



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1637 – Expanded reproductive carrier testing of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions

Applicant: **Murdoch Children’s Research Institute**

Date of MSAC consideration: **28-29 July 2022**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of expanded reproductive carrier testing (ERCT) of couples for joint carrier status of genes associated with autosomal recessive (AR) and X-linked (XL) conditions was received from the Murdoch Children’s Research Institute by the Department of Health and Aged Care.

2. MSAC’s advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness, cost-effectiveness and total cost, MSAC did not support public funding of expanded reproductive carrier testing for joint carrier status of genes associated with autosomal recessive and X-linked recessive conditions (Mackenzie's Mission). MSAC recalled its previous support for individual-based pre-conception carrier testing for cystic fibrosis (CF), spinal muscular atrophy (SMA) and fragile X syndrome (FXS), under MSAC application 1573, which is not yet listed on the MBS. MSAC considered that there was a high unmet need for the proposed testing to inform reproductive decision-making as currently a couple would have to have an affected child before being considered for carrier testing. MSAC considered the proposed ERCT would have an uncertain but very high upfront financial cost to the Commonwealth and uncertain overall costs to the healthcare system. MSAC considered that the societal acceptability of couple-based reproductive carrier testing for the three conditions specified in application 1573 would not necessarily translate to acceptability for testing for many other conditions. Further, the medical and ethical basis of testing for each disease proposed in the gene panel had not been sufficiently explored or resolved. MSAC considered the proposed testing would need to be nationally implemented to ensure equity of access. Implementation on this scale would include components that are typically required as part of population screening programs. In anticipation of a re-application, MSAC asked the Department to investigate whether funding and implementation as a population screening program would be more appropriate, as opposed to

standalone MBS reimbursed services. MSAC advised it would welcome a future re-application addressing its concerns.

Consumer summary

This application from the Murdoch Children's Research Institute requested Medicare Benefits Schedule (MBS) listing of expanded reproductive carrier testing of couples for genes associated with severely disabling or life-limiting autosomal recessive and X-linked recessive conditions.

Autosomal recessive means that a person needs pathogenic (disease-causing) variants in both their copies of a gene – one from each parent – to be affected with the condition. X-linked means that the gene is on the X chromosome, which makes male children more likely to have the condition, because males only have one X chromosome. Given the conditions proposed in this application are autosomal recessive or X-linked, the chances of having an affected child are one in four (25%) if the parents are both carriers of an autosomal recessive condition or the mother is a carrier of an X-linked recessive condition.

The conditions proposed to be tested for are each very rare, but together they affect millions of people in the world. Examples of these conditions are Wilson's disease, degenerative neurological conditions, and Charcot-Marie-Tooth disease.

The application proposed testing reproductive couples that are planning to have a baby or are already pregnant, using a large gene panel of either 1,034 genes or 411 genes. The test would identify which couples are at increased risk of having a child born with one of the conditions associated with pathogenic variants in the genes on the panel. Most of the conditions are severe, with reduced life expectancies and the majority of conditions have few, or no effective treatment options. But some of the conditions on the gene panel are comparatively more mild or have available treatments. Also, the conditions have varying penetrance, which means that for some conditions there is a weaker chance that having pathogenic variants in both their copies of the gene will mean the person actually develops that condition: that is, for some conditions the same genetic variant could result in a child being anywhere from mildly affected to severely affected.

The proposed testing also allows for a fetus to be tested where the couple is found to be at increased risk for a condition, and for testing of existing children of couples found to be at increased risk. Testing would allow couples found to be at increased risk for having a child affected by a condition and their medical practitioner(s) to make more informed decisions about how to plan a pregnancy, or what to do if they are already pregnant. This may include consideration of MBS-reimbursed in vitro fertilisation & pre-implantation genetic diagnosis, adoption, decision to not have a child, or if already pregnant and the fetus is diagnosed with the condition, to make an informed reproductive decision. Couples will require counselling to support their reproductive decision-making. Couples at increased risk may choose to proceed with a pregnancy, but be more informed of the likelihood of having an affected child.

Currently, couples without a family history of one of the conditions tested for are typically only found to be at risk when they have a child affected by one of these conditions. Once an affected child is born and the genetic diagnosis is confirmed (by MBS or state-funded testing), then the parents are tested to determine the risk of having another affected child in subsequent pregnancies. MSAC was uncertain that it was generally socially acceptable to test for such a wide variety of conditions, and considered that the applicant had not provided enough evidence of medical, ethical, and societal acceptance of testing for all the conditions. There is a risk that couples at increased risk for having an affected child may feel pressured to make some reproductive choices over others to avoid having an affected child, for example to use pre-implantation genetic diagnosis, or to terminate a pregnancy if they found out they

were carrying an affected child. MSAC determined that more public consultation needs to be done on this type of genetic testing, and what impacts it may have on people living with some of the conditions being tested for. MSAC considered that it may be more societally acceptable to only test for severe conditions that are life-limiting and have few, or no treatment options, but that this requires more ethical consideration and evidence that it is acceptable to society. MSAC acknowledged that there is a high unmet need for reproductive carrier testing, and that some couples already pay for their own carrier testing.

MSAC also noted that the applicant did not include any information on culturally sensitive approaches to testing, including for Aboriginal and Torres Strait Islander peoples. It also wasn't clear how couples in remote or rural areas would be able to access the testing.

MSAC advised that the value of the test came mostly from the improved basis for reproductive decision making, and accepted that many of these decisions had also been shown to reduce overall costs to the healthcare system. If this testing were supported, it would detect more people with a condition but would also detect people with less severe types of conditions, so MSAC was concerned the value for money of this testing over time may have been overestimated. There would be a very large upfront cost to the MBS to provide the proposed testing, and the assessment may have overestimated the cost offsets, which were based on lifetime healthcare not needed because fewer affected children would be born. MSAC also considered that while the testing had not been proposed as a screening program, implementing it may require things that are typically established to support population screening programs, such as a registry and large-scale data infrastructure. Further work would be needed, especially on ethics and implementation, before MSAC could support this testing if a re-application was submitted.

MSAC's advice to the Commonwealth Minister for Health and Aged Care

MSAC did not support listing expanded reproductive carrier testing of couples for genes associated with autosomal recessive and X-linked conditions on the MBS. MSAC considered that there were substantial ethical implications and implementation issues with such a wide range of conditions and with widespread reproductive carrier testing overall that had not been sufficiently addressed.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this application was for MBS listing of expanded reproductive carrier testing (ERCT) of couples for joint carrier status of genes associated with autosomal recessive (AR) and X-linked recessive (XL) conditions. MSAC noted that this was its first consideration of this application.

MSAC recalled it had previously supported public funding for small-scale reproductive genetic carrier testing for cystic fibrosis (CF), spinal muscular atrophy (SMA) and fragile X syndrome (FXS) (MSAC application 1573), and noted that this will be listed on the MBS in November 2023.

MSAC noted that, although individually rare, as a group AR and XL conditions affect millions of children globally. Many AR and XL conditions are incurable, debilitating and/or result in a significantly shortened life expectancy, resulting in a significant disease and treatment burden to children born with a condition and their families, and to health systems. MSAC also noted that most children with AR or XL conditions are born to couples without a family history of the condition.

MSAC noted that at present in the absence of publicly funded ERCT, couples typically must have a child affected by one of the nominated conditions and only then will they progress to carrier

testing of the parents and cascade testing of at-risk family members. Currently, a child affected by one of the conditions associated with pathogenic variants in the nominated genes listed in ERCT will be genetically diagnosed either through newborn bloodspot screening (comprising approximately 25 conditions, depending on jurisdiction) or later diagnostic testing often using MBS- or State/Territory-funded genetic tests. MSAC also noted consultation feedback describing the pain of losing a young child that could have been avoided had the parents known they were both carriers of an AR gene variant. Thus, MSAC considered there to be a high clinical need for ERCT as it would enable pre-pregnancy decision-making for couples identified as being at high-risk for the nominated conditions. MSAC considered that the value of the test came mostly from the improved basis for reproductive decision making, and accepted that many of these decisions would also reduce overall costs to the healthcare system. MSAC acknowledged the importance of enabling reproductive choices, and that such tests are currently being accessed privately at considerable cost to patients. MSAC considered that the current funding situation leads to inequitable access for those who cannot afford to pay privately. However, MSAC noted that not all couples would choose to have, or be in a position to undergo ERCT. MSAC noted that 'reproductive couple' encompasses gamete donors, and affirmed that this refers to the two individuals who are the genetic parents of the potential child.

MSAC noted that technological advances make it more efficient to screen for hundreds, or even thousands, of AR and XL conditions on the same gene panel per couple. This application included two options for gene panel sizes – 1,034 and 411 gene panels¹, both using next-generation sequencing (NGS) methods.

MSAC noted that the application proposed four MBS items:

- AAAA – Prenatal or preconception carrier testing of a reproductive couple
- BBBB – Prenatal or preconception carrier testing of a reproductive couple, where one or both had previously received AAAA
- EEEE – testing of the fetus
- FFFF – cascade testing of the existing child of an increased risk couple.

MSAC noted that the analysis for items AAAA and BBBB uses a bioinformatics approach that only reports test results for a couple jointly, not for each individual. For each reproductive couple tested and for each condition tested the analysis identifies them as being at low risk of having an affected child (i.e. at least one parent is not a carrier of an AR variant, and the mother is not a carrier of an XL variant), or as being at 'increased risk' (25% risk) of having an affected child (i.e. both parents are carriers of AR variants for the same condition, or the mother is a carrier of an XL variant). Among the general population, a particular couple would typically only be found to be at risk for one heritable condition. However, MSAC noted that ERCT cannot identify the risk of a *de novo* variant resulting in an affected child being born to a couple reported to be low risk for that condition, hence the result is described as "low risk" rather than no risk.

MSAC noted the large scope of the proposed genetic testing, with more than 1000 genes proposed to be included on the larger panel test option, but that most of the conditions associated with these genes are very rare, and questioned if there was sufficient data on the phenotypic severity and penetrance for all of the conditions. MSAC considered that the conditions associated with the genes on the panel vary substantially in severity. MSAC was concerned that some conditions may be mild, and may not be widely perceived to warrant considering terminating a fetus with that condition. MSAC also considered that penetrance varies within and

¹ The ADAR's smaller gene panel contained 410 genes, and in its pre-ESC response the applicant advised the *ELP1* gene had been omitted in error so the revised smaller panel contained 411 genes.

between the conditions, and may not be known for some conditions. MSAC considered that given this variation in severity and penetrance, insufficient evidence had been provided to demonstrate that it would be acceptable ethically and to society to include each of the approximately 1006 unique conditions (and sub-types of conditions) associated with the 1034 genes proposed for the larger panel. MSAC recognised that this would require a substantial body of evidence for the conditions associated with pathogenic variants in the 1034 nominated genes, and considered that it may be simpler to make a case for the acceptability of testing for a smaller number of unequivocally very severe conditions. MSAC was concerned that couples may find it difficult to make a reproductive decision based on the information available for some of the conditions, especially if a prenatal diagnosis (PND) is made. MSAC also considered that the true burden and quality of life were uncertain for many of the panel conditions. In addition, some of the conditions have publicly funded treatments available, although MSAC acknowledged that access to some of these treatments was in part dependent on the accurate diagnosis of the condition. Consequently some treatments have uncertain effectiveness for all affected individuals. MSAC noted that the ERCT panel includes the conditions that are tested for in newborn bloodspot screening programs, which have significant impacts on child health. MSAC noted that the conditions proposed for inclusion were based on a published decision framework, and also that the Mackenzie's Mission gene panel is now listed in PanelApp Australia. However, MSAC considered that the ethical implications around testing for each of these conditions are not yet sufficiently addressed in the application to support public funding. It considered that more consumer consultation was needed, including consumer groups representing people living with the conditions being tested for, to gain better understanding of where the general public, or those individuals living with one of the non-fatal conditions, stands on the issue of ERCT for the conditions that are proposed to be included.

MSAC considered the applicant-developed assessment report (ADAR) did not sufficiently explore the ethical implications of the proposed reproductive carrier testing, which it considered to be a substantial omission given the significance of the ethical issues. MSAC considered that the proposed testing needs to be perceived by the community to be ethically acceptable, and advised that broader public engagement would be required to ensure that large-scale and widespread reproductive carrier testing as a whole is societally and ethically acceptable. MSAC considered that widespread use of ERCT may have potential implications for the genetics of our society over time, as pathogenic variants are progressively removed over generations. MSAC also considered that existing reproductive partner testing following the identification of a proband would already permit equivalent reproductive decision-making to the testing proposed here, and advised that the ethical framework of ERCT needs to be contextualised in relation to all reproductive partner testing that is already supported for public funding.

MSAC considered that ERCT has the risk of being interpreted as commoditising the value of human life and that couples may feel pressured to use the investigation to reduce society's healthcare costs. MSAC also considered that couples identified as being at increased risk may also be unsure of the implications of having a recessive variant for their own health, and considered that counselling would need to clearly explain the lack of health implications of being a carrier of a recessive variant, assuming this to be the case. MSAC advised that, if such testing were to be publicly funded, it would be important to ensure that patient education and counselling are supportive of patient autonomy, confidentiality, and equity of access. MSAC considered that the applicant's proposal to also support an online modality of the educational consent process was appropriate.

MSAC noted the two proposed clinical management algorithms: one for preconception testing and one for prenatal testing. MSAC noted the eligible population for preconception testing would be all couples planning pregnancy in their reproductive years, with first-time couples being a particular focus (approximately 178,000 each year).

MSAC considered the comparator of reproductive carrier testing for CF, SMA and FXS (supported under application 1573) to be appropriate, though noted reproductive carrier testing is also already publicly funded for some conditions as a follow-on to testing patients with signs and/or symptoms of disease and the consequent cascade testing of their relatives. MSAC noted that the panel is proposed to replace reproductive carrier testing for CF/SMA/FXS.

MSAC noted the main source of evidence was the Mackenzie's Mission trial, a project funded by the Medical Research Future Fund (MRFF). The trial is not yet complete, so the ADAR included analysis of interim data. The trial has reviewed data from 5,820 couples (70% of the target population), with 120 couples identified as being at increased risk thus far. MSAC acknowledged the pre-MSAC response stated that although the results are interim, final results are not likely to change substantially. MSAC noted that the commentary was unable to independently verify the data, and assess the risk of bias and conclusions from this trial as reported in the ADAR.

MSAC noted the heterogeneity in interventions across the included studies, inconsistencies reporting genes/conditions across studies, paucity of comparative evidence, and the lack of evidence (or limited evidence) for the comparator for some of the outcomes (e.g. diagnostic test accuracy, safety), small sample sizes for some of the outcomes (e.g. clinical utility, safety), and issues with the use of non-validated measures in safety studies.

MSAC noted the lack of evidence for safety in the studies, but noted that the literature suggests any psychological burden associated with genetic testing rarely reached clinically relevant levels and that any harms that were experienced had generally dissipated by 6 months post-test. MSAC agreed with ESC that false positives and false negatives are likely rare (NGS testing is highly sensitive and specific, with >99% specificity), but noted the ADAR did not address potential medico-legal implications of patients receiving false positive or false negative results. MSAC considered that there is always a risk of *de novo* mutations, and hence there is a risk that ERCT offers false assurance that the offspring will not be affected by a rare genetic condition.

MSAC also noted that Aboriginal and Torres Strait Islander peoples and other ethnicities are typically under-represented in genomic databases informing genotype-phenotype relationships. MSAC considered that this creates uncertainty in the generalisability of the clinical validity of ERCT, as use of databases to assign pathogenicity to the variants found may not accurately predict individual disease risk for populations under-represented in genomic databases. MSAC noted the pre-MSAC response, which stated that there has been "*considerable population admixture over the past 200+ years, with the result that known disease-associated variants that have arisen in other populations may be identified in Aboriginal or Torres Strait Islander people who undergo screening*" and that "*such variants ... can be reported in people from any population with a high degree of confidence regarding their clinical significance*". MSAC considered that although the pre-MSAC response proposed not reporting variants of uncertain significance (VUSs), the proposed services would detect VUSs that are present in Australians on a population scale, and so advised it would be appropriate for a registry of results to be managed as part of the implementation of the proposed testing to improve curation of VUSs in under-represented Australian populations over time. MSAC considered that while reporting to patients could include VUSs, it was important to consider the potential harm in that reporting VUSs could create a diagnostic odyssey for people who otherwise would not have experienced additional healthcare, costs of that healthcare, and additional uncertainty.

MSAC noted that the diagnostic yield of couples identified as being at increased risk of having a child with an AR or XL condition was estimated to be 1.6% for large panel testing (1,034 genes) and 0.4% for the comparator (3 genes).

MSAC noted that the economic evaluation was a cost-effectiveness analysis, which was appropriate. However, the transition probabilities were derived from incomplete unpublished

data from the Mackenzie's Mission trial as the sole data source. MSAC noted the incremental cost-effectiveness ratios (ICERs), including lifetime healthcare costs, indicated dominant cost-effectiveness for both the 1034-gene and 411-gene panels, for both pre-conception and pre-natal testing. MSAC noted that the major drivers of the economic model were the weighted lifetime healthcare cost in the CF/SMA/FXS low-risk arm, the lifetime costs associated with the conditions on the 1034-gene panel, and the probability of affected births in the CF/SMA/FXS low-risk arm.

MSAC noted that for other conditions where treatments have been developed (such as Fabry's disease), the reported incidence has increased over time as patients with less severe disease are identified. MSAC considered that the economic evaluation naively assumed that there would be no reduction in the threshold for severe disease over time. For individuals with mild disease or even no disease manifestation, the clinical benefit of treatments may be reduced or in some cases not beneficial at all. MSAC considered that while the threshold of severe disease reducing over time would result in incidence increasing, there would also be decreasing incidence over time if couples choose to avoid having children with the conditions associated with the genes on the panel. In addition, when increasing detection of less severe cases, MSAC considered it was likely inaccurate that the more conditions detected, the more cost-effective the testing is. MSAC also considered that the potential cost-offsets would occur in the future, increasing the inherent uncertainty that they would be realised. MSAC also noted that the economic evaluation did not include probabilistic sensitivity analyses, which would have been useful for decision-making. MSAC considered that the cost of pregnancy termination was likely underestimated, as it only considered costs to the MBS. MSAC noted the impact of false negatives and false positives in the PND arm were not included in the sensitivity analyses.

MSAC noted the additional cost breakdown provided in the pre-MSAC response, however considered the fee remained too high without sufficient justification. MSAC also considered that the 411-gene panel costs were not sufficiently justified (proposed as \$940.00). MSAC noted the utilisation estimates and estimated uptake rates, and considered that there was substantial uncertainty in the number of services that would be provided.

MSAC noted the upfront financial cost to the MBS of providing this testing, and that the cost-offsets to the PBS and State/Territory hospitals were estimated to also be relatively high. MSAC noted that although the ADAR stated pregnancy terminations would increase, this cost was not included in the utilisation and cost model. MSAC noted updates to the financial analyses to correct transcription errors, and also considered that the financial analyses had not included the offset cost of carrier testing for CF/SMA/FXS, though this is proposed to be replaced by ERCT. MSAC noted that when the cost-offsets of the Commentary's estimated numbers of replaced CF/SMA/FXS tests are included, the financial impact to the MBS ranges from \$42 million in year 1 to \$203 million in year 6, which MSAC considered to represent a very high upfront cost to the MBS to provide this testing. MSAC noted that cost-offsets to the PBS and State/Territory hospitals resulted in an overall estimated cost across the healthcare system as a whole ranging from \$16 million in year 1 to \$22 million in year 6, though also considered that the overall costs to the healthcare system were uncertain, and could be improved through taking into account the current actual uptake of PBS, MBS and other costs that are likely to be avoided. MSAC considered that the financial assessment included multiple under- and overestimates of testing-associated costs and services, and some assumptions were not justified, such as the assumption that 100% of genetic counselling would be funded by the States and Territories with none funded by the MBS. MSAC further considered the cost-offsets from lifetime healthcare costs averted may have been overestimated, because although the interim data suggest that couples will act on this information (i.e. through pre-implantation genetic diagnosis, PND + termination, adoption), there was likely a selection bias in Mackenzie's Mission for higher socioeconomic couples. Overall,

MSAC considered the financial impact to be very high and uncertain, mainly due to uncertainty around the expected uptake and lifetime healthcare costs.

MSAC noted that the proposed large-scale ERCT was similar in scope to a population screening program and therefore irrespective of the ultimate funding mechanism would benefit from having elements that are typically required for a screening program: in particular, the proposed testing should be implemented with a registry of participants and their outcomes, and would require an expert advisory panel, including consumer representation, to continue to oversee the appropriate composition of the gene panel in order to provide transparent oversight. In addition, MSAC noted that irrespective of the implementation approach, the proposed testing will require substantial technology and workforce expansion to implement widespread nationwide testing, with multiple potential implementation issues, including:

- a culturally appropriate approach for Aboriginal and Torres Strait Islander communities
- the need for confirmatory testing for some variants
- the long-term (years to decades) storage and transfer of genomic data.

MSAC noted the applicant had proposed in application 1637 that ERCT be funded through listing on the MBS rather than as a screening program, and that in relation to application 1573 MSAC had noted *“the Chief Medical Officer’s advice that this testing is unlikely to meet the requirements for a population-based screening program”* (1573 Public Summary Document (PSD), page 23). MSAC recalled its advice on application 1573 that *“the application was not for funding of a population-based screening program, but represented reproductive carrier testing as a type of opportunistic testing (meaning, in a medical practitioner’s opinion, the patient’s circumstances clinically warranted the performance of the test)”*, and so it had considered it appropriate to fund the reproductive carrier testing supported under 1573 via the MBS (1573 PSD, page 3). MSAC considered that while the reproductive carrier testing previously supported under application 1573 will be publicly funded through listing on the MBS from 1 November 2023, and although its previous advice that reproductive carrier testing can be considered opportunistic testing may also apply to the ERCT proposed in application 1637, the ERCT proposed in application 1637 represents a substantial increase in the scale of testing (from three conditions to more than 1000). As such, MSAC advised it would be necessary to consider the establishment of certain additional elements that are typically found in screening programs alongside public funding for these services. MSAC therefore questioned the appropriate mechanism to fund and implement large-scale and widespread reproductive carrier testing that would require substantial infrastructure and oversight, given MBS listing does not require programmatic infrastructure. MSAC also noted that Australia’s other screening programs had been implemented on the back of large randomised controlled trials that demonstrated screening confers an advantage from the perspective of the patient, and considered it to be unclear whether equivalent evidence had been provided as part of this application. In anticipation of a re-application, MSAC requested the Department investigate the appropriateness of funding ERCT as a screening program.

MSAC considered that any re-application should include:

- in-depth ethical examination of the appropriateness and societal acceptability of large-scale and widespread reproductive carrier testing
- more ethical consideration and consumer engagement on the societal acceptability of each of the conditions associated with genes proposed to be included in ERCT
- improved description of the clinical impact and treatment for key conditions that could be anticipatorily avoided through the use of ERCT
- consideration of Department advice on the proposed funding mechanism for ERCT

- the feasibility of establishing a registry of participants of their test and pregnancy outcomes
- an outline of the proposed structure and function of a governancy body that would be created to provide transparent oversight of the testing, including changes to the gene list over time
- a description of systems to store and share genomic data among laboratories, especially for future re-use upon recoupling (item BBBB)
- clarification of the proposed requestors for ERCT
- consideration of the proposed healthcare practitioners to deliver pre- and post-test counselling, particularly post-test counselling for couples identified as being at increased risk
- consideration of proposing a smaller, more targeted gene panel, and addressing the issues of disease severity and threshold of penetrance for panel inclusion
- an outline for a quality assurance program (QAP)
- culturally sensitive approaches, including for Aboriginal and Torres Strait Islander people
- how couples from remote and/or rural areas could access the testing and appropriate counselling
- current actual and estimated MBS, PBS, and other costs that are likely to be avoided and (if relevant) estimated increases to these costs, to provide greater confidence of estimated offsets and total net cost
- better fee justification.

MSAC considered that there were further uncertainties that would need to be resolved as part of its consideration of a future re-application, such as the appropriate panel size and composition, the potential for patient-collected samples, the appropriate frequency of testing, and appropriate gestational limits.

MSAC advised that this application provided insufficient evidence for it to support public funding for the proposed testing, though it would welcome a future re-application addressing its concerns.

4. Background

This is the first application for ERCT for determining joint carrier status of selected serious AR and XL genetic conditions. In July 2020, the MSAC supported public funding of application 1573 for three-disease reproductive carrier testing to detect carriers of cystic fibrosis (CF), fragile X syndrome (FXS) and spinal muscular atrophy (SMA). MBS items for the three-condition panel at the time of drafting this ADAR were as per the 1573 PSD. The Commonwealth Government has since announced the supported testing will become available from 1 November 2023².

The ADAR stated that publicly funded reproductive carrier tests are available, however, these are itemised on the MBS only for a small number of specific conditions. The relevant MBS item numbers already implemented include:

- MBS item 73347: Testing of both parents for carrier status of *CFTR* variants, based on an affected fetus.
- MBS item 73349: Testing of a prospective parent for carrier status of *CFTR* variants, when carrier status has been established in the patient's reproductive partner.

The ADAR also included as relevant, MBS items that include not only reproductive carrier testing, but also affected individual testing, fetal testing and cascade testing, and also referred to MBS

² <https://www.health.gov.au/sites/default/files/documents/2022/03/budget-2022-23-portfolio-budget-statements.pdf>

items 73345, 73346 and 73348. The ADAR grouped these MBS items as reproductive carrier testing MBS items.

Further reproductive partner testing has also been supported by MSAC in relation to other diseases, though at the time the ADAR was finalised were yet to be implemented. Aside from reproductive carrier testing supported under 1573, examples of supported reproductive partner testing include:

- 1598: Testing the reproductive partner of a known carrier of a recessive pathogenic or likely pathogenic (P/LP) variant in a gene related to heritable cardiac arrhythmias or channelopathies (listed as MBS item 73418 from 1 July 2022).
- 1599 CCCC: Testing the reproductive partner of a known carrier of a recessive P/LP variant related to heritable cardiomyopathies (listed as MBS item 73394 from 1 July 2022).
- 1600 DDDD: Testing the reproductive partner of a known carrier of a recessive pathogenic variant in a gene related to heritable kidney disease (listed as MBS item 73405 from 1 July 2022).
- 1585 EEEE: Testing the reproductive partner of a known carrier of a recessive pathogenic germline variant in a gene related to a neuromuscular disorder that was detected using a panel test (to be MBS listed from 1 November 2022).

5. Prerequisites to implementation of any funding advice

Advice from the National Pathology Accreditation Advisory Council (NPAAC) highlighted several implementation issues. Firstly, no specific QAP for large reproductive carrier screening panels in Australia or internationally. Secondly, testing at scale would require significant capital costs, and testing may therefore remain limited to a small number of laboratories. Depending on the uptake of the service, this may possibly signify access issues.

6. Proposal for public funding

The applicant proposed the intervention would be offered by different healthcare providers, including general practitioners, obstetricians, midwives, nurses, fertility specialists, and genetics health professionals. As part of a healthcare interaction in preconception or early pregnancy care, the healthcare provider would offer the intervention with pre- and post-test counselling, obtain standard clinical consent, and collect a sample (or advise on how to complete sample collection).

The Ratified PICO noted that “should the requestors for application 1637 be expanded beyond medical practitioners, a justification would need to be provided for each additional requestor type proposed”. The Commentary noted this was not addressed in the ADAR.

The test results would be communicated to the couple as a “low risk” or “increased risk” of having a child affected by one or more of the conditions tested for; this differs from the comparator, under which testing of a second partner is assumed to only occur in the case that the first partner is found to be a carrier of one of the two AR conditions (CF or SMA). The comparator also involves the reporting of results on an individual basis. The treating clinician then needs to determine the potential risk for the couple based on those individual-level results.

The applicant proposed ERCT be publicly funded through the MBS. The post-PASC proposed item descriptors are presented in Table 1.

Where appropriate, the health technology is proposed as a replacement for an existing test (reproductive carrier testing for cystic fibrosis, spinal muscular atrophy and fragile X syndrome, supported by MSAC under application 1573 but not yet implemented), noting some differences

between tests: the previously supported testing consists of sequential testing of a second partner in case the first partner is found to be a carrier of an AR variant, and reports the results on an individual basis, whereas the proposed test is carried out usually simultaneously on both partners, and results are presented for the couple as a whole, and not on an individual basis. The proposed ERCT also tests for carrier status in a far greater number of diseases, and proposes to only report where both partners are carriers for the same disease and therefore at risk of having an affected child, rather than the reporting of 1573 where both positive and negative carrier results would be communicated. The technology would not replace all usage of the existing test, e.g., individuals would not be eligible for the proposed technology but would be able to access testing supported under 1573.

Pre-test counselling should be available to assist in facilitating the standard clinical consent for testing and post-test counselling to deliver and interpret the results. Couples would be required to provide standard clinical consent that they understand how couple testing works, that carrier status for individual genes beyond any for which the couple is found to be at increased risk would not be provided, and that not all increased risk couples can be identified by testing.

Table 1 Proposed new item descriptors for ERCT

Category 6 (Pathology Services) – Group P7 Genetics
<p>MBS item AAAA</p> <p>Prenatal or preconception carrier testing of a reproductive couple where neither genetic contributor has previously received a service to which AAAA or BBBB applies, using characterisation via genomic sequencing and analysis, of germline variants known to cause autosomal recessive and X-linked disorders, reporting the couple's joint risk.</p> <p>Applicable for an individual, only when used in conjunction with the same item performed in a reproductive partner.</p> <p>Available to any reproductive <u>couple pairing</u> only once per reproductive lifetime.</p>
<p>Fee: \$1,050.00 Benefit: 75% = \$787.50 85% = \$962.10</p> <p>Smaller panel Fee: \$940.00 Benefit: 75% = \$705.00 85% = \$852.10</p>
Category 6 (Pathology Services) – Group P7 Genetics
<p>MBS item BBBB</p> <p>Prenatal or preconception carrier testing of a reproductive couple where one or both genetic contributors have previously received a service to which AAAA or BBBB applies and re-use of the data is possible, using characterisation via genomic sequencing and analysis for any genetic contributor who has not previously received a service to which AAAA or BBBB applies, of germline variants known to cause autosomal recessive and X-linked disorders, reporting the couple's joint risk.</p> <p>Applicable for any reproductive <u>couple pairing</u> only once per lifetime.</p>
<p>Fee: \$720.00 Benefit: 75% = \$540.00 85% = \$632.10</p>
Category 6 (Pathology Services) – Group P7 Genetics
<p>MBS item EEEE</p> <p>Testing of a pregnant patient, where both prospective parents are known to be genetic carriers of variants for the same autosomal recessive disorder, or the woman is a carrier of an X-linked disorder, as part of services to which AAAA or BBBB apply (with the exception of the <i>CFTR</i> gene), for the purpose of determining whether pathogenic or likely pathogenic variants are present in the fetus, when requested by a specialist or consultant physician who manages the treatment of the patient.</p> <p>The fetus must be at 25% or more risk of a disorder because of known familial variants.</p> <p>1 test per fetus</p>
<p>Fee: \$1,600.00 1,100 Benefit: 75% = \$1,200.00 825 85% = \$1,512.10 1,012.10</p>

Category 6 (Pathology Services) – Group P7 Genetics

MBS item FFFF

Testing of an individual for an autosomal recessive or X-linked disorder, where:

- a) the biological parents are known (as part of services to which AAAA or BBBB apply) to be:
 - I. both genetic carriers of variants for the same autosomal recessive disorder; or
 - II. one parent is a carrier of an X-linked disorder; and
- b) the individual is of an age that is expected to be pre-symptomatic for the autosomal recessive or X-linked disorder

for the purpose of determining whether familial pathogenic or likely pathogenic variants in the relevant gene are present in the individual, when requested by a specialist or consultant physician who manages the treatment of the individual.

1 test per gene per lifetime

Fee: \$500.00 Benefit: 75% = \$375 85% = \$425

Source: Commentary Executive Summary, Table 1

Where relevant, the out-of-hospital (85%) benefit rates reflect the 1 November 2021 Greatest Permissible Gap (GPG) of \$87.90. All out-of-hospital Medicare services that have an MBS fee of \$586.20 or more will attract a benefit that is greater than 85% of the MBS fee – being the schedule fee less the GPG amount. The GPG amount is indexed annually on 1 November in line with the Consumer Price Index (CPI) (June quarter).

The Commentary stated the MBS descriptors used in the ADAR are largely consistent with the post-PASC item descriptors in the PICO, except for a post-ratification change to EEEE that was made based on the applicant's advice, revising the risk criterion to "The fetus must be at 25% or more risk of a disorder, or the maternal donor has greater than or equal to 55 CGG repeats in *FMR1*".

The proposed item descriptors were reworked during the PASC process, as detailed in the PICO. In brief, item CCCC (re-analysis for characterisation of previously unreported germline gene variants) was considered redundant and removed as the incremental change in composition of the gene panel is likely to be insignificant. Item DDDD (re-testing) was also removed. As detailed in the ratified PICO, PASC initially agreed that Item AAAA could be re-drafted to also allow re-testing otherwise provided under Item DDDD. However, the restriction of testing under Item AAAA to "once per lifetime" was considered mutually exclusive with re-testing, and as such PASC opted to forgo support for re-testing.

The Commentary found two discrepancies in the fees associated with the MBS items presented in the PICO Confirmation (Corrigendum Version) compared to the fees presented in the ADAR. The 85% benefit for MBS item AAAA in the PICO Confirmation does not account for the Greatest Permissible Gap (GPG) and should be \$962.10. This fee has been used throughout the ADAR for the 1034 gene panel. There is also an inconsistency with the fee for MBS item EEEE. The fee in the PICO Confirmation (Corrigendum Version) and this Executive Summary is \$1,600. However, in Section 1.1, this fee has been reduced to \$1,100, and in Section 1.8. the fee has a value of \$1,110. For the purposes of this Commentary, the fee will be assumed to be \$1,100. This has been noted in this Commentary, however the impact of the inconsistent MBS item EEEE fee is minimal to the overall economic evaluation.

7. Population

One PICO set was presented, defining the population as asymptomatic couples of reproductive age (or genetic contributors to a pregnancy) who are planning to become pregnant or in the early stages of pregnancy.

The Commentary considered that the ADAR addresses the requirements of the population description in the confirmed PICO, e.g. the use of gender-neutral language in the MBS item descriptors.

8. Comparator

The comparator is reproductive carrier testing for CF, SMA and FXS.

In July 2020, MSAC supported public funding for reproductive carrier testing for three conditions, CF, SMA and FXS (MSAC application 1573); however, this medical service is not currently available through the MBS. MBS items were not yet implemented at the time of drafting the ADAR.

In the absence of the testing supported under MSAC application 1573, individuals most commonly proceed through the reproductive process without genetic carrier testing for AR or XL conditions. In some instances, genetic carrier testing is conducted in reproductive partners via other MBS items listed above (e.g., MBS items 73347 and 73349) or on a user-pays basis.

The current standard of care (i.e., usual practice without any genetic carrier testing) was also considered.

The Commentary considered that the post-PASC comparator, reproductive carrier testing for CF, SMA and FXS, is appropriate.

The Commentary stated that in response to PASC's suggestion that the applicant review MSAC Application 1671 and present a rationale whether 1671 may be an additional comparator, the applicant responded that given the prerequisite of a >10% risk of being a heterozygous genetic carrier for a condition in 1671, it is likely that 1637 could be used instead of 1671. While this argument seems reasonable, it remains unclear whether and to what extent MSAC Application 1637 could replace 1671 if MSAC supports both applications. It is unclear whether any genes proposed for the 1671 panel would be incremental to those tested under the 1034 or 410 gene panels: most genes in the 1671 panel (according to its PICO) are also included in 1637, except the genes *ELP1* and *GBA* are not included in the gene lists for the 1034 or 410 gene panel provided by the applicant as part of the 1637 ADAR. In the pre-ESC response the applicant clarified that *ELP1* was omitted from both proposed panels in error, though *MPZ* had been included in the 1034 gene panel in error – and stated the correction to 1034 gene and 411 gene panels has minimal impact. The Commentary additionally noted there is a difference in the populations of each application, as the population in MSAC application 1671 includes individuals not necessarily planning pregnancy but at high risk, while MSAC application 1637 includes a general population planning pregnancy or already pregnant.

9. Summary of public consultation input

Prior to consideration by PASC in August 2021, the Department received responses to the consultation survey from three patient/consumer support groups, all of which supported the application. None of the three groups identified any concerns, and they all emphasised the need for appropriate informed consent and counselling.

After PASC, further consultation feedback was received from three individuals (a GP and two carriers/caregivers) and nine organisations:

- Australian Pathology (AP)
- Childhood Dementia Initiative (CDI)

- Fragile X Association of Australia (FXAA)
- Genetic Undiagnosed and Rare Disease (GUARD) Collaborative Australia
- Haemophilia Foundation Australia (HFA)
- Mito Foundation
- Public Pathology Australia (PPA)
- The Royal Australian College of General Practitioners (RACGP)
- The Royal College of Pathologists of Australasia (RCPA)

All nine organisations and three individuals were supportive of the proposed testing.

Advantages of the proposed expanded reproductive carrier testing were:

- It would inform prospective parents who want to know their risk of having offspring with a severe recessive condition, enabling them to make informed reproductive decisions with consequent ability to avoid/minimise associated disease in offspring, including allowing earlier diagnosis of affected babies born to at-risk couples. It would allow a wider range of informed decision-making options.
- It would reduce the financial burden to public health and increase equitable access.
- It represents a major step in reducing the burden of severe genetic disorders in children and would reduce impact on the family including grief from losing an affected child.
- It would identify more affected individuals than the long-established antenatal screening programs for chromosome disorders, which identify only a small proportion of the severe genetic disorders that affect children.
- A non-fixed gene list will allow response to improving knowledge of relevant variants. A nimble yet robust review process with community and consumer engagement is needed.
- It makes sense to restrict initial testing to once per lifetime, with separate items for initial testing and for re-interpretation upon re-partnering, which should be covered.
- Testing existing children of increased risk couples may allow earlier diagnosis and treatment. The fee should be commensurate with similar items (e.g. 73361, at \$400).

Disadvantages of the proposed expanded reproductive carrier testing were:

- The proposed testing will require adequate counselling pre- and post-testing, though there is a lack of funding for genetic counselling in the private sector. Increasing demand for counselling will be a challenge for implementation but should not be a barrier. General practitioners and obstetricians, including rural and remote providers, will need to be up-skilled appropriately for both pre-and post-test counselling.
- It will be hard to ensure consistency of ERCT between providers in the absence of a gene list referred to or identified within the item descriptor.
- The proposed testing would exclude individuals from the opportunity to have the test.
- Males also need to be tested for X-linked conditions (e.g. FXS), as they can pass them on.
- If already pregnant, results may need to be provided sooner than 4 weeks.
- New genes are described at a rate of several dozen per month, however, most if not all of these are associated with very rare conditions. Re-analysis of previously tested couples for new genes will therefore probably not result in a high yield or a favourable cost-benefit ratio as most common recessive and X-linked conditions are already included.
- There will also be logistical and commercial challenges: labs will sometimes receive requests, perform the analysis, and only then discover that the individual has been previously tested, and so the MBS item for initial testing has already been used and extinguished.
- Storage and transfer of genomic data for years/decades is not catered for at present. NPAAC retention requirements refer to 10 years for VCF but only 4 years for FASTQ/BAM. How will one examine 'older' sequence data for 'newer' genetic variants (e.g. CNVs, STRs)

if the FASTQ/BAM file is no longer available? It may be necessary to request NPAAC revisit retention times.

- Transfer of genomic data between laboratories is not catered for well at present. The patient might request reanalysis/updated interpretation at a different pathology practice to the one that performed the original analysis. It's complicated to obtain consent for release of genomic information, and then clumsy to release via one of a range of modalities, which varies with the request. There are difficulties now while referral of genomic testing between labs is still uncommon, though for 50k cases p.a. it will be a challenge.
- The interpretation of "low risk" for certain genetic conditions in ERCT becomes more complex should there be an existing affected family member. Given the nuance required in interpretation in this situation, should ERCT only be made available when requested by clinical geneticists or specialists with experience in genetics?
- Restricting requestors to specialists is unrealistic considering the population scale of the proposed testing, and would likely jeopardise the health benefits of the approach by restricting access. Delivery through a range of health care professionals, including GPs, that have had appropriate training and access to information material, is certainly the preferred option. It is important to note that for high-risk couples appropriate genetic counselling by a suitably skilled professional, such as a genetic counsellor, must be available and should include the meaning of test results and the uncertainty of phenotype/genotype correlations. This should be included as part of the service.

Other comments raised regarding the proposed expanded reproductive carrier testing were:

- Inclusion of patient satisfaction surveys would inform uptake of the service.
- If coupled with cascade testing, could trigger targeted testing to diagnose relatives.
- If the genes proposed in 1671 are fully covered under the gene list for 1637, then the intention of both approaches may be covered in one item.
- Couples that have had ERCT should be excluded from subsequently having the three-condition testing supported under application 1573.
- Appropriate information would need to be available for GPs to provide to patients to make informed decisions.
- The term "carrier testing" will have to be considered, as individual carrier results are not reported under this test. "Couple reproductive genetic risk" might be more appropriate.

Consultation feedback also included proposals for management of the gene list. The RCPA stated that ideally, testing would use a minimum consensus gene list that is created and updated on a regular basis (e.g. every 6 or 12 months), perhaps as part of a more dynamic genetic test registry such as the one used in the UK by the NHS. However, while this would be highly desirable, the appropriate body to provide oversight is unclear. The minimum gene list could not be overseen by the existing applicant committee, but would have to be overseen by MSAC and/or the RCPA. In lieu of that solution, a fixed minimum gene list resembling likely based on the one used by the applicant (i.e. around 1,000 genes) should be implemented. Having an undefined and changeable gene panel is undesirable (as it will make both funding eligibility and compliance difficult). But specifying the genes in the item descriptor is also undesirable (as it will be hard to update). A better approach would be to specify that testing must utilise a gene panel of "X% diagnostic sensitivity in the Australian population". The RCPA stated that if this line of reasoning were accepted, X% could be set at (e.g.) 90%, or 95%, or 99% of what is theoretically possible. That would immediately generate a minimum number of genes that needed to be included in testing to be eligible for the MBS item, without needing to specify exactly which genes. Similarly, PPA proposed the gene list be replaced by a cut-off, e.g. at least 500 or 1000 genes with a carrier prevalence of >0.1% or ACMG tier 4 genes.

10. Characteristics of the evidence base

The ADAR adopted a direct evidence approach to assess the proposed medical intervention with the comparator.

The Commentary noted the presented evidence consisted of provisional data from an ongoing trial of the proposed intervention testing panel, the Australian Reproductive Genetic Carrier Screening Project (also known as “Mackenzie’s Mission” trial) as well as from a systematic review of literature.

To date, 5,820 couples have undergone expanded reproductive carrier testing (excluding couples who had known positive carrier results previously), but the trial has not completed data collection or published any preliminary results. Interim analyses of the trial have been conducted specifically for the ADAR. The results from this trial should be directly relevant to the ADAR as the trial intervention is the same gene/condition list as the proposed intervention in the ADAR, and fully applicable to the Australian context.

The Commentary was unable to access raw unredacted data from the trial, therefore, results and interpretation of the trial data as presented in the ADAR could not be independently reviewed for the Commentary.

A systematic review of evidence was conducted to identify additional evidence on the test accuracy, clinical utility, and safety of expanded reproductive carrier testing of couples for joint carrier status. A total of 37 studies met the inclusion criteria. Key features of the included evidence are summarised in Table 2.

The methodology of the systematic review and reporting of the results were appropriate.

The presence of a risk of bias was detected across all outcomes of interest, with safety outcomes considered at high risk of bias.

The Commentary noted the ADAR did not provide many details on the risk of bias assessment of individual studies. The Commentary identified some issues in the risk-of-bias assessment methodology (e.g., making overall risk of bias ratings when using tools without established overall risk rating or not following the guidance for overall risk rating).

In general, it may be concluded that the evidence for all outcomes was at risk of bias due to the following issues:

- Heterogeneity in interventions tested across studies
- Inconsistencies in reporting of genes/conditions across studies
- Paucity of comparative evidence, lack of evidence (or limited evidence) for the comparator for some of the outcomes (e.g., diagnostic test accuracy, safety)
- Small sample sizes for some of the outcomes (e.g., clinical utility, safety)
- Issues with the use of non-validated measures in safety studies.

Applicability issues were also detected, due to the difference between proposed intervention and interventions tested across studies (number of genes/conditions tested for within the panels) and relatively high socio-economic status of the tested population.

The risk of bias and applicability issues were appropriately discussed throughout the ADAR. The general conclusion is that the evidence presented was at risk of bias for all studied outcomes.

Table 2 Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Test accuracy	1 longitudinal cohort (Mackenzie's Mission) reporting on diagnostic yield, proportion of pregnancies in high-risk couples who underwent CVS/ amniocentesis and were found to be affected by the identified high-risk variant(s) <u>Systematic review:</u> 6 studies reporting diagnostic accuracy 22 studies reporting diagnostic yield 3 studies reporting on the proportion of pregnancies in high-risk couples who underwent CVS/ amniocentesis and were found to be affected by the identified high-risk variant(s)	Mackenzie's Mission: n=5,820 couples <u>Systematic review:</u> Comparative evidence: k=2 Intervention only: k=22 Comparator only: k=1	At risk of bias
Clinical utility	1 longitudinal cohort (Mackenzie's Mission) reporting on reproductive outcomes from at-risk couples' first pregnancy at (pregnant couples) or after (preconception testing) results disclosure <u>Systematic review:</u> 8 studies (7 quantitative, 1 qualitative) reporting on reproductive outcomes of couples at increased risk at (pregnant couples) or after (preconception testing) results disclosure	Mackenzie's Mission: n=120 couples at increased risk <u>Systematic review:</u> Comparative evidence: k=0 Intervention only: k=7 Comparator only: k=1	At risk of bias
Safety	<u>Systematic review:</u> 12 studies reporting psychological harms from positive test results (anxiety, stress and distress, depression and ability to cope, perception of health, fear of stigmatisation, decisional conflict and regret) (No evidence identified for downstream safety outcomes)	Comparative evidence: k=0 Intervention only: k=11 Comparator only: k=1	At risk of bias

CVS=chorionic villus sampling; k=number of studies, n=number of patients
Source: Commentary Executive Summary, Table 2

11. Comparative safety

The Mackenzie's Mission study did not provide evidence for direct safety of the intervention or the comparator.

From the literature search, twelve studies were identified which reported on safety outcomes (11 reporting on the intervention; 1 on the comparator) (Beard et al., 2016; Birnie et al., 2021; Cheng et al., 2020; Clarke et al., 2018; Conijn et al., 2021; Gilmore et al., 2017; Kraft et al., 2018; Propst et al., 2018; Rothwell et al., 2017; Schuurmans et al., 2020; van Dijke et al., 2021; Zhang et al., 2021). The Commentary noted no studies compared safety of the intervention with the comparator.

The Commentary further considered that no comparative evidence was identified, and evidence for the comparator was sparse. The body of evidence was at risk of bias. Validated safety

measures were used in 25% of the studies only. Small sample size of the studies further limited the applicability of results.

Findings on psychological harms associated with the proposed test were mixed. Generally, results indicated that a) any psychological burden rarely reaches clinically relevant levels at any timepoints before, during or after carrier testing, and b) any experienced harms generally dissipate by six months post-test. The only study that examined differences between carriers and non-carriers with validated instruments did not find significant differences in anxiety after receipt of results between the two groups³.

Two studies explicitly compared the safety of expanded reproductive carrier testing with usual care (no carrier testing). No clinically or statistically significant differences in depression and anxiety were experienced in tested participants compared to those receiving standard reproductive care⁴. Those who declined expanded reproductive carrier testing (and therefore underwent usual care) had significantly higher anxiety at test offer and six months following than those who elected to receive testing⁵.

One study also reported that individuals who had higher anxiety or worry at testing offer were more likely to report higher anxiety or worry six months post-test⁶, suggesting that predispositions for a safety outcome (e.g., anxiety) likely moderate harms experienced from testing, which was also articulated in another qualitative study⁷, however this effect was inadequately explored.

The ADAR also noted that while testing for more conditions increases the chances of being identified as a carrier, proposed couple-based results disclosure reduces both the number of carrier results issued and waiting time for results relative to the sequential carrier testing approach used in the comparator.

No evidence on the downstream safety outcomes (harm from “false negatives” or “false positives”) was identified. The ADAR noted that no substantial additional safety issues were expected.

No significant harms of expanded reproductive carrier testing were encountered. The ADAR claimed that the safety of the intervention compared to the comparator was noninferior. This conclusion is likely appropriate, although it may be more fitting to consider it uncertain given the paucity of comparative evidence. Because safety has not been incorporated into the economic model, the impact of the safety clinical claim is not paramount. Importantly, no significant safety issues were identified.

³ van Dijke I, et al. (2021). Couples' experiences with expanded carrier screening: evaluation of a university hospital screening offer. *Eur J Hum Genet*, **29**(8), 1252-1258. doi:10.1038/s41431-021-00923-9

⁴ Kraft SA, et al. (2018). Patient actions and reactions after receiving negative results from expanded carrier screening. *Clinical Genetics*, **93**(5), 962-971. doi:10.1111/cge.13206

⁵ Birnie E, et al. (2021). Couple-based expanded carrier screening provided by general practitioners to couples in the Dutch general population: psychological outcomes and reproductive intentions. *Genetics in Medicine*. doi:10.1038/s41436-021-01199-6

⁶ Birnie E, et al. (2021). Couple-based expanded carrier screening provided by general practitioners to couples in the Dutch general population: psychological outcomes and reproductive intentions. *Genetics in Medicine*. doi:10.1038/s41436-021-01199-6

⁷ Conijn T, et al. (2021). Preconception expanded carrier screening: a focus group study with relatives of mucopolysaccharidosis type III patients and the general population. *Journal of Community Genetics*, **12**(3), 311-323.

12. Comparative effectiveness

Diagnostic yield

The “Mackenzie’s Mission” study results (to date) found a diagnostic yield rate of couples at increased risk for having a child with an AR or X-linked condition of 1.6% for the intervention (i.e., large panel testing 1,034 genes and ~600 conditions) and 0.4% for the comparator (testing for CF, SMA and FXS only).

Similar trends of increased diagnostic yield with increasing panel size were found across the literature. The systematic search identified direct comparative evidence showing that the diagnostic yield of expanded reproductive carrier testing was significantly higher than genetic carrier testing for CF, SMA and FXS only; these findings were supported by three additional studies comparing the intervention and a near-comparator (testing for CF and SMA).

The Commentary considered that the identified evidence was at risk of bias, mainly due to heterogeneity in interventions tested across studies, difference between proposed intervention and interventions tested across studies, and inconsistencies in reporting. Both the “Mackenzie’s Mission” trial and identified literature had issues with applicability and transitivity due to differences in testing gene panels and high socioeconomic status of the tested participants, and these were appropriately discussed in the ADAR.

No meta-analysis was performed due to heterogeneity; the Commentary considered this to be appropriate.

Diagnostic accuracy

The “Mackenzie’s Mission” trial did not provide evidence for accuracy of the intervention or the comparator. In the literature, all panels and methods of analysis for the intervention (next generation sequencing, NGS, and polymerase chain reaction, PCR) reported high analytical sensitivity (>99% across 4 panels) and specificity (>99% across 4 panels). This suggests that, while the panels tested do not represent the exact proposed intervention, the use of similar analysis techniques will also yield high test accuracy. The Commentary noted the analytical validity of NGS has been previously accepted by MSAC (in relation to application 1585).

There was a risk of bias across test accuracy studies arising from small samples and unclear sampling methods/blinding. A lack of evidence on the comparator, and the heterogeneity in the intervention limits the interpretability of results for this outcome.

No meta-analysis was performed due to heterogeneity, which the Commentary considered was appropriate.

Test accuracy – the proportion of pregnancies in high-risk couples that underwent chorionic villus sampling (CVS)/amniocentesis and tested positive to the identified high-risk pathogenic/likely pathogenic variant(s)

The Commentary noted no comparative evidence was identified.

All evidence (the “Mackenzie’s Mission” trial results for the intervention and findings from the literature) for both the intervention and the comparator found >25% of pregnancies of couples at increased risk who underwent chorionic villus sampling (CVS)/amniocentesis were identified as affected. While the affected pregnancy rate is greater than 25% (range, 31.6%-37.5% for the intervention and 26.9% for the comparator), all studies had small sample sizes and the ADAR

noted that it could be expected that with larger samples, the observed proportion would approximate 25%.

No meta-analysis was performed due to heterogeneity; this is appropriate.

Clinical utility

The Commentary noted no comparative evidence was identified.

The Commentary noted the “Mackenzie’s Mission” trial reported the following clinical utility outcomes: 45.8% of non-pregnant couples at increased risk chose to pursue preimplantation genetic diagnosis (PGT) with in vitro fertilisation (IVF). Pregnant couples at increased risk chose prenatal diagnosis (PND) in over 70% of cases. Four of six (66.7%) affected pregnancies were electively terminated and one of six (16.7%) affected pregnancies proceeded; one pregnancy was terminated for other reasons. Results for the trial are not final, which limits interpretability of results (cohort is still in follow-up). Small sample sizes for affected pregnancies across the evidence present potential issues with reliability of findings. Applicability may be limited by a higher socio-economic sample than the general population.

In the literature identified through the systematic review, many couples at increased risk took the reproductive actions of preventing affected children either through pregnancy termination for pregnant couples or IVF with PGT for preconception couples, which is consistent with previous published literature. Couples at increased risk were more likely to take preventative reproductive actions when they were carriers of more severe conditions^{8,9}.

No meta-analysis was performed due to heterogeneity; this is appropriate.

The Commentary stated that in addition to issues such as inconsistencies in reporting and heterogeneity of testing gene panels, there was evidence of a risk of bias related to the small sample size of affected pregnancies. Its magnitude is difficult to estimate. Additional bias may be related to self-selection of couples presenting for reproductive carrier testing, and high socioeconomic status of participants, biasing future reproductive choices, e.g., choice of preimplantation genetic diagnosis.

Clinical claim

The use of expanded reproductive carrier testing of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions at preconception or early pregnancy results in **superior effectiveness** compared with reproductive genetic carrier testing for cystic fibrosis, spinal muscular atrophy and fragile X syndrome based on an increased diagnostic yield.

The Commentary considered the clinical claim to be appropriate.

⁸ Ghioffi CE, et al. (2018). Clinical Utility of Expanded Carrier Screening: Reproductive Behaviors of At-Risk Couples. *J Genet Couns*, **27**(3), 616-625. doi:10.1007/s10897-017-0160-1

⁹ Johansen Taber KA, et al. (2019). Clinical utility of expanded carrier screening: results-guided actionability and outcomes. *Genet Med*, **21**(5), 1041-1048. doi:10.1038/s41436-018-0321-0

13. Economic evaluation

Overview and rationale of the economic evaluation

Based on the clinical claim of superiority in clinical effectiveness, a cost-effectiveness analysis was deemed appropriate. Considering that MSAC found the comparator (RGCT for CF, SMA and FXS) to be cost-effective¹⁰, the economic evaluation presents an incremental value of testing for additional conditions not already covered by the comparator as directed by PASC.

The Commentary agreed that due to a clinical claim of superior effectiveness and either non-inferior or uncertain safety, a cost effectiveness analysis is appropriate. This was confirmed by PASC in the Final PICO that states ‘a cost-effectiveness or cost-utility analysis is most appropriate’.

The ADAR presents cost effectiveness of two ERCT panels (large=1034 genes; small=410 genes) compared to RGCT for CF, SMA and FXS only. The Commentary noted this is in line with PASC advice to assess a range of minimum gene panel sizes.

A summary of the key characteristics of the economic evaluation is detailed in Table 3.

Table 3: Summary of the economic evaluation

Component	Description
Population	Asymptomatic couples of reproductive age (or genetic contributors to a pregnancy) who are planning to become pregnant or in the early stages of pregnancy.
Prior testing	N/A
Comparator	RGCT for CF, SMA and FXS; an additional comparator may be “no RGCT”.
Type(s) of analysis	Cost-effectiveness analysis
Outcomes	Cost per couple identified as high-risk (before offset costs) Cost per couple identified as high-risk (after estimated offset costs)
Time horizon	Lifetime
Computational method	Decision tree
Generation of the base case	Trial based and modelled
Health states	N/A
Cycle length	N/A
Transition probabilities	All transition probabilities have been taken from the Mackenzie’s Mission study
Discount rate	NA
Software	Excel and TreeAge Pro

RGCT=reproductive genetic carrier testing; CF=cystic fibrosis; FXS=fragile X syndrome; SMA=spinal muscular atrophy
Source: Commentary Executive Summary, Table 3

The Commentary conducted a systemic literature review to identify any evaluations of RGCT. The Commentary re-ran the search using the same strategy and found 2 studies from Embase, 4 from Medline and 4,702 from Scopus. The applicant’s search returned 6,133 unique results. The three key Australian studies that assisted in the development of the economic model are largely

¹⁰ Public Summary Document for MSAC Application 1573 – Reproductive carrier testing for cystic fibrosis, spinal muscular atrophy and fragile X syndrome. Available at: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1573-public>

in line with the ADAR model, however these studies only analyse the initial stages of testing, and do not consider the use of additional procedures such as IVF, termination, or CVS/amniocentesis.

Structure of economic evaluation

The model was conducted using a stepped approach. Step 1 was a trial-based analysis, where only the cost of the test and the increased risk rate were considered. All increased risks (1034 gene panel, 410 gene panel and CF/SMA/FXS-only panel) were taken from the Mackenzie's Mission study. Step 2 considered additional costs and probabilities (CVS/amniocentesis, IVF/PGT, termination and lifetime disease burden) to determine the cost effectiveness when all costs and offsets were considered. There were two models developed to estimate the cost effectiveness of preconception and pregnant carrier testing in Step 2.

The economic model consisted of four arms (1034 gene panel, 410 gene panel and CF/SMA/FXS-only panel and standard care) and followed the clinic pathway with payouts for increased risk detected. However, with the updated PICO, the outcome was cost per increased risk couple identified, without any testing strategy, no increased-risk couples could be identified. Thus, the arm of no testing was used to examine the difference in cost to pregnancy rather than cost effectiveness (after estimated offset costs).

The Commentary stated that while the ADAR suggests that the relevant comparator is no testing, MSAC 1573 is the more appropriate comparator (CF/SMA/FXS panel testing) and therefore should be considered as the main comparator, in line with PASC's advice.

The structure was such that it was assumed that while there may be very small numbers of false negative/false positives, these were not included in the structure of the model. This was deemed appropriate as the clinical utility is based on a risk profile from the testing result, and this is covered by the model structure.

Also, false test results were not incorporated into the PND arm as these are considered to have very high accuracy and including these arms would have limited impact on the overall results.

The Commentary considered it appropriate to exclude false negatives and positives in the analysis, however, testing these assumptions in a sensitivity analysis would have been beneficial for providing greater certainty.

The ADAR assumed that the level of PND and termination for other conditions would be consistent across the intervention arms and have not been added in the model.

As the key outcome is cost per identified couple only a single pregnancy per couple was included in the model, while additional pregnancies could be added it would overcomplicate the model and increase uncertainty in the results. This approach is conservative as the benefits realised in the second pregnancy are not incorporated into the model.

Model Inputs

Probabilities and population

Model transition probabilities, variables, and extrapolation

All transition probabilities were taken from the Mackenzie's Mission study. The probabilities of increased risk couple detection were calculated based on the carrier rates reported by the Mackenzie's Mission study for all panels. It was assumed that there would be no increased risk couples identified in the standard care arm.

The Commentary noted that as agreed in the PICO, all transition probabilities have been directly sourced from the Mackenzie's Mission Project. This study is ongoing, and results are not yet publicly available, however the applicant has stated that the findings are considered the most relevant direct evidence. As such, the Commentary was not able to validate or comment on the transition probabilities used in the model that have been sourced from this study.

Health outcomes

The key health outcome from the model was an affected child at birth. While the proportion of affected fetuses determined from PND of pregnant couples at increased risk in the Mackenzie's Mission study was 31.6%, it was still assumed that the probability of an increased risk couple having an affected child was 25%, as this would be the rate for diseases with AR inheritance and the Mackenzie's Mission study PND numbers were too low (n=19) to provide an accurate estimate. The probability of an affected child in the general population was based on the increased risk of the 1034 gene panel and a 25% affected birth rate.

The Commentary considered the assumption for the proportion of affected fetuses determined from PND to be appropriate given this estimate is more conservative than the proportion identified in the Mackenzie's Mission study.

To prevent an affected child, couples could choose to terminate a pregnancy post-receipt of a positive PND result. Couples could also choose to proceed with the pregnancy without further testing. For the other two panels (410 gene panel and CF/SMA/FXS-only panel), the affected birth rate for low risk couples was based on the difference between the increased risk detection in the panel of interest, and the increased risk detection in the 1034 gene panel.

Health care resources and costs

Cost of reproductive genetic carrier testing

The cost of testing for the 1034 gene panel, 410 gene panel and PND testing was based on the results reported in this ADAR. The cost for testing using the CF/SMA/FXS-only panel was based on the cost in the public summary document for MSAC application 1573. Where possible, costs associated with decisions were sourced from the MBS, PBS, and other relevant health care data. However, weighted lifetime cost for affected children were determined from multiple different sources.

The Commentary noted that PASC advised that the assessment should consider the applicant's proposed fee of \$2,100 fee per couple, which it noted may differ based on the results from the time-and-motion study. As noted in section 1.8 of the ADAR, the applicant mentions that a key deviation from the PICO is around the fees proposed for the MBS items. Due to the COVID pandemic, a time-in-motion study was not conducted, therefore, the fee for service estimates is based on staff and resource usage on sample analysis. Using this approach, the fee proposed for item AAAA is \$2,100 per couple, and item EEEE has been reduced to \$1,110.

The Commentary considered there is an inconsistency with the fee for MBS item EEEE. The fee in the PICO Confirmation (Corrigendum Version) and this Executive Summary is \$1,600. However, in Section 1.1, this fee has been reduced to \$1,100 and in Section 1.8. the fee has a value of \$1,110. For the purposes of this Commentary, the fee is assumed to be \$1,100. This has been noted in this Commentary; however, the fee discrepancies have minimal impact on the overall economic evaluation.

The Commentary noted PASC requested that the analysis examine a range of minimum gene list sizes. Therefore, the applicant has also included a gene panel of 410 genes. Whilst the applicant has suggested a fee for this panel, further justification surrounding the fee may be required.

Cost of prenatal diagnosis

A pregnant person is required to undergo either amniocentesis or CVS to obtain a sample if they choose to undergo prenatal testing. The cost of sample collection was based on the average usage from Medicare data. Based on the average cost of MBS items 16600, 16603, and 55703 the cost of sample collection to MBS was estimated as \$131.52 per person. However, there are substantial out of pocket costs associated with this procedure, with commercial institutes charging an estimated \$700.

The ADAR notes that there are substantial out of pocket costs associated with commercial institutes, identified by Sydney Ultrasound for Women. The Commentary considered that as this is a conservative estimate and given that the impact of higher fees for CVS and amniocentesis favours the comparator, this fee may be justified. However, with substantial out of pocket costs, these patients are also likely to meet the Original Medicare Safety Net (OMSN) and/or the Extended Medicare Safety Net (EMSN). For example, if the out of pocket expense is \$553.61 (\$685.31-\$131.52) as described here, then the patient has already reached 24.6% of the current EMSN (\$2,249.80). As such, the costs used in the model may be overestimated but are conservative.

The Commentary considered the model did not account for fetal mortality after CVS. In one study¹¹, the proportion of pregnancies that experience fetal mortality after CVS is 1.3%. This could be an additional complexity that may be useful to further reduce uncertainty in the model. However, it is noted that another study¹² uses this mortality rate in an economic model assessing the cost effectiveness of genetic carrier testing in an Australian population.

With regards to testing the sample, there were two items that could be used to inform cost. One item is for couples with increased risk of CF; the other is the proposed item EEEE presented in this ADAR. Based on the proportion of increased risk couples identified in the Mackenzie's Mission study, the average cost of testing was estimated to be \$1,000.53 per test. This brings the total costs of PND to \$1,101.65.

The Commentary considered that using staff and resource use sample analysis as detailed in the ADAR, the applicant proposes the fee for item EEEE be reduced to \$1,110. Therefore, the total weighted costs of PND will be \$1,006.80 if this fee is used for EEEE.

The cost of PND in the model in both scenarios is \$2,390.53. The methodology to calculate this cost uses the cost of amniocentesis, CVS, and the weighted average of sample testing. As stated in the ADAR, patients undergo either CVS or amniocentesis, and therefore by including both services the costs are double counted. Instead, the Commentary considered the cost of PND should equal the weighted average of sample retrieval for PND plus the weighted average of sample testing ($\$685.13 + \$1,000.53 = \$1,685.66$).

Cost of Termination

There are several methods available for elective termination of pregnancies, including vacuum aspiration/dilation and curettage, mifepristone & misoprostol, and dilation and evacuation (D&E). While mifepristone (&) misoprostol are used in the second trimester, they are only listed for use on the PBS for up to 63 days of pregnancy. For that reason, it is assumed that D&E would be the

¹¹ Lieu TA, et al. (1994). The cost-effectiveness of prenatal carrier screening for cystic fibrosis. *Obstet Gynecol*, **84**(6), 903-912.

¹² Norman R, et al. (2012). Cost-effectiveness of carrier screening for cystic fibrosis in Australia. *J Cyst Fibros*, **11**(4), 281-287. doi:10.1016/j.jcf.2012.02.007

item most likely to be affected by the listing of ERCT. Based on the average cost of MBS items 16530 and 16531, the cost of termination was estimated as \$625 per instance .

The Commentary noted the economic evaluation uses MBS weighted fees to determine the cost of termination, which assumes termination of pregnancy will be exclusively claimed under the MBS. As this service is also likely to be undertaken for public in-patients in public hospitals, the cost of termination may be underestimated.

Cost of IVF/PGT

When a couple is identified at increased risk prior to becoming pregnant, there is an opportunity to undergo IVF with PGT as a reproductive option. There are several MBS items and PBS medicines associated with this process. The total cost of IVF with PGT was estimated to be \$4,855.32 (assuming each patient would only complete one round of IVF).

The Commentary considered these MBS/PBS costs to be accurate. While it is reasonable to assume that patients undergo one round of IVF, the cost of additional IVF rounds should have been tested in a sensitivity analysis.

The cost of IVF/PND used in the economic model was sourced from IVF Australia and is equal to \$13,586. The Commentary noted the total cost associated with IVF/PGT (\$4,855.32) is not used in the economic model and therefore is irrelevant.

Lifetime disease costs

There were no readily accessible data on the lifetime cost of an affected child (for each of the selected conditions) in the Australian population. To determine lifetime cost, the ADAR collated several sources with information on the cost of disease from Australian and international studies. Sources of information were obtained from published literature (Alonso et al., 2008; Azimi et al., 2016; Beauchamp et al., 2019; Chambers et al., 2020; Johnson et al., 2019; Karnon et al., 1999; Norman et al., 2012). The priority of literature searching was based on applicability to the Australian context. If no Australian publication was available, studies from other countries were used. Due to the limited evidence for rare diseases, there were a considerable number of genes on the list that had no costs or carrier frequency associated with them. These were excluded from the determination of the weighted costs, which of course creates some uncertainty in the estimates. The lifetime costs are explored in the sensitivity analysis (and separate models have been created to allow efficient evaluation of this outcome if needed). Where conditions/genes had no published lifetime costs available, but carrier frequency was available, the lifetime costs for that condition was based on the mean lifetime cost in the condition category. All the costs are lifetime costs and converted to the AUD\$ in 2022 (CEMG – EPPI-Centre Cost Converter v.1.4).

The Commentary considered the calculations to determine the lifetime costs for each panel size are appropriate. Due to limited information available on carrier frequencies for rare conditions, weighted average costs have been determined for all conditions with the best available information. We acknowledge that there are a multitude of genes for which weighted costs require calculation, as such it would not be feasible to assess every condition in detail. It is noted that some individual costs are significantly less than costs used in the report i.e. FXS and GDS1. However, other conditions will have higher costs and therefore with so many conditions included in the analysis, the discrepancies in costs will average out for all conditions.

Regarding genetic counselling costs, page 27 of PSD 1573 noted that “The most likely health care professional to conduct genetic counselling using MBS codes is an obstetrician/gynaecologist (OB/GYN), however, other medically trained professionals (GPs or other physicians/consultants) may counsel couples if they are determined to be carriers.” The Commentary noted the cost of genetic counselling is not included in the inputs table; however,

this cost has been used in the economic model. The ADAR assumed that this session would cost \$100 per session, however this assumption requires further clarification. For example, MBS items 104 (\$90.35) and MBS items 44 (\$111.50) may be appropriate alternatives for this cost. This is further addressed in the Financial section.

Results of the base case

Step 1: Trial based economic evaluation on cost per increased risk couple identified

The cost per individual is based on the costs presented in the ADAR and the PSD MSAC 1573. The number of analyses needed to be conducted to identify a carrier was assumed to be the inverse of the increased risk rate reported in the Mackenzie’s Mission study.

The CF/SMA/FXS-only panel resulted in the lowest cost per increased risk couple identified. While the cost per increased risk couple identified was lower for the CF/SMA/FXS-only panel, 171 more tests than the large risk panel needed be conducted to identify an increased risk couple. The 410 gene panel costs more per increased risk couple identified than the 1034 gene panel.

Table 4 Intervention cost per couple in the economic evaluation Step 1

Panel	Increased risk rate	Number of couples needed to be tested to identify an increased risk couple	Cost per increased risk couple identified
CF/SMA/FXS-only panel	0.0043	233	\$97,605
410 gene panel (including CF/SMA/FXS)	0.0134	75	\$140,277
1034 gene panel (including CF/SMA/FXS)	0.0162	62	\$130,021

Source: ADAR, Table 5

Step 2: Modelled estimates on cost per increased risk couple identified (including offsets)

Step 2 incorporated the offsets for further testing, reproductive decisions, and lifetime healthcare costs of affected children. The results of the stepped analysis are presented in the tables below. The pre-ESC response provided updated cost-effectiveness analyses for preconception couples (Table 5) and pregnant couples (Table 6).

Table 5 Results of the cost-effectiveness analysis for preconception couples

Panel	Cost	Incremental Cost	Increased risk couple rate	Incremental Effectiveness	ICER (per increased risk couple identified)
CF/SMA/FXS-only panel	\$5,468.40		0.00185		
1034 gene panel	\$2,362.33	-\$3,106.07	0.0173	0.01545	dominant
411 gene panel	\$2,540.91	-\$2,927.50	0.01394	0.01209	dominant
Standard care	\$6,357.65	\$889.25	0	-0.00185	dominated

Source: Pre-ESC response, Table 2

The results of the modelled economic evaluation preconception demonstrated that the cost per preconception couple was highest in the standard care with the results showing that all testing strategies were less costly than standard care. The results of the economic analysis demonstrated that the 1034 gene panel was the dominant strategy in preconception couples.

Table 6 Results of the cost-effectiveness analysis for pregnant couples

Panel	Cost	Incremental Cost	Increased risk couple rate	Incremental Effectiveness	ICER (per increased risk couple identified)
<i>All options compared against CF/SMA/FXS only testing</i>					
CF/SMA/FXS-only panel	\$5,798.84		0.00162		
1034 gene panel	\$5,693.93	-\$104.91	0.01706	0.01544	dominant
411 gene panel	\$5,240.90	-\$557.94	0.01357	0.01195	dominant
Standard care	\$5,888.40	\$89.56	0	-0.00162	dominated
<i>The 1034 gene panel compared against the 411 gene panel</i>					
411 gene panel	\$5,240.90		0.01357	0.01195	
1034 gene panel	\$5,693.93	\$453.03	0.01706	0.00349	\$129,807.26

Source: Pre-ESC response, Table 1

The results of the modelled economic evaluation in pregnant couples demonstrated that the cost per pregnancy was highest in the standard care with the results showing that both 1034 gene and 410 gene panel testing strategies were less costly than standard care. In this scenario, the 410 gene panel was the most cost-effective approach.

The Commentary considered the results presented in the ADAR are correct. The results demonstrate that both gene panels with 1034 and 410 genes are more effective in identifying increased risk couples and less costly than CF/SMA/FXS testing and standard care.

For simplicity, the effectiveness measure in the decision trees for prenatal and preconceptional scenarios is denoted as either 1 or 0. This is an appropriate method to assess the cost effectiveness in each arm.

Uncertainty analysis: model inputs and assumptions

Sensitivity analysis was carried out in two ways. Given the uncertainty around the lifetime costs of affected children, an additional model was built that assumed the lifetime cost was the same in each arm regardless of the panel being tested for. In this scenario the weighted lifetime cost of the Mackenzie's Mission 1034 gene panel was used. Additional analysis was carried out where the weighted lifetime cost was assumed to be the same at each point and the weighted lifetime cost for the 1034 gene panel using the Invitae carrier frequency was used (\$1,513,726.76).

The Commentary considered that in terms of pregnant couples, when considering the weighted lifetime costs for the conditions identified by Mackenzie's Mission, the 410 gene panel remains most cost-effective. For single weighted lifetime costs across all arms in pregnant couples, the CF/SMA/FXS-only panel was most cost-effective, however the 1034 gene panel was comparatively cost effective. In terms of pre-conceptional couples, the 1034 gene panel remained the dominant strategy when both weighted lifetime costs, and single weighted lifetime costs were adjusted.

Further sensitivity analysis was conducted where a 20% variance was applied to each input variable. Tornado diagrams were developed to explore the model sensitivity. The pregnant couples' model was most sensitive to the weighted lifetime cost in the CF/SMA/FXS low risk arm and the probability of affected child in the CF/SMA/FXS-only low risk (Figure 1). Other key variables that were sensitive to changes in inputs were the probability of carrying out a termination and doing a PND.

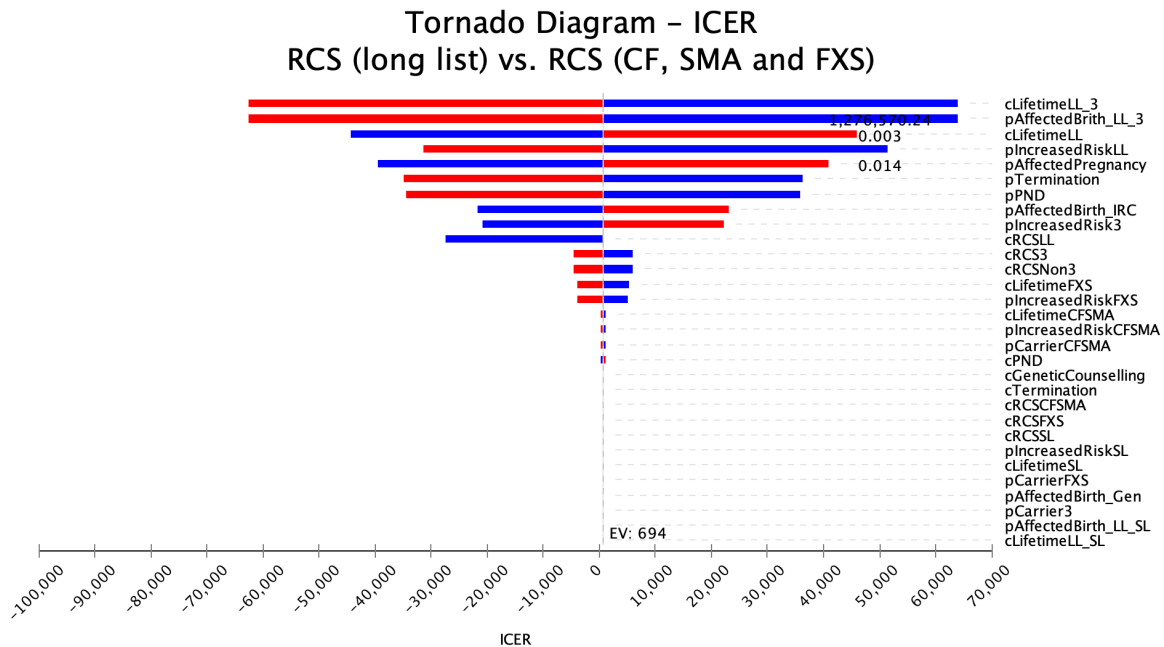


Figure 1 Sensitivity analysis for pregnant couples

Red = high parameter value; blue = low parameter value

As with the pregnant model, the preconception model was most sensitive to the probability of having an affected child in the low risk CF/SMA/FXS-only arm and the probability of increased risk in the 1034 gene panel, but also the lifetime costs associated with the 1034 gene panel (Figure 2). Other key variables that were sensitive to changes in inputs were the probability of undertaking PND and carrying out a termination of pregnancy.

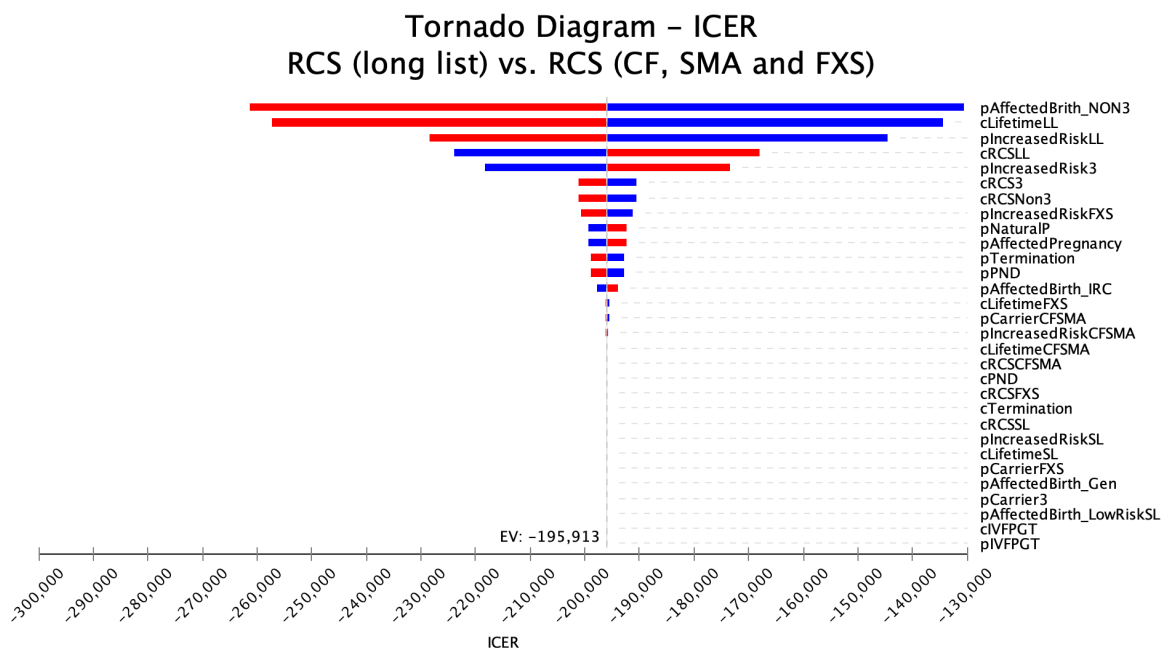


Figure 2 Sensitivity analysis for preconception couples

Red=high parameter value; blue=low parameter value

The Commentary considered this approach to the sensitivity analysis to be acceptable. As mentioned earlier, it would be beneficial to have tested the impact of including false negatives and positive in the model. The key drivers of the model realised through the 20% adjustment of all variables in the economic evaluation are summarised in the table below.

Table 7 Key drivers of the model

Description	Method	Impact
Weighted lifetime cost in the CF/SMA/FXS low risk arm	The lifetime costs were calculated using the average lifetime cost of all conditions, based on best available information.	High
Lifetime costs associated with the 1034 gene panel	The lifetime costs were calculated using the average lifetime cost of all conditions, based on best available information.	High
Probability of affected children in the CF/SMA/FXS-only low risk arm	This probability was calculated by finding the difference in the rate of detecting couples at increased risk in two scenarios and dividing this by the chance of having an affected child. All increased risk rates were sourced from the Mackenzie's Mission Study.	High
Probability of increased risk couple detection in the 1034 gene panel	This probability was calculated by finding the difference in increased risk couple detection rate in two scenarios and dividing this by the chance of having an affected child. All increased risk rates were sourced from the Mackenzie's Mission Study.	Medium
Probability of termination	This probability was sourced from the Mackenzie's Mission Study.	Medium-low
Probability of PND	This probability was sourced from the Mackenzie's Mission Study.	Medium-low

Source: Commentary Executive Summary, Table 8

14. Financial/budgetary impacts

Justification of the selection of approach and data sources

The Commentary assumed the ADAR's financial model costs were calculated based on the 1034 genes versus the 410 gene panel, and in its pre-ESC response the applicant confirmed this, noting the larger panel is the most expensive and a conservative approach overestimating the costs to Government.

The Commentary noted discrepancies in the number of services for AAAA and BBBB, namely, the number of services were incorrectly calculated for couples not individuals. The Commentary updated the net financial implications of ERCT to the MBS, PBS and the Commonwealth government and Net financial implications of ERCT to the MBS. These updates result in a net change in the cost to government of \$818,256,302. The Commentary suggested the applicant review the updated MBS service and cost calculations, additionally, the applicant should update the costs to the Commonwealth government in both the text and tables in the ADAR.

An incidence-based epidemiological approach was used to estimate the financial implications of the introduction of ERCT. The Commentary considered this to be appropriate.

The ADAR did not tabulate the data sources used in the financial model. The Commentary considered it would be beneficial to tabulate and justify all data sources used in the ADAR financial model.

For the financial model the ADAR states that "the number of future births was derived from the Series B projection of the ABS Australian Population Projections."¹³ The Commentary considered use of the Australian Bureau Statistics (ABS), population projections data (Series B) projected medium fertility rate, to be appropriate. An alternative data source is the AIHW mothers and babies report providing key demographics and statistics for Australian mothers and babies¹⁴. A sensitivity analysis with inflated number of pregnancies is presented in the table below to compensate for any uncaptured number of miscarriages that may have led to a lower estimate of people eligible for testing.

¹³ Australian Bureau Statistics. (2018). Population Projections, Australia, 2017 (base) - 2066.

¹⁴ <https://www.aihw.gov.au/reports/mothers-babies/australias-mothers-babies/contents/demographics-of-mothers-and-babies/key-demographics-and-statistics>

Table 8 Estimated number of people eligible for testing using the services proposed when pregnancies are inflated (post ESC table)

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated use at number planning pregnancy 10% (base case)						
Number of services used						
Service AAAA (1034 gene panel)	7,843	31,853	48,437	65,376	82,614	100,098
Service BBBB	0	0	0	1	3	4
Service EEEE	23	95	144	195	246	299
Service FFFF	15	62	94	127	160	194
Total New Services	7,881	32,010	48,676	65,699	83,024	100,595
Estimated use at number planning pregnancy 15%						
Number of services used						
<i>Service AAAA (1034 gene panel)</i>	<i>7,843</i>	<i>31,854</i>	<i>48,441</i>	<i>65,381</i>	<i>82,621</i>	<i>100,107</i>
<i>Service BBBB</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>2</i>	<i>4</i>	<i>7</i>
<i>Service EEEE</i>	<i>23</i>	<i>95</i>	<i>144</i>	<i>195</i>	<i>246</i>	<i>299</i>
<i>Service FFFF</i>	<i>15</i>	<i>62</i>	<i>94</i>	<i>127</i>	<i>160</i>	<i>194</i>
<i>Total New Services</i>	<i>7,881</i>	<i>32,011</i>	<i>48,681</i>	<i>65,705</i>	<i>83,032</i>	<i>100,607</i>
Estimated use at number planning pregnancy 20%						
Number of services used						
<i>Service AAAA (1034 gene panel)</i>	<i>7,843</i>	<i>31,855</i>	<i>48,445</i>	<i>65,387</i>	<i>82,628</i>	<i>100,116</i>
<i>Service BBBB</i>	<i>0</i>	<i>0</i>	<i>1</i>	<i>3</i>	<i>5</i>	<i>9</i>
<i>Service EEEE</i>	<i>23</i>	<i>95</i>	<i>145</i>	<i>195</i>	<i>246</i>	<i>299</i>
<i>Service FFFF</i>	<i>15</i>	<i>62</i>	<i>94</i>	<i>127</i>	<i>160</i>	<i>194</i>
<i>Total New Services</i>	<i>7,881</i>	<i>32,012</i>	<i>48,685</i>	<i>65,712</i>	<i>83,040</i>	<i>100,618</i>

New values updated post ESC added in the rows below in blue italicised text.

The ADAR stated “According to the Australian Institute of Family Studies, the divorce rate in in 2020 was 1.9/1,000 population with a mean of 10 divorces per 1,000 married couples and 15 per 1,000 married couples in women under 45 years of age (used in the analysis)¹⁵. In 2016, 48.6% of divorces involved children under 18. In 2020, just over 22% of marriages involved at least one partner who was previously married; while this is not the proportion of separated people that remarry, it was used as a proxy as this specific detail was not available. Also, it was assumed that these rates were the same for married couples as they were for non-married couples.”

The Commentary considered that considerable uncertainty exists around the use of the divorce rates (1.5% of married couples in women under 45 years) and previously married partner rates (22%) used as proxies in the model. Given at the time of proposed testing it is unknown how many couples were divorced, separated or unmarried, the previously married partner rate (22%) and the divorce rate (1.5%) used to estimate the number of people recoupling and the number of first utilisers in a new couple pairing has been reduced to 0%. The Commentary completed a sensitivity analysis, providing costs to MBS of reducing the divorce and previously married rates to 0% (Table 9). Due to the updated (doubling) to service numbers for items AAAA and BBBB the Commentary updated the sensitivity analysis calculations resulting in a net cost offset for MBS in year one of \$119 (, 2023 net cost to MBS \$63,172,773) and \$4,002 in year six (, 2028 net cost

¹⁵ Australian Bureau of Statistics. (2021). Marriages and Divorces, Australia.

to MBS \$232,941,842), \$6,047 in five years (0.003%). As the reduction in these rates creates minimal net cost savings, these factors are not key drivers or do not significantly impact the financial model and costs overall.

Further, the Commentary stated it is unclear how the re-coupling rate of 22% was estimated from the referenced source. Additionally, greater justification should be provided by the applicant regarding why re-marriages are used as a proxy for establishing new reproductive partnerships (i.e., not all reproductive couples will be married).

Table 9 Net financial implications to MBS when % of people recoupling reduced from 22 to 0% and % of first utilisers in a new couple pairing reduced from 1.5 to 0%

	2023	2024	2025	2026	2027	2028
Cost of listing ERCT	\$9,476,519	\$33,581,512	\$50,559,004	\$67,898,180	\$85,540,984	\$103,433,383
<i>Cost of listing ERCT</i>	<i>\$63,222,311</i>	<i>\$96,140,141</i>	<i>\$129,761,963</i>	<i>\$163,977,334</i>	<i>\$198,681,055</i>	<i>\$233,777,729</i>
<i>Cost offset for MBS</i>	<i>-\$49,657</i>	<i>-\$137,876</i>	<i>-\$260,414</i>	<i>-\$417,922</i>	<i>-\$610,936</i>	<i>-\$839,890</i>
Net cost to MBS	\$9,426,862	\$33,443,637	\$50,298,590	\$67,480,258	\$84,930,046	\$102,593,494
<i>Net cost to MBS</i>	<i>\$63,172,654</i>	<i>\$96,002,265</i>	<i>\$129,501,548</i>	<i>\$163,559,412</i>	<i>\$198,070,120</i>	<i>\$232,937,840</i>

Blue italicised text indicates figures updated by the Commentary
Source: Commentary Executive Summary, Table 9

The financial implications to the MBS over 6 years resulting from the proposed listing of ERCT using the 1034 gene panel are summarised in Table 10.

The Commentary has updated this table to include the following differences from the ADAR: updated number of services for items AAAA and BBBB based on the number of individuals accessing services not the number of couples, updated number of service EEEE (incorrectly transcribed from the applicants utilisation and cost model' excel workbook), updated total number of services, and updated MBS costs and impacts (based on the increase in numbers of services for AAAA and BBBB) and subsequent updated change in costs to government. The impact of these updates resulted in substantial additional costs, for example MBS costs will increase in year 1 by \$53,818,268 and in year 6, \$130,387,597.

Additionally, the Commentary noted that the current comparator is no testing. However, following MSAC supporting the MBS listing of universal RGCT for CF/SMA/FXS; MSAC app 1573, and implementation from 1 November 2023, the changes in use of testing for (CF/SMA/FXS) have been calculated by extrapolating figures used in application 1573.

Table 10 Net financial implications of ERCT to the MBS

Parameter	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated use and cost of the proposed health technology						
Number of people eligible for ERCT	318,510	322,863	326,820	330,397	333,605	336,457
Number of services of ERCT						
Service AAAA (1034 gene panel)	7,843	31,853	48,437	65,376	82,614	100,098
Service AAAA (1034 gene panel)	63,706	96,874	130,752	165,228	200,196	235,560
Service BBBB	0	0	0	4	3	4
Service BBBB	0	0	2	6	8	14
Service EEEE	23	95	144	195	246	299
Service EEEE	95	144	195	246	299	351
Service FFFF	62	94	127	160	194	229
Total New Services	7,928	32,042	48,708	65,732	83,058	100,629
Total New Services	8,000	32,094	48,759	65,783	83,110	100,682
Total New Services	63,863	97,113	131,076	165,641	200,697	236,154
Cost to MBS	\$7,595,720	\$30,781,913	\$46,801,428	\$63,164,443	\$79,816,865	\$96,706,237
Cost to MBS	\$61,413,988	\$93,388,652	\$126,049,044	\$159,287,189	\$192,998,373	\$227,093,834
Change in use and cost of other health technologies						
Change in use of comparator (No testing)	No-comparator	No-comparator	No-comparator	No-comparator	No-comparator	No-comparator
Change in use of comparator (CF/SMA/FXS) (to ceiling of number of AAAA+BBBB services)	-86,313 63,706	86,516	86,720	86,923	87,127	87,330
Cost-offset from comparator services (85% benefit)	-\$21,660,040	-\$29,415,440	-\$29,484,800	-\$29,553,820	-\$29,623,180	-\$29,692,200
Change in use of other related health technologies, e.g. increases in fetal testing, assisted reproductive technologies (ART) (number of services)	1,515	2,313	3,125	3,951	4,788	5,635
Net change increase in costs to MBS for other medical services associated with listing	\$1,808,437	\$2,751,942	\$3,714,921	\$4,694,960	\$5,688,933	\$6,694,279
Cost-offsets to MBS for other medical services associated with listing *	-\$49,660	-\$137,891	-\$260,453	-\$417,994	-\$611,049	-\$840,054

Total Cost to MBS (inc.FFFF)	\$9,404,156	\$38,947,636	\$57,823,393	\$77,093,130	\$96,693,703	\$116,564,729
Net financial impact to MBS (including cost of new services AAAA, BBBB, EEEE, FFFF)	\$9,476,640	\$33,583,924	\$50,567,490	\$67,911,449	\$85,558,583	\$103,453,905
Net financial impact to MBS (including cost of new services AAAA, BBBB, EEEE, FFFF and offsets)*	\$63,172,773	\$96,002,734	\$129,502,298	\$163,561,064	\$198,073,177	\$232,941,842
Net financial impact to MBS (including cost of new services AAAA, BBBB, EEEE, FFFF and offsets)	\$41,512,725	\$66,587,264	\$100,018,712	\$134,010,336	\$168,453,076	\$203,255,859

MBS=Medicare Benefits Schedule

Where data in the ADAR were incorrectly reported this has been stricken through and the values updated by the Commentary added in the row below in blue italicised text.

MSAC's revisions to include cost-offsets from CF/SMA/FXS services replaced are shown in strikethrough and bold green italicised text.

Source: MSAC revisions to Commentary Executive Summary, Table 10.

* = figures sourced from Commentary Executive Summary, Table 11.

Financial impact of listing new ERCT services (items AAAA, BBBB, EEEE, FFFF)

MBS costs

The Commentary noted the discrepancies in the number of services reported for AAAA and BBBB, namely, the number of services were incorrectly calculated for couples not individuals. The Commentary has updated Table 10 above regarding the net financial implications of ERCT to the MBS. These updates result in increased MBS costs in year 1 of \$53,818,268 and in year 6, \$130,387,597. The Commentary suggests the applicant review the updated MBS service and cost calculations, additionally, the applicant should update the costs to the Commonwealth government in both the text and tables.

The ADAR stated that for all items, it was assumed that an 85% benefit would apply (for Items AAAA, BBBB, EEEE the Greatest Permissible Gap was applied). Table 10 presents the costs of all four items associated with ERCT. It was estimated that in the first year of listing the new MBS items would have a net financial implication of \$7.6 million, rising to \$96.7 million in year 6. This equates to a net five-year financial implication of approximately \$228 million.

The ADAR presented the estimated number of other MBS services that are expected to be used in conjunction with ERCT. It was assumed that the first contact with a clinician would be a routine check and would not result in an additional cost to the MBS. Costs of genetic counselling are covered in the additional health budgets, as they are currently not included separately on the MBS. Changes in services associated with ERCT included: increases in CVS/amniocentesis, sibling testing for CFTR, PND for CFTR, terminations, PGT/IVF, genetic counselling, and decreases in hospital, and medical services.

The Commentary noted that additionally, the AR-DRG cost for terminations have not been included (AR-DRG 005Z; \$3,494). Lastly, weighted averages should not be used in the financial impact analysis, and services and benefits should be separately calculated and tables for MBS items 16530 and 16531.

The ADAR presented the net cost to the MBS from associated medical services. When additional items associated with increased risk results are added, the five-year cost of listing is estimated at \$280 million.

The Commentary stated the five-year MBS listing cost of ERCT services and associated services was recalculated based on errors identified in the volume of services costs for MBS item EEEE, and the overestimation of the number of MBS items for CVS (16603), and the omission of the cost of MBS items 21945, 55854 and 60503, resulting in a net cost to the MBS of \$263 million, compared to the ADAR, this represents a reduction of about \$17 million over five years. Further, the doubling of the number of services for AAAA and BBBB results in additional costs to the MBS over 5 years of over \$650 million. The Department further revised the tables to correct transcription errors, and MSAC revised the the tables to include cost-offsets from CF/SMA/FXS services replaced. These updates are reflected in Table 10 above.

Regarding the genetic counselling cost the ADAR noted that "It was assumed that a genetic counsellor session would cost \$100 per session." and this cost was included in the financial model. However, the Commentary noted that page 27 of the 1573 public summary document and the DCAR noted that "The most likely health care professional to conduct genetic counselling using MBS codes is an obstetrician/gynaecologist (OB/GYN), however, other medically trained professionals (GPs or other physicians/consultants) may counsel couples if they are determined to be carriers.". Therefore, genetic counselling session MBS items may include MBS item number 104 "Professional attendance at consulting rooms or hospital by a specialist in the practice" for an initial consultation (Fee: \$90.35 Benefit: 75%=\$67.80, 85%=\$76.80) and 105 for a subsequent consultation (Fee: \$45.40 Benefit: 75%=\$34.05, 85%=\$38.60). Alternatively, MBS item number 44 "Professional attendance by a general practitioner at consulting rooms (other than a service to which another item in the table applies), lasting at least 40 minutes" Fee: \$111.50 Benefit: 100%=\$111.50, could be utilised.

Lastly, the Commentary noted there is additional uncertainty in the utilisation of MBS services for pre-test genetic counselling. The estimated genetic counselling fee of \$100 could be overestimated as MBS items 104, 105 or 44 could be used. A pre-test genetic counselling fee of \$100 is a conservative estimate and appropriate. However, the applicant could undertake a sensitivity analysis regarding this fee.

PBS costs

The listing of ERCT will lead to increased use of pharmaceuticals associated with IVF/PGT. ADAR Table 67 presents the Dispensed Price for Maximum Quantity (DPMQ) and items used in the analysis of costs to the PBS. It was assumed that co-payments would be at the maximum general co-pay level of \$42.50. Table 68 in the ADAR presents the volume of usage associated with super ovulation and embryo retrieval. Table 11 presents the annual costs to the PBS associated with IVF/PGT medicines and the listing of ERCT.

Table 11 Estimated yearly costs to PBS associated with IVF/PGT medicines and the listing of ERCT

Costs for superovulation	2023	2024	2025	2026	2027	2028
follitropin beta	\$67,744.31	\$103,014.83	\$139,042.48	\$175,708.16	\$212,894.90	\$250,507.00
nafarelin	\$31,880.29	\$48,478.49	\$65,433.01	\$82,687.78	\$100,187.75	\$117,887.90
Co Pay	-\$22,045.43	-\$33,523.20	-\$45,247.36	-\$57,179.15	-\$69,280.50	-\$81,520.27
Net cost to PBS	\$77,579.17	\$117,970.12	\$159,228.12	\$201,216.79	\$243,802.16	\$286,874.63

Source: Commentary Executive Summary, Table 12

Cost offsets of ERCT

The listing of ERCT will lead to some cost offsets due to avoiding the birth of seriously ill children. Table 12 outlines the financial implication to the PBS by the listing of ERCT. It is estimated that ERCT will save the PBS between \$13 million and \$86 million per year over the first six years, with a five-year impact of a reduction in cost of \$191,976,042.

Table 12 Net financial implications of ERCT to the PBS

	2023	2024	2025	2026	2027	2028
Cost associated with listing ERCT (1034 gene panel)	\$77,579	\$117,970	\$159,228	\$201,217	\$243,802	\$286,875
Cost savings for PBS	\$13,285,618	-\$23,860,796	-\$36,487,434	-\$51,183,005	-\$67,958,989	-\$86,824,719
<i>Net cost savings for PBS</i>	<i>-\$2,745,298</i>	<i>-\$5,287,970</i>	<i>-\$8,514,088</i>	<i>-\$12,433,400</i>	<i>-\$17,053,517</i>	<i>-\$22,380,648</i>
Net cost to PBS	\$13,208,039	-\$23,742,826	-\$36,328,203	-\$50,981,788	-\$67,715,187	-\$86,537,844
<i>Net cost to PBS</i>	<i>-\$2,667,719</i>	<i>-\$5,170,000</i>	<i>-\$8,354,860</i>	<i>-\$12,232,183</i>	<i>-\$16,809,715</i>	<i>-\$22,093,774</i>

Blue italicised text indicates figures updated by the Commentary
Source: Commentary Executive Summary, Table 13

The Commentary noted the cost offsets for PBS appropriately relate to the offsets afforded by the estimated reduction in the costs of medicines required to manage those with the genetic disorders including SMA and CF. This included the costs of nusinersen loading (year one) and maintenance dosing (year two onwards) for patients with SMA. However, nusinersen calculations did not account for the additional patients who would have received loading doses of nusinersen previously and required annual maintenance dosing. Additionally, the utilisation and cost model excel sheet contained an error in the formula for calculating the CF salbutamol costs, whereby the incorrect cell was selected. This error has been corrected in Table 12 above.

Table 12 outlines the financial implication to the PBS by the listing of ERCT. The Commentary's updated figures estimate that ERCT will save the PBS between \$3 million and \$22 million per year over the first six years, with a five-year impact of a reduction in cost of \$45,234,477 (approximately \$146,741,565 less than the ADAR reported).

The ADAR stated that "ERCS [ERCT] is expected to have considerable impact on state and territory governments' health budgets. Children with rare genetic diseases are almost exclusively treated in public hospitals.

Based on data from the economic model and the conditions identified as high risk in the Mackenzie's Mission study, the costs to state hospital and health services were calculated. There were 60 conditions identified in the Mackenzie's Mission study. The average lifetime costs for these conditions were estimated to be \$1.6 million per individual. For the analysis, it was assumed that 50% of these costs would be incurred in the first two years of life. The number of children affected is based on 25% increased risk, with a 66.7% pregnancy termination rate."

Table 13 provides a summary of the reduction in hospital services due to the listing of ERCT.

Table 13 Reduction in hospital services utilisation

	2023	2024	2025	2026	2027	2028
Reduced number of children affected	57	87	117	148	180	212
Total hospital costs	\$23,351,628	\$58,861,087	\$83,437,735	\$108,495,300	\$133,952,409	\$159,735,749

Source: Commentary Executive Summary, Table 14

The ADAR stated that “the average lifetime costs for these conditions were estimated to be \$1.6 million. For the analysis, it was assumed that 50% of these costs would be incurred in the first two years of life”. However, the Commentary considered this assumption has not been justified.

Table 14 provides a summary of the net costs of listing ERCT on the state government budget. The listing of ERCT will lead to a reduction for state and territory budgets of \$23 million in year one to a saving of \$159 million by year six.

The Commentary noted the net costs of listing ERCT on the state government budget included the cost of genetic counselling. However, for the projected 2024 figures the ADAR identified 48,437 couples, however, despite the increasing number of couples requiring pre-test counselling the total cost of counselling was reduced. Given this calculation error, the cost of counselling from 2024 onwards was recalculated and updated in Table 14 below. Further, this update has a minimal impact on the overall net cost to state and territory governments.

Table 14 Net costs to state and territory governments

	2023	2024	2025	2026	2027	2028
Total cost of counselling	\$147,005	\$78,232 <i>\$223,543</i>	-\$105,592 <i>\$301,723</i>	-\$133,436 <i>\$381,287</i>	-\$161,677 <i>\$461,983</i>	-\$190,240 <i>\$543,601</i>
Total hospital costs	-\$23,351,628	-\$58,861,087	-\$83,437,735	-\$108,495,300	-\$133,952,409	-\$159,735,749
Net cost to state and territory governments	-\$23,204,622	-\$58,637,544	-\$83,136,012	-\$108,114,013	-\$133,490,426	-\$159,192,148

Blue italicised text indicates figures updated by the Commentary

Source: Commentary Executive Summary, Table 15

Due to the error in calculating the number of services for AAAA and BBBB, the Commentary requested that the applicant review and update Table 15, Table 16, Table 17 regarding the total cost to the Commonwealth government. Further, the Commentary suggested the applicant complete a sensitivity analysis regarding the uptake of ERCT. The model assumed that rates of uptake would increase over time as couples became more familiar with the availability of the test, starting at 20% for the first full year of listing (Year 1), rising to a plateau of 70% at Year 6 of listing. However, no justification was provided regarding the assumed rates of uptake. Following update by the applicant of the cost to the Commonwealth government, testing the upper limit of what the financial impact could be, the Commentary added a sensitivity analysis using 100% uptake every year (Table 15). This table does not represent what the rates would be in real practice but provides an indication of the maximum financial outlay to the Commonwealth government in absence of any further information.

Table 15 Cost to Commonwealth government using 100% uptake of testing across all years

	2023	2024	2025	2026	2027	2028
Total cost to MBS	\$16,280,704	\$151,444,493	\$153,515,868	\$155,362,960	\$157,031,369	\$158,523,125
Total cost to PBS	-\$12,758,866	-\$18,892,121	-\$25,390,283	-\$31,951,403	-\$38,568,328	-\$45,234,521
Net cost to Commonwealth government	\$3,521,838	\$132,552,372	\$128,125,585	\$123,411,557	\$118,463,041	\$113,288,604

Source: Commentary Executive Summary, Table 17.

Table 16 summarises the total cost to Commonwealth government through the MBS and PBS. The ADAR stated the listing of ERCT will lead to a saving in state and territory budgets by \$4 million in year one but leading to a cost of approximately \$29 million by year six and total cost of \$86 million over the first five years of listing.

Table 16 Cost to Commonwealth government

	2023	2024	2025	2026	2027	2028
Total cost to MBS	\$9,356,326	\$38,814,357	\$57,571,308	\$76,688,249	\$96,101,517	\$115,750,305
<i>Total cost to MBS</i>	<i>\$9,426,980</i>	<i>\$33,446,030</i>	<i>\$50,307,037</i>	<i>\$67,493,455</i>	<i>\$84,947,535</i>	<i>\$102,613,852</i>
Net cost to MBS (from revised Table 10)	\$41,512,725	\$66,587,264	\$100,018,712	\$134,010,336	\$168,453,076	\$203,255,859
Total cost to PBS	-\$13,208,039	-\$23,742,826	-\$36,328,203	-\$50,981,788	-\$67,715,187	-\$86,537,844
<i>Total cost to PBS</i>	<i>-\$2,667,719</i>	<i>-\$5,170,000</i>	<i>-\$8,354,860</i>	<i>-\$12,232,183</i>	<i>-\$16,809,715</i>	<i>-\$22,093,774</i>
Net cost to Commonwealth government	-\$3,851,713	\$15,071,534	\$21,243,105	\$25,706,461	\$28,386,330	\$29,212,460
<i>Net cost to Commonwealth government</i>	<i>\$6,759,261</i>	<i>\$28,276,030</i>	<i>\$41,952,177</i>	<i>\$55,261,272</i>	<i>\$68,137,820</i>	<i>\$80,520,078</i>
Net cost to Commonwealth government	\$38,845,006	\$61,417,264	\$91,663,852	\$121,778,153	\$151,643,361	\$181,162,085

Blue italicised text indicates figures updated by the Commentary. MSAC's revisions to include cost-offsets from CF/SMA/FXS services replaced, and Department revisions to correct errors in the transcription of MBS costs, are shown in strikethrough and bold green italicised text.

Source: MSAC and Department revisions to Commentary Executive Summary, Table 16

The Commentary noted that errors in nusinersen, salbutamol and counselling costs, errors in the expected usage of drugs associated with IVF/PGT, and the omission of the cost of MBS items 21945, 55854 and 60503, have been accounted for and updated in Table 16 above.

Table 17 summarises the total cost across all government health budgets. The ADAR stated the listing of ERCT will lead to a saving to the government health budgets of \$27 million in year one, rising to \$130 million by year six, and providing a total saving of approximately \$320 million over the first five years of listing.

Table 17 Total cost to government health budgets (for 1034 gene panel)

	2023	2024	2025	2026	2027	2028
Total cost to state governments	-\$23,204,622	-\$58,637,544	-\$83,136,012	-\$108,114,013	-\$133,490,426	-\$159,192,148
Total cost to Commonwealth government	-\$3,851,713	\$15,071,531	\$21,243,105	\$25,706,461	\$28,386,330	\$29,212,460
<i>Total cost to Commonwealth government</i>	<i>\$6,759,261</i>	<i>\$28,276,030</i>	<i>\$41,952,177</i>	<i>\$55,261,272</i>	<i>\$68,137,820</i>	<i>\$80,520,078</i>
<i>Net cost to Commonwealth government (from revised Table 16)</i>	<i>\$38,845,006</i>	<i>\$61,417,264</i>	<i>\$91,663,852</i>	<i>\$121,778,153</i>	<i>\$151,643,361</i>	<i>\$181,162,085</i>
Net cost to government	-\$27,056,336	-\$43,566,013	-\$61,892,907	-\$82,407,552	-\$105,104,096	-\$129,979,688
<i>Net cost to governments</i>	<i>-\$16,445,361</i>	<i>-\$30,361,514</i>	<i>-\$41,183,835</i>	<i>-\$52,852,741</i>	<i>-\$65,352,606</i>	<i>-\$78,672,070</i>
<i>Net cost to governments</i>	<i>\$15,640,384</i>	<i>\$2,779,720</i>	<i>\$8,527,840</i>	<i>\$13,664,140</i>	<i>\$18,152,935</i>	<i>\$21,969,937</i>

Blue italicised text indicates figures updated by the Commentary. MSAC's revisions to include cost-offsets from CF/SMA/FXS services replaced, and Department revisions to correct transcription errors, are shown in strikethrough and bold green italicised text. Source: MSAC and Department revisions to Commentary Executive Summary, Table 18

The Commentary noted errors in nusinersen and counselling costs, errors in the expected usage of drugs associated with IVF/PGT, and the omission of the cost of MBS items 21945, 55854 and 60503, accounted for changes in the costs to the Commonwealth government and have been updated in Table 17 above. These updates resulted in the listing of ERCT leading to a saving to the government health budgets of \$16 million in year one, rising to \$78 million by year six. This equates to a total saving of approximately \$206 million over the first five years of listing (\$114 million less than reported in the ADAR).

Average values for ERCT

The weighted average cost of ERCT services per individual was calculated by the Commentary as \$961.64. This is the weighted cost of the number of utilisations multiplied by its associated 85% benefit (taking into account the greatest permissible gap).

- The total number of ERCT services ranged from 63,863 in the first year, increasing to 235,560 by Year 6.
- The average out-of-pocket cost per individual per ERCT service was not calculated or reported in the ADAR. Estimates would involve uncertainties regarding the number and complexity of services required which may change across an individual's lifetime.

Extended Medicare Safety Net

The Commentary noted the financial implications for the original or extended Medicare Safety Net were not calculated or reported in the ADAR. Due to the degree of uncertainty regarding the number of patients who would reach the Extended Medicare Safety Net it is difficult to estimate the financial implications for the Extended Medicare Safety Net.

15. Other relevant information

The ADAR provided evidence on the effectiveness and validity of the online educational consent process for establishing informed consent of the reproductive partners, as requested by PASC.

The applicant developed an online education and consent process for the Australian Reproductive Genetic Carrier Screening Project (Mackenzie's Mission). The online consent process is supported by access to genetic counsellors; if there are any issues that participants wish to explore further or if there are personal considerations not covered by the online process, a "1800 helpline" is available which allows confidential discussion with a genetic counsellor.

Evidence supporting the validity of this approach for establishing the informed consent of reproductive partners has been collected as part of the Mackenzie's Mission project. Participants complete a 'knowledge check' before viewing the education module (pre-education knowledge) and after viewing the education module (post-education knowledge). The knowledge check consists of 10 statements about ERCT to which participants respond 'true', 'false' or 'unsure'. The number of correctly answered statements are summed to provide a total score out of 10. For the purposes of analysis, 'unsure' responses were recoded as 'incorrect'.

Participants demonstrated a significant increase in knowledge after viewing the education module within the enrolment process. Most participants and couples indicated a positive attitude toward ERCT. For these participants and couples, attitudes toward ERCT matched their choice to have testing.

16. Key issues from ESC to MSAC

Key issues from ESC to MSAC

Clinical issues

- The clinical evidence comes from the interim results of one single-arm Australian study: the Mackenzie's Mission trial. However, the study population was selective (leading to selection bias), not adequately described and data on uptake rates both by couples and among GPs ordering the tests were not provided. Further, little detail about the study design was provided by the applicant, and estimates from this study could not be verified. The number of increased risk couples was very small (n=120).
- Expanded reproductive carrier testing (ERCT) is expected to detect carriers of a substantially larger number of conditions than currently supported reproductive carrier testing (only cystic fibrosis, fragile-X syndrome and spinal muscular atrophy). This would enable prospective parents to make more informed reproductive decisions.
- ERCT is estimated to find that 1.6% of couples are both carriers of variants in the same autosomal recessive (AR) gene or the female is a carrier of a variant in an X-linked (XL) gene, and therefore at increased risk of having an affected child. This compares to 0.4% of couples that would be found to be at increased risk by the comparator. ERCT is anticipated to reduce the number of births affected by AR and XL conditions in Australia.

Economic issues

- The lifetime costs are the major drivers of the economic evaluation.
- 1034-gene and 411-gene panel options are presented for item AAAA. The ICERs including lifetime healthcare costs are dominant for both the 1034-gene and 411-gene panels, for

both pre-conception and pre-natal testing. The larger panel is more cost-effective for pre-conception testing, though the smaller panel is more cost-effective for pregnant couples.

- The proposed out-of-hospital rebates for AAAA (\$962.10 for the 1034-gene panel option; \$852.10 for the 411-gene panel option) are much higher than fees currently charged for private, non-publicly funded reproductive carrier testing (approximately \$600), with insufficient justification provided. Economies of scale would also be expected to lower the cost of this testing.
- Out-of-pocket costs of ERCT could potentially be high.

Financial issues

- The financial cost of providing ERCT is high, however the cost-offsets (primarily to State/Territory hospitals and the PBS) are also substantial, resulting in a net financial saving to Government of adopting ERCT. *Following the meeting, MSAC noted the Department had provided figures correcting transcription errors, and that the estimated cost to the MBS exceeds the estimated cost-offsets, resulting in a net financial spend of adopting ERCT.*
- The budget impact is uncertain, mainly due to uncertainty around the expected uptake and lifetime costs.

Other relevant information

- NPAAC advised there is currently no specific quality assurance program (QAP) for large ERCT panels, in Australia or internationally.
- The proposed testing will be substantial to implement, and there are multiple potential implementation issues.
- Most referring clinicians should be able to provide adequate post-test counselling for couples found to not be at increased risk, however for the 1.6% of couples found to be at increased risk, post-test counselling may be beyond the scope of most referrers.
- ERCT will inevitably detect many variants of uncertain significance (VUSs), though public databases may be insufficient to adequately assign pathogenicity. It is unclear how VUSs will be handled in terms of couple increased risk assignment, and how couples will be counselled around any VUSs detected.
- There are issues around equality of access, since the testing is proposed to only be available to couples, not to individuals.
- The application does not address how rural or remote patients may access the testing.
- The application does not address a culturally appropriate approach for Aboriginal and Torres Strait Islander communities.
- Storage and transfer of genomic data for years/decades is not catered for at present.
- Although the application is seeking public funding through the MBS rather than as a population screening program, it could be considered to be comparable to screening. Therefore, it may be appropriate for ERCT to have a registry and an expert panel, including consumer representation, to provide transparent oversight. ESC considered this to be a central point for MSAC's consideration.
- The testing proposed under this application should be considered in relation to that proposed under MSAC application 1671 – Targeted carrier testing for severe monogenic conditions, which proposes testing in the Ashkenazi Jewish population, and the base case comparator: that supported by Government and proposed under MSAC application 1573 -

Reproductive carrier testing for fragile X syndrome, spinal muscular atrophy and cystic fibrosis.

ESC discussion

ESC noted that this was a new application for MBS listing for expanded reproductive carrier testing (ERCT) of couples for joint carrier status of genes associated with autosomal recessive (AR) and X-linked (XL) conditions. ESC recalled that in July 2020 MSAC supported public funding of application 1573 for three-gene reproductive carrier testing to detect carriers of cystic fibrosis (CF, *CFTR* gene), fragile-X syndrome (FXS, *FMR1* gene) and spinal muscular atrophy (SMA, *SMN1* gene) with an MBS fee of \$400. ESC noted the testing supported under 1573 will be introduced onto the MBS on 1 November 2023. ESC noted that MSAC application 1671 – Targeted carrier testing for severe monogenic conditions – also proposes reproductive carrier testing building on the testing supported under 1573, and is being considered by ESC and MSAC at the same time as this application. ESC recommended that the testing proposed under application 1637 should be considered in relation to that proposed under application 1671, as well as that supported under 1573, which is the base case comparator.

ESC noted that most ERCT to date has focused on targeting specific populations where certain diseases are more prevalent (e.g. founder populations, groups where consanguinity is high and/or isolated geographic areas). However, most children with AR or XL conditions are born to couples without a family history; for example, an estimated 94% of newborns with CF are born to parents with no family history of the disease. ESC noted that PASC requested that, in addition to the proposed ERCT for 1,034 genes (fee of \$1,050 per patient) that was the intervention originally planned in the application, a smaller gene panel also be considered in the assessment: the ADAR added a 410-gene panel (subsequently updated by the pre-ESC response to 411 genes; fee of \$940 per patient). ESC noted the basis for selection of diseases proposed to be included had been published¹⁶. ESC noted that the smaller panel was for “more severe” conditions but queried the basis for selection of the subset included on the smaller panel.

ESC noted that private laboratory fees (i.e., those currently charged to patients on a user-pays basis, in the absence of public funding) for reproductive carrier testing are approximately \$600 per patient – much lower than the \$962.10 (1034-gene panel option; fee \$1050) and \$852.10 (411-gene panel option; fee \$940) out-of-hospital MBS rebates per patient proposed for AAAA. ESC considered the out-of-pocket costs of ERCT could potentially be high, however noted data provided by the Department for publicly funded exome/genome-based testing (MBS items 73358 and 73359) for 2021-22 (YTD as at 31 May 2022) showed high bulk billing rates and relatively low average out-of-pocket costs of [REDACTED] \$[REDACTED]. ESC considered the fees proposed in this application to be high and insufficiently justified by the applicant. ESC considered the proposed fees were not adequately justified, and that a disaggregation of the basis for the proposed fee would be informative: including not only the wet lab costs of conducting the sequencing, quality control, bioinformatics, consumables etc, but also the time taken to interpret and report on the detected variants. ESC commented MSAC could consider tiered cost benchmarks. ESC noted the applicant argued the fee of \$1,050 was appropriate as it was in line with gene panel MBS items (e.g. 20-gene virtual panel for cardiac arrhythmia testing supported by MSAC for \$1200 under Application 1598), however ESC considered the ERCT setting to be different and that it may be inappropriate to benchmark fees for MBS items proposed by this application against fees for existing MBS listed and MSAC supported items for affected individual testing. ESC queried

¹⁶ Kirk EP, et al. (2021). Gene selection for the Australian Reproductive Genetic Carrier Screening Project ("Mackenzie's Mission"). *Eur J Hum Genet*, **29**(1): 79-87.

whether economies of scale would decrease the costs, since the expected utilisation could potentially be high (there are approximately 310,000 mothers giving birth each year in Australia, including approximately 178,000 first-time mothers – a major group of interest for ERCT) and automation in sequencing may occur. ESC noted the applicant stated small revisions to the gene list will not affect the cost of the test.

ESC considered the proposed item descriptors to be linked and rational. ESC noted that BBBB addresses the situation where one member of the couple has previously had ERCT, and will be important.

ESC noted the clinical need for such testing. At present, prospective parents do not have carrier testing for most AR or XL conditions. ESC noted the comparator is reproductive carrier testing for the three most common severe AR and XL conditions (CF, FXS and SMA). ESC noted that ERCT is expected to detect a substantially larger number of conditions, offering prospective parents the value of more informed reproductive decisions. ERCT is estimated to find 1.6% of couples are both carriers of variants in the same AR gene or the mother is a carrier of a variant in an XL gene, and therefore at increased risk of having an affected child. This compares to 0.4% of couples that would be found to be at increased risk by the comparator. ESC noted these figures were in line with the literature (with studies reporting diagnostic yields (DYS) ranging from 0.1% to 11.5%, but most studies' DYS were <6%), and considered them to be reasonable estimates. However, ESC noted the rates reported by the Mackenzie's Mission study and other studies were based on predominantly Caucasian populations, and so emphasised these figures may be less applicable to diverse multicultural samples. ESC considered that although the Mackenzie's Mission study and the literature search had identified issues with applicability and transitivity, similar findings were reported across multiple direct evidence sources, supporting the robustness of the conclusions. ESC noted that ERCT is anticipated to reduce the number of births affected by AR and XL conditions in Australia.

ESC noted that the clinical evidence is from a single Australian trial as part of the Australian Reproductive Genetic Carrier Screening Project (also known as "Mackenzie's Mission"), a \$20 million pilot study launched in 2018. The trial is nearing completion, with interim results presented in the ADAR based on 5,820 couples that have received results to date (excluding a priori known carrier couples). ESC noted that very little detail about the study was provided in the ADAR, and considered that further detail about the study would have allowed ESC to provide a more informed judgement. ESC considered that as the trial involved a selected population with higher socio-economic status (SES), the results may be less generalisable to the general Australian population than claimed by the ADAR. ESC considered information about the following would assist MSAC's decision-making:

- More information about uptake rates.
- Further details about ethnic diversity and SES of participants., including comparison between those who did versus did not take up ERCT.
- More information about the follow-up, which was incomplete. ESC noted that 70% of the couples in the follow-up were in the top two SES quintiles.
- More information about the proportion of invited GPs who are taking part in the study and what their role is.

ESC noted the clinical claim is that ERCT of couples for joint carrier status of genes associated with AR and XL conditions at preconception or early pregnancy results has superior health outcomes compared to ERCT for CF, SMA and FXS alone.

ESC noted that the Mackenzie's Mission study did not provide evidence on comparative safety outcomes. The literature suggests any psychological burden associated with genetic testing rarely

reached clinically relevant levels at any timepoints before, during or after ERCT and that any harms that were experienced had generally dissipated by six months post-test.

ESC noted that, although false positives and false negatives are likely to be rare (NGS testing is highly sensitive and specific, with >99% specificity), the ADAR did not address the potential medicolegal implications of patients receiving false negative results. ESC considered false positives would be rare, and other systems, such as cascade testing, would help to correct false positive results. ESC considered there will be false negatives, i.e. affected children born despite both parents having been tested and not found to be at increased risk, and that these will be for technical reasons but also due to de novo mutations. ESC noted the Mackenzie's Mission trial found the proportion of affected fetuses detected using CVS/amniocentesis was higher than the expected 25%, though considered this may be due to small sample size.

ESC noted that genomic databases are dominated by genomic data of people with European ancestry, and noted that Aboriginal and Torres Strait Islander peoples and other ethnicities are under-represented in genomic databases. ESC considered this creates uncertainty in the clinical validity of ERCT, as use of databases to determine pathogenicity may not predict disease very well for people under-represented in genomic databases.

ESC noted that testing for more conditions increases the chances of a couple being identified as carriers; however, relative to the sequential testing approach used in the comparator, the proposed couple-based results disclosure process reduces both the number of results provided to each couple and the waiting time for results. Findings showed that this procedural difference may relieve some anxiety associated with waiting for results. ESC noted that psychological harms are likely significantly mediated by predispositions for outcomes, although this was inadequately explored. ESC considered that the lack of validated measures and best practice study designs and the small samples reduces the applicability of results.

ESC noted the novel couple-based approach has resulted in testing only being proposed to be available to couples. ESC considered this would include individuals/couples using a gamete donor, provided the gamete donor's DNA is accessible and the donor has consented to its use in this way. ESC considered the couple-based approach creates inequity for individuals planning pregnancy who are not in a couple or do not have access to the gamete donor's DNA.

ESC noted that the interim results of the Mackenzie's Mission study reported key clinical utility outcomes of:

- 45.8% (55/120) of non-pregnant couples at increased risk chose to pursue in vitro fertilisation (IVF) with preimplantation genetic testing (PGT)
- 70.3% (26/37) of pregnant couples at increased risk undertook prenatal diagnosis (PND)
- 66.7% (4/6) of affected pregnancies were terminated
- 16.7% (1/6) of affected pregnancies proceeded.

ESC noted that the literature showed that many couples at increased risk take reproductive actions to avoid having affected offspring. Couples at increased risk were more likely to take preventative reproductive actions when they were carriers of more severe conditions. As the intervention identifies at least 4 times as many couples at increased risk, it can be expected that there will be more affected births averted for the intervention than the comparator (e.g. via IVF with PGT, or PND and termination of affected pregnancies). ESC noted that the results for the Mackenzie's Mission study are not yet final, which limits interpretability of results, as the cohort is still in follow-up. ESC considered that the small sample size for affected pregnancies across the evidence presents potential issues with the reliability of findings.

ESC noted that the economic evaluation was a cost-effectiveness analysis from a healthcare system perspective, using decision trees. ESC noted the economic analyses separated preconception vs pregnant couples, and included two steps: step 1 only incorporating the cost of the test and the increased risk rate, and step 2 including all costs and cost-offsets including lifetime healthcare cost-offsets.

ESC considered that the lifetime cost-offsets are a major component of the economics, though the resources and costs of ERCT would primarily be high upfront (e.g. testing, GP visits), while the cost-offsets would occur much later (and by their nature are uncertain), as a result of any affected births. ESC considered that the diagnostic yield (DY) at the point where the couple's risk is established is not the true DY – true DY would be calculated at the point of pre-natal diagnosis, and would be ~25% of the DY of couples found to be at increased risk.

ESC noted the major drivers of the economic model were the weighted lifetime cost in the CF/SMA/FXS low risk arm, the lifetime costs associated with the diseases on the 1034-gene panel, and the probability of affected births in the CF/SMA/FXS low risk arm. ESC noted the assessment did not include probabilistic sensitivity analyses of the economics, which it considered would be helpful for decision-making.

ESC noted that the ADAR reported that for preconception testing, in step 1 the cost per increased risk couple identified was \$97,605 for CF/FXS/SMA-only testing (the base case comparator), \$140,277 for the 410-gene panel and \$130,021 for the 1034-gene panel (Table 4). The pre-ESC response showed these costs per increased risk couple identified translate in step 2 to dominant incremental cost-effectiveness ratios (ICERs) for both 1034-gene and 411-gene panels relative to the base case comparator, with the larger panel being the most cost-effective (Table 5). ESC considered this to be similar to the dominant ICER per carrier couple detected previously seen for CF/FXS/SMA reproductive carrier testing in Application 1573¹⁷.

ESC noted that in the analysis of pregnant couples, the pre-ESC response's updated analyses showed both 1034-gene and 411-gene panels have dominant ICERs compared to the base case comparator, with the smaller panel being the most cost-effective (Table 6).

ESC noted that the financial modelling included both over- and under-estimates, which the Commentary had revised, though some inaccuracies may remain. ESC noted the Commentary estimated the net financial impact to the MBS of the proposed testing to be \$63 million in year 1 rising to \$233 million in year 6, which ESC considered is high and represents a major investment – but is also uncertain due to the highly uncertain utilisation estimates. ESC noted the analysis of re-coupling used divorce rates, though considered this would not account for births outside marriage or other family structures. ESC noted the uptake rate was modelled as increasing across the years (from 20% in year 1, rising 10% per year to 70% uptake in year 6), and queried whether assumptions relating to uptake rates were sufficiently justified. ESC noted that 20% of all pregnancies end in miscarriage and the proposed testing would take place prior to miscarriage, so considered that basing the estimated population of pregnant women on Australian data on the number of births may have inadequately accounted for miscarriage rates. ESC further noted that increased risk couples who miscarried (5/120 couples at increased risk in the Mackenzie's Mission data so far), or who had not yet taken action on their test results, or who had been reclassified as low risk, were not accounted for in the financial modelling.

ESC noted the Commentary's updated analyses showed while the cost to the MBS of providing ERCT would be substantial, there would be even greater cost-offsets to State/Territory hospitals that provide healthcare for patients with severe genetic conditions (\$159 million cost-offset in

¹⁷ MSAC application 1573 PSD: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1573-public>

year 6), and to the Pharmaceutical Benefits Scheme (PBS) (\$22 million cost-offset in year 6). ESC considered the State/Territory and PBS aspects of the financials had been thoroughly addressed by the ADAR. This results in a net financial saving of adopting ERCT, estimated to be a \$79 million net saving in year 6 (Table 17). *Following the ESC meeting, MSAC noted the Department had provided figures correcting transcription errors, and that the estimated cost to the MBS exceeds the estimated cost-offsets, resulting in a net financial spend of adopting ERCT.*

ESC considered that ERCT has the risk of being interpreted as commoditising the value of human life and couples may feel pressured to use the investigation to reduce society's healthcare costs. Additionally, it may contribute to increasing stigma for those living with genetic conditions included in ERCT testing. It is therefore important that ensuring appropriate test reporting, and patient education and counselling are supportive of patient autonomy, confidentiality and equity of access. ESC considered that the proposed testing needs to be perceived to be acceptable to the community, and that broader public engagement may be required before ERCT proceeds further in Australia. ESC considered there is a need for a parallel independent ethical analysis of ERCT. Ethical issues need to be considered during decision-making, including the four principles of biomedical ethics.

ESC noted implementation issues with the application:

- Advice from the National Pathology Accreditation Advisory Council (NPAAC) highlighted that there is currently no specific quality assurance program (QAP) for large reproductive carrier screening panels in Australia or internationally. Alternatives include established EQA programs for single genes of common disorders, or sample swap with other Australian laboratories.
- Variants in some genes proposed to be included in ERCT can cause different conditions with different modes of inheritance. For example, variants in fumarate dehydrogenase (*FH* gene) can cause the AR disease fumarate deficiency, but also hereditary leiomyomatosis and renal cell carcinoma (HLRCC), an autosomal dominant, hereditary cancer syndrome. ESC considered that the inclusion of such genes means ERCT will uncover people with AD conditions that have significant health implications, so an ethically defensible approach is required to address this, such as an opt-out registry, potentially on a gene-by-gene basis.
- The proposal is seeking public funding through the MBS rather than as a population screening program, although it could be considered to be comparable to screening. Therefore, ESC considered it may be appropriate for ERCT to have a registry and an expert panel. The expert panel would be an independent body providing oversight, including determining the scope of testing and results, such as any changes to the gene list over time, pathogenicity, and approach to variants. The registry could be linked to population level data – the National Cancer Screening Register for participants in cervical and bowel cancer screening could provide a model.
- ESC noted PASC had advised any requestors beyond medical practitioners would need to be justified. The ADAR proposed requestors include midwives, nurses, and other healthcare providers without justification. ESC considered that although oversight would be required when ordering tests, in the context of the suggested establishment of a register and expert panel, it may not be necessary to limit requesting to medical, midwives and nurse practitioners. ESC also considered that most referring clinicians should be able to provide adequate post-test counselling for couples found to not be at increased risk, however for the 1.6% of couples found to be at increased risk post-test counselling may be beyond the scope of most referrers. Many of the diseases proposed to be included in ERCT are rare, and GPs may not have the required expertise to advise couples on each one.

- While many results will be variants known to be pathogenic (or likely pathogenic), or benign (or likely benign), ERCT on a population scale will also detect many variants of uncertain significance (VUSs). ESC noted the applicant suggests the pathogenicity of VUSs can be determined using ClinVar and other public databases, however ESC considered that public databases may not be sufficient to adequately assign pathogenicity for many variants. ESC considered it is unclear how VUSs will be handled in terms of couple increased risk assignment, and how couples will be counselled around any VUSs detected.
- The testing proposed is complex and requires workforce expertise. Though ESC considered that some reproductive carrier testing is already provided in Australia and this may mitigate scalability issues.
- The significant capital costs for this testing at scale and the small expert workforce will likely limit providers to a small number of laboratories. It is difficult to estimate the demand for testing, though ESC noted there are about 310,000 pregnancies per year in Australia, of which approximately 180,000 are first pregnancies – the major group of interest for ERCT. So the scale of testing may provide a challenge where only a small number of laboratories develop the test.
- Transferring genomic data between labs is not well catered for at present. ESC considered the National Approach to Genomic Information Management (NAGIM) blueprint is relevant to this issue, and noted the preliminary recommendations to implement the NAGIM blueprint are being consulted on at present.
- The idea of “risk” may differ for different members of the public. This, and the concept of ERCT more broadly, needs to be communicated to the public appropriately. Potential patients need appropriate information in order to provide informed consent to the test, so they are aware of what results they could receive and what they might mean, even if the chance of receiving an “increased risk” result is low.
- The ADAR does not identify how the referrals, informed consent, testing and counselling will be delivered to remote/rural communities. ESC considered that permitting self-collected samples (e.g. a buccal swab sent through the post) would increase equity of access to ERCT, and recalled self-collected samples had been supported previously in relation to cervical screening¹⁸. However, ESC considered that the diagnostic performance of self-collected samples relative to provider-collected samples would have to be examined in order for self-collected samples to be supported for ERCT. ESC also noted there are problems associated with using self-collected samples, including paternity and informed consent. Moreover, ESC considered that for ERCT, at least in the initial years before it is well known to the public, healthcare-providers collecting the sample would be useful as this contact would ensure information is appropriately communicated to couples.
- The ADAR does not identify how the referrals, informed consent, testing and counselling will be delivered to Aboriginal and Torres Strait Islander communities in a sensitive and culturally safe way. ESC suggested that a co-development and/or co-leading approach with Aboriginal and Torres Strait Islander communities may be appropriate, and would improve uptake of ERCT amongst these communities. ESC suggested that any expert panel overseeing ERCT would benefit from ongoing Aboriginal and Torres Strait Islander representation.
- ESC noted consultation feedback had raised that storage and transfer of genomic data for years/decades is not catered for at present.

¹⁸ MSAC application 1664 PSD: <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1664-public>

17. Applicant comments on MSAC's Public Summary Document

The Applicant acknowledges the concerns raised by MSAC, and appreciates the Committee's recognition of the complexity of implementing expanded reproductive carrier testing (ERCT) at scale in Australia. We particularly note, and are encouraged by, MSAC's reiteration of the unmet clinical need for ERCT, and emphasis on the importance of resolving the current inequity of access to reproductive choice for Australian couples. While the Mackenzie's Mission study has concluded, additional evidence as to reproductive outcomes, psychosocial implications and participant experience will continue to be evaluated, and will inform a future re-submission to MSAC. The Applicant appreciates the complexity of the ethical, cultural and societal implications of ERCT, as raised by MSAC. We continue to build evidence on these issues, and plan to address these concerns in more detail upon re-submission.

However, for a re-submission, some of the suggestions noted by MSAC are optimistic, and/or impossible to achieve with current resourcing. These include, but are not limited to, the evaluation of the severity and acceptability of inclusion of each individual condition. It would be practically inconceivable to amass the evidence of economic and societal acceptability of every included gene variant, condition, and penetrance given their rarity. However, this should not be the basis for MSAC to conclude that a smaller, targeted gene panel would resolve this issue. Without ERCT, hundreds of Australians each year are facing the reality of having children born with severe, debilitating, and life-limiting conditions that impact not only health system expenditure, but the very fabric of these families' lives.

We are particularly pleased that MSAC has requested that the Department of Health and Aged Care investigate the appropriateness of funding ERCT as a screening program, given the infrastructure and oversight required to implement it effectively at a national scale. We are conscious of the challenges of delivering an equitable, consistent, and safe ERCT program at scale nationally. We welcome the opportunity to explore an ERCT national screening program with the Department.

We note that while our initial application was not supported in its current form, MSAC "would welcome a future re-application". We plan to build the evidence from Mackenzie's Mission, address the issues raised where possible, and resubmit for the consideration of MSAC in 2023.

18. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)