

# The Diagnosis of Primary Ciliary Dyskinesia: Putting The European Respiratory/American Thoracic Guideline Into Practice.

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## Study Guide: Diagnosis and Management of Primary Ciliary Dyskinesia (PCD)

This study guide provides a comprehensive overview of Primary Ciliary Dyskinesia (PCD) based on the 2025 joint European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines. It covers the pathophysiology, clinical presentation, diagnostic modalities, and future directions for the disease.

### I. Key Concepts

#### 1. Understanding PCD

- **Definition:** PCD is a rare inherited disease characterized by dysfunctional motile cilia. These organelles are found on the apical epithelial surface of the upper and lower airways, reproductive organs, and the embryonic node.
- **Pathophysiology:** In the airways, motile cilia (approximately 200 per cell) propel liquid and mucus. Dysfunction leads to impaired mucociliary clearance (MCC), resulting in mucus accumulation, bacterial colonization, chronic inflammation, and recurrent sino-oto-pulmonary infections.
- **Prevalence:** Approximately 1:7500, though it may be higher in regions with high rates of consanguinity. It is frequently underdiagnosed or diagnosed late due to non-specific symptoms that overlap with asthma, cystic fibrosis, and immunodeficiencies.

#### 2. Clinical Presentation

Clinicians should look for a combination of patterns rather than a single symptom. Key features include:

- **Neonatal Period:** Unexplained respiratory distress at term; persistent supplemental oxygen requirements.
- **Respiratory System:** Persistent wet cough; early-onset bilateral bronchiectasis (typically middle/lower lobes); chronic rhinosinusitis and perennial rhinitis.

- **Other Systems:** Laterality defects (situs inversus totalis, dextrocardia, heterotaxy), chronic middle ear infections or hearing loss, and reduced fertility (male and female).
- **Rare Features:** Hydrocephalus or ventriculomegaly due to ependymal ciliary dysfunction in the central nervous system.

### 3. Diagnostic Prioritization Tools

To assist non-experts in identifying high-risk patients, two primary symptom-based tools are utilized:

- **PICADAR:** A seven-point questionnaire for patients with a persistent early-onset wet cough. It considers neonatal chest symptoms, NICU admission, situs anomalies, congenital heart defects, perennial rhinitis, and ear/hearing problems.
- **ATS Clinical Criteria (Leigh et al.):** Focuses on four cardinal features: unexplained neonatal distress, year-round cough, year-round nasal congestion, and laterality defects.

### 4. The Diagnostic Battery

Because no single "gold standard" test exists, a combination of tools is used to classify patients as "Confirmed," "Highly Likely," "Suspected," or "Highly Unlikely."

| Test            | Description                                                                   | Specificity/Sensitivity Notes                                                                  |
|-----------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| <b>Genetics</b> | Identifying biallelic pathogenic variants in one of over 65 associated genes. | Confirms diagnosis in ~70% of cases. Sufficient for diagnosis on its own.                      |
| <b>TEM</b>      | Transmission Electron Microscopy analyzes axonemal ultrastructure.            | 99% specific but normal in 20%–30% of genetically confirmed cases.                             |
| <b>nNO</b>      | Nasal Nitric Oxide measurement; low levels are indicative of PCD.             | Highly accurate with velum closure; less accurate with tidal breathing (used for children <5). |
| <b>HSVM</b>     | High-Speed Video Microscopy analyzes ciliary beat pattern and frequency.      | Direct visualization of dyskinesia; post-culture assessment is most sensitive/specific.        |
| <b>IF</b>       | Immunofluorescence uses fluorescent antibodies to identify protein defects.   | Very high sensitivity/specificity; helps resolve variants of unknown significance (VUS).       |

## II. Short-Answer Practice Questions

1. **Why is a genetic diagnosis considered the most critical confirmatory step in the current era?**  
Identifying biallelic pathogenic variants is sufficient to confirm PCD. It is also essential for identifying patients eligible for future curative trials involving mRNA correction or gene editing.
2. **Distinguish between Class 1 and Class 2 TEM defects.** Class 1 defects (e.g., absent outer dynein arms) are confirmatory for PCD. Class 2 defects (e.g., central pair defects or microtubule

disorganisation in <50% of cilia) are only suggestive and require additional evidence from other diagnostic tests.

3. **What are the two methods for measuring Nasal Nitric Oxide (nNO), and which is preferred?** The two methods are velum closure (breath-hold or exhalation against resistance) and tidal breathing. Velum closure is strongly recommended due to higher sensitivity and specificity; tidal breathing is reserved for children under age 5 who cannot perform the former.
  4. **How does PCD affect laterality, and what specific conditions can result?** Dysfunction of embryonic nodal cilia leads to laterality defects, including situs inversus totalis (mirrored internal organs), dextrocardia (heart on the right), and heterotaxy syndromes (often associated with complex heart disease).
  5. **Why is nNO not recommended as a general population screening tool?** Because the prevalence of PCD is low, widespread screening would result in a high rate of false-positive results. It should only be used in patients with a high pretest probability based on clinical history.
  6. **What role does international collaboration play in resource-limited settings?** Collaborative networks (e.g., BEAT-PCD, ERN-LUNG) provide education, procedural training, diagnostic expertise, and access to funding for genetic testing in areas where healthcare infrastructure is insufficient.
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### III. Essay Prompts for Deeper Exploration

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1. **The Evolution of Diagnostic Standards:** Analyze the necessity of the 2025 unified ERS/ATS guidelines. Discuss how advances in genetics and the limitations of previous "gold standard" tests like TEM necessitated a multi-test approach.
  2. **The Complexity of Differential Diagnosis:** Using the case study of the 6-year-old boy who was eventually diagnosed with primary immunodeficiency, discuss why PCD is frequently misdiagnosed and why a negative diagnostic battery for PCD is as clinically valuable as a positive one.
  3. **Future Therapeutic Landscapes:** Explore the link between specific genetic diagnoses and emerging therapies. How might the identification of specific protein defects through IF or genetic variants pave the way for mRNA-based or gene-editing treatments?
  4. **Diagnostic Disparities:** Evaluate the challenges of diagnosing PCD in resource-limited regions. How can symptom-based tools like PICADAR be used to bridge the gap between clinical suspicion and high-cost confirmatory testing?
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### IV. Glossary of Important Terms

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- **Axonemal Ultrastructure:** The complex internal structure of the cilium, typically analyzed via TEM to find defects in dynein arms or microtubules.

- **Biallelic Pathogenic Variant:** Mutations in both copies of a gene (inherited from both parents) that are known to cause disease.
- **Consanguinity:** Genetic relatedness between parents, which increases the prevalence of autosomal recessive disorders like PCD.
- **Dynein Arms (Outer/Inner):** Protein structures within the cilia that provide the "motor" force for movement. Defects here are primary indicators of PCD.
- **GRADE Approach:** A systematic method (Grading of Recommendations, Assessment, Development, and Evaluation) used by the task force to formulate evidence-based clinical guidelines.
- **Heterotaxy:** A condition where internal organs are abnormally arranged (neither situs solitus nor situs inversus), often involving heart defects.
- **Mucociliary Clearance (MCC):** The self-clearing mechanism of the airways where motile cilia move mucus toward the throat to be cleared.
- **PICO Questions:** A framework (Patients, Intervention, Comparison, Outcomes) used to structure clinical research and systematic reviews for the guidelines.
- **Situs Inversus Totalis:** A condition where all major visceral organs are reversed or mirrored from their normal positions.
- **Variants of Unknown Significance (VUS):** Genetic variations where the impact on health is not yet determined, often requiring further protein-level testing (like IF) to confirm pathogenicity.