Clinical Policy Title: Genetic testing for cystic fibrosis

Clinical Policy Number: 02.01.07

Effective Date: April 1, 2015

Initial Review Date: January 2015

Most Recent Review Date: February 17, 2016

Next Review Date: February 2017

Related Policies:

CP# 02.01.09 – Genetic testing, rare diseases

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Coverage policy

I. Keystone First considers the use of the American College of Medical Genetics (ACMG) 23- mutation core panel for cystic fibrosis (CF) to be clinically proven and, therefore, medically necessary when the following criteria are met:

<table>
<thead>
<tr>
<th>Medical necessity criteria</th>
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<tbody>
<tr>
<td>(ONE of the following criteria must be met)</td>
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</table>

- Preconception or prenatal carrier screening in individuals of reproductive age when the results would assist couples in making informed reproductive choices and/or aid in the diagnosis of fetal abnormalities.
**Medical necessity criteria**  
*(ONE of the following criteria must be met)*

<table>
<thead>
<tr>
<th>Criteria</th>
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<tbody>
<tr>
<td>Prenatal testing of at-risk fetuses with bowel hyperechogenicity and/or loop dilatation identified on ultrasound.</td>
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<tr>
<td>Diagnostic confirmation in individuals with signs and symptoms of CF, including but not limited to:</td>
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<tr>
<td>- Infants with an elevated IRT on newborn screening.</td>
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<tr>
<td>- Infants with meconium ileus or other symptoms suggestive of CF who are too young to produce adequate volumes of sweat for a sweat chloride test.</td>
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<tr>
<td>- Individuals who exhibit symptoms of CF but have a negative sweat chloride test.</td>
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<tr>
<td>- Individuals with either of the following:</td>
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<tr>
<td>o Congenital bilateral absence of vas deferens (CBAVD).</td>
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<tr>
<td>o Azooospermia or severe oligospermia (i.e., &lt; 5 million sperm/milliliter) with palpable vas deferens.</td>
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<tr>
<td>Pharmacogenomic testing to identify individuals with the p.Gly551Asp variant who may respond to treatment with ivacaftor (Vertex Pharmaceuticals, Boston, MA).</td>
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II. Keystone First considers the use of other genetic testing for CF to be clinically proven and, therefore, medically necessary after consideration has been given to standard diagnostic evaluation and use of a tiered panel or targeted test sequence for the minimal number of genes needed to establish the diagnosis when any of the following criteria are met:

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><em>(ONE of the following criteria must be met)</em></td>
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<tr>
<td>Predictive testing for a known familial mutation variant (common variant) when the familial CF mutation is known in a blood relative.</td>
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<td>Confirmatory testing with full gene sequence analysis when the ACMG-23 panel is negative and if any of the following applies:</td>
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<td>- Newborn with CF confirmed by elevated IRT and positive sweat tests.</td>
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<td>- Parent of a child with CF wants to know.</td>
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<td>- Parent with known CF or strong clinical suspicion of CF wants to know.</td>
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<tr>
<td>Confirmatory testing with deletion/duplication analysis when sequence analysis is negative but a strong clinical suspicion of CF remains.</td>
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<td>CFTR Poly-T analysis when the following criteria are met:</td>
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<td>- Individual diagnosed with nonclassic CF; or</td>
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<tr>
<td>- Male diagnosed with congenital bilateral absence of vas deferens (CAVD); OR</td>
</tr>
<tr>
<td>- R117H mutation detected on CF standard or expanded panel.</td>
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</table>

III. All genetic tests must be ordered by a trained professional e.g., medical geneticist, developmental-
behavioral pediatrician, condition-specific subspecialist, or neonatologist for neonates in the NICU, who will assure face-to-face genetic consult or counseling by appropriately trained professional(s) to accompany testing.

IV. Genetic counseling services must be provided that are accurate and provide balanced information to afford individuals the opportunity to make autonomous decisions. Every attempt should be made to protect individual rights and genetic and medical privacy rights and to prevent discrimination and stigmatization.

Limitations:

All other uses of genetic testing for CF are not medically necessary, including but not limited to:

- General screening in all newborns.
- General carrier screening in populations other than those considering childbearing or prenatal testing.
- Persons who have undergone previous genetic testing for CF, unless changes in technology or treatments indicate that test result or patient outcomes would change.
- Detection of genetic susceptibility in minors of adult-onset disorders except when such testing impacts clinical management prior to adulthood.
- Use of self-testing home kits due to potential risks associated with genetic testing, such as inappropriate testing, misinterpretation of results, inaccurate or not clinically valid testing, lack of follow-up care and other adverse consequences.

Alternative Covered Services:

- Clinical evaluation.
- Immunoreactive trypsinogen (IRT).
- Pilocarpine iontophoresis of sweat electrolytes (sweat test).
- Semen analysis.
- Transepithelial nasal potential difference.
- Direct intestinal current measurements from rectal suction biopsies.
- Pancreatic stimulation testing for pancreatic duct electrolyte secretion.

Background

Cystic fibrosis (CF) is a life-shortening inherited disease that primarily affects the lungs and digestive system. According to the Cystic Fibrosis Foundation, approximately 1,000 new cases of CF are diagnosed each year in the U.S., and an estimated 30,000 individuals live with the disease (CFF 2013). Most cases are diagnosed by age 2, but the number of new diagnoses in adults is increasing. According to the most recent patient registry data, the median predicted age of survival for people with CF is early 40s (CFF 2013).

CF is an autosomal recessive genetic disorder, meaning two copies of an abnormal gene — one from each parent — must be present in order for the disease or trait to develop (GHR 2012). People with only one copy of the abnormal gene are considered carriers. An additional 10 million people — about one in every 31 Americans — are symptomless carriers of the defective CF gene. They will not develop the disease, but they can pass the abnormal gene to their children (GHR 2012).
Persons with CF have one or more mutations in the gene encoding for the CFTR protein on both alleles of chromosome 7 (GHR 2012). This multifunctional protein is required to regulate the components of sweat, digestive fluids and mucus. The CFTR mutation affects the transport of chloride and sodium across cell membranes, which can result in an imbalance of water absorption, causing dehydration. The liquid depletion results in the presence of thick and sticky mucus that can damage many body organs.

More than 1,900 mutations in the CFTR gene have been reported to the CF Mutation Database (CFC 2011). However, most of these mutations are rare and their functional roles are unclear. The most common mutation is delta F508, which is a deletion of one amino acid at position 508 in the CFTR protein, and accounts for two-thirds of all CF alleles worldwide. The CFTR mutation detection rate varies by test method and ethnic background. While persons of northern European ancestry have the highest rates of CF, CFTR mutations occur across all races and many ethnicities (GHR 2012).

While the American College of Medical Genetics includes prenatal testing of embryos or pre-implantation genetic diagnosis (PGD) for cystic fibrosis, infertility services are not covered under Medicaid. As a consequence pre-natal testing of embryos is not a Medicaid benefit.

Non-genetic testing

Early clinical recognition of CF on the basis of symptoms is desirable but difficult. Only about 10 percent to 15 percent of infants with CF have symptoms at birth. The majority of symptoms are not specific to CF, and misdiagnosis and delay in treatment may occur. The most common phenotypic features include meconium ileus, progressive damage to the respiratory system, chronic digestive system problems associated with pancreatic insufficiency with malabsorption, salt loss syndromes and infertility in males (NHLBI 2014). Variability of these features among unrelated individuals and within families further complicates diagnosis. Some patients may have all the classical manifestations of CF from infancy and have a relatively poor prognosis, while others have much milder disease manifestations. Environmental, non-CFTR genetic mutations, and other unknown factors likely contribute to this variability (Moskowitz 2008).

In the U.S., newborn screening (NBS) for CF is associated with improved growth, cognitive development, survival, and reduced hospitalizations (Grosse 2004). NBS programs for CF use an array of protocols and algorithms. Protocols use measurement of immunoreactive trypsinogen (IRT) in dried blood spots as the initial screen to identify infants at high risk of having CF (Mishra 2005). The specific value used to decide whether IRT is sufficiently elevated to warrant further testing depends on the laboratory kits used, the population screened, and the screening protocols and algorithms employed (Grosse 2004). Single IRT measures lack sufficient specificity resulting in a high number of false positive results (and a correspondingly low positive predictive value), and additional testing is recommended to reduce the potential harms associated with false positive diagnoses (CFF 2014, Mishra 2005). Approximately 90 percent to 95 percent of children with CF without meconium ileus are reported to be detected by IRT- repeat IRT screening (Grosse 2004).

An earlier diagnosis may reduce the expense and anxiety associated with work-up for failure to thrive or other symptoms, but additional benefits of screening will depend on the availability of specialized medical care. False screen-positive and screen-negative results from initial IRT levels may occur, and additional steps (e.g., testing and counseling) are needed to mitigate potential harms (Grosse 2004).
Analysis of sweat electrolytes from pilocarpine iontophoresis (sweat test) is considered diagnostic to confirm or rule out a CF diagnosis (Mishra 2005). The principle indications for performing a sweat test include a positive newborn screening for CF, clinical signs suggestive of CF, or a family history of CF (Mishra 2007). Despite the limited evidence supporting thresholds for defining CF using a sweat test, a value $\geq 60$ mmol/L is considered diagnostic of CF; an interval of 40 mmol/L - 59 mmol/L is considered borderline or possibly carrier status; and <39 mmol/L is considered normal (Mishra 2007). These intervals are applied across all ages and genders but may be less accurate in infants and adults, particularly among some infants who have insufficient quantities of sweat for reliable testing (Mishra 2007, Grosse 2004).

Transepithelial nasal potential difference (NPD) may be used in screening protocols. Direct intestinal current measurements (ICM) from rectal suction biopsies and pancreatic stimulation testing for pancreatic duct electrolyte secretion may be used to confirm CFTR dysfunction when previous testing is inconclusive (Mishra 2005).

Genetic testing

Genetic testing for CFTR mutation (DNA mutation analysis) has expanded our understanding of CFTR functions. New drug therapy is available that targets the genetic cause of CF in individuals with the G551D CFTR variant, and more drugs are in development (Clancy 2014, CFF 2013). At the same time, the complexity of the diagnosis has increased with the recognition of milder phenotypes, patients with no clinical manifestation detected by screening programs, and patients with CF phenotypes with less than two CFTR mutations (Mishra 2007). DNA samples can be obtained from either peripheral blood or a tissue sample, such as cells from the inside of the cheek.

CF-related gene mutations are classified into six groups according to the mechanism by which they disrupt the synthesis, traffic and function of CFTR that is critical for normal organ functioning. These classes are not mutually exclusive, and specific mutations may have characteristics of more than one class (Mishra 2005):

- **Class I mutations** prevent protein synthesis. Mutations in this class include the most severe CF
  - phenotypes.
- **Class II mutations** are defects in protein processing. These mutations include the most common and the first recognized mutation, Delta F508.
- **Class III mutations** disrupt channel regulation or gating.
- **Class IV mutations** disrupt chloride conductance.
- **Class V mutations** result in decreased amounts of CFTR protein.
- **Class VI mutations** reduce CFTR protein stability and increases CFTR channel turnover at the cell surface.

CFTR mutations are further classified depending on the severity of protein dysfunction and clinical effect. Severe mutations result in no protein synthesis or blocked processing (Class I, II, and III), whereas milder mutations show altered conductance or reduced synthesis (Class IV, V, and VI) (Mishra 2005).

An increasingly wide range of techniques is used to identify CFTR gene sequence variations. CFTR gene analyses are performed in specialist clinical molecular genetics laboratories closely associated with clinical genetic services or research facilities, as well as in private laboratories. DNA sequencing
of all coding regions on the gene is the most accurate way to detect mutations but is time consuming and expensive (Mishra 2005). In an effort to standardize the laboratory approach to screening and determine the optimal balance between test performance and costs, the Subcommittee on Cystic Fibrosis Screening, the American College of Medical Genetics (ACMG), and the American College of Obstetricians and Gynecologists (ACOG) developed and subsequently modified a pan-ethnic panel that included all 23 mutations with an allele frequency $\geq 0.1\%$ in the general U.S. population. The test is performed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories, and as such, does not require U.S. Food and Drug Administration (FDA) approval (Moskowitz 2001).

The ACMG 23-mutation panel may miss certain carriers who possess rarer mutations, especially in African-American and Hispanic individuals. Larger mutation panels may be added to accommodate rarer mutations. The FDA has approved several extended panels as 510(k) Class II devices (FDA 2014).

**Diagnosis**

Most commonly, the diagnosis of CF is determined by the presence of or more characteristic phenotypic features of CF plus evidence of an abnormality in CFTR function based on one of the following (Moskowitz 2001):

- Presence of two CFTR pathogenic allelic variants.
- Two abnormal sweat test values (>60 mEq/L).
- Transepithelial nasal potential difference (NPD) measurements characteristic of CF.

The diagnosis of CF may be made in the absence of phenotypic features in newborns by the presence of two disease-causing mutations in CFTR or abnormal sweat chloride value, or prenatally by the presence of two pathogenic variants in CFTR (Moskowitz 2001).

Other genetic testing may be indicated to confirm a diagnosis. For example, predictive testing for known familial mutation variant (common variant) in asymptomatic individuals may be indicated when the familial CF mutation is known in a blood relative. When the ACMG 23 panel is negative, full gene sequence analysis may be needed in newborns with clinical suspicion of CF, for a parent of a child with CF, or for a parent with known CF or strong clinical suspicion of CF. Confirmatory testing with deletion/duplication analysis may be indicated when gene sequence analysis is negative but a strong clinical suspicion of CF remains (Moskowitz 2001).

The poly T tract, a string of thymidine bases located in intron 8 of the CFTR gene, can be associated with CFTR-related disorders depending on its size. Males with congenital bilateral absence of vas deferens (CAVD) or suspected CAVD, individuals with non-classic CF, or adult carriers of ST who wish to further refine their reproductive risks may be appropriate for ST/TG tract typing (Moskowitz 2001).

However, objective testing does not always provide clarity. Genetic counseling and comprehensive educational programs are available for the public and health professionals to help providers and families navigate the diagnostic process and understand the risks and benefits associated with genetic testing (NIHCDCS 1999, Grosse 2004, Langfelder-Schwind 2005, Farrell 2008, CFF 2009, Dequeker 2009).
Searches

Keystone First searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services.
- The Genetic Test Registry: Cystic Fibrosis.

Searches were conducted on December 8, 2014, using the terms "cystic fibrosis/classification" [MeSH] or "cystic fibrosis/diagnosis" [MeSH] or "cystic fibrosis/economics" [MeSH], as well as free text terms for “cystic fibrosis” and “cystic fibrosis transmembrane conductance regulator” limited to articles published in English.

Included were:
- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

Findings

For this policy we identified six systematic reviews and 15 professional guidelines that addressed various aspects of genetic testing for CF, but we found no cost-effectiveness analyses conducted in the U.S. context. Partial cost analyses conducted in a Wisconsin newborn screening program indicated the majority of CF screening costs were offset by savings from a reduction in ordering of sweat tests (Grosse 2004).

Evidence in the published peer-reviewed scientific literature, as well as support from specialty societies and organizations, support the use of CFTR mutation testing to identify those at risk for acquiring CF or having affected children, or for confirming a diagnosis in those who present with signs and symptoms of CF (Farrell 2008, Langfelder-Schwind, et al., 2005; Grosse, et al., 2004).

- **There is sufficient evidence to support using the ACMG 23 mutation panel as a validated test for CFTR analysis.** In selecting a range of mutations to test, consideration should be given to test validity, ethnicity, geography, presence of classic or atypical characteristics, and its intended use (e.g., diagnostic evaluation versus screening versus pharmacogenetic testing). When molecular analysis is used to confirm a diagnosis based on clinical concerns and elevated sweat electrolytes, many mutations may need to be tested, whereas screening programs generally test for mutations associated with the most severe forms of the disease (Mishra 2005). The ACMG 23 mutation panel has an overall 84 percent detection rate of CF carriers in the U.S. pan-ethnic population and is considered the standard test for population-based carrier testing (ACMG 2008, Farrell 2008, Dequeker 2009, Strom 2011, ACOG 2011).
- **There is sufficient evidence to support CFTR mutation testing using the ACMG 23 core**

- **2009, Southern 2009, CADTH 2012, CFF 2013):**
  - Preconception or prenatal carrier screening in individuals of reproductive age when the results would assist couples in making informed reproductive choices and/or aid in the diagnosis of fetal abnormalities.
  - Prenatal testing of embryos or pre-implantation genetic diagnosis (PGD) when either parent has a diagnosis of CF, is a known carrier of a CFTR mutation, or has a family history of CF.
  - Prenatal testing of at-risk fetuses with bowel hyperechogenicity and/or loop dilatation.
  - Newborn screening in infants with an elevated IRT.
  - Diagnostic confirmation in individuals with signs and symptoms of CF, including but not limited to:
    - Infants with meconium ileus.
    - Adults with other diseases associated with CFTR mutations (e.g., males with congenital bilateral absence of the vas deferens (CBAVD), chronic pancreatitis, disseminated bronchiectasis, or atypical chronic rhinosinusitis).

- Pharmacogenomic testing to identify individuals with the p.Gly551Asp variant who may respond to treatment with ivacaftor (trade name Kalydeco, developed as VX-770, Vertex Pharmaceuticals, Boston, MA).

- **There is insufficient evidence to support the routine use of extended mutation panels in the screening or diagnosis of CF.** There are limited data on the penetrance of the rarer mutations and their impact on health outcomes. The ACMG does not recommend the routine use of extended panels (Grody 2001). Extended panels may be needed in select circumstances to reduce diagnostic uncertainty, and choice of a tiered panel or targeted test sequence should be based on the minimal number of genes required to establish the diagnosis. Examples include:
  - Predictive testing for a known familial mutation variant (common variant) when the familial CF mutation is known in a blood relative.
  - Confirmatory testing with full gene sequence analysis when the ACMG-23 panel is negative and any of the following applies:
    - Newborn with CF is confirmed by elevated IRT and positive sweat tests.
    - Parent of a child with CF who wants to know.
    - Parent with known CF or strong clinical suspicion of CF who wants to know.

- Confirmatory testing with deletion/duplication analysis when sequence analysis is negative but a there is a strong clinical suspicion of CF.

- **The evidence is insufficient to support the use of routine newborn genetic screening for CF in all newborns, as no health benefit has been demonstrated in the absence of elevated IRT results.** Screening of healthy infants with no known history of familial CF may be associated with false positives which could affect the infant-parent relationship, give false reassurance from negative tests delaying treatment in CF infants, or cause needless treatment to be given to infants with mild disease who would otherwise not have required treatment (Grosse 2004, Oliver 2009, CADTH 2012). Inclusion of a greater number of CFTR mutations in NBS panels decreases the number of false negative results, but also increases carrier detection and costs of testing and potential follow-up care (Grosse 2004, CADTH 2012).

- **The evidence is insufficient to support the use of carrier screening for CF in the general population, as no health benefit has been demonstrated in individuals other than those**
considering childbearing or prenatal testing. The decision to conduct carrier screening in minors is controversial. Borry et al. found that while most parents and immediate relatives were interested in the carrier status of their children and want their children to be tested before they reach legal majority (and some even in childhood), professional guidelines support deferring carrier testing on the grounds that children should be able to decide for themselves later in life (Borry 2005).

- CF screening programs should be accompanied by an implementation planning process involving specialized CF care centers and specialists in risk communication, including genetic counselors. Genetic counseling should be available before and after testing for anyone who undergoes genetic testing for CF (Kaye 2006, Farrell 2008, Dequeker 2009, ACOG 2011, Langfelder-Schwinder 2014).
### Summary of clinical evidence

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td><strong>Newborn screening (NBS)</strong></td>
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<tr>
<td>CADTH 2012 Key points</td>
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<tr>
<td>• Systematic review of one health technology assessment by the Institute for Health Economics (2007), seven diagnostic studies, and one cost-comparison study.</td>
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<tr>
<td>• Analysis of seven NBS protocols consisting of two- or three-test algorithms using the following tests: IRT, single- or multi-mutation DNA tests, pancreatic-associated protein (PAP) test.</td>
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<tr>
<td>• Overall quality: potential for bias was high or unclear.</td>
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<tr>
<td>• All screening protocols were associated with high sensitivity and specificity, but their positive predictive values were either low or not estimated. Calculation of negative predictive values requires detecting the missed cases clinically, as well as tracking the final diagnostic status of all those with positive screens.</td>
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<tr>
<td>• One economic modelling study: The cost of CF NBS varied from U.S. $4.48 per newborn for the IRT/IRT protocol to U.S. $6.78 per newborn with the IRT/DNA protocol.</td>
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<tr>
<td>• Research evidence of clinical utility is limited, which would inform policy makers about the benefits of adding CF NBS to the current screening panel.</td>
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<tr>
<td>• The decision as to whether to add screening for CF in existing screening panels should consider the benefits, harms, and costs of the available screening protocols.</td>
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<tr>
<td>Southern 2009 Key points</td>
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<tr>
<td>• Systematic review of two RCTs were identified; data from one study (Wisconsin trial) were included.</td>
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<tr>
<td>• Overall quality: low risk of bias.</td>
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<td>• Severe malnutrition was less common among screened participants.</td>
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<tr>
<td>• At age 7, 88% of screened participants and 75% of controls had lung function parameters within normal limits of at least 89% predicted.</td>
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<td>• At diagnosis, chest radiograph scores were significantly better among screened participants; but over time, chest radiograph scores were worse in the screened group (WCXR P = 0.017 and BCXR P = 0.041). Results were no longer significant after adjustment for genotype, pancreatic status, and Pseudomonas aeruginosa-culture results.</td>
<td></td>
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<tr>
<td>• Screening seems less expensive than traditional diagnosis.</td>
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</table>
| Grosse 2004 | **Key points**  
| On behalf of the CDC and CFF | **Clinical validity data:**  
|  | - In the U.S., multi-stage protocols report high sensitivity (>90%). 90% – 95% of children with CF without meconium ileus are detected by IRT-repeat IRT screening. IRT/DNA screening and follow-up protocols that use multiple mutation panels and directly refer children with extremely high IRT values for sweat testing have achieved clinical sensitivity of ≥98%.  
|  | - NBS for CF has moderate false-positive rates relative to other NBS tests.  
|  | - NBS algorithms for CF can result in false-negatives, resulting in delayed diagnosis; causes include low or ambiguous IRT values or DNA mutation not in testing panel used by the screening program.  
|  | **Outcome data:**  
|  | - Systematic review of two RCTs, five studies of screened and unscreened cohorts, and two studies using registry databases in the U.S. and UK.  
|  | - Overall quality: moderate consisting of Level 1 (high quality RCT) or Level 2 (limited quality patient-oriented evidence from cohort studies or other studies with inconsistent findings).  
|  | - NBS improved child survival, growth and cognitive ability, and reduced hospitalizations.  
|  | **Costs:**  
|  | - Based on data from the Wisconsin screening program, average costs = $2.35 for an IRT/DNA algorithm with a single mutation and $3.60 for an IRT/DNA algorithm with a multiple-mutation panel.  
|  | - Conclusions: The health benefits to children with CF outweigh the risk of harm and justify screening for CF.  
|  | - The complex policy decision as to whether to adopt screening also requires consideration of costs, resources, and priorities.  
| Oliver 2004 | **Key points**  
| Cochrane review |  
|  | - Systematic review of studies addressing the impact of disclosing carrier status during routine blood spot screening using a soundly controlled trial or RCT.  
|  | - Overall quality: no studies identified.  
|  | - There is a need to develop and evaluate the effects of interventions to support the disclosure of carrier status to parents following newborn screening.  
| Carrier screening |  
| Borry 2005 | **Key points**  
|  | - Systematic review of 20 studies describing attitudes of minors, parents or health care professionals toward carrier testing in minors in a family context.  
|  | - Overall quality: unclear.  
|  | - Most parents and relatives favor carrier testing before age 18 years. Professional guidelines advise deferring carrier testing on the grounds that children should be able to decide for themselves later in life.  
|  | - This can lead to tensions between parents and health care professionals regarding carrier testing in minors.  
| Hayes 2004 | **Key points**  
|  | - Systematic review of one RCT, two retrospective cohort studies, seven prospective
cohort studies of preconception or prenatal populations.

- Overall quality: High. Limitations included small number of CF carriers and even smaller numbers of affected fetuses represented in each study; populations were largely Caucasian, results in other populations with lower prevalence of CF are likely to be lower.

- Results of population-based studies of genetic screening for CF show:
  - A high acceptance rate among couples who are planning pregnancy or those who are pregnant, particularly when accompanied by appropriate educational materials and genetic counseling.
  - Usefulness when informing a couple’s decisions regarding childbearing or fetal diagnosis.
  - The potential to reduce the incidence of CF, but only through avoidance of pregnancies or therapeutic abortion.
  - No single screening approach is significantly superior.
  - Cost-effectiveness is highly dependent on the cost of the test, the estimated lifetime costs of treating an individual with CF, and the population studied.
  - Does not provide any health benefit other than for individuals considering childbearing or prenatal testing.

Glossary

**Allele** — One of two or more versions of a gene. An individual inherits two alleles for each gene; one from each parent. If the two alleles are the same, the individual is homozygous for that gene. If the alleles are different, the individual is heterozygous. Though the term “allele” was originally used to describe variation among genes, it now also refers to variation among non-coding DNA sequences.

**Autosomal recessive** — Describes a trait or disorder requiring the presence of two copies of a gene mutation (one from each parent) at a particular locus in order to express observable phenotype; specifically refers to genes on one of the 22 pairs of autosomes (non-sex chromosomes).

**Intestinal current measurements (ICM)** — One of the alternative methods for demonstration of defective ion transport. It can be carried out on suction biopsy tissue obtained from the colonic mucosa.

**Medically Necessary** — A service or benefit is Medically Necessary if it is compensable under the MA Program and if it meets any one of the following standards:

- The service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition or disability.
- The service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury or disability.
- The service or benefit will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age.

**Meconium ileus** — Obstruction of the intestine (ileus) due to overly thick meconium, the dark, sticky material that is normally present in the intestine at birth and passed in the feces after birth. The obstruction results from a deficiency of trypsin and other digestive enzymes from the pancreas.

**Nasal potential difference (NPD)** — Measures how well sodium and chloride flow across the mucous membranes in the nose.
**Sweat testing** — A general term that refers to the quantitative or qualitative analysis of sweat to determine electrolyte concentration, conductivity or osmolality for the diagnosis of CF. Also called quantitative pilocarpine iontophoresis sweat chloride testing.

**References**

**Professional society guidelines/others:**


**Peer-reviewed references:**


**Clinical Trials:**

Searched clinicaltrials.gov on December 29, 2014 using search term “CFTR” | Open Studies | Condition: cystic fibrosis. 22 studies found; 6 relevant.

Cystic Fibrosis Related Bone Disease: the Role of CFTR. Available at: http://ClinicalTrials.gov/show/NCT01549314.

 Genetic Modifiers of Cystic Fibrosis Related Diabetes. Available at:
http://ClinicalTrials.gov/show/NCT01113216.

Genetics of Insulin and Incretins in Cystic Fibrosis. Available at: http://ClinicalTrials.gov/show/NCT01852448.

Role of Genetic Factors in the Development of Lung Disease. Available at: http://ClinicalTrials.gov/show/NCT00001532.

The Role of Bacteria and Genetic Variations in Cystic Fibrosis. Available at: http://ClinicalTrials.gov/show/NCT00043225.

Genetic Modifiers of Cystic Fibrosis (CF) Liver Disease. Available at: http://ClinicalTrials.gov/show/NCT00804583.

Centers for Medicare & Medicaid Services (CMS) national coverage determination (NCD):

Searched Medicare Document Types: NCD, MEDCAC, TA, MCD, LCD (Final)
Keyword: cystic fibrosis
Keyword Lookup Type: Entire Document
Keyword Search Type: Exact Phrase
States: Louisiana, Pennsylvania, South Carolina


SUMMARY: The sweat test is an important diagnostic tool in cystic fibrosis and may be covered when used for that purpose. Usage of the sweat test as a predictor of efficacy of sympathectomy in peripheral vascular disease is unproven and, therefore, is not covered.

Local coverage determinations (LCDs):

L33640 Biomarkers Overview Pennsylvania:

L33638 Biomarkers Overview Louisiana:
SUMMARY: Medicare considers genetic testing medically necessary to establish a molecular diagnosis of an inheritable disease when all of the following criteria are met:

- The beneficiary displays clinical features, or is at direct risk of inheriting the mutation in question (pre-symptomatic).
- The result of the test will directly impact the treatment being delivered to the beneficiary.
- After history, physical examination, pedigree analysis, genetic counseling, and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain, such testing can be coverable.

Key limitation: Genetic testing of tissue samples from other family members (e.g., possible/probable carriers) is not statutorily covered by Medicare.

The below table delineates the coverage status for various germline mutations, noting age-related determinations, which reflect relevance to the typical Medicare population, based upon the above bulleted principles. No procedure-to-diagnosis based limitations will be implemented, with the expectation that such sound principles of genetic counseling and testing have been implemented.

<table>
<thead>
<tr>
<th>Categorical Mutations</th>
<th>Coverage Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTR(cystic fibrosis transmembrane conductance regulator) (eg. cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)</td>
<td>Non-covered</td>
</tr>
<tr>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
<td>Non-covered</td>
</tr>
</tbody>
</table>

Commonly submitted codes

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>81220</td>
<td>CTR(cystic fibrosis transmembrane conductance regulator) (eg. cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)</td>
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<tr>
<td>96040</td>
<td>Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family</td>
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<table>
<thead>
<tr>
<th>ICD-9 Code</th>
<th>Description</th>
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</tr>
</thead>
<tbody>
<tr>
<td>277.00</td>
<td>Cystic fibrosis without mention of meconium ileus</td>
<td></td>
</tr>
<tr>
<td>277.01</td>
<td>Cystic fibrosis with mention of meconium ileus</td>
<td></td>
</tr>
<tr>
<td>277.02</td>
<td>Cystic fibrosis with pulmonary manifestations</td>
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</tr>
<tr>
<td>277.03</td>
<td>Cystic fibrosis with gastrointestinal manifestations</td>
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<tr>
<td>277.09</td>
<td>Cystic fibrosis with other manifestations</td>
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<tr>
<td>606.0</td>
<td>Azospermia</td>
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<td>606.1</td>
<td>Oligospermia</td>
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<tr>
<td>752.89</td>
<td>Congenital absence of vas deferens</td>
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<tr>
<td>777.1</td>
<td>Meconium ileus NOS</td>
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<tr>
<td>ICD-10 Code</td>
<td>Description</td>
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<tr>
<td>V18.19</td>
<td>Family hx of other endocrine and metabolic disease</td>
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<tr>
<td>V18.9</td>
<td>Genetic disease carrier</td>
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<tr>
<td>V83.81</td>
<td>Cystic fibrosis gene carrier</td>
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<tr>
<td>E84.0</td>
<td>Cystic fibrosis with pulmonary manifestations</td>
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<td>E84.11</td>
<td>Cystic fibrosis with meconium ileus</td>
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<tr>
<td>E84.19</td>
<td>Cystic fibrosis with other intestinal manifestations</td>
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<td>E84.8</td>
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<td>E84.9</td>
<td>Cystic fibrosis unspecified</td>
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<td>N46.02</td>
<td>Oligospermia</td>
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<td>Q55.4</td>
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<tr>
<td>Z14.1</td>
<td>Genetic carrier, cystic fibrosis</td>
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<tr>
<td>Z83.49</td>
<td>Family history of endocrine, metabolic, and nutritional disease</td>
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<tr>
<td>Z84.81</td>
<td>Family history of carrier of genetic disease</td>
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<table>
<thead>
<tr>
<th>HCPCS Level II</th>
<th>Description</th>
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