CARRIER SCREENING FOR CYSTIC FIBROSIS

Policy Number: PDS - 001
Effective Date: January 01, 2016

Table of Contents

GUIDELINES ................................................................. 1
DEFINITIONS ............................................................. 2
BACKGROUND ............................................................... 2
CLINICAL EVIDENCE ................................................... 4
CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS) .............. 6
APPLICABLE CODING .................................................. 7
REFERENCES ............................................................... 8
POLICY HISTORY/REVISION HISTORY .................................. 9

INSTRUCTIONS FOR USE

Physician Decision Support (PDS) is a lab ordering tool operated by BeaconLBS. This Clinical Guideline supports the Questions and Answers that appear in PDS for tests referenced in this document. UnitedHealthcare reserves the right, in its sole discretion, to modify its Clinical Guidelines as necessary. This Clinical Guideline is provided for informational purposes. It does not constitute a Medical Policy or medical advice.

GUIDELINES

Cystic Fibrosis (CF) carrier screening using a basic targeted mutation panel (fewer than 40 mutations screened) is performed in the following situations:

- Prior to conception or early in pregnancy for all reproductive couples.
- All gamete (egg and sperm) donors.

CF carrier screening using an expanded targeted mutation panel (greater than 40 mutations screened) is performed in the following situations:

- Individuals who have a reproductive partner with CF.
- Individuals who have a reproductive partner with congenital absence of the vas deferens (CAVD).
- Males with CAVD.
- Individuals who have a family history of CF in which the CF mutation has not been identified.

Sequencing of the CFTR gene which is primarily a tool for diagnosis of CF, may be appropriate for carrier screening in the following situations:

- Individuals with a blood relative with CF in whom the familial CF mutation(s) has not been identified and CF carrier screening in the individual using an extended targeted mutation panel was negative.
- Individuals with a blood relative with CF in whom the familial CF mutation(s) has been identified.
and cannot be detected with an extended targeted mutation panel

- Infertile males with CAVD in which carrier screening using an extended targeted mutation panel that included 5T analysis was uninformative.

These recommendations are based upon guidelines from the American College of Obstetricians and Gynecologists (ACOG), the American College of Medical Genetics (ACMG), and the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology.

DEFINITIONS

CF Mutation Panel:

- Base (non-extended): Generally refers to mutation panel composed of ACMG/ACOG recommended 23 mutations. Analysis published in 2008 showed the median number of CF mutations screened in the United States was 32 mutations.¹
- Expanded Panel: Generally refers to a CF mutation panel in which approximately 40 or more CF mutations are analyzed (including the 23 ACMG/ACOG recommended mutations).

Gene Sequencing: Process in which the individual nucleotide bases within the CFTR gene are evaluated to identify mutations. Sequencing of all exons, intron/exon borders, promoter regions and specific intronic regions detects more than 98% of relevant CFTR mutations.

Deletion Analysis: Permits detection of a whole or partial deletion of the CFTR gene.

Congenital Absence of the Vas Deferens (CAVD or CBAVD if bilateral absence): Absence of vas deferens on clinical or ultrasound examination

Family History of Cystic Fibrosis: Blood relative affected with or a known carrier of CF or CAVD.

Known Familial Mutation: CF mutation identified in blood relative

BACKGROUND

Cystic fibrosis (CF) is one of the most common genetic diseases in the Caucasian population. Approximately 1 in every 25 Caucasians is a carrier for this recessive condition, and 1 in 2500 is clinically affected.²,³ CF occurs in all ethnic groups but the carrier frequency and prevalence vary greatly.²,³ The birth prevalence of CF is estimated to be 1 in 9,200 in Hispanic Caucasians; 1 in 10,900 in Native Americans; 1 in 15,000 in African Americans; and 1 in 31,000 in Asian Americans.⁴ CF has a broad clinical presentation ranging from chronic lung disease to pancreatic insufficiency, meconium ileus, failure to thrive, and infertility.²,³ The overall median survival in CF is 37.4 years.⁵

In 1989, CF was found to be caused by mutations in the CF transmembrane conductance regulator (CFTR) gene on chromosome 7.² Since that time, over 1600 CFTR mutations have been identified, although the majority of mutations are rare.⁵,⁶ An individual with no family history of CF and/or no children with CF can still be a CF carrier. A CF carrier will not have CF-related health problems, but may have children affected with the disease if his or her partner is also a CF carrier. When both parents are carriers of CF, there is a 25% (1 in 4) chance with each pregnancy that the child will have cystic fibrosis.²
Table 1 provides the carrier risk rate by racial or ethnic group and the detection rate of the ACOG/ACMG panel of 23 mutations.\textsuperscript{3,7,8} Analysis published in 2008 showed the median number of CF mutations screened in the United States was 32 mutations.\textsuperscript{1}

<table>
<thead>
<tr>
<th>Ethnic Group</th>
<th>Carrier Rate\textsuperscript{3}</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish</td>
<td>1/25</td>
<td>97%\textsuperscript{2}</td>
</tr>
<tr>
<td>Caucasian (non-Hispanic)</td>
<td>1/25</td>
<td>90%\textsuperscript{2}</td>
</tr>
<tr>
<td>Hispanics</td>
<td>1/46</td>
<td>72%\textsuperscript{2}</td>
</tr>
<tr>
<td>African American</td>
<td>1/65</td>
<td>69%\textsuperscript{2}</td>
</tr>
<tr>
<td>Asian American</td>
<td>1/90</td>
<td>55%\textsuperscript{2}</td>
</tr>
<tr>
<td>Native American</td>
<td>1/52</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Molecular Testing**

A number of molecular tests have been developed for use in the identification of CF carriers as well as diagnosis of CF disease and related conditions such as CAVD. CF carrier screening usually refers to targeted mutation analysis interrogating DNA from a blood or buccal swab specimen. Targeted mutation analysis tests for a panel of mutations in the *CFTR* gene which have been reported in CF patients. Both base (non-extended) and expanded panels are available (see Definitions). Some targeted mutation panels include an analysis of a tract of thymidine bases in intron 8 of the *CFTR* gene. Individuals commonly have 5, 7, or 9 thymidines in this region. The 5T variant has been associated with CAVD and therefore is useful for identifying the etiology of disease and implications for reproductive options in males with azoospermia and absence of the vas deferens.

CF mutations also can be identified by sequencing the entire *CFTR* gene or targeting and sequencing one small region of the gene. Full gene sequencing primarily is a tool for diagnosis of CF, however there are rare high risk situations when full gene sequencing may be appropriate to determine carrier status. Sequencing of a targeted region of the *CFTR* gene is useful for carrier screening when there is a known familial mutation that is not included in basic or extended carrier screening panels.

Deletion analysis of the *CFTR* gene is a test which is employed to detect complete or partial deletions of the *CFTR* gene which are not detected by other standard methods such as targeted mutation analysis or sequencing. *CFTR* deletions are rare. Deletion analysis primarily is a tool for diagnosis of CF, however, is appropriate as a carrier screen test if there is a blood relative known to have a *CFTR* deletion. Recently, a variant in the CFTR (*G551D-CFTR*) has been of interest due to the approval of ivacaftor, a drug that potentiates CFTR gating function and is specifically indicated for CF patients with this particular CFTR variant.\textsuperscript{9}

**CFTR-Related Disorders**

CAVD or bilateral absence of the vas deferens (CBAVD) is diagnosed on clinical or ultrasound examination.\textsuperscript{4} Studies have found that approximately 78\% of males with CAVD carry at least one CF mutation or 5T allele. CAVD occurs in men without pulmonary or gastrointestinal manifestations of CF. Assisted reproductive technologies (ART) to manage infertility include microscopic sperm aspiration from the epididymal remnant in conjunction with in vitro fertilization or artificial insemination using donor sperm.

An increased prevalence of *CFTR* mutations has been noted in individuals with idiopathic pancreatitis, bronchiectasis, allergic bronchopulmonary aspergillosis, and chronic rhinosinusitis.\textsuperscript{4}
CLINICAL EVIDENCE

Over the years, carrier screening for CF has evolved from only testing couples with an affected partner to preconception and prenatal carrier screening for all women of reproductive age.

Guidelines and Recommendations

National Institute of Health Consensus Conference

In 1997, a National Institute of Health (NIH) Consensus conference was convened with the objective of providing health care providers, patients, and the general public with a responsible assessment of the optimal practices for genetic testing for CF. The NIH Consensus statement concluded that genetic testing for CF should be offered to:

- Adults with a positive family history of CF
- Partners of people with CF
- Couples currently planning a pregnancy
- Couples seeking prenatal testing

American College of Obstetricians and Gynecologists (ACOG) and American College of Medical Genetics (ACMG)

In 2001, ACOG and ACMG published Preconception and Prenatal Carrier Screening for Cystic Fibrosis: Clinical and Laboratory Guidelines, which recommended a panel of mutations and variants that should be used in tests determining carrier status within the CFTR gene. This guideline contained recommendations that CF carrier testing should be offered to Caucasian and Ashkenazi Jewish populations and should be made available to all other ethnic groups. Additionally, the recommendation was given that CF screening should be offered to individuals with a family history of CF and reproductive partners of individuals who have CF. It was further recommended that carrier testing be performed when they seek preconception counseling or infertility care, or during the first and early second trimester. At that time, a core mutation panel consisting of 25 mutations with a known allele frequency of greater than 0.1% among North American patients with CF was recommended.

After this joint publication in 2001, all subsequent guidelines have come from the individual societies.

In 2004, the ACMG decreased the recommended mutation panel from 25 to 23 mutations.

In 2005, ACOG published an update to their initial guidelines based on additional studies and survey. The following were included in their recommendations:

- Cystic fibrosis carrier screening can be offered to all couples regardless of race or ethnicity as an alternative to selective screening.
- When both partners are of Caucasian, European, or Ashkenazi Jewish ethnicity, cystic fibrosis carrier screening should be offered before conception or early in pregnancy.
- For individuals with a family history of cystic fibrosis, medical records indicating the CFTR mutation in the affected family member should be obtained whenever possible. If the mutation has not been identified, screening with an expanded panel of mutations or, in some cases, complete analysis of the CFTR gene by sequencing may be indicated. Genetic counseling in this situation usually is beneficial.
- Individuals who have a reproductive partner with cystic fibrosis or congenital bilateral absence of the
vas deferens may benefit from screening with an expanded panel of mutations or, in some cases, a complete analysis of the CFTR gene by sequencing.

In 2006, ACMG published technical standards and guidelines for CFTR testing that included the following for indications for testing:

- Diagnostic Testing, possible diagnosis of CF
- Diagnostic Testing, definite diagnosis of CF
- Diagnostic Testing, infants with meconium ileus
- Diagnostic Testing, congenital bilateral absence of the vas deferens (CBAVD) in males
- Carrier Testing, partners of individuals with positive family history
- Carrier Testing, partners of CBAVD males
- Carrier Testing, general population of reproductive couples
- Carrier Testing, premarital population, to assist in selection of a mate
- Carrier Testing, positive family history
- Carrier Testing, gamete donors
- Preimplantation Testing
- Prenatal Diagnostic Testing, positive family history or for couples having a CF mutation in both partners
- Prenatal Diagnostic Testing, echogenic bowel in fetus during second trimester
- Newborn Screening

Most recently, in 2011, ACOG published another update to their guidelines. The following were included in their recommendations:

- It is important that CF screening continues to be offered to women of reproductive age. 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.
- It is prudent to determine if the patient has been previously screened before ordering CF screening that may be redundant. If a patient has been screened previously, CF screening results should be documented but the test should not be repeated.
- Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening.
- Newborn screening panels that include CF screening do not replace maternal carrier screening.
- If a woman with CF wants to become pregnant, a multidisciplinary team should be considered to manage issues regarding pulmonary function, weight gain, infections, and the increased risks of diabetes and preterm delivery.
- For couples in which both partners are carriers, genetic counseling is recommended to review prenatal testing and reproductive options.
- For couples in which both partners are unaffected but one or both has a family history of CF, genetic counseling and medical record review should be performed to identify if CFTR mutation analysis in the affected family member is available.
- If a woman’s reproductive partner has CF or apparently isolated congenital bilateral absence of the vas deferens, the couple should be referred to a genetics professional for mutation analysis and consultation.

Additionally, the 2011 guidelines stated that “Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening because it may yield results that can be difficult to interpret. This type of testing is generally reserved for patients with CF, patients with a family history of CF, 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. Because carrier screening detects most mutations, sequence analysis should only be considered after discussion with a genetics professional to determine if it will be of value to the evaluation after standard screening has been performed.11

American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology14

In 2013, the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology issued “Recommendations for gamete and embryo donation: a committee opinion” which recommended that CF carrier status be performed on all donors.14

National Society of Genetic Counselors

In 2014, the National Society of Genetic Counselors (NSGC) published “Molecular testing for cystic fibrosis carrier status practice guidelines: recommendations of the National Society of Genetic Counselors”. Significant issues impacting CF carrier screening, including family history, partners of known CF carriers or affected individuals, fetal echogenic bowel, and ethnic background were reviewed.2

Highlighted Published Literature

There is evidence to suggest that a pan-ethnic mutation panel may provide a practical test that maximizes sensitivity for the detection of carrier screening for CF in the heterogeneous US population. Using a panel of 50 to 70 CFTR mutations compared to the Standard Mutation Panel, investigators discovered that the 25-mutation panel would have detected 4,398 CF chromosomes (75.3%), whereas the 64-mutation panel detected 4,668 CF chromosomes (81.4%).15 This data showed that there was an increase in sensitivity seen in all groups except Ashkenazi Jews.

Similarly, another group found that for a subset of CFTR mutations in the US population currently receiving carrier testing, the mutation distribution in Caucasians is significantly different from that in Hispanics, African Americans, and Asians.16 In both these studies, the conclusions that as the US population continues to change, a pan-ethnic approach to carrier screening will be essential.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

For Medicare populations, CMS does not pay for screening procedures (tests) performed in the absence of signs or symptoms. (Section 1862(a)(7) of the Social Security Act)

Local or national Medicare does not have a policy specifically addressing genetic testing for CF.
### APPICABLE CODING

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81220</td>
<td>CFTR (Cystic fibrosis transmembrane conductance regulator) (e.g., Cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines)</td>
</tr>
<tr>
<td>81221</td>
<td>CFTR (Cystic fibrosis transmembrane conductance regulator) (e.g., Cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines), known familial variants</td>
</tr>
<tr>
<td>81222</td>
<td>CFTR (Cystic fibrosis transmembrane conductance regulator) (e.g., Cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines), duplication/deletion variants</td>
</tr>
<tr>
<td>81224</td>
<td>CFTR (Cystic fibrosis transmembrane conductance regulator) (e.g., Cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines), intron 8 poly-T analysis (e.g., male infertility)</td>
</tr>
</tbody>
</table>
REFERENCES


<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/05/2015</td>
<td><strong>Annual Policy Review Completed,</strong> changes made:</td>
</tr>
<tr>
<td></td>
<td>• Updated references: Langfelder-Schwind, 2014 and ASRM, 2013.</td>
</tr>
<tr>
<td></td>
<td>• Added sentence in 'Background' section, under 'Molecular Testing': &quot;Recently, a variant in the CTFR (G551D-CFTR)....with this particular variant.&quot; based on the Clancy, 2014 reference.</td>
</tr>
</tbody>
</table>