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# Women's Health in Polycystic Kidney Disease (PKD) - A Focus on Pregnancy & Family Planning



August 2024 US.CORP.D.24.00031

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Improving Awareness & Patient Outcomes

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# Presenters

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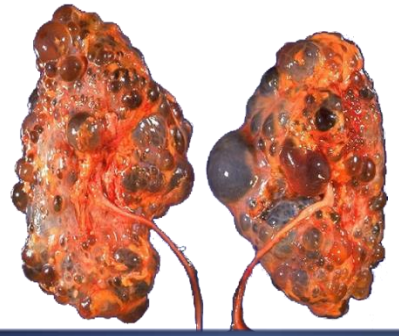
Otsuka Pharmaceutical Development & Commercialization, Inc.

# Objectives

1. Provide an overview of autosomal dominant polycystic kidney disease (ADPKD) epidemiology and disease burden
2. Explain how ADPKD affects pregnancy and family planning, and how pregnancy influences the progression of the disease including long-term outcomes
3. Discuss the risks of fetal and maternal complications
4. Outline general management principles for pregnancy in the setting of ADPKD
5. Review options and resources in relation to family planning

# What Is PKD?

## Polycystic kidney disease (PKD) is a group of monogenic disorders characterized by the propensity to develop numerous renal cysts[1]



- **Syndromic forms**[1,2] → **Rare, recessively inherited**
- **Autosomal dominant (ADPKD)**[3,4]
  - ***PKD1/PKD2*** **(~91%)**
  - ***NMD**** **(~9%)**
- **Autosomal recessive (ARPKD)**[1] → ***PKHD1***

*The "no mutation detected" (NMD) group may contain those patients with mutations in other genes impacting cystic development, such as GANAB.[5]

ADPKD=autosomal dominant PKD; ARPKD=autosomal recessive PKD; GANAB=gene encoding glucosidase II subunit-α; NMD=no mutation detected; PKD=polycystic kidney disease; PKHD1=polycystic kidney and hepatic disease


1. Harris PC and Torres VE. (2009). Annu Rev Med. 60:321-337.
2. Jauregui AR et al. (2005). Exp Cell Res. 305(2):333-342.
3. Heyer CM et al. (2016). J Am Soc Nephrol. 27(9):2872-2884.
4. Irazabal MV et al. (2017). Nephrol Dial Transplant. 32(11):1857-1865.
5. Lanktree MB, Chapman AB. (2017). Nat Rev Nephrol. 13(12):750-768.

# ADPKD Is the Most Common Life-threatening Inherited Renal Disease

## ADPKD does not discriminate on sex, race, ethnicity, or geography[1,2]

- ADPKD affects both sexes equally, and occurs in all ethnicities[3]
- ADPKD is the most common life-threatening inherited renal disease and accounts for up to ~5% of all patients with ESRD[2]
- ADPKD is the fourth leading cause of ESRD in the United States after diabetes, hypertension, and glomerulonephritis[2]
- As many as 1:2000 people worldwide are currently diagnosed with ADPKD,4 and between 1:400 and 1:1000* people living today will be diagnosed with ADPKD in their lifetime[1]

*The higher prevalence value of 1:1000 is believed to be inaccurate because the data are based on a postmortem study and therefore report lifetime morbid risk rather than point prevalence.

ADPKD=autosomal dominant polycystic kidney disease; ESRD=end-stage renal disease.


1. Torres VE, Harris PC. (2009). Kidney Int. 76(2):149-168.
2. United States Renal Data System. 2016 USRDS Annual Data Report Volume 2: ESRD in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2016 (accessed 14 February 2019).
3. Chebib FT, Torres VE. (2016). Am J Kidney Dis. 67(5):792-810.
4. Willey C. DRAFT: The Descriptive Epidemiology of ADPKD in the U.S. 2017.

# ADPKD Is Inherited as an Autosomal Dominant Trait

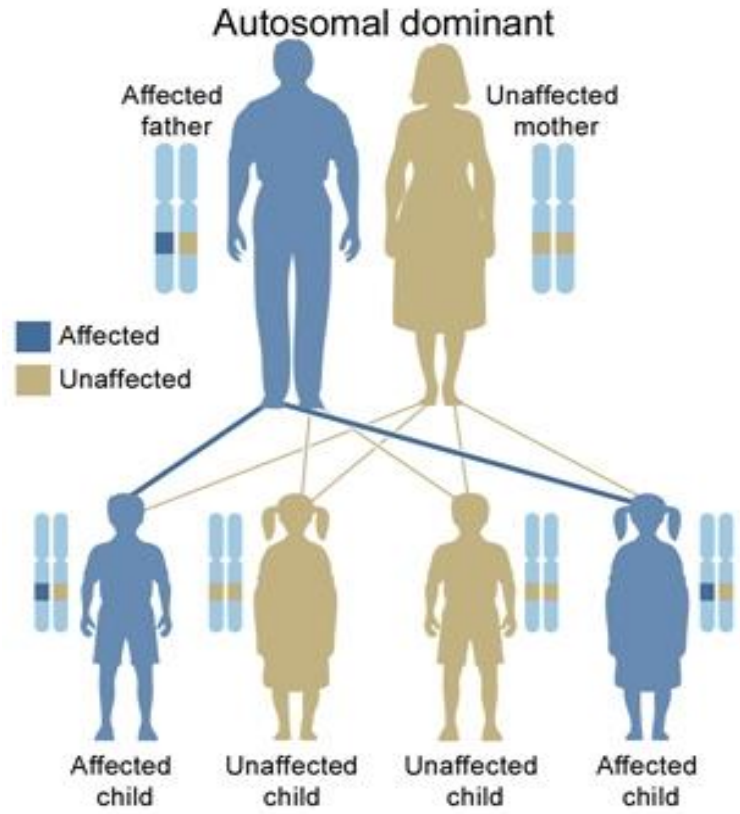



Figure adapted from U.S. National Library of Medicine

Inheritance pattern of autosomal dominant disease[5]

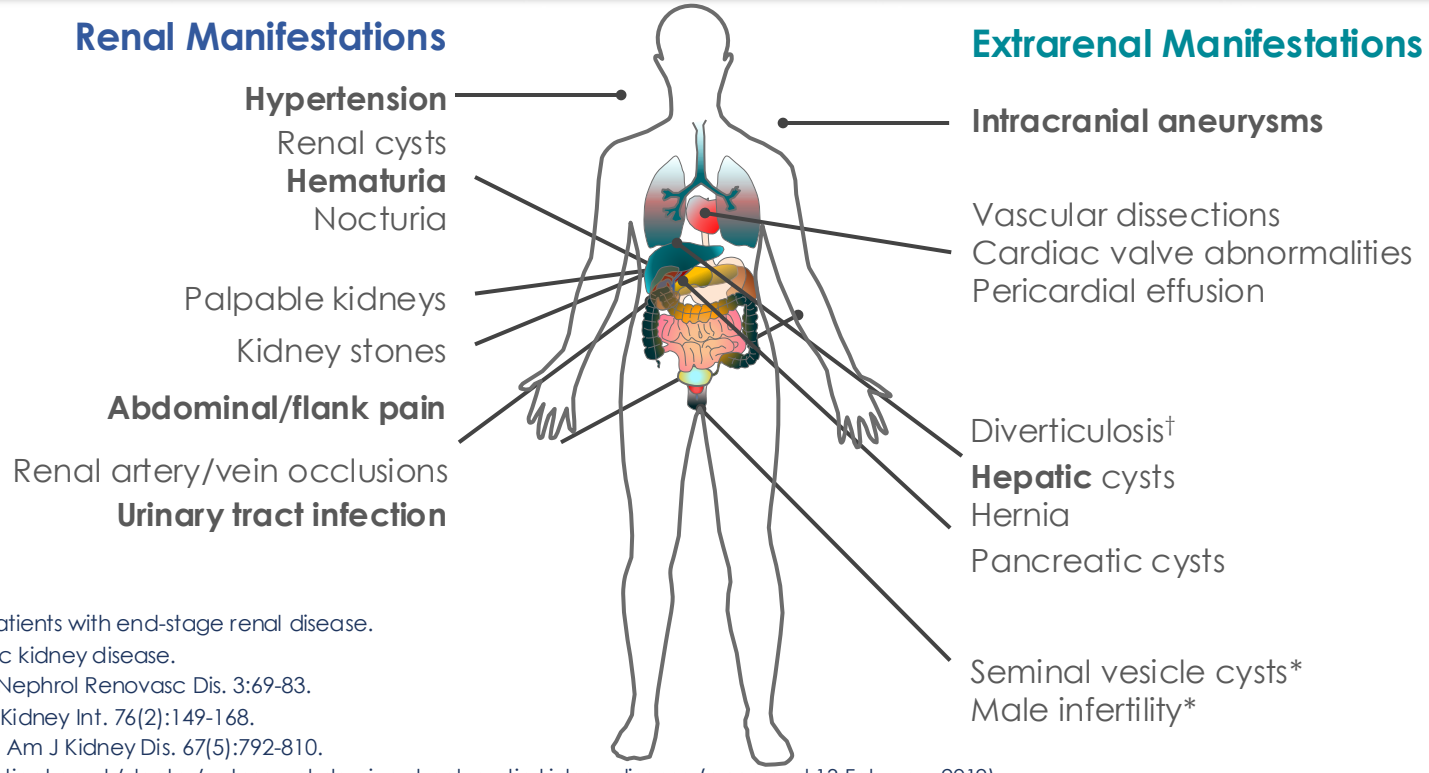
- ADPKD is an autosomal dominant disease with a high degree of penetrance[1]
- A child of an affected parent has a 50% chance of inheriting ADPKD[1]
- In 5% to 10% of cases, ADPKD is caused by a de novo mutation[2,3]
  - In ~10% of newly diagnosed cases, patients report a negative family history[3]
- Disease progression can be highly variable, even among family members with the same mutation[3]
  - Variability suggests a "two-hit" model for ADPKD, in which germ-line and somatic inactivation of both copies of a PKD gene lead to cystogenesis[4]

ADPKD=autosomal dominant polycystic kidney disease.

1. Harris PC, Rossetti S. (2010). *Nat Rev Nephrol.* 6(4):197-206.
2. Grantham JJ. (2009). *Ann TrKidneyansplant.* 14:86-90.
3. Reed B et al. (2008). *Am J Dis.* 52(6):1042-1050.
4. Pei Y et al. (1999). *J Am Soc Nephrol.* 10(7):1524-1529.
5. ADPKD. PKD International. http://www.pkdinternational.org/what-is-pkd/ (accessed 13 February 2019).

# ADPKD Is a Systemic Disease with Multiple Renal and Extrarenal Manifestations

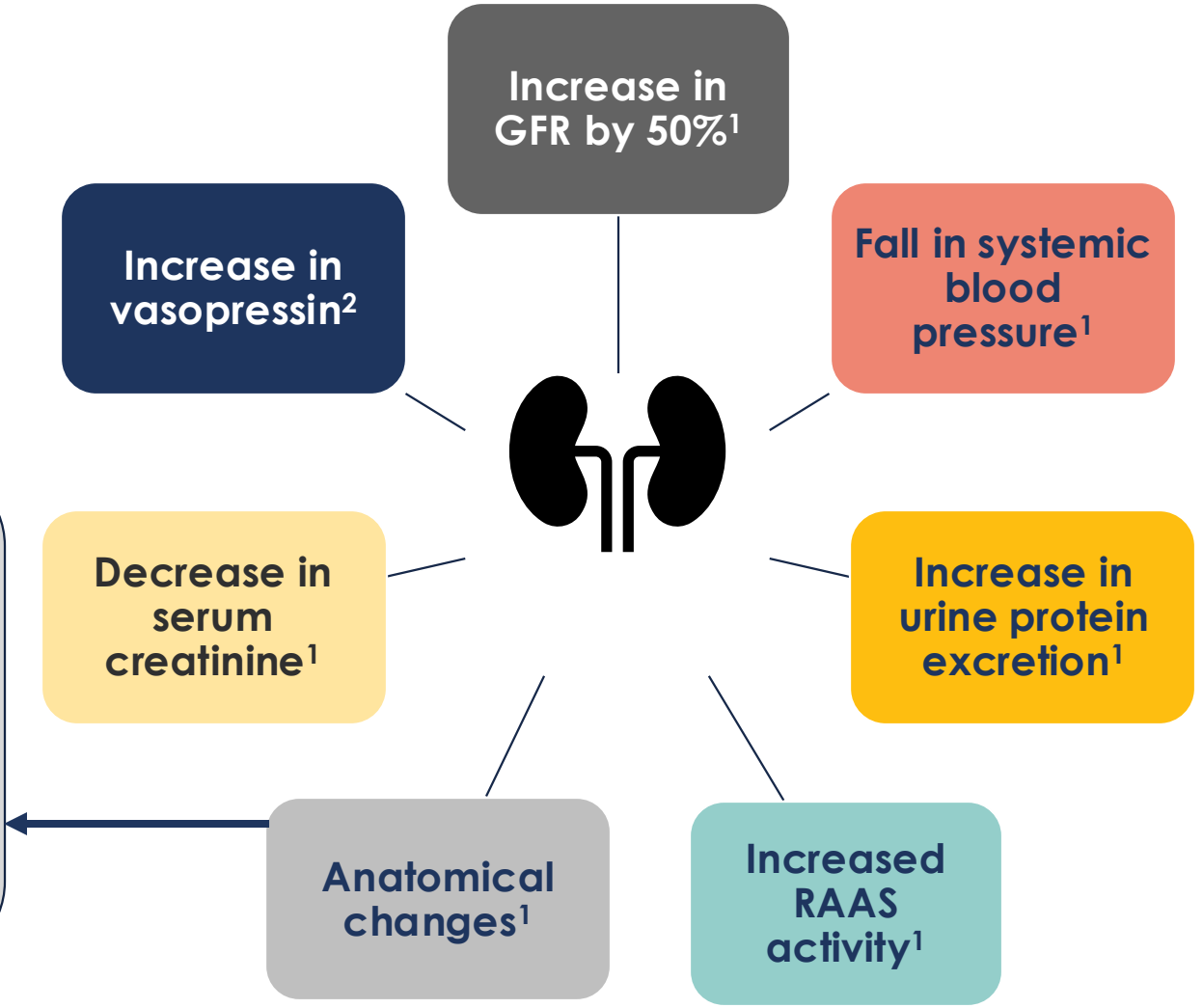
**Renal cysts are the first manifestation of ADPKD and precede changes in kidney function by many years[1–8]**




*In male patients. †Most common in patients with end-stage renal disease.
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. Renal Cystic Disorders. In: Wilcox CS et al. eds. Therapy in Nephrology & Hypertension. 3rd ed. Philadelphia, PA: Saunders; 2008.
8. Chauveau D et al. (1994) Kidney Int. 45:1140-1146.

# Several Anatomical and Physiological Changes Occur in the Kidneys During Pregnancy



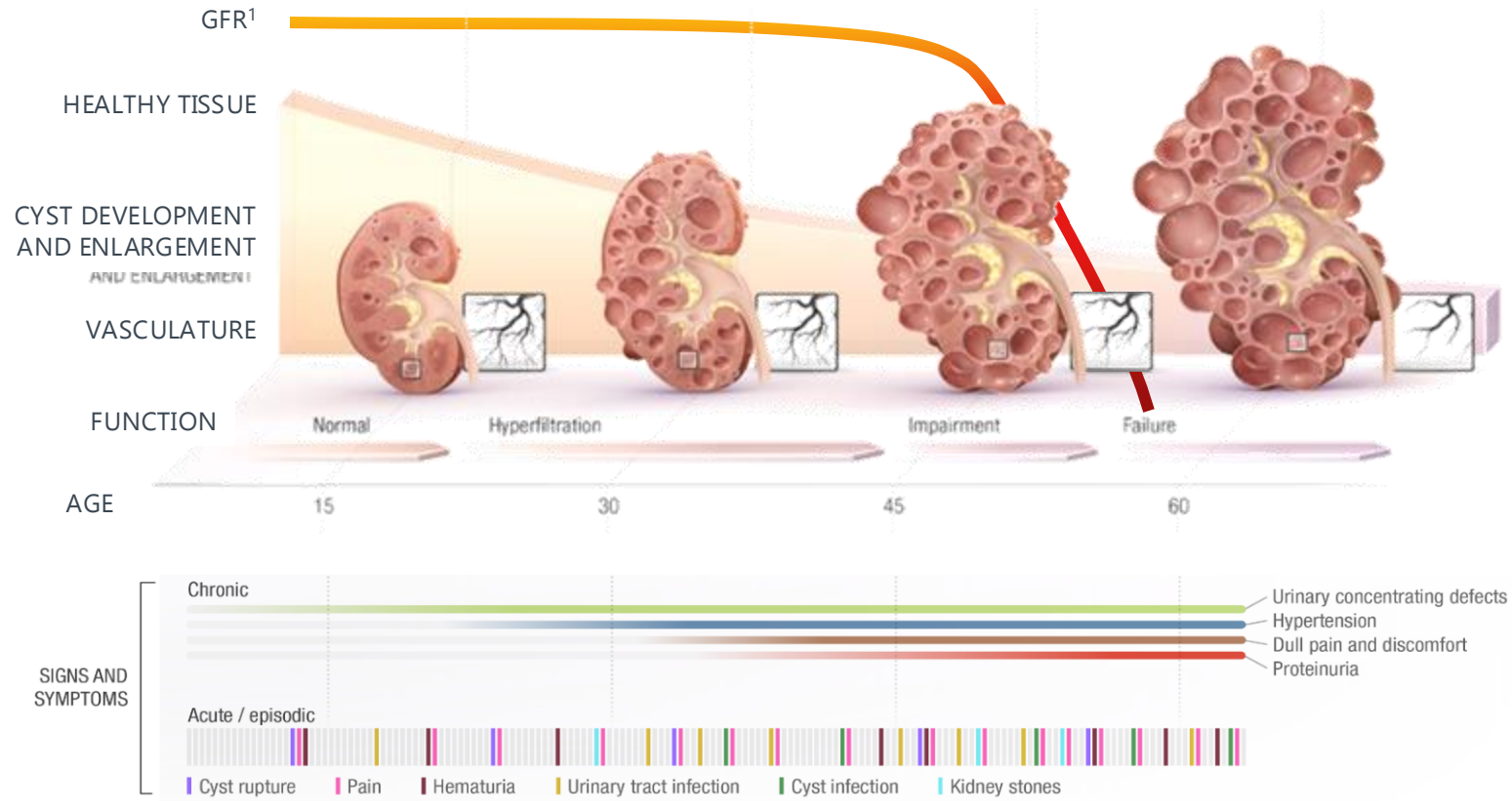

- Increase in kidney size[1]
- Collecting system dilation[4]
- Increase in ureter lengths[4]
- Vascular smooth muscle relaxation[4]
- Hydronephrosis[1,4]
- Urinary stasis[4]
- Pyelonephritis[4]

**Women with ADPKD may have earlier-stage CKD during pregnancy with hypertension, proteinuria, and mild renal impairment[3]**


1. Cerra Z, Krishnan A. (2023). KI Reports.
2. Sayyab MA and Chapman A. (2023). 30(5):454-460.
3. McBride L et al. (2020). Int J Women's Health. 12:409-422.
4. Cheung KL, Lafayette RA. (2013). 20(3):209-214.

# ADPKD Patients Experience a Significant Cyst Burden and Complications

## Kidney Disease Progression in ADPKD[1]






**However, there are no studies evaluating the impact of pregnancy on the progression of total kidney volume and renal outcomes among ADPKD patients[2]**

ADPKD=autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate.

1. Grantham JJ et al. (2011). *Nat Rev Nephrol*. 7(10):556-566.
2. Paek, J, et al. (2022). JASN. 33(11S).

# Does ADPKD Affect Pregnancy?

- All chronic kidney diseases, including ADPKD, are known to be associated with higher risk pregnancies, particularly preeclampsia and prematurity[1]

**However, most women with PKD (80%) have successful and uneventful pregnancies**

- Women with ADPKD **and reduced kidney function** are more likely to have complications during pregnancy compared to women with normal or only mildly impaired renal function[1]
- There is no evidence of impaired female fertility in ADPKD if renal function is normal[1]


1. McBride L, Wilkinson C, Jesudason S. Management of Autosomal Dominant Polycystic Kidney Disease (ADPKD) During Pregnancy: Risks and Challenges. Int J Womens Health. 2020;12:409-422.
2. Polycystic Kidney Disease. https://www.kidney.org/atoz/content/polycystic. National Kidney Foundation. Accessed July 10, 2024.

# ADPKD is Associated with Increased Risk of Maternal Complications

- Hypertension[1,2]
- Acute and Chronic Pain[2]
- Urinary Tract Infection[1]
- Edema[1]
- Preeclampsia[1,2]
- Proteinuria[1]
- Loss of Renal function[1]
- Extra-renal Manifestations[2]


1. Wu M, Wang D, Zand L, et al. Pregnancy outcomes in autosomal dominant polycystic kidney disease: a case-control study. J Matern Fetal Neonatal Med. 2016;29(5):807-812.
2. McBride L, Wilkinson C, Jesudason S. Management of Autosomal Dominant Polycystic Kidney Disease (ADPKD) During Pregnancy: Risks and Challenges. Int J Womens Health. 2020;12:409-422

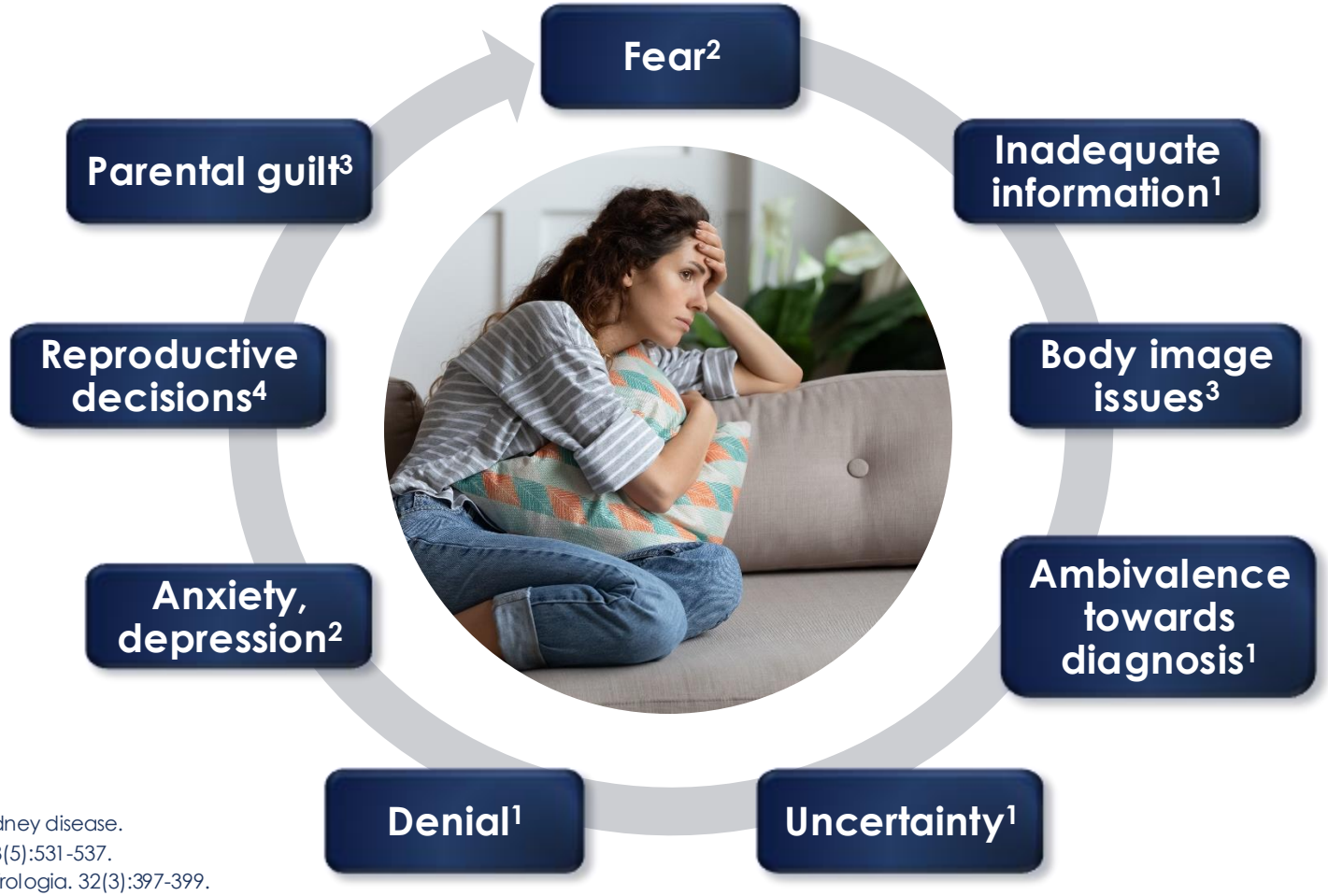
# ADPKD is Associated with Only a Slight Increase In the Risk for Fetal Complications

**Overall, fetal complication rates are similar between women with ADPKD and women without ADPKD[1]**

- Rates of spontaneous abortion and premature birth are comparable[1]
- Fetal complications are more common in ADPKD women ≥ 30 years[1]
- Increased fetal prematurity rates are found in those who develop preeclampsia[1]
- Rates of fetal distress and labor induction for post-term dates are higher in ADPKD pregnancies[1]

1. Wu M, Wang D, Zand L, et al. *J Matern Fetal Neonatal Med*. 2016;29(5):807-812.

# Patients with ADPKD Can Experience a Significant Emotional Burden




ADPKD=autosomal dominant polycystic kidney disease.


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.
3. Sanon Aigbogun M, Oberdhan D, Doane MJ, Rooney J, Inyart BC, Pao CS, Denny AH. Disconnect in Assessments of Autosomal Dominant Polycystic Kidney Disease Burden Between Patients and Physicians: A Survey Study. Int J Nephrol Renovasc Dis. 2021 Apr 13;14:105-115.
4. Sayyab MA and Chapman A. Pregnancy in Autosomal Dominant Polycystic Kidney Disease. Advances in Kidney Disease and Health. VOLUME 30, ISSUE 5, P454-460, SEPTEMBER 2023.

# General Management for Pregnancy in Women with ADPKD[1]

## Pre-Pregnancy

- Timing (i.e. age and fertility)
- Contraception, tubal ligation if not considering pregnancy
- Genetic counseling and considerations of pre-implantation genetic diagnosis (PGD)
- Routine ADPKD management
- Risk stratification
- Consider extra-renal disease screening

## During Pregnancy

- Cease taking ACE Inhibitors and ARBs
- Initiate/continue low-dose aspirin
- Initiate/continue folic acid and iodine

- **Maternal Surveillance**
  - BP, renal function, proteinuria
  - Screen for bacteruria each trimester, treat UTI
  - Consider extra-renal disease

- **Fetal Surveillance**
  - Routine 1st and 2nd trimester screening
  - 3rd trimester fetal growth scan and dopplers

## Post-Pregnancy

- Lactation considerations
- BP management
- Return care to usual providers
- Future pregnancy planning

1. McBride L, Wilkinson C, Jesudason S. Management of Autosomal Dominant Polycystic Kidney Disease (ADPKD) During Pregnancy: Risks and Challenges. Int J Womens Health. 2020;12:409-422.

# Lifestyle Management for ADPKD – Applications in Pregnancy

Blood Pressure < 110/75 mmHg[1]

Decrease salt intake (2.3-3g/day) [1]

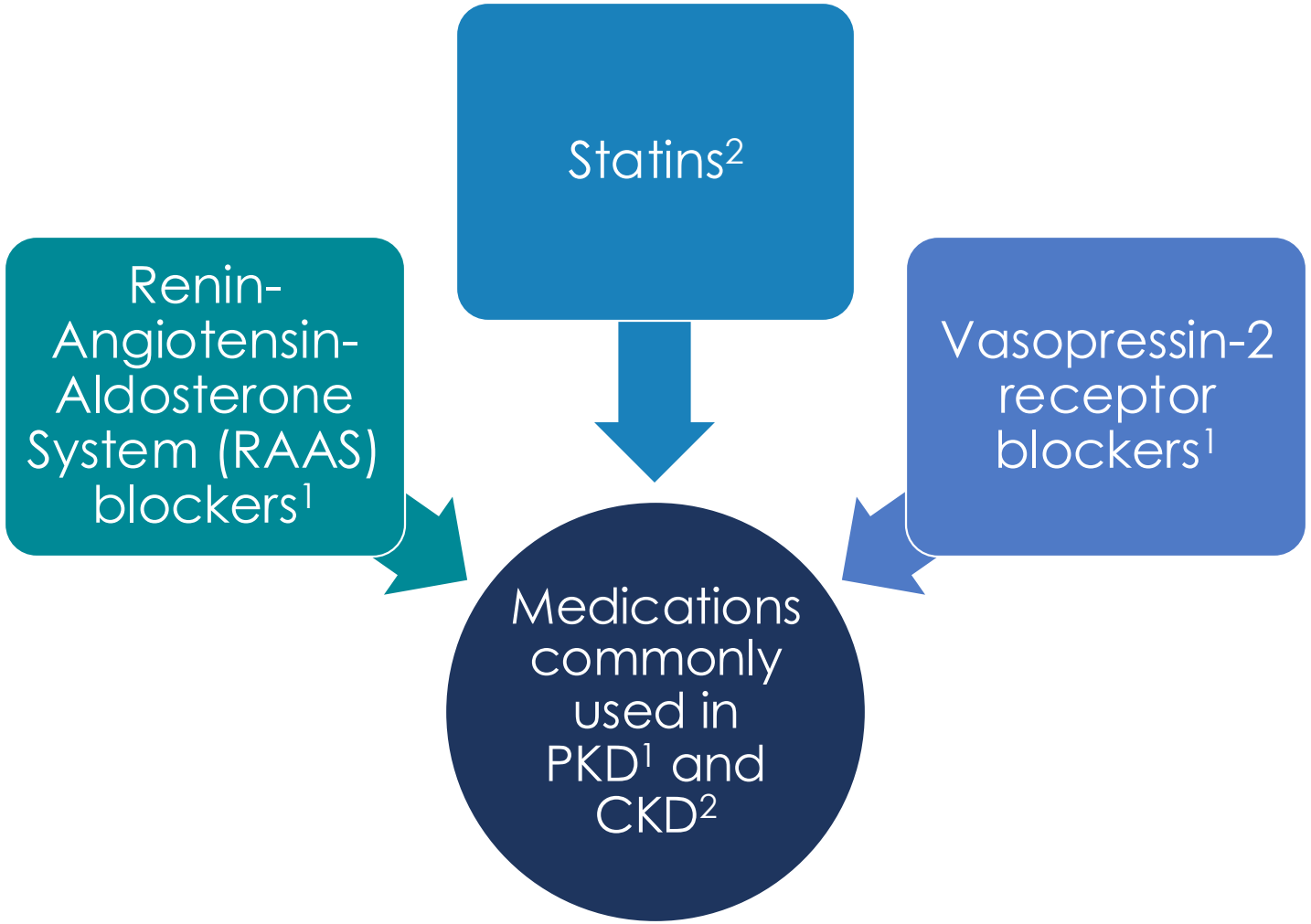
Increased water intake (about 2-3 L urine volume/day) [1]

Avoid excessive caffeine intake[1]

1. Nobakht, Niloofar & Pirzadeh, Afshin & Dolatshahi Pirooz, Amir & Kamgar, Mohammad. (2023). A Young Man with Polycystic Kidneys' Journey to End Stage Kidney Failure.

# Medications Commonly Used in the Management of PKD May Not Be Suitable in Pregnancy

- Medications commonly used in the management of PKD may not be suitable for use in pregnancy[1]
- Timing of medication use (i.e conception, pregnancy, post-partum) and alternative drug class considerations should be discussed[1,3]

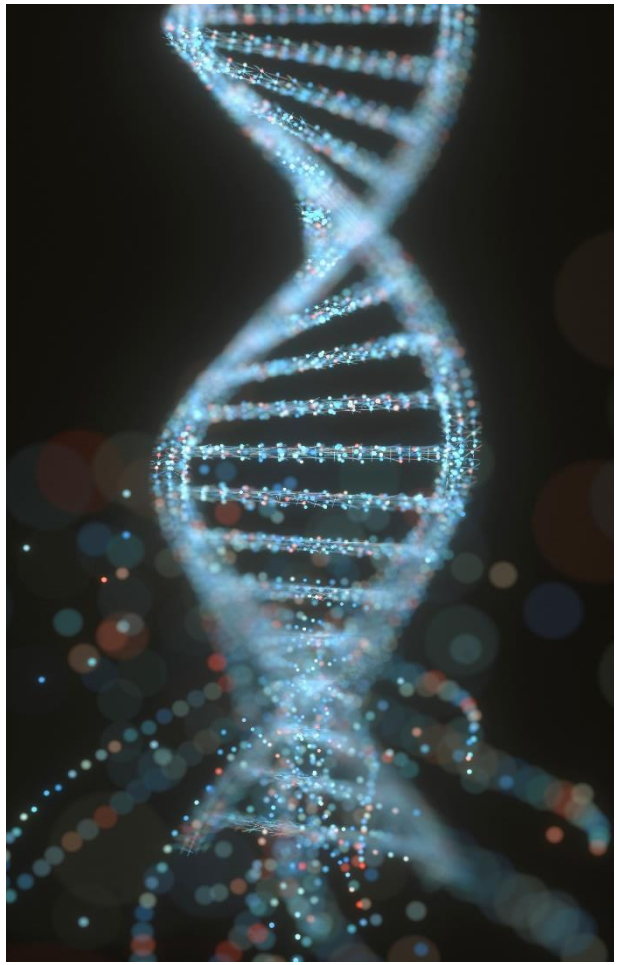



[a]ACEi = angiotensin converting enyme inhibitor. [b]ARB = angiotensin receptor blocker


1. McBride L, Wilkinson C, Jesudason S. Management of Autosomal Dominant Polycystic Kidney Disease (ADPKD) During Pregnancy: Risks and Challenges. Int J Womens Health. 2020;12:409-422
2. Kovell L. Lipid Management Guidelines for Adults with Chronic Kidney Disease 2016.
3. Pregnancy and medicines. Womenshealth.gov

# Indications for Genetic Testing in ADPKD Include Prenatal or Pre-implantation Diagnostics

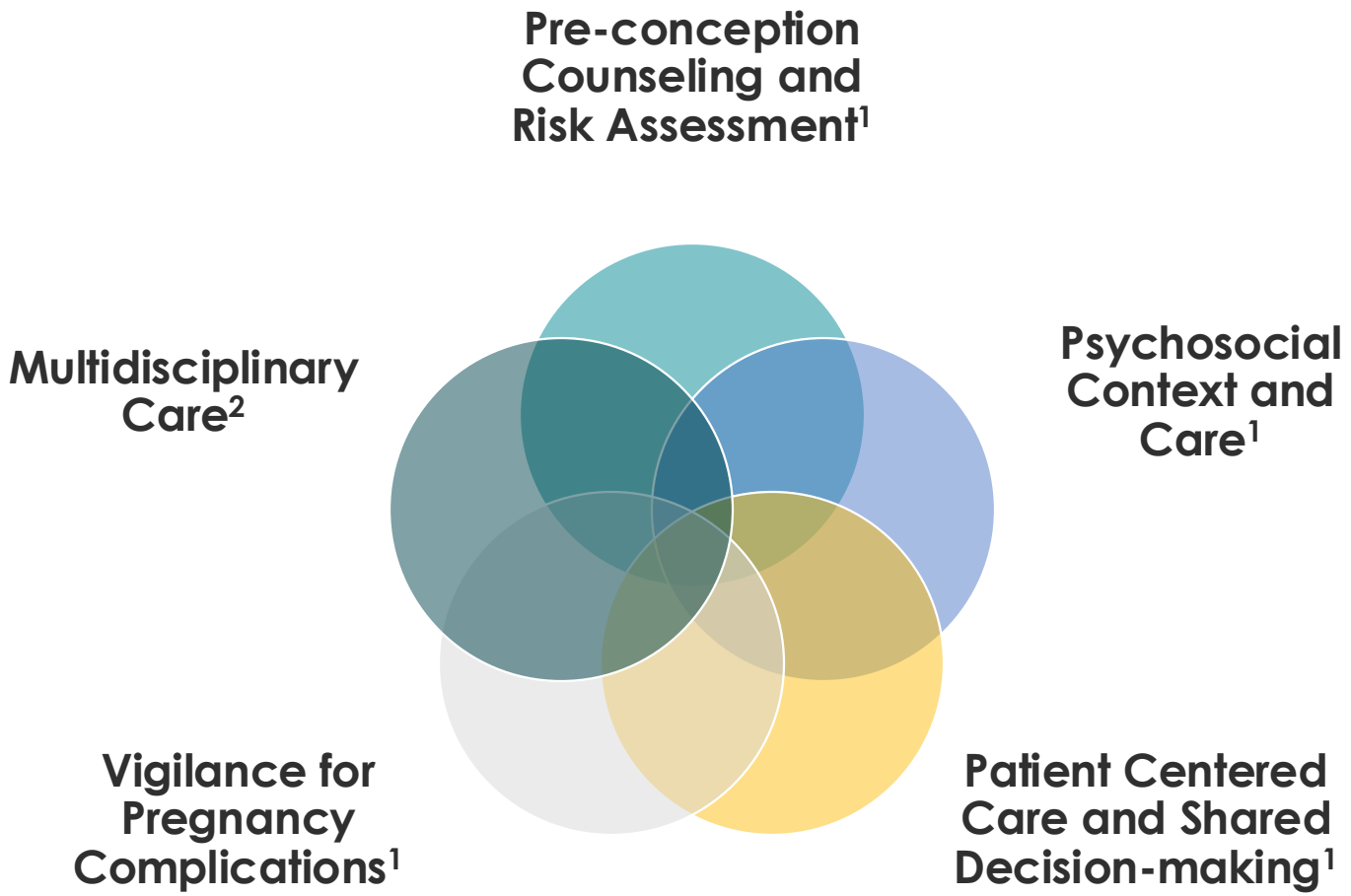
| Indications for Genetic Testing in ADPKD[1] |
|---|
| **Highest impact for clinical genetic testing** |
| Cases where there is doubt regarding diagnosis<br>• *Example*: lack of family history or equivocal imaging findings |
| Cases with high stakes for accurate disease exclusion at an early age<br>• *Examples*: prenatal or preimplantation diagnostics, kidney donation evaluation |
| **Cases in which genetic testing may be appropriate** |
| Risk stratification for initiating disease-modifying therapies |
| Explaining atypical presentations<br>• *Examples*: early and severe disease or discrepancies between imaging findings and decrease in renal function |



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. (2018). *Nephrol Dial Transplant*. Aug 27. doi: 10.1093/ndt/gfy261. [Epub ahead of print].

# Patient Perspectives and Shared Decision-Making in Pregnancy Counselling





1. McBride L, Wilkinson C, Jesudason S. Management of Autosomal Dominant Polycystic Kidney Disease (ADPKD) During Pregnancy: Risks and Challenges. Int JWomens Health. 2020;12:409-422.
2. Sayyab MA and Chapman A. Pregnancy in Autosomal Dominant Polycystic Kidney Disease. Advances in Kidney Disease and Health. VOLUME 30, ISSUE 5, P454-460, SEPTEMBER 2023.

# Resources for ADPKD and Family Planning

PKD FOUNDATION
Polycystic kidney disease

**pkdcure.org/**

- Blog post about choices
- Videos on ADPKD and Pregnancy Considerations and Family Planning and Achieving Reproduction Success

NATIONAL KIDNEY FOUNDATION®

**Kidney.org**


1. https://pkdcure.org/living-with-pkd/pregnancy-and-pkd/
2. https://www.kidney.org/communities

# Summary

1. ADPKD is a progressive, genetic renal disease where numerous cysts form on the kidneys -- causing kidney enlargement, kidney damage, and eventually kidney failure
2. Due to its autosomal dominant genetic pattern of inheritance, ADPKD affects pregnancy and family planning decisions.
3. Several anatomical and physiological changes that occur during pregnancy may affect ADPKD disease progression
4. ADPKD poses only a slight potential of increased rates of fetal complications.
5. Increased maternal complications include hypertension, preeclampsia, and decreased renal function
6. General management principles for women with ADPKD who are considering pregnancy involve informed, shared decision making and inclusion of a multidisciplinary care team
7. Options and resources for families with ADPKD planning to become pregnant include genetic testing and counseling, as well as support from community and nephrology advocacy groups

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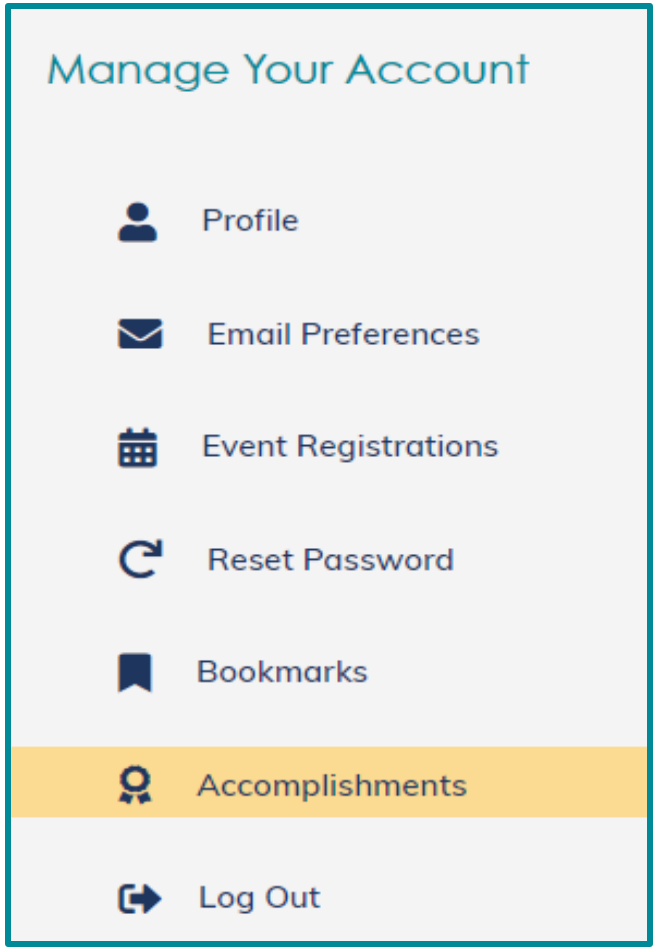


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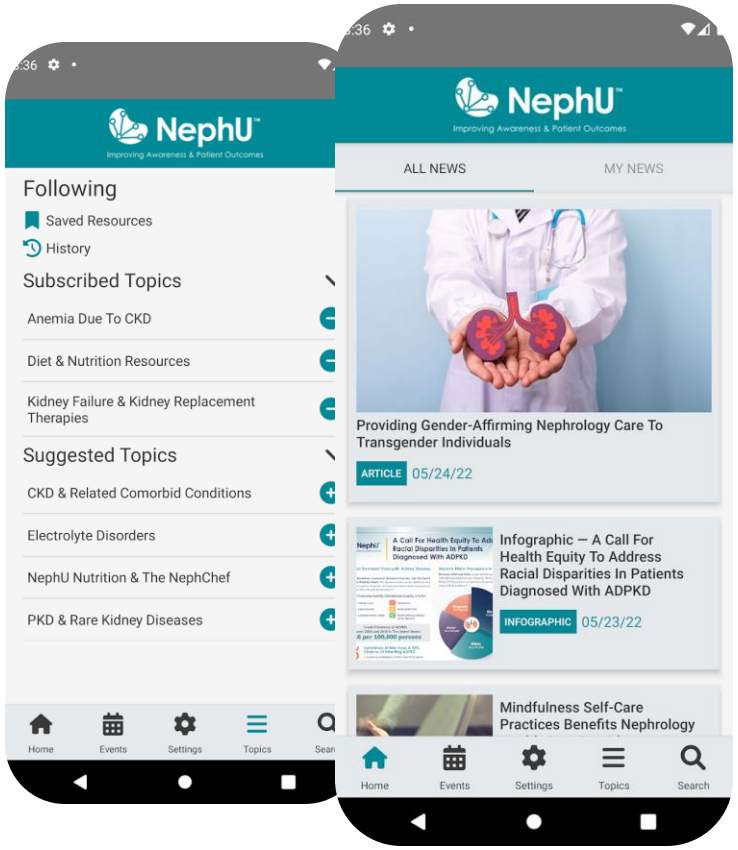


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