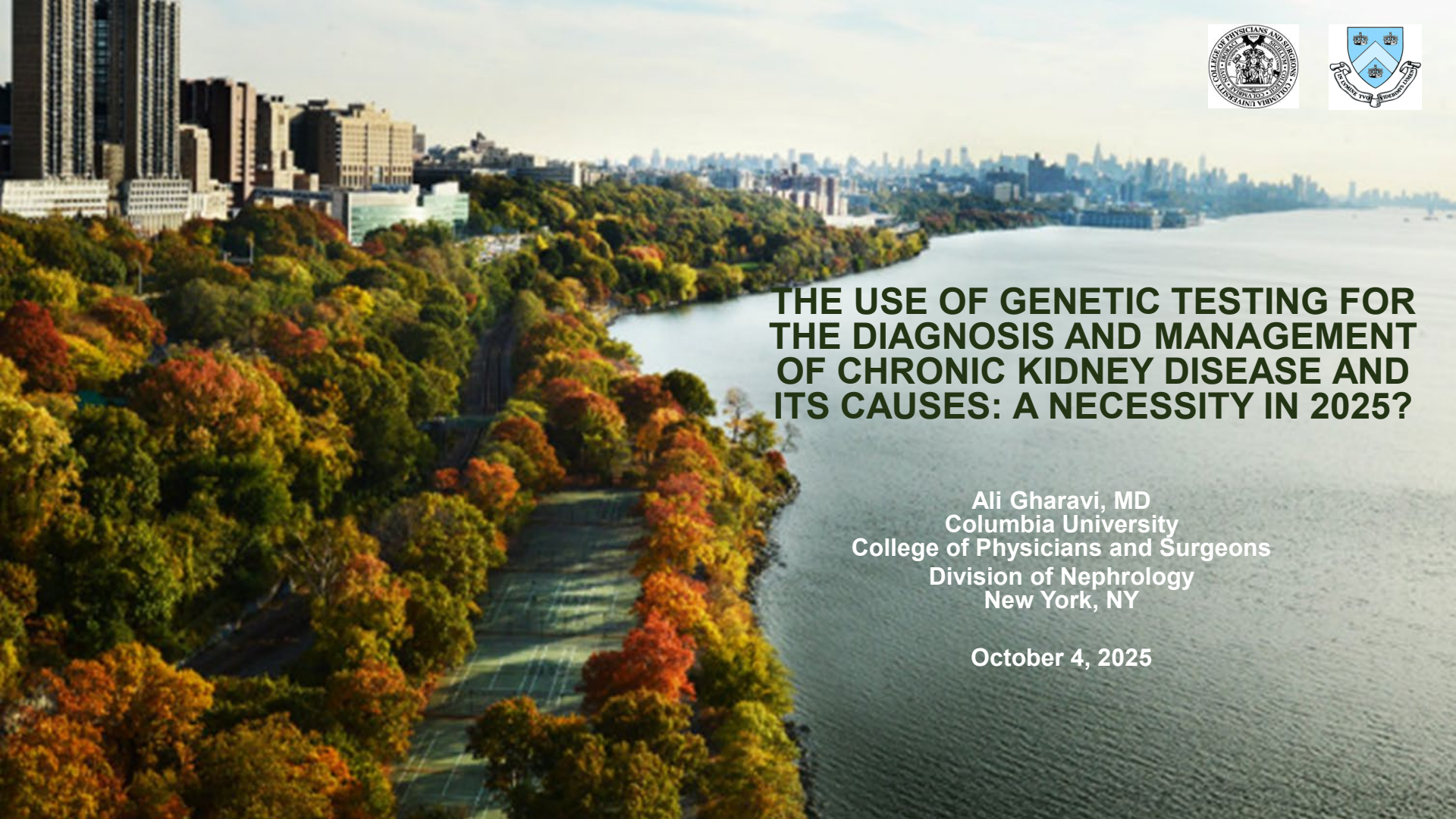

THE USE OF GENETIC TESTING FOR THE DIAGNOSIS AND MANAGEMENT OF CHRONIC KIDNEY DISEASE AND ITS CAUSES: A NECESSITY IN 2025?

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October 4, 2025

Disclosures

- Advisory board Actio, Natera, Novartis, Travere, Vera, Vertex, Calliditas
- Stock options: Actio

Patient Questions

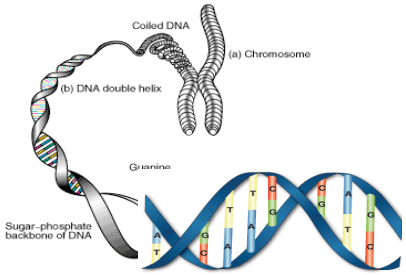
- What is this disease?
- Why do I have this disease?
- What will happen to me?
- What are the treatment options?

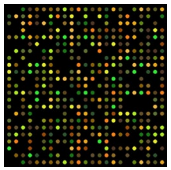
- “Doctor, should we perform genome sequencing to answer some of these questions?”

The Human Genome Sequence

Science Feb 16 2001 & Nature, Feb 15, 2001

The human genome has ~ 3 billion nucleotides (letters)

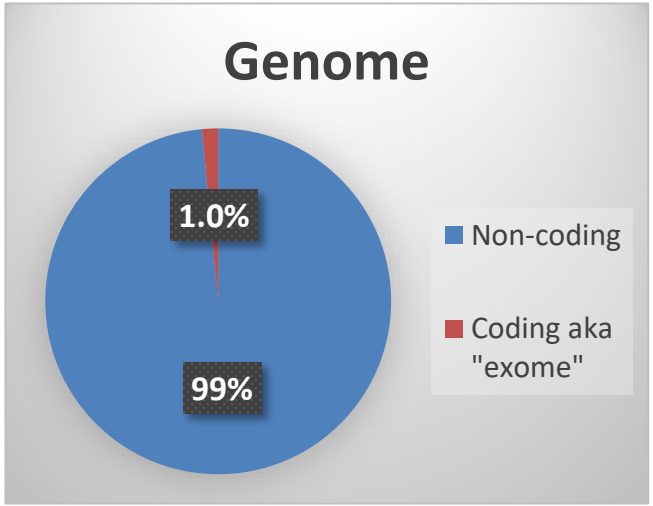


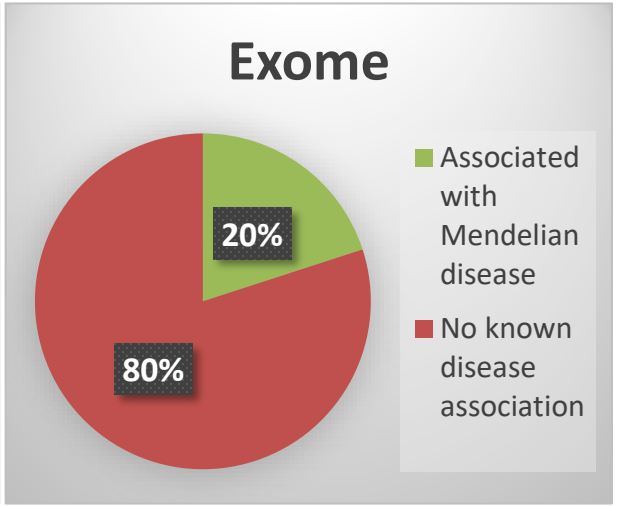


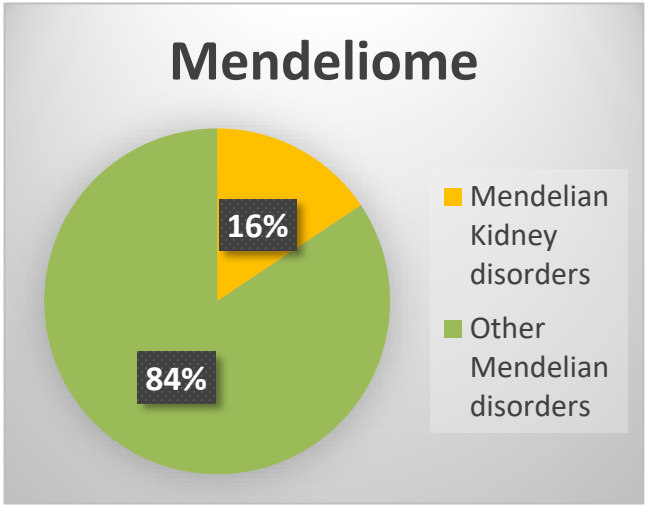
Microarray

DNA sequencers can read genomes in 24 hrs

Targets for Sequencing







There are ~20,000 genes in our genome. The coding portion of genes is called the "exome"

Of the ~20,000 genes, ~4700 are associated with a Mendelian Disorder ("Mendeliome")

Of the ~4700 Mendeliome genes, ~600-700 are associated with a Monogenic nephropathy ("Nephrome")

Utility of Whole Exome Sequencing in Adults with CKD

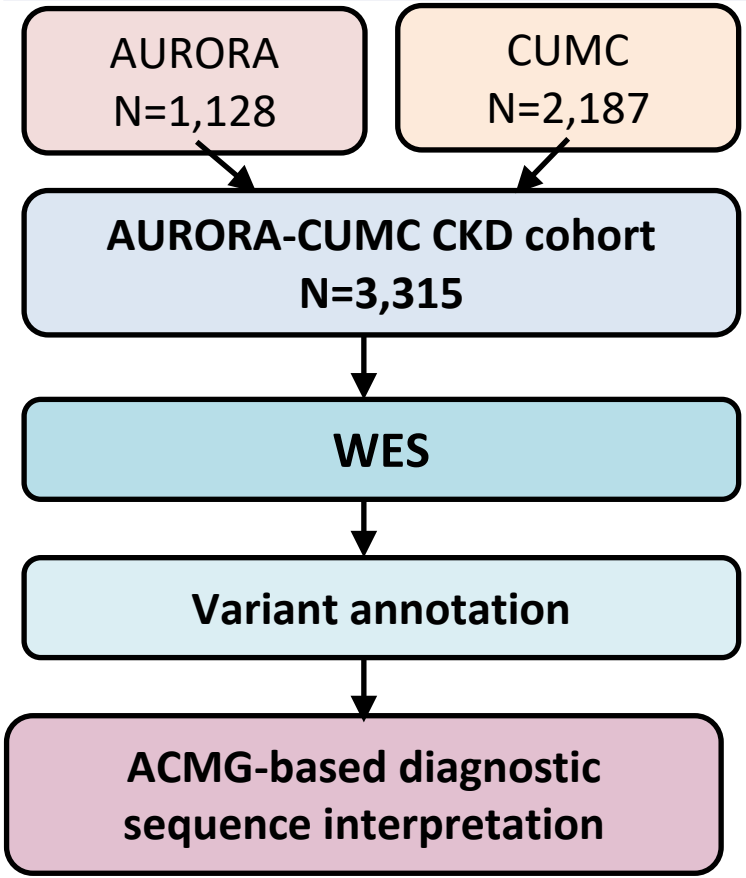


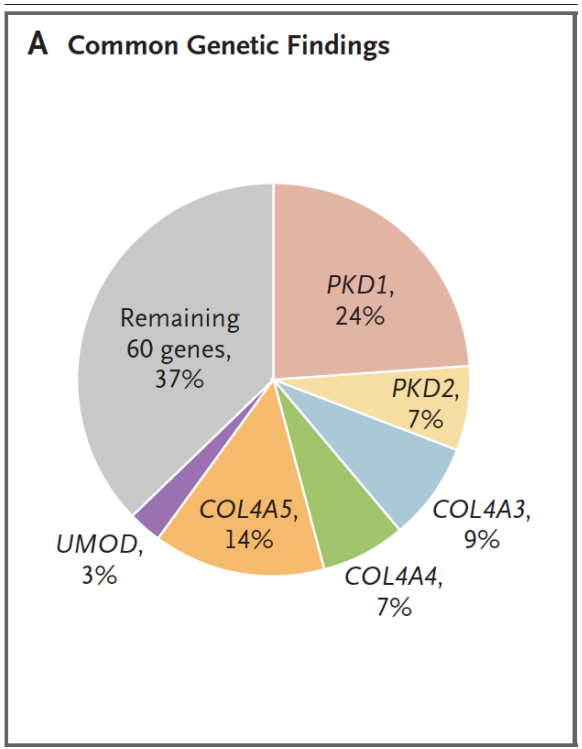
Table 1. Clinical Characteristics of the Patients.*

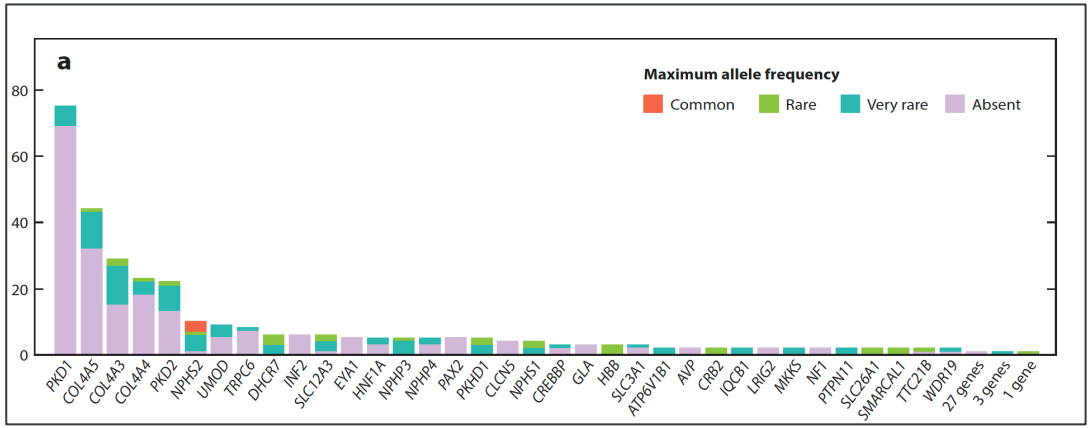
Characteristic	AURORA Cohort (N=1128)	CUMC Cohort (N=2187)	Overall Study Population (N=3315)
	number of patients (percent)		
Age at time of study entry			
0–21 yr	0	278 (12.7)	278 (8.4)
22–44 yr	0	713 (32.6)	713 (21.5)
45–64 yr	560 (49.6)	800 (36.6)	1360 (41.0)
≥65 yr	568 (50.4)	396 (18.1)	964 (29.1)
Sex			
Female	427 (37.9)	945 (43.2)	1372 (41.4)
Male	701 (62.1)	1242 (56.8)	1943 (58.6)
Race or ethnic group†			
White	1023 (90.7)	1113 (50.9)	2136 (64.4)
Hispanic	50 (4.4)	435 (19.9)	485 (14.6)
Black	18 (1.6)	330 (15.1)	348 (10.5)
Asian	20 (1.8)	224 (10.2)	244 (7.4)
Other or unspecified	17 (1.5)	85 (3.9)	102 (3.1)
Clinical diagnosis			
Congenital or cystic renal disease	159 (14.1)	372 (17.0)	531 (16.0)
Glomerulopathy	231 (20.5)	1180 (54.0)	1411 (42.6)
Diabetic nephropathy	184 (16.3)	186 (8.5)	370 (11.2)
Hypertensive nephropathy	193 (17.1)	126 (5.8)	319 (9.6)
Tubulointerstitial disease	212 (18.8)	32 (1.5)	244 (7.4)
Other	50 (4.4)	109 (5.0)	159 (4.8)
Nephropathy of unknown origin	99 (8.8)	182 (8.3)	281 (8.5)
End-stage renal disease‡	1128 (100.0)	1016 (46.5)	2144 (64.7)
Family history of kidney disease§	—	619 (28.3)	—

Groopman EE, Marasa M., et al. *NEJM 2019*

WES: Whole Exome Sequencing

ES Provides a Diagnostic Yield of 9.3% in patients with CKD, N = 3,315

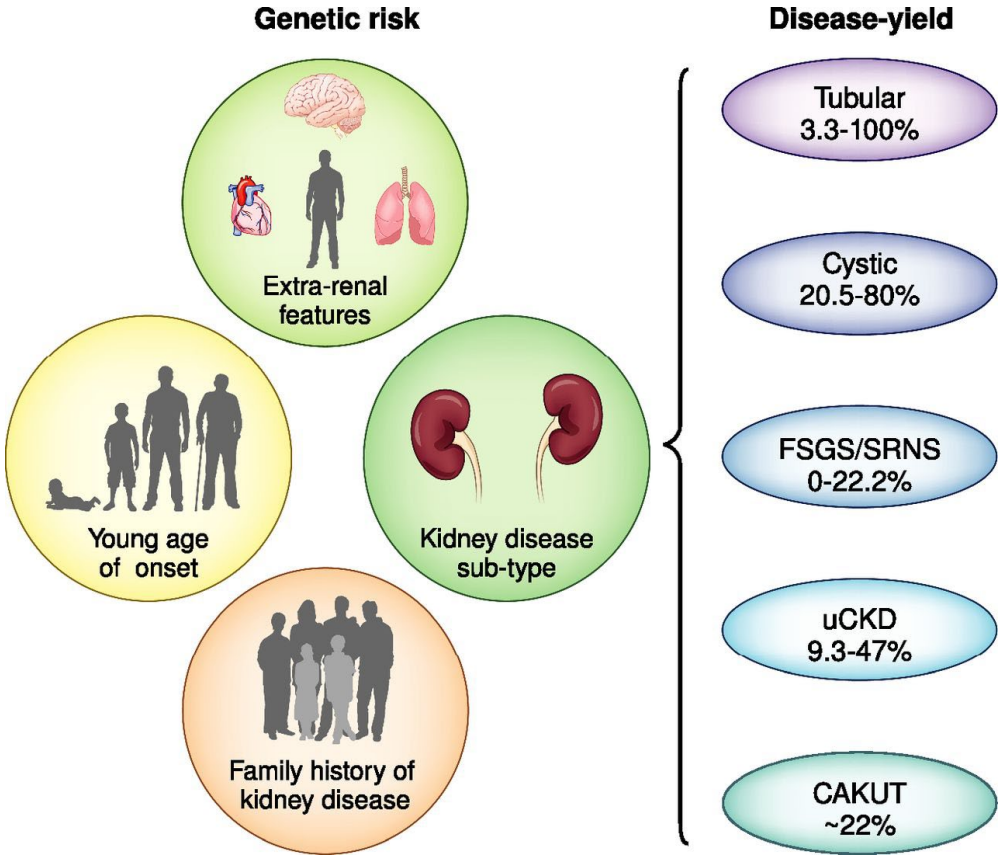




Groopman EE, Marasa M., et al. *NEJM 2019*

Elliott et al., *Ann Rev Med in press*

Clinical Predictors of Diagnostic Yield



Enrico Cocchi et al. CJASN 2020

Case Studies

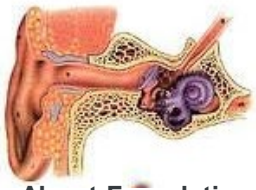
Case

- 46 yo woman with newly diagnosed kidney disease with blood & protein in urine
- Family hx of kidney disease in 2 uncles
- Kidney biopsy: focal segmental glomerulosclerosis (FSGS)
- Exome Sequencing reveals diagnosis of X-linked Alport Syndrome
- Treatment: avoid steroids, refer for new clinical trial
- Screen family members at risk

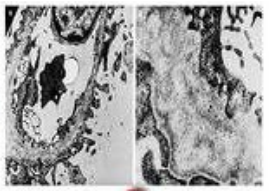
Groopman EE, **Marasa M., et al.** ***NEJM 2019***

Clinical presentation of Classic Alport syndrome

- Hematuria
- Sensorineural hearing loss
- Pathognomonic findings on kidney biopsy
- Anterior lenticonus



Alport Foundation



Genes:

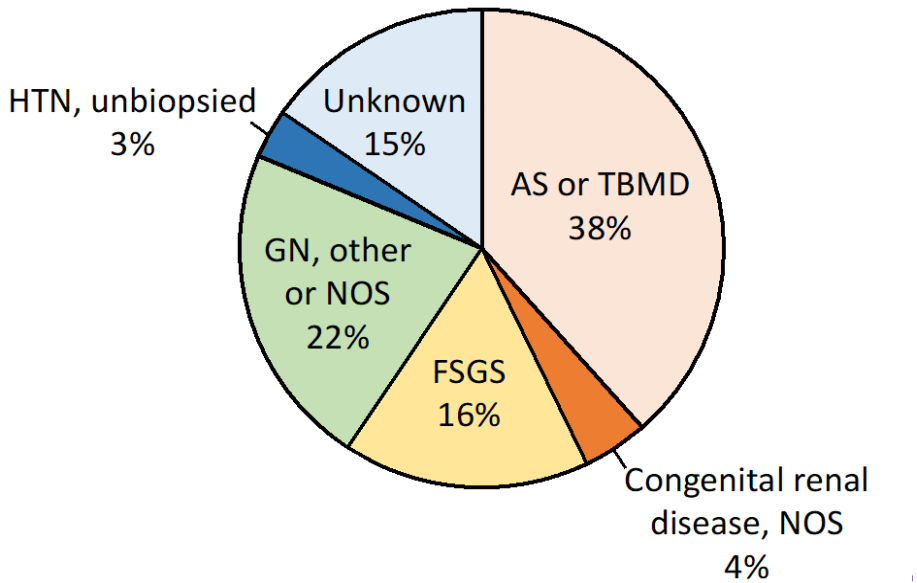
- *Chr. 2 COL4A3* – Dom & Rec
- *Chr. 2 COL4A4* – Dom & Rec
- *Chr. X COL4A5* – X-Linked

Case Studies

Case

- 46 yo with newly diagnosed kidney disease with blood & protein in urine
- Family hx of kidney disease in 2 uncles
- Kidney biopsy: focal segmental glomerulosclerosis (FSGS)
- Exome Sequencing reveals diagnosis of X-linked Alport Syndrome
- Treatment: avoid steroids, refer for new clinical trial
- Screen family members at risk

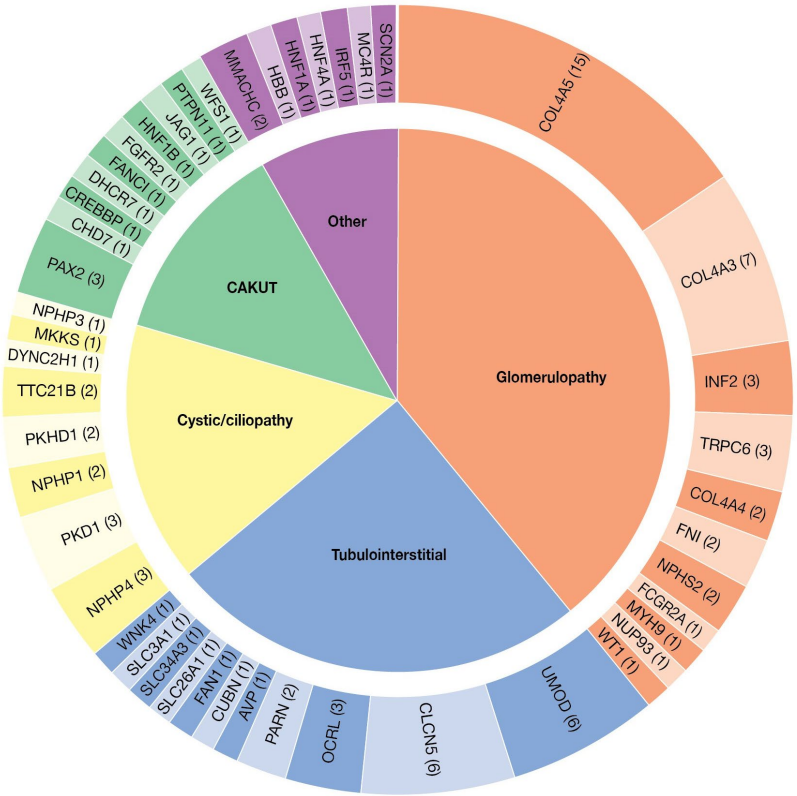
Phenotypes Associated with *COL4A3, COL4A4, or COL4A5* pathogenic variants



Groopman EE, **Marasa M., et al.** ***NEJM 2019***

HTN: hypertension; GN: glomerulonephritis; NOS: not otherwise specified; AS: Alport Syndrome; TBMD: thin basement membrane disease

CKD of Unknown Cause

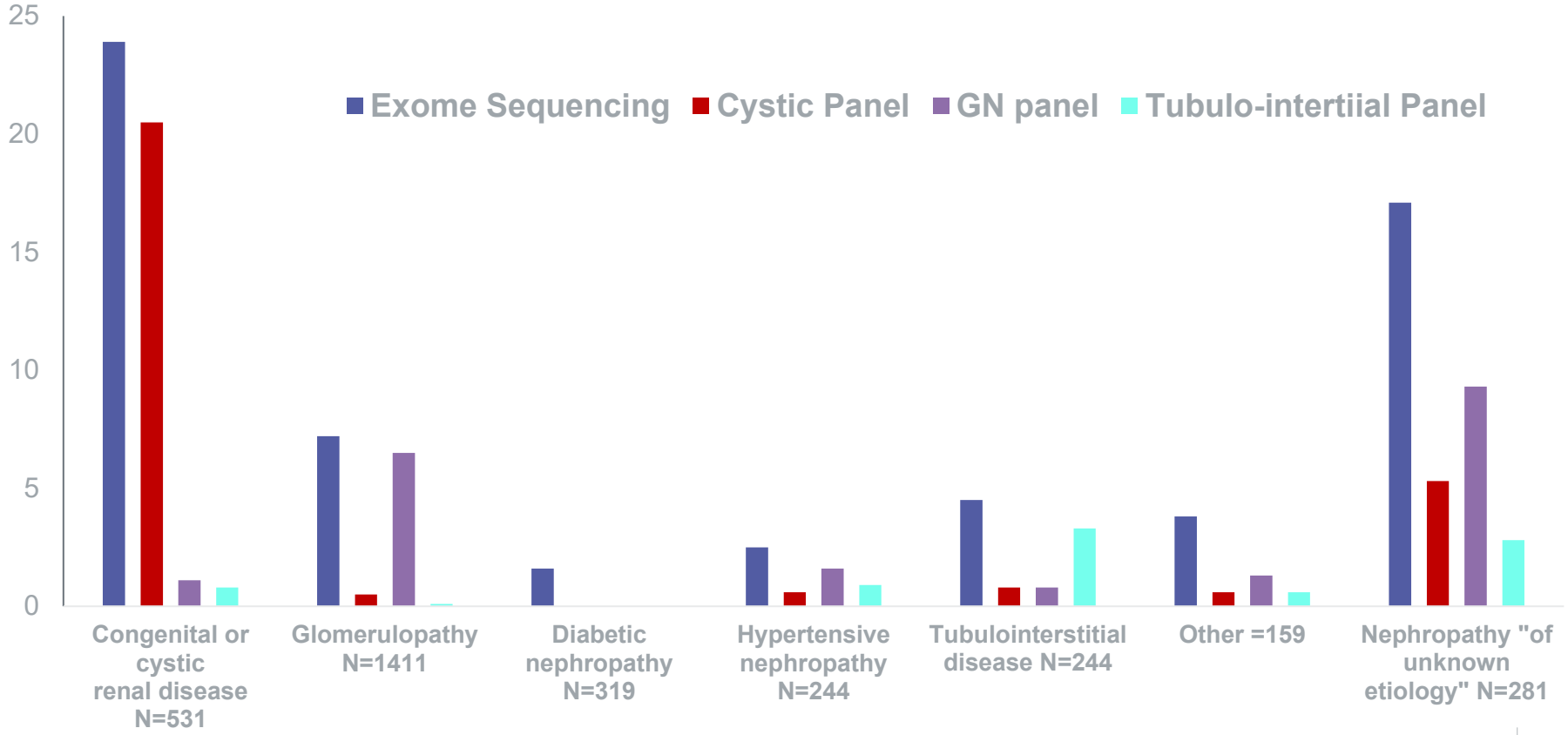


Review of 6 exome sequencing studies of CKD:

- 443 patients
- 22% diagnostic rate
- 47 genetic diagnoses made, of which 29 (62%) represented singleton diagnoses unique to one patient
- *COL4A3-5* mutations accounted for one-third of cases

Hays, et al, Kid International, *2020*

Diagnostic Performance of Exome vs. Panel Sequencing

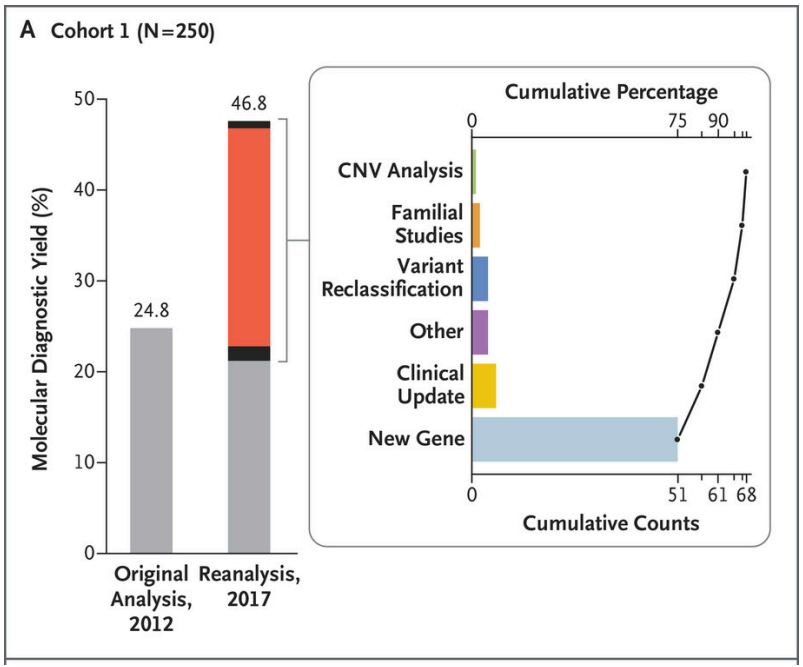


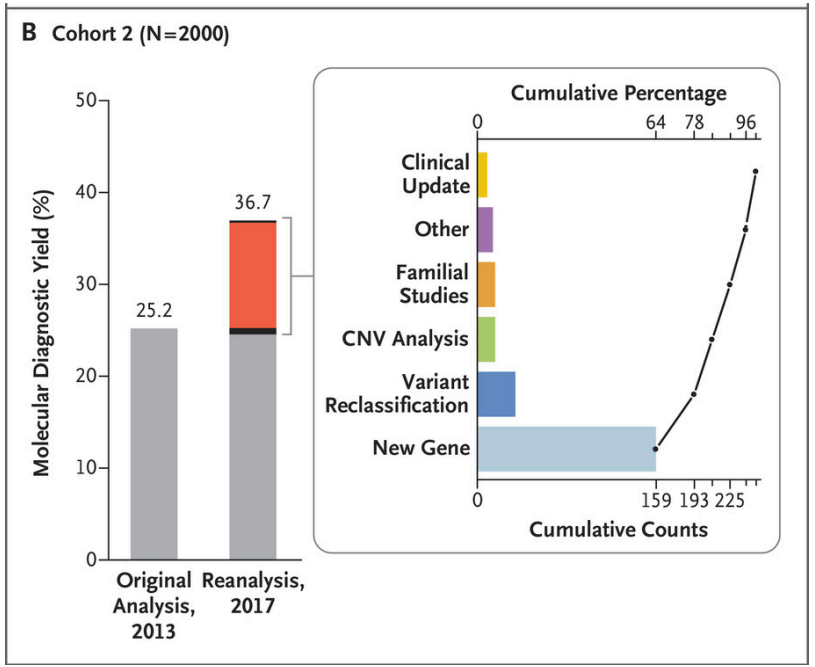
Groopman EE, Marasa M., et al. *NEJM 2019*

What To Do With a Negative Genetic Test?

- **Consider blind spots in sequencing assay**
  - Genes or exons not captured /covered
  - Classes of mutations not readily surveyed by NGS: CNVs, indels, mosaicism, retrotransposition, VNTR
  - Non-coding variants
- **Consider periodic reanalysis of data**
- **Consider alternative inheritance models: e.g. polygenic**
- **Non genetic causes**

Systematic Reanalysis Increases Diagnostic Yields





P Liu et al. N Engl J Med 2019

Genetics in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

OPEN

KDIGO Conference Participants[1]

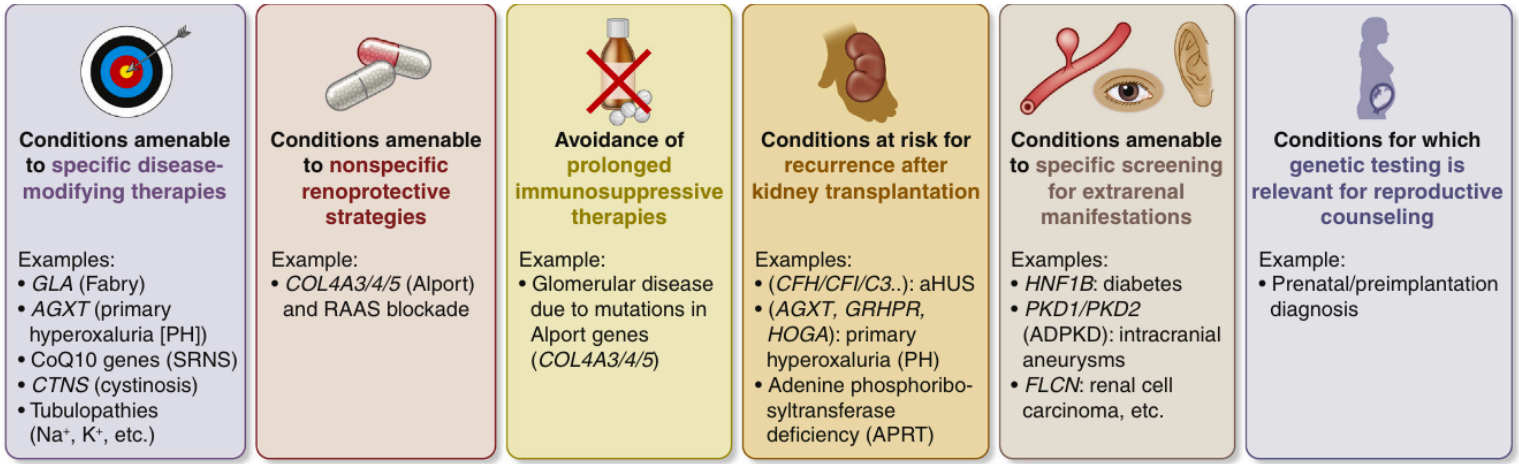


Figure 4 | Actionable genes in kidney diseases. Actionability refers to the potential for genetic test results to lead to specific clinical actions for prevention or treatment of a condition, supported by recommendations based on evidence. ADPKD, autosomal dominant polycystic kidney disease; aHUS, atypical hemolytic uremic syndrome; RAAS, renin–angiotensin–aldosterone system; SRNS, steroid-resistant nephrotic syndrome.

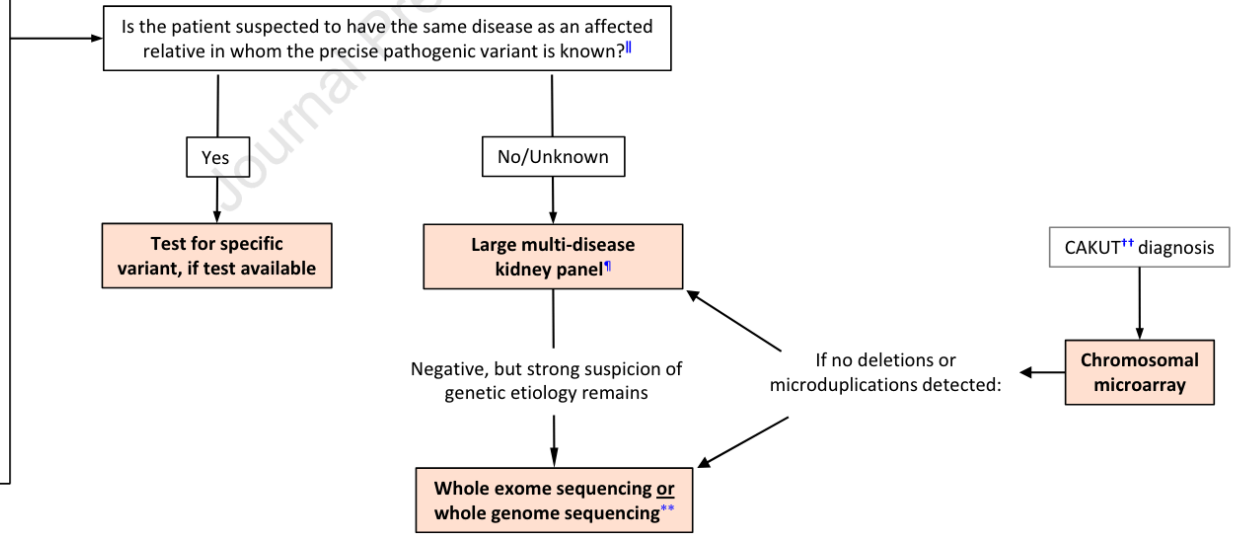
SYMPTOMATIC ADULT and PEDIATRIC PATIENTS

General recommendation for genetic testing

Genetic testing is indicated in all kidney-related abnormalities* where genetic etiology is considered after appropriate clinical evaluation.

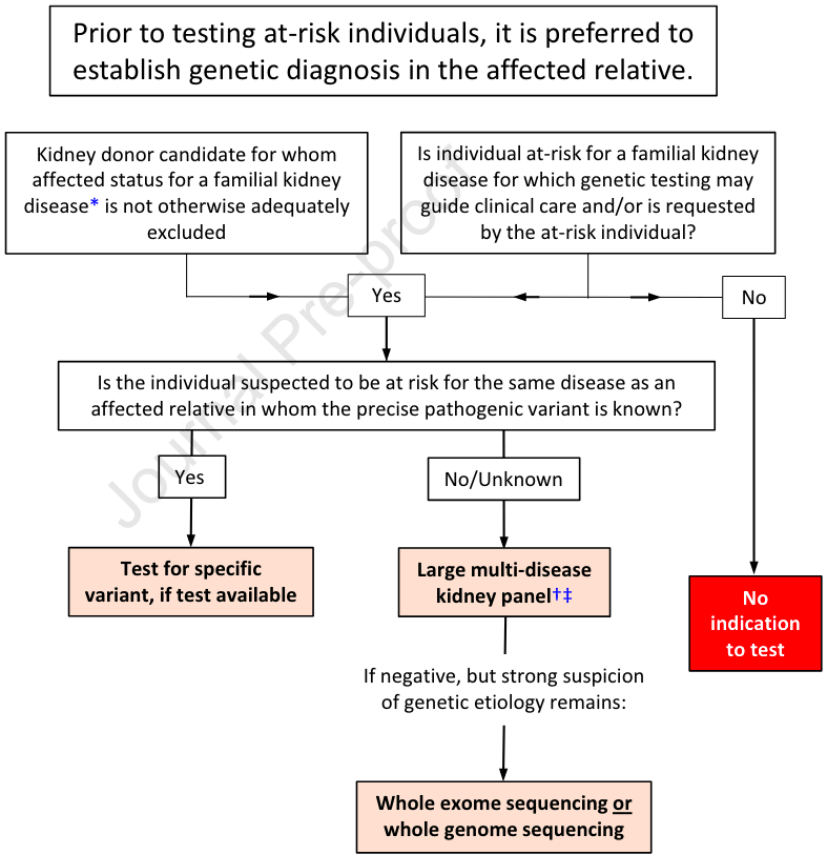
Specific recommendations for genetic testing

- Family History (see†)
- Multi-organ syndrome of unknown etiology
- Atypical clinical disease, to guide therapeutics, or is requested by the individual (reasons may include prognostication, family planning, etc.)
- Kidney biopsy findings suggestive of a genetic cause (e.g.):
  - Chronic TIN‡ with crystals§
  - FSGS without obvious secondary causes
  - Features suggestive of collagen IV nephropathy
  - TMA or idiopathic MPGN
  - Lipidoses
- CKD/ESKD of unknown etiology after a comprehensive clinical evaluation if **ANY** of the following criteria are met:
  - Age < 50 years
  - Patient's blood relative is considering kidney donation
  - Diagnosis may aid in management of extra-renal manifestations
- Evaluation of patients with atypical cystic kidney or liver disease and no family history
- Testing will end a diagnostic odyssey
- Test is for kidney donor evaluation



Franceschini et al., AJKD 2024

AT-RISK ADULT and PEDIATRIC INDIVIDUALS



Franceschini et al., AJKD 2024

Patient Questions

- What is this disease?
- Why do I have this disease?
- What will happen to me?
- What are the treatment options?

- “Doctor, should we perform genome sequencing to answer some of these questions?”

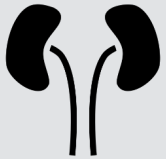
Genome or Exome Sequencing of 5,727 Patients with CKD

CureGN: N= 1913 | Columbia-GN, N=1098 | Columbia-CKD, N= 2716

Diagnostic Yield

Monogenic Nephropathies N= 371 (6.5%)

High-risk *APOL1* Genotypes N= 318 (5.5%)



Kidney Failure

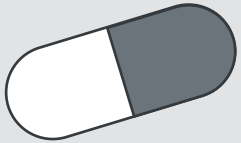
HR = 1.72 (1.38 – 2.14)

HR = 1.67 (1.42 – 1.96)

eGFR Decline

3.31 mL/min/year faster decline

2.50 mL/min/year faster decline



Lack of Complete Remission

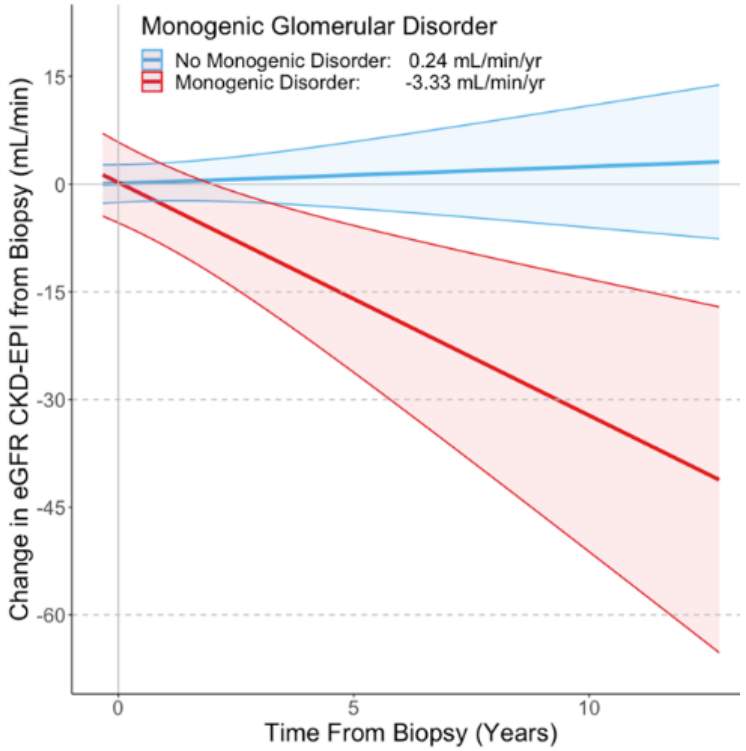
OR = 5.25 (2.56 – 10.77)

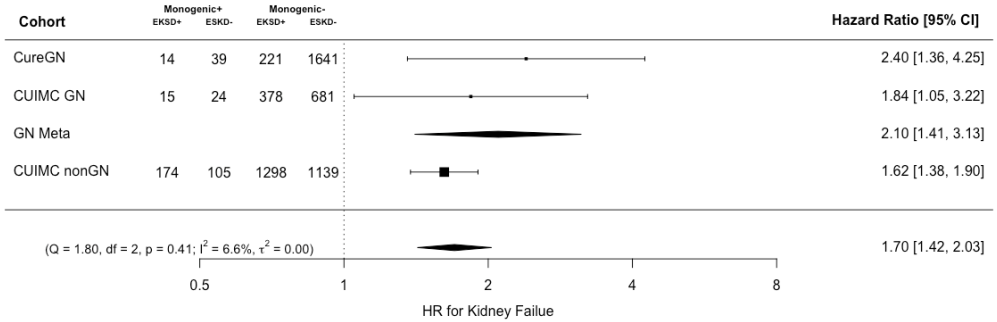
OR = 1.36 (0.79 – 2.31)

Elliot et al., JCI 2024

Mean follow up time 2-5 years

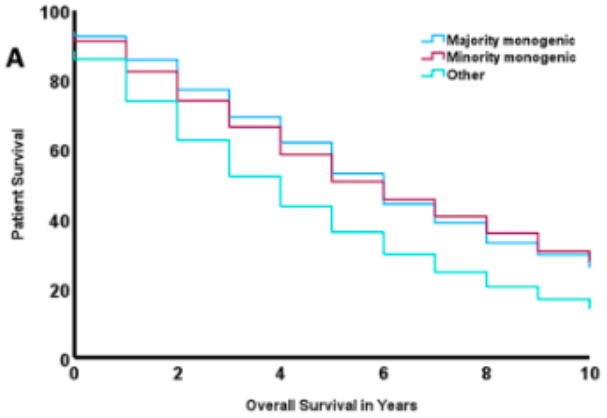
Monogenic Disorder have a Faster Progression to ESKD (5734 adults and children with kidney disease)

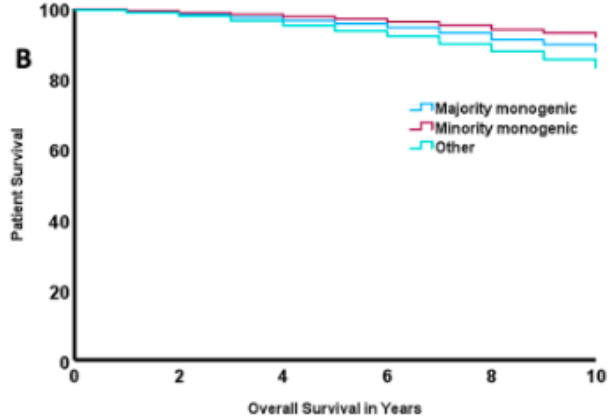




Elliot et al., JCI 2024

Patients with Genetic Diseases May Have Reduced Mortality after Kidney Failure





Number at Risk

Majority Monogenic	2051	1859	1225	784	489	328
Minority Monogenic	1914	1594	1020	630	426	271
Other	47103	38174	22336	12632	6891	3767

Number at Risk

Majority Monogenic	3455	3405	3166	2819	2490	2133
Minority Monogenic	2850	2822	2670	2439	2190	1936
Other	15483	15273	14242	12582	10799	9086

Figure 2. Unadjusted Kaplan Meier curves for patient survival after starting kidney replacement therapy – (**A**) dialysis, (**B**) kidney transplant.

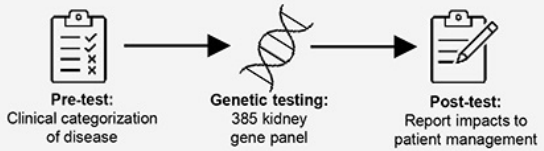
Han et al. Scientific Rep 2024

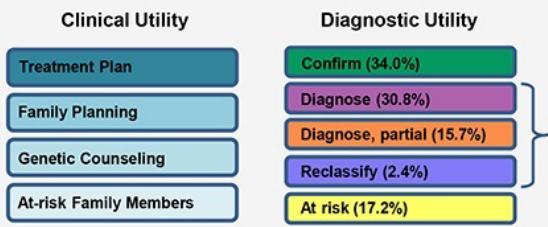
The Clinical Utility of Genetic Testing in the Diagnosis and Management of Adults with Chronic Kidney Disease

JASN
JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY

METHODS

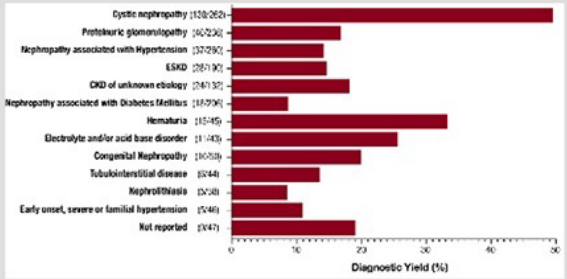
RenaCARE (NCT05846113)
N=1623



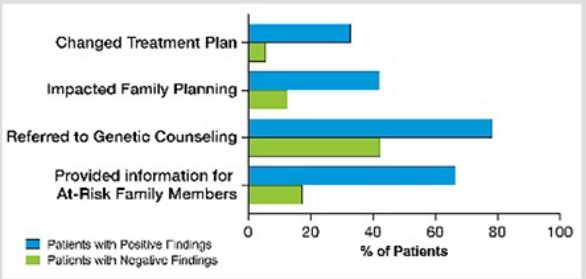


RESULTS

Diagnostic yield = 20.8%
(Range: 8.6% – 49.6% across disease categories)



Management Impacts reported for 90.7% of Patients with Positive Genetic Findings



New* or reclassified diagnosis established in 48.8% of Positive cases
(New: diagnose + diagnose, partial)

CONCLUSION: Genetic testing with a CKD-focused 385-gene panel substantially refined clinical diagnoses and had widespread implications for clinical management.

doi: 10.1681/ASN.0000000000000249

Dahl et al., JASN 2023

Examples of Monogenic Kidney Disease with Specific Therapies

Syndrome	Gene(s)	Therapy
Liddle Syndrome	*SCNN1A, SCNN1B or SCNN1G*	Amiloride
Pseudohyperaldosteronism type II	*KCNJ5*	Thiazide diuretics
Corticosteroid remediable aldosteronism	*CYP11B2/CYP11B1* gene fusion	Glucocorticoids
Familial Hyperaldosteronism, type II	*CLCN2*	Aldosterone antagonists
Familial Hyperaldosteronism, type III	*KCNJ5*	Aldosterone antagonists
Fabry Disease	*GLA*	Alpha-galactosidase enzyme replacement
COQ10 deficiency	*COQ2, COQ6, ADCK2/COQ8B, PDSS2, or MTTL1*	CoQ10 replacement
Primary Hyperoxaluria 1	*AGXT*	RNAi therapy
APOL1 associated nephropathy	*APOL1*	Clinical trials ongoing

A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study

Jesse J Swen, Cathelijne H van der Wouden, Lisanne EN Manson*, Heshu Abdullah-Koolmees, Kathrin Blagec, Tanja Blagus, Stefan Böhringer, Anne Cambon-Thomsen, Erika Cecchin, Ka-Chun Cheung, Vera HM Deneer, Mathilde Dupui, Magnus Ingelman-Sundberg, Siv Jonsson, Candace Joefield-Roka, Katja S Just, Mats O Karlsson, Lidija Konta, Rudolf Koopmann, Marjolein Kriek, Thorsten Lehr, Christina Mitropoulou, Emmanuelle Rial-Sebbag, Victoria Rollinson, Rossana Roncato, Matthias Samwald, Elke Schaeffeler, Maria Skokou, Matthias Schwab, Daniela Steinberger, Julia C Stingl, Roman Tremmel, Richard M Turner, Mandy H van Rhenen, Cristina L Dávila Fajardo, Vita Dolžan, George P Patrinos, Munir Pirmohamed, Gere Sunder-Plassmann, Giuseppe Toffoli, Henk-Jan Guchelaar, on behalf of the Ubiquitous Pharmacogenomics Consortium†*

Gene	PREPARE drug for which actionable DPWG guideline is available
CYP2B6	Efavirenz
CYP2C9	Phenytoin Warfarin
CYP2C19	Citalopram Clomipramine Clopidogrel Escitalopram Imipramine Sertraline Voriconazole
CYP2D6	Amitriptyline Aripiprazole Atomoxetine Clomipramine Codeine Doxepin Flecainide Haloperidol Imipramine Metoprolol Nortriptyline Paroxetine Pimozide Propafenone Tamoxifen Tramadol Venlafaxine Zuclopenthixol
CYP3A5	Tacrolimus
DPYD	5-Fluorouracil, Capecitabine, Tegafur
F5	Estrogen contraceptive, agents
HLA-B	Carbamazepine Oxcarbazepine Phenytoin, Lamotrigine, Abacavir, Flucloxacillin
SLCO1B1	Atorvastatin, Simvastatin
TPMT	6-Mercaptopurine Azathioprine Thioguanine
UGT1A1	Irinotecan
VKORC1	Acenocoumarol, Phenprocoumon, Warfarin

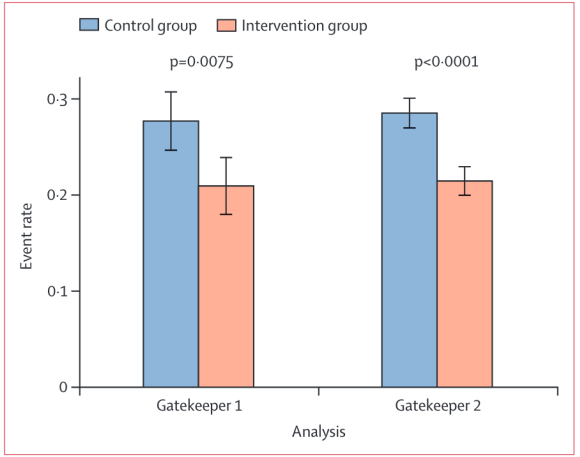


Figure 2: **Frequency of causal clinically relevant adverse drug reactions in patients with an actionable test result**
Error bars represent 95% CIs for event rates. p values for intergroup differences were based on the mixed-effects models used in the primary analysis. An actionable test result was defined as a drug–gene interaction for which the Dutch Pharmacogenetics Working Group guidelines recommended a change to standard-of-care drug treatment.

Swen et al., Lancet 2023

Population Pharmacokinetic Model for Tracrolimus Dosing

A prospective controlled, randomized clinical trial of kidney transplant recipients developed personalized tacrolimus dosing using model-based Bayesian Prediction.

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Methods and cohort

Clinical trial : Two-arm, Randomized, Open-label , single-center
Designed as a superiority study (30%)

OPTIMUS

N=96
Kidney Transplant Recipients

Day 0 — Basiliximab, MMF and steroids

Intervention

N=50
Control
Tacrolimus dosage following Manufacturer's labelling

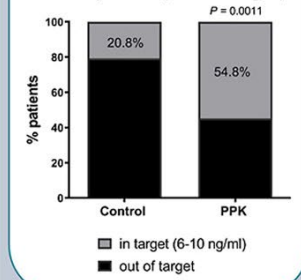
N=46
PPK model
Tacrolimus dosage following
CYP3A4 & CYP3A5 genotype

Next doses calculation:
Previous Tac C_0, CYP3A4 & CYP3A5 genotype, Age and hematocrit

Findings

Primary endpoint:

Proportion of patients within therapeutic target in the first steady-state (30% margin):



Secondary endpoints (90 days of follow-up):

Patients achieved faster tacrolimus therapeutic target concentration (6-10 ng/mL)
5 days (PPK) vs 10 days (Control) $P<0.05$

Patients showed less intra-patient variability
24.7 (PPK) vs 35.8 (Control) $P<0.05$

Patients had a lower number of dose modifications
1 (PPK) vs 2.6 (Control) $P<0.05$

There was a lower percentage of patients with overexposure or infraexposure to tacrolimus
26% (PPK) vs 55% (Control) $P<0.05$

No statistically significant differences were observed in clinical outcomes

Lloberas et al, 2023

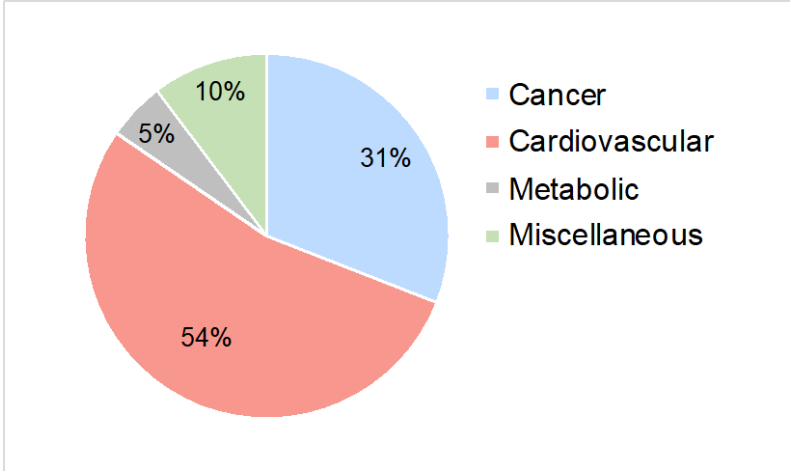
CONCLUSION: PPK-based tacrolimus dosage offers significant superiority for starting tacrolimus prescription over the classical labelling-based dosage according to the body weight, which may optimize Tac-based therapy since the first days after transplantation.

Lloberas et al. Kidney International 2023

Exome Sequencing & Incidental Findings in 1-2% of the population

ACMG STATEMENT | Genetics inMedicine

Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics



N=97

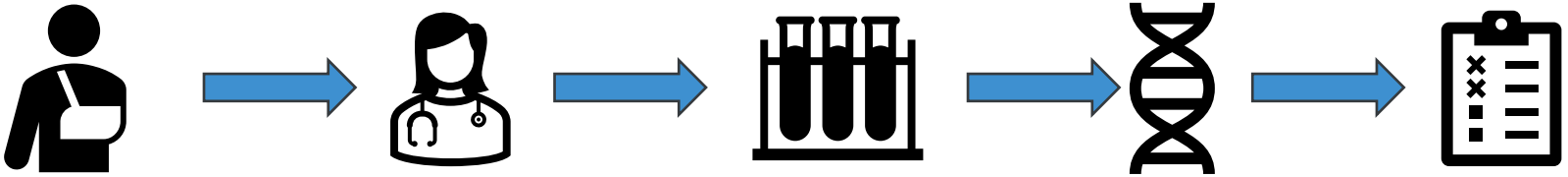
Table 2 Semiquantitative metric to score clinical actionability

Domain	Scores
Severity: what is the nature of the threat to health to an individual carrying a clearly deleterious allele in this gene?	3 = Reasonable possibility of sudden death 2 = Reasonable possibility of death or major morbidity 1 = Modest morbidity 0 = Minimal or no morbidity
Likelihood of disease: what is the chance that a serious outcome will materialize given a deleterious variant (akin to penetrance)?	3 = >40% chance 2 = 5–39% chance 1 = 1–4% chance 0 = <1% chance
Effectiveness of specific interventions: how effective is the selected, specific intervention for preventing or significantly diminishing the risk of harm?	3 = Highly effective 2 = Moderately effective 1 = Minimally effective 0 = Controversial or unknown effectiveness IN = Ineffective/no intervention[a]
Nature of intervention: how risky, medically burdensome, or intensive is a given intervention?	3 = Low risk, or medically acceptable and low-intensity interventions 2 = Moderate risk, moderately acceptable or intensive interventions 1 = Greater risk, less acceptable and substantial interventions 0 = High risk, poorly acceptable or intensive interventions
State of the knowledge base: what is the level of evidence?	A = Substantial evidence, or evidence from a high tier (tier 1) B = Moderate evidence, or evidence from a moderate tier (tier 2) C = Minimal evidence, or evidence from a lower tier (tier 3 or 4) D = Poor evidence, or evidence not provided in the report E = Evidence based on expert contributions (tier 5)

[a]Do not score the remaining categories.

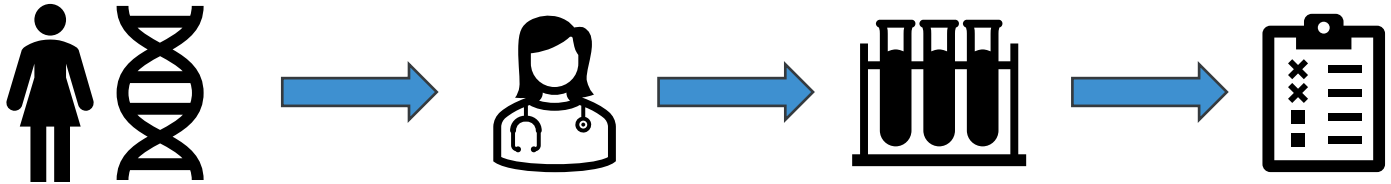
Hunter at. Al, Genet Med 2016

Current Paradigm



patient physician Workup Genetic testing Plan

Future Paradigm



Patient + Genome Sequence physician Workup Plan

Summary

- Monogenic kidney diseases may be present in ~10% of CKD patients
- The prevalence of genetic disease varies by age, family history and clinical diagnosis, and referral population studied
- The detection of genetic disease has many implications for disease management, including therapy
- Other useful information in genetic testing include risk alleles, carrier screening and pharmacogenetics
- Predictive testing for kidney disorders will require better curation of variant databases and may need to be restricted to selected, well studied genes

Online Resources

- **Online Mendelian Inheritance in Man (OMIM.org)**
- **GeneReviews (NCBI Bookshelf)**
- **MedlinePlus/Genetics (formerly genetic home reference, National Library of Medicine)**
- **National Organization for Rare Disorders (NORD)**
- **ClinGen (clinicalgenome.org)**
- **American Society Medical Genetics**