ERS pocket guidelines

Diagnosis of primary ciliary dyskinesia: a European Respiratory Society guideline

From the ERS task force on diagnosis of primary ciliary dyskinesia

ERS EUROPEAN RESPIRATORY SOCIETY

every breath counts

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Table of contents

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It was prepared by Prof. Claudia Kuehni (Bern, Switzerland) and Prof. Jane Lucas (Southampton, UK) under the supervision of the ERS Methodologists Dr. David Rigau and Ms. Thomy Tonia.

Question #1: Which patients should be referred for diagnostic testing?

We recommend that patients are tested for PCD if they have several of the following features: persistent wet cough; situs anomalies; congenital cardiac defects; persistent rhinitis; chronic middle ear disease with or without hearing loss; a history, in term infants, of neonatal upper and lower respiratory symptoms or neonatal intensive care admittance	•Strong recommendation •Moderate quality of evidence
Patients with normal situs presenting with other symptoms suggestive of PCD (as listed above) should be referred for diagnostic testing	•Strong recommendation •Moderate quality of evidence
Siblings of patients should be tested for PCD, particularly if they have symptoms suggestive of PCD (as listed above)	•Strong recommendation •Moderate quality of evidence
We suggest the use of combinations of distinct PCD symptoms and predictive tools (e.g. PICADAR) to identify patients for diagnostic testing	•Weak recommendation •Moderate quality of evidence

Advantages and limitations

- Sensitivity and positive predictive values for individual clinical features are low.
- Combination of suggestive symptoms (e.g. PICADAR score >5) have a higher discriminative value than individual symptoms, but accuracy needs to be assessed in different populations and should further be optimised.

Rationale of recommendation

Predictive values of subsequent tests, such as nasal NO increase significantly if applied to patients with typical symptoms, thus before conducting any diagnostic investigations it is essential to establish that the patient has suggestive symptoms. These data are easy to gather by a clinician taking a detailed clinical history.

Considerations for implementation

It is important that clinicians consider the diagnosis of PCD and refer to a diagnostic reference centre when appropriate. Currently, most patients with PCD are missed or diagnosed late because clinicians have not recognised the typical symptoms.

Question #2: In patients suspected of having PCD, should nasal nitric oxide be used as a diagnostic tool?

Nasal nitric oxide measurement should be used as part of the diagnostic work-up of school children aged >6 years and adults suspected of having PCD, preferably using a chemiluminescence analyser with a velum closure technique	• **Strong recommendation** • **Moderate evidence**
In children aged <6 years suspected of having PCD, we suggest nasal nitric oxide measurement using tidal breathing as part of the diagnostic work-up	• **Weak recommendation** • **Weak evidence**

Advantages and limitations

- nNO is a highly accurate test for PCD when measured via a stationary chemiluminescence analyser using velum closure techniques
- Tidal breathing technique or use of portable analysers have less diagnostic accuracy but may contribute to the diagnostic decision.
- Results are dependent on a number of factors including age, analyser sampling rate and breathing manoeuvre; nNO can be low in healthy infants and the discriminative value is poor in this age group.

Rationale of recommendation

nNO is not sufficiently accurate to rule PCD in or out in isolation. However, it is relatively easy to perform, is non-invasive and is affordable, and is therefore recommended as part of the diagnostic work-up of patients suspected of having PCD aged over 6 years. Its role is less clear for children aged less than 6 years.

Considerations for implementation

In patients without a typical history, nNO has a very low predictive value, and therefore it is not useful as a general screening tool without taking the clinical history into account. Patients presenting with a strong clinical history should undergo further testing, even if nNO is normal.

A standardised approach for making the measurements and reporting the data needs to be agreed (e.g. taking into consideration analyser type, age, breathing manoeuvre).

Question #3: In patients suspected of having PCD, should high-speed video analysis (HSVA) be used as a diagnostic tool?

HSVA, 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** • **Low quality of evidence**
Ciliary beat frequency (CBF) should not be used without assessment of ciliary beat pattern (CBP) in diagnosing PCD	• **Strong recommendation** • **Low quality of evidence**
To improve diagnostic accuracy of HSVA, CBF/P assessment should be repeated after cell culture	• **Strong recommendation** • **Low quality of evidence**

Advantages and limitations

- HSVA is an accurate test for PCD when performed by experienced observers combining ciliary beat frequency measurement and pattern analysis
- Culturing the respiratory cells may contribute to improve the accuracy of HSVA, in particular to rule out false positives

Rationale of recommendation

HSVA is not sufficiently standardised to rule PCD in or out in isolation. The panel took into consideration that the optimal conditions for functional evaluation of cilia remain to be defined and that nasal sampling to obtain ciliated cells can be uncomfortable, but that the test is relatively quick and cost effective.

Considerations for implementation

Assessment of ciliary beating is subjective and the diagnostic technician therefore requires significant experience of normal/ abnormal beating patterns. Diagnostic testing should take place in a specialist PCD centre with a high throughput of samples.

A standardised approach for making the analyses and reporting the data needs to be agreed (e.g. temperature, buffer solutions, number of epithelial edges)

Question #4: In patients suspected of having PCD, should transmission electron microscopy (TEM) be used as a diagnostic tool?

Ciliary ultrastructure analysis by TEM should be used as part of the diagnostic work-up of patients suspected of having PCD.	• **Strong recommendation** • **Low quality of evidence**
Further diagnostic investigations should be performed in patients with normal ultrastructure if the clinical history is strong	• **Strong recommendation** • **Low quality of evidence**
In patients with hallmark ciliary ultrastructure defects for PCD further confirmatory diagnostic investigations are not required [1]	• **Strong recommendation** • **Low quality of evidence**

1. Hallmark ciliary ultrastructure defects for PCD: absence of outer dynein arms, combined absence of inner and outer dynein arms, inner dynein arm absence combined with microtubular disarrangement.

Advantages and Limitations

- TEM is a highly specific test to confirm a diagnosis of PCD with a very low rate of false positives.
- The confidence in the evidence is limited because TEM was also used as part of the reference standard work-up.

Rationale of recommendation

TEM is a highly specific test and can confirm a diagnosis of PCD. Although the equipment is very expensive, samples can be fixed and sent to the centres.

The panel considered that up to 16% of PCD patients have TEM without a detectable defect, thus TEM should not be used in isolation to exclude a diagnosis but that false positives are extremely rare when TEM shows hallmark ciliary ultrastructure defects.

Considerations for implementation

Diagnostic testing should take place in a specialist PCD centre with a high throughput of samples. A standardised approach for making the analyses and reporting the data needs to be agreed (e.g. number of cilia and number of cells to assess)

Patients need to know that TEM does not provide immediate results and that nasal sampling to obtain ciliated cells is moderately uncomfortable.

Question #5: In patients suspected of having PCD, should genotyping be used as a diagnostic tool?

It was not possible to determine the accuracy of genetic testing due to lack of suitable studies. Several studies have identified the genes responsible in patients with confirmed PCD, suggesting that genetic testing identifies the gene in ~65% of cases; this is likely to increase as more genes are identified. Whilst further evidence in a diagnostic setting is required, experts on the task force agreed:

1. Genetic testing to confirm diagnosis can be performed in PCD individuals diagnosed by other means (e.g. HSVA, TEM, IF) or in individuals with high clinical suspicion for PCD (typical clinical findings, low nNO) and no availability of other investigations, such as HSVA, TEM or IF. A negative genetic test does not exclude PCD.

2. Genetic testing can also be performed to establish diagnosis in patients highly suspected of PCD and in whom HSVA, TEM or IF failed to confirm the diagnosis, as can be the case for patients with DNAH11, CCNO, MCIDAS or RSPH gene mutations.

3. Genetic testing and interpretation of results should follow national and international best practice guidelines.

4. Genetic diagnosis has to be consistent with the clinical and TEM/IF/HSVA phenotype, or diagnosis reconsidered if the picture is inconsistent.

5. Allelic segregation analysis within the family (especially in both parents) is important to confirm the genotype in the probands (to differentiate between homozygosity and hemizygosity, and between compound heterozygosity and a complex allele).

6. Genetic testing in probands and in their relatives is helpful for genetic counselling to inform reproductive choices.

7. In the future, genetic testing might be important for genotype specific therapy.

Question #6: In patients suspected of having PCD, should immunofluorescent staining of ciliary proteins (IF) be used as a diagnostic tool?

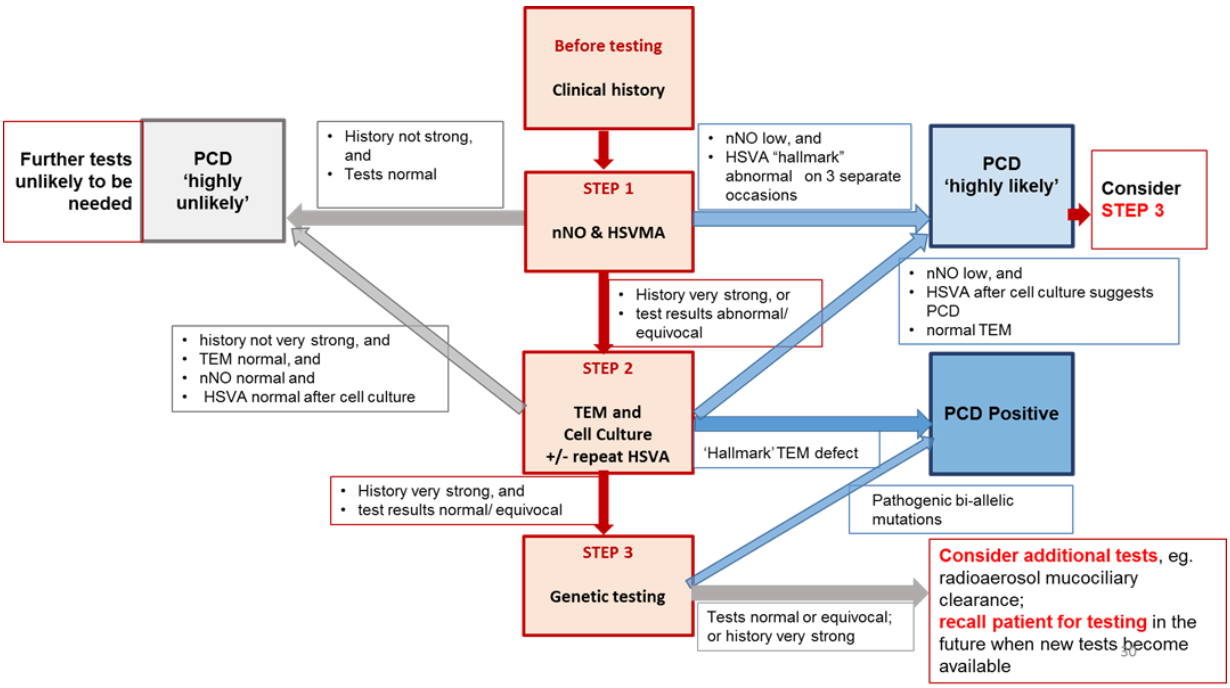
It was not possible to determine the accuracy of immunofluorescence testing due to lack of suitable studies. Task force experts agree that immunofluorescence can be useful in clinical settings. Whilst further evidence in a diagnostic setting is required, experts on the task force agreed:

1. Immunofluorescence is able to confirm pathogenesis of mutations (e.g. missense mutations in genes encoding radial spoke proteins)

2. Immunofluorescence can detect PCD in some cases with normal ultrastructure or subtle ultrastructural defects

3. Immunofluorescence can help establish the diagnosis of PCD in outer and inner dynein arms, tubular disorganisation (CCDC39/CCDC40 mutations), central pair (genes encoding radial spoke proteins) and nexin link defects

Final question: Has the patient got PCD?



Positive diagnosis: For patients with a supportive history of PCD, the following results are confirmatory of a positive diagnosis of PCD:

- Hallmark ciliary ultrastructure defects for PCD (absence of outer dynein arms, combined absence of inner and outer dynein arms, inner dynein arm absence combined with microtubular disarrangement), assessed by TEM.
- Non-ambiguous biallelic mutations in PCD causing genes.

Highly likely diagnosis: In patients with a compatible history of PCD the following diagnostic test results make the diagnosis of PCD highly likely, but do not provide a definitive PCD diagnosis:

- Very low nNO plus HSVA findings consistently suggestive of PCD (e.g. static cilia, circling) on three occasions.
- Very low nNO plus HSVA findings consistent with PCD (e.g. static cilia, circling) following cell culture.

Excluding the diagnosis of PCD: No single test nor combination of tests can exclude a diagnosis of PCD. However, based on the evidence reviewed they agreed that there are conditions under which the diagnosis is 'extremely unlikely', i.e. if the clinical suspicion is only modest and:

- nNO is high/ normal plus normal HSVA, or
- nNO is high/ normal plus normal HSVA following cell culture