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REVIEW

Navigating Genetic Testing in Nephrology: Options and Decision-Making Strategies

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Technological advances such as next-generation sequencing (NGS) have enabled high-throughput assessment of the human genome, supporting the usage of genetic testing as a first-line tool across clinical medicine. Although individually rare, genetic causes account for end-stage renal disease in 10% to 15% of adults and 70% of children, and in many of these individuals, genetic testing can identify a specific etiology and meaningfully impact management. However, with numerous options for genetic testing available, nephrologists may feel uncomfortable integrating genetics into their clinical practice. Here, we aim to demystify the process of genetic test selection and highlight the opportunities for interdisciplinary collaboration between nephrologists and genetics professionals, thereby supporting precision medicine for patients with kidney disease. We first detail the various clinical genetic testing modalities, highlighting their technical advantages and limitations, and then discuss indications for their usage. Next, we provide a generalized workflow for genetic test selection among individuals with kidney disease and illustrate how this workflow can be applied to genetic test selection across diverse clinical contexts. We then discuss key areas related to the usage of genetic testing in clinical nephrology that merit further research and approaches to investigate them.

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Although individually rare, genetic etiologies of kidney disease collectively account for end-stage kidney disease in 10% to 15% of adults and 70% of children.[1,2] Genetic and acquired forms of kidney disease can differ substantially in their prognosis, course, and management, but are often challenging to distinguish from each other using traditional diagnostics alone.[3,4] Moreover, because early-stage kidney disease is frequently clinically silent, individuals may present only when they reach end-stage kidney disease, at which point traditional diagnostics such as renal imaging and renal biopsy may be uninformative or disfavored.[5] Genetic testing can also enable early detection of kidney disease in family members, supporting targeted management and improved outcomes.[6]

Traditionally, geneticists meet with individuals suspected to have a genetic condition and conducted a detailed clinical evaluation, including personal and family history, physical examination, and relevant biochemical, imaging, and/or histopathological testing. Based on the results of this evaluation, focused genetic testing involving 1 or several candidate gene(s) is ordered to confirm the clinically suspected disease. In nephrology, clinicians learn to recognize individuals with features of some monogenic forms of kidney disease, such as Alport syndrome,[7] and refer them for genetic evaluation. Studies now support that genetic testing has the potential to help achieve early and specific diagnosis and personalized management for many more individuals with kidney disease, including those with unknown etiology of disease.[4,8-10] In addition to resolving the diagnostic odyssey, a process that carries significant time, financial, and psychosocial costs for patients with rare diseases and their families,[11,12] genetic diagnosis can also prevent individuals from having to undergo further, potentially invasive tests. Moreover, knowledge of the specific etiology of chronic kidney disease (CKD) can inform clinical management,[4,9,13] and help evaluate living kidney donors.[14]

Massively parallel sequencing, also known as NGS has revolutionized medical genetics by enabling

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high-throughput assessment of variations across the human genome.[15,16] Such technological advancements are shifting practice paradigms in clinical genetics.[17,18] NGS-based tests, such as targeted panels or exome sequencing (ES), are deployed as part of the initial diagnostic workup of individuals with suspected genetic disease,[19,20] with clinical evaluation following up on the genetic test results.[21] Review of NGS-based studies shows that a monogenic cause of a disease can be found in approximately 5% to 30% of adults and 30% of children with CKD, albeit with variable diagnostic yield: higher yields are seen among individuals with a positive family history of CKD, earlier age of CKD onset, and presence of extrarenal features.[4,9,13]

In this shifting landscape, nephrologists are faced with a bevy of different options for genetic testing and may feel insufficiently prepared to choose between them.[22] In this review, we focus on genetic test selection for rare Mendelian forms of kidney disease and refer those interested in other uses of genetic testing to other relevant reviews.[23-25] We also refer readers interested in approaches for genetic testing for unaffected individuals (e.g., unrelated candidate living kidney donors) to relevant reviews on this topic.[14,26] We first provide a detailed overview of the different genetic testing modalities available, focusing on their analytical advantages, drawbacks and indications for their usage. We then build on previous work on applying genomics for kidney disease[6,27] to outline frameworks for genetic test selection among individuals with kidney disease and discuss how they can be applied across different clinical contexts. Finally, we present key areas for further study in clinical genetic testing in nephrology.

TYPES OF GENETIC VARIANTS

Genetic variants are alterations in the DNA sequence relative to the standard (reference) sequence (Figure 1). They can be categorized based on their size (e.g., single-nucleotide variant [SNV] vs. structural variants [SVs]), location (e.g., intronic vs. exonic), impact on the encoded protein (e.g., synonymous vs. nonsynonymous), or clinical significance (e.g., pathogenic vs. benign). These 4 categorizations can be simultaneously applied to any given genetic variant (e.g., a variant can be a single nucleotide change located in an exon, encoding for a synonymous change, and classified as benign). Although the term "mutation" has been used to describe DNA sequence alterations, it has been advised to avoid using this terminology because the term "mutation" implies that a change is disease-causing and has negative connotations (i.e., being popularly associated with the grotesque and disturbing).[28]

Here, we group genetic variants into 4 broad categories based on their size spectrum: SNVs, which alter a single DNA base; insertions and deletions (indels), which can be small ($<$ 50 base pairs) or large ($\geq$ 50 base pairs); variable tandem number repeats, which consist of a variable number of DNA sequence repeats in tandem; and SVs, which are alterations of $\geq$ 1 kilobases of DNA. SNVs encompass single-nucleotide polymorphisms, which are present at frequencies in $\geq$ 1% of individuals in a population, and rarer single DNA base alterations (present in $<$ 1% of individuals in a population).[28] In addition, we discuss epigenetic variants, which are modifications to the DNA molecule or associate proteins that do not alter the DNA sequence but can impact gene expression.

GENETIC TESTING METHODOLOGIES: STRENGTHS AND LIMITATIONS

Genetic technologies vary in their ability to detect different categories of variants (Figure 1, Table 1, and Table 2). The methodologies have evolved, with older methods often having high technical accuracy but being increasingly time- and cost-inefficient as more genes are associated with diseases.

Genetic Testing for SNVs and Small Indels

Sanger Sequencing

For decades, Sanger sequencing was the main methodology to identify SNVs and small indels ($<$ 50 base pairs), which comprise the majority of known causal variants for monogenic forms of kidney diseases (Figure 1). Although Sanger sequencing still has the highest technical sensitivity and specificity for detecting SNVs and indels,[39] its limited scope and low throughput have led to a reduction of its utilization in clinical genetic testing. Currently, Sanger sequencing is typically used for the analysis of 1 or several specific variant(s), such as the detection of founder variants (e.g., the *APOL1* G1 and G2 risk variants) or of a known variant in the setting of familial testing (Table 1 and Table 2). Analysis of 1 or several specific variants can also be performed using targeted genotyping approaches, such as the Taqman assay.[40] Because it is a relatively inexpensive and high-throughput approach, the Taqman assay has been applied to detect known kidney disease risk variants (e.g., the *APOL1* G1 and G2 risk alleles). It is also a potential testing strategy for screening for founder variants, particularly in resource-limited settings.[41]

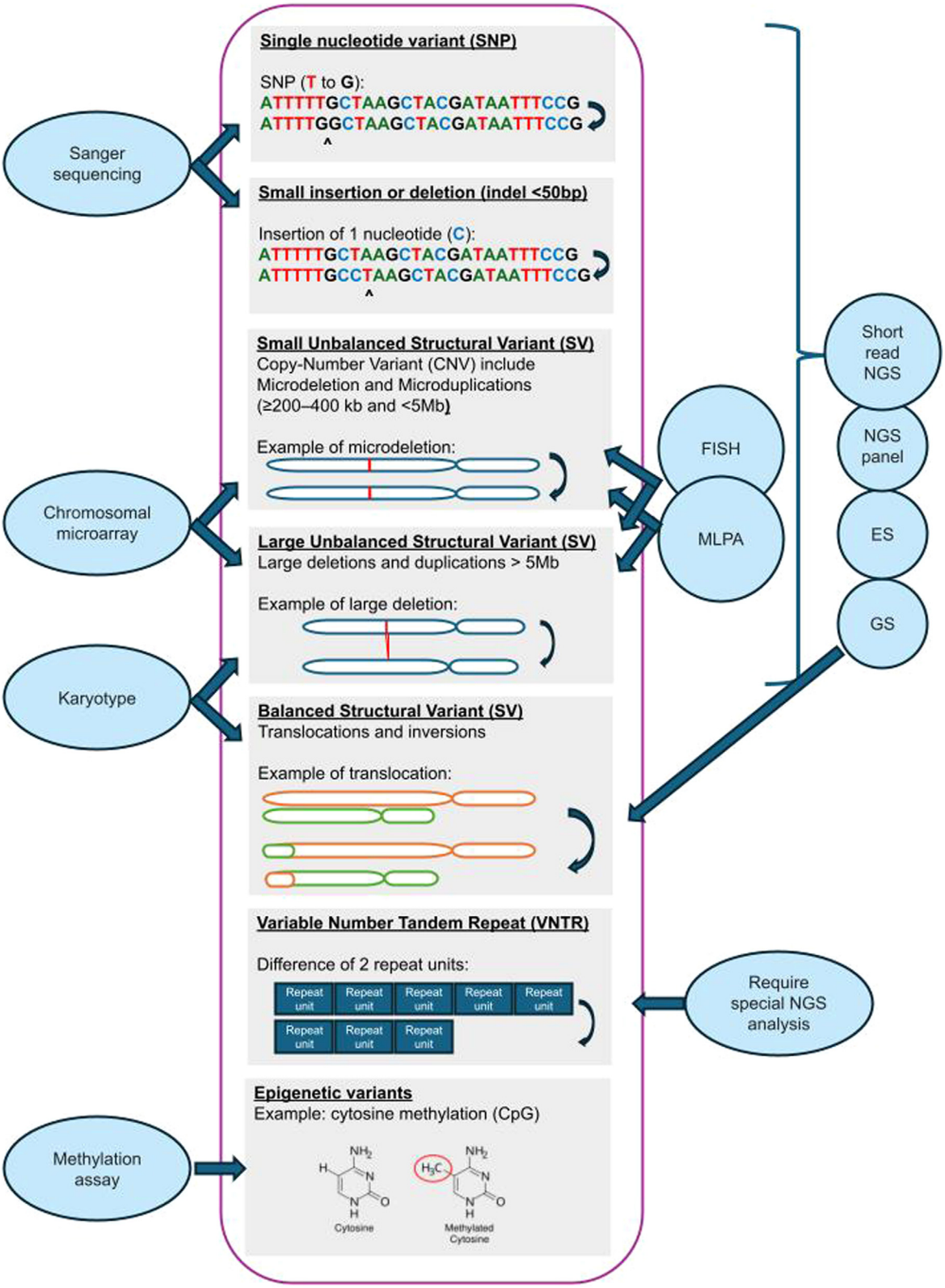

Figure 1. Genetic technologies for variant detection. Different clinical genetic testing modalities are illustrated with the type/s of genetic variants they can detect. ES, exome sequencing; FISH, fluorescent *in situ* hybridization; GS, genome sequencing; MLPA, multiplex ligation probe–dependent amplification; NGS, next-generation sequencing.

Short-Read NGS

NGS enables simultaneous sequencing of multiple segments of DNA, facilitating high-throughput assessment of the human genome. NGS has therefore superseded Sanger sequencing in clinical genetics. NGS can detect SNVs with very high sensitivity and specificity, and

Table 1. Characteristics of different clinical genetic testing modalities

Test	Indications for use	Advantages	Limitations	Turn-around time	Price	Examples of usage	Examples of incidental or secondary findings
Sanger sequencing	Validation of NGS findings Regions poorly assessed by NGS, such as GC-rich and/or highly repetitive regions Individuals with features specific to a form of kidney disease with a single gene etiology Screening for previously identified disease-causal variant in familial cascade testing Identifying known recurrent disease-associated variants	High technical specificity and sensitivity Relatively simple sequence interpretation	Inefficient and costly if used to test long genes or multiple genes	2–5 d	$ (assuming single variant testing)	Confirm frameshift variant detected by NGS Detect a glycine substitution variant in the first exon of *COL4A3*, which has high GC content, in an individual with familial early-onset hematuria and sensorineural hearing loss for whom NGS testing identified no candidate *COL4A3/4/5* variants Identifying *WT1* variant in an individual presenting with steroid-resistant nephrotic syndrome with diffuse mesangial sclerosis on renal biopsy, Wilm's tumor, and ambiguous genitalia *APOL1* G1/G2 risk allele testing	None, as the test solely involves a particular gene/genetic region related to the patient's phenotype
Multiplex ligation probe–dependent amplification (MLPA)	Identifying intragenic CNVs for a single gene or several genes Validation of intragenic CNVs identified by NGS-based CNV calling	High technical accuracy Easy and fast interpretation Can be modified to include methylation testing (MS-MLPA)	Not commercially available for all genes Cannot identify CNVs outside of the genetic regions targeted Cannot detect balanced rearrangements Limited detection of genetic mosaicism	7–14 d	$	Detection of a *COL4A5* deletion as part of genetic testing for X-linked Alport syndrome (case S3) Detection of *NPHP1* deletion in a child presenting with polydipsia, polyuria, and increased echogenicity with reduced corticomedullary differentiation on ultrasound	If used for validation of NGS-called CNV, CNV within a gene associated with a disorder unrelated to the patient's clinical presentation
Karyotype	Detection of chromosomal aneuploidies and balanced chromosomal rearrangements >5 Mb Investigation of infertility, recurrent miscarriages, and/or multiple congenital anomalies (because these can be due to balanced chromosomal rearrangements)	Detects both balanced (e.g., balanced translocations, inversions) and unbalanced (e.g., deletions, duplications) structural variants	Cannot detect uniparental disomy Requires mitotically active (dividing) cells and cell culture	$\leq$ 14 d	$–$$	Confirm diagnosis of Turner syndrome in an individual with short stature, primary amenorrhea, and horseshoe kidney Detect balanced Robertsonian translocation involving chromosome 21 in an individual with a history of multiple miscarriages and a child with trisomy 21 (Down syndrome) with posterior urethral valves[29,30] Detected *de novo* balanced translocation in a fetus with bilateral renal agenesis[31]	Sex chromosome aneuploidy Balanced rearrangements (e.g., inversions or translocations)

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Table 1. (Continued) Characteristics of different clinical genetic testing modalities

Test	Indications for use	Advantages	Limitations	Turn-around time	Price	Examples of usage	Examples of incidental or secondary findings
Fluorescent *in situ* hybridization (FISH)	Investigation for structural variants in known disease-associated genomic regions (targeted by the probe), including microdeletions and microduplications, chromosomal aneuploidies, and balanced rearrangements Identify mosaic structural variants Follow up after chromosomal microarray to give positional information, which can help determine recurrence risk	Detects both balanced (e.g., balanced translocations, inversions) and unbalanced (e.g., deletions, duplications) structural variants in the genomic regions targeted Can detect mosaic structural variants	Cannot detect uniparental disomy Can only detect variants in the genomic regions targeted	≤14 d	$$–$$$ (depending on number of regions targeted)	Prenatal screening for common aneuploidies, such as those involving gains or losses of chromosomes 13, 18, 21, X, and Y Identify 17q12 deletion in a patient with cystic dysplastic kidneys, hypomagnesemia, and intellectual disability Detection of mosaic 22q11.2 deletion (DiGeorge syndrome) in an individual with cleft palate, failure to thrive, and tetralogy of Fallot[32] Identification of a maternally inherited balanced translocation involving chromosomes 19 and 21 on prenatal screening of a family with a history of multiple miscarriages	None
Chromosomal microarray (CMA)	Individuals with CAKUT with or without extrarenal anomalies (case S2) Individuals with multiple congenital anomalies and/or neurodevelopmental delay	Genome-wide CNV detection	Limited technical sensitivity for low-grade genetic mosaicism, and CNVs in regions that are more difficult to capture using array technology (e.g., repetitive elements, pseudogenes) Cannot provide positional information (e.g., whether a duplication is located in tandem [next to] the original copy of the gene or at another site in the genome; position can be determined by karyotyping or FISH)	2–3 wks	$$	Identify 22q11.2 deletion (DiGeorge syndrome) in an individual with unilateral renal agenesis, cleft palate, and immunodeficiency Identify 16p11.2 duplication in an individual with autism, developmental delays, and posterior urethral valves	CNV within a gene associated with a disorder unrelated to the patient's clinical presentation.
Targeted NGS panels	Individuals whose presentation is consistent with a specific clinical subtype of kidney disease Clinical subtypes of kidney disease that have relatively low genetic and/or phenotypic heterogeneity	Can be engineered to provide high coverage of variants in targeted regions, increasing technical sensitivity Assessment of a selected set of genes (i.e., genes associated with a particular clinical subtype of kidney disease) facilitates variant interpretation and reduces risk of secondary genetic findings	Limitations inherent to panel design, including sensitivity-specificity tradeoff for gene selection, inter-laboratory variation in which genes are chosen, and needing to frequently review and update panel (e.g., to add newly identified genes and/or remove genes found to have insufficient evidence of disease association) Low capacity for reanalysis of the genetic data generated Increased potential for VUS to be returned[33]	10–21 d	$–$$	Testing complement pathway–associated genes in a patient with atypical hemolytic uremic syndrome[34] Testing for genes associated with ADPKD in an individual presenting with bilateral enlarged kidneys with multiple cysts and a negative family history (case S1)	None, because the panel is targeted to the patient's specific subtype clinical disease

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Table 1. (Continued) Characteristics of different clinical genetic testing modalities

Test	Indications for use	Advantages	Limitations	Turn-around time	Price	Examples of usage	Examples of incidental or secondary findings
Broad NGS panels	Clinical presentation associated with a wide range of genetic causes	Can be engineered to provide high coverage of variants in targeted regions, increasing technical sensitivity Assessment of most genes known to be associated with kidney diseases	Limitations inherent to panel design, including sensitivity-specificity tradeoff for gene selection, interlaboratory variation in which genes are chosen, and needing to frequently review and update panel (e.g., to add newly identified genes and/or remove genes found to have insufficient evidence of disease association) Low capacity for reanalysis of the genetic data generated Very high potential for VUS to be returned, than targeted NGS panel or ES/GS.[33]	10–21 d	$–$$	Patient with a category of kidney disease that has high genetic heterogeneity Patient with kidney disease of unknown etiology (case S4)	For broad NGS panels that target a general clinical disease category (e.g., monogenic kidney diseases), there can be incidental findings in genes associated with diseases that are associated with the general clinical disease category but are unrelated to the patient's clinical disease subtype
Exome sequencing (short-read)[a] (ES)	Individuals with clinical subtypes of kidney disease that have high genetic heterogeneity Individuals with nonspecific clinical features, including kidney disease of unknown etiology Individuals left undiagnosed by more targeted testing	Genome-wide testing provides higher diagnostic sensitivity than targeted approaches (e.g., single-gene or multigene panel testing) Assessment of the coding regions, which harbor the majority of known disease-causal variants, increases the efficiency of genome-wide analysis than genome sequencing Interrogation of all protein-coding regions supports sequence reanalysis in the case of novel gene discovery Option to receive medically actionable secondary genetic findings	Limited coverage of certain regions and lower detection accuracy for certain types of variants (e.g., indels) than genome sequencing Misses intronic regions unless specifically targeted by the exome capture kit Genome-wide testing can yield multiple candidate variants, increasing the time needed for analysis and follow-up evaluations	2–3 mo	$$	Genetic diagnostic evaluation of individuals with steroid-resistant nephrotic syndrome.[35] Identifying a pathogenic *TMEM67* variant [conveying the genetic diagnosis of NPHP-RC] in an individual with presumed ARPKD.[36] Identifying a cause of disease among individuals with kidney disease of "unknown etiology" (Table 4).[35]	Medically actionable secondary findings, e.g., pathogenic or likely pathogenic variants in the ACMG medically actionable genes.[37]

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Table 1. (Continued) Characteristics of different clinical genetic testing modalities

Test	Indications for use	Advantages	Limitations	Turn-around time	Price	Examples of usage	Examples of incidental or secondary findings
Genome sequencing (short-read)[a] (GS)	Individuals with clinical subtypes of kidney disease that have high genetic heterogeneity Individuals with nonspecific clinical features, including kidney disease of unknown etiology Individuals with nondiagnostic results on previous, more targeted testing	Increased technical and diagnostic sensitivity than ES, reflecting its superior per-base coverage and ability to assess variants in both the coding and noncoding regions Higher sensitivity for structural variants than ES Option to receive medically actionable secondary genetic findings	Generates a large amount of data, conferring substantial interpretative and financial costs (e.g., time for interpretation, cost of data storage, etc.) Noncoding variants can be often challenging to interpret and require further follow up (e.g., functional assays, clinical phenotyping) to help clarify their significance	2–3 mo	$$$	Identifying disease-causal intronic variants, e.g., in an intronic *DGKE* variant in case of genetically unresolved atypical hemolytic uremic syndrome.[31] Genetic testing for ADPKD (because of high sequence homology of *PKD1*).[38] Detection of pathogenic balanced structural rearrangements in cases of multiple congenital anomalies.[31]	Medically actionable secondary findings, e.g., pathogenic or likely pathogenic variants in the ACMG medically actionable genes.[37] CNV within a gene associated with a disorder unrelated to the patient's clinical presentation

ACMG, American College of Medical Genetics and Genomics; ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; CAKUT, congenital anomalies of the kidney and urinary tract; CNV, copy number variant; ES, exome sequencing; GS, genome sequencing; MLPA, Multiplex ligation probe–dependent amplification; MS-MLPA, methylation- Multiplex ligation probe–dependent amplification; NGS, next-generation sequencing; NPHP-RC,nephronophthisis-related ciliopathies; VUS, variant of uncertain significance.
As the absolute cost of genetic testing can vary substantially due to multiple factors, including international differences in healthcare policy, here we only provide the relative costs of the genetic tests discussed, with the number of dollar signs ($) corresponding to higher cost.
[a]Currently, clinical exome sequencing (ES) and genome sequencing (GS) technologies use short-read sequencing, which typically assesses paired DNA segments of 150 base pairs in length. We discuss long-read sequencing approaches in the section "Emerging genetic technologies".

indels with relatively high sensitivity and specificity. NGS can also identify SVs using bioinformatics tools; however, its sensitivity and specificity are lower than for SNVs and are highly variable.[42] Although long-read sequencing methodologies are now starting to be used for rare disease diagnosis (Table 3),[43,44] clinical NGS is currently based on short-read sequencing, which usually assesses paired DNA segments of 150 base pairs in length.[16] For clinical evaluations, the predominantly used tests are targeted and broad panels, ES, and genome sequencing (GS).

Targeted and Broad NGS Panels. Genetic panels analyze a predetermined set of genes associated with a clinical phenotype, with the number of genes assessed reflecting the scope of phenotypes included (Figure 1, Table 1 and Table 2). Targeted panels assess a specific clinical subtype of kidney disease and generally range from 3 to 20 genes; for example, a panel for Alport syndrome consisting of *COL4A3*, *COL4A4*, *COL4A5*, and *COL4A6* genes. Broad panels can cover a wider category of kidney diseases that may include multiple specific clinical subtypes; for example, a panel for steroid-resistant nephrotic syndrome that includes 50 genes associated with hereditary podocytopathies.[79] Of note, there are also broad panels that include multiple forms of monogenic kidney disease that contain hundreds of genes.[80,81] Genetic reports for panels usually include the list of the genes included and the limitations of the test (e.g., exons not sequenced or types of variants not analyzed).

ES. ES refers to the targeted capture of most of the protein-coding regions in the genome (i.e., the exome), allowing a broad search for pathogenic variants in the absence of clinical clues pointing to a specific genetic etiology. ES has highly variable technical sensitivity across the exome, with poor detection capacity for certain clinically relevant regions (Figure 1, Tables 1 and 2).[82] ES can thus have lower diagnostic sensitivity for some variants, for example, in *PKD1* regions with high sequence homology.[83] In addition, ES capture kits can vary in their sequencing coverage for different genes. For example, coverage for the gene *GREB1L*, associated with renal agenesis, varies highly across different ES capture kits.[84] Generally, ES reports do not provide detailed information on the exon-level sequencing coverage for different genes. Thus, for individuals with phenotypes consistent with a genetic kidney disease who have negative ES results, we recommend obtaining this information to help rule out these being false negative results because of insufficient sequencing coverage.

GS. In addition to assessing the noncoding regions, GS provides uniform coverage across the protein-coding

Table 2. Detection capacities of different genetic testing methodologies

Genetic testing methodology	Number of genes or genetic regions analyzed	Methylation	Noncoding variants	SNV	Small Indels	Balanced structural variants	Unbalanced structural variants	Possibility of secondary or incidental finding/s	Genetic mosaicism detection
Sanger sequencing	1 gene	No	Yes	Yes	< 10 bp	No	No	None	Limited
MLPA	< 50 genetic regions	No	Yes	No	No	No	1 kb–15 Mb	Low	No
Karyotype	All	No	Yes	No	No	Yes	> 5 Mb	1–3%	No
FISH	1	No	Yes	No	No	Yes	> 100 kb	None	Yes
Chromosomal microarray	genome-wide	No	Yes	No	No	No	> 50 kb	1–3%	No
Methylation array	Range of 1 to genome-wide	Yes	Yes	No	No	No	No	Low	Limited
Targeted NGS panels	5–250	No	No	Yes	< 100 bp	No	Variable[a]	Low	Yes
Broad NGS panels	350–500	No	No	Yes	< 100 bp	No	Variable[a]	Variable[a]	Yes
Exome sequencing[b]	genome-wide	No	No	Yes	< 100 bp	No	Variable[a]	~3%	Yes
Genome sequencing[b]	genome-wide	No	Yes	Yes	Yes	No	Variable[a]	~3%	Yes

FISH, Fluorescent *in situ* hybridization; MLPA, Multiplex ligation probe–dependent amplification; NGS, next-generation sequencing; SNV, Single nucleotide variants.
[a]Depending on laboratories and often require confirmation with FISH, chromosomal microarray or MLPA.
[b]Short-read sequencing.

regions[85,86]; thus, it is expected to have greater diagnostic sensitivity than ES. This is especially advantageous for the investigation of genes that are more difficult to accurately assess via ES, such as *PKD1*; and GS has been recommended as an effective strategy for the molecular diagnosis of autosomal dominant polycystic kidney disease.[38,87] In addition, GS can include analysis of the mitochondrial genome, enabling unbiased detection of individuals with kidney disease because of mitochondrial DNA variants,[88] further increasing its diagnostic sensitivity.[89]

Genetic Testing for SVs

Karyotyping

Karyotyping was the first technology developed to visualize SVs, and remains a first-line method for the detection of large SVs, including chromosomal aneuploidies, translocations, inversions, and complex rearrangements.[90,91] Examples of usage of karyotyping in nephrology include identifying balanced translocations among individuals with syndromic and isolated congenital anomalies of the kidney and urinary tract and detecting complex rearrangements among individuals with Wilms tumor-aniridia-genital anomalies-retardation syndrome (Table 1).[92]

Fluorescent In Situ Hybridization

In the 1990s, to better identify microdeletions and certain recurrent translocations, fluorescent *in situ* hybridization (FISH) was developed and remains commonly used in molecular diagnostics. Examples of usage of FISH in nephrology include identifying known disease-causal SVs, such as the 22q11.2 deletion associated with DiGeorge syndrome, the *NPHP1* deletion in nephronophthisis,[93] and SVs involving the *TFE3* and *TFEB* genes in renal cell carcinoma.[94]

Multiplex Ligation–Dependent Probe Amplification

In the early 2000s, to increase the number of copy number variants (CNVs) analyzed simultaneously and reduce the cost of CNV detection, multiplex ligation-dependent probe amplification (MLPA) was developed and introduced in clinical care.[95] The sequences targeted by MLPA are 50 to 70 nucleotides long, allowing MLPA to identify single exon CNVs that are too small to be detected by FISH. In addition, MLPA allows the detection of CNVs for up to 50 genetic regions. However, MLPA is not available for all genes and does not provide information on the size of the deletion. Examples of clinical utilization of MLPA in nephrology include detection of pathogenic deletions involving *COL4A5* among individuals with X-linked Alport syndrome[96] and SVs involving the *CFH-CFHR* genomic region among individuals with atypical hemolytic uremic syndrome.[97]

Chromosomal Microarray

Karyotyping, FISH, and MLPA have been largely replaced by chromosomal microarray (CMA) as the first-tier test for individuals with phenotypes that can result from pathogenic CNVs, such as multiple congenital anomalies or neurodevelopmental disorders.[98] Here, we use the term CMA to include 2 different technologies: comparative genomic hybridization arrays and single-nucleotide polymorphism arrays, which can be used to identify unbalanced SVs (Figure 1, Table 1, and Table 2).[99] Unlike FISH or MLPA, which require *a priori* selection of genomic regions to target, CMA offers genome-wide CNV assessment, increasing diagnostic sensitivity, particularly for individuals who present with features that are not specific to a single genomic disorder. In nephrology, CMA detected pathogenic CNVs in approximately 10% of individuals with isolated and syndromic congenital anomalies of the kidney and urinary tract.[100] Moreover, CMA has been reported

Table 3. Emerging genetic technologies

Although the clinical adoption of chromosomal microarray (CMA) and next-generation sequencing (NGS) has revolutionized the diagnosis of rare genetic conditions, approximately 50% to 60% of individuals with suspected Mendelian disease remain unresolved after evaluation with such technologies.[17,45-47] For such individuals left unresolved by standard clinical genetic testing, emerging technologies such as optical genome mapping (OGM), long-read sequencing (LRS), DNA methylation analysis, and RNA sequencing may help achieve a genetic diagnosis, supporting personalized care.
OGM uses imaging of fluorescently labeled mega base–long DNA molecules to identify structural variants (SVs) genome-wide.[48,49] OGM can detect copy number variants (CNVs) less than 25kb in size and balanced rearrangements (e.g., inversions or translocations), which are missed by CMA or NGS, as well as somatic mosaicism. Given its ability to detect a variety of SVs, it has the potential to become a first-line approach for prenatal cytogenetic testing.[50] OGM has been applied to detect such CNVs across individuals with a variety of rare genetic diseases. It identified a mosaic *de novo* deletion and inversion of the *CDKL5* gene in an infant with epilepsy who had previously undergone CMA, targeted panel, exome sequencing (ES), and genome sequencing (GS) testing.[51] OGM also identified a 2.8kb insertion within the *SMARCB1* gene in 2 siblings with atypical teratoid rhabdoid tumor left unresolved by ES with CNV analysis.[52] Currently, there is a clinically approved OGM-based assay for identifying the 3.3kb *D4Z4* repeat array causal for facioscapulohumeral muscular dystrophy (FSHD), which has the potential to replace the traditional time- and labor-intensive Southern blot for FSHD diagnosis.[53] Although OGM offers the ability to detect both balanced and unbalanced SVs of varying sizes in a single test, it has important limitations: it requires high molecular-weight DNA, which is more difficult to extract, does not provide information about the sequence of the SV(s) detected, and its resolution is limited by the spacing of the fluorescent labels along the DNA molecule and the resolution of the imaging photocell.[49,54]
LRS refers to sequencing that yields continuous DNA or RNA reads of between 1kb and 4 megabases.[55] LRS can be targeted to a specific genomic region (i.e., T-LRS) or done across the genome (lrGS). Current commercial LRS technologies include PacBio HiFi sequencing, which uses DNA polymerase–mediated incorporation of fluorescently labeled nucleotides into a circular DNA template to identify the DNA bases present in a particular genomic region; and Oxford Nanopore Technologies (ONT) sequencing, which analyzes changes in electrical current as a single-stranded DNA or RNA molecular travels through a protein nanopore.[56] Although ONT and PacBio sequencing vary in their read lengths and per-base error rates, both offer substantially longer sequence reads than the reads from standard (short-read) NGS. These longer reads enable more accurate detection of variants that can be missed by short-read NGS, such as variants occurring in highly repetitive regions of the genome and repeat expansion variants. LRS also allows for phasing of variants without the need for parental samples, which can help ascertain the variants' pathogenicity. In addition, both technologies can detect alterations in DNA methylation, enabling simultaneous evaluation of the sequence and methylation pattern at a particular genomic region.[57,58] Recent research-level sequencing studies highlight the potential of T-LRS and lrGS for cases left undiagnosed by short-read NGS. As a targeted approach, T-LRS can be used to identify disease-causal variants among genetically unresolved individuals with specific features for a monogenic form of disease. In nephrology, T-LRS led to the identification of the "missing" second variant in *WDR19* in an individual with nephronophthisis, retinal dystrophy, skeletal dysplasia, and hepatic fibrosis in whom an NGS ciliopathy gene panel had identified a single heterozygous pathogenic *WDR19* variant, thus genetically confirming the diagnosis of Senior-Loken syndrome.[59] T-LRS also allowed the identification of intronic variants in individuals with genetically unresolved Gitelman syndrome.[60] T-LRS has also been successfully applied for the genetic diagnosis of autosomal dominant polycystic kidney disease, reflecting its superior detection sensitivity than short-read NGS and multiplex ligation probe–dependent amplification to detect variants in genes such as *PKD1* that have high sequence homology.[61] As a genome-wide approach, lrGS has been shown to provide a molecular diagnosis among pediatric patients with a variety of rare disease phenotypes who had been left undiagnosed by previous genetic testing, reflecting its superior ability to detect SVs and variants in regions poorly captured by short-read NGS.[62] Although LRS has increased technical sensitivity than short-read NGS, as a novel technology, there is a need for standardized analytic pipelines and larger population reference datasets, which can make variant filtering and prioritization challenging. Ongoing initiatives using LRS, such as the All of Us project[63] and the 1000 Genomes project[64] will help address these challenges. In addition, though recent investigations support the diagnostic utility of LRS to resolve cases left undiagnosed by short-read NGS, systematic large-scale comparisons of the diagnostic yield of LRS versus existing genetic testing modalities are needed to inform clinical usage of LRS.
DNA methylation analysis can be performed using methylation arrays or LRS. Certain genetic diseases, including some syndromes involving neurodevelopmental delay and multiple congenital anomalies, result from altered DNA methylation (DNAm).[65] These include syndromic disorders that can present with congenital anomalies of the kidney and urinary tract, such as Kabuki syndrome[66] and CHARGE syndrome.[67] Because these conditions have unique DNAm patterns, known as "episignatures,"DNAm analysis can help achieve a molecular diagnosis for affected individuals.[68] Traditionally, targeted DNAm analysis was performed for individuals with features of a specific imprinting disorder to confirm the clinically suspected diagnosis.[69] Now, genome-wide DNAm analysis emerging as a follow-up test to resolve individuals with variants of uncertain significance (VUS) in genes associated with epigenetic disorders: here, identification of an episignature for a specific disorder supports that the individual has the condition, and can help characterize the functional impact of the VUS (case S2).[70] However, there are important limitations. Although DNAm analysis is typically performed using peripheral blood samples, there is considerable tissue-specific variation in DNAm patterns, limiting the generalizability of the results observed from blood samples.[71] In addition, there is the need to develop consensus technical standards for DNAm testing, because analysis must include correction for factors that can affect DNAm patterns, such as age, sex, and environment.[70] Moreover, existing methylation arrays have a limited ability to detect low-grade genetic mosaicism and can only identify disorders that have known episignatures, lowering the diagnostic sensitivity of DNAm testing.[68] Nonetheless, DNAm analysis has been recently reported to resolve as many as 30% of individuals with features suggestive of a rare neurodevelopmental disorder,[72]a diagnostic yield comparable to those reported for CMA (15%–20%) and ES (30%–40%).[73] These findings support further investigation of the diagnostic utility of DNAm analysis, particularly for individuals with features suggestive of epigenetic disorders and/or with a VUS in a gene associated with a disease that has an episignature.
RNA sequencing (RNA-seq) applies massively parallel sequencing methods to sequence and quantify the different RNA molecules (i.e., the transcriptome) within a cell. RNAseqcan therefore be used to evaluate whether a DNA sequence variant in a given gene impacts RNA splicing and expression of that gene, which can help determine the variant's pathogenicity.[74] For example, in an analysis of nearly 700,000 individuals who underwent clinical NGS for different genetic diseases, incorporating RNA-seq helped resolve 31% of the VUS identified by clarifying their splicing impact.[75] Similarly, RNA-seq of individuals with autosomal dominant polycystic kidney disease with deep intronic VUS detected on GS validated that these variants altered splicing and led to reduced *PKD1* gene expression, supporting their pathogenicity.[76] In addition to resolving VUS, RNA-seq can identify candidate disease-causal genes by identifying genes with altered expression in affected individuals relative to controls.[77] However, there are important caveats. Both individual and experimental factors (e.g., age, sequencing platform) can impact transcriptome profiles, requiring the use of in-house control sets to help ensure accurate analysis. Moreover, because the transcriptome varies substantially between different tissues, it is crucial that samples be taken from the tissue(s) relevant to the disease of interest. Recent studies in mouse models demonstrate that genes associated with monogenic forms of kidney disease showed cell-specific expression patterns, supporting further investigation of the clinical utility of single-cell–based RNA-sequencing nephrology.[78]

to identify disease-causal CNVs in 5% of children with CKD because of causes other than congenital anomalies of the kidney and urinary tract and in 1.1% of adults with all-cause CKD, suggesting that CNVs may contribute more broadly to CKD than traditionally thought.[101]

NGS-Based SVs Identification

Although CMA and MLPA remain the gold standards for identifying CNVs, recent studies suggest that CNVs can be detected with high sensitivity using bioinformatic tools from targeted panels' data; however, their overall performance varies, with lower accuracy reported for single-exon CNVs and CNVs in regions that are more poorly captured by short-read NGS.[102,103] CNVs can be called using bioinformatic methods from ES data. However, GS has superior SV detection ability, and it can identify balanced SVs as well as CNVs.[90] Considering that laboratories vary in whether they perform these analyses, it is important to check the types of variants analyzed when ordering a test.

PRACTICAL CONSIDERATIONS FOR CHOOSING BETWEEN DIFFERENT TESTING MODALITIES

When choosing between different genetic testing modalities, in addition to diagnostic sensitivity, other key considerations include cost, turn-around time, and incidental and secondary findings (Table 1).

Short-Read NGS Limitations

Short-read NGS has limited capacity to identify variants in certain parts of the genome, such as highly repetitive regions (e.g., the complement factor H gene cluster)[104] and regions with high sequence homology (e.g., the *PKD1* gene and its pseudogenes).[105] Short-read sequencing can have limited coverage of certain regions and lower detection sensitivity for certain variants (e.g., indels). To help address these issues, targeted or broad panels are frequently supplemented with other technologies.[106]

The detection of certain variants can be difficult across technologies. For example, in *MUC1*-associated autosomal dominant tubulointerstitial disease, the most commonly known disease-causal variant is an insertion inside a variable tandem number repeat unit of 60 nucleotides (60-mer), which leads to a frameshift and premature truncation of the encoded protein. Considering that Sanger sequencing and standard short-read NGS analyses are unable to detect this variant, identifying it requires long-range polymerase chain reaction and molecular cloning.[107] The variant's initial identification and alternate approaches, including computational pipelines using short-read NGS[108,109] and long-read sequencing[110] have been developed to identify this variant and may be implemented in the future among individuals with suspected *MUC1*-associated autosomal dominant tubulointerstitial disease. Owing to such technical limitations, laboratories often supplement targeted panels with other methodologies to increase their detection sensitivity.[106] Recently, new bioinformatics tools to identify variable tandem number repeats from ES and GS have been reported, which have variable detection accuracy.[111,112]

Variants of Uncertain Significance

A common concern about genetic testing is the possibility of variants of uncertain significance (VUS). Given that most genetic diseases are rare, current guidelines for clinical variant interpretation assess a variant's frequency in the general population versus the disease's known prevalence to help determine its pathogenicity.[113] However, because of multiple factors, including disparities in access to infrastructure and funding, non-European populations have been underrepresented in clinical settings and genomic research such that current population genetic databases do not reflect the diversity of the global population.[114] This underrepresentation complicates variant interpretation, because it can be difficult to gauge the true population prevalence of variants, and leads to higher rates of VUS among non-European individuals undergoing clinical genetic testing.[115-117] Importantly, there are ongoing initiatives to bring genomics to historically underrepresented regions, such as the Human Heredity and Health in Africa Kidney Disease Research Network,[118] Deciphering Diversities - Renal Asian Genetics Network,[119] and Brazilian Network of Pediatric Nephrotic Syndrome.[120] These efforts will help improve our understanding of the genetics of kidney disease across different populations, reducing the current ancestry-based disparities in VUS rates and supporting individuals of diverse backgrounds benefiting equitably from genetic testing.

Per current guidelines, VUS should not inform clinical decision-making.[113] As genome-wide tests, ES and GS may be expected to return more VUS than targeted panels. However, a recent analysis of over 1.5 million genetic tests from 19 clinical laboratories found a higher VUS rate from targeted panels than from ES or GS.[33] This is because of the differences in VUS reporting protocols; currently, panels generally report all VUS, whereas, for ES or GS, laboratories report only highly compelling VUS (e.g., those associated with genetic conditions that have high clinical overlap with the patient's listed phenotype and/or segregate appropriately with the disease in a family). Thus, the higher VUS rates reflect the lower specificity for a particular clinical subcategory of disease.[33] Given that resources needed to allow potential VUS reclassification are often limited, the VUS included on a genetic test report should be carefully reviewed (e.g., by a genetics professional) to help determine which ones merit further investigation.

Secondary Findings

ES and GS can also prompt concern about secondary findings. Although unrelated to the primary testing indication (i.e., kidney disease), secondary findings can enable presymptomatic diagnosis and prevention of medically actionable conditions,[121] and may have meaningful implications for kidney care as well.[122] Given that individuals vary in their preference to receive pretest counseling, it is important to discuss the pros and cons of analysis for these secondary findings and note that individuals can choose to opt out of receiving secondary findings. When choosing between different NGS tests, financial status and insurance coverage should be considered, because insurance coverage for ES or GS is highly variable.[123,124]

The American College of Medical Genetics and Genomics currently recommends that individuals undergoing genomic sequencing (i.e., ES or GS) be assessed for medically actionable secondary genetic findings, even if unrelated to the primary indication for genetic testing.[125,126] The current set of American College of Medical Genetics and Genomics medically actionable genes includes multiple genes associated with adult-onset conditions, such as hereditary cancer predisposition syndromes and cardiomyopathies.[37] Conversely, the European Society of Human Genetics recommends a cautious approach to such "opportunistic" screening, especially among minors.[127] In addition to the ethically complex question of whether to disclose such secondary findings for adult-onset conditions to a pediatric patient, analysis of trio (parents and child) ES or GS data for secondary genetic findings may also identify a parentally inherited variant, leading to parents receiving unprecedented information about their own risk for cancer, cardiovascular disease, or other disorders.[128] Current guidelines by the American College of Medical Genetics and Genomics, the European Society of Human Genetics, and the American Academy of Pediatrics recommend pretest counseling regarding the pros and cons of receiving such secondary genetic findings and providing parents with the option to "opt out" of the investigation and reporting of secondary findings.[129,130]

Laboratory Practices

Considering that each laboratory chooses which genes to include in their targeted or broad panels, panels vary in their gene content and thus, their diagnostic sensitivity and specificity for the associated phenotype. Developing a consensus list of genes associated with monogenic forms of kidney disease can help address this interlaboratory variability[6,27]; and global initiatives, such as the Gene Curation Coalition,[131] are contributing to this goal by assessing the clinical validity of gene-disease associations. In addition, to increasing the test's sensitivity, some laboratories supplement their tests with additional testing methodologies.

Although the advent of consensus guidelines for clinical variant interpretation led to more consistent interpretation across different clinical laboratories, there remains notable interlaboratory variations, affecting the tests' sensitivity.[113,132,133] When choosing a test, it is thus critical to consider the laboratory's expertise in classifying variants in the genes of interest. Laboratories also vary in follow-up testing provided. For example, some laboratories offer testing of family members to help with the potential reclassification of VUS, which is especially relevant if the patient has affected family members. Some laboratories also offer free testing of family members in case of positive genetic findings (i.e., cascade screening). In addition, some laboratories offer virtual panels where analysis of a selected set of genes is performed on ES or GS data, enabling a broader analysis without requiring additional patient DNA samples if the virtual panel testing yields negative results.

Cost

The price of a genetic test reflects not only the costs of sequencing but also those related to processing, storing, and analyzing the resulting genetic data. Broader tests generate larger amounts of data, which often results in a need for more sophisticated bioinformatic tools and greater data storage capacities. This larger amount of genetic data also increases the time and labor needed for variant interpretation. GS generates the largest amount of data that can confer substantial financial and interpretative costs, including for noncoding variants, which can be difficult to interpret and require further clinical and/or experimental follow-up to help ascertain their significance.[134] Nevertheless, investigations of children with suspected genetic diseases suggest that GS might be a more cost-effective tool than ES because of its higher diagnostic sensitivity.[135,136] Accordingly, GS is anticipated to become a first-line tool for clinical genetic testing in nephrology in the future.[137] Practically, the out-of-pocket cost (i.e., the amount paid by the patient) of genetic testing depends on several factors, including the test modality and insurance coverage.[138] Some laboratories promise a maximum out-of-pocket price for their tests to alleviate the fear of "surprise bills." Importantly, coverage for genetic testing varies substantially between countries, reflecting international differences in healthcare policy.[139] Access and costs depend on the test and country requirements, like preauthorization or pretest genetic counseling.[140] Given this variability, we only provide the relative costs of the genetic tests discussed here to each other (Table 1). In the United States, insurance coverage is usually lower for genome-wide testing than more targeted approaches.[124,141,142] For example, insurance coverage for CMA and ES remains variable, with a recent study of 801 pediatric patients with suspected genetic disease reporting that CMA and ES were covered by insurance in 89.6% and 83.4% of patients, respectively.[124] Although single-payer healthcare systems can help address such uneven coverage of genetic testing, they require deciding how to equitably allocate genetic testing in

the setting of finite budgets.[143] To support this goal, frameworks for the prioritization of genetic testing have been proposed in Europe.[144,145] Additional studies are needed to assess the most cost-effective approach for genetic testing of individuals with kidney diseases.

Turn-Around Time

In general, turn-around time is faster for more targeted forms of genetic testing such as Sanger sequencing and targeted panels than ES or GS (Table 1 and Table 2), reflecting that because they analyze a smaller proportion of the genome, fewer candidate variants need to be reviewed by the geneticists. Similarly, because these more targeted genetic modalities assess gene(s) related to the primary indication for testing (i.e., the suspected genetic subtype of kidney disease), there is a lower possibility of incidental and secondary findings.

GENETIC TEST SELECTION FOR INDIVIDUALS WITH KIDNEY DISEASE

In this section, we present a general framework for genetic test selection among individuals with kidney disease (Figure 2). In the featured case study (Table 4, Figure 3), we illustrate how this workflow can be applied to test selection in clinical practice. For readers interested in seeing additional examples across diverse clinical contexts, we provide 4 additional case vignettes in the Supplementary Material (cases S1–S4).

Informed and Shared Choice

Clinicians and patients should engage in shared decision-making throughout the process of genetic test selection, particularly when the evidence for choosing one type of test versus another is equivocal. In addition, we recommend that clinicians consult with a genetics professional (e.g., a genetic counselor and/or clinical geneticist) when faced with complex situations; for example, deciding on next steps for a patient with features consistent with a genetic cause of kidney disease who has nondiagnostic results on initial genetic testing.[6]

Patient With a Known Familial Genetic Diagnosis

Genetic test selection starts by ascertaining whether the individuals' biological relatives have a known genetic diagnosis (i.e., a pathogenic or likely pathogenic variant in a gene associated with the relevant clinical subtype of kidney disease, Figure 2). If so, we recommend that clinicians pursue targeted testing based on the type of variant that has been identified (Table 2); Sanger sequencing would be best for SNVs and small indels, whereas for SVs, MLPA, FISH, or CMA could be used depending on the size of the SV and the availability of MLPA or FISH tests for the familial SV.

Patient With a Disease Associated With One Gene

If the individual does not have a known familial genetic diagnosis, the options depend on the patient's clinical presentation. If the patient's clinical presentation is consistent with a clinical category of genetic kidney disease associated with a single genetic cause (e.g., Fabry disease or cystinosis), then Sanger sequencing, MLPA, or FISH are generally most appropriate (Tables 1 and 2).

Patient With a Disease Associated With Few or Multiple Genes

If the patient's condition may have multiple genetic causes, it can be further divided into those associated with several genes (e.g., Alport syndrome, autosomal dominant polycystic kidney disease) or many genes (e.g., steroid-resistant nephrotic syndrome, renal ciliopathies). For conditions that result from several genes, we suggest a targeted panel with CNV analysis, which offers a specific and sensitive way to detect variants in these genes. We recommend the test chosen include CNV analysis, which can be done on NGS data using bioinformatic methods or through supplementation with MLPA or CMA.

Patient With a Nonspecific Disease

If an individual does not have features consistent with a specific clinical category of genetic kidney disease (e.g., end-stage kidney disease of unknown etiology and no known familial genetic diagnosis), a broad targeted panel, ES, or GS are all reasonable first-line approaches, with clinicians and patients engaging in shared decision-making to determine which test best fits the patient's unique needs (Tables 1–3).

GENETIC RESULTS INTERPRETATION

Results of genetic testing can be diagnostic (positive) or nondiagnostic (negative or inconclusive results).

Diagnostic Results

If a pathogenic or likely pathogenic variant for a genetic disease that explains the patient's clinical presentation is identified, it is a diagnostic result. Diagnostic genetic findings can inform clinical prognosis and management, including evaluation and surveillance for the disease's different manifestations and initiation of targeted therapy. In addition, family members should be offered genetic counseling and cascade testing to determine their disease risk status,

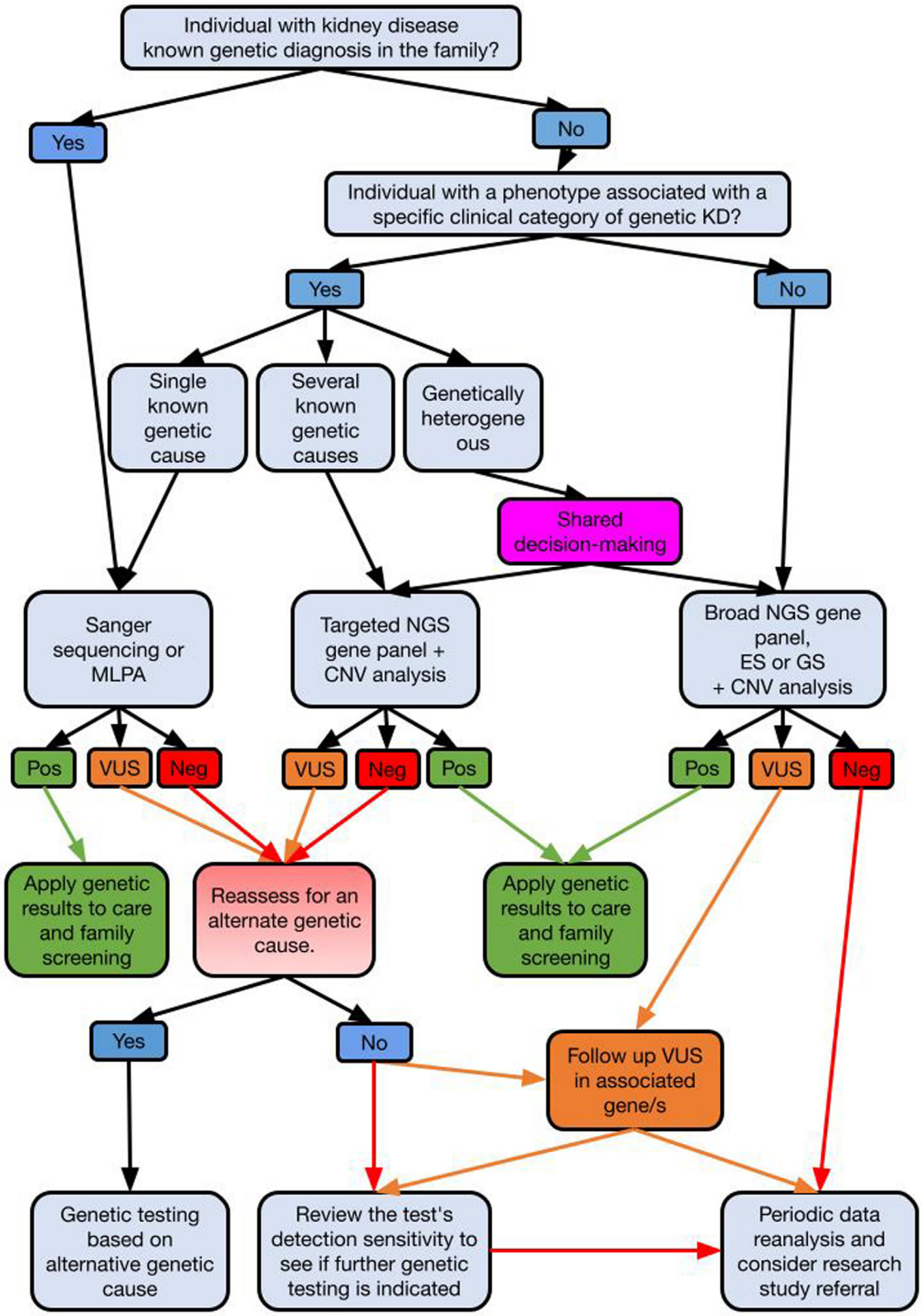

Figure 2. Framework for genetic test selection among individuals with kidney disease. The workflow illustrated here is described in the main text in the section: "Genetic test selection among individuals with kidney disease." ES, exome sequencing; GS, genome sequencing; MLPA, multiplex ligation probe–dependent amplification; Neg, negative; NGS, next-generation sequencing; Pos, positive; VUS, variant of uncertain significance.

inform their subsequent clinical management, and their eligibility to be related living donors for future renal transplantation.[6]

Nondiagnostic Results

Nondiagnostic results include negative results and inconclusive results. Negative results are when no

Table 4. Case study

Case Presentation
GF is a 42-yr-old male with a history of diabetes and hypertension who presents with end-stage kidney disease (ESKD). He reports that his grandmother, mother, and maternal aunt, all of whom are deceased, reached ESKD before the age of 50 yrs, which was presumed to be secondary to diabetes and hypertension. Serum electrolytes and complement studies are unremarkable, and urinalysis shows bland sediment and low-grade proteinuria. Renal imaging reveals shrunken, hyperechogenic kidneys; given these findings and his advanced kidney disease, renal biopsy is not performed. His 51-yr-old sister, KF, wants to donate her kidney to him. KF reports being in good health. She is normotensive and has no anomalies on renal imaging. KF's laboratory values show serum creatinine 0.8 (estimated glomerular filtration rate of 84 ml/min per 1.73 m^2) and fasting glucose of 75 mg/dl; urinalysis is within normal limits. KF notes their family identifies as African American, and she has read that individuals of Western African ancestry may be at higher risk of developing kidney disease. GF and KF ask if any additional tests could help them understand why GF and other members of their family have kidney disease and whether KF can safely donate a kidney to GF.
Genetic Differential Diagnosis
Although diabetic and hypertensive nephropathy are on the differential, GF's personal and family history of ESKD before the age of 50 yrs supports considering monogenic etiologies for his kidney disease. Although his clinical presentation is not specific for a particular category of genetic kidney disease, the absence of certain features can help narrow the differential, for example, the negative complement studies disfavoring a typical hemolytic uremic syndrome or other complement-mediated renal diseases. Given the cooccurrence of diabetes and renal disease in his family, *HNF1B* nephropathy is a possibility: though classically associated with cystic renal disease and diabetes, there is variable expressivity, with some individuals displaying only isolated renal hypoplasia or no structural renal anomalies on imaging.[146,147] In addition, given that GF is an African American of Western African ancestry, *APOL1* nephropathy should also be considered, because approximately 13% of African Americans harbor 2 *APOL1* risk alleles.[148] Although the *APOL1* risk genotype substantially increases kidney disease risk, a minority of individuals with *APOL1* risk genotypes develop kidney disease, suggesting that a "second hit," such as other genetic variant(s) and/or systemic or environmental factors, may be needed to produce disease. A study of over 15,000 individuals with kidney disease found that nearly 10% of individuals with *APOL1* risk genotypes harbored a diagnostic variant for a monogenic form of kidney disease, supporting genetic testing in individuals with suggestive features for monogenic forms of kidney disease even if they are known to have an *APOL1* risk genotype.[149]
Clinical Utility of Genetic Testing
For GF, genetic testing has the potential to pinpoint a specific cause of disease and thereby inform living-related donor selection and posttransplant prognosis and management.[26] Next-generation sequencing –based genetic testing has been reported to identify a monogenic cause in approximately 10% of adults with ESKD of unknown etiology.[150-152] Knowledge of the transplant recipient's primary kidney disease can help determine recurrence risk in the allograft and also identify individuals at increased risk of other common posttransplant complications (e.g., malignancy for *WT1*-associated focal segmental glomerulosclerosis, diabetes among individuals with *HNF1B* nephropathy), helping guide surveillance and choice of posttransplant therapy. In addition, by ascertaining whether family members harbor the disease-causal variant, genetic testing can help determine eligible living-related donors. If genetic testing includes investigation for the *APOL1* risk genotypes and/or other medically actionable disorders,[37] these findings may have clinical utility. For example, knowledge of the *APOL1* risk genotype status can inform about the recurrence risk in the allograft[153] and the donor's risk of developing CKD postdonation.[14]
Although not causal for an individual's renal disease, secondary findings in genes deemed medically actionable can inform management, for example, detection of a hereditary cancer predisposition syndrome informing immunosuppression regimen or identification of a pathogenic variant in *KCNQ1*, associated with long QT syndrome, prompting avoidance of QT-prolonging medications such as macrolide and quinolone antibiotics and azole antifungals.[122] Therefore, individuals should be counseled about the possible utility of receiving medically actionable secondary findings should they choose to pursue genome-wide testing.
Options for Genetic Testing
ESKD of unclear etiology and no specific familial form of kidney disease support a broad approach to genetic testing (Figure 2). GF's options include a broad targeted panel of genes associated with monogenic forms of CKD, virtual panel testing, or genome-wide testing (i.e., exome sequencing [ES] or genome sequencing). Becauseeach of these tests is a reasonable first-line approach,[35] GF and his nephrologist engage in shared decision-making. His nephrologist writes a letter of medical necessity describing how GF has kidney disease of unknown etiology with a family history of kidney disease and the clinical utility of genetic testing in his case and obtains insurance coverage for ES for him.
Results and Next Steps
ES reveals that GF has a pathogenic variant in the *HNF1B* gene. GF is given a genetic diagnosis of *HNF1B* nephropathy, which has meaningful implications for his clinical management. Identification of *HNF1B* nephropathy warrants targeted evaluation and surveillance for extrarenal manifestations, which include liver dysfunction, neuropsychiatric disease, and exocrine pancreatic insufficiency.[147,154] Moreover, because affected individuals have an increased risk of diabetes posttransplant, avoidance of tacrolimus and reduced corticosteroid usage in immunosuppression regimens is advised, and, for those with ESKD and diabetes, combined kidney-pancreas transplant can be considered.
In addition to the pathogenic *HNF1B* variant, GF's ES report notes that he harbors the *APOL1* G1/G1 risk genotype and has a heterozygous pathogenic variant in the *LDLR* gene, associated with autosomal dominant familial hypercholesterolemia. His sister, KF, is found to be negative for the *HNF1B* variant, but does harbor the *APOL1* G1/G1 risk genotype and *LDLR* pathogenic variant. She is counseled that, per population-based studies, individuals with *APOL1* risk genotypes have an ~2-fold increased risk of ESKD post donation, with the caveat that her risk may be lower because the lifetime risk of ESKD decreases as donors age.[155] Despite harboring the *APOL1* risk genotype, she still meets institutional cutoffs for acceptable lifetime risk and decides to proceed with donating her kidney.
As individuals with heterozygous familial hypercholesterolemia, GF and KF are referred to a cardiologist specialized in hereditary dyslipidemias for recommended management, including stringent lipid profile monitoring with a low threshold for initiating pharmacotherapy (e.g., with statins, ezetimibe, or PCSK9 inhibitors).[156] In addition, their familial hypercholesterolemia also informs immunosuppression regimen via supporting minimizing corticosteroid use, given corticosteroids' negative impact on lipid profile.

variants for genetic diseases relevant to the individual's clinical presentation are reported. Inconclusive results are when there are VUS (i.e., variants that are not currently clearly disease-causal or benign) for genetic diseases that could be relevant to the individual's clinical presentation.

Negative Results

For a patient initially suspected to have a specific clinical category of genetic kidney disease, clinicians can reassess the patient to determine if other clinical categories of genetic kidney disease are possible; if so, further genetic testing for these other possible kidney diseases would be indicated. If the clinical impression remains consistent with the originally suspected category of genetic kidney disease, we suggest additional targeted genetic testing to identify variants that may have been missed because of the technical limitations of the initial genetic test used. For patients with nonspecific phenotypes, we suggest routine reanalysis of their genetic data, which may identify disease-causal variants missed in the initial analysis, such as variants identified by newer bioinformatic pipelines or variants in newly discovered disease-associated genes.[157] In

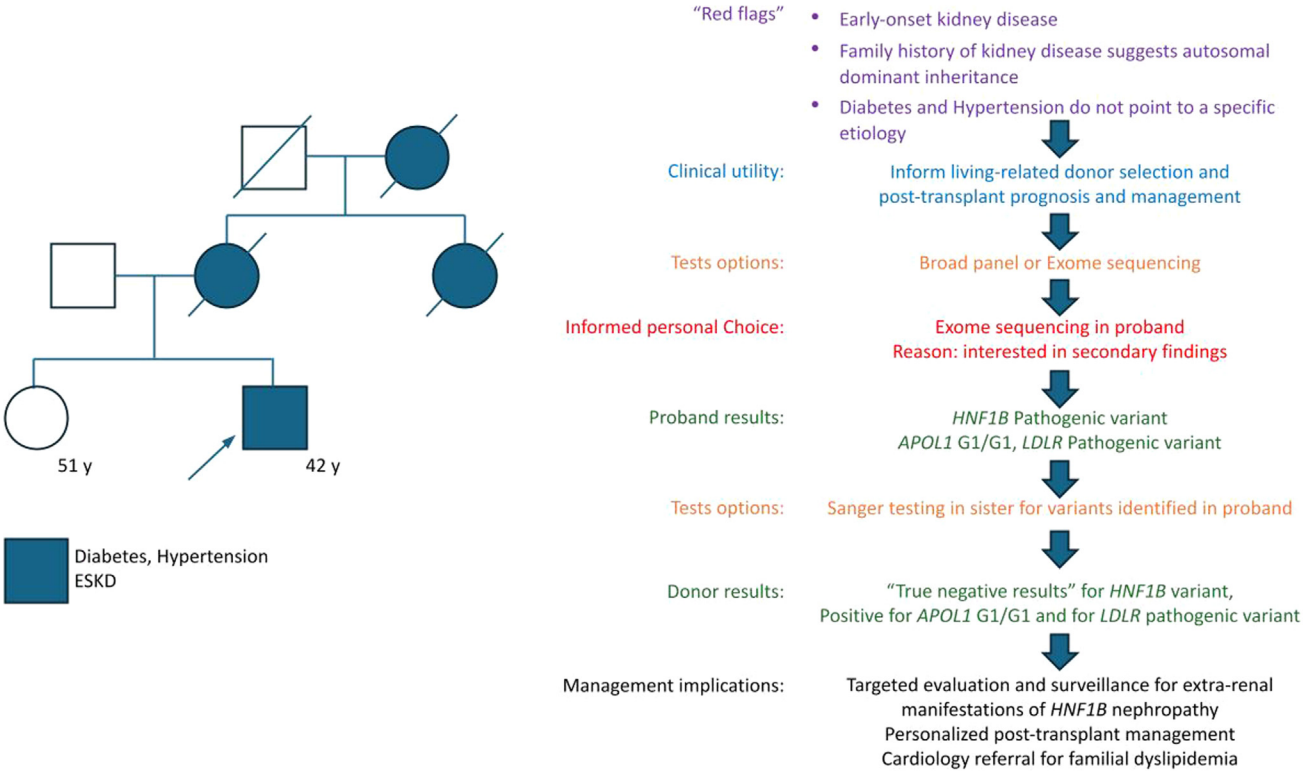

Figure 3. Clinical genetic testing and outcomes for case study. The workflow for clinical genetic testing and associated outcomes for the case described in Table 4 ("Case Study") is shown here. *APOL1* G1/G1, Apolipoprotein L1 gene G1 risk variant homozygote; *HNF1B*, hepatocyte nuclear factor 1 beta gene; *LDLR*, low density lipoprotein receptor gene.

addition, clinicians can consider referring such patients to research studies for further evaluation.[45,46]

Inconclusive Results and Follow-Up for Candidate Variants

For patients with inconclusive results, we suggest consulting with a genetics professional to help inform the next steps regarding the VUS identified.[6,27] If the VUS is deemed compelling, follow-up testing can help resolve its clinical significance. For example, if the VUS is in a gene associated with a genetic disease that has pathognomonic findings (e.g., on physical examination or biochemical testing), identification of these features can provide evidence for the variant's pathogenicity. Familial genetic testing can also help resolve VUS; for example, by identifying *de novo* variants or determining whether the variant segregates appropriately with the disease (i.e., is present in affected family members and absent in unaffected family members). In this case, because family members are being assessed for a single, known variant, we recommend using targeted approaches based on the specific type of variant, for example, Sanger sequencing for a SNV or MLPA/FISH/CMA for a deletion. Other molecular analyses can help inform variant classification, such as RNA analysis to determine the splicing impact of deep intronic variants[60] and DNA methylation testing to assess for a disease's episignature[72] (Table 3). In addition, with time, additional data may emerge that helps resolve a VUS, including observations of the variant in other affected individuals and/or in population databases and experimental assays demonstrating whether the variant has a functional impact. Data-sharing initiatives such as GenomeConnect, where patients can securely share their genetic and clinical data, can support patients and clinicians in learning about such additional data and lead to the resolution of VUS.[158,159]

THE NEED FOR MULTIDISCIPLINARY CARE

Nephrologists are not expected to become expert geneticists. However, to ensure equitable access to genetic testing, all nephrologists should be able to identify patients who may benefit from genetic testing and provide the appropriate referrals. As illustrated by recent reports on the association between genetic education and referral to genetic testing, including genetics education across different stages of medical training will help support this goal.[22,160,161] In addition, there is a growing community of nephrogenetics specialists available to assist clinicians; these include genetic counselors, nephrologists, and geneticists with expertise in the genetics of kidney diseases.[10,140,162-165] In the United States, the National Society of Genetic

Counselors has developed a website to help locate genetic counselors with nephrology expertise (findageneticcounselor.org). Similarly, the European Rare Kidney Disease Center Network has created a resource of nephrogenetics reference centers.[166] Collaboration involving nephrologists and genetics professionals can increase the diagnostic yield of genetic testing,[164,165] supporting its implementation in multiple clinical sites.

FUTURE DIRECTIONS

As genetic technologies continue to advance, there is a need to create evidence-based guidelines for implementing equitable genetic testing in nephrology.[6,27,167] Although expert panels have issued recommendations for genetic testing for certain disorders, such as Fabry disease[168] and steroid-resistant nephrotic syndrome,[169] comparative studies on tests' sensitivity, specificity, turn-around time, cost, and impact of secondary findings are needed to create data-driven frameworks for genetic test selection across different clinical subtypes of kidney disease. There is a need to identify the best implementation strategies to ensure equitable access to genetic testing in nephrology, particularly in resource-limited settings.[170] In addition, research is needed to guide the deployment of other types of genetic types, such as pharmacogenetics,[171] polygenic risk scores,[25,172-175] and relevant comorbidities and medically secondary findings.[122] As the scope and usage of genetic testing in nephrology broaden, tests that provide multiple types of information may become first-line modalities. For example, because GS can simultaneously provide information about SVs, SNVs, and indels in both the coding and noncoding regions and can provide pharmacogenetic information, polygenic risk scores, and information on other comorbidities, it may supersede targeted panels, ES, and CMA.

Because novel gene-disease associations are regularly reported, there is a need to assess the extent to which a given gene is associated with a particular form of kidney disease. Global initiatives such as the Gene Curation Coalition, which includes organizations such as the Clinical Genome Resource Kidney Domain Working Group, Genomics England Panel App, and PanelApp Australia are collaborating to lead efforts to identify genes reported causal for different forms of kidney disease and systematically review and classify their clinical validity.[131,176] For example, the Clinical Genome Resource Kidney Domain Working Group uses a standardized semiquantitative framework to assess the clinical validity of genes associated with a variety of kidney disease subtypes, including congenital anomalies of the kidney and urinary tract, complement-mediated kidney diseases, cystic disease and renal ciliopathies, glomerulopathies, and tubulopathies. Large-scale sequencing studies involving ethnically and clinically diverse patient cohorts should also help to assess gene-disease associations.

Establishing systematic guidelines for variant interpretation is likewise crucial to achieving genomic medicine in nephrology. In addition to determining the clinical validity of different gene-disease associations, there is a growing understanding that accurate variant interpretation requires tailoring variant classification guidelines to specific genes. For example, expert working groups have published recommendations for variant interpretation for Alport syndrome[177] and cystinuria.[178] Analyses of large datasets of patients with well-characterized monogenic forms of kidney diseases will help create sufficiently sensitive and specific gene-specific guidelines and thereby support increased diagnostic yield and reduced rates of VUS on clinical genetic testing.

As variant classification continues to evolve, clinicians and patients must be appropriately counseled regarding the need to periodically reevaluate genetic results, because variant reclassification can meaningfully inform clinical management.[179] Incorporation of artificial intelligence may help by increasing the efficiency of these efforts; however, further study is needed to assess the accuracy of artificial intelligence–based methods in these domains.[180,181] Of note, recent studies in undiagnosed rare disease cohorts highlight that resequencing can identify causal variants that were initially missed because of technical limitations of the original method of genetic testing.[157,182] As genetic technologies advance and sequencing costs continue to decrease, there is a need for further studies to compare the diagnostic yield and cost efficacy of resequencing patient samples versus reanalyzing previously generated sequence data.[183]

CONCLUSION

Genetic testing is emerging as a first-line diagnostic tool in nephrology, with the potential to enable diagnosis and targeted management in a variety of clinical contexts (Table 4, Figure 3, cases S1–S4). New modalities, such as optical genome mapping, long-read sequencing, DNA methylation analysis, and RNA sequencing optical genome mapping, are now being piloted for rare disease diagnosis, including kidney disease (Table 3). In this review, we aimed to provide nephrologists with a practical framework for genetic test selection and support them in integrating genetics into their clinical practices. As the usage of genetic testing in nephrology continues to grow, we anticipate

that multidisciplinary partnerships in clinical practice, scientific research, and medical education will support the development and implementation of evidence-based guidelines that support genetic testing and personalized care for individuals with kidney disease.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Case Vignettes (includes **Cases S1–S4).**

Glossary.

Supplementary References.

REFERENCES

1. Vivante A, Hildebrandt F. Exploring the genetic basis of early-onset chronic kidney disease. *Nat Rev Nephrol*. 2016;12:133–146. https://doi.org/10.1038/nrneph.2015.205
2. Bassanese G, Wlodkowski T, Servais A, et al. The European Rare Kidney Disease Registry (ERKReg): objectives, design and initial results. *Orphanet J Rare Dis*. 2021;16:251. https://doi.org/10.1186/s13023-021-01872-8
3. Liapis H, Gaut JP. The renal biopsy in the genomic era. *Pediatr Nephrol*. 2013;28:1207–1219. https://doi.org/10.1007/s00467-012-2356-9
4. Knoers N, Antignac C, Bergmann C, et al. Genetic testing in the diagnosis of chronic kidney disease: recommendations for clinical practice. *Nephrol Dial Transplant*. 2022;37:239–254. https://doi.org/10.1093/ndt/gfab218
5. Luciano RL, Moeckel GW. Update on the native kidney biopsy: core curriculum 2019. *Am J Kidney Dis*. 2019;73:404–415. https://doi.org/10.1053/j.ajkd.2018.10.011
6. Köttgen A, Cornec-Le Gall E, Halbritter J, et al. Genetics in chronic kidney disease: conclusions from a Kidney Disease: improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2022;101:1126–1141. https://doi.org/10.1016/j.kint.2022.03.019
7. Savige J, Ariani F, Mari F, et al. Expert consensus guidelines for the genetic diagnosis of Alport syndrome. *Pediatr Nephrol*. 2019;34:1175–1189. https://doi.org/10.1007/s00467-018-3985-4
8. Groopman EE, Rasouly HM, Gharavi AG. Genomic medicine for kidney disease. *Nat Rev Nephrol*. 2018;14:83–104. https://doi.org/10.1038/nrneph.2017.167
9. Connaughton DM, Hildebrandt F. Personalized medicine in chronic kidney disease by detection of monogenic mutations. *Nephrol Dial Transplant*. 2020;35:390–397. https://doi.org/10.1093/ndt/gfz028
10. Bogyo K, Vena N, May H, et al. Incorporating genetics services into adult kidney disease care. *Am J Med Genet C Semin Med Genet*. 2022;190:289–301. https://doi.org/10.1002/ajmg.c.32004
11. Bauskis A, Strange C, Molster C, Fisher C. The diagnostic odyssey: insights from parents of children living with an undiagnosed condition. *Orphanet J Rare Dis*. 2022;17:233. https://doi.org/10.1186/s13023-022-02358-x
12. Faye F, Crocione C, Anido de Peña R, et al. Time to diagnosis and determinants of diagnostic delays of people living with a rare disease: results of a Rare Barometer retrospective patient survey. *Eur J Hum Genet*. 2024;32:1116–1126. https://doi.org/10.1038/s41431-024-01604-z
13. Jefferis J, Mallett AJ. Exploring the impact and utility of genomic sequencing in established CKD. *Clin Kidney J*. 2024;17:sfae043. https://doi.org/10.1093/ckj/sfae043
14. Thomas CP, Daloul R, Lentine KL, et al. Genetic evaluation of living kidney donor candidates: a review and recommendations for best practices. *Am J Transplant*. 2023;23:597–607. https://doi.org/10.1016/j.ajt.2023.02.020
15. Voelkerding KV, Dames SA, Durtschi JD. Next-generation sequencing: from basic research to diagnostics. *Clin Chem*. 2009;55:641–658. https://doi.org/10.1373/clinchem.2008.112789
16. Goodwin S, McPherson JD, McCombie WR. Coming of age: ten years of next-generation sequencing technologies. *Nat Rev Genet*. 2016;17:333–351. https://doi.org/10.1038/nrg.2016.49
17. Shashi V, McConkie-Rosell A, Rosell B, et al. The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. *Genet Med*. 2014;16:176–182. https://doi.org/10.1038/gim.2013.99
18. Xue Y, Ankala A, Wilcox WR, Hegde MR. Solving the molecular diagnostic testing conundrum for Mendelian disorders in the era of next-generation sequencing: single-gene, gene panel, or exome/genome sequencing. *Genet Med*. 2015;17:444–451. https://doi.org/10.1038/gim.2014.122
19. Adams DR, Eng CM. Next-generation sequencing to diagnose suspected genetic disorders. *N Engl J Med*. 2018;379:1353–1362. https://doi.org/10.1056/NEJMra1711801
20. Sullivan JA, Schoch K, Spillmann RC, Shashi V. Exome/genome sequencing in undiagnosed syndromes. *Annu Rev Med*. 2023;74:489–502. https://doi.org/10.1146/annurev-med-042921-110721
21. Shashi V, McConkie-Rosell A, Schoch K, et al. Practical considerations in the clinical application of whole-exome sequencing. *Clin Genet*. 2016;89:173–181. https://doi.org/10.1111/cge.12569
22. Rasouly HM, Balderes O, Marasa M, et al. The effect of genetic education on the referral of patients to genetic evaluation: findings from a national survey of nephrologists. *Genet Med*. 2023;25:100814. https://doi.org/10.1016/j.gim.2023.100814
23. Adams SM, Crisamore KR, Empey PE. Clinical pharmacogenomics: applications in nephrology. *Clin J Am Soc*

Nephrol. 2018;13:1561–1571. https://doi.org/10.2215/CJN.02730218

24. Tambur AR, Kosmoliaptsis V, Claas FHJ, Mannon RB, Nickerson P, Naesens M. Significance of HLA-DQ in kidney transplantation: time to reevaluate human leukocyte antigen-matching priorities to improve transplant outcomes? An expert review and recommendations. *Kidney Int*. 2021;100:1012–1022. https://doi.org/10.1016/j.kint.2021.06.026
25. Khan A, Kiryluk K. Polygenic scores and their applications in kidney disease. *Nat Rev Nephrol*. 2025;21:24–38. https://doi.org/10.1038/s41581-024-00886-2
26. Soraru J, Chakera A, Isbel N, et al. The evolving role of diagnostic genomics in kidney transplantation. *Kidney Int Rep*. 2022;7:1758–1771. https://doi.org/10.1016/j.ekir.2022.05.019
27. Franceschini N, Feldman DL, Berg JS, et al. Advancing genetic testing in kidney diseases: report from a national kidney foundation working group. *Am J Kidney Dis*. 2024. 2024;84:751–766. https://doi.org/10.1053/j.ajkd.2024.05.010
28. Jarvik GP, Evans JP. Mastering genomic terminology. *Genet Med*. 2017;19:491–492. https://doi.org/10.1038/gim.2016.139
29. Postolache L, Parsa A, Simoni P, et al. Widespread kidney anomalies in children with Down syndrome. *Pediatr Nephrol*. 2022;37:2361–2368. https://doi.org/10.1007/s00467-022-05455-y
30. Rossetti CM, Simonetti GD, Bianchetti MG, et al. Kidney and urogenital abnormalities in Down syndrome: a meta-analysis. *Ital J Pediatr*. 2024;50:79. https://doi.org/10.1186/s13052-024-01636-7
31. Harewood L, Liu M, Keeling J, et al. Bilateral renal agenesis/hypoplasia/dysplasia (BRAHD): postmortem analysis of 45 cases with breakpoint mapping of two de novo translocations. *PLoS One*. 2010;5:e12375. https://doi.org/10.1371/journal.pone.0012375
32. Halder A, Jain M, Kabra M, Gupta N. Mosaic 22q11.2 microdeletion syndrome: diagnosis and clinical manifestations of two cases. *Mol Cytogenet*. 2008;1:18. https://doi.org/10.1186/1755-8166-1-18
33. Rehm HL, Alaimo JT, Aradhya S, et al. The landscape of reported VUS in multi-gene panel and genomic testing: time for a change. *Genet Med*. 2023;25:100947. https://doi.org/10.1016/j.gim.2023.100947
34. Bu F, Borsa NG, Jones MB, et al. High-throughput genetic testing for thrombotic microangiopathies and C3 glomerulopathies. *J Am Soc Nephrol*. 2016;27:1245–1253. https://doi.org/10.1681/ASN.2015040385
35. Hays T, Groopman EE, Gharavi AG. Genetic testing for kidney disease of unknown etiology. *Kidney Int*. 2020;98:590–600. https://doi.org/10.1016/j.kint.2020.03.031
36. Szabó T, Orosz P, Balogh E, et al. Comprehensive genetic testing in children with a clinical diagnosis of ARPKD identifies phenocopies. *Pediatr Nephrol*. 2018;33:1713–1721. https://doi.org/10.1007/s00467-018-3992-5
37. Miller DT, Lee K, Abul-Husn NS, et al. ACMG SF v3.2 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2023;25:100866. https://doi.org/10.1016/j.gim.2023.100866
38. Mallawaarachchi AC, Hort Y, Cowley MJ, et al. Whole-genome sequencing overcomes pseudogene homology to diagnose autosomal dominant polycystic kidney disease. *Eur J Hum Genet*. 2016;24:1584–1590. https://doi.org/10.1038/ejhg.2016.48
39. Cheng C, Fei Z, Xiao P. Methods to improve the accuracy of next-generation sequencing. *Front Bioeng Biotechnol*. 2023;11:982111. https://doi.org/10.3389/fbioe.2023.982111
40. Hui L, DelMonte T, Ranade K. Genotyping using the TaqMan assay. *Curr Protoc Hum Genet*. 2008;56:2–10. https://doi.org/10.1002/0471142905.hg0210s56
41. Asharam K, Bhimma R, David VA, et al. NPHS2 V260E is a frequent cause of steroid-resistant nephrotic syndrome in black South African children. *Kidney Int Rep*. 2018;3:1354–1362. https://doi.org/10.1016/j.ekir.2018.07.017
42. Gordeeva V, Sharova E, Babalyan K, Sultanov R, Govorun VM, Arapidi G. Benchmarking germline CNV calling tools from exome sequencing data. *Sci Rep*. 2021;11:14416. https://doi.org/10.1038/s41598-021-93878-2
43. Warburton PE, Sebra RP. Long-read DNA sequencing: recent advances and remaining challenges. *Annu Rev Genomics Hum Genet*. 2023;24:109–132. https://doi.org/10.1146/annurev-genom-101722-103045
44. Sanford Kobayashi E, Batalov S, Wenger AM, et al. Approaches to long-read sequencing in a clinical setting to improve diagnostic rate. *Sci Rep*. 2022;12:16945. https://doi.org/10.1038/s41598-022-20113-x
45. Splinter K, Adams DR, Bacino CA, et al. Effect of genetic diagnosis on patients with previously undiagnosed disease. *N Engl J Med*. 2018;379:2131–2139. https://doi.org/10.1056/NEJMoa1714458
46. 100,000 Genomes Project Pilot Investigators, Smedley D, Smith KR, et al. 100,000 genomes pilot on rare-disease diagnosis in health care - preliminary report. *N Engl J Med*. 2021;385:1868–1880. https://doi.org/10.1056/NEJMoa2035790
47. Wright CF, Campbell P, Eberhardt RY, et al. Genomic diagnosis of rare pediatric disease in the United Kingdom and Ireland. *N Engl J Med*. 2023;388:1559–1571. https://doi.org/10.1056/NEJMoa2209046
48. Chan S, Lam E, Saghbini M, et al. Structural variation detection and analysis using Bionanooptical mapping. *Methods Mol Biol*. 2018;1833:193–203. https://doi.org/10.1007/978-1-4939-8666-8_16
49. Lam ET, Hastie A, Lin C, et al. Genome mapping on nanochannel arrays for structural variation analysis and sequence assembly. *Nat Biotechnol*. 2012;30:771–776. https://doi.org/10.1038/nbt.2303
50. Mantere T, Neveling K, Pebrel-Richard C, et al. Optical genome mapping enables constitutional chromosomal aberration detection. *Am J Hum Genet*. 2021;108:1409–1422. https://doi.org/10.1016/j.ajhg.2021.05.012
51. Cope H, Barseghyan H, Bhattacharya S, et al. Detection of a mosaic CDKL5 deletion and inversion by optical genome mapping ends an exhaustive diagnostic odyssey. *Mol Genet Genom Med*. 2021;9:e1665. https://doi.org/10.1002/mgg3.1665
52. Sabatella M, Mantere T, Waanders E, et al. Optical genome mapping identifies a germline retrotransposon insertion in SMARCB1 in two siblings with atypical teratoid rhabdoid

tumors. *J Pathol*. 2021;255:202–211. https://doi.org/10.1002/path.5755

53. Stence AA, Thomason JG, Pruessner JA, et al. Validation of optical genome mapping for the molecular diagnosis of facioscapulohumeral muscular dystrophy. *J Mol Diagn*. 2021;23:1506–1514. https://doi.org/10.1016/j.jmoldx.2021.07.021
54. Dremsek P, Schwarz T, Weil B, Malashka A, Laccone F, Neesen J. Optical genome mapping in routine human genetic diagnostics-its advantages and limitations. *Genes (Basel)*. 2021;12:1958. https://doi.org/10.3390/genes12121958
55. De Coster W, Weissensteiner MH, Sedlazeck FJ. Towards population-scale long-read sequencing. *Nat Rev Genet*. 2021;22:572–587. https://doi.org/10.1038/s41576-021-00367-3
56. Logsdon GA, Vollger MR, Eichler EE. Long-read human genome sequencing and its applications. *Nat Rev Genet*. 2020;21:597–614. https://doi.org/10.1038/s41576-020-0236-x
57. Simpson JT, Workman RE, Zuzarte PC, David M, Dursi LJ, Timp W. Detecting DNA cytosine methylation using nanopore sequencing. *Nat Methods*. 2017;14:407–410. https://doi.org/10.1038/nmeth.4184
58. Flusberg BA, Webster DR, Lee JH, et al. Direct detection of DNA methylation during single-molecule, real-time sequencing. *Nat Methods*. 2010;7:461–465. https://doi.org/10.1038/nmeth.1459
59. Miller DE, Sulovari A, Wang T, et al. Targeted long-read sequencing identifies missing disease-causing variation. *Am J Hum Genet*. 2021;108:1436–1449. https://doi.org/10.1016/j.ajhg.2021.06.006
60. Viering DHHM, Hureaux M, Neveling K, et al. Long-read sequencing identifies novel pathogenic intronic variants in Gitelman syndrome. *J Am Soc Nephrol*. 2023;34:333–345. https://doi.org/10.1681/ASN.2022050627
61. Xu D, Mao A, Chen L, Wu L, Ma Y, Mei C. Comprehensive analysis of PKD1 and PKD2 by long-read sequencing in autosomal dominant polycystic kidney disease. *Clin Chem*. 2024;70:841–854. https://doi.org/10.1093/clinchem/hvae030
62. Cohen ASA, Farrow EG, Abdelmoity AT, et al. Genomic answers for children: dynamic analyses of >1000 pediatric rare disease genomes. *Genet Med*. 2022;24:1336–1348. https://doi.org/10.1016/j.gim.2022.02.007
63. Mahmoud M, Huang Y, Garimella K, et al. Utility of long-read sequencing for All of Us. *Nat Commun*. 2024;15:837. https://doi.org/10.1038/s41467-024-44804-3
64. Gustafson JA, Gibson SB, Damaraju N, et al. High-coverage nanopore sequencing of samples from the1000 Genomes Project to build a comprehensive catalog of human genetic variation. *Genome Res*. 2024;34:2061–2073. https://doi.org/10.1101/gr.279273.124
65. Fahrner JA, Bjornsson HT. Mendelian disorders of the epigenetic machinery: tipping the balance of chromatin states. *Annu Rev Genomics Hum Genet*. 2014;15:269–293. https://doi.org/10.1146/annurev-genom-090613-094245
66. Merdler-Rabinowicz R, Pode-Shakked B, Vivante A, et al. Kidney and urinary tract findings among patients with Kabuki (make-up) syndrome. *Pediatr Nephrol*. 2021;36:4009–4012. https://doi.org/10.1007/s00467-021-05216-3
67. van Ravenswaaij-Arts CM, Hefner M, Blake K, Martin DM. CHD7 disorder. In: Adam MP, Feldman J, Mirzaa GM, et al., eds. *GeneReviews®*. Seattle: University of Washington; 1993. Updated September 29, 2022. Accessed September 25, 2024. http://www.ncbi.nlm.nih.gov/books/NBK1117/
68. Sadikovic B, Levy MA, Kerkhof J, et al. Clinical epigenomics: genome-wide DNA methylation analysis for the diagnosis of Mendelian disorders. *Genet Med*. 2021;23:1065–1074. https://doi.org/10.1038/s41436-020-01096-4
69. Eggermann T, Monk D, de Nanclares GP, et al. Imprinting disorders. *Nat Rev Dis Primers*. 2023;9:33. https://doi.org/10.1038/s41572-023-00443-4
70. Chater-Diehl E, Goodman SJ, Cytrynbaum C, Turinsky AL, Choufani S, Weksberg R. Anatomy of DNA methylation signatures: emerging insights and applications. *Am J Hum Genet*. 2021;108:1359–1366. https://doi.org/10.1016/j.ajhg.2021.06.015
71. Laird PW. Principles and challenges of genomewide DNA methylation analysis. *Nat Rev Genet*. 2010;11:191–203. https://doi.org/10.1038/nrg2732
72. Aref-Eshghi E, Bend EG, Colaiacovo S, et al. Diagnostic utility of genome-wide DNA methylation testing in genetically unsolved individuals with suspected hereditary conditions. *Am J Hum Genet*. 2019;104:685–700. https://doi.org/10.1016/j.ajhg.2019.03.008
73. Srivastava S, Love-Nichols JA, Dies KA, et al. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. *Genet Med*. 2019;21:2413–2421. https://doi.org/10.1038/s41436-019-0554-6
74. Byron SA, Van Keuren-Jensen KR, Engelthaler DM, Carpten JD, Craig DW. Translating RNA sequencing into clinical diagnostics: opportunities and challenges. *Nat Rev Genet*. 2016;17:257–271. https://doi.org/10.1038/nrg.2016.10
75. Truty R, Ouyang K, Rojahn S, et al. Spectrum of splicing variants in disease genes and the ability of RNA analysis to reduce uncertainty in clinical interpretation. *Am J Hum Genet*. 2021;108:696–708. https://doi.org/10.1016/j.ajhg.2021.03.006
76. Dorval G, Le Gac G, Morinière V, et al. Targeted RNAseq from patients' urinary cells to validate pathogenic non-coding variants in autosomal dominant polycystic kidney disease genes: a proof of concept. *Kidney Int*. 2024;106:532–535. https://doi.org/10.1016/j.kint.2024.05.029
77. Frésard L, Smail C, Ferraro NM, et al. Identification of rare-disease genes using blood transcriptome sequencing and large control cohorts. *Nat Med*. 2019;25:911–919. https://doi.org/10.1038/s41591-019-0457-8
78. Park J, Shrestha R, Qiu C, et al. Single-cell transcriptomics of the mouse kidney reveals potential cellular targets of kidney disease. *Science*. 2018;360:758–763. https://doi.org/10.1126/science.aar2131
79. Kopp JB, Anders HJ, Susztak K, et al. Podocytopathies. *Nat Rev Dis Primers*. 2020;6:68. https://doi.org/10.1038/s41572-020-0196-7
80. Mansilla MA, Sompallae RR, Nishimura CJ, et al. Targeted broad-based genetic testing by next-generation sequencing informs diagnosis and facilitates management in patients with kidney diseases. *Nephrol Dial Transplant*. 2021;36:295–305. https://doi.org/10.1093/ndt/gfz173

81. Dahl NK, Bloom MS, Chebib FT, et al. The clinical utility of genetic testing in the diagnosis and management of adults with chronic kidney disease. *J Am Soc Nephrol*. 2023;34:2039–2050. https://doi.org/10.1681/ASN.0000000000000249

82. Patwardhan A, Harris J, Leng N, et al. Achieving high-sensitivity for clinical applications using augmented exome sequencing. *Genome Med*. 2015;7:71. https://doi.org/10.1186/s13073-015-0197-4

83. Ali H, Al-Mulla F, Hussain N, et al. PKD1 Duplicated regions limit clinical utility of whole exome sequencing for genetic diagnosis of autosomal dominant polycystic kidney disease. *Sci Rep*. 2019;9:4141. https://doi.org/10.1038/s41598-019-40761-w

84. Zhao E, Bomback M, Khan A, et al. The expanded spectrum of human disease associated with GREB1L likely includes complex congenital heart disease. *Prenat Diagn*. 2024;44:343–351. https://doi.org/10.1002/pd.6527

85. Lelieveld SH, Spielmann M, Mundlos S, Veltman JA, Gilissen C. Comparison of exome and genome sequencing technologies for the complete capture of protein-coding regions. *Hum Mutat*. 2015;36:815–822. https://doi.org/10.1002/humu.22813

86. Belkadi A, Bolze A, Itan Y, et al. Whole-genome sequencing is more powerful than whole-exome sequencing for detecting exome variants. *Proc Natl Acad Sci U S A*. 2015;112:5473–5478. https://doi.org/10.1073/pnas.1418631112

87. Mallawaarachchi AC, Lundie B, Hort Y, et al. Genomic diagnostics in polycystic kidney disease: an assessment of real-world use of whole-genome sequencing. *Eur J Hum Genet*. 2021;29:760–770. https://doi.org/10.1038/s41431-020-00796-4

88. Schijvens AM, van de Kar NC, Bootsma-Robroeks CM, Cornelissen EA, van den Heuvel LP, Schreuder MF. Mitochondrial disease and the kidney with a special focus on CoQ10 deficiency. *Kidney Int Rep*. 2020;5:2146–2159. https://doi.org/10.1016/j.ekir.2020.09.044

89. Stenton SL, Prokisch H. Genetics of mitochondrial diseases: identifying mutations to help diagnosis. *EBiomedicine*. 2020;56:102784. https://doi.org/10.1016/j.ebiom.2020.102784

90. Yang L. A practical guide for structural variation detection in the human genome. *Curr Protoc Hum Genet*. 2020;107:e103. https://doi.org/10.1002/cphg.103

91. Trask BJ. Human cytogenetics: 46 chromosomes, 46 years and counting. *Nat Rev Genet*. 2002;3:769–778. https://doi.org/10.1038/nrg905

92. Marakhonov AV, Vasilyeva TA, Minzhenkova ME, et al. Complex chromosomal rearrangement involving chromosomes 10 and 11, accompanied by two adjacent 11p14.1p13 and 11p13p12 deletions, identified in a patient with WAGR syndrome. *Int J Mol Sci*. 2023;24:16923. https://doi.org/10.3390/ijms242316923

93. Hildebrandt F, Rensing C, Betz RC, et al. Establishing an algorithm for molecular genetic diagnostics in 127 families with juvenile nephronophthisis. *Kidney Int*. 2001;59:434–445. https://doi.org/10.1046/j.1523-1755.2001.059002434.x

94. Wang XM, Shao L, Xiao H, et al. Lessons from 801 clinical TFE3/TFEB fluorescence in situ hybridization assays performed on renal cell carcinoma suspicious for MiTF family aberrations. *Am J Clin Pathol*. 2023;160:549–554. https://doi.org/10.1093/ajcp/aqad089

95. Stuppia L, Antonucci I, Palka G, Gatta V. Use of the MLPA assay in the molecular diagnosis of gene copy number alterations in human genetic diseases. *Int J Mol Sci*. 2012;13:3245–3276. https://doi.org/10.3390/ijms13033245

96. Hertz JM, Juncker I, Marcussen N. MLPA and cDNA analysis improves COL4A5 mutation detection in X-linked Alport syndrome. *Clin Genet*. 2008;74:522–530. https://doi.org/10.1111/j.1399-0004.2008.01051.x

97. Bu F, Maga T, Meyer NC, et al. Comprehensive genetic analysis of complement and coagulation genes in atypical hemolytic uremic syndrome. *J Am Soc Nephrol*. 2014;25:55–64. https://doi.org/10.1681/ASN.2013050453

98. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet*. 2010;86:749–764. https://doi.org/10.1016/j.ajhg.2010.04.006

99. Vermeesch JR, Brady PD, Sanlaville D, Kok K, Hastings RJ. Genome-wide arrays: quality criteria and platforms to be used in routine diagnostics. *Hum Mutat*. 2012;33:906–915. https://doi.org/10.1002/humu.22076

100. Verbitsky M, Sanna-Cherchi S, Fasel D, et al. Genomic imbalances in patients with pediatric chronic kidney disease. *J Clin Invest*. 2015;125:2171–2178. https://doi.org/10.1172/JCI80877

101. Verbitsky M, Krishnamurthy S, Krithivasan P, et al. Genomic disorders in CKD across the lifespan. *J Am Soc Nephrol*. 2023;34:607–618. https://doi.org/10.1681/ASN.2022060725

102. Moreno-Cabrera JM, Del Valle J, Castellanos E, et al. Evaluation of CNV detection tools for NGS panel data in genetic diagnostics. *Eur J Hum Genet*. 2020;28:1645–1655. https://doi.org/10.1038/s41431-020-0675-z

103. Kerkhof J, Schenkel LC, Reilly J, et al. Clinical validation of copy number variant detection from targeted next-generation sequencing panels. *J Mol Diagn*. 2017;19:905–920. https://doi.org/10.1016/j.jmoldx.2017.07.004

104. Piras R, Valoti E, Alberti M, et al. CFH and CFHR structural variants in atypical hemolytic uremic syndrome: prevalence, genomic characterization and impact on outcome. *Front Immunol*. 2022;13:1011580. https://doi.org/10.3389/fimmu.2022.1011580

105. Rossetti S, Hopp K, Sikkink RA, et al. Identification of gene mutations in autosomal dominant polycystic kidney disease through targeted resequencing. *J Am Soc Nephrol*. 2012;23:915–933. https://doi.org/10.1681/ASN.2011101032

106. Rehm HL. Disease-targeted sequencing: a cornerstone in the clinic. *Nat Rev Genet*. 2013;14:295–300. https://doi.org/10.1038/nrg3463

107. Kirby A, Gnirke A, Jaffe DB, et al. Mutations causing medullary cystic kidney disease type 1 lie in a large VNTR in MUC1 missed by massively parallel sequencing. *Nat Genet*. 2013;45:299–303. https://doi.org/10.1038/ng.2543

108. Fages V, Bourre F, Larrue R, et al. Description of a new simple and cost-effective molecular testing that could simplify MUC1 variant detection. *Kidney Int Rep*. 2024;9:1451–1457. https://doi.org/10.1016/j.ekir.2024.01.058

109. Saei H, Morinière V, Heidet L, et al. VNtyper enables accurate alignment-free genotyping of MUC1 coding VNTR using short-read sequencing data in autosomal dominant tubulointerstitial kidney disease. *iScience*. 2023;26:107171. https://doi.org/10.1016/j.isci.2023.107171

110. Okada E, Morisada N, Horinouchi T, et al. Detecting MUC1 variants in patients clinicopathologically diagnosed with having autosomal dominant tubulointerstitial kidney disease. *Kidney Int Rep*. 2022;7:857–866. https://doi.org/10.1016/j.ekir.2021.12.037

111. Bakhtiari M, Shleizer-Burko S, Gymrek M, Bansal V, Bafna V. Targeted genotyping of variable number tandem repeats with adVNTR. *Genome Res*. 2018;28:1709–1719. https://doi.org/10.1101/gr.235119.118

112. Gelfand Y, Hernandez Y, Loving J, Benson G. VNTRseek-a computational tool to detect tandem repeat variants in high-throughput sequencing data. *Nucleic Acids Res*. 2014;42:8884–8894. https://doi.org/10.1093/nar/gku642

113. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405–424. https://doi.org/10.1038/gim.2015.30

114. Wang Y, He Y, Shi Y, et al. Aspiring toward equitable benefits from genomic advances to individuals of ancestrally diverse backgrounds. *Am J Hum Genet*. 2024;111:809–824. https://doi.org/10.1016/j.ajhg.2024.04.002

115. Chen E, Facio FM, Aradhya KW, et al. Rates and classification of variants of uncertain significance in hereditary disease genetic testing. *JAMA Netw Open*. 2023;6:e2339571. https://doi.org/10.1001/jamanetworkopen.2023.39571

116. Florentine MM, Rouse SL, Stephans J, et al. Racial and ethnic disparities in diagnostic efficacy of comprehensive genetic testing for sensorineural hearing loss. *Hum Genet*. 2022;141:495–504. https://doi.org/10.1007/s00439-021-02338-4

117. Kurian AW, Ward KC, Hamilton AS, et al. Uptake, results, and outcomes of germline multiple-gene sequencing after diagnosis of breast cancer. *JAMA Oncol*. 2018;4:1066–1072. https://doi.org/10.1001/jamaoncol.2018.0644

118. Adu D, Ojo A, H3A-KDRN Investigators, H3A-KDRN Investigators. Overview of the human heredity and health in Africa Kidney disease research network (H3A-KDRN). *Kidney360*. 2021;2:129–133. https://doi.org/10.34067/KID.0002592020

119. Lu L, Yap YC, Nguyen DQ, et al. Multicenter study on the genetics of glomerular diseases among southeast and South Asians: deciphering Diversities - Renal Asian Genetics Network (DRAGoN). *Clin Genet*. 2022;101:541–551. https://doi.org/10.1111/cge.14116

120. Feltran LS, Watanabe A, Guaragna MS, et al. Brazilian Network of Pediatric Nephrotic Syndrome (REBRASNI). *Kidney Int Rep*. 2020;5:358–362. https://doi.org/10.1016/j.ekir.2019.11.007

121. Katz AE, Nussbaum RL, Solomon BD, Rehm HL, Williams MS, Biesecker LG. Management of secondary genomic findings. *Am J Hum Genet*. 2020;107:3–14. https://doi.org/10.1016/j.ajhg.2020.05.002

122. Ma BM, Elefant N, Tedesco M, et al. Developing a genetic testing panel for evaluation of morbidities in kidney transplant recipients. *Kidney Int*. 2024;106:115–125. https://doi.org/10.1016/j.kint.2024.02.021

123. Reuter CM, Kohler JN, Bonner D, et al. Yield of whole exome sequencing in undiagnosed patients facing insurance coverage barriers to genetic testing. *J Genet Couns*. 2019;28:1107–1118. https://doi.org/10.1002/jgc4.1161

124. Zion TN, Berrios CD, Cohen ASA, et al. Insurance denials and diagnostic rates in a pediatric genomic research cohort. *Genet Med*. 2023;25:100020. https://doi.org/10.1016/j.gim.2023.100020

125. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013;15:565–574. https://doi.org/10.1038/gim.2013.73

126. Green RC, Lupski JR, Biesecker LG. Reporting genomic sequencing results to ordering clinicians: incidental, but not exceptional. *JAMA*. 2013;310:365–366. https://doi.org/10.1001/jama.2013.41703

127. de Wert G, Dondorp W, Clarke A, et al. Opportunistic genomic screening. Recommendations of the European Society of Human Genetics. *Eur J Hum Genet*. 2021;29:365–377. https://doi.org/10.1038/s41431-020-00758-w

128. Wilfond BS, Fernandez CV, Green RC. Disclosing secondary findings from pediatric sequencing to families: considering the "benefit to families.". *J Law Med Ethics*. 2015;43:552–558. https://doi.org/10.1111/jlme.12298

129. ACMG Board of Directors. ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. *Genet Med*. 2015;17:68–69. https://doi.org/10.1038/gim.2014.151

130. McCullough LB, Brothers KB, Chung WK, et al. Professionally responsible disclosure of genomic sequencing results in pediatric practice. *Pediatrics*. 2015;136:e974–e982. https://doi.org/10.1542/peds.2015-0624

131. DiStefano MT, Goehringer S, Babb L, et al. The Gene Curation Coalition: A global effort to harmonize gene-disease evidence resources. *Genet Med*. 2022;24:1732–1742. https://doi.org/10.1016/j.gim.2022.04.017

132. Niehaus A, Azzariti DR, Harrison SM, et al. A survey assessing adoption of the ACMG-AMP guidelines for interpreting sequence variants and identification of areas for continued improvement. *Genet Med*. 2019;21:1699–1701. https://doi.org/10.1038/s41436-018-0432-7

133. Amendola LM, Muenzen K, Biesecker LG, et al. Variant classification concordance using the ACMG-AMP variant interpretation guidelines across nine genomic implementation research studies. *Am J Hum Genet*. 2020;107:932–941. https://doi.org/10.1016/j.ajhg.2020.09.011

134. Schwarze K, Buchanan J, Taylor JC, Wordsworth S. Are whole-exome and whole-genome sequencing approaches cost-effective? A systematic review of the literature. *Genet Med*. 2018;20:1122–1130. https://doi.org/10.1038/gim.2017.247

135. Wojcik MH, Lemire G, Berger E, et al. Genome sequencing for diagnosing rare diseases. *N Engl J Med*. 2024;390:1985–1997. https://doi.org/10.1056/NEJMoa2314761

136. Bick D, Jones M, Taylor SL, Taft RJ, Belmont J. Case for genome sequencing in infants and children with

rare, undiagnosed or genetic diseases. *J Med Genet*. 2019;56:783–791. https://doi.org/10.1136/jmedgenet-2019-106111

137. Mallawaarachchi A, Biros E, Harris T, et al. Shaping the future of kidney genetics in Australia: proceedings from the KidGen policy implementation workshop 2023. *Hum Genomics*. 2024;18:88. https://doi.org/10.1186/s40246-024-00656-y
138. Lundquist AL, Pelletier RC, Leonard CE, et al. From theory to reality: establishing a successful kidney genetics clinic in the outpatient setting. *Kidney360*. 2020;1:1097–1104. https://doi.org/10.34067/KID.0004262020
139. Stark Z, Dolman L, Manolio TA, et al. Integrating genomics into healthcare: A global responsibility. *Am J Hum Genet*. 2019;104:13–20. https://doi.org/10.1016/j.ajhg.2018.11.014
140. Thomas CP, Freese ME, Ounda A, et al. Initial experience from a renal genetics clinic demonstrates a distinct role in patient management. *Genet Med*. 2020;22:1025–1035. https://doi.org/10.1038/s41436-020-0772-y
141. Smith HS, Franciskovich R, Lewis AM, et al. Outcomes of prior authorization requests for genetic testing in outpatient pediatric genetics clinics. *Genet Med*. 2021;23:950–955. https://doi.org/10.1038/s41436-020-01081-x
142. Deverka PA, Dreyfus JC. Clinical integration of next generation sequencing: coverage and reimbursement challenges. *J Law Med Ethics*. 2014;42(suppl 1):22–41. https://doi.org/10.1111/jlme.12160
143. Rogowski WH, Grosse SD, Schmidtke J, Marckmann G. Criteria for fairly allocating scarce health-care resources to genetic tests: which matter most? *Eur J Hum Genet*. 2014;22:25–31. https://doi.org/10.1038/ejhg.2013.172
144. Severin F, Borry P, Cornel MC, et al. Points to consider for prioritizing clinical genetic testing services: a European consensus process oriented at accountability for reasonableness. *Eur J Hum Genet*. 2015;23:729–735. https://doi.org/10.1038/ejhg.2014.190
145. Kroese M, Zimmern RL, Farndon P, Stewart F, Whittaker J. How can genetic tests be evaluated for clinical use? Experience of the UK genetic testing network. *Eur J Hum Genet*. 2007;15:917–921. https://doi.org/10.1038/sj.ejhg.5201867
146. Dubois-Laforgue D, Cornu E, Saint-Martin C, et al. Diabetes, associated clinical spectrum, long-term prognosis, and genotype/phenotype correlations in 201 adult patients with hepatocyte nuclear factor 1B (HNF1B) molecular defects. *Diabetes Care*. 2017;40:1436–1443. https://doi.org/10.2337/dc16-2462
147. Clissold RL, Hamilton AJ, Hattersley AT, Ellard S, Bingham C. HNF1B-associated renal and extra-renal disease-an expanding clinical spectrum. *Nat Rev Nephrol*. 2015;11:102–112. https://doi.org/10.1038/nrneph.2014.232
148. Daneshpajouhnejad P, Kopp JB, Winkler CA, Rosenberg AZ. The evolving story of apolipoprotein L1 nephropathy: the end of the beginning. *Nat Rev Nephrol*. 2022;18:307–320. https://doi.org/10.1038/s41581-022-00538-3
149. da Silva Francisco R, Punj S, Vincent L, et al. Prevalence of Mendelian kidney disease among patients with high-risk APOL1 genotypes undergoing commercial genetic testing in the United States. *Kidney Int Rep*. 2024;9:2667–2676. https://doi.org/10.1016/j.ekir.2024.06.028
150. Schrezenmeier E, Kremerskothen E, Halleck F, et al. The underestimated burden of monogenic kidney disease in adults waitlisted for kidney transplantation. *Genet Med*. 2021;23:1219–1224. https://doi.org/10.1038/s41436-021-01127-8
151. Groopman EE, Marasa M, Cameron-Christie S, et al. Diagnostic utility of exome sequencing for kidney disease. *N Engl J Med*. 2019;380:142–151. https://doi.org/10.1056/NEJMoa1806891
152. Ottlewski I, Münch J, Wagner T, et al. Value of renal gene panel diagnostics in adults waiting for kidney transplantation due to undetermined end-stage renal disease. *Kidney Int*. 2019;96:222–230. https://doi.org/10.1016/j.kint.2019.01.038
153. Freedman BI, Locke JE, Reeves-Daniel AM, Julian BA. Apolipoprotein L1 gene effects on kidney transplantation. *Semin Nephrol*. 2017;37:530–537. https://doi.org/10.1016/j.semnephrol.2017.07.006
154. Faguer S, Decramer S, Chassaing N, et al. Diagnosis, management, and prognosis of HNF1B nephropathy in adulthood. *Kidney Int*. 2011;80:768–776. https://doi.org/10.1038/ki.2011.225
155. Grams ME, Sang Y, Levey AS, et al. Kidney-failure risk projection for the living kidney-donor candidate. *N Engl J Med*. 2016;374:411–421. https://doi.org/10.1056/NEJMoa1510491
156. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous familial hypercholesterolemia. *J Am Heart Assoc*. 2019;8:e013225. https://doi.org/10.1161/JAHA.119.013225
157. Tan NB, Stapleton R, Stark Z, et al. Evaluating systematic reanalysis of clinical genomic data in rare disease from single center experience and literature review. *Mol Genet Genom Med*. 2020;8:e1508. https://doi.org/10.1002/mgg3.1508
158. Savatt JM, Azzariti DR, Faucett WA, et al. ClinGen's GenomeConnect registry enables patient-centered data sharing. *Hum Mutat*. 2018;39:1668–1676. https://doi.org/10.1002/humu.23633
159. Savatt JM, Azzariti DR, Ledbetter DH, et al. Recontacting registry participants with genetic updates through GenomeConnect, the ClinGen patient registry. *Genet Med*. 2021;23:1738–1745. https://doi.org/10.1038/s41436-021-01197-8
160. Doreille A, Villié P, Mesnard L. National survey on genetic test prescription in French adult nephrologists: a call for simplification and education. *Clin Kidney J*. 2022;15:1213–1215. https://doi.org/10.1093/ckj/sfac041
161. Mrug M, Bloom MS, Seto C, et al. Genetic testing for chronic kidney diseases: clinical utility and barriers perceived by nephrologists. *Kidney Med*. 2021;3:1050–1056. https://doi.org/10.1016/j.xkme.2021.08.006
162. Alkanderi S, Yates LM, Johnson SA, Sayer JA. Lessons learned from a multidisciplinary renal genetics clinic. *QJM*. 2017;110:453–457. https://doi.org/10.1093/qjmed/hcx030
163. Amlie-Wolf L, Baker L, Hiddemen O, et al. Novel genetic testing model: A collaboration between genetic counselors and nephrology. *Am J Med Genet A*. 2021;185:1142–1150. https://doi.org/10.1002/ajmg.a.62088
164. Mallett A, Fowles LF, McGaughran J, Healy H, Patel C. A multidisciplinary renal genetics clinic improves patient diagnosis. *Med J Aust*. 2016;204:58–59. https://doi.org/10.5694/mja15.01157

165. Elhassan EAE, Murray SL, Connaughton DM, et al. The utility of a genetic kidney disease clinic employing a broad range of genomic testing platforms: experience of the Irish Kidney Gene Project. *J Nephrol*. 2022;35:1655–1665. https://doi.org/10.1007/s40620-021-01236-2

166. ERKNet: The European rare kidney disease reference network. European Union. Accessed December 1, 2024. https://www.erknet.org/index.php?id=home

167. Ambrosino E, Abou Tayoun AN, Abramowicz M, et al. The WHO genomics program of work for equitable implementation of human genomics for global health. *Nat Med*. 2024;30:2711–2713. https://doi.org/10.1038/s41591-024-03225-x

168. Germain DP, Levade T, Hachulla E, et al. Challenging the traditional approach for interpreting genetic variants: lessons from Fabry disease. *Clin Genet*. 2022;101:390–402. https://doi.org/10.1111/cge.14102

169. Trautmann A, Boyer O, Hodson E, et al. IPNA clinical practice recommendations for the diagnosis and management of children with steroid-sensitive nephrotic syndrome. *Pediatr Nephrol*. 2023;38:877–919. https://doi.org/10.1007/s00467-022-05739-3

170. Ilori T, Watanabe A, Ng KH, Solarin A, Sinha A, Gbadegesin R. Genetics of chronic kidney disease in low-resource settings. *Semin Nephrol*. 2022;42:151314. https://doi.org/10.1016/j.semnephrol.2023.151314

171. Tziastoudi M, Pissas G, Raptis G, et al. A systematic review and meta-analysis of pharmacogenetic studies in patients with chronic kidney disease. *Int J Mol Sci*. 2021;22:4480. https://doi.org/10.3390/ijms22094480

172. Vy HMT, Coca SG, Sawant A, et al. Genome-wide polygenic risk score for CKD in individuals with APOL1 high-risk genotypes. *Clin J Am Soc Nephrol*. 2024;19:374–376. https://doi.org/10.2215/CJN.0000000000000379

173. Ali AS, Pham C, Morahan G, Ekinci EI. Genetic risk scores identify people at high risk of developing diabetic kidney disease: A systematic review. *J Clin Endocrinol Metab*. 2024;109:1189–1197. https://doi.org/10.1210/clinem/dgad704

174. Cao R, Schladt DP, Dorr C, et al. Polygenic risk score for acute rejection based on donor-recipient non-HLA genotype mismatch. *PLoS One*. 2024;19:e0303446. https://doi.org/10.1371/journal.pone.0303446

175. Xu L, Gan T, Chen P, et al. Clinical application of polygenic risk score in IgA nephropathy. *Phenomics*. 2024;4:146–157. https://doi.org/10.1007/s43657-023-00138-6

176. Stark Z, Byrne AB, Sampson MG, Lennon R, Mallett AJ. A guide to gene-disease relationships in nephrology. *Nat Rev Nephrol*. 2024. https://doi.org/10.1038/s41581-024-00900-7

177. Savige J, Storey H, Watson E, et al. Consensus statement on standards and guidelines for the molecular diagnostics of Alport syndrome: refining the ACMG criteria. *Eur J Hum Genet*. 2021;29:1186–1197. https://doi.org/10.1038/s41431-021-00858-1

178. Abad Baucells C, Schönauer R, Halbritter J. The genetics of cystinuria - an update and critical reevaluation. *Curr Opin Nephrol Hypertens*. 2024;33:231–237. https://doi.org/10.1097/MNH.0000000000000949

179. Schott C, Colaiacovo S, Baker C, Weir MA, Connaughton DM. Reclassification of genetic testing results: A case report demonstrating the need for structured re-evaluation of genetic findings. *Can J Kidney Health Dis*. 2024;11:20543581241242562. https://doi.org/10.1177/20543581241242562

180. O'Brien TD, Campbell NE, Potter AB, Letaw JH, Kulkarni A, Richards CS. Artificial intelligence (AI)-assisted exome reanalysis greatly aids in the identification of new positive cases and reduces analysis time in a clinical diagnostic laboratory. *Genet Med*. 2022;24:192–200. https://doi.org/10.1016/j.gim.2021.09.007

181. Dai P, Honda A, Ewans L, et al. Recommendations for next generation sequencing data reanalysis of unsolved cases with suspected Mendelian disorders: A systematic review and meta-analysis. *Genet Med*. 2022;24:1618–1629. https://doi.org/10.1016/j.gim.2022.04.021

182. Schobers G, Schieving JH, Yntema HG, et al. Reanalysis of exome negative patients with rare disease: a pragmatic workflow for diagnostic applications. *Genome Med*. 2022;14:66. https://doi.org/10.1186/s13073-022-01069-z

183. van der Geest MA, Maeckelberghe ELM, van Gijn ME, et al. Systematic reanalysis of genomic data by diagnostic laboratories: a scoping review of ethical, economic, legal and (psycho)social implications. *Eur J Hum Genet*. 2024;32:489–497. https://doi.org/10.1038/s41431-023-01529-z