



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1573 – Reproductive carrier testing for cystic fibrosis, spinal muscular atrophy and fragile X syndrome

Applicant: Royal College of Pathologists of Australasia (RCPA)

Date of MSAC consideration: MSAC 79th Meeting, 28-29 July 2020

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 reproductive carrier testing for determining carrier status of cystic fibrosis (CF), spinal muscular atrophy (SMA) and fragile X syndrome (FXS).

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported public funding for reproductive carrier testing to detect CF, SMA and FXS pathogenic variants in women early in pregnancy or intending to become pregnant, and in their reproductive partners as needed. MSAC advised that the value of the test mostly arose from the improved basis for reproductive decision making for those who test positive, and accepted that many of these decisions had also been shown to reduce overall costs to the health care system.

The MSAC-supported MBS items were as follows:

Category 6 (Pathology Services) – Group P7 Genetics
Item number: XXXXX Testing of a patient who is planning pregnancy to identify carrier (heterozygous) status for pathogenic variants in the cystic fibrosis transmembrane conductance regulator (<i>CFTR</i>), survival motor neuron 1 (<i>SMN1</i>) and fragile X mental retardation 1 (<i>FMR1</i>) genes, for the purpose of determining reproductive risk of these conditions. One test per lifetime. Fee: \$400
Category 6 (Pathology Services) – Group P7 Genetics
Item number: YYYYY Testing of a pregnant patient to identify carrier (heterozygous) status for pathogenic variants in the cystic fibrosis transmembrane conductance regulator (<i>CFTR</i>), survival motor neuron 1 (<i>SMN1</i>) and fragile X mental retardation 1 (<i>FMR1</i>) genes, for the purpose of determining reproductive risk of these conditions. One test per lifetime. Fee: \$400
Category 6 (Pathology Services) – Group P7 Genetics
Item number: ZZZZZ Testing of the reproductive partner of a patient who has been found to be a carrier of an autosomal recessive pathogenic variant identified by item XXXXX or YYYYY, for the purpose of determining the couple's reproductive risk of this condition. One test per condition per lifetime. Fee: \$400

Practice note:

The laboratory used to undertake tests for items XXXXX and YYYYY must use a methodology appropriate to the clinical setting with:

- (a) sufficient diagnostic range and sensitivity to detect at least 95% of pathogenic variants likely to be present in the patient; and
- (b) at least 50 of the most frequently encountered cystic fibrosis transmembrane conductance regulator variants in the Australian population.

Not to be claimed in conjunction with items 73300, 73305, 73345, 73346, 73347, 73348, 73349 and 73350.

Consumer summary
<p>The Royal College of Pathologists Australasia applied for public funding through the Medicare Benefits Schedule (MBS) for reproductive carrier testing for three conditions – cystic fibrosis, spinal muscular atrophy and fragile X syndrome – in people who are planning to have a baby or who are already pregnant. These three conditions are the most common inheritable genetic disorders with substantially reduced life expectancy in the Australian population.</p> <p>Reproductive carrier testing can show if someone is a genetic carrier for one of these conditions. If both parents are carriers for either cystic fibrosis or spinal muscular atrophy, there is a chance that their baby will be born with the condition. If the mother is a carrier of fragile X syndrome, there is a chance the baby will be affected. Testing means that people can make a more informed decision about how to plan a pregnancy, or what to do if they are already pregnant.</p> <p>MSAC noted that this type of testing is already available for people who pay for it themselves. This means some people who want this information miss out because they cannot afford the test.</p>

Consumer summary

MSAC acknowledged that people eligible for the test can decide whether or not to be tested. People can also make their own decisions based on the information they receive from the test. For example, some people who find they are likely to have a child with one of these conditions might choose in-vitro fertilisation or adoption, or termination of pregnancy if their fetus is affected, or preparing for the care needs they anticipate if their child has one of these conditions.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported public funding of reproductive carrier testing for fragile X syndrome, spinal muscular atrophy and cystic fibrosis through the MBS. This is because MSAC considered that the test contributes to informed decision-making about reproduction and reduced costs to the health system as a result. MSAC also supported funding the test because it improves equity of access for those who cannot afford to pay privately.

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

MSAC noted that this application was for new MBS items for reproductive carrier testing of couples (who are planning a pregnancy or are in the early stages of a pregnancy) for the monogenic conditions of CF, SMA and FXS.

MSAC advised that the application was not for funding of a population-based screening program, but represented reproductive carrier testing as a type of opportunistic testing (meaning, in a medical practitioner's opinion, the patient's circumstances clinically warranted the performance of the test). MSAC supported the application on the basis that the item descriptor for this carrier testing will be limited to CF, SMA and FXS. MSAC accepted that the testing methodologies used currently would limit the testing to these three conditions:

- MALDI-TOF, allele specific amplification, Sanger sequencing or next-generation sequencing for *CFTR* variants (for CF)
- multiplex ligation-dependent probe amplification (MLPA) probes or qPCR for *SMN1* (for SMA)
- fragment analysis (primed PCR to detect triplet repeat expansion) for FXS.

The specificity of these methods reduces the chance of leakage to testing for other conditions, because of the specific nature of the genetic test for these conditions, noting that next-generation sequencing is currently not widely used in Australian pathology laboratories for SMA or FXS. MSAC accepted that the three identified conditions were the three most common monogenic conditions with substantially reduced life expectancy for those affected.

MSAC considered that there was a clinical need for carrier testing for the identified conditions, and that it could be considered reasonably required for the management of the medical condition of both women early in pregnancy or intending to become pregnant, and for their reproductive partners because this would favourably affect the reproductive decision options available to those who test positive.

MSAC also noted that, currently, clinical or newborn screening through Newborn Bloodspot Screening funded by state and territory governments is available to diagnose affected individuals with CF, and this has been extended in a research program in NSW and the ACT to include SMA. Early detection of either disease can lead to earlier treatments, and thus

improved outcomes for these children. However, MSAC noted there are no pharmacological treatment options for those with FXS, and there are no currently registered curative treatments for any of the three conditions.

MSAC noted that this testing is recommended by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, and is strongly supported by consumer groups.

MSAC acknowledged the ethical issues surrounding applications such as this. MSAC noted that the cost-effectiveness analyses were based on rates of different types of decisions reported in the published literature in women and couples who test positive as carriers of one of the three conditions. However, MSAC also recognised that some couples may choose to not have testing or may choose to have a child born with a condition after being informed by a positive test result.

MSAC acknowledged the current inequity of access to this type of carrier testing, as these conditions often occur in babies of families with no known history. MBS-funded CF and FXS testing is currently only available to those with a family history of these conditions or who are relatives of known carriers. The proposed carrier test for each condition are currently available for consumers who are willing to pay private fees, thus compounding the inequity of access.

MSAC queried the proposed fee of \$400, considering that it may be too low compared with public laboratory costings currently based on combining three different methodologies – one for each condition. If so, there will be some out-of-pocket costs for some consumers, which may affect the equity of access for those who cannot afford to pay any additional costs for the test. MSAC also considered that increasing the fee would have related consequences in increasing costs in the economic evaluations and the budgetary forecasts. On balance, MSAC supported the proposed fee of \$400 because there was insufficient basis to reject the applicant's proposal that the service could be provided for this fee.

MSAC noted that physical adverse events arising from obtaining a test sample for the proposed reproductive carrier tests were likely to be non-significant, due to the relative non-invasiveness of obtaining biological material (i.e. swabs and blood samples). In addition, 17 studies reporting on psychological effects of reproductive carrier testing were identified, mainly measuring test-related anxiety before or during pregnancy, or up to 3 years after testing. Test-related anxiety appeared to decline over time, and no clear patterns in anxiety levels were observed between those who were identified as a carrier and those who were not. On this basis, MSAC concluded that the proposed testing was safe.

MSAC noted that there was insufficient direct evidence to assess the effectiveness of the proposed test. However, based on sufficient indirect evidence, MSAC concluded that the proposed testing would be more effective than no testing. Analytical test performance was strongest for DNA obtained from blood samples rather than from saliva or buccal samples. Further, reproductive carrier testing has greater impacts (for costs and benefits) on individuals affected by decisions based on the test result during pregnancy compared to the individuals being tested for carrier status prior to pregnancy. As such, outcomes including: termination rates, *in-vitro* fertilisation (IVF) rates and pregnancy abstinence rates summarised from the published literature were linked in the economic model. However, due to the scarcity of comparative studies, linked evidence was sourced mostly from single-arm studies.

MSAC noted the economic analysis was a cohort decision-analytic model (decision tree), allowing various chance nodes to determine the proportion of couples that will have a child

with CF, SMA or FXS, as well as possible termination episodes, births arising from IVF, and couples who decide to abstain from pregnancy and potentially adopt a child.

MSAC noted the carrier rate in the general Australian population of 1/25 for CF, 1/40 for SMA and 1/150 for FXS had been applied in the comparator arm of no reproductive carrier testing. With no reproductive carrier testing, the chance of a CF birth is the carrier rate in the female population multiplied by the carrier rate in the male population, multiplied by the probability of a CF birth ($1/25 \times 1/25 \times 1/4$). The same methodology was used to calculate the probability of a SMA birth ($1/40 \times 1/40 \times 1/4$) and an FXS birth ($1/150 \times 1/2$; male carrier status is not relevant for FXS in this setting).

MSAC considered the economic evaluation to be uncertain as evidenced by its sensitivity to rounding because the estimated differences in outcomes across the two arms are close to zero. A value that changes from -0.000001 to 0.000001 can change whether the ICER is dominant (benefits increase and costs decrease), is dominated (benefits decrease and costs increase) or is cost-effective (increased benefits justify the increased costs). However, MSAC accepted that any additional interrogation beyond what ESC had already provided would not affect its overall advice.

Based on studies with small numbers of patients testing positive (and uncertainty in the estimates), MSAC noted that pregnancies were terminated in:

- 66.7%–100.0% of CF-affected pregnancies
- 91.7%–100.0% of SMA-affected pregnancies
- 0%–100% of FXS-affected pregnancies.

Similarly, based on studies with small numbers of patients testing positive (and uncertainty in estimates), MSAC also noted that couples detected as being carriers in preconception reproductive carrier testing intended to pursue alternative reproductive options 89%–100% of the time for CF, 100% for SMA and 74%–100% for FXS.

MSAC also accepted that, although hard to measure, there was also the intrinsic value for couples and women being empowered to control their reproductive options based on the knowledge provided by the test results, particularly if they were found to be carriers.

Based on published rates of these types of informed decisions, MSAC accepted that the cost-effectiveness of the proposed reproductive carrier testing arises from consequential cost offsets to the Pharmaceutical Benefits Scheme (PBS) due to these choices leading to fewer children born with CF, SMA or FXS who would need treatment. MSAC also noted that where carriers are identified, by proceeding with preconception embryo testing, couples would not be faced with deciding whether to terminate a pregnancy or not. MSAC considered that this information was valuable both for pre-conception testing and for pregnant couples who may have been planning subsequent pregnancies. Overall, based on the information provided, MSAC supported reproductive carrier testing of the three conditions in both the early stages of a pregnancy (extending beyond other types of tests offered to pregnant women with similar consequences for the unborn baby) and in the pre-conception setting (to avoid the consequence of women having to become pregnant before being eligible for this carrier testing).

MSAC queried the utilisation estimates provided in the DCAR, which were based on 133,000 women giving birth each year. MSAC considered this may be an underestimate, as the Australian Bureau of Statistics reported that there were 315,147 registered births in 2018, with 4,500 of them multiple births (68 triplets), which equates to 310,579 women giving birth

in 2018. For all Australian women, the total fertility rate was therefore 1.74 births per woman, with 178,493 first-time mothers. MSAC noted that utilisation estimates influence the financial estimates. The other factor that most influence the financial estimates are the annual costs of lumacaftor/ivacaftor (to treat CF) and nusinersen (to treat SMA).

MSAC noted the pre-MSAC response, which stated that genetic counselling for this type of testing does not need to be performed by accredited genetic counsellors. MSAC noted that obstetricians and general practitioners are already providing this counselling to consumers who are paying privately for the test, and for those individuals who are eligible for current test items. With further education of these medical practitioners, the rate of offering this type of testing and counselling is likely to increase.

MSAC supported the department's minor suggestions to the proposed MBS item descriptors. MSAC advised that no changes to the existing MBS items for testing CF and FXS was needed, although expected that their use would decrease.

MSAC noted the high calculated financial impact (\$32,229,986 in year 1, decreasing to \$17,686,723 in year 5), with sensitivity analyses suggesting costs could be as high as \$65 million per year assuming 100% uptake. MSAC considered that the PBS cost-offsets would continue to increase past year 5, due to ongoing treatment regimens for those who would have been born with the conditions. MSAC also considered that the initial uptake rates were overestimated as not all medical practitioners would consider themselves ready to offer testing and counselling from the start of MBS funding. However, MSAC considered that the financial impact would be greater in the first 10 years of testing, as it would include a prevalent pool comprising patients planning pregnancy more than a year ahead, and parents beyond their first pregnancy who are requesting the test, if they did not have access to the test for the births of previous non-affected children. As more people have their carrier status determined, utilisation will likely decrease over time and only be undertaken by first-time parents. MSAC thus accepted that, in the long term (>10 years), the utilisation estimates based on annual incidences will become more accurate.

MSAC accepted that a key driver of the financial impact was likely to be utilisation, and requested that the Department review the estimates in more detail out of session.

MSAC recommended listing, with the caveat that the Department-reviewed financial estimates were within 10%–20% of that proposed in the DCAR; if the reviewed financials were beyond this, MSAC requested that the application return to MSAC for review. Otherwise, the application could be progressed out of session.

Subsequent to the MSAC meeting, the Chair convened an out of session teleconference to discuss the Department's review of the financial estimates.

The following factors for considering the DCAR's utilisation estimates to be underestimates were noted:

- The DCAR estimates omitted the prevalence pool (being based on the annual incidence population of women already pregnant or contemplating pregnancy that year). This prevalence pool would include mothers without an affected child contemplating another pregnancy and women planning a pregnancy more than a year in the future. However, this prevalence pool is likely to be limited to women in a 10-year reproductive window who would consider being tested, and women are more likely to consider testing the closer they are to considering becoming pregnant. No source of estimates could be identified to reflect this varying uptake rate across the prevalence pool beyond the 54% uptake rate assumed for the incidence population.

- The DCAR estimates were based on an observed rate of 54% uptake rate in both subgroups of the incidence population (pre-conception and post-conception). In a setting where couples already have a child with the condition, up to 90% of women would take up the test if offered, which suggests an upper limit to this uptake estimate for the incidence population.

On the other hand, a factor for considering the DCAR's utilisation estimates to be overestimates was the implicit assumption that all medical practitioners would be ready to offer the test from the start of MBS funding. This was considered unlikely, but again no source of estimates could be identified to reflect this contribution to a reduced uptake in the early years of listing.

In relation to the identified difference of 133,000 and 178,493 first-time mothers per year, the authors of the DCAR provided a satisfactory explanation of how the different approaches could be reconciled, and affirmed that the DCAR's approach was intentionally consistent across the economic evaluation and financial analysis.

It was recognised that it was difficult to generate a quantitative basis for many of these additional factors to get an overall impression of their overall consequences for the utilisation estimates. In addition, even though the utilisation estimates might vary, the overall budget implications to the MBS and the PBS would likely vary to a lesser degree. The reason for this is that, if more or less patients get tested for more or less MBS costs, then there will be correspondingly more or less carriers detected, and thus correspondingly more or less PBS cost offsets.

It was concluded, and ratified by MSAC out of session, that there was insufficient basis to advise that the financial estimates might be in error by more than 10%–20% and that further consideration by MSAC was not required. As it is usual practice for MSAC to conduct a predicted versus actual analysis of utilisation 24 months after MBS listing, it was considered that this would be particularly important in this case, mindful that it may take longer to detect the PBS utilisation consequences as the PBS listing may also change in the meantime.

4. Background

This is the first application for reproductive carrier testing for determining carrier status of cystic fibrosis (CF), spinal muscular atrophy (SMA) and fragile X syndrome (FXS). It is informed by a department contracted assessment report (DCAR). MSAC has not previously considered this application.

Reproductive carrier testing of individuals without a family history is currently neither funded, nor reimbursed, in either the private or the public setting in Australia.

The Ratified PICO Confirmation for 1573 stated that MBS funding for CF or FXS genetic testing is currently available only for those affected or who have a family history and for parents of a fetus suspicious for CF with echogenic gut (MBS items 73345, 73346, 73347, 73348, 73349, 73350 [CF]; and 73300, 73305 [FXS]). There is no current MBS funding for SMA testing.

5. Prerequisites to implementation of any funding advice

The National Pathology Accreditation Advisory Council (NPAAC) noted that there is an existing quality framework (External Quality Assurance (EQA) programs and accreditation experience). NPAAC also noted that testing for SMA is conducted by a number of accredited

Australian pathology laboratories without an MBS item or fee. There are EQA programs available.

6. Proposal for public funding

The proposed MBS item descriptor from the DCAR is summarised in Table 1.

Table 1 Proposed MBS items

Category 6 (Pathology Services) – Group P7 Genetics
Item number: XXXXX Testing, requested by a medical practitioner, of a female planning pregnancy to identify carrier (heterozygous) status for pathogenic variants in the cystic fibrosis transmembrane conductance regulator (CFTR), survival motor neuron 1 (SMN1) and fragile X mental retardation 1 (FMR1) genes, for the purpose of determining reproductive risk of these conditions. One test per lifetime. <u>Fee: \$400</u>
Category 6 (Pathology Services) – Group P7 Genetics
Item number: YYYYY Testing, requested by a medical practitioner, of a pregnant female to identify carrier (heterozygous) status for pathogenic variants in the cystic fibrosis transmembrane conductance regulator (CFTR), survival motor neuron 1 (SMN1) and fragile X mental retardation 1 (FMR1) genes, for the purpose of determining reproductive risk of these conditions. One test per lifetime. <u>Fee: \$400</u>
Category 6 (Pathology Services) – Group P7 Genetics
Item number: ZZZZZ Testing, requested by a medical practitioner, of the male reproductive partner of a female who has been found to be a carrier of an autosomal recessive pathogenic variant identified by item XXXXX or YYYYY , for the purpose of determining the couple's reproductive risk of this condition. One test per condition per lifetime. <u>Fee: \$400</u>

Source: Table 11, p5 of DCAR

Practice note:

The laboratory used to undertake tests for items XXXXX and YYYYY must use a methodology appropriate to the clinical setting with:

(a) sufficient diagnostic range and sensitivity to detect at least 95% of pathogenic variants likely to be present in the patient; and

(b) at least 50 of the most frequently encountered cystic fibrosis transmembrane conductance regulator variants in the Australian population.

Not to be claimed in conjunction with items 73300, 73305, 73345, 73346, 73347, 73348, 73349 and 73350.

In its pre-ESC response, the applicant noted that the extent of the CFTR variants nominated in the practice note in the draft item for this application, , is not consistent with the practice notes for the existing CF MBS items (73345-73350), with a requirement for methodologies to identify at least 50, as opposed to 25, of the most frequently CFTR variants in the Australian population. The applicant supports this requirement; however, considered it may necessitate an alignment of the existing and proposed MBS items.

7. Summary of public consultation feedback/consumer issues

Comments were received from seven groups and organisations, noting that:

- the main benefits of the proposed service were:
 - individuals would have the opportunity to be informed of their carrier status
 - equitable access to testing for all prospective parents
 - testing during pregnancy could provide earlier diagnoses and treatment initiation

- there is a cost-benefit for both individuals and the community to allow the opportunity to screen for these conditions compared to non-screening. The Royal Australian and New Zealand College of Obstetricians (RANZCOG) stated, “*reducing the birth incidence at a population level is less expensive than a non-screening approach and managing costs of care, both direct and indirect when such a condition is diagnosed in a child*”
- the main disadvantages of the proposed service were that the concept of genetic carrier screening is more complex to provide pre- and post-test counselling for than other screened conditions
- education should be provided to general practitioners and obstetrician-gynaecologists to detail the importance of carrier screening and for it to be offered to their patients
- a cheek swab/saliva sample could be equally as effective as a blood test and should be considered
- only females need to be tested for carrier status for Fragile X.

Comments were also received from three individuals: their views towards the benefits of the proposed medical service were similar to those listed by the groups and organisations (above), especially the opportunity to be more informed for making decisions to do with family planning, and having affordable access. One of the individuals listed a disadvantage to the proposed service being that it may cause unnecessary anxiety for an individual in having the test performed, in addition to attracting unwanted advice or opinions from others.

8. Proposed intervention’s place in clinical management

Description of the proposed intervention

In-vitro reproductive carrier testing for pathogenic variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*), the survival motor neuron 1 (*SMN1*) and the fragile X mental retardation protein (*FMR1*) genes, for purpose of determining whether the patient is a carrier of a pathogenic variant for CF, SMA or FXS. This test is performed on DNA obtained from a peripheral blood sample, saliva sample or buccal swab (the sample must allow the testing laboratory to extract sufficient DNA for analysis) collected from the tested individual. The samples are delivered to the laboratory for analysis and results are generally obtained within 10 days. Testing is not proposed to be limited to any particular technology.

Description of the medical condition(s)

The target population comprises pregnant women or women who are planning a pregnancy as well as their reproductive male partners, for women who are found to be carriers, and the condition is not X-linked. There is no family history requirement.

Place in clinical management

The DCAR stated that reproductive carrier testing provides an option to determine the risk of having a child with CF, SMA or FXS either during pregnancy or before conception. Reproductive couples identified as high risk (for CF and SMA if both male and female in the couple are identified as carriers and for FXS if a female is a carrier) may be referred to a clinical genetics service or obstetrician to discuss reproductive options. The current and proposed algorithms are located in Figure 1 and Figure 2, respectively.

The DCAR stated that there is a major difference in the clinical management algorithms between those planning a pregnancy and those who are already pregnant in terms of options available if carrier status is confirmed for either CF, SMA or FXS. For those who are already pregnant, options include diagnostic testing of the fetus via amniocentesis or chorionic villus

sampling (CVS) with a further option to terminate the pregnancy, or continue, if the respective disease is confirmed in the fetus.

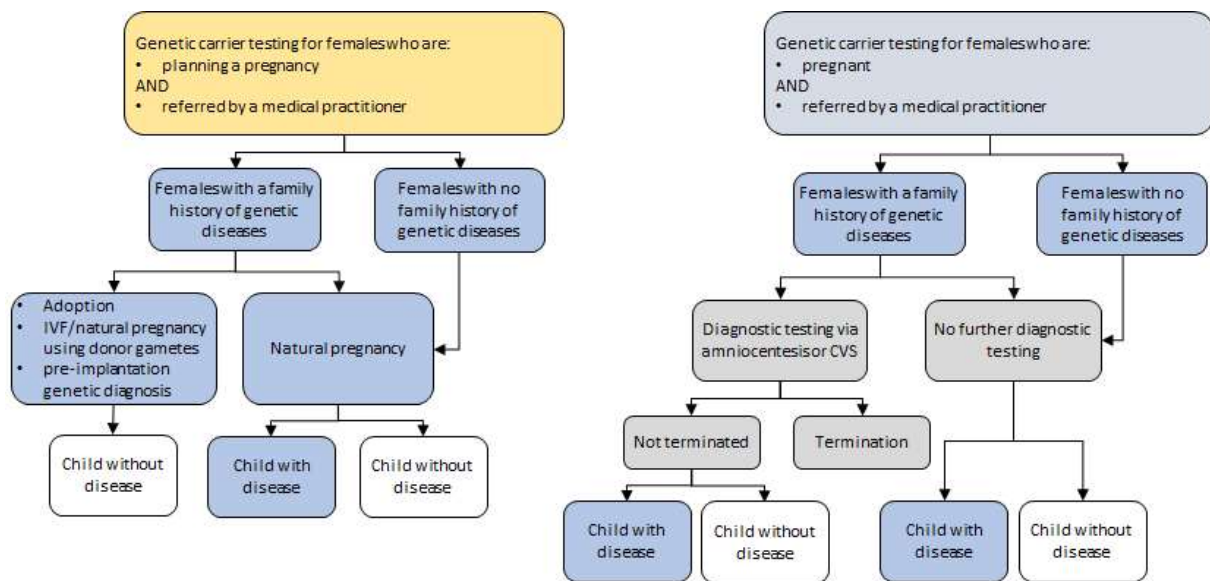


Figure 1 Current clinical management algorithm for reproductive carrier testing for CF, SMA and FXS in females who are planning a pregnancy (left) and for females who are pregnant (right)
Source: Figure 1, p7 of the DCAR

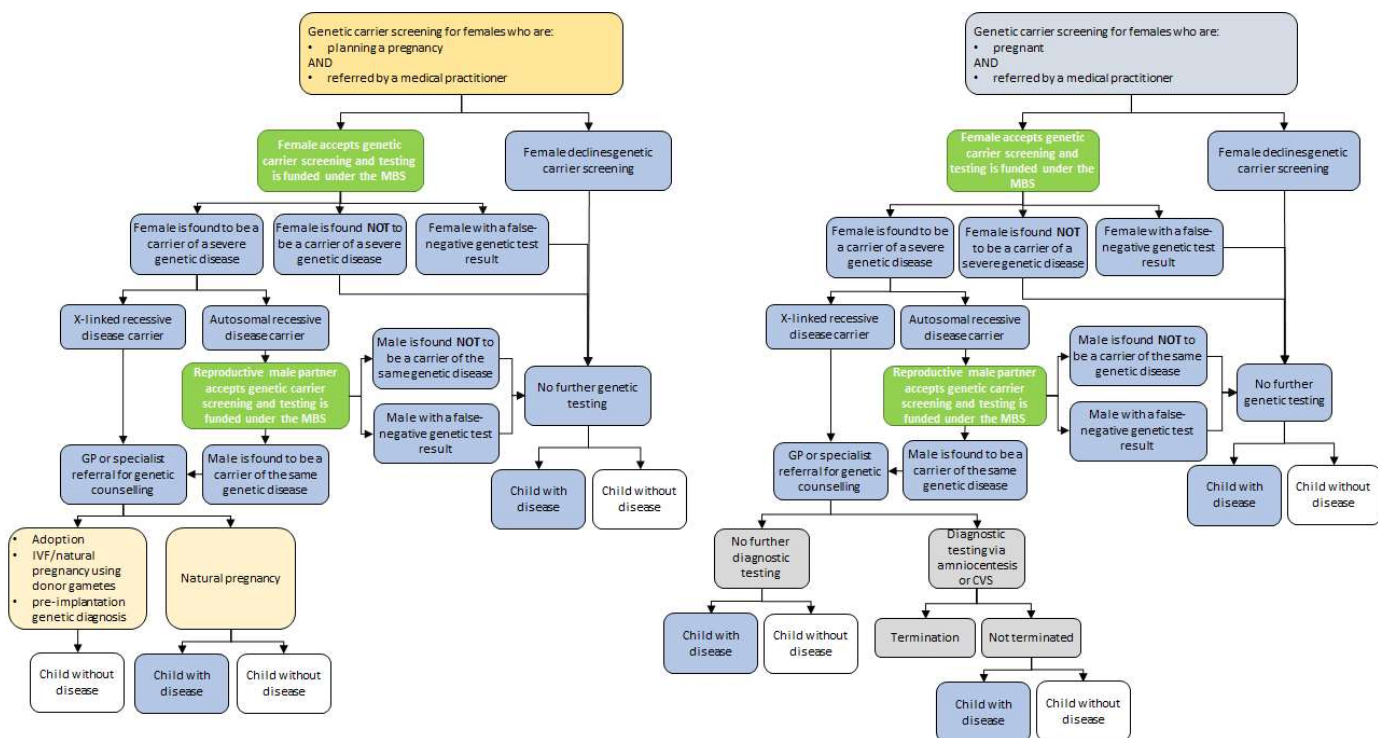


Figure 2 Proposed clinical management algorithm for reproductive carrier testing for CF, SMA and FXS in females who are planning a pregnancy (left) and for females who are pregnant (right)
Source: Figure 2, p8 of the DCAR

9. Comparator

‘No reproductive carrier testing’ is the proposed comparator.

The Ratified PICO Confirmation stated that the existing MBS items for genetic testing for: patients with symptoms of CF or FXS; those with a close family history; and partners of females with CF are not suitable comparators, because they constitute a small minority of the

proposed eligible population, which mostly comprises asymptomatic people without a family history of CF or FXS and SMA.

10. Comparative safety

The evidence base identified in the DCAR is summarised in Table 2. The DCAR stated the three studies assessing analytical validity studies were assessed to be of low-medium risk of bias. For clinical utility, most included studies were assessed to be at medium or high risk of bias using the case-series critical appraisal checklist.

Table 2 Key features of the linked evidence approach of the DCAR

Type of evidence	Description
Diagnostic accuracy (analytical validity)	Three studies reported analytical validity of reproductive carrier testing for CF, SMA or FXS that were predominantly based on next generation sequencing (NGS). One Australian study reported detection rates of non-NGS based test with these estimates appearing to be obtained from the test service provider.
Clinical validity	No studies evaluating comparative clinical validity of reproductive carrier testing for CF, SMA or FXS were identified by the literature search.
Therapeutic efficacy (clinical utility)	One ecological study reporting on reproductive carrier testing for CF, with a comparator relevant to this assessment (Castellani 2016) was identified. Due to the paucity of comparative evidence, the selection criteria were broadened to also include large population cohorts (either single-arm cohorts or case series) without a comparator. Therefore, a total of one ecological cohort study, three single-arm cohort studies and nine case series were included in the assessment of clinical utility.
Therapeutic effectiveness	Therapeutic effectiveness of the proposed medical service was not considered as carriers of pathogenic variants in the <i>CFTR</i> , <i>SMN1</i> and <i>FMR1</i> genes do not require a therapeutic intervention as such. Reproductive carrier testing offers the tested couple information on the risk of having children with these diseases and gives them the opportunity to choose other reproductive options, if desired.

^a reference standard available; ^b reference standard not available

Source: Table 2, pxviii of the DCAR

Test adverse events

The DCAR stated that no adverse events directly attributable to the proposed reproductive carrier testing panel are considered applicable, due to the relative non-invasiveness and safety of methods of obtaining samples (i.e., swabs and blood samples).

Adverse events from change in management

The DCAR stated that studies reporting on the proportion of pregnant women who chose prenatal diagnostic testing by amniocentesis or CVS following a positive reproductive carrier test in both partners (CF, SMA) or in the female alone (FXS) were 56%-100% for CF (subsequent pregnancies 32%), 91%-100% for SMA, and 41%-100% for FXS (subsequent pregnancies 28%).

The DCAR stated that psychological adverse events from reproductive carrier testing, such as anxiety caused by testing, appeared to decline over time, and no clear patterns in anxiety levels were observed between test-positive carriers and test-negatives.

11. Comparative effectiveness

No direct evidence to assess reproductive carrier testing for CF, SMA and FXS compared to no reproductive carrier testing was identified.

Linked evidence

Analytical validity

The DCAR stated that no studies were found that evaluated the analytical validity of multiplex ligation-dependent probe amplification (MLPA) or quantitative fluorescent multiplex polymerase chain reaction (PCR) for analysing the 50 most common pathogenic variants of *CFTR*; *SMN1* copy number analysis via multiplex ligation-dependent probe amplification (MLPA) or qPCR for exon 7, and expansion of the *FMR1* gene CGC repeat region by sizing and triplet repeat primed PCR. The literature search found three studies on the analytical validity of next generation sequencing (NGS) based reproductive carrier tests for CF, SMA and FXS (Table 3).

Table 3 Key features of the included evidence on analytical validity of genetic tests for carriers of CF, SMA and FXS

Study	Disease assessed	Samples used	Study summary	Key outcome(s)
Hogan 2018	CF, SMA and FXS	<i>CFTR</i> : patient and cell lines <i>SMN1</i> : 120 patients and 8 cell lines <i>FMR1</i> : 40 cell lines ¹	Analytical validation of a 235-gene NGS based ECS with full coverage across coding regions, targeted assessment of pathogenic noncoding variants, panel-wide CNV calling, and specialised assays for technically challenging genes including PCR and capillary electrophoresis for CGG repeats of <i>FMR1</i> .	Analytical sensitivity and specificity ² Reproducibility
Loukas 2015	CF	<i>CFTR</i> validation subset: 23 samples with previously characterised genotype from CDC plus five samples from Coriell Cell Repository The <i>CFTR</i> application set: 824 consecutive cases and 12 samples from CF positive neonates	Study assessed three genotyping assays: (i) The commercial Cystic Fibrosis Genotyping Assay (Abbott CE-IVD kit), (ii) 92% NGS panel consisting of partially sequencing of <i>CFTR</i> gene and detection of the deletion of exons 2 and 3, and (iii) 100% NGS panel including the complete coding region, three deep intronic mutations as well as large genomic rearrangements.	Analytical sensitivity and specificity ² Reproducibility
Feng 2017	SMA	6,738 de-identified blood samples submitted to Baylor Genetics Laboratory for carrier testing for a panel of diseases, including SMA, by NGS, qPCR, and MLPA	Paralogous gene copy number analysis by ratio and sum (PGCNARS) for SMA carrier testing based on short-read NGS data. This method was rigorously validated and compared to results generated by MLPA or qPCR. In addition, the g.27134T>G SNP associated with 2 + 0 SMA carrier status and pathogenic <i>SMN1</i> sequence variants were also analysed.	Analytical sensitivity and specificity Reproducibility

NGS=next generation sequencing, ECS=expanded carrier screen, CDC=Centre for Disease Control and Prevention, SNP=single nucleotide polymorphism, CF=cystic fibrosis, SMA=spinal muscular atrophy, FXS=fragile X syndrome

¹ Details of samples used and reference data for pathogenic variants of three listed genes analysed in this study are listed in Appendix F

² Positive and negative percent agreement of results when compared with a reference data

Source: Table 12, pp18-19 of the DCAR

The DCAR stated that all NGS-based panels provide high analytical validity and reproducibility. No studies evaluating analytical validity of other methods for reproductive carrier testing of CF, SMA and FXS were identified. Additionally no studies were found that compared the analytical validity of different sample types, investigated comparative analytical performance across different assay options, or reported likelihood ratios.

The DCAR noted that one study conducted in Australian population reported the detection rates for reproductive carrier testing of CF, SMA and FXS to be 90%, 95% and >99%, respectively.

Clinical validity

The DCAR stated that no studies reporting on clinical validity (clinical sensitivity and specificity, positive and negative predictive values) of reproductive carrier testing for CF, SMA and FXS versus no reproductive carrier testing were identified in the systematic search.

In its pre-ESC response, the applicant noted the lack of clinical and analytical validity peer-reviewed evidence identified during the assessment process; however, considered this is to be expected for the following reasons, and should not be used as an indication of the validity or not of the proposed testing:

- First and foremost, clinical validity is difficult to assess in reproductive carrier testing, in that carriers do not have the disease. The only feature that identifies them as carriers is the presence of a genetic variant, which can only be determined by testing.
- Reproductive carrier testing using non-NGS based methods has been a well-established methodology for at least the last decade in both Australian and international laboratories.
- Allele-specific amplification for cystic fibrosis genotyping, sizing and triplet repeat primed PCR1 for *FMR1* repeat expansions (fragile X syndrome, FXS), and MLPA2 or qPCR for spinal muscular atrophy (SMA) copy number testing are all accepted as the gold standard for testing for these disorders. The same tests are used whether the indication is for reproductive carrier testing or diagnostic testing.
- The NGS studies referenced in the document have used genotyping, fragment analysis and qPCR/MLPA to confirm the NGS results, reflecting the acceptance of these methods as the existing gold standard.
- In Australia, there are diagnostic kits for cystic fibrosis (CF) and FXS approved by the TGA, a process that would have required a demonstration of both analytical and clinical utility. This information should be available in the test kit inserts or websites and would be expected to be identified in search of unpublished and grey literature, most likely using different search terms to those used in the assessment.
- Individual testing labs in Australia have been participating for many years in EQA programs using these methods. They have performed their in-house validations/verifications as part of routine use. However, this routine quality control is not considered to be original work, and would, therefore, be unlikely to be identified in the published literature.

Therapeutic efficacy (change in management)

The DCAR stated that one ecological cohort study with significant methodological limitations reported a decrease in CF birth prevalence over a period of 21 years correlated to reproductive CF carrier testing.

Following reproductive carrier testing, the proportion of pregnancies in carrier couples resulting in an affected child ranged from 11-17% in CF carrier couples and was reported to be 2% in SMA carrier couples. In pregnancies affected by FXS, 17-100% of children affected by a premutation and 43-67% of children affected by a full mutation were born.

Carrier couples detected in preconception reproductive carrier testing intended to pursue alternative reproductive options in 89-100% for CF, 100% for SMA, and 74-100% for FXS.

Pregnancy was terminated in 67-100% of CF-affected pregnancies, 92-100% of SMA-affected pregnancies, and 0-100% of FXS-affected pregnancies.

Carrier couples detected through prenatal reproductive carrier testing pursued increased pregnancy decision options (in form of prenatal diagnosis performed through amniocentesis or CVS) in 56-100% for CF, 91%-100% for SMA, and 41-100% for FXS.

Therapeutic effectiveness (health benefit from change in management)

The DCAR stated that the therapeutic effectiveness of the proposed medical service was not considered as carriers of pathogenic variants in the *CFTR*, *SMN1* and *FMR1* genes do not require a therapeutic intervention as such. Reproductive carrier testing offers the tested couple information on the risk of having children with these diseases and gives them the opportunity to choose other reproductive options, if desired.

Clinical claim

The clinical claim was that reproductive carrier testing using a genetic panel for CF and SMA in couples and for FXS in females, is inferior in terms of safety and superior in terms of clinical effectiveness, compared to no reproductive carrier testing. The claim of inferiority was based on adverse psychological effects from reproductive carrier testing and prenatal diagnostic test-associated risk of miscarriage. The claim of superiority was based on an increase in informed reproductive decision-making options being available to couples and a forecast reduced number of births of children with CF, SMA and FXS.

Based on the evidence profile (summarised in Table 4, Table 5 and Table 6), the DCAR suggested that, relative to no reproductive carrier testing, the test and associated interventions has uncertain safety and superior effectiveness.

Table 4 Balance of clinical benefits and harms of reproductive carrier testing for CF compared to no reproductive carrier testing, and as measured by the critical patient-relevant outcomes in the key studies

Outcomes Follow-up	Participants (studies)	Quality of evidence (GRADE) ^{a,b}	Effect	Comments
Proportion of children born with CF	38,160 carrier tests (2 studies) 1,112,620 tested newborns (1 study)	⊕⊕⊕⊕	One ecological cohort study from Italy reported a statistically significant difference in annual CF prevalence decrease between two geographic regions with and without reproductive carrier testing. One Australian study reported 11.2% of pregnancies in carrier couples resulted in a child with CF (25% of CF-affected pregnancies as detected by PNDx), and a US study reported 16.7% of pregnancies in carrier couples resulted in a child with CF.	Downgraded by 1 point overall due to some concerns about the methodological quality of the studies, some concerns about the indirectness and some concerns about the imprecision.
Increased future reproductive options	28,571 tests (2 studies)	⊕⊕⊕⊕	89-100% pursued IVF with PGT-M (26% in the subsequent pregnancies)	Downgraded by 2 points overall due to serious concerns about methodological quality, indirectness, inconsistency, some concerns about imprecision.
Termination of pregnancy	38,160 tests (2 studies)	⊕⊕⊕⊕	One Australian study and one US study reported 75% and 67% termination rates in affected pregnancies, respectively. The termination rate was 100% for the subsequent pregnancies in the US study.	Downgraded by 1 point overall due to some concerns about methodological quality and indirectness.
Decision options for current reproduction/ Number of PNDx ^c	38,160 tests (2 studies)	⊕⊕⊕⊕	55.6-100% One Australian study indicated that all pregnant women with a high risk of having a child affected by CF required PNDx, while one US study indicated that proportion would be 56% in the first pregnancy and 32% in the subsequent pregnancies.	Downgraded by 2 points due to some concerns about the methodological quality, some concerns about indirectness, some concerns about imprecision and serious concerns about inconsistency.
Proportion of women requiring PNDx	38,160 tests (2 studies)	⊕⊕⊕⊕	55.6-100% One Australian study indicated that all pregnant women with a high risk of having a child affected by CF required PNDx, while one US study indicated that proportion would be 56% in the first pregnancy and 32% in the subsequent pregnancies.	Downgraded by 2 points due to some concerns about the methodological quality, some concerns about indirectness, some concerns about imprecision and serious concerns about inconsistency.
Psychological adverse events - anxiety before or during pregnancy	4746 (5 studies)	⊕⊕⊕⊕	Two studies indicated no anxiety (in a whole cohort or when compared between carrier and non-carriers), two studies suggested a slight increase in anxiety in carriers or couples that were tested sequentially rather than concurrently, and one study suggested a decrease in anxiety after receiving educational information.	Downgraded by 2 points due to serious concerns relating to the methodological quality and serious imprecision (in relation to the variable direction of effect).
Psychological adverse events - anxiety Follow-up range: 3 months to 3 years	1488 (5 studies)	⊕⊕⊕⊕	Four studies suggested that anxiety did not appear to differ between carriers and non-carriers and in one study reported a declining anxiety score for carriers when contacted one year after receiving test results.	Downgraded by 1 point overall for some concerns relating to the methodological quality of the studies and imprecision.

^a GRADE Working Group grades of evidence (Guyatt et al., 2013); ^b for cohort studies, the GRADE rating commenced at moderate certainty of evidence; ^c outcomes of decision options for current pregnancy and impact on the number of PNDx were assessed together as they evaluated the same concepts.

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊕ **Moderate quality:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊕⊕ **Low quality:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

⊕⊕⊕⊕ **Very low quality:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CF=cystic fibrosis; IVF=*in-vitro* fertilisation; PGT-M=preimplantation genetic testing for monogenic conditions; PNDx=pre-natal diagnostic testing

Source: Table 29, pp66-67 of DCAR

Table 5 Balance of clinical benefits and harms of reproductive carrier testing for SMA compared to no reproductive carrier testing, and as measured by the critical patient-relevant outcomes in the key studies

Outcomes Follow-up	Participants (studies)	Quality of evidence (GRADE) a,b	Effect	Comments
Proportion of children born with SMA	119,611 tests (2 studies)	⊕⊕⊕⊖	0% of affected pregnancies in one Australian study and 8.3% in one Taiwanese study.	Well conducted and reported studies (based on the NOS assessment). No downgrading of the evidence; there was a small concern about imprecision, but not serious enough to downgrade by 1 point.
Increased future reproductive options	2,412 tests (1 study)	⊕⊖⊖⊖	100% PGT-M.	Downgraded by 2 points overall due to serious concerns about methodological quality, indirectness, some concerns about imprecision.
Termination of pregnancy	128,043 tests (3 studies)	⊕⊕⊕⊖	Most carrier couples in one Australian and one Taiwanese study decided to terminate a SMA-affected pregnancy (91.7-100% termination rate). No affected pregnancies were found in an Israeli study of carrier testing for SMA.	Well conducted and reported studies (based on the NOS assessment). No downgrading of the evidence; there was a small concern about imprecision, but not serious enough to downgrade by 1 point.
Decision options for current reproduction/ Number of PNDx ^c	119,611 tests (2 studies)	⊕⊕⊕⊖	91.5-100% One Australian and one Taiwanese single-arm cohort studies estimated that most pregnant women with a high risk of having a child affected by SMA required PNDx.	Well conducted and reported studies (based on the NOS assessment). No downgrading of the evidence; there was a small concern about imprecision, but not serious enough to downgrade by 1 point.
Proportion of women requiring PNDx	119,611 tests (2 studies)	⊕⊕⊕⊖	91.5-100% One Australian and one Taiwanese single-arm cohort studies estimated that most pregnant women with a high risk of having a child affected by SMA required PNDx.	Well conducted and reported studies (based on the NOS assessment). No downgrading of the evidence; there was a small concern about imprecision, but not serious enough to downgrade by 1 point.
Psychological adverse events - anxiety during pregnancy	392 (1 study)	⊕⊖⊖⊖	One study indicated that most participants (98.7%) who underwent carrier testing responded favourably to the experience and one patient responded unfavourably due to added anxiety.	Downgraded by 2 points due to serious concerns relating to the methodological quality and use of an unvalidated tool to assess outcome.

^a GRADE Working Group grades of evidence (Guyatt et al., 2013); ^b for cohort studies, the GRADE rating commenced at moderate certainty of evidence; ^c outcomes of decision options for current pregnancy and impact on the number of PNDx were assessed together as they evaluated the same concepts.

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⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

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⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

NOS=Newcastle-Ottawa Scale; PGT-M=preimplantation genetic testing for monogenic conditions; PNDx=prenatal diagnostic testing; SMA=spinal muscular atrophy

Source: Table 30, pp67-68 of DCAR

Table 6 Balance of clinical benefits and harms of reproductive carrier testing for FXS compared to no reproductive carrier testing, and as measured by the critical patient-relevant outcomes in the key studies

Outcomes Follow-up	Participants (studies)	Quality of evidence (GRADE) a,b	Effect	Comments
Proportion of children born with FXS	82,790 tests (7 studies)	⊕⊖⊖⊖	High inconsistency in the proportions reported (33-100% for fetuses affected with a FM). Decisions to carry on with the pregnancy were influenced by the knowledge of the child's sex and, in case of PM, by the uncertainty about the severity of the condition.	Downgraded by 2 points due to serious concerns about methodological quality (case series only), indirectness and imprecision.
Increased future reproductive options	26,231 tests (5 studies)	⊕⊖⊖⊖	11.8-100% of PM carriers pursued IVF with PGT-M	Downgraded by 2 points overall due to serious concerns about methodological quality, indirectness, inconsistency, some concerns about imprecision.
Termination of pregnancy	82,790 tests (7 studies)	⊕⊖⊖⊖	High inconsistency in the proportions reported (50-100% for fetuses affected with a FM, and 33% in subsequent pregnancies in one study). Decisions to carry on with the pregnancy were influenced by the knowledge of the child's sex and, in case of PM, by the uncertainty about the severity of the condition.	Downgraded by 2 points overall due to serious concerns about methodological quality and indirectness and some concerns about inconsistency and imprecision.
Decision options for current reproduction/ Number of PNDx ^c	82,790 (7 studies)	⊕⊖⊖⊖	FM: 0-100% PM: 40.8-100% IM: 43.8% High inconsistency in the proportions reported. Decisions were influenced by the knowledge of the child's sex (lower PNDx rates for female fetuses).	Downgraded by 2 points due to serious concerns about methodological limitations, indirectness, and inconsistency. Some concerns about imprecision.
Proportion of women requiring PNDx	82,790 tests (7 studies)	⊕⊖⊖⊖	FM: 0-100% PM: 40.8-100% IM: 43.8% High inconsistency in the proportions reported. Decisions were influenced by the knowledge of the child's sex (lower PNDx rates for female fetuses).	Downgraded by 2 points due to serious concerns about methodological limitations, indirectness, and inconsistency. Some concerns about imprecision.
Psychological adverse events - anxiety Follow-up: up to 1 month after receiving test result	1328 (3 studies)	⊕⊖⊖⊖	Two Australian studies indicated that there was no difference in anxiety between tested and non-tested groups at 1 month while one study indicated that carriers felt quite anxious after receiving a positive result	Downgraded by 2 points due to some concerns regarding methodological quality and serious concerns about imprecision

^a GRADE Working Group grades of evidence (Guyatt et al., 2013); ^b for cohort studies, the GRADE rating commenced at moderate certainty of evidence; ^c outcomes of decision options for current pregnancy and impact on the number of PNDx were assessed together as they evaluated the same concepts.

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊖ **Moderate quality:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

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⊕⊖⊖⊖ **Very low quality:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

FXS=fragile X syndrome; IVF=*in-vitro* fertilisation; PGT-M=preimplantation genetic testing for monogenic conditions; PNDx=prenatal diagnostic testing

Source: Table 30, pp68-69 of DCAR

12. Economic evaluation

A cost-effectiveness analysis (and cost-utility analysis) was undertaken by the DCAR to evaluate reproductive carrier testing for CF, SMA and FXS (Table 7). The economic analysis was generated by a stepped economic evaluation presenting the results for both the cost effectiveness (cost/CF carrier couple detected, cost/SMA carrier couple detected and cost/FXS carrier detected), as well as by initial and subsequent pregnancies, and cost utility analysis (cost/QALY gained). It adopted the structure proposed by Norman et al 2012¹ for the cost effectiveness of CF testing.

The DCAR stated that the population in the economic evaluation was any woman or couple of reproductive age that may be pregnant or planning pregnancy, for whom the knowledge of carrier status and whether the foetus or the potential foetus could express the relevant CF, SMA or FXS gene is of benefit. This knowledge has utility for the couple in deciding pregnancy options such as *in-vitro* fertilisation (IVF), termination or abstaining from pursuing pregnancy, which creates further cost savings for the healthcare system and benefits for the family.

Table 7 Summary of the economic evaluation

Perspective	Healthcare
Comparator	No reproductive carrier testing
Type of economic evaluation	Cost-effectiveness Cost-utility
Sources of evidence	Systematic review of linked evidence
Time horizon	Lifetime
Outcomes	CF carrier couples detected SMA carrier couples detected FXS carriers detected Change in terminations Change in IVF utilisation QALYs
Methods used to generate results	Cohort decision analytic model (utilising lifetime costs and benefits derived from other microsimulation and Markov models)
Health states	8 health states CF Baby SMA Baby FXS Baby Termination Infant Mortality IVF Abstention Other Baby
Discount rate	5%
Software packages used	Microsoft Excel 365

Source: Table 3, pxxi of DCAR

¹ Norman, R., van Gool, K., Hall, J., Delatycki, M., et al. (2012). Cost-effectiveness of carrier screening for cystic fibrosis in Australia. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society*, 11(4), 281-287

Key structural and input assumptions of the model in the DCAR are summarised below.

- The rates of CVS, termination, IVF, and choosing not to have further children were sourced from the identified clinical studies and aggregated for use in the model.
- The long-term costs and benefits of CF and SMA were derived from submissions to the PBAC, each comparing best supportive care with ivacaftor or lumacaftor/ivacaftor for CF or with nusinersen for SMA; the long-term costs and benefits of FX were derived from a French study (Chevreul et al., 2015).
- The number of subsequent pregnancies was determined using a methodology adopted from a previously published model (Norman et al., 2012).
- Long-term benefits of births other than CF, SMA and FXS were estimated as the utility in the average Australian population over the average lifespan of a newborn.
- CVS and other testing options were not captured in the comparator arm or the false negative arm, as any tests would not be due to test status and would have occurred regardless of carrier status.
- The model structure did not capture carrier status knowledge outside of the proposed reproductive carrier testing, or the possible indirect identification of carrier status of other disorders or risk status. It is possible that carrier status is identified through testing for other disorders or risk status (e.g. risk for breast cancer) and CF, SMA and FXS carrier status could be identified through these other tests. Also, testing for CF, SMA and FXS carrier status may also indirectly identify carriers of other diseases, depending on the type of genetic test used. It was considered outside of the scope of the DCAR to quantify these consequences.
- The costs for genetic counselling and IVF were assumed, but shown to have little impact on the model by the sensitivity analyses.
- The probability of birth with a genetic disorder is mutually exclusive. A cohort of CF births is removed from the cohort who could be born with SMA or FXS. While there is a possibility a birth could have two genetic disorders, the probability is low and with limited evidence would only increase uncertainty and complexity of the model.

The stepped evaluation examined the cost-effectiveness of:

- Step 1: carrier testing for each disease alone, assessing initial pregnancies only, and assessing the pre-conception and post-conception populations separately
- Step 2: carrier testing across all three diseases, assessing initial pregnancies only, and assessing the pre-conception and post-conception populations separately
- Step 3: carrier testing across all three diseases, assessing initial pregnancies only, and combining the pre-conception and post-conception populations
- Step 4: carrier testing across all three diseases, assessing across initial and subsequent pregnancies, and combining the pre-conception and post-conception populations.

The Step 1 cost effectiveness (per carrier couple detected) and Step 2 cost utility estimates of reproductive carrier testing for CF, SMA and FXS, stratified by pre-conception and post-conception testing, in initial pregnancies only, are shown in Table 8.

Table 8 Incremental costs and benefits of reproductive carrier testing compared with no testing (pre-conception testing and post-conception testing)

	Costs	CF carrier couples detected (/100,000)	SMA carrier couples detected (/100,000)	FXS carriers detected (/100,000)	QALY gained
Pre-conception testing					
Carrier testing	\$575.89	121.82	53.022	660	17.94
No testing	\$595.07	0	0	0	17.89
Difference	-\$19.19	121.82	53.022	660	0.04
ICER/ICUR	-	Dominates	Dominates	Dominates	Dominates
Post-conception testing					
Carrier testing	\$785.57	121.82	53.022	660	17.91
No testing	\$595.07	0	0	0	17.89
Difference	\$190.50	121.82	53.022	660	0.02
ICER/ICUR	-	\$156,373*	\$359,286*	\$28,664*	\$11,145

CF=cystic fibrosis, FXS=fragile X syndrome, ICER=incremental cost effectiveness ratio, ICUR=incremental cost utility ratio, QALY=quality adjusted life year, SMA=spinal muscular atrophy

Note: ICER/ICUR results were calculated before the incremental costs and benefits were rounded.

Source: Adapted from Table 4, pxxiii-xiv of DCAR

*This is the cost/100,000 couples detected, therefore the incremental cost (e.g for CF \$190.50) was multiplied by 100,000 and divided by the number of CF carrier couples detected (which was already a factor of 100,000).

The overall costs and outcomes, and incremental costs and outcomes as calculated for the carrier testing strategy and no testing strategy, and using the base case assumptions for Step 4, are shown in Table 9 for the cost-utility analysis and Table 10 for the cost-effectiveness analysis.

Table 9 Incremental costs and effectiveness of reproductive carrier testing compared with no testing (cost utility)

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICUR
Carrier testing	\$391.25	-\$259.91	17.93	0.02	Dominates
No testing	\$651.16		17.91		

ICUR=incremental cost utility ratio, QALY=quality adjusted life year

Source: Table 4, pxxiv of DCAR

Table 10 Incremental costs and effectiveness of reproductive carrier testing compared with no testing (cost effectiveness)

	Cost	Incremental cost	Effectiveness (CF, SMA, FXS carriers detected, /100,000)	Incremental effectiveness	ICER
CF carrier couples detected					
Carrier testing	\$391.25	-\$259.91	126.54	126.54	Dominates
No testing	\$651.16		0		
SMA carrier couples detected					
Carrier testing	\$389.45	-\$261.71	55.07	55.07	Dominates
No testing	\$651.16		0		
FXS carriers detected					
Carrier testing	\$387.01	-\$264.14	660	660	Dominates
No testing	\$651.16		0		
Combined CF carrier couples detected, SMA carrier couples detected, FXS carriers detected					
Carrier testing	\$391.25	-\$259.91	841.61	841.61	Dominates
No testing	\$651.16		0		

CF=cystic fibrosis, FXS=fragile X syndrome, ICER=incremental cost effectiveness ratio, QALY=quality adjusted life year, SMA=spinal muscular atrophy

Source: Adapted from Table 5, ppxiv-xxv of DCAR (as corrected in Addendum)

The modelled results were most sensitive to the sensitivity of the CF test, the cost of the test, the CF carrier rate in the male population, the male testing rate and the specificity of the test for CF, SMA and FXS (Table 11).

Table 11 Key drivers of the economic model

Description	Method/Value	Impact
Sensitivity – CF test	90%	High, favours intervention
Cost of test	\$400 as determined by the applicant	Indeterminant
Carrier rate (males) - CF	4%	High, favours comparator
Male testing rate	94%	Indeterminant for initial & subsequent testing; favours intervention for initial pregnancy testing
Specificity – CF test	1	High, favours intervention
Specificity – SMA test	1	High, favours intervention
Specificity – FXS test	1	High, favours intervention

CF=cystic fibrosis, FXS=fragile X syndrome, SMA=spinal muscular atrophy

Source: Table 6, pxxv of DCAR

13. Financial/budgetary impacts

The DCAR used an epidemiological approach to estimate the financial implications to the MBS of the introduction of reproductive carrier testing for CF, SMA and FXS to the MBS as being from just under \$35 million per year to just over \$35 million per year over the first 5 years of listing (Table 12).

Table 12 Total costs to the MBS associated with reproductive carrier testing for CF, SMA and FXS

	2021	2022	2023	2024	2025
Test					
Number of services	85,906	86,110	86,313	86,516	86,720
Sub-total cost	\$34,362,478	\$34,443,822	\$34,525,159	\$34,606,489	\$34,687,813
Associated MBS costs					
CVS testing	\$66,513	\$66,670	\$66,827	\$66,985	\$67,142
Genetic counselling	\$53,825	\$53,952	\$54,080	\$54,207	\$54,334
IVF	\$441,073	\$442,118	\$443,162	\$444,207	\$445,251
Pathology tests	-\$864	-\$866	-\$868	-\$870	-\$872
Lung function tests	-\$3,432	-\$3,440	-\$3,448	-\$3,456	-\$3,465
Clinical visits	-\$23,448	-\$23,503	-\$23,559	-\$23,614	-\$23,670
Endoscopy	-\$137	-\$137	-\$137	-\$138	-\$138
Sweat chloride test	-\$11	-\$11	-\$11	-\$11	-\$11
Sub-total cost	\$533,519	\$534,782	\$536,046	\$537,309	\$538,572
Financial implications for the MBS	\$34,895,997	\$34,978,604	\$35,061,205	\$35,143,799	\$35,226,385

CF=cystic fibrosis, CVS=chorionic villus sampling, IVF=*in-vitro* fertilisation, FXS=fragile X syndrome, MBS=Medicare Benefits Schedule, SMA=spinal muscular atrophy

Source: Table 8, pxxv-xxvi of DCAR

The DCAR then stated that reproductive carrier testing for CF, SMA and FXS would save the PBS between \$2,666,010 and \$17,539,662 per year over the first five years (Table 13). These savings may increase as more expensive treatments for these disorders are listed on the PBS, expanding the eligible patient population. The PBS savings per year increase over the five years and would further increase as treatment expenditure for these therapies increases as the incident patient population is included in the prevalent treated population and mortality is significantly decreased. Table 13 reports net financial implications to the MBS and the PBS of \$32,229,986 in the first year, decreasing to \$17,686,723 in the fifth year.

Table 13 Total combined cost to the Australian healthcare system for the listing of reproductive carrier testing for CF, SMA, and FXS

	2021	2022	2023	2024	2025
MBS costs of tests	\$34,362,478	\$34,443,822	\$34,525,159	\$34,606,489	\$34,687,813
Associated MBS costs	\$533,519	\$534,782	\$536,046	\$537,309	\$538,572
PBS costs (savings)	\$2,666,010	\$6,371,290	\$10,085,326	\$13,808,117	\$17,539,662
Net financial implications for the MBS and the PBS	\$32,229,986	\$28,607,317	\$24,975,878	\$21,335,682	\$17,686,723

CF=cystic fibrosis, FXS=fragile X syndrome, MBS=Medicare Benefits Schedule, PBS=Pharmaceutical Benefits Scheme, SMA=spinal muscular atrophy

Source: Table 9, pxxvi of DCAR

The sensitivity analyses of the financial analyses in the DCAR tested the impact of the miscarriage rate, the proportion of couples planning pregnancy and the probability that the male of the couple is tested if the female of the couple is identified as a carrier (for MBS costs only), and the cost of IVF (when more than one cycle of IVF is required), the cost and utilisation of genetic counselling, and the annual cost of lumacaftor/ivacaftor (for both MBS costs and combined MBS and PBS costs). The DCAR considered that the financial analyses over five years were minimally impacted when these parameters are changed.

The key drivers of the financial analyses were identified as the cost of the test and the number of individuals utilising the test. As such, the base case uptake rate of 54% was also tested in

these sensitivity analyses. The net cost to the MBS ranged from \$0 (uptake 0%) to \$65 million a year (100% uptake).

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Ethical issues	Significant ethical issues need to be considered during decision making, including potential impacts on human rights.
Uncertainty in clinical validity in population	The evidence for how well pathological variants detected in the genotype of carriers predict clinical phenotype (disease severity) in their offspring is very uncertain for the three conditions, including for people in sub-populations currently under-represented in genomic databases (such as Aboriginal and Torres Strait Islanders).
Uncertainty in clinical utility estimates	The estimated proportions of detected at-risk couples for the three conditions who could make use of increased reproductive options, including termination, are uncertain.
Definition of therapeutic effectiveness	The assessment group considered that therapeutic effectiveness was not relevant for this application. Instead, the aim of the requested carrier testing is to inform reproductive decision making for couples, but there are uncertainties in how the consequences of this is estimated in this DCAR as direct evidence on informed decision making was not included in the report. Adequate genetic counselling is likely to be key for addressing this.
The economic and financial estimates are built on very uncertain clinical utility estimates	The modelled economic evaluation and the large annual budget implications for the MBS are both highly uncertain. The DCAR argues for incremental cost per case averted to be used in MSAC decision making to compensate for the uncertainty regarding the incremental cost per QALY calculations and results. However, MSAC may find it difficult to place a value on cases averted.
The reproductive carrier testing could create demand for a formal screening program if there is no appropriate support framework	MSAC and the Department will need to consider strategies to minimise the risk of reproductive carrier testing creating an expectation for a population-based screening program in order to better support couples and practitioners in obtaining optimal outcomes based on the test results generated.
The Department suggested that the MBS item could include risk criteria to access the test (such as family history)	If pursued, the economic model will need to account for a narrower eligible population. Consideration will also need to be given to how any MBS items arising from this application might require flow-on amendments to affected existing items.

ESC discussion

ESC noted that this application was for new Medicare Benefits Schedule (MBS) items for reproductive carrier testing of couples (who are planning or in early stages of pregnancy) for the monogenic conditions of cystic fibrosis (CF), spinal muscular atrophy (SMA) and fragile X syndrome (FXS).

ESC noted PASC's concern regarding this proposed targeted carrier testing becoming a screening program without a proper support framework, and the Chief Medical Officer's advice that this testing is unlikely to meet the requirements for a population-based screening program. ESC thus considered that MSAC and the Department would need to consider strategies to minimise the risk of this carrier testing creating the need for the supporting framework as would be expected from such a screening program.

ESC noted the public consultation feedback from seven groups and organisations, which supported the application. ESC also noted the feedback from three consumers who had a child with one of the conditions. No feedback from a consumer with one of the conditions was received. ESC noted the benefits of carrier testing from a consumer perspective, such as couples being able to make an informed choice and access to early treatment if children are born with either CF, FXS or SMA. However, ESC also noted the significant ethical issues surrounding this application, including the burden for couples when deciding to take the test and when acting on test positive results. Further, ESC noted the broader issues around valuing diversity in the population and the juxtaposition of considering children born with these conditions to be leading a worthwhile life whilst also suggesting these patients are a burden on the healthcare system. There are also known variations in condition prevalence by ethnicity, with CF and SMA being more common in European ancestry than other ancestry. ESC also acknowledged possible variations across states and territories to pregnancy termination options. Public involvement and input from other perspectives would help with the justification of the conditions and genes selected for testing and with the consequences of more informed reproductive decision-making. ESC cited the 2 October 2015 *Report of the IBC on Updating Its Reflection on the Human Genome and Human Rights* by the International Bioethics Committee of the United Nations Educational Scientific and Cultural Organisation (UNESCO)² for a fuller discussion of ethical considerations relevant to this application.

ESC noted that a national consent form for genomic testing is being developed by the Department, including with respect to privacy and confidentiality. ESC considered that, in general, applications for genomic testing should acknowledge this or another suitable consent form. ESC also considered that acceptable samples could include postal buccal swaps to address equity of access issues for consumers living in remote areas.

ESC noted the Department's suggestion that the MBS item descriptor could include risk criteria to access the test, such as family history. ESC considered that including family history as a criterion would not achieve the intent of the application, since not all couples know their family history. The consumer feedback also raised this criterion as being inappropriate for the same reason. ESC considered that if such limitations to carrier testing were to be pursued, both the modelled economic evaluation and the financial analyses would need to consider a narrower eligible population. ESC also noted that some existing MBS items related to genetic testing in the context of CF and FXS, and suggested that any new items arising from this application might require flow-on considerations for some of these items.

ESC noted there was uncertainty around the size of the eligible population that would take up testing, as 'a female planning pregnancy' is vague and could include any woman of child-bearing age; PASC had therefore previously considered that the population could be underestimated by the approach taken for the estimates in the Application Form. The approach in the DCAR linked the number of pre-conception tests to the number of pregnancies in a year (an incidence-based approach) rather than reflecting the larger prevalence pool, which was the source of concern to PASC. The Department had since suggested using the volume of use of the existing MBS items (currently based on history of condition or prenatal ultrasound results) to estimate the size of the eligible population, but considered this to possibly lead to an underestimate. ESC considered using risk criteria from existing MBS items to estimate the size of the eligible population to be inappropriate, as not everyone currently has access to the extent of testing specified by the proposed MBS items.

² <https://unesdoc.unesco.org/ark:/48223/pf0000233258>

ESC noted that there were no studies that evaluated the comparative clinical validity of reproductive carrier testing for CF, SMA or FXS. The assessment group clarified that there were no studies with clinical information about affected people identified through reproductive carrier testing to evaluate how well the genotype of the carrier couple predicts the phenotype in their offspring. As such, the consequences of variations in penetrance and expressivity for the natural histories of these conditions are not well understood. ESC thus considered the clinical validity of the proposed testing to be highly uncertain. ESC acknowledged that high-quality evidence could be difficult to obtain due to the low prevalence of each of the three conditions.

ESC noted the assessment group's conclusion that therapeutic effectiveness was not applicable to this assessment, as informed reproductive decision making for couples was the aim of carrier testing. ESC agreed with the assessment group that adequate, non-directive pre- and post-test genetic counselling would be crucial to ensure couples were able to make an informed choice, and agreed that the application did not address this issue in depth. ESC considered that general practitioners need meaningful training and clear governance on how to counsel patients, and counselling needs to be well prepared. ESC also considered that the need for additional genetic counselling may result in inequity and access issues for some couples.

ESC considered that the estimated proportions of detected at-risk couples for the three conditions who could make use of increased reproductive options, including changes in the proportions of prenatal testing of the fetus and terminations, are very uncertain. Most studies were non-comparative, and the single comparative assessment was an ecological study in CF. Many of the results expressed as proportions were subject to wide variation and were likely to be imprecise due to being based on small denominators given the rarity of the conditions. Prior to the meeting, an ESC member sought clarification as to whether further analyses could help reduce uncertainty of the clinical utility estimates; specifically whether meta-analysis of estimated proportions for each of the clinical decisions could be undertaken. This resulted in additions to the Addendum to the DCAR, in which the assessment group considered that the populations were too heterogeneous to combine for most of the clinical utility outcomes, but provided meta-analyses for the estimated carrier rates for CF and FXS (insufficient data for SMA). This resulted in sensitivity analyses for the economic model using the pooled estimates and confidence intervals for the carrier rate estimates for CF and FXS. Despite the additional analyses, ESC considered that the clinical utility remains very uncertain.

Similarly, ESC considered that there were mixed results across the studies in terms of safety, with no strong signals for either an increase or a decrease in the anxiety of detected carriers (noting that the studies available on safety were also non-comparative and did not include participants who were not offered testing).

ESC noted that proposed MBS items did not specify the appropriate test methodology, which could therefore include any options available in Australia with the necessary quality assurance. ESC also noted that the pre-ESC response from the applicant suggested that the TGA-approved test kits for CF and FXS would have included information relevant to both analytical validity and clinical utility and that this information would have been included in the test kit inserts or websites. However, such information was not provided for independent verification. ESC considered that the costs of testing may continue to fall, so a regular reassessment of the proposed fee may be appropriate.

ESC considered that the results of the modelled economic evaluation and the large annual budget implications for the MBS were both highly uncertain. ESC noted that the DCAR argued for incremental cost per case averted to be used in MSAC decision making to compensate for the uncertainty regarding the incremental cost per quality-adjusted life year (QALY) calculations and results. However, ESC considered that MSAC may find it difficult to place a value on cases averted.

ESC considered the two-part structure of the model to be appropriate: first to estimate the proportions of changed decisions (for example, the use of IVF and terminations) and their associated costs, and second to estimate the longer-term costs and outcomes (for example, the utilities and costs associated with CF and SMA were derived from submissions to the PBAC for recently listed PBS medicines for these two conditions). ESC also agreed with the DCAR that the longer-term utility estimates assigned to “IVF babies” and “other babies” was appropriately set to the average health of babies born without any of these three conditions rather than assuming they had full health.

ESC noted that the economic modelling did not include additional carrier status (in addition to CF, SMA and FXS status) identified through testing. The DCAR argued that not including these cost offsets and benefits (utilities) means the cost-effectiveness of carrier testing is conservative and underestimates the true cost-effectiveness of testing. ESC disagreed with this, as additional costs and harms (disutilities) would then also need to be considered.

ESC sought clarification of some of the results reported from the modelled economic evaluation; specifically, in Tables 4, 54 and 55. This resulted in additions to the Addendum to the DCAR, with associated changes in the corresponding tables of this ESC Report as required.

ESC noted that, as for the economic evaluation, estimated cost off-sets from reduced use of PBS-listed medicines were an important contributor to the estimates of financial implications. The financial implications to the MBS and the PBS were not estimated to be cost saving due to its shorter time horizon than for the economic evaluation. The main sources of uncertainty were the size of the eligible population, the uptake of testing and the fee for the test.

15. Other significant factors

Ethical considerations

Reproductive carrier testing poses specific ethical considerations as these tests are used to enable reproductive choices and family planning based on the risk of having a child with an inheritable disease. Given this, the DCAR applied the predominant framework in the field of biomedical ethics: the ‘Four Principles of Biomedical Ethics’ approach. These four principles comprise respect for autonomy, non-maleficence, beneficence and justice.

- **Informed choice and counselling:** As autonomy requires adequate information, counselling before and after reproductive carrier testing is crucial. Pre-test information must be complete and balanced, otherwise no meaningful reproductive choice is possible. Couples may feel a pressure to consider reproductive carrier testing if the offer from physicians is suggestive and unclear about the opportunity to freely decline it.
- **Testing of partners:** In the case of FXS testing, the female partner carries the whole burden of guilt if testing positive, as her reproductive male partner would not need to undergo reproductive carrier testing for FXS, due to X-linked dominant inheritance.
- **Disability rights critique of reproductive carrier testing:** The disability rights critique holds that selective termination of a pregnancy after prenatal diagnosis is problematic,

as living with disabling traits need not be detrimental to an individual's prospects of leading a worthwhile life, or to the families in which they grow up, or to society at large. Reproductive carrier testing may send to society the message that it would have been better if those living with the targeted condition had not been born.

- Access to testing and treatment: In Australia, access to medical services is generally adequate and equitable, although access problems in rural areas, including to genetic testing services, have been reported. In reproductive carrier testing, not everyone is offered the same services, information and support (as they would in an organised screening program), with a potential risk of inequity.
- Privacy and confidentiality: Individuals have the right to privacy and may choose to reveal information about their carrier status to their partner and medical personnel, but this information must be kept confidential by medical personnel except as permitted by law. Ethical dilemmas can occur when a clinician is torn between maintaining the confidentiality of test results and informing family members of their own risk of having a child with a hereditary disease. In the case of carriers, there is only a risk for family members if they are going to have children.
- The principles of non-maleficence and beneficence entail that the risks of harm should be outweighed by the probable benefits before a genetic test is accepted into general practice.

The DCAR concluded that the above ethical considerations suggest that reproductive carrier testing should only be offered on the MBS in conjunction with non-directive pre- and post-test genetic counselling from accredited counsellors.

In its pre-ESC response, the applicant highlighted that patients should be counselled; however, in the setting of reproductive carrier testing, this does not need to be performed by accredited counsellors. The applicant referenced the statement in the DCAR:

“The most likely health care professional to conduct genetic counselling using MBS codes is an obstetrician/gynaecologist (OB/GYN), however, other medically trained professionals (GPs or other physicians/consultants) may counsel couples if they are determined to be carriers.”

The applicant considered that this statement more accurately reflects current clinical practice in Australia and the 2020 position statement from the Human Genetic Society of Australasia³.

Legal implications

Termination of pregnancy is regulated by the states and territories. Therefore, whether pregnancy termination is lawful when CF, SMA or FXS is prenatally diagnosed could differ between states and territories. This might need to be considered in the decision-making process.

16. Applicant comments on MSAC's Public Summary Document

The College would like to take this opportunity to thank the Department and the MSAC for their assistance in moving this application forward to a successful outcome that will deliver great benefits to all Australians planning, or in the early stages of, pregnancy. In addition, the College notes concerns raised regarding targeted carrier testing becoming a *de facto* screening program without a support framework in place. The College offers its assistance in this matter, noting that the MSAC and the Department may need to consider strategies to minimise the risk of this carrier testing creating the need for the supporting framework as would be expected from such a screening program.

³ <https://www.hgsa.org.au/documents/item/11030>

17. Further information on MSAC

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