GUIDELINES
This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder contract. Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards. This guideline is solely for explaining correct procedure reporting and does not imply coverage and reimbursement.

DESCRIPTION
Cystic fibrosis (CF) is a recessive genetic disorder (i.e., an individual needs to inherit a copy of a genetic variant from both parents in order to have the disease). It is characterized by impairment in the transport of chloride and sodium across cell membranes, which can result in an imbalance of water absorption, thereby causing dehydration. The liquid depletion results in the presence of thick and sticky mucus that causes blockage of ducts and tubes in various organs, including the lungs, pancreas, liver, and intestines.

CF affects approximately 30,000 individuals in the United States, and 70,000 worldwide. While the overall birth prevalence in the United States is approximately 1 in 3500, prevalence rates vary by ethnicity, with whites having the highest rates at 1 in every 3000 births. Lower prevalence is observed in Asians (1 in 35,000), African Americans (1 in 15,000), Hispanic Americans (ranging from 1 in 9200 to 1 in 13,500), and Native Americans (1 in 10,900). In 2011, the average age of survival for individuals with CF was 36.8 years. While CF affects males and females equally, males have a greater median survival.

A majority of CF treatments target CF symptoms and include pancreatic enzyme supplements for pancreatic-insufficient patients, antibiotics to reduce infections, and medications that alter mucus consistency. CF is caused by presence of a variant on both copies of the cystic fibrosis transmembrane conductance regulator (ATP-binding cassette sub-family C, member 7) (CFTR) gene. Variants in this gene result in impairment of the CFTR protein, which serves as a chloride channel allowing transport of chloride and sodium through the cell membrane. More than 1900 variants have been described in the CFTR gene. However, most of these variants are rare and their functional role has not been elucidated.

Genetic testing for CFTR has a number of different applications, which include carrier testing and screening, prenatal diagnosis, preimplantation genetic diagnosis (PGD), newborn screening, and identification of individuals who will benefit from specific drug therapies. A number of clinical laboratories in the United States offer testing for CFTR variants. Laboratories typically offer a panel of 23 common CFTR variants that is recommended by the American College of Medical Genetics (ACMG), as well as testing for additional variants depending upon the laboratory. Full gene sequencing, deletion analysis, and targeted testing for known familial variants are also available.

POLICY
Genetic testing (CFTR gene) for cystic fibrosis (CF) (81220-81224) does not require prior authorization when determined to be medically necessary as the medical criteria and guidelines shown below are met.

HMO, PPO, Individual Marketplace, Elite, Advantage
Genetic testing (CFTR gene) for cystic fibrosis (CF) is considered medically necessary when the following criteria for each panel are met:

- CF standard mutation panel (ie, 23-25 mutations) for ANY of the following:
  - Couple planning pregnancy or seeking prenatal care; OR
  - Family history of CF; OR
  - Positive newborn screen for CF, or signs and symptoms of CF are present and sweat chloride test is positive, intermediate, inconclusive or cannot be performed (e.g., infant is too young to produce adequate volumes of sweat); OR

- CF expanded mutation panel (ie, more than 25 mutations) for ANY of the following:
  - Family history of CF; AND
    - CF standard mutation panel is negative; OR
    - Known familial mutation which is not included on CF standard mutation panel; OR
  - Individual whose reproductive partner is any of the following:
    - Affected with CF; OR
• A known CF carrier; OR
• Male with congenital bilateral absence of vas deferens (CBAVD); OR
  o Male with CBAVD; OR
  o Positive newborn screen for CF or signs/symptoms of CF are present; AND
    o Standard mutation panel for CF is negative; AND
    o Sweat chloride test is positive, intermediate, inconclusive or could not be performed (e.g., infant is too young to produce adequate volumes of sweat)
• Complete CFTR gene analysis by sequencing (e.g., MiSeqDx Cystic Fibrosis Clinical Sequencing Assay) when the following criteria are met:
  o Determination of genotype for treatment with Kalydeco (ivacaftor) or Orkambi (lumacaftor/ivacaftor) in an individual with CF; OR
  o Family history of CF; AND
    o CF standard mutation panel is negative; OR
    o Known familial mutation which is not included on CF standard mutation panel; OR
  o Individual diagnosed with CF; OR
  o Individual whose reproductive partner is any of the following:
    o Affected with CF; OR
    o A known CF carrier; OR
    o Male with CBAVD; OR
  o Male diagnosed with CBAVD; OR
  o Positive newborn screen for CF, or signs/symptoms of CF are present; AND
    o Standard mutation panel for CF is negative; AND
    o Sweat chloride test is positive, intermediate, inconclusive or cannot be performed (e.g., infant is too young to produce adequate volumes of sweat)
• CFTR intron 8 poly-T analysis when the following criteria are met:
  o Individual diagnosed with nonclassic CF; OR
  o Male diagnosed with CBAVD; OR
  o R117H mutation detected on CF standard or expanded panel
• Site specific mutation when the individual to be tested has a first- (ie, parent, full-sibling, child) or second-degree (ie, aunt, uncle, grandparent, grandchild, niece, nephew, half-sibling) blood relative with known CFTR mutations that are not included on the CF standard mutation panel or CF expanded panel (Testing strategy: test for specific known familial mutation[s])

Genetic testing for cystic fibrosis (CF) is non-covered for any indication or test other than those listed above including, but may not limited to, the following:
• An at-risk (unaffected) individual or affected individual when a family member has been tested for mutations and received a result of VUS (also known as unclassified variant or variant of uncertain significance)
• Direct-to-consumer (DTC) genetic testing
• Parental carrier screening when affected child has a positive CF newborn screening result
• Screening for cystic fibrosis mutations that extend beyond the standard mutation panel recommended by the ACMG

CODING/BILLING INFORMATION
The appearance of a code in this section does not necessarily indicate coverage. Codes that are covered may have selection criteria that must be met. Payment for supplies may be included in payment for other services rendered.

<table>
<thead>
<tr>
<th>CPT CODES</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>81220</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; common variants (e.g., ACMG/ACOG guidelines)</td>
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<tr>
<td>81221</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; known familial variants</td>
</tr>
<tr>
<td>81222</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; duplication/deletion variants</td>
</tr>
<tr>
<td>81223</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; full gene sequence</td>
</tr>
<tr>
<td>81224</td>
<td>CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; intron 8 poly-T analysis (e.g., male infertility)</td>
</tr>
</tbody>
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TAWG REVIEW DATES: 07/26/2018

REVISION HISTORY EXPLANATION
07/26/18: Genetic testing (CFTR gene) for cystic fibrosis (CF) (81220-81224) does not require prior authorization when determined to be medically necessary as the medical criteria and guidelines in the policy are met. Policy created to reflect most current clinical evidence per The Technology Assessment Working Group (TAWG).
REFERENCES/RESOURCES
Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services
Ohio Department of Medicaid http://jfs.ohio.gov/
Centers for Medicare and Medicaid Services, Healthcare Common Procedure Coding System, HCPCS Release
and Code Sets
Industry Standard Review
Hayes, Inc.