Considerations for the implementation of reproductive genetic carrier screening

This document has been prepared at the request of the Australian Government Department of Health to present a candid appraisal of perceived barriers to the implementation of expanded reproductive genetic carrier screening (ERGCS) in Australia. These barriers can be broadly categorised into issues regarding **health system infrastructure** (laboratory capacity; clinical service provision; clinical utility; data management) and **ethical/legal/regulatory issues** (policy framework; equity of access; public knowledge). Potential delivery models are also presented.

Background

At present in Australia, ERGCS is available from commercial providers on a user-pays basis. Companies offer varied gene lists and have differing reporting policies. Public funding for testing for cystic fibrosis (CF), fragile X syndrome (FXS) and spinal muscular atrophy (SMA), will be available through the MBS from November 2023. MSAC application 1637 proposes public funding for ERGCS for a larger number of conditions. It presents evidence from the MM project that screening for >1,000 genes associated with severe childhood-onset autosomal recessive and X-linked conditions would identify ~2.0% of screened couples as having an increased (generally 1 in 4) risk of having an affected child. The health economic analysis suggested screening would be highly cost effective, and the diagnostic yield from the CF/FXS/SMA testing would be <20% of the yield from a panel of >1,000 genes. **For a more detailed analysis of the implementation considerations of CF/FXS/SMA testing versus ERGCS, see Appendix 1**.

Potential issues / barriers for ERGCS

1. Laboratory capacity

The genetic testing required to implement ERGCS is specialised and <10 Australian laboratories currently possess the technical capacity and expertise. At present, no single service could deliver ERGCS at the volumes required for population scale implementation. Laboratories need time to prepare and confidence about the volume of testing they would receive to commit to deliver ERGCS at scale. Involvement of both public and private sector laboratories will be needed to achieve the volume of testing required, particularly as ERGCS demands a short turnaround time for results, especially if the couple are pregnant.

2. Clinical service provision

The MM project has demonstrated that pre-test information and consent can be successfully provided to most reproductive couples online. This needs to be supported by administrators and Genetic Counsellors to answer questions, follow up relevant family history information, and enable access for those unable to use the online resources. Genetic Counsellors are also needed to provide education and support to requesting practitioners, particularly GPs, in order for them to feel comfortable to offer ERGCS. The MM couple-based model means that post-test services can be focused on those found to have an increased risk, for whom the information is important for reproductive decision making. Additional clinical resources (genetic counsellors, clinical geneticists, and sub-specialist physicians in the relevant conditions) will be needed to support increased chance couples in particular, with respect to reproductive decision making, testing of existing children and other family members as necessary. These demands will be in addition to an already overstretched Genetics workforce. There will be additional demands on maternal-fetal medicine services for prenatal diagnostic testing, and on pre-implantation genetic testing services, which are currently almost exclusively within the private sector.

3. Clinical utility

The design of the screening program is key to delivering a cost-effective service that provides clinically useful information to reproductive couples and with the necessary supports. At present, ERGCS providers vary as to their screening approach and this can create significant workload impacts on clinical services. For example, there is wide variation in the genes included in panels, which can lead to complex genetic counselling scenarios. Creating national guidelines to standardise the approach to ERGCS, with a focus on clinical utility, will minimise the harms and maximise the benefits of ERGCS.

4. Data management

ERGCS at population scale will generate large amounts of genetic data (~2 petabyte per annum[1]). This data will be quantitatively larger, but not qualitatively different, from existing genetic testing data. As most accredited providers are reliant on scalable cloud infrastructure, the quantity of data generated will not exceed existing technical capacity, although there will need to be an evaluation of costs for short- and long-term storage; reprocessing; compression; and archiving. As an indication, Mackenzie's Mission data storage amounts to ~120TB data (compressed BAM, FASTQ, VCF) per 10,000 individuals, which would cost ~$AUD4400 per month in active storage, or 1/10 of this in deep archive (not readily accessible for reanalysis/sharing). There are existing State/Territory policies regarding genomic data management and further NPAAC/NATA requirements for retention of data applied to accredited laboratories. ERGCS at scale raises additional policy considerations in relation to: data custodianship; interoperability of laboratory systems; accessibility between laboratories and jurisdictions; sharing of data to permit reanalysis in the case of re-partnering; and potential re-use of data (for clinical and/or research purposes). Some of these considerations will be explored in the context of the National Approach to Genomic Information Management (NAGIM) implementation.

5. Policy framework

Ideally, unified national policies to support the implementation of ERGCS will ensure standardised approaches to diagnostic, clinical and data processes, and underpin a standardised approach that protects consumers from differing experiences based on service provider. Exact requirements will depend on the model for implementation. Existing Australian speciality society guidelines are limited – the most relevant is the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) guideline, C-Obs 63, which is endorsed by the Human Genetics Society of Australasia (HGSA). Currently, the Royal Australasian College of Pathologists (RCPA) and HGSA are jointly developing guidelines on the CF/FXS/SMA testing and plan to develop guidelines for expanded carrier testing. We are not aware of any existing State or Federal government policies regarding ERGCS.

6. Equity of access

Currently there is marked inequity of access to ERGCS[2]. To ensure ERGCS is available to any Australian couple that wishes to access it, there will need to be extensive infrastructural preparation: information/education materials need to be available in the major community languages as well as in English; provisions are needed for those less able to access online resources, who speak other languages, or who have a learning disability. Special consideration needs to be given to the needs of Aboriginal and Torres Strait Islander peoples, with specific engagement of Indigenous leaders to ensure the ERGCS program addresses Community needs. It is noted, too, that current genomic reference databases (e.g. gnomAD) predominantly represent Western European

[1] Assuming 140,000 couples accessing ERGCS per annum, ~8GB per exome

[2] SJ Robson et al, 2020, AZJOG 60(6) 976-979 https://doi.org/10.1111/ajo.13206

ethnicities, and are poorly representative of Australian ethnic diversity. With current research efforts including the Australian Genetic Diversity Database and National Indigenous Genomics Network, it is hoped this need will be addressed in coming years. The technical approach to CF testing in the CF/FXS/SMA screen is particularly compromised by the poor representation of genomic reference databases, as it involves variant panels to target 'known pathogenic variants' derived from these databases. The ERGCS methodology provides the sequence of the entire genes of interest, and so permits the identification and evaluation of variants beyond this limited panel.

7. Public knowledge of ERGCS

If ERGCS is publicly funded, there would be benefits of an awareness campaign, ideally from the Federal and State Departments of Health about ERGCS, similar to other such campaigns for example for bowel cancer screening. This would support consistency and clarity of messaging, mitigate the risk of misinformation, and address concerns of technology- and/or genomic-hesitant sectors of the community who may balk at such interventions.

Possible approaches to implementation

1. Item number only

Public funding and delivery of ERGCS via a set of item numbers will assist in addressing equity of access to ERGCS in that cost would no longer be a barrier to screening. However, this approach is likely to be problematic in that a Medicare item number would cover the cost of the test but not the necessary support services. This model does not provide funding for patient and practitioner information/education resources, nor does it cover development and training for laboratory and clinical services and other necessary genomics infrastructure. Without funding for these services harms due to inadequate supports around testing may occur including inequities due to language, cultural and other barriers.

2. A program-based approach

A program-based approach to implementation of ERGCS would enable the development of a standardised program for provision of ERGCS across Australia. The main advantages would be delivery of a consistent service nationally, development of capacity ahead of implementation and better management of equity issues. However, this approach may have additional up-front costs and may initially be more complex to implement.

Possible models include:

2a. A screening approach similar to the National Cervical Screening Program, with Federal government coordination, including management of a website for information provision and pre-test consent, and delivery of testing by laboratories under a contract system. This would have the advantages that uniform standards could be set (including requirements for reporting policies), appropriate data security standards and data sharing policies could be mandated, and laboratories providing services under contract would have certainty about test volumes and requirements. Associated post-test clinical support services could be managed centrally or at a local level.

2b. A system akin to newborn bloodspot screening, with a single laboratory service providing testing in each State or Territory – noting this could include a single service covering more than one jurisdiction, as is the case for newborn bloodspot screening. Associated clinical services including genetic counsellors could be part of the central service or could be associated with health services in a distributed fashion. This would require agreement by all States and Territories and would make it difficult to make use of private sector capacity. A national reference body would be needed to ensure consistency of service across the country. The online components could still be centrally managed, or could be based with the State/Territory services.

Appendix 1 - Modelling the health system implementation considerations of publicly funded reproductive genetic carrier testing.

The Medical Services Advisory Committee (MSAC) has supported public funding for Application No. 1573, "Reproductive carrier testing for cystic fibrosis (CF), spinal muscular atrophy (SMA) and fragile X syndrome (FXS)" (CF/FXS/SMA testing) which will be available from November 2023. An application for "Expanded Reproductive Carrier Testing of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions", Application No. 1637 was considered by MSAC July 2022.

These two approaches to reproductive genetic carrier testing are markedly different. Beyond the scope of genes/conditions tested, where CF/FXS/SMA testing focusses on the three conditions, and expanded reproductive genetic carrier screening (ERGCS) on 1000+ genes for 750+ conditions, the model of testing between the two applications differs. In the CF/FXS/SMA model, testing is undertaken sequentially on the individual members of the reproductive couple (i.e. genetic contributors to proposed offspring, including donors): first the female, then if she returns an increased chance result, the male. ERGCS approach in Application No 1637 has a couple-based approach, where analysis of the data and reporting is conducted simultaneously on both the female and the male.

These two approaches will have different implications for health system implementation of carrier testing at scale. The sequential carrier testing model will have significant implications for implementation around both laboratory burden, and pre- and post-test genetic counselling:

- The laboratory-based analysis of an individual's carrier status (particularly in carrier testing involving hundreds or thousands of genes) is significant. Analysis of the data from a couple significantly reduces laboratory genetic curation burden at scale.
- If a sequential carrier testing screen returns a carrier status on the female, this will require post-test genetic counselling, administration of male testing – and further counselling if both parties present as an increased-chance couple collectively.
- Most couples currently accessing reproductive carrier testing are pregnant (69% of female individuals tested were pregnant in Archibald et al[4]). To make sequential testing logistically feasible in the context of CF/FXS/SMA carrier screening, considerable genetic counselling / clinical administration support needs to be in place to identify and prioritise pregnant females and ensure the male receives testing concurrently, to avoid identification of an affected child beyond the point of legal termination, which differs across the jurisdictions. The current wording of CF/FXS/SMA MBS item precludes this contingency – permitting testing of the male only on identification of a female carrier. It is not yet clear how the logistics of this process will be managed at a national scale, nor how the genetic counselling workforce could deliver the service at current capacity[8].

Reproductive couple-based carrier testing enables screening of both reproductive partners at the same time and is useful when a large number of genes are screened, which comes with a high chance for a carrier result. Whilst couple-based carrier screening provides a comprehensive couple reproductive risk assessment in a more-timely manner, retesting is needed when members of the couple re-partner.

Based on data from the Australian Institute of Health and Welfare, and the Australian Bureau of Statistics, we expect approximately 300,000 babies born every year (see 'data inputs' and references

below). Based on the total fertility rate, 182,000 babies per annum will be born to new couples, 140,000 of which would choose to undertake reproductive carrier testing based on known consumer decisions about current prenatal carrier testing choices[3,7]. These data enable extrapolation of the number of increased chance individuals and couples identified nationally with reproductive carrier testing, and calculation of the potential health system impacts:

CF/FXS/SMA testing carrier **females** per annum nationally: 7,113 (5.08% individual carrier status[4])

CF/FXS/SMA testing increased chance **couples** per annum nationally: 1,169 (0.83% couple carrier status[5])*

ERGCS increased chance **couples** per annum nationally: 2,100 (1.5% couple carrier status[6])

Based upon these data, the outcomes of publicly funded reproductive genetic carrier testing can be estimated for each jurisdiction:

Reproductive genetic carrier testing outcomes by jurisdiction	Couples accessing screening annually	Increased chance women CF/FX/SMA testing	Increased chance couples CF/FX/SMA testing	Number pregnant CF/FX/SMA testing	Potential prenatal CF/FX/SMA testing	Potential terminations CF/FX/SMA testing	Increased chance couples ERGCS	Number pregnant ERGCS	Potential prenatal ERGCS*	Potential terminations ERGCS*
New South Wales	44,366	2,255	370	256	187	27	665	459	336	49
Victoria	35,922	1,826	300	207	151	22	539	372	272	39
Queensland	28,291	1,438	236	163	119	17	424	293	214	31
South Australia	8,939	454	75	51	38	5	134	93	68	10
Western Australia	15,341	780	128	88	65	9	230	159	116	17
Tasmania	2,617	133	22	15	11	2	39	27	20	3
Northern Territory	1,654	84	14	10	7	1	25	17	13	2
Australian Capital Territory	2,884	147	24	17	12	2	43	30	22	3
Nationally	**140,014**	**7,117**	**1,169**	**807**	**557**	**85**	**2,100**	**1,449**	**1,061**	**153**

Assumptions to the above calculations:

- Application 1573 for CF/FXS/SMA testing states that carrier couples pursued prenatal diagnosis performed through amniocentesis or CVS in 56-100% for CF, 91%-100% for SMA, and 41-100% for FXS.
- Application 1573 states that pregnancy was terminated in 67-100% of CF-affected pregnancies, 92-100% of SMA-affected pregnancies, and 0-100% of FXS-affected pregnancies.
- To calculate potential interventions, the median of these ranges was applied and multiplied against the proportion of increased chance couple for each condition, based carrier frequency (Application 1573 DCAR table 8). ¼ pregnancies were assumed to be affected.
- As data as to intervention choices of increased chance couples is not yet available from Mackenzie's Mission, the rates for CF, SMA and FXS have been applied.

It should be noted that currently few Australians know their carrier status – many couples planning pregnancy (not just first-time mothers) would access carrier testing initially. Based on the data inputs (table below) this suggests as many as **232,000** Australian couples may choose to undertake reproductive carrier testing – or **1.7x the jurisdictional figures** represented above.

* Note Archibald et al estimate a couple carrier status rate of 0.42%, significantly lower than the 0.83% cited in the 1573 PSD – which is probably a result of the inclusion of small FMR1 expansions which are not included in the ERGCS calculations. For conservatism, the higher rate has been used for health impact calculations.

Data inputs

Data inputs	Data	Source
Number of mothers (2019)	298,567	Reference 1
Number of babies (2019)	303,054	Reference 1
TFR Australia (2019)	1.657	Reference 2
Proportion of mothers accessing screening	77.0%	Reference 3
Births by state/territory breakdown, 2019		Reference 2
New South Wales	96,909	
Victoria	78,463	
Queensland	61,795	
South Australia	19,526	
Western Australia	33,510	
Tasmania	5,716	
Northern Territory	3,613	
Australian Capital Territory	6,300	
Australia	305,832	

References

1 https://www.aihw.gov.au/reports/mothers-babies/australias-mothers-babies-2017-data-visualisations/contents/demographics-of-mothers-and-their-babies/key-demographics

2 https://www.abs.gov.au/statistics/people/population/births-australia/latest-release

3 https://www.aihw.gov.au/reports/mothers-babies/australias-mothers-babies/contents/summary

4 Archibald et al, Genetics in Medicine 20 (5) May 2018

5 MSAC Application 1573 Public Summary Document, Table 8 DCAR

6 Mackenzie's Mission study data (unpublished)

7 Delatycki et al, Eur J Hum Genet, 27: 669-70, 2019.

8 Nisselle et al, Australian Genomics, Genomic Workforce, Education and Ethics Program. Technical Report – Professional Status Survey of Genetic Counsellors and Clinical Geneticists. May 2018.