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From Theory to Reality: Establishing a Successful Kidney Genetics Clinic in the Outpatient Setting

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Abstract

Background Genetic testing in nephrology is increasingly described in the literature and several groups have suggested significant clinical benefit. However, studies to date have described experience from established genetic testing centers or from externally funded research programs.

Methods We established a *de novo* kidney genetics clinic within an academic adult general nephrology practice. Key features of this effort included a pipeline for internal referrals, flexible scheduling, close coordination between the nephrologist and a genetic counselor, and utilization of commercial panel-based testing. Over the first year, we examined the outcomes of genetic testing, the time to return of genetic testing, and out-of-pocket cost to patients.

Results Thirty patients were referred and 23 were evaluated over the course of five clinic sessions. Nineteen patients underwent genetic testing with new diagnoses in nine patients (47%), inconclusive results in three patients (16%), and clearance for kidney donation in two patients (11%). On average, return of genetic results occurred 55 days (range 9–174 days) from the day of sample submission and the average out-of-pocket cost to patients was $155 (range $0–$1623).

Conclusions We established a kidney genetics clinic, without a pre-existing genetics infrastructure or dedicated research funding, that identified a new diagnosis in approximately 50% of patients tested. This study provides a clinical practice model for successfully incorporating genetic testing into ambulatory nephrology care with minimal capital investment and limited financial effect on patients.

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Introduction

Genetic testing is increasingly available in medicine as a result of advances in sequencing technology and diminishing cost. Several recent studies have suggested a significant benefit for genetic testing in nephrology, with results leading to novel diagnoses, changes in disease management, and preparation for kidney transplant. In these initial studies, genetic testing yielded a diagnosis in approximately 10% of the general adult CKD population and in approximately 40%–60% of patients with a family history suggestive of inherited kidney disease (1–4). There is a call to make genetic testing more routine in outpatient nephrology clinics (5,6); however, the initial studies were from programs with established genetic testing centers with associated research funding (1–4,7–9).

In order for genetic testing to truly take hold in nephrology, genetic testing capabilities and utilization need to be distributed more broadly. Barriers to the establishment of more widespread kidney genetics clinics include the perceived need for significant capital investment, concern regarding cost to the patient, administrative time dealing with insurance companies, and access to genetic counselors (6,10–13). To address these concerns and to provide a blueprint for clinic development, we initiated a *de novo* outpatient kidney genetics clinic within an academic adult general nephrology practice and monitored its effect over 1 year.

Materials and Methods

We identified the following criteria as necessary for a successful kidney genetics clinic: genetic testing could result in clinical benefit for the patient or a family member, the cost of the testing is reasonable for the patient, minimal administrative effort is required to obtain the testing, results are returned in an efficient manner, interpretation is provided by the physician, and genetic counseling is available when needed.

The key components of the clinic included a supportive administration, a physician with an interest in inherited kidney disease, and a part-time genetic

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counselor whose administrative efforts were later transitioned to a genetic counseling assistant. Referrals to the clinic were primarily made internally from the Massachusetts General Hospital (MGH) general adult nephrology practice, an academic practice comprised of two full-time clinical nephrologists and 12 part-time nephrologists. Additional referrals were made from other regional nephrology practices, the MGH kidney transplant program, and the MGH pathology department. Retrospective review of the demographic and clinical data in this study were approved by the MGH Institutional Review Board (2020P002464). The study adheres to the Declaration of Helsinki and informed consent was waived by the Institutional Review Board for all patients. Explicit consent was obtained for those patients described in more detail in the discussion using the following form (https://clinicalgenome.org/tools/consent-resources/one-page-consent-form) (14).

Physician Oversight

A single nephrologist with an interest, but no formal training, in genetic kidney disease coordinated the clinic. The time commitment consisted of administrative efforts to initiate and advertise the clinic, correspondence with local nephrologists regarding potential patients, five half-day clinics over the year, and follow-up with patients on the basis of the results of the testing.

Part-time Genetic Counselor

A genetic counselor, contributed from a small team within the MGH Department of Medicine tasked with helping clinics integrate genomic medicine approaches, joined the clinics on a part-time basis. The genetic counselor facilitated consent for genetic testing, acted as a liaison with the commercial testing agency for sample submission and cost assessment, functioned as a valuable resource for interpretation of results, and provided genetic counseling and coordination of care for actionable results. The total estimated effort from the genetic counselor in the first year was 10%, with more effort in the first half of the year.

Genetic Counseling Assistant

In the second half of the year, the clinic transitioned many of the administrative roles taken on by the genetic counselor to a genetic counseling assistant. Genetic counseling assistants have the potential to address the high demand for genetic counselors through task sharing to allow genetic counselors to focus on higher-level activities (15,16). In this case, the genetic counseling assistant facilitated test requisitions, sample submission, and coordination of payment for the commercial testing.

Clinic Structure

A dedicated half-day clinic session focused on genetic testing occurred once every 2 to 3 months (Figure 1). The clinics were conducted in the same physical space as the general nephrology practice, with sessions scheduled on a rolling basis to ensure that at least four to five patients would be evaluated per session. The patients were reviewed before the visit by both the physician and the genetic counselor to determine (*1*) the potential utility of genetic testing and (2) the best testing platform. The clinic was structured to be inclusive and referring physicians were encouraged to refer any adult patient they felt might benefit from genetic testing. Patients were scheduled if there was a known family history of kidney disease, a young age at presentation, an unexplained nephropathy, cystic disease or electrolyte disorder, or if the patient had a personal preference to be seen. If initial review suggested a low likelihood of a genetic disorder, the nephrologist reached out to the referring physician to discuss further.

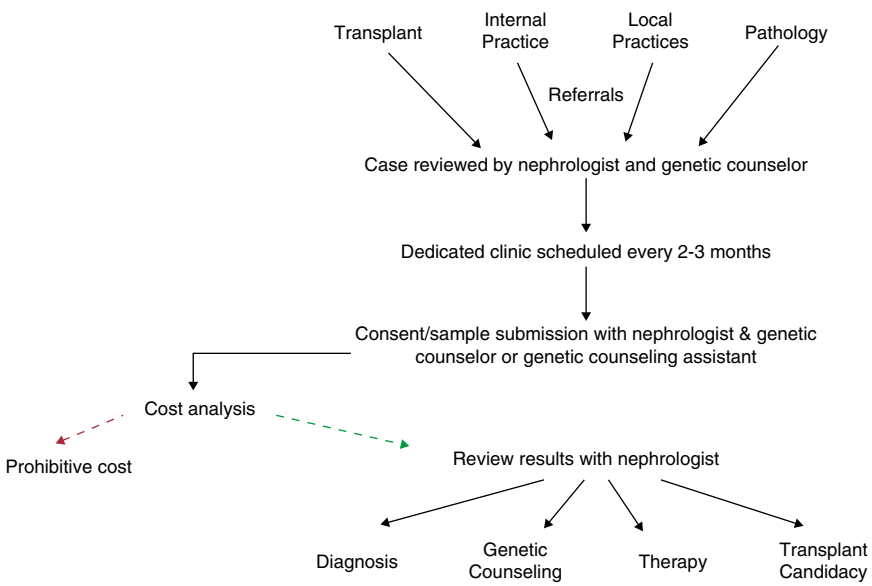

Figure 1. | **Kidney genetics clinic workflow.** Patients were referred through multiple pathways and cases were reviewed before the clinic visit. The commercial testing platform coordinated with the insurance company to determine coverage or cost to the patient. Samples were processed if cost was acceptable to the patient.

Genetic Testing

We pursued phenotype-driven panel testing or focused exome panel testing on the basis of the patient's clinical presentation. Although there are a number of commercial testing platforms, our tests were sent to two sites: one with multiple precurated diagnostic panels on the basis of phenotype (Blueprint Genetics, Helsinki, Finland) and a second that allowed designer panels with results on up to 150 genes on an exome platform (XomeDxSlice; GeneDx, Gaithersburg, MD). During the patient visit, a blood sample was collected and submitted for commercial testing after obtaining informed consent. The prior authorization process for testing coverage was performed independently between the testing company and the patient's insurance. Testing proceeded if there was no cost to the patient. For patients where there was an estimated cost to the patient, testing was placed on hold until this cost had been discussed with the patient and a decision was made whether or not to proceed. Pathogenicity of variants was determined by the commercial vendor upon review of known variants, genetic conservation, and prediction of changes to protein structure. In patients where novel variants were identified and classified as variants of uncertain significance (VUS), the clinic coordinated segregation analyses of additional affected and unaffected family members to clarify pathogenicity.

Return of Genetic Testing Results

The genetic counselor and physician initially discussed the outcome of the testing to determine the next steps needed to complete the evaluation. The physician communicated the results to the patients, initially by phone, then in a follow-up visit in person to review the results. Additional genetic counseling, local or at this institution, was arranged when needed.

Results

Thirty patients were referred to the clinic during the first year, 19 from the MGH general nephrology practice, six from local nephrology practices, three from the MGH kidney transplant program, and one from the MGH pathology department (Figure 1). None of the patients had a prior genetic diagnosis. After initial patient review, it was determined that three of these patients were not appropriate for genetic testing on the basis of a perceived low likelihood of a genetic disorder and four patients have yet to present to the clinic. Of the 23 patients seen in clinic, ten were men and 13 were women, with an average age of 43.5 years and a range of 25–76 years. Most patients were unrelated, except for three patients from one family. Nineteen patients underwent genetic testing, 12 by GeneDx and seven by Blueprint Genetics, whereas four have yet to undergo testing due to cost.

The average cost to the patients who underwent genetic testing was $155 with a range of $0 to $1623. Twelve of the 19 patients tested did not have any out-of-pocket cost ($0). On average, test results returned in 55 days from the day of sample submission, with a range of 9–174 days. Testing in two patients took notably longer than all other patients (140 and 174 days) due to difficulty making contact with one patient and patient-driven cancellation of testing, then reinitiation months later with a new insurance plan in the other. Excluding these two patients, the average time between sample submission and report date was 42 days. The average time to return of results once testing was initiated at the commercial facility was 25 days, thus it took an average of 17 days to coordinate insurance coverage or out-of-pocket payment before the initiation of testing.

Overall outcomes of genetic testing in the first year are shown in Figure 2. A new diagnosis was established in nine out of the 19 patients tested (47%). Cost and testing results for the patients with new diagnoses are shown in Table 1. New diagnoses included two patients with Gitelman syndrome, two patients with autosomal dominant interstitial kidney disease, and one patient each with Alport syndrome, thin basement membrane nephropathy/Alport syndrome spectrum, polycystic kidney disease, hypomagnesemia due to a 17q12 microdeletion syndrome including *HNF1B*, and

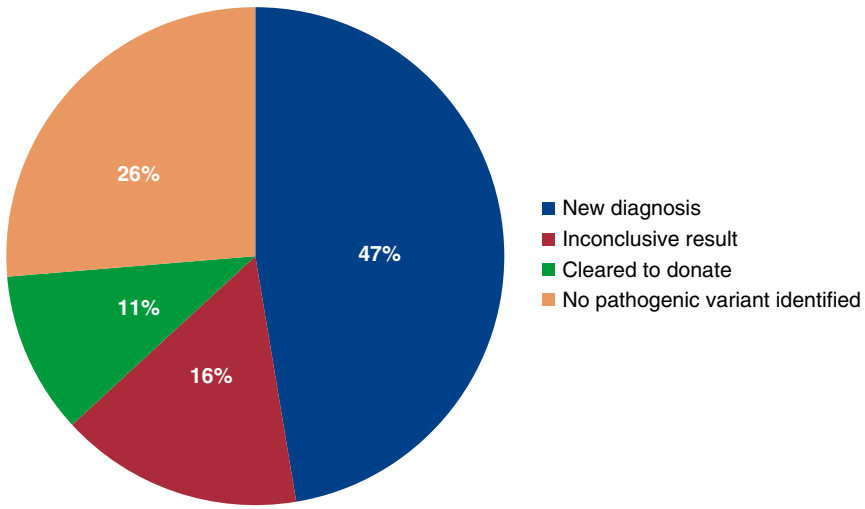

Figure 2. | Genetic testing resulted in a new diagnosis in nearly 50% of patients tested in the first year (N=9/19). All samples were sent for commercial gene panel testing. Inconclusive results consisted of variants of uncertain significance, or a single heterozygous variant in a recessive disease gene. Cleared to donate is a subset of the no pathogenic variant identified category.

Table 1. Summary of patients with new clinical diagnoses after genetic testing (*n*=9)

Patient	Family History	Cost to Patient, $	Diagnosis	Gene	Transcript	Genomic Coordinates (GRCh37)	Zygosity	DNA Change	Protein Change	Classification
1	Multiple	1623	ADIKD	*UMOD*	NM_003361.2	16:20360507	HET	c.116C>A	p.A39D	Pathogenic
2	Multiple	0	ADIKD	*UMOD*	NM_003361.2	16:20360507	HET	c.116C>A	p.A39D	Pathogenic
3	Multiple	14	Alport	*COL4A5*	NM_033380.1	X:107939580	HEMI	c.5048G>A	p.R1683G	Pathogenic
4	Multiple	0	TBMN/ Alport	*COL4A4*	NM_000092.4	2:227973304	HET	c.728G>A	p.G243E	Pathogenic
5	No	250	Gitelman	*SCL12A3*	NM_000339.2	16:56947205	COMP HET	c.2981G>A	p.C994W	Pathogenic
				SCL12A3	NM_000339.2	16:56903649	COMP HET	c.514T>C	p.T172R	Pathogenic
6	No	250	Gitelman	*SCL12A3*	NM_000339.2	16:56899381	COMP HET	c.237_238dup	p.R80Pfs*35	Pathogenic
				SCL12A3	NM_000339.2	16:56920278	COMP HET	c.1928C>T	p.P643L	Pathogenic
7	Multiple	250	PKD	*PKD1*	NM_001009944.2	16:2160152	HET	c.5014_5015del	p.A1672Gfs*98	Pathogenic
8	No	0	Deletion syndrome	*HNF1B* + other genes	Multiple	17:34856055	HET	17q12 deletion	Multiple	Pathogenic
9	Multiple	0	Mitochondrial	*MT-TL1*	NC_012920.1	N/A	HETplas	m.3243A>G	N/A	Pathogenic

Cost is in US dollars. ADIKD, Autosomal Dominant Interstitial Kidney Disease; HET, heterozygous; HEMI, hemizygous; TBMN, Thin Basement Membrane Nephropathy; COMP HET, compound heterozygote; PKD, Polycystic Kidney Disease; HETplas, heteroplasmic.

Table 2. Summary of patients with inconclusive results (*n*=3)

Patient	Family History	Cost to Patient, $	Gene	Transcript	Genomic Coordinates (GRCh37)	Zygosity	DNA Change	Protein Change	Classification
10	Multiple	0	*CACNA1D*	NM_000720.2	3:53762060	HET	c.3914C>T	p.A1305V	VUS
11	Yes	0	*CYP24A1*	NM_000782.4	20:52790103	HET	c.18_21dupCAAG	p.S8QfsX99	Likely Pathogenic
12	Yes	300	*NPHS2*	NM_014625.3	1:179526214	HET	c.686G>A	p.R229Q	VUS

Cost is in US dollars. HET, heterozygous; VUS, Variant of uncertain significance.

FSGS secondary to a mitochondrial cytopathy. Novel variants were identified in *UMOD* and in *COL4A4*. Longitudinal follow-up of the patient with the *COL4A4* variant and additional screening of affected family members is necessary to refine the diagnosis of thin basement membrane nephropathy versus autosomal dominant Alport syndrome.

Three of the 19 patients tested (16%) had inconclusive results, either with a VUS or a single heterozygous variant in a recessive disease gene (Table 2). In each case, the variant identified correlated with the phenotype, but either did not meet criteria to be classified as pathogenic or a variant on the second allele was not identified. Patient 10 was referred for polyuria, hypertension (HTN), and hypokalemia, with a family history of HTN and hypokalemia. A heterozygous VUS was found in the *CACNA1D* gene, in which pathologic variants are associated with primary hyperaldosteronism (17,18). Patient 11 was referred for hypophosphatemia and nephrolithiasis. A likely pathogenic duplication in *CYP24A1* was identified. Biallelic variants in this gene lead to infantile hypercalcemia (19,20), whereas monoallelic findings can result in kidney stone formation (21–23). Patient 12 was referred with a history of biopsy-proven FSGS. Genetic testing revealed a VUS in the *NPHS2* gene (24,25). Testing of additional affected family members in each of these three cases may help clarify the significance of these initial genetic findings.

Two of the 19 patients tested (11%) were potential kidney donors, one a sibling in the family with the newly identified uromodulin variant and the other with a family history of nephrolithiasis. Genetic testing was negative in both potential donors, facilitating future donation. The results of the five remaining patients with negative testing (26%) are shown in Table 3. Four of these patients were felt to have a low to moderate probability of finding a genetic variant and no further testing is planned, whereas one patient with a strong family history of early onset hypertension and will undergo follow-up whole-exome sequencing (WES).

Discussion

Our experience in the first year of a kidney genetics clinic is consistent with recent studies that demonstrate the potential clinical benefit of genetic testing in outpatient nephrology (1,2,4). We were able to start a successful *de novo* genetics clinic within the framework of an existing academic adult nephrology practice with minimal capital investment and without a pre-existing testing platform or dedicated research funding. As this was a pilot project without significant advertising, only 30 patients were referred in the first year. We have subsequently experienced an increase in referrals with increased awareness of the clinic. A part-time genetic counselor was an essential part of the clinic, counseling patients and serving as a liaison with the testing laboratory for sample coordination and insurance coverage. Halfway through the year, the majority of the administrative responsibilities were transitioned to a genetic counseling assistant.

Commercial gene panel testing on the basis of phenotype resulted in a new diagnosis in approximately 50% of patients tested in our clinic, comparable with studies using whole-exome testing (1). Recent studies show that insurance coverage for WES remains limited in adult patients (26) with cost more than double that of panel testing (27). We chose panel-based testing as an initial strategy to reduce cost and to expedite results. This approach also minimized the likelihood of secondary or incidental findings such as *BRCA* variants, because only the genes included in the panels were analyzed and reported, even in the exome-based panels. Using this strategy, cost to the patient was not prohibitive as 12 out of 19 patients tested had no out-of-pocket

Table 3. Summary of patients with negative testing results (*n*=5)

Patient	Family History	Cost to Patient, $	Indication for Testing	Follow-Up Plan
13	No	250	Weak	None
14	No	0	Moderate	None
15	No	0	Moderate	None
16	No	0	Moderate	None
17	Multiple	0	Strong	Whole-exome sequencing

Cost is in US dollars.

cost and the average cost in all patients tested was $155. It remains difficult to predict which patients will receive coverage and there is variability in preferred or accepted insurance carriers across different commercial testing providers. Regardless, the average time to acquire prior authorization or negotiate out-of-pocket cost to the patient before initiation of testing in this study was only 17 days.

When testing was not covered by insurance, the maximum out-of-pocket cost for patients varied across commercial testing platforms. The maximum out-of-pocket cost for the designer gene panel on the basis of the exome platform was $2000, compared with a maximum cost of $250 using standard or nonexome-based gene panels. When out-of-pocket cost was prohibitive for exome-based panel testing, several patients were willing and able to pay $250 out of their own pockets to proceed with standard panel-based testing. In our experience, the nonexome-based panels were both cost-efficient and effective, whereas the exome-based panels came at an increased cost, but offered designer capability when required. Recent studies have shown that WES may increase the yield of panel-based testing (28), and accordingly one out of 19 patients in this study will undergo follow-up WES. Outside of the research setting, we believe that initial screening with more affordable and focused panel-based testing, followed by more comprehensive WES in patients with a strong family history of disease and negative panel testing, is an effective approach. Accurate phenotyping, a positive family history or unexplained kidney disease, and presentation at a young age are all characteristics that may help reduce negative test results and overall cost.

In addition to diagnostic benefit, test results affected clinical management in multiple patients. For patient 8, the genetic diagnosis affected the patient's understanding of her condition and her subsequent health care decision making. She had a history of seizures, bipolar disorder, and long-term muscle weakness, and presented for evaluation of persistent and severe hypomagnesemia in the setting of presumed Gitelman syndrome. Testing revealed the 17q12 microdeletion syndrome, a 1.3-Mb deletion of 15 genes including the *HNF1B* gene, variation in which can lead to kidney dysplasia and hypomagnesemia (29,30). Prior studies have shown that this microdeletion can lead to both kidney and neuropsychiatric disease (31,32), tying together her overall medical history. These findings were communicated to her local psychiatrist, she underwent further genetic counseling locally and she decided against having children in the future.

In a second patient, the diagnosis affected the referring physician's treatment approach. Patient 9 was referred in the setting of biopsy-proven FSGS, proteinuria, CKD3, HTN, and hearing loss in young adulthood. Her mother has ESKD, diabetes, and stroke at a young age and she has a sister with hearing loss. Genetic testing revealed a heteroplasmic pathogenic *MT-TL1* variant A3243G, previously shown to result in mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke–like episodes (33) with variable additional phenotypes including FSGS, kidney failure, and hearing loss (34,35). The characterization of a familial mitochondrial cytopathy will have significant clinical effect on both the patient and her family members, including audiologic evaluation and management, cardiac testing,

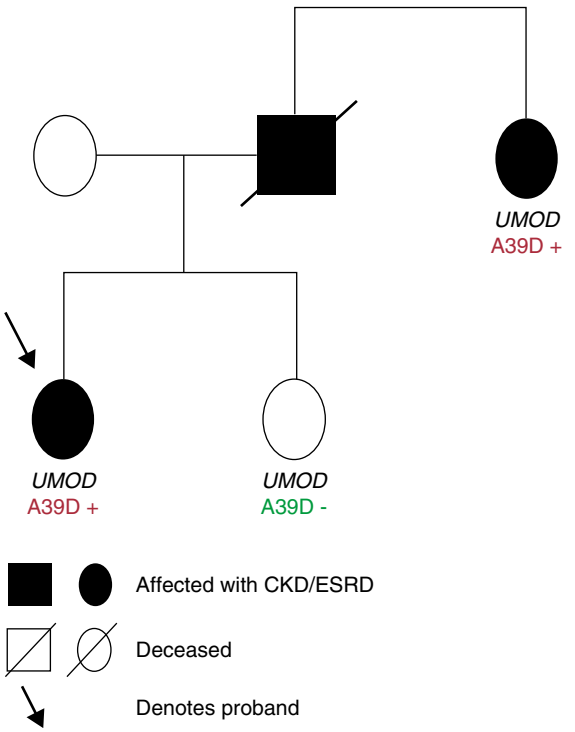

Figure 3. | Genetic testing identified the etiology and facilitated evaluation of a famliy member as a kidney donor in this family with CKD. Additional genetic testing revealed that the proband's paternal aunt with ESKD had the same uromodulin (*UMOD*) variant, whereas her sister did not, allowing her sister to be evaluated as a potential kidney donor.

and avoidance of certain medications (36). In her case, steroids will be avoided for treatment of her FSGS, additional disease-specific therapies can be considered (37), and she was referred for enrollment in clinical trials.

In a third case, the genetic diagnosis had implications for kidney transplantation. Patient 1 presented with biopsy-proven interstitial nephritis and progressive stage 4 CKD. Her sister was denied evaluation as a transplant donor as their father and a paternal aunt also had significant kidney disease of unknown etiology (Figure 3). Genetic testing revealed a novel uromodulin variant. Testing of her paternal aunt, currently on dialysis, revealed the same variant whereas the variant was absent in her sister, facilitating her evaluation as a future kidney donor. Taken together, these three examples show that genetic testing in nephrology can be useful both for diagnosis and clinical management.

There were some limitations to the generalizability of this strategy. First, the majority of our patients were referred from within Massachusetts, where the rate of health insurance coverage is high. The cost of genetic testing is decreasing, although widespread testing may remain cost-prohibitive for some individuals in other parts of the United States or internationally, and efforts to assure access to thorough and equal testing for patients of all socioeconomic status and ethnicities are necessary. Further, we were initially afforded 10% effort from a genetic counselor and subsequently 5% effort from a genetic counseling assistant

as part of an effort to integrate genomics into clinical medicine by the Department of Medicine at MGH. These resources may not be available at all institutions, but these experiences underscore the successful use of a shared and centrally hired genetic counselor, as opposed to hiring a full-time genetic counselor for each clinic. With limited genetic counseling resources nationwide, we demonstrate a new approach for service delivery of genetic counseling that can serve as a model for improving access to genetics services in other clinics and institutions.

In summary, we describe the first-year results of a new kidney genetics clinic established within an academic adult general nephrology practice that yielded a new diagnosis in approximately 50% of patients tested, with limited out-of-pocket cost to patients (approximately $150) and return of test results in <2 months. We hope this study provides both motivation and a framework for additional kidney genetics clinics across the country to enhance the scope and clinical benefit of genetic testing in the field of nephrology.

Disclosures

All authors have nothing to disclose.

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Author Contributions

K. Armstrong, A. Lundquist, R. Pelletier, H. Rehm, E. Rhee, and W. Williams conceptualized the study; A. Lundquist and R. Pelletier were responsible for data curation and formal analysis; C. Leonard was responsible for project administration; A. Lundquist was responsible for methodology, supervision, and wrote the original draft; and all authors reviewed and edited the manuscript.

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