



## CLINICAL MEDICAL POLICY and PRIOR-AUTHORIZATION POLICY

<b>Policy Name:</b>	Genetic Testing for Cystic Fibrosis
<b>Policy Number:</b>	MD-006-MD-PA
<b>Approved By:</b>	Medical Management
<b>Provider Notice Date:</b>	07/01/2016
<b>Original Effective Date:</b>	04/14/2016
<b>Annual Approval Date:</b>	05/01/16
<b>Revision Date:</b>	05/16/16
<b>Products:</b>	Pennsylvania Medicaid
<b>Application:</b>	All participating hospitals and providers
<b>Page Number(s):</b>	1 of

### Disclaimer

***Gateway Health<sup>SM</sup> (Gateway) clinical medical payment and/or prior-authorization policy is intended to serve only as a general reference resource regarding payment and coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.***

### **POLICY STATEMENT:**

Gateway provides coverage under the laboratory benefits of the company's Medicaid products for medically necessary genetic testing for Cystic Fibrosis utilizing appropriate mutation panels.

Genetic testing coverage is provided when the information is needed to adequately assess risk in the Gateway member; and the information is expected to make an impact on the member's treatment plan or the responsible family member/legal guardian intends to use the information in making decisions about his/her care or treatment plan.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness or condition. Each person's unique clinical circumstances warrants individual consideration, based upon review of applicable medical records.

### **DEFINITIONS:**

**Prior Authorization Review Panel (PARP)** — A panel of representatives from within the PA Department of Human Services who have been assigned organizational responsibility for the review, approval and denial of all PH-MCO prior authorization policies and procedures.

### **Carrier**

Individuals that 'carry' a genetic change that can cause a disease. Carriers typically show no signs of the disorder,

however, they can pass on the genetic variation to their children, who may develop the disorder or become carriers themselves.

### **Diagnostic Testing**

When genetic testing is performed to identify a genetic condition or disease causing signs or symptoms currently or will cause signs and symptoms in the future.

### **Newborn Screening**

Testing performed on infants one to two days after birth to determine if the infant has a certain disease known to cause issues with health and development.

### **Prenatal screening**

Testing performed during pregnancy to help identify fetuses that may have a certain disease.

## **PROCEDURES**

Gateway considers genetic testing for Cystic Fibrosis (CF) medically necessary for members in which alternative biochemical or other clinical tests to definitively diagnose carrier status are not available or if available provided an indeterminate result. The following criteria must be met:

### 1. Diagnostic or Confirmatory Testing

- a) Confirmation of a diagnosis of Cystic Fibrosis when the diagnosis is in doubt (e.g., individuals with a negative sweat chloride test) but have symptoms of Cystic Fibrosis; *or*
- b) Diagnosis for otherwise healthy males with infertility issues due to congenital bilateral absence of the vas deferens (CBAVD)

Genetic testing for the diagnosis of Cystic Fibrosis Transmembrane Regulator (CFTR) mutation related disorders is considered medically necessary if the medical appropriateness criteria are met.

### 2. Carrier Testing

- a) Carrier testing should only be performed in adults and only once per lifetime;
- b) Persons with a positive family history of Cystic Fibrosis (e.g., member has a previously affected child with CF); *or*
- c) One or both persons with a 1st degree relative identified as a Cystic Fibrosis carrier; *or*
- d) Both prospective parents who are Gateway members seeking prenatal care or who are planning a pregnancy; *or*
- e) Reproductive partners that are Gateway members of persons with Cystic Fibrosis;
- f) As part of routine care in women who are pregnant or wanting to become pregnant
- g) One or both members are in a population known to have a carrier rate that exceeds a threshold considered appropriate for testing for Cetic testing or expanded screening panels for CFTR mutations to determine the *carrier status* of an individual may be considered medically necessary if medical necessity has been confirmed by appropriately trained health care providers (genetics) when the paternal family history is unknown or the parent is unavailable but comes from a population at significantly increased carrier risk.

In accordance with the 2011 ACOG update on carrier screening for CF, Gateway recognizes the following

recommendations:

- When a member has been screened previously, the CF screening results should be documented but the test should not be repeated; AND
  - Complete analysis of the CFTR gene by DNA sequencing is not appropriate for routine carrier screening.
  - Prenatal Diagnostic Testing
  - Fetuses when both parents have any combination of either of a diagnosis of CR, are a known carrier of a CFTR mutation, or have family history of CF; *or*
  - Prenatal diagnosis where ultrasound demonstrates fetal meconium ileus, echogenic bowel, or obstructed bowel
3. Pre- and post- genetic counseling as an adjunct to genetic testing itself is considered medically necessary.
  4. Gateway considers genetic carrier and diagnostic testing for Cystic Fibrosis medically necessary for the indications listed above. Any other condition, will require case-by-case review.
  5. Post-payment Audit Statement  
The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Gateway at any time pursuant to the terms of your provider agreement.
  6. The place of service for this service is outpatient
  7. Governing Bodies Approval
    - a) Genetic tests are laboratory developed tests that do not require premarket approval by the FDA. These types of tests are regulated by the Centers for Medicare & Medicaid as part of the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The regulations of the CLIA Amendments do not include validation of specific tests but rather there is procedural compliance.
    - b) Additional information is available online at:  
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm124105.htm>.

**CODING REQUIREMENTS:**

Diagnosis Codes

ICD-10 Codes	Description
E84.0	Cystic fibrosis with pulmonary manifestations
E84.1	Cystic fibrosis with intestinal manifestations
E84.11	Meconium ileus in Cystic Fibrosis
E84.19	Cystic fibrosis with other intestinal manifestations
E84.8	Cystic fibrosis with other manifestations
E84.9	Cystic fibrosis, unspecified
Q55.3	Atresia of Vas Deferens (Code first associated cystic fibrosis)
Z13.71	Encounter for non-procreative screening for genetic disease carrier status
Z14.1	Cystic Fibrosis carrier

Z31.430	Encounter for genetic testing of female for genetic disease carrier status for procreative management
Z31.440	Encounter for genetic testing of male for genetic disease carrier status for procreative management
Z31.5	Encounter for genetic counseling
Z33.1	Pregnant state, incidental
Z34.00	Encounter for supervision of normal pregnancy
Z34.01	Encounter for supervision of normal first pregnancy, first trimester
Z34.02	Encounter for supervision of normal first pregnancy, second trimester
Z34.03	Encounter for supervision of normal first pregnancy, third trimester
Z34.80	Encounter for supervision of other normal pregnancy, unspecified trimester
Z34.81	Encounter for supervision of other normal pregnancy, first trimester
Z34.82	Encounter for supervision of other normal pregnancy, second trimester
Z34.83	Encounter for supervision of other normal pregnancy, third trimester
Z34.90	Encounter for supervision of normal pregnancy, unspecified, unspecified trimester
Z34.91	Encounter for supervision of normal pregnancy, unspecified, first trimester
Z34.92	Encounter for supervision of normal pregnancy, unspecified, second trimester
Z34.93	Encounter for supervision of normal pregnancy, unspecified, third trimester
Z36	Encounter for antenatal screening of mother

#### Procedure Codes

CPT Code	Description
81220	CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) (e.g. Cystic Fibrosis) gene analysis; common variants (e.g. ACMOG/ACPG guidelines)
81221	CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) (e.g. Cystic Fibrosis) gene analysis; common variants (e.g. ACMOG/ACPG guidelines); known familial variants
81222	CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) (e.g. Cystic Fibrosis) gene analysis; common variants (e.g. ACMOG/ACPG guidelines); duplication/deletion variants
81223	CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) (e.g. Cystic Fibrosis) gene analysis; common variants (e.g. ACMOG/ACPG guidelines); full gene sequence
81224	CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) (e.g. Cystic Fibrosis) gene analysis; common variants (e.g. ACMOG/ACPG guidelines); intron 8 pol-T analysis (e.g. male infertility)

#### **LITERATURE SUMMARY**

Cystic Fibrosis is a rare genetic disease, found in about 30,000 people in the United States and 70,000 worldwide. The disease is an example of a recessive disease, meaning that a person must have a mutation in both copies of the Cystic

Fibrosis gene to have Cystic Fibrosis. If a person only has one copy of the CF gene and the other copy is normal, the person does not have CF but is considered a CF carrier. About 10 million people in the United States are CF carriers.

There are more than 1,900 mutations in the CF gene. Many of the mutations are common while others are rare and found in a relatively few persons. The disease occurs mostly in whites whose ancestors came from northern Europe, although it affects all races and ethnic groups. Accordingly, it is less common in African Americans, Native Americans, and Asian Americans. Approximately 2,500 babies are born with CF each year in the United States. Also, about 1 in every 20 Americans is an unaffected carrier of an abnormal "CF gene."

The most common test for CF is called the sweat test. It measures the amount of sodium chloride in the sweat. In this test, an area of the skin (usually the forearm) is made to sweat by using a chemical called pilocarpine and applying a mild electric current. To collect the sweat, the area is covered with a gauze pad or filter paper and wrapped in plastic. After 30 to 40 minutes, the plastic is removed, and the sweat collected in the pad or paper is analyzed. Higher than normal amounts of sodium and chloride suggest that the person has Cystic Fibrosis. The sweat test may not work well in newborns because they do not produce enough sweat. In that case, another type of test, such as the immune-reactive trypsinogen test (IRT), may be used. In the IRT test, blood drawn 2 to 3 days after birth is analyzed for a specific protein called trypsinogen. Positive IRT tests must be confirmed by sweat and other tests. Also, a small percentage of people with CF have normal sweat chloride levels. They can only be diagnosed by chemical tests for the presence of the mutated gene. Some of the other tests that can assist in the diagnosis of CF are chest X-rays, lung function tests, and sputum (phlegm) cultures. Stool examinations can help identify the digestive abnormalities that are typical of CF.

In 1989, the responsible gene, the CF transmembrane conductance regulator (CFTR) was mapped to chromosome 7, and the most common gene mutation, F508del, was identified. To date there are over 1,500 mutations identified in the CFTR gene, many of which are rare mutations. The standard core mutation analysis of the CFTR gene recommended by the American College of Medical Genetics (ACMG) includes 23 mutations that identify the majority of prevalent mutations. This panel can identify about 97% of mutations in Ashkenazi Jewish individuals, 90% in Caucasians, 69% in African-Americans and 57% in Hispanic-Americans.

The normal gene product of Cystic Fibrosis is a transmembrane conductance regulator (CFTR) that allows the normal passage of chloride, along with sodium to make a salt into and out of certain cells, including those that line the lungs and pancreas. Mutations in the normal gene protein can affect the CFTR protein quantitatively, qualitatively, or both. As a result, these cells produce thick, sticky mucus and other secretions. The mucus clogs the lungs, causing breathing problems. Affected individuals also have frequent lung infections, which eventually damage the lungs and contribute to early death. The thickened digestive fluids made by the pancreas are prevented from reaching the small intestine, where they are needed to digest food.

The American College of Obstetricians and Gynecologists (2001) has issued similar recommendations on genetic carrier testing for CF. ACOG recommends that obstetricians should offer CF screening to:

1. For routine carrier screening, complete analysis of the CF transmembrane regulator (CFTR) gene by DNA sequencing is not appropriate.
2. Maternal carrier screening is not replaced by newborn screening panels that include CF screening.
3. If a woman with CF wishes to become pregnant, a multidisciplinary team may assist in management of issues regarding pulmonary function, weight gain, infections, and higher risks for diabetes and preterm delivery.
4. When both parents are CF carriers, they should undergo genetic counseling to review prenatal testing

and reproductive options.

5. When neither parent is affected by CF, but one or both has a family history of CF, CFTR mutation analysis in the affected family member may be identified from medical record review, and the couple should undergo genetic counseling.
6. If a woman's reproductive partner has CF or apparently isolated congenital bilateral absence of the vas deferens, mutation analysis and consultation by a geneticist is recommended.

ACOG also recommends that screening should be made available to couples in other racial and ethnic groups. To date, over 900 mutations in the CF gene have been identified. As it is impractical to test for every known mutation, the ACMG Accreditation of Genetic Services Committee has compiled a standard screening panel of 25 CF mutations, which represents the standard panel that ACMG recommends for screening in the U.S. population (Grody, et al, 2001). This 25-mutation panel incorporates all CF-causing mutations with an allele frequency of greater than or equal to 11% in the general U.S. population, including mutation subsets shown to be sufficiently predominant in certain ethnic groups, such as Ashkenazi Jews and African Americans. This standard panel of mutations is intended to provide the greatest pan-ethnic detectability that can practically be performed.

In 2002, the American College of Medical Genetics (ACMG) published the following recommended indications for CF genetic testing (revised 2004):

1. Diagnostic testing - possible diagnosis of CF, definite diagnosis of CF, infants with meconium ileus, or males with congenital bilateral absence of the vasa deferentia (CBAVD)
2. Carrier testing - partners of individuals with positive family history of CF, partners of males with congenital bilateral absence of the vasa deferentia (CBAVD), general population of reproductive couples, persons with a positive family history of CF, or gamete donors
3. Preimplantation testing
4. Prenatal diagnostic testing - positive family history, couples having a CF mutation in both partners, or fetus with echogenic bowel during second trimester
5. Newborn screening

Cystic Fibrosis (CF) is the most common life-threatening autosomal recessive condition in the non-Hispanic white population. Carrier rates are 1 in 24 in the Ashkenazi Jewish population and 1 in 25 in the non-Hispanic white general population. In 2011, ACOG issued an update on carrier screening for CF and the Committee on Genetics concluded that it is important that CF screening continues to be offered to women of reproductive age, and that because it is difficult to assign a single ethnicity to individuals, it is reasonable to offer CF carrier screening to all patients.

Current guidelines, revised by the ACMG in 2004 and reaffirmed in 2013, use a 23-mutation panel and were developed after assessing the initial experiences upon implementation of CF screening into clinical practice. Using the 23-mutation panel, the detection rate is 94% in the Ashkenazi Jewish population and 88% in the non-Hispanic white general population.

The ACMG and the American College of Obstetricians and Gynecologists (ACOG) both recommend carrier screening for Ashkenazi Jewish individuals for:

- Tay-Sachs disease (disease incidence 1/3000; carrier frequency 1/30),
- Canavan disease (1/6,400; 1/40), and
- Cystic Fibrosis (1/2,500-3,000; 1/29) and
- Familial Dysautonomia (1/3,600; 1/32)

In addition, the ACMG recommends that the following also be offered to all individuals of Ashkenazi Jewish descent who are pregnant, or considering pregnancy:

- Fanconi anemia (group C) (1/32,000; 1/89), and
- Niemann-Pick (type A) (1/32,000; 1/90), and
- Bloom syndrome (1/40,000; 1/100), mucopolidosis IV (1/62,500; 1/127), and
- Gaucher disease (1/900; 1/15).

The ACOG's update on carrier screening for CF (2011) provided the following recommendations. 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.

ACOG published an update on carrier screening for CF (2014). They have determined that screening is most efficacious in non-Hispanic white and Ashkenazi Jewish populations. Because testing is offered for only the most common mutations, a negative screening test result reduces, but does not eliminate, the chance of being a CF carrier and having an affected offspring. In addition, 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.

### **Policy Source(s)**

American College of Obstetricians and Gynecologists Committee on Genetics. (2011; reaffirmed 2014). ACOG committee opinion No. 486: Update on carrier screening for Cystic Fibrosis. Accessed on February 23, 2016 from <http://acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-G>.

Ramsey B, Banks-Schlegel S, Accurso F, Boucher R, Cutting G, Engelhardt J, et al. (2012). Future directions in early Cystic Fibrosis lung disease research; An NHLBI workshop report. *American Journal of Respiratory Critical Care Medicine*, 185 (8), 887 - 892. Accessed on February 24, 2016 from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3360572/>

Winifred S. Hayes, Inc. GTE Overview. (2013, March; last update search May 2015). *Cystic Fibrosis Transmembrane Regulator (CFTR) for Cystic Fibrosis*.

Grody WW, Cutting GR, Klinger KW, et al. and the American College of Medical Genetics Accreditation of Genetic Services Committee, Subcommittee on Cystic Fibrosis Screening. Laboratory standards and guidelines for population-based Cystic Fibrosis carrier screening. *American College of Medical Genetics Policy Statements. Genetics Med.* 2001;3(2):149-154. Accessed on February 24, 2016 from: [https://www.researchgate.net/publication/12052480\\_Grody\\_WW\\_et\\_al\\_Laboratory\\_standards\\_and\\_guidelines\\_for\\_population-based\\_cystic\\_fibrosis\\_carrier\\_screening\\_Genetics\\_Med\\_3\\_149-154](https://www.researchgate.net/publication/12052480_Grody_WW_et_al_Laboratory_standards_and_guidelines_for_population-based_cystic_fibrosis_carrier_screening_Genetics_Med_3_149-154)

American College of Obstetricians and Gynecologists. (ACOG). Committee on Genetics. ACOG Committee Opinion No. 442: Preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent.

Obstet Gynecol. 2009 Oct; 114 (4): 950-3. (Replaces No. 298, August 2004). Reaffirmed 2014. Accessed on February 24, 2016 from: <http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Genetics/Preconception-and-Prenatal-Carrier-Screening-for-Genetic-Diseases-in-Individuals-of-Eastern-European>.

American College of Medical Genetics. Technical standards and guidelines for CFTR mutation testing. 2006 ed. Bethesda (MD): ACMG; 2006. Accessed on February 22, 2016 from: [https://www.acmg.net/Pages/ACMG\\_Activities/stds-2002/cf.htm](https://www.acmg.net/Pages/ACMG_Activities/stds-2002/cf.htm).

Segal I, et al. Cystic Fibrosis transmembrane conductance regulator ion channel function testing in recurrent acute pancreatitis. *J Clin Gastroenterol* 2008 Aug;42(7):810-4. Available at: <http://journals.lww.com/jcge/pages/articleviewer.aspx?year=2008&issue=08000&article=00009&type=abstract>. Accessed on March 1, 2016.

Grosse SD, Khoury MJ. What is the clinical utility of genetic testing? *Gen in Med*. July 2006;8(7):448-450. Accessed on February 23, 2016 from: [http://www.cdc.gov/genomics/hugenet/file/print/pub\\_clinicalUtility.pdf](http://www.cdc.gov/genomics/hugenet/file/print/pub_clinicalUtility.pdf)

Hayes GTE Overview. Cystic Fibrosis Transmembrane Regulator (CFTR) for Cystic Fibrosis. May 30, 2013. Updated May 13, 2015