Clinical Policy Title: Genetic testing for cystic fibrosis

Clinical Policy Number: 02.01.07

Effective Date: April 1, 2015
Initial Review Date: January 21, 2015
Most Recent Review Date: February 15, 2017
Next Review Date: February 18

Policy contains:
- Cystic fibrosis transmembrane conductance regulator (CFTR) gene testing.
- Genetic counseling.

CP# 02.01.09 Genetic testing, rare diseases

ABOUT THIS POLICY: Prestige Health Choice has developed clinical policies to assist with making coverage determinations. Prestige Health Choice’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Prestige Health Choice when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Prestige Health Choice’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Prestige Health Choice’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Prestige Health Choice will update its clinical policies as necessary. Prestige Health Choice’s clinical policies are not guarantees of payment.

Coverage policy

Prestige Health Choice 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 (ONE of the following criteria must be met)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
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<tr>
<td>Prenatal testing of embryos or pre-implantation genetic diagnosis (PGD) when either parent has a diagnosis of CF, is a known carrier of a cystic fibrosis transmembrane conductance regulator (CFTR) mutation or has a family history of CF.</td>
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<td>Prenatal testing of at-risk fetuses with bowel hyperechogenicity and/or loop dilatation identified on ultrasound.</td>
</tr>
<tr>
<td>Diagnostic confirmation in individuals with signs and symptoms of CF, including but not limited to:</td>
</tr>
<tr>
<td>- Infants with an elevated immunoreactive trypsinogen (IRT) on newborn screening.</td>
</tr>
<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>
</tr>
<tr>
<td>- Individuals who exhibit symptoms of CF but have a negative sweat chloride test.</td>
</tr>
</tbody>
</table>
**Medical necessity criteria**

ONE of the following criteria must be met

- Individuals with either of the following:
  - Congenital bilateral absence of vas deferens (CBAVD).
  - Azoospermia or severe oligospermia (i.e., <5 million sperm/milliliter) with palpable vas deferens.

Pharmacogenomic testing to identify individuals with the p.Gly551Asp variant and/or the Phe508del mutation who may respond to treatment with ivacaftor (Kalydeco®, lumacaftor or both drugs in combination (Orkambi® Vertex Pharmaceuticals, Boston, MA).

Prestige Health Choice 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>
<th>Predictive testing for a known familial mutation variant (common variant) when the familial CF mutation is known in a blood relative.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmatory testing with full gene sequence analysis when the ACMG-23 panel is negative and any of the following applies:</td>
</tr>
<tr>
<td>- Newborn with CF confirmed by elevated IRT and positive sweat tests.</td>
</tr>
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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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<tr>
<td>CFTR Poly-T analysis when the following criteria are met:</td>
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<tr>
<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>
</tr>
</tbody>
</table>

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. Genetic counseling services must be provided that are accurate and provide balanced information to afford individuals the opportunity to make autonomous decisions.

The patient or guardian has a desire for engagement with the integrated multidisciplinary team that is documented in the clinical record. Every attempt should be made to protect individual rights and genetic and medical privacy rights and to prevent discrimination and stigmatization.

The test results will directly impact management (i.e., as a result of the test, effective treatment may be offered that will alter the course of disease or outcomes). The test is an analytically and clinically valid test (i.e., supported by peer-reviewed published research). Consideration has been given to standard diagnostic evaluation and use of tiered panel or targeted test sequence for minimal number of genes to establish the diagnosis.

**Limitations:**

...
Coverage determinations are subject to benefit limitations and exclusions as delineated by the state Medicaid authority. The Florida Medicaid website can be accessed at http://ahca.myflorida.com/Medicaid/.

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 nasal measurements from rectal suction biopsies.
- Pancreatic stimulation testing for pancreatic duct electrolyte secretion.

**Background**

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 United States, 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 in years of survival for people with CF is early age 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).

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 United States, 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 ≥ 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 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 ≥ 0.1 percent 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).

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,
We included:

- 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 5T who wish to further refine their reproductive risks may be appropriate for 5T/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**

Prestige Health Choice 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 (CMS).

We conducted searches on January 8, 2016. Searched terms were: "genetic testing (MeSH)"; "cystic fibrosis (MeSH)" and "laboratory test."

We included:

- **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, 2005; Grosse, 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 mutation panel for the following (Moskowitz, 2001; Grosse, 2004; Hayes, 2004; Mishra, 2005; ACMG, 2008; Dequeker, 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 is 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 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-Schwind, 2014).

**Policy updates:**

Elborn (2016) noted that the development and delivery of drugs that improve the clearance of mucus from the lungs and treat the consequent infection, in combination with correction of pancreatic insufficiency and undernutrition by multidisciplinary teams, have resulted in remarkable improvements in quality of life and clinical outcomes in patients with cystic fibrosis, with median life expectancy now older than 40 years.
An ongoing clinical study (Knowles, 2015) examines modifier genes that may play a role in the development of CF liver disease. The study is using a combination of serum evaluation, pulmonary function tests, and other historical information to identify the modifier genes that influence disease severity and may ultimately lead to a better understanding of CF liver disease. It is anticipated the manipulation of these modifier genes may useful in the development of new treatments for CF.

The PROSPECT trial (Rowe, 2015) aims to identify genetic markers that may reflect the impact of emerging CFTR modulator therapies that directly target defective CFTR genes. It is postulated that partial restoration of CFTR function might impact CF disease progression and might be followed clinically by CF-related disease biomarkers to monitor disease progression, and document the mechanistic effects of CFTR modulators and other relevant therapies in individuals with CF.

**Summary of clinical evidence:**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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| Elborn (2016) | **Key points:**  
  - The development and delivery of new CF drugs has resulted in remarkable improvements in quality of life and clinical outcomes with median life expectancy now older than 40 years.  
  - Innovative and transformational therapies that target the basic defect in cystic fibrosis have recently been developed and are effective in improving lung function and reducing pulmonary exacerbations.  
  - Further small molecule and gene-based therapies are being developed to restore CFTR function.  
  - These therapies promise to be disease modifying and to improve the lives of people with cystic fibrosis. |
| Knowles (2015) | **Genetic Modifiers of Cystic Fibrosis (CF) Liver Disease**  
  - Clinical trial of modifier genes that may play a role in the development of CF liver disease.  
  - Study aims to examine the genetic makeup of CF patients who are considered to have severe liver disease to see if any modifier genes influence the hepatic dysfunction.  
  - The identification of modifier genes that influence disease severity may ultimately lead to a better understanding of CF liver disease, and may be useful in the development of new treatments. |
| Rowe (2015) | **A Two-Part Multicenter Prospective Longitudinal Study of CFTR-dependent Disease Profiling in Cystic Fibrosis (PROSPECT)**  
  - Study of CF biomarkers that might reflect partial restoration of CFTR function and can be used to monitor disease progression (PROSPECT trial).  
  - Aim is to evaluate the mechanistic effects of CFTR modulators and other relevant therapies in individuals with CF |
| CADTH (2012) | **Key points:** |
| Newborn screening for cystic fibrosis | Systematic review of one health technology assessment by the Institute for Health Economics (2007), seven diagnostic studies, and one cost-comparison study.  
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.  
Overall quality: potential for bias was high or unclear.  
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.  
One economic modeling 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.  
Research evidence of clinical utility is limited, which would inform policymakers about the benefits of adding CF NBS to the current screening panel.  
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. |
|---|---|
| Southern (2009) Newborn screening for cystic fibrosis | Key points:  
Systematic review of two RCTs; data from one study (Wisconsin trial) met inclusion criteria.  
Overall quality: low risk of bias.  
Severe malnutrition was less common among screened participants.  
At age 7, 88% of screened participants and 75% of controls had lung function parameters within normal limits of at least 89% predicted.  
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.  
Screening seems less expensive than traditional diagnosis. |
| Grosse (2004) Newborn screening for cystic fibrosis | Key points:  
Clinical validity data:  
In the U.S., multistage 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). |
<table>
<thead>
<tr>
<th>Study</th>
<th>Key points:</th>
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<tbody>
<tr>
<td>Oliver (2004)</td>
<td>Disclosing to parents newborn carrier status identified by routine blood spot screening</td>
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<tr>
<td></td>
<td>Systematic review of studies addressing the impact of disclosing carrier status during routine blood spot screening using a soundly controlled trial or RCT.</td>
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<td></td>
<td>Overall quality: no studies identified.</td>
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<td>There is a need to develop and evaluate the effects of interventions to support the disclosure of carrier status to parents following newborn screening.</td>
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<td>Borry (2005)</td>
<td>Attitudes towards carrier testing in minors</td>
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<td></td>
<td>Systematic review of 20 studies describing attitudes of minors, parents, or health care professionals toward carrier testing in minors in a family context.</td>
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<tr>
<td></td>
<td>Overall quality: unclear.</td>
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<td>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.</td>
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<td></td>
<td>This can lead to tensions between parents and health care professionals regarding carrier testing in minors.</td>
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<td>Hayes (2004)</td>
<td>Genetic carrier testing for cystic fibrosis</td>
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<tr>
<td></td>
<td>Systematic review of one RCT, two retrospective cohort studies, seven prospective cohort studies of preconception or prenatal populations.</td>
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<tr>
<td></td>
<td>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.</td>
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<tr>
<td></td>
<td>Results of population-based studies of genetic screening for CF show: o 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.</td>
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<td></td>
<td>o Usefulness when informing a couple’s decisions regarding childbearing or fetal diagnosis.</td>
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<td></td>
<td>o The potential to reduce the incidence of CF, but only through avoidance of pregnancies or therapeutic abortion.</td>
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<td></td>
<td>o No single screening approach is significantly superior.</td>
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<td></td>
<td>o 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.</td>
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<tr>
<td></td>
<td>o Does not provide any health benefit other than for individuals considering childbearing or prenatal testing.</td>
</tr>
</tbody>
</table>
References

Professional society guidelines/other:


Peer-reviewed references:


CMS National Coverage Determination (NCDs):


Local Coverage Determinations (LCDs):

L35062 Biomarkers. CMS Medicare Coverage Database website. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=35062&ver=44&CoverageSelection=Both&ArticleType=All&PolicyType=Final&s=All&KeyWo
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>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>81220</td>
<td>CTR(cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines)</td>
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<thead>
<tr>
<th>ICD-10 Code</th>
<th>Description</th>
<th>Comments</th>
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<tbody>
<tr>
<td>E84.0</td>
<td>Cystic fibrosis with pulmonary manifestations</td>
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<tr>
<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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<tr>
<td>E84.8</td>
<td>Cystic fibrosis with other manifestations</td>
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<td>E84.9</td>
<td>Cystic fibrosis unspecified</td>
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<tr>
<td>N46.01</td>
<td>Azoospermia</td>
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<td>N46.02</td>
<td>Oligospermia</td>
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<tr>
<td>Q55.4</td>
<td>Congenital absence of vas deferens</td>
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<td>Z14.1</td>
<td>Genetic carrier, cystic fibrosis</td>
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<td>Z84.81</td>
<td>Family history of carrier of genetic disease</td>
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<tr>
<th>HCPCS Level II</th>
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