Guidelines for Diagnosis and Treatment of Primary Ciliary Dyskinesia

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Disclosure of Conflict of Interest (over the past 2 years)

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I have no conflict of interest.
What is Primary Ciliary Dyskinesia (PCD)

- Mostly autosomal recessive disease
- Prevalence of 1:10,000 to 1:30,000
- Dyskinetic cilia lead to mucus stasis and chronic infection in upper and lower respiratory tracts, bronchiectasis, lung transplant, death
- Long term outcomes not well defined
Diagnosis of Primary Ciliary Dyskinesia

- Delayed diagnosis - symptoms overlap with other diseases - CF, immune, aspiration, “daycare-itis”

Key clinical PCD symptoms in children¹:
1. Year-round, wet cough starting <6 months old
2. Year-round nasal congestion starting <6 months old
3. Unexplained neonatal respiratory distress, >24 hours of supplemental O₂ or pressure support
4. Organ laterality defect (Situs inversus or ambiguus)

¹Leigh et al. Annals ATS, 2016
Diagnosis of Primary Ciliary Dyskinesia

- Gold-standard diagnosis was transmission electron microscopy (TEM) analysis of ciliary ultrastructure
- TEM normal in 30% of PCD\(^1\)

Diagnosis of Primary Ciliary Dyskinesia

PCD Diagnosis

- nNO
- Genetics
- EM
- HSVM
- IF
Diagnosis of Primary Ciliary Dyskinesia

- Not every center can perform each test:
  - Proper nitric oxide devices not widespread
  - TEM failure rates are high, misinterpreted
  - HSVM not routinely done in North America
  - Genetics often not reimbursed
  - Immunofluorescence rarely done
Guidelines and Consensus

- **PCD Diagnosis:**

- **PCD Therapeutics:**
ATS Committee Composition

- 30 international PCD experts - pediatric & adult pulmonology, ENT, neonatology, radiology, genetics, cardiology, expert methodologist, PCD patients/parents

- 4 PICO questions on PCD diagnostic testing compared against:
  - “Reference Standard” of Classic TEM defect and/or 2 pathogenic mutations in one PCD gene
  - In those with a high clinical probability of PCD (at least 2 of 4 key clinical features)
Should an extended genetic panel (testing >12 genes) be used as a diagnostic test in patients with a high probability of PCD?

- As replacement of classic TEM ciliary defect and/or standard genetic panels testing ≤12 PCD genes.
# of coding exons in each of the genes implicated in Human PCD

Comparison with CFTR

- 2007 - 9 PCD genes
- 2019 - 42 PCD genes
- 2015 - extended gene panels commercially available
  - \(\leq 12 \rightarrow >34\) genes

Courtesy M. Zariwala, UNC.
PICO1 – PCD Genetic Testing

- Prospective, multi-site, cohort - Leigh et al (2017)\(^1\)
  - 534 consecutively referred children for PCD suspicion

- 26 gene PCD panel vs TEM and/or ≤12 gene panel
  - **Sensitivity 80%, specificity 99.5%**

- 4 case-series: Sensitivity increases with number genes
  - 71% for 12 genes\(^2\)
  - 94% for 32 genes + del/dup testing\(^3\)

PICO1: Should extended gene panel testing be used to replace EM and/or standard gene panels?

- In patients with high clinical probability of PCD, we suggest using an extended genetic panel as a diagnostic test over TEM &/or standard genetic panels.

- **Conditional recommendation** - Highly feasible, prognosis through genotype, family planning

**Limitations of genetic testing:**

- NOT a rule out test
- NEED 2 in same PCD gene, arising in trans
- Variants of unknown significance are non-diagnostic, require local genetic specialists for support
PICO2 – nNO Testing

- Should a low nasal nitric oxide level be used as a diagnostic test for PCD, in adult and pediatric patients ≥5 years old, who are at high probability of having PCD?
  - With chemiluminescence technology
  - After ruling out cystic fibrosis
  - As a replacement of reference standard of classic TEM structural ciliary defect and/or biallelic causative mutations in PCD genes
PICO2 – nNO Testing

- nNO <77 nL/min in PCD:
  - Unknown mechanism
  - If ≥5yo, cooperative to blow into resistor, using SOP

- Good screening test:
  - Non-invasive, rapid, feasible
  - Inexpensive to patients
  - Immediate results

PICO2 – nNO Testing: Meta-Analysis

- 12 populations, >1400 patients
- Chemiluminescence devices
- Cooperative, CF ruled out

**Pooled Sensitivity 98%, Specificity 96%**
- vs classic TEM defects and/or genetics

Shapiro et al. Annals ATS, 2017
PICO2: Should nNO testing be used to replace TEM and/or standard gene panels?

- In cooperative patients ≥5 years old, with high clinical probability of PCD and with CF excluded, we suggest using nNO testing as a diagnostic test over TEM and/or genetics - Conditional recommendation

- Comment: nNO values may be transiently decreased with acute viral respiratory infection:
  - NEED low nNO on 2 separate occasions
  - NEED to use a proven SOP
Limitations to nNO Testing:

- Lacking diagnostic nNO cut-offs for <5 years old by tidal breathing, but normal tidal values (>77 nL/min) are very reassuring
- Need normal nNO levels in disease controls
- Devices not Health Canada approved
- Rare examples of normal nNO in PCD (RSPH1)
- **NOT** a screening tool for general populations
PICO3 – HSVM Testing

Should digital high speed videomicroscopy with ciliary beat pattern analysis (HSVM) be used as a PCD diagnostic test in patients in patients with high clinical probability of PCD?

- As a replacement of reference standards of classic TEM structural ciliary defect and/or biallelic causative mutations in PCD genes.
PICO3 – HSVM Testing

- HSVM is a stand-alone PCD diagnostic technique in European (UK) centers
- Capture ciliary motion at >400 frames per second, perform slow-motion review of beat pattern
- Strongly recommended in ERS guidelines – 3 repeats or after cellular regrowth

HSVM equipment setup
Courtesy of M. Chilvers, UBC
Center outside of UK shows poorly diagnostic accuracy

- Non-standard interpretation techniques: Qualitative CBP description vs semi-quantitative Dyskinesia Score
- No data on repeat HSVM results at separate visits
- 2 studies used HSVM after cell regrowth, 50% success
- All compared to TEM diagnoses, no genetic testing

3Papon et al. Orphanet J Rare Dis, 2012.  
Pooled Sensitivity 97.3%, Specificity 96.5%, but very large confidence interval:

- Great variation in certainty of results
- Accuracy likely lower when include PCD diagnosed by genetics
- Poor test feasibility across many centers
- Blinded, inter-rater HSVM agreement is poor in healthy control samples

Shoule HSVM be used to replace EM and/or PCD gene testing?

- **We suggest NOT using HSVM** as a replacement diagnostic test in patients who are at high probability of having PCD - **Conditional recommendation**
- This is a research-based test that works well in PCD centers that are highly experienced with HSVM.
- The lack of feasibility, standardization, and successful cellular regrowth protocols make this test extremely difficult to perform across various clinical centers.
PICO4 – CBF and Non-HSVM Recording

Should 1) ciliary waveform analysis using light microscopy without high speed recording or 2) ciliary beat frequency (CBF), be used as a PCD diagnostic test, in patients with high clinical probability of PCD?

- As replacement of reference standards of classic TEM structural ciliary defect and/or biallelic causative mutations in PCD genes.
Screening with light microscopy and non-HSVM recording (<120 fps) of fresh cells, before more PCD tests.

Look for subjectively abnormal beat.

No studies in PCD diagnosed by current TEM or genetic standards.

No prospective studies >15 years for CBP by non-HSVM techniques.

No official recommendation as no reviewable evidence.
Should CBF alone replace EM and/or PCD gene testing?

In 3 studies, 458 patients:
- “Normal” CBF varies greatly between labs
- No genetic PCD diagnoses, only TEM
- **Sensitivity 68-100%, specificity 61-78%**

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<th>Study</th>
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<th>FP</th>
<th>FN</th>
<th>TN</th>
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<td>0.77 [0.72, 0.82]</td>
</tr>
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</table>

Should CBF alone replace EM and/or PCD gene testing?

- **We suggest NOT using CBF measurement** as a diagnostic test in patients who are at high probability of having PCD.

- **Conditional recommendation**
Summary of Diagnostic Recommendations

No single test will accurately diagnose all forms of PCD

- Rarely normal, ≥5 years old
- ≥70% detection
- 30% normal in PCD
- False +/- results
- Limited centers

nNO $ FEAS+++ Genetics $$ FEAS++++ EM $$ FEAS++ HSVM $$$ FEAS- IF $$ FEAS+
Suggested PCD Diagnostic Algorithm

At least 2 of the 4 key clinical features for PCD:
- Unexplained neonatal respiratory distress in term infant
- Year-round daily cough beginning before 6 months of age
- Year-round daily nasal congestion beginning before 6 months of age
- Organ laterality defect

No → PCD Unlikely

Yes

Access to nNO testing (with chemiluminescence device and standardized protocol) at specialty center
AND Cooperative patient ≥5 years old, capable of performing nNO testing maneuver

Yes to both (preferred pathway)
- Nasal nitric oxide measurement

No to either
- Extended genetic testing panel

Suggested PCD Diagnostic Algorithm

Nasal nitric oxide measurement*

- Low nNO level
  - Diagnosis of PCD, if CF is excluded. Advise repeat nNO to verify low value.
  - Pursue additional corroborative PCD testing:
    - Extended genetic panel testing (first line)
    - TEM of ciliary ultrastructure

- Normal nNO level
  - Unlikely PCD diagnosis
  - Pursue genetic testing if strong clinical features

Extended genetic testing panel†

- Biallelic pathogenic variants in PCD-associated gene
  - Diagnosis of PCD
  - Electron microscopy of ciliary ultrastructure
    - Recognized ciliary ultrastructural defect
      - Diagnosis of PCD
    - Normal ciliary ultrastructure
      - PCD Still Possible

- Single pathogenic variant in PCD-associated gene
  - Diagnosis of PCD

- No pathogenic variants in PCD-associated genes
  - Inadequate sample or indeterminate analysis
    - Unknown
      - Consider repeat TEM or referral to PCD specialty center

*CF ruled out
†Including >12 genes, plus deletion/duplication testing
Guidelines and Consensus

- **PCD Diagnosis:**

- **PCD Therapeutics:**
Completing the Ciliary Phenotype

- Retinal examination in RPGR, visual deficits, or family history of retinal/ciliary blindness
- Genetics consultation with syndromic features
- Consider abdominal/cardiac ultrasounds for laterality issues in all PCD patients (200X risk of CHD):
  - Occult cardiac septal defects, L-TGA
  - If spleen anomalies: Howell-Jolly Body test
  - If intestinal malrotation: surgical consult

Routine Monitoring in PCD

- Respirology + PFT’s + sputum cultures: 2-4 times/year
  - AFB/NTM cultures every 2 years & prn
  - IgE/ABPA testing prn
- Otolaryngology: 1-2 times/year children, prn adults
  - Audiology: At diagnosis, then per ENT
- Chest radiography: Every 2-4 years & prn
- Chest computed tomography: Consider after 5-7 yrs

Prospective Studies in PCD Therapeutics
Routine Therapies in PCD

- Airway clearance: Daily (clapping, handhelds, vest)
- Standard, Pneumococcal, Influenza vaccines
- RSV immunoprophylaxis: Consider monthly in first winter for high risk patients (long O₂ need)
- Infection control: General hospital infection control policies recommended**

**Depending upon exposures to CF patients

**Antibiotics:** As needed for acute exacerbations
- Mild – broad spectrum oral agent ≥14 days
- Moderate/Severe – IV therapy for ≥14 days
- Inhaled antibiotics not studied

**Initial* P. aeruginosa* airway culture eradication suggested, though not studied**

*Shapiro et al. Pediatr Pulmonol. 2016*
Case by Case Therapies in PCD

- Chronic oral suppressive antibiotics
  - Azithromycin:
    • Benefits in CF & Non-CF bronchiectasis\(^1\)
    • Requires NTM surveillance\(^2\)
    • European PCD trial complete, awaiting results\(^3\)

- Chronic inhaled suppressive antibiotics
  - Chronic *P. aeruginosa* colonization

Case by Case Therapies in PCD

- Inhaled bronchodilators: unclear benefits in PCD\(^1\)
- Inhaled hypertonic saline - 2 non-CF adult studies:
  - No benefit or limited positive benefits vs NS\(^2\)
  - Small PCD study – no benefit in SGRQ\(^3\)
  - International trial with inhaled HS + ENaC inhibitor + ivacaftor complete, awaiting results\(^4\)
- Inhaled Dnase – 2 non-CF adult studies:
  - No benefit or more exacerbations, worse PFT’s\(^5\)

Therapies Not Recommended in PCD

- Inhaled corticosteroids
  - Reserved for PCD with airway reactivity or asthma
- IVIG - unless proven humoral dysfunction
  - Isolated IgA or IgG subclass deficiency does not justify IVIG therapy in PCD
- Lobectomy – Poor prognostic factor, lower PFT’s in adults with PCD.

Routine ENT Therapies in PCD

- Lacking any prospective data on ENT in PCD
  - Recurrent otitis media + effusion is very common
  - Monitor regularly for hearing deficits:
    - PE tubes with deficits or speech/language delay
    - 80-100% have normal hearing post-PE tubes
    - Post-operative otorrhea not worse than non-PCD
    - Topical therapy for future otitis media

Routine ENT Therapies in PCD

- Chronic rhino-sinusitis is omnipresent in PCD:

- Need regular surveillance:
  - Nasal endoscopy for polyps
  - Consider chronic nasal steroids
  - Daily sinus irrigation in PCD after ESS improves quality of life\(^1\)
  - Does sinus therapy help lungs?

\(^1\) Alanin MC et al. Int Forum Allergy Rhinol. 2017
Conclusion

- PCD diagnosis in North America rests primarily on nasal nitric oxide and genetic testing.
- Other PCD diagnostic tests should remain in expert research settings for now.
- PCD monitoring and therapeutics are borrowed from CF experiences, but PCD clinical trial results are arriving soon...