Introduction

Cystic fibrosis testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFTR Targeted Mutation Analysis</td>
<td>81220</td>
</tr>
<tr>
<td>CFTR Known Familial Mutation Analysis</td>
<td>81221</td>
</tr>
<tr>
<td>CFTR Sequencing</td>
<td>81223</td>
</tr>
<tr>
<td>CFTR Deletion/Duplication Analysis</td>
<td>81222</td>
</tr>
<tr>
<td>CFTR Poly T Tract (5T) Genotyping</td>
<td>81224</td>
</tr>
</tbody>
</table>

What is cystic fibrosis

Definition

Classic cystic fibrosis (CF) is a genetic disorder that causes chronic lung disease, pancreatic insufficiency, and male infertility.1,2 It is caused by mutations in the CFTR gene.1

Prevalence

CF affects approximately 1 in 3200 live births of northern European background.1 While CF is most common in this background, it can occur in any ethnic group.2

Inheritance

CF is an autosomal recessive condition. Males and females are equally likely to be affected.1 If both parents are carriers of CF, the risk for a pregnancy to be affected is 1 in 4 (25%).1 If one partner is affected with CF and the other partner is a carrier, the risk for a pregnancy to be affected is 1 in 2 (50%). Preimplantation and prenatal diagnosis are available for couples known to be at-risk.
Prognosis and Treatment

Patient registry data from 2017 indicate that the median predicted survival for people with classic CF is about 44 years. Treatment advances continue to extend the life of patients with CF. Several therapies in development or currently available target specific CFTR gene mutations, such as the FDA-approved Kalydeco™ for people with the G551D and other approved mutations, Orkambi™ for people with two copies of F508del; and Symdeko® for people with two copies of F508del or a single copy of 26 other specific mutations. The genotype must be confirmed by molecular genetic testing in order to direct CFTR mutation-specific therapies.

Detection

Most signs of CF cannot be identified on prenatal ultrasound examination. However, pregnancies in which fetal echogenic bowel is identified on ultrasound are at an increased risk to be affected with CF. Prenatal diagnosis for CF can be performed on a sample from chorionic villus sampling (CVS) or amniocentesis:

- If both parents are known carriers, a mutation panel that includes both parental mutations is typically the test of choice.
- If only one parent is a carrier, or if testing is indicated because of echogenic bowel, testing with a large mutation panel or sequencing and deletion/duplication analysis offers greater sensitivity.

Newborn screening (NBS) programs include screening for CF, though the screening protocol may vary by state.

CFTR-related disorders and CF screen-positive, inconclusive diagnosis

Several other conditions that share some clinical similarities to CF, are also caused by mutations in the CFTR gene, but do not meet the diagnostic criteria for CF. These are called “CFTR-related disorders” and include congenital bilateral absence of vas deferens (CBAVD/CAVD), acute recurrent or chronic pancreatitis, and some respiratory tract conditions such as bronchiectasis, sinusitis, and nasal polyps.

CBAVD is frequently identified after semen analysis shows absent sperm (azoospermia). CBAVD is often caused by one severe CFTR mutation and one mild mutation (including the 5T allele). At least one CFTR mutation can be found in up to 80% of men with CAVD. Because of this association, CFTR analysis is routinely performed for men with azoospermia.

CF screen-positive, inconclusive diagnosis (CF-SPID), also referred to as CFTR-related metabolic syndrome (CRMS) "is used to describe an infant with an elevated trypsinogen on newborn screening, sweat chloride values ≤60 mEq/L, and up to two CFTR variants, at least one of which is not clearly categorized as a pathogenic variant and therefore not meeting diagnostic criteria for CF. These infants are typically asymptomatic, and knowledge of the natural history of CRMS continues to evolve."
Test information

Introduction

Testing for cystic fibrosis tests may include CFTR mutation panels, CFTR sequencing, CFTR deletion/duplication analysis, intron 8 poly-T analysis, or CFTR known-familial mutation analysis.

CFTR mutation panels

The American College of Medical Genetics has defined a panel of 23 common, pan-ethnic mutations that occur at a frequency of at least 0.1% in patients with cystic fibrosis. While this panel was created for carrier screening purposes, the CF diagnostic guidelines also endorse its use in that setting for most patients. Laboratories performing mutation panel testing routinely include all of these mutations. Many laboratories expand their panels with more mutations intended to increase the detection rate, particularly in non-Caucasian populations. Expanded mutation panels generally test for 70 or more CFTR mutations. The detection rates of expanded panels vary by laboratory and depend on the mutations included and the patient's ethnicity.

CFTR sequencing

CFTR sequencing detects more than 97% of mutations. Sequencing is generally performed in reflex to normal mutation panel results, and reserved for specific situations in which a mutation panel is insufficient.

CFTR deletion/duplication analysis

CFTR deletion/duplication analysis identifies mutations that sequencing would not find. This test is generally performed in reflex to normal sequencing results.

CFTR known familial mutation analysis

Once the mutations in affected or carrier family members have been identified, other relatives and at-risk pregnancies can be tested for those mutations. Mutation panels are often used in this situation, as long as they include the family mutation(s). If a family mutation is rare or unique, testing targeted for that mutation may be needed.

Intron 8 poly-T analysis

Intron 8 poly-T analysis identifies the number of thymidine bases in intron 8 of the CFTR gene. The three common variants are 5T, 7T, and 9T. The 5T variant is considered a mild mutation with reduced penetrance, while 7T and 9T are considered normal variants.

Testing is typically done in reflex to the identification of an R117H mutation by CFTR mutation panel testing. The 5T variant also modifies the effect of the R117H mutation if the two mutations are located on the same chromosome. R117H is a mild
CFTR mutation included in the standard panel recommended by the American College of Medical Genetics. If R117H is identified by CF testing, reflex testing for the 5T variant is indicated to provide information relevant to genetic counseling.

**5T variant analysis**

5T variant analysis may also be included in CFTR testing panels when the testing is done specifically to evaluate a man with CAVD. The 5T variant is more commonly found in men with CAVD in the absence of other symptoms of CF. In one large study, 25% of men with CAVD who had CFTR mutations identified had at least one copy of the 5T variant identified.

**Guidelines and evidence**

**Introduction**

This section includes relevant guidelines and evidence pertaining to cystic fibrosis testing.

**American College of Obstetrics and Gynecology**

Evidence-based guidelines from the American College of Obstetrics and Gynecology (ACOG) (2017) recommend that CF carrier screening using a mutation panel be offered to all couples who are pregnant or planning a pregnancy or those with a family history of CF.

ACOG adds, “Cystic fibrosis is more common among the non-Hispanic white population compared with other racial and ethnic populations; however, because of the increasing difficulty in assigning a single ethnicity to individuals, in 2005, the American College of Obstetricians and Gynecologists recommended offering cystic fibrosis carrier screening to all patients.”

These ACOG guidelines state:

- “Cystic fibrosis carrier screening should be offered to all women who are considering pregnancy or are currently pregnant.
- If the patient is a cystic fibrosis carrier, then her partner should be tested. During pregnancy, concurrent screening of the patient and her partner is suggested if there are time constraints for decisions regarding prenatal diagnostic evaluation.
- Current guidelines, revised by the American College of Medical Genetics and Genomics in 2004, recommend use of a panel that contains, at a minimum, the 23 most common mutations. A number of expanded mutation panels are now commercially available and can be considered to enhance the sensitivity for carrier detection, especially in non-Caucasian ethnic groups.
- Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening. This type of testing generally is reserved for patients with
cystic fibrosis, patients with negative carrier screening result but a family history of
cystic fibrosis (especially if family test results are not available), males with
congenital bilateral absence of the vas deferens, or newborns with a positive
newborn screening result when mutation testing (using the standard 23-mutation
panel) has a negative result.

- For couples in which both partners are unaffected but one or both has a family
  history of cystic fibrosis, genetic counseling and medical record review should be
  performed to determine if CFTR mutation analysis in the affected family member is
  available.

- If a woman’s reproductive partner has cystic fibrosis or apparently isolated
  congenital bilateral absence of the vas deferens, the couple should be provided
  follow-up genetic counseling by an obstetrician–gynecologist or other health care
  provider with expertise in genetics for mutation analysis and consultation.

- If both partners are found to be carriers of a genetic condition, genetic counseling
  should be offered."

**American Society for Reproductive Medicine in partnership with the Society for
Male Reproduction and Urology**

Consensus-based guidelines from the American Society for Reproductive Medicine in
partnership with the Society for Male Reproduction and Urology (2018) recommend
cystic fibrosis testing for men with CAVD and their partners, stating:11

- “…failure to identify a CFTR abnormality in a man with CBAVD does not exclude a
  mutation entirely, because 10%–40% are undetectable using common clinically
  available methods. During comprehensive screening with CFTR gene sequencing
  (as opposed to the commonly used delta F508, 30-mutation, or 100-mutation
  panels), a small fraction of CBAVD men will have no identifiable mutations.” “Before
  any treatments using sperm from a man with CBAVD or congenital unilateral
  absence of the vas deferens (CUAVD), testing should be offered to his female
  partner to exclude the possibility (~4%) that she too may be a carrier.”

- These guidelines do not specify a preferred testing methodology.

**Cystic Fibrosis Foundation**

Consensus-based guidelines from the Cystic Fibrosis Foundation (2017) outline the
ways in which a CF diagnosis can be established (see below). Characteristic features
of CF include chronic sinopulmonary disease (such as persistent infection with
characteristic CF pathogens, chronic productive cough, bronchiectasis, airway
obstruction, nasal polyps, and digital clubbing), gastrointestinal/nutritional abnormalities
(including meconium ileus, pancreatic insufficiency, chronic pancreatitis, liver disease,
and failure to thrive), salt loss syndromes, and obstructive azoospermia in males (due
to CAVD).2
When at least one characteristic feature is present, a diagnosis of CF can be established by:

- Two abnormal sweat chloride values; or
- Identification of two CF-causing CFTR gene mutations; or
- Characteristic transepithelial nasal potential difference (NPD)

In the absence of symptoms, a CF diagnosis can be established in:

- A newborn with two CF-causing CFTR gene mutations identified via newborn screening

"Individuals who are screen-positive and meet sweat chloride criteria for CF diagnosis should undergo CFTR genetic testing if the CFTR genotype was not available through the screening process or is incomplete." "Even in the presence of a positive sweat test, the identification of 2 CF-causing mutations should be confirmed in a clinical genetics laboratory capable of performing in-depth genetic analysis when required to further define CF risk (eg, the length of polyT tracts with the c.350G>A [legacy:R117H] CFTR mutation). Confirmation of genetic testing results with an FDA-approved companion diagnostic test also has additional value in therapy selection and access."\(^2\)

These guidelines further state that, “Individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, and sweat chloride values in the intermediate range (30-59 mmol/L) on 2 separate occasions may have CF. They should be considered for extended CFTR gene analysis and/or CFTR functional analysis.”\(^2\)

**Society of Obstetricians and Gynaecologists of Canada**

No US evidence-based guidelines have been identified that specifically address CF prenatal diagnosis for echogenic bowel. However, it is standard practice and evidence-based guidelines from the Society of Obstetricians and Gynaecologists of Canada (SOGC, 2005) state:\(^{12}\)

- “Grade 2 and 3 echogenic bowel is associated with both chromosomal and nonchromosomal abnormalities. Expert review is recommended to initiate the following:…laboratory investigations that should be offered, including fetal karyotype, maternal serum screening, DNA testing for cystic fibrosis (if appropriate), and testing for congenital infection (II-2 A).” [Evidence level II-2: “Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.” Recommendation classification A: “There is good evidence to support the recommendation for use of a diagnostic test, treatment, or intervention.”]

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Criteria
Introduction

Requests for cystic fibrosis testing are reviewed using these criteria.

CFTR Standard Panel Testing

• Genetic Counseling:
  o Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous genetic testing for CFTR mutation(s), AND

• Diagnostic Testing for Symptomatic Individuals:
  o Individuals with an intermediate range/equivocal sweat chloride test (30-59mmol/L), or
  o Individuals with a negative sweat chloride test when symptoms of CF are present, or
  o Infants with meconium ileus or other symptoms indicative of CF and are too young to produce adequate volumes of sweat for sweat chloride test, or
  o Infants with an elevated IRT value on newborn screening, or
  o Males with oligospermia/azoospermia/congenital absence of vas deferens (CAVD)⁶, OR

• Mutation Identification to Guide Pharmacologic Therapy Selection
  o Individuals who meet diagnostic criteria for CF and are eligible for FDA-approved CFTR mutation-specific therapies, OR

• Carrier Screening:
  o Be of reproductive age and have potential and intention to reproduce, OR

• Prenatal Testing:
  o Either biological parent has a diagnosis of CF, or
  o Family history of CF in a first degree relative, or
  o Both parents are carriers of CF mutations included in the panel, or
  o Echogenic bowel has been identified on ultrasound in a fetus, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.
CFTR Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Testing:
  - No previous genetic testing for the known CFTR family mutation(s), AND

- Diagnostic Testing for Symptomatic Individuals:
  - Individuals who have a suspected diagnosis of cystic fibrosis and the familial mutations to be tested were identified in a 1st degree biologic relative with CF, OR

- Mutation Identification to Guide Pharmacologic Therapy Selection
  - Individuals who meet diagnostic criteria for CF and are eligible for FDA-approved CFTR mutation-specific therapies, OR

- Carrier Screening:
  - Be of reproductive age and have potential and intention to reproduce, and
  - Familial CFTR mutation(s) in known biologic relative, OR

- Prenatal Testing:
  - Either biological parent is a known carrier of a CFTR mutation, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

CFTR Sequencing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
  - Previous CFTR standard panel was negative (no mutation found) or only one mutation was found, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Individuals with a negative or equivocal sweat chloride test, and unexplained COPD or bronchiectasis with unexplained chronic or recurrent sinusitis and abnormal pulmonary function tests (PFTs), or
  - Infants with meconium ileus or other symptoms indicative of CF and are too young to produce adequate volumes of sweat for sweat chloride test, or
• Infants with an elevated IRT value on newborn screening and 0 or 1 mutations identified on standard panel testing, OR

• Mutation Identification to Guide Pharmacologic Therapy Selection
  o Individuals who meet diagnostic criteria for CF and are eligible for CFTR FDA-approved genotype-based therapies, or
  o No CFTR mutations that have FDA-approved genotype-based therapies identified by standard panel testing, OR

• Carrier Screening:
  o Be of reproductive age and have potential and intention to reproduce, and
  o An individual with a family history of CF with an unknown mutation, or
  o An individual whose reproductive partner is a known CF carrier, has a diagnosis of CF, or has a diagnosis of CAVD, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

**CFTR Deletion/Duplication Analysis**

• Genetic Counseling:
  o Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous CFTR deletion/duplication testing, and
  o Previous CFTR gene sequencing was negative (no mutation found) or only one mutation was found, and
  o No known familial mutation, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

**CFTR Intron 8 Poly T Analysis**

• Genetic Counseling:
  o Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous CFTR intron 8 poly T testing, AND

• Diagnostic Testing:
- CFTR mutation analysis performed and R117H mutation detected, or
- Diagnosis of male infertility (congenital absence of vas deferens [CAVD], obstructive azoospermia), or
- Diagnosis of non-classic CF, OR

- Carrier Testing:
  - CFTR mutation analysis performed and R117H mutation detected, AND

- Rendering laboratory is a qualified provider of service per the Health Plan policy.

**Note** This guideline does not apply to CFTR testing for individuals with pancreatitis. CFTR testing for this indication is addressed by the guideline *Genetic Testing for Hereditary Pancreatitis*.

**References**


