Primary Ciliary Dyskinesia Genetic Testing

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Primary ciliary dyskinesia (PCD) genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedure addressed by this guideline	Procedure code
Primary ciliary dyskinesia known familial mutation analysis	81403
Miscellaneous primary ciliary dyskinesia gene analysis	81479
Primary ciliary dyskinesia multi gene panel	81479, 81443

Criteria

Requests for PCD genetic testing are reviewed using the following criteria.

Known familial mutation analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous genetic testing that would detect the familial mutation(s), AND
- Diagnostic Testing or Carrier Testing:
  - Known disease-causing mutation in a PCD-related gene identified in a 1st, 2nd, or 3rd degree biological relative, AND
- Rendering laboratory is a qualified provider of services per the Health Plan policy.

Single Gene Analysis

- Genetic Counseling:

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  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous analysis of the requested gene, AND
- Diagnostic Testing for Symptomatic Individuals:
  - A diagnosis of PCD is suspected, but has not been confirmed, and
  - Clinical findings suggest the requested gene is the likely cause for the member's symptoms, and
  - High suspicion for PCD based on having at least two of the following:
    - Unexplained neonatal respiratory distress as a term infant, with lobar collapse and/or need for respiratory support with CPAP (continuous positive airway pressure) and/or oxygen for >24 hours, and/or
    - Daily cough that is year-round and has been present since infancy or bronchiectasis on chest CT, and/or
    - Daily nasal congestion that is year-round and has been present since infancy or pansinusitis on sinus CT, and/or
    - Situs abnormality, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Multi-Gene Panel Testing

When a multi-gene panel is being requested and will be billed with a panel CPT code (e.g. 81479), the panel is medically necessary when the following criteria are met:

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing of the genes included on the panel, AND
- Diagnostic Testing for Symptomatic Individuals:
  - A diagnosis of PCD is suspected, but has not been confirmed, and
  - Alternate etiologies have been considered and ruled out when possible (e.g., cystic fibrosis, immunodeficiency), and
  - Absence of features suggestive of a complex genetic syndrome (e.g., retinitis pigmentosa, digital anomalies, cystic kidneys) for which more targeted testing is available, and
  - High suspicion for PCD based on having two or more of the following
    - Unexplained neonatal respiratory distress as a term infant, with lobar collapse and/or need for respiratory support with CPAP and/or oxygen for >24 hr, and/or
    - Daily cough that is year-round and has been present since infancy or bronchiectasis on chest CT, and/or

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    - Daily nasal congestion that is year-round and has been present since infancy or pansinusitis on sinus CT, and/or
    - Situs abnormality, AND
- Rendering laboratory is a qualified provider of service per Health Plan policy.

Other Considerations

Broad ciliopathy panels or immunodeficiency panels may not be medically necessary when a narrower panel is available and more appropriate based on the clinical findings.

Billing and Reimbursement

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
    - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g. 81479, 81443*).
    - When use of a panel code is not possible, each billed component procedure will be assessed independently.
    - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
    - When the test is billed with multiple stacked codes, only sequencing of the following genes may be considered for reimbursement:
        - DNAH5
        - DNAH11
        - CCDC39
        - DNAI1

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What is primary ciliary dyskinesia?

Primary ciliary dyskinesia (PCD) is a genetic disorder that causes chronic lung disease, situs abnormalities, and male infertility[1]

Prevalence

PCD is expected to affect approximately 1 in 7,500-20,000 births.[2,3] Limitations in diagnostic methods make it difficult to determine if the published incidence is accurate.[1]

Symptoms

- Pulmonary disease: Neonatal respiratory distress occurs in approximately 75% of full-term babies with PCD. Chronic airway infection with a cough, sputum, and wheezing are present in most children by early childhood. Bronchiestasis usually develops by adulthood.[1]
- Sinus infections and nasal congestion: Sinus symptoms are often noted in the first few months of life. Sinus infections are a frequent issue for adults with PCD.[1]
- Chronic/recurrent ear infection: Ear infections are most common in young children before they reach school age.[1] Chronic ear infections often lead to conductive hearing loss and can affect speech development.[1]
- Male infertility: Abnormal sperm motility causes the majority of males with PCD to be infertile. Women can also have a reduction in fertility due to impaired ciliary function in the oviduct.[1]
- Situs abnormalities: Situs inversus totalis (all internal organs are arranged in a mirror image of what occurs normally) occurs in 40-50% of individuals with PCD.[1] Heterotaxy (internal organs develop on the opposite side of the body as what occurs normally) occurs in approximately 12% of individuals with PCD.[1] Heterotaxy can involve a single organ or multiple organs. Complex cardiac defects are more common in individuals with heterotaxy than the general population.[4]

Cause

PCD is caused by genetic mutations that affect the function of motile cilia. Motile cilia are involved in directing the movement of fluids and other materials along cell surfaces. Motile cilia play roles in embryogenesis, reproduction, and airway clearance.[2]

A few disorders can include PCD along with other features. X-linked oral-facial-digital type I syndrome caused by a mutation in OFD1, and X-linked Retinitis Pigmentosa and PCD caused by a mutation in RPGR are two such disorders.[1,5]

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Inheritance

The majority of the genes associated with PCD show autosomal recessive inheritance.

Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

A few genes associated with PCD have been shown to display autosomal dominant or X-linked inheritance.[1]

Diagnosis

Diagnostic testing for PCD is only recommended for individuals with a high suspicion for PCD based on clinical history. No diagnostic testing is recommended for individuals without major clinical features of PCD.[6]

PCD symptoms can overlap with other health conditions including: cystic fibrosis (CF), immunodeficiency, pulmonary aspiration, asthma, and recurrent viral respiratory infections. CF may be differentiated from PCD, as individuals with CF "typically do not have neonatal respiratory distress or chronic otitis media, nor do they have daily cough until lung disease has significantly progressed. Nonetheless, children being evaluated for PCD should undergo sweat chloride testing at a laboratory certified to perform sweat chloride measurements. Similarly, various immunodeficiencies may also present with chronic upper and lower respiratory tract infections, though not typically with daily, year-round symptoms."[6]

"There no single gold standard diagnostic test for PCD."[4] A combination of clinical history and diagnostic tests is often required to make a diagnosis."[5]

Diagnosis of PCD can be limited by an individual's access to diagnostic procedures. The recommended tests, other than genetic testing, are typically found at testing centers that specialize in PCD. Transmission electron microscopy (TEM), high-speed video microscopy analysis (HVMA) and nasal nitric oxide (nNO) measurement are often recommended when available. Both TEM and HVMA require a high level of training and experience to perform and interpret. False positives and false negatives are common when these tests are performed without sufficient expertise.[5,6]

Nasal nitric oxide (nNO) measurement is a recommended part of a diagnostic work-up for individuals 5-6 years of age or older who are suspected to have PCD.[4,5] An nNO value of less than 77nl/min is suggestive of PCD, but some individuals with known PCD

have a normal or high nNO level.[4,5] nNO testing requires confirmatory testing since low values can be caused by infection or sinusitis.[6]

Transmission electron microscopy (TEM) of ciliary cross sections from nasal epithelium allows for a definitive diagnosis of PCD.[4] This analysis can confirm, but is unable to rule out, a diagnosis. At least 30% of individuals with PCD may not be identified by this method.[4] If the member's clinical history strongly suggests PCD, and TEM is non-diagnostic, other diagnostic testing is recommended.[4]

High-speed video microscopy analysis (HVMA) may be used in a PCD work-up with CBF/CBP (ciliary beat frequency/ciliary beat pattern) assessment. CBF of less than 11 beats per second has been suggested as a cutoff value.[4] This testing is not sufficiently standardized to rule in or rule out PCD in isolation.[4,6]

Multi-gene panels are commonly used to establish a diagnosis in individuals suspected to have PCD. More than 50 genes have been implicated in PCD.[7] Next-generation sequencing is expected to identify biallelic pathogenic mutations in 70-80% of individuals with PCD.[6]

Management

The main components of PCD management include airway clearance, infection control, and the elimination of inflammatory triggers.[2,4] Lung transplantation may be an option for individuals that develop end-stage lung disease.[4] Individuals with PCD are recommended to have routine monitoring of their pulmonary symptoms and for early diagnosis of infection.[8]

Survival

Lung disease varies considerably among individuals with PCD.[1] Some adults seem to have stable lung function over time, while others have a progressive disease course and develop end-stage lung disease.[4]

Test information

PCD genetic testing consists of known familial mutation analysis, next generation sequencing, or multi-gene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Given that the majority of cases cannot be easily categorized into subtypes and genetic testing is a first-tier diagnostic test for PCD, a comprehensive panel approach is acceptable for individuals whose clinical history is highly suspicious for PCD.

Genes commonly included on multi-gene panels include: DNAH5, DNAH11, CCDC39, DNAI1, CCDC40, CCDC103, SPAG1, ZMYND10, ARMC4, and CCDC151.[1]

Guidelines and evidence

American Thoracic Society Clinical Practice Guideline for the Diagnosis of Primary Ciliary Dyskinesia

The American Thoracic Society (ATS, 2018) evidence-based Clinical Practice Guideline for the Diagnosis of Primary Ciliary Dyskinesia stated:[6]

- An extended genetic panel is suggested over TEM ciliary testing in the diagnostic evaluation of PCD based on concern for accuracy and accessibility of TEM testing. Genetic testing is expected to yield a higher sensitivity, is more feasible, and provides the added benefit of family planning information. This recommendation was made with an acknowledgment that the overall evidence is limited in regards to the impact on long-term clinical outcomes.

- A few studies have allowed for a comparison of sensitivities for different sizes of genetic panel tests for PCD. As a whole, the sensitivity of genetic panel testing for establishing a PCD diagnosis increased as the panel size increased. When 12 genes were tested, the sensitivity was 71.9%, while the sensitivity for a 32 gene panel that included deletion/duplication analysis and used the same population was 93.9%.
- When available, nNO testing should precede genetic testing or TEM testing for individuals 5 years of age or older with a clinical history suspicious for PCD. Low nNO values require verification (measured low on two separate occasions) when used as a PCD diagnostic test, as infections or sinusitis can decrease nNO values. A diagnosis of PCD made using nNO should be confirmed by other testing. Individuals with normal nNO levels should only have further diagnostic testing if strong clinical features of PCD are present.
- The use of CBP/F analysis by HSVM is not recommended as a diagnostic test for PCD. Standardization of this type of testing for PCD is insufficient and access is limited to select few testing centers

European Respiratory Society Task force Guideline

The European Respiratory Society (ERS, 2017) released evidence-based guidelines for the diagnosis and management of children with PCD that stated:[8]

- Nasal NO measurement is recommended as a screening test for individuals with a clinical history suspicious for PCD. Some individuals with PCD have normal nNO levels, so "patients presenting with a strong clinical history should undergo further testing, even if nNO is normal (weak recommendation)"
- "High speed video analysis, including ciliary beat frequency and beat pattern analysis, should be used as part of the diagnostic work-up of patients suspected of having PCD (weak recommendation)."
- "Ciliary ultrastructure analysis by transmission electron microscopy should be used as part of the diagnostic work-up of patients suspected of having PCD (strong recommendation)."
  - "Further diagnostic investigations should be performed in patients with normal ultrastructure if the clinical history is strong (strong recommendation)."
  - "In patients with hallmark ciliary ultrastructure defects for PCD further confirmatory diagnostic investigations are not required (strong recommendation)."
- Genetic testing can be used to confirm a diagnosis, or can be used when there is high clinical suspicion for PCD but other diagnostic testing was unavailable or unable to establish a diagnosis.
- A proposed diagnostic algorithm recommends nNO and HSVMA with CBF/P as a first tier test for screening individuals with clinical history suspicious for PCD. If these tests are normal, further testing is not needed. If the results are abnormal or equivocal, TEM and cell culture should be completed. If a diagnosis can be made based on a defect found by TEM, no further testing is needed. If TEM is suggestive of PCD or the

TEM results are normal or equivocal but the individual's history is strongly suggestive of PCD, genetic testing for PCD is recommended.

Primary Ciliary Dyskinesia Foundation

The Primary Ciliary Dyskinesia Foundation (PCDF, 2016) released guidelines for the diagnosis, monitoring and treatment of individuals with PCD.[5] These guidelines included age-dependent diagnostic criteria for PCD and major clinical criteria. The recommendations for diagnostic testing suggest using a combination of diagnostic tests.

PCD Diagnostic Criteria[5]

- "Newborns (0-1 month of age)
  - Situs inversus totalis and unexplained neonatal respiratory distress at term birth plus at least one of the following:
  - Diagnostic ciliary ultrastructure on electron micrographs
  - Biallelic c mutations in one PCD-associated gene
  - Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions
- Children (1 month to 5 years)
  - Two or more major PCD clinical criteria ... plus at least one of the following (nasal nitric oxide not included in this age group, since it is not yet sufficiently tested):
  - Diagnostic ciliary ultrastructure on electron micrographs
  - Biallelic mutations in one PCD-associated gen
  - Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions
- Children 5-18 years of age and adults
  - Two or more major PCD clinical criteria...plus at least one of the following:
  - Nasal nitric oxide during plateau <77 nl/min on 2 occasions, >2 months apart, with cystic fibrosis excluded
  - Diagnostic ciliary ultrastructure on electron micrographs
  - Bialelic mutations in one PCD-associated gene
  - Persistent and diagnostic ciliary waveform abnormalities on high-speed videomicroscopy, on multiple occasions"

Four major PCD clinical criteria include:[5]

- "Unexplained neonatal respiratory distress (at term birth) with lobar collapse and/or need for respiratory support with CPAP and/or oxygen for >24 hr.
- Any organ laterality defect—situs inversus totalis, situs ambiguous, or heterotaxy.
- Daily, year-round wet cough starting in the first year of life or bronchiectasis on chest CT.
- Daily, year-round nasal congestion starting in first year of life or pansinusitis on sinus CT."

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Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for primary ciliary dyskinesia testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

References

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