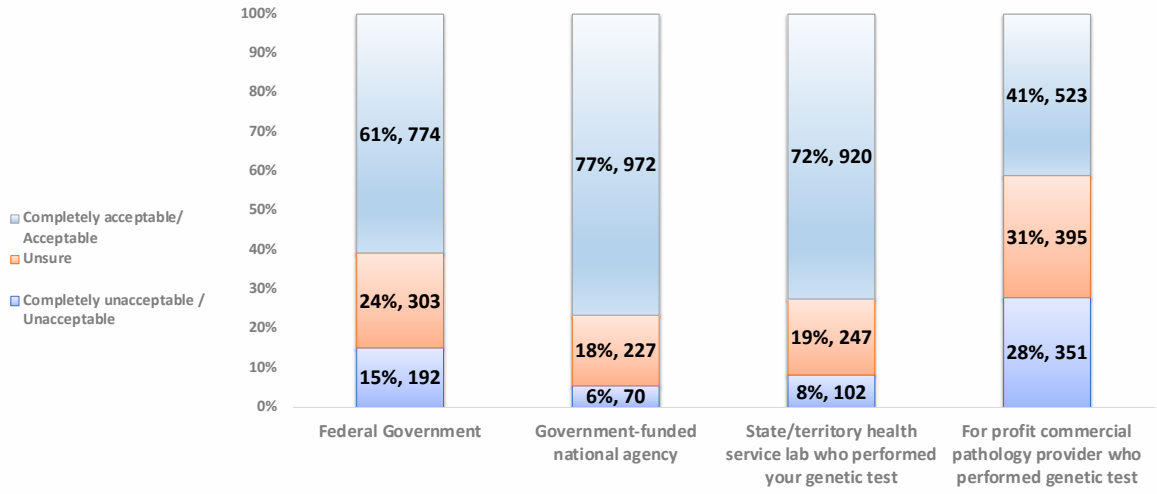

Figure 17: Societal acceptability genomic data management and governance

The survey results suggest that there is generally high public acceptability of long-term retention of genomic data generated from clinical interventions, and secondary use of this data for healthcare

and research. This supports the recommendation for establishing a long-term data governance framework for an organised RGCS program, with explicit informed consent of the data donors.

Conclusion

This report presents a comprehensive plan for the design and delivery of a National RGCS Program in Australia. Drawing on evidence from MM and three targeted priority projects, it demonstrates that equitable, large-scale delivery of RGCS is both achievable and cost effective. The findings provide a clear pathway forward for a national model that addresses longstanding disparities in access and supports informed reproductive decision-making for all Australians.

MM showed that a digitally enabled, simultaneous screening model can be successfully implemented across Australia, with participation from all states and territories, including rural and remote regions. It confirmed that the majority of increased chance couples identified would not have been detected using the currently Medicare funded three-gene panel, reinforcing the value of expanding the scope of screening. Importantly, the model proved acceptable to both participants and healthcare professionals, with high satisfaction, low decision regret and strong public support for broad, publicly funded RGCS.

The accompanying priority projects helped clarify the system-level requirements for implementation, including digital infrastructure, clinical service design, workforce development, data governance, and the equitable delivery of downstream reproductive services. Together, these projects identified core assumptions and operational considerations essential for sustainability and inclusion. This includes investment in a secure digital platform, accessible educational resources, a national genomic data registry, and systems for culturally responsive and regionally appropriate care.

The recommended model supports informed reproductive choice by focusing on conditions with clear reproductive utility, avoiding unnecessary anxiety or ambiguity. It emphasises autonomy, cultural safety, and community engagement especially with Aboriginal and Torres Strait Islander peoples, culturally and linguistically diverse communities, and those in regional and remote settings. It also ensures mechanisms are in place for timely disclosure of results, access to genetic counselling, and referral to the full range of reproductive options.

To realise these benefits, early and sustained investment in program infrastructure and governance is essential. Establishing a National RGCS Program will require collaboration between government, clinical services, laboratories, technology partners, and communities. Ongoing monitoring and evaluation will also be critical to ensure quality, responsiveness, and long-term impact.

The vision set out in this report is one of a future where all Australians of reproductive age can access meaningful, accurate, and timely information to guide their reproductive decision-making. Implementing the recommendations outlined here will address longstanding inequities in genomic healthcare. Now is the time to build on the foundation laid by MM and move confidently toward national implementation.

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Appendices

APPENDIX I – Working Group Members

Working Group	Name	Affiliation
Education and Awareness	Kirsten Boggs (CHAIR)	Australian Genomics, Sydney Children's Hospital Network, University of New England
	Alison Archibald	Australian Genomics, Murdoch Children's Research Institute, Macquarie University, The University of Melbourne
	Bronwyn Terrill	Australian Genomics, Centre for Population Genomics
	Bethany Wadling	ALIGN, Royal Hospital for Women
	Amy Nisselle	Murdoch Children's Research Institute, University of Melbourne
	Samantha Edwards	Harry Perkins Institute of Medical Research, University of Western Australia
	Belinda McClaren	Murdoch Children's Research Institute, University of Melbourne
	Anaita Kanga-Parabia	Murdoch Children's Research Institute, University of Melbourne
	Georgie Hollingsworth	Harry Perkins Institute of Medical Research, University of Western Australia and Office of Population Health Genomics, WA Department of Health
Information Management	Tiffany Boughtwood (CHAIR)	Australian Genomics
	Kirsten Boggs	Australian Genomics, Sydney Children's Hospital Network, University of New England
	Tessa Mattiske	Australian Genomics
	Sarah Casauria	Australian Genomics
	Marie-Jo Brion	Australian Genomics
	Oliver Hofmann	University of Melbourne Centre for Cancer Research
	Andrew Patterson	University of Melbourne Centre for Cancer Research
Laboratory	Edwin Kirk (CHAIR)	NSW Health Pathology Randwick, Sydney Children's Hospital Randwick, University of New South Wales
	Corrina Cliffe	Douglas Hanly Moir Pathology
	Sebastian Lunke	Victorian Clinical Genetics Service
	Richard Allcock	PathWest Laboratory Medicine, WA Department of Health
	Marina Barbic	Douglas Hanly Moir Pathology

	Kirsten Boggs	Australian Genomics, Sydney Children's Hospital Network, University of New England
	Kathryn Friend	SA Pathology, Woman and Children's Health Network
	Chiyan Lau	Pathology Queensland
	Abhijit Kulkarni	Genomic Diagnostics
	Nigel Laing	University of Western Australia and Harry Perkins Institute of Medical Research
Clinical	Alison Archibald (CHAIR)	Australian Genomics, Murdoch Children's Research Institute, Macquarie University, The University of Melbourne
	Kirsten Boggs	Australian Genomics, Sydney Children's Hospital Network, University of New England
	Joanne Kelley	Mercy Perinatal
	Lisa Hui	Mercy Perinatal, The University of Melbourne
	Lucinda Freeman	Master of Genetic Counselling Program, University of Technology Sydney
	Julie McGaughran	Genetic Health Queensland
	Erica Brown	The Royal Women's Hospital, Victoria
	Erin Tutty	Murdoch Children's Research Institute, The University of Melbourne
	Jill Kennedy	Genetic Health WA, King Edward Memorial Hospital
	Amy Howat	Fetal Maternal Assessment Unit, Campbelltown Hospital
Other medical specialties	Martin Delatycki (CHAIR)	Victorian Clinical Genetics Services/Murdoch Children's Research Institute
	Michelle Farrar	Sydney Children's Hospital Randwick, University of New South Wales
	John Massie	The Royal Children's Hospital Melbourne, University of Melbourne
IVF/PGT	Martin Delatycki (CHAIR)	Victorian Clinical Genetics Services/Murdoch Children's Research Institute
	Sharyn Stock Myer	Virtus
	Tristan Hardy	Monash IVF/ReproMed
	Roger Hart	Fertility Specialists of WA
	Rachel Rodgers	Royal Hospital for Women/IVF Australia
	Jana Karatas	IVF Australia
Aboriginal and Torres Strait Islander Consultation	Tiffany Boughtwood (CHAIR)	Australian Genomics
	Louise Lyons	Australian Genomics, ALIGN
	Johanna Barclay	ALIGN
	Bethany Wadling	ALIGN, Royal Hospital for Women

	Harry Miller Snr.	ALIGN Governance
	Kirsten Boggs	Australian Genomics, Sydney Children's Hospital Network, University of New England

APPENDIX II – Scenario-Based Prompt

Scenario A

"Imagine you are 30 years old, and you and your partner have decided you would like to start a family in the near future. You visit your doctor to discuss what you might need to do to prepare for this. They mention a screening test available called genetic carrier screening. This test can help work out the chances of you having children with a serious genetic condition.

The doctor directs you to a website which has information about the test, the possible results, and the testing process. You can order a testing kit through the website. The test uses a saliva sample from you and your partner to find out if you both are carriers of a serious genetic condition that may affect your children. About 2% of Australian couples will have an increased chance of having children with a genetic condition.

The website explains that carriers are people who are healthy but have a change in their DNA that means they can pass on a genetic condition to their children. If both you and your partner are carriers for the same condition, you have a 1 in 4 (or 25%) chance each pregnancy of having ~~a~~ children affected by the condition. Genetic conditions can be serious, reducing the child's quality of life, or shortening the life of the child. Most people who are carriers do not have a family history of the genetic condition they carry."

If you and your partner are found to be carriers, there are options available to help you have children without the condition.

You can choose whether or not you would like to have the test."

APPENDIX III – Case Study – The National Cancer Screening Register

The National Cancer Screening Register (NCSR) was established to streamline and consolidate the management of cancer screening programs across Australia. It combines multiple state and territory-based screening registers for cervical and bowel cancers into a single, national system. The NCSR is the first digital health system in Australia to comprehensively link all relevant population screening stakeholders: Commonwealth and state health authorities, GOs, specialists, public and private pathology services, and the participant.

Key Details:

1. **Announcement and Budget:** The NCSR was announced in the 2015–16 Budget with an initial allocation of $148.4 million, later increased to $178.3 million for the period 2015–20. By the time of implementation, the total budget was expanded to $236 million. Telstra Health was awarded the contract to manage the system, which included both the building and operational costs over five years. Although the breakdown of ongoing maintenance costs isn't publicly available, operational aspects such as system updates, data management, and cybersecurity were likely part of the extended budget. *(Tender documents unavailable via AusTender).*
2. **Purpose**: The NCSR aims to:
    - Create a unified electronic health record for individuals participating in cervical and bowel cancer screening.
    - Improve the efficiency, data accuracy, and clinical decision-making processes of cancer screening programs.
    - Allow for future integration of additional cancer screening programs.
3. **Timeline**:
    - **Contract Awarded:** May 2016.
    - **Planned Launch:** May 2017.
    - **Actual Launch:** Delayed until December 2017, which resulted in additional project costs.
4. **Key Functionalities**:
    - The NCSR creates a single-electronic health record for every Australian participating in cancer screening programs. This record includes details of their participation history, screening results, follow-up actions, and reminders for future screenings.
    - Provides participants and healthcare professionals access to real-time screening data, enabling informed clinical decisions.
    - Automatically processes screening results from laboratories, reducing manual data entry errors.

- Facilitates follow-up actions for abnormal results, ensuring timely intervention.
- The NCSR tracks participation rates and outcomes, which can help evaluate program effectiveness. This data supports national public health initiatives, providing insights into participation levels, demographic information, and potential areas for improvement in screening programs.
- While it currently supports cervical and bowel cancer screenings, the NCSR has the capability to expand and include additional population-based screening programs, such as breast cancer or lung cancer screening, in the future.

The establishment of the NCSR was seen as a major reform, improving national coordination, data consistency, and accessibility for participants and healthcare professionals. However, challenges related to project delays (detailed below) and additional costs were noted during its implementation.

Healthcare Provider Portal

Released in Oct 2020, the Healthcare Provider Portal for the NCSR is designed to support healthcare professionals by providing access to essential screening information and enabling streamlined management of patient care. The portal is accessed via PRODA (Provide Digital Access) which is an online identity verification and authentication system that lets you securely access a range of government online services for providers.

Key functionalities include:

1. **Access to Screening Records**:
    - Healthcare providers can view patient screening histories for cervical and bowel cancer, enabling informed decisions and monitoring over time.
2. **Patient Enrolment and Management**:
    - Providers can enrol patients, update contact details, and manage screening preferences, including opt-ins and opt-outs.
3. **Clinical Decision Support**:
    - The portal provides reminders and notifications to assist providers in managing patient screening schedules and follow-ups.
4. **Requesting and Viewing Results**:
    - Providers can request screening results, such as HPV tests or Faecal Occult Blood Tests (FOBT), directly from the portal.
5. **Follow-Up and Notifications**:
    - The system helps send invitations and reminders for screenings and follow-up actions. Providers can also order replacement bowel screening kits for patients.
6. **Integration with Practice Management Software**:

- The portal integrates with systems like **Best Practice** (Jan 2021), **MedicalDirector** (Aug 2021), and **Communicare** (Dec 2021), allowing seamless access to patient screening data within established workflows.

Participant Portal

Launched in late 2020, the **Participant Portal** allows individuals to manage their cancer screening participation with ease. Its functionalities empower participants to stay engaged in their health management.

1. **View Screening History**:
    - Participants can access their screening history for bowel and cervical cancer, providing a clear view of their health journey.
2. **Update Personal Information**:
    - Participants can update contact details to ensure they receive timely reminders and screening results.
3. **Manage Participation Preferences**:
    - Users can opt in or out of screening programs and set notification preferences (e.g., email, phone).
4. **Receive Invitations and Reminders**:
    - The portal sends personalised invitations and reminders, promoting timely participation in screenings.
5. **Access Educational Resources**:
    - Participants can access information on the importance of regular screenings and how to interpret results.
6. **Integration with My Health Record**:
    - The Participant Portal is integrated with Australia's **My Health Record**, allowing for seamless communication between individuals and healthcare providers.

Integration with Pathology services

The NCSR integrates with pathology laboratories to enhance the efficiency and accuracy of cancer screening programs.

1. **Automated Result Submission**:
    - Pathology labs electronically submit test results (e.g., HPV tests) directly to the NCSR, ensuring timely record updates.
2. **Result Tracking**:
    - Healthcare providers can access test results via the Healthcare Provider Portal, ensuring timely follow-up with patients.

3. **Centralised Data Management**:
    - By integrating with pathology services, the NCSR consolidates data from multiple sources, improving decision-making for healthcare providers.
4. **Standardised Reporting**:
    - Standardised formats for pathology results enhance data consistency and reliability.

Data Collected

1. **Personal Information**:
    - Name, date of birth, contact details (to send reminders and invitations), Medicare number, and other identifiers necessary to link records.
2. **Clinical Information**:
    - Screening results (e.g., HPV test for cervical screening or fecal occult blood test for bowel screening).
    - Past test history, such as Pap smear results and any follow-up actions or diagnostic tests.
    - Information on any treatments received following a positive screening result.
3. **Participation and Attendance**:
    - Records of when participants were invited for screening and whether they attended or completed the tests. The system tracks compliance and can trigger reminders if a participant misses an appointment or test.
4. **Health Professional Interactions**:
    - Data on interactions between participants and healthcare professionals, including when results were shared or follow-up consultations were held.

Key Challenges to Implementation

The implementation of the **National Cancer Screening Register (NCSR)** experienced delays due to several key factors:

1. **Technical Challenges**: The development of the register involved integrating multiple state and territory cervical screening registers, along with the National Bowel Cancer Screening Program, into one centralised platform. This complex integration posed significant technical challenges, particularly around data migration, system security, and ensuring the functionality of the platform for both healthcare providers and participants.
2. **Legislative Delays**: The legislation required to establish the NCSR was delayed. Although Telstra Health had already begun working on the project, the enabling legislation (for the My Health Records Act amendments to facilitate the NCSR) faced delays in parliamentary approval, which slowed down the entire project.

3. **Vendor Transition and Coordination Issues**: The transition of responsibility for cancer screening registers from state and territory management to a centralised, national system under Telstra Health also caused operational delays. Coordination between different stakeholders, including healthcare providers, laboratories, and government agencies, proved to be a complicated process.
4. **Stakeholder Concerns**: Concerns were raised about privacy and data security, given the sensitivity of health data being centralised into a single system. Addressing these concerns required further attention and adjustments to ensure compliance with data protection laws.

Public Health Impact

- By centralising and digitising the cancer screening data, the NCSR enhances data reliability and helps **increase participation rates** in the national cancer screening programs. It also provides a framework for public health analysis, supporting the **early detection of cancer** and improving survival rates by ensuring timely follow-ups.

This system, despite some initial delays, is considered a significant step toward improving cancer screening outcomes across Australia.

Other information/links:

https://www.ncsr.gov.au/

https://www.ncsr.gov.au/about-us/privacy-policy.html

https://www.telstrahealth.com/sectors/population-health/

National Cancer Screening Register Data Access and Release Policy (Oct 2018)

MJA perspectives article: Supporting health care providers in cancer screening: the role of the National Screening Register (July 2023)

https://www.anao.gov.au/work/performance-audit/procurement-national-cancer-screening-register

APPENDIX IV – Input Data for Genomic Data Management Modelling for an Organised RGCS Program

Metric	WGS (30X)	WES (100X)	REF	Notes
bp	3,000,000,000	105,000,000	1	WES calc as '2-5% genome'; panel numbers calculated
Variants	5,000,000	175,000	2	0.16% var in WGS; panel numbers calculated
Comp time (hours)	24	2	2	FASTQ to VCF; panel numbers calculated
Storage				
Storage – FASTQ (GB)	80.00	5.00	2	
Storage – BAM (GB)	100.00	8.00	2, 8	
Storage – VCF (GB)	1.00	0.10	2	
Storage - Σ (GB)	181.00	13.10	2	
Data transfer (sec)	1448.00	104.80	2	1 gigabit / sec internet = 125MB/s
Data transfer (min)	24.13	1.75	2	
Cost – Active Storage per Month				
AWS S3 standard per month	6.79	0.49	2, 3	$USD 0.025 per GB per mth = $AUD 0.0375
Google Cloud cloud storage	6.24	0.45	2, 4	$USD 0.023 per GB per mth = $AUD 0.0345
Microsoft Azure premium	40.73	2.95	2, 5	$USD 0.15 per GB per mth = $AUD 0.225
On prem active storage	4.525	0.33	OH	$USD 0.3 per GB per year = $AUD 0.025 per month
Cost – Cold Storage				
AWS Cold Storage	36.2	2.62	9	20% active storage
On prem			OH	Cold storage on tape - $200/TB/yr
Compression				
CRAM (30 – 50% compression)	90.5	6.55	7, 8	CRAM 3.1 reliably 50% now
Cost AWS S3 standard per month CRAM	3.39	0.25		Cost full dataset CRAM
Data Retention Requirements				
FASTQ or BAM	4 years – NPAAC		6	BAM not FASTQ because compute requirements to realign
VCF	25 years	Utilisation triple screen: 95% 25-44. Assume 25Y retention. See utilisation summary updated.		

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2. 3billion: https://3billion.io/blog/big-data-among-big-data-genome-data
3. AWS pricing calculator: https://calculator.aws/#/
4. Google pricing calculator: https://cloud.google.com/products/calculator
5. Microsoft Azure pricing calculator: https://azure.microsoft.com/en-au/pricing/calculator/
6: NPAAC: Requirements for the retention of laboratory records and diagnostic material Table 6 - genetics
7. CRAM. https://www.ga4gh.org/product/cram/
8. CRAM – 2: https://academic.oup.com/bioinformatics/article/38/6/1497/6499262?login=false
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APPENDIX V – Genomics Acceptability: Public Perspectives

Section 4: Your Genetic Data

If you have a genetic test it can look at all of your DNA or only parts of it, which creates a lot of genetic data.

A medical scientist or doctor will examine your genetic data to identify which changes in your DNA are important to your health or your family's health.

You will receive a genetic test result which tells you information about what these changes mean you and your family.

Genetic data is the full set of information from your DNA. This looks like a giant code (Image 1).

Genetic test results summarise the important information about your health that were found by looking at your DNA. They are often medical reports (Image 2).

Image 1: Your genetic data

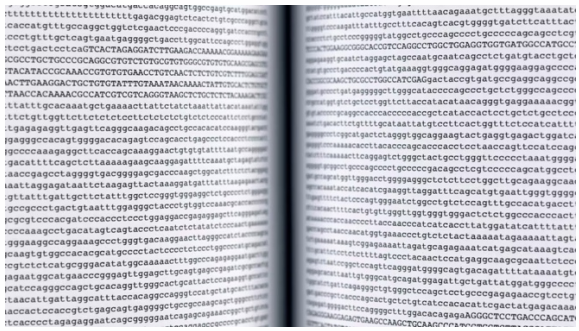
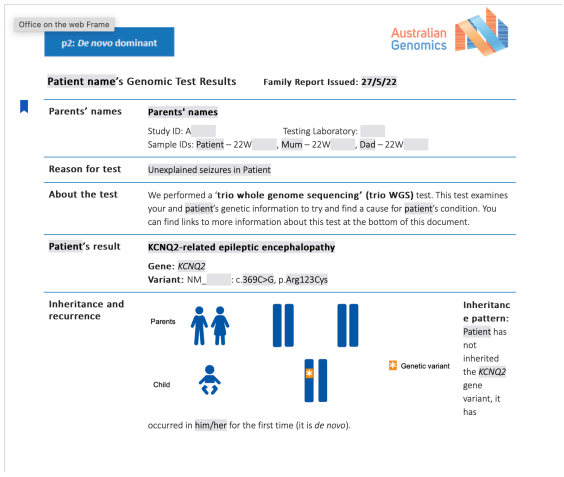


Image 2: Your genetic test result



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p2: *De novo* dominant

Australian Genomics

Patient name's Genomic Test Results **Family Report Issued: 27/5/22**

Parents' names	**Parents' names** Study ID: A Testing Laboratory: Sample IDs: Patient – 22W , Mum – 22W , Dad – 22W
Reason for test	Unexplained seizures in Patient
About the test	We performed a '**trio whole genome sequencing' (trio WGS)** test. This test examines your and patient's genetic information to try and find a cause for patient's condition. You can find links to more information about this test at the bottom of this document.
Patient's result	**KCNQ2-related epileptic encephalopathy** **Gene:** *KCNQ2* **Variant:** NM_ : c.369C>G, p.Arg123Cys
Inheritance and recurrence	Parents Child Genetic variant **Inheritance pattern:** Patient has not inherited the *KCNQ2* gene variant, it has occurred in him/her for the first time (it is *de novo*).

In these questions we are talking about using and storing your genetic data (your genetic code), not the genetic test result.

Use of your genetic data for medical care

When your doctor orders a genetic test, your genetic data is compared with data from other people to get a diagnosis.

This helps experts (medical scientists or doctors) figure out which changes in your DNA might be important for your health or linked to certain conditions.

4.1. Your genetic data (not your personal details e.g., name and address) could be made available to doctors to help diagnose other patients.

How acceptable is this to you?

completely unacceptable, unacceptable, unsure, acceptable, completely acceptable.

I. Would you like to comment further? [question is optional]

4.2. Your genetic data (not your personal details e.g., name and address) could be made available to medical services to improve their genetic testing.

How acceptable is this to you?

completely unacceptable, unacceptable, unsure, acceptable, completely acceptable

I. Would you like to comment further? [question is optional]

Use of your medical genetic data for research

A patient's genetic data can be useful for health and medical research.

In health and medical research, scientists study what makes people healthy and why they might have health conditions or disabilities. Findings from this research can help people by leading to better treatments, better ways to identify a health condition, or better ways to deliver health services.

By looking at genetic data in many different people, scientists can learn more about the genetic causes of a range of health conditions.

The research may not directly benefit the person providing the data, but could help other patients in the future.

If you are offered a genetic test, your doctor/health professional could also ask you if your genetic data (not your personal details or your results) can be used in medical research?

4.3 How acceptable is sharing your genetic data for medical research, with your consent?

completely unacceptable, unacceptable, unsure, acceptable, completely acceptable

4.4 How acceptable would it be to have a discussion about research when you are having a medical test?

completely unacceptable, unacceptable, no opinion unsure, acceptable, completely acceptable

I. Would you like to comment further? [question is optional]

4.3. Your health professional could ask you about using your data (not your personal details e.g., name and address) in research at different times. When would it be acceptable to you?

completely unacceptable, unacceptable, no opinion unsure, acceptable, completely acceptable

- *In the first discussion with my doctor/healthcare professional when I consent to do the test*
- *When I receive my genetic test result*
- *At another time (after my appointment where I have received my test result)*

- *Never - I do not want my doctor to ask me about the use of my genetic data for research when I am getting a medical test*

i. Would you like to comment further? [question is optional]

Storing your genetic data after a genetic test

After a genetic test, a patient's genetic data is often securely stored by the lab who did the test, or it may be deleted after a few years.

Storing genetic testing data in a secure database for a long period of time could allow experts (e.g., medical scientists or doctors) to use your genetic data for healthcare purposes or for medical research, to help other people.

Your genetic data would usually be stored in a secure way without personal details attached.

It could be stored and managed by some different organisations or agencies.

4.4. How acceptable would you find a database/storehouse that is managed by:

For each option rate:

completely unacceptable, unacceptable, unsure, acceptable, completely acceptable

- *Federal Government [grid]*
- *Government-funded national agency e.g. CSIRO, Australian Digital Health Agency, a national genetics agency[grid]*
- *Your State/Territory health service lab who performed your genetic test[grid]*
- *For-profit commercial pathology provider who performed your genetic test[grid]*
- *None of these - my data should be deleted after the test [Exclusive]*
- *Other [open text box]*

4.5. Genetic data is stored in a secure way without personal details attached. However, as with all data, there is always a small chance it could be lost or accessed without permission. Would this change your decision to have the test?

- *Would definitely change*
- *likely to change*
- *uncertain*
- *not likely to change*
- *Would definitely not change*