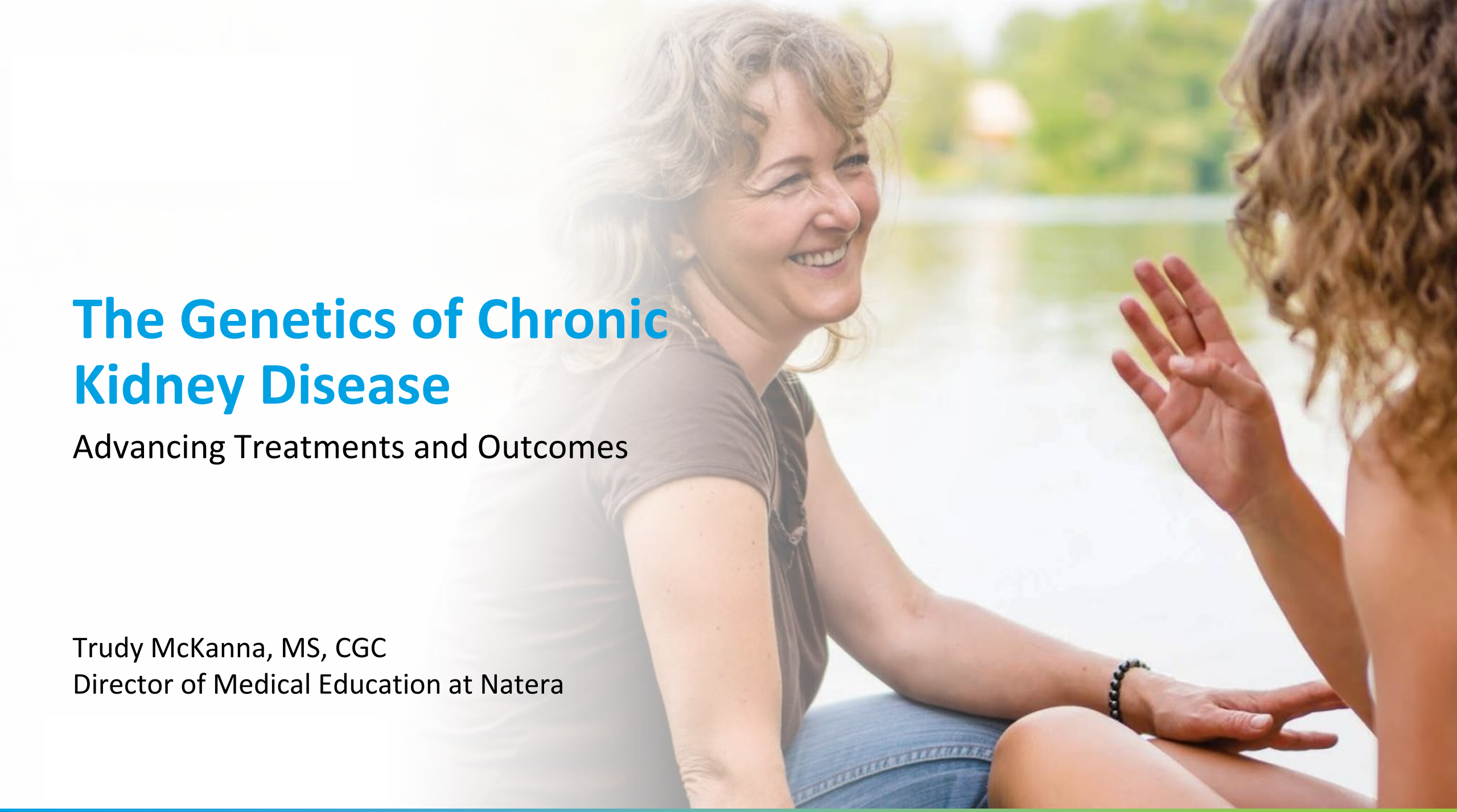
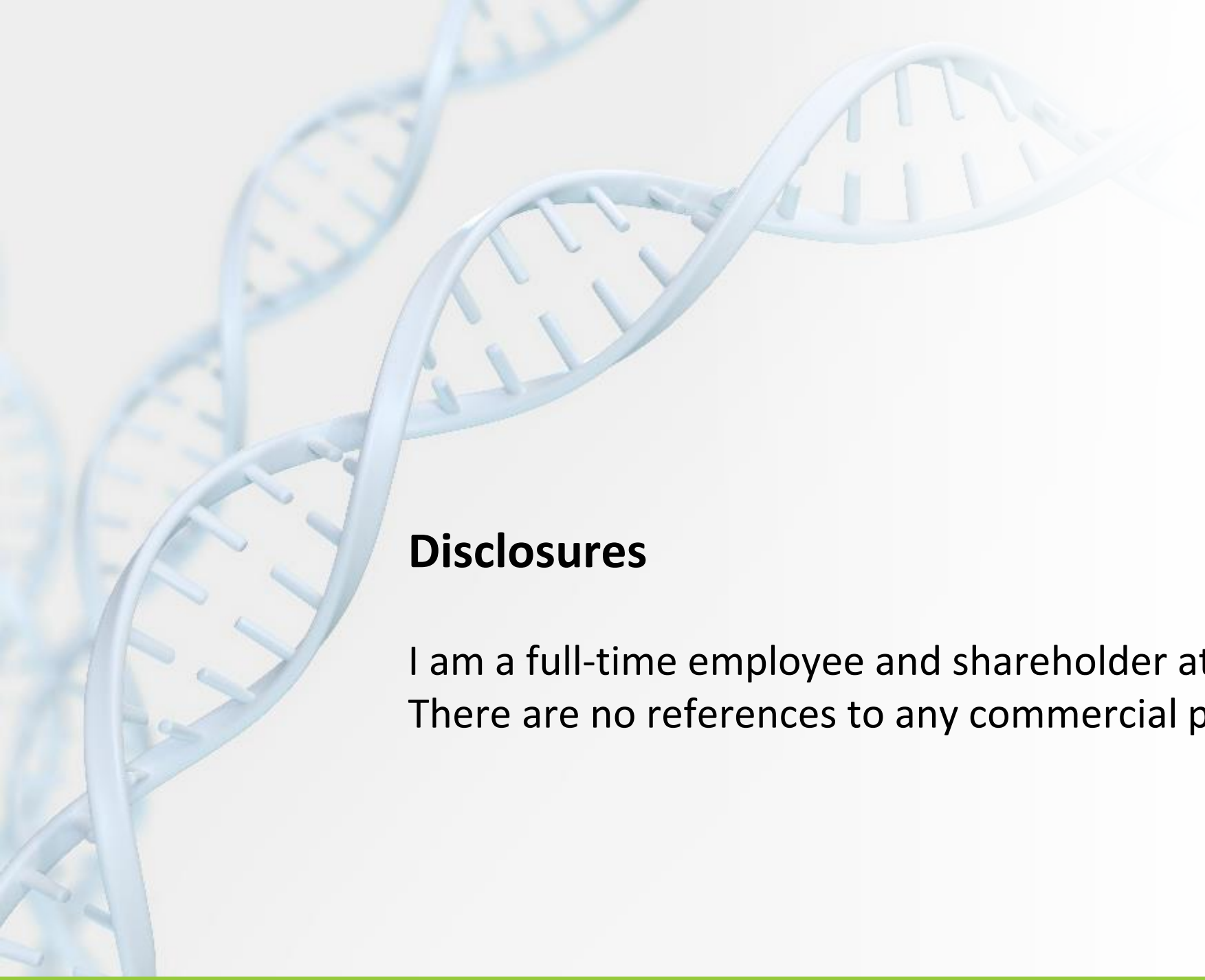
The Genetics of Chronic Kidney Disease

Advancing Treatments and Outcomes



Trudy McKanna, MS, CGC
Director of Medical Education at Natera



Disclosures

I am a full-time employee and shareholder at Natera, Inc.
There are no references to any commercial products in this presentation

Objectives

1. Identify common and rare genetic etiologies for monogenic chronic kidney disease (CKD).
2. Summarize some targeted therapies for monogenic CKD and discuss opportunities for future advancements.

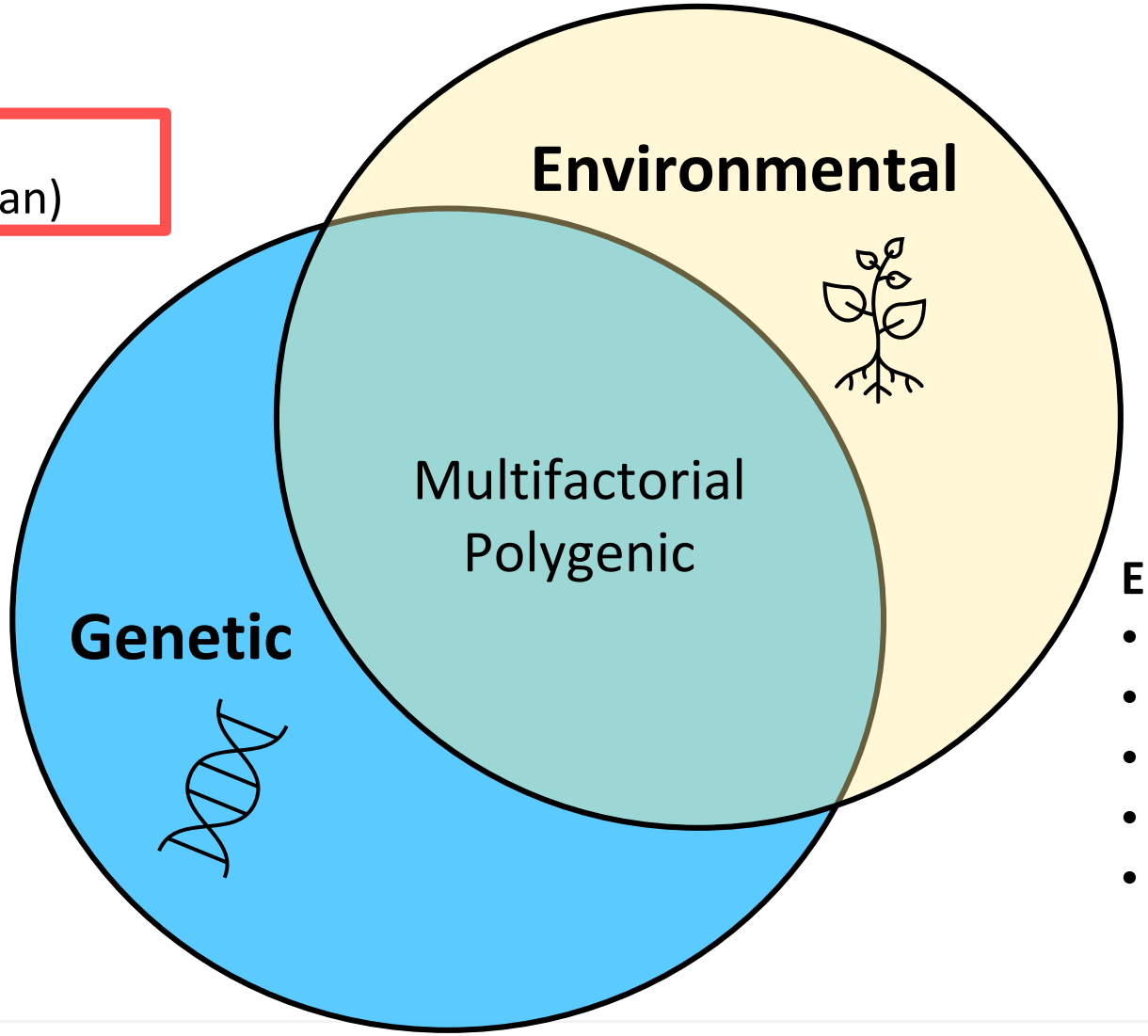
Agenda

1. Renal genetics overview
2. Clinical utility of renal genetic testing
3. Case examples
4. Future directions

What Causes Kidney Disease?

Genetic Influences:

- Single-gene disorders (monogenic, Mendelian)
- Polygenic disorders
- Epigenetic effects



Environmental Influences:

- Teratogen exposure
- Postnatal infection
- Medication
- Comorbidities
- Trauma

Genetic CKD may differ in prognosis and treatment

CKD affects **>10%** of the world's population

~25% of patients with CKD have a family history

Most pediatric CKD has a genetic cause

10% of end-stage renal disease (ESRD) has an "unknown" etiology

Groopman E et al NEJM 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Diagnostic Utility of Exome Sequencing for Kidney Disease

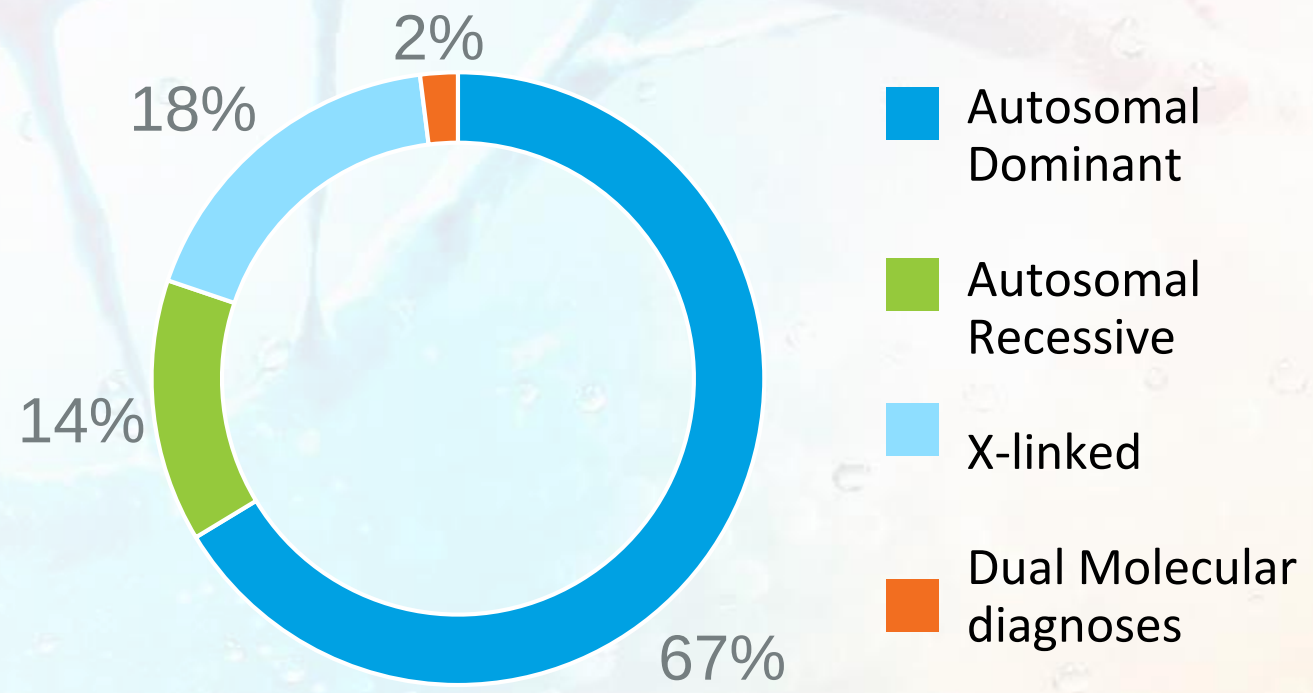
E.E. Groopman, M. Marasa, S. Cameron-Christie, S. Petrovski, V.S. Aggarwal, H. Milo-Rasouly, Y. Li, J. Zhang, J. Nestor, P. Krithivasan, W.Y. Lam, A. Mitrotti, S. Piva, B.H. Kil, D. Chatterjee, R. Reingold, D. Bradbury, M. DiVecchia, H. Snyder, X. Mu, K. Mehl, O. Balderes, D.A. Fasel, C. Weng, J. Radhakrishnan, P. Canetta, G.B. Appel, A.S. Bomback, W. Ahn, N.S. Uy, S. Alam, D.J. Cohen, R.J. Crew, G.K. Dube, M.K. Rao, S. Kamalakaran, B. Copeland, Z. Ren, J. Bridgers, C.D. Malone, C.M. Mebane, N. Dagaonkar, B.C. Fellström, C. Haefliger, S. Mohan, S. Sanna-Cherchi, K. Kiryluk, J. Fleckner, R. March, A. Platt, D.B. Goldstein, and A.G. Gharavi

Groopman et al. N Engl J Med (2019) 380;2

9.3% of CKD can be attributed to a genetic etiology

Results

- 307/3315 individuals had genetic variants identified = **9.3%**
- Accounted for 66 different monogenic disorders
- 2/3 of the conditions were autosomal dominant
- 2% had more than 1 genetic disorder



Groopman et al. N Engl J Med (2019) 380;2

Who should be tested?

Table 2. Diagnostic Yield and Heterogeneity of Genetic Diagnoses across Clinical Diagnostic Categories.

Clinical Diagnosis	Sequencing Performed	Diagnostic Variants Present	Diagnostic Yield	Distinct Monogenic Disorders Detected	Singleton Genetic Diagnoses
	number of patients		*percent*	*number*	
Congenital or cystic renal disease	531	127	23.9	27	20
Glomerulopathy	1411	101	7.2	23	14
Diabetic nephropathy	370	6	1.6	3	2
Hypertensive nephropathy	319	8	2.5	6	4
Tubulointerstitial disease	244	11	4.5	10	9
Other	159	6	3.8	4	2
Nephropathy of unknown origin	281	48	17.1	28	17
Total	3315	307	9.3	66*	39*

* A total of 27 genetic diagnoses were found multiple times, 21 of which were found among patients in different clinical diagnostic subgroups.

1Connaughton et al. Kidney international (2019) 95, 914-928
2Gharavi et al. N Engl J Med (2019) 380;2

In 89%, a genetic diagnosis had implications for clinical management

Table 4. Diagnostic Utility and Clinical Implications of Genetic Findings in the 167 Patients in the CUMC Cohort with Genetic Diagnoses.

Diagnostic Utility of Genetic Findings	Patients	Distinct Monogenic Disorders Detected	Singleton Genetic Diagnoses	Genetic Diagnosis with Implications for Clinical Management*
		number		*number (percent)*
Confirmed suspected hereditary cause	45	12	5	34 (76)
Discerned specific subcategory of condition within broader clinical disease category	65	36	24	58 (89)
Reclassified disease	18	11	7	18 (100)
Identified molecular cause for undiagnosed condition	39	22	11	39 (100)
Total	167	55†	35†	149 (89)

Groopman et al. N Engl J Med (2019) 380;2

Clinical Utility of Renal Genetic Testing

- Confirm or reclassify clinical diagnosis
- Target therapies or workup
- Provide diagnosis for unknown etiology
- Family counseling and planning
- Extrarenal referrals
- Clinical trials

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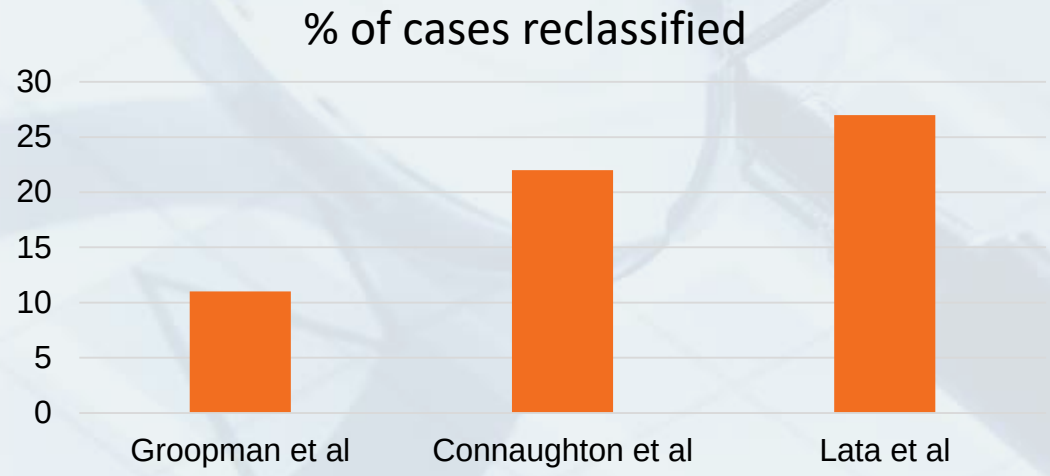
Clinical diagnosis = genetic diagnosis?

Utility

- Provide patient and family with a definitive cause and mutation[1]
- Identify specific mutation
- Negative result may be useful
- Discover dual diagnoses

Support

- Up to 1 in 4 clinical diagnoses may be reclassified by genetic test results[2-4]



[1]Vivante and Hildebrandt. Nat Rev Nephrol 12(3): 133-146
[2]Groopman et al. NEJM 380;2 2019
[3]Connaughton et al. Kidney international (2019) 95, 914-928
[4]Lata et al. Ann Intern Med. 168; 2 (2019)

Case example: Reclassification[1]

NPH in adult-onset ESRD

- Nephronophthisis (NPH) is typically thought to have childhood onset
- Large study: 88% of adult patients were diagnosed with something other than NPH

- 61 y.o Caucasian woman develops CKD in her 40s, ESRD at 61
- Diagnosis: kidney damage due to high blood pressure
- Genetic testing results: homozygous *NPHP1* mutations
- Clinical diagnosis ≠ genetic diagnosis

Clinical significance:

- ✔ Removal of incorrect diagnosis
- ✔ Better prognostication
- ✔ Identification of other at-risk relatives

"…these results warrant wider application of genetic testing in adult-onset ESRD."

Snoek R et al. J Am Soc Nephrol 29: 1772-1779, 2018

Clinical Utility of Renal Genetic Testing

Confirm or reclassify clinical diagnosis

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Personalized treatment or prevention

Avoid unnecessary procedures, tests, and treatments

- Support or eliminate biopsy
- Plan transplant management
- Genetic forms of Steroid Resistant Nephrotic Syndrome (SRNS) are less likely to recur (4-8% v. 30%)[1,2]
  - Reduce immunosuppression and reduce risk of infectious complications
- ACE inhibitors may slow renal failure in Alport[3]
  - Avoid immunosuppression
- *HNF1B*-related Congenial Abnormalities of Kidney and Urinary Tract (CAKUT)
  - Elevated liver function tests
  - Lifestyle and diabetes management

[1]Mann N et al. JASN 2019
[2]Warejko j et al. Clin J Am Soc Nephrol 13: 53-62.
[3]Stokman M et al. doi:10.1038/nrneph.2016.87
[4]Armstrong and Thomas. Curr Opin Nephrol Hypertens 2019; 28:183-194

Case example: aHUS

Prevent transplant loss with correct diagnosis and treatment

- Atypical Hemolytic Uremic Syndrome (aHUS) is a rare but treatable cause of acute kidney injury
- Many patients have a genetic cause leading to abnormal complement pathway activation, which causes kidney damage
- Susceptible to recurrence after transplant

- Patient lost first kidney transplant–treated with only plasma exchanges
- Received second transplant, aHUS recurred and was successfully treated with eculizumab

Clinical significance:

- ✔ Graft loss due to missed diagnosis
- ✔ Second transplant preserved due to appropriate treatment
- ✔ Inheritance pattern leads to identification of other at-risk relatives

Fayek S et al. Trans Proc 52: 146-152 (2020)
Stokman M et al. doi:10.1038/nrneph.2016.87

Clinical Utility of Renal Genetic Testing

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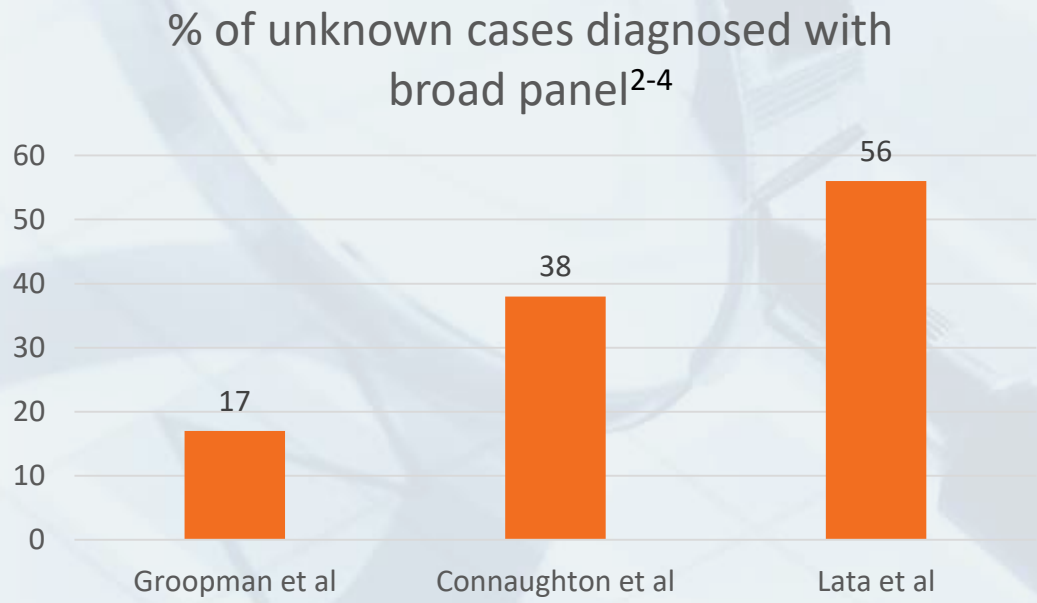
Up to 36% of adult CKD is undiagnosed[1]

Utility

- Symptoms may be mild, non-specific, atypical
  - No family history
  - No biopsy, or undetermined results
- The “hypertension” basket
- Could rate be even higher?

Impact



[1]Connaughton D and Hildebrant F. Nephrol Dial Transplant (2019) 1-8
[2]Groopman et al. *NEJM* 380;2 2019
[3]Connaughton et al. *Kidney international* (2019) 95, 914-928
[4]Lata et al. Ann Intern Med. 168; 2 (2019)

Case example: Unknown to known

Autosomal Dominant Tubulointerstitial Disease (ADTKD)

- 30 year old woman presents with elevated serum creatinine
- Family history of ESRD in her mother, onset at age 60
- Ultrasound is normal
- Clinical diagnosis: ESRD of unknown etiology
- Genetic testing: *UMOD* mutation = ADTKD

Clinical significance:

- ✔ Familial CKD diagnosed
- ✔ UMOD associated with risk for gout, and may benefit from specific medications

Clinical Utility of Renal Genetic Testing

Confirm or reclassify clinical diagnosis

Target therapies or workup

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Family counseling and planning

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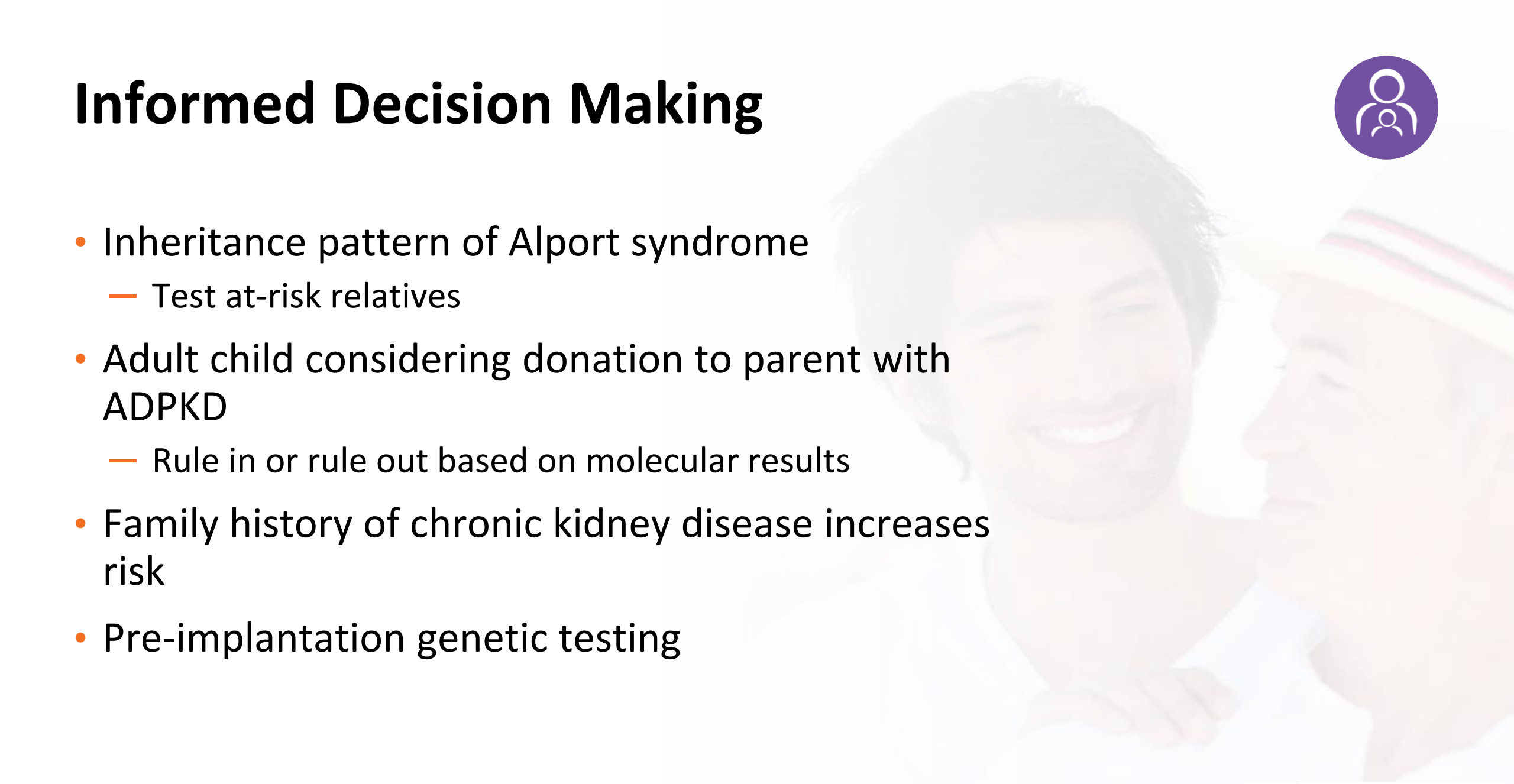
Clinical trials

Informed Decision Making



- Inheritance pattern of Alport syndrome
  - Test at-risk relatives
- Adult child considering donation to parent with ADPKD
  - Rule in or rule out based on molecular results
- Family history of chronic kidney disease increases risk
- Pre-implantation genetic testing

Clinical Utility of Renal Genetic Testing

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Early Detection and Management

- Alport syndrome/*COL4A3-5* disease[1]
  - Vision and hearing referrals
- CAKUT
  - Certain genes may be associated with deafness, hypoparathyroidism
  - *HNF1B:* maturity onset diabetes of the young (MODY)[2]
- Nephronophthisis
  - *NPHP5:* Risk for blindness due to retinitis pigmentosa

[1]Groopman et al. NEJM 380;2 2019
[2]Vivante and Hildebrandt. Nat Rev Nephrol 12(3): 133-146

Clinical Utility of Renal Genetic Testing

Confirm or reclassify clinical diagnosis

Target therapies or workup

Provide diagnosis for unknown etiology

Family counseling and planning

Extrarenal referrals

Clinical trials

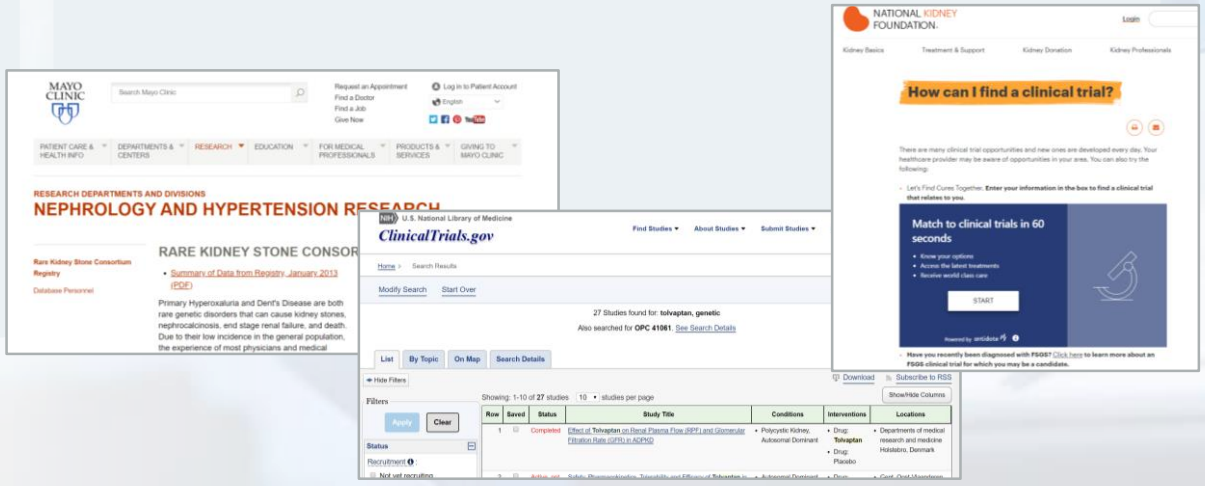
Disease- or Gene-specific Trials

Utility

- Enrollment in studies often requires confirmed diagnosis
- Genotype-phenotype studies
- Pharmaceutical trials
- Novel gene discovery

Impact

- More studies needed to continue to find genes associated with CKD
- Support from professional and patient organizations, academic institutions



Case examples

Case Example #1: Diagnosis → Treatment

Meet John, 79 yo male with ESRD

- ESRD developed in his late 60s; thought to be secondary to his 5-year history of diabetes and hypertension
- Underwent kidney transplant from living related donor (42 yo daughter)
- No known family history of significance

Post-Transplant

- Creatinine remained elevated
  - ~2.4 mg/dL 4 weeks post-transplant (normal 0.9-1.3 mg/dL)
- Clinician pursued genetic testing panel

Case 1: Results

Test Results

FINAL RESULTS SUMMARY

Positive

A homozygous pathogenic variant in the *APRT* gene was detected.

FINDINGS: POSITIVE VARIANT(S)

Gene	Kidney-Associated Disease(s)	Inheritance	Variant	Zygosity	Classification
APRT	Adenine Phosphoribosyltransferase Deficiency	Autosomal Recessive	c.259C>T (p.Arg87*)	**Homozygous**	**Pathogenic**

Case 1: Clinical Utility

- Identification of the cause of John’s kidney disease
- Modification of John’s treatment plan
  - Immediately began treatment with allopurinol
  - Dietary changes initiated
- Avoiding further injury to John’s graft
  - Creatinine at 1.5 mg/dL following several months of treatment
- Informing familial risks and potentially preventing ESRD in John’s relatives

Case Example #2—Reclassification

- 67 y/o African American male
  - Proteinuria
  - Elevated serum creatinine
- Diagnosis: Hypertension
- Medications
  - Anti-hypertensives
- Family Hx
  - Negative for renal disease, sickle cell trait or disease

Case 2: Results

- Homozygous G2/G2 APOL1 variants

FINAL RESULTS SUMMARY

Positive

A homozygous risk allele variant in the *APOL1* gene was detected.

FINDINGS: POSITIVE VARIANT(S)

Gene	Kidney-Associated Disease(s)	Inheritance	Variant	Zygosity	Classification
APOL1	Focal Segmental Glomerulosclerosis 4; Susceptibility to End-Stage Renal Disease	Complex	c.1164_1169del (p.Asn388_Tyr389del) (G2 allele)	**Homozygous**	**Risk Allele**

Multifactorial: APOL1 Mutations

Lifetime risk for ESRD in AA population

Incidence of 2 APOL1 risk alleles in AA

Of those with APOL1 develop CKD

- Individuals with two APOL1 variants (risk alleles) have a 7 to 30-fold increased risk of developing kidney disease
- Two-hit hypothesis?

APOL1: Clinical Utility

- Genetic diagnosis made without a biopsy

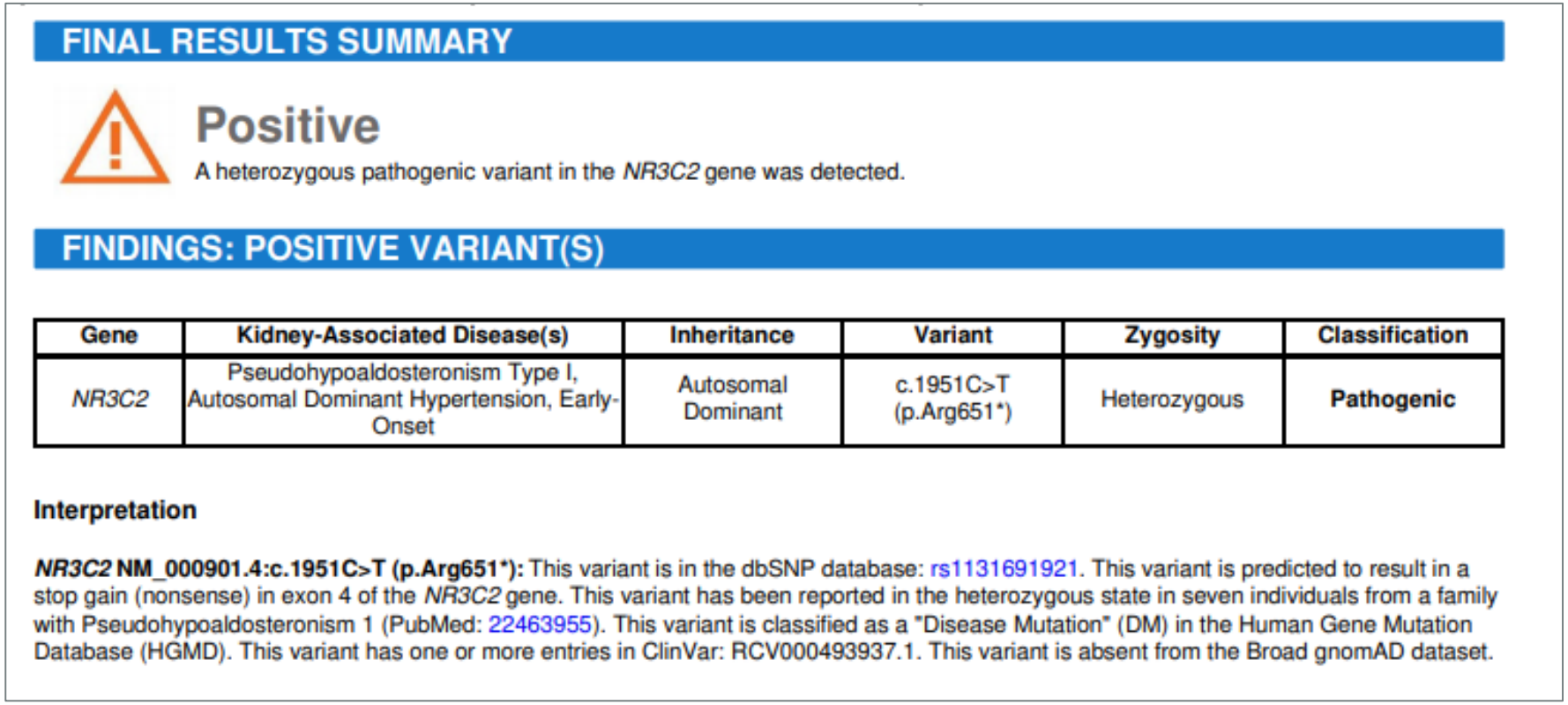
- The presence of the homozygous APOL1 risk alleles in this case argues against an immunological cause of FSGS, allowing for the avoidance of immunosuppression

- Risk assessment for family members/donor counseling if necessary

Case Example #3: Unknown to Known

- 63-year-old woman referred for slowly elevating creatinine (1.35-1.5 mg/dL)
- Sodium: 130 mEq/L [135-145]
- Potassium: 5.6 mmol/L [3.6-5.2]
- Family history: no history of kidney disease or autoimmune disease
- Renal ultrasound: confirmed unilateral complex cyst
- Genetic testing performed for evaluation of cystic kidney disease

Positive: PHA1



FINAL RESULTS SUMMARY

Positive

A heterozygous pathogenic variant in the *NR3C2* gene was detected.

FINDINGS: POSITIVE VARIANT(S)

Gene	Kidney-Associated Disease(s)	Inheritance	Variant	Zygosity	Classification
NR3C2	Pseudohypoaldosteronism Type I, Autosomal Dominant Hypertension, Early-Onset	Autosomal Dominant	c.1951C>T (p.Arg651*)	Heterozygous	**Pathogenic**

Interpretation

***NR3C2* NM_000901.4:c.1951C>T (p.Arg651*):** This variant is in the dbSNP database: rs1131691921. This variant is predicted to result in a stop gain (nonsense) in exon 4 of the *NR3C2* gene. This variant has been reported in the heterozygous state in seven individuals from a family with Pseudohypoaldosteronism 1 (PubMed: 22463955). This variant is classified as a "Disease Mutation" (DM) in the Human Gene Mutation Database (HGMD). This variant has one or more entries in ClinVar: RCV000493937.1. This variant is absent from the Broad gnomAD dataset.

- Pseudohypoaldosteronism type 1 (PHA1), is an electrolyte disorder that typically begins in infancy and is characterized by hyponatremia and hyperkalemia
- Mutations in the *NR3C2* gene lead to a nonfunctional or abnormally functioning mineralocorticoid receptor protein. As a result, sodium reabsorption and potassium secretion are both decreased.

PHA1: Clinical Utility

Provides a genetic diagnosis for clinical picture

Patient improved with electrolyte therapy

Family members may want genetic testing

Future Directions

Opportunities

- Identification of new disease spectrums and presentations
  - Redefining Alport syndrome spectrum
- Genomics provides new opportunities for drug discovery
- Improved transplant outcomes

Challenges

- GWAS studies have not always had success to date
  - Genes identified do not have a clear target for drug
  - Link to pathogenesis not well understood
- Variant interpretation
- Payer coverage/demonstration of health economic utility

Thank You!

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