Clinical Genetic Testing in Nephrology: Core Curriculum 2024

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Implementation of clinical genetic testing into the routine diagnostic workup of patients with kidney disorders can improve care when employed with proper patient selection. Due to advances in technology, testing with curated gene panels associated with kidney diseases are commercially available, are relatively inexpensive, and have quick turnaround time. While this may reduce barrier to entry, their adoption into routine nephrology care may be hindered when practitioners do not have comfort and experience ordering or interpreting these tests. Identifying patients who may have a monogenic etiology of their kidney disease will increase the diagnostic yield of testing, avoid unnecessary use of resources, and reduce anxiety around unclear or secondary findings. Genetic testing can end one's diagnostic odyssey and help identify other family members at risk. Additionally, obtaining a genetic result can aid diagnostic precision, enhance understanding of disease, and may allow for alterations in treatment plans and screening for extrarenal manifestations of disease as well as clarify prognosis and aid in family planning. In this Core Curriculum, using a case-based approach, we highlight these and other topics in clinical genetic testing to enhance utilization in the general nephrology patient population.

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The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

Chronic kidney disease (CKD) can be attributed to multiple environmental and medical risk factors, and the heritability of kidney disease has been well observed. About 25% of patients with CKD/end-stage kidney disease (ESKD) are found to have a positive family history. Although some of this relationship is due to shared societal or environmental factors, between 10% and 65% of patients with a family history of kidney disease will have a monogenic etiology identified based on the characteristics of the cohort interrogated. More stringent selection criteria for genetic testing will result in a higher positive (or solve) rate. Recent investigations implementing genetic testing in a general CKD cohort in both academic and community settings have demonstrated a diagnostic yield of 9%-20% in adults. These data suggest that patients with genetic kidney disease are likely underrecognized.

Utilization of genetic testing in the routine care of patients with CKD has many potential benefits and challenges. A recent position statement by KDIGO recommended that genetic testing be implemented in the routine workup of CKD and urged clinicians to "think genetic." KDIGO identified many areas for improvement, including defining CKD of unknown etiology, identifying specific patient populations who would most benefit from testing, and standardizing kidney disease–associated genes interrogated during testing and the terminology for genetic kidney diseases.

Sequencing of the first human genome was a multinational effort that cost over half a billion dollars and spanned over a decade. Due to advances in technology, a human genome can now be sequenced rapidly and relatively inexpensively. Improvements in low-cost, massively parallel, high-throughput sequencing have allowed the implementation of genetic testing in routine clinical care. Over 600 genes have been implicated in monogenic kidney disease. There are now many commercial services available that test for hundreds of monogenic kidney diseases for less than $500 out-of-pocket cost if not covered by insurance. Because this cost may still be out of reach for patients, some companies in addition offer no-cost or highly subsidized testing. Testing usually includes genetic counseling as part of the service, allowing for use of genetic testing outside of major medical centers. However, despite the potential benefits of genetic tests many nephrologists may not feel comfortable with their ordering or interpretation.

We will focus this review on genetic diagnosis of monogenic kidney diseases, distinguish between disease-associated risk alleles and monogenic kidney disease, and offer guidance for implementing genetic testing in routine nephrology care. For a detailed discussion about the scientific basis of discovering a monogenic versus complex disease we refer the reader to prior AJKD Core Curriculums. This installment in *AJKD*'s Core Curriculum in Nephrology will

familiarize readers with the use of genetic testing in caring for patients with kidney disease in routine clinical practice.

Additional Readings

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Benefits of Genetic Testing

Genetic testing in the diagnostic workup of kidney disorders has many potential benefits. Providing a precise diagnosis may end a patient's diagnostic odyssey and allow for cascade testing to identify affected family members. It is apparent that the utilization of genetic testing can also change management and potentially alter the course of disease. The diagnostic yield of genetic testing has been highest when used in specifically curated pediatric populations such as nephrotic syndrome and focal segmental glomerulosclerosis (FSGS), congenital anomalies of the kidney and urinary tract (CAKUT), and cystic kidney disease.

The pediatric literature has identified pathologic variants involved in podocyte signaling, architecture, and function in patients with steroid-resistant nephrotic syndrome. Identification of these variants in pediatric and young adult patients has allowed sparing of immunosuppressive therapy. Individuals with a genetic cause of FSGS are at minimal risk of recurrence after transplant compared with primary FSGS, and there are implications for peritransplant immunosuppression and postoperative management including plasma exchange.

Testing in a general adult CKD population has also been fruitful. Identification of a pathologic variant can have direct treatment implications, provide prognostic data, and alter management. Enzyme replacement therapy may be used in Fabry's disease (*GLA*), CoQ10 replacement in coenzyme Q–related nephropathies, and vitamin B_{12} replacement in proteinuria related to Imerslund-Gräsbeck syndrome (*CUBN*). Identification of a pathologic variant may also help inform prognosis in patients with imaging suggestive of polycystic kidney disease. Patients with a *PKD1*/*PKD2* variant will have more severe kidney disease than those with more uncommon gene variants such as *GANAB*, *ALG8*, *ALG9*, and *IFT140*.

In some cases, identifying a pathologic variant may allow forgoing a kidney biopsy, such as genetic FSGS or certain types of tubulointerstitial disease (ADTKD-*UMOD*). As some diseases have extrarenal manifestations, identification of a pathologic variant may lead to screening for other features of disease, such as diabetes in someone with hypomagnesemia due to a pathologic variant in *HNFB1*, ocular or auditory changes in patients with *COL4A* variants, or malignancy (*WT1*, *VHL*, *TSC1*, *TSC2*). In those wanting to start a family, identification of a pathologic variant can inform the risk of passing the disease on to their offspring and aid in the counseling for preimplantation genetic testing.

In patients undergoing kidney transplant, identification of a genetic cause for recipient CKD can help screen/inform living-related donors. Posttransplant monitoring intensity can also be modified based on low (genetic FSGS) or high (genetic atypical hemolytic uremic syndrome [aHUS]) risk of recurrence and may influence the decision for dual kidney/liver transplant (aHUS, primary hyperoxaluria type 1 [*AGXT*]).

Data obtained from genetic testing afford nephrologists the opportunity to provide a precise diagnosis and generate new knowledge. In a large study employing genetic testing in a general CKD cohort, 20.8% had positive findings (with a range of 8.6% to 49.6% depending on the kidney disease category), and 48.8% of these patients were provided with a new diagnosis or had a previous diagnosis reclassified. Positive findings changed management in 90.7% of patients, including altering treatment plans (32.9%), referral to genetic counseling (78.3%), referral of family members for genetic testing (66.5%), and initiation of discussions around family planning (42.2%). A positive genetic finding provided a new diagnosis in 71.1% of patients who already had undergone a kidney biopsy and allowed 3% of patients to forgo a kidney biopsy.

When genetic testing was performed in a general CKD cohort, variants in *PKD1* (24-26.2%) and *PKD2* (7%-8.8%) were most identified consistent with autosomal dominant polycystic kidney disease (ADPKD) as the most common cause of adult genetic kidney disease. Surprisingly, the next most common variants were in genes related to collagen 4 (*COL4A3* [5.8%-9%], *COL4A4* [7%-7.2%], *COL4A5* [5%-15%]), which has broadened our understanding the role of collagen 4 in kidney disease. *COL4A3/4/5* variants have been increasingly identified in adults with FSGS, mild cystic kidney disease, and a subset with familial IgA nephropathy, suggesting these variants result in pleiotropic expression of kidney disease.

In providing a genetic diagnosis, KDIGO is likely to recommend a 2-part "dyadic" naming schema, combining both the clinical condition with the gene name: (ie, ADPKD-*PKD1*, autosomal dominant polycystic kidney disease [ADTKD]-*MUC1*, etc). Aside from diagnostic precision, this new naming schema will allow more rapid identification of patient cohorts that may be eligible for therapy or clinical trials in the future.

Although therapies for monogenic kidney disease are currently limited, a better understanding of disease pathogenesis will allow our field to move away from categorizing diseases based on pathologic descriptions of common final pathways (ie, FSGS) and more toward disease mechanisms (FSGS-*COL4A4*), which has promise to guide future investigations and therapeutic advancement.

Additional Readings

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Patient Identification

Case 1: *A 20-year-old woman presents for evaluation of proteinuria found on routine health examination. Her serum creatinine is 1.1 mg/dL and estimated glomerular filtration rate (eGFR) is 50 mL/min/1.73 m^2. Urinalysis and urinary sediment examination is bland. Her 24-hour urine protein collection demonstrates 2.5 g/24 hours. Her family history is notable for ESKD in her mother by age 35 and CKD in her older brother of unknown etiology. Her renal sonogram shows normal sized kidneys bilaterally without cysts or anatomical abnormalities.*

Question 1: What elements of her presentation increase the likelihood of a diagnostic result with genetic testing?
(a) Young age of onset
(b) Strong family history
(c) CKD of unclear etiology
(d) Potential for primary glomerular etiology
(e) All of the above

For the answer to this question, see the following text.

It is helpful to identify which patients are appropriate for genetic testing by developing a gestalt pretest probability based on the potential yield in certain patient populations. Prior studies have demonstrated wide variability in diagnostic yield due to differences in their patient cohorts. Individuals with a young age at presentation, a strong family history not easily explained by more common etiologies and typically defined as presence of kidney disease in 1 or more first-degree relatives, or multiple extrarenal manifestations suggesting an overarching syndrome should be considered for genetic testing (Fig 1). Patients with biopsy findings indicative of a genetic disease, including unexplained chronic tubulointerstitial disease, FSGS without obvious secondary causes, or abnormalities of glomerular basement membrane consistent with collagen IV nephropathy, should also be offered genetic testing.

Certain categories of kidney disease have also demonstrated a higher yield, including cystic kidney disease

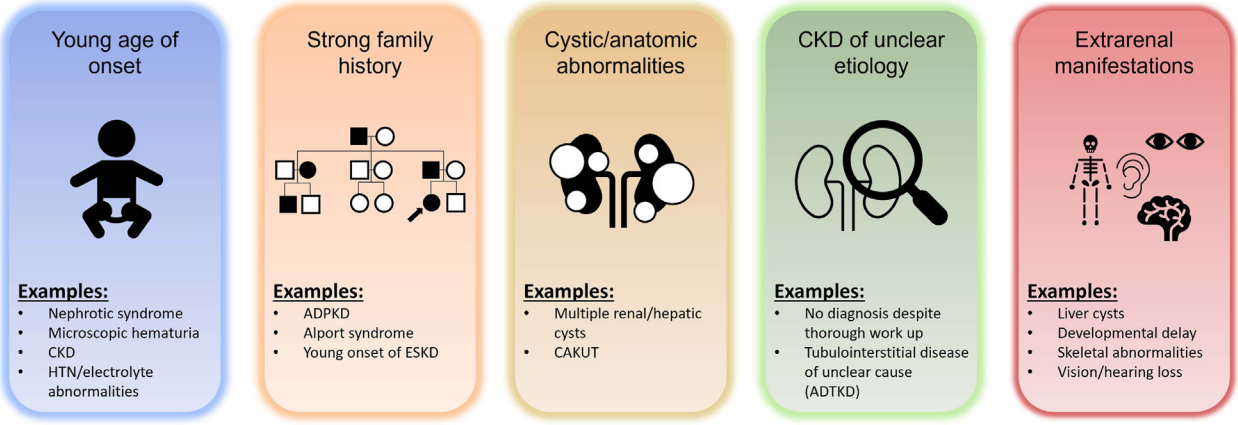

Figure 1. Patient characteristics that increase the diagnostic yield of genetic testing. Identifying patients with a high pretest probability of having a genetic etiology of their kidney disorder will allow for more targeted and effective use of clinical genetic testing. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ADTKD, autosomal dominant tubulointerstitial kidney disease; CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; ESKD, end-stage kidney disease; HTN, hypertension.

(23.9%-49.6%), proteinuric kidney disease suggesting a primary glomerulopathy (7.2%-16.9%), tubulointerstitial disease (4.5%-13.6%), and CKD of unknown etiology (17.1-18.2%). The genetic yield in patients diagnosed with diabetic nephropathy (1.6%-8.7%) or hypertensive nephropathy (2.5%-14.2%) was modest; however, 22% and 31% of the positive findings, respectively, were 2 high-risk *APOL1* alleles. Given the low yields, it may be that the risk for diabetic and hypertensive kidney disease will be better defined by polygenic (genome-wide) risk scores, but the value of a gene panel containing *APOL1* is also highlighted.

In the patient in Case 1, her young age of onset of non-nephrotic range proteinuria and early development of ESKD in primary family members is suggestive of a genetic etiology of her proteinuric kidney disease. Therefore, the answer to the question is (e), all of the above. Additionally, the results of her genetic testing may allow her to forgo a kidney biopsy in the future.

Pretest Considerations and Counseling

Case 1, continued: *In discussing this patient's options, you explain that genetic testing may provide a diagnosis for her kidney disease. Although she is eager to get an explanation, she is self-employed and worried about her ability to get health insurance in the future.*

Question 2: How do you counsel her?

(a) She will be unable to get health insurance if a pathologic variant is identified.
(b) It is illegal for health insurance companies to deny her coverage based on the results of genetic testing.
(c) It is illegal for life insurance companies to deny her coverage based on the results of genetic testing.
(d) It is illegal for disability insurance companies to deny her coverage based on the results of genetic testing.

For the answer to this question, see the following text.

It is important to become familiar with the characteristics of the type of genetic test one chooses to order, and special attention should be paid to providing pretest counseling to patients to allow informed consent and set expectations (Table 1).

The ordering clinician should review the list of genes being interrogated to ensure that the gene(s) of interest will be evaluated if there is a specific disease(s) in mind before testing. Pretest and posttest genetic counseling should be available and offered. Counseling can be extremely helpful in the case of a positive or inconclusive result. The ordering clinician should be aware if secondary findings and variants of uncertain significance (VUS) will be reported (to be discussed later).

It is important that patients are informed about the limitations of genetic testing. It should be communicated that the results may not provide a definitive diagnosis or may be unclear and lead to further testing. A positive or inconclusive result may lead to a request for additional testing of family members (cascade testing).

Table 1. Considerations Before ordering Genetic Testing

Clinician Considerations	Patient Considerations
"Gestalt" pretest probability	Testing may not provide a definitive diagnosis/result(s) may be unclear.
Review genes on panel if ordering t-NGS	Result(s) may require screening for other diseases.
Is genetic counseling available if needed?	Testing may discover unexpected or secondary findings.
Will VUS or secondary findings be reported?	Positive result(s) may have implications for other family members.
Is informed consent required?	Positive result(s) may affect insurability for various types of insurances (health insurance excluded).

It is important that the ordering clinician be aware of various testing characteristics before obtaining genetic testing. In addition, patients must be appropriately counseled regarding the expectations of genetic testing with special attention paid to the insurability implications for younger patients.
Abbreviations: t-NGS, targeted next-generation sequencing; VUS, variant of uncertain significance.

The American College of Medical Genetics and Genomics (ACMG) recommends that all clinical genetic testing also include screening for highly penetrant genetic disorders with established interventions for prevention and/or treatment (actionable genes). Most of these genes are not included on commercial kidney gene panels, and a positive finding can add complexity to discussion of the test results. Currently 81 genes are on the ACMG's list. Examples include genes associated with an increased risk for breast and ovarian cancer (*BRCA1*, *BRCA1*), hereditary cancer syndromes (Lynch syndrome, Li-Fraumeni syndrome), familial hypercholesterolemia (*LDJR*, *APO8*, *PCSK9*), and various cardiac diseases (hypertrophic cardiomyopathy/dilated cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia, arrhythmogenic right ventricular cardiomyopathy and various channelopathies). Nephrology-specific actionable genes included in appropriate kidney panels are *VHL* (Von Hippel-Lindau syndrome), *WT1* (*WT1*-related Wilms tumor), and *TSC1*/*TSC2* (tuberous sclerosis complex).

The Genetic Information Nondiscrimination Act (GINA), which passed in 2008 in the United States, prohibits health insurance and most employers from discriminating against patients based on their genetic data, so the answer to the Question 2 is (b). However, other forms of insurance—such as life and disability insurance—are not covered under GINA, and patients may be disqualified for these types of coverage based on the results of genetic testing. Informing patients, especially those who are young, during pretest counseling about this possibility is essential.

Currently 13 states require informed consent to perform genetic testing, so it is critical to be aware of all

local requirements before testing. Even when formal informed consent is not required, it is helpful to provide the patient with an information sheet documenting the discussion of the risks, benefits, and limitations of testing.

Additional Reading

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Types of Genetic Tests

Case 1, continued: *After discussing the risks and benefits your patient agrees to genetic testing.*

Question 3: What type of test should you order?
(a) Whole-genome sequencing
(b) Whole-exome sequencing
(c) Targeted next-generation sequencing (kidney gene panel)
(d) Sanger sequencing of *NPHS1*

Case 4: *A 28-year-old man with a history of obesity, diabetes mellitus type 2, hypertension, and provoked deep-vein thrombosis after meniscus repair 1 month ago, which is now treated with apixaban, presents to your clinic for evaluation of CKD found on perioperative laboratory testing. His serum creatinine is 1.3 mg/dL with an eGFR of 49 mL/min/1.73 m^2. The urinalysis is notable for microscopic hematuria with 8-10 red blood cells per high-power field. His urine albumin-creatinine ratio is 1,050 mg/g. His family history is notable for ESKD secondary to Alport syndrome diagnosed by biopsy in his father and paternal uncle.*

Question 4: What testing should you pursue in this patient?
(a) Renal biopsy
(b) Whole-exome sequencing
(c) Targeted next-generation sequencing (kidney gene panel).
(d) Testing of *COL4A3*, *COL4A4*, *COL4A5*

For the answers to these questions, see the following text.

Details of genetic testing techniques are beyond the scope of this Core Curriculum. However, a basic knowledge of the different techniques is required to facilitate understanding of their strengths and limitations (Fig 2). In the past, a clinician would have to identify specific genes of interest to be sequenced individually, base by base, via Sanger sequencing. Although this approach may still be appropriate in limited cases, it is burdensome, time consuming, and requires the ordering clinician to have a detailed knowledge of various genetic disorders and their specific associated variant(s).

Advances in technology have allowed for the sequencing of multiple genes simultaneously. This next-generation sequencing (NGS, also known as massively parallel sequencing) has allowed for significant reductions in the time and cost of genetic testing. Using NGS, many institutional and commercial laboratories offer curated kidney gene panels of genes associated with monogenic kidney disease (known as targeted NGS: t-NGS). Some panels are phenotype driven and thus narrow in scope (ie, cystic or nephrotic disease panels). Other panels are broad, encompassing most kidney-specific genetic diseases. The use of a broader panel may result in more VUS being reported. Because many genes are sequenced simultaneously, the ordering clinicians may focus on identifying appropriate patients for genetic testing rather than knowledge of all the genes involved in causing a specific condition, such as nephrotic syndrome.

Although t-NGS will be adequate for most clinical testing, there are certain circumstances when it will be either unnecessary or inadequate. In individuals with a known familial disease-causing variant, sequencing of the specific variant(s) or gene(s) of interest would be sufficient for diagnostic purposes and avoid the detection of secondary variants or VUS, which can hinder diagnostic clarity. However, t-NGS may be inadequate for detecting diseases characterized by significant chromosomal structural variations, including large or whole gene deletions, insertions, or chromosomal rearrangements (CAKUT, DiGeorge syndrome, multiorgan manifestations, nephronophthisis-*NPHP1*). In these circumstances, other techniques such as chromosomal microarray may be required and will likely necessitate referral to a specialized center.

Special mention should be made of ADTKD-*MUC1*: the most common variant for this disease is due to a cytosine in the variable number tandem repeat (VNTR) region and requires specific testing at a specialized laboratory. If there is strong suspicion for ADTKD and testing with t-NGS has been unrevealing, the provider should consider referral to a center specializing in genetic kidney disease.

Because t-NGS is limited by the genes included on the precurated panel, it is possible that individuals may have a negative t-NGS test while still having a monogenic kidney disease. Their gene may not be included in the panel or other technical limitations of the testing method may arise (a false negative). In ADPKD-*PKD1*,

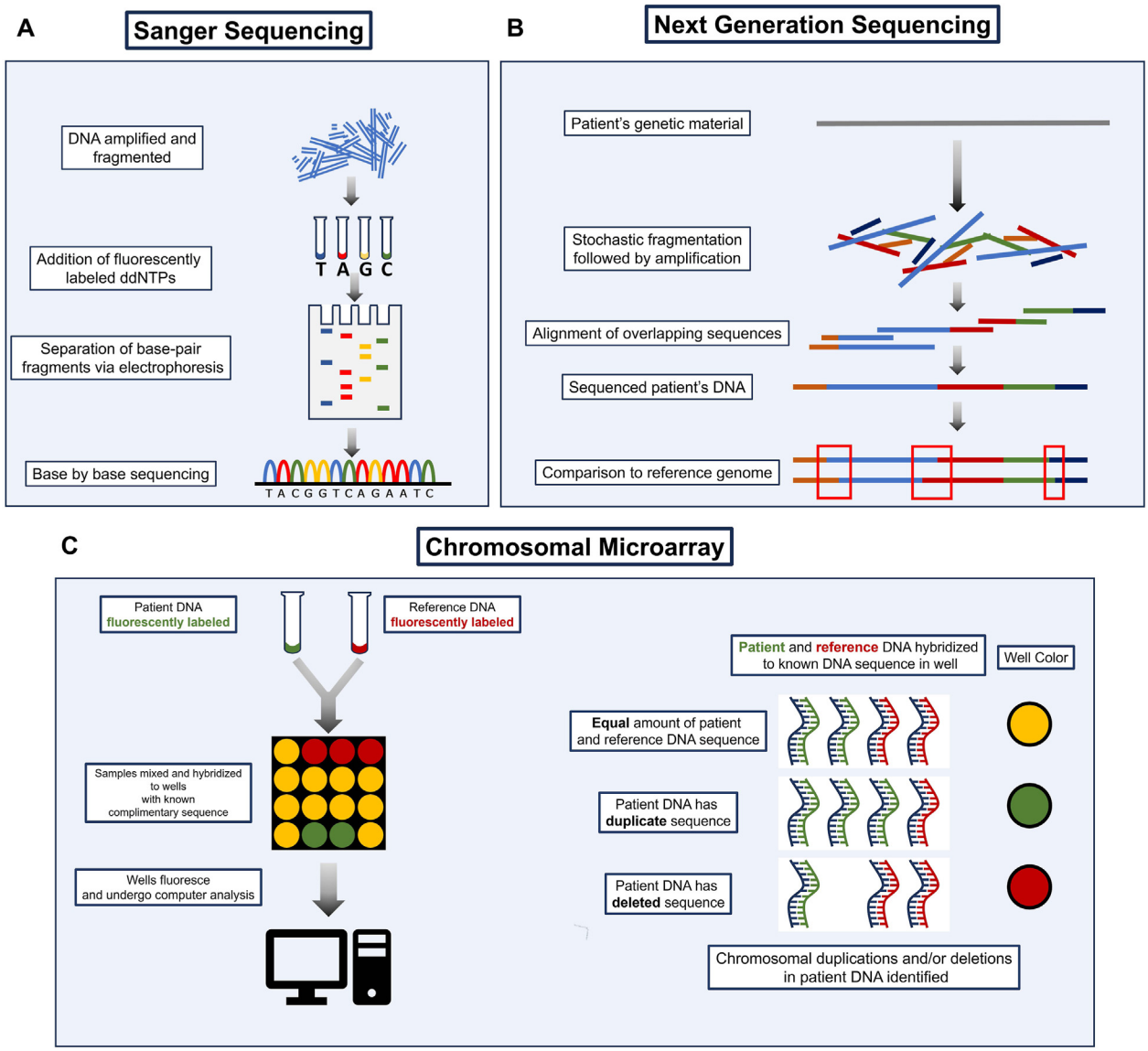

Figure 2. Simplified schematic comparing Sanger sequencing, next-generation sequencing, and chromosomal microarray. In all techniques, DNA is extracted from a patient sample and subsequently fragmented and amplified. (A) Sanger sequencing. Fluorescently labeled dideoxynucleotides (ddNTPs) are incorporated into the sample which is then separated based on base pair length via electrophoresis. The DNA is then sequenced base by base. Best used for targeted analysis for a specific variant. (B) Next-generation sequencing. DNA is stochastically fragmented and then amplified. Adaptors are added to the fragments which allow them to hybridize with reference library oligonucleotides and fluorescently labeled nucleotides are added (steps not pictured). Overlapping base pairs between fragments are then aligned, allowing rapid sequencing of the entire sample which is then compared to the reference genome to assess for variants. This simultaneous sequencing of large sequences of DNA allows for rapid sequencing of many different genes. (C) Chromosomal microarray. Patient and reference DNA are fluorescently labeled different colors. DNA is then amplified, fragmented, and placed into wells where both patient and reference DNA hybridize to known complimentary sequences. Proportion of patient to reference DNA is detected by the color each well fluoresces allowing computer analysis to identify sequences that are duplicated or deleted. Best used in diseases with significant chromosomal structural variants including large or whole gene deletions, insertions, or rearrangements.

family-specific, ultrarare variants that are not included in large databases are common, and individuals with classic imaging findings of polycystic kidney disease may be misled by a negative t-NGS report. Review of reported VUS or referral for more specialized testing may be warranted if there is no identification of a suspected genetic variant.

This field is rapidly evolving, so institutions frequently update their gene lists to reflect the most recent advances in the literature. In cases where t-NGS is negative

despite a strong clinical suspicion, a more unbiased approach—such as personalized curation of whole-exome sequencing (WES) or whole-genome sequencing (WGS) in a kidney genetics center—is preferred (Fig 3). Although WES or WGS may be performed to increase diagnostic yield, it is important to remember that commercially available WES or WGS may still only evaluate a limited number of genes. WES interrogates the 1% of the genome encoding for proteins that contains most of the disease-causing variants; WGS can also evaluate for variants in noncoding DNA.

For a more detailed discussion, we refer the reader to the recently published report by the National Kidney Foundation working group on advancing genetic testing in kidney disease for guidance on which patients would benefit from genetic testing and which testing modalities to use (Fig 4).

The latter 2 cases highlight situations where different types of genetic testing should be employed. In Case 3, there is a high gestalt pretest probability that the patient may have a genetic etiology for her CKD, but no specific disease has been identified. In these situations, the answer is (c): targeted NGS will allow the patient to have multiple monogenic kidney disease genes interrogated simultaneously. WGS or WES would likely also provide an answer, but they may be more expensive and may not be fully optimized for sequencing of the gene of interest.

In Case 4, the patient's phenotype is concerning for Alport syndrome, which is consistent with his family history. Although a renal biopsy has been considered the gold standard, a positive genetic test may allow certain individuals for forgo this procedure, especially when it is contraindicated, as with this patient who is being treated

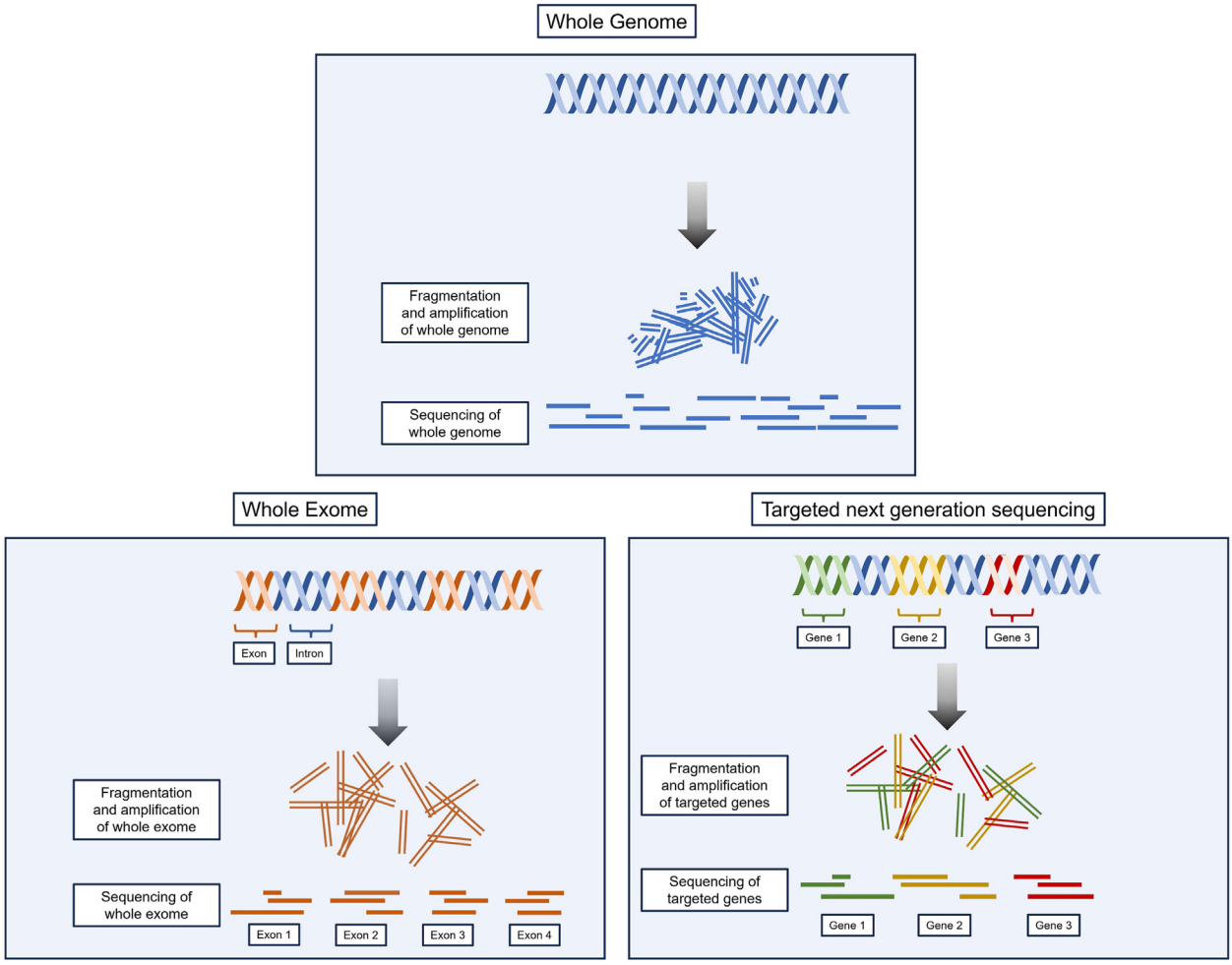

Figure 3. Comparison between WGS, WES, and t-NGS. WGS, as the name implies, includes sequencing of the entire genome. WES sequences all exons, the approximately 1% of the genome-encoding proteins. With t-NGS, the exons of a precurated list of genes are sequenced. For most cases, t-NGS will be sufficient; however, if t-NGS is negative and the suspicion of a genetic disorder is higher, WES or WGS can be considered. Abbreviations: t-NGS, targeted next-generation sequencing; WES, whole-exome sequencing; WGS, whole genome sequencing.

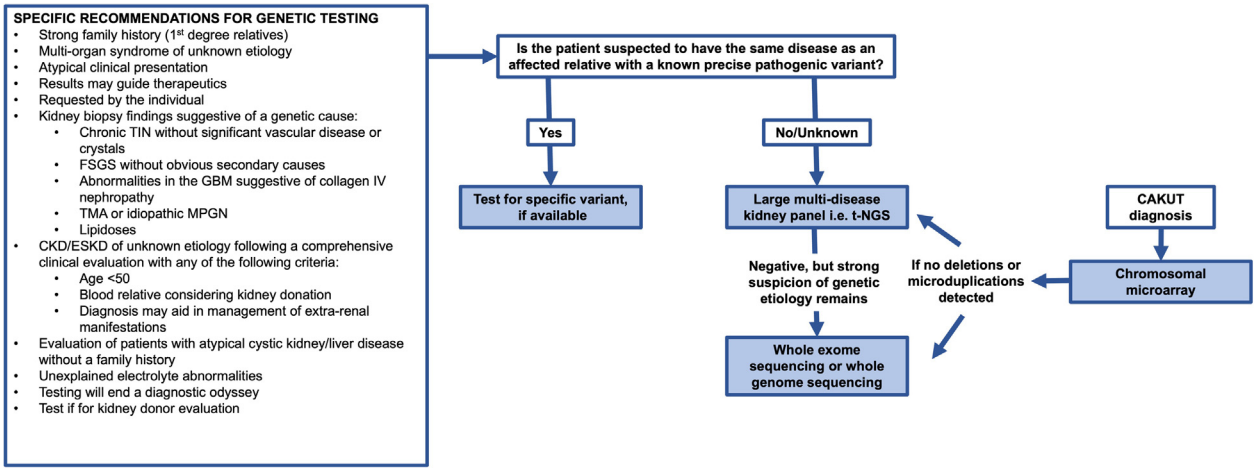

Figure 4. National Kidney Foundation genetic testing algorithm for patients with kidney disease. Specific scenarios in which patients should undergo genetic testing with appropriate testing modalities recommended. In conditions, such as CAKUT, where copy number variants, microdeletions, duplications, or rearrangements are suspected, chromosomal microarray is suggested and may require consultation with a genetics center. Abbreviations: CAKUT, congenital anomalies of the kidneys and urinary tracts; CKD, chronic kidney disease; ESKD, end stage kidney disease; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; MPGN, membranoproliferative glomerulonephritis; TIN, tubulointerstitial nephritis; TMA, thrombotic microangiopathy; t-NGS, targeted next-generation sequencing. Adapted from Franceschini N, Feldman D, Berg JS, et al. Advancing genetic testing in kidney diseases: report from a National Kidney Foundation Working Group. *Am J Kidney Dis*. Published online July 19, 2024. doi:10.1053/j.ajkd.2024.05.010

with anticoagulation. Alport syndrome is associated with variants of *COL4A3*, *COL4A4*, and *COL4A5*. *COL4A5* is X-linked, making this an unlikely diagnosis in this case. Both autosomal dominant and recessive cases of *COL4A4* and *COL4A3* have been described and seem more likely to be causal in this case, so sequencing of these genes will be the most efficient way to assess for the presence of Alport syndrome in this patient. The answer is (d). If a specific familial variant was known, then genetic testing for this specific variant could be performed to further streamline testing and reduce the risk of secondary findings. If a t-NGS panel is used, one can request that only pathologic or likely pathologic variants be reported (no VUS included).

Additional Readings

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Interpretation of Genetic Testing Results

Case 5: *A 40-year-old woman with no past medical history initially has presented to your clinic for evaluation of proteinuria on routine health maintenance testing. The 24-hour urine protein collection confirmed 3.9 g/24 hours. She has a normal serum creatinine, serum albumin, and eGFR. Because of her nephrotic range proteinuria, she underwent a renal biopsy that demonstrated FSGS. She has had no improvement in her creatinine concentration despite treatment with 60 mg of prednisone (1 mg/kg dose).*

Due to her lack of response to corticosteroids, the patient underwent genetic testing via t-NGS. Results are as shown:

Gene	*COL4A3*
Associated disease(s)	*COL4A3*-related Alport syndrome
Inheritance	AD and AR
Variant	Missense, c.88G>C (p.Gly30Arg)
Zygosity	Heterozygous
Classification	Likely pathogenic

Question 5: How do you interpret these findings?
(a) Incidental finding.
(b) The patient has classic Alport syndrome.
(c) The patient may have a form of genetic FSGS.
(d) The patient needs intensification of her immunosuppression.

Case 6: *A 50-year-old man with hypertension and diabetes mellitus type 2 is seen in your clinic for evaluation of CKD and proteinuria. His serum creatinine is 1.4 mg/dL, eGFR is 45 mL/min/1.73 m^2, and urine albumin-creatinine ratio is 800 mg/g. His renal sonogram is notable for a small, simple cyst in the right upper pole and left lower pole. His father and uncle both developed ESKD in their late 60s and early 70s, respectively, though both had poorly controlled hypertension and diabetes and were avid smokers.*
Due to his family history, he requests genetic testing, and you order a t-NGS kidney disease gene panel, which reveals the following:

Gene	*PKD1*
Associated Disease(s)	ADPKD
Inheritance	AD
Variant	Missense, c.12905G>A (p.Ser4302Asn)
Zygosity	Heterozygous
Classification	Uncertain

Question 6: How do you interpret these findings?
(a) The patient has ADPKD.
(b) The patient does not have ADPKD.
(c) The patient should undergo whole-genome sequencing.
(d) The patient should undergo whole-exome sequencing.

For the answers to these questions, see the following text.

Inheritance and Zygosity

Although most testing facilities include genetic counseling as part of their services, basic familiarity with disease heritability and variant nomenclature/reporting will aid the clinician in interpreting many genetic testing results on their own. (A more detailed discussion regarding variant reporting and interpretation is beyond the scope of this Core Curriculum.)

Genetic inheritance can be X-linked, Y-linked, *autosomal dominant* (AD), *autosomal recessive* (AR), or mitochondrial (maternal). Chromosomes 1-22 are autosomes, and generally an individual has 2 copies of each. AD disease occurs when a single disease-causing allele is sufficient for disease, and in AR disorders 2 pathologic alleles are required for disease. Alleles associated with *X-linked* (XL) diseases are found on the X chromosome with disease expression more common in men. Genotypes with 1 disease causing allele are known as *heterozygous* whereas genotypes with 2 disease causing alleles are known as *homozygous*. *Compound heterozygotes* are genotypes with 2 unique disease-causing alleles. Women with 1 XL pathologic variant are known as *carriers*, or heterozygotes. Disease expressivity in these women may vary from a very mild phenotype to significant disease due to variability in X chromosome inactivation.

Similarly, individuals with 1 disease-causing variant of an AR condition may have very mild expression of disease but do not have all the disease features. For example, patients with 2 disease-causing variants in *SLC34A3*, encoding the sodium-dependent phosphate cotransporter 2c, will have hereditary hypophosphatemic rickets with hypercalciuria, but carriers with a single disease-causing variant may have nephrocalcinosis, kidney stones, and hypercalciuria.

Variants

DNA sequences consist of long strands of nucleotides that can be modified to make the final coding sequence of the associated protein. Before translation, some nucleotide sequences (introns) are removed, and the remaining sequences (exons) are spliced together, forming the final transcript. The reading frame of this transcript consists of nucleotide triplets known as codons. There are 64 possible 3-nucleotide combinations that encode for 1 of 20 different amino acids (AA) or 3 stop codons. Due to the redundancy of this system, a single nucleotide variation may not always result in a changed AA. However, due to various biochemical differences between AAs (size, charge, polarity, etc) a single AA change may have a large or small effect on proper protein function.

The Human Genome Variation Society has established standards for the annotation of genetic variants (Fig 5; Table 2). *Synonymous* variants result in a single nucleotide substitution resulting in an unchanged AA. Sometimes these variants may still be disease causing if the change occurs in an area critical for proper protein function such as near a splice site because the splice site may be abolished if a modification occurs at the first or second intronic base (intron-exon boundary). *Missense* variants are a single nucleotide substitution that results in an AA change whereas a *nonsense* variant creates a stop codon, prematurely terminating the sequence and resulting in a truncated protein. A *nonframeshift* variant is the insertion/deletion of nucleotides in a multiple of 3 and allowing for transcription of subsequent codons distal to the site. A *frameshift* variant is the insertion/deletion of nucleotides not in a multiple of 3, which will shift the reading frame of all subsequent codons distal to the site. Lastly, single nucleotide substitutions located at the intron/exon boundary may affect proper splicing of the exon leading to splice site variants.

Variant Interpretation

All individuals have variants compared to the reference genomes, and most variants are benign. The more rare a variant, the more likely it is to cause monogenic disease.

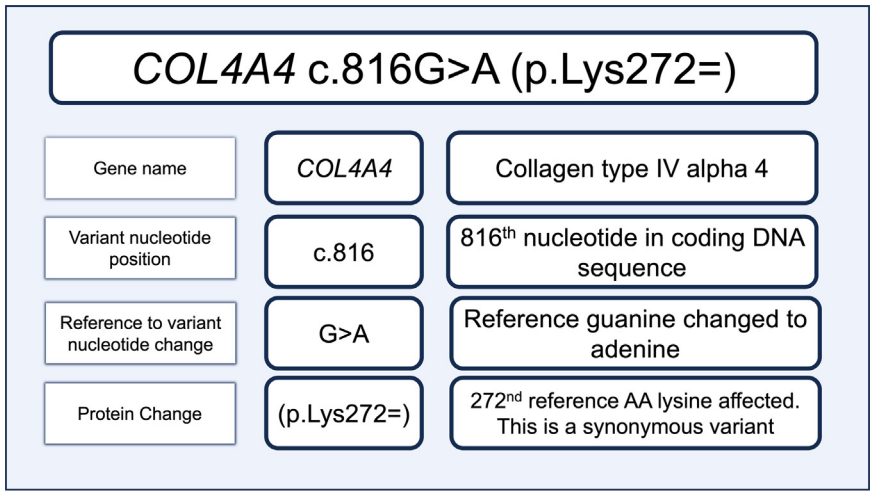

Figure 5. Explanation of variant annotation and reporting nomenclature. The Human Genome Variation Society establishes the standard for variant annotation and reporting which can appear overwhelming to the untrained eye. The italicized gene name abbreviation is followed by the variant nucleotide position including the reference and corresponding variant nucleotide separated by ">." It is then followed by the reference protein, its amino acid position and corresponding variant protein. "=" denotes a synonymous variant, "X" or "ter" denotes a stop codon. Abbreviation: AA, amino acid.

When identified, variants of interest are compared to a large database comprising genomes from thousands of individuals to help determine a variant's relevance. The largest resource, known as the Genome Aggregation Database (gnomAD), consists of whole-genome or whole-exome sequencing from more than 800,000 individuals. Although this is still a predominantly European dataset, the diversity is increasing.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology provide criteria to categorize variants as pathogenic, likely pathogenic, benign, likely benign, and uncertain significance. The term "likely" is used when there is >90% certainty that the variant is either pathogenic or benign. Some of these criteria include whether the variant is known to be associated with a specific disorder, results in a change that will affect critical protein function (ie, truncating or frameshift variant), or has a frequency consistent with the disease frequency in the population. In any given gene it is important to know the type of variant that causes disease. For example, in ADTKD-*UMOD*, only variants that cause protein misfolding will cause disease whereas a loss of function variant in *UMOD* may not be disease-causing. This contrasts with *PKD1*in which a loss of function variant is almost always associated with disease.

Variants of Uncertain Significance

As the name implies, VUS are variants whose significance in disease cannot be conclusively resolved based on the given data. They may be the most challenging to consider. In general, a diagnosis or clinical decision making should not be based on a VUS alone. This designation may be given to variants that are rare, are not yet reported in the reference databases, or do not meet criteria based on prediction modeling alone for disease association. Many disease-causing variants, such as some *PKD1* variants in ADPKD, for example, are ultrarare and thus may not meet ACGM criteria for disease causation without segregation analysis of affected and unaffected family members, so they will be listed as a VUS.

Establishing a proper genotype-phenotype fit will give context to the VUS because it will help determine whether a VUS in the gene in question could explain the patient's presentation. This will be further enhanced by paying particular attention to the heritability of the disease in question. In settings where there are multiple affected family members, cascade testing may lead to reclassification. The decision to reclassify a VUS as potentially disease-causing should be made with support of a multidisciplinary board of clinicians, geneticists, and genetic counselors. A discussion of gene function and its associated pathology is typically included in the report to assist the ordering provider. Genetic counseling is also typically available by the reporting laboratories to help the ordering provider navigate VUS results, if desired.

Returning to our patients above, in Case 5 the patient has steroid-resistant nephrotic syndrome in the setting of biopsy-proven FSGS. She has a proper genotype-phenotype fit: *COL43/4/5* variants have been increasingly reported in adult FSGS, especially in patients who are unresponsive to immunosuppression. The variant is a missense variant and can have an AD inheritance, which

Table 2. Variant Types Resulting From Single or Oligonucleotide Change(s)

Variant Type	Definition	Nucleotide Change	Nomenclature: Coding DNA	Nomenclature: Protein	Comments	Implication
Substitution (*synonymous*)	Single nucleotide substitution resulting in unchanged AA	ATG AGA (ref) c. 1 2 3 4 5 6 Met Arg p. 1 2 ATG AGG (var) Met **Arg**	c.6**A>G**	p.Arg2= or p.Arg2Arg	• 6th nucleotide adenine changed to guanine • Variant occurs at 2nd codon • Both AGA and AGG encode arginine • Protein sequence is not affected	• No change in AA • *Likely benign*
Substitution (*missense*)	Single nucleotide substitution changing AA	ATG AGA Met Arg ↓ ATG ATA Met **Ile**	c.5**G>T**	p.Arg2Ile	• 5th nucleotide guanine changed to thymine • 2nd codon encoded arginine; variant encodes isoleucine (Ile)	• AA changed • *Potentially pathogenic*
Substitution (*nonsense*)	Single nucleotide substitution creating a stop codon	ATG AGA (ref) Met Arg ↓ ATG TGA (var) Met STOP	c.4**A>T**	p.Arg2**Ter** or p.Arg2**X**	• 4th nucleotide adenine changed to thymine • 2nd codon encoded arginine; variant encodes a premature stop codon	• Truncated protein • *Pathogenic* in majority of disease mechanisms
Insertion/deletion (*frameshift*)	Insertion or deletion of # nucleotides (# ≠ multiple of 3)	ATG AGA CAG T Met **Arg** Gln ↓ ATG **GAC AGT** Met **Asp Ser**	c.4**delA**	p.Arg2**fs**	• 4th nucleotide adenine deleted, causing a shift in the reading frame • Reading frame no longer encodes the intended protein and by chance will reach a stop codon	• Truncated/altered protein all AAs distal to frame shift are changed • *Pathogenic* in majority of disease mechanisms
Insertion/deletion (*nonframeshift*)	Insertion or deletion of # nucleotides (# in multiples of 3)	ATG AGA CAG T Met **Arg** Gln ↓ ATG **CAG** Met **Gln**	c.4_6delAGA	p.Arg2del	• 4th through 6th nucleotides deleted, causing loss of Arg but no frameshift	• AA deleted • *Potentially pathogenic* if critical AA
Substitution (*splice variant*)	Single nucleotide substitution and intron/exon boundary	AAGgtaatt… Lys *intron* ↓ AAGttaatt… Lys *intron*	c.21+1G>T		• 1st intronic nucleotide (guanine) changed to thymine • No protein consequence is defined given intronic variant	• Truncated protein expected • Splice site abolished if 1st or 2nd intronic base modified • *Pathogenic* in majority of disease mechanisms

Various examples using the Human Genome Variation Society guidelines for reporting variants are explained including their potential implications. Please note, introns are denoted in lowercase. Abbreviation: AA, amino acid. Adapted with permission of the copyright holder (Wolters Kluwer Health, Inc) from: Aron AW, Dahl NK, Besse W. A Practical Guide to Genetic Testing for Kidney Disorders of Unknown Etiology. *Kidney360*. 2022;3(9):1640-1651. doi:10.34067/KID.0007552021

further supports that variant as being clinically relevant. Finally, although the classification is reported as "likely pathogenic," this classification is given when variants are thought to have a >90% certainty of being pathogenic. Therefore, the answer is (c): this patient has a genetic form of FSGS, and it is unlikely that escalating courses of immunosuppression will affect her disease course.

In Case 6, the patient, who has a family history of ESKD, has requested genetic testing for his CKD, which has revealed a VUS in *PKD1*. He does not have a proper genotype-phenotype fit: he has 2 cysts by ultrasound at the age of 50, and his normal kidney size would rule out ADPKD. Furthermore, a missense variant is not always pathogenic in ADPKD. Although he has family history of ESKD, their conditions are more easily explained by other etiologies. If there were a more compelling suspicion of ADPKD—such as a high cyst burden in the patient and/or family members—cascade testing to determine the presence of this VUS in affected family members could be considered. However, given his lack of phenotype-genotype fit, it is likely that this patient's VUS is an incidental finding and is not contributing to his CKD, so the answer is (b).

Additional Reading

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Risk Alleles

Case 7: *A 40-year-old Black man with hypertension and CKD stage G2A1 has requested genetic testing due a strong family history of ESKD.*
His results are as follows:

Gene	*APOL1*
Associated disease(s)	Susceptibility to ESKD and FSGS
Inheritance	Complex
Zygosity	Heterozygous
Variant	G1
Classification	Risk allele

Question 7: How do you interpret the results?
(a) He has FSGS.
(b) He is at increased risk for developing ESKD.
(c) He is not at increased risk for developing ESKD.
(d) He has a 2 *APOL1* risk alleles.

For the answer to this question, see the following text.

Monogenic disease-causing alleles are rare and have high penetrance, or a high effect on disease. For example, a disease-causing variant in *PKD1* is usually associated with a clinical diagnosis of ADPKD. By contrast, risk alleles are more common and generally have only a modest effect on disease. A good example of this is IgA nephropathy in which an accumulation of multiple risk alleles correlates with earlier disease progression. Each risk allele is not pathogenic in isolation. *APOL1* risk alleles are unusual in that they are common (35% of the US Black population) and have a large effect size in increasing risk of disease.

APOL1 risk alleles are more common in individuals with West African ancestry and explain about 70% of the increased incidence of ESKD in individuals with a high-risk genotype. Risk alleles, denoted G1 and G2, confer increased resistance to *Trypanosoma brucei* infection, the pathogen responsible for African sleeping sickness, compared with the wild-type allele (G0). Individuals with a high-risk genotype or 2 risk alleles (G1/G1, G2/G2, or compound heterozygous G1/G2) are at a significant increased risk for development/progression of CKD when faced with a clinical "second hit," perhaps related to a high interferon state, resulting in a worse prognosis with primary FSGS, lupus nephritis, hypertension-attributed nephropathy, HIV-associated nephropathy, and likely COVID-19–associated nephropathy. High-risk *APOL1* genotypes are frequently found in cases of collapsing FSGS associated with HIV and SARS-CoV2 infection.

APOL1 risk variants will be frequently encountered with clinical genetic testing of individuals with kidney disease. In fact, 35% of Black Americans have 1 risk allele, and 14% have 2 risk alleles. Our patient in Case 7 has a single risk allele, with a heterozygous genotype (G0/G1). A single risk allele does not confer an increased risk of developing CKD/ESKD, so the answer is (c). Individuals with high-risk *APOL1* genotypes should be screened/monitored for clinical second hits that can be treated, such as hypertension, HIV infection, and lupus. Although there are currently no targeted therapies for *APOL1*-associated nephropathy, there are many therapeutics in the pipeline, and this will hopefully change in the future.

Additional Reading

- Egbuna O, Zimmerman B, Manos G, et al. Inaxaplin for proteinuric kidney disease in persons with two *APOL1*

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Implications in Kidney Donation

Due to variable penetrance, individuals with a pathogenic variant may not always have clinical manifestations of disease. Living kidney donors are known to have an increased risk of developing hypertension, proteinuria, and CKD/ESKD due to their acquired reduced nephron mass after donation nephrectomy. Screening living-related donors of patients with known monogenetic kidney disease has been able to identify donors with pathogenic variants and help better inform them of their risk of developing CKD/ESKD after donation, especially in young donors who are not old enough to have developed clinical manifestations of disease.

Genetic testing in living kidney donation becomes complicated in the case of risk alleles such as *APOL1* because the presence of a high-risk genotype increases the risk of but does not guarantee the development of CKD/ESKD. After being informed of their potential increased risk, some related donors still elect to proceed with donation whereas others have demonstrated dissatisfaction with being precluded from donation of their kidney to a loved one. Deceased donor grafts with high-risk *APOL1* genotypes have reduced survival compared with low-risk genotypes.

There currently is no consensus among transplant centers regarding accepting living donors with high-risk *APOL1* genotypes. Long-term outcomes for high-risk genotype living donors are not well-established, but they are being actively investigated by the APOLLO study (*APOL1* Long-term Kidney Transplant Outcomes Network, NCT03615235), which should provide better information about the risks once the results are available.

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Preimplantation Genetic Testing

Case 8: *A 30-year-old man with ADPKD, hypertension, and Mayo Imaging Class 1D kidneys and a truncating PKD1 variant has presented to your clinic for a routine follow-up visit. He states that he is hoping to start a family soon. Many of his family members developed ESKD in their 50s because of ADPKD, and he is worried about his children inheriting this disease.*

Question 8: Which of the following statements is true?
(a) Unfortunately, there is nothing that can be done; there is a 25% risk that his offspring with have a *PKD1* variant.
(b) Preimplantation genetic testing may be utilized to reduce the risk of passing a pathogenic variant to his offspring.
(c) The risk of his offspring developing ADPKD is low.

For the answer to this question, see the following text.

A diagnosis of genetic kidney disease has potential implications for individuals who are planning to have children. Unlike genetic counselors, nephrologists are significantly less likely to offer family planning advice. However, as genetic testing becomes implemented routinely in general nephrology practice, nephrologists may be called upon by their patients to offer initial family planning guidance.

Preimplantation genetic testing (PGT) refers to the testing of embryos after in vitro fertilization (IVF) to assess for the presence of disease-causing variant(s); this allows embryos that do not have the potential for passing on the disorder to be selected for implantation. PGT requires a priori knowledge of the specific pathogenic variant in the potential parent(s), so that embryos that do not harbor the genetic disorder in question and are otherwise normal can undergo selective transfer. PGT thus minimizes the likelihood of facing the difficult decision to terminate a pregnancy if the disorder is found later.

Currently, prenatal testing has been applied to over 500 conditions. In nephrology, ADPKD, Alport syndrome and ARPKD being the most common indications, making the correct answer (b).

IVF poses unique technical considerations and clinical challenges in persons with kidney disease. Although IVF can be safe in women with early CKD, fertility treatment with repeated exposure to estrogens may lead to

enlargement of liver cysts, an important consideration for women with ADPKD. Ovarian hyperstimulation syndrome, a known complication of IVF, increases the risk of acute kidney injury due to hemodynamic insults. In addition, pregnancy can accelerate CKD progression, and women with CKD are at higher risk of preeclampsia, intrauterine growth restriction, and premature delivery.

The decision to use PGT to avoid highly penetrant genetic disorders may be straightforward for some, but its implementation in genetic diseases that still allow a high quality of life or in risk alleles is less clear. Also, in the United States most infertility treatments including PGT are expensive and may not be covered by insurance, limiting access to this technology. This poses significant ethical considerations because this may create a socioeconomic genetic divide leading to a disproportionate burden of genetic disease on those of lower socioeconomic status.

Currently, the Ethics Committee of the American Society of Reproductive Medicine supports a policy of "reproductive liberty," deferring to the clinician to weigh the risks and benefits of PGT for various disease types. While the use of PGT is highly regulated, there are currently no laws governing which diseases are appropriate for PGT in the United States, and no official recommendations exist from kidney disease organizations.

In Case 9the patient has a 50% chance of passing on his pathogenic *PKD1* variant to his offspring. His clinical course (hypertension with large kidneys at a young age) and family history of early onset ESKD suggest that his familial variant is associated with aggressive disease. Genetic counseling to discuss PGT will allow him to fully consider his options.

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Conclusions

The widespread availability of clinical genetic testing promises to enhance the care of patients with kidney disease. Routine use in carefully selected patients will help provide more diagnostic clarity/precision, generate new knowledge for further research, identify patients who may qualify for future treatments, help modify treatment plans, inform patients and potential kidney donors about their risk for developing CKD/ESKD, and provide counseling for family planning. Just as the nephrology community has learned to rely on renal pathologists for assistance interpreting a kidney biopsy, there should be ongoing discussion of complex genetic cases involving geneticists, genetic counselors, and researchers, who may all provide valuable insights. Both the KDIGO consensus statement and NKF working group report include statements about the need for this growing field, including educating a larger workforce with expertise in genetics, genomics, and computational research, conducting more studies with diverse populations, integrating genetics into clinical trials, and forming interdisciplinary expert boards.

Article Information

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