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# Initial experience from a renal genetics clinic demonstrates a distinct role in patient management

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**Purpose:** A Renal Genetics Clinic (RGC) was established to optimize diagnostic testing, facilitate genetic counseling, and direct clinical management.

**Methods:** Retrospective review of patients seen over a two-year period in the RGC.

**Results:** One hundred eleven patients (mean age: 39.9 years) were referred to the RGC: 65 for genetic evaluation, 19 for management of a known genetic disease, and 18 healthy living kidney donors (LKDs) and their 9 related transplant candidates for screening. Forty-three patients underwent genetic testing with a diagnosis in 60% of patients including 9 with Alport syndrome, 7 with autosomal dominant polycystic kidney disease (ADPKD), 2 with genetic focal segmental glomerulosclerosis (FSGS), 2 with *PAX2*-mediated CAKUT, and 1 each with autosomal recessive polycystic kidney disease (ARPKD), Dent, Frasier, Gordon, Gitelman, and Zellweger syndromes. Four of 18 LKDs were referred only for

*APOL1* screening. For the remaining 14 LKDs, their transplant candidates were first tested to establish a genetic diagnosis. Five LKDs tested negative for the familial genetic variant, four were positive for their familial variant. In five transplant candidates, a genetic variant could not be identified.

**Conclusion:** An RGC that includes genetic counseling enhances care of renal patients by improving diagnosis, directing management, affording presymptomatic family focused genetic counseling, and assisting patients and LKDs to make informed decisions.

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## INTRODUCTION

Kidney diseases encompass a spectrum of disorders that may be limited to a subset of tubular transport pathways or are associated with a more global decline in kidney function. In turn, diseases associated with an overall decline in kidney function may arise from abnormalities in kidney and urinary tract development, specific defects in ciliary structure or function, or disorders that begin as tubulointerstitial or glomerular disease processes. The vast and varied phenotypic spectrum of these disorders includes several monogenic renal diseases as well as acquired disorders that can, at least superficially, resemble different genetic conditions.

With mapping of the human genome and advances in genetic sequencing technology, an increasing number of genetic causes of renal disease have been identified.<sup>1</sup> It has become evident that many genetic diseases are present in individuals without an apparent family history of kidney disease, often reflecting the nonrecognition of affected family members, possibly from variable or subtle disease expression or nonpenetrance. In addition, occasionally family history cannot be ascertained (adoptees) or be misleading (misattributed paternity). Finally, genetic diseases from pathogenic variants that arise de novo or with autosomal recessive

inheritance are less likely to have a family history. However, once a genetic diagnosis is confirmed this information can substantially enhance the management of patients and their families by affording the ability to screen family members at risk for disease and offering them targeted genetic counseling and testing including prenatal counseling and assessment. Providing preconception counseling also becomes possible.

While genetic disorders are acknowledged as the most common cause of renal diseases in children, their role in adults, except for those with polycystic kidney disease, is frequently overlooked.<sup>2</sup> Even when considered, the dearth of certified genetic counselors (CGCs) who can provide timely counseling appointments can become an impediment to optimal patient management. Furthermore, the pressure of a busy clinic load with the inability to routinely extend the time available for evaluation and management of more complicated cases, especially those that have been on a diagnostic odyssey, often limits the ability to provide disease-focused or genotype-directed care. Additionally, in the field of living related renal transplantation identifying the genetic basis of kidney disease in the patient with end-stage renal disease (ESRD) can assist in the screening of the related living donor.<sup>3</sup> Testing living donors of recent African ancestry for the

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*APOL1* risk alleles G1 and G2 is also a consideration, given the emerging data on the risk of kidney disease.<sup>4,5</sup>

To help with a perceived need within our own practice, we established a Renal Genetics Clinic (RGC) with physicians who had a strong interest and clinical expertise in a broad range of renal genetic disorders and a CGC whose practice was limited to nephrology and cardiology. The renal genetics practice consisted of two adult nephrologists, one focused on polycystic kidney disease and another who saw all the remaining patients. The RGC worked closely with a pediatric nephrologist with an interest in developmental disorders and a clinical genetics provider with an interest in lysosomal storage disorders. The dedicated RGC operated weekly and all new referrals for a genetic diagnosis met the nephrologist and the CGC for clinical review and formulation of a differential diagnosis. Patients who underwent genetic testing returned to the RGC at least once for counseling and discussion of test results, and if appropriate, returned to their referring nephrologist. The goals of the clinic were:

1. To offer genetic counseling and testing services for patients, presymptomatic family members, and health-care providers
2. To assess the need for and facilitate genetic testing for kidney disease suspected to have an inherited basis
3. To offer consultative and ongoing management advice for inherited tubulopathies, ciliopathies, familial renal stone disease, and genetic glomerular diseases
4. To oversee the management of rare multisystem inherited diseases with a renal component such as Fabry disease, cystinosis, and tuberous sclerosis, and coordinate specialist consultative services
5. To help with the transition to an adult nephrology practice for patients with genetic renal disease who have been referred by their pediatric nephrology providers
6. To evaluate kidney transplant candidates and their related asymptomatic living donors for inherited renal disease to increase the safety and informed choice of living donation

## MATERIALS AND METHODS

We performed a retrospective review of all patients who were evaluated in the RGC between January 2017 and December 2018. We collected information, including demographic data, the clinical features of the disease, and family history (a family member in this context is an individual genetically related to the patient). The study was approved by the University of Iowa Institutional Review Board (IRB 201810847). The study adheres to the Declaration of Helsinki and informed consent was waived by the IRB.

For the purposes of this analysis, we classified patients by the following four broad phenotypes: congenital anomalies of the kidney and urinary tract (CAKUT), ciliopathy and tubulointerstitial diseases, tubular transport disorders including nephrolithiasis and nephrocalcinosis, and glomerular diseases. We classified genetic variants using criteria developed by the American College of Medical Genetics and

Genomics (ACMG) as benign (B), likely benign (LB), variant of unknown significance (VUS), likely pathogenic (LP), and pathogenic (P).<sup>6</sup> We assessed the effect of genetic testing, when performed, on establishing or confirming a diagnosis and attempted to determine the impact of the genetic test results on patient management.

## RESULTS

In total, 111 patients from 88 pedigrees were referred to the RGC for consultation with a renal genetics physician and/or the CGC during this time period. Fifty-two patients were male and 59 were female ranging in age from 1 to 79 years, with 16 patients under the age of 25 and a mean of 39.9 years. In this cohort, 65 patients from 57 pedigrees were referred for assistance with establishing a genetic diagnosis. Of these referrals, 39 came from internal nephrologists (pediatric nephrology: 5 and adult nephrology: 34), 15 referrals were from external nephrologists, and 11 were self-referrals. Nineteen patients with a known genetic disease were referred for continued management of their condition and 18 living donors and 9 related recipient candidates were referred for assessment of living donor genetic risk. The clinical features of the patients referred for consideration of a genetic diagnosis are shown in Supplementary Table S1.

Of the patients referred for a genetic diagnosis, 58 were considered candidates for genetic testing and 43 proceeded to counseling and testing. In 41 patients genetic testing was performed with a 264-gene (Supplementary Table S2) renal panel (KidneySeq™ V3, Iowa Institute of Human Genetics [IIHG], <https://medicine.uiowa.edu/humangenetics/kidneyseq>). With KidneySeq™, targeted capture of coding exons and splice sites of renal disease genes are performed with RNA baits and then subjected to massively parallel sequencing and bioinformatic processing as previously described.<sup>3,7</sup> For one patient, testing for Fabry disease (OMIM 301500) was performed at Mount Sinai, New York, and for another patient, testing was limited to *APOL1* risk alleles, G1 and G2 (IIHG). Outcomes of patients who underwent genetic testing with positive results are shown in Table 1. In 26 of 43 patients (60%), we identified pathogenic or likely pathogenic variants and were thus able to confirm a genetic diagnosis. Positive diagnoses included nine with Alport disease (four autosomal dominant: OMIM 104200 and five X-linked: OMIM301050), seven with autosomal dominant polycystic kidney disease (ADPKD) (OMIM 173900 and 613095), two with genetic focal segmental glomerulosclerosis (FSGS) (*TRPC6*: OMIM 603965, *APOL1*: OMIM 612551), two with *PAX2*-mediated CAKUT (OMIM 120330), and one each with autosomal recessive polycystic kidney disease (ARPKD) (OMIM 263200), Dent (OMIM 300009), Frasier (OMIM 136680), Gordon (OMIM 614495), Gitelman (OMIM 263800), and Zellweger spectrum (OMIM 601539) syndromes. In an additional five patients, the identified variants corresponded to the phenotype but did not meet criteria to be classified as pathogenic or likely pathogenic. These included two patients with suspected ADPKD, each of whom carried a VUS in *PKD1*. It is possible that the VUSs in these two patients are

**Table 1** Patients (n = 31) with positive genetic variants are shown arranged by phenotype categories.

Subject	Clinical features	FH	Sex/age/ ethnicity	Genetic testing	ACMG criteria	Genetic diagnosis	Impact of genetic diagnosis
<b>Tubular transport</b>							
15	Hypokalemia, nephrocalcinosis	N	M/40/ EUR	<i>SLC12A3</i> p.Gly741Arg— homozygous	Pathogenic (P51, P53, PM2, PM3, PP3)	Gitelman syndrome	Altered clinical diagnosis
24	Nephrocalcinosis	Y	M/41/ EUR	<i>CLCN5</i> p.Arg704Ter	Pathogenic (PV51, P51, PM2, PP3)	X-linked Dent disease	Establish a diagnosis, cascade screening, recurrence risk
33	Resistant HTN childhood onset	Y	F/23/EUR	<i>CYP11B1</i> p.Phe79Ile	Likely pathogenic (P51, PM2, PP3)	Carrier for 11 $\beta$ -hydroxylase deficiency	Exclude other monogenic forms of resistant hypertension
55	Hyperkalemia	Y	M/56/ EUR	<i>KIFHL3</i> p.Arg496His; <i>SLC3A1</i> p.Glu321Valfs*6	Likely pathogenic (P51, PM2, PP2, PP3, PP5)	Gordon syndrome	Establish a diagnosis, cascade screening, initiated thiazides
57	Hypokalemia	N	F/62/EUR	<i>SLC12A3</i> p.Cys994Tyr	Likely pathogenic (P51, PP2, PP3, PP5)	Carrier for Gitelman syndrome	Diagnosis not confirmed; treat as Gitelman
<b>Glomerular</b>							
3	Microscopic hematuria	Y	M/31/ EUR	<i>COL4A5</i> p.Gly1415Asp	Likely pathogenic (PM1, PM2, PP2, PP3, PP5)	X-linked Alport nephropathy	Initiated ACEI, discuss prognosis
25	Proteinuria, ESRD, kidney transplant	Y	M/59/ EUR	<i>COL4A5</i> p.Gly1143Ser	Likely pathogenic (PM1, PM2, PM5, PP3, PP5)	X-linked Alport nephropathy	Cascade screening
29–1	Alport syndrome (biopsy)	Y	F/59/EUR	<i>COL4A3</i> p.Gly934Arg	Likely pathogenic (PM1, PM2, PP1, PP3)	Autosomal dominant Alport nephropathy	Cascade screening
38	Deafness, retinal dystrophy, podocyte myeloid bodies	Y	M/54/ EUR	<i>PEX1</i> p.Gln1192Stop; <i>PEX1</i> p.Ile989Thr; <i>PEX1</i> p.Pro674Leu	Pathogenic (PV51, PM2, PP3, PP5) VUS (PM2, PP3, PP5) VUS (PM2, PP3)	Zellweger spectrum disorder	Establish a diagnosis, treatment
39–2	Chronic kidney disease	Y	M/33/ EUR	<i>COL4A5</i> p.Cys1521Ser	Likely pathogenic (PM1, PM2, PP1, PP3, PP5)	X-linked Alport nephropathy	Establish a diagnosis, cascade screening, recurrence risk
39–3	Microhematuria, proteinuria	Y	M/28/ EUR	<i>COL4A5</i> p.Cys1521Ser	Likely pathogenic (PM1, PM2, PP1, PP3, PP5)	X-linked Alport nephropathy	Establish a diagnosis, cascade screening, recurrence risk
42–1	Microscopic hematuria	Y	M/4/EUR	<i>COL4A4</i> p.Gly622Argfs*35	Likely pathogenic (PV51, PM2, PP1, PP3)	Autosomal dominant Alport nephropathy	Establish a diagnosis, cascade screening, recurrence risk
42–2	Microhematuria, proteinuria, and TBMD	Y	F/36/EUR	<i>COL4A4</i> p.Gly622Argfs*35	Likely pathogenic (PV51, PM2, PP1, PP3)	Autosomal dominant Alport nephropathy	Establish a diagnosis, cascade screening, recurrence risk
42–3	ESRD, kidney transplant	Y	M/78/ EUR	<i>COL4A4</i> p.Gly622Argfs*35	Likely pathogenic (PV51, PM2, PP1, PP3)	Autosomal dominant Alport nephropathy	Establish a diagnosis, cascade screening, recurrence risk
53	CKD 5, global glomerulosclerosis	Y	F/30/AFR	<i>APOL1</i> G1/G2	Risk alleles	Alport nephropathy	Prognostic information
59	Microhematuria, ESRD	Y	M/34/ EUR	<i>COL4A5</i> p.Gln1234Ter	Pathogenic (PV51, P51, PM2, PM4, PP3)	X-linked Alport nephropathy	Establish a diagnosis, family planning, cascade screening
65	Focal segmental glomerulosclerosis	N	F/26/EUR	<i>TRPC6</i> p. Asn125Ser	Likely pathogenic (P51, PP3, PP5)	Autosomal dominant FSGS	Establish a diagnosis, avoid steroids
69	ESRD, delayed female puberty	N	F/15/EUR	<i>WTT1</i> c.745+5G>A	Likely pathogenic (P51, PM2, PP3, PP5)	Fraser syndrome	Establish a diagnosis, prophylactic gonadectomy
<b>Cilopathy</b>							
4–2	Bilateral renal cysts	Y	M/33/ EUR	<i>PKD1</i> p.Tyr2622Ter	Likely pathogenic (PV51, PM2)	Autosomal dominant polycystic kidney disease	Family planning, prognostic information, tolvaptan
19–1	Bilateral renal cysts, liver cysts	Y	F/38/EUR	<i>PKD2</i> p.Tyr311Leufs*2	Pathogenic (PV51, PM2, PP1, PP3, PP5)	Autosomal dominant polycystic kidney disease	Prognostic information, cascade screening
19–2	Bilateral renal cysts, liver cysts	Y	F/20/EUR	<i>PKD2</i> p.Tyr311Leufs*2	Pathogenic (PV51, PM2, PP1, PP3, PP5)	Autosomal dominant polycystic kidney disease	Prognosis, cascade screening, family planning
21	Cystic kidney disease	N	F/21/EUR	<i>PKD1</i> p.Thr2250Met	VUS (PM1, PP3)	Not established	Family screening and segregation analysis
35–1	Bilateral renal cysts, enlarged kidneys	N	F/12/EUR	<i>PKHD1</i> c.390+1G>T; <i>PKD1</i> p.Leu1106Val	Pathogenic (PV51, PM2, PP2); likely benign (BP4, BP6)	Carrier for ARPKD	Likely ARPKD based on cascade screening
40–1	Asymptomatic	Y	F/28/EUR	<i>PKD1</i> p.Tyr2004Thrfs*112	Pathogenic (PV51, PM2, PP3)	Autosomal dominant polycystic kidney disease	Establish a diagnosis, family planning, treatment

Table 1 continued

Subject	Clinical features	FH	Sex/age/ethnicity	Genetic testing	ACMG criteria	Genetic diagnosis	Impact of genetic diagnosis
48	CKD 3, congenital hepatic fibrosis	Y	F/27/EUR	<i>PKHD1</i> p.Arg375Trp; <i>PKHD1</i> p.Ile222Leu	Likely pathogenic (P51, PM1, PM2, PM3); likely pathogenic: PM1, PM2, PM5, PP2, PP3	Autosomal recessive polycystic kidney disease	Establish a diagnosis
58	Renal and liver cysts, ESRD, HTN	Adopted	M/50/EUR	<i>PKD1</i> p.Ala2332Trpfs*7	Pathogenic (PV51, PS1, PM2, PP3)	Autosomal dominant polycystic kidney disease	Recurrence risk, cascade screening, prognosis, treatment
60	Bilateral renal cysts	Y	F/41/EUR	<i>PKD1</i> p.Val1105Gly	VUS (PM1, PM2, PP3)	Not established	Family screening and segregation analysis
68	Bilateral renal cysts	N	M/23/EUR	<i>PKD1</i> p.Val1144Alafs*68	Pathogenic (PV51, PM2, PP3)	Autosomal dominant polycystic kidney disease	Establish a diagnosis, cascade screening, prognosis, tolvaptan
70	Bilateral renal cysts, liver cysts	N	F/43/EUR	<i>PKD2</i> p.Leu409Argfs*42	Pathogenic (PV51, PM2, PP3)	Autosomal dominant polycystic kidney disease	Establish a diagnosis, prognosis, cascade screening
<b>CAKUT</b>							
12	Unilateral atrophy versus hypoplasia	Y	F/48/EUR	<i>PAX2</i> p.Arg140Leu	Likely pathogenic (PM1, PM2, PP1, PP2, PP3)	<i>PAX2</i> -mediated CAKUT	Establish a diagnosis, evaluate for eye disease, recurrence risk
52	Multicystic dysplastic kidney	Y	F/7/EUR	<i>PAX2</i> p.His62Tyr	Likely pathogenic (PM1, PM2, PP2, PP3)	<i>PAX2</i> -mediated CAKUT	Cascade screening, recurrence risk

ACEI angiotensin-converting enzyme inhibitor, ACMG American College of Medical Genetics and Genomics, AFR African/African American, AJ Ashkenazi Jewish, ARB Angiotensin 2 receptor blocker, ARPKD autosomal recessive polycystic kidney disorder, CAKUT congenital anomaly of the kidney or urinary tract, CKD chronic kidney disease, EA East Asian, ESRD end-stage renal disease, EUR Caucasian, FH family history, FSGS focal segmental glomerulosclerosis, HTN hypertension, LAT Hispanic or Latino, MA American Indian or Alaska Native, TBM thin basement membrane disease, VUS variant of unknown significance.

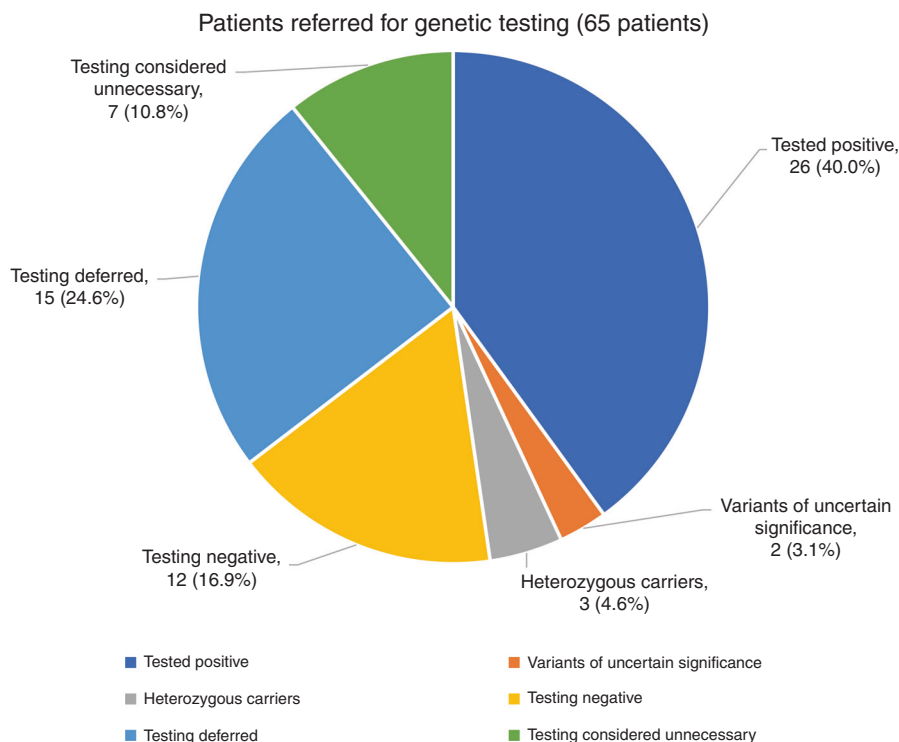
disease causing and may be reclassifiable as LP/P if segregation analysis can be performed in these families or if functional studies on these missense variants are completed. The remaining three patients each carried a single heterozygous pathogenic variant in an autosomal recessive disease (*SCL12A3* in possible Gitelman: OMIM 263800; *PKHD1* in a possible ARPKD: OMIM 263200 and *CYP11B1* in a possible congenital adrenal hyperplasia: OMIM 202010). In 16 patients genetic testing was deferred: 4 because of limited genetic testing elsewhere, 4 due to insurance decline, 6 due to patient choice or expected out of pocket expense, 1 due to presumed genetic diagnosis based on family screening, and 1 was deferred by the RGC for later consideration. A summary of testing results is illustrated in Figure 1.

We tested nine kidney transplant candidates, seven with a comprehensive genetic test panel (KidneySeq™ V3), one with an atypical hemolytic uremic syndrome (aHUS)/C3G panel (Genetic Renal Panel, Molecular Otolaryngology and Renal Research Labs, University of Iowa), and one for ADTKD (Wake Forest University, Winston-Salem, NC) (Table 2). We identified genetic variants that could account for their kidney disease in five recipient candidates, which permitted the screening of nine related living donor candidates for the familial genetic variant and, in turn, allowed five potential donors in whom the disease-causing variant was excluded to be accepted as living donors. In another five transplant candidates, genetic testing was negative, which nevertheless facilitated the counseling of living donors and their subsequent decision to donate. Four donor candidates who had positive genetic testing following familial screening were offered counseling and did not proceed with organ donation. In two of these, their transplant candidate had a VUS in a relevant gene for FSGS, *ARHGAP24*, and despite the lack of certainty about its role in the transplant candidate's kidney disease, it was prudent to counsel the donor candidates, who carried the VUS, against donating. Four living kidney donors (LKDs) were referred only for *APOL1* screening with two testing positive for two high-risk alleles. The donors were counseled before and after testing and offered the option of donating after a thorough explanation of the known effects of *APOL1* risk status in the general population and in living donors.<sup>4,5,8,9</sup>

Finally, we had 19 patients with a variety of known genetic renal diseases including aHUS, Fabry disease, cystinosis, and tuberous sclerosis who were referred to the clinic for continued management (Table 3). These included the prescription and monitoring of chronic therapies such as eculizumab, cysteamine, agalsidase beta, and everolimus; periodic surveillance for potential or known disease manifestations; and the coordination of specialist care.

DISCUSSION

In the practice of medicine, establishing a clinical or laboratory diagnosis is generally a prerequisite for appropriate management of a patient, including prognostication and guiding therapy. Many diseases that present as one of the distinct renal



**Fig. 1 Outcome of genetic clinic visit in 65 patients referred for genetic evaluation.** See Table 1. Forty-three patients were tested and of those tested, 58% had a genetic diagnosis established (tested positive). Actual numbers and percentages (in parentheses) for each category are shown. Three patients had one pathogenic variant for an autosomal recessive disorder (heterozygous carrier) that fit the phenotype. In seven patients, the preliminary evaluation concluded that genetic testing would not be informative (testing considered unnecessary).

phenotypes such as glomerular disorders, tubulointerstitial diseases, cystic kidney diseases, tubular transport disorders, and disorders of renal development are single-gene disorders. Genetic renal diseases may be diagnosable with traditional testing methods such as ultrasound imaging in the setting of a positive family history as in the case of ADPKD or a renal biopsy with a low plasma  $\alpha$ -galactosidase in a male with suspected Fabry disease. However, genetic testing often provides diagnostic certainty for many other renal diseases, especially when their presentation is nonclassic or when standard studies are merely suggestive but not diagnostic. In the case of progressive chronic kidney diseases with no distinctive imaging finding, a renal biopsy may not offer enough etiologic information and if the presentation is late there is often nonspecific tubulointerstitial fibrosis and glomerulosclerosis obscuring the characteristic findings that may have been present. Genetic testing also offers other advantages as it can be performed at any stage of the disease including presymptomatically and is noninvasive and cost effective.

With the advent of more efficient sequencing technologies with high-throughput bioinformatic processing, there are several options available for the clinician wishing to establish a genetic diagnosis. When a single-gene disorder such as Fabry disease is suspected, the relevant gene can be screened by polymerase chain reaction (PCR)-based sequencing of coding exons, which is available at several clinical testing

laboratories.<sup>10</sup> More often a genetic diagnosis is suspected but the exact nature of the genetic disease is unknown, or due to considerable locus heterogeneity in disease causation, more broad-based testing is necessary. These broader methods take advantage of next-generation sequencing methods and are either phenotype focused (e.g., FSGS panel, ciliopathy panel, nephrolithiasis panel) or more comprehensive and thereby include all or nearly all genes implicated in monogenic renal diseases (comprehensive targeted gene panel such as Kidney-Seq™) or even the exome.<sup>7,11,12</sup>

As stated previously, establishing a diagnosis is a vital part of the management of a patient, even if the diagnosis does not lead to a specific therapy. Some patients with rare genetic disorders have been on a diagnostic odyssey, and having a diagnosis avoids unnecessary testing and continued uncertainty.<sup>13,14</sup> Furthermore, with a diagnosis comes the ability to provide a meaningful prognosis and, if appropriate, counseling for family members who may be at risk. In some situations, the recognition that a common renal disease like FSGS may be genetic in origin can also have an impact on management. For example, autosomal dominant FSGS from heterozygous missense or loss-of-function variants in *COL4A3* and *COL4A4* (cases 29–1 and 42–3) or ADPKD from *PKD2* variants (cases 19–1 and 19–2) predicts a slowly progressive disease with very late development of ESRD.<sup>15–17</sup> Conversely, the identification of pathogenic null variants in *PKD1* with a resulting high ProPKD score may identify



**Table 2** Outcome of testing in kidney transplant recipients (n = 10) and their related (n = 14) living donor candidates.

Clinical features		Living donors							Impact of genetic diagnosis	
Subject	FH	Sex/age/ethnicity	Genetic testing	ACMG criteria	Genetic diagnosis	Subject	Sex/age/ethnicity	Relation to recipient	Donor clinical evaluation	
Microhematuria, proteinuria, TBMD	Y	F/59/EUR	COL4A3 p.Gly934Arg	LP: PM1, PM2, PP1, PP3	AD Alport	29–2	M/51/EUR	Brother	Microhematuria	Positive for familial variant, not allowed to donate
FSGS-ESRD	Y	M/67/EUR	ARHGAP24 p. Gly493Arg	VUS: PM2, PP3	None	76–2	M/25/EUR	Son	Negative	Positive for ARHGAP24 variant, not allowed to donate
Heavy proteinuria ESRD	N	M/59/EUR	Negative		None	77–2	F/19/EUR	Daughter	Negative	Positive for ARHGAP24 variant, not allowed to donate
Interstitial nephritis	Y	M/45/EUR	MUC1 insC in VNTR	LP: PV51, PS1, PM2, PP3	ADTKD-MUC1	78–2	F/43/EUR	Sister	Negative	Negative for any causal variants, allowed to donate
ADPKD	N	M/28/EUR	PKD1 p.Glu2771Lys; Glu154Gln (AR)	P: PS1, PM1, PM2, PP3, PP5	ADPKD-PKD1	79–2	F/26/EUR	Sister	Negative	Negative for familial MUC1, allowed to donate
C3 glomerulopathy	N	M/25/AFR	CFH p.Ser884Tyr	VUS: PM2, PP3	None	80–2	F/44/EUR	Aunt	Negative	Negative for familial CFH variant; allowed to donate
FSGS-ESRD	Y	M/54/EUR	Negative (incl. MUC1)		None	81–2	M/22/EUR	Son	Negative	Negative for any causal variants, allowed to donate
Proteinuria, hematuria, ESRD	Y	F/37/EUR, LAT	MYO1E p. Glu154Gln (AR)	VUS: PM2, PP3	None	82–2	M/35/EUR, LAT	Brother	Negative	Negative for causal variants, allowed to donate
ESRD, bland urine	Y	F/61/EUR	CLCNKB p.Gly164Arg; NPHP4 p.Phe729Ser	VUS: PM2, PP3; VUS: PM2, PP3;	None	83–2	F/40/EUR	Daughter	Negative	Negative for causal variants, allowed to donate
Bilateral VUR, MCDK	N	M/1/EUR	Negative		None	84–2	M/36/EUR	Father	Few cysts	Affected son negative for causal variants

Living donors who underwent testing for APOL1 risk alleles alone are not included. Subject 29–1 is also in Table 1. ACMG American College of Medical Genetics and Genomics, AD autosomal dominant, ADPKD autosomal dominant polycystic kidney disease, ADTKD autosomal dominant tubulointerstitial kidney disease, AFR African/African American, AR autosomal recessive, ESRD end-stage renal disease, EUR Caucasian, FH family history, FSGS focal segmental glomerulosclerosis, LAT Hispanic or Latino, LP likely pathogenic, MCKD medullary cystic kidney disease, P pathogenic, TBMD thin basement membrane disease, VUR vesicoureteric reflux, VUS variant of unknown significance.

**Table 3 Patients with a known genetic disease referred to the clinic for disease management (n = 19).**

Subject number	Sex/age/ethnicity	FH	Diagnosis	Basis for diagnosis	Genetic testing	Testing lab	ACMG criteria	Reason for referral
1	F/50/EUR	Yes—multiple	Fabry disease	Low α-GAL A; positive family history	GLA p.Arg227Gln	Mount Sinai, New York, NY	LP: PM1, PM2, PP2, PP3, PP5	Renal biopsy
4–1	F/56/EUR	Yes—multiple	ADPKD	Cystic kidneys, positive family history		IHG (Kidneyseq™), Iowa City, IA		CKD f/u
6	M/21/EUR	Yes—multiple	Fabry disease	Low α-GAL A; positive family history	GLA p.Ser297Tyr	Mount Sinai, New York, NY	LP: PM1, PM2, PM5, PP2, PP3	CKD f/u
7	M/29/EUR	No	Cystinosis	Fanconi syndrome, renal rickets and corneal crystals in infancy		Not done		Cysteamine Rx, manage disease
8	F/59/EUR	Yes—multiple	Fabry disease	Slit lamp, positive family history	GLA p.Trp204Ter	Mount Sinai, New York, NY	P: PV51, PM1, PM2, PP3	CKD f/u
9	M/54/AFR	Yes—multiple	Fabry disease	Low α-GAL A; positive family history	GLA p.Trp340Ter	Mount Sinai, New York, NY	P: PV51, PM1, PM2, PP3	CKD f/u
10	M/47/EUR	Yes—multiple	Fabry disease	Low α-GAL A; positive family history	GLA p.Ala29GlyfsTer2	Mount Sinai, New York, NY	P: PV51, PM1, PM2, PP3	CKD f/u
11	F/27/EUR	Yes—sister	Cystinosis	Bone marrow biopsy positive for cystine crystals		Not done		Cysteamine Rx
19	F/23/EUR	No	Tuberous sclerosis	Clinical criteria		Not done		Manage renal AMLs
26	F/32/EUR	No	Tuberous sclerosis + TMA in pregnancy	TSC: clinical criteria	TSC 1c.1029+3A>G; PLG p.Trp200Ala	CHG, Cambridge, MA; MORL (Genetic Renal Panel), Iowa City, IA	VUS: PM2, PP3, PP5; VUS: PP3	Manage tuberous sclerosis
27	M/18/EUR	Yes—multiple	Fabry disease	Kidney biopsy	GLA p.Cys63Arg	Mount Sinai, New York, NY	LP: PM1, PM2, PM5, PP2, PP3	CKD f/u
28	M/34/EUR	No	Fabry disease	Symptoms; positive family history	GLA p.Gly260Glu	Mount Sinai, New York, NY	LP: PM1, PM2, PM5, PP2, PP3	CKD f/u
31	M/24/EUR	No	Unilateral renal aplasia	Antenatal and postnatal imaging		Not done		CAKUT f/u
37	M/59/EUR	Yes—multiple	Suspected Fabry, no manifestation	Low α-GAL A; positive family history	GLA p.Ala143Thr	Mount Sinai, New York, NY	LP: PM1, PM5, PP2, PP3, PP5	Referred for renal biopsy
62	F/79/EUR	Yes—multiple	Familial hypocalcemic hypercalcemia	Hypercalcemia, positive family history	CaSR p.Pro55Leu	Mayo Medical Lab, Rochester, MN	LP: PM1, PM2, PP2, PP3, PP4, PP5	Post-test genetic counseling
66	F/34/EUR	Yes—sister	aHUS	TMA, genetic screening	CFH p.Leu1189Argfs*2	MORL (Genetic Renal Panel), Iowa City, IA	P: PV51, PM2, PP3	aHUS post-transplant f/u
67	M/30/EUR	No	None	Asymptomatic	Negative for NPHP1 variant	IHG (Kidneyseq™), Iowa City, IA		Preconception counseling, spouse with NPHP1 deletion
74	F/40/EUR	No	aHUS	TMA, genetic screening	CFI p.Tyr369Ser	MORL (Genetic Renal Panel), Iowa City, IA	LP: PM1, PM2, PP3, PP5	aHUS post-transplant f/u
75	F/38/EUR	No	aHUS	TMA, genetic screening	CFH p.Glu625Ter	MORL (Genetic Renal Panel), Iowa City, IA	P: PV51, PM2, PP3	aHUS post-transplant f/u

Genetic screening in these patients was performed prior to referral. ACMG American College of Medical Genetics and Genomics, ADPKD autosomal dominant polycystic kidney disease, AFR African/African American, aHUS atypical hemolytic uremic syndrome, AML angiomylipoma, CAKUT congenital anomalies of kidney and urinary tract, CHG Center for Human Genetics, CKD chronic kidney disease, EUR Caucasian, f/u follow up, FH family history, IHG Iowa Institute of Human Genetics, LP likely pathogenic, MORL Molecular Otolaryngology and Renal Research Laboratories, P pathogenic, TMA thrombotic microangiopathy, TSC tuberous sclerosis, VUS vesicoureteric reflux, VUS variant of unknown significance, α-GAL A α-galactosidase A.

ADPKD patients who require frequent follow up and who may benefit from tolvaptan therapy.<sup>18</sup> Genetic FSGS can present like primary FSGS with nephrotic syndrome and diffuse foot process effacement on renal biopsy (case 64 FSGS-*TRPC6*) but is generally unresponsive to steroids.<sup>19</sup> Genetic variants that typically cause CAKUT or tubulointerstitial diseases may also be identified in patients with FSGS, likely a manifestation of secondary FSGS in the context of reduced nephron mass, as we report here in at least one family member of case 12.<sup>20</sup>

Confirming a genetic diagnosis can be helpful in tailoring therapy for a patient. The identification of a likely pathogenic variant in *KLHL3* confirmed a diagnosis of Gordon syndrome (case 55) prompting the use of low-dose thiazide diuretic rather than chronic furosemide and sodium polystyrene sulfonate, which up to that point had been ineffective. In Fabry disease, a heterozygous female may have normal plasma  $\alpha$ -galactosidase activity and unrecognized end organ disease and identifying the familial genetic variant in a female may therefore prompt cardiac testing or a renal biopsy.<sup>21,22</sup> In other situations, specific treatment strategies require knowledge of not only the underlying gene but also the specific genetic variant. For example, while enzyme replacement therapy (agalsidase beta) can be offered to any patient with Fabry disease, specific amenable variants in the *GLA* gene can be rescued by the pharmacologic chaperone migalastat (case 28).<sup>23,24</sup> Similarly, some genetic causes of FSGS (e.g., *COQ2*, *COQ6*, *ADCK4*) may respond to CoQ10, offering a cheap and innocuous treatment.<sup>25,26</sup>

A genetic diagnosis may also offer specific management strategies in the post-transplant period or predict a risk of recurrent disease following a kidney transplant. Genetic FSGS, except for *NPHS1*-mediated disease, is considered to have a low risk of recurrence in the post-transplant setting.<sup>27</sup> Atypical HUS from *CFH* and *CFI* variants requires perioperative and likely lifelong complement blockade to prevent post-transplant recurrence, and based on identified variants, we have continued eculizumab in three cases (cases 74, 75, and 76). In another case diagnosed as possible aHUS when severe thrombotic microangiopathy occurred during pregnancy, genetic testing identified only a VUS in *PLG*, and we withdrew eculizumab one year after a successful kidney transplant (case 26).

A genetic diagnosis may also permit the earlier recognition of extrarenal manifestations of disease such as cardiac disease in Fabry disease (case 9, left ventricular hypertrophy [LVH], dilated aortic root), or allow strategies to prevent the development of future severe complications (e.g., prophylactic gonadectomy for future gonadoblastoma risk in an XY female with Frasier syndrome, case 69). In some cases genetic testing may even uncover a new genetic basis for renal disease. Case 38 was referred to us with asymptomatic proteinuria, impaired kidney function, and zebra bodies in podocytes but a normal plasma  $\alpha$ -galactosidase. We noted that he also had pigmentary retinal dystrophy, bilateral sensorineural hearing loss, tremors, bradykinesia, myoclonus, and cerebellar

signs. He did not have an identifiable genetic variant when tested with KidneySeq™, a targeted renal gene panel with 264 genes, but was found to have compound heterozygous variants in *PEX1* when tested with OtoSCOPE™, a multigene panel of hearing loss genes.<sup>7,28</sup> Variants in *PEX1* cause a peroxisomal biogenesis disorder manifesting as one of a group of conditions called Zellweger spectrum disorder.<sup>29</sup> This disease accounts for the auditory, visual, and central nervous system (CNS) manifestations and is thought to explain the renal phenotype. However, proteinuric chronic kidney disease (CKD) with podocyte inclusions has not been recognized previously in this condition although crystalline inclusions have been seen in affected livers.<sup>30</sup>

Finally, the confirmation of the genetic basis of a disease, which may have been previously suspected to be sporadic, can prompt at-risk family members to be screened for disease. This occurred for case 39–3, the sibling of 39–2, who was prompted to see a physician for the first time following the identification of familial Alport disease and who was discovered to have stage 3 CKD with microscopic hematuria together with the identified familial *COL4A5* variant.

With respect to living kidney donors, it is important to ascertain the cause of kidney disease in the related recipient, so that the living donor can be screened for genetic disease if appropriate.<sup>31</sup> Unfortunately, too often the cause of ESRD in patients on the transplant waitlist is unknown or assumed and the increased risk of ESRD postdonation in related living donors may reflect a missed genetic disease.<sup>32,33</sup> In the case of the gene *APOL1*, the inheritance of two copies of the risk alleles G1 or G2 substantially increases the risk of ESRD in patients of sub-Saharan African ancestry who have hypertension, HIV, sickle cell disease, or systemic lupus erythematosus (SLE).<sup>8,9</sup> Preliminary studies suggest that living donors with two *APOL1* risk variants may have a lower estimated glomerular filtration rate (eGFR) and possibly a higher risk of ESRD postdonation.<sup>5</sup> In our opinion, all at-risk living donors should be offered genetic counseling and the option of *APOL1* genetic testing before they are accepted as living kidney donors.

There are several barriers to genetic testing in the typical nephrology practice. First, many genetic disorders have an incomplete or overlapping phenotype and may phenocopy an acquired disease, thus causing a genetic disease to go unrecognized. Alport gene variants are now considered to be the most common genetic cause of adult onset FSGS and yet many of these patients do not have the typical syndromic manifestations of sensorineural deafness or lenticonus.<sup>34</sup> Other classic syndromic conditions such as nail patella syndrome and renal coloboma syndrome may also present with isolated FSGS without skeletal or ocular manifestations, respectively.<sup>20,35</sup> Second, although there have been tremendous advances in the ability to rapidly sequence and interpret variants in the human exome and genome, an understanding of the power and limitations of sequencing technology has not reached the practicing clinician. Furthermore, the rapidly changing landscape of testing labs and capabilities makes it

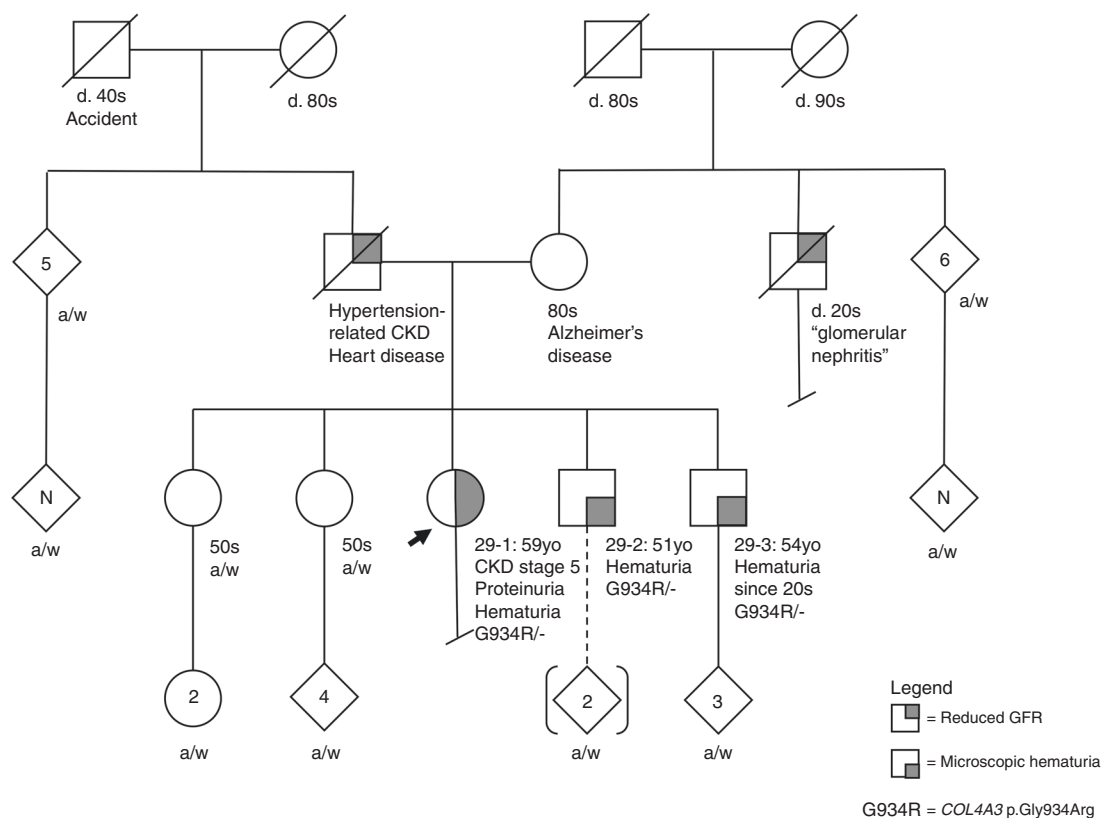


challenging for a clinician to determine the best testing approach (i.e., single-gene vs. limited panel vs. comprehensive panel vs. exome) or how and where to have genetic testing done. Since it is considered a new and emerging technology, even though it is cost-efficient, some insurance payers require preauthorization, which can again dampen a clinician's enthusiasm for ordering these tests. Finally, the genetic test results, especially when scored based on ACMG criteria, can be confusing to the clinician when a series of variants of unknown significance (VUS) are reported in genes that may not even be relevant to the patient's disease.

A CGC is a vital part of any genetics clinic.<sup>36,37</sup> Patients may be referred for consideration of genetic testing and if the indication for testing is not clear, a nephrologist with experience in renal genetic diseases should evaluate the patient to formulate a differential diagnosis and determine whether genetic testing is indicated. If the patient is agreeable to genetic testing, he or she should be seen by a CGC prior to genetic testing. Genetic counseling involves obtaining a detailed medical and family history, performing a risk assessment for the patient, and providing education, psychosocial counseling, and support. The implications of a genetic diagnosis on the patient's prognosis, medical management, familial risk, and risk of recurrence following kidney transplant are also discussed. Patients are informed of the current policies in place that protect them from

discrimination based on a genetic testing result. Currently, the Genetic Information Nondiscrimination Act (GINA) of 2008 protects them from health insurance and employment discrimination. However, it does not cover life insurance, long-term care insurance, or disability insurance and is not protective in companies with fewer than 15 employees. It is important for patients to understand the benefits, risks, and limitations of a genetic test to make an informed decision.

Once the genetic test report is available, the test results are communicated to the patient as soon as practical, ideally with a follow-up visit. Genetic counseling should again be offered at this point to ensure the patient understands the implications of the results. It is important to note that in some cases identified genetic variants may not rise to the level of pathogenicity required to establish causality. Therefore, additional studies including segregation analysis within an affected family can provide further evidence to support pathogenicity of the identified variant. We were able to demonstrate segregation of the identified variant in pedigree 19 and pedigree 29, which helped establish pathogenicity (Figure 2). Sometimes, genetic variants that could explain the phenotype may be difficult to identify, as is the case with large gene segmental deletions or duplications that may not be detected with a standard bioinformatic pipeline.<sup>38</sup> In addition, if phenotype-limited gene panels are used the causal gene may not be included in the selected panel chosen such that a



**Fig. 2** Pedigree chart for subjects 29-1, 29-2, and 29-3. The identified heterozygous genetic variant COL4A3 p.Gly934Arg (G934R) was initially classified as a variant of unknown significance (VUS) (American College of Medical Genetics and Genomics [ACMG] criteria: PM1, PM2, PP3) but following segregation analysis was reclassified as likely pathogenic (ACMG: PM1, PM2, PP1, PP3). CKD chronic kidney disease, GFR glomerular filtration rate.

negative result would need to be interpreted with caution. Since panels and exomes typically focus on coding exons and their associated splice sites, a negative result may also arise because the causal variant is in an untranslated portion of a gene that is not assessed in the sequencing strategy. This may also be an explanation for the identification of just one causal variant in an autosomal recessive disease. For example, in two large studies, only one pathogenic variant was identified in ~9% of patients with Gitelman syndrome and in 21% of patients with ARPKD.<sup>39,40</sup> We were only able to identify a single heterozygous pathogenic variant in each of three patients with suspected autosomal recessive disease (cases 33, 35–1, and 57).

### Summary

As a growing number of genes become implicated in kidney diseases associated with a variety of renal phenotypes that present at all ages, an RGC may become increasingly relevant. Ideally, such a clinic would include an adult and pediatric nephrologist with an interest in genetic renal disorders and a CGC. Developing the clinical expertise in the assessment, diagnosis, and treatment of renal genetic diseases offers the potential for specific disease management and/or genotype-directed care. The genetics clinic can serve primarily as a consultative service to determine if genetic testing is necessary and then identify the appropriate testing strategy and facilitate testing where indicated. In other situations, where chronic disease-specific care or coordination of specialist management of a multisystem disease is required, the genetics clinic can provide this long-term care. An RGC can also determine the appropriate screening strategy for presymptomatic testing of related family members, especially living donor candidates where excluding renal disease is of vital importance. In this study, we demonstrate a role for the RGC in these areas with a high rate of genetic confirmation of diagnosis, although it is a single-center study of patients predominantly of European ancestry. Nevertheless, given the obvious benefits, we believe that a specialized RGC will have an increasingly important place in the evaluation and care of patients with a wide variety of kidney diseases.

### SUPPLEMENTARY INFORMATION

The online version of this article (<https://doi.org/10.1038/s41436-020-0772-y>) contains supplementary material, which is available to authorized users.

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### DISCLOSURE

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