Supplemental Appendix

Supplement to: Nestor, J *et al.* Return of Genetic Results in Adult Nephrology: Lessons Learned from a Pilot Study in a Diverse Urban Population

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Section S1- SUPPLEMENTARY METHODS

Study design and protocol

The Columbia University Medical Center (CUMC) Genetic Studies of Chronic Kidney Disease (CKD) (IRB #AAAC7385) is a genetic research and biobanking protocol (established in 2003; PI: Ali Gharavi) recruiting patients seen by the Division of Nephrology, and has been previously described[1,2]. In 2015, the study protocol and informed consent were revised for the first time to include the option for re-contact in the event a "medically relevant" finding was identified. Participants were also made aware that if there was a clinically actionable finding identified in the research laboratory, confirmatory re-testing in a Clinical Laboratory Improvement Amendments of 1988 (CLIA)-certified laboratory would be necessary, using a newly collected blood sample. Beginning in January 2017, participants enrolled prior to January 2015, were met by a member of our research team at one of their subsequent nephrology follow-up appointments and given the opportunity to reconsent to participation with this new clause included. This required additional amendments to the IRB.

The workflow was iteratively developed based on feasibility, challenges encountered with the introduction of Return of Results in nephrology care, alongside provider feedback. The strategies implemented to address various obstacles faced with Return of Results informed the final optimized workflow.

The optimized final workflow:

1. Genetic Sequence Analysis

We developed an in-house pipeline to analyze sequence data for patients enrolled in our genetic biobank study. The major steps included exome sequencing, bioinformatics processing, variant annotation and sequence interpretation, and are detailed in our earlier publications[1, 2].

Exome sequencing (ES):
ES data was captured using: the Agilent SureSelectXT Human All Exon V4 (51 Mb) kit[1], yielding mean sequence coverage 110x, with on average 99% of target bases in a given sample achieving at least 10x coverage; or Roche NimbleGen SeqCap Exome EZ v3.0 kit or the IDT xGen Exome Research Panel v1.0 kit[2], yielding mean sequence coverage 111x, with on average 97% of target bases in a given sample achieving at least 10x coverage. These coverages are in the range of those achieved using commercially available exome capture kits for clinical-level sequencing[3-5].

Gene- and variant-level prioritization:
To facilitate identification of variants potentially causal for nephropathy, we manually curated a list of 625 genes associated with Mendelian forms of genitourinary disease[6]. The list was generated by querying the Online Mendelian Inheritance in Man (OMIM)[7] and Orpha.net[8] databases for genes associated with Mendelian forms of kidney and genitourinary disease, followed by manual review of the primary literature to assess the strength of evidence supporting each gene-disease association and characterize the relevant molecular genetic and clinical attributes of the gene-disease pairs.

Actionable findings included: primary diagnostic-variants classified as Pathogenic or Likely Pathogenic per the American College of Medical Genetics and Genomics (ACMG) criteria[9] potentially explicative for patients' nephropathy; and secondary-known and expected pathogenic variants in the 59 genes recommended by the ACMG for return as medically actionable secondary findings[10].

Case-level interpretation:
We next identified participants with actionable primary (diagnostic) or secondary findings who opted for re-contact if a "medically relevant" findings were detected. To verify that primary diagnostic findings were indeed explicative of the patient's kidney disease, we conducted an in-depth review of these participants' electronic health records. This involved summarizing the individual's clinical history and relevant data (e.g., biochemical studies, imaging and histopathology). Then, we consulted with their referring nephrologist to discuss the individual's phenotype. Each variant selected for return also underwent secondary review by a team of nephrologists, research scientists, and a molecular geneticist to confirm its pathogenicity.

2. Notify referring nephrologist

In this study, we did not return Variants of Uncertain Significance to patients or providers. Such cases were routinely presented to the referring nephrologist during quarterly "Nephrology Genetic Sign Out Rounds". In these conferences, the genetic findings were assessed in the clinical context with the patient's provider. Additional testing (e.g., urine studies for a patient with a suspicious variant detected in *CLCN5* which is associated with Dent disease, etc.) and further follow-up were at times requested for these "candidate variant(s). If additional testing yielded data that was compelling enough to make the variant diagnostic (i.e., Pathogenic or Likely Pathogenic by the ACMG criteria), the provider was updated accordingly. Furthermore, as part of the workflow, sequence data is routinely re-analyzed as new genes and variants continued to be discovered.

Adult (aged ≥ 18) participants of the aforementioned parent study with actionable genetic variants detected on research-grade exome sequencing (ES)[1,2], who opted to re-contact if a "medically relevant" finding was identified, were considered eligible for re-contact.

3. Participant Re-contact

Following initial revisions to the biobank study protocol in January 2015, pre-pilot efforts began in 2015 through 2016 to re-contact participants for Return of Results, beginning with the first 5 adult participants identified to be eligible. For these initial cases, we notified the referring nephrologists of the preliminary finding and recommended them to order clinical testing for confirmation of the research results. Providers expressed to us their concerns. Specifically, they cited not knowing how and from where to order clinical genetic testing, limited time in their clinical workflows to counsel patients on the benefits of confirming the genetic findings, and a lack of confidence in their ability to discuss research findings recommend clinical testing without disclosing the genetic variant, and adequately explaining the risks and benefits of clinical genetic testing. Therefore, we asked the nephrologists how they would like their patients who participated in the biobank protocol to be re-contacted in the event they were identified to have an actionable finding, and they expressed their preference for a clinician member of the study protocol to laisse between the research team and the clinical faculty. Therefore, the remaining individuals of the pilot cohort (99/104) were re-contacted by the Precision Nephrology Fellow, a trainee of the Division's nephrology fellowship program, who continues to work alongside the clinical faculty as a practicing clinician, and a member of the Gharavi laboratory. The Precision Nephrology Fellow re-contact the majority of participants (99 of 104) in the pilot cohort, between January 2017 and July 2019.

After alerting the referring nephrologist that a research-grade medically relevant finding was detected in their patient, study participants were re-contacted by the study team to notify them that a clinically actionable finding was identified and would require confirmation using a new secondary sample for clinical re-testing in a CLIA-certified laboratory before the findings could be disclosed. The initial re-contact method utilized by the study team was a telephone call to the participant alerting them that an actionable research-level finding was detected and inviting them to return to CUMC for a pre-test counseling visit and the opportunity to clinically validate the research findings. The telephone call was placed by a nephrologist on the study team (initially M.M., then after January 2017, J.G.N., the Precision Nephrology Fellow, who is an American Board of Internal Medicine-certified nephrologist who is bilingual in Spanish and English). Midway through the study, feedback from providers revealed their concerns, which included a physician's responsibility to notify patients of potentially actionable findings, possible psychosocial impact of the genetic findings on patients and families (e.g., anxiety, depression, stigmatization, loss/increase cost of insurance coverage, etc.), desires to respect the rights of some patients to no longer want to know about the genetic findings, and their inability to proper instruct patients who contacted them with questions or concerns after receiving the telephone call. Thus, the nephrologists suggested notifying participants with a letter, instead of a telephone call. The re-contact letter was developed in collaboration with the clinicians and approved by the Institutional Review Board (IRB). The letter was sent to the remaining eligible participants along with an enclosed "refusal form" that participants could complete and return (using the self-addressed stamped envelope included with the letter) to the research team if they were not interested in learning more about the genetic findings. Based on the mixed response

rates from either re-contact method, we adopted a standardized re-contact approach for the return of results workflow: sending the re-contact letter (**see Re-contact Letter**), followed by up to two subsequent telephone calls (**see Re-contact Telephone Script**) to all participants the who did not respond after 30 days. This standardized approach was utilized for 21 pilot participants. We made reasonable efforts to re-contact participants, consistent with recent consensus statements [11-13]. In cases where we were unable to re-contact the study participant by telephone or by mail correspondence, the Precision Nephrology Fellow notified the referring nephrologist, and requested their assistance contacting the participant. The nephrologists often had insight on the status of the patient (e.g., deceased, relocated, etc.). The patient was considered lost to follow-up if these measures failed.

Pre-test counseling and clinical re-testing for participants who underwent research-grade exome sequencing:

Pre-test counseling consisted of an in-person visit, with the Precision Nephrology Fellow, that typically lasted approximately 30 minutes. During this visit, participants were reminded that the research-grade findings required re-testing for CLIA-confirmation before the results could be disclosed as they were not-yet validated. They were also given an in-depth overview of the potential risks and benefits of clinical (CLIA-certified) genetic testing including limitations of genetic tests (e.g., varying resolution and analytic sensitivity between modalities), variant interpretation and shifting classification based on periodic reanalysis, potential loss of privacy, and federal protections against genetic discrimination provided through the Genetic Information Nondiscrimination Act (GINA). Discussions were tailored to the participant based on their perceived knowledge gap and health literacy, and the category of their genetic finding (e.g., primary diagnostic versus medically actionable secondary findings), to ensure their informed consent.

Following these discussions, written consent was obtained from participants who opted for clinical re-testing. A new blood sample was collected and participants were immediately scheduled for their second in-person visit, for post-test counseling visit, approximately eight weeks later. The option to schedule the follow-up post-test counseling visit during the pre-test counseling encounter was intended to facilitate the process of scheduling the appointment for the participant. When participants' expressed concerns returning for a second visit or reported a scheduling conflicts, efforts were made Precision Nephrology fellow to minimize additional travel to the hospital. This included rescheduling participants' other appointments (e.g., medical appointments, procedures, treatments, etc.) so that they may fall on the same day as the Return of Results visit.

A second blood sample was then sent to the New York Genome Center (NYGC) or to Columbia University's Personalized Genomics Laboratory for clinical-grade targeted dideoxy terminator (Sanger) sequencing of the variant(s). Early on, providers expressed concern about possible high out-of-pocket costs to patients who pursue clinical genetic

testing to confirm the research findings. Therefore, to prevent financial limitations impacting the participants' decision to validate the research findings, the Division's research funds covered the full cost of CLIA-sequencing* for this pilot cohort.

*Note- this may not be a scalable solution with further expanded use of genetic testing. To address this, other strategies we implemented in our workflow included procedures to facilitate providers' efforts to pursue prior authorizations with the insurance companies and to inform their decision on ordering clinical genetic testing.
They included:
1. Development of a templated "letter of medical necessity" for providers suspicious of a hereditary nephropathy and interested in ordering clinical genetic testing
2. Providing nephrologists with estimates of the full cost of different genetic tests (e.g., clinical grade ES for probands and trios; cost of a targeted cystic kidney disease panel through different commercial laboratories, etc.)
3. Alerting providers of which commercial laboratories offer financial counseling and prior-authorization services and can offer estimates of out-of-pocket costs and likelihood of insurance coverage
4. Leveraging opportunities to do increasingly conduct research-level sequencing within a CLIA-certified environment

For patients who had relocated out-of-state and unable to return for clinical re-testing, efforts would be made to assist them in finding a genetic counselor locally so that they may order the appropriate confirmatory genetic testing.

Clinical-grade genetic testing through participation in the eMERGE study:

In 2016, a subset of biobank participants was dually consented for research-grade and clinical-grade sequencing. Clinical sequencing was offered through their participation in the Electronic Medical Records and Genomics (eMERGE) Network's Phase III study, where sequencing was performed using the eMERGE-*seq* platform, a next generation sequencing (NGS) panel of 74 actionable genes.

Clinical interpretation for the eMERGE Network for our recruitment site was at Baylor College of Medicine (CAP# 8004250/CLIA#45D2027450). Using the eMERGE-seq Version 2 NGS Panel, Baylor cited the following quality control metrics of the sequencing data: > 70% of reads aligned to target, >99% target base covered at > 20x, > 98% target base covered at > 40x, average coverage of target bases > 200x. Baylor provided Columbia University with clinical interpretation for variants classifies as Pathogenic and Likely Pathogenic per the ACMG criteria[9], for the following 74 genes: *ACTA2, ACTC1, APC, APOB, ATM, BMPR1A, BRCA1, BRCA2, CACNA1A, CACNA1S, CFH, CHEK2, COL3A1, COL5A1, DSC2, DSG2, DSP, FBN1, GLA, HNF1A, HNF1B, KCNE1, KCNH2, KCNJ2, KCNQ1, LDLR, LMNA, MC4R, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH11, MYH7, MYL2, MYL3, MYLK, NF2, OTC, PALB2, PCSK9, PKP2, PMS2, POLD1, POLE, PRKAG2, PTEN, RB1, RET, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM43, TNNI3, TNNT2, TP53, TPM1, TSC1, TSC2, TTR, UMOD, VHL, and WT1*.

As sequencing for these participants was performed in a clinical-grade environment, participants with diagnostic findings (putative variants in kidney-related genes) identified on ES, also identified on this NGS panel, did not require the additional step of clinical re-testing. These patients were re-contacted by letter and up to 2 follow-up telephone calls after 30 days. However, these patients were instead invited for a Return of Results visit with the nephrogenetics team.

4. Return of clinically confirmed results and post-test counseling

In this Return of Results visit, the nephrogenetics team, consisting of the Precision Nephrology fellow and a senior faculty member with expertise in hereditary forms of kidney disease (A.G.G, K.K., S.S.C.), met with patients to provide post-test counseling and a comprehensive clinical consultation. After in-depth review of the clinical and familial histories, and physical examination, the confirmed genetic findings were disclosed. Inheritance, cascade screening and family counseling options were discussed in details. The implications of the genetic findings (whether primary diagnostic or medically actionable secondary findings) were then explained to the patient, in the context of their kidney disease. This comprehensive consultation typically lasted 60 minutes. Participants received a standardized clinical consultation note that detailed the genetic findings and listed the management recommendations (**see Nephrogenetics Consultation Note Template**), along with a copy of the CLIA-confirmed variant report for them to share with their providers and family members. Whenever indicated, we also provided participants with a simplified informational note to share with at-risk family members (**see Family Letter**), that included the variant(s) details, the associated condition, and the inheritance.

Remote consultations:

In the event a participant relocated, and chose to undergo confirmatory genetic testing locally, steps were included to support the new local nephrologists with Return of Results using telephone consultations with the provider, the patient, and/or both parties. A detailed summary of the discussions would then be sent to the local nephrologist outlining the management recommendations based on the genetic diagnosis.

5. *Clinical application of findings*

After the Return of Results visit, the genetic diagnosis, along with tailored medical management and referral recommendations, were reviewed one-on-one with the referring nephrologist. Individuals with actionable secondary findings were also referred to the appropriate specialist for subsequent care. An expert referrals list was developed that included genetic counselors, clinical geneticists and field experts (e.g., genetic ophthalmology, oncologists specialized in hereditary cancer syndromes, a genetic and maternal-fetal medicine expert, etc.). The consultation notes, and the CLIA-confirmed genetic test report, then became part of the individual's medical record.

Re-contact Letter

[DATE]

Dear [PATIENT NAME],

On [DATE], you volunteered to participate in our genetic study. The research team has informed me that there may be findings that **may be relevant to your health**. However, New York State requires confirmation of research results by a clinically-certified (CLIA*) laboratory before they are given to you.

If you are interested in learning more about the option to confirm this finding, you can schedule a **free visit** with my research colleague, [PROVIDER].

[PROVIDER] will help with arranging for confirmatory testing, which involves a repeat blood draw. The repeat testing in an outside clinically-certified (CLIA) laboratory is voluntary and takes approximately 6-8 weeks. CLIA-confirmed results will be discussed with you in person. Confirmed results will also be added to your medical record so that you and your physicians can refer to them in the future.

Please note, the test to confirm the research result is **free of charge** for individuals who choose to participate in the *Return of Results Study*. This study requires participants to provide informed consent and is intended to help us develop best practices for sharing genetic results with our patients.

Please call XXX-XXX-XXX to schedule a free visit to meet [PROVIDER]. If you have any questions, please feel free to call us or email us [TELEPHONE NUMBER; EMAIL ADDRESS].

If you do not want to learn more about how to confirm the research findings, please complete the attached form and return it to us by mail using the enclosed postage-paid envelope.

Sincerely,

[TREATING NEPHROLOGIST]

**The Clinical Laboratory Improvement Amendments (CLIA) of 1998 regulates that all clinical laboratories be certified by their state and the Center for Medicare and Medicaid Services (CMS), to ensure they meet the highest quality standards for diagnostic testing*

Re-contact Telephone Script

Telephone Recruitment Script

Attached to Protocol:
Principal Investigator:
IRB Protocol Title:

Patient Name:

STEP 1: Calling the Potential Participant

Hello, I am _____ from the Department of Medicine at [INSTITUTION]. May I please speak to_____?

If desired person is not available:	Is there a better day and time to reach (Mr. / Ms.)_____? ➢ **Note days and times**:_____ Thank you. I will call back then. ➢ **End call**
When desired person gets on the phone:	Hello (Mr./Ms.) _____. I am _____ from the Department of name of authorized study team member Medicine at [INSTITUTION]. We are contacting you to follow-up on a letter sent to your home by Dr. [NAME OF THE TREATING NEPHROLOGIST]. Did you receive that letter? ➢ ***IF NO, go to STEP 2a*** ➢ ***IF YES, go to STEP 2b***

STEP 2: Confirming receipt of letter

STEP 2a **Patient states they <u>did not</u> receive the letter**	Ok, the letter we sent stated that you previously volunteered to participate in one of our genetic studies and chose the option to be contacted if your preliminary results suggested the need for confirmatory testing. Dr. [NAME OF THE TREATING NEPHROLOGIST] has been notified by the research team that you have preliminary genetic results, which **may** be important to your health. But the results must first be confirmed in a special CLIA lab before they can be shared with you and with Dr. [NAME OF THE TREATING NEPHROLOGIST], and that requires a repeat blood test for confirmatory testing. Confirmatory testing is voluntary and if you would like to learn more about it, we invite you to come in and meet with [XXX], one of our physicians. She can discuss confirmatory testing with you in more detail. **The visit with her is free**. And if you decide that you would like to do the confirmatory testing when you meet with her, the results take about 6 to 8 weeks to get back. Plus, we offer to pay the cost for the CLIA test for those who agree to take part in our return of results study, which involves completing questionnaires about your opinions on genetic testing.

	Would you like to come in and meet with [XXX]? ➢ ***IF NO, go to STEP 3a*** ➢ ***IF YES, go to STEP 3b***
STEP 2b **Patient states they did receive the letter**	Good. Then as you know, Dr. [NAME OF THE TREATING NEPHROLOGIST] was notified by the research team that you have preliminary genetic results that **may** be important to your health, but the results must be confirmed with a repeat blood sample before they can be shared with you and with Dr. [NAME OF THE TREATING NEPHROLOGIST]. Confirmatory testing is voluntary and if you would like to learn more about it, we invite you to come in and meet with [XXX] one of our physicians. She can discuss confirmatory testing with you in more detail. **The visit with her is free**. And if you decide that you would like to do the confirmatory testing when you meet with her, the results take about 6 to 8 weeks to get back. Plus, we offer to pay the cost for the CLIA test for those who agree to take part in our return of results study, which involves completing questionnaires about your opinions on genetic testing. Would you like to come in and meet with [XXX]? ➢ ***IF NO, go to STEP 3a*** ➢ ***IF YES, go to STEP 3b***
STEP 3: Scheduling a visit for discussion on confirmatory testing	
STEP 3a **IF interrupted or strong immediate refusal**	No problem, but may I ask why not? ➢ Write down response given for why patient is not interested in coming in to meet with [XXX] to discuss the option to undergo confirmatory genetic testing _____ ➢ If no reason is provided, give the following options: ❑ No time ❑ Too stressful ❑ I don't want to learn this information ❑ Other *(please specify)*: _____ Thank you for your time, (Mr./Ms.) PATIENT NAME. Please call us at [TELEPHONE] if you have any questions.
STEP 3b **Schedule confirmatory test visit**	Great. What day would you like to come in? ➢ **Note day and time**:_____ Thank you for your time, (Mr./Ms.) PATIENT NAME. Please call us at [TELEPHONE] if you have any questions. ➢ **End Call**

- ***Record date & time below:***

Thank you very much for your time. ***End call.***

Nephrogenetics Consultation Note Template

Name:
MRN:
Date of Birth:
Date of Encounter:

Referring Nephrologist:
Primary Care Physician:

Reason for Consultation: NAME OF INDEX is a 57-year old female with long standing hematuria, subnephrotic range proteinuria and CKD V presenting today for a return of genetic results visit.

Clinical History:
History of Present illness-
[SUMMARIZED]

In November of 2015, the patient presented to Columbia University for a second opinion as her renal insufficiency progressed. [PROVIDER NAME] suspected the patient had a hereditary glomerulopathy, but the etiology remained unknown. She was managed conservatively with RAAS blockade (lisinopril 40mg po qD) and the slides of her original biopsy were requested for review at Columbia University (see below).

ROS:
+hearing loss

Diagnostic evaluation-
A. Imaging studies: Renal ultrasound from [DATE} reviewed, unremarkable
B. Relevant laboratory studies: [DETAILED]
C. Histopathology:
   Renal biopsy [ACCESSION #] [ORIGINAL DATE]
   Performed at INSTITUTION, re-read at Columbia University by [PATHOLOGIST NAME] on [DATE]
      1. Glomerulosclerosis with diffuse GBM thinning
      2. Tubular atrophy, interstitial fibrosis & interstitial inflammation
      3. Arterio- & arteriolosclerosis
D. Other studies, including prior genetic testing: N/A

Family History:
Father- hearing loss and advanced CKD
The patient reports her father never went on to require RRT and passed away in 2010 at the age of 72 from “heart failure”

Mother- currently alive at age 78, with hypercholesterolemia

Sister- currently alive at age 51, with hearing loss as reported by the index

Brother-currently alive at age 51, with no known medical problems

Social History:

Works as an executive administrator
Has no children
Lives alone
Denies toxic habits

Physical Exam:
BP 139/87 mm Hg (upright)
No dysmorphologies noted on exam

Genetic Workup:
The patient was enrolled in the Genetic Studies of Kidney Disease-a genetic studies and biobanking protocol on [DATE]. On research-grade exome sequencing, she was found to be heterozygous for a variant in the Collagen, Type IV, Alpha-A (*COL4A5*) gene. These findings were confirmed by targeted dideoxy terminator (Sanger) sequencing in a CLIA-certified laboratory in December 2017 (see variant details below).

Genetic Diagnosis:

The patient was found to have a novel missense variant in *COL4A5*:c.3017G>A:p.G1006D. Putative variants in the *COL4A5* gene are associated with X-linked Alport syndrome (OMIM Phenotype MIM #301050). The variant was classified as Likely Pathogenic under current American College of Medical Genetics and Genomics (ACMG) guidelines for clinical sequence interpretation (Richards *et al.,* 2015) based on the following:

The variant occurs at a highly conserved glycine residue in the triple helical domain, a known functional domain of the collagen protein (PM1). It is absent in large control population databases, including gnomAD and DiscoverEHR (PM2), and is a novel missense substitution at the same amino acid residue as previously reported pathogenic variant, p.G1006V. The p.G1006V was found segregating in family (2 generations; 5 members: 2 unaffected, 3 affected) with a milder form of Alport Syndrome: affected members displayed hematuria and hearing loss, and did not report visual impairment (Barker et. al., 2001) (PM5). The variant is a missense variant in a disease where missense mutations are a known mechanism of disease (i.e., Gly-Xaa-Yaa substitutions are a well-established mechanism of COL4A-associated nephropathy) (PP2) and was predicted to be deleterious by multiple *in silico* algorithms, including CADD, Polyphen-2-HumVar, SIFT, and MetaSVM (PP3). Finally, the patient's clinical presentation and family history are highly specific for *COL4A*-associated nephropathy/Alport syndrome (PP4).

The genetic findings detailed above, along with the patient's clinical course and family history, strongly support a genetic diagnosis of X-linked Alport syndrome, a subtype of *COL4A*-associated nephropathy.

Therapeutic Implications:
COL4A-associated nephropathy encompasses a wide spectrum of clinical phenotypes, including isolated FSGS and Alport syndrome (X-linked and autosomal forms) (Stokman *et al.,* 2016). Disease severity similarly varies within Alport spectrum phenotypes, ranging from isolated microscopic hematuria with stable renal function, to early- onset end-stage-renal disease (ESRD) with visual and auditory impairment.

Among individuals with X-linked Alport syndrome, ESRD can occur anytime between the second and sixth decades of life, with varying degrees of hearing loss and ocular changes. As obligate heterozygotes, females generally show a milder disease course than affected males. However, studies to date have demonstrated that over 95% of females develop hematuria, 8-30% develop ESRD, and up to a third (4-40%) having sensorineural hearing loss (Savige *et al.,* 2013; Tan *et al.,* 2010; Dagher *et al.,* 2001; Jais *et al.,* 2003). The type of putative variant may also modulate disease severity. Though loss-of-function variants in *COL4A3/4/5* genes are generally associated with more severe disease compared to missense variants (e.g., later onset of ESRD, less frequent and less severe audiologic and ocular involvement) (Bekheirnia *et al.,* 2010; Savige *et al.,* 2016), interruptions of the glycine helix, such as in the case of the patient's genetic findings, are also disruptive, which is consistent with the patient's advanced CKD and subjective hearing loss.

Given the patient's progressive decline in renal function, we recommend that she undergo evaluation for renal allograft transplantation. Determination of inheritance information is important in this patient who is considering living-related donors, potentially from her sister (first choice) and her brother (second choice). We therefore recommend additional genetic screening of her mother and siblings (father is deceased) to confirm the inheritance of the *COL4A5* variant and have referred the patient for additional genetic counseling.

Finally, we recommend that the patient undergo formal ophthalmologic evaluation, informing the ophthalmologist that she has Alport syndrome. We also recommend formal audiologic evaluation given her reported subjective hearing loss. The patient will be referred to [PROVIDER NAME] in the Department of Ophthalmology's Genetic Eye Clinic and to [PROVIDER NAME], an otolaryngologist with expertise in Alport syndrome.

Family Counseling:
The patient has no children. However, as we explained to her, we suspect she has a X-linked disease, meaning that this variant was transmitted to her by her father. In X-linked disorders, all female offspring of affected males are obligate carriers. We recommend that the patient's sister, undergo thorough evaluation with a nephrologist, as well as genetic testing; if the sister is found to have the same *COL4A5* variant, we also recommend she undergo formal ophthalmologic and audiologic evaluations.

As a reportedly healthy middle-aged adult male, the patient's brother, is unlikely to have the same putative variant. Nevertheless, we recommend he also undergo a comprehensive evaluation with a nephrologist, as he is a possible renal donor.

Incidental Findings: Not applicable

Continuous review: Not applicable

Variant Details: Gene: *COL4A5* (OMIM Gene # 303630)
RefSeq Transcript: NM_000495 (Build: GRCh37/hg19) Exon: 35
gDNA change: chr.X:g.107868935G>A
cDNA change: c.3017G>A
Peptide change: p.G1006D
Zygosity: Heterozygous
Disease Association: X-linked Alport Syndrome (OMIM Phenotype MIM # 301050)

Summary:

This is a 57yo F with long standing hematuria, subnephrotic range proteinuria and glomerulosclerosis with GBM thinning noted on renal biopsy. She reports longstanding subjective hearing loss and has a family history of renal disease and hearing loss (father). On clinical-grade targeted testing, the patient was found to have a LP variant in the *COL4A5* gene, deemed diagnostic for X-Linked Alport syndrome in a female. Given her advanced CKD, the patient should be evaluated for transplantation, and that her sister undergoes genetic screening as part of their donor evaluations.

Physician To-Do List:

1. Referred for transplant evaluation
2. Referred to [PROVIDER NAME] for genetic counseling and cascade screening
3. Referred to [PROVIDER NAME] in the Department of Ophthalmology
4. Referred to [PROVIDER NAME] in the Department of Otolaryngology

Family Letter Template

To Whom It May Concern:

The purpose of this letter is to inform you that an inherited genetic condition was identified in a member of your family. We recommend showing this letter to your primary care provider.
A genetic risk factor for <Disease Name> was identified in a member of your family. Any blood-related family member (parents, siblings, aunts, uncles, cousins, grandparents) may have the same genetic risk factor.

Here is the technical information about the genetic risk factor identified in your family member:

Disease	Inheritance	Gene	Position[a]	Variant	Zygosity	Notes	Interpretation
<Disease Name>		<Gene Name>					

[a]NCBI ____

Here are some common questions to help you to better understand:

1. What effect does this genetic risk factor have?

This genetic risk increases individuals' chance to develop <Disease Specific Risks>.
Not all individuals with this risk factor will develop the condition. You and your family member may or may not have already developed this disease.

2. How likely am I to have the genetic risk factor?

This genetic risk factor is transmitted from parents to children. Children and siblings of people with this genetic risk factor have a chance to also have it. If a person does not have the genetic risk factor, then they cannot pass it on to their children. Based on our discussion with your family member, you may have inherited this genetic risk factor.

3. What will happen if I have the genetic risk factor?

The genetic testing is able to identify if you have a specific genetic change that puts you at risk of developing the disease. However, this test cannot predict if you will develop the disease or exactly when. If you have this genetic risk factor, <Disease Specific Screenings> is recommended to enable early detection and treatment.

4. What action should I take?

We suggest you to have a genetic counselor evaluation to discuss about being tested for this genetic risk factor and/or to receive information for specific health screening. **Genetic testing is the only way to know if you have the genetic risk factor.** As the symptoms vary and can appear late in life, you may have a chance to develop <Disease Name> even if you do not think you have it. Your primary care provider can refer you to genetic counseling. Alternatively, you can find a genetic counselor through this website: www.findageneticcounselor.com

Finally, if you have additional questions, need assistance finding a genetic counselor, or are interested in learning more about our genetic research studies, please feel free to contact us at [TELEPHONE NUMBER; EMAIL ADDRESS].

Sincerely,

Dr. [PROVIDER]

Estimation of cost for Development and Implementation of Return of Results Workflow

To evaluate the fixed study startup cost of this pilot study, we calculated direct labor costs, converted into an annual full-time equivalent (FTE) based on individual compensation levels of the different study team members, in addition to the other direct and indirect costs involved in developing and implementing the Return of Results Workflow over 31 months.

The study team was made up of eight individuals with different skill sets. They included four faculty members (3 nephrologists and 1 molecular pathologist), two research scientists, one research staff member (a trained clinical nephrologist who holds a position as "Project Coordinator Level II") and one research trainee (the Precision Nephrology fellow, an ABIM board-certified nephrologist) sponsored by institutional research training awards.

DIRECT COSTS

1. **Labor:**

Estimates of productivity (in hours)

Labor costs were based on retrospective estimates of hours dedicated by each study member in the completion of specific tasks associated with developing the Return of Results Workflow (in study year 1 (2017): Y1) and then implementing it (in study years 2 (2018) and 3 (2019): Y2 and Y3). Each study member was asked to provide a conservative approximation of hours (productivity) they dedicated to specific tasks, per calendar year (12 months). Tasks associated with this pilot study included:

A. Development of the Return of Results Workflow (Y1) -
Drafting and submitting the study amendments to the IRB, verifying that primary diagnostic findings were indeed explicative of the patient's kidney disease and confirming the pathogenicity of the actionable secondary findings identified through our variant annotation pipeline, conducting in-depth review of each participants' EHRs, defining the individual steps of the workflow in collaboration with clinicians, and developing communication and data management tools.
-When available, hour estimates were cross-referenced with user logs (i.e., RedCap's user activity monitoring).

B. Implementation of the Return of Results Workflow (Y2, Y3) -
Re-contacting attempts for participants (e.g., drafting letters, obtaining signatures from faculty members, labeling and mailing letters, calling study participants, coordinating in-person visits for clinical re-testing and/or Return of Results visits, etc.), counseling and evaluating patients during up to two visits, processing specimens for clinical re-testing, reviewing the literature of the identified genetic syndromes to provide clinicians with up-to-date management recommendations based on published evidence and consensus guidelines, drafting detailed consultation notes for providers, discussing cases with the

referring nephrologists at different steps of the workflow (e.g., during case-level interpretation of candidate variants at “genetic sign out rounds”, at one-on-one meetings when implementing the genetic findings into clinical care, at monthly educational conferences intended to support nephrologists’ education, etc.), and coordinating subsequent patients’ follow-up care (e.g., arranging follow-up visits, referrals, familial testing, additional genetic counseling, entering data into the EHR, etc.).
-Of note, for certain tasks (e.g., meeting patients for pre-test counseling, clinical consultation and post-test counseling, note writing) time logs were used prospectively, and the minimum and maximum time spent on those specific tasks, averaged.

The hours provided by each study team member, performing each task, were then totaled and categorized by the individual’s compensation levels (e.g., faculty compared to research scientists/research staff compared to the research trainee). For example, if one faculty member spent 17 hours on one task, and the other three faculty members each spent an hour on the same task, the total hours dedicated to that specific task was 20 hours.

Annual Compensation

Then, annual compensations (i.e., salary or training awards) were estimated for each member of the study teams. For faculty, a National Institute of Health (NIH) salary cap of $187,000 (for fiscal years 2017 and 2018) was used as a conservative estimate for the faculty members. In addition, Columbia University’s average annual salary for both research scientists, and research staff member who holds the position of “Project Coordinator, Level II” was $60,000 during the same fiscal years.

The research trainee held a non-salary position. Thus, the direct costs per year for this study team member was based on the specific institutional research training awards the Precision Nephrology fellow received during those same years. Specifically, during Y1, the research trainee was supported by the Division’s T32 award, and the direct costs were $64,228/year, which included a stipend ($54,228), training related expenses (TRE) ($4500), tuition fees ($4,500), and a travel budget ($1000). In Y2 and Y3, the research trainee was supported by Columbia University’s Clinical & Translational Science Awards (CTSA) program TL1 award, and the direct costs were $68,378/year, which included a stipend ($57,528), TRE ($5350), tuition fees ($4,500), and a travel budget ($1000).

Fringe Expenses

Using Columbia University’s fringe rate of 30.3% (for 2017 through 2019 fiscal years), we added the fringe expense based on the direct salary of the faculty, research scientists and research staff members. The fringe expense was not added to the direct labor costs of the research trainee.

Available Hours and Full-Time Equivalent (FTE)

Available hours were calculated based on institutional policies. For faculty and for the research trainee, the estimated time available for productive work was assumed to be 2000 hours/year, based on 40 hours/week for 50 weeks/year, considering holidays, vacation and sick time. For the research scientists and the research staff member, available hours were estimated to be 1750 hours/year, based on 35 hours/week, for 50 weeks/year.

Finally, FTEs were calculated based on total hours dedicated to each task, divided by the available hours of each team member category (e.g., 2000 hours/year for the faculty and the research trainee versus 1750 hours/year for the research scientists and the research staff member). Direct labor costs were then calculated based on the FTE, at each level of compensation (i.e., faculty versus research scientists/research staff versus research trainee).

2. **Sequencing Costs**:

Other direct costs included the cost of targeted dideoxy terminator (Sanger) sequencing (rate based on the number of variants requiring clinical conformation), and shipment costs, for 30 samples that went to the NYGC for clinical re-testing. An additional 11 samples were sent to Columbia University's Personalized Genomics Laboratory for confirmatory Sanger sequencing (no associated shipment costs). The sequencing cost for the 7 study participants dual enrolled in the eMERGE study, was covered by the eMERGE Network. Since these patients were part of a large multicenter study, the individual sequencing costs for these 7 participants is not yet available, and therefore, was not included in this analysis.

Of note, the cost of research-grade exome sequencing was $350 per exome, and was conducted by Columbia University's Institute of Genomic Medicine. However, these costs were incurred prior to this pilot study, and thus, are also not included in this analysis.

INDIRECT COSTS

Additional overhead expenses were also included in our calculations. Based on institutional policies, 60% indirect (overhead) costs (for fiscal years 2017 through 2019) was added to the salary with fringe for salaried study team members (e.g., faculty, research scientists and research staff members). This expense was not added for the research trainee. Instead, per NIH policy, Facilities and Administrative (F&A) costs of 8% were added to the Precision Nephrology fellow's direct trainee costs.

The fixed startup costs were then calculated for each year of the study.

Section S2- SUPPLEMENTARY RESULTS

This is an ongoing sequencing study. To date, we identified 213 individuals with medically relevant findings, 205 (96%) of whom were included in earlier publications[1, 2], while the remaining 8 participants were sequenced in the intervening periods.

Reasons for participant ineligibility through the pilot workflow

Reasons for ineligibility for recontact through this pilot workflow included the following: Pediatric (age < 18 years) participants will have results returned through a separate pediatrics workflow (*n* = 22); participants who did not opt to re-contact during time of original consent (*n* = 5); and participants enrolled prior to January 2015 who have not as of yet re-consented to the study with the revised consent form (*n* = 73). Of note, study participants consented prior to the protocol update are routinely notified of the new consent clause, and invited to re-consent with the new Return of Results option clause, when they present to nephrology follow-up appointments. Participants that are not reached in follow-up visits will be notified of the updated consent clause by mail correspondence and invited to update their preference on re-contact. Also, a Pediatric Return of Results Workflow is being developed for the re-contact of all pediatric cases.

Of the remaining 113 adult participants, 9 additional participants were excluded after review of the EHR revealed these individuals had undergone clinical genetic testing, outside of the nephrology Return of Results Workflow, since the time of original enrollment. Interestingly, these 9 individuals had medically actionable secondary findings in genes included in the ACMG 59 list. Moreover, 6 of these 9 participants were dually recruited in the eMERGE Network's Phase III study and therefore, also underwent clinical-grade sequencing using the NGS panel. As part of the eMERGE study, these 6 participants were notified of the positive findings by letter and invited to schedule a visit for post-test counseling with a genetic counselor, with field expertise in hereditary cardiovascular or cancer syndromes. Of note, eMERGE-participants with diagnostic (primary) findings explicative of their nephropathy, we included in this Return of Results Workflow.

Importantly, for all 9 cases, clinical testing identified the same genetic finding detected in our study. These cases are described in further detail in **Table S3**. For all 9 individuals', their referring nephrologist was informed that research-grade ES identified the same genetic finding as the variant(s) identified by clinical genetic testing, so that they may inform the patient. Our pilot cohort was made up of the remaining 104 eligible individuals (**Table 1**; **Table S1**).

Table S1: Clinical phenotype and genetic spectrum of the 104 pilot study participants

Clinical diagnosis				
CONGENITAL OR CYSTIC KIDNEY DISEASE (*n* = 9)				
Gene	**OMIM Gene MIM #**	**Genetic Diagnosis**	**OMIM Phenotype MIM #**	**Participant Count**
EYA1	601653	Branchiootorenal syndrome 1 with or without cataracts	113650	2
PAX2	167409	Glomerulosclerosis focal segmental 7; Papillorenal syndrome	616002; 120330	1
PKD1	601313	Polycystic kidney disease 1	173900	2
UMOD	191845	Autosomal dominant tubulointerstitial kidney disease, *UMOD*-associated	609886;162000; 603860	1
HNF1B	189907	Renal cysts and diabetes syndrome	137920	1
TSC1	605284	Tuberous sclerosis-1	191100	1
PKHD1	606702	Polycystic kidney disease, autosomal recessive	263200	1
GLOMERULOPATHY (*n* = 54)				
Gene	**OMIM Gene MIM #**	**Genetic Diagnosis**	**OMIM Phenotype MIM #**	**Count**
CRB2	609720	Focal segmental glomerulosclerosis 9	616220	2
COL4A3	120070	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780; 141200	8
COL4A4	120131	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780; 141200	12
COL4A5	303630	Alport syndrome, X-linked	301050	15
INF2	610982	Glomerulosclerosis focal segmental 5	613237	1
NPHS1	607100	Nephrotic syndrome type 1	256300	1
NPHS2	600995	Nephrotic syndrome type 2	600995	1

TRPC6	603652	Glomerulosclerosis focal segmental 2	603965	5
WT1	607102	Nephrotic syndrome type 4	256370	1
SALL1	602218	Townes-Brocks syndrome 1	107480	1
CREBBP	600140	Rubinstein-Taybi syndrome 1	180849	1
DSP	125647	Arrhythmogenic right ventricular dysplasia 8	604400	1
SCN5A	600163	Brugada syndrome 1; Long QT syndrome 3	601144; 603830	1
PMS2	600259	Colorectal cancer hereditary nonpolyposis type 4	614337	1
BRCA2	600185	Breast-ovarian cancer, familial 2	612555	3
DIABETIC NEPHROPATHY (*n* = 3)				
Gene	**OMIM Gene MIM #**	**Genetic Diagnosis**	**OMIM Phenotype MIM #**	**Count**
HNF1A	142410	MODY type III	600496	2
MYCN	164840	Feingold syndrome 1	164280	1
TUBULOINTERSTITIAL DISEASE (*n* = 11)				
Gene	**OMIM Gene MIM #**	**Genetic Diagnosis**	**OMIM Phenotype MIM #**	**Count**
ATP6V1B1	192132	Renal tubular acidosis with deafness	267300	1
CLCN5	300008	Dent disease	300009	1
SLC12A3	600968	Gitelman syndrome	263800	2
SLC4A1	109270	Renal tubular acidosis distal, autosomal dominant	179800	1
SLC5A2	182381	Renal glucosuria	233100	1
UMOD	191845	Autosomal dominant tubulointerstitial kidney disease, *UMOD*-associated	609886;162000; 603860	4
HNF1B	189907	Renal cysts and diabetes syndrome	137920	1
NEPHROPATHY OF UNKNOWN ORIGIN (*n* = 26)				
Gene	**OMIM Gene MIM #**	**Genetic Diagnosis**	**OMIM Phenotype MIM #**	**Count**
APOE	107741	Lipoprotein glomerulopathy	611771	1

CLCN5	300008	Dent disease	300009	3
COL4A3	120070	Alport syndrome, autosomal dominant/recessive; Thin basement membrane disease	203780; 141200	1
COL4A5	303630	Alport syndrome, X-linked	301050	2
HBB	141900	Sickle cell disease	603903	1
MC4R	155541	Obesity autosomal dominant	601665	1
MYH9	160775	Epstein syndrome; Fechtner syndrome	153650; 153640	1
NPHS2	600995	Nephrotic syndrome type 2	600995	1
PKD1	601313	Polycystic kidney disease 1	173900	1
PAX2	167409	Glomerulosclerosis focal segmental 7; Papillorenal syndrome	616002; 120330	2
UMOD	191845	Autosomal dominant tubulointerstitial kidney disease, *UMOD*-associated	609886;162000; 603860	1
NPHP4	607215	Nephronophthisis 4	606966	2
COL4A5	303630	Alport syndrome, X-linked	301050	1*
NPHP3	607215	Nephronophthisis 3	604387	
HNF1A	142410	MODY type III	600496	1
HNF4A	600281	MODY type 1	125850	1
TRPC6	603652	Glomerulosclerosis focal segmental 2	603965	1
PTPN11	176876	Noonan syndrome 1	163950	1
PKHD1	606702	Polycystic kidney disease, autosomal recessive	263200	2
PKP2	602861	Arrhythmogenic right ventricular dysplasia 9	609040	1
BRCA2	600185	Breast-ovarian cancer, familial 2	612555	1
Other (*n* = 1)				
Gene	**OMIM Gene MIM #**	**Genetic Diagnosis**	**OMIM Phenotype MIM #**	**Count**
GLA	300644	Fabry disease	301500	1

*Patient with a dual molecular diagnoses

Eight participants had known pathogenic variants in genes included in the ACMG 59 as medically actionable secondary findings: *DSP* (*n* = 1), *SCN5A* (*n* = 1), *PKP2* (*n* = 1), *PMS2* (*n* = 1), and in *BRCA2* (*n* = 4). Ninety-six participants had primary diagnostic findings encompassing 34 genes, including one participant with dual molecular diagnoses (Alport syndrome, X-linked and Nephronophthisis 3).

Note: The clinical diagnoses are displayed by rows. The eight participants with actionable findings in the ACMG 59 genes are highlighted in grey.

Description of case where the research-level genetic finding was not confirmed on clinical re-testing

In one case of a female with a heterozygous deletion of exon 37 in *COL4A5*, the results were not confirmed due to a technical limitation of the confirmatory test modality used (i.e., limited analytical sensitivity for detection of copy number variations with Sanger sequencing). Due to the high suspicion that the research finding was causal, this patient was referred for genetic counseling to discuss the options for further clinical-grade genetic testing using a commercial panel with robust coverage of the relevant gene, which included deletion/duplication analysis of *COL4A5*. Ultimately, the patient chose to defer this option citing a lack of interest.

Reasons for participants' refusal to return for Return of Results

Six individuals failed to return for their results. One participant failed to show up to a scheduled appointment ("No Show") and could not be subsequently reached by telephone or email to re-schedule. Another individual did not want to schedule a return of results visit despite multiple attempts, twice citing a lack of time. The remaining four participants cited they were not interested in returning because they already knew their clinical diagnosis: One participant, diagnosed with FSGS, revealed they had previously undergone clinical-grade genetic testing through a different academic institution, and knew of the genetic finding in the *TRPC6* gene, which was not documented in our hospital's electronic health record; when asked, they stated they withheld this information because they wanted to "see if you would find the same variant". Two individuals, both clinically diagnosed with Autosomal dominant Polycystic kidney disease (ADPKD), declined to comment regarding whether they too underwent clinical genetic testing. One participant with a diagnostic finding in *UMOD* also stated he knew his diagnosis clinically.

For all 6 participants, the CLIA-confirmed findings were shared with their referring provider and entered into the electronic health record, either following the post-test counseling visit or if they declined to return.

Table S2: Fixed start-up costs for the development and implementation of the Return of Results Workflow in this pilot study

In total, eight study team members worked approximately 1452 total hours to develop and implement the Return of Results Workflow for nephrology, over 31 months. The total fixed start-up cost for this pilot study was estimated to be $92,249.31. This includes $80,160.61 of total labor costs (direct + indirect).

In Y1, approximately 406 hours were devoted to tasks relating to development of the workflow. Of the 406 hours, 44% (approximately 180 hours) was dedicated to genetic data analysis, which included variant-level and case-level review, while 23% (approximately 92 hours) was spent on the development of the communication tools (See Re-contact Letter, Re-contact Telephone Script, Nephrogenetics Consultation Note Template and Family Letter Template in Section S1). The total cost of Y1 was $30,675.51.

During Y2 and Y3, approximately 1046 hours were devoted to the implementation of the workflow. Of the 1046 hours, 650 hours (62%) was dedicated to clinical application of the genetic findings (e.g., clinical evaluation with post-test counseling, literature review, coordinating follow-up care, meeting with faculty to discuss the genetic findings, etc.) for this pilot cohort. In addition, the cost of clinical genetic testing at the NYGC ranged from $250 to $450, depending on the number of variants validated. The cost of clinical re-testing for 30 participants through the NYGC was $8,238.70 ($7900 for clinical sequencing of 34 variants in 30 participants; $338.70 for sample shipping). The cost of clinical genetic testing at Columbia University's Personalized Genomics Laboratory was $350 for Sanger confirmation of a single variant. The cost of clinical re-testing for 11 participants (11 variants) through the Personalized Genomics Laboratory was $3,850 (no sample shipment required). Therefore, the total cost of clinical grade confirmatory sequencing for the 41 participants that only underwent research-grade ES was $12,088.70. The total estimated cost for Y2 and Y3 was $61,573.80. (**Table S2**).

Note: Forty-one participants had only research-grade sequencing and required clinical re-testing that was done at a CLIA-certified laboratory (the New York Genome Center or Columbia University's Personalized Genomics Laboratory)

Description	Time (hours)	Full Time Equivalents (FTE)			Total FTE	Total costs*
		Faculty (*n* = 4)	Research Scientists (*n* = 2)/ Research Staff (*n* = 1)	Precision Nephrology Fellow (*n* = 1)		
IRB Approval/ Amendments	74	0	0.01	0.03	0.04	$3,943.45
Development of communication tools	92	0.01	0.01	0.03	0.05	$5,849.71
Variant-level review	70	0.03	0.01	0	0.04	$12,410.52
Training tools development	20	0	0.01	0	0.01	$1,429.58
Recruitment personnel training	40	0	0.02	0	0.02	$2,859.15
Clinical (Case-level) review	110	0	0.01	0.05	0.06	$4,183.10
Return of Results Development Total in Y1	**406**	**0.04**	**0.07**	**0.11**	**0.21**	**$30,675.51**
RedCap design and production	100	0	0.01	0.05	0.05	$4,037.96
Participant re-contact	100	0	0.01	0.05	0.05	$4,383.51
Pre-test counseling	41	0	0.01	0.02	0.02	$1,859.44
Clinical re-testing	20	0	0	0.01	0.01	$738.48
Return of results	90	0.02	0	0.03	0.05	$9,643.36
Clinical application of findings	650	0.01	0	0.33	0.33	$27,160.77
Data entry/cleaning	45	0	0	0.02	0.02	$1,661.59
Additional Direct Costs	-	-	-	-	-	-
CLIA-sequencing	N/A	N/A	N/A	N/A	N/A	$11,750.00
Specimen shipment	N/A	N/A	N/A	N/A	N/A	$338.70
Return of Results Implementation Total in Y2 and Y3	**1046**	**0.03**	**0.02**	**0.47**	**0.53**	**$61,573.80**
Total	**1452**	**0.07**	**0.09**	**0.58**	**0.74**	**$92,249.31**

*Total costs include direct labor costs (Salary with Fringe (30.3%) and indirect costs (60% overhead) for faculty, research scientists and research staff; the research trainee's direct trainee costs along with indirect costs (8% Facilities and Administrative costs)

Table S3: Faculty (Salary)-
Hours, FTE and Direct Costs with Fringe + Indirect Costs

Description	Faculty					
	Hours	FTE	Salary	Fringe expense	Indirect costs*	Total labor costs**
			$187,000	30.3%	60%	
IRB Approval/ Amendments	4	0.00	$374.00	$113.32	$292.39	$779.72
Development of communication tools	12	0.01	$1,122.00	$339.97	$877.18	$2,339.15
Variant-level review	60	0.03	$5,610.00	$1,699.83	$4,385.90	$11,695.73
Training tool development	0	-	-	-	-	-
Recruitment personnel training	0	-	-	-	-	-
Clinical case review	0	-	-	-	-	-
RedCap design and production	0	-	-	-	-	-
Participant re-contact	0	-	-	-	-	-
Pre-test counseling	0	-	-	-	-	-
Clinical re-testing	0	-	-	-	-	-
Return of results	40	0.02	$3,740.00	$1,133.22	$2,923.93	$7,797.15
Clinical application of findings	20	0.01	$1,870.00	$566.61	$1,461.97	$3,898.58
Data entry/cleaning	0	-	-	-	-	-
TOTAL Y1 & Y2 & Y3	**136**	**0.07**	$12,716.00	$3,852.95	$9,941.37	$26,510.32

*Indirect costs: 60% overhead costs
**Total labor costs: direct (salary with fringe) and indirect costs

Table S4: Research Scientists/Research Staff (Salary)- Hours, FTE and Direct Costs with Fringe + Indirect Costs

Description	Research Scientists/Project Coordinator (Level II)					
	Hours	FTE	Salary	Fringe expense	Indirect costs*	Total labor costs**
			$60,000	30.3%	60%	
IRB Approval/Amendments	20	0.01	$685.71	$207.77	$536.09	$1,429.58
Development of communication tools	20	0.01	$685.71	$207.77	$536.09	$1,429.58
Variant-level review	10	0.01	$342.86	$103.89	$268.05	$714.79
Training tools development	20	0.01	$685.71	$207.77	$536.09	$1,429.58
Recruitment personnel training	40	0.02	$1,371.43	$415.54	$1,072.18	$2,859.15
Clinical case review	10	0.01	$342.86	$103.89	$268.05	$714.79
RedCap design and production	10	0.01	$342.86	$103.89	$268.05	$714.79
Participant re-contact	20	0.01	$685.71	$207.77	$536.09	$1,429.58
Pre-test counseling	10	0.01	$342.86	$103.89	$268.05	$714.79
Clinical re-testing	0	-	-	-	-	-
Return of results	0	-	-	-	-	-
Clinical application of findings	0	-	-	-	-	-
Data entry/cleaning	0	-	-	-	-	-
TOTAL Y1 & Y2 & Y3	**160**	**0.09**	**$5,485.71**	**$1,662.17**	**$4,288.73**	**$11,436.62**

*Indirect costs: 60% overhead costs
**Total labor costs: direct (salary with fringe) and indirect costs

Table S5: Research trainee (Precision Nephrology Fellow)- Hours, FTE and Direct Trainee costs + Indirect Costs

Description	Research trainee (Precision Nephrology fellow)					
	Hours	FTE	Direct Trainee costs	Fringe expense	Indirect costs*	Total labor costs**
			Y1: $64,228 Y2: $68,378 Y3: $68,378	**N/A**	**8%**	
IRB Approval/Amendments	50	0.03	$685.71	-	$128.46	$1,734.16
Development of communication tools	60	0.03	$685.71	-	$154.15	$2,080.99
Variant-level review	0	-	$342.86	-	-	-
Training tools development	0	-	$685.71	-	-	-
Recruitment personnel training	0	-	$1,371.43	-	-	-
Clinical case review	100	0.05	$3,211.40	-	$256.91	$3,468.31
RedCap design and production	90	0.05	$3,077.01	-	$246.16	$3,323.17
Participant re-contact	80	0.04	$2,735.12	-	$218.81	$2,953.93
Pre-test counseling	31	0.02	$1,059.86	-	$84.79	$1,144.65
Clinical re-testing	20	0.01	$683.78	-	$54.70	$738.48
Return of results	50	0.03	$1,709.45	-	$136.76	$1,846.21
Clinical application of findings	630	0.32	$21,539.07	-	$1,723.13	$23,262.20
Data entry/cleaning	45	0.02	$1,538.51	-	$123.08	$1,661.59
TOTAL Y1 & Y2 & Y3	**1,156**	**0.58**	**$ 39,086.73**	**-**	**$3,126.94**	**$42,213.67**

*Indirect costs: 8% F&A costs
**Total labor costs: direct and indirect costs

Table S6: Examples of the clinical utility of ACMG 59 genes in participants who underwent clinical genetic testing and had their genetic results returned outside of the Return of Results Workflow

Below are 9 participants, excluded in the pilot cohort, who had known pathogenic variants in the 59 genes recommended by the ACMG for return as medically actionable secondary findings for individuals undergoing genome-wide sequencing[10]. These patients underwent clinical genetic testing and were found to have the same genetic findings as the one we detected on research-grade ES. There clinically confirmed results were returned outside of this workflow. To further assess the opportunities and challenges of assessing genetic results, including the capacity of genome-wide sequencing to detect variants diagnostic for otherwise medically actionable conditions not directly explicative for patients' nephropathy, we conducted a broader survey of cases who had participated in our genetic study. Therefore, to determine the clinical implications of the genetic diagnoses on nephrology care in these 9 cases, we assessed: 1) the extent of the known phenotypic concordance (the column, "Known Clinical Features Consistent with the ACMG 59 Gene Disorder"); 2) the greater implications of these genetic findings to their care, such as surveillance and/or management strategies available based on the findings (column titled "Clinical Implications"); and 3) the potential implications of the findings to nephrologic care (in the column, "Potential Implications for Nephrologic care") based on review of the literature of management recommendations, detailed in **Table S6.**

Age range (years)	Clinical Diagnosis	Gene/ Genetic Diagnosis (OMIM Phenotype MIM #)	Known Clinical Features Consistent with the ACMG 59 Gene Disorder	Clinical Implications	Potential Implications to Nephrology Care
≥ 50	Glomerulopathy	*BRCA2*/ Breast-ovarian cancer, familial, 2 (612555)	Prostate Cancer	Poly (ADP ribosome) polymerase (PARP) inhibitor olaparib and platinum-based chemotherapy[14] for metastatic castration-resistant prostate cancer	Management of immunosuppression dosing for primary glomerular disease or for transplantation
22-49	Nephropathy of unknown etiology	*BRCA2*/ Breast-ovarian cancer, familial, 2 (612555)	Kidney failure s/p DDRT with a history of VTE	Initiation of cancer surveillance[15], annual breast exams in male carriers[16]	
≥ 50	Nephropathy of unknown etiology	*TP53*/ Li-Fraumeni syndrome (151623)	DCIS s/p lumpectomy; family history of cancer (brother diagnosed with leukemia)	Tamoxifen or raloxifene therapy, Bilateral mastectomy and prophylactic bilateral oophorectomy[17]	
≥ 50	Other (Nephrolithiasis)	*MSH2*/ Colorectal cancer hereditary nonpolyposis type 1 (120435)	Colon cancer s/p colectomy, family history of uterine and breast	Transvaginal ultrasound with endometrial biopsy,	

			cancer (mother)	prophylactic hysterectomy and salpingo-oophorectomy, maintenance of aspirin therapy[18-21]	
≥ 50	Nephropathy of unknown etiology	*PKP2*/ Arrhythmogenic right ventricular dysplasia 9 (609040)	HTN, severe aortic valve disease s/p AVR, and stage V CKD	Increased clinical screening[22], Anti-arrhythmic therapy[23] and AICD placement for primary or secondary prevention[24, 25]	
≥ 50	Nephropathy of unknown etiology	*PKP2*/ Arrhythmogenic right ventricular dysplasia 9 (609040)	Kidney failure s/p DDRT		
≥ 50	Glomerulopathy	*KCNQ1*/ Long QT syndrome 1 (192500)	CAD s/p angioplasty, CABG, and AVR; family history of CAD (sister)	Anti-arrhythmic therapy with beta blockade[26-28] and AICD placement for primary or secondary prevention[25, 26], avoid drugs known to prolong the QT interval, cause torsade de pointes or deplete potassium or magneseium[26, 27, 29]	Diuretic and dialysis prescription adjustment to avoid electrolyte disturbance and optimize electrolyte and volume management

≥ 50	Glomerulopathy	*MYBPC3*/ Cardiomyopathy hypertrophic 4 (115197)	Severe Left Ventricular Hypertrophy; family history of HTN and CVA (father)	Serial electrocardiograms, transthoracic echocardiograms and an initial ambulatory (Holter) electrocardiographic monitoring[30, 31], avoidance of high dose diuretics, venodilators, and arterial vasodilators that can exacerbate degree of ventricular obstruction[30]	
22-49	Glomerulopathy	*LDLR*/ Familial hypercholesterolemia (143890)	CAD, portal hypertension requiring portocaval shunt at age 7, aortic stenosis, hypothyroidism and DM, kidney failure s/p dual DDRT and liver transplant	LDL goal < 70 with high intensity statins +/- ezetimibe[32]	Statin use in kidney failure patients*, and consideration for maximally-tolerated statin dosing

CKD: Chronic Kidney Disease; HTN: Hypertension; VTE: Venous thromboembolism; s/p: status-post; AVR: Aortic valve replacement; AICD: Automatic implantable cardioverter-defibrillator; DDRT: Deceased donor kidney transplant; CAD: Coronary artery disease; CABG: Coronary artery bypass grafting; CVA: Cerebrovascular accident; DM: diabetes mellitus; LDL: Low-density lipoprotein

*Use of statin therapy for cardioprotection in CKD and kidney failure populations has been studied in three prospective studies: 4D Study (diabetes mellitus and Kidney failure)[33]; AURORA Study (Kidney failure)[34]; SHARP Study (CKD, Kidney failure)[35]. Based on these findings, and various post-hoc analyses, the 2013 Kidney Disease: Improving Global Outcomes (KDIGO)[36] guidelines did not recommend initiation of statin treatment in dialysis patients, but agreed with continuing statin therapy if patients already on statins. In 2015, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) working group convened and issued a commentary in agreement with that position[37]. The 2018 American College of Cardiology and American Heart Association Task Force issued Clinical Practice Guidelines for Cholesterol management[32] also agreed with this recommendation. However, these guidelines also identified CKD (eGFR 15-59 mL/min/1.73m$_2$) and Heterozygous Familial Hypercholesterolemia as high-risk conditions. Therefore, identifying CKD and kidney failure patients with Familial Hypercholesterolemia is a priority, and further study is needed to determine if treatment escalation with higher doses of statin and use of adjuvant therapies (e.g., ezetimibe, PCSK9 Inhibitors, etc.) for lower LDL-level targets reduce atherosclerotic cardiovascular disease events.

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