KIDNEYCODE: A Genetic Testing Program for Patients with Chronic Kidney Disease

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Authors and Disclosures

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SM, JM and CJM are employees of Reata Pharmaceuticals
KR is an employee of Invitae
BW (has entered details into ASN portal)
ARC has participated in an advisory board and has been a speaker for Reata Pharmaceuticals

*K**ID**NEYCODE is not intended to promote any Reata Pharmaceuticals, Inc. product or clinical program. This presentation is for informational purposes only.*

Introduction

RATIONALE – Genetic Testing

In a recent whole-exome sequencing (WES) study, approximately 10% of patients had a genetic cause of their chronic kidney disease (CKD), many of which were previously undiagnosed or mis-diagnosed[1]

6% of patients previously diagnosed with focal segmental glomerular sclerosis (FSGS) had a mutation in *COL4A3, 4*, or *5*, and therefore had Alport syndrome (AS)

Additionally, smaller WES-based gene panels have been used to screen patients for specific types of glomerular and cystic CKDs[2]

This gene panel approach provides diagnostic precision results similar to WES, with the benefit of simpler data analysis and test result reporting[3]

The International Society of Nephrology recommends the adoption of genetic testing to provide precision medicine based on individual risk[4], and with continued advances in DNA sequencing technology, genetic testing is feasible for routine clinical evaluation[5]

However, genetic testing in adults with CKD remains an under-used diagnostic tool[5], and knowledge of genotype-phenotype associations of CKD remains a critical barrier to progress in kidney research[4]

AIM

To facilitate a personalized, precision medicine-based approach to CKD diagnosis, and contribute to the global understanding of genetic causes of CKD

APPROACH

A sponsored, no-charge genetic testing program, including genetic counseling, was designed for use in a subset of patients with CKD defined by a specific set of inclusion criteria

1. Groopman EE, N Engl J Med. 2019 2. Yao T, Clin J Am Soc Nephrol. 2019 3. Gribouval O, Kidney Int. 2018 4. Levin A, Lancet. 2017 5. Harris P, Kidney Int. 2018

Methods

K**ID**NEYCODE is a no-charge genetic testing program and is a joint project between Reata Pharmaceuticals and Invitae

K**ID**NEYCODE uses Invitae's Progressive Renal Disease panel that includes 18 genes

The panel is designed to enable diagnosis of three specific rare monogenic causes of CKD:

- Alport syndrome (AS)
- Polycystic kidney disease (PKD) due to mutations in *PKD2* or *PKHD1*
- Focal segmental glomerular sclerosis (FSGS)

Progressive Renal Disease Panel					
Condition	**FSGS**		**AS**	**PKD**	**Other**
Genes	*ACTN4*	*LMX1B*	*COL4A3*	*PKD2*	*HNF1A* – Maturity-onset diabetes of the young (MODY), type 3
	ANLN	*MYO1E*	*COL4A4*	*PKHD1*	
	*APOL1**	*NPHS1*	*COL4A5*		*PAX2* – Papillorenal syndrome
	CD2AP	*NPHS2*			
	CRB2	*TRPC6*			
	INF2				

**SEQUENCING ASSAY*APOL1 was added to the panel after the cutoff date for the current analysis*

Invitae's sequencing assay uses next-generation sequencing (NGS) techniques performed with blood or saliva samples on an Illumina platform

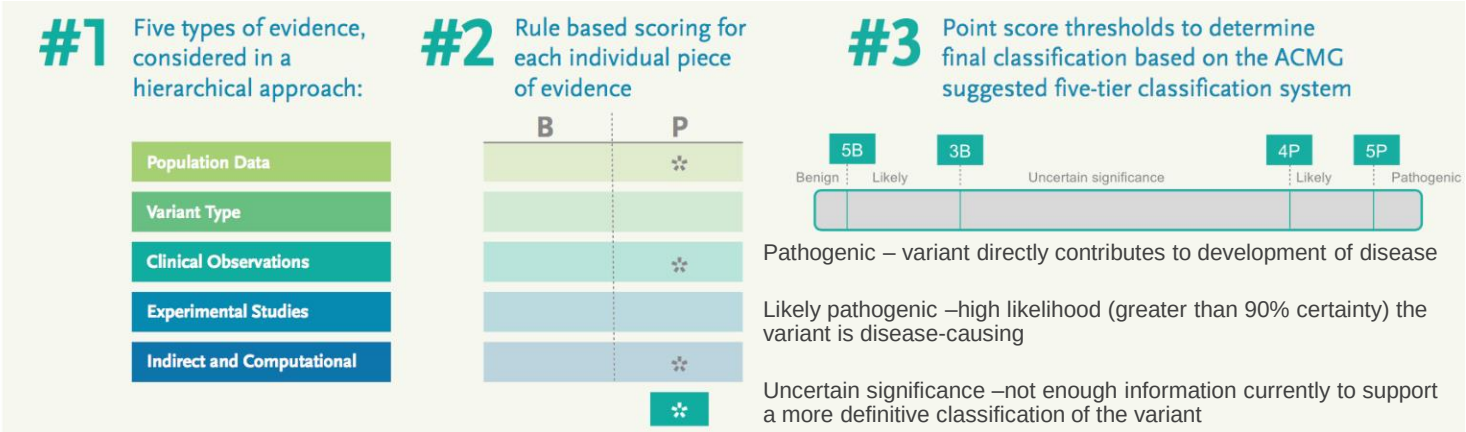
The assay includes both full-gene sequencing and intragenic deletion/duplication analysis. The assay targets the coding exons and flanking 10 base pairs of intronic sequences

The platform detects:

- Single nucleotide variants (SNVs);
- Small insertions and deletions - reliably detects deletions/duplications of ≥4 exons;
- Copy number variants (CNVs);

Average read depth is 150x; 20x min read depth for reported regions

VARIANT INTERPRETATION[1,2] (Sherloc)



Pathogenic – variant directly contributes to development of disease

Likely pathogenic –high likelihood (greater than 90% certainty) the variant is disease-causing

Uncertain significance –not enough information currently to support a more definitive classification of the variant

De-identified variant results are reported to ClinVar[3]

1. Nykamp K, Genet Med. 2017 2. Richards S, Genet Med. 2015 3. Landrum MJ, Nucleic Acids Res. 2018

Program Details

REQUIRED ELIGIBILITY

eGFR ≤ 90mL/min/1.73m^2

AND

At least one of the following:

- □ Hematuria
- □ Family history of kidney disease

OR

At least one of the following:

- □ Suspected or biopsy-confirmed AS
- □ Suspected or biopsy-confirmed FSGS
- □ Family member of a patient with a biopsy-confirmed or suspected diagnosis of AS
- □ Family member of a patient with a biopsy-confirmed or suspected diagnosis of FSGS

REQUESTED CLINICAL INFORMATION

- □ Diabetic related
- □ Hypertension related
- □ IgA Nephropathy (IgAN)
- □ FSGS
- □ AS
- □ ADPKD
- □ Familial hematuria
- □ Benign familial hematuria
- □ Congenital familial hematuria
- □ Benign hereditary nephritis
- □ Thin basement membrane nephropathy (TBMN)

GENETIC COUNSELING

Genetic counseling is available to physicians and patients at no additional charge:

- Physicians: directly via Invitae's Client Services
- Patients: through a third-party company, Gene Matters™

AS: Alport syndrome FSGS: focal segmental glomerular sclerosis ADPKD: autosomal dominant polycystic kidney disease

Program Use and Patient Characteristics

Tests results were collected between August 22, 2019 and September 2, 2020 in the United States

1098 tests were ordered by 510 physicians

676 test results available for analysis

Required Eligibility Criteria	Total Reported	P/LP		VUS	
	N	N	%	N	%
eGFR < 90 mL/min/1.73m^2	297	75	25	87	29
Hematuria	301	105	35	95	32
Family history of kidney disease	262	97	35	87	33
Suspected/biopsy-confirmed FSGS/AS	31	8	26	9	29
Family member of patient with biopsy-confirmed/suspected FSGS/AS	510	168	33	139	28

Majority of patients have been a family member of patient with suspected or biopsy-confirmed AS or FSGS

eGFR < 90 mL/min/1.73m^2, hematuria, and family history of kidney disease were common inclusion criteria met to qualify for the program

P: Pathogenic LP: Likely Pathogenic VUS: Variant of Uncertain Significance

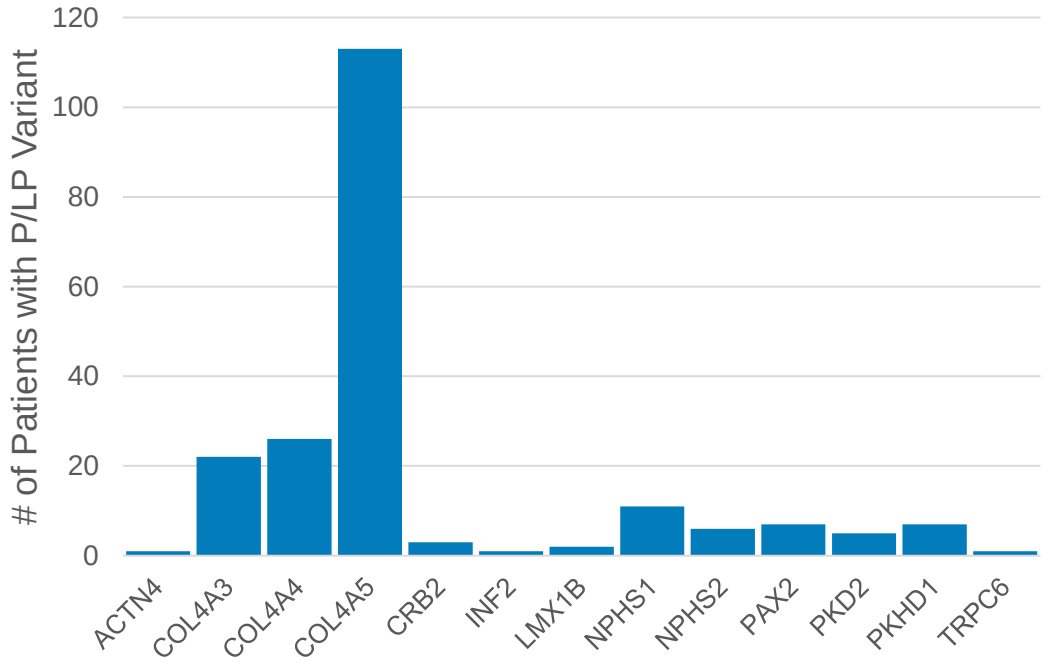
Variant Interpretation

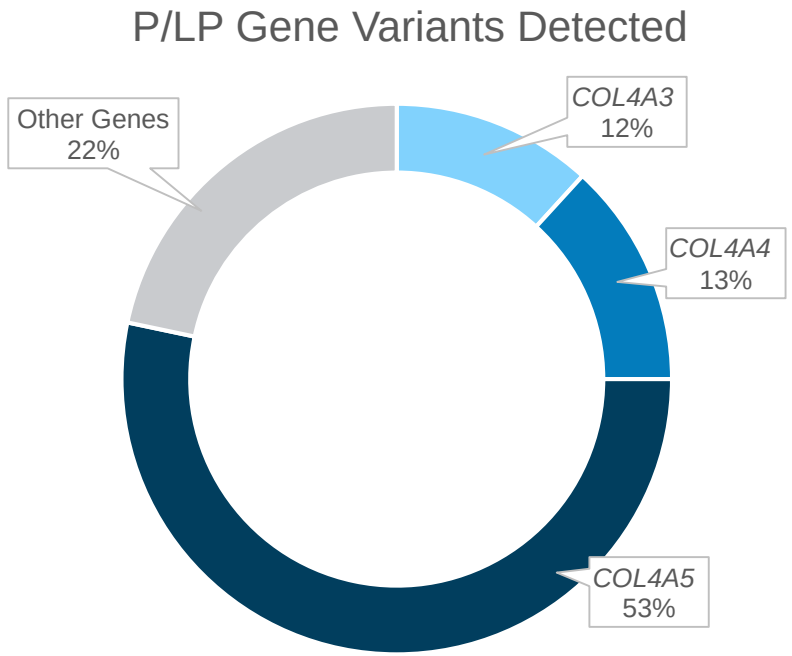
Whole Data Set

- 58% of patients had a variant in at least one of the 17 genes tested*
- Of those with variants detected, 42% had pathogenic (P), 13% had likely pathogenic (LP), and 80% had a variant of uncertain significance (VUS)

Gene Level

- Number of P/LP variants are indicated for each gene below
- Most P/LP variants detected were in *COL4A3, 4, or 5* (78% of all P/LP genes detected)





**APOL1 was added to the panel after the cutoff date for the current analysis*

COL4A3/4/5 Variants: Previous Diagnosis

63% of patients who previously reported a diagnosis of AS leading to CKD had a P/LP *COL4A* variant

Familial hematuria (38%) and TBMN (24%) were frequently reported prior diagnoses of patients with a P/LP *COL4A* variant

Other prior diagnoses of patients with a P/LP *COL4A* variant included FSGS, hypertension related CKD, and IgAN

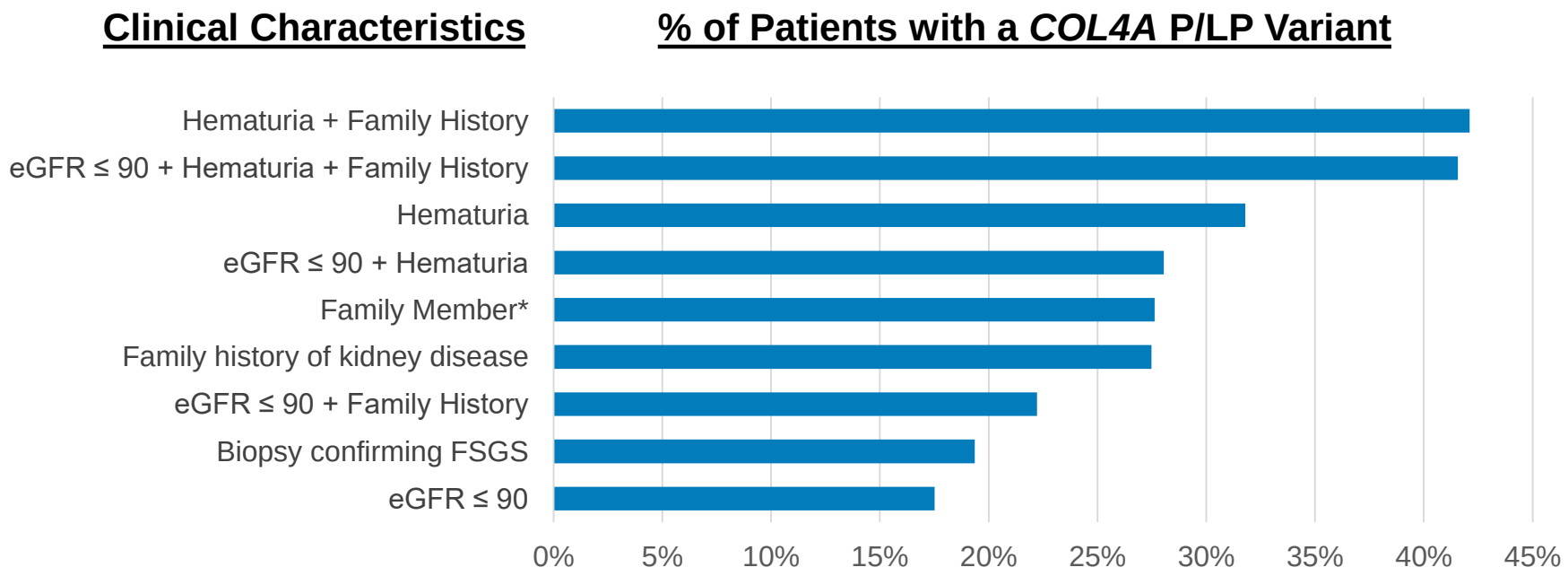
Prior Diagnosed Forms of CKD	Patients with a *COL4A* variant		No *COL4A* variant detected
	P/LP	VUS	
Alport Syndrome	67	19	20
Familial hematuria	24	21	19
TBMN	11	15	19
FSGS	9	10	110
Hypertension related	4	4	25
IgA nephropathy	3	2	4
ADPKD	0	4	24
Congenital familial hematuria	3	2	4
Benign familial hematuria	2	2	5
Benign hereditary nephritis	3	2	8
Diabetic related	0	0	10

P: Pathogenic LP: Likely Pathogenic VUS: Variant of Uncertain Significance

Detection Rates in *COL4A3/4/5* Variants

Clinical characteristics were predictive of finding a P/LP variant in one of the *COL4A* genes

Family history of CKD and hematuria were the strongest predictors



* Family member of a patient with suspected or biopsy-confirmed AS or FSGS

Conclusions

With 1098 tests ordered in 12 months, K**ID**NEYCODE has been used extensively, signifying the utility of genetic testing in patients with CKD

30% of patients who met the eligibility requirements had a P/LP variant in one of the genes on the Progressive Renal Disease panel

P/LP variants in *COL4A 3, 4 & 5* were the most frequently observed P/LP variants in the patient population defined by the K**ID**NEYCODE eligibility criteria (78%)

Presence of hematuria and a family history of CKD were strong predictors of a P/LP *COL4A* variant

Required clinical eligibility criteria mimic clinical presentation of patients with AS, potentially indicating a selection bias favoring testing of AS patients and family members

For more information and ordering protocol, visit: www.Invitae.com/chronic-kidney-disease