

THE BEAT

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U.S. News & World Report Ranks North Carolina Children's Hospital as One of the Nation's Top 10 for Children with Respiratory Disorders

May 30, 2008. North Carolina Children's Hospital, an affiliate of the University of North Carolina, Chapel Hill Medical Center (UNC), has been ranked a top ten facility for children's respiratory health. This honor comes as no surprise to the PCD community who experience first-hand the benefits of UNC's dedication to research in PCD, cystic fibrosis and other disorders of the airways. Congratulations UNC!

For more information:
www.usnews.com/pediatrics

Check out the Website for new features:

- Registration and information about the **6th Annual PCD Family Education Weekend**, July 18-20 in Durham, NC

- New PCDF-sponsored **online patient forum**

www.pcdfoundation.org

Genetic Counseling: More Than a Risk Assessment

By Guest Contributor Brissa Martin, Genetic Counselor, Ambry Genetics

Anyone who's ever had a child diagnosed with a genetic disorder can attest to the overwhelming and contradictory emotions that develop from this experience. On one hand, you feel relieved because a diagnosis was finally made and now you and your physician can concentrate on the appropriate treatment. On the other hand, the realization that this will be a permanent diagnosis and the effect it will have on your family's life may add a new level of anxiety. Your physician might only have time to give you a brief explanation about the disorder, its inheritance, and risks for future offspring. A session with a genetic counselor during this difficult time can be very beneficial.

Genetic counselors are unique health care professionals with specialized graduate degrees and experience in the areas of medical genetics and counseling. Their role is to help patients cope with both the medical and the psychosocial aspects of genetic disease and the risks associated with it.

By its very nature, genetic information is often complex and highly technical. Genetic counselors have specialized skills that allow them to evaluate their patients level of understanding and decide how to explain complicated terminology. An important goal of every genetic counseling session is to make sure patients truly understand the information presented so they are able to make informed decisions about their healthcare. The reality and challenges of dealing with a genetic condition often make a family feel like they are the only ones going through such difficult experience. A genetic counselor can help find support groups specific to their diagnosis or even connect individual patients or families with other families dealing with the same disorder. Another complication associated with a genetic diagnosis is the fact that once an individual is diagnosed, the diagnosis has implications for the family as a whole. Genetic counselors help their patients with the difficult task of communicating with extended family about personal or reproductive risks and can even coordinate genetic testing for family members who would like to have more information about their genetic status.

The field of genetics is growing and changing at a rapid pace. This explosion in our knowledge of genetics has created opportunities for genetic counselors to work in a variety of settings. Many molecular diagnostic laboratories, such as Ambry Genetics, currently have genetic counselors in their staff. Their scientific knowledge and clinical expertise gives genetic counselors the ability to help physicians and other genetic counselors interpret genetic testing results, recommend appropriate testing strategies, find Information about specific mutations, and inform them about research projects that could benefit their patients.

Genetic counselors have many responsibilities to fulfill in their interactions with families or individuals who have received a genetic diagnosis. They must be able to understand and explain in simple terms the complicated nature of a genetic disorder, provide appropriate genetic risk information and facilitate independent decision-making, all these while supporting their patients psychosocially to make sure they are coping with the implications of the disorder in an appropriate manner. For more information about genetic counseling or to find a genetic counselor near you, visit the National Society of Genetic Counselors (NSGC) website: www.nsgc.org

PCD Fact Versus Fiction: 7 Myths About PCD

From time-to-time it is useful to try to clear up some common misconceptions about PCD. The topics below are “frequent offenders”—issues that come up time and time again and cause considerable confusion.

Myth 1: Only Males Can Have (or be diagnosed with) PCD

This interesting interpretation of the medical literature comes as a great surprise to the estimated 50% of female individuals in the PCD community whose diagnosis has been confirmed both by biopsy and genetic testing. This misconception is most likely the result of misinterpreting the literature with regard to PCD and male infertility and mistakenly assuming the relationship between male infertility and PCD means that only males are affected or can be diagnosed. The fact is that PCD is equally represented in both genders and can be diagnosed—without regard to sperm tail function—by ciliary biopsy and/or genetic testing.

Myth 2: PCD is *Not* a Progressive Disorder

The definition of a progressive disorder is one that continuously increases in extent or severity over time. The evidence that lung disease in PCD progresses in severity is unequivocal—lung disease in PCD gets worse over time. This can be seen by the fact that infants with PCD typically do not have severe (or end-stage) lung disease, but many adult PCD patients do. Although it is not uncommon for newly diagnosed families to be told otherwise, ***PCD is a progressive disorder*** and, like similar disorders, requires early aggressive intervention to slow disease progression.

Myth 3: PCD, Kartagener Syndrome and Immotile Cilia Syndrome are Separate Disorders

Primary ciliary dyskinesia refers to genetic (inherited) disorders of the structure and/or function of motile cilia. There are multiple genetic defects that result in the disorder called PCD. These defects may result in PCD with cilia that are dyskinetic (have impaired motion), PCD with totally immotile (or apparently totally immotile) cilia, or PCD with organ reversal, called Kartagener syndrome. People with PCD caused by *identical genetic mutations* may present with any of these defects. Together, they represent the spectrum of disease presentation in PCD and are not considered separate disorders. A useful way of thinking about this is that Kartagener syndrome is a form of or subset of primary ciliary dyskinesia.

Some History and A Note About the Term “Syndrome”: *A syndrome is simply a set of observable symptoms or clinical signs where the underlying cause of the symptoms may not yet be known. Kartagener syndrome is an example of this. The syndrome was named for Dr. Manes Kartagener based on his observation of a group of patients with bronchiectasis, sinus disease and situs inversus. Dr. Kartagener did not know what the underlying cause for these diverse symptoms was, he simply observed an association and gave the observation a name. Years later, Bjorn Afzelius, a Ph.D. ultrastructuralist, noticed that a number of the male patients he was evaluating for infertility had bronchiectasis and sinus disease and about half of them also had situs inversus. Noting that sperm motility was impaired, Dr. Afzelius theorized that maybe ciliary (sperm tails are flagella, a structure related to cilia) activity was the underlying cause for all of these symptoms and named his observation “immotile cilia syndrome.” Like Dr. Kartagener, Dr. Afzelius was not able at that time to positively identify the underlying cause. He simply made an observation of associated symptoms and suggested “immotile cilia” as a possible cause. As technology improved, it became possible to visualize the internal structure of cilia and flagella and the underlying cause for both Dr. Kartagener’s and Dr. Afzelius’s syndromes was revealed—ultrastructural defects leading to impaired (dyskinetic) ciliary function. Over time, it became clear that most affected individuals did not have truly immotile cilia (this is actually quite rare even though many patients are told they have immotile cilia) but rather dyskinetic cilia and it appeared that these defects were inherited. The name of these two syndromes was changed to **primary** (reflecting their inherited/genetic nature) **ciliary dyskinesia** (impaired motility) to more accurately describe the actual cause of the disorder.*

It is not unusual for syndrome names to change or become obsolete once the underlying disease cause has been identified. An example of this is “Down syndrome,” now preferably referred to as “trisomy 21” to reflect the actual underlying cause of the symptoms. In the case of PCD, multiple syndrome names have caused confusion among affected individuals and health care providers. The bottom line is that the terms Kartagener syndrome, immotile cilia syndrome and PCD all refer to a disorder of inherited defects of ciliary ultrastructure and/or function and they are not distinct or mutually exclusive disease categories.

Myth 4: Kartagener Syndrome (PCD with reversed organs) is the Most Severe Form of PCD

Please see Myth #3. Lack of ciliary motility during embryonic development leads to random organ placement in PCD. One possible organ arrangement is called *situs inversus*, or complete mirror-image placement of the chest and abdominal organs. In PCD, there is a roughly equal chance of being born with normal organ placement or with *situs inversus*. The underlying disease of PCD is the same—regardless of organ arrangement. For most people with *situs inversus*, the mirror-image placement of the organs does not affect organ function or disease severity. Kartagener syndrome simply means PCD with *situs inversus*. It does not imply more severe disease—it is simply a different manifestation of random organ placement related to underlying PCD.

In the past, it was believed that people with PCD had either “normal” *situs* or *situs inversus*. Kartagener syndrome specifically refers to PCD with *situs inversus*. We now know that there is a third option, which is neither PCD with normal *situs* nor PCD with *situs inversus* (Kartagener syndrome). In this third option, which is relatively rare, the ciliary motility defects in PCD lead to a number of complex and diverse *situs*/organ arrangements that are neither normal *situs*, nor *situs inversus*. These complex and diverse arrangements are known as *situs ambiguus* (or “ambiguous”) or heterotaxy. Conditions associated with organ development or function related to *situs ambiguus*, like congenital heart defects, may result in clinical complications that contribute to more severe disease. Because *situs ambiguus* appears to be less common than *situs inversus* or normal *situs* in PCD and because there are a number of unique defects that may be related to *situs ambiguus*, it is difficult to say at this point how significantly *situs ambiguus* may contribute to PCD disease severity.

Myth 5: People with Immotile Cilia Syndrome Have the Most Severe Form of PCD

Please see Myth #3. Many individuals with PCD have been told they have “immotile cilia” or “immotile cilia syndrome.” As the “history” section in Myth # 3 indicates, this is due in part to the use of outdated terminology and may not accurately reflect their true level of ciliary motility. Regardless of level of ciliary motility, all forms of PCD confer structural and/or functional defects of motile cilia. All of these defects lead to impaired mucociliary clearance and its consequences—lung, ear, sinus infections, *situs* abnormalities, etc. There is no credible evidence that “immotile” cilia confer any more severe disease than “dysmotile” cilia. Bottom line—if your cilia aren’t doing their job, regardless of why, you will have problems with mucociliary clearance leading to chronic hypersecretion, inflammation and infection. Although there appear to be some individuals with PCD who have totally immotile cilia, research has demonstrated that the outdated term immotile cilia syndrome has little if any true clinical relevance and should be abandoned in favor of the more relevant term primary ciliary dyskinesia.

Myth 6: ‘Ciliary Dyskinesia’ and ‘Primary Ciliary Dyskinesia’ Are the Same Thing

As mentioned above, if your cilia don’t work—regardless of the reason—you will have most likely have problems with mucociliary clearance. The “primary” in primary ciliary dyskinesia refers to inherited, consistent and permanent defects in ciliary structure or function that are the result of genetic defects. Cilia can also be damaged by external (acquired rather than inherited) causes. For instance, every time you have a cold, chances are your cilia will show evidence of acquired defects (compound cilia are a good example of an acquired ciliary defect). Acquired defects tend to be less consistent in physical appearance (different defects in different cilia) and less consistent over time (different defects may show up in specimens collected at different times). In contrast, inherited defects show up consistently throughout the biopsy sample and do not change over time. This is because inherited PCD defects are the result of absent or faulty gene products (proteins) that are necessary to build and/or regulate cilia. If your body does not produce these proteins or produces a defective copy, it is a permanent and global (affects every structure that contains the protein) problem. In contrast, acquired defects may affect only specific areas and may improve over time when the offending external irritant is removed. Both PCD and ciliary dyskinesia result in respiratory symptoms, but the underlying cause and future outlook are very different, so it is important to distinguish between inherited versus acquired forms of ciliary dysfunction.

Myth 7: It Is Possible for Some Cilia to Work and Others Not to Work in PCD

As mentioned above, inherited defects like those found in PCD are global. If you are not producing the protein necessary to build or maintain functioning cilia, all structures containing that protein will be impacted. Cilia in PCD will not selectively work in some areas, but not work in others. In contrast, ciliary structure and function may be selectively affected in otherwise healthy individuals who are experiencing secondary or acquired insults to their cilia like infection, irritant exposure, and/or inflammation.

As our understanding of PCD grows, we can anticipate that some of the myths surrounding it will be clarified or will simply disappear. Until that time, the PCD Foundation (PCDF) will continue to provide information that is as accurate and up-to-date as possible. Please feel free to contact the PCDF with questions or concerns.

Clinical Genetic Testing for PCD: Clarification of Statistics

In our February 08 newsletter, we quoted outdated statistics regarding genetic testing for PCD:

“There are known PCD-causing mutations on two genes linked to the production of outer dynein arm (ODA) protein: DNAI1 and DNAH5). Together, the mutations on these two genes account for approximately 10% of all cases of PCD and close to 30% of ODA-related PCD.”

Recent publications paint a rosier picture and indicate that currently available molecular genetic testing for PCD may identify up to **38%** of all cases of PCD and **63%** of PCD caused by outer dynein arm defects.

Patient Story Feature

A Lifetime of PCD: Laura's Story

Laura Slaney has been dealing with the consequences of primary ciliary dyskinesia (PCD) her entire life. Diagnosed with Kartagener syndrome (a subset of PCD characterized by situs inversus) at age six, Laura brings the valuable insight of lifelong experience to the PCD patient group.

As an infant, Laura was plagued by constant nasal drainage, sore throats and ear infections. Early treatment and intervention focused on ear and sinus problems, with myringotomy tubes, nasal-antral window placement in the sinuses, frequent sinus suctioning, removal of the tonsils and adenoids and lots of antibiotic therapy. At age six, an allergist noted Laura's cough and her parents realized the cough had been present since birth. At that point, the family was referred to St. Louis Children's Hospital, where a diagnosis of Kartagener syndrome was made. Laura's parents were told she would be lucky to live to 12 years of age.



Laura continued to have frequent upper and lower respiratory infections, complicated by allergies. At age 10, a right lower lobectomy was performed due to severe bronchiectasis. Laura continued to be active, but noticed that she did not have the stamina of other children and sometimes had to sit on the sidelines rather than participate. She was started on gamma globulin therapy to boost her immune system, but didn't notice much response. Her physicians suggested that the family move to Arizona from St. Louis to minimize the impact of allergies on her disease and eventually the family did move west, settling in California. Laura remembers getting allergy relief for about two years, then reverting back to similar allergy problems.

It is not unusual for people with PCD to get some relief in the late adolescent and early adult years, the so-called "Cinderella period," and Laura experienced some diminishment of her symptoms between ages 13 and 35. She was not healthy per se, but was sick less frequently and experienced fewer infections requiring hospitalization and IV antibiotic therapy. She focused on exercise, pursuing jogging, hiking, backpacking and swimming.

Things changed dramatically when Laura turned 35. She had enrolled in a Pulmozyme® study and was forced to withdraw because of hemoptysis (coughing up blood). She had numerous emergency room visits and narrowly avoided being placed on a ventilator. Cultures revealed that she had contracted *Mycobacterium avium* complex (MAC). She battled on and off with treatment for atypical mycobacterium for the next decade and also survived breast cancer during this time. With declining pulmonary function, she finally decided it was time to go on disability at age 45.

Even with the appropriate diagnosis, the role of ciliary function in causing Laura's symptoms was not fully understood until she was an adult. Contact with other patients through an internet forum and through the PCD Foundation helped her to find the answers she was looking for. That and her strong faith in God have carried her this far. She doesn't worry about the future—she knows she's in good hands.

**Sixth-Annual PCD
Family Education Weekend**

July 18-20, 2008 Marriott Research Triangle Park, Durham, NC

Registration forms are now available for the PCDF 6th Annual Family Education Weekend. The format and program will be similar to past meetings. Program details will be posted to the PCDF website as they are available. Check online for updates. Access forms at: www.pcdfoundation.org or email/call the PCDF at info@pcdfoundation.org or 623-215-2032.

**The PCD Foundation
Announces Family Education Weekend
Travel Grant Program**

The PCD Foundation is pleased to announce the PCDF Family Education Weekend Grant Program to assist individuals interested in attending the Sixth Annual PCDF Family Education Weekend in Durham, North Carolina from July 18-20, 2008.

PCDF Family Education Weekend is the most anticipated event of the year for members of the PCD community. It provides the opportunity for patients, caregivers, health professionals and interested individuals to learn about PCD from experts and to interact with other families. Every effort is made to keep registration and lodging costs low to allow as many people as possible to attend. This year, tough economic times may make the cost of attendance even more prohibitive. For this reason, the PCDF will offer travel assistance grants for PCDF Family Education Weekend. The grants will be need-based and will range from \$150 to \$500. Grant funds can be used toward registration, lodging or travel expenses. Grants will only be awarded to conference attendees.

To apply for a grant, please complete the grant application form which can be accessed on the PCDF website at www.pcdfoundation.org (in the scrolling news bar) or by contacting the PCDF for a hard copy. Send completed forms no later than June 20, 2008 via:

Email: info@pcdfoundation.org

Fax: 623-215-6670

Mail: PCD Foundation
c/o Lynn Ehrne
61 Lake Meadow Drive
Rochester, NY 14612

Grant awardees will be notified by June 30, 2008.

News From the Primary Ciliary Foundation

PCD Foundation
Primary Business Address:
29252 N 22nd Lane

Phone: 612-965-3116
Email: info@pcdfoundation.org

We're on the Web!!!

www.info@pcdfoundation.org

*The PCD Foundation
Education & Advocacy for
People with Primary Ciliary
Dyskinesia*

The Beat Editorial Staff
Michele Manion

Contributors to this Issue
Johnny L Carson, PhD
Michele Manion
Laura Slaney

Send Comments/Questions/Submissions to:
The Beat
C/O PCD Foundation
29252 N. 22nd Lane
Phoenix, AZ 85085
info@pcdfoundation.org
(623) 215-2032

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Journal Watch NEW ARTICLES OF INTEREST TO THE PCD COMMUNITY

The National Library of Medicine (NLM) maintains a database of peer-reviewed articles from international medical journals. The peer-review process means that the article is subject to vigorous critical review by a panel of experts prior to being accepted for publication. This information can be accessed by the public at: <http://www.ncbi.nlm.nih.gov/PubMed> or by typing "entrez pubmed" into your internet provider search function.

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