



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1216.1 – Cystic Fibrosis Transmembrane Regulator (CFTR) testing

Applicant: The Royal College of Pathologists of Australia

Date of MSAC consideration: MSAC 69th Meeting, 6-7 April 2017

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

1. Purpose of application

A resubmission requesting Medicare Benefits Schedule (MBS) listing of the testing for hereditary mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene was received from the Royal College of Pathologists of Australasia (RCPA) by the Department of Health (the Department).

The resubmission requested the creation of six new items on the MBS for identifying the presence of the CFTR gene in three key patient groups:

- prenatal cystic fibrosis;
- people suspected to have cystic fibrosis (CF) or CFTR-related disorders; and
- partners and family members of people with at least one known CFTR mutation, tested for the purpose of reproductive planning.

2. MSAC's advice to the Minister

After considering the evidence presented in relation to safety, clinical effectiveness and cost-effectiveness, MSAC supported public funding of diagnostic testing for hereditary mutations in the CFTR gene. MSAC accepted that, pending some refinements to the proposal, the proposed service is safe, leads to improvements in overall health outcomes, and is acceptably cost-effective.

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

An application requesting MBS listing of diagnostic testing for hereditary mutations in the CFTR gene was considered by MSAC in July 2015. MSAC deferred the application to seek better definitions and prevalence estimates of the intended populations in addition to a re-evaluation of the clinical and cost-effectiveness in the intended populations to be tested (see MSAC [Public Summary Document Application 1216](#), July 2015).

Overall MSAC considered that the issues identified were addressed appropriately in the resubmission. MSAC noted the proposed service applies to three key population groups:

- prenatal CF diagnosis;
- people suspected to have CF or CFTR-related disorders; and
- partners and family members of people with at least one known CFTR mutation for the purpose of reproductive planning (cascade testing).

MSAC noted that six MBS items were proposed, one for each specific population:

1. Diagnosis of a (new) case of CF, including:
 - i. Patients with classic CF symptoms
 - ii. Patients with non-classic CF symptoms
 - iii. Men with congenital bilateral absence of the vas deferens
2. In a fetus with ultrasonic evidence of echogenic gut, where CFTR variants have not been identified in the parents
3. Parents of a fetus with ultrasonic evidence of echogenic gut
4. Cascade testing of family members, following diagnosis of a case of CF or a CFTR carrier
5. Partner of a CF patient or CFTR carrier to assess risk to potential offspring
6. Prenatal testing of a fetus, where the parents are known to have one or more pathogenic CFTR variants. This would include fetuses with echogenic gut, where at least one mutation is identified in a parent.

MSAC recalled that the clinical evidence for prenatal CF testing and testing of people suspected to have CF or CFTR-related disorders was considered at its July 2015 meeting. MSAC noted that it had previously accepted the relative safety and effectiveness of CFTR testing in these groups.

MSAC noted that the resubmission included CFTR cascade testing for the purpose of reproductive planning as an additional population. MSAC noted that additional information presented in the resubmission in relation to safety issues in the CFTR cascade testing population focused on psychological and social impacts on carriers and their families. Overall, although no comparative evidence was available, MSAC considered that the presented evidence was relatively consistent and indicated that a positive cascade carrier test result is a shock for most people, particularly if a decision regarding termination of pregnancy needed to be made quickly. However, within a short period of time, these individuals' anxiety levels soon approximate those of people who are determined to be non-carriers.

MSAC noted that no direct evidence was available to assess diagnostic accuracy in the cascade carrier population and the linked evidence approach used did not provide any additional evidence to support diagnostic performance (analytical accuracy or clinical validity). Although there was heterogeneity in the direct evidence available in regards to clinical decision-making, MSAC acknowledged that overall, carrier testing is likely to have some impact on future reproductive choices and is likely to result in fewer CF-affected children being born. MSAC also noted that pre-implantation genetic diagnosis is likely to lead to more unaffected live births.

MSAC noted that cost-effectiveness was assessed using separate models for each of the six populations, as well as an aggregated model for proposed listings 1, 4, 5 and 6. MSAC noted that the model for the cascade testing populations resulted in an incremental cost-effectiveness ratio (ICER) of \$514 per additional mutation status known and \$1,253 per additional familial carrier identified. MSAC noted that these estimates were sensitive to the carrier rate, with a higher carrier rate reducing the ICER. MSAC noted the complexity of the aggregated model, which estimated an ICER of \$194,941 per CF birth averted. MSAC noted that the combined use of proposed listings 2 and 3 resulted in an ICER of \$85,323 per CF

birth averted. Overall MSAC considered that CFTR testing appears to be cost-effective or cost-saving when the costs of CF management are considered.

MSAC noted the combined epidemiological and market approach used to estimate the utilisation of each of the six proposed items. MSAC noted that based on these estimates, the predicted MBS expenditure for these items is approximately \$1.3 million per year. MSAC advised that the utilisation estimates were uncertain and noted that data from the 2011 RCPA survey suggests that actual usage and expenditure would be approximately twice these estimates. MSAC were concerned about the potential for use beyond the intended populations in the proposed listings and that there is no limit to repeat testing.

MSAC noted that CFTR testing as in the proposed listing is usually funded by the States and Territories as well as private expenditure. MSAC considered that listing of this service on the MBS would involve cost-shifting from these existing funding sources but that it would address existing concerns of access and equity.

MSAC recommended several amendments to the proposed MBS item descriptors to provide greater clarity. MSAC suggested that in order to comply with the legislation governing the MBS, items 2 and 6 need to specify that testing is in a pregnant woman to identify CFTR gene variants in the fetus (rather than testing of the fetus). MSAC proposed amendments to item 4 to clarify that the item is intended for testing in an individual where the CFTR gene variant is already known. MSAC also proposed changes to the wording of item 5 to clarify that it is intended for testing of the partner of an individual known to be a carrier of a pathogenic CFTR gene variant (as identified in the applicant's pre-MSAC response).

MSAC advised that the overall frequency of CFTR gene mutations is likely to decrease as a result of the proposed MBS items, which will affect the cost-effectiveness of cascade testing. MSAC questioned whether cost-effectiveness in the cascade population may need to be reassessed in the future in light of these changes. MSAC also noted that the prevalent mix of CFTR mutations in Australia is likely to continue to change with the changing population. As such it is important to ensure that testing continues to target the top 95% of prevalent CFTR mutations.

MSAC supported MBS funding, accepting that, with some refinements to the proposal, testing for hereditary cystic fibrosis mutations is safe, leads to improved health outcomes overall, and is acceptably cost effective.

4. Background

Application 1216 was considered at the July 2015 MSAC meeting. MSAC deferred the application to seek better definitions and prevalence estimates of the intended populations and re-evaluation of the clinical and cost effectiveness in the intended populations to be tested.

5. Prerequisites to implementation of any funding advice

CFTR mutation testing is currently undertaken in all States and Territories, diagnostic laboratories should be National Association of Testing Authorities (NATA) accredited to perform CFTR mutation tests.

6. Proposal for public funding

In the previous consideration, MSAC requested clearer MBS item descriptors for the proposed service including restrictions on eligibility and genetic counselling requirements. Abbreviated item descriptors are shown in Table 1.

Table 1 Proposed MBS item descriptors (abbreviated)

Testing of an individual for pathogenic CFTR variants for the purpose of investigating, making or excluding a diagnosis of cystic fibrosis or a CFTR related disorder. The individual must have clinical or laboratory findings suggestive of cystic fibrosis or a CFTR related disorder. Fee: \$500
Testing of a fetus for pathogenic CFTR variants for the purpose of investigating, making or excluding a diagnosis of cystic fibrosis or a CFTR related disorder. The fetus must have ultrasonic findings of echogenic gut, with unknown family CFTR variants. Fee: \$500
Testing of a prospective parent for pathogenic CFTR variants for the purpose of determining the risk of their fetus having pathogenic CFTR variants. This is indicated when the fetus has ultrasonic evidence of echogenic gut. Fee: \$500
Testing of an individual with a laboratory-established family history of pathogenic CFTR variants, for the purpose of determining whether the individual is an asymptomatic genetic carrier of a CFTR variant. Fee: \$250
Testing of an individual for pathogenic CFTR variants for the purpose of determining the reproductive risk of the individual with their reproductive partner. Either the individual, or their reproductive partner, must be already known to have one or more pathogenic CFTR variants. Fee: \$500
Testing of a fetus for known familial CFTR variants for the purpose of investigating, making or excluding a diagnosis of cystic fibrosis or a CFTR related disorder, in the following situation: Where the fetus is at 25% or more risk of cystic fibrosis. Fee: \$250

CFTR = cystic fibrosis transmembrane conductance regulator

The applicant's pre-MSAC response noted that the descriptors do not refer to test sensitivity which may allow diagnostic laboratories to test for any number of pathogenic variants (from two variants to the whole gene). The application suggested that the testing laboratory use a testing method that can detect at least 95% of pathogenic CFTR variants prevalent in the Australian population.

The applicant's pre-MSAC response also noted that the fifth item in Table 1 seems to allow paying \$500 for testing an individual who is already known to have pathogenic mutation(s). The intent for this item was to be limited to use for the partner of the person with known mutation(s), not the person with known mutation(s) themselves.

7. Summary of Public Consultation Feedback/Consumer Issues

See Public Summary Document for Application 1216 on the MSAC website.

8. Proposed intervention's place in clinical management

The application presented numerous clinical management algorithms for CFTR testing across different populations to help define the place of the intervention in current and proposed clinical management.

9. Comparator

The comparator, no prenatal CFTR mutation testing, is identical to the previous Application 1216. In the economic analysis, ‘current clinical practice’ is the nominated comparator.

10. Comparative safety

All studies were non-comparative and could not address the question of safety and effectiveness of cascade testing compared to no testing.

A small body of evidence investigating the psychological impacts of testing and being a carrier found that a positive test result on cascade carrier testing is a shock for most people. However, with adequate time to process the information prior to reproductive decisions, anxiety levels soon approximate anxiety levels among non-carriers. As testing and knowing carrier status can have psychological effects, it is important to ensure appropriate counselling and supports are in place around a testing program.

Cascade testing is likely to have slightly inferior safety in terms of psychological impact of testing and possible adverse events and consequences from prenatal diagnosis (PND), pre-implantation genetic diagnosis (PGD) and termination of pregnancy (TOP) as a result of being identified as a carrier.

11. Comparative effectiveness

No studies were identified assessing comparative diagnostic performance in the appropriate population.

For therapeutic effectiveness (health benefit from change in management), the largest study ($n = 240$) had consistently better PGD outcomes than the smaller studies, which increased the weighted average. The results showed that a live unaffected birth was the outcome in 36.6% of PGD cycles, and the average number of cycles per couple was between 1 and 2.15. Although no comparative studies were identified, it cannot be assumed that the comparator (no PGD) would be associated with CF births, as couples have other alternatives such as PND, not having children or adopting.

Overall, carrier testing is likely to have an impact on future reproductive choices, and it is likely to result in fewer CF-affected children being born. However, given that the acceptability between reproductive options varies (ie. PGD, termination) it cannot be assumed that every couple will make the same decision when armed with the same information.

Clinical claim

Cascade carrier testing offers relatives of people with at least one known CFTR mutation the opportunity to determine their mutation status and make informed reproductive choices.

12. Economic evaluation

For each of the proposed listings, two economic analyses were presented. The first set of analyses, in the main body of the report, compare the proposed MBS listings to a scenario where no CFTR testing is available, to identify the inherent value of CFTR testing. A second set of analyses compare the proposed MBS-funded listings to current CFTR testing practice in State government funded or private practice.

For the collective use of proposed listings 1, 4, 5 and 6, the ICER was estimated as \$194,941 per CF birth averted. For the concurrent use of the proposed listings 2 and 3, the ICER was estimated as \$85,323 per CF birth averted.

13. Financial/budgetary impacts

The estimated use of CFTR testing and associated MBS expenditure of the proposed MBS listings is shown in Table 2.

Table 2 Projected numbers of CFTR tests associated with each proposed listing, and associated MBS costs

	2017	2018	2019	2020	2021
<u>Listing 1:</u> for diagnosis of index cases	1,105	1,110	1,114	1,119	1,123
MBS costs (85% of fee): \$425/test	\$469,625	\$471,750	\$473,450	\$475,575	\$477,275
<u>Listings 2 and 6:</u> diagnosis of CF in a fetus with FEB or carrier parents	224	225	226	227	228
MBS costs (85% of fee): \$425/test*	\$95,200	\$95,625	\$96,050	\$96,475	\$96,900
<u>Listing 3:</u> tests in parents of a fetus with FEB	442	444	446	447	449
MBS costs (85% of fee): \$425/test	\$187,850	\$188,700	\$189,550	\$189,975	\$190,825
<u>Listing 4:</u> cascade testing of family members of index cases or carriers	1,276	1,282	1,287	1,292	1,297
MBS costs (85% of fee): \$212.50/test	\$271,150	\$272,425	\$273,488	\$274,550	\$275,613
<u>Listing 5:</u> partner testing of index cases or carriers	552	555	557	559	561
MBS costs (85% of fee): \$425/test	\$234,600	\$235,875	\$236,725	\$237,575	\$238,425
Total number of tests	3,599	3,616	3,630	3,644	3,658
Total MBS costs (85% of fees)	\$1,258,425	\$1,264,375	\$1,269,263	\$1,274,150	\$1,279,038

CF = cystic fibrosis, CFTR = cystic fibrosis transmembrane conductance regulator; epi = epidemiological approach, MBS = Medicare Benefits Scheme, FEB = fetal echogenic bowel

These estimates were derived using a combination of epidemiological estimates and data from Western Australia on CFTR tests conducted in 2015, and represent testing specifically associated with the proposed listings. These estimates are significantly lower than the overall CFTR test use that was identified in the RCPA Survey conducted in 2011. If the number of tests estimated to be undertaken is based on the RCPA data (excluding those identified as screening tests, primarily for newborn screening) then usage and expenditure would be approximately twice the estimates above.

14. Key issues from ESC for MSAC

An application requesting MBS listing of diagnostic testing for hereditary mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene was originally considered by MSAC in July 2015. MSAC deferred the application to seek better definitions and prevalence estimates of the intended populations and re-evaluation of the clinical and cost effectiveness in the intended populations to be tested. The table below outlines how the issues raised by MSAC have been addressed in the resubmission.

Issues raised by MSAC	Addressed?	How has it been addressed? (Or why not)
Seek better definitions of intended populations	Yes	MBS item descriptors provided by RCPA, to provide basis for population groups.
Seek better prevalence estimates of the intended populations	Yes	Tables with prevalence of each of the populations were included, where available.
Seek more accurate data relating to the expected number of patients tested for each purpose	Yes	Clinical data were sought for populations 1, 2, 3, 5 and 6 in MSAC Application 1216, these populations were addressed in a fit-for-purpose manner. A full assessment of population 4 was provided.
More accurate data relating to diagnostic yield for each class of test in each intended population	Yes	A rapid review was performed to assess the diagnostic yield of CFTR testing in the different populations.
Cost-effectiveness analysis for each of the intended populations	Yes	Individual models for each population were included, as well as an integrated model.
Clearer MBS item descriptors including restrictions on eligibility and genetic counselling requirements	Yes	Clearer MBS item descriptors were developed in consultation with the RCPA CFTR Working Group.
Consider including cascade testing for reproductive planning	Yes	Safety, effectiveness and cost-effectiveness of this population were assessed.
Consider including routine antenatal screening for reproductive planning purposes	No	The RCPA did not request MBS items for people with less than 6% risk of being a CFTR carrier.
Consider impact of next-generation sequencing	Partially	The RCPA suggested a complete review of NGS, as the implications will be much broader than just CFTR. However, if one mutation, rather than two mutations, is found after a test with 95% sensitivity, the expectation was that NGS may be used to test for very rare mutations. The accuracy of using NGS was also considered.
Consider impact of non-invasive prenatal testing	No	The RCPA suggested that there is unlikely to be any evidence for NIPT in the near future for CF. NIPT emerging technology and costs were estimated to be significantly higher than MBS rebates requested.
Consider impact of preimplantation genetic diagnosis	Yes	The re-assessment included data on the clinical and cost-effectiveness of PGD, in collaboration with assessment 1165.1.

Abbreviations: CFTR = cystic fibrosis transmembrane conductance regulator; RCPA = Royal College of Pathologists of Australasia; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; NGS = next-generation sequencing; NIPT = non-invasive prenatal testing

The proposed service would be used in three key patient populations:

- prenatal CF testing;

- people suspected to have CF or CFTR-related disorders; and
- partners and family members of people with at least one known CFTR mutation, tested for the purpose of reproductive planning.

ESC noted that under the current legislation (Health Insurance Act 1973) the fetus is not a patient but the mother is a patient and fetal testing required collection of a sample from the mother.

ESC noted that six items are proposed, one for each specific population to prevent leakage and/or de facto screening:

1. Diagnosis of (new) case of cystic fibrosis, including:
 - (i) Patients with classic CF symptoms
 - (ii) Patients with non-classic symptoms
 - (iii) Men with congenital bilateral absence of the vas deferens (CBAVD)
2. In a fetus with ultrasonic evidence of echogenic gut, where CFTR variants have not been identified in the parents
3. Parents of a fetus with ultrasonic evidence of echogenic gut
4. Cascade testing of family members, following diagnosis of a case of cystic fibrosis or CFTR carrier
5. Partner of a CFTR patient or carrier to assess risk to potential offspring
6. Prenatal testing of a fetus, where the parents are known to have one or more pathogenic CFTR variants. This would include fetuses with echogenic gut, where at least one mutation is identified in a parent.

ESC noted that cascade testing (item 4) was a new population that had not been included in the previous application. ESC noted that the requested fee is lower in this population. The clinical evidence for all other populations was provided in application 1216.

Ivacaftor is currently listed on the Pharmaceutical Benefits Scheme (PBS) for patients with G551D mutation in the CFTR gene on at least one allele. Testing for this CFTR mutation is not currently reimbursed under the MBS. ESC advised that CFTR testing under item 1 can be used to qualify patients for access to ivacaftor under the PBS.

ESC noted that the item descriptor specifies that the testing laboratory uses a testing method that can detect at least 95% of pathogenic CFTR variants prevalent in the Australian population. ESC noted that is equivalent to a 18 panel test. ESC questioned whether this wording (at least 95% sensitivity) may leave the item open to interpretation by diagnostic laboratories. ESC also noted that there was no limit proposed for repeat testing for false negatives and that the frequency of repeat testing using an expanded panel would be difficult to identify as it would be claimed under the same item numbers.

ESC noted that there is limited evidence on the safety of CFTR cascade testing and none of it is comparative. In considering the safety issues associated with cascade testing, ESC noted the importance of psychological and social impacts on carriers and their families.

ESC noted that insufficient direct evidence is available to assess CFTR carrier testing. The linked evidence approach taken in the assessment found no evidence for diagnostic performance (accuracy or clinical validity) in the appropriate population (cascade carrier testing) so no conclusions could be drawn about diagnostic accuracy. ESC noted the heterogeneity of the identified direct evidence on clinical decision making and that the linked evidence on clinical decision making was in a population who had already been diagnosed as CF carriers. ESC acknowledged that carrier testing is likely to have some impact on future reproductive choices and may result in fewer children with CF being born, but that

uncertainty remains regarding this claim. ESC noted that CFTR testing may not be acceptable to all and not every couple will make the same decision when provided with the same information.

ESC noted that four scenarios are tested in the economic evaluation using different mutation panels and that cost-effectiveness was sensitive to the sensitivity of the mutation panel. ESC noted that the economic evaluation assesses the proposed listings versus a scenario where no CFTR testing is available. However, ESC considered that the incremental outcomes generated from such analyses would not be realised if the service is MBS listed, as CFTR testing already occurs in practice (with mixed availability and funding arrangements). ESC noted that an additional scenario accounting for the cost-shifting from states and private expenditure to the MBS was provided in Appendix I of the assessment report.

Economic models for each of the six populations were provided, as well as an aggregated model combining costs and outcomes across populations 1, 4, 5 and 6. ESC noted that there were advantages to having a combined model for all populations, however, ESC considered that an integrated model showing the step by step incremental benefit of funding for proband/index populations with cascade testing subsequently added would be more informative and would be consistent with the approach preferred in MSAC's Clinical Utility Card. ESC noted the models were variously sensitive to a number of factors including the time horizon, the incidence of CF in the fetal echogenic bowel population, termination of pregnancy rates and carrier rates.

ESC noted that the models were all short term with no cost savings from future costs related to treating children with CF. ESC noted that this was a conservative approach. ESC noted that the economic model does not quantify the costs and outcomes associated with identifying gated mutations and facilitation treatment with ivacaftor.

ESC noted that the aggregated economic model suggested that were CFTR testing listed for populations 1, 4, 5 and 6, the ICER would be approximately \$194,941 per CF birth averted. If CFTR testing were listed for populations 2 and 3, the approximate ICER is \$85,323 per CF birth averted.

If listed, MBS expenditure on CFTR testing is estimated at around \$1.5 million per year. ESC noted that CFTR testing as in the proposed listings is usual practice, currently funded by state governments and private expenditure and most of the downstream benefits are already being realised, therefore the decision to fund testing on the MBS concerns access and equity.

ESC questioned whether the numbers of patients in the budget estimates were reasonable. In particular, ESC noted that the cascade testing population was a relatively small fraction of the overall population, with relatively small budget implications. However, ESC considered that the actual population for cascade testing could be much larger. ESC questioned whether cascade testing should be specifically linked to use for reproductive planning to prevent usage beyond the intent of the listing.

ESC advised that patients would require genetic counselling, which is not currently reimbursed on the MBS. ESC questioned whether this would be funded by the states and territories and noted that the economic evaluation used MBS items 132 and 133 for initial and subsequent visits.

ESC noted that the main issues for consumers are the current inequitable access across states and territories, out of pocket costs for patients, and the psychosocial cost of decision-making for parents. ESC noted that it is unclear how funding for this service is currently managed by the states and considered that this was a policy issue.

15. Other significant factors

Nil.

16. Applicant's comments on MSAC's Public Summary Document

The applicant had no comment.

17. Further information on MSAC

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