* Protocol

MSAC 1216

**Testing for hereditary mutations in the Cystic Fibrosis conductance Transmembrane Regulator (CFTR) gene**

**October 2014**

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## 1. Background

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. The MSAC advises the Australian Minister for Health on the evidence relating to the safety, effectiveness and economic considerations associated with new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

Adelaide Health Technology Assessment (AHTA), as part of its contract to the Medical Services Advisory Committee, will undertake an assessment of the evidence pertaining to diagnostic testing for hereditary mutations in the Cystic Fibrosis conductance Transmembrane Regulator (CFTR) gene.

### Cystic Fibrosis and CFTR testing

Cystic Fibrosis (CF) and other CFTR-related disorders are the most common autosomal recessive disorder in Caucasians, with a frequency of about 1 in 2500 - 2800 live births worldwide and a carrier frequency of 1 in 25 in Australia (Bell et al. 2011; Ratjen & Döring 2003). Progressive respiratory disease is the major cause of morbidity and mortality among young people with CF. In Australia, the mean life expectancy of people with CF increased from 12.2 to 27.9 years for males and from 14.8 to 25.3 years for females, between 1979 and 2005 (Reid et al. 2011).

CF and CFTR related disorders are caused by mutations in a 230 kb gene on chromosome 7, encoding a polypeptide that is 1480 amino acids long, called the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene ([Ratjen & Döring 2003](#_ENREF_15)). Disease expression varies by class of CFTR mutation, along with genetic modifiers and environmental factors ([Moskowitz et al. 2008](#_ENREF_10)). Non-classic CF develops when there is at least one ‘mild’ mutation that results in partial functionality of the CFTR protein. Some of these mutations are linked to diseases of one organ, such as late onset pulmonary disease, congenital bilateral absence of the vas deferens (CBAVD), or idiopathic pancreatitis ([Knowles & Durie 2002](#_ENREF_6)). Worldwide, the most common mutation in the *CFTR* gene is caused by a three base-pair deletion which results in the loss of phenylalanine at position 508 (F508del). It accounts for approximately 70 per cent of CFTR mutations worldwide, but its frequency varies between different ethnic groups.

CF is clinically diagnosed with supporting evidence of a CFTR abnormality, either by sweat chloride measurement or mutations in the *CFTR* gene known to cause CF. An elevated immunoreactive trypsinogen (IRT) level during the newborn screening test can replace clinical features as a diagnostic criterion in newborns. Diagnosis is usually simple, and occurs following newborn screening or clinical presentation with an elevated sweat chloride level. However, in some situations the combined information makes the diagnosis difficult, e.g. mild symptoms and a (borderline) positive sweat test and a new CFTR sequence variation of unknown significance ([Farrell et al. 2008](#_ENREF_3)).

The identification of CFTR mutations in affected individuals can lead to:

1. Additional diagnostic surety for a lifelong, expensive and complex condition.
2. Changed family planning options (e.g. if the parents of the CF patient want more children).
3. More treatment options. Currently most CF treatment is not mutation specific but there are therapies currently available (and more in development) that are tailored to a specific CFTR gene mutation, e.g. Ivacaftor for the G551D mutation ([O'Reilly & Elphick 2013](#_ENREF_14)).

Ruling out CFTR mutations in (unaffected) individuals will not affect the clinical management of these individuals as they are currently not monitored for signs or symptoms.

Diagnostic testing for hereditary mutations in the *CFTR* gene occurs in three distinct groups/clinical indications:

1. In people with a high clinical suspicion of CF;
2. For prenatal CF diagnosis; and
3. In partners of people with known CFTR mutations and for the purpose of reproductive planning.

### 1.2 Purpose of this document

In its draft form, the main objectives of the protocol were to:

1. clarify the standard approach taken by MSAC’s contracted assessors, including defining the relevant clinical questions;
   1. clarifying the role of genetic testing for hereditary mutations in the CFTR gene in current clinical practice;
2. provide an opportunity for discussion of clinical and methodological issues; and
3. clarify timelines associated with this project.

These matters have now been addressed and clarified. This current document encompasses the decisions and feedback that occurred on the protocol subsequent to PASC review and public consultation. This finalised *research* protocol provides a framework to outline the methods that will be used to identify, appraise and synthesise the available evidence on genetic testing for hereditary mutations in the CFTR gene.

Once finalised, the protocol should not be altered as it provides the structure for the entire assessment process.

### 1.3 Objectives of the review

To carry out a structured assessment of genetic testing for hereditary mutations in the CFTR gene based on:

* **clinical effectiveness** 
  + *Direct evidence*: impact on health outcomes - do the people who had the test have better health outcomes?
  + *Linked evidence*:
    - diagnostic accuracy - This involves comparing test results against a reference standard (‘truth’), which may be determined by pathology findings or clinical outcome
    - impact on clinical decision making - measured as the change in treatment decision made by clinicians in response to the information provided by the test
    - effectiveness of treatment – does treatment of those people with a diagnosis change their health outcomes?
* **safety**
* **economic considerations**

## 2. Assessment methodology

### 2.1 Approach to test evaluation

A systematic literature review will be conducted to assess the safety and effectiveness of CFTR mutation testing.

The effectiveness of a diagnostic test depends on whether it improves patient outcomes. This can be assessed by studies, ideally randomised controlled trials, which directly investigate the impact of the test on health outcomes. However, this type of evidence is often lacking.

In these cases, a ‘linked evidence approach’ can be used, where key elements of the diagnostic-to-treatment pathway are linked. These elements include:

* Diagnostic test performance (test accuracy) - sensitivity, specificity and accuracy
* Impact on clinical decision making - does clinical decision–making change as a result of the test?
* Impact of the treatment of diagnosed patients on health outcomes - do patients receiving the test directly benefit from any subsequent change in management?

If there is no direct evidence (e.g. clinical trials) available to assess the impact of CFTR testing on patient outcomes a linked evidence approach will be undertaken. The methods are outlined in the MSAC (2005) *Guidelines for the assessment of diagnostic technologies* and in the decision framework published by Merlin et al. (2013). ([Merlin et al. 2013](#_ENREF_7))

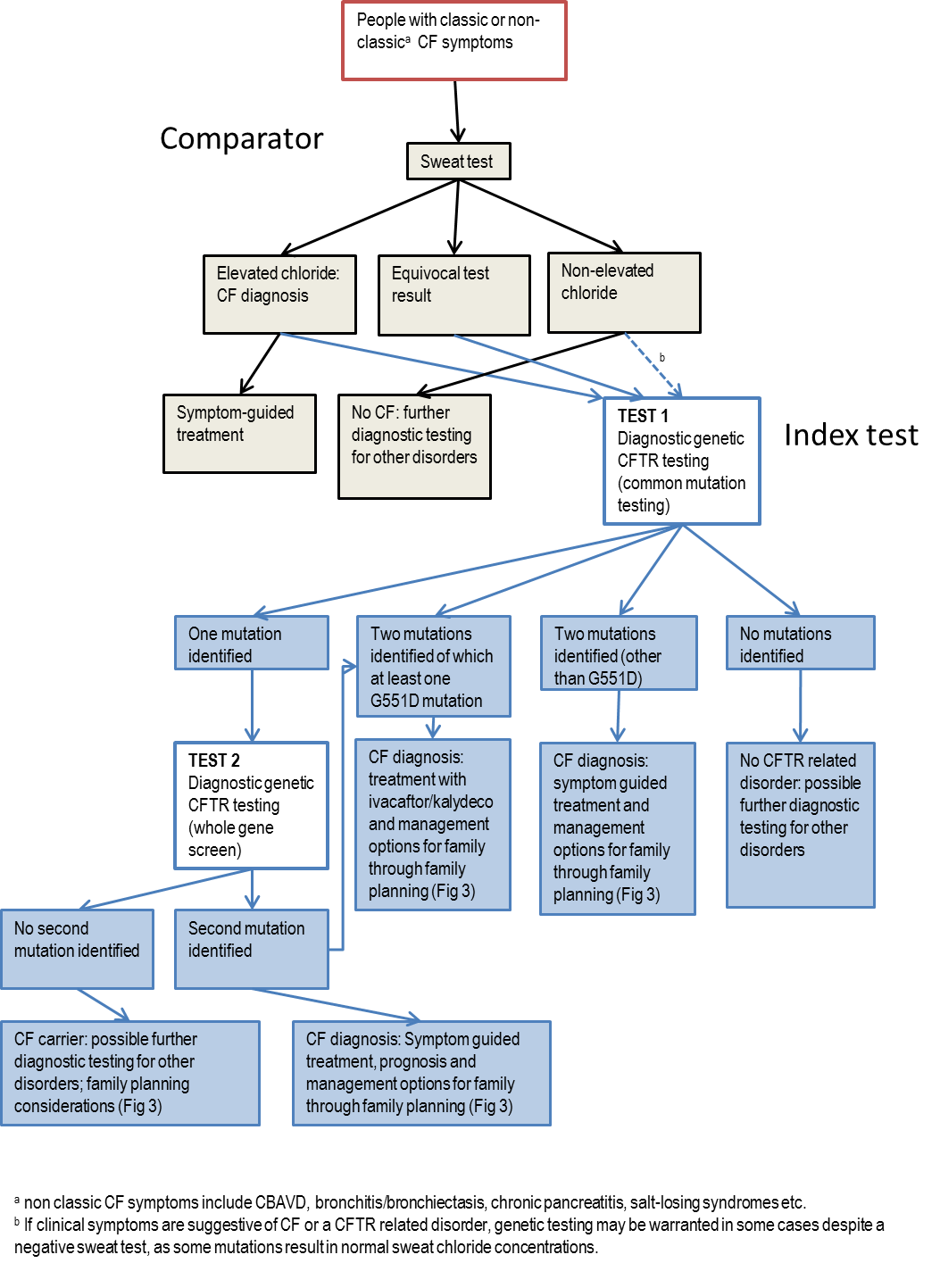
### 2.2 Development of clinical questions

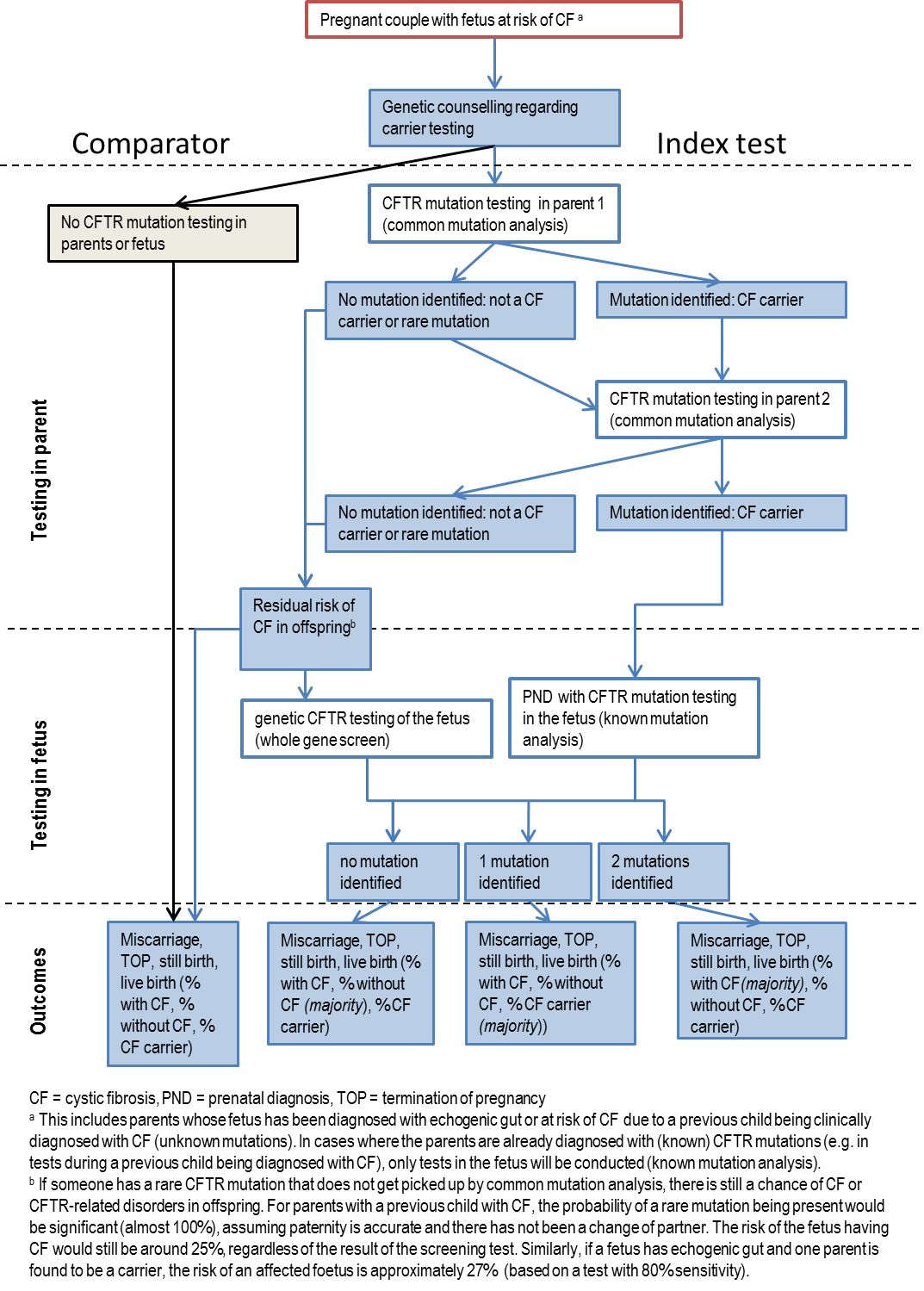
The PICO (Population, Intervention, Comparator, Outcomes) criteria[[1]](#footnote-1) are used to develop well-defined clinical questions for each review. The PICO are also used to define the criteria that will be used to determine what type of scientific literature will be included in the systematic literature review. This involves focusing the question on the following four elements:

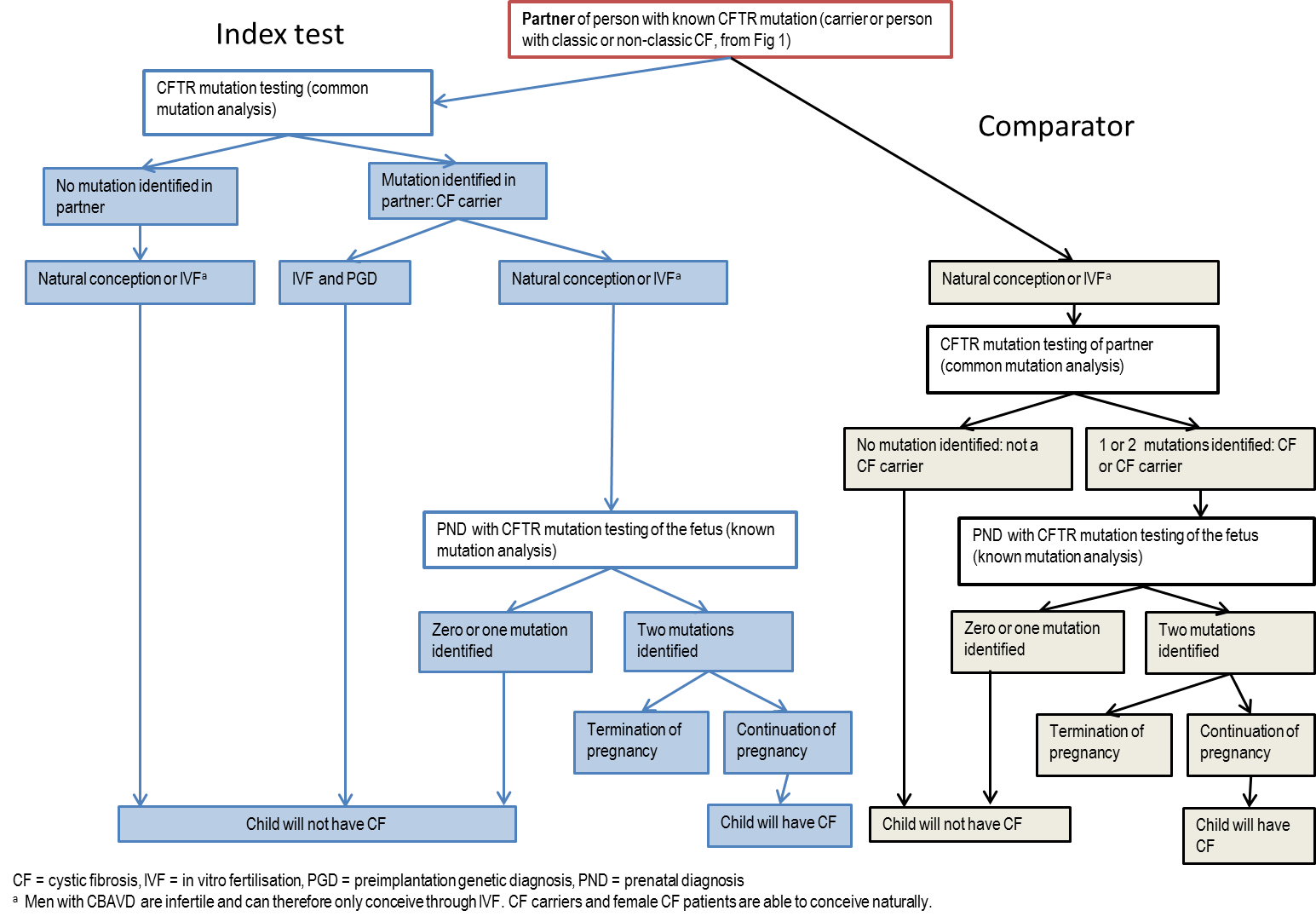
* the target population for the intervention;
* the intervention being considered;
* the comparator or current intervention ie that mostly likely to be replaced or supplemented by the new intervention; and
* the clinical outcomes that are most relevant to assess safety and effectiveness.

Clinical questions are partly defined through the development of flow charts. Flowcharts help define the place of the intervention in clinical management. This includes whether the new intervention will be used incrementally or will replace a current intervention. This assists with identifying the correct comparator for the new intervention. The flowcharts (per group/indication) agreed to by the Protocol Advisory Sub-Committee of the MSAC are shown below in Figures 1, 2 and 3.

Figure 1 Clinical pathway for use of a genetic CFTR test to identify mutations in people with a high clinical suspicion of CF

Figure 2 Clinical pathway for use of a genetic CFTR test in pregnant couples to determine the CF status of the fetus



Figure 3 Clinical pathway for use of a genetic CFTR test to inform reproductive planning, prior to conception (plus PGD or pre-natal CFTR testing) versus pre-natal CFTR testing

Outlined below is the approach formulated according to the information provided in the application from the Royal College of Pathologists of Australasia (RCPA), discussions of the Protocol Advisory Sub-Committee (PASC) of the MSAC, and communication between the contracted assessment group, the MSAC Secretariat, and the relevant policy area from the Department of Health (Table 1).

Table 1 Overview of approach to be taken to assessing the benefit of CFTR testing for the different populations

|  |  |  |  |
| --- | --- | --- | --- |
| **Population requested to be assessed in application** | **Clinical pathway** | **How this has been or will be assessed** | **Summary of approach**  **(PICO box)** |
| 1. Newborns found to have one CFTR mutation on newborn screening and had positive sweat test | - | PASC suggested that all neonates currently identified as having one CFTR mutation from newborn screening, would be further investigated (receive additional genetic tests) within the public health system, funded by the States and Territories. As this testing is already considered standard practice, and parents would currently not be funding the testing themselves, it was considered that this indication would not need to be examined.  A discussion will be provided on CFTR testing within this population, but a systematic review will not performed. | Discussion |
| 2. Patients with symptoms of classic cystic fibrosis | Figure 1 and, if using the information for reproductive planning, Figure 3 | Within this population, information on CFTR mutations may assist: (1) in determining eligibility for ivacaftor, or (2) for reproductive planning.  The health benefit of testing for (1) above has already been examined in the submission to the PBAC for ivacaftor. Therefore, only the accuracy of CFTR testing for this indication will need to be examined in the MSAC assessment.  The benefit of testing this population for reproductive planning will be examined in the contracted assessment of Pre-implantation genetic diagnosis (MSAC 1165). PASC agreed that it need not be re-examined specifically for CFTR. Therefore, only the accuracy of CFTR testing for this indication will be assessed.  The financial implications associated with the genetic testing of patients with symptoms of classic cystic fibrosis will be evaluated. | Accuracy (Table 3)  Financial impact |
| 3. Patients with chronic symptoms of non-classic cystic fibrosis | Figure 1 | As per population 2 above. | Accuracy (Table 3)  Financial impact |
| 4. Men with congenital absence of the vas deferens | Figure 1 and Figure 3 | Considered to have symptoms of non-classic CF. The key benefit of testing within this population would be to inform reproductive planning.  The benefit of testing for this purpose will be examined in the contracted assessment of Pre-implantation genetic diagnosis (MSAC 1165). PASC agreed that this need not be re-examined specifically for CFTR. Therefore, only the accuracy of testing for this indication will be assessed and the financial implications of providing this testing will be estimated. | Accuracy (Table 3)  Financial impact |
| 5. Prenatal diagnosis of couples who have a previous child with CF or CFTR-related disorder, or who are found to be carriers of a CFTR mutation | Figure 2 | This population has not been assessed elsewhere. Therefore, a systematic review will be performed assessing the safety and effectiveness of prenatal testing of couples, and, if they are found to be carriers, genetic testing of the fetus, and possible termination of pregnancy.  A discussion will be provided on the psychological impact of termination of pregnancy, and the psychological impact of caring for a child with CF.  Cost-effectiveness will likely be determined by cost per case avoided, with a discussion on the lifetime cost of treating a person with CF. | Safety, effectiveness and cost-effectiveness (Table 4 and Table 5)  Linked evidence analysis:  Accuracy (Table 6 and Table 7)  Change in management (Table 8 and Table 9)  Impact of change in management (Table 10)  Financial impact |
| 6. Fetuses with an echogenic gut | Figure 2 | As per population 5 above. | As above. |
| **Additional population accepted by PASC** | **Clinical pathway** | **How this has been or will be assessed** | **Summary of approach** |
| 7. Partners of someone who is known to have CF or be a carrier of a CFTR mutation | Figure 3 | The benefit of testing to inform reproductive planning will be examined in the contracted assessment of Pre-implantation genetic diagnosis (MSAC 1165), and PASC agreed it need not be re-examined specifically for CFTR. Therefore, only the accuracy of testing for this indication will be assessed and the financial implications of providing this testing will be estimated. | Accuracy (Table 3)  Financial impact |

**Research questions:**

Diagnostic accuracy only:

1. **What is the diagnostic accuracy of CFTR mutation testing in patients with a high clinical suspicion of CF?**
2. **What is the diagnostic accuracy of CFTR mutation testing in partners of CF carriers?**

Safety and effectiveness:

1. **What is the safety, effectiveness and cost-effectiveness of prenatal CFTR mutation testing of couples carrying a fetus with a high clinical suspicion of CF, in comparison to determining the diagnosis of the child after the birth?**
2. **What is the safety, effectiveness and cost-effectiveness of CFTR mutation testing of a fetus conceived by parents that are both CF carriers, in comparison to determining the diagnosis of the child after the birth?**

Sub-questions (for a linked evidence approach) to questions 3 and 4:

Diagnostic accuracy

* What is the diagnostic accuracyof CFTR mutation testing in parents of a fetus suspected of CF?
* What is the diagnostic accuracy of CFTR mutation testing in fetuses where both parents are CF carriers?

Change in management

* Does prenatal CFTR mutation testing (common mutation analysis) affect the clinical management of a pregnancy where the fetus is suspected of having CF, in comparison to determining the diagnosis of the child after the birth?
* Does CFTR mutation testing of a fetus conceived by parents that are both CF carriers affect the clinical management of the pregnancy, in comparison to determining the diagnosis of the child after the birth?

Effectiveness of change in management

* If there are alterations in the clinical management (e.g. termination of pregnancy) and treatment options available to parents of a fetus suspected of CF, does this have an impact on the health outcomes of the parents?

### 2.3 Literature search

The aim of the initial search is to identify existing health technology assessment (HTA) reports on genetic testing of the CFTR gene. The electronic databases and websites of international HTA agencies that will be searched are found in Appendix A.

#### 2.3.2 Search strategies

Search strategies are generally developed using the key elements of the clinical questions. These are outlined in Section 2.2. Table 2 contains suggestions on search terms for this review.

See Appendix A for the databases and websites that will be searched for appropriate literature.

Table 2 Suggested search terms for CFTR mutation testing

|  |  |
| --- | --- |
| **Element of clinical question** | **Search terms** |
| Population & Intervention | ((CFTR OR cystic fibrosis conductance transmembrane regulator) OR ((cystic fibrosis OR cystic fibrosis [MeSH]) AND (gene OR gene\* OR carrier\* OR prenatal OR antenatal OR fetus\* OR foetus\* OR fetal OR foetal))) AND ((screen\* OR test\* OR diagnos\*) OR ("Cystic Fibrosis Transmembrane Conductance Regulator/diagnostic use"[Mesh] OR "Cystic Fibrosis/prevention and control"[Mesh] OR ("Cystic Fibrosis/diagnosis"[Mesh] AND "Cystic Fibrosis/genetics"[Mesh])))  OR  (“cystic fibrosis”[Text Word] AND ("genetic testing"[MeSH Terms] OR genetic screening[Text Word]) |
| Comparator (if applicable) | - |
| Outcomes (if applicable) | - |
| Limits | Publication date from 01/01/1989 to 10/2014, NOT (Animals NOT (Animals + humans)) |

MeSH = Medical Subject Heading, based on a Medline/PubMed platform

### 2.4 Selection criteria for evidence

In general, studies will be excluded if they:

* Do not address the research question
* Do not provide information on the pre-specified target population
* Do not address one of the pre-specified outcomes and/or provided inadequate data on these outcomes
* Are studies in other languages than English that were of a lower level of evidence (than the studies in English)
* Do not have the appropriate study design

The criteria for selecting the research evidence that will address each of the relevant research questions are outlined in Tables 3 – 10. These criteria are defined *a priori* in order to minimise any bias associated with study selection in the systematic literature review.

Initial eligibility of the research evidence will be undertaken on the basis of the collated study citations and will be *conservatively* determined by one reviewer (ie if unclear from the abstract, or if the reviewer is unsure, the full text paper will be ordered anyway). One reviewer will then assess each of the retrieved full text articles for eligibility, with another assessing those over which there is doubt. In addition, the second reviewer will independently review a random 20% sample of the collated evidence base in order to re-confirm study eligibility. When discordant results are obtained and consensus cannot be reached between the reviewers, a third reviewer will independently assess the paper in question and the majority decision will prevail. A PRISMA flowchart will be used to describe the selection process for all the included studies. A list of studies which meet the inclusion criteria but are subsequently excluded from the review will be appended to the final report.

Table 3 Selection criteria for the diagnostic accuracy of CFTR mutation testing in patients with a high clinical suspicion of CF and partners of CF carriers (Question 1 & 2; diagnostic accuracy only questions)

|  |  |
| --- | --- |
| Population | 1. Patients with classical CF symptoms 2. Patients with non-classic CF symptoms (CBAVD, bronchitis / bronchiectasis, chronic pancreatitis, salt-losing syndromes etc.) 3. Partners of CF carriers |
| Intervention | Diagnostic CFTR mutation testing (common mutation analysis, if necessary followed by whole gene screen) |
| Evidentiary Standard | Whole gene sequencing (in association with copy number analysis to include whole gene deletions or partial gene deletions and duplications) |
| Outcomes | Analytic validity: test-retest reliability, invalid/uninterpretable test results  Clinical validity: sensitivity, specificity, false positive rate, false negative rate, negative predictive value, positive predictive value (by reference to the evidentiary standard) |
| Study design | Level I to level III-3 diagnostic study designs in Table 12 |
| Search period | As the first CFTR mutations were identified around 1989, the search period will be 1/1989 – 10/2014 |
| Language | Studies in languages other than English will only be translated if they represent a higher level of evidence than that available in the English language evidence-base |
| **RQ1. What is the diagnostic accuracy of CFTR mutation testing in patients with a high clinical suspicion of CF?**  **RQ2. What is the diagnostic accuracy of CFTR mutation testing in partners of CF carriers?** | |

Table 4 Selection criteria for evidence assessing the safety and effectiveness of CFTR mutation testing in parents with a fetus suspected of CF

|  |  |
| --- | --- |
| Population | 1. Parent with a fetus showing echogenic gut on second trimester ultrasound 2. Parent with a fetus at risk of CF due to a previous child being clinically diagnosed with CF (unknown mutations) |
| Intervention | CFTR mutation testing (common mutation analysis) in the parents and in some cases PND + CFTR mutation testing (known mutation analysis or whole gene screen) in the fetus |
| Comparators | No prenatal CFTR mutation testing and diagnosis of the child after the birth |
| Outcomes | Miscarriage rate, rate of termination of pregnancy, reason for termination of pregnancy *(if applicable)*, rate of still birth, rate of live birth, % change in patients proceeding to PND  % change in method of CF diagnosis in child/fetus, parental psychological health, parental quality of life |
| Study design | Randomised or non-randomised controlled trials, cohort studies, case series, or systematic reviews of these study designs |
| Search period | As the first CFTR mutations were identified around 1989, the search period will be 1/1989 – 10/2014 |
| Language | Studies in languages other than English will only be translated if they represent a higher level of evidence than that available in the English language evidence-base |
| **RQ3. What is the safety, effectiveness and cost-effectiveness of prenatal CFTR mutation testing of couples carrying a fetus with a high clinical suspicion of CF, in comparison to determining the diagnosis of the child after the birth?** | |

Table 5 Selection criteria for evidence assessing the safety and effectiveness of CFTR mutation testing of a fetus conceived by parents that are both CF carriers.

|  |  |
| --- | --- |
| Population | Fetuses where both parents have been identified as CF carriers (parents identified due to: signs/symptoms of CF in themselves, a previous child with CF, or due to investigations following an echogenic gut in the fetus) |
| Intervention | PND followed by CFTR mutation testing (whole gene screen in fetuses with echogenic gut where common mutations are not identified in parents and known mutation analysis and possible whole gene screen for fetuses whose parents are carriers) with the option of TOP if the fetus is affected |
| Comparators | No prenatal CFTR mutation testing and diagnosis of the child after the birth |
| Outcomesa | Physical harms directly associated with testing procedure  % with CF, % without CF, % CF carrier |
| Study design | Randomised or non-randomised controlled trials, cohort studies, case series or systematic reviews of these study designs |
| Search period | As the first CFTR mutations were identified around 1989, the search period will be 1/1989 – 10/2014 |
| Language | Studies in languages other than English will only be translated if they represent a higher level of evidence than that available in the English language evidence-base |
| **RQ4. What is the safety, effectiveness and cost-effectiveness of CFTR mutation testing of a fetus conceived by parents that are both CF carriers, in comparison to determining the diagnosis of the child after the birth?** | |

a Note: this assessment will not be formally assessing the impact of CFTR testing on the life expectancy, morbidity, quality of life, or functional status of children with CF as the expected disease course is known and the test is unable to affect the course of the disease (except with regard to a parental decision of termination of pregnancy - *addressed in Table 4*).

**Sub-questions (for a linked evidence approach):**

A full linked evidence approach might be necessary to answer research questions 3 and 4**:**

DIAGNOSTIC ACCURACY

Table 6 Selection criteria for the accuracy of CFTR mutation testing in parents with a fetus suspected of CF (research question 3)

|  |  |
| --- | --- |
| Population | 1. Parent with a fetus showing echogenic gut on second trimester ultrasound 2. Parent with a fetus at risk of CF due to a previous child being clinically diagnosed with CF (unknown mutations) |
| Intervention | CFTR mutation testing (common mutation analysis) in the parents and in some cases PND + CFTR mutation testing (known mutation analysis or whole gene screen) in the fetus |
| Evidentiary Standard | Clinical diagnosis (newborn screening + symptoms) after the birth |
| Outcomes | Analytic validity: test-retest reliability, invalid/uninterpretable test results  Clinical validity: sensitivity, specificity, false positive rate, false negative rate, negative predictive value, positive predictive value (by reference to the evidentiary standard) |
| Study design | Level I to level III-3 diagnostic study designs in Table 12 |
| Search period | As the first CFTR mutations were identified around 1989, the search period will be 1/1989 – 10/2014 |
| Language | Studies in languages other than English will only be translated if they represent a higher level of evidence than that available in the English language evidence-base |
| **What is the diagnostic accuracy of CFTR mutation testing in parents of a fetus suspected of CF?** | |

Table 7 Selection criteria for the accuracy of CFTR mutation testing in fetuses were both parents are CF carriers (research question 4)

|  |  |
| --- | --- |
| Population | Fetuses where both parents have been identified as CF carriers (parents identified due to: signs/symptoms of CF in themselves, a previous child with CF, or due to investigations following an echogenic gut in the fetus) |
| Intervention | PND followed by CFTR mutation testing (whole gene screen in fetuses with echogenic gut where common mutations are not identified in parents and known mutation analysis and possible whole gene screen for fetuses whose parents are carriers) with the option of TOP if the fetus is affected |
| Evidentiary Standard | Clinical diagnosis (newborn screening + symptoms) after the birth |
| Outcomes | Analytic validity: test-retest reliability, invalid/uninterpretable test results  Clinical validity: sensitivity, specificity, false positive rate, false negative rate, negative predictive value, positive predictive value (by reference to the evidentiary standard) |
| Study design | Level I to level III-3 diagnostic study designs in Table 12 |
| Search period | As the first CFTR mutations were identified around 1989, the search period will be 1/1989 – 10/2014 |
| Language | Studies in languages other than English will only be translated if they represent a higher level of evidence than that available in the English language evidence-base |
| **What is the diagnostic accuracy of CFTR mutation testing in fetuses where both parents are CF carriers?** | |

CHANGE IN MANAGEMENT

Table 8 Selection criteria to determine the impact of testing on the clinical management of pregnancies where the fetus has suspected CF (research question 3)

|  |  |
| --- | --- |
| Population | 1. Parent with a fetus showing echogenic gut on second trimester ultrasound 2. Parent with a fetus at risk of CF due to a previous child being clinically diagnosed with CF (unknown mutations) |
| Intervention | CFTR mutation testing (common mutation analysis) in the parents and in some cases PND + CFTR mutation testing (known mutation analysis or whole gene screen) in the fetus |
| Comparators | No prenatal CFTR mutation testing and diagnosis of the child after the birth |
| Outcomes | % change in patients proceeding to PND  % change in method of CF diagnosis in child/fetus |
| Study design | Randomised trials, cohort studies, case series or systematic reviews of these study designs |
| Search period | As the first CFTR mutations were identified around 1989, the search period will be 1/1989 – 10/2014 |
| Language | Studies in languages other than English will only be translated if they represent a higher level of evidence than that available in the English language evidence-base |
| **Does prenatal CFTR mutation testing (common mutation analysis) affect the clinical management of a pregnancy where the fetus is suspected of having CF, in comparison to determining the diagnosis of the child after the birth?** | |

Table 9 Selection criteria to determine the impact of testing on the clinical management of pregnancies where both parents are CF carriers (research question 4)

|  |  |
| --- | --- |
| Population | Fetuses where both parents have been identified as CF carriers (parents identified due to: signs/symptoms of CF in themselves, a previous child with CF, or due to investigations following an echogenic gut in the fetus) |
| Intervention | PND followed by CFTR mutation testing (whole gene screen in fetuses with echogenic gut where common mutations are not identified in parents and known mutation analysis and possible whole gene screen for fetuses whose parents are carriers) with the option of TOP if the fetus is affected |
| Comparators | No prenatal CFTR mutation testing (and diagnosis of the child after the birth, *where relevant*) |
| Outcomes | % change in termination of pregnancy rate; live births - % with CF, % without CF, % CF carrier |
| Study design | Randomised trials, cohort studies, case series or systematic reviews of these study designs |
| Search period | As the first CFTR mutations were identified around 1989, the search period will be 1/1989 – 10/2014 |
| Language | Studies in languages other than English will only be translated if they represent a higher level of evidence than that available in the English language evidence-base |
| **Does CFTR mutation testing of a fetus conceived by parents that are both CF carriers affect the clinical management of the pregnancy, in comparison to determining the diagnosis of the child after the birth?** | |

EFFECTIVENESS OF CHANGE IN MANAGEMENT

Table 10 Selection criteria to determine the impact of change in management in parents with a fetus suspected of CF

|  |  |
| --- | --- |
| Population | 1. Parent with a fetus showing echogenic gut on second trimester ultrasound 2. Parent with a fetus at risk of CF due to a previous child being clinically diagnosed with CF (unknown mutations) |
| Intervention | Termination of pregnancy |
| Comparators | No termination of pregnancy: caring for a child with CF |
| Outcomes | Parental psychological health, parental quality of life |
| Study design | Randomised trials, cohort studies, case series or systematic reviews of these study designs |
| Search period | As the first CFTR mutations were identified around 1989, the search period will be 1/1989 – 10/2014 |
| Language | Studies in languages other than English will only be translated if they represent a higher level of evidence than that available in the English language evidence-base |
| **If there are alterations in clinical management (e.g. termination of pregnancy) and treatment options available to parents of a fetus suspected of CF, does this have an impact on the health outcomes of the parents?** | |

### 2.5 Assessment of individual eligible studies

Evidence retrieved from the above searches will be assessed according to the NHMRC Dimensions of Evidence (NHMRC 2000) which are listed in Table 11.

There are three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified for a particular intervention. The last two require expert clinical input as part of their determination. Study quality will be evaluated and reported using an appropriate instrument for quality assessment: studies of clinical validity will be assessed by QUADAS-2 ([Whiting et al. 2011](#_ENREF_20)), case series will be assessed using the IHE checklist ([Moga et al. 2012](#_ENREF_9)) and for randomised and non-randomised controlled trials and observational studies the assessment will be done using the Downs and Black checklist ([Downs & Black 1998](#_ENREF_2)).

Table 11 Dimensions of evidence

|  |  |
| --- | --- |
| Type of evidence | Definition |
| Strength of the evidence  Level  Quality  Statistical precision | The study design used, as an indicator of the degree to which bias has been eliminated by design.\*  The methods used by investigators to minimise bias within a study design.  The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect. |
| Size of effect | The distance of the study estimate from the “null” value and the inclusion of only clinically important effects in the confidence interval. |
| Relevance of evidence | The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used. |

\*See Table 12

Table 12 Designations of levels of evidence according to type of research question ([Merlin, Weston & Tooher 2009](#_ENREF_8))

|  |  |  |
| --- | --- | --- |
| **Level** | **Intervention1** | **Diagnostic accuracy2** |
| I3 | A systematic review of level II studies | A systematic review of level  II studies |
| II | A randomised controlled trial | A study of test accuracy with: an independent, blinded comparison with a valid reference standard,4 among consecutive persons with a defined clinical presentation5 |
| III-1 | A pseudo-randomised controlled trial  (i.e. alternate allocation or some other method) | A study of test accuracy with: an independent, blinded comparison with a valid reference standard,4 among non-consecutive persons with a defined clinical presentation5 |
| III-2 | A comparative study with concurrent controls:  ▪ Non-randomised, experimental trial6  ▪ Cohort study  ▪ Case-control study  ▪ Interrupted time series with a control group | A comparison with reference standard that does not meet the criteria required for  Level II and III-1 evidence |
| III-3 | A comparative study without concurrent controls:  ▪ Historical control study  ▪ Two or more single arm study7  ▪ Interrupted time series without a parallel control group | Diagnostic case-control study5 |
| IV | Case series with either post-test or pre-test/post-test outcomes | Study of diagnostic yield (no reference standard)8 |

Explanatory notes

1 Definitions of these study designs are provided on pages 7-8 How to use the evidence: assessment and application of scientific evidence ([NHMRC 2000](#_ENREF_13)) and in the accompanying Glossary.

2 These levels of evidence apply only to studies of assessing the accuracy of diagnostic or screening tests. To assess the overall effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes ([MSAC 2005](#_ENREF_11); [Sackett & Haynes 2002](#_ENREF_18)). The evidence hierarchy given in the ‘Intervention’ column should be used when assessing the impact of a diagnostic test on health outcomes relative to an existing method of diagnosis/comparator test(s). The evidence hierarchy given in the ‘Screening’ column should be used when assessing the impact of a screening test on health outcomes relative to no screening or alternative screening methods.

3 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

4 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study ([Whiting P 2003](#_ENREF_19)).

5 Well-designed population based case-control studies (eg. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice ([Mulherin & Miller 2002](#_ENREF_12)).

6 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C with statistical adjustment for B).

7 Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

8 Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms (and other outcomes) are rare and cannot feasibly be captured within randomised controlled trials, in which case lower levels of evidence may be the only type of evidence that is practically achievable; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question eg. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Note C: Each individual study that is attributed a “level of evidence” should be rigorously appraised using validated or commonly used checklists or appraisal tools to ensure that factors other than study design have not affected the validity of the results.

### 2.6 Data extraction and synthesis of evidence

Data will be extracted by the evaluators into evidence tables which will be designed specifically for this review.

For each study, these tables will outline the level of evidence, quality assessment, authors, publication year, location, study design, study population characteristics, type of intervention, patient inclusion/exclusion criteria, outcomes assessed and follow-up period.

Descriptive statistics will be extracted or calculated for all safety and effectiveness outcomes in the individual studies – including numerator and denominator information, means and standard deviations, medians and inter-quartile ranges. The power of individual controlled studies to detect a clinically important effect will be calculated, assuming that α = 0.05.

Relative risk/rate ratio (RR), absolute risk differences, number needed to diagnose and associated 95% confidence intervals will be calculated from individual comparative studies containing count data. Mean differences and 95% confidence intervals will be extracted or calculated for normally distributed continuous outcomes in individual studies using the independent t-test. In the analysis of diagnostic accuracy, calculations of sensitivity, specificity, negative and positive predictive values of tests, false positive and false negative rates, as well as 95% confidence intervals, will be undertaken where possible.

Meta-analyses of randomised controlled trials and of diagnostic accuracy studies will be conducted, where appropriate, and tested for heterogeneity and publication bias. Sensitivity analyses (particularly analysing the impact of study quality) and stratification on known confounders will occur where necessary.

Where meta-analysis cannot or should not be conducted, a narrative meta-synthesis of the data will be undertaken.

Meta-analyses and all statistical calculations and testing will be undertaken using the biostatistical computer package, Stata version 12.

### 2.7 Assessment of the body of evidence

In addition to the individual studies, the overall body of evidence will be assessed. For the assessment of test accuracy, an evidence rating from A (excellent) to D (poor) will be assigned to each of the components in the body of evidence matrix provided in Table 13, adapted from the NHMRC FORM grading system ([Hillier et al. 2011](#_ENREF_4)).

Table 13 Body of evidence assessment matrix

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Component** | **A** | **B** | **C** | **D** |
| **Excellent** | **Good** | **Satisfactory** | **Poor** |
| **Evidence base1** | one or more level I studies with a low risk of bias or several level II studies with a low risk of bias | one or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias | one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias | level IV studies, or level I to III studies/SRs with a high risk of bias |
| **Consistency2** | all studies consistent | most studies consistent and inconsistency may be explained | some inconsistency reflecting genuine uncertainty around clinical question | evidence is inconsistent |
| **Generalisability** | population/s studied in body of evidence are the same as the target population for the guideline | population/s studied in the body of evidence are similar to the target population for the guideline | population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population3 | population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population |
| **Applicability** | directly applicable to Australian healthcare context | applicable to Australian healthcare context with few caveats | probably applicable to Australian healthcare context with some caveats | not applicable to Australian healthcare context |

SR = systematic review, several = more than two studies

1 Level of evidence determined from the NHMRC evidence hierarchy – Table 12  
2 If there is only one study, rank this component as ‘not applicable’.

3For example, results in adults that are clinically sensible to apply to children OR psychosocial outcomes for one cancer that may be applicable to patients with another cancer

For the research questions where the health outcomes associated with CFTR mutation testing need to be assessed, a balance sheet of clinical benefits and harms will be constructed based on the GRADE Profile (ACCP) table (Table 14, Table 15). The health outcomes pre-specified as critical for analysis in the benefit:harm balance sheet are:

1. Research Question 3: termination of pregnancy rate, live birth rate, parental quality of life, parental psychological health
2. Research Question 4: physical harms from testing procedure, CF diagnostic status (% with CF, % without CF, % CF carrier)

Table 14 Balance of clinical benefits and harms associated with Research Question 3

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Question 3: What is the safety, effectiveness and cost-effectiveness of prenatal CFTR mutation testing of couples carrying a fetus with a high clinical suspicion of CF, in comparison to determining the diagnosis of the child after the birth?** | | | | | | | | | | | | |
| **Quality assessment** | | | | | | | **Summary of Findings** | | | | | |
| **Participants (studies) Follow up** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Overall quality of evidence** | **Study event rates (%)** | | **Relative effect** (95% CI) | | **Anticipated absolute effects** | |
| **With Control** | **With Intervention** | **Risk with Control** | **Risk difference with Intervention** (95% CI) |
| **<Health outcome>** | | | | | | | | | | | | |
|  |  |  |  |  |  |  |  |  |  | | **Study population** | |
|  |  |
| **Low** | |
|  |  |
| **Moderate** | |
|  |  |
| **<Health outcome>** | | | | | | | | | | | | |
|  |  |  |  |  |  |  |  | |  |  | **Study population** | |
|  |  |
| **Low** | |
|  |  |
| **Moderate** | |
|  |  |

Table 15 Balance of clinical benefits and harms associated with Research Question 4

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Question 4: What is the safety, effectiveness and cost-effectiveness of CFTR mutation testing of a fetus conceived by parents that are both CF carriers, in comparison to determining the diagnosis of the child after the birth?** | | | | | | | | | | | | | |
| **Quality assessment** | | | | | | | **Summary of Findings** | | | | | | |
| **Participants (studies) Follow up** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** | **Overall quality of evidence** | **Study event rates (%)** | | **Relative effect** (95% CI) | | **Anticipated absolute effects** | | |
| **With Control** | **With Intervention** | **Risk with Control** | **Risk difference with Intervention** (95% CI) | |
| **<Health outcome>** | | | | | | | | | | | | | |
|  |  |  |  |  |  |  |  |  |  | | **Study population** | | |
|  |  | |
| **Low** | | |
|  |  | |
| **Moderate** | | |
|  |  | |
| **<Health outcome>** | | | | | | | | | | | | | |
|  |  |  |  |  |  |  |  | |  |  | **Study population** | | |
|  | |  |
| **Low** | | |
|  | |  |
| **Moderate** | | |
|  | |  |

### 2.8 Economic evaluation

If there is insufficient evidence regarding the safety and/or effectiveness of diagnostic CFTR mutation testing, or if there is no expected change in management following the intervention, an economic evaluation will not be undertaken.

In cases where there will be no full assessment of the safety and/or effectiveness of CFTR mutation testing, e.g. for reproductive planning, only the financial implications of the test will be explored.

Table 16 presents the type of economic evaluation that will be undertaken, should there be enough data to reach a conclusion regarding the comparative safety and effectiveness of diagnostic CFTR mutation testing. The financial impact of CFTR testing in this population will also be estimated.

In the economic evaluation, the economic outcome of interest will be the cost per case of CF avoided. It was considered inappropriate to construct a cost/QALY outcome for this economic evaluation as it would require competing value judgements concerning the parental quality of life associated with termination of pregnancy or of bringing a child with CF into the world. Similarly, as two lives are affected by this health intervention – and what might be of benefit to the parent could be interpreted as a harm to the child, and vice versa – an assessment of the societal value of these options could only be done with a proper ethical analysis.

Table 16 Classification of an intervention for determination of economic evaluation to be presented

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | **Comparative effectiveness versus comparator** | | | | |
| Superior | | Non-inferior | Inferior | |
| **Comparative safety versus comparator** | Superior | CEA/CUA | | CEA/CUA | Net clinical benefit | CEA/CUA |
| Neutral benefit | CEA/CUA\* |
| Net harms | None^ |
| Non-inferior | CEA/CUA | | CEA/CUA\* | None^ | |
| Inferior | Net clinical benefit | CEA/CUA | None^ | None^ | |
| Neutral benefit | CEA/CUA\* |
| Net harms | None^ |

Abbreviations: CEA = cost-effectiveness analysis, CUA = cost-utility analysis

\* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

## 3. Proposed assessment timeframes

The proposed time frame for this review is as follows:

|  |  |
| --- | --- |
| Systematic review protocol finalised | October 2014 |
| Project plan due | 7 November 2014 |
| Draft contracted assessment due | 16 March 2015 |
| Final contracted assessment due | 30 April 2015 |
| Rejoinder to applicant comments | 5 May 2015 |
| ESC meeting | 11 – 12 June 2015 |

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Appendix A  
Health Technology Assessment Websites **\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_**

|  |  |
| --- | --- |
| INTERNATIONAL |  |
| International Network of Agencies for Health Technology Assessment | http://www.inahta.org/ |
| AUSTRALIA |  |
| Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) | <http://www.surgeons.org/for-health-professionals/audits-and-surgical-research/asernip-s/> |
| Centre for Clinical Effectiveness, Monash University | <http://www.monashhealth.org/page/Health_Professionals/CCE/> |
| Centre for Health Economics, Monash University | <http://www.buseco.monash.edu.au/centres/che/> |
| AUSTRIA |  |
| Institute of Technology Assessment / HTA unit | <http://www.oeaw.ac.at/ita> |
| CANADA |  |
| Institut national d’excellence en santé et en services sociaux (INESSS) | <http://www.inesss.qc.ca/en/publications/publications>/ |
| Alberta Heritage Foundation for Medical Research (AHFMR) | http://www.ahfmr.ab.ca/ |
| Alberta Institute of Health Economics | <http://www.ihe.ca/> |
| The Canadian Agency for Drugs And Technologies in Health (CADTH) | <http://www.cadth.ca/index.php/en/> |
| The Canadian Association for Health Services and Policy Research (CAHSPR) | <https://www.cahspr.ca/en/about/vision> |
| Centre for Health Economics and Policy Analysis (CHEPA), McMaster University | <http://www.chepa.org/> |
| Centre for Health Services and Policy Research (CHSPR), University of British Columbia | <http://www.chspr.ubc.ca/> |
| Institute for Clinical and Evaluative Studies (ICES) | <http://www.ices.on.ca/> |
| Saskatchewan Health Quality Council (Canada) | <http://www.hqc.sk.ca/> |
| DENMARK |  |
| Danish National Institute Of Public Health | <http://www.si-folkesundhed.dk/?lang=en> |
| FINLAND |  |
| Finnish National Institute for Health and Welfare | <http://www.thl.fi/en/web/thlfi-en/> |
| FRANCE |  |
| L’Agence Nationale d’Accréditation et d’Evaluation en Santé (ANAES) | <http://www.anaes.fr/> |
| GERMANY |  |
| German Institute for Medical Documentation and Information (DIMDI) / HTA | <http://www.dimdi.de/static/en/> |
| Institute for Quality and Efficiency in Health Care (IQWiG) | [http://www.iqwig.de](http://www.iqwig.de/) |
| THE NETHERLANDS |  |
| Health Council of the Netherlands Gezondheidsraad | <http://www.gezondheidsraad.nl/en/> |
| NEW ZEALAND |  |
| New Zealand Health Technology Assessment (NZHTA) | <http://www.otago.ac.nz/christchurch/research/nzhta/> |
| NORWAY |  |
| Norwegian Knowledge Centre for the Health Services | [http://www.kunnskapssenteret.no](http://www.kunnskapssenteret.no/) |

|  |  |
| --- | --- |
| SPAIN |  |
| Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud “Carlos III”I/Health Technology Assessment Agency (AETS) | <http://www.isciii.es/> |
| Andalusian Agency for Health Technology Assessment (Spain) | <http://www.juntadeandalucia.es/> |
| Catalan Agency for Health Technology Assessment (CAHTA) | [http://www.gencat.cat](http://www.gencat.cat/) |
| SWEDEN |  |
| Center for Medical Health Technology Assessment | <http://www.cmt.liu.se/?l=en&sc=true> |
| Swedish Council on Technology Assessment in Health Care (SBU) | <http://www.sbu.se/en/> |
| SWITZERLAND |  |
| Swiss Network on Health Technology Assessment (SNHTA) | <http://www.snhta.ch/> |
| UNITED KINGDOM |  |
| National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA) | <http://www.hta.ac.uk/> |
| NHS Quality Improvement Scotland | <http://www.nhshealthquality.org/> |
| National Institute for Clinical Excellence (NICE) | <http://www.nice.org.uk/> |
| The European Information Network on New and Changing Health Technologies | <http://www.euroscan.bham.ac.uk/> |
| University of York NHS Centre for Reviews and Dissemination (NHS CRD) | <http://www.york.ac.uk/inst/crd/> |
| UNITED STATES |  |
| Agency for Healthcare Research and Quality (AHRQ) | [http://www.ahrq.gov/clinic/techix.htm](http://www.ahrq.gov/)l |
| Harvard School of Public Health | <http://www.hsph.harvard.edu/> |
| Institute for Clinical and Economic Review (ICER) | <http://www.icer-review.org/> |
| Institute for Clinical Systems Improvement (ICSI) | [http://www.icsi.org](http://www.icsi.org/) |
| Minnesota Department of Health (US) | <http://www.health.state.mn.us/> |
| National Information Centre of Health Services Research and Health Care Technology (US) | <http://www.nlm.nih.gov/nichsr/nichsr.html> |
| Oregon Health Resources Commission (US) | <http://www.oregon.gov/oha/OHPR/HRC/Pages/index.aspx> |
| Office of Health Technology Assessment Archive (US) | <http://ota.fas.org/> |
| U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec) | <http://www.bcbs.com/blueresources/tec/> |
| Veteran’s Affairs Research and Development Technology Assessment Program (US) | <http://www.research.va.gov/default.cfm> |

Appendix B

Literature Sources

Electronic bibliographic databases will be searched to find relevant studies (those meeting the inclusion criteria) addressing each of the research questions developed for this MSAC assessment. These databases are described in Table B.1.

As the first CFTR mutations were identified around 1989, the search period will be January 1989 to October 2014 ([Kerem et al. 1989](#_ENREF_5); [Riordan et al. 1989](#_ENREF_17)).

Table B.1 Bibliographic databases

|  |  |
| --- | --- |
| Electronic database | Time period |
| Cochrane Library – including, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Database, the NHS Economic Evaluation Database | 1/1989 – 10/2014 |
| Current Contents | 1/1989 – 10/2014 |
| Embase | 1/1989 – 10/2014 |
| PubMed | 1/1989 – 10/2014 |
| Web of Science – Science Citation Index Expanded | 1/1989 – 10/2014 |
| Cinahl | 1/1989 – 10/2014 |
| Econlit | 1/1989 – 10/2014 |
| Scopus | 1/1989 – 10/2014 |

Additional literature – peer-reviewed or grey literature – will be sought from the sources outlined in Table B.2, and from the health technology assessment agency websites provided in Table A.1. Websites of specialty organisations will also be searched for any potentially relevant information (Table B.3).

Table B.2. Additional sources of literature

|  |  |
| --- | --- |
| Source | Location |
| *Internet* |  |
| NHMRC- National Health and Medical Research Council (Australia) | http://www.nhmrc.gov.au/ |
| US Department of Health and Human Services (reports and publications) | http://www.hhs.gov/ |
| New York Academy of Medicine Grey Literature Report | http://www.greylit.org/ |
| Trip database | [http://www.tripdatabase.com](http://www.tripdatabase.com/) |
| Current Controlled Trials metaRegister | <http://controlled-trials.com/> |
| National Library of Medicine Health Services/Technology Assessment Text | <http://text.nlm.nih.gov/> |
| U.K. National Research Register | http://www.nihr.ac.uk/Pages/NRRArchive.aspx |
| Google Scholar | http://scholar.google.com/ |
| Australian and New Zealand Clinical Trials Registry | www.anzctr.org.au |
| *Pearling* |  |
| All included articles will have their reference lists searched for additional relevant source material |  |

Table B.3. Specialty Websites

|  |  |
| --- | --- |
| Cystic Fibrosis Australia | http://www.cysticfibrosis.org.au/ |
| Cystic Fibrosis Foundation (US) | www.cff.org/ |
| Cure4CF Foundation (US) | http://www.cure4cf.org/ |
| Australian Heart/Lung Transplants Association | http://www.ahlta.com.au/ |
| Lung Foundation Australia | http://lungfoundation.com.au/ |

Appendix C  
Critical appraisal checklists  
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**Case series –** **IHE Checklist**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Yes** | **No** | **Unclear** |
| **Study objective** |  |  |  |
| 1. Is the hypothesis/aim/objective of the study stated clearly in the abstract, introduction, or methods section? |  |  |  |
| **Study population** |  |  |  |
| 2. Are the characteristics of the participants included in the study described? |  |  |  |
| 3. Were the cases collected in more than one centre? |  |  |  |
| 4. Are the eligibility criteria (inclusion and exclusion criteria) for entry into the study explicit and appropriate? |  |  |  |
| 5. Were participants recruited consecutively? |  |  |  |
| 6. Did participants enter the study at a similar point in the disease? |  |  |  |
| **Intervention and co-intervention** |  |  |  |
| 7. Was the intervention clearly described in the study? |  |  |  |
| 8. Were additional interventions (co-interventions) clearly reported in the study? |  |  |  |
| **Outcome measure** |  |  |  |
| 9. Are the outcome measures clearly defined in the introduction or methods section? |  |  |  |
| 10. Were relevant outcomes appropriately measured with objective and/or subjective methods? |  |  |  |
| 11. Were outcomes measured before and after intervention? |  |  |  |
| **Statistical analysis** |  |  |  |
| 12. Were the statistical tests used to assess the relevant outcomes appropriate? |  |  |  |
| Results and conclusions |  |  |  |
| 13. Was the length of follow-up reported? |  |  |  |
| 14. Was the loss to follow-up reported? |  |  |  |
| 15. Does the study provide estimates of the random variability in the data analysis of relevant outcomes? |  |  |  |
| 16. Are adverse events reported? |  |  |  |
| 17. Are the conclusions of the study supported by results? |  |  |  |
| 18. Are both competing interests and sources of support for the study reported? |  |  |  |

**Checklist for appraising the quality of intervention studies**

**STUDY QUALITY ASSESSMENT CHECKLIST**

Suitable for trials, cohorts and case-control studies assessing interventions

**(**[**Downs & Black 1998**](#_ENREF_2)**)–adapted)**

**Reporting**

1. Is the hypothesis/aim/objective of the study clearly described?

|  |  |
| --- | --- |
| yes |  |
| no |  |

1. Are the main outcomes to be measured clearly described in the Introduction or Methods section?

|  |  |
| --- | --- |
| yes |  |
| no |  |

1. Are the characteristics of the patients included in the study clearly described?

|  |  |
| --- | --- |
| yes |  |
| no |  |

1. Are the interventions of interest clearly described?

|  |  |
| --- | --- |
| yes |  |
| no |  |

1. Are the distributions of principal confounders in each group of subjects to be compared clearly described?

|  |  |
| --- | --- |
| Yes (all) |  |
| Partially |  |
| no |  |

1. Are the main findings of the study clearly described?

|  |  |
| --- | --- |
| yes |  |
| no |  |

1. Does the study provide estimates of the random variability in the data for the main outcomes?

|  |  |
| --- | --- |
| yes |  |
| no |  |

1. Have all important adverse events that may be a consequence of the intervention been reported?

|  |  |
| --- | --- |
| yes |  |
| no |  |

1. Have the characteristics of patients lost to follow-up been described?

|  |  |
| --- | --- |
| yes |  |
| no |  |

1. Have the actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes, except where the probability value is less than 0.001?

|  |  |
| --- | --- |
| yes |  |
| no |  |

***External validity***

All the following criteria attempt to address the representativeness of the findings of the study and whether they may be generalised to the population from which the study subjects were derived.

1. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

1. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

1. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

***Internal validity - Bias***

1. Was an attempt made to blind study subjects to the intervention they have received?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

1. Was an attempt made to blind those measuring the main outcomes of the intervention?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

1. If any of the results of the study were based on “data dredging”, was this made clear?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

1. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

1. Were the statistical tests used to assess the main outcomes appropriate?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

1. *Was compliance with the intervention/s reliable?*

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

1. *Were the main outcome measures used accurate (valid and reliable)?*

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

***Internal validity – Confounding (selection bias)***

1. Were the patients in different intervention groups (trials and cohort studies) recruited from the same population?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

1. Were study subjects in different intervention groups (trials and cohort studies) recruited over the same period of time?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

1. Were study subjects randomised to intervention groups?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

1. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

1. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

1. Were losses of patients to follow-up taken into account?

|  |  |
| --- | --- |
| yes |  |
| no |  |
| unable to determine |  |

*[Note: Power item (no 27) has been omitted but a statistical calculation to determine whether the study is adequately powered (to determine whether the observed difference is statistically significant) can be performed]*

**Subscale Scores**

Reporting =

External validity =

Bias =

Confounding =

**Overall Quality**

Determination of total overall quality of the study will depend on the reviewers’ views and the weight they place on the components of quality. These might vary according to intervention being reviewed or the outcome being assessed in the study eg for subjective outcomes more weight may be placed on item 14 (blinding study subjects).

Internal validity of the study is usually captured by the bias and confounding subscales. These components are important as they help you determine whether you can have confidence that the study results are accurate.

External validity helps the reviewer determine whether the study results can be applied more generally.

Reporting gives an idea as to whether the study’s main flaw is poor reporting, which might be the reason it scores poorly on the other methodological components.

A weighting or threshold may be applied to each of these components, or only one or two components may be used, to make the decision as to whether the study is poor quality, low-moderate quality, moderate quality, moderate-high quality or high quality.

For example, some reviewers may only choose to report on the bias domain. Others may require a cut-off of 5/7 for bias and 4/6 for confounding plus an overall quality score > 20 to be a high quality study. And yet others may choose to indicate that no study was high quality if item 14 was ‘no’.

There is no hard and fast method used to allocate studies to the different quality descriptors, the only caveat is that when reviewing multiple studies the approach should be consistent across all studies appraised, so that the critical appraisal is standardised.

**QUADAS-2 checklist**

|  |  |
| --- | --- |
| **Domain 1: Patient selection** | |
| **A. Risk of bias** |  |
| Describe patient selection |  |
| Was a consecutive or random sample of patients enrolled? | Yes/No/Unclear |
| Did the study avoid inappropriate exclusions? | Yes/No/Unclear |
| **Could the selection of patients have introduced bias?** | **RISK: LOW/HIGH/UNCLEAR** |
| **B. Concerns regarding applicability** |  |
| Describe included patients (prior testing, presentation, use of index test and setting) |  |
| **Is there concern that the included patients do not match the review question?** | **CONCERN: LOW/HIGH/UNCLEAR** |

|  |  |
| --- | --- |
| **Domain 2: Index test** |  |
| **A. Risk of bias** |  |
| Describe the index test and how it was conducted and interpreted |  |
| Were the index test results interpreted without knowledge of the reference standard? | Yes/No/Unclear |
| **Could the conduct or interpretation of the index test have introduced bias?** | **RISK: LOW/HIGH/UNCLEAR** |
| **B. Concerns regarding applicability** |  |
| **Is there concern that the index test, its conduct, or interpretation differ from the review question?** | **CONCERN: LOW/HIGH/UNCLEAR** |

|  |  |
| --- | --- |
| **Domain 3: Reference standard** |  |
| **A. Risk of bias** |  |
| Describe the reference standard and how it was conducted and interpreted |  |
| Is the reference standard likely to correctly classify the target condition? | Yes/No/Unclear |
| Were the reference standard results interpreted without knowledge of the results of the index test? | Yes/No/Unclear |
| **Could the reference standard, its conduct, or interpretation have introduced bias?** | **RISK: LOW/HIGH/UNCLEAR** |
| **B. Concerns regarding applicability** |  |
| **Is there concern that the target condition as defined by the reference standard does not match the review question?** | **CONCERN: LOW/HIGH/UNCLEAR** |

|  |  |
| --- | --- |
| **Domain 4: Flow and Timing** |  |
| **A. Risk of bias** |  |
| Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram) |  |
| Describe the time interval and any interventions between index test(s) and reference standard |  |
| Was there an appropriate time interval between index test(s) and reference standard? | Yes/No/Unclear |
| Did all patients receive a reference standard? | Yes/No/Unclear |
| Did patients receive the same reference standard? | Yes/No/Unclear |
| Were all patients included in the analysis? | Yes/No/Unclear |
| **Could the patient flow have introduced bias?** | **RISK: LOW/HIGH/UNCLEAR** |

Risk of bias and applicability judgements (QUADAS-2; ([Whiting et al. 2011](#_ENREF_20))

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **RISK OF BIAS** | | | | **APPLICABILITY CONCERNS** | | |
| **Patient selection** | **Index test** | **Reference standard** | **Flow and timing** | **Patient selection** | **Index test** | **Reference standard** |
|  |  |  |  |  |  |  |  |

☺Low Risk ☹High Risk ? Unclear Risk

1. Richardson WS, Scott MD, Wilson MC et al. (1995) The well built clinical question: a key to evidence based decisions. *ACP Journal Club*, 123, ppA-12. [↑](#footnote-ref-1)