Genetic Testing for Cystic Fibrosis

Humana

Medicaid Medical Coverage Policy

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Table of Contents

Description

Cystic fibrosis (CF) is an inherited disorder that causes severe damage to the lungs, pancreas and sweat glands. CF is the result of mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. It is characterized by the production of abnormally viscous mucus produced by the affected glands bringing about infections, inflammation, respiratory failure and other complications.

The diagnosis of CF is a multistage process. For infants, it involves newborn screening (NBS) (eg, immunoreactive trypsinogen [IRT] and/or genetic testing), sweat chloride testing and additional genetic testing, when appropriate. Genetic testing is utilized for additional indications aiding in the diagnosis of an individual with signs and symptoms of the disease and carrier screening for reproductive decision-making.

***CFTR* gene mutation panels** analyze multiple CF pathogenic variants (mutations) simultaneously. The CF standard panel, which had been the testing of choice, included only 23 of the most common mutations based on the population in the United States; however, with the advancement of technology, laboratories now incorporate the 23 variants plus numerous additional genes.

Complete (or full) *CFTR* gene analysis by sequencing utilizes next-generation sequencing (next-gen sequencing, NGS) to provide a comprehensive scan of the *CFTR* gene and should not be used for routine screening testing. One application of the technology is to detect the presence of *CFTR* mutations to determine who may benefit from treatment with *CFTR* modulators. These prescription drugs include:

- **Kalydeco (ivacaftor)** is indicated for an individual 1 month of age or older who have one of the following mutations in the *CFTR* gene:

    - 2789+5G→A, 3272-26A→G, 3849+10kbC→T, 3945L, 5977F, 711+3A→G, A1067T, A455E, D110E, D110H, D1152H, D1270N, D579G, E193K, E56K, E831X, F1052V, F1074L, G1069R, G1244E, G1349D, G178R, G551D, G551S, K1060T, L206W, P67L, R1070Q, R1070W, R117C, R117H, R347H, R352Q, R74W, S1251N, S1255P, S549N, S549R, S945L or S977F

- **Orkambi (lumacaftor/ivacaftor)** has been US Food & Drug Administration (FDA) approved for an individual 1 year of age or older who are homozygous for the F508del mutation in the *CFTR* gene

- **Symdeko (tezacaftor-ivacaftor)** is prescribed for an individual 6 years of age or older who have one of the following mutations in the *CFTR* gene:

    - Homozygous F508del, A1067T, A455E, D110E, D110H, D1152H, D1270N, D579G, E193K, E56K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R1070W, R117C, R347H, R352Q, R74W, S945L, S977F, 2789+5G-->A, 3272-26A-->G, 3849+10kbC-->T, 711+3A-->G

- **Trikafta (elexacaftor-tezacaftor-ivacaftor)** is used for an individual 2 years of age or older who have at least one F508del mutation in the *CFTR* gene

***CFTR* deletion/duplication testing** may be initiated by the laboratory as a reflex test following *CFTR* gene sequencing. This type of testing has been proposed for CF to identify the absence (deletion) of a segment of DNA and/or the presence of an extra segment (duplication) of DNA in a coding region.

Reflex testing for the 5T allele may be initiated by the laboratory, known as reflex testing, when the *R117H* mutation has been detected on *CFTR* genetic testing. This type of testing is not recommended for routine screening.

Single site CF genetic testing analyzes specific *CFTR* pathogenic variants that have been detected in an affected (diagnosed) blood relative.

Coverage Determination

<u>*CFTR* Gene Mutation Panel Testing</u>
Humana members may be eligible under the Plan for ***CFTR* gene mutation panel testing for CF** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**

- For reproductive decision-making regardless of personal or family history or ethnicity; **OR**

- Individual to be tested diagnosed with bronchiectasis, idiopathic chronic or recurrent acute pancreatitis

Complete *CFTR* Gene Analysis
Humana members may be eligible under the Plan for **complete *CFTR* gene analysis by sequencing and/or deletion/duplication analysis*** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested diagnosed with congenital absence of vas deferens (CAVD); **OR**
- Individual to be tested diagnosed with CF or exhibits signs/symptoms of CF and *CFTR* gene mutation panel is negative; **OR**
- Individual to be tested is diagnosed with CF and is under consideration for treatment with the following *CFTR* modulators:
    - Kalydeco (ivacaftor)
    - Orkambi (lumacaftor-ivacaftor)
    - Symdeco (tezacaftor-ivacaftor)
    - Trikafta (elexacaftor-tezacaftor-ivacaftor); **OR**
- Infant with positive NBS by serum IRT:
    - Inconclusive *CFTR* gene mutation panel testing; **AND**
    - Sweat chloride test is abnormal (at least 60 mmol/L), intermediate (30-59 mmol/L), inconclusive or cannot be performed (eg, infant is too young to produce adequate volumes of sweat)

***Testing strategy:** If only one or no pathogenic variant is found by sequencing analysis, proceed to deletion/duplication analysis. Refer to Coverage Limitations section when deletion/duplication information is obtained as part of the sequencing procedure but submitted as an independent analysis.

Reflex CF Genetic Testing
Humana members may be eligible under the Plan for **reflex CF genetic testing for 5T allele** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- *CFTR* gene analysis has detected the *R117H* mutation

Single Site CF Genetic Testing
Humana members may be eligible under the Plan for **single site CF genetic testing** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**

- Individual to be tested has a first- or second-degree relative with a known *CFTR* pathogenic variant(s). **Testing Strategy**: Test appropriate affected family member first for familial mutations with CFTR gene mutation panel testing for CF unless unavailable for testing (eg, deceased, declines genetic testing or unable to contact) or incomplete previous CF genetic testing

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for **genetic testing for CF** for any indication or test other than those listed above including, but may not limited to, the following:

- Carrier screening in an individual who is not of reproductive age; **OR**
- Complete *CFTR* gene sequencing or 5T allele genotyping for routine carrier screening; **OR**
- Parental carrier screening when an affected child has a positive CF newborn screening (NBS) result

These are considered experimental/investigational as they are not identified as widely used and generally accepted for any other proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **genetic testing for CF** for any of the following:

- Deletion/duplication information is obtained as part of the sequencing procedure but submitted as an independent analysis
- Individual to be tested has an affected first-, second- or third-degree relative with a negative genetic testing result for the associated condition; **OR**
- Individual to be tested is unaffected and an affected first-, second- or third-degree relative who is available for genetic testing; **OR**
- KFV detection analysis using either of the following methods:
    - Multigene panel that includes the KFV; **OR**
    - Sequencing, deletion/duplication analysis or large genomic rearrangement analysis (conducted individually, as comprehensive testing or sequentially) without KFV results of a first, second- or third-degree relative

These are considered **not medically necessary**.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)	
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants	
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants	
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence	
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)	
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
S0265	Genetic counseling, under physician supervision, each 15 minutes	

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Appendix

Appendix A
Pre- and Post-Test Genetic Counseling Criteria

Pre- and post-test genetic counseling performed by any of the following qualified medical professionals
Genetic counselor who is board-certified or board-eligible by the American Board of Medical Genetics and Genomics (ABMGG) or American Board of Genetic Counseling, Inc (ABGC) and is not employed by a commercial genetic testing laboratory; **OR**
Genetic clinical nurse (GCN) or advanced practice nurse in genetics (APNG) who is credentialed by the Genetic Nursing Credentialing Commission (GNCC) or the American of Nurses Credentialing Center (ANCC) and is not employed by a commercial genetic testing laboratory; **OR**
Medical geneticist who is board-certified or board-eligible by ABMGG; **OR**
Treating physician who has evaluated the individual to be tested and has completed a family history of three generations

Appendix B
Family Relationships

Degree of Relationship	Relative of the Individual to be Tested
First-degree	Child, full-sibling, parent
Second-degree	Aunt, uncle, grandchild, grandparent, nephew, niece, half-sibling
Third-degree	First cousin, great aunt, great-uncle, great-grandchild, great-grandparent, half-aunt, half-uncle

Change Summary

01/01/2025 New Policy