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Understanding Polycystic Kidney Disease:

An Overview of PKD

Always talk with your doctor about your condition and any changes in your condition. Also discuss with your doctor any changes in your diet as well as the medications you are taking and any side effects that may occur.

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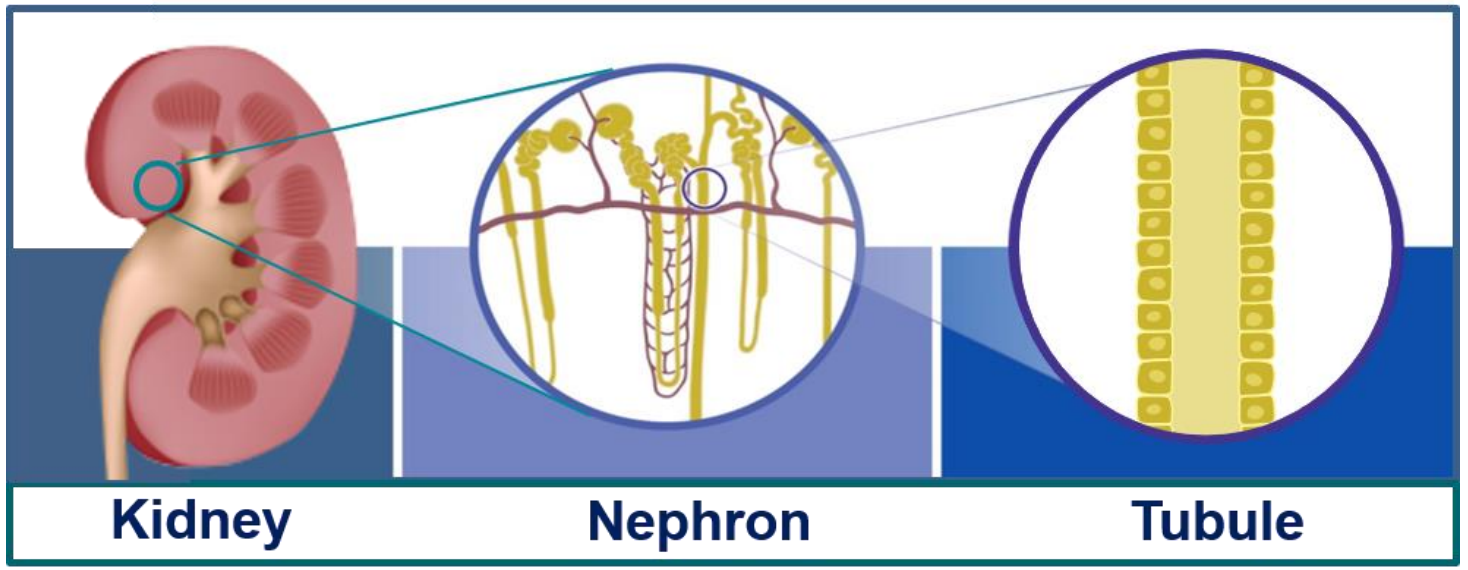
Speakers are employees and/or paid consultants of Otsuka Pharmaceutical Development & Commercialization, Inc.

What Do Your Kidneys Do?

How do my kidneys work?

- Inside each kidney there are millions of filtering units called nephrons.
- In each nephron there are two parts that make up a filter: a glomerulus and a tubule.
- First, the glomerulus filters your blood; secondly the tubule returns needed nutrients to your blood and removes wastes that you do not need.

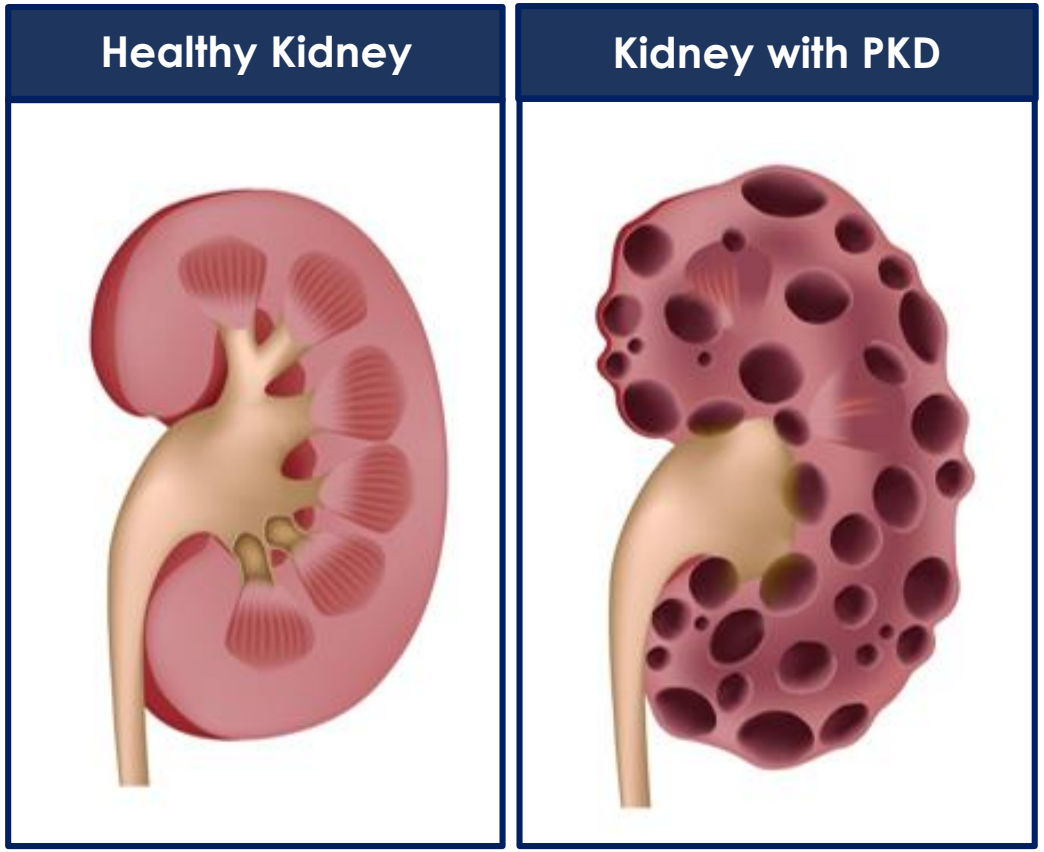
The main job of your kidneys is to clean your blood.



1. National Institute of Diabetes and Digestive and Kidney Disease. Health Information, Kidney Disease, Your Kidneys & How They Work. https://www.niddk.nih.gov/health-information/kidney-disease/kidneys-how-they-work. Accessed on May 5th, 2021.

What is Polycystic Kidney Disease (PKD)?

Polycystic kidney disease (PKD) can be broken down into two groups



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- Autosomal Dominant Polycystic Kidney Disease (ADPKD) – "Adult PKD"
- Autosomal Recessive Polycystic Kidney Disease (ARPKD) – "Childhood PKD"

1. Bergmann C (2018). Frontiers in Pediatrics. 5:221.

How Common is Polycystic Kidney Disease (PKD)?

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- Most common life-threatening genetic kidney disease[1]
- Over 140,000 Americans have been diagnosed with ADPKD[2]
- Can occur in 1 out of 400 to 1 out of 1,000 children born in the United States[3]
- Affects over 13 million people world wide[4]
- People living with ADPKD are from all over the world with all different backgrounds[3]

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

- Rare form of PKD, occurring in about 1 out of 20,000 children born in the general population[5]
- The true frequency or number of children affected by this disease is unknown as some affected babies may die before a true diagnosis is made[5]

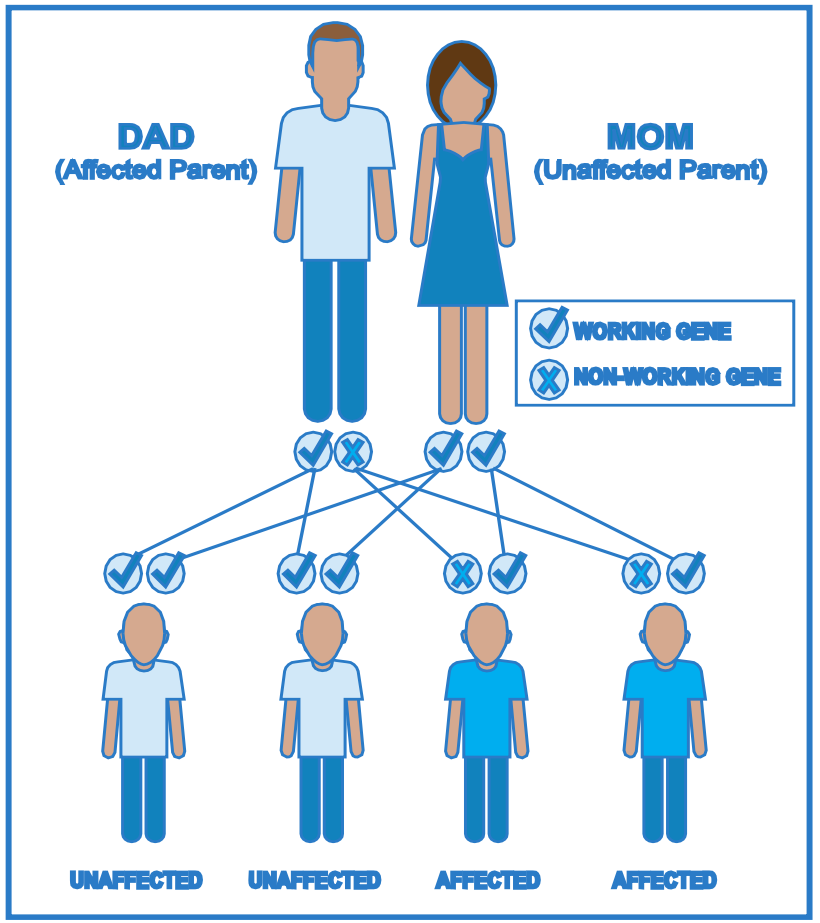
1. Torres VE et al. (2007). *Lancet.* 369:1287-1301.
2. Willey et al. (2019). *Kidney Diseases* 5:107–117.
3. Torres VE, Harris PC. (2009). *Kidney Int*. 76(2):149-168..
4. Sweeney WE Jr and Avner ED. (2014). *Pediatr Res*. 75(1–2):148-157.
5. Bergmann C (2018). *Frontiers in Pediatrics*. 5:221.

A Closer Look at PKD:
Autosomal Dominant Polycystic Kidney Disease (ADPKD)

This is the **most common** type of PKD

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- **Type 1:** Damage to the PKD1 gene → Median age of death or kidney failure is 53 years old[1]
- **Type 2:** Damage to the PKD2 gene → Median age of death or kidney failure is 69 years old[1]



- Each child born from an affected parent has a 50/50 chance of getting the damaged gene.
- Individuals that get a damaged PKD1 gene will have more cysts in their kidneys.
- Individuals that get a damaged PKD1 gene will have kidney damage sooner and need treatment for kidney failure earlier in their life.

PKD1=polycystic kidney disease gene 1; *PKD2* = polycystic kidney disease gene 2

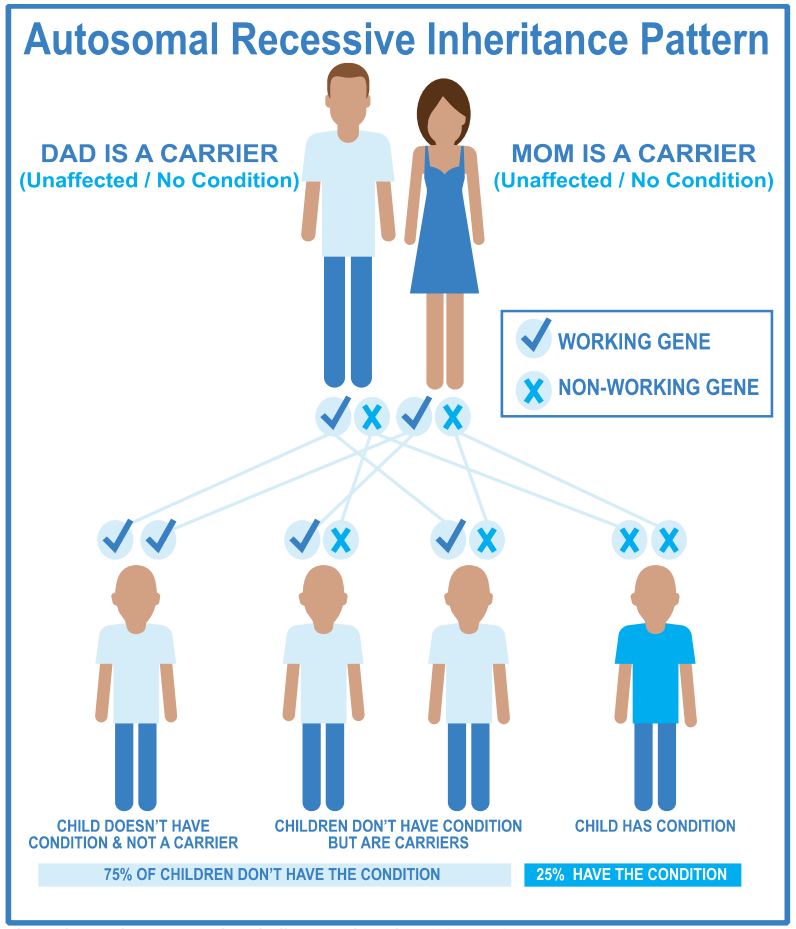
1. Hateboer N et al. (1999). *Lancet*. 353(9147):103-107.

A Closer Look at PKD
Autosomal Recessive Polycystic Kidney Disease (ARPKD)

This is the **less common** type of PKD

Autosomal Recessive Polycystic Kidney Disease (ARPKD) — Damage to PKHD1 gene — About 1/3 of children with ARPKD will develop kidney failure

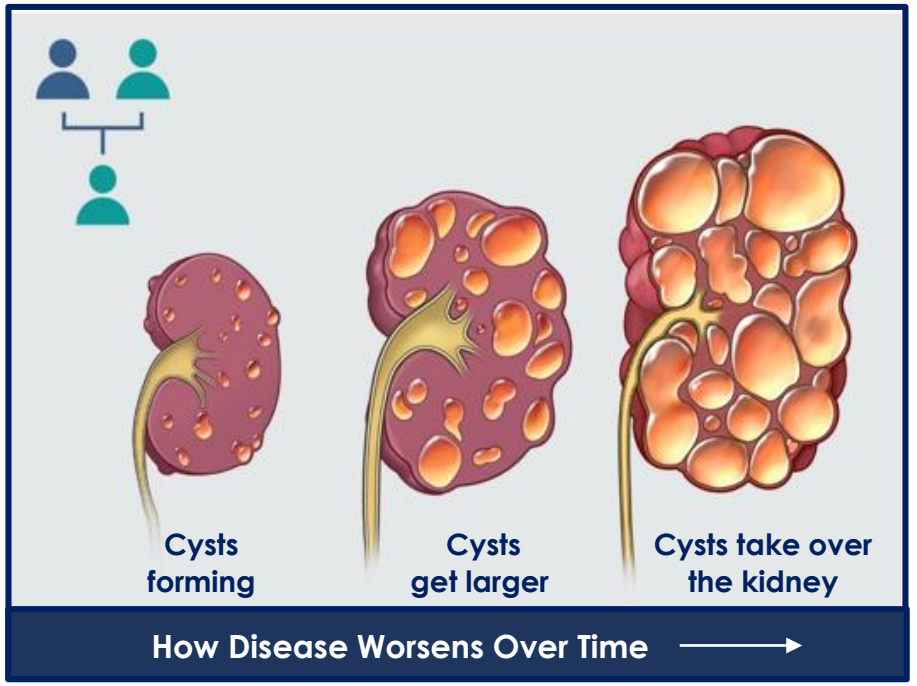
- This form of PKD is rare and this damaged gene is passed on from one generation to the next.
- The damaged gene can only be passed on if both parents have the damaged gene. The parents are referred to as "carriers" of the damaged gene.
- In families where both parents have the damaged gene, every child has a 25% chance of getting the disease.
- Unlike the more common form, ARPKD may "skip a generation".



1. Bergmann C (2018). *Frontiers in Pediatrics*. 5:221.

Polycystic Kidney Disease (PKD): An Overview

- Polycystic Kidney Disease or PKD is a genetic disease (can be passed down through generations in families).
- In PKD, certain kidney cells are damaged which leads to multiple cysts developing, (fluid filled sacs).
- These cysts expand over time and cause the kidneys to become large.
- Ultimately, when there are too many cysts the kidney stops working properly, people with PKD then suffer kidney failure.



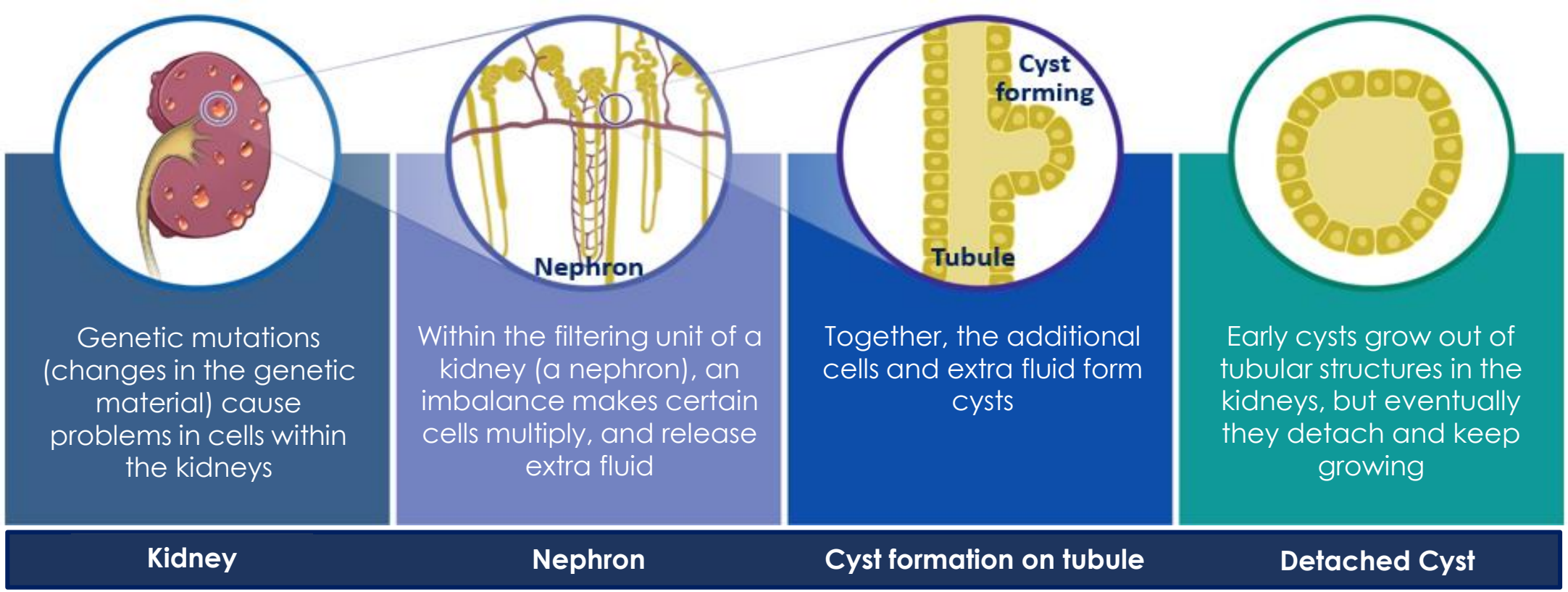
Did you know?

A healthy kidney is about the size of a fist

A polycystic kidney can grow as large as a football

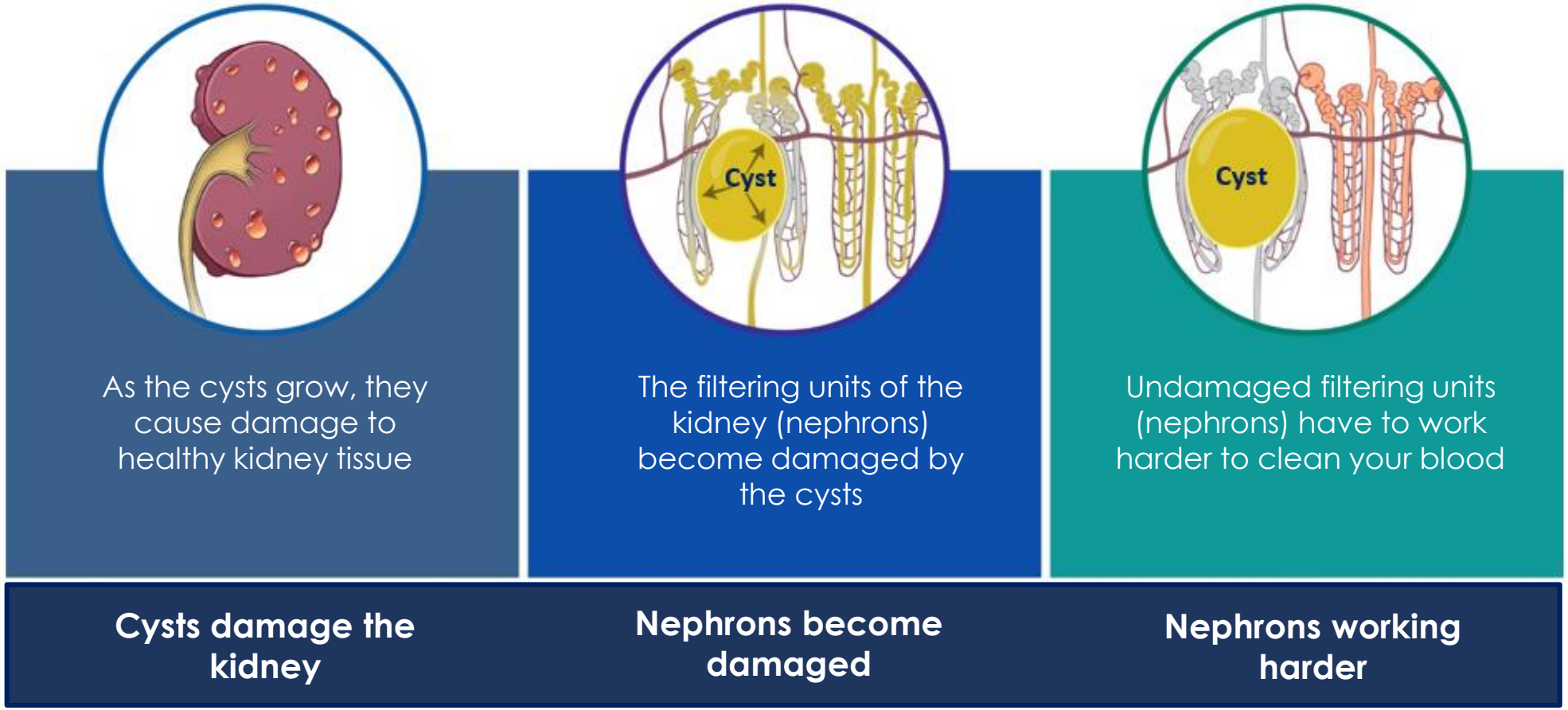
1. Grantham JJ et al. (2011). *Nat Rev Nephrol.* 7(10):556-566.

A Closer Look: How a Cyst Forms in the Kidney



1. Grantham JJ et al. (2011). *Nat Rev Nephrol.* 7(10):556-566.

How Disease Progression Leads to Kidney Damage and Ultimately Kidney Failure



1. Grantham JJ et al. (2011). *Nat Rev Nephrol.* 7(10):556-566.

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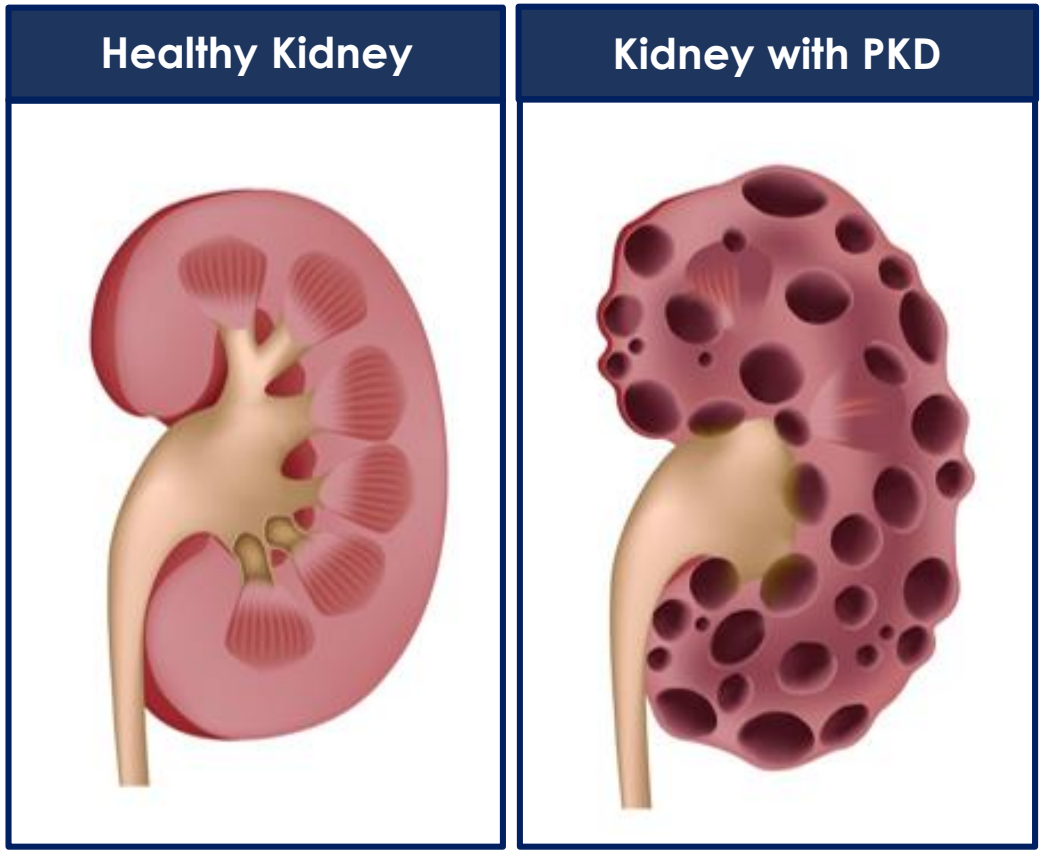
Diagnosis of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

What is Polycystic Kidney Disease (PKD)?

Polycystic kidney disease (PKD) can be broken down into two groups



Autosomal Dominant Polycystic Kidney Disease (ADPKD) – "Adult PKD"

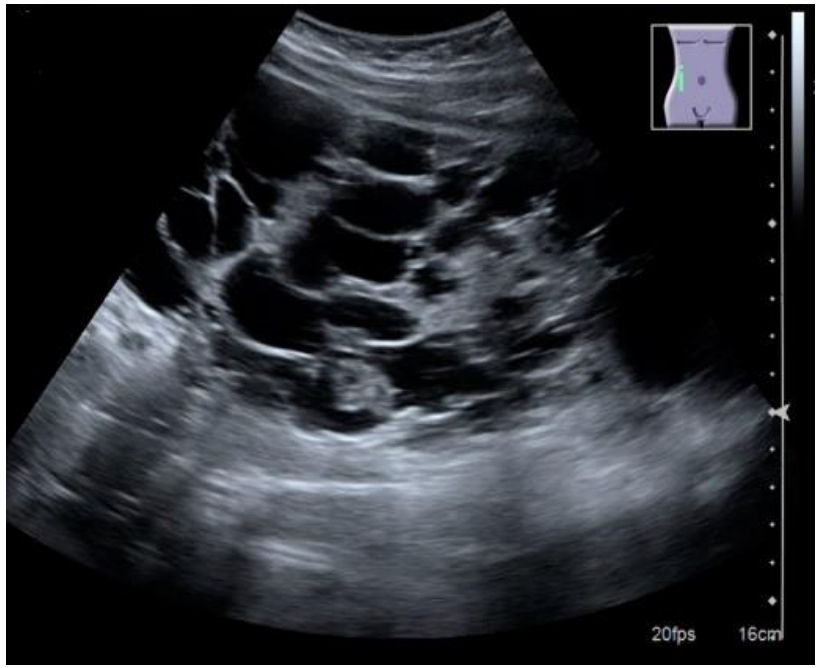
Autosomal Recessive Polycystic Kidney Disease (ARPKD) – "Childhood PKD"

1. Bergmann C (2018). Frontiers in Pediatrics. 5:221

Diagnosis of Autosomal Dominant Polycystic Kidney Disease (ADPKD) by Ultrasound

Imaging plays a role in accurately diagnosing ADPKD[1]

- The only way to find out if you have ADPKD is to be screened or tested for it.[2]
- Talk with your doctor about being screened, especially if you are having symptoms such as high blood pressure or pain (side and lower back) which are often caused by the disease.[2]
- Also talk to your doctor if family members have had kidney disease.[1]
- Even without symptoms, if you have ADPKD your kidneys are being damaged by the disease.[2]
- To diagnose ADPKD, generally a doctor will want to have an ultrasound taken of your kidneys.[1]
- Ultrasound imaging does not use dyes or radiation. This imaging test is like the one used in pregnant women; thus, it is very safe.[1]



Ultrasound image of kidney

1. Chebib FT and Torres VE. (2016). *Am J Kidney Dis*. 67(5):792-810.
2. Grantham JJ et al. (2011). *Nat Rev Nephrol.* 7(10):556-566.

Role of Genetic Testing in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

The Role of Genes in ADPKD

- How sick you may become depends on the type of damaged gene that was passed to you.[1]
- The genetics and the mutations, (the damaged part of your gene) are very complex in ADPKD.[2]
- Evaluating a new patient or family requires complete genetic testing of both genes.[2]

When to have Genetic Testing for ADPKD[2]

There are doubts about your diagnosis

- *Lack of family history*
- *Imaging is unclear*

?

When the doctors need to be 100% sure their patient does not have ADPKD

- *Family Planning*
- *Kidney Donation*

?

ADPKD=autosomal dominant polycystic kidney disease; DNA=deoxyribonucleic acid; PKD=polycystic kidney disease gene.

1. Lee KB. (2016). *Kidney Res Clin Pract*. 35(2):67-68.
2. Lanktree MB, et al. (2019). *Nephrol Dial Transplant*. 34: 1453–146o.

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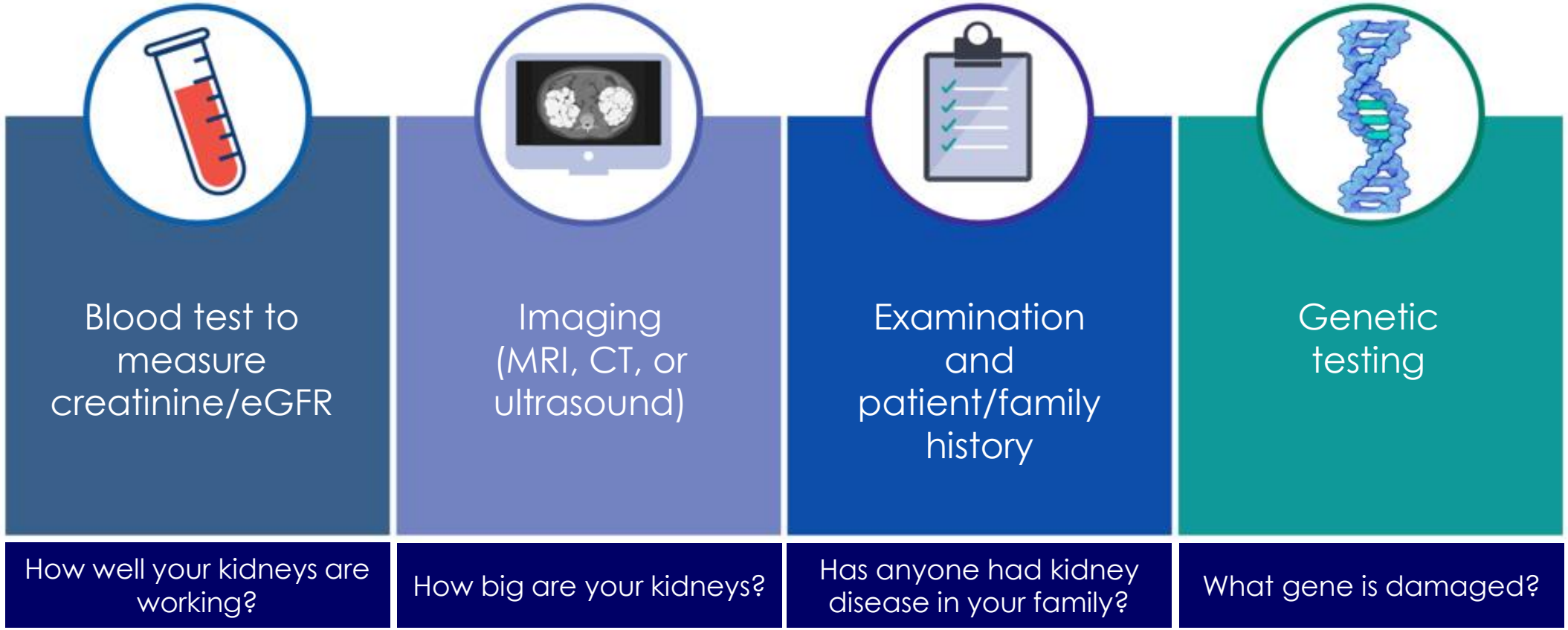
How Your Autosomal Dominant Polycystic Kidney Disease (ADPKD) May Advance Over Time

Information Collected to Help Understand Disease Progression in ADPKD

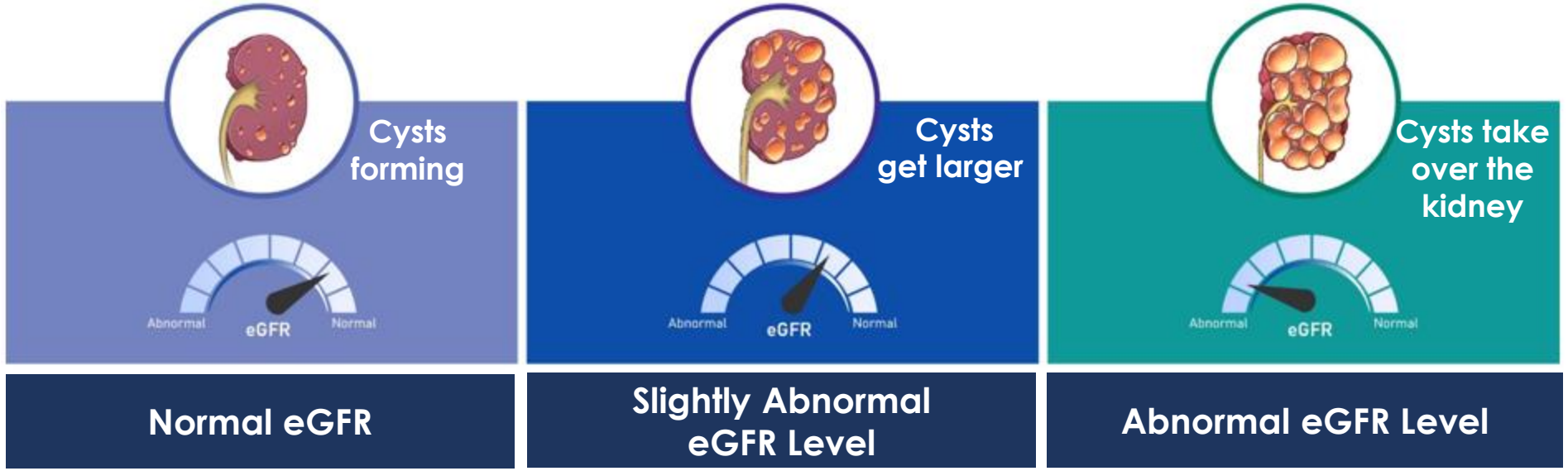


ADPKD=autosomal dominant polycystic kidney disease; MRI=magnetic resonance imaging; CT=computerised tomography; eGFR=estimated glomerular filtration rate

1. Gansevoort RT et al. (2016). *Nephrol Dial Transplant*. 31(3):337-348.

Kidney Function is Determined by a Blood Test

- A blood test is performed to measure creatinine levels in your blood.
  - Creatinine is a waste product that the kidneys typically "clean out".
  - Everyone has creatinine in their bloodstream, but higher than normal levels could mean your kidneys are not working as well as they should.
- In early stages of disease, cysts are forming in your kidneys, but your kidneys can work harder to keep the kidneys functioning.
- Therefore, early in the disease, your blood test may not tell you how much damage your kidney really has.



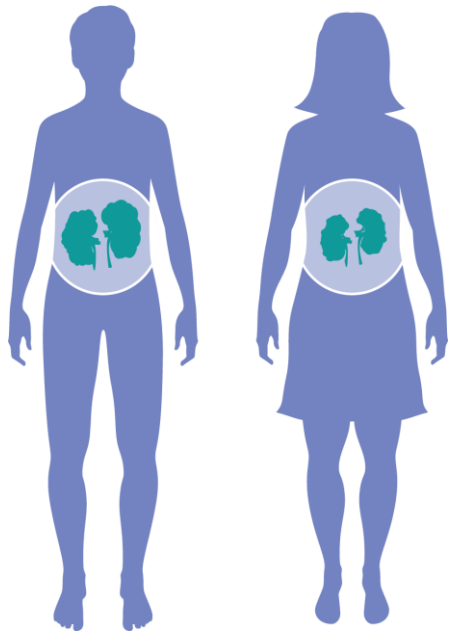
eGFR=estimated glomerular filtration rate

1. Grantham JJ et al. (2011). *Nat Rev Nephrol.* 7(10):556-566.

Reasons For Disease Changes with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Why does ADPKD develop more quickly in some people than others?

- There are several things that can help predict whether someone's disease may progress faster than other ADPKD patients.
- Large kidneys, or your doctor may refer to high total kidney volume (TKV)
- Hypertension (high blood pressure) before the age of 35.
- Visible blood in the urine.
- Having complications with kidneys -- like a cyst that bursts or frequent UTIs, before the age of 35.
- Kidney function gets worse earlier in your life as measured by a blood test called estimated Glomerular Filtration Rate (eGFR).
- Having a specific type of damaged gene compared to others.

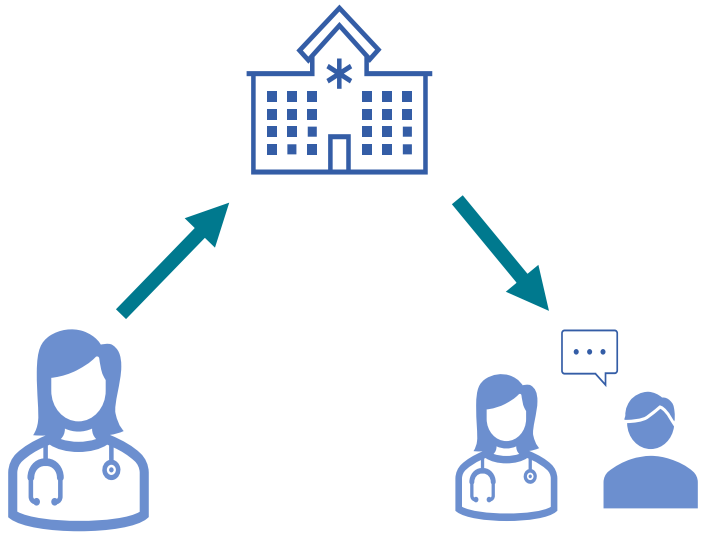


1. Gansevoort RT et al. (2016). *Nephrol Dial Transplant.* 31(3):337-348.

Kidney Size is Measured with Imaging

Types of Imaging

- **Magnetic resonance imaging (MRI)** – the large tube scanner uses a magnet, sound waves and a computer to create an image.
- **Computed tomography scan (CT or CAT)** – this scanner typically looks like a large donut and uses x-rays and a computer to create an image.



Determining Kidney Size

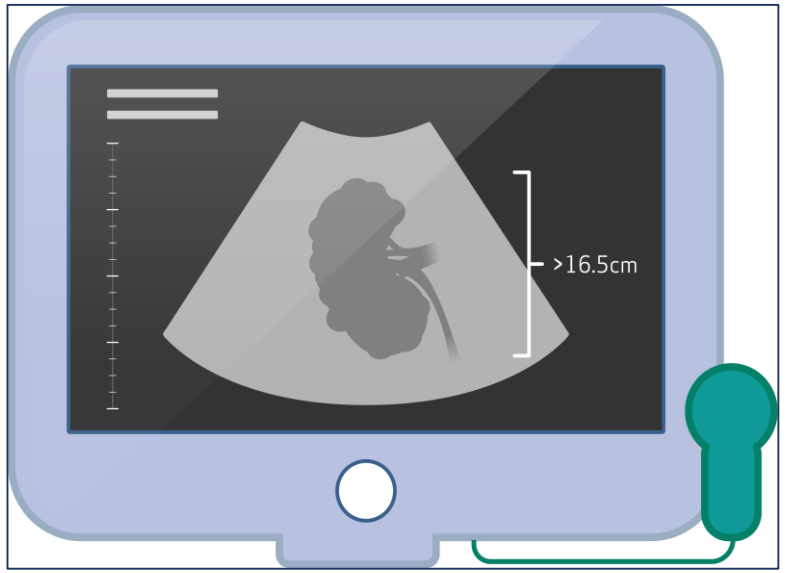
- Your kidney doctor works with a radiology team, who specializes in imaging.
- Measurements taken during the imaging tests; help calculate the volume of the kidneys (how big they are compared to a healthy kidney).
- Knowing how big your kidneys are at the time of your imaging scan, can help predict how badly your kidneys are being damaged and how close you are to kidney failure.

1. Gansevoort RT et al. (2016). Nephrol Dial Transplant. 31(3):337-348.

Kidney Size Can Also be Measured by Ultrasound

Ultrasound Imaging

- If an MRI or CT scan is not an option, your doctor may perform an ultrasound.
  - Ultrasound imaging does not use dyes or radiation.
  - This imaging test is like the one used in pregnant women; however, they will be taking pictures of your kidneys.
- Kidney length is measured and can help doctors predict how badly your kidneys are being damaged and how quickly you may reach kidney failure.



MRI=magnetic resonance imaging; CT=computerised tomography

1. Bhutani et al (2015). Kidney Int. 88(1): 146–151.

Patient Medical History and Genetic Testing

Gathering family history and genetic testing to understand the severity of ADPKD

- Family history, (knowing which family members have had kidney disease and at what age their kidneys failed) can help determine what type of damaged gene you inherited.[1]
- Evaluating a new patient or family requires complete genetic testing of both genes.[2]
- If a family member went on dialysis or had a kidney transplant because their kidneys had failed before the age of 55, this is most likely "type 1" PKD, a more severe form of disease.[3]
- If family members did not have kidney failure until after the age of 70, this is most likely "type 2" PKD, a less severe form of the disease.[3]

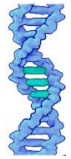
ADPKD=autosomal dominant polycystic kidney disease ; *PKD* = polycystic kidney disease

1. Gansevoort RT et al. (2016). Nephrol Dial Transplant. 31(3):337-348.
2. Lanktree MB, et al. (2019). *Nephrol Dial Transplant*. 34: 1453–146o.
3. Cornec-Le Gail E et al (2016). *J Am Soc Nephrol.* 27:942-951.

What Other Factors May Affect How Quickly Your Disease Gets Worse?

Lab Tests

- Blood pressure
- Blood in the urine
- Kidney function



Genetic Factors

- Damaged *PKD1* gene
- Damaged *PKD2* gene

Environmental Factors

- Too much caffeine
- Too much protein
- Not enough water
- Smoking
- Unhealthy weight

Imaging Scans

- Measure kidney size
- Look for kidneys getting larger

PKD1=polycystic kidney disease gene 1; *PKD2* = polycystic kidney disease gene 2

1. Gansevoort RT et al. (2016). *Nephrol Dial Transplant.* 31(3):337-348.

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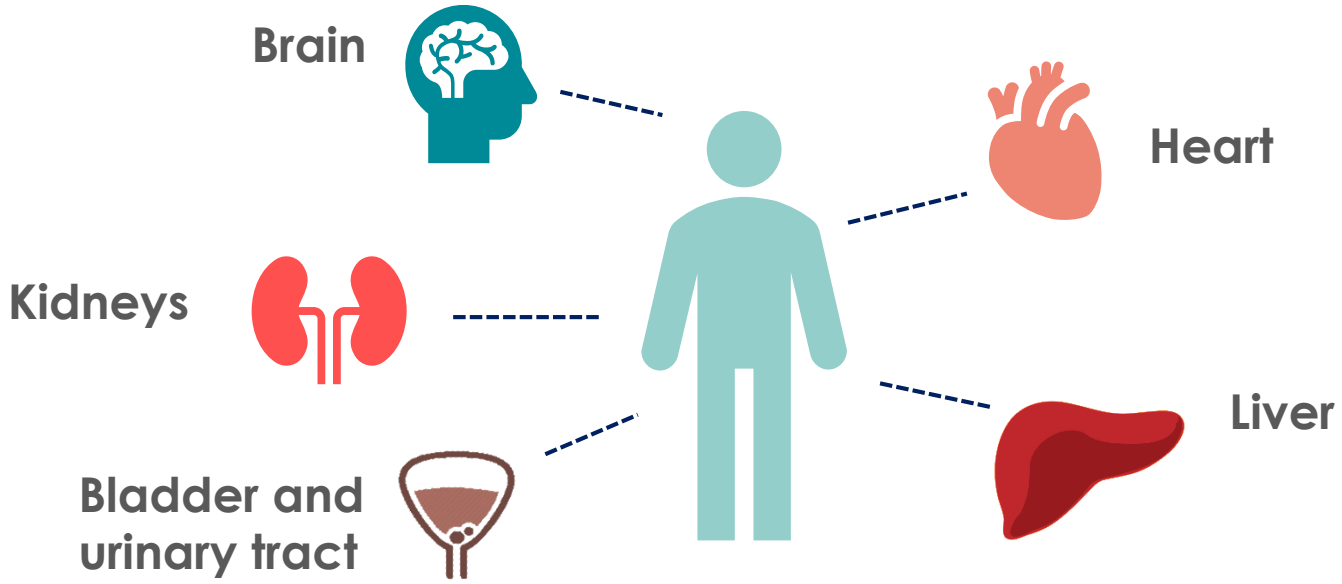
How Autosomal Dominant Polycystic Kidney Disease (ADPKD) Affects Your Body

Autosomal Dominant Polycystic Kidney Disease (ADPKD) Affects the Whole Body, Not Just Kidneys

Kidney cysts are one of the first signs of ADPKD.
The appearance of cysts can be found years before kidney damage is detected.[1–8]

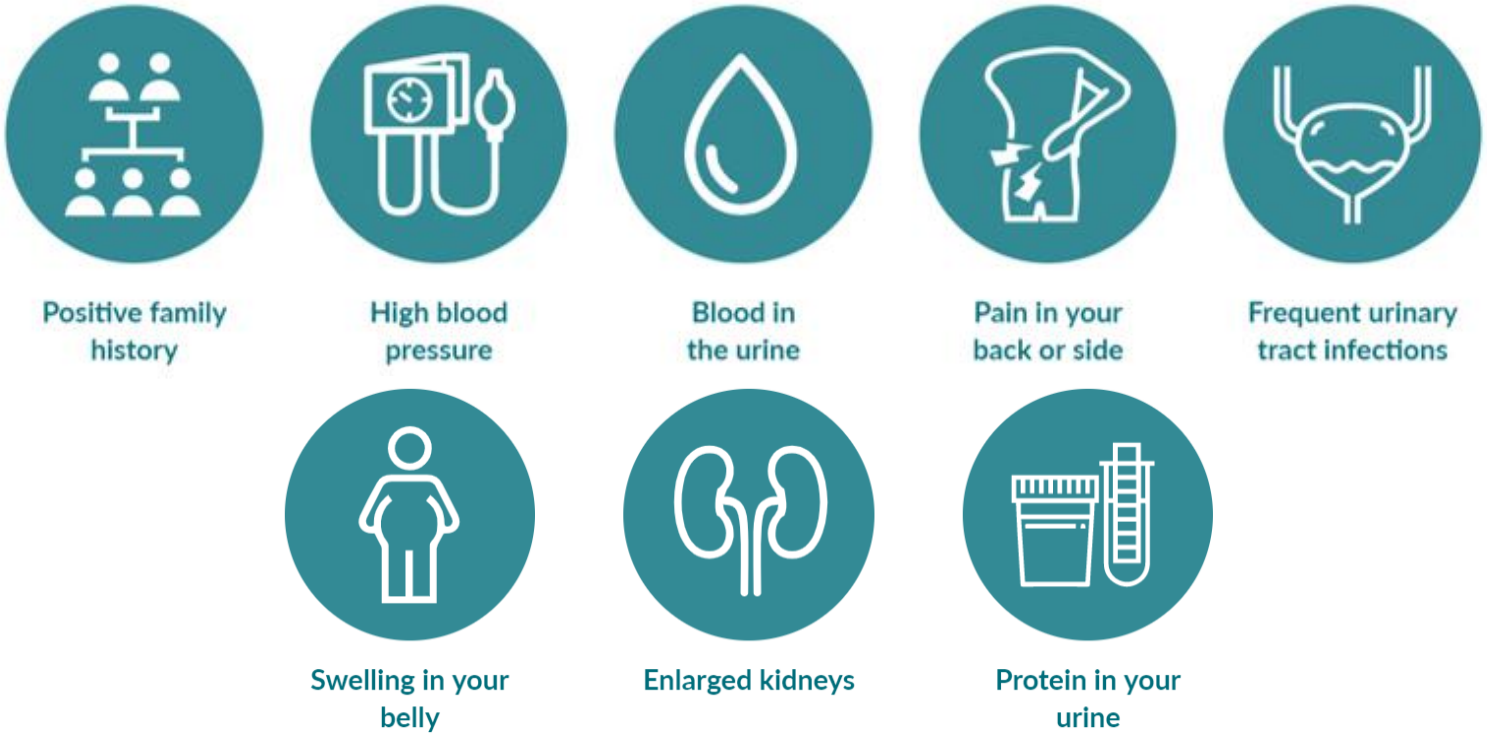


ADPKD= autosomal dominant polycystic kidney disease.

1. Halvorson CR et al. (2010). *Int J Nephrol Renovasc Dis*. 3:69-83.
2. Torres VE, and Harris PC. (2009). *Kidney Int*. 76(2):149-168.
3. Chebib FT and Torres VE. (2016). *Am J Kidney Dis*. 67(5):792-810.
4. Patient Platform. http://www.patient.co.uk/doctor/autosomal-dominant-polycystic-kidney-disease (accessed 13 February 2019).
5. Luciano RL and Dahl NK. (2014). *Nephrol Dial Transplant*. 29(2):247-254.
6. Mikolajczyk AE, et al. (2017). *Clin Gastroenterol Hepatol*. 15(1):17-24.
7. Chapman AB and Rahbari-Oskui FF. (2008) Renal Cystic Disorders. In: Wilcox CS et al. eds. *Therapy in Nephrology & Hypertension.* 3rd ed. Philadelphia, PA: Saunders.
8. Chauveau D et al. (1994) *Kidney Int.* 45:1140-1146.

Signs & Symptoms of Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Common Signs of ADPKD



1. ADPKD Questions: About ADPKD. Diagnosis. What are the signs and symptoms of ADPKD? https://www.adpkdquestions.com/adpkd-diagnosis. Accessed on Dec. 10th 2021.

High Blood Pressure in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- Approximately 70% of individuals with ADPKD will have high blood pressure.[1]
- Approximately 20% to 30% of children with ADPKD will have high blood pressure.[2]
- More men with ADPKD develop high blood pressure than women.[3]
- High blood pressure generally is found before any change in kidney function can be discovered.[3]
- Blood pressure goes up earlier in life in patients with ADPKD than those patients who do not have ADPKD.[3]
- High blood pressure can cause your heart to become bigger which can cause more problems, such as thickening of the walls of your heart's main pumping chamber.[4]

1. Halvorson CR et al. (2010). *Int J Nephrol Renovasc Dis*. 3:69-83.
2. Ecder T and Schrier RW. (2001). *J Am Soc Nephrol*. 12(1):194-200.
3. Kelleher CL et al. (2004). *Am J Hypertens*. 17(11):1029-1034.
4. Chebib FT and Torres VE. (2016). *Am J Kidney Dis*. 67(5):792-810.

Controlling High Blood Pressure

- High blood pressure can cause heart problems and can damage your kidneys faster.[1]
- A large clinical study showed lower blood pressure targets were beneficial for ADPKD patients.[1]
- Your doctor may control your blood pressure with medications and have a target for your blood pressure that would be lower than people without ADPKD.[2]

Recommended Blood Pressure Levels[2]	18- to 50-year-old ADPKD patients with at least 60% of kidney function **Target BP ≤110/75**	Other patients **Target BP ≤130/85**
Ways to Help Lower Blood Pressure[2]	**Medications** 	**Dietary Approaches** 

ADPKD=autosomal dominant polycystic kidney disease; BP=blood pressure

1. Schrier et al. (2014). *N Engl J Med*. 371(24):2255-2266.
2. Chebib FT & Torres VE. (2018). *Clin J Am Soc Nephrol* 13:1765–1776.

Blood in the Urine is Common for Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- Visible blood in the urine occurs in 43% of patients with ADPKD and may be the first sign of the disease.[1]
- Usually caused by bleeding from a cyst that connects to the urinary tract and bladder.[2,3]
- Having blood in your urine at an early age, may be an indication that your ADPKD is getting worse faster than other patients.[1,3]

1. Gabow PA et al (1992). *Kidney Int*. 41:1311-3119.
2. Grantham JJ et al. (2009). *Ann Transplant*. 14(40):86-90.
3. Grantham JJ et al. (2006). *Clin J Am Soc Nephrol*. 1(1):148-157.

Pain is Most Frequent Complaint of Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

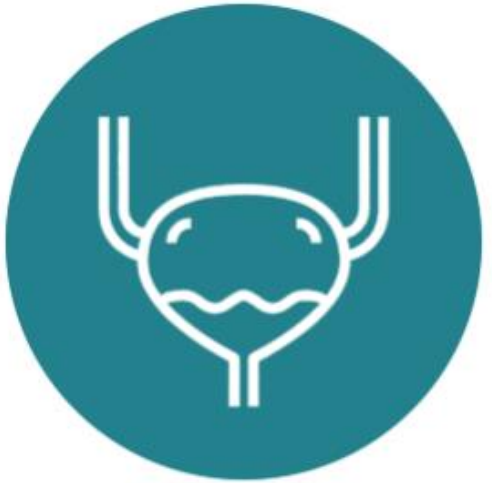
- Pain is caused when cysts grow larger or cause complications.
- Approximately 60% of patients with ADPKD report pain at some point.
- Almost a third of patients have either daily or constant lower back pain.
- You may have to take medication to control your pain.
- Talk to your doctor about your symptoms.

Pain in your back or side

1. Bajwa ZH et al. (2004). *Kidney Int*. 66(4):1561-1569.

Urinary Tract and Cyst Infections Can Develop with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- 60% of patients with ADPKD will develop a urinary tract infection.[1]
- Cyst infections require treatment with specific antibiotics.[2]
- You may have to take the antibiotics for a longer period of time.
- You may also have to take antibiotics in larger doses to treat the infection.[3]



1. .Idrizi A et al. (2011). *Med Arh.* 65(4):213-215.
2. Schwab et al. (1987). *Am J Med.* 82:714-718.
3. PKD Clinic. http://www.pkdclinic.org/urinary-tract-infection.html (accessed 14 February 2019).

Kidney Stones are Common in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- Approximately 20% of patients with ADPKD develop kidney stones.[1,2]
- Treatment of kidney stones is like that for patients without ADPKD:[3]
  - Increased water intake
  - Medication treatment
  - Surgical removal
  - Using shock waves to break up the kidney stone into small pieces

Kidney stone

1. Halvorson CR et al. (2010). *Int J Nephrol Renovasc Dis*. 3:69-83.
2. Nishiura JL et al. (2009). *Clin J Am Soc Nephrol*. 4:838-844.
3. Pearle MS et al. (2014). *J Urology.* 192:316-324.

Cysts on the Liver Can Develop with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- Liver cysts are the most common type of cyst, other than kidney cysts, for patients with ADPKD.[1]
- You may get more cysts in your liver as you get older.[1]
- Females are more likely to have liver cysts than males.[1]
- Most liver cysts do not make you feel sick or cause damage to your liver[2]; however, cysts in your liver may make your pain worse and make you feel fuller after a meal.[1]

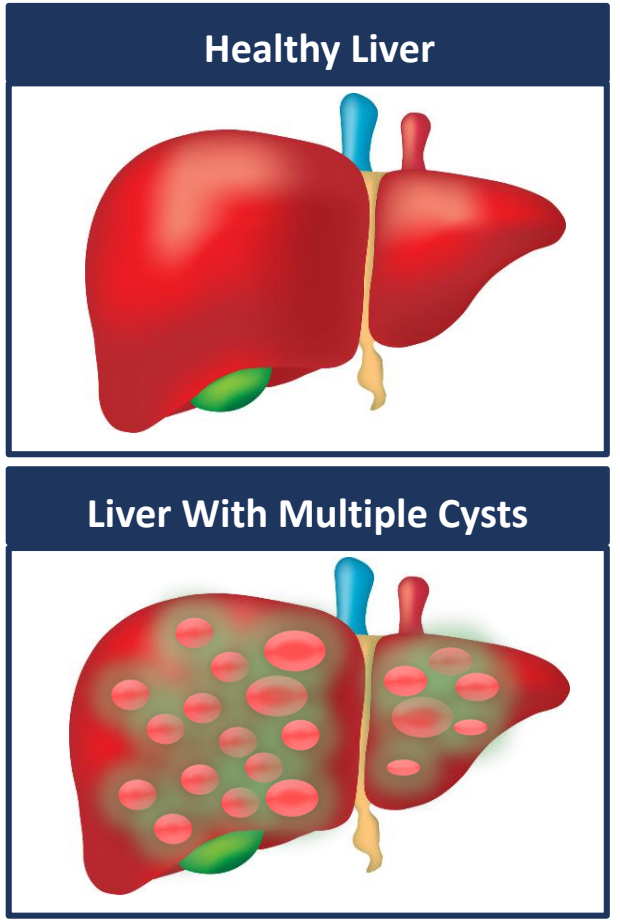
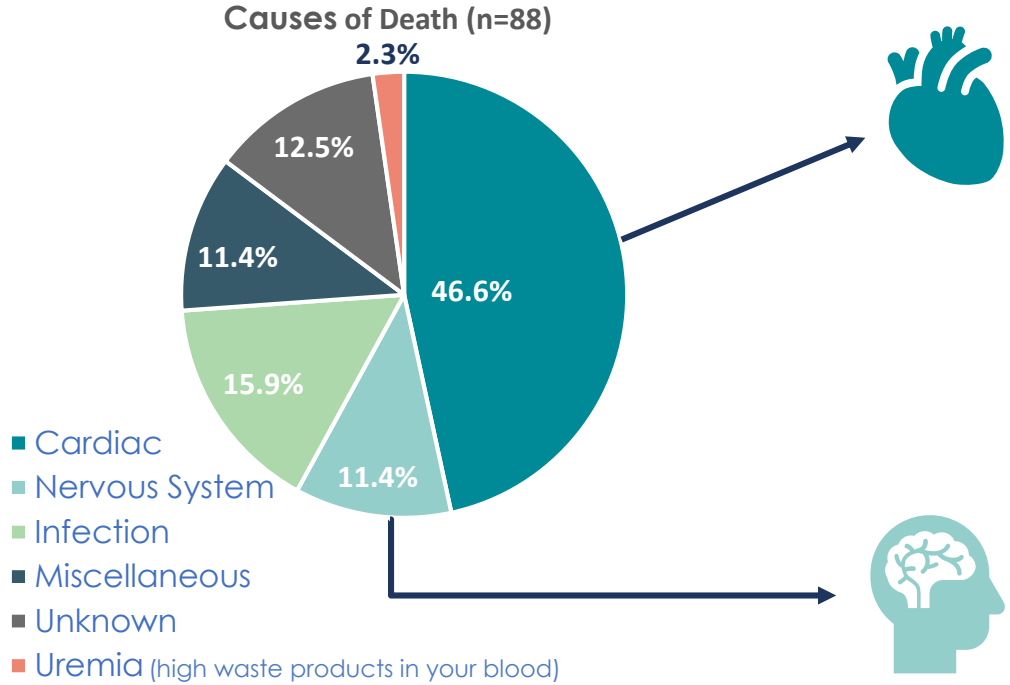


Image adapted from https://www.biobanking.com/wp-content/uploads/2018/11/liver-2934612_1280-1.png

1. Bae KT et al. (2006). *Clin J Am Soc Nephrol* 1:64-69.
2. Torres VE et al. (2007). *Lancet*. 369(9569):1287-1301.

Most Common Causes of Death in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Kidney damage and failure lead to heart and/or blood vessel disease and other complications[1-3]



- Cardiovascular disease, (heart and/or blood vessel disease) is the most common cause of death in patients with ADPKD.
- High blood pressure can lead to cardiovascular disease.
- This is why your doctor wants to keep your blood pressure low to reduce your risk.

- Some nervous system conditions such as brain aneurysms, are more common in patients with ADPKD compared to the general public.
- If you have a family history of brain aneurysms, your doctor may order a special brain scan.

ADPKD=autosomal dominant polycystic kidney disease; CNS= central nervous system

1. Fick GM et al. (1995). *JASN*. 5:2048-2056.
2. Rahman E et al. (2009). *Saudi J Kidney Dis Transpl*. 20(5):806-810.
3. Orskov B et al. (2012). *Nephrol Dial Transplant*. 27:1607-1613.

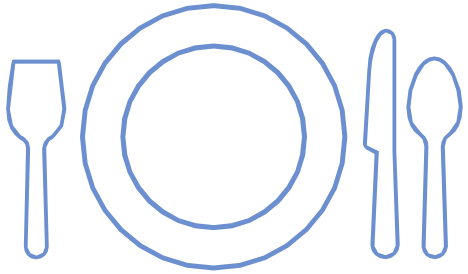
Ways to Help You Manage Your Heart Health

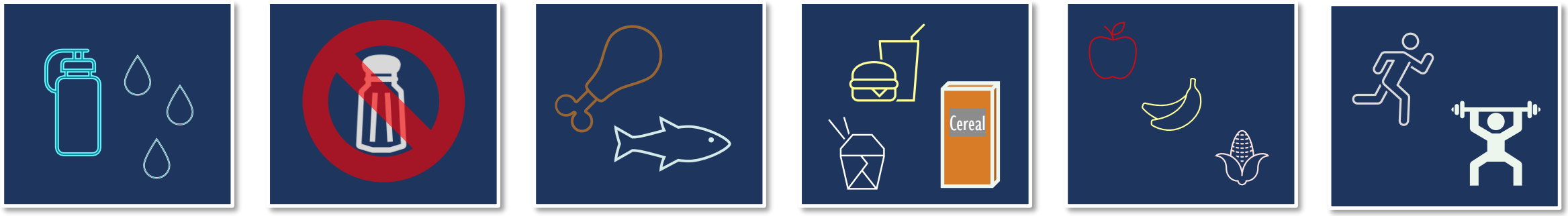
- Lower blood pressure[1]
- Stop smoking[1]
- Lower cholesterol levels[1]
  - Changes in your cholesterol (blood fats) increase the chance of getting heart disease.
  - Your doctor might want to lower your bad cholesterol levels to lower your chance of getting heart disease.

*Alternatives, such as a cholesterol absorption blocker should be considered if the patient is unable to tolerate statins; ADPKD=autosomal dominant polycystic kidney disease; LDL= low density lipoprotein

1. American Heart Association. *My Life Check. Life's Simple 7* [Online]. Available at: https://www.heart.org/en/healthy-living/healthy-lifestyle/my-life-check--lifes-simple-7. Accessed on November 26, 2019.
2. Chebib FT & Torres VE. (2018). *Clin J Am Soc Nephrol* 13:1765–1776.

The Importance of Diet in Kidney and Heart Health

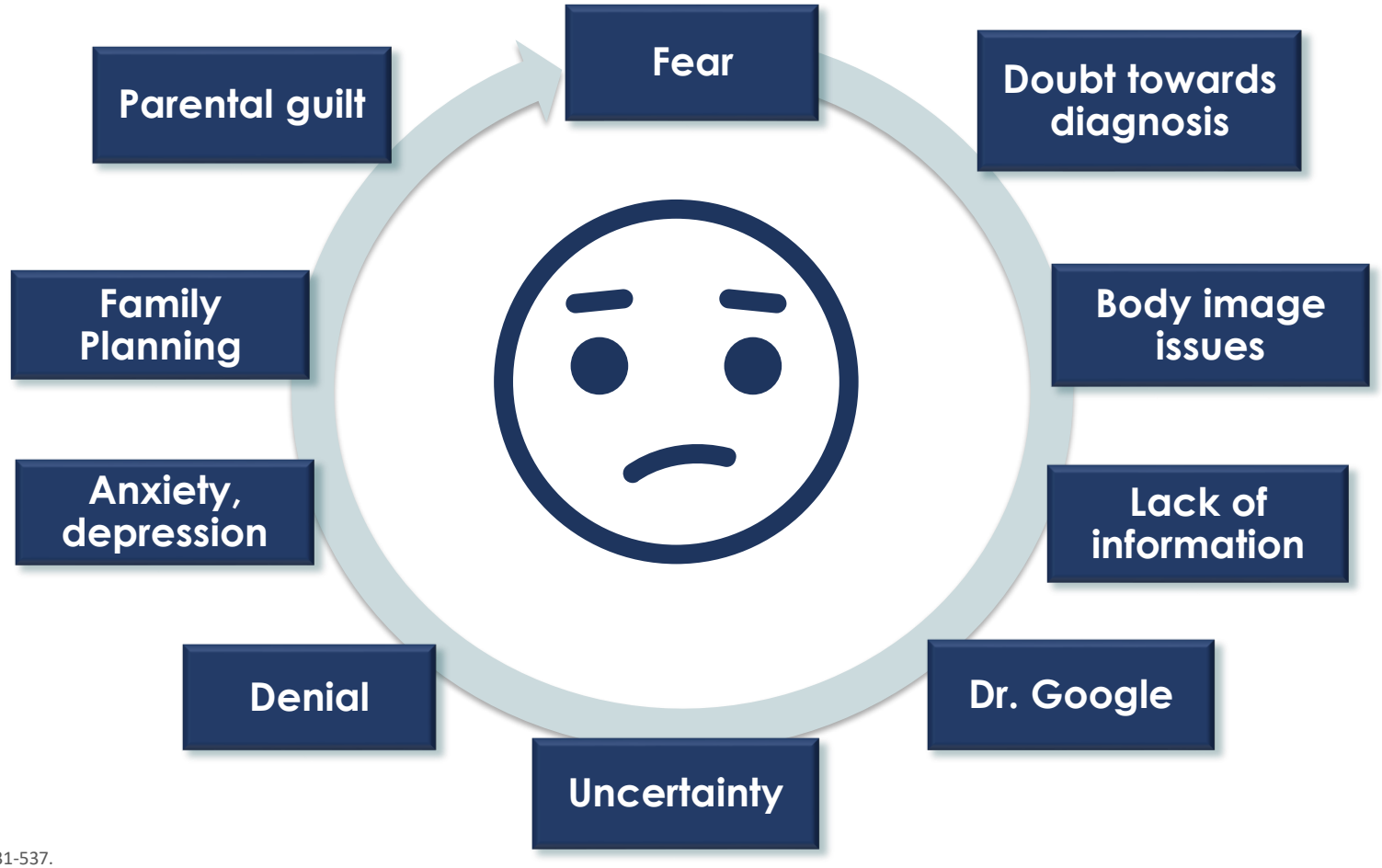




Your doctor may talk to you about ways you can maintain a kidney and heart healthy diet.

1. Chebib FT et al. (2018). *J Am Soc Nephrol*. 29(10):2458-2470.

Emotional Impact of Autosomal Dominant Polycystic Kidney Disease (ADPKD)



1. Baker A et al. (2015). *Clin Kidney J.* 8(5):531-537.
2. Pérez-Dominguez T et al. (2012). *Nefrologia.* 32(3):397-399.

How Does Autosomal Dominant Polycystic Kidney Disease (ADPKD) Affect You Day-to-Day

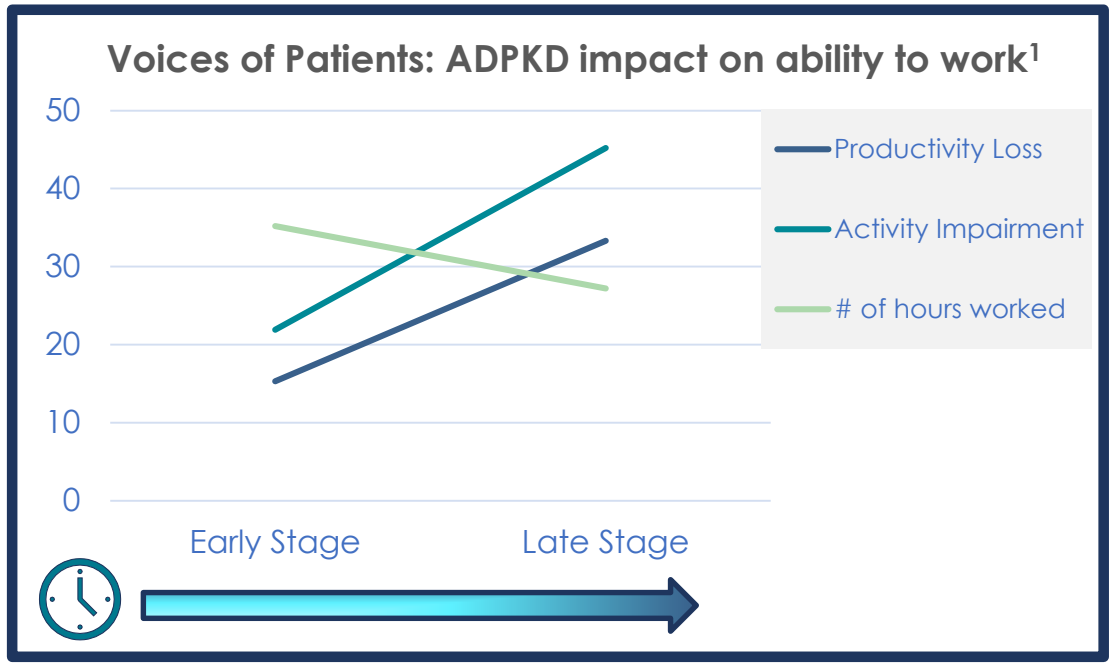
Voices of Patients: Impact of ADPKD on Daily Life[1]

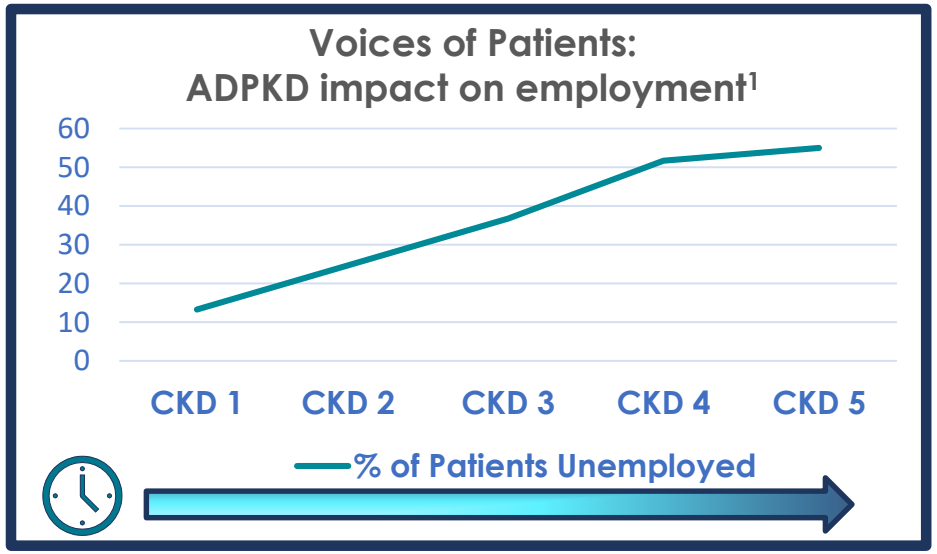
	Early-Stage Patients	Late-Stage Patients
Moderate Impact	27.8 %	34.2 %
Strong Impact	10.6%	19.2%
Very Strong Impact	6.7%	21.7%

Majority of patients (early stage or late stage) reported having to make modifications to their daily lives because of ADPKD.

1. Sanon et al. Patient Voice in Autosomal Dominant Polycystic Kidney Disease (ADPKD): Findings from a Large Cross-sectional Survey in the United States. Poster presented at National Kidney Foundation Spring Clinical Meeting; 2019 May 08-12; Boston, MA.

How Does Autosomal Dominant Polycystic Kidney Disease (ADPKD) Affect Your Ability to Work?





CKD=chronic kidney disease

1. Sanon et al. Work Productivity Loss in Patients with ADPKD: Findings from a Large Cross-sectional Survey in the United States. Poster presented at National Kidney Foundation Spring Clinical Meeting; 2019 May 08-12; Boston, MA.

Summary

- **Understanding the main job of your kidneys and what can happen to your kidneys during PKD**
  - The main job of your kidneys is to clean your blood
  - There are two main types of PKD: Autosomal Dominant (ADPKD) and Autosomal Recessive (ARPKD) both types cause multiple cysts to form and grow within a person's kidneys
  - If you have PKD, there is a good chance you will need dialysis or a kidney transplant at some point in your life
- **Screening/Diagnosis and progression of disease**
  - Typically, an ultrasound is used to diagnose ADPKD, but sometimes genetic testing may be performed
  - Everyone's PKD is different. There are many things that can affect how quickly your kidneys will reach the point of failure.
- **How ADPKD affects your body**
  - Remember, even when there are no symptoms, PKD is still damaging your kidneys
  - Physical burden, emotional burden, reduced quality of life
- **Your ADPKD Healthcare Team**
  - ADPKD is a complex condition. That's why you may have a variety of healthcare providers in your treatment team, including: Nephrologist, PCP, Nutritionist, Nurse, Cardiologist, Urologist, Pharmacist
  - It's important to take steps to manage the disease early. Doing so may help you manage some of the complications that occur as the disease gets worse

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Understanding Polycystic Kidney Disease:
An Overview of PKD