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Application 1637:

Expanded reproductive carrier testing of couples for joint carrier status of genes associated with autosomal recessive and
X-linked conditions

# Ratified

#  PICO Confirmation

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

Table 1 PICO for expanded reproductive carrier testing of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions in asymptomatic couples (or genetic contributors to a pregnancy) who are planning to become pregnant or in early stage of pregnancy

| **Component** | **Description** |
| --- | --- |
| Population | Asymptomatic couples of reproductive age (or genetic contributors to a pregnancy) who are planning to become pregnant or in early stage of pregnancy. |
| Prior tests | None |
| Intervention | Expanded reproductive carrier testing of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions at preconception or early pregnancy |
| Comparator/s | Reproductive carrier testing for cystic fibrosis, spinal muscular atrophy and fragile X syndrome |
| Reference standard | Not available |
| Outcomes | Outcomes that relate to the direct safety of the health technology or comparator:* Psychological harms from positive test results
* Harms from test outcomes that subsequently prove to be false (false negative or false positive)

Clinical utility:* Affected births/affected births averted
* Uptake of actions based on informed reproductive decision (e.g. donor gametes, pre-implantation genetic diagnosis, termination, adoption)

Test accuracy outcomes:* Diagnostic accuracy
* Diagnostic yield among the test population for determining carrier status (number of high-risk results/number of couples tested)
* The proportion of pregnancies in high-risk couples that underwent chorionic villus sampling/amniocentesis and tested positive to the identified high-risk pathogenic/likely pathogenic variant(s)

Cost-effectiveness & financial impact:* Cost per couple identified as high-risk (before offset costs)
* Cost per couple identified as high-risk (after estimated offset costs)
* Cost of informed reproductive decisionmaking in couples who are both identified as carriers for a condition (comparison of existing management and proposed management)
* Number & cost of couples who will undergo re-testing
* Number and cost of testing existing children of high-risk couples

Total Australian Government health care costs:* The total number and costs of terminations for high-risk couples

Healthcare resource use:* Total number of couple tests and cost of the couple testing program
* Number and cost of additional medical practitioner consultations (e.g., pre-test and post-test counselling, genetic counselling)
* Number and cost of preimplantation genetic diagnoses and in-vitro fertilisation cycles for each subsequent pregnancy (in preconception testing and subsequent pregnancies of a high-risk couple)
* Number and cost of prenatal fetal testing (i.e., chorionic villus sampling or amniocentesis and confirmatory diagnostic genotyping following a high-risk carrier test result)
 |
| Assessment questions | What is the safety, effectiveness and cost-effectiveness of expanded reproductive carrier testing of couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions at preconception or early pregnancy versus reproductive carrier testing for cystic fibrosis, spinal muscular atrophy and fragile X syndrome in asymptomatic couples (or genetic contributors to a pregnancy)? |

## Purpose of application

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

The clinical claim is that expanded reproductive carrier testing of couples for joint carrier status results in superior health outcomes compared to the comparator/standard practice, i.e., female-first reproductive carrier testing for cystic fibrosis, spinal muscular atrophy and fragile X syndrome. When implemented, expanded reproductive carrier testing is claimed to reduce the incidence of autosomal recessive and X-linked genetic disorders.

## PICO criteria

### Population

#### The testing population

The target or testing population for expanded reproductive carrier testing of couples for joint carrier status of genes associated with autosomal resessive and X-linked conditions are couples who are planning to become pregnant or are in the first trimester of pregnancy. In the majority of cases, this will involve a male and female partner being tested concurrently. However, in some instances where a donor gamete or embryo may be planned to be used or may have been used to conceive a pregnancy, the expanded reproductive carrier testing would be performed on the genetic contributors to that pregnancy/planned pregnancy if the donors are available and willing to provide a DNA sample and undergo expanded reproductive carrier testing. The aim is to provide the couple with information about their risk of having children with certain autosomal resessive and X-linked genetic conditions.

*PASC confirmed the population to be asymptomatic reproductive couples (or genetic contributors to a pregnancy) who are planning to become pregnant or are in the early stages of pregnancy.*

*PASC emphasised the need for gender-neutral language to be utilised in the MBS item descriptors and in counselling materials.*

#### The proband population (i.e. test positive population)

Most autosomal and X-linked recessive conditions cannot be cured, and almost all are expressed phenotypically in affected indviduals by reproductive age (Costa, Scriver, & Childs, 1985). Although these conditions are identified as rare diseases individually (affecting less than five in 10,000 people (Rare Voices Australia, 2020)), they are not collectively rare and affect millions of people globally. Exact prevalence data in the scientific literature are conflicting due to the variety of conditions, but Kumar, Radhakrishnan, Chowdhary, and Giampietro (2001) estimated that genetic disorders accounted for almost 1 in 5 paediatric emergency department visits in a New York health center. Ropers (2012) estimated that, assuming a birth prevalence of severe recessive disorders between 0.25-0.5%, 1-2% of couples would have an increased risk of having a child affected by an autosomal recessive or X-linked condition. The applicant estimates that over one million people in Australia are affected directly or indirectly by a genetic condition. A study by Bell et al. (2011) demonstrated that over 97% (101/104) of people were carriers of a severe recessive condition; however, in reality this is likely to be closer to 100% as they only analysed 448 conditions. In this study, the average carrier burden of severe recessive substitutions, indels, and gross deletion disease variants was of 2.8 per genome (291 in 104 samples) (Bell et al., 2011).

*PASC noted the assumptions and calculations used to estimate the population size eligible for the proposed intervention.*

Autosomal recessive conditions occur when a pathogenic variant in the same gene is inherited from each parent. In the rest of this document pathogenic variant is simply referred as ‘variant’. If the child only has one copy of a gene variant inherited from one parent, he or she will not be affected but will be a carrier. If the parents are both carriers for a variant in the same gene, which is associated with an autosomal recessive condition (i.e. both of them have one normal copy and one copy of the gene with a variant), then their children will have 1 out of 4 (25%) risk of being affected by the condition.

For many conditions, there are multiple different associated genes but in almost all cases of autosomal recessive conditions, the parents must carry variants in the same gene for there to be an increased risk of having an affected child.

In X-linked conditions the gene with the variant is located on the X chromosome. Thus, if the mother is a carrier, their male offspring have a 50% risk of being affected. Female offspring have a 50% risk of inheriting the copy of the gene with the variant and also being a carrier (Genetics Home Reference), but are generally either not affected by the condition or are more mildly affected than a male with the variant; thus the overall risk of having an affected child is close to 1 in 4. The father is not tested for X-linked conditions because he would be expected to be identified as being affected if he had a condition arising from a variant in a gene on the X chromosome.

There are two known X-linked genes (*EFNB1* and *PCDH19*) for which males are generally asymptomatic whereas females are symptomatic. There is also one known X-linked gene (*SHOX*) that is located in part of the X chromosome that is also present on the Y chromosome – there are two such regions, known as the pseudoautosomal regions, and the severe condition associated with variants in *SHOX* is inherited as though it were an autosomal recessive condition. Thus, limited analysis of X-linked genes in males is required.

The intervention is intended for asymptomatic couples. It is assumed that carriers do not exhibit symptoms, and that the penetrance of the variants included in the test panel is high, with strong confidence in genotype-phenotype relationship. However, Australian population frequencies for the great majority of conditions on the list are not known, according to the applicant.

A prior positive family history, i.e., of an individual affected by of one of the diseases included in the test in one of the couple’s family, does not preclude a couple from accessing expanded reproductive carrier testing, in case they have an increased risk for another condition. The couple would, however, have a greater probability of being identified as “high risk” for the known condition. Being at risk for more than one condition is rare; the risk of an additional condition may be either population risk, or higher risk. The vast majority of at-risk couples will be at risk for one condition alone, but the likelihood of being at risk for more than one condition is higher in populations with low genetic variation, and in consanguineous relationships.

Similarly, couples with a previous index case of a child with a monogenic disease and identified as carriers would be eligible for testing. Reproductive options that are already in place would apply in relation to the previously known condition in the family.

The Royal Australian College of General Practitioners’ (RACGP) guidelines recommend that all women of reproductive age should be considered for preconception care, including providing the opportunity for carrier testing of genetic conditions and referral for genetic counselling based upon risk factors (The Royal Australian College of General Practitioners, 2016). This recommendation for carrier testing pre-pregnancy or in early pregnancy is also made by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and the Human Genetics Society of Australasia (HGSA).

In Australia, potentially eligible people are currently able to obtain carrier testing on a user-pays basis. MSAC recently supported the MBS listing of universal reproductive carrier testing for three conditions (cystic fibrosis, spinal muscular atrophy, and fragile X syndrome; MSAC application 1573 (Medical Services Advisory Committee, 2020a)), though these MBS items have not yet been implemented. If supported by Government and listed on the MBS, this testing would be offered as opportunistic testing for all women who are planning a pregnancy or are in the early stages of pregnancy, with subsequent testing of their reproductive partner if found to be a carrier for the recessively inherited disorders cystic fibrosis or spinal muscular atrophy. Additionally, MBS items for cystic fibrosis carrier testing are already available in certain situations (see details in the Comparator section).

The test results of the proposed medical technology are issued for a particular couple. Individual results are not disclosed to the tested participants. While it is proposed that expanded reproductive carrier testing would be performed once in a lifetime to couples, there may be a need for repeat testing in the following cases:

1. A person previously tested as part of a different couple, but forms a new reproductive couple. Ideally, their stored data would be re-analysed or combined with the test results of the new reproductive partner. However, difficulties may arise if the original testing was performed by a different laboratory using different analysis and reporting methods. In those circumstances, re-testing of both partners is required. Alternatively, the new partner sample could be referred to the laboratory that performed the initial testing and analysis.
2. If both reproductive partners had been previously tested as part of a different couple, their results may be re-analysed if it is possible to access both of their stored data.
3. Re-analysis of a couple’s data after minimum 5 years since last analysis or re-analysis. As new information becomes available, some variants may be reclassified in their pathogenicity and according to this new information, the variant may become “not reportable”. It may therefore be useful to re-analyse the data of the particular couple if there is a large gap between pregnancies.
	1. Similarly, couples may need to be re-tested after a minimum five-year horizon if there are technological advances in genomic sequencing. Also, as the list of genes is expanded based on new findings, some couples who were tested using targeted panels may need to be re-tested. The applicant noted that this is likely to be a small number of patients as most couples will have completed their reproductive period in a short period of time and not need additional panel testing.

*A post-PASC meeting was held between the Department and the applicant. At the post-PASC meeting, the applicant stated that given the anticipated interval between pregnancies for most couples who remain together, the re-analysis item CCCC was considered redundant as the incremental change in composition is likely to be insignificant. There is still a need to have an item for couples forming a new relationship where one has been tested previously.*

The pace at which gene lists change would make requests for re-analysis rare within the typical period during which most couples are reproducing. This is particularly the case because any new genes that are added are likely to be associated with very rare conditions that will not greatly increase the proportion of couples identified as having an increased risk of having an affected child.

#### Cascade testing

The application does not request cascade testing of family members in case of a high-risk test result for the condition(s) in a couple. Additionally, family members of a couple at high-risk who might be considered for cascade testing would be equally eligible for the proposed MBS items.

*PASC queried whether limited cascade testing of existing children of high-risk couples may be required in the short term for diagnostic purposes. At the post-PASC meeting the applicant confirmed where a couple was identified as high-risk, there is a need for a cascade test item for existing children who may be presymptomatic for that condition. An appropriate item descriptor and fee should be proposed for such testing (see item FFFF).*

An MBS item is also proposed for prenatal fetal testing of a sample from amniocentesis or chorionic villus sampling in diagnostic studies of a fetus where both prospective parents have been identified as high-risk carriers for an autosomal recessive condition or the woman has been identified as a carrier of an X-linked recessive disorder.

### Intervention

The proposed health technology is investigative and would be a part of preconception or early pregnancy care. The proposed test will determine the carrier status of a reproductive couple for a minimum set of genes contributing to autosomal recessive and X-linked genetic conditions, and predict the couple’s risk of having a child affected by at least one of the conditions.

The proposed health technology is genomic sequencing and analysis of germline gene variants known to cause autosomal recessive and X-linked conditions, testing for hundreds of genetic conditions simultaneously. Methodologically, “genomic sequencing” is used to refer to whole exome sequencing, whole genome sequencing, or panel sequencing of genes such as those identified by the Australian Reproductive Genetic Carrier Screening Project (also known as “Mackenzie’s Mission”). The applicant presented a peer-reviewed publication describing in detail the process of selecting genes for the Australian Reproductive Genetic Carrier Screening Project testing panel, which is the basis of the current application (Kirk et al., 2021).

*PASC confirmed the intervention is expanded carrier testing of reproductive couples for joint carrier status of genes associated with autosomal recessive and X-linked conditions at preconception or early pregnancy, through sequencing of a minimum set of genes to identify pathogenic or likely pathogenic variants, and report the combined couple risk only. Different testing options include whole genome sequencing, whole exome sequencing, and targeted sequencing through a large gene panel. PASC noted that some genes may be challenging to analyse using next-generation sequencing methods and may require additional test methodologies.*

There is no consensus on which autosomal and X-linked recessive conditions should be included in a testing panel for reproductive health. The inclusion criteria, where reported in the literature, are that the condition should have a well-defined phenotype and a serious impact on the affected individual and their family, be able to be diagnosed prenatally, and that testing for the condition is perceived to be acceptable to the target population and the community (Archibald et al., 2018). For this application, a condition list that was applicable to the Australian population has been decided upon, using rigorous scientific methods and based on the condition being life-limiting or disabling, with childhood onset, such that couples would be likely to take steps to avoid having an affected child; and/or be one for which early diagnosis and intervention would substantially change the outcome. Strong evidence for gene-phenotype relationship was required: genes were only included if there was strong evidence for an association, using the internationally recognised ClinGen consortium criteria (Strande et al., 2017). Candidate genes were identified from the Online Mendelian Inheritance in Man (OMIM) catalog and via review of 23 commercial and published gene lists. Genes were reviewed by 16 clinical geneticists using a standard operating procedure, in a process overseen by a multidisciplinary committee that included clinical geneticists, genetic counsellors, an ethicist, a parent of a child with a genetic condition and scientists from diagnostic and research backgrounds.

Prevalence of the condition was not considered, on the grounds that the costs associated with using massively parallel sequencing to test >500 genes are not substantially higher than for a panel of only a few hundred genes.

The applicant states that the test is proposed to be offered by different healthcare providers, including general practitioners, obstetricians, midwives, nurses, fertility specialists, and genetics health professionals. The healthcare provider must be able to perform appropriate pre- and post-test counselling and obtain an standard clinical consent. A person (either with their partner or by themselves) who is planning to become pregnant or is in the early stages of pregnancy would access healthcare in relation to their planned or current pregnancy, and their healthcare provider would provide preconception or early pregnancy care. As part of that patient management, the clinician would provide information with regards to carrier testing for recessive genetic conditions (The Royal Australian College of General Practitioners, 2016). The healthcare provider can obtain a sample (if both genetic contributors are present at the healthcare interaction), provide sample kits, or advise on how to access sample kits.

The sample collection procedure can be by a buccal swab, which can be performed in people’s homes. The rationale for making the test available in the patient’s home is that the reproductive partner may not be available for sampling at the interaction with the healthcare professional. The buccal swab is a simple procedure that can be carried out with ease by the patient. Blood sampling methods can also be used for collecting the sample, as the female partner may be having other investigations pre-pregnancy or in early pregnancy. The test panel is currently being offered as a National Association of Testing Authorities (NATA)-accredited test by three Australian laboratories (Class 3 IVD under Therapeutic Goods Administration (TGA) regulations). Pre-test counselling should be available to assist in facilitating the standard clinical consent for testing and post-test counselling to deliver and interpret the results.

Couples would be required to provide standard clinical consent that they understand how couple testing works, that carrier status for individual genes beyond any for which the couple is found to be at high risk would not be provided, and that not all high-risk couples can be identified by testing.

The applicant has developed an online education and consent process for the Australian Reproductive Genetic Carrier Screening Project. This tool will be further evaluated through a combination of qualitative research and surveys. Based on preliminary feedback and data, the applicant expects to be able to provide evidence supporting the validity of this approach for establishing the informed consent of the reproductive partners. The online consent process is supported by access to genetic counsellors; if there are any issues that participants wish to explore further or if there are personal considerations not covered by the online process, a “1800 helpline” is available which allows confidential discussion with a genetic counsellor.

If either partner withdraws consent at any stage, analysis to determine the risk for autosomal recessive conditions will not be possible. However, if the male partner withdraws consent, it would still be possible to analyse and report data for X-linked conditions for the woman.

*PASC noted the Department’s advice that the expanded reproductive carrier test is proposed to be reported as a combined risk applicable to the couple pairing, but that the carrier status of each individual in the reproductive couple is unknown, and there are ethical implications in the withholding of genetic information from an individual. It may impact future pregnancies should they be undertaken with a different reproductive partner, or should the individual mistakenly believe that the results apply to themselves as an individual, and not as a specific couple pairing. PASC noted the applicant has advised that this can be managed through the provision of testing/re-analysis for new couple pairings, as well as informed consent processes, but that the Department remains concerned as re-testing or re-analysis may not be available (if the new reproductive partner cannot access the MBS, or is unwilling to take the test), and is concerned that proposed online consent processes may be insufficient. PASC discussed the process of obtaining informed consent from both members of the reproductive couple, and noted that there were options for both verbal consent for individuals attending a medical appointment, and an online consent process. PASC welcomed the option of online consent for persons who would otherwise have difficulties presenting for the pre-test counselling in person as it may improve equity of access, but raised concerns about the level of health literacy, technologic literacy, and English language skills required to participate in the online consent process. The applicant confirmed information materials would be available in multiple languages. PASC requested that the evidence on the effectiveness and validity of the applicant’s online education and consent process for establishing informed consent of the reproductive partners be included in the assessment.*

*PASC queried whether there are security implications and privacy risks associated with the collection and long-term storage of personal genomic data, especially if transferring data from one provider to another. It was considered that, providing that the data were stored in Australia and followed current genomic data management standards and legislation, the proposal should not pose significant issues to security and privacy.*

Where appropriate, the health technology is proposed as a replacement for an existing test (reproductive carrier testing for cystic fibrosis, spinal muscular atrophy and fragile X syndrome, supported by MSAC but not yet implemented), noting some differences between tests: the existing test consists of sequential testing of a partner in case the female is found to be a carrier and reports the results on an individual basis, whereas the proposed test is carried out simultaneously on both partners, and results are presented for the couple as a whole, and not on an individual basis. The technology would not replace all usage of the existing test, e.g., individual females would not be eligible for the proposed technology but would be able to access the existing test.

The test results are communicated to the couple as a “low risk” or “high risk” of having an affected child. High risk refers to the situation where both members of a couple are identified as carriers of a pathogenic or likely pathogenic variant in the same autosomal recessive gene and/or the woman as a carrier of a pathogenic or likely pathogenic variant in an X-linked gene. Rarely, couples may be at high risk for more than one condition. For a large panel like the one proposed, gene-by-gene listing of low risk results would be unwieldy and hard to read. High-risk results contain detailed information about the specific variant(s) identified and the consequences of the result. “Low risk” means that the couple has not been found to each have a pathogenic or likely pathogenic variant in the same autosomal recessive gene and the woman has not been found to have a pathogenic or likely pathogenic variant in an X-linked gene. The dichotomisation is the same for all reproductive couples.

*At the post-PASC meeting, the applicant confirmed that where a couple is identified as high-risk, there is a need for a cascade test item for existing children who may be presymptomatic for that condition. An appropriate fee should be proposed for such testing, based on advice from the applicant as to whether data on the specific familial variants identified would be accessible following couple testing (in which case testing can be for the known familial variants) or inaccessible (in which case testing would be single gene sequencing for the relevant gene/s).*

For most couples, the starting point is that they are at population risk for each condition (this may be modified by factors such as family history, as discussed above, or consanguinity). A low-risk result means that the possibility of a couple having an affected child is below population risk for each tested condition.

Once reported, it is very important for the couple and their health care practitioner to understand that, apart from X-linked recessive conditions, the result is only valid for the couple. Should either have a child with a different partner, the result would not be meaningful for assessment of future risk of autosomal recessive conditions in their offspring. It is therefore essential for both partners to be listed on the report.

Individual test results are not communicated to those tested; the chance of an individual not being a carrier of any one of the tested conditions is well under 50% (Dr Swaroop Aradhya, Invitae, Personal Communication, August 2019 based on the Invitae RCS panel of around 300 genes).

*PASC noted concerns about the ethical implications of withholding of genetic information from an individual, as the results are reported for the couple and not on individual basis, however considered that this could be addressed through the informed consent process.*

*At the post-PASC meeting, it was discussed that the analysis methodology for assessing couple-risk does not identify the carrier status of each individual (for autosomal recessive conditions). This precludes the delivery of information that may relate to carrier status for an individual e.g those associated with increased cancer predisposition in heterozygotes. Individuals undergoing testing to inform reproductive decision-making may still require other tests to inform their personal risk; this should be highlighted during the consent process.*

Population frequencies of each condition are also not described in the test report, as they are not known for the majority of the conditions and reporting residual risks for the small subset of the included conditions for which information is available would not be meaningful.

**Other relevant considerations**

It is anticipated that there will be updates to the gene list over time, and for this reason specification of a particular list of genes for testing is not desirable. It is more likely that genes will be added than removed from the list but there are a variety of reasons why either could occur:

* Availability of new information, such as reports of additional cases strengthening the evidence for gene-phenotype relationship and ‘new’ disease genes being identified.
* Development of new treatments or introduction of newborn screening resulting in the clinical impact of a condition changing.
* Technical developments that make it possible to test for additional conditionsthat currently are not able to be tested for using massively parallel sequencing technology.

Addition (or subtraction) of genes over time will not raise costs or have any impact on the fee, as it is likely that the proportional change within the foreseeable future will be small, and additions can be accommodated for the same test cost.

*PASC noted that the application did not list the genes that would be included in the test, and this list is anticipated to be updated over time. PASC considered that the absence of a minimum gene list would create inconsistencies between test providers. PASC requested a list of essential or minimum genes for the gene panel be provided (not necessarily a complete list). In line with other MSAC applications, PASC advised this could be be achieved through a reference to a website link to an expert-curated and dynamic gene list. At the post-PASC meeting it was discussed that the minimum gene list could be provided as a publication via the HGSA, or as a stand-alone item within PanelApp. Estimates of the frequency of variants in the genes in the population should be listed, at least for the more common conditions. It was also requested that conditions that cannot be tested through a next-generation sequencing panel, such as gene features requiring triple repeat primer PCR or Southern blotting, are explicitly listed to ensure they are included in the test, or state if only one methodology is proposed.*

*PASC discussed the absence of an external quality assurance scheme for the proposed gene panel. It was queried whether individual schemes for some of the expected conditions (e.g., cystic fibrosis, spinal muscular atrophy, fragile X syndrome) may be appropriate. At the post-PASC meeting, the applicant confirmed a quality assurance program is in development for the proposed testing.*

### Comparator(s)

In July 2020, the MSAC supported public funding for reproductive carrier testing to detect three conditions (cystic fibrosis, spinal muscular atrophy, and fragile X syndrome (Medical Services Advisory Committee, 2020a)). This medical service is not currently available through the MBS, and the MBS items were not yet implemented at the time of drafting this PICO Confirmation. The previously supported pre-pregnancy testing is sequential, with one partner tested first and if found to be a carrier for the recessively inherited diseases cystic fibrosis or spinal muscular atrophy, then the reproductive partner would also be tested.

*PASC noted that the main comparator is reproductive carrier testing for three conditions (cystic fibrosis, spinal muscular atrophy and fragile X syndrome, MSAC Application 1573). PASC considered that although MSAC had supported Application 1573, its implementation was pending. PASC advised the base case should use testing as per 1573 as the comparator, though an additional comparator may be “no reproductive carrier testing”. PASC suggested that the applicant review MSAC Application 1671 and present a rationale whether 1671 may be a further additional comparator.*

Several pathology services also currently offer carrier testing on a user-pays basis (except for haemoglobinopathies for which testing is funded under MBS item 65081), which can be ordered by a healthcare provider or can be ordered directly by the consumer (e.g., eugenelabs.com). Depending on the test provider:

* Testing may look for a limited number of conditions (e.g., cystic fibrosis, fragile X syndrome, spinal muscular atrophy) or test for an expanded range of conditions (i.e., >100)
* Genetic counselling may or may not be available.

The applicant has indicated that the proposed expanded reproductive carrier testing would be, at least partially, a replacement technology for the reproductive carrier testing of three conditions.

Additionally, carrier genetic testing for cystic fibrosis for reproductive purposes is also available on the MBS in situations listed in Table 2.

Table 2 Existing MBS items for cystic fibrosis genetic testing for reproductive purposes by reproductive stage

|  |  |
| --- | --- |
| Reproductive stage | Cystic fibrosis (pathogenic *CFTR* variants) |
| Prior to pregnancy | If known family historya, to determine carrier status (item 73348)To determine reproductive risk, if reproductive partner is known carriera (item 73349) |
| Early pregnancy | If one or both prospective parents are known carriersa, to determine whether fetus is affected (item 73350)If ultrasound evidence of echogenic gut (items 73346 and 73347b) |

Source: MBS Online

a Of pathogenic *CFTR* variant/s

b Item 73346 is for testing of a pregnant patient whose carrier status of pathogenic *CFTR* variants, and that of their reproductive partner, are unknown, for the purposes of determining whether pathogenic *CFTR* variants are present in the fetus. Item 73347 is for testing of a prospective parent for pathogenic *CFTR* variants for the purpose of determining the risk of their fetus having pathogenic *CFTR* variants. Both of these item numbers require ultrasound evidence of echogenic gut.

The item descriptors of these MBS items and their fees are listed in Table 3.

Table 3 Existing MBS items for cystic fibrosis genetic testing for reproductive purposes

| Item number | Category 6 – PATHOLOGY SERVICES; Group P7 – Genetics |
| --- | --- |
| 73346 | Testing of a pregnant patient whose carrier status for pathogenic cystic fibrosis transmembrane conductance regulator variants, as well as their reproductive partner carrier status is unknown, for the purpose of determining whether pathogenic cystic fibrosis transmembrane conductance regulator variants are present in the fetus, in order to make or exclude a diagnosis of cystic fibrosis or a cystic fibrosis transmembrane conductance regulator related disorder in the fetus when requested by a specialist or consultant physician who manages the treatment of the patient, not being a service associated with a service to which item 73350 applies.The fetus must have ultrasonic findings of echogenic gut, with unknown familial cystic fibrosis transmembrane conductance regulator variants.**Fee:** $500.00 **Benefit:** 75% = $375.00 85% = $425.00 |
| 73347 | Testing of a prospective parent for pathogenic cystic fibrosis transmembrane conductance regulator variants for the purpose of determining the risk of their fetus having pathogenic cystic fibrosis transmembrane conductance regulator variants. This is indicated when the fetus has ultrasonic evidence of echogenic gut when requested by a specialist or consultant physician who manages the treatment of the patient, not being a service associated with a service to which item 73345, 73348, or 73349 applies.**Fee:** $500.00 **Benefit:** 75% = $375.00 85% = $425.00 |
| 73348 | Testing of a patient with a laboratory-established family history of pathogenic cystic fibrosis transmembrane conductance regulator variants, for the purpose of determining whether the patient is an asymptomatic genetic carrier of the pathogenic cystic fibrosis transmembrane conductance regulator variants that have been laboratory established in the family history, not being a service associated with a service to which item 73345, 73347, or 73349 applies.The patient must have a positive family history, confirmed by laboratory findings of pathogenic cystic fibrosis transmembrane conductance regulator variants, with a personal risk of being a heterozygous genetic carrier of at least 6%. (This includes family relatedness of: parents, children, full-siblings, half-siblings, grand-parents, grandchildren, aunts, uncles, first cousins, and first cousins once-removed, but excludes relatedness of second cousins or more distant relationships).**Fee:** $250.00 **Benefit:** 75% = $187.50 85% = $212.50 |
| 73349 | Testing of a patient for pathogenic cystic fibrosis transmembrane conductance regulator variants for the purpose of determining the reproductive risk of the patient with their reproductive partner because their reproductive partner is already known to have pathogenic cystic fibrosis transmembrane conductance regulator variants requested by a specialist or consultant physician who manages the treatment of the patient, not being a service associated with a service to which item 73345, 73347, or 73348 applies.**Fee:** $500.00 **Benefit:** 75% = $375.00 85% = $425.00 |
| 73350 | Testing of a pregnant patient, where one or both prospective parents are known to be a genetic carrier of pathogenic cystic fibrosis transmembrane conductance regulator variants for the purpose of determining whether pathogenic cystic fibrosis transmembrane conductance regulator variants are present in the fetus in order to make or exclude a diagnosis of cystic fibrosis or a cystic fibrosis transmembrane conductance regulator related disorder in the fetus, when requested by a specialist or consultant physician who manages the treatment of the patient, not being a service associated with a service to which item 73346 applies.The fetus must be at 25% or more risk of cystic fibrosis or a cystic fibrosis transmembrane conductance regulator related disorder because of known familial cystic fibrosis transmembrane conductance regulator variants.  **Fee:** $250.00 **Benefit:** 75% = $187.50 85% = $212.50 |

Source: MBS Online

Explanatory note PN.7.3 related to items 73346, 73347, 73348, 73349, 73350:

Cystic fibrosis gene testing

(1) For any particular patient, item 73347, 73348 and 73349 is applicable not more than once in a lifetime.

(2) For any particular patient, item 73346 and 73350 is applicable not more than once in a pregnancy.

(3) The testing laboratory used to undertake tests for items 73346, 73347, 73348, 73349 and 73350 must use a cystic fibrosis transmembrane conductance regulator methodology appropriate to the clinical setting with:

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

   (b) with at least 25 of the most frequently encountered cystic fibrosis transmembrane conductance regulator variants in the Australian population.

The applicant considers that MBS items 73348, 73349 and 73350 are not complete comparators because expanded reproductive carrier testing is aimed at all couples in the community who seek reproductive carrier testing irrespective of family history. Items 73346 and 73347 are not complete comparators either as they only relate to testing of parents whose fetus has signs of cystic fibrosis on ultrasound, and expanded reproductive carrier testing would generally occur at an earlier reproductive stage (either pre-pregnancy or in early pregnancy, prior to prenatal fetal diagnostic tests) regardless of ultrasound findings.

While expanded reproductive carrier testing is likely to replace items 73346, 73347 and 73349 in practice, it will also involve sequencing the entire *CFTR* gene (also potentially looking for deletions in the gene). Items 73346, 73347, 73348, 73349 and 73350 would be included as part of the normal pathway of the comparator (based on current utilisation and the proportion of pregnancies with a fetus with signs of cystic fibrosis on ultrasound). Item 73350 could still be used to determine whether a fetus is affected by cystic fibrosis.

### Reference standard

The applicant noted that no reference standard for the proposed investigative technology was available. The MSAC guidelines explicitly state that the accuracy of the proposed test would need to be demonstrated by direct, from test to health outcomes evidence showing a health benefit resulting from use of the test, or a clinical utility standard. However, in the case of genetic testing, the analytical validity of next generation sequencing has previously been accepted by MSAC.

*PASC noted no reference standard was available for the proposed medical service.*

The applicant acknowledged that false positive and false negative results are possible. False positives are expected to be very rare, because the process of variant curation is deliberately biased to favour specificity over sensitivity, to minimise the chance that a couple will be wrongly told they are at high risk of having an affected child. False negatives are more likely to occur, and at a large scale of testing are inevitable. This relates in part to the bias in favour of specificity, and particularly relates to the difficulties of interpreting novel variants in the absence of previously reported affected individuals with the variant. Specifically, it is almost impossible to classify a previously unreported missense variant as Likely Pathogenic or Pathogenic. There are some variant types that are not well detected by the laboratory methods in use (for example, small copy number variants) and there can be gaps in coverage in any massively parallel sequencing assay.

It is important that the referring clinician and the couple understand that the test does not completely remove the possibility of an affected child. This issue is an important part of the consent process. It should be noted that even a notional assay with 100% sensitivity and specificity would still not completely remove the chance of an affected child, since *de novo* variants may arise (a well-known issue for spinal muscular atrophy but also possible in other conditions) or other rare mechanisms such as uniparental isodisomy could result in an affected child even though only one parent is a carrier.

In practice it is extremely rare that a couple found to be at low risk is offered any further investigation or reproductive intervention. The exception is where there is a family history of a condition that changes the interpretation of a low risk result. An example of this is where spinal muscular atrophy is present in a participant as “2/0” rather than the common “1/0” genotype. This terminology refers to two copies of the *SMN1* gene on one chromosome and a *SMN1* deletion on the other chromosome (2/0), and is termed as a silent carrier. A 1/0 refers to a patient with one copy of the *SMN1* gene on one chromosome and a *SMN1* deletion on the corresponding chromosome. These genetic differences can result in a false negative result that can be rectified if the laboratory knows about that family history and further investigation can identify the couple to be at high risk.

In cases where paternity is uncertain, there is a risk that testing of the incorrect male may provide an erroneous result. Misidentification of the reproductive partner could also lead to false positives or false negatives; receiving a sample from the wrong individual is a potential source of error for all laboratory assays.

As for sample contamination, the applicant noted that, in their experience with >20,000 genetic tests performed using DNA collected at home using swabs, it was a very rare occurrence. The instructions provided with the swabs have undergone a process of development and refinement so that they are clear and easy to follow, with a low failure rate (<1%). Admixture of samples from two individuals is very rare and is easy to detect in massively parallel sequencing data – even low levels of contamination result in samples failing quality control metrics. Where the quantity or quality of extracted DNA does not meet requirements, recollection is required. Depending on the circumstances (particularly whether there is already an ongoing pregnancy, and taking gestational age into account if so) consideration is given to arranging for collection of a sample of peripheral blood as an alternative.

### Outcomes

The following outcomes were suggested for evaluating clinical effectiveness and safety of expanded reproductive carrier testing:

Outcomes that relate to the direct safety of the health technology or comparator:

* Psychological harms from positive test results
* Harms from test outcomes that subsequently prove to be false (false negative or false positive)

Clinical utility:

* Affected births/affected births averted
* Uptake of actions based on informed reproductive decision (e.g. donor gametes, pre-implantation genetic diagnosis, termination, adoption)

Test accuracy outcomes:

* Diagnostic accuracy
* Diagnostic yield among the test population for determining carrier status (number of high-risk results/number of couples tested)
* The proportion of pregnancies in high-risk couples that underwent chorionic villus sampling/amniocentesis and tested positive to the identified high-risk pathogenic/likely pathogenic variant

Cost-effectiveness & financial impact:

* Cost per couple identified as high-risk (before offset costs)
* Cost per couple identified as high-risk (after estimated offset costs)
* Cost of informed reproductive decisionmaking in couples who are both identified as carriers for a condition (comparison of existing management and proposed management)
* Number & cost of couples who will undergo re-testing

Total Australian Government health care costs:

* The total number and costs of terminations following high-risk results

Healthcare resource use:

* Total number of couple tests and cost of the couple testing program
* Number and cost of additional health practitioner consultations (e.g., pre-test and post-test counselling, genetic counselling)
* Number and cost of preimplantation genetic diagnoses and in-vitro fertilisation cycles for each subsequent pregnancy (in preconception testing and subsequent pregnancies of a high-risk couple)
* Number and cost of prenatal fetal testing (i.e., chorionic villus sampling or amniocentesis and confirmatory diagnostic genotyping following a high-risk carrier test result)

*PASC noted the outcomes listed in the draft PICO, and comments received by the applicant.*

*The applicant suggested adding two clinical utility outcomes: affected births/affected births averted, and actions based on informed reproductive decisions, such as donor gametes, pre-implantation genetic diagnosis, termination or adoption.*

*Additionally, the applicant suggested replacing the outcome “diagnostic yield of the fetal test population (confirmed diagnoses/number of tests performed), with population weighting reflecting the proportion of autosomal recessive and X-linked conditions tested for”, with “the proportion of pregnancies in high-risk couples that underwent chorionic villus sampling/amniocentesis and tested positive for the identified high-risk pathogenic/likely pathogenic variant”.*

*PASC discussed the difficulties of calculating the costs of affected births averted, noting uncertainties in the population estimates as well as cost estimates. Notwithstanding these difficulties, the cost-effectiveness of carrier testing will need to include cost offsets in order to establish the estimated net financial impact of testing. PASC considered that the cost of informed reproductive decisionmaking is an important outcome to report as this metric has previously been accepted by MSAC, but that the economic and financial analyses needed to extend beyond this to incorporate cost-offsets.*

## Assessment framework

The assessment framework is depicted in Figure 1.

**Figure 1 Assessment framework**

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: adverse events due to testing; 7: adverse events due to treatment

ERCT=expanded reproductive carrier testing; PGT=pre-implantation genetic testing; QALY=quality-adjusted life-years

*PASC confirmed that the assessment framework proposed in the draft PICO is appropriate.*

## Clinical management algorithms

The clinical management algorithm for the comparator is depicted in Figure 2 and Figure 3. It follows a female-first approach, where male partner is only tested if the female is found to be a carrier of cystic fibrosis or spinal muscular atrophy (Medical Services Advisory Committee, 2020b).



**Figure 2 Current management preconception care**

Figure notes: CF=cystic fibrosis; CVS=chorionic villus sampling; FN=false negative; FXS=fragile X syndrome; GP=general practitioner; IVF=*in vitro* fertilisation; PGT=preimplantation genetic testing; SMA=spinal muscular atrophy

**Figure 3 Current management preconception care**

Figure notes: CF=cystic fibrosis; CVS=chorionic villus sampling; FN=false negative; FXS=fragile X syndrome; GP=general practitioner; IVF=*in vitro* fertilisation; PGT=preimplantation genetic testing; SMA=spinal muscular atrophy

The proposed clinical management algorithm is depicted in Figure 4 and Figure 5. The participants are tested simultaneously as a couple, and test report is issued for the tested couple, not for individual participants.

**Figure 4 Current clinical management early pregnancy care**

Figure notes: CF=cystic fibrosis; CVS=chorionic villus sampling; GP=general practitioner; FN=false negative; FXS=fragile X syndrome; SMA=spinal muscular atrophy



Figure 5 Proposed management early pregnancy care

Figure notes: CVS=chorionic villus sampling; ERCT=expanded reproductive carrier testing

Amniocentesis/CVS for collection of fetal cells for further prenatal diagnostic genetic testing

*PASC advised that the clinical management algorithms may include pre-test counselling by a medical practitioner, as well as the option of re-analysis of previous data in the proposed clinical management.*

## Proposed economic evaluation

Based on the clinical claim of superiority in clinical effectiveness, a cost-effectiveness or cost-utility analysis would be appropriate (Table 2). Considering that MSAC found the comparator (reproductive carrier testing for cystic fibrosis, spinal muscular atrophy, and fragile X syndrome) to be cost-effective (Medical Services Advisory Committee, 2020a), the economic evaluation should capture the incremental value of testing for all additional conditions not already covered by the comparator.

Table 4 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

| Comparative safety- |  | Comparative effectiveness |  |  |
| --- | --- | --- | --- | --- |
| Inferior | Uncertaina | Noninferiorb | Superior |
| Inferior | Health forgone: need other supportive factors | Health forgone possible: need other supportive factors | Health forgone: need other supportive factors | ? Likely CUA |
| Uncertaina | Health forgone possible: need other supportive factors | ? | ? | ? Likely CEA/CUA |
| Noninferiorb | Health forgone: need other supportive factors | ? | CMA | CEA/CUA |
| Superior | ? Likely CUA | ? Likely CEA/CUA | CEA/CUA | CEA/CUA |

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis

? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis

a ‘Uncertainty’ covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations

b An adequate assessment of ‘noninferiority’ is the preferred basis for demonstrating equivalence

*PASC confirmed that a cost-effectiveness or cost-utility analysis is most appropriate.*

*PASC considered that the cost-effectiveness of testing would be influenced by the size and diagnostic yield of the minimum panel size chosen (and fee for conducting the test if this varies with panel size), and requested that the analyses examine a range of minimum gene list sizes.*

## Proposal for public funding

The applicant is proposing expanded reproductive carrier testing to be publicly funded through the MBS. In the application form the applicant proposed two MBS item descriptors, for couples where neither partner has previously been tested, and where one/both partners have previously been tested.

| Category 6 (Pathology Services) – Group P7 Genetics |
| --- |
| Non-invasive expanded carrier screening testing of an asymptomatic couple (or genetic contributors to a pregnancy), either pre-pregnancy or prenatal, to determine their autosomal recessive and X-linked recessive single gene carrier status for conditions identified by the Australian Reproductive Genetic Carrier Screening Project. |
| Fee: $TBC |

| Category 6 (Pathology Services) – Group P7 Genetics |
| --- |
| Non-invasive expanded carrier screening testing of an asymptomatic couple (or genetic contributors to a pregnancy), either pre-pregnancy or prenatal, to determine their autosomal recessive and X-linked recessive single gene carrier status of conditions identified by the Australian Reproductive Genetic Carrier Screening Project, where one or both genetic contributors have previously been tested. |
| Fee: $TBC |

Following advice at the pre-PASC meeting from the applicant and the Department, the Assessment Group proposed a revised set of five MBS item descriptors for PASC’s consideration: two for testing couples, where neither partner has previously been tested and where one/both partners have previously been tested, one for repeat analysis at a minimum interval of 5 years, and one for prenatal fetal diagnostic testing.

The applicant estimated the couples-test would cost approximately $2,100 per couple, and the test where one or both genetic contributors have previously been tested to cost approximately $720. The true cost of the procedure remains to be ascertained during a time and motion study, which forms part of a pivotal study (Clinicaltrials.gov trial number NCT04157595), and will be presented in the applicant-developed assessment report (ADAR).

*PASC noted the proposed MBS item descriptors. PASC requested the MBS item descriptors be reviewed, in line with the following concerns:*

* *MBS items should be provided per individual and not per couple, as each member of the couple is a Medicare beneficiary.*
* *PASC requested a detailed justification of the fees be provided. PASC noted that the ongoing research includes a time and motion study into the costs of the procedure, and requested the results be included in the assessment report. PASC advised the proposed fee for fetal testing should include the cost of maternal cell contamination.*
* *PASC noted that item 73358 involving whole exome sequencing (WES) or whole genome sequencing (WGS) has a fee of $2,100, and that if the fee for couple WES were $2,100 then this equates to $1,050 per exome. PASC noted the fee may differ in the assessment report based on the results from the time-and-motion study. PASC advised that should this be the case, the assessment should explore sensitivity to the fee in a sensitivity analysis. PASC also queried whether the need for additional methods to assess some genes may involve additional costs.*

The committee may wish to consider the appropriate requestor/s for the proposed tests.

*PASC noted inconsistencies between the proposed MBS items in terms of requestor. PASC requested the requesting provider(s) be specified in all proposed items. At the post-PASC meeting, it was noted that for application 1573 the proposed requestor group was ‘medical practitioners’. Should the requestors for application 1637 be expanded beyond medical practitioners, a justification would need to be provided for each additional requestor type proposed.*

| Category 6 (Pathology Services) – Group P7 Genetics |
| --- |
| MBS item AAAAPrenatal or preconception carrier testing of a reproductive couple where neither genetic contributor has previously received a service to which AAAA or BBBB applies, using characterisation via genomic sequencing and analysis, of germline variants known to cause autosomal recessive and X-linked disorders, reporting the couple’s joint risk.Applicable for any reproductive couple pairing only once per lifetime. |
| Fee: $2,100.00 Benefit: 75% = $1,575.00 85% = $2,015.30 |

Associated note: “Genomic sequencing and analysis” = exome, genome, or panel sequencing of genes such as identified by the Australian Reproductive Genetic Carrier Screening Project."

Wording and fee based on item 73358.

*PASC advised a minimum list of genes would need to be nominated, but that they did not need to be listed within the item descriptor – a reference to a published list would be acceptable.*

*PASC agreed re-test item DDDD could be merged into AAAA with some rewording of AAAA.*

| Category 6 (Pathology Services) – Group P7 Genetics |
| --- |
| MBS item BBBBPrenatal or preconception carrier testing of a reproductive couple where one or both genetic contributors have previously received a service to which AAAA or BBBB applies and re-use of the data is possible, using characterisation via genomic sequencing and analysis for any genetic contributor who has not previously received a service to which AAAA or BBBB applies, of germline variants known to cause autosomal recessive and X-linked disorders, reporting the couple’s joint risk.Applicable for any reproductive couple pairing only once per lifetime. |
| Fee: $720.00 Benefit: 75% = $540.00 85% = $635.30 |

Associated note: “Genomic sequencing and analysis” = exome, genome, or panel sequencing of genes such as identified by the Australian Reproductive Genetic Carrier Screening Project."

Fee as proposed by the applicant.

| Category 6 (Pathology Services) – Group P7 Genetics |
| --- |
| MBS item CCCCRe-analysis of genomic data obtained in performing a service to which AAAA or BBBB applies, for characterisation of previously unreported germline gene variants known to cause autosomal recessive and X-linked disorders and reporting the couple’s joint risk, if:1. the re-analysis is performed at least 18 months after:
2. a service to which item AAAA or BBBB applies; or
3. a service to which this item applies; and
4. the re-analysis is requested by a specialist, consultant physician or general practitioner who manages the treatment of the patient.

Applicable for any reproductive couple pairing only twice per lifetime. |
| Fee: $589.90 Benefit: 75% = $442.45 85% = $506.50 |

Associated note: “Genomic sequencing and analysis” = exome, genome, or panel sequencing of genes such as identified by the Australian Reproductive Genetic Carrier Screening Project."

Wording and fee based on item 73292 and across other items, e.g., 73346.

*PASC noted concerns about the practicality of accessing archived data (items BBBB and CCCC) for re-use or re-analysis, resulting in possible privacy issues and data compatibility issues.*

*PASC noted the wording and fee for the re-analysis item were based on item 73292 involving genome-wide microarraying. PASC suggested alignment to item 73360 (re-analysis of WES/WGS data)would be more appropriate.*

*PASC noted the inconsistency between items CCCC (re-analysis) and DDDD (re-testing) in frequency restrictions (18 months versus 5 years respectively), and variation in utility restrictions (items AAAA, BBBB once per lifetime, item CCCC twice per lifetime, item DDDD no utility restrictions). PASC considered that it would be rare for the same couple to require re-analysis during their reproductive lifetime, but that any restrictions should be consistent. PASC advised the frequency of testing for item AAAA should be amended to ‘once during the reproductive lifetime of the couple’ (or similar) to be consistent with the application, though commented that if the applicant proposed to instead use ‘once per five years’ that this would need to be justified in the assessment report.*

*At the post-PASC meeting, the applicant stated that given the anticipated interval between pregnancies for most couples who remain together, the re-analysis item CCCC was considered redundant as the incremental change in composition of the gene panel is likely to be insignificant.*

| Category 6 (Pathology Services) – Group P7 Genetics |
| --- |
| MBS item DDDDPrenatal or preconception carrier testing of a reproductive couple using characterisation, via genomic sequencing and analysis, of germline variants known to cause autosomal recessive and X-linked disorders and reporting the couple’s joint risk, if:1. this service is performed at least 5 years after a service to which AAAA or BBBB or CCCC applies; and
2. re-analysis of genomic data is not possible/applicable; and
3. the re-testing is requested by a specialist, consultant physician or general practitioner who manages the treatment of the patient.
 |
| Fee: $2,100.00 Benefit: 75% = $1,575.00 85% = $2,015.30 |

Associated note: “Genomic sequencing and analysis” = exome, genome, or panel sequencing of genes such as identified by the Australian Reproductive Genetic Carrier Screening Project."

Wording and fee based on item 73358 may be needed where panels are being conducted. This item could be merged into AAAA if AAAA’s wording included “or the same reproductive couple’s most recent service to which AAAA or BBBB or CCCC applies was performed at least 5 years earlier”.

*PASC agreed re-test item DDDD could be merged into AAAA with some rewording of AAAA.*

| Category 6 (Pathology Services) – Group P7 Genetics |
| --- |
| MBS item EEEETesting of a sample from amniocentesis or chorionic villus sampling, including targeted assessment of specific regions for constitutional genetic abnormalities in diagnostic studies of a fetus where both prospective parents have been identified as carriers for the same autosomal recessive disorder, or the woman is a carrier of an X-linked disorder, as part of services to which AAAA or BBBB or CCCC or DDDD applies.1 test per affected fetus |
| Fee: $1,800.00 Benefit: 75% = $1,350.00 85% = $1,715.30 |

Wording and fee based on item 73292 and MSAC Application 1573.

*PASC advised the proposed fee for fetal testing should include the cost of maternal cell contamination. PASC noted the wording for the fetal testing item was based on item 73292 involving genome-wide microarraying. PASC suggested alignment to an item for prenatal diagnosis (e.g., 73350) would be more appropriate.*

*At the post-PASC meeting, the applicant confirmed that where a couple is identified at high-risk, there is a need for a cascade test item for existing children who may be presymptomatic for that condition. An item descriptor should be proposed for such testing.*

*PASC advised that where the parental variant was in the CFTR gene, fetal cascade testing is already available under MBS item 73350. A restriction has been added to reflect that prenatal testing for CFTR should use MBS item 73350 rather than this item.*

### Post-PASC item descriptors

*After consideration by PASC and the post-PASC meeting, the following set of four revised item descriptors are proposed to be used in the applicant-developed assessment report (ADAR):*

* *AAAA revised to specify ‘reproductive lifetime’, incorporate DDDD, be per person rather than per couple, and use the applicant’s proposed fee per couple (halved per individual).*
* *BBBB revised to specify ‘reproductive lifetime’*
* *CCCC removed*
* *DDDD removed (because it is merged into AAAA)*
* *EEEE reworded to be based on 73350*
* *FFFF new item for cascade testing of existing children of high-risk couples*

| Category 6 (Pathology Services) – Group P7 Genetics |
| --- |
| MBS item AAAAPrenatal or preconception carrier testing of a reproductive couple where neither genetic contributor has previously received a service to which AAAA or BBBB applies, using characterisation via genomic sequencing and analysis, of germline variants known to cause autosomal recessive and X-linked disorders, reporting the couple’s joint risk.Applicable for an individual, only when used in conjunction with the same item performed in a reproductive partner.Available to any reproductive couple pairing only once per reproductive lifetime. |
| Fee: $1,050.00 Benefit: 75% = $787.50 85% = $962.10 |

| Category 6 (Pathology Services) – Group P7 Genetics |
| --- |
| MBS item BBBBPrenatal or preconception carrier testing of a reproductive couple where one or both genetic contributors have previously received a service to which AAAA or BBBB applies and re-use of the data is possible, using characterisation via genomic sequencing and analysis for any genetic contributor who has not previously received a service to which AAAA or BBBB applies, of germline variants known to cause autosomal recessive and X-linked disorders, reporting the couple’s joint risk.Applicable for any reproductive couple pairing only once per lifetime. |
| Fee: $720.00 Benefit: 75% = $540.00 85% = $632.10 |

| Category 6 (Pathology Services) – Group P7 Genetics |
| --- |
| MBS item EEEETesting of a pregnant patient, where both prospective parents are known to be genetic carriers of variants for the same autosomal recessive disorder, or the woman is a carrier of an X-linked disorder, as part of services to which AAAA or BBBB apply (with the exception of the *CFTR* gene), for the purpose of determining whether pathogenic or likely pathogenic variants are present in the fetus, when requested by a specialist or consultant physician who manages the treatment of the patient.The fetus must be at 25% or more risk of a disorder, or the maternal donor has greater than or equal to 55 CGG repeats in *FMR1*.1 test per fetus |
| Fee: $1,600.00 Benefit: 75% = $1,200.00 85% = $1,512.10 |

*PASC noted the applicant’s advice that the 25% risk threshold in item EEEE will lead to the exclusion of FMR1 where the mother carries less than a threshold number of CGG repeats. PASC considered that Fragile-X Syndrome (FXS) should not be excluded from fetal testing, and agreed to revise this to “The fetus must be at 25% or more risk of a disorder, or the maternal donor has greater than or equal to 55 CGG repeats in FMR1” (as incorporated above).*

| Category 6 (Pathology Services) – Group P7 Genetics |
| --- |
| MBS item FFFFTesting of an individual for an autosomal recessive or X-linked disorder, where:* 1. the biological parents are known (as part of services to which AAAA or BBBB apply) to be:
		1. both genetic carriers of variants for the same autosomal recessive disorder; or
		2. one parent is a carrier of an X-linked disorder; and
	2. the individual is of an age that is expected to be pre-symptomatic for the autosomal recessive or X-linked disorder

for the purpose of determining whether familial pathogenic or likely pathogenic variants in the relevant gene are present in the individual, when requested by a specialist or consultant physician who manages the treatment of the individual.1 test per gene per lifetime |
| Fee: $500.00 Benefit: 75% = $375 85% = $425 |

*PASC noted that MSAC had recently for application 1585 supported fetal testing items at fees of $1600 (for known, familial variant, i.e. fetal cascade testing) and $1800 (where the fetal variant is unknown). The PASC secretariat requested the applicant advise whether or not parental variant data would be accessible for cascade testing under the unique couple analysis method to be used in this testing. In its email of 12 November 2021, the applicant advised that: “In the MM couple-based carrier screening we only report the variants seen in autosomal genes that the two members of the reproductive couple have in common (eg both are carriers of CF or SMA). We will report the variants for genes that they have in common. It is important to note that laboratories will report the specific variants for couples found to be at increased risk (for both partners if autosomal recessive, for the female if X-linked). This means that the information will be available to inform any subsequent testing.” The applicant also further confirmed regarding the existing sibling testing item, that “The $500 per variant would be appropriate for single variant testing.”*

*Please note that the Department has also updated the 85% benefits in this set of post-PASC item descriptors to reflect the 1 November 2021 update to the Greatest Permissible Gap.*

## Summary of public consultation input

The Department received responses to the consultation survey from three patient/consumer support groups: PKD Australia, an organisation established to find a cure for polycystic kidney disease; Fragile X Association of Australia, and the GUARD Collaborative Australia, consisting of SWAN Australia, Genetic Alliance Australia, and Genetic Support Network of Victoria. All three groups supported the application. None of the three groups identified any concerns, and they all emphasised the need for appropriate informed consent and counselling.

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

*PASC noted that support was received from PKD Australia (patient/consumer support group), from a clinician/research scientist on behalf of Fragile X Association of Australia, and from the GUARD Collaborative Australia (consumer advocate and patient support leader). PASC also noted some implementation issues raised by the National Pathology Accredication Advisory Council (NPAAC).*

## Next steps

*PASC advised that the application required substantial editing. The applicant may resubmit the application to PASC out of session.*

*PASC noted the applicant has elected to progress its application as an ADAR (Applicant Developed Assessment Report).*

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