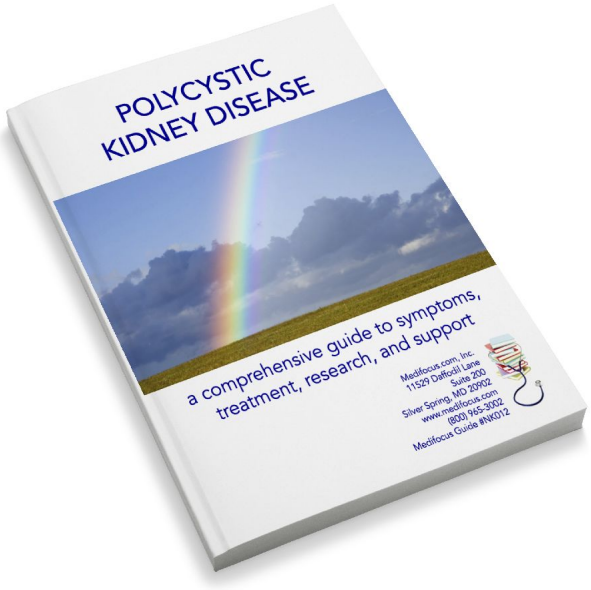
Preview of the Medifocus Guidebook on: Polycystic Kidney Disease

Updated January 30, 2017



This document is only a SHORT PREVIEW of the **Medifocus Guidebook on Polycystic Kidney Disease**. It is intended primarily to give you a general overview of the **format and structure** of the Guidebook as well as select pages from each major Guidebook section listed in the Table of Contents.

To purchase the **COMPLETE** Medifocus Guidebook on Polycystic Kidney Disease (139 pages; Updated January 30, 2017), please:

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Table of Contents

1 - Background Information

Introduction

Chronic or life-threatening illnesses can have a devastating impact on both the patient and the family. In today's new world of medicine, many consumers have come to realize that they are the ones who are primarily responsible for their own health care as well as for the health care of their loved ones.

When facing a chronic or life-threatening illness, you need to become an educated consumer in order to make an informed health care decision. Essentially that means finding out everything about the illness - the treatment options, the doctors, and the hospitals - so that you can become an educated health care consumer and make the tough decisions. In the past, consumers would go to a library and read everything available about a particular illness or medical condition. In today's world, many turn to the Internet for their medical information needs.

The first sites visited are usually the well known health "portals" or disease organizations and support groups which contain a general overview of the condition for the layperson. That's a good start but soon all of the basic information is exhausted and the need for more advanced information still exists. What are the latest "cutting-edge" treatment options? What are the results of the most up-to-date clinical trials? Who are the most notable experts? Where are the top-ranked medical institutions and hospitals?

The best source for authoritative medical information in the United States is the National Library of Medicine's medical database called PubMed®, that indexes citations and abstracts (brief summaries) of over 7 million articles from more than 3,800 medical journals published worldwide. PubMed® was developed for medical professionals and is the primary source utilized by health care providers for keeping up with the latest advances in clinical medicine.

A typical PubMed® search for a specific disease or condition, however, usually retrieves hundreds or even thousands of "hits" of journal article citations. That's an avalanche of information that needs to be evaluated and transformed into truly useful knowledge. What are the most relevant journal articles? Which ones apply to your specific situation? Which articles are considered to be the most authoritative - the ones your physician would rely on in making clinical decisions? This is where *Medifocus.com* provides an effective solution.

Medifocus.com has developed an extensive library of *MediFocus Guidebooks* covering a wide spectrum of chronic and life threatening diseases. Each *MediFocus Guidebook* is a

high quality, up- to-date digest of "professional-level" medical information consisting of the most relevant citations and abstracts of journal articles published in authoritative, trustworthy medical journals. This information represents the latest advances known to modern medicine for the treatment and management of the condition, including published results from clinical trials. Each *Guidebook* also includes a valuable index of leading authors and medical institutions as well as a directory of disease organizations and support groups. *MediFocus Guidebooks* are reviewed, revised and updated every 4-months to ensure that you receive the latest and most up-to-date information about the specific condition.

About Your MediFocus Guidebook

Introduction

Your *MediFocus Guidebook* is a valuable resource that represents a comprehensive synthesis of the most up-to-date, advanced medical information published about the condition in well-respected, trustworthy medical journals. It is the same type of professional-level information used by physicians and other health-care professionals to keep abreast of the latest developments in biomedical research and clinical medicine. The *Guidebook* is intended for patients who have a need for more advanced, in-depth medical information than is generally available to consumers from a variety of other resources. The primary goal of a *MediFocus Guidebook* is to educate patients and their families about their treatment options so that they can make informed health-care decisions and become active participants in the medical decision making process.

The *Guidebook* production process involves a team of experienced medical research professionals with vast experience in researching the published medical literature. This team approach to the development and production of the *MediFocus Guidebooks* is designed to ensure the accuracy, completeness, and clinical relevance of the information. The *Guidebook* is intended to serve as a basis for a more meaningful discussion between patients and their health-care providers in a joint effort to seek the most appropriate course of treatment for the disease.

Guidebook Organization and Content

Section 1 - Background Information

This section provides detailed information about the organization and content of the *Guidebook* including tips and suggestions for conducting additional research about the condition.

Section 2 - The Intelligent Patient Overview

This section of your *MediFocus Guidebook* represents a detailed overview of the disease or condition specifically written from the patient's perspective. It is designed to satisfy the basic informational needs of consumers and their families who are confronted with the illness and are facing difficult choices. Important aspects which are addressed in "The Intelligent Patient" section include:

- The etiology or cause of the disease
- Signs and symptoms
- How the condition is diagnosed
- The current standard of care for the disease
- Treatment options

- New developments
- Important questions to ask your health care provider

Section 3 - Guide to the Medical Literature

This is a roadmap to important and up-to-date medical literature published about the condition from authoritative, trustworthy medical journals. This is the same information that is used by physicians and researchers to keep up with the latest developments and breakthroughs in clinical medicine and biomedical research. A broad spectrum of articles is included in each *MediFocus Guidebook* to provide information about standard treatments, treatment options, new clinical developments, and advances in research. To facilitate your review and analysis of this information, the articles are grouped by specific categories. A typical *MediFocus Guidebook* usually contains one or more of the following article groupings:

- *Review Articles:* Articles included in this category are broad in scope and are intended to provide the reader with a detailed overview of the condition including such important aspects as its cause, diagnosis, treatment, and new advances.

- *General Interest Articles:* These articles are broad in scope and contain supplementary information about the condition that may be of interest to select groups of patients.

- *Drug Therapy:* Articles that provide information about the effectiveness of specific drugs or other biological agents for the treatment of the condition.

- *Surgical Therapy:* Articles that provide information about specific surgical treatments for the condition.

- *Clinical Trials:* Articles in this category summarize studies which compare the safety and efficacy of a new, experimental treatment modality to currently available standard treatments for the condition. In many cases, clinical trials represent the latest advances in the field and may be considered as being on the "cutting edge" of medicine. Some of these experimental treatments may have already been incorporated into clinical practice.

The following information is provided for each of the articles referenced in this section of your *MediFocus Guidebook:*

- Article title
- Author Name(s)
- Institution where the study was done
- Journal reference (Volume, page numbers, year of publication)

- Link to Abstract (brief summary of the actual article)

Linking to Abstracts: Most of the medical journal articles referenced in this section of your *MediFocus Guidebook* include an abstract (brief summary of the actual article) that can be accessed online via the National Library of Medicine's PubMed® database. You can easily access the individual abstracts online via PubMed® from the "electronic" format of your *MediFocus Guidebook* by clicking on the corresponding URL address that is provided for each cited article. If you purchased a printed copy of a *MediFocus Guidebook*, you can still access the article abstracts online by entering the individual URL address for a particular article into your web browser.

Section 4 - Centers of Research

We've compiled a unique directory of doctors, researchers, medical centers, and research institutions with specialized research interest, and in many cases, clinical expertise in the management of the specific medical condition. The "Centers of Research" directory is a valuable resource for quickly identifying and locating leading medical authorities and medical institutions within the United States and other countries that are considered to be at the forefront in clinical research and treatment of the condition.

Inclusion of the names of specific doctors, researchers, hospitals, medical centers, or research institutions in this *Guidebook* does not imply endorsement by Medifocus.com, Inc. or any of its affiliates. Consumers are encouraged to conduct additional research to identify health-care professionals, hospitals, and medical institutions with expertise in providing specific medical advice, guidance, and treatment for this condition.

Section 5 - Tips on Finding and Choosing a Doctor

One of the most important decisions confronting patients who have been diagnosed with a serious medical condition is finding and choosing a qualified physician who will deliver high-level, quality medical care in accordance with curently accepted guidelines and standards of care. Finding the "best" doctor to manage your condition, however, can be a frustrating and time-consuming experience unless you know what you are looking for and how to go about finding it. This section of your Guidebook offers important tips for how to find physicians as well as suggestions for how to make informed choices about choosing a doctor who is right for you.

Section 6 - Directory of Organizations

This section of your *Guidebook* is a directory of select disease organizations and support groups that are in the business of helping patients and their families by providing access to information, resources, and services. Many of these organizations can answer your questions, enable you to network with other patients, and help you find a doctor in your geographical area who specializes in managing your condition.

2 - The Intelligent Patient Overview

POLYCYSTIC KIDNEY DISEASE

Introduction to Polycystic Kidney Disease

What is Polycystic Kidney Disease?

Polycystic kidney disease (PKD) is characterized by fluid-filled cysts that form in both kidneys (*bilaterally*) and eventually lead to kidney failure in mid-late adulthood in the majority of affected individuals. It is the most common life threatening genetic disorder caused by a single gene and affects between 1 in 400-1,000 people worldwide. Polycystic kidney disease is the fourth most common cause of kidney failure. It is associated with many complications and is generally not diagnosed until years after the cysts have begun to form. The diagnosis of PKD is typically straightforward. Where there is a known family history of PKD, the hallmark indicator in imaging modalities is bilaterally enlarged kidneys with numerous cysts, often accompanied by the presence of liver cysts. The major cause of morbidity and mortality in PKD is progressive renal dysfunction, which leads to kidney failure or end-stage renal disease (ESRD). Approximately one-half of PKD patients undergo renal replacement therapy (dialysis) or kidney transplantation by the age of 60.

How do the Kidneys Work?

The kidneys are two bean-shaped organs, each about the size of a fist [approximately 5" long (14 cm.) x 3" wide (8 cm.) x 2" thick (5 cm.)], that are located in the upper part of the abdomen on each side of the spine. Each weighs 10-12 ounces (280-340 grams). Their main function is to balance the volume of fluids and minerals in the body (*homeostasis*) by filtering the blood and retaining necessary fluid and nutrients while expelling wastes and toxins in the urine.

The kidney is made up of several components, including:

- *Capsule* - the fibrous membrane covering of the kidney
- *Cortex* - the outer region of the kidney that surrounds the internal *medulla*. The cortex is composed of *nephrons* that are the basic structural and functional filtration units of the kidney.
- *Nephrons* are long, tubular structures and are divided into various parts according to their location and function. There are approximately one million nephrons in each kidney. The actual removal of waste from the kidneys starts in the nephrons. Nephrons are made up of *glomeruli*, tiny blood vessels that are attached to *tubules*, tiny tubes that receive filtered fluid

from the glomeruli and then continue the filtration process.

- *Medulla* - innermost part of the kidney. It contains cone-shaped regions called *pyramids* where a significant portion of urine concentration occurs.

- *Pelvis* - a collection area for filtered waste. The pelvis is connected to the pyramids by chambers called *calyses*.

Blood flows into the kidney and is forced into the nephrons where it is filtered first by the glomeruli. After the blood is filtered in the glomeruli (and now called a *filtrate*), it is forced under pressure into the tubules where the next level of filtration occurs. Essential nutrients and water are returned to the circulation while excess water and unwanted waste and toxins are removed and turned into urine. After collection in the renal pelvis, the urine drains via the *ureters* into the bladder and from there it is expelled from the body through the *urethra*.

The kidneys play several important roles in maintaining a healthy body including:

- Regulating the balance of nutrients, water, salts, and electrolytes in the body
- Reabsorbing essential nutrients and water back into circulation
- Producing several hormones that are essential for vital body functions such as:

    - *erythropoietin* (EPO), a hormone that helps in the formation of red blood cells
    - *renin*, a hormone that helps to regulate blood pressure and the body's metabolism of salt as well as facilitating the production of other hormones

- Removing waste products from the body including:

    - *blood urea nitrogen* (BUN) - nitrogen that comes from *urea*, a waste product that is filtered out of the blood by the kidneys
    - *creatinine* - a substance removed so efficiently by the kidneys, that an estimate of kidney function can usually be made by measuring creatinine levels in the blood

Development of Renal Cysts

Cysts in PKD usually begin as outpouchings (like blisters) anywhere along the length of a nephron. Approximately 70% of the cysts detach from the nephron when they are small and proceed to enlarge, filling either with clear fluid or fluid that may contain blood cells. In patients with PKD, hundreds to thousands of cysts can develop that range from the size of a pinhead to the size of a grapefruit (10-20 cm. in diameter). In extreme cases, the kidney may expand to be as large as a football and weigh up to 38 pounds. The continual enlargement of cysts crowds out healthy kidney tissue. The kidneys may quadruple in size before kidney function is affected at which point renal function rapidly declines.

In addition, normal kidney tissue can be actively destroyed and fibrous tissue can form in its place,

resulting in a condition called *interstitial fibrosis*. The combination of cysts and progressive interstitial fibrosis is thought to accelerate chronic renal failure.

Several factors are related to cyst formation in the kidney, but exactly what triggers the process is unclear. Three of the factors that have been identified include:

- Increased production of cells lining the cyst wall that continue to reproduce throughout life and enable the cyst to enlarge.
- Increased production of fluid by the cells forming the cyst.
- Abnormal *basement membrane* structure and function. The basement membrane is a thin layer of tissue upon which the cysts rest. In PKD the makeup of the basement membrane is abnormal, the tissue is thicker than usual, and attachment to the cyst wall is increased.

Hypertension (high blood pressure) is closely associated with PKD due to the increased burden placed on the blood vessels from inadequately filtered blood. It is often one of the earliest symptoms of PKD and develops in most patients by the age of 20 or 30.

Risk factors for a more rapid decline in kidney function in people with PKD include:

- Male gender
- Onset of hypertension before 35 years of age
- Women with three or more pregnancies
- Presence of gross hematuria (blood in the urine) in men before the age of 30

Polycystic kidney disease does not affect fertility in women and most women with PKD complete successful pregnancies. However, some men with PKD develop conditions that may affect their fertility, such as:

- Necrospermia (sperm in the semen are not alive)
- Immotile sperm (sperm do not move well or at all)
- Seminal vesicle cysts
- Ejaculatory duct cysts

Incidence of Polycystic Kidney Disease

Polycystic kidney disease affects approximately 600,000-700,000 people in the United States and approximately 12.5 million people worldwide. PKD account for up to 7-10% of people who are on *dialysis*, a treatment that provides mechanical filtration of the blood in lieu of kidneys that are no longer functional.

Additional information about PKD:

- PKD is the most common inherited "monogenic" (one gene) kidney disease in the world.
- PKD affects one 500-1000 births.
- Approximately 5,000 to 6,000 new cases of PKD are diagnosed each year in the U.S.
- 40% of the cases diagnosed yearly in the U.S. are people of age 45 or less.

- 5-10% of people with PKD have no known familial history of PKD.
- Approximately 50% of patients diagnosed with autosomal dominant polycystic kidney disease (ADPKD) progress to end-stage renal disease by the age of 60.
- Polycystic kidney disease is the fourth leading cause of kidney failure and appears to affect all races and genders equally.

Types of Polycystic Kidney Disease

There are three types of polycystic kidney disease:

- Autosomal Dominant PKD (ADPKD)
- Autosomal Recessive PKD (ARPKD)
- Acquired Cystic Kidney Disease (ACKD)

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

The term "autosomal dominant" means that a child can inherit a disease or condition if only one of their parents carries the gene for the disease. Autosomal dominant polycystic kidney disease (ADPKD) is the most common form of polycystic kidney disease and is responsible for 85-90% of all PKD cases. It is also the most common "monogenic" (from one mutated gene) inherited cause of kidney failure and accounts for up to 5% of all cases of end-stage renal disease (ESRD) in the U.S. Because of its late age of onset, ADPKD in general has previously been called "adult onset polycystic kidney disease". There are two types of ADPKD:

- Type I - the genetic mutation for Type I ADPKD is found on chromosome 16 and affects the production of a protein called *polycystin 1*. Type I ADPKD is a more severe form than Type II ADPKD and is associated with an earlier age at onset and a shorter life expectancy. Symptoms of Type I PKD typically develop between the ages of 30 and 40, but can begin in childhood. Fifty percent of patients with type 1 PKD will develop end-stage renal disease requiring replacement therapy by dialysis or kidney transplantation when they reach their 50s and this percentage rises as patients reach their 60's and 70's. Type I PKD is responsible for approximately 85% of cases of ADPKD and is characterized by:
    - cysts that typically appear when individuals are in their 20's but may not be symptomatic
    - fairly rapid disease progression
    - high likelihood of end-stage renal disease (ESRD) in the fifth or sixth decade
- Type II - The genetic mutation for Type II ADPKD is found on chromosome 4 and affects the production of *polycystin 2* and is responsible for approximately 15% of cases. It is characterized by:
    - later age at diagnosis than Type I PKD
    - slower disease progression than Type I PKD
    - delayed onset of ESRD (74 years old vs. 54 years old for Type I PKD)
    - reduced prevalence of hypertension
    - lower cyst burden

Regardless of which gene is involved, the same clinical profile results for both conditions namely renal cysts, extra-renal cysts, inguinal hernias, intracranial aneurysms, and cardiac valve abnormalities. The major difference between them is that Type II PKD is less severe.

Children can also be affected by ADPKD. It may be present in as many as 1 out of 1,000 newborns. Children may be diagnosed with ADPKD either *in utero* or after birth. The PKD Foundation notes that there are different characteristics of ADPKD for children who are diagnosed in the first year of life or after the first year of life. Children who are diagnosed with ADPKD *before* their first birthdays are more likely to have:

- A mother with ADPKD
- Brothers and sisters who have been diagnosed with ADPKD before the first year of life
- Diagnosis of large kidneys before birth but often no sign of cysts
- A high risk of developing hypertension in childhood

Children who are diagnosed with ADPKD *after* their first birthdays are more likely to have:

- A mother or father with ADPKD
- Kidney cysts, though the kidneys may not be enlarged
- A high likelihood of normal kidney function throughout childhood and into their twenties

PKD may be discovered in children if:

- The kidneys are large enough to cause a lump that can be palpated
- There is an abnormal finding of urine in the blood
- Hypertension is found during a routine check-up
- A child experiences flank pain with fever (may indicate an infected cyst)
- A child has anemia or growth problems

Usually ADPKD is not discovered until individuals are in their 30s or 40s and have experienced an asymptomatic childhood. Interestingly, it is not uncommon for individuals with ADPKD to report no known history of PKD in any family members. Indeed, some researchers suggest that a significant number of individuals affected by ADPKD (up to 10%) lack a family history of the disease. They theorize that this subgroup of individuals may either develop a "de novo" (new) mutation or actually have family members with mild, undiagnosed Type II ADPKD.

Unless otherwise noted, when the term "PKD" is used in the Medifocus Guidebook, it refers to ADPKD.

Autosomal Recessive Polycystic Kidney Disease

The term "autosomal recessive" means that a child can only inherit a disease or condition only if *both* of the parents carry the gene for the disease. Autosomal recessive polycystic kidney disease (ARPKD) is a rare inherited form of the disease with an estimated incidence of 1 per 20,000 people. This type of polycystic kidney disease is a cause of perinatal death because the kidneys enlarge to such an extent that the lungs cannot function properly after birth. Because of the early

onset of symptoms, this form of PKD has also been called "infantile PKD".

Approximately 50% of cases of ARPKD are diagnosed *in utero* (prenatally). ARPKD causes more severe illness in children than ADPKD and results in three times as many children with kidney failure as ADPKD. The American Association of Kidney Patients (AAKP) notes that complications of ARPKD may begin *in utero* and include:

- Oligohydramnios (insufficient amniotic fluid)
- Enlarged kidneys that may affect lung development and cause breathing problems at birth
- Hypertension (a common complication)
- Risk of dehydration (since kidneys do not effectively conserve water or salt)
- Risk of anemia (because of reduction in kidney function)
- Failure to thrive
- Congenital Hepatic Fibrosis (CHF) - fibrotic tissue in the liver that causes scarring and may result in loss of liver function. CHF also causes malformation of the bile ducts in the liver, which may lead to an elevated risk of gallstones. In addition, CHF restricts flow in the portal vein that carries blood to the liver, resulting in elevated pressure in the portal vein (*portal hypertension*). CHF occurs with some degree of severity in all patients with ARPKD since the genetic defect causing ARPKD affects both the kidneys and the liver.

Severity of the disease varies from extreme, where infants may die hours or days after birth due to respiratory difficulties or respiratory failure, to moderate where individuals develop symptoms only in adulthood. The ARPKD/CHF Alliance notes that neonatal death occurs in up to 50% of cases and is typically caused by underdeveloped lungs (pulmonary hypoplasia) secondary to oligohydramnios. Most children who survive usually develop renal failure and liver fibrosis, often in the first decade of life. Congenital hepatic fibrosis becomes an increasing concern with age.

The prognosis for children with ARPKD has improved with earlier diagnosis and intervention. Children who survive mechanical ventilation as newborns, have improved rates of survival. The ARPKD/CHF Alliance notes that the five-year survival rate is 80-95% for infants who survive the first 4 weeks after birth. Survival into adulthood has increased due to improvements in mechanical ventilation, control of hypertension, more effective management of end-stage renal disease (ESRD), and kidney transplantation.

Acquired Cystic Kidney Disease

Acquired cystic kidney disease (ACKD) is not inherited, but develops most commonly in patients who have been on long-term dialysis treatment. Approximately 90% of people with ACKD have been on dialysis for five years or more. It is found in up to 20% of patients with ESRD. Typically, the size of the kidneys is normal despite the presence of cysts. Patients with ACKD have a two-fold risk of developing renal cell carcinoma compared to the general population.

Other Inherited Cystic Kidney Diseases

Medullary Cystic Kidney Disease

Medullary cystic kidney disease (MCKD) is an autosomal dominant hereditary condition that typically appears in older adults. Cysts form only in the center portion (medulla) of each kidney

resulting in shrunken, scarred kidneys and eventual loss of kidney function. There also may be interstitial fibrosis. It is characterized by excessive urine production and loss of sodium. Symptoms of MCKD include:

- Excessive urination
- Low blood pressure (hypotension)
- Night-time urination (nocturia)
- Craving for salt
- Weakness

Familial Nephronophthisis

Familial nephronophthisis (NPH) is an autosomal recessive hereditary condition form of polycystic kidney disease, which is more severe than MCKD, and often leads to kidney failure in children. Both kidneys are shrunken in size and renal cysts are situated at the border of the medulla and cortex of the kidney. It is characterized by growth retardation, polyuria (frequent urination), loss of salt, anemia, and progressive renal insufficiency. Unlike MCKD, NPH may be associated with extrarenal complications, such as eye problems. There are three types of NPH - infantile, juvenile, and adolescent.

Causes of Polycystic Kidney Disease

There are several factors that contribute to the development of polycystic kidney disease (PKD). Although the exact process has not yet been determined, three factors are thought to be involved with PKD:

- Genetic factors
- Cellular factors
- Hormonal factors

Genetic Factors

If one or both parents pass down an abnormal gene to the fetus at conception, a genetically transmitted disease can occur. If acquiring the abnormal gene from *one* parent is enough to produce the disease in the child, it is defined as a *dominant* gene. In these cases, one of the parents also has the disease. When both parents must possess the abnormal gene in order for the child to develop the disease, it is defined as a *recessive* gene. In these cases, the parents do not have the disease themselves but both carry the abnormal gene. The chances of inheriting a dominant gene are much higher than inheriting a recessive gene. If a child receives one abnormal gene for a recessive disease, he/she will not develop the disease but may pass that recessive gene down to his/her children.

Autosomal *dominant* PKD (ADPKD) is the most common inherited form of polycystic kidney disease. If one parent has the disease, there is a 50% chance of passing the disease to each child. If both parents have the disease, there is a 75% chance that each child will have the disease. Transmission is not sex-linked (not associated with the gender of the affected parent). It is thought that in about 10-25% of cases, a new mutation of the gene that causes PKD spontaneously occurs in a fetus which results in ADPKD.

Autosomal *recessive* PKD is inherited through a recessive gene meaning that both parents carry the abnormal gene even though neither one of them may have clinical evidence of the disease. Each child that is born has a 25% chance of having the disease.

Scientists have recently begun to identify the process that triggers the formation of cysts. They have located 2 genes related to ADPKD which are mutated: one gene (PKD1) on chromosome 16 and another gene (PKD2) on chromosome 4. They have also identified the proteins that each of these genes produces: *polycystin 1* produced by PKD1 and *polycystin 2* produced by PKD2. When both of these genes are normal, they foster normal kidney growth and development and inhibit formation of cysts, however, if either gene is mutated, it can lead to cyst formation. Cyst formation may be related to inadequate levels of polycystin.

It appears that other factors besides the known mutations alone may influence the development of PKD. One theory is known as the "two-hit theory" and is based on the *Knudsen hypothesis*. According to this hypothesis, while the genetic mutation is necessary for the development of PKD, it is not sufficient to cause cyst formation. While the identity of the second trigger is currently unknown, it is believed to possibly be a mutation in an individual tubular cell in the kidney that somehow allows the proliferation of renal tubular cells to start forming cysts. The timing and frequency of the activation of the second genetic mutation determine the time of onset and rate of progression of cyst formation and may also play a role in the different characteristics of the time of onset that distinguish Types I and II ADPKD.

For more information about genetic mutations and PKD, please click on the following link: http://www.ccjm.org/content/76/2/97.full

Since the first gene related to PKD (PKD1) was identified in 1994, researchers have discovered that there are several types of genetic mutations associated with different forms of polycystic kidney diseases.

- In 2002, the gene responsible for ARPKD on chromosome 6, called PKHD1 was discovered.
- Familial nephronophthisis is caused by a mutation of the NPH1, NPH2, NPH3, NPH4, and NPH5 genes.
- Medullary cystic kidney disease is caused by a mutation in either the MCKD1 or MCKD2 gene.

Cellular Factors

In every cell in the body there is a delicate balance between cellular reproduction and proliferation and cellular death (apoptosis). It is thought that part of the progressive destruction of normal kidney tissue in ADPKD and ARPKD is due to abnormally persistent *apoptosis* (cell death) that may allow the cystic process to continue unchecked.

Recent evidence appears to implicate a protein called *mammalian target of rapamycin* (mTOR) that regulates various functions of cells, including cell growth, cell proliferation, and cell survival. Some studies have shown that increased mTOR involvement may be one of the mechanisms related to the dysfunction of normal cellular activity in individuals with PKD. There is currently extensive research into the role of mTOR in PKD as well as the potential for drugs called *mTOR*

inhibitors to reverse or slow the progression of PKD.

Hormonal Factors

A hormone called *epidermal growth factor* (EGF) appears to be involved with cyst formation in PKD. There is a high concentration of EGF in cystic fluid, and it may be a trigger for the proliferation of cystic cells, since certain cells lining the cysts appear to be very sensitive to being stimulated by EGF.

Extrarenal Manifestations of Polycystic Kidney Disease

There are several extra-renal manifestations of PKD that will be discussed in detail below in the "Diagnosis of PKD" section, including:

- Hypertension
- Cysts on the liver and other organs
- Acute and chronic pain
- Urinary tract infections
- Kidney stones
- Mitral valve prolapse
- Inguinal, abdominal, and umbilical hernias
- Colonic diverticulae (outpouches of the colon)
- Intracranial aneurysm
- Bleeding cysts
- Hematuria (blood in the urine)
- Bronchiectasis (pulmonary obstruction)

Polycystic Kidney Disease and Pregnancy

According to the National Kidney Foundation, 80% of women with PKD who have normal renal function and no hypertension have successful and uncomplicated pregnancies. However, the risk for serious complication rises in the presence of decreased kidney function and hypertension. In approximately 40% of pregnancies, women who experienced hypertension before pregnancy develop *preeclampsia* (elevated blood pressure and protein in the urine), a life threatening condition for mother and baby. In general, women with PKD should be aggressively monitored throughout their pregnancy.

Fetuses should be followed with ultrasound to detect the presence of kidney cysts in utero as well as other complications including:

- Uteroplacental insufficiency (insufficient blood flow to the placenta)
- Intrauterine growth retardation (restricted fetal growth)
- Oligohydramnios (deficiency of amniotic fluid)

To read more about fertility issues and pregnancy in PKD, please click on the following link: http://www.ncbi.nlm.nih.gov/pubmed/18215709

The **Intelligent Patient Overview** in the complete **Medifocus Guidebook on Polycystic Kidney Disease** also includes the following additional sections:

- **Diagnosis of Polycystic Kidney Disease**
- **Treatment Options for Polycystic Kidney Disease**
- **Nutritional and Lifestyle Interventions in Polycystic Kidney Disease**
- **Quality of Life and Psychosocial Considerations in Polycystic Kidney Disease**
- **New Developments in Polycystic Kidney Disease**
- **Questions to Ask Your Health Care Provider about Polycystic Kidney Disease**

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3 - Guide to the Medical Literature

Introduction

This section of your *MediFocus Guidebook* is a comprehensive bibliography of important recent medical literature published about the condition from authoritative, trustworthy medical journals. This is the same information that is used by physicians and researchers to keep up with the latest advances in clinical medicine and biomedical research. A broad spectrum of articles is included in each *MediFocus Guidebook* to provide information about standard treatments, treatment options, new developments, and advances in research.

To facilitate your review and analysis of this information, the articles in this *MediFocus Guidebook* are grouped in the following categories:

- Review Articles - 33 Articles
- General Interest Articles - 48 Articles
- Drug Therapy Articles - 4 Articles
- Surgical Therapy Articles - 5 Articles
- Clinical Trials Articles - 9 Articles
- Kidney Transplantation Articles - 9 Articles
- Dialysis Therapy Articles - 1 Articles

The following information is provided for each of the articles referenced in this section of your *MediFocus Guidebook:*

- Title of the article
- Name of the authors
- Institution where the study was done
- Journal reference (Volume, page numbers, year of publication)
- Link to Abstract (brief summary of the actual article)

Linking to Abstracts: Most of the medical journal articles referenced in this section of your *MediFocus Guidebook* include an abstract (brief summary of the actual article) that can be accessed online via the National Library of Medicine's PubMed® database. You can easily access the individual abstracts online via PubMed® from the "electronic" format of your *MediFocus Guidebook* by clicking on the URI that is provided for each cited article. If you purchased a printed copy of the *MediFocus Guidebook*, you can still access the abstracts online by entering the individual URI for a particular abstract into your computer's web browser.

Recent Literature: What Your Doctor Reads

Database: PubMed <January 2012 to July 2017 >

Review Articles

1.

Recommendations for the use of tolvaptan in autosomal dominant polycystic kidney disease: a position statement on behalf of the ERA-EDTA Working Groups on Inherited Kidney Disorders and European Renal Best Practice.

Authors: Gansevoort RT; Arici M; Benzing T; Birn H; Capasso G; Covic A; Devuyst O; Drechsler C; Eckardt KU; Emma F; Knebelmann B; Le Meur Y; Massy ZA; Ong AC; Ortiz A; Schaefer F; Torra R; Vanholder R; Wiecek A; Zoccali C; Van Biesen W

Institution: Department of Nephrology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.; Department of Nephrology, Hacettepe University Faculty of Medicine, Ankara, Turkey.; Department II of Internal Medicine and Centre for Molecular Medicine Cologne, University of Cologne, Cologne, Germany.; Department of Renal Medicine, Aarhus University Hospital, Aarhus, Denmark Department of Biomedicine, Aarhus University, Aarhus, Denmark.; Department of Nephrology, Second University of Naples, Naples, Italy.

Journal: Nephrol Dial Transplant. 2016 Mar;31(3):337-48. doi: 10.1093/ndt/gfv456. Epub 2016 Jan 29.

Abstract Link: http://www.medifocus.com/abstracts.php?gid=NK012&ID=26908832

2.

Optimising the management of polycystic kidney disease.

Authors: Keenan D; Maxwell AP

Journal: Practitioner. 2016 Feb;260(1790):13-6, 2.

Abstract Link: http://www.medifocus.com/abstracts.php?gid=NK012&ID=27032221

The **Guide to the Medical Literature** in the complete **Medifocus Guidebook on Polycystic Kidney Disease** includes the following sections:

- Review Articles - 33 Articles
- General Interest Articles - 48 Articles
- Drug Therapy Articles - 4 Articles
- Surgical Therapy Articles - 5 Articles
- Clinical Trials Articles - 9 Articles
- Kidney Transplantation Articles - 9 Articles
- Dialysis Therapy Articles - 1 Articles

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4 - Centers of Research

This section of your *MediFocus Guidebook* is a unique directory of doctors, researchers, medical centers, and research institutions with specialized research interest, and in many cases, clinical expertise in the management of this specific medical condition. The *Centers of Research* directory is a valuable resource for quickly identifying and locating leading medical authorities and medical institutions within the United States and other countries that are considered to be at the forefront in clinical research and treatment of this disorder.

Use the *Centers of Research* directory to contact, consult, or network with leading experts in the field and to locate a hospital or medical center that can help you.

The following information is provided in the *Centers of Research* directory:

- **Geographic Location**
    - United States: the information is divided by individual states listed in alphabetical order. Not all states may be included.
    - Other Countries: information is presented for select countries worldwide listed in alphabetical order. Not all countries may be included.
- **Names of Authors**
    - Select names of individual authors (doctors, researchers, or other health-care professionals) with specialized research interest, and in many cases, clinical expertise in the management of this specific medical condition, who have recently published articles in leading medical journals about the condition.
    - E-mail addresses for individual authors, if listed on their specific publications, is also provided.
- **Institutional Affiliations**
    - Next to each individual author's name is their **institutional affiliation** (hospital, medical center, or research institution) where the study was conducted as listed in their publication(s).
    - In many cases, information about the specific **department** within the medical institution where the individual author was located at the time the study was conducted is also provided.

Centers of Research

United States

AZ - Arizona

Name of Author	Institutional Affiliation
Andrews PE	Department of Urology, Mayo Clinic Hospital, Phoenix, AZ, USA.
Humphreys MR	Department of Urology, Mayo Clinic, Phoenix, Arizona. Electronic address: tyson.mark@mayo.edu.
Tyson MD	Department of Urology, Mayo Clinic, Phoenix, Arizona. Electronic address: tyson.mark@mayo.edu.
Wisenbaugh ES	Department of Urology, Mayo Clinic Hospital, Phoenix, AZ, USA.

CA - California

Name of Author	Institutional Affiliation
Kalantar-Zadeh K	Harold Simmons Center for Chronic Disease Research and Epidemiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA.
Lukowsky LR	Harold Simmons Center for Chronic Disease Research and Epidemiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA.
Shillingford JM	Molecular, Cellular, and Developmental Biology, University of California-Santa Barbara, CA 93106-9610, USA.
Weimbs T	Molecular, Cellular, and Developmental Biology, University of California-Santa Barbara, CA 93106-9610, USA.

CO - Colorado

Name of Author	Institutional Affiliation

The **Centers of Research** in the complete **Medifocus Guidebook on Polycystic Kidney Disease** includes the following sections:

- Centers of Research for relevant states in the United States
- Centers of Research listed for relevant countries outside the United States

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5 - Tips on Finding and Choosing a Doctor

Introduction

One of the most important decisions confronting patients who have been diagnosed with a serious medical condition is finding and choosing a qualified physician who will deliver a high level and quality of medical care in accordance with currently accepted guidelines and standards of care. Finding the "best" doctor to manage your condition, however, can be a frustrating and time-consuming experience unless you know what you are looking for and how to go about finding it.

The process of finding and choosing a physician to manage your specific illness or condition is, in some respects, analogous to the process of making a decision about whether or not to invest in a particular stock or mutual fund. After all, you wouldn't invest your hard eared money in a stock or mutual fund without first doing exhaustive research about the stock or fund's past performance, current financial status, and projected future earnings. More than likely you would spend a considerable amount of time and energy doing your own research and consulting with your stock broker before making an informed decision about investing. The same general principle applies to the process of finding and choosing a physician. Although the process requires a considerable investment in terms of both time and energy, the potential payoff can be well worth it--after all, what can be more important than your health and well-being?

This section of your Guidebook offers important tips for how to find physicians as well as suggestions for how to make informed choices about choosing a doctor who is right for you.

Tips for Finding Physicians

Finding a highly qualified, competent, and compassionate physician to manage your specific illness or condition takes a lot of hard work and energy but is an investment that is well-worth the effort. It is important to keep in mind that you are not looking for just any general physician but rather for a physician who has expertise in the treatment and management of your specific illness or condition. Here are some suggestions for where you can turn to identify and locate physicians who specialize in managing your disorder:

- **Your Doctor** - Your family physician (family medicine or internal medicine specialist) is a good starting point for finding a physician who specializes in your illness. Chances are that your doctor already knows several specialists in your geographic area who specialize in your illness and can recommend several names to you. Your doctor can also provide you with information about their qualifications, training, and hospital affiliations.

The **Tips on Finding and Choosing a Doctor** in the complete **Medifocus Guidebook on Polycystic Kidney Disease** includes additional information that will assist you in locating a highly qualified and competent physician to manage your specific illness.

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6 - Directory of Organizations

American Association of Kidney Patients
3505 E. Frontage Road; Suite 315; Tampa, FL 33607
800.749.2257
info@aakp.org
www.aakp.org

American College of Surgeons
633 N. Saint Clair Street; Chicago, IL 60611
800.621.4111; 312.202.5000
postmaster@facs.org
www.facs.org

American Kidney Fund
6110 Executive Boulevard; Suite 1010; Rockville, MD 20852
301.881.3052; 800.638.8299
helpline@akfinc.org
www.akfinc.org

American Society of Transplant Surgeons
2461 South Clark St. Suite 640 Arlington, VA 22202
703.414.7870
www.asts.org

ARPKD/CHF Alliance
POB 70; Kirkwood, PA 17536
717.529.5555; 800.708.8892
info@arpkdchf.org
www.arpkd.org

Children's Organ Tranplant Association
2501 West COTA Drive Bloomington, IN 47403
800.366.2682
cota@cota.org
www.cota.org

The **Directory of Organizations** in the complete **Medifocus Guidebook on Polycystic Kidney Disease** includes a list of selected disease organizations and support groups that are helping people diagnosed with Polycystic Kidney Disease.

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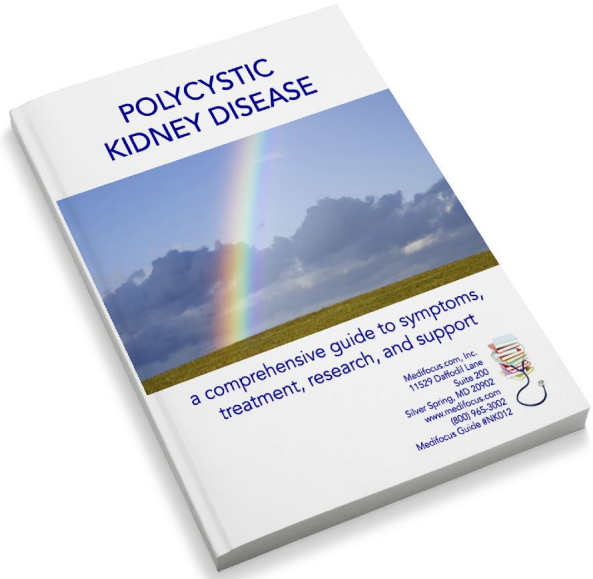

This document is only a SHORT PREVIEW of the **Medifocus Guidebook on Polycystic Kidney Disease**. It is intended primarily to give you a general overview of the **format and structure** of the Guidebook as well as select pages from each major Guidebook section listed in the Table of Contents.

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