Cystic Fibrosis Testing

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.

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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 Caucasian newborns.\(^1\) While CF is most common in Caucasians, 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

Patient registry data from 2016 indicate that the median lifespan for people with classic CF is about 47 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 and Orkambi™ for people with two copies of deltaF508.

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 offers greater sensitivity.

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

CFTR-related disorders

Several other conditions share some clinical similarities to CF, are also caused by mutations in the CFTR gene, but do not meet the diagnostic criteria for classic 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.

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.\(^7\) While this panel was created for carrier screening purposes, the CF diagnostic guidelines also endorse its use in that setting for most patients.\(^2\) 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.\(^1\)

CFTR sequencing

CFTR sequencing detects more than 98% of mutations.\(^1\) 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 performed in reflex to normal sequencing results.\(^1\)

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.\(^1\) Mutation panels are often used in this situation, as long as they include the family mutation. If the family mutation is rare or unique, testing for just 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.\(^1\) The 5T variant is considered a mild mutation with reduced penetrance, while 7T and 9T are considered normal variants.\(^1\)

Testing is typically done in reflex to the identification of an R117H mutation by CFTR mutation panel testing.\(^1,7-9\) The 5T variant also modifies the effect of the R117H mutation if the two mutations are located on the same chromosome.\(^7\) R117H is a mild CFTR mutation included in the standard panel recommended by the American College of Medical Genetics.\(^7-9\) If R117H is identified by CF testing, reflex testing for the 5T variant is indicated to provide information relevant to genetic counseling.\(^1,7-9\)

5T variant analysis

5T variant analysis may also be performed alone or included in CFTR testing panels when the testing is done specifically to evaluate a man with CAVD.\(^1,8\) 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.\textsuperscript{10}

**Guidelines and evidence**

**Introduction**

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

**American College of Obstetrics and Gynecology and American Society for Reproductive Medicine**

Evidence-based guidelines from the American College of Obstetrics and Gynecology (ACOG) (2005\textsuperscript{9}, limited update 2011\textsuperscript{11}) and the American College of Medical Genetics and Genomics (ACMG) (2004)\textsuperscript{7} 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 “It is becoming increasingly difficult to assign a single ethnicity to individuals. It is reasonable, therefore, to offer CF carrier screening to all patients. Screening is most efficacious in the non-Hispanic white and Ashkenazi Jewish populations.” \textsuperscript{9}
- These guidelines state that expanded mutation screening or sequencing may be beneficial in:
  - An individual with a family history of CF with an unknown mutation\textsuperscript{7,9}
  - An individual whose reproductive partner is a known CF carrier, has CF, or has CAVD\textsuperscript{7,9}

**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 (2008) recommend cystic fibrosis testing for men with CAVD and their partners, stating:\textsuperscript{12}

- “A man with CBAVD should be assumed to harbor a CFTR mutation. Therefore, before any treatments using his sperm, testing should be offered to the female partner to exclude the possibility (approximately 4%) that she too may be a carrier. All such couples should be offered genetic counseling.” These guidelines do not specify a preferred testing methodology.
**Cystic Fibrosis Foundation**

Consensus-based guidelines from the Cystic Fibrosis Foundation (2017)² 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).

These guidelines 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.”

**When at least one characteristic feature is present, a diagnosis of CF can be confirmed by:**

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

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

- A newborn with two CFTR gene mutations identified via newborn screening
- A pregnancy found to have two CFTR mutations on prenatal testing

**American College of Obstetrics and Gynecology**

Evidence-based guidelines from the American College of Obstetrics and Gynecology (2011)¹¹ recommend: “For couples in which both partners are carriers, genetic counseling is recommended to review prenatal testing and reproductive options.” In the discussion, ACOG adds that for “A woman [who] is a carrier of a CF mutation and her partner is unavailable for testing or paternity is unknown. Genetic counseling to review the risk of having an affected child and prenatal testing options and limitations may be helpful.”

**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)¹³ state: “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.”]

Criteria

Introduction

Requests for cystic fibrosis testing are reviewed using these criteria.

CFTR Standard Panel Testing

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy)\(^{14}\), AND
- Previous Genetic Testing:
  - No previous genetic testing for CFTR mutation(s), AND
- Diagnostic Testing for Symptomatic Individuals:
  - Individuals with an intermediate range/equivocal sweat chloride test (30-59mmol/L), or
  - Individuals with a negative sweat chloride test when symptoms of CF are present, 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, or
  - Males with oligospermia/azoospermia/congenital absence of vas deferens (CAVD)\(^{8,15,16}\), OR
- Carrier Screening:
  - Be of reproductive age and have potential and intention to reproduce, OR
- Prenatal Testing:
  - Either biological parent has a diagnosis of CF, or
  - Family history of CF in a first degree relative, or
  - Both parents are carriers of CF mutations, or
• 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 known CFTR family mutation(s), or
  - Previous CFTR panel testing was not inclusive of known family mutation, AND

• Carrier Screening:
  - 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 a negative 23 mutation panel, OR

• Carrier Screening:
- An individual with a family history of CF with an unknown mutation, or
- 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:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
  - No previous CFTR deletion/duplication testing, and
  - Previous CFTR gene sequencing was negative (no mutation found) or only one mutation was found, and
  - 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:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

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

- Diagnostic Testing:
  - 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


