Revision log
Coding Implications

CONCERT GENETIC TESTING: RESPIRATORY

See Important Reminder at the end of this policy for important regulatory and legal information.

OVERVIEW

This policy addresses the use of diagnostic tests for disorders that affect the lungs.

For additional information see the Rationale section.

The tests, CPT codes, and ICD codes referenced in this policy are not comprehensive, and their inclusion does not represent a guarantee of coverage or non-coverage. Please see the Concert Platform for additional registered tests.

POLICY REFERENCE TABLE

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2024, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

The tests, CPT codes, and ICD codes referenced in this policy are not comprehensive, and their

inclusion does not represent a guarantee of coverage or non-coverage. Please see the Concert Platform for additional registered tests.

CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Alpha-1 Antitrypsin Deficiency			
SERPINA1 Common Variant Analysis or Sequencing and/or Deletion/Duplication Analysis	Alpha-1 Antitrypsin (AAT) Mutation Analysis (Quest Diagnostics)	81332, E88.01	4
	SERPINA1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81479, E88.01	
Cystic Fibrosis			
Diagnostic *CFTR* Sequencing and/or Deletion/Duplication Analysis	Cystic Fibrosis Complete Rare Variant Analysis, Entire Gene Sequence (Quest Diagnostics)	81223, E84.0-9, P09, Q55.4, R94.8, Z13, Z31, Z34, Z82.79, Z83, Z84	1, 3
	Cystic Fibrosis Gene Deletion or Duplication (Quest Diagnostics)	81222, E84.0-9, P09, Q55.4, R94.8, Z13, Z31, Z34, Z82.79, Z83, Z84	
CFTR Intron 9 PolyT and TG Analysis (previously called Intron 8 polyT/TG)	*CFTR* Intron 8 Poly-T Analysis (Quest Diagnostics)	81224, E84.0-9, P09, Q55.4, R94.8, Z13, Z31, Z34, Z82.79, Z83, Z84	2
Other Covered Lung Disorders			
Other Covered Lung Disorders	See list below	81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408	5, 6, 7

RELATED POLICIES

This policy document provides criteria for testing related to respiratory disorders. Please refer to:

- ***Specialty Testing: Multisystem Genetic Conditions*** for criteria related to diagnostic tests for genetic disorders that affect multiple organ systems (e.g. whole exome and genome sequencing, chromosomal microarray, and multigene panels for broad phenotypes).
- ***General Approach to Laboratory Testing*** for related to respiratory testing, including known familial variant testing, that is not specifically discussed in this or another non-general policy.

back to top

CRITERIA

It is the policy of health plans affiliated with Centene Corporation® that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

ALPHA-1 ANTITRYPSIN DEFICIENCY

SERPINA1 Common Variant Analysis or Sequencing and/or Deletion/Duplication Analysis

I. *SERPINA1* common variant analysis or sequencing and/or deletion/duplication analysis to establish a diagnosis of alpha-1 antitrypsin (AAT) deficiency is considered **medically necessary** when:

A. The member/enrollee has any of the following:

1. Abnormally low (less than 120 mg/dL) or borderline (90-140 mg/dL) alpha-1 antitrypsin levels (as measured by nephelometry), **OR**
2. Early-onset emphysema (45 years of age or younger), **OR**
3. Emphysema in the absence of additional risk factor (e.g., smoking, occupational dust exposure), **OR**

4. Emphysema with prominent basilar hyperlucency, **OR**
5. Otherwise unexplained liver disease, **OR**
6. Necrotizing panniculitis, **OR**
7. C-ANCA positive vasculitis (i.e., granulomatosis with polyangiitis), **OR**
8. Bronchiectasis without evident etiology, **OR**
9. A sibling with known AAT deficiency.

II. Current evidence does not support *SERPINA1* common variant analysis or sequencing and/or deletion/duplication analysis to establish a diagnosis of alpha-1 antitrypsin deficiency for all other indications.

view rationale

back to top

CYSTIC FIBROSIS

Diagnostic *CFTR* Sequencing and/or Deletion/Duplication Analysis

I. *CFTR* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of cystic fibrosis is considered **medically necessary** when:

A. The member/enrollee has a positive (greater than or equal to 60 mmol/L) or inconclusive (30-59 mmol/L) sweat chloride test, **OR**

B. The member/enrollee has a positive newborn screen for cystic fibrosis as indicated by elevated immunoreactive trypsinogen, **OR**

C. The member/enrollee has symptoms of cystic fibrosis from at least **TWO** different organ systems:

1. Sinus (e.g. chronic sinusitis, nasal polyps), **OR**
2. Lower respiratory (e.g., bronchiectasis, chronic or recurrent lower airway infection, allergic bronchopulmonary aspergillosis), **OR**
3. Gastrointestinal (GI)/lumen (e.g., meconium ileus, distal intestinal obstruction syndrome, abnormal motility, rectal prolapse), **OR**

4. Gastrointestinal (GI)/hepatobiliary (e.g., pancreatic insufficiency, recurrent pancreatitis, elevated liver enzymes, ecchymosis, cirrhosis, prolonged neonatal jaundice, fat soluble vitamin deficiencies), **OR**
5. Reproductive (e.g., male (sex assigned at birth) infertility because of obstructive azoospermia, female (sex assigned at birth) infertility), **OR**
6. Other symptoms of cystic fibrosis (e.g., hyponatremic dehydration, failure to thrive, pseudo-Bartter syndrome, aquagenic wrinkling of skin, digital clubbing).

II. Current evidence does not support *CFTR* sequencing and/or deletion/duplication analysis to establish or confirm a diagnosis of cystic fibrosis for all other indications.

view rationale

back to top

CFTR Intron 9 PolyT and TG Analysis **(previously called Intron 8 polyT/TG Analysis)**

I. *CFTR* intron 9 polyT and TG analysis in a member/enrollee is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of cystic fibrosis, **AND**

B. The member/enrollee has an R117H variant in the *CFTR* gene.

II. Current evidence does not support *CFTR* intron 9 polyT and TG analysis in a member/enrollee with a diagnosis of cystic fibrosis for all other indications.

view rationale

back to top

OTHER COVERED LUNG DISORDERS

Other Covered Lung Disorders

The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.

I. Genetic testing to establish or confirm one of the following genetic lung disorders to guide management is considered **medically necessary** when the member/enrollee demonstrates clinical features[1] consistent with the disorder (the list is not meant to be comprehensive, see II below):

   A. Familial Pulmonary Fibrosis

   B. Primary Ciliary Dyskinesia

   C. Pulmonary lymphangioleiomyomatosis (LAM)

   D. Pulmonary alveolar proteinosis (PAP)

II. Current evidence does not support enetic testing to establish or confirm the diagnosis of all other lung disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in the *General Approach to Laboratory Testing* (see policy for criteria).

[1]Clinical features for a specific disorder may be outlined in resources such as GeneReviews, OMIM, National Library of Medicine, Genetics Home Reference, or other scholarly source.

back to top

RATIONALE

SERPINA1 Common Variant Analysis or Sequencing and/or Deletion/Duplication Analysis

American Thoracic Society and European Respiratory Society

The American Thoracic Society and European Respiratory Society published a joint statement on the diagnosis and management of individuals with alpha-1 antitrypsin deficiency (2003) which provided recommendations for diagnostic testing.

A normal range of plasma alpha-1 antitrypsin (measured via nephelometry) is 83/120 - 200/220 mg/dL. Individuals with borderline normal levels of plasma alpha-1 antitrypsin (90-140 mg/dL) or with abnormally low levels (below 120 mg/dL) should be evaluated for alpha-1 antitrypsin deficiency (p. 826 and 827).

"The following features should prompt suspicion by physicians that their patient may be more likely to have AAT deficiency:

- Early-onset emphysema (age of 45 years or less)
- Emphysema in the absence of a recognized risk factor (smoking, occupational dust exposure, etc.)
- Emphysema with prominent basilar hyperlucency
- Otherwise unexplained liver disease
- Necrotizing panniculitis
- Anti-proteinase 3-positive vasculitis (C-ANCA [anti-neutrophil cytoplasmic antibody]-positive vasculitis)
- Family history of any of the following: emphysema, bronchiectasis, liver disease, or panniculitis
- Bronchiectasis without evident etiology…" (p. 820)

The statement also recommended that individuals with a sibling with AAT deficiency should also be offered genetic testing (p. 827).

back to top

Diagnostic CFTR Sequencing and/or Deletion/Duplication Analysis

Cystic Fibrosis Foundation

Consensus-based guidelines from the Cystic Fibrosis Foundation (2017) outline the ways in which a CF diagnosis can be established (see below). Characteristic features of CF include chronic sinopulmonary disease (such as persistent infection with characteristic CF pathogens, chronic productive cough, bronchiectasis, airway obstruction, nasal polyps, and digital clubbing), gastrointestinal/nutritional abnormalities (including meconium ileus, pancreatic insufficiency, chronic pancreatitis, liver disease, and failure to thrive), salt loss syndromes, and obstructive azoospermia in males (due to congenital absence of the vas deferens, or CAVD).

These guidelines state that, "Individuals presenting with a positive newborn screen, symptoms of CF, or a positive family history, and sweat chloride values in the intermediate range (30- 59 mmol/L) on 2 separate occasions may have CF. They should be considered for extended *CFTR* gene analysis and/ or *CFTR* functional analysis" (p. S8).

Sosnay et. al

A consensus statement from the 2015 Cystic Fibrosis Foundation Consensus Conference authored by Sosnay et al. (2017) establishes the following as suspicious symptoms for CF in

individuals who may not have received screening for cystic fibrosis, or who may have received a false negative NBS test:

Table II. Clinical signs/symptoms that may signify CF (p. S53)

Presenting conditions	**Common as first presentation of CF**	**Uncommon as first presentation of CF***
Family history	Sibling or parent with CF	Parent of a child diagnosed with CF
Sinus	Chronic sinusitis, nasal polyps	
Lower respiratory	Bronchiectasis, chronic or recurrent lower airway infection (especially *Pseudomonas* infection)	ABPA, nontuberculous mycobacterial infection, asthma, chronic obstructive pulmonary disease
GI/lumen	Meconium ileus, distal intestinal obstruction syndrome	Abnormal motility, rectal prolapse
GI/hepatobiliary	Pancreatic insufficiency, recurrent pancreatitis	Elevated liver enzymes, ecchymosis, cirrhosis, prolonged neonatal jaundice, fat soluble vitamin deficiencies (may present as ecchymosis, anemia, edema, night-blindness, skin rash)

Reproductive	Male infertility because of obstructive azoospermia (CBAVD)	Female infertility
Other	Hyponatremic dehydration,failure to thrive	Pseudo-Bartter syndrome, aquagenic wrinkling of skin, digital clubbing

ABPA, allergic bronchopulmonary aspergillosis; GI, gastrointestinal.

back to top

CFTR Intron 9 PolyT and TG Analysis **(previously called Intron 8 poly-T/TG Analysis)**

American College of Medical Genetics and Genomics (ACMG)

ACMG has recommended that all R117H positive results require reflex testing for the 5T/7T/9T variant in the polythymidine tract at intron 8 in *CFTR* gene. For R117H/5T positive heterozygotes, testing of parents is recommended to determine the inheritance of the R117H and the 5T variant (i.e., cis vs. trans position). For diagnostic testing, and particularly for testing for CBAVD in males with infertility, it is recommended that the intron 8 variant be included in the testing panel (p. 1294).

back to top

NOTE – this is from 2025.1 Lung Disorders…..I did not include Multisystem Inherited, Intel Disab….Revision Log.

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	03/23	03/23
Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Policy Reference Table: under "SERPINA1 Common Variant…" added "E88.01". For Background and Rationale; under "SERPINA1 Known Familial Variant Analysis: replaced "inheritance patterns" with "genetic testing".	10/23	10/23

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Semi-annual review. Updated title to reflect V2.2024 version. In *SERPINA1* Common Variant Analysis or Sequencing and/or Deletion/Duplication Analysis criteria, updated criteria to better align with current guidelines, allowing for an expansion to coverage. In *SERPINA1* Known Familial Variant Analysis criteria, moved criteria to policy "Genetic Testing: General Approach to Genetic and Molecular Testing" to consolidate criteria for known familial variant tests. Minor rewording for clarity throughout. Coding, reference-table, background and references updated.	04/24	04/24
Semi-annual review. Updated title to reflect V1.2025 version. Evidence-Based Donor-Derived Cell-free DNA for Lung Transplant Rejection: NEW criteria based on LCD guidelines. Emerging Evidence Donor-Derived Cell-free DNA for Lung Transplant Rejection: NEW Criteria set created for lung cancer diagnostic algorithmic tests for which clinical validity has not been established.	11/24	11/24
Annual review. Policy name changed from "Concert Genetic Testing: Lung Disorders" to Concert Genetic Testing: Respiratory. Policy incorporated criteria for CFTR Intron 9 PolyT and TG Analysis (previously called Intron 8 polyT/TG Analysis) and Diagnostic CFTR Sequencing and/or Deletion/Duplication Analysis that was previously in Concert Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay. "Investigational" policy statements changed to state "current evidence does not support." Policy reference table, rationale, background, coding, and references updated.	11/25	12/25

REFERENCES

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2. Deignan JL, Astbury C, Cutting GR, et al. CFTR variant testing: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22(8):1288-1295. doi:10.1038/s41436-020-0822-5
3. Sosnay PR, White TB, Farrell PM, et al. Diagnosis of Cystic Fibrosis in Nonscreened Populations. *The Journal of Pediatrics*. 2017;181:S52-S57.e2. doi:10.1016/j.jpeds.2016.09.068
4. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168(7):818-900. doi:10.1164/rccm.168.7.818

5. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
6. Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: https://omim.org/
7. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: https://medlineplus.gov/genetics/.

back to top

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If

there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.