

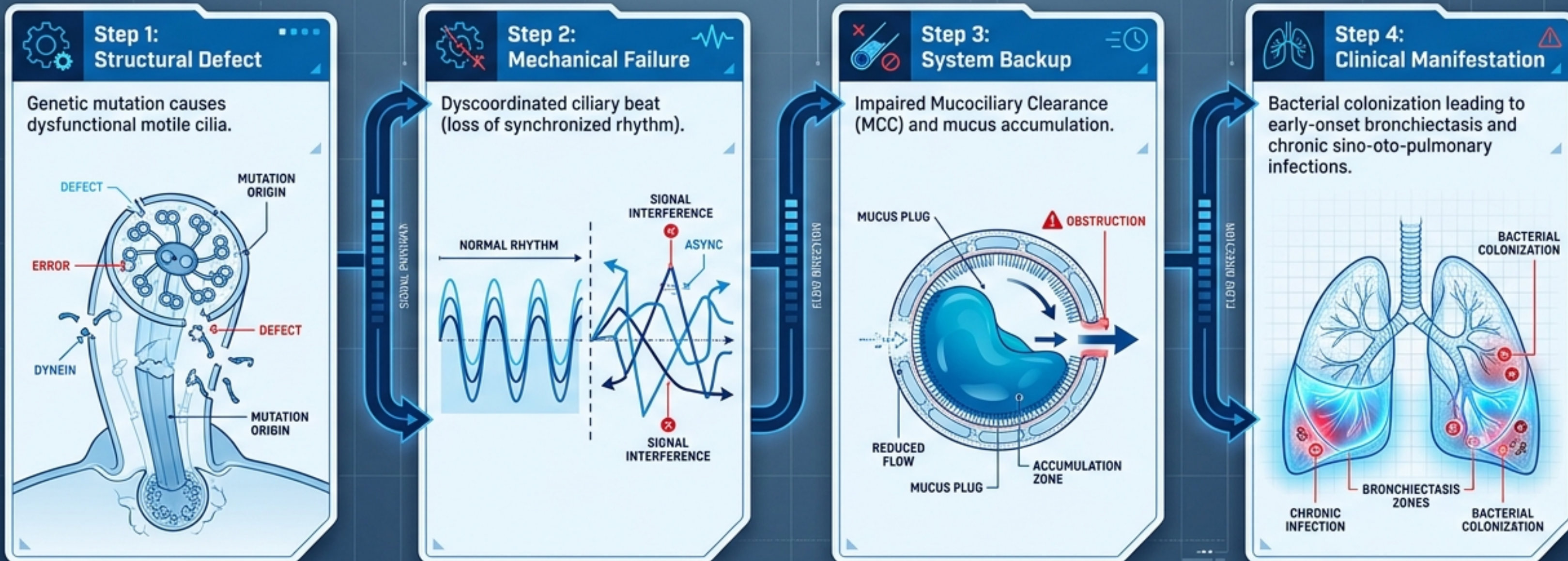
The PCD Diagnostic Blueprint

Translating the Unified ERS/ATS Guidelines into a Clinical Pathway

Standardizing the identification and multimodal diagnosis of Primary Ciliary Dyskinesia.

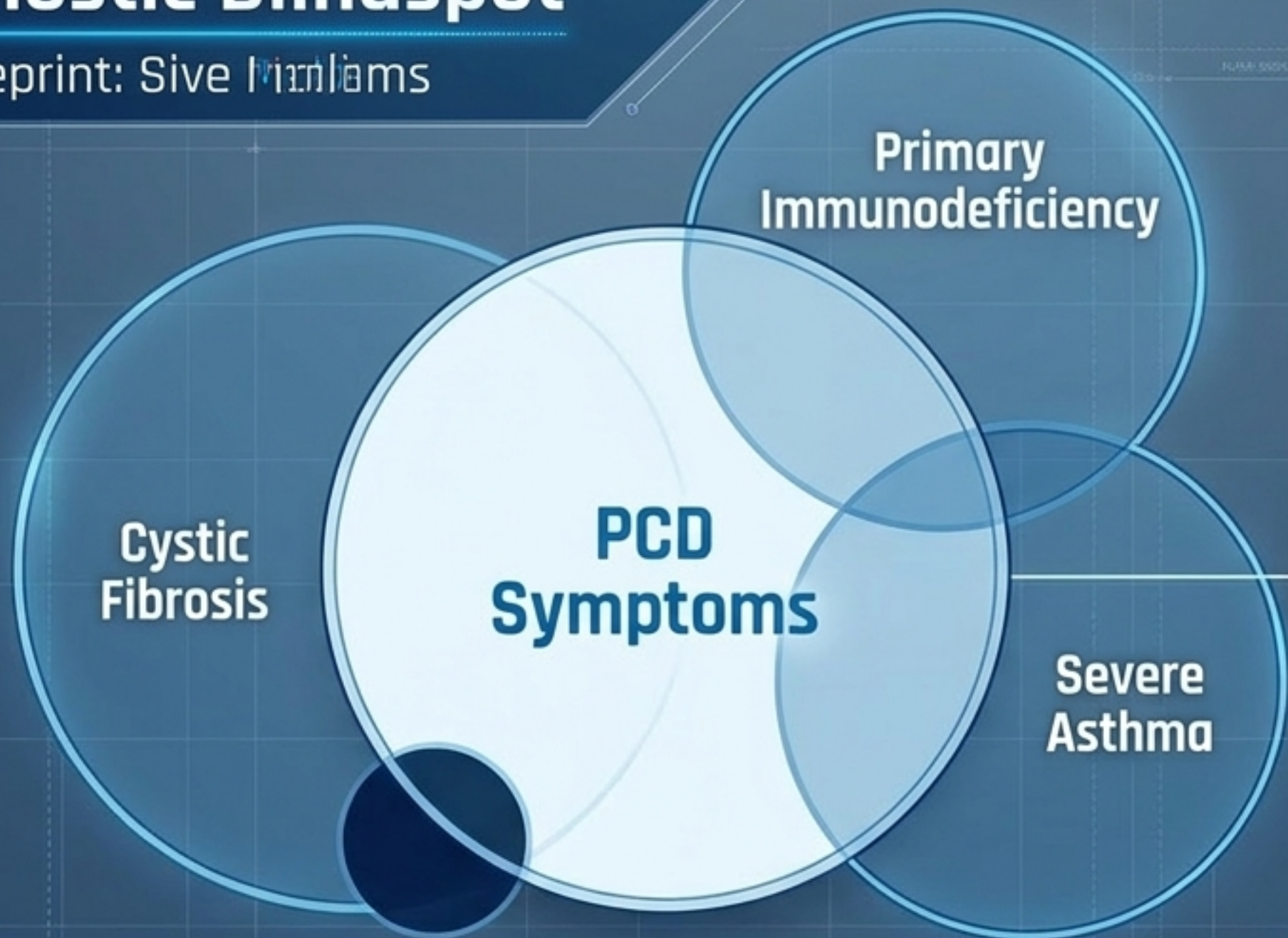
The Architecture of Failure

The Pathology Chain Reaction



The Diagnostic Blindspot

Diagnostic Blueprint: Sive Immunams



Prevalence: 1:7,500

Severe underdiagnosis indicated by registry data.

Key Insight: PCD symptoms are common and non-specific in pediatrics. Patients face years of recurrent infections and multiple physician visits before targeted evaluation.

The Consequence: Late diagnosis prevents early intervention (age < 8), which is proven to preserve lung function throughout childhood.

One Disease, One Global Standard

Historical ATS Guidelines

Historical ERS Guidelines



Standardization

Enables integrated registry data collection and standardizes care delivery globally.



The Shift

The newly published joint ERS/ATS guidelines provide the first unified, evidence-based (GRADE approach) diagnostic framework.



Future Readiness

Facilitates international clinical trials for emerging, targeted gene therapies.

The Clinical Presentation Dashboard

Neonatal (0-1 Month)



- Unexplained respiratory distress at term
- NICU admission for persistent supplemental oxygen
- Situs anomalies (laterality defects)

Childhood



- Persistent, early-onset wet cough
- Persistent perennial rhinitis
- Chronic ear or hearing problems

Adult / Systemic



- Early-onset bilateral bronchiectasis (middle/lower lobes)
- Male and female sub-fertility/infertility

Note: A specific symptom does not trigger evaluation; the PATTERN of presentation does.

Triage & Pre-Test Probability

Pathway A: PICADAR Score



Prerequisite: Persistent early-onset wet cough.



Neonatal chest symptoms



NICU admission



Situs anomalies



Congenital heart defects



Rhinitis



Chronic ear issues

Pathway B: ATS Clinical Criteria



- ✓ Unexplained neonatal distress
- ✓ Early-onset year-round cough
- ✓ Early-onset year-round nasal congestion
- ✓ Laterality defects

Clinical Rule: These are screening tools to prioritize referral to specialized centers, not definitive diagnostic tests. They excel at identifying patients with laterality defects but may miss atypical presentations.

The Diagnostic Toolkit Matrix

	Mechanism	Guideline Recommendation	Caveats
Genetics	Identifies biallelic variants	 Confirmatory	Diagnostic yield is ~70%.
TEM	Axonemal ultrastructure	 Confirmatory (Class 1)	Normal in 20-30% of confirmed cases.
nNO	Nasal nitric oxide levels	Strong (Velum closure)	Reduced in CF/Immunodeficiency. Not a general screen.
HSVM	Direct visualization of beat pattern	Strong	High cost, requires in-vitro culture expertise.
IF	Fluorescent protein tagging	Strong	Highly specialized, relies on known protein panels.

Genetic Sequencing: The Primary Anchor



**70%
Yield**

Confirmed

The Standard

Identifying pathogenic biallelic variants in a known PCD-associated gene (over 65 identified) is sufficient to confirm diagnosis.

The Imperative

Beyond diagnosis, genetic confirmation is critical for enrolling patients in ongoing pre-clinical trials (mRNA correction, gene editing, read-through therapies).

The Gap

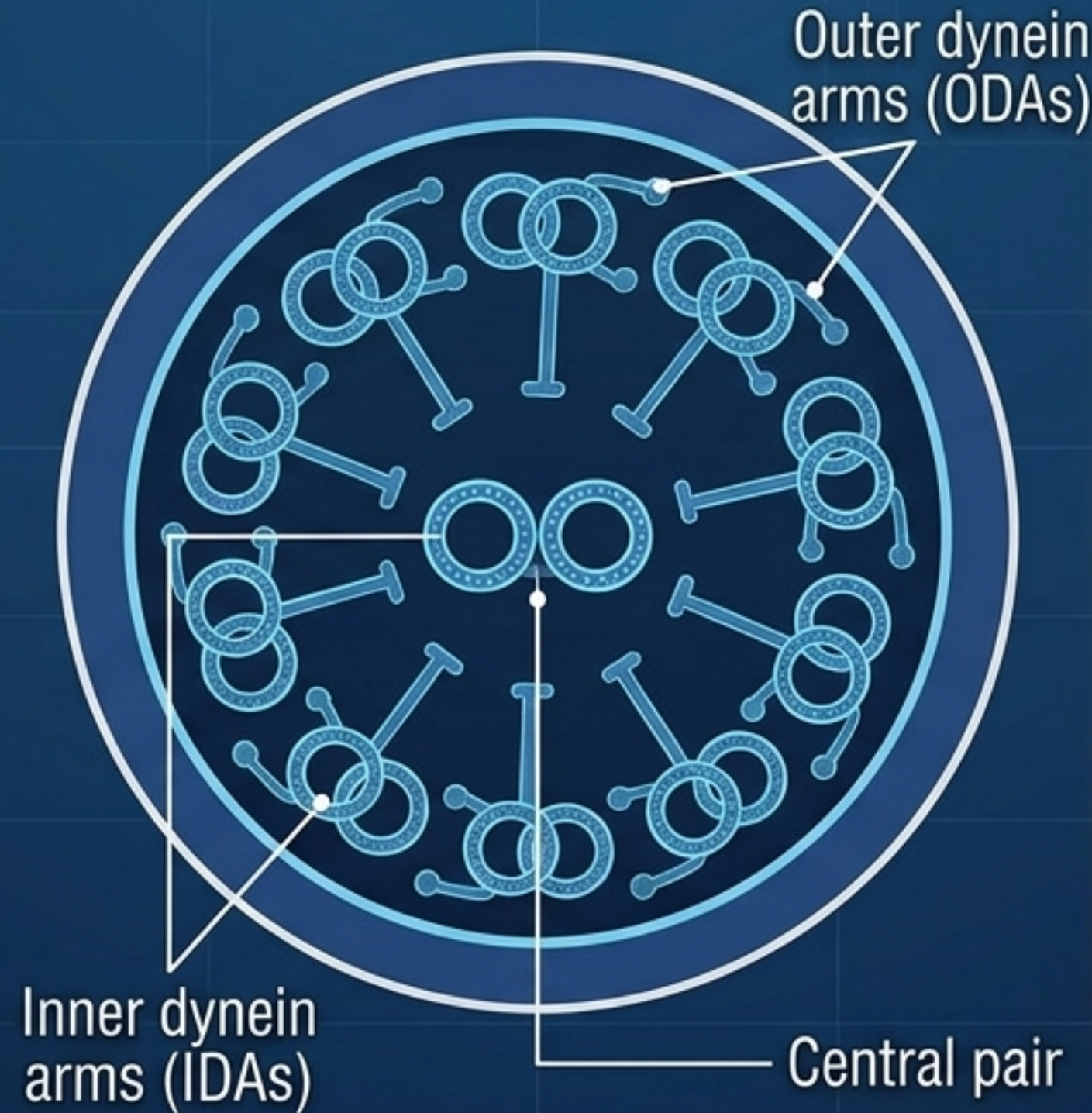
When genetics are inconclusive (the remaining 30%), the diagnostic cascade relies on the advanced adjunct tests.

Transmission Electron Microscopy (TEM)

Highly specific (99%) but requires immense expertise. Not a substitute for genetics.

Class 1 Defects (Confirms Diagnosis)

- Outer dynein arm (ODA) absence
- Inner and outer dynein arm absence
- Inner dynein arm absence + microtubular disorganization



Class 2 Defects (Suggestive, Requires Support)

- ODA defects in <50% of cross-sections
- Central pair defects
- Microtubule disorganization (with IDAs present)

nNO: The Flow-Rate Caveat

Mechanism: nNO levels are significantly lower in PCD patients. Requires a chemiluminescent device.
Standard cutoff: 77 nL/min.



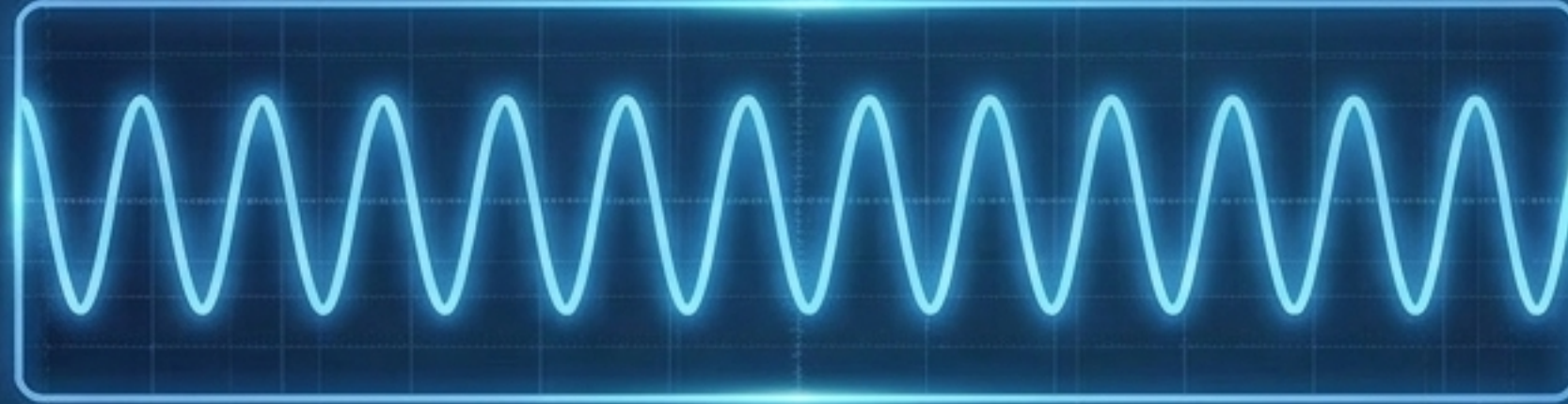
- Recommendation: Strong (Moderate certainty).
- Application: Patients > 5 years old.
- Profile: Highly sensitive and specific.



- Recommendation: Conditional (Very low certainty).
- Application: Infants and young children < 5.
- Profile: Highly variable. Elevated risk of misclassifying non-PCD patients.

High-Speed Video Microscopy (HSVM)

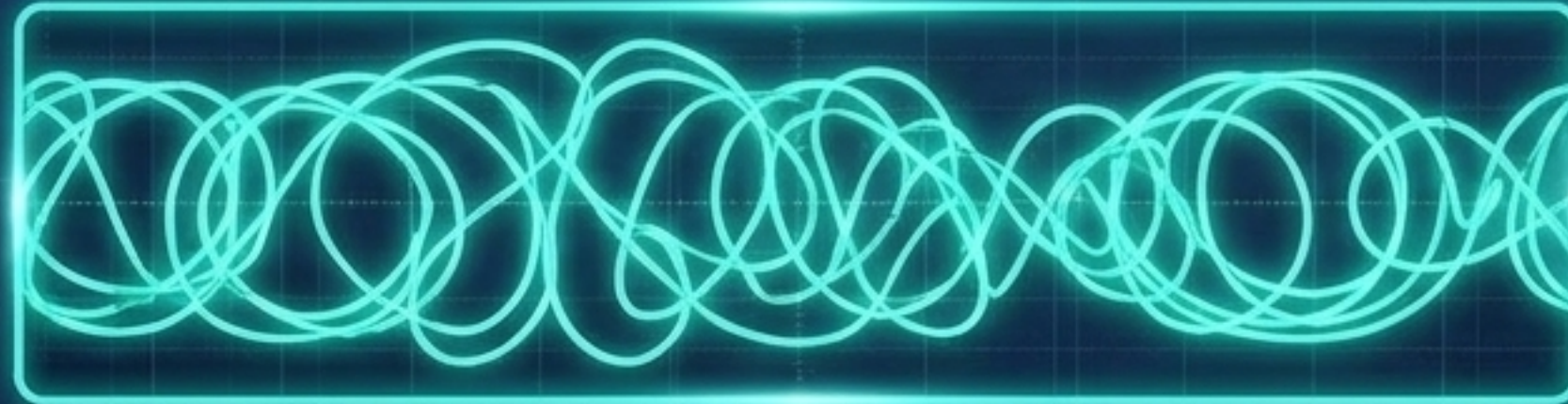
Healthy Cilia



Stasis



**Rotational /
Disorganized**

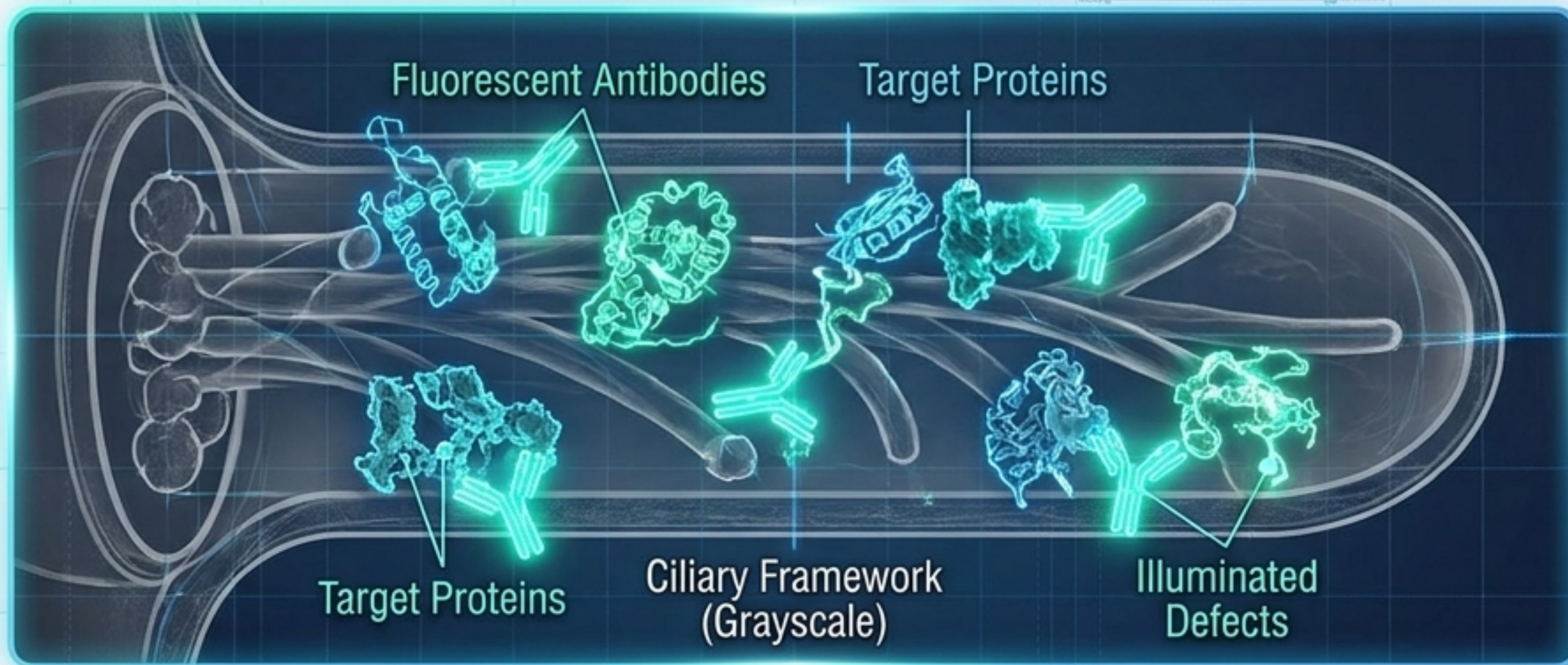


Mechanism: Direct light microscopy visualization of ciliary beat pattern, frequency, and amplitude. (Highest accuracy post-culture).

The Superpower: Crucial for diagnosing PCD when TEM appears perfectly normal.

Key Targets: Specifically resolves variants in DNAH11, HYDIN, and RSPH1 genes, which exhibit distinct dysfunctional rotational patterns invisible to structural TEM analysis.

Immunofluorescence (IF): Illuminating the Blindspots



Mechanism

Applies fluorescently tagged antibodies to nasal brushing samples to identify absent or mis-localized proteins.

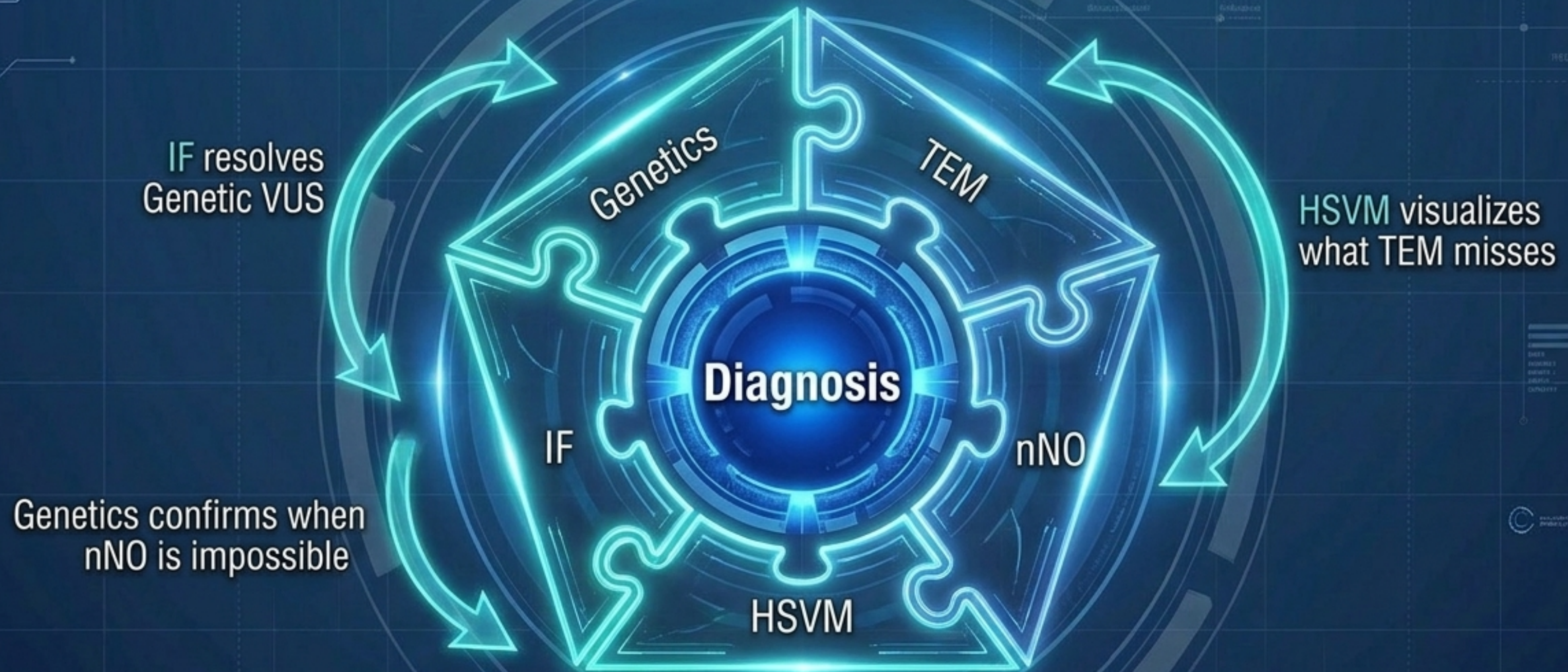
Recommendation

Strong (High certainty of evidence).
Highly accurate without adding undue test burden.

Clinical Utility

The ultimate tool for resolving Variants of Unknown Significance (VUS) in genetic sequencing. Confirms disease pathology when TEM is normal but genetics are ambiguous.

The Multimodal Arsenal



The Core Insight: No single diagnostic test possesses 100% sensitivity and specificity. The guideline mandates a composite approach. Tests are deployed sequentially to cover overlapping diagnostic blindspots.

Standardized Diagnostic Outcomes



CONFIRMED

Biallelic pathogenic variants OR
Class 1 TEM defect.



HIGHLY LIKELY

High clinical suspicion + consistent positive
adjunct tests (HSVM, IF, nNO) without
definitive Genetics/TEM.



SUSPECTED

Incomplete testing or borderline results
requiring ongoing surveillance or in-vitro
culture.



HIGHLY UNLIKELY

Negative results across a robust,
multi-modal testing matrix.

Patient Profile 01: The Classic Presentation



Demographics

4yo Female.
Term birth, 10 days NICU.



Clinical Picture

Chronic wet cough, persistent nasal congestion, recurrent otitis media, delayed speech.

Pre-Test Triage

Pre-Test Triage

PICADAR Score = 8 | ATS Criteria = 3/4

Test Matrix



N/A

nNO: Unable to perform



Genetics:
Biallelic pathogenic
DNAH5 in trans



TEM: Absent
Outer Dynein Arms
(Class 1)

OUTCOME:
CONFIRMED PCD.
Local specialist
center referral.

Patient Profile 02: The False Flag



Demographics

6yo Male.
Preterm (35 wks).
Below 3rd percentile growth.



Clinical Picture

Recurrent wet cough (started late at 18mo), scattered rhonchi, early digital clubbing.

Test Matrix



nNO

62 nL/min
(Velum closure).



Genetics

Gene panel
clear.



TEM

Normal
ultrastructure.



HSVM & IF

Normal beat pattern
and localization.

Key Takeaway

Low nNO occurs in Immunodeficiency and CF.
Negative multimodal tests prevented misdiagnosis.

OUTCOME: HIGHLY UNLIKELY.
Re-evaluated -> Diagnosed with
Primary Immunodeficiency.

Patient Profile 03: Resolving Ambiguity



Demographics

13yo Male.
Term birth, 5 days oxygen support.



Clinical Picture

Chronic otorrhea, right lower lobe crackles, sibling with similar symptoms.

Test Matrix



nNO



Positive/Low:
20 nL/min.



TEM



Negative: Normal
ultrastructure.



HSVM



Positive: Disorganized/
rotational beat.



Genetics



Inconclusive: HYDIN
Variants of Unknown
Significance (VUS).



IF



Positive: Absent
SPEF2 localization.

Key Takeaway

Initially designated 'Highly Likely,' upgraded to Confirmed once IF data allowed re-classification of the VUS to pathogenic.

OUTCOME:
CONFIRMED PCD.

Diagnostics in Resource-Limited Settings



The Challenge

Multimodal diagnostic matrices require intense capital and specialized expertise unavailable in many regions.

Strategy 1: Maximized Triage

Heavy reliance on validated, low-cost screening tools (PICADAR, ATS Criteria) to fiercely prioritize testing resources.

Strategy 2: International Hubs

Utilizing global collaborations (BEAT-PCD, ERN-LUNG) for remote procedural training, diagnostic reads, and funded genetic sequencing.

The Horizon of PCD Diagnostics

Knowledge Gaps: Despite recent guidelines, the diagnostic pathway continues to evolve.

Optical Coherence Tomography (OCT) & Radiolabelled Tracking

For ultra-high-resolution imaging and mucociliary clearance assessment.

Advanced In-Vitro Culture

Next-generation airway epithelial cell culture techniques to simulate respiratory environments.

Machine Learning & Digital Augmentation

Automated pipeline analysis for TEM and IF image sets to reduce human error.

The Clinical Mandate

01

01 | Recognize the Pattern

PCD is not a single symptom. Utilize PICADAR and ATS criteria to identify patterns of neonatal distress, laterality, and chronic wet cough.

02

02 | Deploy the Toolkit

Abandon the search for a single silver bullet. Diagnosis requires a multi-modal matrix of Genetics, TEM, nNO, HSVM, and IF working sequentially.

03

03 | Secure the Future

Early, accurate, genetically confirmed diagnosis is the prerequisite for preserving childhood lung function and unlocking access to next-generation gene therapies.