



Australian Government

Department of Health

RATIFIED PICO

Initial consideration – August 2019 PASC

Second (final) consideration - December 2019 PASC

Application 1573:

Opportunistic genetic carrier testing for three severe heritable diseases, being cystic fibrosis, spinal muscular atrophy and fragile X syndrome

Summary of PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Please note: It is correct (anti-discriminatory) practice to avoid gender-based language in PICOs and MBS item descriptors. In this document, the terms 'female' and 'male' are used for ease of interpretation only (i.e. to differentiate specific tests, and inform utilisation and costing analyses). Gender-neutral language would be used in any final item descriptors.

Component	Description
Patients	<ul style="list-style-type: none"> A female who is planning a pregnancy, for the purpose of determining the risk of cystic fibrosis (CF), spinal muscular atrophy (SMA) or fragile X syndrome (FXS) in her offspring. A pregnant female, for the purpose of determining the risk of CF, SMA or FXS in her offspring. A male reproductive partner of a female who has been found through genetic carrier testing to be a carrier of the cystic fibrosis transmembrane conductance regulator (<i>CFTR</i>) or survival motor neuron 1 (<i>SMN1</i>) genes, either at pregnancy planning or during pregnancy.
Prior tests	None
Interventions	<ul style="list-style-type: none"> An in vitro diagnostic (IVD) test, which includes analysis of three genes, to detect genomic alterations and assess whether the patient is a carrier of CF, SMA or FXS. For the male reproductive partner, an IVD test for gene analysis and detection of genomic alterations, to determine if they are also a carrier of CF or SMA.
Comparator	No opportunistic genetic carrier testing
Outcomes	<p><u>Effectiveness/clinical utility:</u></p> <ul style="list-style-type: none"> Impact on increased decision options for future reproduction Proportion of children born with CF, SMA or FXS (noting not all CF genotypes will be screened for) <p><i>Post-conception (pre-natal) testing</i></p> <ul style="list-style-type: none"> Impact on increased pregnancy decision options for current reproduction Termination of pregnancy rate due to presence of specific pathogenic variants (in pregnant females) <p><u>Safety:</u></p> <ul style="list-style-type: none"> Psychological adverse events from genetic testing or no genetic testing Psychological effects of test results which subsequently prove to be false Proportion of pregnant females who require diagnostic testing for CF, SMA or FXS by amniocentesis or chorionic villus sampling following a positive genetic carrier test, with or without a positive test from their reproductive partners as appropriate

Component	Description
	<p data-bbox="440 149 646 178"><u>Analytical validity:</u></p> <ul data-bbox="488 201 1370 541" style="list-style-type: none"> <li data-bbox="488 201 1370 264">• Analytical sensitivity and specificity, including at least 50 of the most common pathogenic variants of <i>CFTR</i> <li data-bbox="488 285 1224 315">• Comparative analytical performance of different sample types <li data-bbox="488 336 1370 495">• Comparative analytical performance across different assay options likely to be offered in the bundle of tests used to perform the requested test across the three identified diseases, including any commercially available panel (<i>noting technology is rapidly changing, so it is recommended only limited time be allocated to this</i>) <li data-bbox="488 516 716 546">• Likelihood ratios <p data-bbox="440 567 618 596"><u>Clinical validity:</u></p> <ul data-bbox="488 617 964 693" style="list-style-type: none"> <li data-bbox="488 617 894 646">• Clinical sensitivity and specificity <li data-bbox="488 667 964 697">• Positive and negative predictive values <p data-bbox="440 718 688 747"><u>Healthcare resources:</u></p> <ul data-bbox="488 768 1260 1045" style="list-style-type: none"> <li data-bbox="488 768 976 798">• Number and cost of gene carrier testing <li data-bbox="488 819 1084 848">• Number and cost of testing reproductive partners <li data-bbox="488 869 1260 898">• Number and cost of additional medical practitioner consultations <li data-bbox="488 919 1068 949">• Number and cost of genetic counselling services <li data-bbox="488 970 1198 999">• Number and cost of caring for a person with CF, SMA or FXS <li data-bbox="488 1020 906 1050">• Cost per quality-adjusted life year <p data-bbox="440 1071 695 1100"><i>Pre-conception testing</i></p> <ul data-bbox="488 1121 1377 1310" style="list-style-type: none"> <li data-bbox="488 1121 1377 1310">• Number and cost of pre-implantation genetic diagnoses (PGD) and in-vitro fertilisation (IVF) cycles for <u>each subsequent pregnancy</u> in confirmed female carriers of FXS and confirmed carrier couples of CF and SMA (<i>noting that this cost is also involved in any subsequent pregnancy for patients who only present after the birth of an affected child, so inclusion as a financial factor for application 1573 may not be fair</i>) <p data-bbox="440 1331 829 1360"><i>Post-conception (pre-natal) testing</i></p> <ul data-bbox="488 1381 1284 1491" style="list-style-type: none"> <li data-bbox="488 1381 1284 1444">• Number and cost of amniocentesis or chorionic villus sampling, and confirmatory diagnostic genotyping following a positive test <li data-bbox="488 1465 906 1495">• Number and cost of terminations

POPULATION

The proposed patient populations include the offer of genetic carrier testing to:

1. A female who is planning a pregnancy, for the purpose of determining the risk of cystic fibrosis (CF), spinal muscular atrophy (SMA) or fragile X syndrome (FXS) in her offspring.
2. A pregnant female, for the purpose of determining the risk of CF, SMA or FXS in her offspring.
3. A male reproductive partner of a female who has been found through genetic carrier testing to be a carrier of the cystic fibrosis transmembrane conductance regulator (*CFTR*) or survival motor neuron 1 (*SMN1*) genes, either at pregnancy planning or during pregnancy.

If a female is found to be a carrier of a pathogenic variant (mutation) of the fragile X mental retardation 1 (*FMR1*) gene, her reproductive male partner would not need to undergo genetic carrier testing for FXS, due to X-linked dominant inheritance. However, PASC noted the mutation may not necessarily be causing the syndrome.

The proposed patient population is based on the Royal Australian and New Zealand College of Obstetricians and Gynaecologists' (RANZCOG) and World Health Organisation's (WHO) recommendations for early detection. These recommendations endorse opportunistic genetic carrier testing information to be provided to all females who are planning a pregnancy or are pregnant, regardless of family history (Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2015).

PASC's First Consideration

PASC accepted the proposed population, but acknowledged "planning pregnancy" may be difficult to define, with associated difficulties in calculating population size. The cohort of women "planning pregnancy" could mean all women of reproductive age. This would result in a large underestimate in the early years of implementation.

PASC noted multigravida women would be eligible for opportunistic genetic carrier testing if their other children were born before carrier testing was available, and queried whether these women were captured in population estimates.

PASC also noted difficulties in estimating the male reproductive partner population if a woman has a different male reproductive partner for subsequent births after the initial genetic carrier testing assessment.

This is an increased cost to the system. There will be an increase in the proportion of pregnancies deemed high-risk if opportunistic genetic carrier testing is implemented, which would be no cost to the patient at the point of care. Currently, this is a cost for the patient.

The assessment group reported it was a challenge to estimate the cohort “planning a pregnancy”. However, an estimate has been provided for each year, based on available literature which suggests about 49% of people plan a pregnancy, with the remainder being the first pregnancy trimester cohort. It has been assumed that, from year 3, second time mothers will appear in the population, and have been removed from the estimates. These estimates should be used cautiously, due to many complexities, including the number of diseases, which may be included in any gene test.

After PASC’s first consideration (December 2019), the applicant provided the following information (italicised dot-points below):

- *Australian and international experience is that two thirds of women do not present for screening until they are already pregnant. This indicates that concerns about the entire population of women of reproductive age presenting for screening are likely to be unfounded. (Archibald et al (2018), Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: outcomes of 12,000 tests, Genetics in Medicine, vol 20, pages 513–523).*
- *The Royal College of Pathologists of Australasia (RCPA) has advised that wording of the item descriptor should be “Asymptomatic women, with or without a family history.....”, otherwise women who are at even higher risk due to a family history would be discriminated against. In addition, the wording as it stands “asymptomatic females with no family history of severe heritable diseases...” may imply that a woman with a family history of another severe condition would not be eligible for screening (e.g. a woman with a family history of CF would therefore not be eligible to be screened for fragile X or SMA).*
- *These concerns have been addressed in the revised item descriptor, which should be reflected in the proposed population in the PICO: Opportunistic testing of an asymptomatic female to identify carrier (heterozygous) status for at least three (3) severe heritable disease genes, which must include 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. All tested genes must be limited to those where the genetic condition is highly penetrant and affected individuals have severe adverse health impacts, predicted to significantly shorten lifespan. Limited to females who are either planning a pregnancy or who are pregnant.*

PASC’s Second Consideration

PASC confirmed the three populations eligible for the proposed opportunistic (i.e. not screening) genetic carrier testing.

Figure 1 outlines the estimated population eligible for the proposed carrier testing over a 12-month period. This estimation is based on a series of assumptions including:

1. Females who are pregnant:
 - Using the birth rate* estimates from 2017, 309,142 females were pregnant in 2017 (Australian Bureau of Statistics, 2019a). This estimate has been adjusted for plurality** (population reduced by 1.5%) and miscarriages (population increased by age-specific miscarriage rate) (Australian Bureau of Statistics, 2019b; Magnus, Wilcox, Morken, Weinberg, & Håberg, 2019). The resulting number gives an estimated population size of 352,464.

- The resulting number is adjusted further by the estimated opportunistic genetic carrier testing take-up rate. This rate (54%) is a weighted average of four studies (two international studies and two Australian studies) on take-up rates for opportunistic genetic testing in cancer and CF (Ioannou et al., 2014; Keogh et al., 2014; Keogh et al., 2017; Quinlivan, Battikhi, & Petersen, 2014). This results in an estimated 190,362 females in the first year likely to take up genetic testing for CF, SMA and/or FXS.
2. Females who are planning a pregnancy:
- Less than half of the pregnancies in Australia are planned, with one Australian study showing 49% of all pregnancies were planned (Marie Stopes International, 2008). Based on the number of pregnancies in 2017, approximately 172,707 females would have planned their pregnancy.
 - It is assumed that all couples seek medical advice from a GP or obstetrician if a pregnancy is planned.
 - Furthermore, only 54% of females planning a pregnancy would take up opportunistic genetic carrier testing prior to conception. This results in an estimated 93,277 females (who will be planning a pregnancy in the first year of MBS funding) who would likely take up opportunistic genetic testing prior to pregnancy.

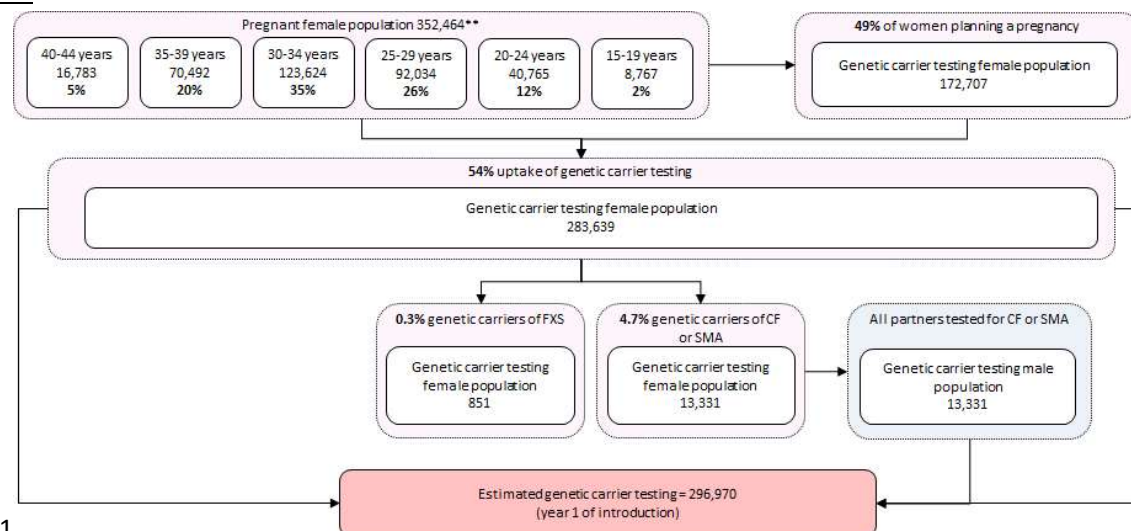
In addition, the estimated eligible population for opportunistic genetic carrier testing needs to include the number of reproductive males requiring opportunistic testing as a result of their female partner being identified as a carrier of an autosomal recessive pathogenic variant for CF and/or SMA. These male reproductive partners would be advised to undergo genetic carrier testing to determine the couple's risk of having a baby with a severe genetic disease.

As 5% of females are estimated to be carriers of either CF, SMA or FXS, this equates to 14,182 females. Approximately, 13,331 out of 14,182 (96%) female carriers have pathogenic variants of the *CFTR* or *SMN1* genes, the remainder being carriers of pathogenic variants of the *FMR1* gene (Archibald et al., 2018). Hence, the estimated number of males that would require opportunistic carrier testing is 13,330. Pathogenic variants of the *FMR1* gene are dominantly inherited via the X chromosome, hence male partners are exempt from this genetic test where the female is identified as being a carrier.

Based on the number of males and females eligible for genetic carrier testing, approximately 296,970 people will require testing for CF, SMA, and FXS. This estimate is based on assessing carrier status of males for CF and SMA only.

It is noted that females may have more than one reproductive partner in their lifetime, which would increase the number of males needing to be tested. However, there is no literature which suggests what proportion this would be.

Figure 1: Process for determining the estimated population size for genetic carrier testing for CF, SMA or FXS



**Adjusted for pregnancy plurality and age-specific miscarriage rates. The rate at which twins and triplets are born is 1.5% according to ABS 2017 data. This rate is applied consistently across all age groups. Higher rates of plurality occur in IVF related pregnancies and has not been accounted for in this report. Plurality greater than triplets is not included in this population estimate, since it is a very rare occurrence. This variance may result in an overestimation of the population size. Age-specific miscarriage rates were derived from a 2019 Norwegian study (Magnus et al., 2019).
Source: Australian Bureau of Statistics (2018).

Table 1 estimates the eligible population for the proposed opportunistic genetic carrier testing over the next six years. It is based on the 2016 AIHW pregnancy rates which showed an average annual change of 2,752 pregnant females over a span of 10 years (2006-2016). This rate (2,752) has been applied to each subsequent year to predict the number of pregnant females for the years 2017 to 2022.

Furthermore, as a female only requires the test once per lifetime, those having their second pregnancy in year 3 onwards (assuming year 1 was their first pregnancy) have been removed each year from year 3 onwards. It is noted some females have three or more pregnancies, however over a six year projection, this proportion is considered too small to include in the modelling.

Table 1: Estimated eligible population for genetic carrier testing for CF, SMA and FXS

Year	Number of pregnant females each year†	+	Number of females planning a pregnancy**	=	Total number of females eligible for opportunistic genetic testing	×	54% genetic testing uptake by females planning a pregnancy	-	Number of females in their second pregnancy*	=	Total number of females eligible for opportunistic genetic testing	+	Number of males eligible for opportunistic genetic testing§	=	Total population eligible for opportunistic genetic testing
1	352,464		172,707		525,171		283,639				283,639		13,331		296,970
2	355,216		174,056		529,272		285,853				285,853		13,435		299,289
3	357,968		175,404		533,372		288,068		63,581		224,487		10,551		235,038
4	360,720		176,753		537,473		290,283		64,077		226,205		10,632		236,837
5	363,472		178,101		541,573		292,497		64,574		227,924		10,712		238,636
6	366,224		179,450		545,674		294,712		65,070		229,642		10,793		240,435

100% of estimated number of females eligible for opportunistic testing in year 1 and 2.
 * 33.4% of pregnancies in a single year are women in their second pregnancy (HealthEngine, 2009). It is assumed that all these females did not have the genetic test for their first pregnancy.
 † Based annual change of 2,752 females. This is the average rate change in the number of pregnant females over a 10-year period (2006-2016) (Australian Institute of Health and Welfare, 2018).
 ** 49% of pregnancies are planned.
 § 5% of eligible females are carriers of CF, SMA or FXS, out of which 94% are CF or SMA carriers. All reproductive male partners (100%) of females that are CF or SMA carriers, require carrier testing.

Prior test

No prior tests are required for the proposed opportunistic genetic carrier panel testing for CF, SMA or FXS. *A priori* risk assessment will be required for carrier testing of any other severe heritable disease to be incorporated into the requested panel.

INTERVENTION

The proposed intervention is genetic carrier panel testing for pathogenic variants in the *CFTR*, *SMN1* and *FMR1* genes. Multiplex ligation-dependent probe amplification (MLPA) or quantitative fluorescent multiplex polymerase chain reaction (PCR) is used for analysing the 50 most common pathogenic variants of *CFTR*; *SMN1* copy number analysis via MLPA or qPCR for exon 7, and expansion of the *FMR1* gene CGC repeat region by sizing and triplet repeat primed PCR (MSAC, 2015; Sonic Genetics, 2015).

- CF is caused by inheriting two copies of pathogenic variants in the autosomal recessive *CFTR* gene which results in excessive mucous accumulation. This leads to recurrent respiratory tract inflammation and infection causing permanent lung damage, liver disease, pancreatic exocrine insufficiency, and infertility in men (National Institutes of Health, 2019). Approximately one in 2,500 babies are born with CF (Cystic Fibrosis Australia, 2017). Over 3,200 people are currently living with CF and one in 25 people are carriers of CF genes in Australia (Better Health Channel; Ruseckaite R, 2019)

The high incidence rate is attributable to the 25% chance of having a child with CF, when both parents are carriers. Newborn screening currently involves testing for CF using reactive immunotrypsin (IRT), and not genetic testing initially. On the basis of a positive IRT screening result, genetic testing (with or without sweat chloride concentration testing) is then performed on the infant. The CF phenotype can be variable, depending on the pathogenic variant <https://thorax.bmj.com/content/60/7/558>. There are over 2000 known *CFTR* variants; existing newborn screening assesses the 50 most common variants which are associated with 99% of CF cases, and which are proposed to also be tested in the current application.

- SMA is a genetic condition caused by inheriting two mutated copies of the autosomal recessive *SMN1* gene. It presents with a range of symptoms and has a variable rate of progression and age of onset. SMA is classified into types 1 to 4, with type 1 being more severe and prominent at a younger age and type 4 being adults with a normal life expectancy with no severe disability (Better Health Channel, 2016). In Australia, one in 10,000 babies are born with SMA, out of which 60-70% have the most severe form (Type 1). Based on this incidence rate and the 2017 ABS data (Australian Bureau of Statistics, 2018), it may be assumed that approximately 31 babies were born with SMA out of which 22 babies may have type 1 SMA. One in 35 people are carriers in Australia and they have a 25% chance of having a baby with SMA if their partner is also a carrier (Spinal Muscular Atrophy Australia Inc., 2017).

- FXS is caused by X-linked dominant inheritance of pathogenic variants in the *FMR1* gene, from either the mother or father, which reduces or stops the production of the fragile X mental retardation protein (FMRP). This protein is vital for developing neural synapses. The presentation of pathogenic variants in the *FMR1* gene varies according to the expansion of the CGG triplet repeat (a DNA segment) in the *FMR1* gene. This DNA segment is usually repeated 5 to 40 times in the *FMR1* gene. People with 55 to 200 repeats of the CGG segment display *FMR1* gene pre-mutation symptoms, such as learning disabilities, autism, ovarian insufficiency, ataxia/tremor and mental disorders (like anxiety or depression). People with the full FX syndrome have more than 200 repeated CGG segments (i.e. full mutation FXS). This is a severe form that presents as mild to moderate intellectual disability, anxiety, hyperactive and attention deficit disorder, seizures, and changes in physical features (U.S. National Library of Medicine, 2012). However, whilst women may inherit the full mutation *FMR1* gene, they may or may not be affected. Approximately 1/3 of women with an inherited full mutation are clinically affected but their symptoms are typically less severe than in males due to X-chromosome inactivation. In Australia, approximately one baby is born with the full mutation *FMR1* gene every week affecting approximately one in 3,600 males and 1 in 6,000 females (The Fragile X Association of Australia). In addition, pre-mutation expansions of the *FMR1* gene are found in approximately one in 209 females and one in 430 males (Birch, Cohen, & Trollor, 2017). Also, there are approximately 100,000 carriers of the *FMR1* gene in Australia out of which one in 140-250 are female and one in 250-800 are male (Jewell J A, 2018; The Fragile X Association of Australia).

PASC's First Consideration

PASC accepted the proposed intervention, but commented that if this testing is set up as a formal screening program, it would need to be systematic, so all eligible women would be invited for testing (which they may decline). If the intervention is implemented as opportunistic testing, PASC acknowledged that some women would miss out on testing, and some may also choose not to be screened.

PASC acknowledged the request to expand sampling to include saliva and buccal swabs (in addition to blood). PASC considered that isolating DNA from blood is the gold standard, but advised that alternative sampling methods can be useful for some patients. PASC acknowledged that laboratories would have to validate the method (e.g. through NPAAC and NATA) if using a sampling material other than blood.

PASC also noted the addition of other test methods (e.g. next-generation sequencing), but there was no explanation why these were added.

The applicant prefers that the item descriptor remains "testing method agnostic": the addition of other validated test methods (e.g. NGS) or alternate sample types is acceptable practice.

PASC's Second Consideration

PASC confirmed the proposed intervention, noting the purpose of the test:

- *is limited to determining the risk of CF, SMA or FXS;*
- *each person tested is to be tested once per lifetime; and*
- *requesting the test is not to be limited to specialists.*

PASC noted this application is for opportunistic testing, not a formal screening program.

PASC noted that any sample type is accepted (e.g. saliva sample or buccal swab, as well as blood sample). PASC advised that the sample type does not need to be mentioned, but rather a statement that the sample must allow the testing laboratory to extract sufficient DNA for analysis.

PASC noted the proposal did not limit testing to any specific technology.

The proposed genetic carrier testing would be accessible via referral from a medical practitioner. 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) is first collected from the eligible female. The samples are delivered to the genetic services centre for analysis and results are obtained within 10 days.

If the female is found to be positive for a pathogenic variant in the autosomal recessive SMN1 or CFTR genes, the female's male reproductive partner would also be recommended to undergo single gene testing for the same pathogenic variant to determine a pregnancy's or their fetus' (if already pregnant) overall risk of CF or SMA. Male reproductive partners of females with an identified pathogenic variant in the FMR1 gene do not need to be tested for FXS due to its X-linked dominant mode of inheritance. If a female is a carrier of a pathogenic variant of the *FMR1* gene, the couple would be managed as a high-risk couple. Therefore, knowing the male carrier status would not affect clinical management in this situation. The probability of a male partner also having an undetected *FMR1* pre-mutation expansion is very low.

Couples are classified as high risk (1 in 4 chance of having an affected offspring) if autosomal recessive pathogenic variants in the genes for either CF or SMA are found in both individuals. If the female is a carrier of a pathogenic variant in the *FMR1* gene, the couple is also considered to be at a high risk (1 in 2 chance of the offspring inheriting this pathogenic variant). Couples identified as high risk of having an affected child would be referred to a clinical geneticist or obstetrician to discuss reproductive options. Reproductive options include:

- If genetic carrier testing is undertaken prior to pregnancy:
 - Natural conception (with or without diagnostic testing of the fetus)
 - In vitro fertilisation (IVF) with pre-implantation genetic diagnosis
 - Use of donor sperm, egg, or embryo
 - Adoption
 - Not having children
- If genetic carrier testing is undertaken during early pregnancy (≤ 12 weeks)
 - Natural progression of pregnancy (with or without diagnostic testing of the fetus)
 - Diagnostic testing of the fetus via chorionic villus sampling or amniocentesis, with pregnancy management decisions made on the basis of the test result
 - Preparation for the possibility of a having a child with genetic condition

Genetic carrier testing is only required to be undertaken once in a female's life, and if found to be a carrier of an autosomal recessive genetic disease, will also be recommended to be done once in her reproductive male partner's life. If the female is a carrier of CF or SMA, and the male reproductive partner changes, genetic testing of the new partner would need to be undertaken if not previously performed.

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 with echogenic gut (73345, 73347, 73348, 73349, 16600, 16603, 73300, 73305). There is no current MBS subsidy for SMA carrier testing. Females and their partners who do not meet the current MBS criteria, can access genetic testing services on a user-pays basis.

According to RANZCOG and RACGP guidelines, the proposed medical service is frequently referred by medical practitioners and accessed by patients on a user-pays basis.

COMPARATOR

‘No opportunistic genetic carrier testing’ is the proposed comparator.

As mentioned above, MBS-subsidised genetic testing is available for:

- patients with symptoms of CF or FXS
- those with a close family history; and
- partners of females with CF.

These 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.

PASC’s Second Consideration

PASC confirmed the comparator is ‘no opportunistic genetic carrier testing’.

PASC noted the inclusion of ‘user-pays genetic testing’ in the clinical management algorithm. PASC advised this should not be considered the comparator for the economic evaluation, but may be relevant for financial analyses.

OUTCOMES

PASC’s First Consideration

PASC noted existing MBS FXS item 73305 is for repeat analysis by Southern blot, when MBS item 73300 is non-diagnostic. PASC advised that Southern blotting is an old technology, which does not need to be included as a back-up test for this application.

Regarding analytical validity, PASC advised that the 50 loci (proposed to be screened for CF) will cover 99% of pathogenic variants in the Australian population.

Regarding healthcare resources, PASC advised that the “cost of additional diagnostic fetal testing in at-risk couples” should be added.

PASC’s Second Consideration

PASC recommended the following minor changes to the outcomes:

- *Removal of “adverse events from obtaining a carrier test sample”, because PASC considered these adverse events were unlikely.*
- *Analytical sensitivity and specificity - PASC recommended including >50 CF loci, equivalence of sample types, and equivalence of assays, but removing the rate of repeat testing.*

- *Clinical sensitivity and specificity - PASC noted that a false-negative result in a woman would mean no testing of male reproductive partner.*
- *PASC recommended removing the “number of, and cost of obtaining, an appropriate sample” from outcomes, because it would be negligible.³³*
- *PASC recommended modifying the “number and cost of pre-implantation genetic diagnoses (PGD) and in-vitro fertilisation (IVF) cycles for each subsequent pregnancy, in confirmed asymptomatic female carriers of FXS and confirmed asymptomatic carrier couples of CF and SMA”. PASC considered this would occur without testing, after an affected child was born.*
- *PASC advised that outcomes should be presented in hierarchical importance, with the most important (and achievable/available) outcomes being listed as the priority. Lower level (and/or unachievable) outcomes should be listed, but an explanation given if data on those outcomes is unlikely to be available/achievable. This will assist MSAC’s decision making.*

PATIENT-RELEVANT OUTCOMES

From a patient perspective, genetic carrier testing for severe heritable diseases including CF, SMA and FXS, offers insight into the probability of having a child with these diseases. In general, disease testing offers information to couples planning a pregnancy or in early pregnancy. Couples deemed at high risk for CF, SMA or FXS through carrier testing will have the opportunity to choose other reproductive options, or avoid having children with these diseases after using pre-implantation genetic diagnosis. Also, if these couples choose to have children without considering alternative options, they would be prepared and informed prior to birth by enabling early diagnosis and treatments as necessary.

From a clinical perspective, knowing the couple’s risk and type of hereditary disease is important because of its prognostic and therapeutic implications for the child, and other family members. Accurate genetic panel testing for these diseases would provide clinicians with information on whether there is a need for additional diagnostic fetal testing in identified at-risk couples, and if necessary treatments for children of high-risk parents. This information would also assist clinicians in providing information and genetic counselling on other reproductive options.

The following outcomes are considered relevant to the assessment of the comparative effectiveness and safety for females planning a pregnancy or are in early stages of pregnancy.

Effectiveness/clinical utility:

- Proportion of children born with or without CF, SMA or FXS
- Impact on increased decision options for future reproduction

During pregnancy

- Termination of pregnancy rate due to presence of specific pathogenic variants identified through amniocentesis or CVS
- Impact on increased pregnancy decision options for current reproduction
- Impact on the number of diagnostic genetic tests performed through amniocentesis or chorionic villus sampling (CVS)
- Comparison of genotype of a child diagnosed pre-natally or post-natally with CF, SMA or FXS with that predicted by carrier testing

Safety:

- Proportion of pregnant women who require diagnostic testing for CF, SMA or FXS by amniocentesis or chorionic villus sampling following a positive genetic carrier test, with or without a positive test from their reproductive partners as appropriate
- Psychological adverse events from genetic carrier testing or no genetic carrier testing
- Psychological effects of test results which subsequently prove to be false

Analytical validity¹:

- Analytical sensitivity and specificity, including at least 50 of the most common pathogenic variants of *CFTR*
- Comparative analytical performance of different sample types
- Comparative analytical performance across different assay options likely to be offered in the bundle of tests used to perform the requested test across the three identified diseases, including any commercially available panel
- Likelihood ratios

Clinical validity²:

- Clinical sensitivity and specificity
- Positive and negative predictive values

HEALTHCARE SYSTEM OUTCOMES

Availability of genetic carrier testing for CF, SMA and FXS for females planning a pregnancy or during pregnancy, and (as necessary) their partners, will have implications for the Australian healthcare system.

It will likely involve additional consultations with clinicians, so females and their reproductive male partners understand what information the testing provides, and also to receive results. If results are positive for a pathogenic variant, referrals will be made for consultations with genetic counselling services and/or fetal management clinics (comprising obstetricians, neonatologists and other specialists, as necessary). Additional diagnostic testing of the fetus and/or in vitro fertilisation services will be anticipated where a couple are identified as carriers.

An Australian study showed the total disease burden for CF, SMA and FXS was estimated to be 59,332 disability-adjusted life years (DALYs) at the current pre-conception genetic testing rate (5%) for adults aged 18-25 years. The same study also showed an approximate 25% reduction in CF, SMA or FXS cases, preventing 491 cases (out of 1988 forecasted births) due to pre-conception carrier screening (Zhang et al., 2019).

¹Analytical validity: the reproducibility and repeatability of the assay, that is, the ability of the test to measure gene expression accurately and reliably.

² Clinical validity: measures the test's ability to predict the presence or absence of disease, that is, the sensitivity, specificity, and positive and negative predictive values, in this case.

Equal access, via MBS funding, to the proposed genetic carrier testing, provides couples with opportunities to choose other reproductive options and hence potentially reduce the number of births affected by CF, SMA or FXS. If so, this would result in a cost-saving for the MBS and PBS and other healthcare use (e.g. public/private hospitalisation and/or non-admitted patient sessions, private health care insurance). For females, or couples, found not to be carriers (i.e. receiving a low risk result), the impact on health care resources will be the cost of the test or MBS fee.

Healthcare resources:

- Number and cost of gene carrier testing
- Number and cost of testing the reproductive partners
- Number and cost of additional medical practitioner consultations
- Number and cost of genetic counselling services and fetal management clinic attendances
- Number and cost of caring for a person with CF, SMA or FXS
- Cost-effectiveness (cost per quality-adjusted life year)
- Cost of additional diagnostic fetal testing in at-risk couples

Pre-conception testing

Number and cost of pre-implantation genetic diagnoses (PGD) and in-vitro fertilisation (IVF) cycles for each subsequent pregnancy in confirmed female carriers of FXS and confirmed carrier couples of CF and SMA.

Post-conception (pre-natal) testing

- Number and cost of amniocentesis or chorionic villus sampling, and confirmatory diagnostic genotyping following positive genetic carrier test(s)
- Number and cost of terminations

Under 'Healthcare resources', PASC considered whether the following should be included: *"Number and cost of pre-implantation genetic diagnoses (PGD) and in vitro fertilisation (IVF) cycles for each subsequent pregnancy, in confirmed asymptomatic female carriers of FXS and confirmed asymptomatic carrier couples of CF and SMA"*. However, PASC concluded this would be difficult to cost and include (i.e. how would you know how many subsequent pregnancies a person has or wants). The same cost would be incurred after the birth of an affected child in a non-screened patient, so PASC did not consider this specific to carrier testing.

CURRENT AND PROPOSED CLINICAL MANAGEMENT ALGORITHMS

Current clinical management algorithm for identified population

Under the current clinical management pathway, females who are planning a pregnancy or are in early stages of pregnancy and if necessary, their male reproductive partners, are referred for genetic carrier testing by their medical practitioner. If they wish to be tested, the service is currently performed on a user-pay basis. For the purpose of the economic evaluation, this should be assumed to be 0%. For the purpose of financial impact/analysis, this should only affect the extent of estimated financial cost offsets.

Figure 2 presents the current clinical management algorithm for genetic carrier testing for females. A multidisciplinary healthcare team treats the disease symptoms as affected individual's progress with age. These diseases significantly affect their quality of life and are associated with increased healthcare costs.

PASC's Second Consideration

PASC confirmed the clinical management algorithms, but noted the potential problem of false-negative results in female testing. This would incorrectly lead to no reproductive partner testing, with the result that a child is born with the condition. PASC advised that this possibility should be included in the algorithm. The applicant acknowledged the risk of false-negative results, but confirmed that the post-test probability of being a carrier (and hence having an affected child) is markedly reduced by having the test. The applicant agreed this should be recorded in the algorithm.

Proposed clinical management algorithm for identified population

Figure 3 presents the proposed clinical management algorithm for genetic carrier testing for CF, SMA and FXS for females. The difference between the current and proposed clinical algorithm is access to genetic carrier testing that is MBS subsidised (proposed clinical management algorithm).

Figure 2: Current clinical management algorithm

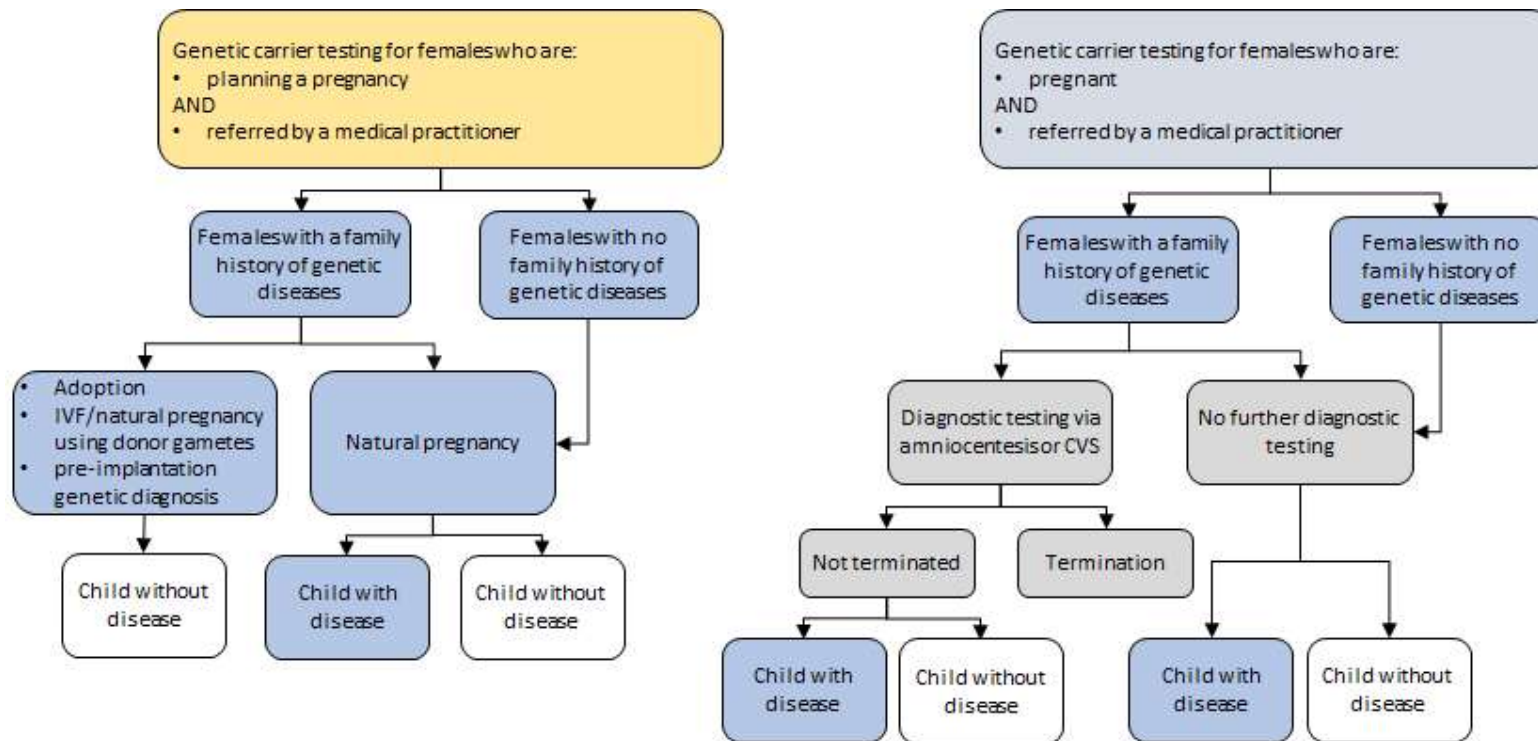
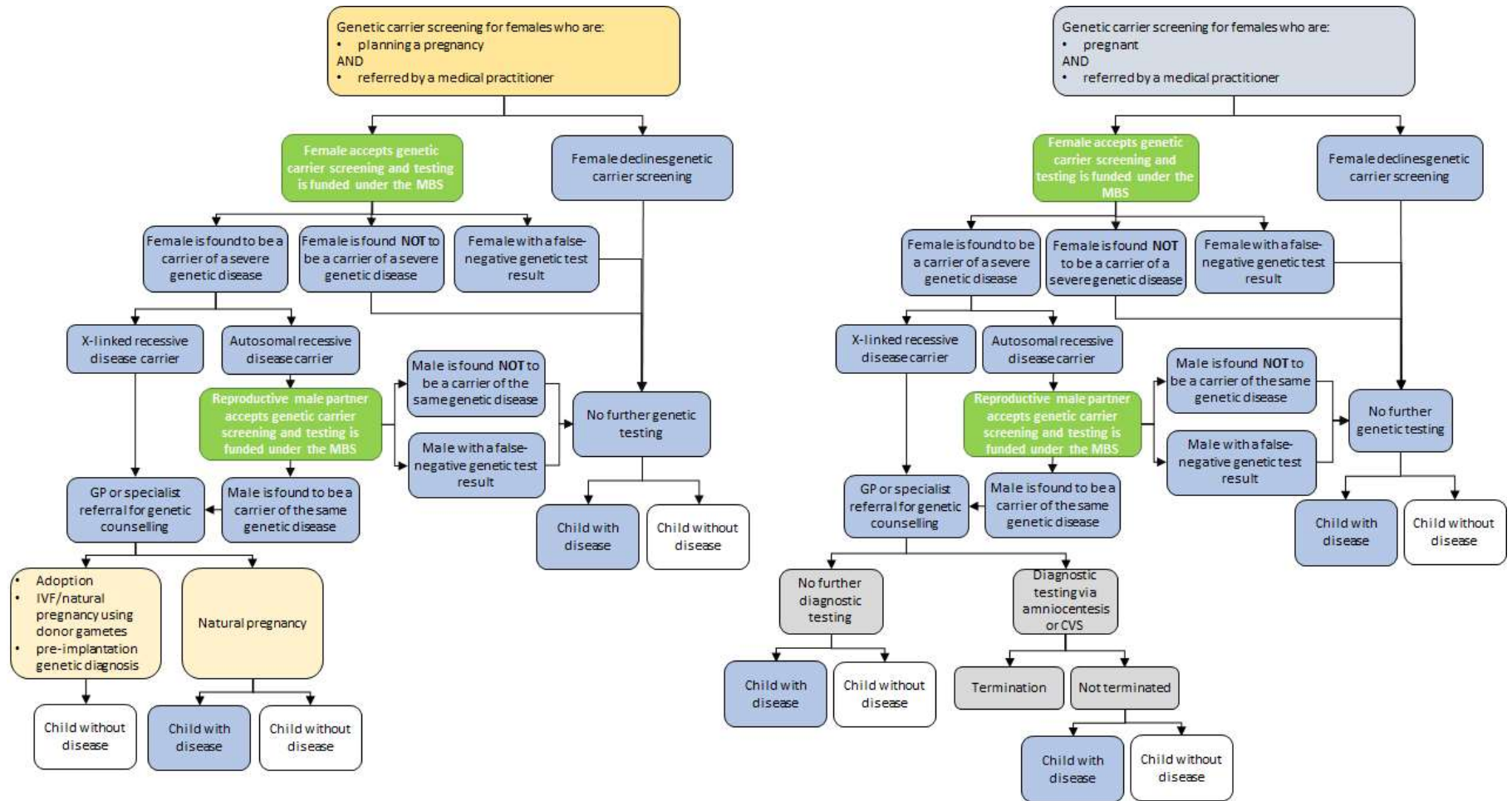


Figure 3: Proposed clinical management algorithm



PROPOSED ECONOMIC EVALUATION

PASC's Second Consideration

PASC confirmed the economic evaluation should be a cost-effectiveness/cost-utility analysis.

PASC confirmed that separate economic evaluations will be needed for pre-conception and pre-natal (at least first trimester) testing, which will need to be aggregated.

The clinical claim is that genetic panel carrier testing for CF, SMA and FXS for females, is inferior in terms of safety and superior in terms of clinical effectiveness, compared to no genetic carrier testing.

According to the *Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee: Investigative*, the required economic analysis is therefore a cost-effectiveness and/or cost-utility analysis. This type of analysis will determine the incremental cost per extra unit of health outcome achieved, expressed in quality-adjusted life years (QALYs) because of a reduction in the number of babies born with the identified diseases.

For the economic evaluation of gene testing, QALYs should be calculated for each of the endpoint outcomes. If QALYs cannot be calculated, the measure of effectiveness can be expressed in life years or other outcomes. The economic evaluation could start with CF as the 'exemplar' disease (carrier rate 1:25) and then add FXS (1:57 carrier rate) and SMA (1:149 carrier rate) as necessary on the basis of also having clinical utility.

Separate economic evaluations will be required for preconception and pre-natal (at least first trimester) testing.

At its first consideration (August 2019), PASC advised that three separate economic evaluations were not needed for each gene, and at PASC's second consideration (December 2019), PASC clarified that pre-conception and pre-natal testing needed to be separated. There are precedents for the testing of three genes (Australian trials and modelling; United Kingdom data; Israeli data; etc). These data and models could be utilised, rather than repeating/re-modelling costs for each gene.

PROPOSED MBS ITEM DESCRIPTOR/S AND MBS FEES (If relevant)

Two separate MBS items are proposed: One for females, and a subsequent one for males who have a female reproductive partner who has been shown to carry a pathogenic variant in genes related to CF or SMA.

PASC's First Consideration

PASC noted the pre-PASC changes to the item descriptor (from that originally proposed in the application form), with changes shown in red in the proposed descriptor below. PASC noted these changes were made in consultation between the applicant and the Department.

PASC accepted that, clinically, additional genes beyond the originally-requested three may be valid.

PASC noted there would be no additional cost if more than three genes were tested.

PASC was inclined to recommend reverting to the genes specified in the original application form's item descriptor (i.e. a three-gene test for CF, SMA and FXS). However, PASC acknowledged there may be problems with doing so, and deferred to additional advice from the Department.

Following the first PASC meeting, the Department advised that the intervention is a combined panel, which would always result in the possibility of identifying more than one type of disease carrier or diseased person. Reverting to 'three condition-only gene testing' may reverse MSAC's intent to support efficiencies through the Clinical Utility Card (CUC) format.

If MSAC Executive determines it is appropriate to limit this application to "three gene only" carrier testing (therefore leaving it up to pathology providers to offer more genes if they wish, without the item descriptor explicitly mentioning this), wording for the male partner item will need careful phrasing.

A query was also raised about whether the words "at least three" in the item descriptor would create standardisation and implementation issues, but PASC did not express any concern.

PASC did express concern about wording: "predicted to significantly shorten lifespan", given FXS does not significantly shorten an individual's lifespan. The applicant agrees that "predicted to significantly shorten lifespan" is not sufficient, and suggested adding "or result in significant disability". This is added to the proposed MBS item descriptor below.

PASC noted the applicant's suggestion that the proposed 'Practice Note' be expanded to add other assessments for at-risk patients (see 'Practice Note' under the MBS item descriptors below). PASC considered this problematic, as it assumes/requires clinical knowledge of a patient's genetic disease risk. It is also at odds with a standardised screening program (if this application was to progress as a formal screening program).

PASC's Second Consideration

PASC confirmed the MBS item descriptor should specify that the test can be requested by a 'medical practitioner'.

PASC confirmed that 'once per lifetime testing' is suitable.

PASC noted that the need for genetic counselling may be urgent if a woman is already pregnant when tested. PASC reinforced there is no MBS rebate for genetic counselling, noting this service is supported by alternative funding in the public sector. PASC noted this particular workforce may already be overstretched, with access for patients being limited.

PASC advised that it is not suitable to limit testing to the first trimester (for testing during pregnancy). A couple may want testing in the later stages of pregnancy, in order to plan for the birth of an affected child. PASC recommended removing this limitation from the item descriptor.

PASC noted the potential inequity of access between males and females for the proposed testing. The item descriptors for females would not prevent a pathology provider also testing additional genes (at no extra cost), but the provider would restrict testing to pathogenic variants CFTR and SMN1 in the male partner.

For example, a pathogenic variant for Tay-Sachs disease could be identified in the female, but the male reproductive partner could not be tested for that variant under the proposed wording for item ZZZZ.

PASC recommended the following alternative wording for MBS item ZZZZ: “Testing of the male reproductive partner of a female who has been found to be a carrier of an autosomal recessive pathogenic variant identified by items XXXXX or YYYYY, for the purpose of determining the couple’s reproductive risk of these conditions”.

This would result in a small increase in estimated numbers for male carrier testing.

PASC noted the male reproductive partners of females who are CF carriers are already eligible for MBS-funded testing (item 73349) if referred by a specialist, with a higher MBS rebate (\$500).

PASC queried whether the \$500 rebate amount should be reviewed (and decreased), in line with current application 1573.

PASC discussed the non-inclusion of FMR1 pathogenic variant testing of male reproductive partners. FXS is X-dominant, and can therefore be inherited from either the mother or the father. PASC discussed whether excluding FMR1 pathogenic variant testing of male partners would result in an affected child being born because the male partner (who has not been tested) has an undetected FMR1 pre-mutation expansion.

PASC concluded that, if a woman is a carrier of a pathogenic variant of the FMR1 gene, the couple would be managed as a high-risk couple. Therefore, knowing the male carrier status would not affect management in this situation. PASC also acknowledged that the probability of a male partner also having an undetected FMR1 pre-mutation expansion is highly unlikely.

PASC noted the Department’s proposal that a further addition be made to the ‘Practice Note’ (i.e. not to be claimed in conjunction with items 73300, 73345–73350 (the current FXS and CF testing items).

PASC expressed concern about the proposed MBS fee proposed, in the absence of more detailed (demonstrated) justification, given genetic testing is a rapidly changing field, with decreasing costs.

The applicant advised that the cost/price of carrier testing using ‘Prepair’ is based on current costs of testing, and while it may be true that costs may fall in future, it would be difficult to test at a fee below the proposed pricing structure in this application.

The proposed (amended) draft item descriptors are as follows:

Category 6 (Pathology Services) – Group P7 Genetics
<p>Item number: XXXXX</p> <p>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.</p> <p>One test per lifetime.</p> <p><u>Fee: \$400</u></p>
Category 6 (Pathology Services) – Group P7 Genetics
<p>Item number: YYYYY</p> <p>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.</p> <p>One test per lifetime.</p> <p><u>Fee: \$400</u></p>
Category 6 (Pathology Services) – Group P7 Genetics
<p>Item number: ZZZZZ</p> <p>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.</p> <p>One test per condition per lifetime.</p> <p><u>Fee: \$400</u></p>

Practice note:

The laboratory used to undertake tests for items XXXX 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, 73345, 73346, 73347, 73348, 73349 and 73350.

Male reproductive partners of females who are CF carriers are currently eligible for MBS-subsidised genetic testing (MBS item 73349) if referred by a specialist. The proposed items are not restricted to specialists requesting the items. This is considered appropriate by the applicant, given the current

population may be seen by a general practitioner (particularly rural patients, as well as couples seeking pre-pregnancy planning advice).

An estimated breakdown of costs associated with the application is provided in Table 2.

Table 2: Estimated breakdown of genetic panel costs

Equipment and resources	Per test
Kit, probes, reagents, ancillary reagents	\$260.00
Labour medical (consultant pathologist)	\$50.00
Labour scientific	\$40.00
Labour on-costs	\$15.00
Depreciation, overheads	\$25.00
Admin, IT	\$10.00
Total	\$400.00

OTHER ISSUES

PASC's First Consideration

At its first pass through PASC (August 2019), PASC highlighted broader policy issues associated with this application. These issues were resolved by MSAC Executive (October 2019), in consultation with the Department, and confirmed by PASC's second consideration (December 2019).

The MBS does not generally fund screening programs, and cost-effectiveness of screening programs is still being evaluated. In addition, screening programs must follow national guidelines, which would need to be considered during any evaluation.

PASC noted the lack of consultation feedback on this application, and suggested more consultation be undertaken with the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and relevant consumer/patient advocacy organisations.

After PASC's first consideration, it was suggested that feedback be sought from the Royal Australian College of General Practitioners (RACGP) and Rural Doctors' Association of Australia (RDAA).

The applicant agreed that other stakeholders be consulted, adding RANZCOG has a policy that is supportive of carrier screening (in this case, 'opportunistic testing').

At PASC's first consideration (August 2019), PASC requested advice be sought from MSAC Executive, confirming (together with the Department) that this application is for 'opportunistic testing' [as opposed to a formal screening program], and [as a separate issue] the words "at least three" are appropriate).

Following PASC's second consideration (December 2019), broader stakeholder consultation should be undertaken (in particular, with RANZCOG and relevant consumer/patient advocacy organisations, but also with RACGP and RDAA).

Interval between the two PASC meetings [September to November 2019]

Following PASC's first consideration (August 2019), the Department and applicant confirmed this application is for opportunistic genetic carrier testing, and not a formal screening program. This document has been amended accordingly.

In addition, the Department and applicant discussed progression of this application through the post-PASC evaluation process. The application has reverted to MSAC consideration of three conditions only (being CF, SMA and FXS).

It is proposed that, due to differences in treatment pathways, separate evaluations be undertaken (in the one application) relating to the pre-conception and post-conception (pre-natal) populations. This will allow ESC and MSAC to consider relative benefits of carrier testing between (and across) the two groups, within a single application.

In October 2019, MSAC Executive was consulted and agreed to this approach.

CONSULTATION FEEDBACK

PASC's Second Consideration

PASC noted there was no additional consultation feedback at the application's second pass through PASC (December 2019).

PASC confirmed it would assist the evaluation stage of this application if RANZCOG and relevant consumer/patient advocacy organisations were consulted, as well as RACGP and RDAA for metropolitan and rural GP requesters.

NEXT STEPS

PASC's Second Consideration

Upon ratification of PICO 1573, the application can PROCEED to the pre-Evaluation Sub-Committee (ESC) stage.

The applicant has elected to progress this application through a DCAR (Department-contracted assessment report).

PASC discussed whether the Clinical Utility Card (CUC) format was relevant to application 1573, and concluded it was not.

REFERENCES

1. Archibald, A. D., Smith, M. J., Burgess, T., Scarff, K. L., Elliott, J., Hunt, C. E., . . . Amor, D. J. (2018). Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: outcomes of 12,000 tests. *Genet Med*, 20(5), 513-523. doi:10.1038/gim.2017.134
2. Australian Bureau of Statistics. (2018). *3301.0 - Births, Australia, 2017*. Retrieved from <https://www.abs.gov.au/ausstats%5Cabs@.nsf/0/8668A9A0D4B0156CCA25792F0016186A?Opendocument>
3. Australian Bureau of Statistics. (2019a). *Births, summary, by state*. Retrieved from http://stat.data.abs.gov.au/Index.aspx?DatasetCode=BIRTHS_SUMMARY#
4. Australian Bureau of Statistics. (2019b). *Confinements, by nuptiality, by state*. Retrieved from http://stat.data.abs.gov.au/Index.aspx?DatasetCode=BIRTHS_SUMMARY#
5. Australian Institute of Health and Welfare. (2018). *Australia's mothers and babies 2016*. Retrieved from Canberra: <https://www.aihw.gov.au/getmedia/7a8ad47e-8817-46d3-9757-44fe975969c4/aihw-per-97.pdf.aspx?inline=true>
6. Better Health Channel. Cystic fibrosis (CF). Retrieved from <https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/cystic-fibrosis-cf?viewAsPdf=true>
7. Better Health Channel. (2016). Spinal muscular atrophy (SMA). Retrieved from <https://www.betterhealth.vic.gov.au/health/conditionsandtreatments/spinal-muscular-atrophy-sma>
8. Birch, R. C., Cohen, J., & Trollor, J. N. (2017). Fragile X-associated disorders: Don't miss them. *Australian Family Physician*, 46(7), 487-491. Retrieved from <https://www.racgp.org.au/afp/2017/july/fragile-x-associated-disorders-don%E2%80%99t-miss-them/#10>
9. Cystic Fibrosis Australia. (2017). What is CF. Retrieved from <https://www.cysticfibrosis.org.au/about-cf/what-is-cf>
10. HealthEngine. (2009). Birth Statistics. Retrieved from <https://healthengine.com.au/info/birth-statistics#c11>
11. Ioannou, L., McClaren, B. J., Massie, J., Lewis, S., Metcalfe, S. A., Forrest, L., & Delatycki, M. B. (2014). Population-based carrier screening for cystic fibrosis: a systematic review of 23 years of research. *Genet Med*, 16(3), 207-216. doi:10.1038/gim.2013.125
12. Jewell J A. (2018). Fragile X Syndrome. Retrieved from <https://emedicine.medscape.com/article/943776-overview#a7>
13. Keogh, L. A., Fisher, D., Sheinfeld Gorin, S., Schully, S. D., Lowery, J. T., & Ahnen, D. J., et al.,. (2014). How do researchers manage genetic results in practice? The experience of the multinational Colon Cancer Family Registry. *Journal of community genetics*, 5(2), 99–108. doi:10.1007/s12687-013-0148-y
14. Keogh, L. A., Niven, H., Rutstein, A., Flander, L., Gaff, C., & Jenkins, M. (2017). Choosing not to undergo predictive genetic testing for hereditary colorectal cancer syndromes: expanding our understanding of decliners and declining. *Journal of behavioral medicine*, 40(4), 583–594. doi:10.1007/s10865-016-9820-0
15. Magnus, M. C., Wilcox, A. J., Morken, N., Weinberg, C. R., & Håberg, S. E. (2019). Role of maternal age and pregnancy history in risk of miscarriage: prospective register based study. *BMJ*, 364, l869. doi:10.1136/bmj.l869
16. Marie Stopes International. (2008). Real Choices: Women, contraception and unplanned pregnancy. Retrieved from <https://www.mariestopes.org.au/wp-content/uploads/Real-Choices-Key-Findings.pdf>
17. MSAC. (2015). *Testing for hereditary mutations in the cystic fibrosis transmembrane conductance regulator(CFTR) gene (1216)*. Retrieved from

[http://www.msac.gov.au/internet/msac/publishing.nsf/Content/D54C11627FEA9785CA25801000123BDC/\\$File/1216-MSAC-CA-CFTR.pdf](http://www.msac.gov.au/internet/msac/publishing.nsf/Content/D54C11627FEA9785CA25801000123BDC/$File/1216-MSAC-CA-CFTR.pdf)

18. National Institutes of Health. (2019). *Genetics Home Reference: Your Guide to Understanding Genetic Conditions*. U.S. National Library of Medicine Retrieved from <https://ghr.nlm.nih.gov/condition/cystic-fibrosis#inheritance>
19. Quinlivan, J., Battikhi, Z., & Petersen, R. (2014). What Factors Impact upon a Woman's Decision to Undertake Genetic Cancer Testing? *Frontiers in Oncology*, 3(325). doi:10.3389/fonc.2013.00325
20. Ruseckaite R, A. S., Ranger T, Dean J, Gardam M, Bell S, Burke N on behalf of the Australian Cystic Fibrosis Data Registry. (2019). *The Australian Cystic Fibrosis Data Registry Annual Report, 2017* (20). Retrieved from
21. Sonic Genetics. (2015). Our Tests: Carrier Screening Panel (CF, SMA and Fragile X). Retrieved from <https://www.sonicgenetics.com.au/tests/carrier-screening-panel-cf-sma-fragile-x/>
22. Spinal Muscular Atrophy Australia Inc. (2017). *Fact Sheet*. Victoria. Retrieved from <https://smaaustralia.org.au/support-services/sma-facts>
23. The Fragile X Association of Australia. FAQ's. Retrieved from <https://fragilex.org.au/resources/faqs/>
24. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. (2015). *Prenatal screening and diagnostic testing for fetal chromosomal and genetic conditions*. Retrieved from
25. U.S. National Library of Medicine. (2012, 11/06/2019). Genetics Home Reference: Your Guide to Understanding Genetic Conditions - Fragile X Syndrome. Retrieved from <https://ghr.nlm.nih.gov/condition/fragile-x-syndrome>
26. Zhang, L., Bao, Y., Riaz, M., Tiller, J., Liew, D., Zhuang, X., . . . Lacaze, P. (2019). Population genomic screening of all young adults in a health-care system: a cost-effectiveness analysis. *Genetics in Medicine*. doi:10.1038/s41436-019-0457-6