



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1671 - Targeted carrier testing for severe monogenic conditions

Applicant: **Royal College of Pathologists of Australasia (RCPA)**

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 targeted carrier testing for nine severe monogenic conditions was received from the Royal College of Pathologists of Australasia (RCPA) 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 supported the creation of a new Medicare Benefits Schedule (MBS) item for reproductive carrier testing of individuals who are of reproductive age and who identify as being of Ashkenazi Jewish descent to detect genetic variants known to cause nine severely disabling and/or life-threatening monogenic conditions that are highly prevalent in this community. From the public consultation input received in the context of this application, MSAC was confident that such individuals within this community would be capable of this necessary self-identification, and would be prepared to do so. MSAC considered that this testing would only be clinically effective for people of Ashkenazi Jewish descent, but that future applications to MSAC could propose testing of other groups at increased risk for specific heritable conditions, relative to the general population. MSAC also supported related MBS items for reproductive partner testing (for non-Ashkenazi Jewish partners) and fetal testing, but advised that the proposed re-analysis item is not required and was therefore not supported. MSAC advised that the value of supported tests mostly arises from the improved basis for reproductive decision-making, and accepted that many of these decisions had also been shown to consequently reduce overall costs to the healthcare system.

Consumer summary

This is an application from the Royal College of Pathologists of Australasia (RCPA) requesting Medicare Benefits Schedule (MBS) listing of reproductive carrier genetic testing for specific variants in 12 genes relating to 9 severe conditions that are much more commonly found in the Ashkenazi Jewish population than in the general population. The conditions are Tay-Sachs disease, Canavan disease, Familial dysautonomia, Mucopolysaccharidosis type IV, Glycogen storage disease type 1, Fanconi anaemia type C, Gaucher disease type 1, Niemann Pick disease type A and Bloom syndrome. The test would also include testing for variants that cause Cystic Fibrosis, Spinal muscular atrophy and Fragile-X syndrome, though as reproductive carrier testing for these conditions in the general population has already been supported by MSAC and will be MBS listed from 1 November 2023, the comparative safety, clinical effectiveness and cost-effectiveness of testing for these conditions under the proposed intervention was not examined again as part of this application.

People with Ashkenazi Jewish ancestry have a one in five chance (20%) of being a genetic carrier for at least one of these conditions. These conditions are all caused by variants found within a single gene (monogenic) and are either autosomal recessive or X-linked. Autosomal recessive means that an affected person needs to inherit two copies (one from each parent) of the altered gene to have the condition. X-linked means the gene is on the X chromosome, meaning that male children (who carry only one X chromosome) are more commonly affected. Because the conditions are inherited in an autosomal recessive or X-linked recessive way, the chances of having an affected child are one in four (25%) if the parents are carriers.

The nine conditions are all severe and cause shortened life expectancy as few, if any, curative treatments are available. Having a child born with these conditions causes significant burden to affected children and their families, to society and to the healthcare system. Many Ashkenazi Jewish people currently pay for reproductive carrier testing themselves, and some people can access charity-funded testing. Therefore, access is largely limited to those who can afford to pay for it.

The application proposed testing for a panel of specific genetic variants that are more common in the Ashkenazi Jewish population. MSAC considered it appropriate to limit panel testing to this group of people, as the panel test is not designed to detect any other variants. Most people who have Ashkenazi Jewish heritage are aware of their ethnicity and self-identify as being Ashkenazi Jewish, and MSAC considered that they would be prepared to self-identify to receive reproductive carrier testing.

Where both people in a reproductive couple are of Ashkenazi Jewish descent, they would both be able to use the panel test. But where a person of Ashkenazi Jewish descent has a reproductive partner of non-Ashkenazi Jewish descent, then that partner is not necessarily likely to have the variants that are more common in the Ashkenazi Jewish population.

If the Ashkenazi Jewish partner is found to have a variant (or variants), then their non-Ashkenazi Jewish partner can be tested. This test needs to check all variants in the same gene (or genes) in which the Ashkenazi Jewish partner has a genetic variant, as opposed to only the specific genetic variants that are more common in the Ashkenazi Jewish population. MSAC considered that supporting this test for non-Ashkenazi Jewish reproductive partners would allow couples in which only one reproductive partner is of Ashkenazi Jewish descent to make informed reproductive decisions.

MSAC also supported fetal testing for couples who are at risk of having a child affected by one of these conditions.

MSAC considered the proposed genetic testing to be effective in that it enabled people to make improved reproductive choices, it is very good value for money, and there were no safety

Consumer summary

concerns about the testing. MSAC considered the cost to the MBS to publicly fund this testing was acceptable.

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

MSAC supported Medicare Benefits Schedule (MBS) listing of reproductive carrier testing for specific genetic variants that cause nine severe conditions commonly found in the Ashkenazi Jewish population, and MBS items for the testing of reproductive partners of Ashkenazi Jewish people (who are not Ashkenazi Jewish) and fetal testing. MSAC considered the testing to be safe, effective and good value for money, and that it has an acceptable total cost to the MBS.

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

MSAC noted that this was a new application for targeted reproductive carrier testing for specific founder variants in 12 genes associated with nine severe autosomal recessive and X-linked recessive monogenic conditions much more commonly found in the Ashkenazi Jewish population than in the general population, these nine conditions being: Tay-Sachs disease (TSD), Canavan disease, familial dysautonomia, mucopolysaccharidosis type IV, glycogen storage disease type 1, Fanconi anaemia type C, Gaucher disease type 1, Niemann Pick disease type A and Bloom syndrome. MSAC noted these recessive genetic conditions are responsible for significant morbidity and mortality in affected individuals; one in five (20%) of Ashkenazi Jewish individuals who undergo genetic testing will be carriers for one or more of these conditions. Couples in the general population planning pregnancy would typically be at very low risk for having an affected child and the risk would be of having only one of these conditions. MSAC noted the applicant proposed that the test in practice would also include testing for variants that cause Cystic fibrosis (CF), Spinal muscular atrophy (SMA) and Fragile-X syndrome (FXS). However since testing for these conditions has previously been supported for public funding (MSAC application 1573), the current assessment does not include a reanalysis of the three supported tests.

MSAC noted that the proposed test was a genetic panel test, performed in National Association of Testing Authorities- (NATA-) accredited laboratories with appropriate supervision arrangements. MSAC noted the proposal is method-agnostic. Currently, carrier testing in the Ashkenazi Jewish population is undertaken on a user-pays basis or through small-scale programs funded by private organisations for targeted populations, such as New South Wales high school students. MSAC thus considered there to be inequity of access to reproductive carrier testing and noted the high community demand in the Ashkenazi Jewish population to access such testing given the known severity of the nominated conditions.

MSAC noted the proposed MBS item descriptors, and that in them Ashkenazi Jewish ethnicity is characterised indirectly, by requiring individuals to have "greater than 10% risk" of being a carrier of the conditions in the testing panel to be eligible for testing, which MSAC considered unclear and potentially leading to leakage. MSAC noted that the applicant's pre-MSAC response emphasised that the genetic variants proposed to be included in the test (1671 PICO, Table 2) were specifically chosen to cater to individuals of Ashkenazi Jewish descent and would be of limited value in other populations. MSAC agreed that the test would only be effective for people with Ashkenazi Jewish descent, noting that these founder variants are not seen in the Sephardic Jewish population or other populations. MSAC considered that explicitly stating the test is for individuals of Ashkenazi Jewish descent would reduce potential confusion as to the appropriate persons to receive this test, and that for existing tests where the eligible population is defined based on pre-test increased risk, the population is defined unambiguously. MSAC also noted the

applicant's pre-MSAC response, which acknowledged ESC's concerns about the appropriateness of defining testing eligibility based on ethnicity but considered that this testing represents positive discrimination for a previously under-catered-for group. MSAC acknowledged the potential perceived harms in explicitly describing the eligible test population based on ethnicity, though considered that most people of Ashkenazi Jewish heritage are aware of their heritage and already self-identify as being Ashkenazi Jewish, including to access existing privately funded reproductive carrier testing. On balance, MSAC advised that it was appropriate that 'the patient of reproductive age' as described in the MBS item descriptor should be explicitly described as being of Ashkenazi Jewish descent.

MSAC acknowledged that there are other specific populations that have a higher than general population-risk for certain severe or life-limiting conditions, and advised it would welcome applications for genetic testing in these populations providing the increased pre-test risk can be adequately defined and evidenced. MSAC removed practice note 1 on AAAA, as this reflected the applicant's initial proposal that the test be generalised across all ethnicities, which the applicant no longer proposed after PASC consideration.

MSAC noted that the applicant's pre-MSAC response agreed with ESC's suggestion to remove "asymptomatic" and make MBS item AAAA also available to symptomatic individuals. MSAC considered that individuals symptomatic for one or more of the listed conditions should not be ineligible to receive reproductive carrier testing to assess their carrier status for the remaining listed conditions, and so agreed this was appropriate. MSAC also considered that reproductive partner testing should be available to the partners of not only individuals who are carriers of the conditions listed in item AAAA, but also the partners of individuals who are affected by one of these conditions. MSAC therefore advised CCCC should be amended to also include the partners of individuals affected by these conditions. MSAC noted that the economic and financial analyses had not included the partners of individuals affected by these conditions, but considered that the impact would be low.

MSAC noted that the AAAA practice note recommended simultaneous testing of any reproductive partners not already tested where the couple is already pregnant, and considered that simultaneous testing of reproductive partners is appropriate if the reproductive partner of the identified carrier is also at high risk (i.e., also of Ashkenazi Jewish descent and so also able to access AAAA).

MSAC noted that reproductive partners who do not have Ashkenazi Jewish heritage are very unlikely to carry one of the specific founder variants tested in AAAA. For these reproductive partners, CCCC provides sequencing of the gene (or genes) in which their Ashkenazi Jewish reproductive partner has been found to have a variant (or variants). MSAC further noted that reproductive carrier testing for CF, SMA and FXS will in future be available under the items supported under application 1573, which will be higher volume and cheaper testing. MSAC considered that where the Ashkenazi Jewish partner has a CF/SMA/FXS variant, it would therefore be more cost-effective to provide reproductive partner testing under the items supported in 1573 than whole gene sequencing under CCCC, and advised that testing for the reproductive partners of Ashkenazi Jewish individuals affected by or carriers of CF/SMA/FXS variants should be done under 1573 items and not under CCCC. MSAC advised that the reproductive partners of Ashkenazi Jewish individuals affected by or carriers of the remaining conditions described in item AAAA should remain eligible for both gene sequencing under CCCC and carrier testing under the 1573 items. MSAC noted the assessment had assumed reproductive partner testing under CCCC would replace services under 1573 items for all conditions on the panel, so the financial analysis will have overestimated the cost of CCCC services and overestimated the offset from 1573 services replaced.

MSAC noted the application proposed MBS item EEEE for re-analysis of the initial results, and recalled that it had previously supported re-analysis for “previously unreported germline variants” (e.g., MBS item 73360) in the context of exome/genome sequencing. MSAC advised re-analysis was not appropriate for this testing as, although the items are method-agnostic, in line with current clinical practice and the proposed schedule fees it is unlikely they will be used for exome/genome sequencing. Therefore all tested variants would be reported upfront and no unreported variants would remain for potential future re-analysis.

MSAC noted AAAA was proposed to be requestable “by or on behalf of a medical practitioner who manages the treatment of the patient”, and CCCC “by or on behalf of a specialist or consultant physician who manages the treatment of the patient”. MSAC considered that appropriate requestors for reproductive carrier testing include general practitioners, so restriction of CCCC to a specialist was not appropriate. Consistent with this advice, MSAC also recalled that for reproductive carrier testing supported under application 1573 it had supported referrals by medical practitioners without restriction. MSAC noted that GGGG was proposed to be requestable “by a consultant physician practising as a clinical geneticist”. MSAC considered that the usual requestors for fetal testing are clinical geneticists, maternal-fetal medicine specialists and obstetricians, and advised GGGG should be requestable by specialist or consultant physicians.

MSAC noted that the proposed GGGG item descriptor stated that “the pregnancy is a singleton pregnancy” but considered MBS item GGGG should be eligible in pregnancies with more than one fetus, as this is routine clinical practice. MSAC advised that in the case of multiple pregnancies, it intended fetal testing to be billed on a per fetus basis. MSAC noted that billing per fetus for multiple pregnancies was not included in the economic or financial analyses, but considered the impact would be low.

MSAC noted that item GGGG was proposed to be available “where both prospective parents are known to be affected by or carriers of autosomal recessive variants or one parent is known to be affected by or a carrier of an X-linked pathogenic variant/s”. MSAC considered that usually both parents’ genotypes are known, but where one parent is affected or a carrier and the other parent is unavailable for testing, the treating practitioner and provider together with the patient may decide to pursue fetal testing based on the patient’s circumstances. MSAC therefore advised that GGGG should not necessarily require both parents’ genotypes be known beforehand for autosomal recessive variants. MSAC considered that its expansion of item GGGG to include where only one parent’s genotype is known is clinically appropriate and would likely have minimal overall impact to the economic and financial analyses.

MSAC considered that the cost for laboratories to test only a small pre-defined set of single nucleotide polymorphisms (SNPs) would be small, and agreed it was appropriate that AAAA had a proposed fee only a small amount greater than the CF/SMA/FXS testing, which has a fee of \$400, and accepted the applicant’s proposed fee of \$425 for AAAA. MSAC considered that the proposed fee of \$1200 for testing non-Ashkenazi Jewish reproductive partners under CCCC is appropriate given the test provided under AAAA would not be suitable for non-Ashkenazi Jewish partners, and so the test requires sequencing of the whole of the gene (or genes) in which the Ashkenazi Jewish reproductive partner is a known carrier. MSAC therefore advised it supported a fee of \$1200 for CCCC in line with its previously supported fees for gene sequencing in reproductive partners. MSAC agreed with ESC and the applicant in the pre-MSAC response that a fee of \$100 was much too low to cover the cost of fetal testing under GGGG. MSAC advised it supported a fee of \$1600 for GGGG, in line with its previously supported fees for variant-specific fetal testing (1585 CCCC).

MSAC noted the PICO and economic analysis had restricted the population of couples and fetal testing to pregnancies in the first trimester. MSAC considered it would be inappropriate to

impose gestational age limits because there is variation across Australia in laws relating to termination of pregnancy. MSAC noted that many tests are done by amniocentesis in the second trimester and considered that a restriction based on gestational age could inadvertently limit the potential obstetric/neonatal value in knowing a child will be affected or not. MSAC also noted that GGGG was proposed to be restricted to “one test per pregnancy” but considered that the risk of potential leakage of testing for item GGGG is rare as patients do not have diagnostic tests more than once in a pregnancy if avoidable. MSAC also noted that testing of chorionic villus samples may in rare cases be inconclusive due to significant maternal cell contamination, in which case testing of an amniocentesis sample may also be required. MSAC thus advised that frequency restriction on GGGG should be removed.

MSAC considered that this type of testing does not normally require hospital treatment or accommodation, and therefore advised that it should be classified as Type C under the *Private Health Insurance (Benefits Requirements) Rules 2011*.

MSAC supported the following MBS item descriptors:

Table 1 MSAC’s supported MBS items

Category 6 (Pathology Services)	Group P7 Genetics
MBS item AAAA	
Characterisation of germline pathogenic or likely pathogenic gene variants:	
(a) in at least the following genes:	
(i) ASPA	
(ii) BLM	
(iii) CFTR	
(iv) ELP1	
(v) FANCA	
(vi) FANCC	
(vii) FANCG	
(viii) FMR1	
(ix) G6PC1	
(x) GBA1;	
(xi) HEXA;	
(xii) MCOLN1;	
(xiii) SLC37A4;	
(xiv) SMN1; and	
(xv) SMPD1	
(b) in a patient of reproductive age who is of Ashkenazi Jewish descent for the purpose of ascertaining their carrier status for:	
(i) Bloom syndrome	
(ii) Canavan disease	
(iii) Cystic fibrosis	
(iv) Familial dysautonomia	
(v) Fanconi anaemia type C	
(vi) Fragile-X syndrome	
(vii) Gaucher disease	
(viii) Glycogen storage disease type I	
(ix) Mucolipidosis type IV	
(x) Niemann-Pick disease type A	

- (xi) Spinal muscular atrophy
- (xii) Tay-Sachs disease

Applicable once per lifetime.

Fee: \$425.00 **Benefit:** 75% = \$318.75 85% = \$361.25

Category 6 (Pathology Services) – Group P7 Genetics

MBS item CCCC

Whole gene sequencing of a gene or genes described in item AAAA, in a patient who is the reproductive partner of an individual who is affected by or a known genetic carrier of one or more conditions described in item AAAA other than cystic fibrosis, fragile-X syndrome or spinal muscular atrophy, for the purpose of determining the couple's combined reproductive risk of the conditions, if:

- (a) the patient is not eligible for a service to which item AAAA applies; and
- (b) the patient has not received a service to which item AAAA applies; and
- (c) the patient has not received a service to which this item applies for the purpose of determining their reproductive risk with their current reproductive partner.

Applicable once per couple per lifetime.

Fee: \$1,200.00 **Benefit:** 75% = \$900.00 85% = \$1,112.10*

Category 6 (Pathology Services) – Group P7 Genetics

MBS item GGGG

Testing of a pregnant patient, where at least one prospective parent is known to be affected by or is a genetic carrier of one or more conditions described in item AAAA, for the purpose of determining whether familial variant/s are present in the fetus, if:

- (a) the detection is requested by a specialist or consultant physician; and
- (b) the fetus is at 25% or more risk of inheriting a condition described in item AAAA.

Fee: \$1,600.00 **Benefit:** 75% = \$1,200.00 85% = \$1,512.10*

* = 85% benefit reflects 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).

AAAA Practice Note: Where the couple is already pregnant and both patients are of Ashkenazi Jewish descent, concurrent testing of any partner(s) not already tested is recommended.

MSAC noted and agreed with the clinical management algorithm.

MSAC noted that Ashkenazi Jewish individuals are at a >10% personal risk of being a heterozygous genetic carrier of a clinically significant disorder associated with pathogenic or likely pathogenic variants of the genes in the testing panel. MSAC considered there to be high clinical need for this testing, as the conditions have a severe impact on the affected child and their family, as well as society. MSAC noted in gauging the demand that in 2016, Australia's total Jewish population was approximately 117,903 with the majority being Ashkenazi Jewish, and there were 1,224 annual births among the Jewish population¹.

¹ David Graham (2019). The Jewish Population of Australia – Key findings from the 2016 Census. Available at: https://jca.org.au/wp-content/uploads/2022/05/Graham-Narunsky-2019-Australia-2016-Census-Report.Final_.pdf

MSAC considered the base case comparator (reproductive carrier testing for CF/SMA/FXS, previously supported under Application 1573) to be appropriate, noting that this testing will be listed on the MBS on 1 November 2023.

MSAC noted that the application could not identify any studies that met the inclusion criteria for assessing direct test to health outcomes or evidence of targeted carrier testing for severe monogenic conditions compared to genetic carrier testing for CF, SMA and FXS, or to no genetic carrier testing. Therefore, a linked evidence approach was adopted, which identified 18 studies, though all 18 studies were assessed as having a high risk of bias.

MSAC noted ESC's concern about the potential for psychological harm in undergoing pre-implantation genetic diagnosis, but noted the lack of evidence for this. MSAC noted a school-based study showed low levels of anxiety regarding this genetic testing. MSAC noted that there was no comparative evidence identified for the safety of targeted carrier testing for severe monogenic conditions compared with genetic carrier testing for CF, SMA and FXS. On balance, MSAC advised the testing was likely safe, though it acknowledged that some uncertainty remained regarding the potential psychological harms of reproductive carrier testing.

MSAC noted that an evaluation of school-based TSD testing programs in the Ashkenazi Jewish population showed that these programs have high levels of participation (>98%), and that no Australian testing program participant has had a TSD-affected child, representing 100% health outcomes effectiveness in this cohort. Thus, MSAC considered it reasonable to assume superior effectiveness of the proposed carrier testing relative to the comparator as it would identify more carriers and provide more people with informed reproductive choices.

MSAC noted that the economic evaluation was a cost-effectiveness analysis. MSAC considered that the value of the test mostly arose from the improved basis for reproductive decision-making, and accepted that many of these decisions had also been shown to consequently reduce overall costs to the healthcare system. MSAC noted that the proposed testing (items AAAA and CCCC) has dominant cost-effectiveness when lifetime healthcare costs are taken into account, and when only the costs of testing are taken into account the incremental cost-effectiveness ratio (ICER) is \$2 per affected birth averted. MSAC agreed with ESC that testing in the preconception stage was more cost-effective (in the sense of resulting in a lower ICER per affected birth averted) than pre-natal testing (notably for TSD).

MSAC noted that the model calculations used an artificial population of 100,000 patients along with assumptions about the proportions of preconception versus prenatal reproductive carrier testing, and made assumptions about the share of couples requiring a combination of AAAA & CCCC (i.e. reproductive couples in which one partner is not Ashkenazi Jewish and so ineligible for AAAA) in order to generate outcomes in term of the number of potentially affected births and the lifetime healthcare costs associated with these conditions. The main drivers of the model were the specificity of genetic carrier testing for severe monogenic conditions and the lifetime costs of healthcare. MSAC noted ESC's concern that the proportion of preconception versus pre-natal testing (base case: 20% vs 80%) was based on a general population estimate, and that the proportion of preconception testing may be an additional driver of cost-effectiveness that had been insufficiently explored. MSAC noted the rejoinder included calculations showing that adjusting the uptake rate by 10% results in a maximum 26% change in the total financial costs of listing. MSAC considered that individuals of Ashkenazi Jewish descent may have heightened awareness of their risk of conditions and greater uptake of preconception testing and so the estimated uptake may be an underestimate.

MSAC noted the financial impact to the MBS was estimated at \$220,919 in year 1 (assumed 2021-22) decreasing to \$111,338 in year 6 (assumed 2026-27; noting the financial impact assumes an average annual financial saving to the MBS of \$91,884 from 1 November 2023,

associated with the listing of CF/SMA/FXS testing supported under MSAC 1573), MSAC also noted a small potential increase in financial cost to the States/Territories for terminations. MSAC considered these to be reasonable estimates, and advised they resulted in an acceptable financial cost.

MSAC noted advice from the National Pathology Accreditation Advisory Council (NPAAC) that there is no specific external quality assurance (EQA) program for this particular panel in Australia or internationally, and considered that testing would need to follow standard technology-based EQA.

4. Background

The Royal College of Pathologists of Australasia (RCPA) submitted MSAC Application 1671 for Medicare Benefits Schedule (MBS) funding of targeted genetic carrier testing for severe monogenic conditions that, although relatively rare in the broader Australian population, are highly prevalent in certain ethnic groups. As submitted, the application sought the listing of new MBS items for genetic testing for any severe monogenic condition prevalent in any subpopulation, plus CF, SMA and FXS. The RCPA envisaged referrers and providers would determine the conditions to be tested for based on their patient's ethnic heritage, as informed by published, publicly accessible gene variant lists.

Following the PASC meeting, the applicant agreed to limit this application to patients of Ashkenazi Jewish heritage. The intervention was consequently limited to variants in genes associated with the following nine conditions, plus those associated with CF, SMA and FXS:

- Bloom Syndrome (BS)
- Canavan disease (CD)
- Familial dysautonomia (FD)
- Fanconi anaemia type C (FA)
- Gaucher disease (GD)
- Glycogen storage disease type 1 (GSD1)
- Mucopolysaccharidosis type IV (MLD)
- Niemann Pick Disease type A (NPD)
- Tay-Sachs Disease (TSD)

MSAC has not previously considered the use of targeted carrier testing for the nine severe monogenic conditions nominated in this application. ESC and MSAC considered a related application, MSAC Application 1637, for expanded reproductive carrier testing of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions at the June and July 2022 meetings respectively (i.e., the same meetings at which MSAC Application 1671 was considered).

In July 2020, MSAC supported public funding of application 1573 for three-gene reproductive carrier testing to detect CF, FXS and spinal muscular SMA. In Budget 2022-23, the Australian Government agreed to the listing of items supported under MSAC Application 1573 from 1 November 2023.

At the time of drafting this Department-Contracted Assessment Report (DCAR), no MBS items were listed for the three-condition panel supported in MSAC application 1573 (Medical Services Advisory Committee (MSAC), 2020).

Genetic testing for CF is currently available through the MBS under certain circumstances (MBS items 73345, 73346, 73347, 73348, 73349, 73350).

5. Prerequisites to implementation of any funding advice

Genetic testing for disease should be undertaken in a National Association of Testing Authorities (NATA) accredited laboratory. NPAAC advised that expertise for this testing already exists as it is currently undertaken in Australia. NPAAC advised that there is no specific EQA program for this panel in Australia or internationally, and that alternatives include established EQA programs for single genes of common disorders, or sample swap with other Australian laboratories.

6. Proposal for public funding

The applicant proposed the intervention be publicly funded through the MBS. Proposed new MBS item descriptors (as considered by PASC) are presented in Tables 2-5.

Testing would be delivered only by National Association of Testing Authorities (NATA)-accredited pathology laboratories (as defined in the MBS Pathology Services Table) by referral only by registered medical practitioners in line with other tests in the MBS Pathology Services Table. Interpretation of results would be provided by approved practising pathologists with appropriate scope of practice, or medical scientists under supervision in an accredited medical pathology service. All women considering pregnancy and where they or their reproductive partner have a >10% personal risk should be referred for antenatal testing by either their treating general practitioner or obstetrician.

Several changes were made to the MBS item descriptors following a post-PASC meeting.

PASC agreed with the following items:

- Item AAAA (Table 2)
- Item CCCC (Table 3)
- Item EEEE (Table 4)
- Item GGGG (Table 5).

PASC removed the applicant's proposed item BBBB, testing of pregnant patients, on the basis that pregnant patients are of reproductive age and so would be able to access publicly funded testing under proposed item AAAA.

PASC removed Item FFFF, interpretation of genetic carrier test results, on the basis that it would be unnecessary to support medical practitioners in providing advice to couples, given this is encompassed under other consultation items.

At the post-PASC meeting, the applicant agreed that a separate item for the cascade testing of first-degree biological relatives (DDDD) is not needed as this population has >10% personal risk and so is already captured under AAAA.

Table 2 Proposed item descriptor for targeted carrier testing

Category 6 (Pathology Services) – Group P7 Genetics
MBS item AAAA
<p>Testing of asymptomatic individuals of reproductive age, for the presence of pathogenic or likely pathogenic variants in order to ascertain their carrier status, in a panel of genes causing severe monogenic disorders that must include the <i>CFTR</i>, <i>SMN1</i>, <i>FMR1</i>, <i>HEXA</i>, <i>ASPA</i>, <i>ELP1</i>, <i>MCOLN1</i>, <i>G6PC1</i>, <i>SLC37A4</i>, <i>FANCA</i>, <i>FANCC</i>, <i>FANCG</i>, <i>GBA1</i>, <i>SMPD1</i>, and <i>BLM</i> genes, requested by or on behalf of a medical practitioner who manages the treatment of the patient.</p> <p>Individuals must have a >10% personal risk of being a genetic carrier of any of the clinical disorders associated with pathogenic or likely pathogenic variants of genes in the testing panel, namely Cystic Fibrosis, Spinal Muscular Atrophy, Fragile X Syndrome, Tay Sachs Disease, Canavan disease, Familial dysautonomia, Mucopolidosis Type IV, Glycogen storage disease type 1, Fanconi anaemia type C, Gaucher disease, Niemann Pick Disease type A, and Bloom Syndrome.</p> <p>One test per lifetime.</p>
Fee: \$425

Practice Note 1: For individuals of Ashkenazi Jewish ancestry, the panel *must also* include *HEXA*, *ELP1*, *SMPD1*, *ASPA*, *FANCC*, *BLM* and *MCOLN1*. Additional genes may also be included in the panel using standardised pathology lists of genes according to ethnic risk. The reference source for these gene lists will be provided by the applicant. **Practice Note 2:** where the couple is already pregnant, concurrent testing of any partner(s) not already tested is recommended.

Table 3 Proposed item descriptor testing of the reproductive partner

Category 6 (Pathology Services) – Group P7 Genetics
MBS item CCCC
<p>Genetic testing of the reproductive partner of an individual who has a >10% personal risk of being a heterozygous genetic carrier of serious clinical disorders associated with pathogenic or likely pathogenic variants of genes as described in AAAA, for all variants within the relevant gene(s) in which their reproductive partner carries a variant, for the purpose of determining the couple's reproductive risk of this condition. The tested individual must not have received a service described in AAAA. Requested by or on behalf of a specialist or consultant physician who manages the treatment of the patient.</p> <p>One test per couple per lifetime.</p>
Fee: \$1200

Table 4 Proposed item descriptor for re-analysis of genetic test results arising from previously performed

Category 6 (Pathology Services) – Group P7 Genetics
MBS item EEEE
<p>Re-analysis of genetic test results arising from testing previously performed under Items AAAA, for the purpose of identifying previously unreported pathogenic or likely pathogenic variants in genes included on the gene panel to determine genetic carrier status, where the pathogenicity of these variant(s) was not known at the time of the previous analysis.</p> <p>Performed at least five years after a service to which AAAA, or BBBB, or DDDD applies.</p> <p>Applicable only twice per lifetime.</p>
Fee: \$ 100

Note: As it was agreed at the post-PASC meeting that BBBB and DDDD are not required, the descriptor for EEEE was amended to remove reference to BBBB and DDDD (blue strikethrough font).

While the fee for Item EEEE was designated in the application and PICO confirmation at \$100, this fee does not align with the fee of \$500.00 for similar items previously supported under MSAC 1585 and 1599. It was not possible to include item EEEE in the financial estimates model,

as the impact and prevalence of currently unknown pathogenic or likely pathogenic variants is inherently uncertain.

Table 5 Proposed item descriptor for fetal testing

Category 6 (Pathology Services) – Group P7 Genetics
MBS item GGGG
Testing of a pregnant patient, where one or both prospective parents are known to be affected by or carriers of known pathogenic variant/s causative of a disease tested for in AAAA, for the purpose of determining whether familial variants are present in the fetus, if: (a) The pregnancy is a singleton pregnancy; and (b) The detection is requested by a consultant physician practising as a clinical geneticist; and (c) The fetus is at 25% or more risk of inheriting a monogenic variant known to cause a disease tested for in AAAA.
One test per pregnancy.
Fee: \$ 100

As with Item EEEE, PASC advised that the fee for GGGG will need to be increased. A proxy for this fee would be MBS item CCCC in MSAC 1585 which was set at \$1600. As the appropriateness of this fee has not been discussed by PASC, ESC or MSAC in the context of this application, the original applicant proposed fee of \$100 was included as the base case in the evaluation, and the higher fee of \$1600 was included in a sensitivity analysis.

7. Population

One PICO set was defined in the PICO confirmation. The target population for carrier testing is people of Ashkenazi Jewish ancestry who have a >10% risk of being a heterozygous genetic carrier of any of the nine severe autosomal recessive and X-linked conditions: Tay Sachs Disease (TSD), Canavan disease (CD), Familial dysautonomia (FD), Mucopolysaccharidosis Type IV (MLD), Glycogen storage disease type 1 (GSD1), Fanconi anaemia type C (FA), Gaucher disease type 1 (GD), Niemann Pick Disease type A (NPD), and Bloom Syndrome (BS).

At present, genetic testing has been recommended by MSAC in the general population for two autosomal recessive genes responsible for SMA, CF, and the X-linked gene for FXS (supported by MSAC in Application 1573); however, this medical service will not be reimbursed through the MBS until 1 November 2023. In practice, the additional genes proposed for the new panel will be offered together with the already supported testing for SMA, CF and FXS under the items proposed in this application, and provide additive benefits of genetic testing in the at-risk population.

There is no clinical management pathway for individuals prior to receiving the intervention. Carrier testing is designed to identify individuals at-risk for being a carrier of one or more of the nominated conditions.

In Australia, genetic testing for the nominated severe monogenic disorders is currently accessible to some at-risk individuals in the Ashkenazi Jewish population via the following pathways:

- cohort high-school-based preconception testing
- preconception testing prior to marriage
- antenatal testing early in pregnancy

Carrier testing in the Ashkenazi Jewish population is currently undertaken by individuals either on a user-pays basis, or in small-scale programs funded by private organisations, which are mostly limited to high school students.

Couples identified as being at high risk of having an affected child would be referred to a clinical geneticist, maternal-fetal medicine service, a specialist obstetrician, or to a genetics health professional under appropriate medical supervision.

It is likely that the introduction of this service prior to conception would increase the use of services such as *in vitro* fertilisation and preimplantation genetic diagnosis. The introduction of carrier testing for couples who are already pregnant may increase services such as chorionic villus sampling or amniocentesis and termination.

The assessment report addresses the requirements of the ratified PICO (PICO Advisory SubCommittee, 2021).

8. Comparator

The base case comparator for the proposed carrier testing is genetic carrier testing for SMA, CF, and FXS, as supported by MSAC (Medical Services Advisory Committee (MSAC), 2020).

9. Summary of public consultation input

Input was received from one individual and one organisation, the Victorian Clinical Genetics Service (VCGS). Feedback was mixed, with both supportive and unsupportive perspectives received, however both responses did not agree with testing eligibility being defined by ethnicity. Following PASC, input was received from Private Pathology Australia (PPA), Australian Genomics Health Alliance (AGHA), Australian Pathology (AP), Human Genetics Society of Australasia (HGSA), Royal Australian College of General Practitioners (RACGP) and SMA Australia.

The advantages of the proposed testing were stated to be:

- Preconception genetic testing may facilitate disease prevention and, in the context of IVF, may avoid suffering and child loss.
- MBS funding of preconception genetic testing would promote equity of access.
- MBS funding of preconception genetic testing may reduce the cost of caring for children with severe disease.

The disadvantages of the proposed testing were stated to be:

- It is difficult to gauge an individual's pre-test risk of severe monogenic disorders.
- Defining the population by ethnic ancestry may become ineffective as some patients may not know their ethnic ancestry, may be from multiethnic backgrounds or, may have a partner of a different ethnicity that is not captured in the proposed population.

The following other points were raised:

- The population may be extended to include all prospective parents or other ethnicities with high risk for severe monogenic conditions.
- The targeted gene panel should be broad to target the commonly occurring autosomal recessive conditions with increased incidence compared to the general population.

- In the prenatal test setting both partners should be tested concurrently.

10. Characteristics of the evidence base

No studies met the inclusion criteria for assessing the direct from test to health outcomes or evidence of targeted carrier testing for severe monogenic conditions compared to genetic carrier testing for CF, SMA, and FXS, or to no genetic carrier testing.

A linked evidence approach was therefore attempted. Eighteen studies reporting on the diagnostic yield of targeted genetic testing, change in reproductive decision-making, health outcomes, and safety were identified (Table 6). None of these studies had a relevant comparator.

Table 6 Key features of the included evidence

Criterion	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in evidence base
Diagnostic yield	Case series and ecological studies reporting carrier frequency and couple carrier frequency	☒ k=11 n>100,624	High risk
Change in patient management	Case series and an ecological study reporting reproductive decision-making	☒ k=2 n>125,223	High risk
Health outcomes	Ecological study	☒ k=1 n=NR	High risk
Safety	Cross-sectional studies and a before-after study on the psychological harms of targeted carrier testing	☒ k=3 n=521	High risk
Safety of downstream changes in management	Cross-sectional, cohort and qualitative studies on the psychological harms of PGD	☒ k=3 n=54	At risk of bias

k=number of studies, n=number of patients.

NR=not reported; PGD=preimplantation genetic diagnosis

11. Comparative safety

Three studies reporting on the psychological harms of targeted carrier testing for TSD and other conditions offered through Australian Jewish high-school programs in Sydney (Barlow-Stewart et al., 2022)² and Melbourne (Curd et al., 2014³; Ioannou et al., 2010⁴) were identified. Measures included anxiety scales (State Trait Anxiety Inventory, STAI), predicted feelings, Decision Regret Scale, and impact of event on detected carriers. Overall, psychological harms such as anxiety and decision regret were rare; most participants scored below clinically significant thresholds.

Concern tended to decrease after the genetic information session part of the program. In a follow up study 5-11 years after carrier testing, no differences in anxiety and decision regret were observed between carriers and non-carriers.

² Barlow-Stewart K, et al. (2003). A genetic screening programme for Tay-Sachs disease and cystic fibrosis for Australian Jewish high school students. *J Med Genet*, **40**(4), e45.

³ Curd H, et al. (2014). High school Tay-Sachs disease carrier screening: 5 to 11-year follow-up. *J Community Genet*, **5**(2), 139-146.

⁴ Ioannou L, et al. (2010). Evaluation of a multi-disease carrier screening programme in Ashkenazi Jewish high schools. *Clin Genet*, **78**(1), 21-31.

Key limitations include low level of evidence (two cross-sectional and one before-after study) without a comparator, risk of bias present in all three studies, and that none of the studies was adequately powered to detect clinically significant differences. Notwithstanding some concerns regarding the particular setting of the three studies (i.e., Jewish high-school programs), they are most likely applicable to the population of interest, considering that they were conducted in Australia and in populations with a high proportion of Ashkenazi Jewish ancestry. The certainty of evidence (GRADE) was graded as very low quality.

Three studies reporting on the psychological harms of preimplantation genetic diagnosis conducted in Sydney (Karatas et al., 2010a⁵; Karatas et al., 2011⁶; Karatas et al., 2010b⁷), were presented as supplementary evidence only, due to several applicability issues (conducted in the general population, treatment performed due to severe monogenic conditions, albeit different conditions than the nine conditions tested in this assessment). The evidence suggested preimplantation genetic diagnosis may increase anxiety in women, which tends to return to baseline levels if successful pregnancy is established. Some women experienced significant emotional burden and clinically significant psychological distress during the process. Depression scores did not increase significantly during the treatment.

Key limitations include limited applicability (as discussed above), low level of evidence (one cross-sectional, one longitudinal cohort and one qualitative study) without a comparator, risk of bias present in all three studies, and that none of the studies was adequately powered to detect clinically significant differences. The certainty of evidence (GRADE) was graded as very low quality.

No other evidence on the safety of downstream consequences of targeted carrier testing for severe monogenic conditions was identified.

No comparative evidence for the safety of targeted carrier testing for severe monogenic conditions compared with genetic carrier testing for CF, SMA and FXS or with no genetic testing was identified. Considering both the proposed intervention and comparator 1 use similar technology, the two interventions are likely of similar safety. However, Ioannou et al. (2010) reported that, compared with a historical cohort that only tested for TSD, increasing the number of conditions tested, increased predicted negative feelings if a study participant was to be detected as a carrier.

12. Comparative effectiveness

No direct test to health outcomes evidence was identified for targeted carrier testing for severe monogenic conditions compared to genetic carrier testing for CF, SMA and FXS, or to no genetic testing. A linked evidence approach was therefore attempted.

The only *test accuracy* measure for targeted carrier testing for severe monogenic conditions was diagnostic yield in the Ashkenazi Jewish population. Eleven studies were identified, none had a relevant comparator. All studies were considered to be at high risk of bias. The results, including the variability (range) of carrier frequencies for individual diseases reported across studies, are summarised in Table 7. The certainty of evidence (GRADE) was graded as very low quality.

⁵ Karatas JC, et al. (2010a). Psychological adjustment, knowledge and unmet information needs in women undergoing PGD. *Hum Reprod*, **25**(6), 1481-1489.

⁶ Karatas JC, et al. (2011). A prospective study assessing anxiety, depression and maternal-fetal attachment in women using PGD. *Hum Reprod*, **26**(1), 148-156.

⁷ Karatas JC, et al. (2010b). Women's experience of pre-implantation genetic diagnosis: a qualitative study. *Prenat Diagn*, **30**(8), 771-777.

Table 7 Variability of carrier frequencies of severe monogenic conditions across the studies

Study ID	Carrier frequency								
	TSD	CD	FD	MLD	GSD1	FA	GD	NPD	BS
Akler et al. (2020) ⁸	1 in 28	1 in 50	1 in 33	1 in 99	1 in 94	1 in 96	1 in 17	1 in 102	1 in 121
Cecchi et al. (2019) ⁹	1 in 33	NR	NR	NR	NR	NR	NR	NR	NR
Fares et al. (2008)	NR	1 in 82	1 in 29	1 in 67	NR	1 in 77	1 in 17	1 in 103	1 in 157
Hantash et al. (2006) ¹⁰	NR	NR	NR	1 in 103	NR	NR	NR	NR	NR
Howell et al. (2004) ¹¹	NR	1 in 46 (95% CI 1 in 30 to 1 in 77)	NR	NR	NR	NR	NR	NR	NR
Lew et al. (2011) ¹²	1 in 23	NR	NR	NR	NR	NR	NR	NR	NR
Scott et al. (2010) ¹³	1 in 27.4	1 in 55.0	1 in 30.7	1 in 88.6	1 in 64.1	1 in 100.3	1 in 15.2	1 in 115.0	1 in 133.7
Shao et al. (2015) ¹⁴	1 in 29	1 in 85	1 in 42	1 in 63	1 in 85	1 in 85	1 in 14	1 in 171	1 in 136
Singer et al. (2020) ¹⁵	1 in 43	1 in 63	1 in 37	NR	NR	NR	NR	NR	NR
Zlotogora et al. (2016) ¹⁶	1 in 45	1 in 63	1 in 38	NR	NR	NR	NR	NR	NR
Range	1 in 23 to 1 in 45	1 in 46 to 1 in 82	1 in 29 to 1 in 42	1 in 63 to 1 in 103	1 in 64.1 to 1 in 94	1 in 77 to 1 in 100.3	1 in 14 to 1 in 17	1 in 102 to 1 in 171	1 in 121 to 1 in 157

BS=Bloom syndrome; CD=Canavan disease; CI=confidence interval; FA=Fanconi anaemia type C; FD=familial dysautonomia; FXS=fragile X syndrome; GD=Gaucher disease; GSD1=glycogen storage disease type 1; MLD=mucopolidosis type IV; NPD=Niemann-Pick disease type A; NR=not reported; TSD=Tay-Sachs disease

Change in management was addressed in two studies reporting on reproductive decision-making. Both studies were single-arm and at high risk of bias. One study reported all three carrier

⁸ Akler G, et al. (2020). Lessons learned from expanded reproductive carrier screening in self-reported Ashkenazi, Sephardi, and Mizrahi Jewish patients. *Mol Genet Genomic Med*, **8**(2), e1053.

⁹ Cecchi, AC, et al. (2019). Screening for Tay-Sachs disease carriers by full-exon sequencing with novel variant interpretation outperforms enzyme testing in a pan-ethnic cohort. *Mol Genet Genomic Med*, **7**(8), e836.

¹⁰ Hantash, FM, et al. (2006). Rapid one-step carrier detection assay of mucopolidosis IV mutations in the Ashkenazi Jewish population. *J Mol Diagn*, **8**(2), 282-287

¹¹ Howell, VM, et al. (2004). Carrier screening for Canavan disease in Australia. *J Inherit Metab Dis*, **27**(2), 289-290.

¹² Lew, R., et al. (2011). Tay-Sachs disease preconception screening in Australia: self-knowledge of being an Ashkenazi Jew predicts carrier state better than does ancestral origin, although there is an increased risk for c.1421 + 1G > C mutation in individuals with South African heritage. *J Community Genet*, **2**(4), 201-209.

¹³ Scott, SA, et al. (2010). Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases. *Hum Mutat.*, **31**(11), 1240-1250.

¹⁴ Shao Y, et al. (2015). Evaluation of two-year Jewish genetic disease screening program in Atlanta: insight into community genetic screening approaches. *J Community Genet*, **6**(2), 137-145.

¹⁵ Singer, A, et al. (2020). Impact of a national genetic carrier-screening program for reproductive purposes. *Acta Obstet Gynecol Scand*, **99**(6), 802-808.

¹⁶ Zlotogora J, et al. (2016). The Israeli national population program of genetic carrier screening for reproductive purposes. *Genet Med*, **18**(2), 203-206

couples detected through their program elected to pursue prenatal diagnosis in subsequent pregnancies (Shao et al., 2015). Singer et al. (2020) reported the number of pregnancy terminations due to genetically affected fetuses (Table 8).

The certainty of evidence (GRADE) was graded as very low quality.

Table 8 Rates of prenatal diagnosis, pregnancy termination and affected live-born children with selected diseases in 2014-2017 (Singer et al., 2020)

Study ID	Risk of bias	Condition tested for	Carrier frequency	Prenatal testing (n)	Pregnancy terminations (n)	Observed affected births (n)
Singer et al. (2020)*	High	TSD (AJ, North African and Balkan Jews)	n=2,872/124,499 1 in 43	123	21	4
		CD (AJ)	n=1,310/82,244 1 in 63	24	6	1
		FD (AJ and Balkan Jews)	n=2,214/82,453 1 in 37	68	18	2

AJ=Ashkenazi Jewish; CD=Canavan disease; FD=familial dysautonomia; NPD=Niemann-Pick disease type A; TSD=Tay-Sachs disease

For evidence of health outcomes, one ecological study studied the relationship between Jewish high-school students testing programs for TSD and the incidence of TSD-affected births in Sydney and Melbourne (Lew et al., 2012¹⁷). The overall ratio of Jewish to non-Jewish TSD-affected births was 1:5 compared with the expected ratio of 1:2 (Table 9). The authors noted that no Jewish TSD carrier identified through the testing program had a TSD-affected child during that period, and no parents of TSD-affected Jewish children had participated in testing. Additionally, no program participants were parents of TSD-affected children.

The study was at high risk of bias. The number of events was low, suggesting possible imprecision issues. The study had an ecological design, therefore, direct causality could not be established. The level of evidence was low (NHMRC level IV). No comparative evidence was identified. The certainty of evidence (GRADE) was graded as very low quality.

Table 9 Expected and observed TSD-affected births in Sydney and Melbourne, 1995-2011 (Lew et al., 2012)

Study ID	Risk of bias	Population	Expected births (n)	Observed births (n)	Rate ratio (95% CI)
Lew et al. (2012)	High	Jewish	4.1	2	0.49 (0.06-1.76)
		Non-Jewish	7.4	10	1.35 (0.65-2.49)

CI=confidence interval; TSD=Tay-Sachs disease

No comparative evidence for the effectiveness of targeted carrier testing for severe monogenic conditions compared with genetic carrier testing for CF, SMA and FXS or with no genetic testing was identified.

Clinical claim

The use of targeted carrier testing for severe monogenic conditions, each with high risk for significant morbidity and or early mortality, in a population with individuals at >10% risk for being

¹⁷ Lew RM, et al. (2012). Tay Sachs disease in Australia: Reduced disease incidence despite stable carrier frequency in Australian Jews. *Med J Aust*, **197**(11), 652-654.

a carrier of one or more of the nominated conditions results in uncertain effectiveness compared with genetic carrier testing for CF, SMA and FXS based on the paucity of evidence: no comparative evidence was identified. If considering naïve comparisons, it could be assumed that testing for additional conditions would identify additional carriers, resulting in superior effectiveness.

The use of targeted carrier testing for severe monogenic conditions in the at-risk population results in superior effectiveness compared with no genetic carrier testing.

The use of targeted carrier testing for severe monogenic conditions in the at-risk population results in uncertain safety compared with genetic carrier testing for CF, SMA and FXS based on the paucity of evidence: no comparative evidence was identified. There is, however, the risk of having an affected child following natural conception if not testing for genetic conditions.

The use of targeted carrier testing for severe monogenic conditions in the at-risk population results in inferior safety compared with no genetic carrier testing. There is, however, the background risk of having an affected child following natural conception if not testing for genetic conditions.

13. Economic evaluation

A cost-effectiveness analysis (CEA) was conducted. The economic evaluation presents an incremental value of genetic carrier testing for all 9 severe monogenic conditions compared to 3 monogenic conditions (CF/SMA/FXS) genetic carrier testing.

A summary of key characteristics of the economic evaluation is provided in Table 10.

Table 10 Summary of the economic evaluation

Component	Description
Perspective	Health care system perspective
Population	<p>This application proposes testing in the at risk population, as reflected in the below identified subpopulations.</p> <ol style="list-style-type: none"> 1. Asymptomatic individuals with a >10% a priori aggregate personal risk of being a heterozygous genetic carrier of a variant in any of the following autosomal recessive and X-linked genes: <i>HEXA, ASPA, ELP1, MCOLN1, G6PC1, SLC37A4, FANCA, FANCC, FANCG, GBA1, SMPD1, BLM</i> 2. Reproductive partners of individuals described in population 1, where either partner is in the first trimester of pregnancy. 3. Reproductive partners of individuals described in population 1, where carrier status of an autosomal recessive condition associated with pathogenic or likely pathogenic variants of the genes described in (1) has been confirmed 4. First trimester diagnostic testing of the potentially affected singleton foetus in a couple identified from any of (1), (2) and (3) as both being carriers of an autosomal condition, or one partner is a carrier of an X-linked condition, associated with pathogenic or likely pathogenic variants of the genes described in (1).
Prior testing	No prior tests as all populations for testing are asymptomatic
Comparator	<p>Comparator one: genetic carrier testing for CF/SMA/FXS</p> <p>Comparator two: no genetic carrier testing</p>
Type(s) of analysis	Cost-effectiveness analysis
Outcomes	Primary outcome for all scenarios is the cost per affected birth for all severe monogenic and X-linked conditions (including lifetime costs). Secondary outcomes include cost per informed reproductive decision, cost per additional IVF & preimplantation genetic diagnosis event, number of terminations, cost per termination etc.
Time horizon	Lifetime
Computational method	Decision tree analysis
Generation of the base case	Modelled evaluation
Health states	N/A
Cycle length	N/A
Transition probabilities	Sources outlined.
Discount rate	N/A
Software	Excel

Overall results of the economic evaluation are detailed in Table 11 for carrier testing compared with the testing for SMA, CF, and FXS only comparator for initial and subsequent pregnancies.

Table 11 Results of the economic analysis (carrier testing compared with CF/SMA/FXS testing only, initial and subsequent pregnancies)

	Cost	Incremental cost	Effectiveness (expected number of affected individuals)	Incremental effectiveness (reduction in expected number of affected individuals)	ICER
Difference in overall costs (all monogenic conditions) – total cost per reproductive couple					
Carrier Testing	\$1,880.71	-\$925.29	467	106	Dominant
CF/SMA/FXS Testing only	\$2,806.00		573		

ICER=incremental cost-effectiveness ratio

The model was conducted using a stepped approach, presenting results for the cost effectiveness (cost of affected birth averted) against the comparator, and for initial (preconception and prenatal) and subsequent pregnancies. Lifetime costs of care were considered in addition to testing costs per couple, and all costs were inflated to 2022 AUD. Key assumptions are outlined in Table 12.

Table 12 Assumptions incorporated into the model structure

Assumption	Method to address assumption
An artificial population of 100,000 has been used throughout the model calculations	Assessing events per 100,000 patients ensures data can be extrapolated for future use.
If a diagnosis is confirmed for one gene, it is assumed the fetus will not carry the gene for another genetic disease.	The probability that a foetus carries two of the twelve target genes (CF, SMA and/or FXS) is very low. In a study by Archibald et al 2017, from a population of 12,000 tested couples, only five couples carried both CF and SMA (0.0004), 2 couples carried CF (0.0001) and FXS and 1 couple carried SMA and FXS (0.000083). If babies are born with these co-morbidities, the costs and benefits accrued by these individuals are highly uncertain, due to the lack of data, and thus would increase the uncertainty of the model. This same principle is applied to all the assessed genetic disorders.
IVF and abstention are not options for couples identified as carriers' post-conception	Conception has already occurred, and as such, the couple cannot abstain from conception. Likewise, if conception has already occurred, the embryo cannot be genetically manipulated and thus cannot be fertilised in-vitro.
CVS and other testing options are not captured in comparator arm two	Any additional testing, such as CVS testing, in the comparator arm would occur with or without the knowledge of carrier status. As such, these tests have not been included in the economic evaluation. Including these costs provide no additional benefit to the assessment and create additional uncertainty.
CVS and other testing options are not captured in the False Negative arm	It may be possible that couples who have been assessed as a negative carrier but are actually a carrier (false negative) may request a CVS test due to other reasons not directly related to CF, SMA or FXS. As these reasons are not directly associated with carrier testing they have not been included in the economic evaluation due to providing no additional benefit to the assessment and creating additional uncertainty.
Structure does not capture individuals identifying carrier status outside of carrier testing program	Identifying carrier status outside of carrier testing creates additional uncertainty to the assessment and does not provide benefit in assessing the cost-effectiveness of MBS listing of carrier testing.

Assumption	Method to address assumption
Carrier rates for males are the same as female carriers	Due to insufficient data and given the principle that the model tests for both couples and individuals, the carrier rate is assumed to be the same for both males and females alike.
The probability of having a child that is either male and/or female is 50%.	The probability of having an affected child with an x-linked disorder equals the probability that the child is affected multiplied by the probability that the child is either male or female. This is because x-linked disorders only result in an affected child where the child is male. For simplicity, it is assumed that there is an equal chance of giving birth to a male or female.
The test sensitivity and specificity for TSD, CD, FD, MLD, GSD1, FA, GD, NPD and BS is equal to the sensitivity and specificity for CF genetic diagnosis tests	Given it is assumed that the genetic carrier testing panel is assessed in a single session, with one (agnostic) testing instrument, it is assumed that the sensitivity and specificity would be equal for all tests.
The probability that couples undertake CVS testing for TSD, CD, FD, MLD, GSD1, FA, GD, NPD and BS is the same as CF.	There is insufficient data for these genetic diseases and as such, using the CF CVS probability for all missing values is a reliable assumption.
The probability that couples undertake IVF testing for TSD, CD, FD, MLD, GSD1, FA, GD, NPD and BS is the same as CF.	There is insufficient data for these genetic diseases and as such, using the CF IVF probability for all missing values is a reliable assumption.
The probability that couples terminate pregnancies with MLD, GSD1, FA, GD, NPD and BS is the equal to CF.	There is insufficient data for these genetic diseases and as such, using the CF termination probability for all missing values is a reliable assumption.
The probability that couples that abstain from pregnancies with TSD, CD, FD, MLD, GSD1, FA, GD, NPD and BS is the same as CF.	There is insufficient data for these genetic diseases and as such, using the CF abstention probability for all missing values is a reliable assumption.

CF=Cystic Fibrosis, FXS=Fragile X Syndrome, SMA=Spinal Muscular Atrophy, TSD=Tay Sachs Disease, CD=Canavan disease, FD= Familial dysautonomia, MLD= Mucopolidosis Type IV, GSD1=Glycogen storage disease type 1, FA=Fanconi anaemia type C, GD=Gaucher disease, NPD=Niemann Pick Disease type A, BS=Bloom Syndrome, CVS=Chorionic villus sampling, IVF=in vitro fertilisation.

Source: DCAR, Table 44

Step 1 involved separately analysing the stand-alone costs per affected birth for all conditions in preconception and prenatal populations. Step 2 considered the total cost of preconception genetic carrier testing and prenatal genetic carrier testing against the comparator one, by considering the cumulative proportions of outcomes in each scenario (baby with condition, baby without condition, IVF, abstain, infant mortality, termination). Preconception and prenatal populations were combined in Step 3 and were labelled as initial pregnancies. Step 4 combined costs and events for initial and subsequent pregnancies, to determine the current and future impact of carrier testing beyond initial pregnancies. This stepped analysis is outlined in Tables 13-16 below for carrier testing compared to CF/SMA/FX testing.

Table 13 details the results of the first step in the stepped analysis whereby stand-alone costs and effectiveness were calculated for each condition.

Table 13 Approach to the stepped analysis - Step 1, Initial pregnancies, stand-alone costs and effectiveness for preconception and prenatal testing compared to CF/SMA/FXS testing

Population and circumstances of use	Results	
	Preconception	Pre-natal
Step 1 – calculate stand-alone costs and effectiveness (births averted)		
TSD Births Only		
Costs		
Carrier Testing	\$526.16	\$848.80
CF/SMA/FXS Testing Only	\$463.61	\$463.61
Incremental costs	\$62.56	\$385.20
TSD births (/100,000 births)		
Carrier Testing	8	35
CF/SMA/FXS Testing Only	40	40
Incremental effectiveness	32	5
ICER (cost/TSD births averted)	\$1.93	\$80.17
CD Births Only		
Costs		
Carrier Testing	\$457.81	\$540.28
CF/SMA/FXS Testing Only	\$127.25	\$127.25
Incremental costs	\$330.56	\$413.03
CD births (/100,000 births)		
Carrier Testing	3	13
CF/SMA/FXS Testing Only	16	16
Incremental effectiveness	13	3
ICER (cost/CD births averted)	\$26.10	\$153.78
FD Births Only		
Costs		
Carrier Testing	\$579.36	\$1,055.14
CF/SMA/FXS Testing Only	\$754.65	\$754.65
Incremental costs	-\$175.29	\$300.49
FD births (/100,000 births)		
Carrier Testing	5	23
CF/SMA/FXS Testing Only	28	28
Incremental effectiveness	23	5
ICER (cost/FD births averted)	Dominant	\$59.60
MLD Births Only		
Costs		
Carrier Testing	\$429.37	\$430.96
CF/SMA/FXS Testing Only	\$3.86	\$3.86
Incremental costs	\$425.50	\$427.10
MLD births (/100,000 births)		
Carrier Testing	0	1
CF/SMA/FXS Testing Only	3	3

Population and circumstances of use	Results	
	Preconception	Pre-natal
Incremental effectiveness	2	1
ICER (cost/MLD births averted)	\$210.01	\$359.55
GSD1 Births Only		
Costs		
Carrier Testing	\$498.08	\$717.85
CF/SMA/FXS Testing Only	\$301.83	\$301.83
Incremental costs	\$196.25	\$416.02
GSD1 births (/100,000 births)		
Carrier Testing	54	193
CF/SMA/FXS Testing Only	195	195
Incremental effectiveness	141	2
ICER (cost/GSD1 births averted)	\$1.39	\$194.63
FA Births Only		
Costs		
Carrier Testing	\$438.09	\$453.66
CF/SMA/FXS Testing Only	\$45.27	\$475.17
Incremental costs	\$392.82	-\$21.51
FA births (/100,000 births)		
Carrier Testing	1	2
CF/SMA/FXS Testing Only	4	4
Incremental effectiveness	3	2
ICER (cost/FA births averted)	\$124.08	Dominant
GD Births Only		
Costs		
Carrier Testing	\$465.14	\$507.83
CF/SMA/FXS Testing Only	\$119.24	\$119.24
Incremental costs	\$345.90	\$388.59
GD births (/100,000 births)		
Carrier Testing	15	40
CF/SMA/FXS Testing Only	77	77
Incremental effectiveness	63	37
ICER (cost/GD births averted)	\$5.53	\$10.60
NPD Births Only		
Costs		
Carrier Testing	\$438.09	\$23.82
CF/SMA/FXS Testing Only	\$474.78	\$45.27
Incremental costs	-\$36.69	-\$21.46
NPD births (/100,000 births)		
Carrier Testing	1	2
CF/SMA/FXS Testing Only	4	4
Incremental effectiveness	3	2

Population and circumstances of use	Results	
	Preconception	Pre-natal
ICER (cost/NPD births averted)	Dominant	Dominant
BS Births Only		
Costs		
Carrier Testing	\$440.94	\$463.12
CF/SMA/FXS Testing Only	\$65.28	\$65.28
Incremental costs	\$375.66	\$397.84
BS births (/100,000 births)		
Carrier Testing	0	1
CF/SMA/FXS Testing Only	2	2
Incremental effectiveness	2	1
ICER (cost/BS births averted)	\$192.90	\$348.45

BS=Bloom Syndrome, CD=Canavan disease, CF=Cystic Fibrosis, FA=Fanconi anaemia type C, FD=Familial dysautonomia, FXS=Fragile X Syndrome, GD=Gaucher disease, GSD1=Glycogen storage disease type 1, ICER=Incremental Cost Effectiveness Ratio, IVF=In vitro fertilisation, MLD=Mucopolipidosis Type IV, NPD=Niemann Pick Disease type A, SMA=Spinal Muscular Atrophy, TSD=Tay Sachs Disease

Table 14 details the results of step 2 in the stepped analysis whereby cumulative costs and effectiveness were calculated for each condition.

Table 14 Approach to the stepped analysis - Step 2, initial pregnancies, cumulative costs and effectiveness for preconception and prenatal carrier testing compared to CF/SMA/FXS testing

Population and circumstances of use	Results	
	Pre-conception	Pre-natal
Step 2 – calculate cumulative costs and effectiveness (events averted) for all monogenic conditions		
Combined Monogenic Disease		
Costs		
Carrier Testing	\$1,049.13	\$2,279.14
CF/SMA/FXS Testing Only	\$2,414.64	\$2,601.75
Incremental costs	-\$1,365.51	-\$322.61
TSD births (/100,000 births)		
Carrier Testing	8	35
CF/SMA/FXS Testing Only	40	40
Incremental effectiveness	32	5
ICER (cost/TSD births averted)	Dominant	Dominant
CD births (/100,000 births)		
Carrier Testing	3	13
CF/SMA/FXS Testing Only	16	16
Incremental effectiveness	13	3
ICER (cost/CD births averted)	Dominant	Dominant
FD births (/100,000 births)		
Carrier Testing	5	23
CF/SMA/FXS Testing Only	28	28
Incremental effectiveness	23	5
ICER (cost/FD births averted)	Dominant	Dominant
MLD births (/100,000 births)		

Population and circumstances of use	Results	
	Pre-conception	Pre-natal
Carrier Testing	0	1
CF/SMA/FXS Testing Only	3	3
Incremental effectiveness	2	1
ICER (cost/MLD births averted)	Dominant	Dominant
GSD1 births (/100,000 births)		
Carrier Testing	54	193
CF/SMA/FXS Testing Only	195	195
Incremental effectiveness	141	2
ICER (cost/GSD1 births averted)	Dominant	Dominant
FA births (/100,000 births)		
Carrier Testing	1	2
CF/SMA/FXS Testing Only	4	4
Incremental effectiveness	3	2
ICER (cost/FA births averted)	Dominant	Dominant
GD births (/100,000 births)		
Carrier Testing	15	40
CF/SMA/FXS Testing Only	77	77
Incremental effectiveness	63	37
ICER (cost/GD births averted)	Dominant	Dominant
NPD births (/100,000 births)		
Carrier Testing	1	2
CF/SMA/FXS Testing Only	4	4
Incremental effectiveness	3	2
ICER (cost/NPD births averted)	Dominant	Dominant
BS births (/100,000 births)		
Carrier Testing	0	1
CF/SMA/FXS Testing Only	2	2
Incremental effectiveness	2	1
ICER (cost/BS births averted)	Dominant	Dominant

BS=Bloom Syndrome, CD=Canavan disease, CF=Cystic Fibrosis, FA=Fanconi anaemia type C, FD=Familial dysautonomia, FXS=Fragile X Syndrome, GD=Gaucher disease, GSD1=Glycogen storage disease type 1, ICER=Incremental Cost Effectiveness Ratio, IVF=In vitro fertilisation, MLD=Mucopolidosis Type IV, NPD=Niemann Pick Disease type A, SMA=Spinal Muscular Atrophy, TSD=Tay Sachs Disease

Table 15 details the results of step 3 in the stepped analysis whereby combined prenatal and preconception for initial pregnancies costs and effectiveness were calculated for each condition.

Table 15 Approach to the stepped analysis - Step 3, combined prenatal and preconception carrier testing for initial pregnancies costs and effectiveness compared to CF/SMA/FXS testing

Step 3 – calculate prenatal and preconception cost effectiveness (combined)	
Pre & Post-conception (Combined)	
Costs	
Carrier Testing	\$2,033.14
CF/SMA/FXS Testing Only	\$2,564.33
Incremental costs	-\$531.19
TSD births (/100,000 births)	
Carrier Testing	30
CF/SMA/FXS Testing Only	40
Incremental effectiveness	10
ICER (cost/TSD births averted)	Dominant
CD births (/100,000 births)	
Carrier Testing	11
CF/SMA/FXS Testing Only	16
Incremental effectiveness	5
ICER (cost/CD births averted)	Dominant
FD births (/100,000 births)	
Carrier Testing	19
CF/SMA/FXS Testing Only	28
Incremental effectiveness	8
ICER (cost/FD births averted)	Dominant
MLD births (/100,000 births)	
Carrier Testing	1
CF/SMA/FXS Testing Only	2
Incremental effectiveness	1
ICER (cost/MLD births averted)	Dominant
GSD1 births (/100,000 births)	
Carrier Testing	164
CF/SMA/FXS Testing Only	194
Incremental effectiveness	30
ICER (cost/GSD1 births averted)	Dominant
FA births (/100,000 births)	
Carrier Testing	2
CF/SMA/FXS Testing Only	4
Incremental effectiveness	2
ICER (cost/FA births averted)	Dominant
GD births (/100,000 births)	
Carrier Testing	35
CF/SMA/FXS Testing Only	76
Incremental effectiveness	41
ICER (cost/GD births averted)	Dominant
NPD births (/100,000 births)	
Carrier Testing	2

Step 3 – calculate prenatal and preconception cost effectiveness (combined)	
CF/SMA/FXS Testing Only	4
Incremental effectiveness	2
ICER (cost/NPD births averted)	Dominant
BS births (/100,000 births)	
Carrier Testing	1
CF/SMA/FXS Testing Only	2
Incremental effectiveness	1
ICER (cost/BS births averted)	Dominant
Terminations (/100,000 births)	1060
Carrier Testing	273
CF/SMA/FXS Testing Only	-786
Incremental effectiveness - births averted (/100,000 births)	\$0.68
ICER (cost/additional termination)	IVF (/100,000 births)
IVF (/100,000 births)	
Carrier Testing	496
CF/SMA/FXS Testing Only	142
Incremental effectiveness - births averted (/100,000 births)	-354
ICER (cost/additional IVF birth)	\$2

BS=Bloom Syndrome, CD=Canavan disease, CF=Cystic Fibrosis, FA=Fanconi anaemia type C, FD=Familial dysautonomia, FXS=Fragile X Syndrome, GD=Gaucher disease, GSD1=Glycogen storage disease type 1, ICER=Incremental Cost Effectiveness Ratio, IVF=In vitro fertilisation, MLD=Mucopolipidosis Type IV, NPD=Niemann Pick Disease type A, SMA=Spinal Muscular Atrophy, TSD=Tay Sachs Disease

Table 16 details the results of step 4 in the stepped analysis whereby combined prenatal and preconception for initial and subsequent pregnancies costs and effectiveness were calculated for each condition.

Table 16 Approach to the stepped analysis - Step 4, initial and subsequent pregnancies, results for preconception and prenatal carrier testing combined costs and events compared to CF/SMA/FXS testing

Population and circumstances of use	Results
Initial and subsequent pregnancies	
Costs	
Carrier Testing	\$1,880.71
CF/SMA/FXS Testing Only	\$2,806.00
Incremental costs	-\$925.29
TSD births averted (/100,000 births)	
Carrier Testing	28
CF/SMA/FXS Testing Only	44
Incremental effectiveness	15
ICER (cost/TSD births averted)	Dominant
CD births averted (/100,000 births)	
Carrier Testing	11
CF/SMA/FXS Testing Only	17
Incremental effectiveness	6
ICER (cost/CD births averted)	Dominant

Population and circumstances of use	Results
FD births averted (/100,000 births)	
Carrier Testing	18
CF/SMA/FXS Testing Only	30
Incremental effectiveness	12
ICER (cost/FD births averted)	Dominant
MLD births averted (/100,000 births)	
Carrier Testing	1
CF/SMA/FXS Testing Only	3
Incremental effectiveness	1
ICER (cost/MLD births averted)	Dominant
GSD1 births averted (/100,000 births)	
Carrier Testing	201
CF/SMA/FXS Testing Only	212
Incremental effectiveness	12
ICER (cost/GSD1 births averted)	Dominant
FA births averted (/100,000 births)	
Carrier Testing	2
CF/SMA/FXS Testing Only	4
Incremental effectiveness	3
ICER (cost/FA births averted)	Dominant
GD births averted (/100,000 births)	
Carrier Testing	30
CF/SMA/FXS Testing Only	83
Incremental effectiveness	53
ICER (cost/GD births averted)	Dominant
NPD births averted (/100,000 births)	
Carrier Testing	2
CF/SMA/FXS Testing Only	4
Incremental effectiveness	3
ICER (cost/NPD births averted)	Dominant
BS births averted (/100,000 births)	
Carrier Testing	1
CF/SMA/FXS Testing Only	3
Incremental effectiveness	2
ICER (cost/BS births averted)	Dominant
Termination of pregnancy (/100,000 births)	
Carrier Testing	740
CF/SMA/FXS Testing Only	299
Incremental effectiveness	-441
ICER (cost savings/Termination)	\$2
IVF (/100,000 births)	
Carrier Testing	652

Population and circumstances of use	Results
CF/SMA/FXS Testing Only	156
Incremental effectiveness	-497
ICER (cost savings/IVF)	\$2

BS=Bloom Syndrome, CD=Canavan disease, CF=Cystic Fibrosis, FA=Fanconi anaemia type C, FD=Familial dysautonomia, FXS=Fragile X Syndrome, GD=Gaucher disease, GSD1=Glycogen storage disease type 1, ICER=Incremental Cost Effectiveness Ratio, IVF=In vitro fertilisation, MLD=Mucopolidosis Type IV, NPD=Niemann Pick Disease type A, SMA=Spinal Muscular Atrophy, TSD=Tay Sachs Disease

The base case analysis of the cost-effectiveness analysis focuses on MBS item AAAA, where at risk individuals are tested and are partnered with other at-risk individuals (i.e., reproductive partnerships where both members are Ashkenazi Jewish). However, an additional analysis was conducted to assess the cost-effectiveness of carrier testing where at risk individuals are partnered with individuals who are themselves not at risk (i.e., reproductive partnerships where only one member is Ashkenazi Jewish) and therefore where these partners use MBS item CCCC if they agree to be tested. To determine the cost-effectiveness of carrier testing in the scenario including CCCC, the same model was used for MBS item AAAA, however, the general population carrier frequency was used to determine the risk of reproductive partners who would be tested using MBS item CCCC, and the cost of the reproductive partner test was also amended accordingly to align with the proposed fee for CCCC. It was assumed that between MBS Item AAAA and CCCC, 75% of the utilisation of item AAAA would occur where the reproductive partner is also at risk while 25% would occur in mixed couples (where the reproductive partner would utilise MBS item CCCC if they agree to be tested). These proportions were used to weight the cost-effectiveness outcomes of the two models to obtain an overall ICER.

Table 17 Monogenic disease births averted – Carrier Testing compared with CF/SMA/FXS testing (Testing costs)

Intervention	Cost	Incremental cost	Effectiveness (expected number of affected individuals)	Incremental effectiveness (reduction in expected number of affected individuals)	ICER
AAAA testing					
Carrier Testing	\$234.54	\$234.54	467	96	\$2.44
CF/SMA/FXS Testing Only	\$0.00		563		
AAAA testing in mixed couples scenario (CCCC testing for reproductive partner)					
Carrier Testing	\$245.69	\$245.69	430	122	\$2.01
CF/SMA/FXS Testing Only	\$0.00		552		
Weighted cost-effectiveness (Monogenic disease births averted)¹					
Carrier Testing	\$237.33	\$237.33	458	103	\$2.31
CF/SMA/FXS Testing Only	\$0.00		560		

¹ Weighted by 75% AAAA testing and 25% CCCC testing – based on assumption 25% of couples have only one individual at risk

Table 18 Monogenic disease births averted – Carrier Testing compared with CF/SMA/FXS testing (lifetime costs)

Intervention	Cost	Incremental cost	Effectiveness (expected number of affected individuals)	Incremental effectiveness (reduction in expected number of affected individuals)	ICER
AAAA testing					
Carrier Testing	\$1,880.71	-\$687.11	467	96	Dominant
CF/SMA/FXS Testing Only	\$2,567.83		563		
AAAA testing in mixed couples scenario (CCCC testing for reproductive partner)					
Carrier Testing	\$1,499.11	-\$972.87	430	122	Dominant
CF/SMA/FXS Testing Only	\$2,471.98		552		
Weighted cost-effectiveness (Monogenic disease births averted)¹					
Carrier Testing	\$1,785.31	-\$758.55	458	103	Dominant
CF/SMA/FXS Testing Only	\$2,543.87		560		

¹ Weighted by 75% AAAA testing and 25% CCCC testing – based on assumption 25% of couples have only one individual at risk

The assessment group provided a combined cost-effectiveness analysis also including GGGG in the post-ESC addendum to the DCAR (Table 19).

Table 19 Monogenic disease births averted – Carrier testing compared with CF/SMA/FXS testing (lifetime costs), also including GGGG (at fee \$1600)

Intervention	Cost	Incremental cost	Effectiveness (expected number of affected individuals)	Incremental effectiveness (reduction in expected number of affected individuals)	ICER
AAAA testing					
Opportunistic Testing	\$1,547.12	-\$1,594.85	225	453	Dominant (\$-3.52)
CF/SMA/FXS Testing Only	\$3,141.97		678		
CCCC testing					
Opportunistic Testing	\$793.02	-\$750.89	139	363	Dominant (\$-2.07)
CF/SMA/FXS Testing Only	\$1,543.91		502		
Weighted cost-effectiveness (Monogenic disease births averted)					
Opportunistic Testing	\$1,358.60	-\$1,383.86	203	431	Dominant (\$-3.21)
CF/SMA/FXS Testing Only	\$2,742.46		634		
GGGG testing					
Opportunistic Testing	\$431,181.37	-\$105,783.12	51,206	11,428	Dominant (\$-9.26)
CF/SMA/FXS Testing Only	\$536,964.49		62,633		
Weighted cost-effectiveness (Monogenic disease births averted)					
Opportunistic Testing	\$80,488.97	-\$20,603.76	9593	2455	Dominant (\$-8.39)
CF/SMA/FXS Testing Only	\$101,092.73		12048		

Source: Addendum to the DCAR.

For the sensitivity analysis, each parameter was adjusted by $\pm 10\%$, and where probabilities ranged between 0% and 100%, the maximum adjustment was to 100% as the upper bound and 0% as the lower bound. This allowed a systematic approach in identifying the key drivers of the model. The main outcomes of the model including cost per births averted for all genetic diseases were analysed in line with parameter changes to assess key drivers of the model.

The top 10 drivers of the model were reported for initial and initial and subsequent pregnancies combined against no testing. Overall, the main drivers of the model were the specificity of genetic carrier testing for severe monogenic conditions and the lifetime costs of care for BS. These are further described in the table below.

Table 20 Key drivers of the model

Description	Base case value	SA value	Impact
Specificity	1.0	+10% = 1.0 -10% = 0.9	Medium
BS lifetime cost of care	\$2,716,730.12	+10% = \$29,884,030 -10% = \$2,445,057	Medium

ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year

Additionally, the impact of different testing costs and utilisation of genetic counselling was analysed. The change in utilisation and costs of these services had little impact on the overall results and are detailed further in Section 3 – Cost-effectiveness analysis.

14. Financial/budgetary impacts

The financial impact analysis assumes an epidemiological approach to calculating overall costs to healthcare budgets, including MBS and hospital costs.

The financial implications to the MBS resulting from the proposed listing of genetic carrier testing for all nine severe monogenic conditions over 6 years from 2021-22 to 2026-27 are summarised in Table 21. The MBS annual expenditure for carrier testing is expected to be \$175,598 decreasing to \$158,522 from 2021-2022 to 2026-2027, and \$212,120 a year on average with associated MBS costs resulting from increased utilisation of chorionic villus sampling (CVS) testing/amniocentesis, genetic counselling, IVF plus PGD and condition-specific treatment costs. However, the decrease in number of affected births results in a decrease in MBS costs associated with treatment concerning the nine monogenic conditions.

While the known hospitalisation costs for CF are large, this DCAR assesses the impact of the additional nine severe monogenic conditions and therefore CF costs are not an appropriate focus associated with the intervention. Rather, the primary focus of the DCAR is on the value proposition of the addition of other diseases beyond CF/SMA/FXS into the genetic testing panel to justify the increased cost of testing over those estimated for 1573. As such, treatment costs and utilisation (sourced from the Department) have been considered for all monogenic conditions where data is available.

The utilisation of carrier testing, and CF/SMA/FXS testing in the population that could otherwise access the proposed carrier testing services is demonstrated below. A separate Ashkenazi Jewish and non-Ashkenazi Jewish population has been determined to assess the uptake of MBS Items CCCC. This is because reproductive partner testing (CCCC) only applies to those who are the reproductive partner of an individual who is at risk of being a carrier and those who have not received a service described in AAAA (as per the item descriptor in the PICO).

The item for reanalysis (EEEE) has not been considered in the analysis, as the impact and prevalence of currently unknown pathogenic or likely pathogenic variants is inherently uncertain. Therefore, any assumed uptake of this item would also be uncertain.

Table 21 Net financial implications of genetic carrier testing for 9 severe monogenic conditions to the MBS

	2021-2022	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
Estimated use and cost of carrier testing						
Number of people eligible for testing (preconception and prenatal)	451	442	433	424	416	407
Number of services (preconception and prenatal)	309	303	297	291	285	279
Ashkenazi Jewish reproductive individuals (item AAAA)	232	227	223	218	214	209
Non-Ashkenazi Jewish reproductive individuals (item CCCC)	77	76	74	73	71	70
Cost to MBS (item AAAA)	\$83,742.72	\$82,092.01	\$80,441.31	\$78,790.61	\$77,188.83	\$75,587.04
Cost to MBS (item CCCC)	\$85,933.36	\$84,239.47	\$82,545.59	\$80,851.71	\$79,208.02	\$77,564.34
Cost to MBS (item GGGG)	\$5,921.58	\$5,804.85	\$5,688.13	\$5,571.41	\$5,471.01	\$5,370.61
Sub total cost of testing to the MBS	\$175,597.65	\$172,136.34	\$168,675.04	\$165,213.73	\$161,867.86	\$158,521.99
Estimated use and cost of CF/SMA/FXS testing						
Number of services (preconception and prenatal)	260	255	250	245	240	235
Ashkenazi Jewish reproductive individuals	195	191	187	183	180	176
Non-Ashkenazi Jewish reproductive individuals	65	64	62	61	60	59
Services (item XXXXX – MSAC 1573)	0	0	84	124	121	118
Services (item YYYYY – MSAC 1573)	0	0	72	106	103	101
Services (item ZZZZ – MSAC 1573)	0	0	11	15	15	15
Cost to MBS (item XXXXX – MSAC 1573)	\$0.00	\$0.00	\$28,589.21	\$41,995.50	\$41,107.19	\$40,218.88
Cost to MBS (item YYYYY – MSAC 1573)	\$0.00	\$0.00	\$24,449.86	\$35,930.51	\$35,186.23	\$34,441.95
Cost to MBS (item ZZZZ – MSAC 1573)	\$0.00	\$0.00	\$3,573.06	\$5,249.62	\$5,201.02	\$5,152.42
Sub total cost of testing to the MBS (CF/SMA/FXS)	\$0.00	\$0.00	\$56,612.13	\$83,175.62	\$81,494.44	\$79,813.25
Associated MBS costs – carrier testing						
CVS Testing/Amniocentesis	\$2,010.31	\$1,971.10	\$1,931.90	\$1,892.69	\$1,854.65	\$1,816.60
Genetic Counselling	\$1,064.85	\$1,043.86	\$1,022.87	\$1,001.88	\$981.51	\$961.15
IVF & PGD	\$43,490.39	\$42,625.35	\$41,760.31	\$40,895.27	\$40,055.87	\$39,216.47

	2021-2022	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
Condition-specific treatment costs	\$895.06	\$877.59	\$860.11	\$842.64	\$825.68	\$808.72
Combined cost of carrier testing (associated MBS costs)	\$47,460.61	\$46,517.91	\$45,575.20	\$44,632.49	\$43,717.72	\$42,802.94
Combined Cost of Carrier Testing (MBS and associated MBS costs)	\$223,058.26	\$218,654.25	\$214,250.23	\$209,846.22	\$205,585.58	\$201,324.94
Associated MBS costs – CF/SMA/FXS testing						
CVS Testing/Amniocentesis	\$0.00	\$0.00	\$321.30	\$472.16	\$462.73	\$453.29
Genetic Counselling	\$0.00	\$0.00	\$162.60	\$238.89	\$234.07	\$229.24
IVF & PGD	\$0.00	\$0.00	\$5,483.06	\$8,054.23	\$7,889.86	\$7,725.50
Condition-specific treatment costs	\$2,139.38	\$2,097.21	\$1,937.83	\$1,840.66	\$1,803.25	\$1,765.84
Combined cost of CF/SMA/FXS testing (associated MBS costs)	\$2,139.38	\$2,097.21	\$7,904.79	\$10,605.95	\$10,389.91	\$10,173.87
Combined Cost of CF/SMA/FXS testing (MBS and associated MBS costs)	\$2,139.38	\$2,097.21	\$64,516.91	\$93,781.56	\$91,884.34	\$89,987.12
Difference in costs						
Total (carrier testing compared with CF/SMA/FXS testing)	\$220,918.89	\$216,557.04	\$149,733.32	\$116,064.65	\$113,701.24	\$111,337.82

CF= Cystic Fibrosis, FXS= Fragile X Syndrome, SMA= Spinal Muscular Atrophy, MBS= Medicare Benefits Schedule.

The financial implications to State and Territory budgets include costs of termination. As mentioned above, although hospital separation, length of stay and cost data is available for the CF-specific DRGs, the focus of the DCAR are the additional nine severe monogenic conditions. Additionally, the hospital costs for all other monogenic conditions were not captured in this assessment due to limited data, and therefore savings due to births averted attributed to carrier testing may be underestimated. Therefore, the impact of reducing these costs due to carrier testing should result in further future cost savings.

Table 22 Net financial implications of genetic carrier testing for 9 severe monogenic conditions to State and Territory budgets

	2021-2022	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
Estimated utilisation of carrier testing						
Number of people eligible for testing (preconception and prenatal)	451	442	433	424	416	407
Number of services (preconception and prenatal)	309	303	297	291	285	279
Associated State and Territory costs – carrier testing						
Termination of pregnancy	\$6,050.99	\$5,932.98	\$5,814.97	\$5,696.96	\$5,582.45	\$5,467.94
Associated State and Territory costs – CF/SMA/FXS testing						
Termination of pregnancy	\$0.00	\$0.00	\$843.65	\$1,239.79	\$1,215.02	\$1,190.24
Difference in costs						
Total (testing compared with CF/SMA/FXS testing)	\$6,050.99	\$5,932.98	\$4,971.32	\$4,457.17	\$4,367.43	\$4,277.70

The combined MBS and State and Territory costs of carrier testing to the healthcare budget is outlined below.

Table 23 Total cost of carrier testing

	2021-2022	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
Combined costs to the healthcare budget						
Carrier testing	\$229,109.25	\$224,587.23	\$220,065.20	\$215,543.18	\$211,168.03	\$206,792.87
CF/SMA/FXS testing	\$2,139.38	\$2,097.21	\$65,360.56	\$95,021.36	\$93,099.36	\$91,177.36
Difference in costs						
Total (testing compared with CF/SMA/FXS testing)	\$226,969.87	\$222,490.02	\$154,704.64	\$120,521.82	\$118,068.67	\$115,615.51

As demonstrated above, carrier testing costs the healthcare budget an additional \$159,728 per year on average when compared with CF/SMA/FXS testing. When compared with no testing there is a significant increase in costs to the healthcare of \$215,843 per year on average, however it is noted that this is a conservative estimate as hospitalisation costs for the listed monogenic conditions have not been considered.

15. Other relevant information

Nil.

16. Key issues from ESC to MSAC

Main issues for MSAC consideration

Clinical issues:

The proposed test for AAAA is an amplicon-specific gene panel examining specific variants that are more prevalent in the Ashkenazi Jewish population. The item descriptor defines eligibility based on identified risk rather than ethnicity, which seems acceptable, though MSAC should note the proposed services are intended for the Ashkenazi Jewish population, and that in practice referring practitioners will determine testing eligibility based on their patient's ethnicity. MSAC will need to consider the appropriateness of defining testing eligibility based on a de facto requirement of Ashkenazi Jewish ancestry. The evidence for risk in other ethnicities (or consanguineous cases) was not examined as part of this application.

This testing represents positive discrimination for a previously under-catered-for group, but also raises ethical concerns that affording access to publicly funded testing to people of select ethnicities and omitting others could result in actual or perceived systemic discrimination.

When already pregnant, simultaneous testing of both reproductive partners is proposed where both partners are eligible for AAAA. However, reproductive partners not eligible for AAAA are proposed to be tested sequentially using gene sequencing under CCCC where their partner is first found to have a variant in any gene or genes using AAAA. Sequential testing for partners not eligible for AAAA would be more cost-effective and have a lower financial impact than simultaneous testing, though simultaneous testing of both partners may be more clinically appropriate.

Gene panel testing is proposed to only be available to asymptomatic individuals, making individuals with a known condition listed in AAAA but who might still be at risk of also being a carrier for other conditions, ineligible for gene panel testing. ESC recommended the deletion of this requirement.

The re-analysis item (EEEE) may be unnecessary. While the item descriptor for AAAA is method-agnostic, the fee is expected to support an amplicon-specific gene panel test. As such, it is unlikely there will be unreported variants.

The fee for fetal testing item GGGG should be \$1,600, in line with similar MBS items. The item descriptor should also reflect the risk that the fetus has the disease, rather than is a carrier.

The only test accuracy measure was diagnostic yield in the Ashkenazi Jewish population. Eleven studies were identified, but none had a relevant comparator, and all studies were at high risk of bias.

Economic issues:

The proposed testing (items AAAA and CCCC) has dominant cost-effectiveness both when only the cost of providing testing is taken into account, and also when lifetime healthcare costs are considered.

The fee for item AAAA (\$425) is reasonable considering the proposed gene panel is an amplicon-specific panel, only examining specific genetic variants that are prevalent in people of Ashkenazi Jewish ancestry.

The economic model does not account for people who are carriers for more than one disease, yet in the Ashkenazi Jewish population this is a substantial proportion of people (e.g., 10.1% of this population are carriers for two conditions and 2.5% are carriers for three conditions).

Some of the inputs in the economic evaluation were uncertain, including that a number of probabilities (such as rates of *in vitro* fertilisation [IVF] and termination of pregnancy) are based on the international Ashkenazi Jewish population. However, there may be inter-country cultural

differences from the Australian Ashkenazi Jewish population that could lead to different proportions in Australia.

The cost effectiveness analysis of item GGGG considered at ESC was a standalone analysis that arrived with the rejoinder and had not been integrated into the AAAA and AAAA+CCCC analysis. Some of the results of the GGGG analysis and the assumptions on probabilities underlying the analysis merited further investigation, and the assessment group provided a post-ESC addendum: ESC considered the updates to the combined model with GGGG did not appear to change any of the conclusions of the model.

Testing in the preconception stage was more cost effective than pre-natal testing (ICER per birth averted was lower for preconception testing than pre-natal testing). Thus, the proportion of preconception vs pre-natal testing (base case 20% : 80%) may be an additional driver of cost savings. The addendum's economic and financial sensitivity analysis around the rates of preconception and pre-natal testing showed that efficiency gains can be made by increasing the proportion of preconception testing, as testing earlier reduces downstream costs.

Financial issues:

Uptake for genetic testing for high school students with Ashkenazi Jewish ancestry is up to three times higher than what was used in the financial analyses as an assumption for preconception testing. ESC noted that increasing the preconception proportion of testing increases the financial cost of testing to the healthcare budget, though is more cost-effective.

Other relevant information:

NPAAC advised there is currently no specific EQA program for this panel in Australia or internationally – alternatives include using established EQA programs for single genes or sample swaps with other Australian laboratories.

Application 1637 also proposes reproductive carrier testing, and is being concurrently being considered by MSAC. The services proposed under Application 1573 will be introduced onto the MBS on 1 November 2023. ESC considered this application should be considered in relation to the testing proposed and supported under 1637 and 1573 respectively.

ESC additionally noted that supporting targeted carrier testing for severe monogenic conditions may contribute to increasing stigma for those living with genetic conditions included in the proposed panel testing and may be at odds with efforts to change society under the social model of disability.

ESC discussion

ESC noted that this was a new application for Medicare Benefits Schedule (MBS) listing of targeted carrier testing for twelve genes associated with nine severe autosomal recessive and X-linked monogenic conditions: Tay-Sachs disease (TSD), Canavan disease (CD), Familial dysautonomia (FD), Mucopolysaccharidosis Type IV (MLD), Glycogen storage disease type 1 (GSD1), Fanconi anaemia type C (FA), Gaucher disease type 1 (GD), Niemann Pick disease type A (NPD) and Bloom Syndrome (BS). ESC noted the proposed testing is incremental to that for Cystic Fibrosis (CF), Spinal Muscular Atrophy (SMA) and Fragile-X Syndrome (FXS), previously supported by MSAC under application 1573 – but that these genes and diseases are also included in the proposed item descriptor as the proposed testing would replace CF/SMA/FXS only testing in practice.

ESC noted that the base case comparator for the proposed carrier testing is genetic carrier testing for CF/SMA/FXS, which MSAC supported in application 1573 in July 2020. ESC noted PASC had permitted an alternative comparator of “no genetic testing”, as the MBS items for Application 1573 testing were yet to be supported by Government at the time. ESC noted the

Government has now supported this testing and it will be introduced to the MBS on 1 November 2023, therefore ESC considered that the alternative comparator is no longer relevant.

ESC noted and accepted the proposed clinical management algorithm.

While the item itself is method agnostic, ESC noted the test proposed for item AAAA is an amplicon-specific gene panel test targeting specific variants (“hotspots”) that are prevalent in individuals of Ashkenazi Jewish ancestry. ESC noted the item descriptor defines eligibility as those with at least a 10% a priori risk of being a genetic carrier, but that in practice referring medical practitioners will infer this risk based on whether or not their patient is of Ashkenazi Jewish ancestry.

ESC noted that some individuals in the Ashkenazi Jewish population already undertake the proposed genetic panel test through private funding.

ESC queried the appropriateness of using Ashkenazi Jewish ancestry as a de facto eligibility criterion, as people with ancestry other than Ashkenazi Jewish (or unknown ancestry) will effectively not be eligible for this testing, though may also be at risk for one or more of the named conditions. ESC noted that although the risk of the listed diseases may be unknown in other ethnic groups, this does not equate to “low risk”. ESC noted that in cases involving consanguinity, these individuals are also at an increased risk of rare hereditary disorders.

ESC also noted that although the reproductive partner of a person eligible for AAAA would be eligible to access sequential testing under CCCC, the proposed approach would not support testing partners for other variants/genes for which the reproductive partner has an a priori risk of being a genetic carrier due to their own ethnic heritage. ESC queried whether this was equitable.

ESC noted that the applicant originally proposed that other high-risk ethnic groups also be included, but had agreed to restrict the PICO to the Ashkenazi Jewish population, citing a lack of evidence supporting the inclusion of other ethnic groups. ESC noted that the evidence being considered for this application only relates to the Ashkenazi Jewish population, and therefore considered that other populations are outside the scope of this consideration, though applications for other populations at increased risk could be lodged in the future when evidence becomes available for those populations. ESC considered that MSAC will need to consider the appropriateness of defining testing eligibility based on a de facto requirement of Ashkenazi Jewish ancestry. ESC considered that this testing represents positive discrimination for a previously under-catered-for group, and that the variants included on the panel are specifically chosen to cater to individuals of Ashkenazi Jewish descent. In contrast, ESC also considered public funding for the proposed services could result in actual or perceived systemic discrimination towards other groups that are not eligible. Additionally, not affording access to other under-catered for groups may perpetuate knowledge gaps of genetic variants and conditions prevalent in those groups (for example, Aboriginal and Torres Strait Islander peoples).

ESC considered that restriction on the basis of ethnicity would be inappropriate, and that the current eligibility proposal based on risk instead is acceptable. ESC considered that if testing cannot be judged by MSAC to be acceptably targeted to the individuals for whom the panel is designed, then a consequence would be that testing without restriction would have reduced cost-effectiveness and increased financial impact. ESC noted other organisations do not support ethnically targeted carrier testing. For example, the recently published revised American College of Medical Genetics and Genomics (ACMG) guidelines on carrier testing¹⁸ state “restricting

¹⁸ Gregg, A.R., et al. (2021). Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*, **23**: 1793–1806.

carrier screening by using socially defined ethnic constructs or by self-identified ancestry is both inequitable and scientifically flawed”. The ACMG guidelines state that while carrier testing for targeted genes in selected ethnic populations was appropriate in the past, massively parallel sequencing allows for a wider panel of genes to be tested without the need to identify the a priori risk based on ethnic background.

ESC noted that item AAAAA is proposed to be restricted to asymptomatic individuals. ESC considered that individuals with an existing condition (of those listed in AAAAA) may still be at risk of being a carrier for other listed conditions, and recommended “asymptomatic” in AAAAA be removed. ESC’s changes to AAAAA are reflected below (Table 24).

Table 24 ESC’s revisions to the item descriptor for targeted carrier testing

Category 6 (Pathology Services) – Group P7 Genetics
MBS item AAAAA
Testing of asymptomatic individuals of reproductive age, for the presence of pathogenic or likely pathogenic variants in order to ascertain their carrier status, in a panel of genes causing severe monogenic disorders that must include the <i>CFTR</i> , <i>SMN1</i> , <i>FMR1</i> , <i>HEXA</i> , <i>ASPA</i> , <i>ELP1</i> , <i>MCOLN1</i> , <i>G6PC1</i> , <i>SLC37A4</i> , <i>FANCA</i> , <i>FANCC</i> , <i>FANCG</i> , <i>GBA1</i> , <i>SMPD1</i> , and <i>BLM</i> genes, requested by or on behalf of a medical practitioner who manages the treatment of the patient.
Individuals must have a >10% personal risk of being a genetic carrier of any of the clinical disorders associated with pathogenic or likely pathogenic variants of genes in the testing panel, namely Cystic Fibrosis, Spinal Muscular Atrophy, Fragile X Syndrome, Tay Sachs Disease, Canavan disease, Familial dysautonomia, Mucopolidosis Type IV, Glycogen storage disease type 1, Fanconi anaemia type C, Gaucher disease, Niemann Pick Disease type A, and Bloom Syndrome.
One test per lifetime.
Fee: \$425

Practice Note 1: For individuals of Ashkenazi Jewish ancestry, the panel *must also* include *HEXA*, *ELP1*, *SMPD1*, *ASPA*, *FANCC*, *BLM* and *MCOLN1*. Additional genes may also be included in the panel using standardised pathology lists of genes according to ethnic risk. The reference source for these gene lists will be provided by the applicant. Practice Note 2: where the couple is already pregnant, concurrent testing of any partner(s) not already tested is recommended. ESC’s deletion is in green strikethrough.

ESC noted stakeholder feedback that the fee for item AAAAA should be \$1,200, to be consistent with the fee for item CCCC. ESC noted the fee is comparable to that for other similar amplicon-specific gene panels. ESC considered that increasing the fee for AAAAA to \$1,200 may support providers to use whole genome or exome sequencing and the use of a virtual panel, in line with previous gene panels where a \$1,200 fee has been supported by MSAC to permit such methods. However, ESC noted the applicant’s consistent advice that this gene panel test will use amplicon-specific methods rather than whole gene sequencing. ESC therefore considered the applicant’s proposed fee of \$425 to be reasonable given the intended amplicon-specific testing methods.

ESC noted that where already pregnant, simultaneous testing of both partners is recommended in the practice note for AAAAA, where both partners are eligible for AAAAA. ESC noted the item descriptor for CCCC proposes sequential testing to inform whether partner testing is needed in the non-Ashkenazi Jewish partner and if so the relevant gene/s to be sequenced under CCCC. ESC considered sequential testing would be more cost-effective and have lower budget impact than simultaneous testing, and noted the DCAR used sequential testing in its costings in line with the item descriptor. However, ESC also noted the RCPA’s feedback that concurrent testing of both partners is desired due to best clinical practice, and queried whether simultaneous testing would be more clinically appropriate.

ESC noted that recoupling was accounted for in reproductive partner testing, through the proposed “one test per couple per lifetime” restriction on CCCC.

For proposed item CCCC for reproductive partner testing, ESC noted that Ashkenazi Jewish partners will be independently eligible for AAAA, and so CCCC will be used by non-Ashkenazi Jewish partners only. ESC considered that whole gene sequencing of the relevant gene/s is appropriate because reproductive partners may have other variants beyond the variants associated with Ashkenazi Jewish ancestry, and also because this would be in line with MSAC’s recent support for reproductive partner testing using whole gene sequencing in other applications. ESC therefore considered the fee of \$1,200 is appropriate in line with the required methodology.

ESC considered having a re-analysis item (EEEE) may be unnecessary, given the proposed genetic panel test (AAAA) is likely to be amplicon-specific (i.e., for ‘hotspots’ only) and therefore there will not be any unreported variants. If MSAC does support a re-analysis item, a fee of \$500 would be more aligned with other MSAC-supported re-analysis items.

ESC noted the PICO stated a fee of \$100 for GGGG is too low, but had not revised the base case fee upwards to a specific figure. ESC noted RCPA and Australian Pathology feedback that \$100 is below the cost of providing fetal testing under GGGG, and that the DCAR had included sensitivity analyses at a fee of \$1,600. ESC considered \$1,600 to be the more appropriate fee for GGGG.

ESC also noted that the wording of GGGG describes the risk that the fetus is a carrier, rather than has a disease. ESC considered that in clinical practice fetal testing would only occur where both parents are known carriers of an autosomal recessive variant or one parent, the female partner, is a known carrier of an X-linked variant. While ESC’s comment aligns with the population for GGGG recommended by PASC, ESC noted the item descriptor presented to it supports testing of a broader population – it supports testing of a pregnant patient where only one parent was a known carrier of an autosomal recessive variant, and where the fetus is at $\geq 25\%$ risk of inheriting a variant, i.e. being a carrier rather than affected by the disease. ESC considered that preventing the birth of carriers is not an endpoint of fetal testing, and requested the item descriptor be amended to more clearly describe the requirement for parental testing prior to fetal testing, including to describe the eligible fetus as being at $\geq 25\%$ risk of inheriting the disease rather than at $\geq 25\%$ risk of being a carrier. In effect, this would restrict eligibility to the population recommended by the PICO and align with ESC’s comments concerning clinical practice.

ESC’s changes to GGGG are reflected below (Table 25).

Table 25 ESC's revisions to the item descriptor for fetal testing

Category 6 (Pathology Services) – Group P7 Genetics
MBS item GGGG
<p>Testing of a pregnant patient, where one or both prospective parents are known to be affected by or carriers of <u>autosomal recessive variants or one parent is known to be affected by or a carrier of an X-linked</u> known pathogenic variant/s causative of a disease tested for in AAAA, for the purpose of determining whether familial variants are present in the fetus, if:</p> <p>(a) The pregnancy is a singleton pregnancy; and</p> <p>(b) The detection is requested by a consultant physician practising as a clinical geneticist; and</p> <p>(c) The fetus is at 25% or more risk of inheriting a monogenic variant known to cause a disease tested for in AAAA.</p> <p>One test per pregnancy.</p>
Fee: \$400 <u>\$1,600</u>

ESC's additions are in green underlined text, and deletions in green strikethrough.

ESC noted the potential for psychological harm of preimplantation genetic diagnosis, but noted the lack of evidence supporting this. Further, ESC noted that there was no comparative evidence identified for the safety of targeted carrier testing for severe monogenic conditions compared with genetic carrier testing for CF, SMA and FXS.

ESC noted that the only test accuracy measure for targeted carrier testing for severe monogenic conditions was the diagnostic yield in the Ashkenazi Jewish population. Eleven studies were identified, but none had a relevant comparator, and all studies were considered to be at high risk of bias.

ESC noted that for the economic evaluation no comparative evidence was available, so a linked evidence approach was used. ESC noted that the economic evaluation was a cost-effectiveness analysis using a decision tree and a stepped approach, which ESC considered to be appropriate for MBS items AAAA and CCCC.

ESC noted that the primary outcome of the model was cost per affected birth, while secondary outcomes were:

- Cost of informed reproductive decision
- Cost per additional IVF and pre-implantation genetic diagnosis event.
- Number of terminations
- Cost per termination

ESC noted that these outcomes were reported both with and without lifetime costs as requested by PASC, because lifetime costs are expected to be considerable (as done in the assessment of Application 1573).

ESC noted that the economic evaluation involved the following stepped approach:

- Step 1: stand-alone costs per affected birth (reported separately for preconception and pre-natal testing)
- Step 2: total costs of Step 1 compared with comparators, using cumulative proportions of reproductive decision outcomes (Baby with condition; Baby without condition; IVF; Abstain; Infant mortality; Termination)
- Step 3: combined preconception and pre-natal
- Step 4: costs and events for initial plus subsequent pregnancies

ESC noted that this was based on the approach by Norman et al. (2012)¹⁹ for CF carrier testing, and is consistent with the approach undertaken in application 1573.

ESC noted that in the economic model, the cumulative outcome represents patients flowing through for the first cycle to determine the costs and events associated with a fetus being affected by one condition (for example CF). When a baby with that one condition is not born, the model flows through again for testing against the next condition and so on. Thus in the model, only one cost of testing is assumed so the denominator is weighted for each subsequent condition. ESC noted that this means that in the model patients can only be a carrier for one disease, not multiple diseases. ESC noted a one study had reported 30.2% of individuals with Ashkenazi Jewish ancestry were carriers for at least one genetic condition, 10.1% were carriers for two conditions and 2.5% were carriers for three conditions²⁰. Therefore, ESC considered that although individual conditions may be rare on a population level, a substantial proportion of people with Ashkenazi Jewish ancestry will be carriers for more than one of the conditions tested for. ESC noted the economic model assumed people would only be a carrier for a single disease, which it considered was inappropriate given the substantial proportion of Ashkenazi Jewish individuals who are carriers for multiple diseases. ESC considered it would have been ideal for the economic analyses to account for multiple carriers, though this would likely have minimal impact on the ICER as the numbers are small.

ESC noted that in the model, downstream consequences are different for each outcome depending on whether one or both parents are carriers or if an 'affected individual' is born. ESC noted that because the model did not consider quality-of-life decrements in the risks of testing, this favours the intervention relative to no testing.

ESC considered that due to insufficient data there was significant uncertainty in many input assumptions, in particular that a number of probabilities (such as rates of in vitro fertilisation [IVF] and termination of pregnancy) are based on the international Ashkenazi Jewish population. If there are inter-country cultural differences in this population, it may impact these proportions for Australia.

ESC noted the cost-effectiveness analyses showed that, when only carrier testing costs were considered, genetic carrier testing for the nine conditions dominated the base case comparator (based on negative incremental costs and a reduction in the number of affected individuals) – this was true of both the scenario where each partner was Ashkenazi and the mixed couples scenario (where the reproductive partner used item CCCC resulting in a weighted cost-effectiveness of 75% of the cost of AAAA + 25% of the cost of CCCC). Carrier testing for nine conditions was also dominant when lifetime costs were taken into account.

ESC noted that analyses incorporating GGGG (fetal testing) had been provided as a standalone analysis that formed part of the rejoinder and had not been integrated into the AAAA and AAAA+CCCC analyses. For GGGG, ESC noted that while the economic evaluation still utilised a stepped approach (as described above), steps 3 and 4 were redundant given that this item is only relevant to pre-natal testing. ESC noted that the GGGG model assumed both partners were Ashkenazi Jewish with only one partner assumed to be a known carrier (but not diagnosed with the condition) and the other at high risk due to Ashkenazi Jewish ancestry.

¹⁹ Norman R, et al. (2012). Cost-effectiveness of carrier screening for cystic fibrosis in Australia. *J Cyst Fibros*, **11**(4), 281-287.

²⁰ Lizarin GA, et al. (2013). An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. *Genet Med*. **15**(3):178-86.

ESC noted that the GGGG modelling had assigned a carrier risk of 0.5 to the second partner, though ESC considered that fetal testing would only be conducted where both parents (AR) or the mother (XL) are already known carriers. ESC noted the rejoinder's modelling for GGGG found that use of this item resulted in incremental costs that were positive and there an increase in the number of affected individuals relative to the two comparators, which would imply that this item was dominated by both comparators. ESC noted the rejoinder's results showed GGGG was also dominated when lifetime costs were taken into account. ESC noted that only a limited time was available to it to evaluate the analysis for item GGGG as it arrived. Post-ESC it was noted that some of the results of the GGGG analysis and the assumptions on probabilities underlying the analysis merited further investigation. The HTA group provided a post-ESC addendum with updates to the combined model with GGGG, which ESC considered to be useful though the updates do not appear to change any of the conclusions of the model.

ESC noted that testing in the preconception stage was more cost-effective (in the sense of resulting in a lower ICER per averted birth) than pre-natal testing (notably for TSD). For instance, the ICER for incremental cost per TSD birth averted was \$1.93 for preconception testing and \$80.17 for pre-natal testing. Thus ESC considered the proportion of preconception vs pre-natal testing (base case: 20% vs 80%) may be an additional driver of cost-effectiveness that had been insufficiently explored. ESC noted that the addendum also provided sensitivity analyses exploring the effect of varying this ratio on the economic and financial analyses. ESC noted that the addendum's analyses showed that as the proportion of preconception testing increases, the cost-effectiveness increases, as does the financial impact to the healthcare budget. ESC considered that this is an important sensitivity analysis as it shows efficiency gains can be made by increasing the proportion of preconception testing. ESC also noted that quality of life was not considered in this assessment as it was in previous assessments, so considered the benefits of testing earlier may have been underestimated.

ESC noted the applicant's pre-ESC comment that between 50%-70% of Jewish high school students in Sydney and Melbourne attend schools that offer genetic carrier testing for TSD, where the reported testing uptake within multi-disease Ashkenazi Jewish testing programs is high, up to 99%²¹ – and that this is approximately three times higher than the uptake rate in the DCAR's financial analyses. ESC considered the estimated uptake may be too low, though noted the rejoinder's results showing that adjusting the uptake rate by 10% results in a maximum 26% change in the total financial costs of listing.

ESC noted that the financial modelling used an epidemiological approach to estimate utilisation. The annual cost to the MBS for the testing was calculated to be \$175,598 in year 1, decreasing to \$158,522 by year 6. ESC also noted additional costs to the MBS each year of about \$223,058 due to increased use of chorionic villus sampling testing/amniocentesis, genetic counselling and IVF plus pre-implantation genetic diagnosis (which is a significant cost of about \$44,000 per year). However, ESC noted that if there is a decrease in the number of affected births, this results in a decrease in MBS costs associated with treatment concerning the nine monogenic conditions. ESC noted that the overall budget impact to the healthcare system is estimated to be from \$229,109 in year 1 to \$206,793 by year 6. ESC considered this to be low.

ESC noted some errors in the financials, which it considered will lead to an underestimate of the financial costs of carrier testing.

²¹ Lew RM, et al. (2012). Tay Sachs disease in Australia: reduced disease incidence despite stable carrier frequency in Australian Jews. *Med J Aust*, **197**: 652-654.

ESC noted NPAAC's advice that there is no specific existing External Quality Assurance (EQA) program for this gene panel in Australia or internationally, though an alternative would be to use existing EQA programs for single genes, and/or inter-laboratory sample exchanges. All testing should be conducted in National Association of Testing Authorities (NATA)-accredited laboratories and by appropriately qualified personnel.

ESC noted that public funding of the proposed services may contribute to increasing stigma for those living with genetic conditions included in the proposed panel testing. It noted that it may complicate or prevent efforts to change societal perceptions and improve the lived experience of those with such conditions under the social model of disability.

ESC noted that Application 1637 – Expanded Reproductive Carrier Testing of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions (Mackenzie's Mission) – is concurrently being considered by MSAC and that Application 1573 - Reproductive carrier screening for CF, SMA and FXS – will be introduced onto the MBS on 1 November 2023. ESC considered that this application should be considered in relation to Applications 1637 and 1573.

17. Applicant comments on MSAC's Public Summary Document

The College's Working Party would like to express their delight in MSAC approving public funding targeted reproductive carrier testing for these severe monogenic conditions, and would like to take this opportunity to thank the Department for its assistance throughout the assessment process.

18. Further information on MSAC

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