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Clinical Utility of Genetic Testing in the Precision Diagnosis and Management of Pediatric Patients with Kidney and Urinary Tract Diseases

Nasim Bekheirnia,[1] Kevin E. Glinton,[2] Linda Rossetti,[2] Joshua Manor,[2] Wuyan Chen,[3] Dolores J. Lamb,[4] Michael C. Braun,[1] and Mir Reza Bekheirnia[1,2]

Abstract

Background As genetic testing increasingly integrates into the practice of nephrology, our understanding of the basis of many kidney disorders has exponentially increased. Given this, we recently initiated a Renal Genetics Clinic (RGC) at our large, urban children's hospital for patients with kidney disorders.

Methods Genetic testing was performed in Clinical Laboratory Improvement Amendments–certified laboratories using single gene testing, multigene panels, chromosomal microarray, or exome sequencing.

Results A total of 192 patients were evaluated in this clinic, with cystic kidney disease (49/192) being the most common reason for referral, followed by congenital anomalies of the kidney and urinary tract (41/192) and hematuria (38/192). Genetic testing was performed for 158 patients, with an overall diagnostic yield of 81 out of 158 (51%). In the 16 out of 81 (20%) of patients who reached a genetic diagnosis, medical or surgical treatment of the patients were affected, and previous clinical diagnoses were changed to more accurate genetic diagnoses in 12 of 81 (15%) patients.

Conclusions Our genetic testing provided an accurate diagnosis for children and, in some cases, led to further diagnoses in seemingly asymptomatic family members and changes to overall medical management. Genetic testing, as facilitated by such a specialized clinical setting, thus appears to have clear utility in the diagnosis and counseling of patients with a wide range of kidney manifestations.

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Introduction

Genetic testing has increasingly integrated into the practice of different specialties in medicine and surgery. Within the field of nephrology, in particular, the availability of such testing led to the rapid growth and expansion of our knowledge of the clinical spectrum of monogenic kidney diseases. The genetic etiology of kidney diseases, such as polycystic kidney disease, Alport syndrome, several forms of monogenic steroid-resistant nephrotic syndrome (SRNS), and nephronophthisis has grown and can now be identified in a significant portion of affected individuals. In patients with SRNS, 30% of those diagnosed before age 25 will have a pathogenic variant in one of 30 known SRNS genes (1). Even in a condition not commonly associated with genetic causes, such as nephrolithiasis, around 15% of individuals have a specific underlying genetic etiology (2). Given the growing number of recognized disease-causing gene defects, multigene panels are now available and, in some cases, can provide adequate diagnostic coverage (3). Similarly, exome sequencing (ES) has immense utility in the diagnosis of adults and children with a variety of disorders (4,5).

With the expanding number of candidate genes and the increasing complexity of genetic testing available, the need for more comprehensive diagnostic evaluations for such patients has also increased. To address this need, a Renal Genetics Clinic (RGC) at Texas Children's Hospital (TCH) was formed in February 2015. Patients are referred from a variety of care settings, including the Pediatric Nephrology Clinic and various inpatient/outpatient services at TCH. Through this clinic, patients undergo a thorough genetic evaluation with a focus on kidney-specific malformations, complications, or diseases. Furthermore, given the nature of the clinic, family members of affected individuals can be evaluated, allowing us to provide guidance, if needed, for family planning. Extensive research shows the key roles genetic defects play in pediatric kidney disorders, and a growing number of studies are evaluating the utility of clinical genetics evaluation and

[1]Section of Pediatric Renal Disease, Department of Pediatrics, Baylor College of Medicine, Houston, Texas
[2]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas
[3]PreventionGenetics Diagnostic Laboratory, Marshfield, Wisconsin
[4]Department of Urology, Englander Institute for Precision Medicine and Center for Reproductive Genomics, Weill Cornell Medicine, New York, New York

Correspondence: Dr. Mir Reza Bekheirnia, Departments of Pediatrics/Molecular and Human Genetics, Baylor College of Medicine 1102 Bates St., Suite 245, Houston, TX 77030. Email: bekheirn@bcm.edu

genetic testing in the clinical practice (6,7). However, there is still a need to expand the knowledge in the intersection of clinical nephrology and clinical genetics. The specific objective of this study is to assess the role of clinical genetics in precision diagnosis and management of early onset pediatric kidney diseases. We hypothesized that genetic evaluation improves patient care in pediatric nephrology. Diagnostic yield and effect on medical management is reported for the first 4 years of this clinic's operations.

Materials and Methods

Study Participants

Patients were all evaluated within the RGC at TCH. The clinic was initially held on only one half day per month, but this was increased to a full clinical day monthly after approximately 18 months. Patients were referred by pediatric nephrologists on the basis of their expert opinions. Patients were interviewed and examined by a clinical geneticist, and appropriate genetic testing was recommended on the basis of their clinical history, presentation, and family history. Pretest counseling was provided. Patients consented for ES on the basis of the performing Clinical Laboratory Improvement Amendment (CLIA) laboratories' consent forms that include secondary findings (medically actionable and carrier status). The genetic variants reported in this study were classified only by CLIA laboratories. Reported variants by CLIA laboratories were evaluated by a clinical geneticist during clinical visits, aiming to provide a clinical diagnosis and to discuss pertinent management. Clinical information on subjects was collected retrospectively for the period of February 2015 to June 2019. All patients seen during this timeframe were eligible to participate. Institutional-review-board approval was obtained to perform a retrospective cross-sectional study to investigate the yield and effect of genetics evaluation. The outcome of the study was defined as the "impact" of genetic evaluation on diagnosis and management of patients, and this impact was classified into five categories: (*1*) effect on medical and/or surgical treatment (L1), (2) change of medical diagnosis (L2), (*3*) providing diagnostic certainty (L3), (*4*) subsequent evaluation of other body-system involvement (L4), and (*5*) cascade family member testing (L5). This definition, with the associated categories, has not been previously published; however, it is proposed as a future methodology for other RGCs, because it provides an overarching scoring system to combine impact stratification between clinical genetics and pediatric nephrology. The scoring system was created by a clinical geneticist and a pediatric nephrologist. To minimize the bias regarding scoring of the outcome, a pediatric nephrologist, blinded to the identifiers, reviewed the allocated scores.

Definition of Proteinuria and Nephrotic Syndrome

Patients with proteinuria and hematuria were referred from pediatric nephrology service at TCH. Proteinuria was defined as urinary protein excretion >100 mg/m^2 per day or 4 mg/m^2 per hour. Nephrotic-range proteinuria was defined as ≥1000 mg/m^2 per day or 40 mg/m^2 per hour. Microscopic hematuria was defined as the presence of more than five red blood cells per high-power field (40× magnification). CKD was defined on the basis of fulfilling one of the following clinical criteria (8):

- GFR of <60 ml/min per 1.73 m^2 for >3 months with implications for health, regardless of whether other CKD markers are present.
- GFR >60 ml/min per 1.73 m^2 that is accompanied by evidence of structural damage or other markers of functional kidney abnormalities, including proteinuria, albuminuria, renal tubular disorders, or pathologic abnormalities detected by histology or inferred by imaging. ESKD was defined as a GFR <15 ml/min per 1.73 m^2.

Genetic Testing

Testing performed by CLIA laboratories include disease-specific panels (Supplemental Table 1), chromosomal microarray (CMA), expanded next-generation sequencing panels (Total BluePrint), and ES (trio or proband only [when both parents were not available]). When appropriate, combinations of these tests were also performed to optimize diagnostic yield in cases with atypical or unclear phenotypes. Overall, for patients with isolated hematuria or proteinuria, specific panels were recommended first. For cystic kidney with suspicion of autosomal dominant polycystic kidney disease (ADPKD), a PKD panel was recommended. For patients with congenital anomalies of the kidney and urinary tract (CAKUT), ESKD of unknown etiology, and suspected nephronophthisis, broad genetic testing was recommended. Specific panels were also recommended for specific rare kidney diseases (*e.g.*, Gitelman syndrome and renal tubular acidosis). In general, for CAKUT, we tried to order CMA first and use ES when CMA was not diagnostic. For proteinuria, when we did not have an identifiable genetic variant by the panel, ES was recommended (9). Comparison analysis of detection rate between different testing modalities was not performed because the choice of genetic testing was not randomized, and, therefore, is biased to compare the detection rate of different genetic testing modalities. We expect that broad genetic testing (*e.g.*, CMA/ES) has a higher yield; however, this requires further investigation and depends on other factors, such as patient population and reasons for referral. Genomic DNA was isolated from peripheral leukocytes obtained *via* venipuncture or, less commonly, from saliva.

Interpretation of Genetic Findings

Sequencing or copy number data were generated in CLIA-certified laboratories, and data were reviewed and interpreted by clinical molecular geneticists at the performing laboratories. The reported results were correlated with clinical and family history of the patients, and a final diagnosis was confirmed by a clinical geneticist at RGC. American College of Medical Genetics and Genomics guidelines were followed throughout this process for consistent interpretation (10).

Venn-Diagram Generation

The scoring system was processed by the library in Pandas. Because this is a five-class comparison, circular Venn diagrams are challenging. Therefore, oval-shaped Venn diagrams were chosen. Modified application-programming-

interface calls were used in the Python environment to create the Venn diagram in this manuscript.

Results

A total of 192 patients were evaluated in this clinic from February 2015 to June 2019 (Table 1). Patients ranged in age from 1 day of life to 25 years of age, with a mean age of 8.7 years (SD, 6.0 years). Patients were from diverse ethnic backgrounds. The most common reason for referral was cystic kidney disease in 49 patients (26%), followed by CAKUT in 41 patients (21%), 38 patients with hematuria (20%), and 21 patients with proteinuria (11%). A further 43 patients (23%) were seen for "other" clinical diagnoses, including nephronophthisis, nephrocalcinosis, developmental delay combined with kidney disease, or overlapping phenotypes (Supplemental Table 2). Of the 192 patients, three were asymptomatic with a positive family history of ADPKD. Considering the ethics of genetic screening in asymptomatic children, genetic testing was only recommended for their affected parent. In addition, parents of two patients were not interested in genetic testing at the initial visit. Genetic testing was performed for 158 of 187 patients (85%). We were not able to perform genetic testing for 29 individuals (12 because of insurance denial, 16 families were not interested in pursuing genetic testing, and one was not available at the time of testing). Information regarding detection rates of different tests among variable indications for referral can be found in Supplemental Table 3. Among 158 patients, 81 (51%) had positive diagnostic results (Table 2). The type of genetic testing (*e.g.*, panel, CMA, ES, and Total BluePrint) and post-test recommendations are summarized in Table 2. In an additional five patients, the patients' phenotypes were partially explained by genetic workup (Supplemental Table 4).

Among 158 patients, 115 variants of uncertain significance were detected in 42 patients. These variants were all reviewed by a clinical geneticist, their significance was reevaluated on the basis of the patient's history, and further recommendations were provided to clarify their significance. The challenges of interpretation of these variants of uncertain significance are summarized in Supplemental Table 5.

Given the breadth of diagnoses encountered, no single test was universally applicable to every patient. Different tests, or a combination of tests, were recommended and completed for patients depending on the specificity of their clinical phenotype or reported history through different CLIA laboratories. For patients with CAKUT (41 patients; tests completed for 33), for instance, CMA or a combination of CMA with ES ultimately led to a diagnostic yield of 42% (14/33; including the partially diagnosed cases). However, in patients who presented with cystic kidney, the use of a multigene panel was the most successful approach to provide a genetic diagnosis in 79% (15/19) patients. Multigene panel testing also had a high detection rate for patients with proteinuria (seven out of ten patients; 70%) and hematuria (ten out of 15 patients; 67%).

Our testing approach led to the identification of pathogenic or likely pathogenic single nucleotide variants (SNVs) in 34 genes (Table 2). Similarly, 11 different pathogenic or likely pathogenic copy number variants (CNVs) were also identified, ranging from single exon deletions to large megabase-sized deletions of multiple genes. Pathogenic SNVs or CNVs were found most commonly in *PKD1* (15), followed by *COL4A5* (14), *HNF1B* (4), *COL4A4* (4), *WT1* (4), and *PKHD1* (4). Secondary findings of *BRCA2* pathogenic variants were identified in two families; they were provided with appropriate genetic counseling.

Pathogenic or likely pathogenic variants in *PKD1*, their strength, and age of diagnoses are summarized in Table 3. Out of 15 variants in *PKD1*, seven are truncating, four are missense, one was a partial gene deletion, one was an in-frame indel, and two were splice-site variants that likely do not cause truncation, but cause exon skipping. Missense variants all have a Combined Annotation Dependent Depletion score of >20, which put them in the top 1% of deleterious variants in the human genome. Therefore, these variants are likely to put the patients at high risk of progression. However, truncating variants pose a higher chance of reaching ESKD at a younger age (11).

Table 1. Demographics and indications for referrals among 192 patients evaluated at Renal Genetics Clinic between 2/2015 and 6/2019

Characteristic	Value
Sex, *n* (%)	
Male	102 (53)
Female	90 (47)
Total patients evaluated, *n*	192
Ethnicity, *n* (%)	
White	67 (35)
Latino	67 (35)
Black	29 (15)
Mixed	25 (13)
Other	3 (2)
Asian	1 (0.1)
Age at evaluation	
Mean (SD) in yr	8.7 (6.0)
Range	1 d–25 yr
Initial indications for referral, *n* (%)	
Cystic kidney disease	49 (26)
Congenital anomalies of the kidney and urinary tract	41 (21)
Other	43 (23)
Hematuria	38 (20)
Proteinuria	21 (11)

Effect on Precision Diagnosis and Management

To assess the effect of genetic testing and evaluation on patients' management, each patient with a positive result was scored according to a five-level scoring system as defined in the *Methods*. Out of 81 positive diagnostic results, 16 (20%) affected immediate medical or L1, and 12 (15%) prior L2 Details regarding L1 and L2 effects on management are summarized in Table 4. The most common indication of referral among these patients with L1 impact was nephrotic syndrome or proteinuria, a condition where medication adjustment, by avoiding immunosuppression, became possible. Other immediate benefits of genetic evaluation included surgical decision making regarding the need for prophylactic (patient number RGC-0034) or therapeutic nephrectomy (RGC-0186) in patients with pathogenic variants in *WT1*. In three patients (RGC-0118, RGC-0185, and RGC-

Table 2. Demographics, genetic information, and effect on management for patients with diagnostic genetic results

Patient Number	Sex	Age(yr)	L1	L2	L3	L4	L5	Type of Genetic Testing (1, 2, 3, 4, 5)[a]	Gene/Locus	Genetic Finding (SNV/Indel/CNV)	Phenotype (Indication for Referral)	Comment
RGC-0001	F	10	−	−	+	+	−	1	*PKD1*	NM_001009944.2: c.7987C>T (p.Q2663*) (het)	Bilateral renal cysts	
RGC-0003	M	0.8	−	−	+	+	+	4	*PKD1*	Partial PKD1 gene deletion (at least exons 27–38) (het) (novel)	Bilateral renal cysts	Subsequently mother was found have cysts in her kidneys
RGC-0004	M	13	−	−	+	+	+	2	*HNF1B*	arr[GRCh37]2q36.3 (227999132_228097605)x1	Chromosomal abnormality	Deletion was found to be maternally inherited
RGC-0009	M	10	−	−	+	+	+	1	*PKD1*	NM_001009944.2: c.7483T>C (p.C2495R) (het)	Bilateral renal cysts and duplicated collecting system	Symptomatic sibling tested positive for KFM
RGC-0010	M	16	−	−	−	+	+	1	*COL4A5*	NM_000495.4: c.152G>T (p.G51V) (hem)	Hematuria and proteinuria	Symptomatic sibling tested positive for KFM
RGC-0013	M	3	−	−	−	+	−	1	*COL4A5*	NM_000495.4: c.3197G>C (p.G1066A) (hem)	Alport syndrome	
RGC-0014	F	10	−	−	+	+	−	2	1q21 del	arr[GRCh37]1q21.1q21.2 (146618988–147825855)x1	Learning disability, VUR, cataracts, microcephaly	Patient also has 16p11.2 0.521 Mb duplication
RGC-0018	M	1.5	−	−	+	+	−	2	*HNF1B*	arr[GRCh37] 17q12 (34842059–36214026)x1	Unilateral multicystic dysplastic kidney, VUR, hypercalcemia, developmental delay, hypotonia	
RGC-0019	F	16	−	−	+	−	−	2, 3	*WDR19*	NM_025132: c.3703G>A (p.E1235K) (het) arr[GRCh37] 4p14 (39215680–39219295)x1	ESKD, dysautonomia, migraines, choledochal and pancreas cyst	
RGC-0021	F	2.7	−	−	+	+	+	2, 4	*PKD1*	NM_001009944.2: c.1259A>G (p.Y420C) (het)	Cystic kidney and Chiari malformation	*PKD1* variant is *de novo*
RGC-0026	F	4	−	−	+	−	+	2, 4	*EYA1*	arr[GRCh37]8q13.2q13.3 (69901440–72586292)x1	Branchio-oto-renal syndrome	*EYA1* variant is *de novo*
RGC-0029	M	2.9	−	−	+	+	−	1	*PKD1*	NM_001009944.2: c.2659delT (p.W887Gfs*11) (het)	Bilateral renal cysts	
RGC-0030	F	1.5	+	−	+	−	+	1	*NPHS2*	NM_014625: c.790G>C (p.E264Q) (het), and c.779T>A (p.V260E) (het)	Infantile nephrotic syndrome	Phase of the variants were determined (opposite chromosomes), subsequently symptomatic siblings tested positive for these variants
RGC-0032	M	12	−	−	+	−	+	2, 4	*DYRK1A*	NM_001396: c. 501delA (p.G168fs) (het)	Intellectual disability and hypospadias	*DYRK1A* variant is *de novo*
RGC-0034	F	2.6	+	−	+	+	+	1, 2, 4	*WT1*	NM_024426.4: c.1390G>A (p.D464N) (het)	Atypical HUS	*WT1* variant is *de novo*
RGC-0039	F	7	−	−	+	+	+	2, 4	*COL4A3*	NM_000091: c.1407delA (p.G470fs) (het) and c.40_63del (p.L14_L21del) (het)	Hereditary nephritis	Each variant is inherited from one parent

Table 2. (Continued)

Patient Number	Sex	Age(yr)	L1	L2	L3	L4	L5	Type of Genetic Testing (1, 2, 3, 4, 5)[a]	Gene/Locus	Genetic Finding (SNV/Indel/CNV)	Phenotype (Indication for Referral)	Comment
RGC-0041	M	15	−	−	+	−	+	2	22q11 triplication	arr[GRCh37]22q11.1q11.21 (17289827–18640328)x3	Facial asymmetry, imperforate anus, neurogenic bladder	This triplication is *de novo*
RGC-0043	M	11	−	−	+	−	+	2, 4	*KAT6B*	NM_012330: c.3280delG (p.E1094fs) (het)	Bilateral undescended testes, a mild hypospadias, and Ohdo syndrome	*KAT6B* variant is *de novo*
RGC-0046	M	3	+	−	+	−	−	1	*NPHS2*	NM_014625: c.790G>C (p.E264Q) (het), and c.779T>A (p.V260E) (het)	Positive family history of infantile nephrotic syndrome	Avoid immune suppression
RGC-0047	F	2	+	−	+	−	−	1	*NPHS2*	NM_014625: c.790G>C (p.E264Q) (het) and c.779T>A (p.V260E) (het)	Infantile nephrotic syndrome	Avoid immune suppression
RGC-0050	M	18	−	−	+	−	+	2, 4	*TMEM67*	NM_153704: c. 515G>T (p.R172L) (het) and c.1021G>A (p.G341R) (het) (novel)	Joubert syndrome	Each variant is inherited from one parent
RGC-0052	M	0.8	−	−	+	+	+	2, 4	*NSD1*	NM_022455.4: c.3423_3424insCC (p.N1142PfsX11) (het) (novel)	Macrosomia and nephromegaly	*NSD1* variant is *de novo*
RGC-0054	M	1.9	+	−	+	−	+	2, 4	*PLCE1*	NM_016341.3: c.4675_4678delTTAG (p.L1559fs) (hom) (novel)	Nephrotic-range proteinuria	Each variant is inherited from one parent
RGC-0055	M	10	−	−	+	+	−	1	*PKD1*	NM_001009944.2: c.7483T>C (p.C2495R) (het)	Family history of ADPKD, bilateral cystic kidney disease, and duplicated collecting system	
RGC-0058	M	3	−	−	−	+	−	1	*ATP6V0A4*	NM_020632.2: c.1231G>T (p.D411Y) (hom)	Distal renal tubular acidosis	Hearing evaluation was normal
RGC-0063	F	3	−	−	−	+	−	1	*PKD1*	NM_001009944.2: c.7111del (p.V2371Cfs*11) (het)	Bilateral renal cysts	Echocardiogram
RGC-0066	F	19	−	+	−	+	+	2, 4	*USP9X*	NM_001039590.2: c.5606_5607dupTC (p.V1870SfsX37) (het) (novel)	Hypertension and Townes–Brocks syndrome	*USP9X* variant is *de novo*
RGC-0067	M	4.9	−	−	+	+	+	2, 4	*COL4A5*	NM_000495: c.5034T>A (p.C1678X) (hem) (novel)	Hematuria and thin basement membrane nephropathy	*COL4A5* variant is maternally inherited
RGC-0068	M	14	−	+	−	+	+	2, 4	*OCRL*	NM_000276.3: c.2531_2539delGAGAACTC TinsAAG (p.R844_L847delinsQV) (hem) (novel)	Cataracts and proteinuria	*OCRL* variant is maternally inherited, subsequently sibling tested positive for KFM
RGC-0070	F	13	−	+	−	+	−	2, 3	*NPHP4*	NM_015102.3: c.3611C>T (p.P1204L) (hom)	CKD	

Table 2. (Continued)

Patient Number	Sex	Age(yr)	L1	L2	L3	L4	L5	Type of Genetic Testing (1, 2, 3, 4, 5)[a]	Gene/Locus	Genetic Finding (SNV/Indel/CNV)	Phenotype (Indication for Referral)	Comment
RGC-0072	M	11	−	−	+	+	−	2, 3	*PKD1*	NM_001009944: c.9859_9861del (p.L3287del) (het)	Bilateral renal cysts	
RGC-0075	F	14	−	−	+	+	−	2, 3	*DCDC2*	NM_016356: c.383C>G (p.S128X) (hom)	ESKD and liver fibrosis	
RGC-0076	M	4	−	−	−	+	+	1	*COL4A5*	NM_000495.4: c.1948G>A (p.G650S) (hem)	Alport syndrome	Siblings tested negative for KFM
RGC-0077	F	6	−	−	+	+	+	1	*PKD1*	NM_001009944.2: likely pathogenic c.8948+1G>T (het), VUS c.955GG>C (p.Vl3184L) (het)	Bilateral renal cysts	Each variant in *PKD1* is inherited from one parent
RGC-0078	F	1.9	−	−	+	+	+	1	*PKD1*	Likely pathogenic c.9829C>T (p.R3277C) (het), VUS c.3494A>G (p. D1165G) (het)	Bilateral renal cysts	Each variant in *PKD1* is inherited from one parent
RGC-0080	M	12	+	−	+	−	+	1	*PKHD1*	NM_138694.3: likely pathogenic (c.3761_3762delinsG) (p.A1254Gfs*49) (het), VUS c.4292G>A (p.C1431Y) (het)	Bilateral renal cysts	Pseudodominant ARPKD, each variant is inherited form one parent; both father and paternal aunt are clinically diagnosed with ARPKD
RGC-0081	M	13	−	−	−	+	+	2, 4	*COL4A5*	arr[GRCh37]Xq22.3 (107802035–107802303)x0 (Novel)	Alport syndrome, developmental delay, autism, ADHD	This deletion is maternally inherited
RGC-0083	M	16	+	+	−	+	+	2, 4	*COL4A5*	NM_000495: c.3059dupT (p.G1021fs) (hem) (novel)	FSGS	Both patient and his affected mother's diagnosis has been changed and avoid immune suppression
RGC-0084	F	4.9	+	−	+	−	+	2, 4	*RMND1*	NM_017909: c.713A>G (p.N238S) (het) and c.533C>T (p.T178M) (het)	CKD, congenital hearing loss, and developmental delay	Each variant is inherited from one parent
RGC-0085	M	0.5	−	−	+	−	+	2, 4	*CASK*	NM_003688: c.1721dupA (p.S575fs) (hem) (novel)	Microcephaly, dysmorphic features, right club feet, neurologic dysfunction, hypotonia, pontocerebellar hypoplasia, and right cryptorchidism	Variant in *CASK* is *de novo*
RGC-0086	M	0.2	−	−	+	+	−	2	1q23.2q25.1 deletion	arr[GRCh37]1q23.2q25.1 (160369890–175796325)x1	Multiple congenital anomalies including dysplastic ears, dysplastic kidney, bilateral undescended testes, dysmorphic features, and abnormality of the shape of hands	

Table 2. (Continued)

Patient Number	Sex	Age(yr)	L1	L2	L3	L4	L5	Type of Genetic Testing (1, 2, 3, 4, 5)[a]	Gene/Locus	Genetic Finding (SNV/Indel/CNV)	Phenotype (Indication for Referral)	Comment
RGC-0087	M	9	−	−	+	+	+	1	*PKD1*	NM_001009944.2: c.11017–10C>A (IVS37–10C>A) (het)	Bilateral renal cysts	*PKD1* variant is inherited from father; subsequently, father and PGF were diagnosed with ADPKD
RGC-0088	F	6	−	−	−	+	−	1	*PKD1*	NM_001009944.2: c.6806C>G (p.S2269*) (het)	Bilateral renal cysts	
RGC-0090	F	18	−	−	−	+	−	1	*COL4A5*	NM_000495.4: c.4602del (p.Y1535Ifs*13) (het) (novel)	Alport syndrome	
RGC-0091	M	8	−	−	+	+	−	2, 3	*PKD1*	NM_001009944.2: c.8043_8046delCTCG (p.S2682Afs*2) (het) (novel)	Bilateral renal cysts	
RGC-0092	F	2	−	−	−	+	+	2, 4	*PKHD1*	NM_138694.3: pathogenic variant c.3761_3762delCCinsG (het), VUS c.10666C>T (p.R3558C) (het)	Bilateral renal cysts	One variant is inherited from one parent and the other one is *de novo*
RGC-0097	F	17	−	−	+	+	+	4	*COL4A5*	NM_033380.1: c.3631G>A (p.G1211R) (het)	Hereditary nephritis	*COL4A5* variant is *de novo*
RGC-0100	M	15	−	−	+	+	−	1	*HNF1B*	NM_000458.2: c.513G>A (p.W171X) (het)	Bilateral renal cysts	
RGC-0101	M	16	−	−	−	+	−	1	*COL4A5*	arr[GRCh37]Xq22.3 (107868501–107869156)x0 (novel)	Alport syndrome	
RGC-0105	F	8	−	+	−	+	−	1	*COL4A4*	NM_000092.4: c.1334G>C (p.G445A) (het) and c.2570C>T (p.P857L) (het)	Steroid-sensitive nephrotic syndrome	
RGC-0108	M	15	+	+	−	−	+	1, 4	*OCRL*	NM_000276.3: c.239delG (p.S80MfsX26) (hem) (novel)	Proteinuria	*OCRL* variant was maternally inherited
RGC-0110	M	5	−	−	+	+	+	5	*WDR19*	NM_025132: pathogenic c.1122_1123insT (p.P375fs) (het) (novel) and VUS c.817A>G (p.N273D) (het)	ESKD	Each variant in *WDR19* is inherited from one parent
RGC-0112	M	14	−	−	+	+	−	2	*NPHP1*	arr[GRCh37]2q13 (110862477–110970270)x1	CKD	
RGC-0113	F	6	−	+	−	+	+	2, 4	*PKD2*	NM_000297.3: c. 965G>A (p.R322Q) (het)	VUR, duplicated collecting system, and bilateral cystic kidney	*PKD2* variant is paternally inherited
RGC-0115	F	7	−	−	+	+	−	1	*PKD2*	NM_000297.3: c.2614C>T (p.R872*) (het)	Unilateral renal cysts	
RGC-0116	F	1	−	−	+	+	+	1, 2, 5	*RPS19*	NM_001022: c.185G>A (p.R62Q) (het)	CKD and Diamond–Blackfan anemia	*RPS19* variant is *de novo*

Table 2. (Continued)

Patient Number	Sex	Age(yr)	L1	L2	L3	L4	L5	Type of Genetic Testing (1, 2, 3, 4, 5)[a]	Gene/Locus	Genetic Finding (SNV/Indel/CNV)	Phenotype (Indication for Referral)	Comment
RGC-0117	M	0.16	−	−	+	+	+	2, 4	*BBS12*	NM_152618.2: pathogenic c.1115_1116delTT (p.F372*) (het), and VUS c.1277G>A (p.C426Y) (het)	Polydactyly and bilateral renal cysts	Each variant in *BBS12* is inherited from one parent
RGC-0118	M	9	+	+	−	+	+	2, 4	*KCNJ1*	NM_000220.3: c.924C>A (p.C308*) (hom)	Renal dysplasia	Both parents are heterozygous for variant in *KCNJ1*
RGC-0120	M	17	−	−	−	+	+	2, 4	*INVS*	NM_014425.3: c.2695C>T (p.R899*) (hom)	Nephronophthisis	Both parents are heterozygous for variant in *INVS*
RGC-0124	F	17	−	−	−	+	−	1	*COL4A4*	NM_000092.4: c.1580del, (p.G527Vfs*126) (het)	Microscopic hematuria	
RGC-0128	M	2	−	−	−	+	−	1	*PKD1*	NM_01009944.2: c.8016+2T>C (IVS21+2T>C) (het)	Bilateral renal cysts	
RGC-0129	M	14	−	−	−	−	+	2, 4	*SLC7A9*	NM_014270.4: c.419T>C (p.F140S) (het) and c.164T>A (p.V55E) (het) (novel)	Cystine stones and dysplastic kidney	Each variant in *SLC7A9* is inherited from one parent
RGC-0132	F	17	−	−	+	+	−	1	*PKD1*	NM_001009944.2: c.11712+1G>A (het)	Bilateral renal cysts	
RGC-0143	M	2	+	−	+	−	+	1	*NPHS1*	NM_004646.3; c.1747G>A (p.S910P) (het) (likely pathogenic), and c.1747G>A (p.E583K) (het) (VUS)	Nephrotic syndrome	Avoid immune suppression
RGC-0145	M	16	−	+	−	−	+	1	*NEK8*	NM_178170.2: c.1523T>A (p.Met508Lys) (het), and c.673G>C (p.Asp225His) (het)	Cystic kidney disease	Clinical diagnosis of ARPKD was changed to nephronophthisis
RGC-0147	M	14	−	−	−	+	+	2, 4	*KCNJ1*	NM_000220.3: c.924C>A, (p.C308*) (hom)	Bartter syndrome	Both parents are heterozygous for variant in *KCNJ1*
RGC-0152	F	10	−	−	+	+	−	1	*COL4A5*	NM_000495.4: c.994_998delinsTCCC (p.Q332Sfs*14) (het) (novel)	Alport syndrome	
RGC-0156	M	14	−	−	+	+	+	1	*COL4A5*	NM_000495.4: c.4688+1G>T (hem)	Alport syndrome	*COL4A5* variant is maternally inherited and sibling was tested negative for KFM
RGC-0157	M	12	−	−	+	−	+	1	*COL4A4*	NM_000092.4; c.1325G>C (p.G442A) (het)	Microscopic hematuria	
RGC-0159	M	2	−	−	+	−	−	1	*COL4A4*	NM_000092.4: c.1697–1G>A (het)	Microscopic hematuria	
RGC-0160	M	5	−	−	+	−	+	1	*AVPR2*	NM_000054.4: c.337C>T (p.R113W) (hem)	Diabetes insipidus	Subsequently sibling was tested positive for KFM

Table 2. (Continued)

Patient Number	Sex	Age(yr)	L1	L2	L3	L4	L5	Type of Genetic Testing (1, 2, 3, 4, 5)[a]	Gene/Locus	Genetic Finding (SNV/Indel/CNV)	Phenotype (Indication for Referral)	Comment
RGC-0162	F	8	−	−	+	−	−	1	*COL4A5*	NM_000495.4: c.2678G>A (p.G893D) (het)	Microscopic hematuria	
RGC-0164[b]	M	1.3	−	+	−	+	+	4	*HNF1B*	Arr[GRCh37]17q12 (34856055–36248918)x1dn	Bilateral renal cysts	This deletion is *de novo* and secondary finding of *BRCA2* is maternally inherited
RGC-0171	M	2	+	−	+	+	+	2, 4	*WT1*	NM_024426.4: c.1432+4C>T (het)	Proteinuria, recurrent UTI, and hypospadias	*WT1* variant was *de novo*
RGC-0182	F	11	−	+	−	+	−	1	*COL4A5*	NM_000495: c.557G>A (p.Gly186Asp) (het) (novel)	Microscopic hematuria	Familial diagnosis of FSGS changed to Alport syndrome
RGC-0183	F	16	−	−	+	+	−	1	*SLC12A3*	NM_000339; c.1001G>A (p.R334Q) (hom)	Gitelman syndrome	
RGC-0185	F	0.1	+	−	+	−	−	2, 5	*TPRM6*	NM_017662.4: c.5488–1G>C (hom) (novel)	Hypomagnesemia	Hypocalcemia and hypomagnesemia are due to defect in intestinal absorption of magnesium
RGC-0186	M	0.9	+	−	−	+	−	1	*WT1*	NM_0024426.3: c.1288C>T (p.R430*) (het) (novel)	Bilateral Wilms tumor	Impacted nephrectomy
RGC-0190	F	10	+	−	+	+	+	2, 4	*WT1*	NM_024426.4: c.1432+5 G>A (het)	ESKD and nephrotic range proteinuria	CMA revealed patient is XY female, and *WT1* variant is *de novo*
RGC-0191	F	11	+	−	+	−	−	1	*CACNA1S*	NM_000069.2: c.3715C>G (p.R1239G) (het)	Hypokalemia	Treatment with acetazolamide
RGC-0192	M	18	−	+	−	+	+	1, 2, 4	*COL4A5*	NM_000495.4: c.4298–20T>A (hem) (novel)	Hematuria and proteinuria	*COL4A5* variant is maternally inherited

L1, effect on medical and/or surgical treatment; L2, change of medical diagnosis; L3, providing diagnostic certainty; L4, subsequent evaluation of other body-system involvement; L5, cascade family member testing; SNV, single nucleotide variant; CNV, copy number variant; F, female; M, male; het, heterozygous; KFM, known familial mutation; hem, hemizygous; del, deletion; VUR, vesicoureteral reflux; HUS, hemolytic uremic syndrome; ins, insertion; hom, homozygous; ADPKD, autosomal dominant polycystic kidney disease; VUS, variant of uncertain significance; ARPKD, autosomal recessive polycystic kidney disease; ADHD, attention deficit hyperactivity disorder; PGF, paternal grandfather; UTI, urinary tract infection; CMA, chromosomal microarray.
[a]Numbers represent the following testing types: 1, panel; 2, CMA; 3, proband exome sequencing; 4, trio exome sequencing; 5, Total BluePrint.
[b]Patient had a secondray finding of pathogenic variant in BRCA2.

Table 3. Genetic information and the strength of the genetic variants for patients diagnosed with pathogenic *PKD1* variant

Family Identifier	Variant	Type of Variant	Indication for testing	Age of Diagnosis	CADD Score
RGC-001	c.7987C>T (p.Q2663*) (het)	Stop gain	Family history of cystic kidney disease but not definitive for ADPKD and symptomatic	2 yr	Truncating
RGC-003	Partial *PKD1* gene deletion (at least exons 27–38) (het)	Partial gene deletion	No family history, but symptomatic	3 mo	NA
RGC-009	c.7483T>C (p.C2495R) (het)	Missense	Family history of ADPKD and symptomatic	9 yr	24.2
RGC-0021	c.1259A>G (p.Y420C) (het)	Missense	No family history but symptomatic	18 mo	23.6
RGC-0029	c.2659delT (p.W887Gfs*11) (het)	Frameshift	No family history but symptomatic	2 yr	Truncating
RGC-0055	c.7483T>C (p.C2495R) (het)	Missense	Family history of ADPKD, bilateral cystic kidney disease, and duplicated collecting system	10 yr	24.2
RGC-0063	c.7111del (p.V2371Cfs*11) (het)	Frameshift	Positive family history of ADPKD and symptomatic	1 yr	Truncating
RGC-0072	c.9859_9861del (p.L3287del) (het)	In-frame deletion	Family history of kidney disease and symptomatic	10 yr	NA
RGC-0077	Likely pathogenic c.8948+1G>T (het) (novel), VUS c.9550G>C (p.V3184L) (het)	Splice site, Missense	Family history of cystic kidney disease but not definitive for ADPKD and symptomatic	Prenatal	33 23.9
RGC-0078	Likely pathogenic c.9829C>T (p.R3277C) (het), c.3494A>G (p.D1165G) (het)	Missense	Family history of cystic kidney disease but not definitive for ADPKD and symptomatic	Prenatal	23.9 24.6
RGC-0087	c.11017–10C>A (IVS37–10C>A) (het)	Splice site	No family history but symptomatic	5 yr	Predicted to skip exon 38 likely to be nontruncating (12)
RGC-0088	c.6806C>G (p.S2269*) (het)	Stop gain	Family history of ADPKD and symptomatic	6 yr	Truncating
RGC-0091	c.8043_8046delCTCG (p.S2682Afs*2) (het)	Frameshift	Family history of kidney disease and symptomatic	6 yr	Truncating
RGC-0128	c.8016+2T>C (IVS21+2T>C) (het) (novel)	Splice site	Family history of cystic kidney disease but not definitive for ADPKD and symptomatic	2 yr	Truncating
RGC-0132	c.11712+1G>A (het)	Splice site	Family history of cystic kidney disease but not definitive for ADPKD and symptomatic	16 yr	Truncating (13)

CADD, Combined Annotation Dependent Depletion; het, heterozygous; ADPKD, autosomal dominant polycystic kidney disease; NA, not applicable; VUS, variant of uncertain significance.

0191), targeted treatment recommendations with directed pharmacotherapy (indomethacin, magnesium, and acetazolamide) became possible after identification of underlying genetic diagnosis (*KCNJ1*, *TPRM6*, and *CACNA1S*).

Among 12 patients with L2 impact, four diagnoses were changed from FSGS to Alport syndrome. Additionally, in 53 patients, diagnostic certainty became possible only with genetic testing (L3). Other effects on management included evaluation of other body organ systems (L4) and cascade family testing (L5) in 58 and 47 patients, respectively. Although cascade testing should have been done for every patient with kidney disease attributable to an autosomal dominant genetic variant, this was not possible in some families due to health-insurance coverage of parents or other family members. In three families, reproductive genetic counseling immediately affected the family's decision making for their family planning. Figure 1 summarizes the overlaps and relationships between five levels of the proposed scoring system. Other important effects on management included screening of potential living related kidney donors, planning for solid organ transplantation, and accurate genetic counseling. The discovery of inherited pathogenic variants in autosomal dominant disease genes led, for instance, to the discovery of previously unrecognized clinical abnormalities in parents (*e.g.*, patients RGC-0003 and RGC-0087) and the illumination of unusual inheritance patterns (*e.g.*, pseudodominance in patient RGC-0080).

Table 4. Details of effect on management (L1 and L2) among patients with diagnostic results

Patient Identifier	L1/L2	Initial Diagnosis	Changed Diagnosis	Variant Found	Effect on Management
RGC-0030	L1	Infantile nephrotic syndrome		*NPHS2*	Avoidance of immune suppression
RGC-0034	L1	Atypical HUS		*WT1*	Bilateral nephrectomy, pelvic MRI, tapering eculizumab
RGC-0046	L1	Positive family history of infantile nephrotic syndrome		*NPHS2*	Avoidance of immune suppression
RGC-0047	L1	Infantile nephrotic syndrome		*NPHS2*	Avoidance of immune suppression
RGC-0054	L1	Nephrotic-range proteinuria		*PLCE1*	Avoidance of immune suppression
RGC-0066	L2	Townes–Brocks syndrome	*USP9X*-related disorder	*USP9X*	
RGC-0068	L2	FSGS	Lowe syndrome	*OCRL*	
RGC-0070	L2	Developmental delay and kidney problem	Nephronophthisis	*NPHP4*	
RGC-0080	L1	ARPKD/ADPKD		*PKHD1*	Pseudodominant ARPKD
RGC-0083	L1, L2	FSGS	Alport syndrome	*COL4A5*	Avoidance of immune suppression
RGC-0084	L1	Mitochondrial disease		*RMND1*	Kidney transplantation is indicated for patients with RMND1 variants if needed
RGC-0105	L2	Nephrotic syndrome	Alport syndrome	*COL4A4*	
RGC-0108	L1, L2	Proteinuria/Alport syndrome	Dent syndrome	*OCRL*	Avoidance of immune suppression, management related to Dent disease
RGC-0113	L2	CAKUT	ADPKD	*PKD2*	
RGC-0118	L1, L2	CAKUT	Bartter syndrome	*KCNJ1*	Indomethacin treatment recommended and DEXA bone scan showed low bone density
RGC-0143	L1	Nephrotic syndrome		*NPHS1*	Avoidance of immune suppression
RGC-0145	L2	Polycystic kidney disease	Nephronophthisis	*NEK8*	Clinical diagnosis of ARPKD was changed to nephronophthisis
RGC-0164[a]	L2	Cystic kidney disease	17q12 deletion syndrome	*HNF1B* and *BRCA2*	Secondary finding of *BRCA2*
RGC-0171	L1	Proteinuria	*WT1*-associated disease	*WT1*	Followed by cancer prevention clinic
RGC-0182	L2	FSGS	Alport syndrome	*COL4A5*	
RGC-0185	L1	Hypomagnesemia		*TRPM6*	Hypocalcemia and hypomagnesemia are due to defect in intestinal absorption of magnesium
RGC-0186	L1	Wilms tumor	*WT1*-associated syndrome		Affected surgical nephrectomy of patient
RGC-0190	L1	Renal failure, proteinuria	*WT1*-associated syndrome	*WT1*	CMA revealed patient is XY female. Risk of gonad blastoma in an XY female patient was discussed
RGC-0191	L1	Periodic hypokalemic paralysis		*CACNA15*	Treatment with Acetazolamide
RGC-0192	L2	CKD	Alport syndrome	*COL4A5*	

L1, effect on medical and/or surgical treatment; L2, change of medical diagnosis; HUS, hemolytic uremic syndrome; MRI, magnetic resonance imaging; ARPKD, autosomal recessive polycystic kidney disease; ADPKD, autosomal dominant polycystic kidney disease; CAKUT, congenital anomalies of the kidney and urinary tract; DEXA, dual-energy x-ray absorptiometry; CMA, chromosomal microarray.
[a]Patient had a secondray finding of pathogenic variant in BRCA2.

Discussion

In this study, the detection rate (81/158, 51%) and the clinical utility of genetic evaluation/testing was demonstrated for pediatric kidney disorders in an RGC setting. In 31% (25/81) of the patients with positive results, immediate medical/surgical treatment was affected, or the prior diagnoses (achieved by either biopsy or clinical evaluation) were changed.

This clinic is staffed by several pediatric nephrologists with an interest in inherited kidney diseases, a clinical geneticist, and a genetic counselor, and is supported by a strong clinical and human genetics program at Baylor

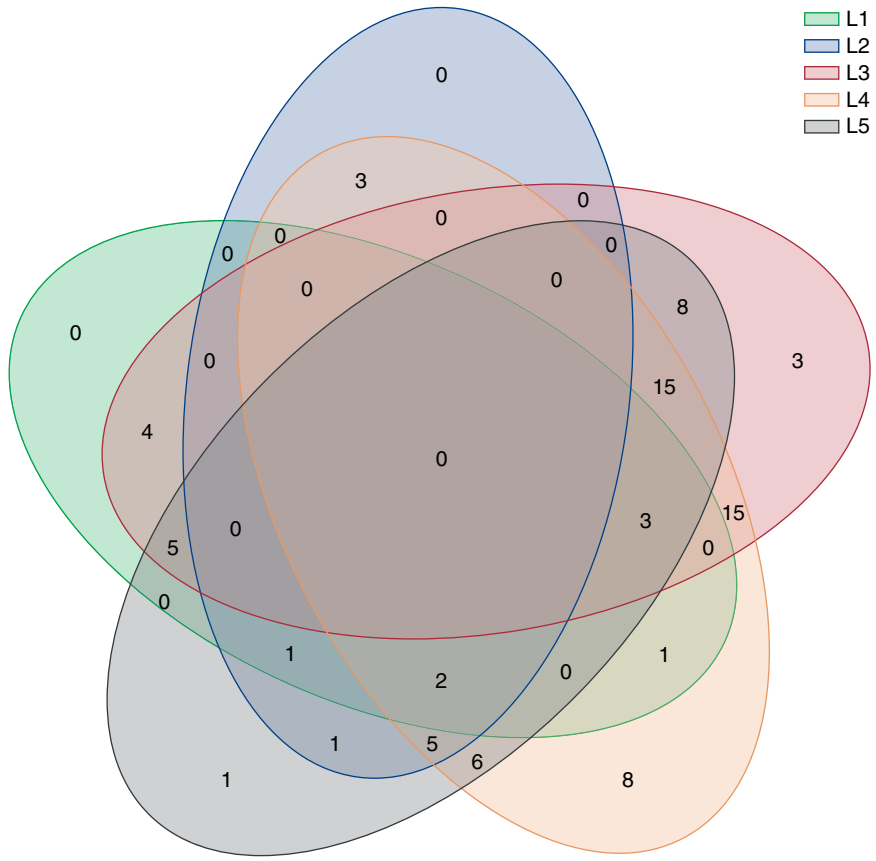

Figure 1. | **Overlaps between L1, L2, L3, L4, and L5 are demonstrated as a Venn diagram.** In 3 patients both L1 and L2 were noted. L1, effect on medical and/or surgical treatment; L2, change of medical diagnosis; L3, providing diagnostic certainty; L4, subsequent evaluation of other body-system involvement; L5, cascade family member testing.

College of Medicine. The detection rate of 51% is within the range of other centers around the world and in the United States. We believe the detection rate can vary on the basis of the reasons for referral and the number of patients assessed. The clinical impact scoring system proposed in this study can potentially be applicable to other centers.

RGCs are the optimal mechanism for integrating a comprehensive genetic evaluation with appropriate molecular testing on a clinical basis (14). This kind of clinic also allows for a family-centered approach, where unaffected relatives may also be evaluated and counseled on their risks for kidney disease. Examples of these clinics in Australia, the United Kingdom, and China showed diagnostic yields of 46% (15), 42% (16), and 42% (7), respectively. In the United States, there are several kidney genetics clinics. In a recent publication, a detection rate of 60% was identified among 41 patients who are mostly in the adult age range (17).Our diagnosis yield is at the same scale, and the variations in detection rate could be explained by following factors. First, the indications of referral among these different clinic models are not the same. Second, broad genetic testing options were available in our center. Lastly, patients were referred with rigorous initial evaluation by pediatric nephrologists. A less-stringent referral criterion may lead to a larger number of patients being seen with a higher number of total positive diagnoses, but with an overall lower diagnosis rate.

Our testing approach used various combinations of targeted panels, CMA, and ES (by CLIA laboratories). This resulted in the identification of pathogenic SNVs in 34 different genes and 11 unique pathogenic CNVs. Of these changes, 21 are novel and have not previously been reported in published databases (Table 2). These novel variants, although not previously reported, are classified as pathogenic or likely pathogenic on the basis of American College of Medical Genetics and Genomics criteria by board-certified clinical molecular geneticists at CLIA-certified laboratories. In terms of testing performance, our diagnostic yield is higher than the reported yield of ES for adult patients with kidney disease in one study (18), although a higher detection rate was reported in another study with more selective criteria for testing (17).Overall, these findings may highlight the increased contribution of genetic abnormalities in the pediatric population. The diagnostic rate of CAKUT in this cohort is higher than that expected from the literature (19). This is likely due to stringent referral criteria that select patients who are syndromic.

Our patients were placed into one of five categories on the basis of their clinical presentation and presumed diagnosis. Each category varied in terms of which genetic testing was felt to be the most appropriate both initially and upon follow-up. For instance, panel testing (known to be cost-effective and specific) was very useful in cases of both cystic

kidney disease and hematuria. For patients with cystic kidneys in particular, a panel appeared to be a good initial diagnostic choice because of the high prevalence of *PKD1* pathogenic variants. If this test result was negative, or if patients had other concerning physical or clinical abnormalities, expanded testing could be pursued with ES or CMA. This allowed us to identify diagnostic variants in genes not previously considered. For instance, a patient initially referred for cystic kidney disease was later found to have a pathogenic variant in *HNF1B*, more commonly associated with CAKUT (patient RGC-0164); whereas another patient was diagnosed with biallelic variants in *BBS12*, indicative of Bardet–Biedl syndrome (patient RGC-0117).

Although ADPKD can be diagnosed by imaging studies, genetic diagnoses add certainty and might be the only option for an accurate diagnosis in young children. In this study, only children with cystic kidneys who had a positive family history or clinical suspicion of ADPKD underwent genetic testing. As shown in recent literature (20,21), genotype information in patients with ADPKD can provide prognostic value and can also be used to manage patients differently on the basis of newly developed therapies. Certainly, this is true when the patients reach the age of 18 when therapy can be provided, if indicated.

Most importantly, genetic evaluation resulted in recommendations for immediate medical or surgical treatment in 20% (16/81) of patients. In addition, the original diagnosis in 15% (12/81) of patients was changed. The benefits of L1 impact on management included targeted therapies and preventing the use of inappropriate treatments (*i.e.*, corticosteroids where there was no expectation of benefit). We compared diagnosis pre- and postgenetic evaluation and concluded that genetic testing improved diagnostic accuracy given that the diagnosis might be different from what was previously achieved by clinical or pathologic evaluations. The change of diagnosis from FSGS to Alport syndrome, reported in this study, was also published by other investigators (22). Additional benefits included reducing the use of invasive diagnostic procedures, such as kidney biopsy. Reduction of genetic testing costs will ultimately result in the precise diagnosis of patients for whom an initial syndromic diagnosis was not clinically suspected. In addition to a confirmatory diagnosis, a genetic diagnosis may also provide prognostic information, establish a targeted surveillance of other organs, and facilitate kidney transplant and reproductive planning (6).

However, this study has the following limitations. First, the design of this study is retrospective and there is still a need for larger, prospective studies similar to the recent research published from an Australian group (23). Second, we did not study the patients' viewpoints of genetic or genomic testing. Third, although our study included a range of diagnoses, the relatively small overall number/type of patients evaluated in this clinic may affect generalization of our data. Fourth, only a pediatric population was studied. Finally, although we have investigated the health effects of genetic testing, the economic effect of this testing in kidney disease was not studied.

Strengths of this study include the following: (*1*) the ability to perform advanced clinical genetic testing for a large proportion of our patients; (*2*) the diversity of the cohort, specifically their ethnicity, kidney phenotypes, and clinical diagnoses; (*3*) access to world-class pediatric nephrology and clinical genetics groups; and (*4*) affiliation with one of the largest children's hospitals in the United States.

In conclusion, results of RGC in a single center is summarized to define the effect of genetic testing and evaluation on management of patients in a pediatric nephrology clinical setting. An overall detection rate of 51% is in line with other reports across the world and in the United States. A new classification for the effect of clinical genetic evaluation on management of patients is provided. In 20% of the patients, medical or surgical management was modified, and clinical diagnosis was changed to a more accurate genetic diagnosis in 15% of the patients.

Disclosures

W. Chen reports receiving other from PreventionGenetics LLC, during the conduct of the study, and other from PreventionGenetics LLC, outside the submitted work. D.J. Lamb reports receiving other from Celmatix, and other from Fellow, outside the submitted work. All remaining authors have nothing to disclose.

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Author Contributions

M.R. Bekheirnia was responsible for funding acquisition and validation; M.R. Bekheirnia and N. Bekheirnia were responsible for formal analysis and resources; M.R. Bekheirnia, N. Bekheirnia, and M.C. Braun were responsible for investigation; M.R. Bekheirnia, N. Bekheirnia, M.C. Braun, and K. E. Glinton were responsible for methodology; M.R. Bekheirnia, N. Bekheirnia, M.C. Braun, K.E. Glinton, and D.J. Lamb provided supervision; M.R. Bekheirnia, N. Bekheirnia, W. Chen, K.E. Glinton, J. Manor, and L. Rossetti were responsible for data curation; M.R. Bekheirnia, N. Bekheirnia, and K.E. Glinton conceptualized the study and were responsible for project administration and visualization; and all authors wrote the original draft and reviewed and edited the manuscript.

Supplemental Material

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Supplemental Table 1. Panels (utilized in this study) and the genes included in each of them.

Supplemental Table 2. "Other" indications for referral.

Supplemental Table 3. Detection rates of different tests among indications for referral.

Supplemental Table 4. Impact on management in patients with partial diagnosis.

Supplemental Table 5. Demographics, phenotype, genetic variants' information, clinician's comments and recommendations for patients without diagnostic result who were found to have variants of uncertain significance (VUS).

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N.B. and K.E.G. contributed equally to this work.