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Genetic Testing in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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This program is paid for by Otsuka Pharmaceutical Development & Commercialization, Inc.

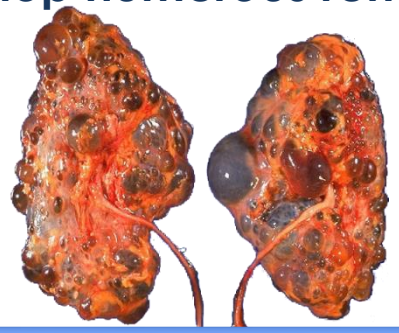
Speakers are employees and/or paid consultants for Otsuka Pharmaceutical Development & Commercialization, Inc.

Objectives

- Overview of ADPKD
  - *PKD1 and PKD2* gene structure
  - Additional genes implicated in ADPKD
- Understand when genetic testing is indicated and is most appropriate in ADPKD
  - Limitations of the information
- Understand the different types of molecular genetic tests available
  - Commercially available options
- Understand the information provided within a clinical genetics report
- Interpret genetic sequencing results
  - Focus on VUS findings
- Role of genetic counseling
- Key takeaways

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.

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 Inherited as an Autosomal Dominant Trait

Inheritance pattern of autosomal dominant disease[5]

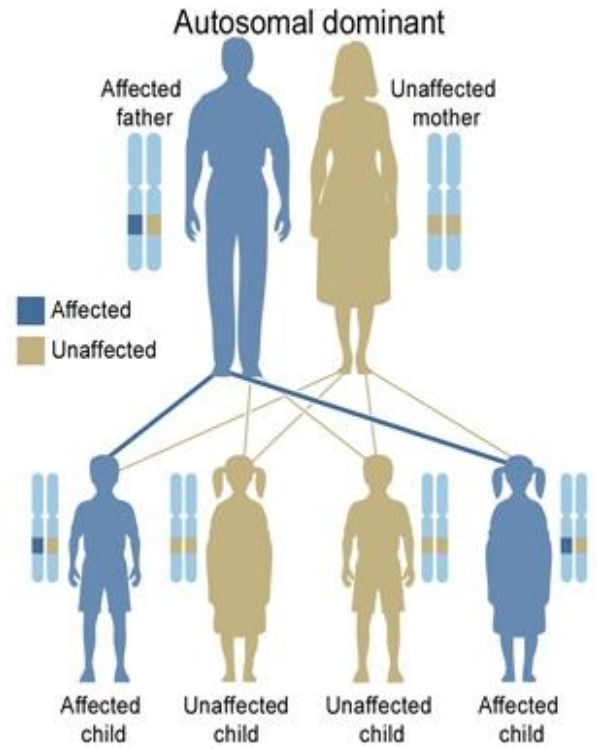


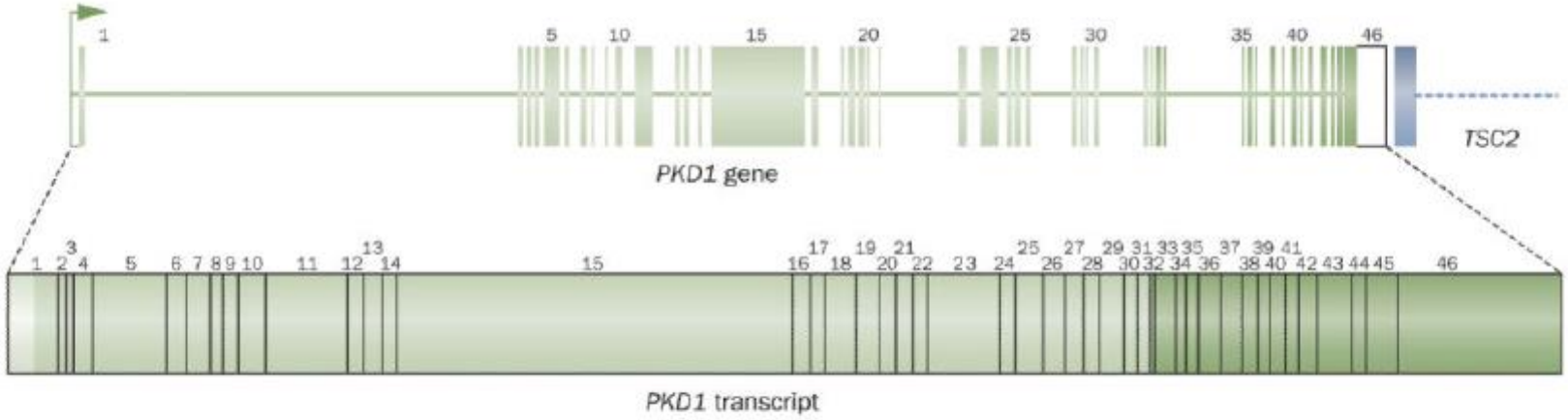
Figure adapted from U.S. National Library of Medicine

- 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 Transplant.* 14:86-90. 3. Reed B et al. (2008). *Am J Kidney 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).

Genomic structure of *PKD1*



PKD1 – 16p13.3

Spans a genomic region of 52kb

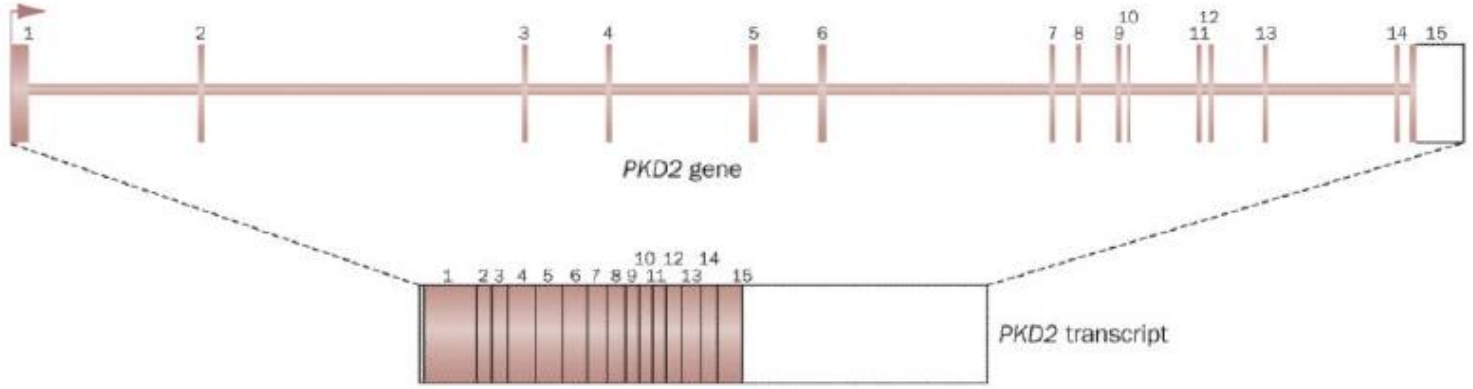
mRNA – 14kb

46 exons

6 pseudogenes – highly homologous to 5’ portion on chr16 (exon 1-33) 99% identity

1. Harris PC, Rossetti S. (2010) Nat Rev Nephrol. Apr;6(4):197-206.

Genomic structure of *PKD2*



PKD2 – 4q21

Spans a genomic region of 68kb

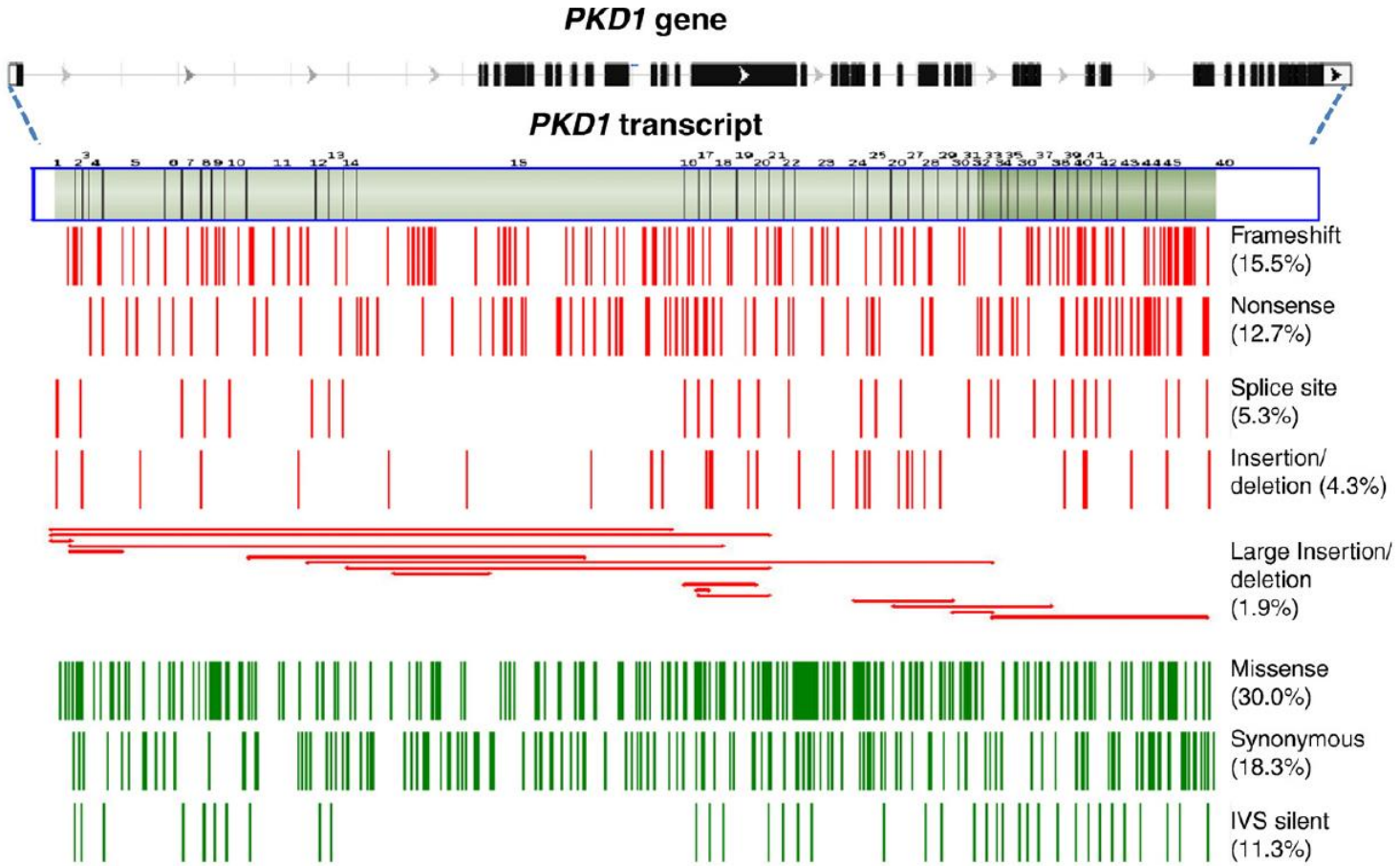
mRNA – 2.9kb

15 exons

No known pseudogenes

1. Harris PC, Rossetti S. (2010) Nat Rev Nephrol. Apr;6(4):197-206.

Disease causing mutations identified in *PKD1*



- ADPKD: high level of allelic heterogeneity – Polymorphism in *PKD1*
- Pseudogenes & High GC content - Locus specific amplification is required
- Any single fully inactivating variant to *PKD1* or *PKD2* causes ADPKD
- No single pathogenic variant accounts for >2% of families
- >1650 PKD1 pathogenic variants described in the PKDF ADPKD Variant Database

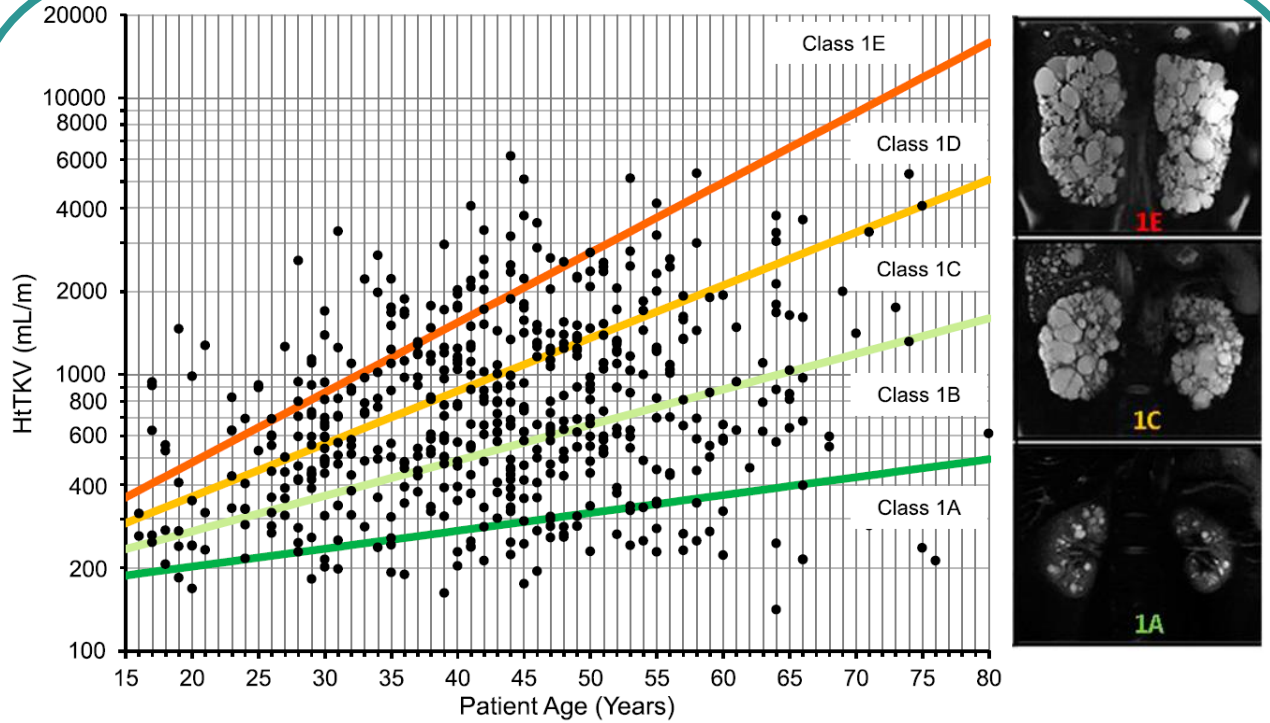
1. Ying-Cai Tan et al. (2011),Biochimica et Biophysica Acta (BBA) 1812, 10, 1202-1212

Additional genes which cause ADPKD

- ***GANAB*** – Identified as a causal gene in 2016 by WES. Encodes the Glucosidase IIα Subunit. Causes ADPKD and ADPLD.[1]
- ***DNAJB11*** – Identified as a causal gene in 2018 by WES. DNAJB11 is a co-factor of BiP, a key chaperone in the endoplasmic reticulum controlling folding, trafficking, and degradation of secreted and membrane proteins. DNAJB11-associated disease is a phenotypic hybrid of ADPKD and ADTKD, characterized by normal-sized cystic kidneys and progressive interstitial fibrosis resulting in late-onset ESRD.[2]
- ***ALG9*** – Identified as a causal gene in 2019 by WES. Kidney and liver cysts.[3]
- ***IFT140*** – Identified as a causal gene in 2022 by WES. IFT140 is a core component of the intraflagellar transport-complex A, responsible for retrograde ciliary trafficking and ciliary entry of membrane proteins. The distinctive monoallelic phenotype is mild PKD with large cysts, limited kidney insufficiency, and few liver cysts. The proximity of IFT140 to PKD1 (~0.5 Mb) in 16p13.3 can cause diagnostic confusion, and *PKD1* variants could modify the IFT140 phenotype.[4]

1. Porath B, et al.(2016) *Am J Hum Genet*. Jun 2;98(6):1193-1207.
2. Cornec-Le Gall E, et al. (2018) *Am J Hum Genet*.102(5):832-844.
3. Besse W, et al. (2019) *J Am Soc Nephrol*. 30(11):2091-2102.
4. Senum SR, et al. (2022) *Am J Hum Genet*.;109(1):136-156.

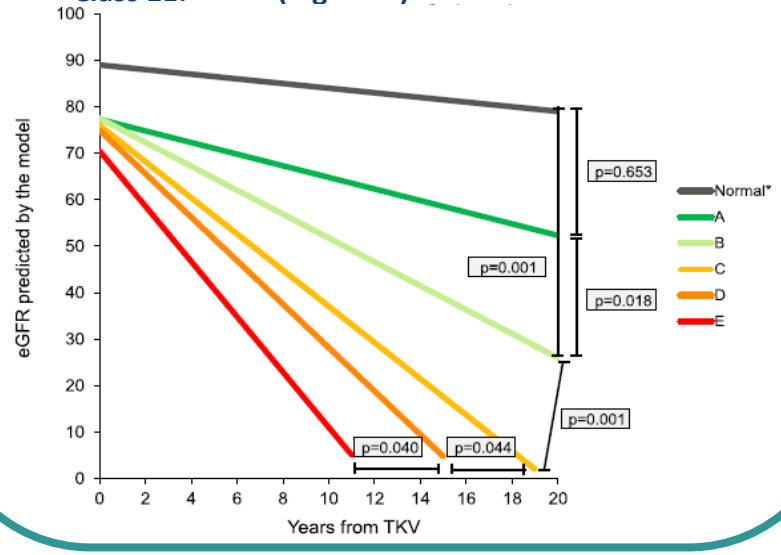
Baseline htTKV predicts risk of kidney function decline



Magnetic resonance images correspond to three 41-year-old patients with various kidney sizes. Top image corresponds to Class 1E, middle image corresponds to Class 1C, and the bottom image corresponds to Class 1A.[1]

Expected Annual Kidney Growth & Risk Stratification

- **Class 1A: 1.5% (low risk)**
- **Class 1B: 1.5-3.0% (intermediate risk)**
- **Class 1C: 3-4.5% (high risk)**
- **Class 1D: 4.5-6% (high risk)**
- **Class 1E: >6% (high risk)**



eGFR=estimated glomerular filtration rate; htTKV=height-adjusted total kidney volume.

1. Irazabal MV et al. *J Am Soc Nephrol*. 2015; 26(1): 160–72

The PROPKD Score Enables Stratification of Risk of Progression to ESRD

PROPKD Score[1,2]	
Being male	1 point
Hypertension before 35 years of age:	2 points
First urological event (macroscopic hematuria, flank pain, or cyst infection) before 35 years of age:	2 points
PKD2 mutation:	0 points
Non truncating PKD1 mutation:	2 points
Truncating PKD1 mutation:	4 points
A score of ≤3 excludes progression to ESRD before the age of 60 years with a negative predictive value of 81.4%	
A score of >6 predicts rapid disease progression with ESRD onset before the age of 60 years with a positive predictive value of 90.9%	
For those with an intermediate score (4–6 points), the prognosis is unclear	

Sum = PROPKD Score

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

1. Cornec-Le Gall E et al. (2016). *J Am Soc Nephrol*. 27(3): 942–51.
2. Adapted from Gansevoort RT et al. (2016). *Nephrol Dial Transplant*. 31(3): 337–48.

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When is genetic testing indicated in ADPKD?

Indications for Genetic Testing in ADPKD

Clinical genetic testing in ADPKD is currently of highest impact in cases in which the diagnosis is unclear or there are high stakes for accurate disease exclusion at an early age[1]

Scenarios in which genetic testing is clinically indicated[1]

- Suspected ADPKD with no apparent familial history
- Suspected ADPKD with equivocal renal imaging findings
- ADPKD exclusion in young (< 25 years old) at-risk patients:
  - Evaluation of living related kidney donation
  - Obtaining life or disability insurance
- Prenatal and preimplantation genetic diagnosis

Evolving indications for genetic testing

- Classifying high-risk patients for clinical trials or novel disease-modifying therapy[1]
- Revealing the underlying cause of undetermined end-stage renal disease[2]
- Optimizing pre- and post-kidney transplant management[2]
- Including in clinical trials[3]
- Determining the cause of atypical clinical presentations[1]:
  - Early and severe disease
  - Inconsistencies between imaging findings and decrease in renal function
  - Asymmetric, unilateral, segmental, or lopsided cystic kidneys
  - Noticeable intrafamilial variability
  - Suspected somatic mosaicism
  - Syndromic forms of cystic kidney disease

1. Lanktree M, et al. (2019). *Kidney Int Rep*. 4:995-1003
2. Ottlewski I et al. (2019). *Kidney Int.* 96(1):222-30.
3. Cornec-Le Gall et al. (2018). *Am J Kidney Dis*. 72(2):302-308

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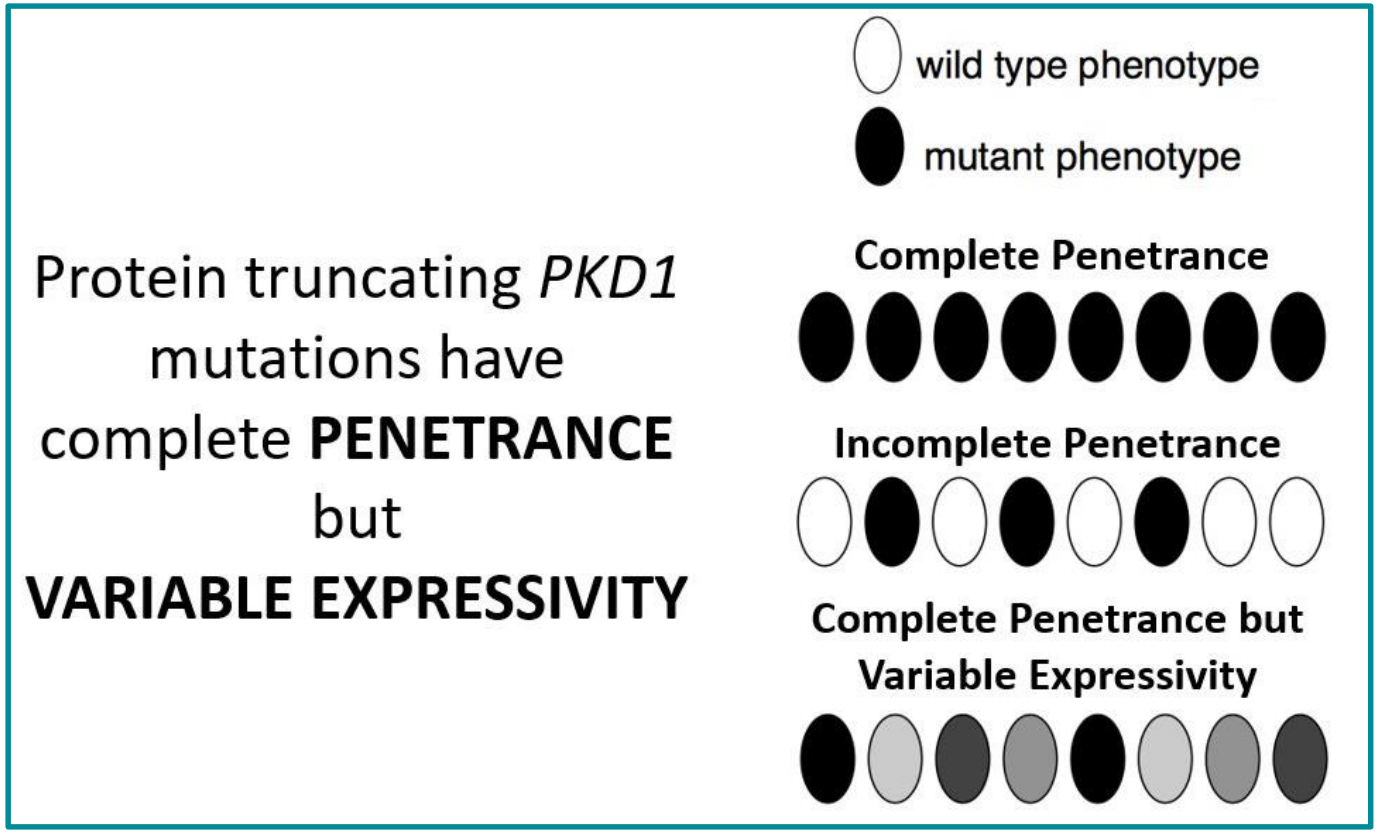
What are some of the limitations of ordering a genetic test in a patient with suspected ADPKD?

Limitations of Genetic Information [in ADPKD]

- While mutation type is accurate at a population level, it can lack accuracy at an individual level[1]
- Mutation type lacks individual prognostic value
- 10-15% of cases have no identifiable *PKD1* or *PKD2* mutation[2]



Lanktree MB et al. *Clin J Am Soc Nephrol*. 2021;16(3):374-383. Adapted from Twitter feed by Matthew Lanktree

1. Chebib F, et al. (2021). *Am J Kidney Dis*. 78(2):282-292
2. Lanktree M, et al. (2019). *Kidney Int Rep*. 4:995-1003

Limitations of Genetic Information [in ADPKD]

- 10-15% of cases have no identifiable *PKD1* or *PKD2* mutation[1]
- Toronto Genetic Epidemiologic Study of Polycystic Kidney Disease[2]
  - 570 (41%) patients in the study cohort had protein-truncating *PKD1* mutations
  - Median follow-up of patients with kidney volume imaging was 2.1 years

18%
of patients with protein-truncating *PKD1* mutations had mild disease based on clinical and imaging assessment

- Classes 1A and 1B were used as a proxy to define mild disease

Mild Kidney disease is not a rare phenotype associated with protein-truncating *PKD1* mutation

Among those with protein-truncating *PKD1* mutations

9% did not require KRT until age >65 y

5% had CKD stages 2–4 at age ≥60 y

On average, protein-truncating *PKD1* mutations are associated with severe ADPKD; however, the data indicate that mutation class alone cannot be used to predict disease severity in individual patients with complete certainty

1. Lanktree M, et al. (2019). *Kidney Int Rep*. 4:995-1003
2. Lanktree MB et al. *Clin J Am Soc Nephrol*. 2021;16(3):374-383.

To Test… or Not to Test?

- Experts recommend diagnosis by imaging criteria[1]
  - Role for genetic testing in certain situations
- Genetic testing alone lacks *individual* prognostic value[1]
  - Imaging incorporates effect of not just germline mutation but also additional "hits" that may alter individual patient's disease

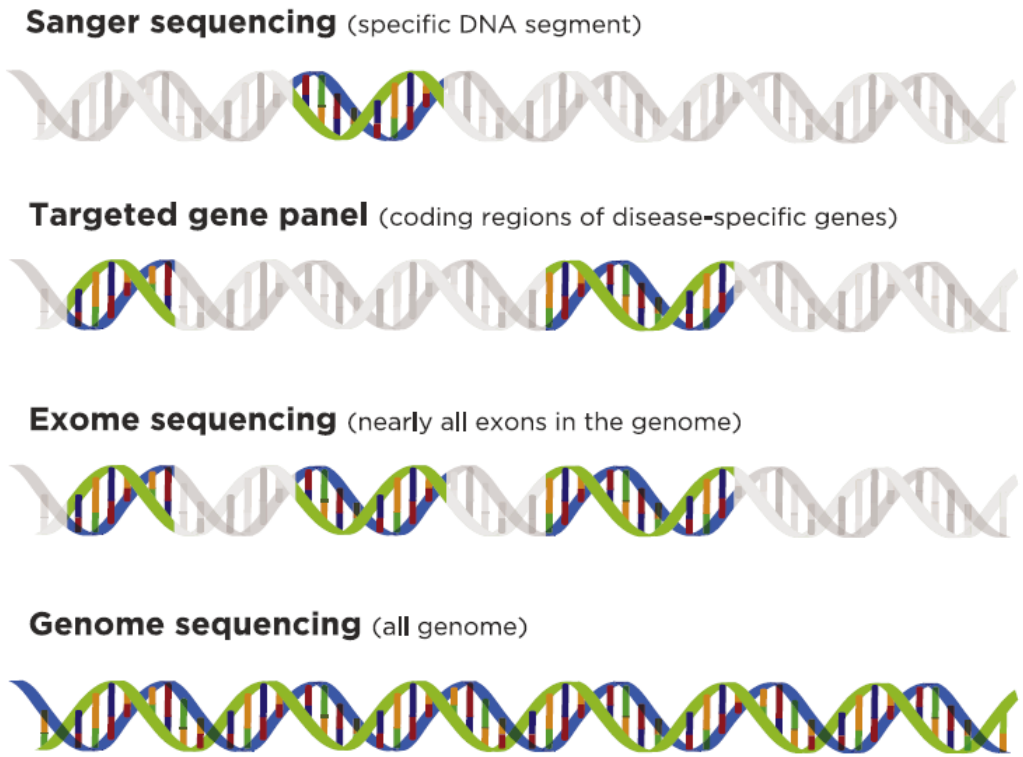
1. Chebib F, et al. (2021). *Am J Kidney Dis*. 78(2):282-292

Molecular Genetic Tests

Look for changes in one or more genes using a process known as DNA sequencing[1]

- ***Sanger Sequencing***
  - First generation sequencing limited to narrow portion of the gene
  - Look for any changes in a single or few genes

- ***Next Generation Sequencing (Next-Gen)***
  - Targeted panel sequencing
  - Whole Exome Sequencing (WES) – exons (coding part) comprise 1-2% of genome but ~85% of genetic variants
  - Whole Genome Sequencing (WGS) - looks for variations in the introns and non-coding regions as well as the exons



1. Knoers et al. (2022) *Niaphrol Dial Transplant.* 37:239-254
2. Images adapted from: Devarajan P et al. (2022) *Kidney Medicine .4(4) 100435.*

Commercially Available Genetic Tests

- Be sure to order tests that contains the specific genes of interest for ADPKD: *PKD1, PKD2, IFT140, PKHD1, GANAB*, *DNAJB11*, *ALG9*, *TCF2 (*HNF1B)
- Some commercial panels lack testing for *PKD1*, and therefore should not be used
- Some targeted NGS panels are disease type specific (i.e., for cystic kidney disease, or glomerulonephritis, etc) and some contain almost all known kidney genes. The later are easier to use.

What is in a genetic report?

- **Patient identifiable & clinical information**
  - Name, DOB, MRN
- **Clinical details and phenotype information**
  - Test that is being requested
  - Clinical indication
- **Genetics Result**
  - Result conclusion and overall result interpretation
  - Variant details
  - AMCG variant classification
- **Interpretation of results**
  - Supporting evidence
  - Clinical recommendations
- **Methodology details, limitations and disclaimers**
  - Gene lists/coverage
  - Technical limitations

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Key features of the sequencing results

- **Description of Mutation** - gene location and predicted change in protein sequence
- **Population Frequency in gnomAD** - more rare, more likely to be significant
- **Inheritance** - AR (autosomal recessive), AD (autosomal dominant), X-linked
- **Classification (Based on ACMG guidelines) -** no variants reported, variant of unknown significance, likely pathogenic, pathogenic
- **Incidental Findings** - Actionable findings in accordance with ACMG

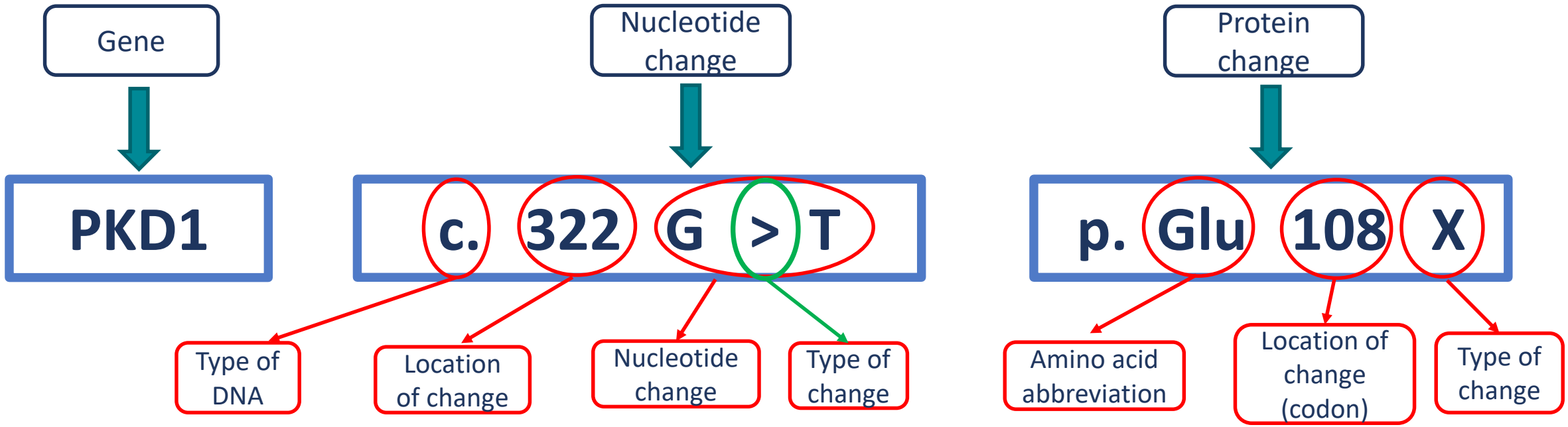
Five Tier Variant Classification System: ACMG Standards & Guidelines[1]

- ***Benign*** - sufficient evidence that an HCP can conclude it is not the cause of the patient's disorder
- ***Likely benign*** - sufficient evidence that an HCP can conclude that it is not the cause of the patient's disorder *when combined* with other information
- ***Uncertain significance*** - should **not** be used in clinical decision making
- ***Likely pathogenic*** - sufficient evidence that an HCP can use molecular testing data in clinical decision making when *combined with other evidence* of disease in question
- ***Pathogenic*** - met criteria informed by empirical data such that an HCP can use molecular testing data for clinical decision making

1. Richards S, et al. (2015) *Genetics in Medicine.* 17:5 :405-24

How to interpret a Genetic test result

PKD1 c.322G>T (p.Glu108X)



Determining Causality

- If the patient has a P or LP mutation in a cystic kidney or liver gene associated with autosomal dominant disease, then the case is “solved”
- If there are no P or LP mutations listed and the pre-test probability is high, then look at the VUS panel.

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How does an HCP interpret a negative genetic result when a patient's phenotype appears to strongly align with diagnostic indication?

How does the HCP interpret a VUS in the gene for which the diagnostic test was ordered?

What does it mean for the patient?

How does the HCP handle this situation?

Strategies for Ordering/Interpreting Targeted NGS panel data for ADPKD

- Order testing with Variants of Uncertain Significance (VUS) **included** because *PKD1* mutations maybe private (unique to a certain family)
- If you find a pathogenic/likely pathogenic mutation and your pre-test probability of ADPKD was high, then you have made a diagnosis
- If you find a variant of unknown significance, determine if it is rare. Since ADPKD is 1/1000 (.001), and a single mutation in *PKD1* is only likely to account for a small fraction of the total, a variant present in a frequency higher than in .0001 (10^{-4}) it is unlikely to be disease causing
- If your pre-test probability was high but the VUS is only borderline rare, you may consider treating it like a hypomorphic allele and/or testing other family members
- Other data (conserved among species, computational modeling may be helpful)

Case 1: Cystic Kidneys but no family history of ADPKD

- Clinical Hx: 34 y/o man diagnosed with cystic kidneys as a child while undergoing tx for lymphoma. No family history of kidney disease. PMH includes obesity, HTN (3-4 yrs), uric acid stones.
- Clinical Dx: ADPKD at high risk of progression (Mayo imaging class 1E, TKV 4600 cc) and stage 3 CKD. **High Pre-test probability of ADPKD, *PKD1* mutation**

FINAL RESULTS SUMMARY

Negative

This test is negative for known renal-disease causing variants. See below for additional findings of potential clinical relevance.

ADDITIONAL FINDINGS: CARRIER VARIANT(S)

This following heterozygous variant(s) were detected in this individual. As the associated condition(s) are inherited in an autosomal recessive manner, these variant(s) are not sufficient to cause disease by themselves.

Gene	Kidney-Associated Disease(s)	Inheritance	Variant	Zygosity	Classification
BBS1	Bardet-Biedl syndrome 1	Autosomal Recessive	c.1169T>G (p.Met390Arg)	Heterozygous	**Pathogenic**
NPHS2	Nephrotic Syndrome, Type 2	Autosomal Recessive	c.686G>A (p.Arg229Gln)	Heterozygous	**Likely Pathogenic**

ADDITIONAL FINDINGS: VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS)

Variants of uncertain significance (VUS) are common and the American College of Medical genetics and Genomics (ACMG) does NOT recommend that a VUS be used in clinical decision making. A VUS means that a change in the DNA was detected, but there is not enough information to determine whether or not it results in disease. Medical management should be based on the patient's personal and/or family history.

Gene	Inheritance	Variant	Zygosity	Classification
PKD1	Autosomal Dominant	c.6657_6671dup (p.Arg2220_Pro2224dup)	Heterozygous	Unknown Significance

Sample Genetic report from Dr. Dahl

Is the *PKD1* VUS likely to be disease-causing?

In this case:

- High pre-test probability and high likelihood that the VUS is likely to be disease-causing

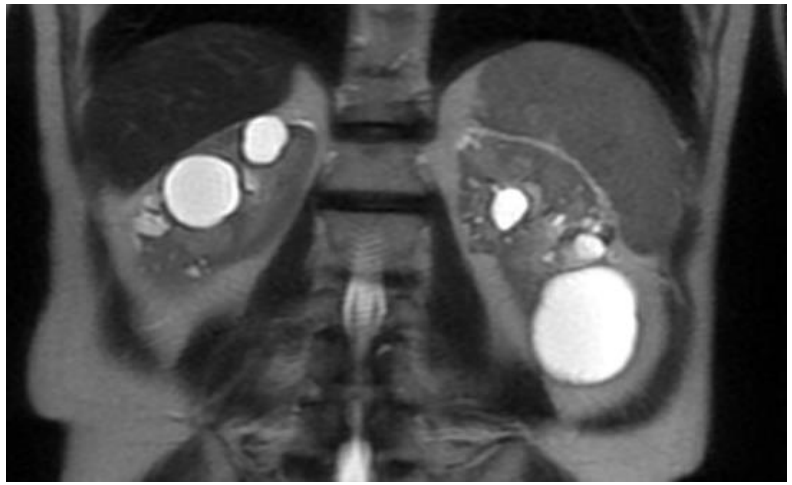
- The provider is satisfied that to have confirmed the clinical diagnosis

- May be reasonable to check back in a few years to see if this variant has been reclassified

1. The PKD Mutation Database Entrance Page (mayo.edu)

Case 2: More Cysts than Expected, Equivocal Family History

- 56 y/o man with FHx of a brain aneurysm (mom). The patient has hypertension, and bilateral kidney cysts, but preserved renal function.
- MRI: TKV 750 cc, htTKV 428
- Mayo Class 1B



Negative

This test is negative for known renal-disease causing variants. See below for additional findings of potential clinical relevance.

ADDITIONAL FINDINGS: CARRIER VARIANT

The following heterozygous variant was detected in this individual. For any gene that is associated with an autosomal recessive condition, the variant is not sufficient to cause the condition by itself. For any gene that is associated with both autosomal recessive and autosomal dominant conditions, the variant has been interpreted as a carrier variant based on the current evidence and/or clinical information provided. Clinical correlation is recommended on an individual basis.

Gene	Condition(s)	Inheritance	Variant(s)	Zygosity	Classification
SI	Sucrase-Isomaltase Deficiency	Autosomal Recessive	c.3370C>T (p.Arg1124*)	Heterozygous	**Pathogenic**

ADDITIONAL FINDINGS: VARIANTS OF UNCERTAIN SIGNIFICANCE (VUS)

Variants of uncertain significance (VUS) are common and the American College of Medical Genetics and Genomics (ACMG) does NOT recommend that a VUS be used in clinical decision making. A VUS means that a change in the DNA was detected, but there is not enough information to determine whether or not it results in disease. Medical management should be based on the patient's personal and/or family history.

Gene	Condition(s)	Inheritance	Variant(s)	Zygosity	Classification
PKD1	Polycystic Kidney Disease 1	Autosomal Dominant	c.5210C>T (p.Thr1737Ile)	Heterozygous	Unknown Significance

Sample Genetic report

Is the VUS in *PKD1* clinically relevant?

Gene	Condition(s)	Inheritance	Variant(s)	Zygosity	Classification
PKD1	Polycystic Kidney Disease 1	Autosomal Dominant	c.5210C>T (p.Thr1737Ile)	Heterozygous	Unknown Significance

***PKD1* NM_001009944.3:c.5210C>T (p.Thr1737Ile):**
This variant is in the dbSNP database: rs773343118. This variant is predicted to result in a single amino acid substitution (missense) of Thr to Ile at codon 1737 in exon 15 of the *PKD1* gene. This variant has not been reported as associated with a clinical condition in the Human Gene Mutation Database (HGMD). This variant has been observed at a frequency of less than 0.01% (5/238990 alleles) in the Broad gnomAD dataset. The highest allele frequency that this variant has been observed at in any sub-population with available data is 0.03% in the Other population. There are no homozygous control individuals for this variant. The Broad Institute gnomAD database (>120,000 Individuals with no known severe, pediatric onset disease) was used for this analysis.

1. Sample Genetic report from Dr. Dahl

Is the VUS in *PKD1* clinically relevant?

In this case:
- Allele frequency (MAF) is higher than .0001 in other and African/African American populations
- No clinical significance listed in ClinVar
- Not listed in the Mayo Database

- Low to Medium pre-test probability
- Test result is equivocal to negative

Unlikely that this is more than a hypomorphic allele at best. NGS panel may have missed the true mutation, or this panel may not contain the gene of interest.

Clinically the provider reassured the patient that he had a low risk of progressive loss of renal function. Discussed a screening kidney ultrasound (mom) for further evaluation.

Additional Limitations to Consider

- Significant pseudogene interference and/or reciprocal changes between the *PKD1* gene and its six pseudogenes can occur and may impact genetic test results[1]
- Reading depth (mean sequencing depth) can impact the likelihood that a mutation will be detected by a genetic test and varies amongst commercially available platforms[2]
- Non-coding variants that may impact an ADPKD phenotype may not be detected with whole-exome sequencing modalities, which are designed to sequence exomes (coding region)[2]
- Detected variants are compared against data found in variation databases (e.g., ClinVar, HGMD, Mayo's ADPKD Variant Database) or the medical literature to determine the likelihood of pathogenicity[2]
  - Does the lab search for matches in every database before classifying a variant?
- Labs can employ steps to improve accurate detection of variants in genes affected by segmental duplication and high pseudogene interference[2]
  - Does the lab mention the possibility of pseudogene interference, test limitations, and solutions to more accurately analyze affected regions?

1. Natera Renasight clinical genetic report /www.natera.com/organ-health/renasight-genetic-testing/ . Accessed June 2022.
2. Blueprint Genetics website. https://blueprintgenetics.com/tests/panels/nephrology/polycystic-kidney-disease-panel/#panel_strength-heading. Accessed on 16 June 2022.

Role of Genetic Counseling

- Counseling is recommended both pre- & post-testing for all patients
- Provides patients and their families with an understanding of the opportunities and limitations
- Ensures informed consent is obtained
- Post-test counseling should be provided by a licensed genetic counselor
  - Offers guidance regarding implications of results for disease risk
  - Psychosocial implications
  - Recommendations for family screening

Key Takeaways

- Growing expectation that nephrologists will need to meet minimal competencies in genetics
- A genetic result does not supersede clinical judgement
  - One data point that should be used in context with the other information
- Variant reclassification is dynamic
- Collaboration between ordering physician & clinical laboratory is essential
- The value of genetic testing
  - Identify and/or confirm cause of disease
    - Can provide differential diagnosis in patients with ADPKD-like phenotype
    - Body of evidence linking genotype/phenotype associations still being enriched and is reliant on a voluntary, time-intensive exercise
    - Novel genes implicated in ADPKD are still being identified
    - >1650 pathogenic mutations have been identified in the *PKD1* gene, and some of these are missed with NGS modalities
  - May aid in individual treatment planning
  - Mutation type lacks *individual* prognostic value
    - Imaging incorporates the germline mutation and subsequent “hits” to individualize prognostication

Questions from the Field

- *PKD1* variant of unknown significance indicated on report, patient presenting with ADPKD phenotype – whose responsibility is it to report phenotypic association with PKD1 variant?
- How are databases maintained?
- Who contacts patient when variants are reclassified?
- What to do when a report comes back with a VUS? How do we use this information?
- HCPs have questions around the accuracy of genetic testing, why some insurance plans are requiring it now, and how they can best help the patient understand the results.
- Providers get back a negative result which prevents them from treating the patients. However, in reality they may be true ADPKD patients that should be on therapy. Providers become unsure how to proceed… results are coming back non-PKD1, non PKD2 and sometimes inconclusive.
- What are the differences between the various commercially available testing platforms?

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