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

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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 nephropthisis 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

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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 from pediatric nephrology service at TCH. Proteinuria was defined as urinary protein excretion >100 mg/m² per day or 4 mg/m² per hour. Nephrotic-range proteinuria was defined as ≥1000 mg/m² per day or 40 mg/m² 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 m² for >3 months with implications for health, regardless of whether other CKD markers are present.
- GFR >60 ml/min per 1.73 m² 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 m².

Genetic Testing

Testing performed by CLIA laboratories include diseasespecific 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.

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 Deletion 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).

**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-
| Patient Number | Sex | Age(yr) | L1 | L2 | L3 | L4 | L5 | Type of Genetic Testing (1, 2, 3, 4, 5) | Gene/Locus | Genetic Finding (SNV/Indel/CNV) | Phenotype (Indication for Referral) | Comment |
|----------------|-----|---------|----|----|----|----|----|----------------------------------------|------------|----------------------------------|------------------------------------|---------|
| RGC-0001       | F   | 10      |    |    | +  | +  | -  | 1                                      | PKD1       | NM_001009944.2: c.7987C>T       | Bilateral renal cysts              |         |
| RGC-0003       | M   | 0.8     |    |    | +  | +  | 4  | 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]2q23.3                | Chromosomal abnormality            |         |
| RGC-0009       | M   | 10      |    |    | +  | +  | +  | 1                                      | PKD1       | NM_001009944.2: c.7483T>C       | 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           | Hematuria and proteinuria          |         |
| RGC-0013       | M   | 3       |    |    | -  | -  | +  | 1                                      | COL4A5     | NM_000495.4: c.3197G>C          | Alport syndrome                    | Patient also has 16p11.2 0.521 Mb duplication |
| RGC-0014       | F   | 10      |    |    | +  | +  | -  | 2                                      | 1q21 del   | arr[GRCh37]1q21.1q21.2          | Learning disability, VUR, cataracts, microcephaly | Unilateral multicystic dysplastic kidney, VUR, hypercalcemia, developmental delay, hypotonia |
| RGC-0018       | F   | 1.5     |    |    | +  | +  | +  | 2                                      | HNF1B      | arr[GRCh37]17q12                | Unilateral multicystic dysplastic kidney, VUR, | Unilateral multicystic dysplastic kidney, VUR, hypercalcemia, developmental delay, hypotonia |
| RGC-0019       | F   | 16      |    |    | +  | -  | -  | 2, 3                                   | WDR19      | NM_025132: c.3703G>A           | ESKD, dysautonomia, migraines, choledochal and pancreas cyst | PKD1 variant is de novo |
| RGC-0021       | F   | 2.7     |    |    | +  | +  | +  | 2, 4                                   | PKD1       | c.1299A>G (p.Y430C)           | Cystic kidney and Chiari malformation | EYAI variant is de novo |
| RGC-0026       | F   | 4       |    |    | +  | +  | -  | 2, 4                                   | EYAI       | arr[GRCh37]6q22.33            | Branchio-oto-renal syndrome         |         |
| RGC-0029       | M   | 2.9     |    |    | +  | +  | -  | 1                                      | PKD1       | NM_001009944.2: c.2659delT      | Bilateral renal cysts              |         |
| RGC-0030       | F   | 1.5     |    |    | +  | -  | -  | 1                                      | NPHS2      | c.790G>C                      | Infantile nephrotic syndrome        |         |
| RGC-0032       | M   | 12      |    |    | +  | +  | -  | 2, 4                                   | DYRK1A     | NM_001396.4: c.501delA         | Intellectual disability and hypospadias | DYRK1A variant is de novo |
| RGC-0034       | F   | 2.6     |    |    | +  | +  | +  | 1, 2, 4                                | WTI        | NM_002442.4: c.1390G>A         | Atypical HUS                        | WTI variant is de novo |
| RGC-0039       | F   | 7       |    |    | +  | +  | 2  | 4                                      | COL4A5     | NM_000091: c.1407delA          | Hereditary nephritis                | Each variant is inherited from one parent |

*Tables are generated based on the provided data*
| Patient Number | Sex | Age(yr) | L1 | L2 | L3 | L4 | L5 | Type of Genetic Testing (1, 2, 3, 4, 5) | 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.799T>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.799T>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_02455.4: c.3423_3424insCC (p.N1142fsX11) (het) (novel) | Macrosomia and nephromegaly | NSD1 variant is de novo |
| RGC-0054      | M   | 1.9     | +  | -  | +  | -  | +  | 2, 4                                | PLCE1      | NM_016341.3: c.4675_4678delTTTAG (p.L1599fs) (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.7111delC (p.V2371Cfs*11) (het) | Bilateral renal cysts | Echocardiogram |
| RGC-0066      | F   | 19      | +  | -  | +  | +  | +  | 2, 4                                | USP9X      | NM_001039590.2: c.5606_5607delGC (p.R844_L845delinsQV) (hem) (novel) | Hypertension and Townes–Brock 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_2539delGAGAAGTCT (p.R844L) (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 | |
| Patient Number | Sex | Age(yr) | L1 | L2 | L3 | L4 | L5 | Type of Genetic Testing (1, 2, 3, 4, 5) | 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 | Siblings tested negative for KFM |
| RGC-0076       | M   | 4       |    |    |    | +  | +  | 1                             | COL4A5      | NM_000495.4:c.1948G>A (p.G650S) (hem) | Alport syndrome | Each variant in PKD1 is inherited from one parent |
| RGC-0077       | F   | 6       |    |    |    | +  | +  | 1                             | PKD1        | NM_001009944.2:c.8948G>T(p.R3277C) (het), VUS c.955GG>C (p.V13184L) (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 | Pseudodominant ARPKD, each variant 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.Y1431Y) (het) | Bilateral renal cysts |         |
| RGC-0081       | M   | 13      |    |    |    | +  |   | 2, 4                          | COL4A5      | arr[GRCh37]Xq22.3(107802035–107802303)x0 (Novel) | Alport syndrome, developmental delay, CKD, FSGS, ADHD | This deletion is maternally inherited |
| RGC-0083       | M   | 16      |    |    | +  | -  |   | 2, 4                          | COL4A5      | NM_000495: c.3059delT (p.G1021fs) (hem) (novel) |               | 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                             | 1q23.2p25.1 deletion | arr[GRCh37]1q23.2p25.1(160369890–175796325)x1 | Multiple congenital anomalies including dysplastic ears, dysplastic kidney, bilateral undescended testes, dysmorphic features, and abnormality of the shape of hands |         |
| Patient Number | Sex | Age(yr) | L1 | L2 | L3 | L4 | L5 | Type of Genetic Testing (1, 2, 3, 4, 5) | 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 (107868901–107869156)x0 (novel) | Alport syndrome                  |         |
| RGC-0105       | F   | 8       |    |    |    |    |    | 1                                     | COL4A4     | NM_000992.4:c.1334G>C (p.G445A) (het) and c.2570C>T (p.R857L) (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 Each variant in WDR19 is inherited from one parent |
| RGC-0110       | M   | 5       |    |    |    |    |    | 5                                     | WDR19      | NM_025132: pathogenic c.1122_1123insT (p.P376fs) (het) (novel) and VUS c.817A>G (p.N273D) (het) | ESKD                              |         |
| RGC-0112       | M   | 14      |    |    |    |    |    | 2                                     | NPHP1      | arr[GRCh37]2q13 (110862477–110907207)x1 (novel) | 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          |
| Patient Number | Sex | Age(yr) | L1 | L2 | L3 | L4 | L5 | Type of Genetic Testing (1, 2, 3, 4, 5)* | 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.G527Vs*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.673G>A, c.1523T>A (p.V510P) (het) | Cystine stones and dysplastic kidney | Each variant in SLC7A9 is inherited from one parent |
| RGC-0132      | F   | 17      |    |    | +  | +  |    | 1                             | PKD1           | NM_00009944.2: c.673G>A (p.Asp225His) (het) | Bilateral renal cysts            |                                     |
| RGC-0143      | M   | 2       |    |    |    |    |    | 1                             | NPHS1          | NM_014425.3: c.2695C>T (p.R899*) (hom) | Nephrotic syndrome               | Avoid immune suppression          |
| RGC-0145      | M   | 16      |    |    |    |    |    | 1                             | NEK8           | NM_014425.3: c.2695C>T (p.R899*) (hom) | Cystic kidney disease            | Clinical diagnosis of ARPKD was changed to nephronophthisis |
| RGC-0147      | M   | 14      |    |    |    |    |    | 2, 4                           | KCNJ1          | NM_014270.4: c.673G>A, c.1523T>A (p.V510P) (het) | Bartter syndrome                | Both parents are heterozygous for variant in KCNJ1 |
| RGC-0152      | F   | 10      |    |    |    |    |    | 1                             | COL4A5         | NM_000092.4: c.1325G>C (p.G442A) (het) | Alport syndrome                 |                                     |
| RGC-0156      | M   | 14      |    |    |    |    |    | 1                             | COL4A5         | NM_000092.4: c.1325G>C (p.G442A) (het) | 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.1325G>C (p.G442A) (het) | Microscopic hematuria            |                                     |
| RGC-0160      | M   | 5       |    |    |    |    |    | 1                             | AVPR2          | NM_000092.4: c.1325G>C (p.G442A) (het) | Diabetes insipidus               | Subsequently sibling was tested positive for KFM |
| Patient Number | Sex | Age(yr) | L1 | L2 | L3 | L4 | L5 | Type of Genetic Testing (1, 2, 3, 4, 5)* | 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      | 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                   | Hypocalcemia and hypomagnesemia are due to defect in intestinal absorption of magnesium |
| RGC-0185      | F   | 0.1     | +  | -  | +  | -  | -  | 2, 5                                   | TPM6       | NM_017662.4: c.5488–1G>C (hom) (novel) | Hypomagnesemia                       |         |
| 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_0024426.4: c.1432+5G>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.R1239C) (het) | Hypokalemia                           | Treatment with acetazolamide        |
| RGC-0192      | M   | 18      | -  | -  | +  | +  | +  | 1, 2, 4                                | COL4A5     | NM_000495.4: c.4298–207>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.

*Numbers represent the following testing types: 1, panel; 2, CMA; 3, proband exome sequencing; 4, trio exome sequencing; 5, Total BluePrint.

*Patient had a secondray finding of pathogenic variant in BRCA2.
targeted treatment recommendations with directed pharmacotherapy (indomethacin, magnesium, and acetazolamide) became possible after identification of underlying genetic diagnosis (KCNJ1, TPM6, and CACNA1S).

Among 12 patients with L2 impact, four diagnoses were not applicable; VUS, variant of uncertain significance.

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

| Family Identifier | Variant Type | 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-0013          | c.1259A>G (p.Y420C) (het) | Missense | No family history but symptomatic | 18 mo | 23.6 |
| RGC-0021          | c.2699delT (p.W887Gfs*11) (het) | Frameshift | Family history of ADPKD, bilateral cystic kidney disease, and duplicated collecting system | 2 yr | Truncating |
| RGC-0029          | c.7483T>C (p.C2495R) (het) | Missense | Family history of ADPKD, bilateral cystic kidney disease, and duplicated collecting system | 10 yr | 24.2 |
| RGC-0055          | c.7111del (p.V2371Cfs*11) (het) | Frameshift | Positive family history of ADPKD and symptomatic | 1 yr | Truncating |
| RGC-0072          | c.9859_9861del (p.L3267del) (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 |
| RGC-0078          | 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 |
| 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.

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).
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.

### 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 | WTI | 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 | NPHS4 |
| RGC-0080 L1        | ARPKD/ADPKD | PKHD1 | Avoidance of immune suppression |
| RGC-0083 L1, L2    | FSGS | Alport syndrome | COLA4A5 |
| RGC-0084 L1        | Mitochondrial disease | RMND1 | Kidney transplantation is indicated for patients with RMND1 variants if needed |
| RGC-0105 L2        | Nephrotic syndrome | Alport syndrome | COLA4A4 |
| RGC-0108 L1, L2    | Proteinuria/Alport syndrome | Dent syndrome | OCRL |
| RGC-0113 L2        | CAKUT | ADPKD | PKD2 |
| RGC-0118 L1, L2    | CAKUT | Bartter syndrome | KCNJ1 |
| RGC-0143 L1        | Nephrotic syndrome | NPHS1 | Avoidance of immune suppression |
| RGC-0145 L2        | Polycystic kidney disease | NPHS2 | Clinical diagnosis of ARPKD was changed to nephronophthisis |
| RGC-0164a L2       | Cystic kidney disease | 17q12 deletion syndrome | HNF1B and BRCA2 |
| RGC-0171 L1        | Proteinuria | WT1-associated disease | WT1 |
| RGC-0182 L2        | FSGS | Alport syndrome | COLA4A5 |
| RGC-0185 L1        | Hypomagnesemia | TRPM6 |
| RGC-0186 L1        | Wilms tumor | WT1-associated syndrome | Hypocalcemia and hypomagnesemia are due to defect in intestinal absorption of magnesium |
| RGC-0190 L1        | Renal failure, proteinuria | WT1 | Affected surgical nephrectomy of patient |
| RGC-0191 L1        | Periodic hypokalemic paralysis | CACNA15 | CMA revealed patient is XY female. Risk of gonad blastoma in an XY female patient was discussed |
| RGC-0192 L2        | CKD | Alport syndrome | COLA4A5 |

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.

*aPatient had a secondary 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.
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 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-00164); 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 Cematix, 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
This article contains supplemental material online at http://kidney360.asnjournals.org/lookup/suppl?doi=10.34067/KID.0002272020/-/DCSupplemental.
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 found to have variants of uncertain significance (VUS).

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

| Panel Name                                               | Genes                                                                 |
|----------------------------------------------------------|-----------------------------------------------------------------------|
| Nephrotic Syndrome (NS)/Focal Segmental Glomerulosclerosis (FSGS) Panel | ACTN4, ANKFY1, ANLN, APOL1, ARHGAP24, ARHGDIA, CD2AP, CDK20, COL4A3, COL4A4, COL4A5, COL4A6, COQ2, COQ6, COQ8B, CRB2, CUBN, DGKE, DHC1, EMP2, FAT1, GAPVD1, GON7, INF2, ITGA3, ITGB4, ITSN1, ITSN2, KANK1, KANK2, KANK4, KAT2B, KIRREL1, LAGE3, LAMA5, LAMB2, LMX1B, MAGI2, MYH9, MYO1E, NFKB2, NPHS1, NPHS2, NUP107, NUP133, NUP160, NUP205, NUP93, OSGEP, PAX2, PDSS2, PLCE1, PTPRO, SCARB2, SGPL1, SMARCA1, TBC1D8B, TNS2, TP53RK, TRKPB, TRIM8, TRPC6, TTC21B, WDR4, WDR73, WT1, XPO5, YRDC |
| Alport syndrome Panel                                    | COL4A3, COL4A4, COL4A5, COL4A6                                       |
| Autosomal Dominant Polycystic Kidney Disease (ADPKD) Panel | DNAJB11, GANAB, HNF1B, PKD1, PKD2                                    |
| Recessive Polycystic Kidney Disease (ARPKD) Panel        | DZIP1L, PKHD1                                                        |
| Hereditary cystic kidney disease panel                  | ANK6B, CEP164, CEP290, CEP83, COL4A1, CRB2, DCDC2, DICER1, DNAJB11, DZIP1L, GANAB, GLIS2, HNF1B, IFT172, INVS, IQCB1, JAG1, LRP5, MAPK8P1, MUC1, NEK8, NOTCH2, NPHP1, NPHP3, NPHP4, OFD1, PAX2, PKD1, PKD2, PKHD1, RPGRIP1L, SDCCAG8, SEC61A1, TMEM67, TSC1, TSC2, TTC21B, UMOD, VHL, WDR19, ZNF423 |
| Nephrotic Syndrome                                      | NPHS1, NPHS2, WT1, PLCE1, LAMB2                                      |
| Autosomal Dominant and Recessive Polycystic Kidney Disease (ADPKD and ARPKD) Panel | DNAJB11, DZIP1L, GANAB, HNF1B, PKD1, PKD2, PKHD1                   |
| Distal Renal Tubular Acidosis Panel                     | ATP6V0A4, ATP6V1B1, CA2, SLC4A1                                      |
| Atypical Hemolytic Uremic syndrome (s-HUS) panel         | C3, CFB, CFH, CFHR1, CFHR3, CFHR5, CFI, DGKE, MCP, THBD              |
| Panel                                                                 | Genes                                                                 |
|----------------------------------------------------------------------|----------------------------------------------------------------------|
| Tuberous Sclerosis Complex Panel                                      | TSC1, TSC2                                                           |
| Microscopic Hematuria (custom panel)                                  | ACTN4, ADCY10, APOL1, C1QA, C1QB, C1QC, C3, CASR, CD2AP, CFH, CFI, CLCN5, CLDN14, CLDN16, CLDN19, COL4A3, COL4A4, COL4A5, COL4A6, CYP24A1, FN1, INF2, MUC1, MYH9, MYO1E, NPHS2, OCRL, SEC61A1, SLC34A1, SPRY2, VHL |
| Neurohypophyseal Diabetes Insipidus and Nephrogenic Diabetes Insipidus Panel | AQP2, AVP, AVPR2                                                     |
| Custom Glycosuria panel                                               | SLC5A2, SLC5A2                                                       |
| Nephrolithiasis and Nephrocalcinosis Panel                           | ADCY10, AGXT, APRT, ATP6V0A4, ATP6V1B1, CA2, CASR, CLCN5, CLDN16, CLDN19, CYP24A1, FAM20A, GRHPR, HNF4A, HOGA1, HPRT1, KCNJ1, OCRL, SLC12A1, SLC22A12, SLC26A1, SLC2A9, SLC34A1, SLC3A1, SLC4A1, SLC7A9, SLC9A3R1, VDR, XDH |
| Nephrolithiasis Panel                                                | ADCY10, AGXT, ALPL, APRT, ATP6V0A4, ATP6V1B1, CA2, CASR, CLCN5, CLDN16, CLDN19, CYP24A1, FAM20A, GPHN, GRHPR, HOGA1, HPRT1, KCNJ1, MOCOS, MOCS1, OCRL, PREPL, SLC12A1, SLC22A12, SLC26A1, SLC2A9, SLC34A1, SLC3A1, SLC4A1, SLC7A9, SLC9A3R1, UMOD, VDR, XDH |
| Alagille syndrome                                                     | ABCB11, ABCB4, ABCC2, ABCG5, ABCG8, ACOX2, AKR1C4, AKR1D1, ALDOB, AMACR, ATP8B1, BAAT, CC2D2A, CFTR, CLDN1, CYP27A1, CYP7A1, CYP7B1, DCCD2, DGUOK, DHCR7, EHHADH, FAH, GNAS, GPBAR1, HNF1B, HSD17B4, HSD3B7, INVS, JAG1, KMT2D, LIPA, MKS1, MPV17, MYO5B, NOTCH2, NPC1, NPC2, NPHP1, NPHP3, NPHP4, NR1H4, PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, PKD1L1, PKHD1, POLG, SCP2, SERPINA1, SLC10A1, SLC10A2, SLC25A13, SLC27A5, SLC51A, SLC51B, SMPD1, TALDO1, TJP2, TMEM216, TRMU, UGT1A1, UTP4, VIPAS39, VPS33B |
| Bartter syndrome panel                                               | BSND, CASR, CLCNKA, CLCNKB, GNAI1, KCNJ1, MAGED2, SLC12A1, SLC12A3 |
| Wilms tumor                                                           | WT1                                                                 |
| Periodic Paralysis Panel                                             | CACNA1S, KCNJ1, RYR1, SCN4A                                          |

Total blue print panel: [https://www.bcm.edu/research/medical-genetics-labs/test_detail.cfm?testcode=1390](https://www.bcm.edu/research/medical-genetics-labs/test_detail.cfm?testcode=1390)
Supplemental Table 2. "Other" indications for referral are summarized in this table

| Name of disease                              | Number |
|----------------------------------------------|--------|
| Hypertension                                 | 2      |
| CKD                                          | 2      |
| Rhabdomyolysis                               | 2      |
| Diamond-Blackfan anemia                      | 1      |
| Nephronophthisis                             | 3      |
| Bilateral Wilms Tumor                        | 1      |
| Renal Tubular Acidosis                       | 1      |
| Bartter syndrome                             | 2      |
| Diabetes insipidus                           | 2      |
| Hypokalemic paralysis                        | 1      |
| Glycosuria                                   | 1      |
| Hyperuricemia and nephropathy                | 1      |
| Townes brock syndrome                        | 1      |
| Nephrocalcinosis                             | 5      |
| Macrocephaly and low muscle tone             | 1      |
| Alagille syndrome                            | 1      |
| Gitelman syndrome                            | 1      |
| a-HUS                                        | 3      |
| Micropenis                                    | 1      |
| Mitochondrial                                | 1      |
| Bilateral renal angiomyolipoma               | 1      |
| Hypophosphatemia                             | 1      |
| VACTERL                                      | 1      |
| Hyperoxaturia                                | 1      |
| Hypomagnesemia                               | 2      |
| Hypocalcemia                                 | 1      |
| Autism and renal artery stenosis             | 1      |
| Joubert                                      | 2      |

Total: 43
Supplemental Table 3. Detection rates of different tests among indications for referral

Cystic Kidney disease total of 49

|                  | Total number | Positive | VUS | Negative |
|------------------|--------------|----------|-----|----------|
| Panel            | 19           | 15       | 2   | 2        |
| CMA              | 3            | 0        | 0   | 3        |
| CMA/ES           | 13           | 4        | 7   | 2        |
| ES               | 3            | 3        | 0   | 0        |
| Not done         | 11           |          |     |          |

(3 asymptomatic patients with family history of ADPKD, 4 insurance denial, 1 patient not available, 3 patients not interested to pursue genetic testing)

CAKUT total of 41

|                  | Total Number | Positive | VUS | Negative |
|------------------|--------------|----------|-----|----------|
| Panel            | 0            | 0        | 0   | 0        |
| CMA              | 9            | 5        | 0   | 4        |
| CMA/ES           | 22           | 8*       | 12  | 2        |
| ES               | 1            | 1        | 0   | 0        |
| Total Blueprint  | 1            | 0        | 1   | 0        |
| Not done         | 8            |          |     |          |

(7 not interested, 1 insurance denial)

*Includes three partially diagnosed cases

Hematuria Total number of 38

|                  | Total number | Positive | VUS | Negative |
|------------------|--------------|----------|-----|----------|
| Panel            | 15           | 10       | 4   | 1        |
| CMA              | 2            | 0        | 1   | 1        |
| Panel and ES     | 1            | 1        | 0   | 0        |
| CMA/ES           | 12           | 7        | 2   | 3        |
| Panel and CMA and ES | 1   | 1        | 0   | 0        |
| ES               | 1            | 1        | 0   | 0        |
| Not done         | 6            |          |     |          |

(3 not interested to pursue genetic testing, 3 insurance denial)
### Proteinuria total number of 21

|                  | Total number | Positive | VUS | Negative |
|------------------|--------------|----------|-----|----------|
| Panel            | 10           | 7        | 2   | 1        |
| CMA              | 0            | 0        | 0   | 0        |
| Panel and CMA    | 1            | 0        | 1   | 0        |
| CMA/ES           | 8            | 5        | 2   | 1        |
| CMA and Panel and Total Blueprint panel | 1 | 0 | 1 | 0 |
| Not done         | 1            |          |     | 1 (patient was not interested to pursue genetic testing) |

### Other indications total number of 43

|                  | Total number | Positive | VUS | Negative |
|------------------|--------------|----------|-----|----------|
| Panel            | 11           | 5        | 3   | 3        |
| CMA              | 4            | 2        | 0   | 2        |
| CMA/ES           | 14           | 8        | 6   | 0        |
| Panel and CMA, and ES | 1 | 0 | 1 | 0 |
| Total BluePrint  | 3            | 1        | 1   | 1        |
| CMA and Total Blueprint | 1 | 1 | 0 | 0 |
| Panel and CMA and Total Blueprint | 1 | 1 | 0 | 0 |
| Not done         | 8            |          |     | 0        |
|                  |              |          |     | 4 (not interested to pursue genetic testing, 4 due to insurance) |
Supplemental Table 4. Impact on management in patients with partial diagnosis

| Patient Number | L1 | L2 | L3 | L4 | L5 | Type of genetic testing (1,2,3,4,5) | Partial diagnosis | Gene/locus | SNV | Phenotype |
|----------------|----|----|----|----|----|---------------------------------|------------------|------------|-----|-----------|
| RGC-0022       | -  | -  | -  | -  | -  | 2,4                             | Hearing Loss     | GJB2       | NM_004004.5; c.35delG, (p.G12VfsX2) and c.416G>A, (p.S139N) | Proteinuria, PUV, bilateral hearing loss |
| RGC-0023       | -  | -  | +  | -  | -  | 2,4                             | Cataract         | CHMP4B     | NM_176812.4; c.508_510delGAA, (p.E170del) (Het) | Cataract and proteinuria |
| RGC-0036       | -  | -  | +  | -  | -  | 2,4                             | Sickle cell anemia | HBB        | NM_000518.4; c.20A>T, (p.E7V)(Hom) | Sickle cell anemia and proteinuria |
| RGC-0106       | -  | -  | -  | +  | +  | 2,4                             | DD               | NAA15      | NM_057175.3; c.439C>T(p.Q147X) (Het) | Syndromic CAKUT |
| RGC-0133       | -  | -  | +  | -  | -  | 2,4                             | DD               | CHMP1A     | NM_002768.4; c.88C>T(p.Q30X) (Hom) | Hyperoxaluria, DD, non-verbal, wheelchair bound |

L1, impact on medical or surgical treatment; L2, change of medical diagnosis; 3, providing diagnostic certainty; 4, subsequent evaluation for other body system involvement; 5, cascade family member testing; CNV, copy number variant; DD, developmental delay; PUV, posterior urethral valve; SNV, single nucleotide variant. Type of testing; 1, panel; 2, CMA; 3, proband ES; 4, trio ES; 5, Total blueprint panel.
Supplement 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)

| Patient ID | Gender | Age | Phenotype   | Gene   | Variant                                           | gnomAD | CADD score | Clinician’s comment | Recommendation                          |
|------------|--------|-----|-------------|--------|--------------------------------------------------|--------|------------|--------------------|----------------------------------------|
| RGC-0007   | M      | 4   | Cystic kidney | PKD1   | NM_001009944; c.971G>T,(p.R324L)(Het) (inherited from father) | 0      | 13.07      | Paternal kidney US recommended |                                        |
| RGC-0007   | M      | 4   | Cystic kidney | TRPC6  | NM_004621; c.2116G>A, p.V706I (Het) (inherited from mother) | 2/250230 | 28         | Recessive disorder and only one heterozygous variant |                                        |
| RGC-0007   | M      | 4   | Cystic kidney | LAMB2  | NM_002292; c.5233G>A, (p.A1745T)(Het) (inherited from mother) | 0      | 24.5       | Recessive disorder and only one heterozygous variant |                                        |
| RGC-0007   | M      | 4   | Cystic kidney | MYO1E  | NM_004998; c.1615C>A, (p.L539M)(Het) (inherited from father) | 0      | 16.21      | Recessive disorder and only one heterozygous variant |                                        |
| RGC-0007   | M      | 4   | Cystic kidney | ITGA8  | NM_003638; c.1492A>G (p.M498V)(Het)(inherited from mother) | 1/251076 | 0.876      | Inherited from the affected mother but variant predicted benign and phenotype does not match with dysplastic kidney in the mother |                                        |
| RGC-0011   | M      | 2   | Cystic kidney | PKD1   | NM_001009944; c.8119G>A (p.V2707M) (Het) (inherited from father) | 0      | 9.007      | Paternal kidney US recommended |                                        |
| RGC-0011   | M      | 2   | Cystic kidney | PKD1   | NM_001009944; c.4151C>T (p.T1384I) (Het) (inherited from father) | 0      | 24.5       | Paternal kidney ultrasound recommended |                                        |
| RGC-0011   | M      | 2   | Cystic kidney | PKD1   | NM_001009944; c.3239C>A (p.P1080H) (Het) (inherited from mother) | 2/214486 | 23.5       | Maternal kidney US recommended |                                        |
| RGC-0012 | F  | 16.8 | Hematuria | 2  | TRPC6 and YAP1 | arr[hg19] 11q22.1 (101,450,649-102,064,511)x3 | NA | NA | TRPC6 might be disrupted therefore this VUS might have clinical consequences (clinical significance of a duplication of these or any genes in this region is not currently known. This region in its entirety is not known to vary in copy number in normal population) | Annual UA and follow up with nephrology |
| RGC-0016 | M  | 17.1 | Kidney stone | 3 | TRPC6 | NM_004621; c.1678G>A (p.A560T) (Het) (inherited from mother) | 0  | 17.98 | VUS inherited from unaffected mother | Follow up in 2 years for reanalysis of tES |
| RGC-0016 | M  | 17.1 | Kidney stone | 3 | SLC4A4 | NM_001098484; c.149G>C (p.G50A) (Het) (inherited from mother) | 390/249120 | 20.6 | Recessive disorder and only one heterozygous variant | Follow up recommended |
| RGC-0025 | M  | 18   | Proteinuria  | 3  | COL4A5 | NM_033380.1; c.2180C>G (p.P727R) (inherited from mother) | 0  | 27.3 | Phenotype does not match Alport and mother does not have microscopic hematuria | |
| RGC-0027 | F  | 16   | CAKUT       | 3  | IL17RD | NM_017563.3; c.8C>G (p.P3R) (Het) (inherited from father) | 0  | 26.1 | Phenotype does not fit with Kallmann syndrome but VUS could contribute to kidney anomaly | Testing of family members/paternal kidney ultrasound recommended |
| RGC-0040 | F  | 3.4  | CAKUT       | 3  | CHD7  | NM_017780; c.8378C>G (p.A2739G) (Het) (inherited from father) | 4/244694 | 24  | Phenotype does not fit | |
| RGC-0040 | F  | 3.4  | CAKUT       | 3  | PKD2  | NM_000297; c.2420G>A (p.R807Q) (Het) (inherited from father) | 754/251136 | 26.1 | Phenotype does not fit | |
| RGC-0040 | F  | 3.4  | CAKUT       | 3  | PKD1  | NM_001009944; c.6749C>T | 0  | 23.5 | Phenotype does not fit | |
| Patient ID | Gender | Age | Diagnosis | Gene | Mutation | Description | Age at Diagnosis | Final Diagnosis |
|------------|--------|-----|-----------|------|----------|-------------|-----------------|----------------|
| RGC-0040   | F      | 3.4 | CAKUT     | MSR1 | arr 8p22(16032346-16073395)x1 | NA | NA | Likely benign |
| RGC-0040   | F      | 3.4 | CAKUT     | MSR1 | arr 8p22(15965430-16021863)x3 | NA | NA | Likely benign, Inherited from mother |
| RGC-0048   | F      | 9.8 | CAKUT     | LRP2 | NM_004525; c.2456G>A (p.R819H)(Het)(inherited from father) | 27/251146 | 25.1 | Patient does not have full phenotype of Donnai-Barrow Syndrome |
| RGC-0048   | F      | 9.8 | CAKUT     | LRP2 | NM_004525; c.403G>A (p.D135N)(Het)(inherited from mother) | 0 | 24 |  |
| RGC-0048   | F      | 9.8 | CAKUT     | PKD1 | NM_001009944; c.10325C>T (p.A3442V)(Het) (inherited from father) | 1/244174 | 12.83 | Phenotype does not fit |
| RGC-0048   | F      | 9.8 | CAKUT     | PKD1 | NM_001009944; c.5530G>C (p.G1844R)(Het)(inherited from father) | 0 | 21.3 | Phenotype does not fit |
| RGC-0048   | F      | 9.8 | CAKUT     | SLC7A9 | NM_014270; c.814G>A (p.V272M) (Het) (inherited from father) | 0 | 13.93 | Recessive disorder and only one heterozygous variant |
| RGC-0048   | F      | 9.8 | CAKUT     | FRAS1 | NM_025074; c.6584A>G (p.E2195G)(Het)(inherited from father) | 238/280120 | 22.4 | Two FRAS1 variants on the same chromosome |
| RGC-0048   | F      | 9.8 | CAKUT     | FRAS1 | NM_025074;c.9553G>A (p.G3185R)(Het)(inherited from father) | 197/279136 | 24.8 |  |
| RGC-0048   | F      | 9.8 | CAKUT     | NPHP1 | NM_000272; c.830G>A (p.R277Q)(Het) (inherited from mother) | 173/282608 | 2.723 | Recessive disorder and only one heterozygous variant |
| RGC-0059   | F      | 12  | CAKUT     | CC2D2A | NM_001080522; c.2597A>G, (p.N866S)(Het)(inherited from mother) | 45/280162 | 16.74 | Recessive disorder and only one heterozygous variant |
| RGC-0059 | F | 12 | CAKUT | 3 | PKHD1 | NM_138694; c. 5750A>G, (p. Q1917R)(Het)(inherited from father) | 0 | 32 | Recessive disorder and only one heterozygous variant |
| RGC-0059 | F | 12 | CAKUT | 3 | ITGA8 | NM_003638; c. 1336G>A, (p. V446I)(Het)(inherited from mother) | 126/282842 | 2.758 | Recessive disorder and only one heterozygous variant |
| RGC-0064 | M | 12 | CAKUT | 3 | NID1 | NM_002508.2; c.3680dupC (p.G1228RfsX9)(Het)(inherited from father) | 0 | 6.445 | VUS seems likely pathogenic, affected sibling positive |
| RGC-0064 | M | 12 | CAKUT | 3 | NID1 | NM_002508.2; c.1297C>T (p.R433X)(Het)(inherited from mother) | 0 | 12.17 | VUS seems likely pathogenic, affected sibling positive |
| RGC-0065 | F | 1 | Other (Nephromegaly and Nephrocalcinosis) | 3 | CRB2 | NM_173689.5; c.1298C>T (p.P433L)(Het) | 124/282294 | 15.97 | Recessive disorder and only one heterozygous variant |
| RGC-0065 | F | 1 | Other (Nephromegaly and Nephrocalcinosis) | 3 | LIG4 | NM_002312.3; c.686A>G (p.H229R)(Het) | 178/281618 | 23.3 | Recessive disorder and only one heterozygous variant |
| RGC-0065 | F | 1 | Other (Nephromegaly and Nephrocalcinosis) | 3 | PSAT1 | NM_051797.2; c.94T>C (p.Y32H)(Het) | 5/280748 | 25.2 | Recessive disorder and only one heterozygous variant |
| RGC-0065 | F | 1 | Other (Nephromegaly and Nephrocalcinosis) | 3 | COL4A5 | NM_000495.4; c.4450T>C (p.Y1484H)(Het) | 0 | 25.4 | Unrelated to patient's phenotype |
| RGC-0065 | F | 1 | Other (Nephromegaly and Nephrocalcinosis) | 3 | SH3YL1 | Arr 2p25.3 (66097-239712)x1 | NA | NA | Non disease-associated regions No parental follow-up recommended |
| RGC-0065 | F | 1 | Other (Nephromegaly and Nephrocalcinosis) | 3 | NUP52CL | Arr Xp22.3 (106384817-106398144)x1 | NA | NA | Non disease-associated regions No parental follow-up recommended |
| RGC-0069 | M | 2.3 | Proteinuria | 1,2 | CD2AP | NM_012120.2; c.1286_1288dup (p.E429dup)(Het) | 126/250158 | 3.562 | In-frame duplication IES recommended |
| RGC-0094 | F | 3.5 | CAKUT | 3 | COL4A5 | NM_000495.4; c.2600T>C (p.L867T)(Het) | 2/182030 | 16.49 | Unrelated to patient's phenotype |

*VUS* means variant of uncertain significance.
| ID      | Age | Diagnosis  | Genes                | Chromosome     | Variant Details                                      | p-value | Odds Ratio | Comment                                                                 |
|---------|-----|------------|----------------------|----------------|-----------------------------------------------------|---------|-------------|------------------------------------------------------------------------|
| RGC-0095| M   | 9          | Cystic kidney        | PKD1           | NM_001009944.2; c.8498C>A (p.P2833H) (Het)           | 0       | 6.179       | Conserved codon, seems likely pathogenic                              |
| RGC-0096| M   | 10.7       | Cystic Kidney        | PKD1           | NM_001009944.2; c.10810 G>A (p.E3604K) (Het) (inherited from father) | 0       | 22.9        | Seems likely pathogenic based on PKDB and Clinvar                    |
| RGC-0096| M   | 10.7       | Cystic Kidney        | Portion of PLEKHA7, ABCC8 and 6 other genes | arr[GRCh37] 11p15.1(16957123_17439236)x3 (inherited from father) | NA      | NA          | Paternal kidney US recommended                                        |
| RGC-0096| M   | 10.7       | Cystic Kidney        | Portion of VCX3A, entire HDHD1, STS, VCX, and PNPLA4 | arr[GRCh37] Xp22.31(6453036_8131810)x2 (inherited from mother) | NA      | NA          | Patient affected by Arthrogryposis and VCX3A is disrupted             |
| RGC-0099| M   | 1.5        | CAKUT                |                | arr[GRCh37] (X)x1~2,(Y)x1 (Mosaic gain) (155186Kb) associated with mosaic Klinefelter syndrome | NA      | NA          | 20-30% mosaicism                                                       |
| RGC-0103| M   | 0.01       | CAKUT                | FAT1           | NM_005245.3; c.7014C>A (p.S2338R) (Het) (inherited from mother) | 7/280606 | 4.937       | Follow up                                                             |
| RGC-0103| M   | 0.01       | CAKUT                | FAT1           | NM_005245.3; c.9320G>T (p.C3107F) (Het) (inherited from mother) | 5/249052 | 24.9        | Follow up                                                             |
| RGC-0103| M   | 0.01       | CAKUT                | PPEF1          | arr[GRCh19] Xp22.13 (18821936-18822035)x0             | NA      | NA          | No disease association                                                |
| RGC-0104| F   | 14.8       | Proteinuria          | MYO1E          | NM_004998.3; c.2627C>G (p.T876R) (Het) (inherited from mother) | 400/282482 | 20.8       | Recessive disorder and only one heterozygous variant                 |
| RGC-0104| F   | 14.8       | Proteinuria          | PLCE1          | NM_016341.3; c.2032A>G (p.M678V) (Het) (inherited from father) | 280/280870 | 23.6       | Recessive disorder and only one heterozygous variant                 |
| RGC-0107| F   | 5.3        | CAKUT                | BICC1          | NM_001080512.2; c.707A>G                                | 8/282402 | 3.304       | Paternal kidney US recommended                                        |
| Patient   | Sex | Age | Phenotype                          | Gene  | Variant Description                      | mtDNA | Probability | Phenotype overlap |
|-----------|-----|-----|------------------------------------|-------|------------------------------------------|-------|-------------|-------------------|
| RGC-0109  | M   | 15.6| Other (Hyperuricemic and nephropathy) | WT1   | NM_024426.4; c.358G>A (p.G120S) | Het   | 0           | 22.4             | No phenotype overlap |
| RGC-0109  | M   | 15.6| Other                              | WDR19 | NM_025132.3; c.7C>T (Het) | 54/275970 | 0.436 | Recessive disorder and only one heterozygous variant |
| RGC-0109  | M   | 15.6| Other                              | PKHD1 | NM_138694.3; c.2744C>T (p.A915V)(Het) | 0 | 26.3 | No phenotype overlap (kidneys not enlarged) |
| RGC-0109  | M   | 15.6| Other                              | PKHD1 | NM_138694.3; c.7675G>C (p.V2559L)(Het)(inherited from mother) | 280/282300 | 9.628 | Predicted benign |
| RGC-0111  | F   | 0.01| CAKUT                              | COL4A4| NM_000092.4; c.3394C>G (p.P1132A)(Het)(inherited from father) | 1/248216 | 25.4 | No phenotype overlap |
| RGC-0111  | F   | 0.01| CAKUT                              | LAMB2 | NM_002292.3; c.4224+19G>C (Het)(inherited from father) | 3031/279460 | 4.844 | Recessive disorder and only one heterozygous variant |
| RGC-0122  | M   | 4   | Hematuria                          | COL4A3| NM_000091.4; c.1483C>T (p.H495Y)(Het)(inherited from father) | 202/280910 | 0.689 | Kidney biopsy showed TBM | Testing other siblings |
| RGC-0122  | M   | 4   | Hematuria                          | FN1   | NM_212482.1; c.3626C>T (p.T1209I)(Het)(inherited from father) | 2/251442 | 24.4 | Biopsy does not fit |
| RGC-0125  | F   | 14  | Other(a-HUS)                       | THBD  | NM_003361; c.1456G>T (p.D486Y)(Het) | 2115/276574 | 1.136 | Reanalyze ES |
| RGC-0125  | F   | 14  | Other(a-HUS)                       | DGKE  | NM_003647; c.303G>C (p.K101N)(Het) | 39/282288 | 22.9 | Recessive disorder and only one heterozygous variant |
| RGC-0125  | F   | 14  | Other(a-HUS)                       | GANAB | NM_198335.2; c.1652A>C (p.N551T)(Het)(inherited from father) | 0 | 22.3 | No family history on paternal side, and positive family history from maternal side |
| RGC-0125 | F   | 14 | Other(a-HUS)    | 1,3 | ALMS1 | NM_015120.4; c.9463A>T(p.T3155S)(Het)(inherited from father) | 65/249098 | 24.7 | Recessive disorder and only one heterozygous variant |
|----------|-----|----|----------------|-----|-------|-------------------------------------------------------------|----------|------|---------------------------------------------------|
| RGC-0125 | F   | 14 | Other(a-HUS)    | 1,3 | TRIOBP| NM_0010391412; c.6632A>T(p.Q2211L)(Het)(inherited from father) | 40/280310 | 28.2 | Recessive disorder and only one heterozygous variant |
| RGC-0125 | F   | 14 | Other(a-HUS)    | 1,3 | GRHPR | NM_012203.1; c.374G>A(p.R125Q)(Het)(inherited from father)    | 78/282832 | 29.7 | Recessive disorder and only one heterozygous variant |
| RGC-0125 | F   | 14 | Other(a-HUS)    | 1,3 | DGKE  | NM_003647.2; c.303G>C(p.K101N)(Het)(inherited from father)    | 39/282288 | 23.2 | Recessive disorder and only one heterozygous variant |
| RGC-0126 | M   | 17 | Proteinuria     | 1,2,5| CFH   | NM_000186.3; c.2270A>C(p.N757T)(Het)                          | 0        | 0.112| No phenotype overlap                                     |
| RGC-0126 | M   | 17 | Proteinuria     | 1,2,5| CD2AP | NM_012120.2; c.164A>C(p.K55T)(Het)                            | 63/282798 | 30   | Fits with biopsy report and family history              |
| RGC-0126 | M   | 17 | Proteinuria     | 1,2,5| NPHS2 | NM_014625; c.725C>T(p.A242V)(Het)                             | 1962/281850 | 25.3 | Recessive disorder and only one heterozygous variant |
| RGC-0126 | M   | 17 | Proteinuria     | 1,2,5| LAMB2 | NM_004646; c.2740G>A(p.G914A)(Het)                            | 0        | 27.7 | Although patient has two variants in LAMB2, Family history of proteinuria in this patient suggest AD mode of inheritance |
| RGC-0126 | M   | 17 | Proteinuria     | 1,2,5| LAMB2 | NM_004646; c.1193C>T(p.T398I)(Het)                            | 694/282716 | 7.968| Parental testing for KFM in LAMB2                      |
| RGC-0130 | M   | 20 | Cystic kidney   | 3    | SEC61A1| NM_013336.3; c.554C>G(p.T185S)(Het)(de novo)                 | 0        | 28.4 | Patient's phenotype has overlap with reported phenotype associate with this gene |
| RGC-0136 | F   | 7  | CAKUT          | 3    | MT-RNR2| m.2872C>T(Homoplasmic)(inherited from mother)                | 0        | NA   | Mother also homoplasmic suggesting that this           |
| Reference | Sex | Age | Diagnosis | Gene | Variant | Allele Count | Risk Score | Result | Comments |
|-----------|------|-----|-----------|------|---------|-------------|------------|--------|----------|
| RGC-0138 | F    | 16  | CAKUT     | GJB3 | NM_024009.2; c.223C>T (p.R75C)(Het) | 42/282762 | 29.7      | Mother does not have hearing loss |
| RGC-0138 | F    | 16  | CAKUT     | WFS1 | NM_006005.3; c.527T>C (p.V176A)(Het) | 3/250700 | 22.4      | Mother does not have hearing loss |
| RGC-0138 | F    | 16  | CAKUT     | GATA3| NM_0010022951; c.828C>T (p.R276W)(Het) | 0       | 32        | Patient's phenotype has overlap with reported phenotype associated with this gene, patient has hypoparathyroidism |
| RGC-0138 | F    | 16  | CAKUT     | NPHS1| NM_004646.3; c.7C>A (p.L3M)(Het) | 8/185830 | 4.560     | Recessive disorder and only one heterozygous variant |
| RGC-0139 | M    | 15  | Cystic kidney | PRKD1 | NM_007242.2; c.1947T>G (p.F649L)(Het) | 2/250352 | 11.83     | Mother reported to have heart disease |
| RGC-0139 | M    | 15  | Cystic kidney | PKD1 | NM_001009944.2; c.7061A>C (p.Q2354P)(Het) | 0       | 27.1      | Likely the cause of ADPKD, there is history of ADPKD in father |
| RGC-0139 | M    | 15  | Cystic kidney | PKD1 | NM_001009944.2; c.6097G>A (p.A2033T)(Het) | 11/275498 | 23.2      | there is history of ADPKD in father |
| RGC-0140 | F    | 8   | CAKUT     | KIAA1109 | NM_015312.3; c.822-3T>C (Het)(inherited from father) | 2/247734 | 6.412     | Recessive disorder and only one heterozygous variant |
| RGC-0140 | F    | 8   | CAKUT     | COL4A4| NM_000092.4; c.2985C>T (p.P995=)(Het)(inherited from father) | 19/280864 | 0.112     | |
| RGC-0140 | F    | 8   | CAKUT     | FANCC| NM_000136.2; c.998T>C (p.L333P)(Het)(inherited from father) | 2/249760 | 22.4      | Recessive disorder and only one heterozygous variant |
| RGC-0140 | F    | 8   | CAKUT | 3    | AHI1 | NM_017651.4; c.1621G>T (p.D541Y)(Het)(inherited from mother) | 0                | 24.2 | Recessive disorder and only one heterozygous variant |
| RGC-0140 | F    | 8   | CAKUT | 3    | TMTC3| NM_181783.3; c.10A>G (p.I4V)(Het)(inherited from father)    | 13/276640        | 12.9 | Recessive disorder and only one heterozygous variant |
| RGC-0140 | F    | 8   | CAKUT | 3    | CFH  | NM_000186.3; c.506A>G (p.H169R)(Het)(inherited from father) | 3/251074         | 0.014| No phenotype overlap                                  |
| RGC-0141 | F    | 0.9 | Other (Hypocalcemia) | 3    | TRPC6| NM_004621.5; c.101T>C (p.M34T) (Het)(inherited from father) | 2/199782         | 24.5 | Father does not have kidney disease                  |
| RGC-0141 | F    | 0.9 | Other (Hypocalcemia) | 3    | SLC12A1| NM_000338.2; c.2282G>A (p.R761Q)(Het)(inherited from mother) | 26/282292        | 22.7 | Recessive disorder and only one heterozygous variant |
| RGC-0141 | F    | 0.9 | Other (Hypocalcemia) | 3    | INVS | NM_014425.3; c.2822A>G (p.H941R)(Het)(inherited from mother) | 1/251378         | 6.868| Recessive disorder and only one heterozygous variant |
| RGC-0141 | F    | 0.9 | Other (Hypocalcemia) | 3    | ITGA8| NM_003638.1; c.1156T>C (p.F386L)(Het)(inherited from mother) | 14/282834        | 22.4 | Recessive disorder and only one heterozygous variant |
| RGC-0141 | F    | 0.9 | Other (Hypocalcemia) | 3    | APOL1| NM_003661.3; c.334C>T (p.R112C)(Het)(de novo)               | 4/251190         | 11.68| Variant discussed with experts and seems benign       |
| RGC-0142 | F    | 0.5 | Other (a-HUS) | 1.4  | CFH  | NM_000186.3; c.3357C>G (p.D1119E)(Het)(inherited from mother) | 3/282870         | 11.94| Patient has homozygous CFHR3-CFHR1 deletion          |
| RGC-0142 | F    | 0.5 | Other (a-HUS) | 1.4  | ITGA8| NM_003638.2; c.840T>C (p.S280=)(Het)(inherited from father)  | 215/282194       | 7.427| Recessive disorder and only one heterozygous variant |
| RGC-0148 | F    | 2   | Hematuria | 1    | ACTN4| NM_004924.5; c.751C>T (p.R251W)(Het)(inherited from father) | 3/143328         | 32   | Paternal kidney evaluation                           |
| RGC-0149 | M | 3 | Hematuria | 1 | COL4A4 | NM_000092.4; c.1442G>T (p.G481V)(Het)(inherited from mother) | 1/143110 | 26 | Segregation study suggests this variant causes hematuria in this family |
| RGC-0150 | M | 1.6 | Other (DI) | 1 | AVPR2 | NM_000054.4; c.910+5G>T (intronic)(Hem) | 0 | 9.197 | Segregation study suggests this variant causes DI in this family |
| RGC-0153 | F | 9 | Other (Glycosuria) | 1 | SLC5A2 | NM_00304.3; c.1665+4A>T (Het)(inherited from father) | 0.003% | 19.57 | Determine father’s phenotype |
| RGC-0158 | M | 8 | Hematuria | 1 | COL4A3 | NM_000091.4; c.4445C>T (p.A1482V)(Het) | 223/143266 | 22.5 | May describe phenotype |
| RGC-0158 | M | 8 | Hematuria | 1 | NPHS1 | NM_004646.3; c.2614G>A (p.V872I)(Het) | 3/143174 | 18.54 | Pt also has nephrotic syndrome and also has a pathogenic variant in NPHS2 |
| RGC-0169 | M | 2 | Cystic kidney | 1 | PKD1 | NM_001009944.2; c.7146C>G (p.S2382R)(Het) | 0 | 23.3 | Reported in autism but there was not concern about DD or ASD in this patient |
| RGC-0169 | M | 2 | Cystic kidney | 1 | NPHP1 | NM_000272.3; duplication of whole gene | NA |  |  |
| RGC-0170 | F | 5 | Proteinuria | 1 | CUBN | NM_001081.3; c.2677A>G (p.T893A)(Het) | 146/143296 | 4.896 | Phase of the two VUSs are unknown Parents did not provide samples |
| RGC-0170 | F | 5 | Proteinuria | 1 | CUBN | NM_001081.3; c.5285T>G, c.5285T>G (p.V1762G)(Het) | 12/282422 | 5.578 | Phase of the two VUSs are unknown Follow up |
| RGC-0170 | F | 5 | Proteinuria | 1 | NPHS1 | NM_004646.3; c.710T>C (p.L237P)(Het) | 4/251428 | 31 | Recessive disorder and only one heterozygous variant |
| RGC-0170 | F | 5 | Proteinuria | 1 | PAX2 | M_003990.4; c.809G>A (p.R270H)(Het) | 7/251366 | 29.2 | Ophthalmology evaluation |
| RGC-0170 | F | 5 | Proteinuria | 1 | PLCE1 | NM_016341.3; c.642A>T (p.Q214G)(Het) | 293/280000 | 10.49 | Recessive disorder and only one |
|   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|
| RGC-0170 | F | 5 | Proteinuria | 1 | SMARCAL1 | M_014140.3; c.1196C>T (p.T399M)(Het) | 353/282896 | 0.899 | Recessive disorder and only one heterozygous variant |
| RGC-0170 | F | 5 | Proteinuria | 1 | WDR73 | NM_032856.3; c.481G>T (p.V161F)(Het) | 5/248808 | 11.65 | Recessive disorder and only one heterozygous variant |
| RGC-0174 | M | 14 | Other (Alagille syndrome) | 1 | JAG1 | NM_000214.2; c.776G>T (p.G259V)(Het)(VUS) | 0 | 26.6 | tES recommended |
| RGC-0180 | F | 5 | Proteinuria | 1 | INF2 | NM_022489.3; c.2851C>T (p.R951W)(Het) | 1/154628 | 23.6 | Father had trace of protein in dipstick Testing of siblings for INF2 |
| RGC-0184 | M | 4 | Proteinuria | 3 | EVC2 | arr[GRCh37]4p16.2(5616917_5699833)x3 | NA | NA | Parental testing recommended |
| RGC-0187 | F | 4 | Cystic kidney | 3 | PUF60 | NM_078480.2; c.1292C>T (p.P43L)(Het)(inherited from father) | 0 | 22.5 | Father does not have kidney disease |
| RGC-0187 | F | 4 | Cystic kidney | 3 | GLIS2 | NM_032975.2; c.1244C>T (p.R415L) (Het)(inherited from mother) | 21/1/176552 | 26.8 | Recessive disorder and only one heterozygous variant |
| RGC-0187 | F | 4 | Cystic kidney | 3 | ARHGEDIA | NM_001301242.1; c.544A>G (p.T182A)(Hom)(both parents are carrier) | 1/249280 | 6.032 | Seems disease causing Testing of siblings recommended |
| RGC-0187 | F | 4 | Cystic kidney | 3 | FLNA | NM_001456.3; c.1399C>T (p.R467C)(Het)(inherited from mother) | 1/177746 | 23.6 | Mother unaffected |

DI, Diabetes insipidus; Es, Exome sequencing; PKDB, Autosomal Dominant Polycystic Kidney Disease Mutation Database; RBP, Retinol-binding Protein; TBM, Thin basement membrane; UA, Urine analysis; US, Ultrasound. Type of the testing; 1, panel; 2, CMA; 3, proband ES; 4, trio ES; 5, Total Blueprint panel.
Supplemental Table 1. Panels (utilized in this study) and the genes included in each of them are summarized below.

| Panel                                                                 | Genes                                                                 |
|----------------------------------------------------------------------|----------------------------------------------------------------------|
| Nephrotic Syndrome (NS)/Focal Segmental Glomerulosclerosis (FSGS) Panel | ACTN4, ANK FY1, ANLN, APOL1, ARHGAP24, ARHGDIA, CD2AP, CDK20, COL4A3, COL4A4, COL4A5, COL4A6, COQ2, COQ6, COQ8B, CRB2, CUBN, DGKE, DLC1, EMP2, FAT1, GAPVD1, GON7, INF2, ITGA3, ITGB4, ITSN1, ITSN2, KANK1, KANK2, KANK4, KAT2B, KIRREL1, LAGE3, LAMA5, LAMB2, LMX1B, MAFB, MAGI2, MYH9, MYO1E, NEU1, NFKB2, NPHS1, NPHS2, NUP107, NUP133, NUP160, NUP205, NUP93, OSGEP, PAX2, PDSS2, PLCE1, PTPRO, SCARB2, SGPL1, SMARCAL1, TBC1D8B, TNS2, TP53RK, TPRKB, TRIM8, TRPC6, TTC21B, WDR4, WDR73, WT1, XPO5, YRDC |
| Alport syndrome Panel                                              | COL4A3, COL4A4, COL4A5, COL4A6                                      |
| Autosomal Dominant Polycystic Kidney Disease (ADPKD) panel          | DNAJB11, GANAB, HNF1B, PKD1, PKD2                                  |
| Recessive Polycystic Kidney Disease (ARPKD) panel                   | DZIP1L, PKHD1                                                       |
| Hereditary cystic kidney disease panel                             | ANKS8, CEP164, CEP290, CEP83, COL4A1, CRB2, DCDC2, DICER1, DNAJB11, DZIP1L, GANAB, GLIS2, HNF1B, IFT172, INVS, IQCB1, JAG1, LRPP5, MAPKBP1, MUC1, NEK8, NOTCH2, NPHP1, NPHP3, NPHP4, OFD1, PAX2, PKD1, PKD2, PKHD1, RPGRIP1L, SDCCAG8, SEC61A1, TMEM67, TSC1, TSC2, TTC21B, UMOD, VHL, WDR19, ZNF423 |
| Nephrotic Syndrome                                                  | NPHS1, NPHS2, WT1, PLCE1, LAMB2                                     |
| Autosomal Dominant and Recessive Polycystic Kidney Disease (ADPKD and ARPKD) Panel | DNAJB11, DZIP1L, GANAB, HNF1B, PKD1, PKD2, PKHD1 |
| Distal Renal Tubular Acidosis Panel                                | ATP6V0A4, ATP6V1B1, CA2, SLC4A1                                     |
| Atypical Hemolytic Uremic syndrome (s-HUS) panel                    | C3, CFB, CFH, CFHR1, CFHR3, CFHR5, CFI, DGKE, MCP, THBD            |
| Panel                                                                 | Genes                                                                 |
|----------------------------------------------------------------------|----------------------------------------------------------------------|
| Tuberous Sclerosis Complex Panel                                     | TSC1, TSC2                                                          |
| Microscopic Hematuria (custom panel)                                | ACTN4, ADCY10, APO1, C1QA, C1QB, C1QC, C3, CASR, CD2AP, CFH, CFI, CLCN5, CLDN14, CLDN16, CLDN19, COL4A3, COL4A4, COL4A5, COL4A6, CYP24A1, FN1, INF2, MUC1, MYH9, MYO1E, NPHS2, OCRL, SEC61A1, SLC34A1, SPRY2, VHL |
| Neurohypophyseal Diabetes Insipidus and Nephrogenic Diabetes Insipidus Panel | AQP2, AVP, AVPR2                                                    |
| Custom Glycosuria panel                                             | SLC5A2, SLC5A2                                                      |
| Nephrolithiasis and Nephrocalcinosis Panel                          | ADCY10, AGXT, APRT, ATP6V0A4, ATP6V1B1, CA2, CASR, CLCN5, CLDN16, CLDN19, CYP24A1, FAM20A, GRHPR, HNF4A, HOCA1, HPRT1, KCNJ1, OCRL, SLC12A1, SLC22A12, SLC26A1, SLC26A9, SLC34A1, SLC34A3, SLC3A1, SLC4A1, SLC7A9, SLC9A3R1, VDR, XDH |
| Nephrolithiasis Panel                                               | ADCY10, AGXT, ALPL, APRT, ATP6V0A4, ATP6V1B1, CA2, CASR, CLCN5, CLDN16, CLDN19, CYP24A1, FAM20A, GRHPR, HOCA1, HPRT1, KCNJ1, MOCOS, MOCS1, OCRL, PREPL, SLC12A1, SLC22A12, SLC26A1, SLC26A9, SLC34A1, SLC34A3, SLC3A1, SLC4A1, SLC7A9, SLC9A3R1, UMOD, VDR, XDH |
| Alagille syndrome                                                   | ABCB11, ABCB4, ABCC2, ABCG5, ABCG8, ACOX2, AKR1C4, AKR1D1, ALDOB, AMACR, ATPB1, BAAT, CC2D2A, CFTR, CLDN1, CYP27A1, CYP7A1, CYP7B1, DCCD2, DGUOK, DHCR7, EHHADH, FAH, GNAS, GPBAR1, HNF1B, HSD17B4, HSD3B7, INS, JAG1, KMT2D, LIPA, MKS1, MPV17, MY05B, NOTCH2, NPC1, NPC2, NPHP1, NPHP3, NPHP4, NR1H4, PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, PKD1L1, PKHD1, POLG, SCPE, SERPINA1, SLC10A1, SLC10A2, SLC25A13, SLC27A5, SLC51A, SLC51B, SMPD1, TALDO1, TJP2, TMEM216, TRMU, UGT1A1, UTP4, VIPAS39, VPS33B |
| Bartter syndrome panel                                             | BSND, CASR, CLCNKA, CLCNKB, GNAII, KCNJ1, MAGED2, SLC12A1, SLC12A3 |
| Wilms tumor                                                        | WT1                                                                |
| Periodic Paralysis Panel                                           | CACNA1S, KCNJ1, RYR1, SCN4A                                         |

Total blue print panel: https://www.bcm.edu/research/medical-genetics-labs/test_detail.cfm?testcode=1390
Supplemental Table 2. "Other" indications for referral are summarized in this table

| Name of disease                          | Number |
|------------------------------------------|--------|
| Hypertension                            | 2      |
| CKD                                      | 2      |
| Rhabdomyolysis                           | 2      |
| Diamond-Blackfan anemia                  | 1      |
| Nephronophthisis                         | 3      |
| Bilateral Wilms Tumor                    | 1      |
| Renal Tubular Acidosis                   | 1      |
| Bartter syndrome                         | 2      |
| Diabetes insipidus                       | 2      |
| Hypokalemic paralysis                    | 1      |
| Glycosuria                               | 1      |
| Hyperuricemia and nephropathy            | 1      |
| Townes brock syndrome                    | 1      |
| Nephrocalcinosis                         | 5      |
| Macrocephaly and low muscle tone         | 1      |
| Alagille syndrome                        | 1      |
| Gitelman syndrome                        | 1      |
| a-HUS                                    | 3      |
| Micropenis                                | 1      |
| Mitochondrial                            | 1      |
| Bilateral renal angiomyolipoma           | 1      |
| Hypophosphatemia                         | 1      |
| VACTERL                                  | 1      |
| Hyperoxaturia                            | 1      |
| Hypomagnesemia                           | 2      |
| Hypocalcemia                             | 1      |
| Autism and renal artery stenosis         | 1      |
| Joubert                                  | 2      |
|                                          | 43     |
Supplemental Table 3. Detection rates of different tests among indications for referral

### Cystic Kidney disease total of 49

| Test Type | Total Number | Positive | VUS | Negative |
|-----------|--------------|----------|-----|----------|
| Panel     | 19           | 15       | 2   | 2        |
| CMA       | 3            | 0        | 0   | 3        |
| CMA/ES    | 13           | 4        | 7   | 2        |
| ES        | 3            | 3        | 0   | 0        |
| Not done  | 11           |          |     |          |

(3 asymptomatic patients with family history of ADPKD, 4 insurance denial, 1 patient not available, 3 patients not interested to pursue genetic testing)

### CAKUT total of 41

| Test Type | Total Number | Positive | VUS | Negative |
|-----------|--------------|----------|-----|----------|
| Panel     | 9            | 0        | 0   | 0        |
| CMA       | 9            | 5        | 0   | 4        |
| CMA/ES    | 22           | 8*       | 12  | 2        |
| ES        | 1            | 1        | 0   | 0        |
| Total Blueprint | 1 | 0 | 1 | 0 |
| Not done  | 8            |          |     |          |

*Includes three partially diagnosed cases

### Hematuria Total number of 38

| Test Type | Total Number | Positive | VUS | Negative |
|-----------|--------------|----------|-----|----------|
| Panel     | 15           | 10       | 4   | 1        |
| CMA       | 2            | 0        | 1   | 1        |
| Panel and ES | 1 | 1 | 0 | 0 |
| CMA/ES    | 12           | 7        | 2   | 3        |
| Panel and CMA and ES | 1 | 1 | 0 | 0 |
| ES        | 1            | 1        | 0   | 0        |
| Not done  | 6            |          |     |          |

(3 not interested to pursue genetic testing, 3 insurance denial)
### Proteinuria total number of 21

|                      | Total number | Positive | VUS | Negative |
|----------------------|--------------|----------|-----|----------|
| Panel                | 10           | 7        | 2   | 1        |
| CMA                  | 0            | 0        | 0   | 0        |
| Panel and CMA        | 1            | 0        | 1   | 0        |
| CMA/ES               | 8            | 5        | 2   | 1        |
| CMA and Panel and Total Blueprint panel | 1 | 0 | 1 | 0 |
| **Not done**         | **1**        | **0**    | **1** | **0**    |

(patient was not interested to pursue genetic testing)

### Other indications total number of 43

|                      | Total number | Positive | VUS | Negative |
|----------------------|--------------|----------|-----|----------|
| Panel                | 11           | 5        | 3   | 3        |
| CMA                  | 4            | 2        | 0   | 2        |
| CMA/ES               | 14           | 8        | 6   | 0        |
| Panel and CMA, and ES| 1            | 0        | 1   | 0        |
| Total Blueprint      | 3            | 1        | 1   | 1        |
| CMA and Total Blueprint | 1        | 1        | 0   | 0        |
| Panel and CMA and Total Blueprint | 1 | 1 | 0 | 0 |
| **Not done**         | **8**        | **0**    | **4** | **4**    |

(4 not interested to pursue genetic testing, 4 due to insurance)
### Supplemental Table 4. Impact on management in patients with partial diagnosis

| Patient Number | L1 | L2 | L3 | L4 | L5 | Type of genetic testing (1,2,3,4,5) | Partial diagnosis | Gene/locus | SNV | Phenotype |
|----------------|----|----|----|----|----|-----------------------------------|------------------|------------|----|-----------|
| RGC-0022       | -  | -  | +  | -  | +  | 2,4                               | Hearing Loss     | GJB2       | NM_004004.5; c.35delG, (p.G12VfsX2) and c.416G>A, (p.S139N) | Proteinuria, PUV, bilateral hearing loss |
| RGC-0023       | -  | -  | +  | -  | +  | 2,4                               | Cataract         | CHMP4B     | NM_176812.4; c.508_510delGAA, (p.E170del) (Het) | Cataract and proteinuria |
| RGC-0036       | -  | -  | +  | -  | +  | 2,4                               | Sickle cell anemia | HBB        | NM_000518.4; c.20A>T, (p.E7V)(Hom) | Sickle cell anemia and proteinuria |
| RGC-0106       | -  | -  | -  | +  | +  | 2,4                               | DD               | NAA15      | NM_057175.3; c.439C>T (p.Q147X) (Het) | Syndromic CAKUT |
| RGC-0133       | -  | -  | +  | -  | +  | 2,4                               | DD               | CHMP1A     | NM_002768.4; c.88 C>T (p.Q30X) (Hom) | Hyperoxaluria, DD, non-verbal, wheelchair bound |

L1, impact on medical or surgical treatment; L2, change of medical diagnosis; L3, providing diagnostic certainty; L4, subsequent evaluation for other body system involvement; L5, cascade family member testing; CNV, copy number variant; DD, developmental delay; PUV, posterior urethral valve; SNV, single nucleotide variant. Type of testing; 1, panel; 2, CMA; 3, proband ES; 4, trio ES; 5, Total blueprint panel.
Supplement 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)

| Patient ID | Gender | Age | Phenotype     | Testing (1,2,3,4, 5) | Gene       | Variant                                                                                           | gnomAD | CADD score | Clinician’s comment | Recommendation                      |
|------------|--------|-----|---------------|----------------------|------------|---------------------------------------------------------------------------------------------------|--------|------------|---------------------|-------------------------------------|
| RGC-0007   | M      | 4   | Cystic kidney | 3                    | PKD1       | NM_001009944; c.971G>T, (p.R324L)(Het) (inherited from father)                                  | 0      | 13.07      | Paternal kidney US recommended                                                                 |
| RGC-0007   | M      | 4   | Cystic kidney | 3                    | TRPC6      | NM_004621; c.2116G>A, p.V706I (Het) (inherited from mother)                                     | 2/250230 | 28         | Recessive disorder and only one heterozygous variant                                            |
| RGC-0007   | M      | 4   | Cystic kidney | 3                    | LAMB2      | NM_002292; c.5233G>A, (p.A1745T)(Het) (inherited from mother)                                  | 0      | 24.5       | Recessive disorder and only one heterozygous variant                                            |
| RGC-0007   | M      | 4   | Cystic kidney | 3                    | MYO1E      | NM_004998; c.1615C>A, (p.L539M)(Het) (inherited from mother)                                   | 0      | 16.21      | Recessive disorder and only one heterozygous variant                                            |
| RGC-0007   | M      | 4   | Cystic kidney | 3                    | ITGA8      | NM_003638; c.1492A>G (p.M498V)(Het)(inherited from mother)                                     | 1/251076 | 0.876      | Inherited from the affected mother but variant predicted benign and phenotype does not match with dysplastic kidney in the mother |
| RGC-0011   | M      | 2   | Cystic kidney | 3                    | PKD1       | NM_001009944; c.8119G>A (p.V2707M) (Het) (inherited from father)                                | 0      | 9.007      | Paternal kidney US recommended                                                                   |
| RGC-0011   | M      | 2   | Cystic kidney | 3                    | PKD1       | NM_001009944; c.4151C>T (p.T1384I) (Het) (inherited from father)                                | 0      | 24.5       | Paternal kidney ultrasound recommended                                                           |
| RGC-0011   | M      | 2   | Cystic kidney | 3                    | PKD1       | NM_001009944; c.3239C>A (p.P1080H) (Het) (inherited from mother)                               | 2/214486 | 23.5       | Maternal kidney US recommended                                                                  |
| ID     | Sex | Age | Condition | Exon | Gene | Description | VUS Status | Clinical Significance | Comments |
|--------|-----|-----|-----------|------|------|-------------|------------|-----------------------|----------|
| RGC-0012 | F   | 16.8 | Hematuria  | 2    | TRPC6 and YAP1 | arr(hg19) 11q22.1 (101,450,649-102,064,511)x3 | NA         | NA                   | TRPC6 might be disrupted therefore this VUS might have clinical consequences (clinical significance of a duplication of these or any genes in this region is not currently known. This region in its entirety is not known to vary in copy number in normal population. This region in its entirety is not known to vary in copy number in normal population. Follow up recommended) | Annual UA and follow up with nephrology |
| RGC-0016 | M   | 17.1 | Kidney stone | 3    | TRPC6 | NM_004621; c.1678G>A (p.A560T) (Het) (inherited from mother) | 0          | 17.98 | VUS inherited from unaffected mother | Follow up in 2 years for reanalysis of iES |
| RGC-0016 | M   | 17.1 | Kidney stone | 3    | SLC4A4 | NM_001098484; c.149G>C (p.G50A)(Het)(inherited from mother) | 390/249120 | 20.6 | Recessive disorder and only one heterozygous variant | |
| RGC-0025 | M   | 18   | Proteinuria | 3    | COL4A5 | NM_033380.1; c.2180C>G (p.P727R) (inherited from mother) | 0          | 27.3 | Phenotype does not match Alport and mother does not have microscopic hematuria | Follow up recommended |
| RGC-0027 | F   | 16   | CAKUT | 3    | IL17RD | NM_017563.3 c.8C>G (p.P3R) (Het)(inherited from father) | 0          | 26.1 | Phenotype does not fit with Kallmann syndrome but VUS could contribute to kidney anomaly | Testing of family members/paternal kidney ultrasound recommended |
| RGC-0040 | F   | 3.4  | CAKUT | 3    | CHD7  | NM_017780; c.8378C>G (p.A2793G)(Het)(inherited from father) | 4/244694 | 24 | Phenotype does not fit | |
| RGC-0040 | F   | 3.4  | CAKUT | 3    | PKD2  | NM_000297; c.2420G>A (p.R807Q)(Het)(inherited from father) | 754/251136 | 26.1 | Phenotype does not fit | |
| RGC-0040 | F   | 3.4  | CAKUT | 3    | PKD1  | NM_00109944; c.6749C>T | 0          | 23.5 | Phenotype does not fit | |
| Patient ID | Gender | Age  | Diagnosis | Genes | Variants | Location | Reference | Phenotype | Comments |
|------------|--------|------|-----------|-------|----------|----------|-----------|-----------|----------|
| RGC-0040   | F      | 3.4  | CAKUT     | MSR1  | c.2456G>A | NM_004525 | 27/251146 | Likely benign | Inherited from mother |
| RGC-0048   | F      | 9.8  | CAKUT     | LRP2  | c.403G>A  | NM_004525 | 0         | Patient does not have full phenotype of Donnai-Barrow Syndrome | Brain MRI was normal, urine beta 2 microglubin is high, RBP recommended |
| RGC-0048   | F      | 9.8  | CAKUT     | LRP2  | c.2456G>A | NM_004525 | 0         | Phenotype does not fit | Paternal kidney US recommended |
| RGC-0048   | F      | 9.8  | CAKUT     | PKD1  | c.5530G>C | NM_001009944 | 0         | Phenotype does not fit | Paternal kidney US recommended |
| RGC-0048   | F      | 9.8  | CAKUT     | PKD1  | c.5184G>A | NM_001009944 | 0         | Recessive disorder and only one heterozygous variant | Recessive disorder and only one heterozygous variant |
| RGC-0048   | F      | 9.8  | CAKUT     | FRAS1 | c.814G>A  | NM_001009944 | 0         | Two FRAS1 variants on the same chromosome | Two FRAS1 variants on the same chromosome |
| RGC-0048   | F      | 9.8  | CAKUT     | FRAS1 | c.9553G>A | NM_001009944 | 197/279136 | Recessive disorder and only one heterozygous variant | Recessive disorder and only one heterozygous variant |
| RGC-0048   | F      | 9.8  | CAKUT     | NPHP1 | c.830G>A  | NM_001009944 | 173/282608 | Recessive disorder and only one heterozygous variant | Recessive disorder and only one heterozygous variant |
| RGC-0059   | F      | 12   | CAKUT     | CC2D2A| c.1709G>A | NM_001009944 | 45/280162 | Recessive disorder and only one heterozygous variant | Recessive disorder and only one heterozygous variant |
| ID     | Gender | Age | Clinical Feature                  | Gene       | Variant Description                  | Frequency | p-value | Comment                                                                 |
|--------|--------|-----|-----------------------------------|------------|--------------------------------------|-----------|---------|-------------------------------------------------------------------------|
| RGC-0059 | F      | 12  | CAKUT                             | PKHD1      | NM_138694; c. 5750A>G, (p.Q1917R)(Het)(inherited from father) | 0         | 32      | Recessive disorder and only one heterozygous variant                   |
| RGC-0059 | F      | 12  | CAKUT                             | ITGA8      | NM_003638; c. 1336G>A, (p.V446I)(Het)(inherited from mother) | 0         | 2.758   | Recessive disorder and only one heterozygous variant                   |
| RGC-0064 | M      | 12  | CAKUT                             | NID1       | NM_002508.2; c.3680dupC (p.G1228RfsX9)(Het)(inherited from father) | 0         | 6.445   | VUS seems likely pathogenic, affected sibling positive                 |
| RGC-0064 | M      | 12  | CAKUT                             | NID1       | NM_002508.2; c.1297C>T (p.R433L) (Het) | 0         | 12.17   | Brain MRI, testing siblings                                           |
| RGC-0065 | F      | 1   | Other (Nephromegaly and Nephrocalcinosis) | CRB2       | NM_173689.5; c.1298C>T (p.P433L)(Het) | 124/282294 | 15.97   | Recessive disorder and only one heterozygous variant                   |
| RGC-0065 | F      | 1   | Other (Nephromegaly and Nephrocalcinosis) | LIG4       | NM_002312.3; c.686A>G (p.H229R)(Het) | 178/281618 | 23.3    | Recessive disorder and only one heterozygous variant                   |
| RGC-0065 | F      | 1   | Other (Nephromegaly and Nephrocalcinosis) | PSAT1      | NM_058179.2; c.94T>C (p.Y32H)(Het) | 5/280748   | 25.2    | Recessive disorder and only one heterozygous variant                   |
| RGC-0065 | F      | 1   | Other (Nephromegaly and Nephrocalcinosis) | COL4A5     | NM_000495.4; c.4450T>C (p.Y1484H)(Het) | 0         | 25.4    | Unrelated to patient's phenotype                                      |
| RGC-0065 | F      | 1   | Other (Nephromegaly and Nephrocalcinosis) | SH3YL1     | Arr 2p25.3 (66097-239712)x1 | NA       | NA      | Non disease-associated regions                                        |
| RGC-0065 | F      | 1   | Other (Nephromegaly and Nephrocalcinosis) | NUP52CL    | Arr Xp22.3 (10638417-106398144)x1 | NA       | NA      | Non disease-associated regions                                        |
| RGC-0069 | M      | 2.3 | Proteinuria                       | CD2AP      | NM_012120.2; c.1286_1288dup (p.E429dup)(Het) | 126/250158 | 3.562   | In-frame duplication                                                   |
| RGC-0094 | F      | 3.5 | CAKUT                             | COL4A5     | NM_000495.4; c.2600T>C (p.L867T)(Het) | 2/182030  | 16.49   | Unrelated to patient's phenotype                                      |

**Legend:**
- **Gender:** M (Male), F (Female)
- **Age:** in years
- **Clinical Feature:** CAKUT (Congenital Anomalies of the Kidney and Urinary Tract)
- **Gene:** Name of the gene
- **Variant Description:** Description of the variant
- **Frequency:** Number of occurrences
- **p-value:** Statistical significance
- **Comment:** Additional information about the variant's status or its effect on the patient's phenotype.
| Case ID   | Sex | Age | Diagnosis   | Genes Involved                                                                 | Gene | Probe | p-value | BMID | Testing recommended |
|----------|-----|-----|-------------|-------------------------------------------------------------------------------|------|-------|---------|------|---------------------|
| RGC-0095 | M   | 9   | Cystic kidney | PKD1, NM_001009944.2; c.8498C>A (p.P2833H) (Het)                           |      |       | 6.179   |      | Testing affected mother |
| RGC-0096 | M   | 10.7| Cystic Kidney | PKD1, NM_001009944.2; c.10810 G>A (p.E3604K) (Het)(inherited from father) |      |       | 22.9    |      | Paternal kidney US recommended |
| RGC-0096 | M   | 10.7| Cystic Kidney | Portion of PLEKHA7, ABCG8 and 6 other genes                                   |      |       | NA      |      | Patient affected by Arthrogryposis and VCX3A is disrupted |
| RGC-0099 | M   | 1.5 | CAKUT       | Portion of VCX3A, entire HDHD1, STS, VCX, and PNPLA4                       |      |       | NA      |      | Follow up |
| RGC-0103 | M   | 0.01| CAKUT       | FAT1, NM_005245.3; c.7014C>A (p.S2338R) (Het)(inherited from mother)         |    7/280606 | 4.937 |         |      | Follow up |
| RGC-0103 | M   | 0.01| CAKUT       | FAT1, NM_005245.3; c.9320G>T (p.C3107F)(Het)(inherited from mother)          |    5/249052 | 24.9 |         |      | No disease association |
| RGC-0104 | F   | 14.8| Proteinuria | MYO1E, NM_004998.3; c.2627C>G (p.T876R)(Het)(inherited from mother)          |    400/282482 | 20.8 |         |      | Recessive disorder and only one heterozygous variant |
| RGC-0104 | F   | 14.8| Proteinuria | PLCE1, NM_0016341.3; c.2032A>G (p.M678V)(Het)(inherited from father)         |    280/280870 | 23.6 |         |      | Recessive disorder and only one heterozygous variant |
| RGC-0107 | F   | 5.3 | CAKUT       | BICC1, NM_001080512.2; c.707A>G                                            |    8/282402 | 3.304 |         |      | Paternal kidney US recommended |
| Family  | Gender | Age | Diagnosis                          | Gene   | Variant | Exon | Depth | Distance | p-value | Risk  | Notes                                                                 |
|---------|--------|-----|------------------------------------|--------|---------|------|-------|-----------|---------|-------|-----------------------------------------------------------------------|
| RGC-0109 | M      | 15.6| Other (Hyperuricemic and nephropathy) | WT1    | NM_024426.4; c.358G>A (p.G120S)(Het) | 5    | 0     | 22.4      | No phenotype overlap |
| RGC-0109 | M      | 15.6| Other                              | WDR19  | NM_025132.3; c.*7C>T (Het)          | 5    | 54/275970 | 0.436     | Recessive disorder and only one heterozygous variant |
| RGC-0109 | M      | 15.6| Other                              | PKHD1  | NM_138694.3; c.2744C>T (p.A915V)(Het) | 5    | 0      | 26.3      | No phenotype overlap (kidneys not enlarged) |
| RGC-0109 | M      | 15.6| Other                              | PKHD1  | NM_138694.3; c.7675G>C (p.V2559L)(Het)(inherited from mother) | 5    | 280/282300 | 9.628     | Predicted benign |
| RGC-0111 | F      | 0.01| CAKUT                              | COL4A4 | NM_000092.4; c.3394C>G (p.P1132A)(Het)(inherited from father) | 3    | 1/248216 | 25.4      | No phenotype overlap |
| RGC-0111 | F      | 0.01| CAKUT                              | LAMB2  | NM_002292.3; c.4224+19G>C(Het)(inherited from father) | 3    | 3031/279460 | 4.844     | Recessive disorder and only one heterozygous variant |
| RGC-0122 | M      | 4   | Hematuria                          | COL4A3 | NM_000091.4; c.1483C>T (p.H495Y)(Het)(inherited from father) | 3    | 202/280910 | 0.689     | Kidney biopsy showed TBM Testing other siblings |
| RGC-0122 | M      | 4   | Hematuria                          | FN1    | NM_212482.1; c.3626C>T (p.T1209I)(Het)(inherited from father) | 3    | 2/251442 | 24.4      | Biopsy does not fit |
| RGC-0125 | F      | 14  | Other (a-HUS)                      | THBD   | NM_000361; c.1456G>T (p.D486Y)(Het) | 1,3  | 2115/276574 | 1.136     | Reanalyze ES |
| RGC-0125 | F      | 14  | Other (a-HUS)                      | DGKE   | NM_003647; c.303G>C (p.K101N)(Het) | 1,3  | 39/282288 | 22.9      | Recessive disorder and only one heterozygous variant |
| RGC-0125 | F      | 14  | Other (a-HUS)                      | GANAB  | NM_198335.2; c.1652A>C (p.N551T)(Het)(inherited from father) | 1,3  | 0      | 22.3      | No family history on paternal side, and positive family history from maternal side |
| RGC-0125 | F  | 14 | Other(a-HUS) | 1,3 | ALMS1 | NM_015120.4; c.9463A>T (p.T3155S)(Het)(inherited from father) | 65/249098 | 24.7 | Recessive disorder and only one heterozygous variant |
|----------|----|----|-------------|-----|-------|---------------------------------------------------------------|-----------|------|--------------------------------------------------|
| RGC-0125 | F  | 14 | Other(a-HUS) | 1,3 | TRIOBP | NM_0010391412; c.6632A>T (p.Q2211L)(Het)(inherited from father) | 40/280310 | 28.2 | Recessive disorder and only one heterozygous variant |
| RGC-0125 | F  | 14 | Other(a-HUS) | 1,3 | GRHPR | NM_012203.1; c.374G>A (p.R125Q)(Het)(inherited from father) | 78/282832 | 29.7 | Recessive disorder and only one heterozygous variant |
| RGC-0125 | F  | 14 | Other(a-HUS) | 1,3 | DGKE | NM_003647.2; c.303G>C (p.K101N)(Het)(inherited from father) | 39/282288 | 23.2 | Recessive disorder and only one heterozygous variant |
| RGC-0126 | M  | 17 | Proteinuria | 1,2,5 | CFH | NM_000186.3; c.2270A>C (p.N757T)(Het) | 0 | 0.112 | No phenotype overlap |
| RGC-0126 | M  | 17 | Proteinuria | 1,2,5 | CD2AP | NM_012120.2; c.164A>C (p.K55T)(Het) | 63/282798 | 30 | Fits with biopsy report and family history |
| RGC-0126 | M  | 17 | Proteinuria | 1,2,5 | NPHS2 | NM_014625; c.725C>T (p.A242V)(Het) | 1962/281850 | 25.3 | Recessive disorder and only one heterozygous variant |
| RGC-0126 | M  | 17 | Proteinuria | 1,2,5 | LAMB2 | NM_004646; c.2740G>A (p.G914A)(Het) | 0 | 27.7 | Although patient has two variants in LAMB2, Family history of proteinuria in this patient suggest AD mode of inheritance Parental testing for KFM in LAMB2 |
| RGC-0126 | M  | 17 | Proteinuria | 1,2,5 | LAMB2 | NM_004646; c.1193C>G (p.T398I)(Het) | 694/282716 | 7.968 | Parental testing for KFM in LAMB2 |
| RGC-0130 | M  | 20 | Cystic kidney | 3 | SEC61A1 | NM_013336.3; c.554 C>G (p.T185S)(Het)(de novo) | 0 | 28.4 | Patient's phenotype has overlap with reported phenotype associate with this gene |
| RGC-0136 | F  | 7  | CAKUT       | 3  | MT-RNR2 | m.2872C>T (Homoplasmic) (inherited from mother) | 0 | NA | Mother also homoplasmic suggesting that this |
| Reference | Gender | Age | Condition | Gene | Mutation | Minor Allele Frequency | Description |
|-----------|--------|-----|-----------|------|----------|-----------------------|-------------|
| RGC-0138  | F      | 16  | CAKUT     | GJB3 | NM_024009.2; c.223C>T (p.R75C)(Het)(inherited from mother) | 42/282762 29.7 | Mother does not have hearing loss |
| RGC-0138  | F      | 16  | CAKUT     | WFS1 | NM_006005.3; c.527T>C (p.V176A)(Het)(inherited from mother) | 3/250700 22.4 | Mother does not have hearing loss |
| RGC-0138  | F      | 16  | CAKUT     | GATA3| NM_0010022951; c.826C>T (p.R75C)(Het) | 0 32 | Patient's phenotype has overlap with reported phenotype associate with this gene, patient has hypoparathyroidism |
|           |        |     |           |      |          |                       | KFM testing of other family members |
| RGC-0138  | F      | 16  | CAKUT     | NPHS1| NM_004646.3; c.7C>A (p.L3M)(Het) | 8/185830 4.560 | Recessive disorder and only one heterozygous variant |
| RGC-0139  | M      | 15  | Cystic kidney | PRKD1| NM_002742.2; c.1947T>G (p.F649L)(Het)(inherited from mother) | 2/250352 11.83 | Mother reported to have heart disease |
| RGC-0139  | M      | 15  | Cystic kidney | PKD1 | NM_001009944.2; c.7061A>C (p.Q2354P)(Het)(inherited from father) | 0 27.1 | Likely the cause of ADPKD, there is history of ADPKD in father |
|           |        |     |           |      |          |                       | Testing of siblings for specific variant in PKD1 |
| RGC-0139  | M      | 15  | Cystic kidney | PKD1 | NM_001009944.2; c.6097G>A (p.A2033T)(Het)(inherited from father) | 11/275498 23.2 | there is history of ADPKD in father |
|           |        |     |           |      |          |                       | Testing of siblings for specific variant in PKD1 |
| RGC-0140  | F      | 8   | CAKUT     | KIAA1109| NM_015312.3; c.822-3T>C (Het)(inherited from father) | 2/247734 6.412 | Recessive disorder and only one heterozygous variant |
| RGC-0140  | F      | 8   | CAKUT     | COL4A4| NM_000092.4; c.2985C>T (p.P995=(Het)(inherited from father) | 19/280864 0.112 | |
| RGC-0140  | F      | 8   | CAKUT     | FANCC| NM_000136.2; c.988T>C (p.L333P)(Het)(inherited from father) | 2/249760 22.4 | Recessive disorder and only one heterozygous variant |
| Sample ID  | Gender | Age | Condition       | Gene       | Mutation Description                           | Allele Count | Probability | Notes                                                                 |
|------------|--------|-----|-----------------|------------|-----------------------------------------------|--------------|-------------|----------------------------------------------------------------------|
| RGC-0140   | F      | 8   | CAKUT           | AHI1       | NM_017651.4; c.1621G>T (p.D541Y)(Het)(inherited from mother) | 0            | 24.2        | Recessive disorder and only one heterozygous variant                  |
| RGC-0140   | F      | 8   | CAKUT           | TMTC3      | NM_181783.3; c.10A>G (p.I4V)(Het)(inherited from father)   | 13/276640    | 12.90       | Recessive disorder and only one heterozygous variant                  |
| RGC-0140   | F      | 8   | CAKUT           | CFH        | NM_000186.3; c.506A>G (p.H169R)(Het)(inherited from father) | 3/251074     | 0.014       | No phenotype overlap                                                  |
| RGC-0141   | F      | 0.9 | Other (Hypocalcemia) | TRPC6      | NM_004621.5; c.101T>C (p.M34T)(Het)(inherited from father) | 2/199782     | 24.5        | Father does not have kidney disease                                  |
| RGC-0141   | F      | 0.9 | Other (Hypocalcemia) | SLC12A1    | NM_000338.2; c.2282G>A (p.R761Q)(Het)(inherited from father) | 26/282292    | 22.7        | Recessive disorder and only one heterozygous variant                  |
| RGC-0141   | F      | 0.9 | Other (Hypocalcemia) | INVS       | NM_014425.3; c.2822A>G (p.H941R)(Het)(inherited from mother) | 1/251378     | 6.868       | Recessive disorder and only one heterozygous variant                  |
| RGC-0141   | F      | 0.9 | Other (Hypocalcemia) | ITGA8      | NM_003638.1; c.1156T>C (p.F386L)(Het)(inherited from mother) | 14/282834    | 22.4        | Recessive disorder and only one heterozygous variant                  |
| RGC-0141   | F      | 0.9 | Other (Hypocalcemia) | APOL1      | NM_003661.3; c.334C>T (p.R112C)(Het)(de novo)              | 4/251190     | 11.68       | Variant discussed with experts and seems benign                       |
| RGC-0142   | F      | 0.5 | Other (a-HUS)   | CFH        | NM_000186.3; c.3357C>G (p.D1119E)(Het)(inherited from mother) | 3/282870     | 11.94       | Patient has homozygous CFHR3-CFHR1 deletion                          |
| RGC-0142   | F      | 0.5 | Other (a-HUS)   | ITGA8      | NM_003638.2; c.840T>C (p.S280)(Het)(inherited from father) | 215/282194   | 7.427       | Recessive disorder and only one heterozygous variant                  |
| RGC-0148   | F      | 2   | Hematuria       | ACTN4      | NM_004924.5; c.751C>T (p.R251W)(Het)(inherited from father) | 3/143328     | 32           | Paternal kidney evaluation                                           |
| ID      | Sex | Age | Phenotype          | Gene | Mutation Details                                      | RawAF | Genomic AF | Notes                                                                 |
|---------|-----|-----|--------------------|------|------------------------------------------------------|-------|-------------|------------------------------------------------------------------------|
| RGC-0149 | M   | 3   | Hematuria          | COL4A4 | NM_000092.4; c.1442G>T (p.G481V)(Het)(inherited from mother) | 1/143110 | 26          | Segregation study suggests this variant causes hematuria in this family |
| RGC-0150 | M   | 1.6 | Other (DI)        | AVPR2 | NM_000054.4; c.910+5G>T (intronic)(Hem)             | 0     | 9.197       | Segregation study suggests this variant causes DI in this family        |
| RGC-0153 | F   | 9   | Other (Glycosuria)| SLC5A2 | NM_00304.3; c.1665+4A>T (Het)(inherited from father) | 0.003% | 19.57       | Determine father’s phenotype                                             |
| RGC-0158 | M   | 8   | Hematuria          | COL4A3 | NM_000091.4; c.4445C>T (p.A1482V)(Het)             | 223/143266 | 22.5       | May describe phenotype                                                  |
| RGC-0158 | M   | 8   | Hematuria          | NPHS1 | NM_004646.3; c.2614G>A (p.V872I)(Het)             | 3/143174 | 18.54       | Pt also has nephrotic syndrome and also has a pathogenic variant in NPHS2 |
| RGC-0169 | M   | 2   | Cystic kidney     | PKD1  | NM_001099944.2; c.7146C>G (p.S2382R)(Het)         | 0     | 23.3        | Reported in autism but there was not concern about DD or ASD in this patient |
| RGC-0169 | M   | 2   | Cystic kidney     | NPHP1 | NM_000272.3; duplication of whole gene             | NA    |             |                                                                         |
| RGC-0170 | F   | 5   | Proteinuria       | CUBN   | NM_001081.3; c.2677A>G (p.T893A)(Het)             | 146/143296 | 4.896       | Phase of the two VUSs are unknown Parents did not provide samples      |
| RGC-0170 | F   | 5   | Proteinuria       | CUBN   | NM_001081.3; c.5285T>G, c.5267T>G, (p.V1762G)(Het) | 12/282422 | 5.578       | Phase of the two VUSs are unknown Follow up                             |
| RGC-0170 | F   | 5   | Proteinuria       | NPHS1  | NM_004646.3; c.710T>C (p.L237P)(Het)              | 4/251428 | 31          | Recessive disorder and only one heterozygous variant                   |
| RGC-0170 | F   | 5   | Proteinuria       | PAX2   | M_003990.4; c.809G>A (p.R270H)(Het)              | 7/251366 | 29.2        | Ophthalmology evaluation                                                |
| RGC-0170 | F   | 5   | Proteinuria       | PLCE1  | NM_016341.3; c.642A>T (p.Q214G)(Het)            | 293/280000 | 10.49       | Recessive disorder and only one                                        |
| RGC-0170 | F  | 5   | Proteinuria | 1   | SMARCAL1 | M_014140.3; c.1196C>T (p.T399M)(Het) | 353/282896 | 0.899 | Recessive disorder and only one heterozygous variant |
|----------|----|-----|-------------|-----|----------|--------------------------------------|------------|-------|-------------------------------------------------|
| RGC-0170 | F  | 5   | Proteinuria | 1   | WDR73    | NM_032856.3; c.481G>T (p.V161F)(Het) | 5/248808   | 11.65 | Recessive disorder and only one heterozygous variant |
| RGC-0174 | M  | 14  | Other (Alagille syndrome) | 1 | JAG1 | NM_000214.2; c.776G>T (p.G259V)(Het)(VUS) | 0          | 26.6  | tES recommended |
| RGC-0180 | F  | 5   | Proteinuria | 1   | INF2    | NM_022489.3; c.2851C>T (p.R951W)(Het) | 1/154628  | 23.6  | Father had trace of protein in dipstick Testing of siblings for INF2 |
| RGC-0184 | M  | 4   | Proteinuria | 3   | EVC2    | arr[GRCh37]4p16.2(5616917_5699833)x3 | NA        | NA    | Parental testing recommended |
| RGC-0187 | F  | 4   | Cystic kidney | 3 | PUF60 | NM_078480.2; c.1292C>T (p.P43L)(Het)(inherited from father) | 0          | 22.5  | Father does not have kidney disease |
| RGC-0187 | F  | 4   | Cystic kidney | 3 | GLIS2  | NM_032975.2; c.1244C>T (p.R415L) (Het)(inherited from mother) | 21/176552 | 26.8  | Recessive disorder and only one heterozygous variant |
| RGC-0187 | F  | 4   | Cystic kidney | 3 | ARHGDIA | NM_001301242.1; c.544A>G (p.T182A)(Hom)(both parents are carrier) | 1/249280  | 6.032 | Seems disease causing Testing of siblings recommended |
| RGC-0187 | F  | 4   | Cystic kidney | 3 | FLNA   | NM_001456.3; c.1399C>T (p.R467C)(Het)(inherited from mother) | 1/177746  | 23.6  | Mother unaffected |

DI, Diabetes insipidus; Es, Exome sequencing; PKDB, Autosomal Dominant Polycystic Kidney Disease Mutation Database; RBP, Retinol-binding Protein; TBM, Thin basement membrane; UA, Urine analysis; US, Ultrasound. Type of the testing; 1, panel; 2, CMA; 3, proband ES; 4, trio ES; 5, Total Blueprint panel.