

Primary Ciliary Dyskinesia (PCD)

Primary ciliary dyskinesia (PCD) is a rare, inherited, genetic disorder of motile (moving) cilia. Cilia are tiny hairlike structures on the cells in the body. Motile cilia perform an important role in the nose, ears, and airways within the lungs, working to remove unwanted inhaled particles and germs. PCD causes frequent respiratory infections starting at a very early age that result in lifelong, progressive lung, sinus and ear disease. People with PCD benefit from early diagnosis and treatment to hopefully limit permanent lung damage. PCD diagnosis remains challenging, but faster and more reliable diagnostic methods and the development of expert centers around the world are improving both diagnosis and care for people with PCD.



normal cilia

What causes PCD?

PCD is an inherited disorder, meaning that people born with the disease receive a mutated (abnormal) gene from both parents. In PCD, mutations in the genes responsible for building cilia and controlling their function result in cilia that do not work effectively. *Dyskinesia*, or impaired movement, is the most common ciliary defect seen in PCD. Other defects may lead to not having enough cilia on each airway cell, which can also cause the clinical symptoms seen in PCD.

Motile cilia are very complex organelles (little organs) and are outgrowths on the surfaces of cells that line the upper (ears, nose and throat) and lower (lungs) respiratory tract. Each of these cells contains approximately 200 cilia that normally beat very fast in a coordinated fashion. Cilia are covered by a mucus “blanket” that traps unwanted inhaled particles and germs. The beating cilia underneath this blanket move the mucus to larger airways and the back of the throat where it is coughed out or swallowed. This is called *mucociliary clearance* and is one main way our bodies defend our lungs and maintain good respiratory health. Without properly functioning cilia, mucociliary clearance is severely impaired, and germ-filled mucus stays in the ears, nose, sinuses, and airways of the lungs, causing inflammation and repeated infections.

In addition to problems with mucociliary clearance, people with PCD can have abnormalities in the development or placement of their internal organs because the special cilia that direct placement of these organs do not move normally. Therefore, abdominal organ placement might be:

- Normal organ arrangement—the heart points to the left, the stomach and spleen are on the left side of the body, and the liver is on the right. This arrangement is called *situs solitus*.
- The most common organ arrangement abnormality, *situs inversus totalis*, results in completely reversed chest and abdominal organs that are a mirror image of normal placement.

- A small percentage of affected people do not have *situs solitus* or *situs inversus totalis*, but have organ placement that is between normal and mirror image. This is called *situs ambiguus*—or *heterotaxy* if there are also serious heart defects. *Situs ambiguus* can affect only the organs in the chest, only those in the abdomen, or organs in both. It can be mild or severe and may result in additional health issues for people with PCD. Congenital heart defects (CHD) are 200 times more common in PCD patients with *situs ambiguus* or *heterotaxy*.

What are the signs and symptoms of PCD?

Symptoms of PCD start very early in life, usually during the first year, and include:

- Neonatal respiratory distress (trouble breathing shortly after birth) in full-term babies, usually requiring oxygen therapy, and often lasting days to weeks
- Daily, year-round, nasal congestion
- Daily, year-round, wet (mucus-producing) cough
- Chronic middle ear fluid and ear infections that can lead to hearing loss or speech difficulties
- Chronic sinus infections
- “Sidedness” differences (*situs inversus totalis* or *situs ambiguus/heterotaxy*), including congenital heart defects
- Male infertility (inability to make a woman pregnant), since sperm tails use the same genes as motile cilia
- Reduced fertility in women (inability to get pregnant) related to cilia dysfunction in the Fallopian tubes

While the main symptoms of PCD are related to the respiratory tract, motile cilia are also found in the open spaces (ventricles) of the brain and the spinal column, so these can be affected, too. In rare cases, enlarged ventricles or too much fluid in the brain, called hydrocephalus, may occur with PCD. In very rare cases, eye conditions like retinitis pigmentosa can also occur.

How is PCD diagnosed?

PCD diagnosis is challenging. There is no single test that can provide a reliable diagnosis for all cases, so expert centers rely on several tests and observations to confirm a diagnosis. The types of tests available may vary by country and by what is covered by insurers and health services. The ATS has clinical guidelines for healthcare providers for the diagnosis of PCD published in 2018.¹

- **Clinical History**—The most helpful first step is careful attention to patient history and symptoms. Unlike other breathing disorders with similar symptoms, PCD symptoms almost always begin very early in life, often just after birth, and do not go away when the weather changes or respond as well to standard asthma or allergy treatments.
- **Ciliary Biopsy**—A biopsy showing the internal structure of cilia using transmission electron microscopy (TEM) is the classic test for diagnosing PCD. This is a minor procedure, done by scraping ciliated cells from surfaces inside the nose or lower airways. Ciliary biopsy using TEM is expensive and requires a high level of expertise not available at many healthcare centers. Because of this, TEM results can be inconclusive and not all structural defects related to PCD may be detected. Approximately 30% of people with PCD will have a normal TEM biopsy result.
- **Nasal Nitric Oxide Testing**—For reasons not yet fully understood, most people with PCD have extremely low levels of a gas called nasal nitric oxide (nNO) in their sinus cavities. Over the past decade, research has shown that measuring nNO (a quick and painless test) can be useful for PCD screening and diagnosis. nNO measurement is not an FDA-approved method for diagnosing PCD, so it must be done as part of a research study at sites with specialized equipment and training.
- **Genetic Testing**—Most of the genes known to carry PCD-causing defects are included in genetic testing available from a number of sources. Since we do not yet know all the genes associated with PCD, a negative genetic test cannot completely rule out PCD. However, it is estimated that it can positively identify about 70-80% of all cases. The price of genetic testing for PCD has come down significantly, and it is hoped that as this test becomes cheaper and more reliable, it will be more widely available to the global PCD community.
- **High-speed Videomicroscopy (HSVM)**—This technology is used to look at cilia's beat pattern and frequency, and can confirm a PCD diagnosis in specialized European PCD centers. Like TEM, HSVM requires a high degree of specialized skill and training, and is not routinely available in North American centers.

How is PCD treated?

To date, there are few evidence-based treatments for PCD, and patients rely on the expert consensus of doctors and researchers for recommendations. In 2016, the PCD Foundation, together with the North American PCD research group, published a North American PCD Consensus Statement in *Pediatric Pulmonology*. This document represents current best practices as defined by the North American Genetic Disorders of Mucociliary Clearance (Research) Consortium and by the PCD Foundation Clinical and Research Centers Network. In 2020, the

first large clinical trial in PCD showed prophylactic azithromycin can decrease the number of annual respiratory exacerbations in adults and children with PCD.²

What is the long-term outlook for people with PCD?

Over time, chronic inflammation and infection damage the airways permanently, causing irreversible widening and scarring called bronchiectasis (which may require a CT scan of the lungs to be seen). By adulthood, nearly every person with PCD will have bronchiectasis. As bronchiectasis progresses, infections worsen and can sometimes lead to respiratory failure. Some people with PCD may need lung transplantation if their lungs fail. (For more information, see ATS Patient Information Series *Bronchiectasis* at www.thoracic.org/patients) There is currently no cure for PCD, but there are several promising medical treatments that may slow its progress. While quality of life can be severely affected for people with PCD, there is a wide range of disease progression and long-term outlook in patients, and there is no average "life expectancy." With the recent launch of the PCD Foundation Clinical Registry in 2020, long-term patient outcomes will be tracked across North American PCD centers to help to identify which aspects of PCD care provide clinical benefit to patients. If you have PCD, contact the PCD Foundation about being a part of this registry.

Authors: Adam Shapiro, MD, Stephanie Davis, MD, Michele Manion, Kathryn Briones

Reviewers: Marianna Sockrider, MD, DrPH, Wilfredo De Jesus Rojas, MD, FAAP

1. Shapiro AJ, Davis SD, Polineni D, et al. Diagnosis of Primary Ciliary Dyskinesia. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med.* 2018;197(12):e24-e39.

2. Kobbernagel HE, Buchvald FF, Haarman EG, et al. Efficacy and safety of azithromycin maintenance therapy in primary ciliary dyskinesia (BESTCILIA): a multicentre, double-blind, randomised, placebo-controlled phase 3 trial. *Lancet Respir Med.* 2020;8(5):493-505.

Rx Action Steps

- ✓ If you think you or a relative might have PCD, contact the PCD Foundation for more information or ask your healthcare provider to refer you to a PCD Foundation Clinical Center.

Healthcare Provider's Contact Number:

Resources

American Thoracic Society

- www.thoracic.org

PCD Foundation

- www.pcdfoundation.org

PCD Family Support Group (UK)

- <http://pcdsupport.org.uk/>

National Organization for Rare Diseases (NORD)

- www.rarediseases.org

This information is a public service of the American Thoracic Society. The content is for educational purposes only. It should not be used as a substitute for the medical advice of one's healthcare provider.

