Abstract # 281

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

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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]
  - 16% 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

METHODS

- Sponsored, no-charge genetic testing is being offered through a program K**ID**NEYCODE, a joint project between Reata Pharmaceuticals and Invitae

GENE PANEL

- K**ID**NEYCODE uses Invitae's Progressive Renal Disease panel that includes 17 genes (below)
- The panel is designed to enable diagnosis of three specific rare monogenic causes of CKD:
  - Alport syndrome (AS);
  - Polycystic kidney disease (PKD);
  - 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*	*PAX2* – Papillorenal syndrome
	CD2AP	*NPHS1*	*COL4A5*		
	CRB2	*NPHS2*			
	INF2	*TRPC6*			

SEQUENCING ASSAY

- 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

- Variant interpretation uses a weighted score-based refinement of the ACMG-AMP variant classification criteria (Sherloc)[6] – population data, variant type, clinical observations, experimental studies, and indirect computational methods are considered; and a rule-based scoring of each individual piece of evidence is done
- Point score thresholds determine final classification based on ACMG suggested five-tier classification system[7]
- Pathogenic (P) and likely pathogenic (LP) variants, and variants of uncertain significance (VUS) are reported to the physician ordering the test
  - 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 information results are reported to ClinVar[8]

Required Program Eligibility		
eGFR ≤ 90mL/min/1.73m²		*At least one of the following*
AND		
At least one of the following:	**OR**	□ Suspected or biopsy-confirmed AS or FSGS
□ Hematuria		□ Family member of a patient with a biopsy-confirmed or suspected diagnosis of AS or FSGS
□ Family history of kidney disease		
Optional Clinical Information		
Has a patient ever been diagnosed with any of the following forms of CKD:		
□ Diabetic related		□ Familial hematuria
□ Hypertension related		□ Benign familial hematuria
□ IgA nephropathy (IgAN)		□ Congenital familial hematuria
□ FSGS		□ Benign hereditary nephritis
□ AS		□ Thin basement membrane disease (TBMD)
□ ADPKD		

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™

PROGRAM USE

- Tests results were collected between August 22, 2019 and May 13, 2020 in the United States
- 736 tests were ordered by 390 physicians
- 679 patient-deidentified results have been collected (455 test results available for analysis)

PATIENT CHARACTERISTICS

	Total Reported	P/LP		VUS	
	N	N	%	N	%
eGFR < 90 mL/min/1.73m²	201	51	25	83	41
Hematuria	196	70	36	88	45
Family history of kidney disease	173	63	36	76	44
Suspected/biopsy-confirmed FSGS/AS	28	7	25	9	32
Family member of patient with biopsy-confirmed/suspected FSGS/AS	348	117	34	128	37

This table shows the clinical characteristics of patients who qualified for genetic testing based on the required program eligibility criteria. Gene variants identified in each eligibility criteria category is also shown. P/LP: pathogenic or likely pathogenic variant; VUS: variant of uncertain significance.

- Majority of patients tested to date have been a family member of patient with suspected or biopsy-confirmed AS or FSGS
- eGFR less than 90 mL/min/1.73m², hematuria, and family history of kidney disease were common inclusion criteria met to qualify for the program

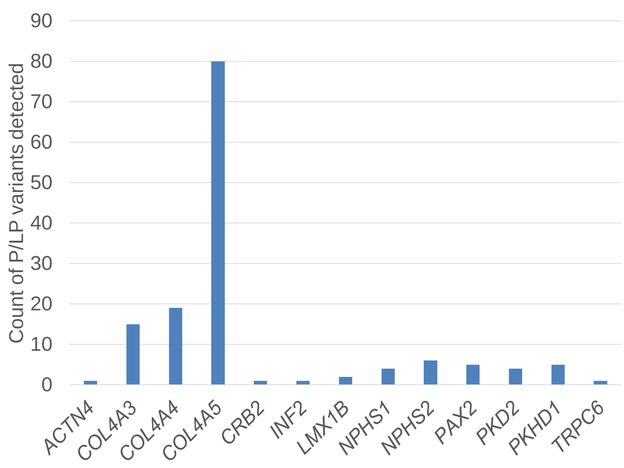
VARIANT INTERPRETATION

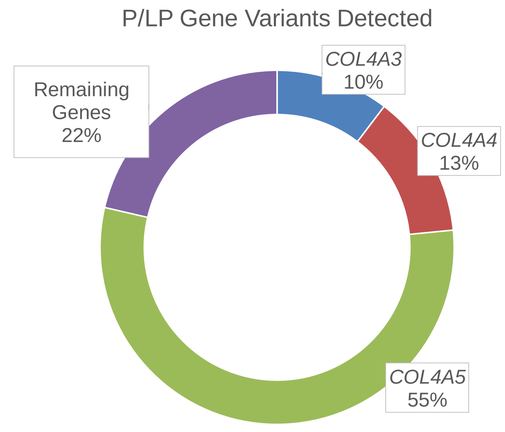
WHOLE DATA SET

- 61% of patients had a variant in at least one of the 17 genes tested
- Of those with variants detected, 40% had pathogenic (P), 10% had likely pathogenic (LP), and 63% had a variant of uncertain significance (VUS)

GENE LEVEL

- Count 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)





COL4A3/4/5 VARIANTS

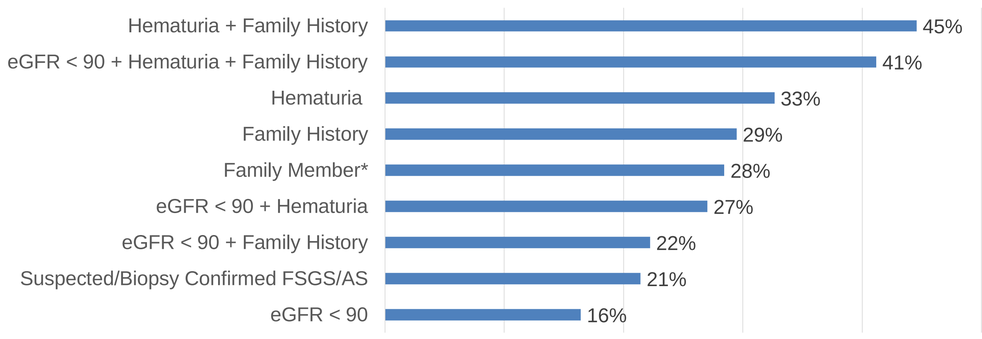
PREVIOUS DIAGNOSES

- Most patients (82%) who previously reported a diagnosis of AS leading to CKD had a *COL4A* variant
- Familial hematuria (76%) and TBMD (64%) were frequently reported prior diagnoses of patients with a *COL4A* variant
- Other prior diagnoses of patients with a *COL4A* variant included FSGS, hypertension related CKD, and IgAN

Prior Diagnosed Forms of CKD	Number of patients with *COL4A* variant	
	Total (P/LP/VUS)	None
FSGS	13	89
AS	65	14
Familial hematuria	31	10
TBMD	23	13
Hypertension related	7	15
ADPKD	3	12
IgAN	4	4
Congenital familial hematuria	4	2
Benign hereditary nephritis	3	3
Benign familial hematuria	2	4
Diabetic related	0	6

DETECTION RATES

- 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

CONCLUSION

- With 736 tests ordered in 9 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
- Variants in *COL4A 3, 4* and *5* were the most frequently observed 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 *COL4A* variant
- Required clinical eligibility criteria mimics 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

DISCLOSURES

KR is an employee and stockholder of Invitae Inc.
SM, LMH, JM, and CJM are employees and stockholders of Reata Pharmaceuticals.
PD, GB, KG, BW, and AC are consultants to Reata Pharmaceuticals.

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Presented at the European Renal Association – European Dialysis and Transplant Association June 6-9, 2020; Milan, Italy.