Review

The Art and Science of Genetic Counseling in Nephrology

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The recognition that up to 10% of individuals with kidney diseases might obtain a genetic diagnosis has led to genetic testing (GT) becoming a critical component of nephrology practice. Genetic counselors have expertise in providing genomic services, which include genetic counseling and testing. They play a crucial role by helping patients estimate their genetic risks, understand the effect of results, and coordinate follow-up care. Nephrologists are in a pivotal position to offer genomic services directly to their patients or to refer them to genetic counseling before or after GT. Nephrologists should therefore be able to identify patients who would benefit most from these services. To effectively refer patients, nephrologists should be able to explain the genetic counseling process and its relevance to the patient. This review aims to help build a collaborative relationship between nephrologists and genetic counselors. It introduces and expands upon the topics genetic counselors cover during genetic counseling sessions, including how they support patients in understanding the implications of genetic findings, decision making related to GT, and the psychosocial aspects of living with a genetic diagnosis. By integrating genetic counseling into nephrology, patients with kidney diseases can receive comprehensive care tailored to their genetic and clinical needs.

Kidney360 6: 1230–1244, 2025. doi: https://doi.org/10.34067/KID.0000000825

Introduction

Renal care is inherently multidisciplinary, and genetic counselors should be an integral part of the care team for individuals with kidney disease. A rising number of newly established renal genetic clinics worldwide highlights the benefits of collaborations between genetic counselors and nephrologists in the pediatric and adult settings.[1–6] Obtaining a genetic diagnosis for kidney disease can have tangible clinical benefits, such as selecting targeted treatment options, personalizing prognostication, and identifying eligible living-related donors for transplantation.[7–11] Genetic testing (GT) benefits are only increasing with the growth of genetically stratified clinical trials, expanding opportunities for targeted therapies and treatment options for this patient population.[12–14] Genomic research in nephrology led to the discovery of many genes associated with kidney diseases and the revelation that genetic forms of kidney disease are prevalent.[10,11,15–19] A genetic diagnosis can be reached in approximately 10% of individuals with CKD and remains largely undetected by other clinical methods.[11] However, a key challenge for nephrologists is accurately identifying patients most likely to benefit from GT and counseling.[20–22] To best incorporate GT into the standard-of-care practice, nephrologists must develop the skills necessary to engage with genomic services and clinicians, including genetic counselors.

To foster a strong partnership between nephrologists and genetic counselors, both must understand each other's roles and effectively communicate them to their patients. This review seeks to demystify the genetic counseling process and provide nephrologists with the knowledge to refer patients to genetic counselors or deliver genetic counseling services themselves. This guide begins by highlighting the red flags nephrologists should recognize to identify individuals most likely to benefit from GT. Key concepts of pretest counseling (*i.e.*, before GT) and post-test counseling (*i.e.*, after receiving genetic test results), incorporating examples of language used by genetic counselors in discussion with patients, as well as examples of publicly available resources, are then outlined. Readers are also referred to prior reviews about the types of genetic tests recommended for individuals with kidney diseases.[23–25]

Identifying Individuals Who Can Most Benefit from Genomic Services

On the basis of cohort studies and expert opinions, patients with certain characteristics are more likely to have a genetic diagnosis than others.[11,15–17] Specific clinical findings, or red flags, should prompt a clinician to consider a genetic etiology (Figure 1). However, individuals not meeting those criteria might also benefit from GT. It is also important to recognize that, as more research is performed

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Published Online Ahead of Print: April 23, 2025

and data are collected, the inclusion criteria and characteristics of this patient population may change. Currently, on the basis of published guidelines and data, these red flags include:

1. An unusual clinical course, including a particularly young age of onset (younger than 50 years without known risk factors), rapid progression of disease (*i.e.*, kidney disease progressing more rapidly than expected based on known clinical features and underlying risk factors), or a severe presentation (*e.g.*, early-onset severe hypertension).[23–29]
2. Syndromic presentation, the presence of multiple, independently affected organ systems (as opposed to kidney failure leading to the dysfunction of other organs).[23,26,30] An example of a syndrome is autosomal recessive or X-linked Alport syndrome in male patients, which is typically associated with glomerulopathy, hearing loss, and ocular abnormalities.[31] These three features are all independent effects of pathogenic variants in one of the three genes, *COL4A3,-4,* and *-5*, leading to abnormal protein expression in different cell types, rather than secondary complications of each other (*i.e.*, the glomerulopathy does not cause hearing loss).
3. While shared environmental factors sometimes explain the clustering of a disease in a family, a positive family history is significantly associated with an increased risk of a genetic etiology.[11]
4. The category or specific type of kidney disease. For example, cystic kidney disease,[32] FSGS,[33,34] and CKD of unknown etiology[35] are each associated with a higher diagnostic yield than diabetic nephropathy.[11]
5. Suspicion of a genetic condition based on clinical presentation, such as a specific constellation of features (*e.g.*, a suspected clinical diagnosis of recessive or X-linked Alport syndrome based on clinical features or family history), a biopsy result (*e.g.*, biopsy consistent with a diagnosis of Fabry disease),[36] or specific patterns of electrolyte dysregulation (*e.g.*, hypokalemia and hypomagnesemia suggestive of Gitelman syndrome).[37]

Patient and Clinician Motivations for Pursuing GT

Both clinicians' and patients' motivations and perspectives should be considered when discussing the risks and benefits of GT and genetic results. The pretest counseling process should be a conversation where the clinician obtains information about the patient's motivations, concerns, and hopes for pursuing GT. Even without clinical indications, the presence of patient motivations warrants a thorough discussion of GT options (Figure 2).

Examples of shared motivations include obtaining confirmation of the diagnosis and its prognosis; enabling treatment decisions; ensuring extrarenal surveillance as needed; determining eligibility for clinical trials[8,11,12]; and, in the context of transplant planning, determining if a living relative may be an appropriate donor.[7,38–40] The confirmation of a genetic diagnosis can provide additional information about kidney disease prognosis. For patients with autosomal dominant polycystic kidney disease, genetic results can be incorporated into the Predicting Renal Outcome in Polycystic Kidney Disease tool to aid in more personalized prediction of the progression of kidney disease.[41] Similarly, clarifying the disease etiology may enable informed and confident decisions about treatment, as

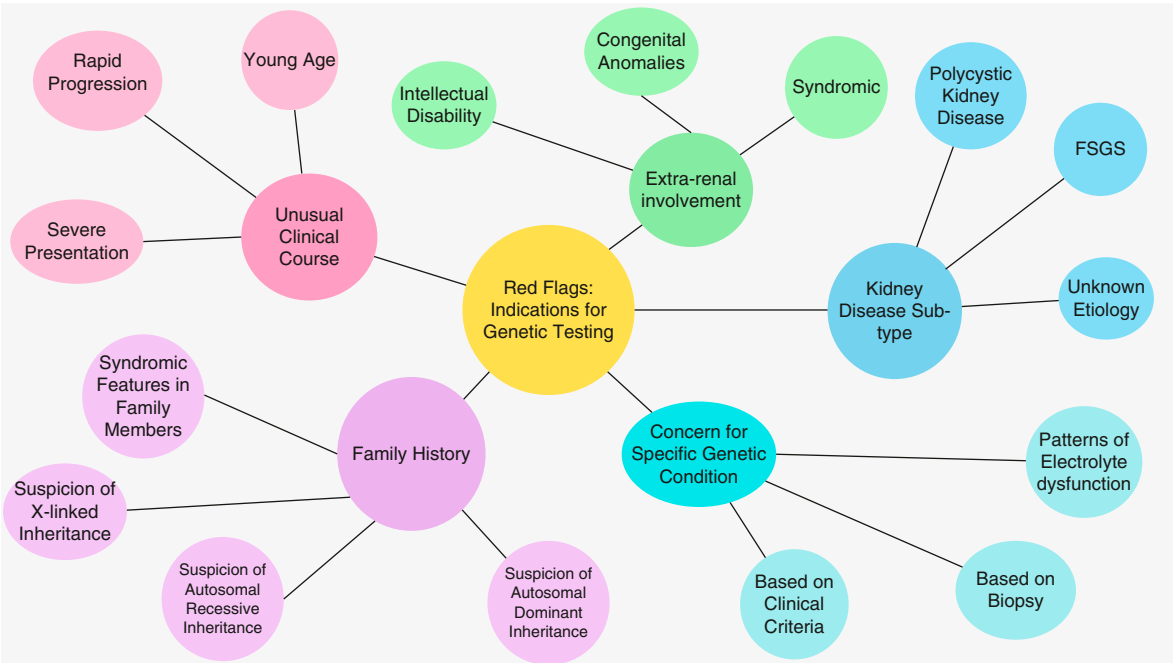

Figure 1. Red flags of genetic etiology. The five colors represent the five categories of information indicative of a genetic etiology. The presence of any one of these categories is sufficient to raise suspicion of a genetic basis for kidney disease.

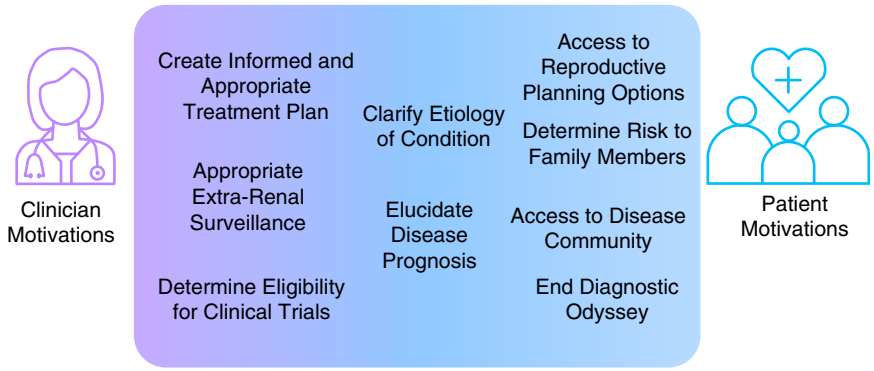

Figure 2. Clinicians' and patients' motivations for genetic evaluation. Clinicians' (purple) and patients' (blue) motivations to pursue GT are diverse and not always overlapping. There are no hierarchical relationships between the different motivations. GT, genetic testing.

exemplified by genetically confirmed steroid-resistant nephrotic syndrome.[42] In the context of transplantation planning, GT can also inform about the risk of recurrence after transplantation (*e.g.*, atypical hemolytic uremic syndrome and FSGS) and the need for a dual organ transplant (*e.g.*, liver and kidney transplant in patients with amyloidosis and atypical hemolytic uremic syndrome).[43]

A patient's personal or a relative's past experiences with genetics, social and cultural identification, and the media's representation of genetics all help shape patients' motivations toward testing. Patients often focus on familial implications, such as learning if their family members are at increased risk of kidney disease. As such, a genetic diagnosis provides patients the opportunity to make informed reproductive decisions, including the option of prenatal GT (by chorionic villus sampling or amniocentesis) or prepregnancy GT, such as preimplantation GT. In addition, patients may want to alleviate the frustration and uncertainty of a prolonged diagnostic journey.[44–46] A genetic diagnosis may enable patients to connect with others with similar health conditions or experiences.

When considering patient motivation for GT, it is critical to recognize personal and implicit biases and how that may influence a clinician's portrayal and access to GT. Medically underserved or mistreated groups are equally interested in GT,[47,48] and clinicians should refrain from assuming individuals' opinions about GT. A systematic review examining the attitudes and beliefs of Black individuals regarding race-targeted GT revealed that, despite existing mistrust and various barriers, there is a consistent interest in GT among them.[49] Similarly, in nephrology specifically, Black individuals have voiced their interest in *APOL1* GT.[50–52]

Pretest Genetic Counseling

Pretest counseling is a critical component of genomic services and involves four areas: (*1*) eliciting a personal medical history, (*2*) obtaining a family medical history, (*3*) calculating the odds of a genetic etiology and selecting a test on the basis of it, and (*4*) obtaining informed consent for GT (Figure 3A). Pretest counseling should be viewed as a preparation for the return of results, if the patient opts to get tested. The limitations and potential follow-up steps that will be discussed during post-test genetic counseling should also be a part of pretest counseling.

Personal Medical History

A comprehensive personal medical history is essential for identifying any red flags in a patient that are suggestive of a genetic disorder (Figure 1).[53] It is important to start from the prenatal period, asking about congenital anomalies involving other organ systems (*e.g.*, heart defects and polydactyly) and continuing into early childhood to potentially identify intellectual disability or learning disabilities, if present. Targeted, specific questions are key to eliciting this critical information. For instance, asking about the age of onset of symptoms or when abnormal laboratory test results were first reported can help determine whether the disease began at an atypically young age, or progressed rapidly. This aspect of pretest genetic counseling is fundamental to genomic services (Table 1).

Family History

A comprehensive family history is key to estimating the probability of a genetic etiology, understanding the patient's motivations, and selecting the appropriate GT (Table 1). Before ordering GT, a three-generation family history is recommended to assess for kidney disease as well as other conditions, such as cancer and cardiovascular diseases, which could be returned as secondary findings depending on the GT modality selected.[54] It is important to explain the reasons a comprehensive family history is collected and reassure the patient that more information can be added at a later time, so they will not be stressed by the interrogation.

A comprehensive family history helps identify clinical features suggesting variable expressivity or reduced penetrance of a genetic condition. For example, *HNF1B*-associated nephropathy, which is associated with variable expressivity, can present with dysplastic kidney, early-onset diabetes, autism, or any combination of those features.[55] The age at which family members die should be considered in the context of disease onset and progression. Recognizing transmission patterns can suggest certain modes of inheritance, thereby informing the risk assessment (Figure 4 and Supplemental File 1).

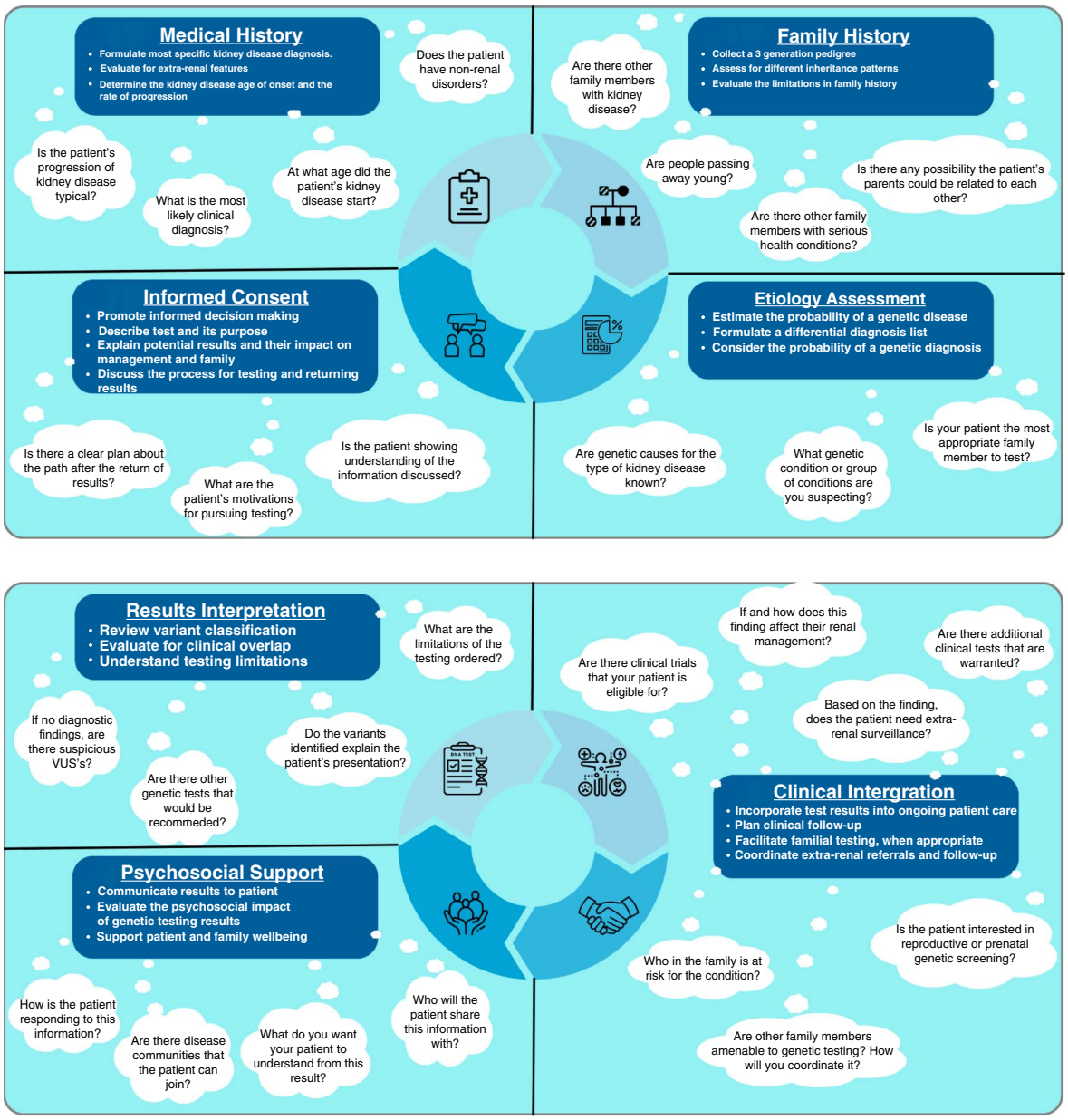

Figure 3. Pretest and post-test counseling. (A) The components of pretest counseling. (B) The components of post-test counseling. The goals of the counseling session are depicted in rectangular shapes. Questions that the clinicians should ask themselves are depicted in the white clouds. VUS, variants of uncertain significance.

While a thorough and complete family history is important, it often has limitations because of gaps in knowledge. Estrangement, unwillingness to share health information within the family, limited family size, and adoption can limit a patient's knowledge about their family's medical history. Therefore, an uninformative family history alone is not sufficient to reduce the probability of a genetic etiology, making it essential to explore family dynamics when assessing genetic risk (Table 1). Family histories are instrumental in calculating the odds of a positive genetic test result, guiding GT choices, and interpreting genetic results (see below).

Etiology Assessment and Test Selection

The distinct advantages and limitations of various testing methodologies should be considered during pretest genetic counseling and have been previously reviewed.[8,24,25] Having a thorough differential diagnosis can help estimate the probability of a genetic etiology and determine appropriate genetic test selection. Test selection must account for technical limitations specific to the suspected genetic condition and the goal of the testing (*i.e.*, patient and clinician motivations). For instance, some genetic panels for cystic diseases do not include *PKD1* because of the technical difficulties of sequencing this

Table 1. Questions to ask a patient for identification of red flags of genetic conditions

Topic	Concept	Examples of Questions
Personal history	Personal history of extrarenal	Do you have any history of birth defects, such as a heart defect or missing or extra fingers? Did you ever need to have surgery or be hospitalized after birth? Do you have any other health conditions other than kidney disease? At what age were they diagnosed? Are you aware if you met your developmental milestones, such as walking and talking on time? Did you have any developmental delays? Did you ever need any extra services such as early intervention or an individualized educational plan (IEP) in school? Did you have a hard time in school or have any learning disabilities?
	GT	Have you or any of your family members ever been told that you have a genetic condition? Have you or any of your family members ever had GT?
Family history	Family history of kidney disease	Do any of your family members have kidney disease or any kidney problems? Did anyone in your family need dialysis or a kidney transplant? How old were the family members when they first developed signs of kidney disease? How old were they when they developed kidney failure?
	Family history of extrarenal conditions	Does anyone in your family have a chronic or severe health condition? Are there any health conditions that you notice are running in your family? Are there any family members with intellectual disability or developmental issues? Are there any family members who were very sick as children or needed surgeries? Did anyone in the family pass away suddenly of unknown cause? Is there anything else that you want to share about your family or family health history?
	Family structure	How old are your family members living until (specifically close family members such as parents and siblings) and what did they pass away from? Were you or anyone else in the family adopted? Is it possible that your parents are related to each other by blood, like cousins or second cousins? What ancestry or ethnicity does your mom's side of the family identify with? Your dad's side? Do you share health information with your family or do people tend to be more private about their health? Do you have contact with that family member or that side of the family?

GT, genetic testing.

gene.[56] Similarly, when considering autosomal dominant tubulointerstitial kidney disease, the clinician should address the technical challenges in analyzing the *MUC1* gene, which requires specialized testing approaches.[57] Weighing the probability of a genetic etiology, testing motivations, and technical limitations enables informed, shared decision making between the patient and the clinician regarding genetic test selection.

The cost of GT should also be considered when selecting a GT modality, and the options should be discussed with the patient. While a broad test, such as exome sequencing, is typically more expensive because of increased time and labor requirements, multiple targeted GTs (one after the other to reach a diagnosis) can also become costly.[24] Health insurance coverage for genetic tests varies by test type, insurance provider, and insurance plan. Letters of medical necessity, highlighting the clinical utility and validity of the GT, can be useful in documenting medical necessity and obtaining coverage.[58] It is important to discuss GT options with patients, even if there may be financial barriers. Many commercial GT laboratories offer financing options, such as capped out-of-pocket costs, and need-based financial assistance, making GT accessible to most patients.[6] Collaboration between genetic counselors and nephrologists is the best way to help the patient obtain health insurance coverage.

Informed Consent

If the decision is made to pursue GT during the pretest genetic counseling appointment, the final step is obtaining informed consent (Figure 3A). The critical components of informed consent include a description of the test, why testing is recommended, the types of possible results (including the potential for a negative result, variants of uncertain significance [VUS], positive result, and secondary and incidental findings), how results will be returned, their potential effect on health management and family members, and the potential risk of genetic discrimination and legal protections (Table 2).[59] Informed consent should be tailored to the patient's specific motivations for GT. It is the ordering clinician's responsibility to recognize and address any misconceptions, miscommunications, or lack of understanding a patient may have regarding GT.

Informed consent should be tailored to each patient and should be adjusted on the basis of the indication for testing. For example, the clinical implications for GT are drastically different for an individual with kidney disease who is suspected to have a genetic condition compared with a currently healthy individual who is seen for cascade testing for a known genetic condition in the family. Similarly, when considering cascade testing of potential living-related transplant donors, it is important to discuss the potential effect that GT could have on their eligibility to be a donor, in addition to insurance implications. The informed consent process should address the clinical implications of all possible results pertaining to the patient's current circumstances.

Informed consent for GT typically extends beyond ethical recommendations and includes a legal component, which varies across countries and states.[60] For example, in the United States, some states have specific informed consent documentation procedures required by law, and the physical location of the patient should be considered in the case of telemedicine. Similarly, legal protections for individuals who have had GT vary, and their limitations should be addressed when obtaining informed consent. In the United States, a federal law, the Genetic Information Nondiscrimination Act, was passed in 2008, prohibiting discrimination by employers and health insurance on the basis of an individual's genetic information, including family medical history and genetic test results.[61] Although other countries have also passed such legal protections, they are not universal, and it is the ordering clinician's responsibility to be knowledgeable on the laws surrounding GT and informed consent in their governing area.

Assent for GT

GT in pediatric patients necessitates unique ethical considerations, and there are distinct legal requirements for obtaining informed consent for GT. In addition to obtaining consent from their parent or legal guardian, assent for GT should be obtained for all children between the ages of 7 and 17 years at a developmentally appropriate level. As children mature, especially during adolescence, they should be more involved in discussions about GT and its potential implications.[62] When considering broad, diagnostic GT in minors, it is important to discuss potential incidental and secondary findings, particularly regarding adult-onset conditions. Current guidelines strongly recommend preserving the child's future decisional autonomy by deferring GT for adult-onset conditions until the individual can make independent choices. Whenever possible, clinicians should encourage age-appropriate discussions involving the minor around the full spectrum of GT results.[62] Similarly, when working with adults who lack decisional capacity, such as those with intellectual disability, consent should be obtained from their legal guardian, but it is important to balance patient autonomy through patient-centered communication tailored to cognitive abilities.[63]

Post-Test Genetic Counseling

Post-test genetic counseling (*i.e.*, return of genetic results) includes three components: (*1*) results interpretation, (*2*) clinical integration and continuation of care, and (*3*) psychological support (Figure 3B). The first two components aim at planning the consultation. The consultation should focus on explaining the results and their effect on the care of the patient and their relatives and providing psychosocial support for the patient and their families.

Understanding the Genetic Result

While the reports issued by each laboratory look different, key information is always present (Table 3): the test modality (*e.g.*, Sanger sequencing for a specific variant versus next-generation sequencing); the overall conclusion of the test; and technical aspects, such as the test's limitations, gene coverage, and interpretation methods used in variant analysis. If variants are reported, the report includes the gene(s) in which they were identified (using the HUGO Gene Nomenclature Committee[64]); a description of the genetic variant(s), such as location on the chromosome and effect on the protein; variant(s) zygosity; and variant(s) classification according to American College of Medical Genetics and Genomics criteria.[25,54] Supporting evidence, such as references to scientific literature or databases used to classify the variant, is usually included. Some reports also include clinical implications of the findings, recommendations for referral, and implications for family members.

In the case of a positive genetic result, the first step is to evaluate the concordance between the genetic diagnosis and clinical presentation (Figure 5) and to determine whether the results are diagnostic, incidental, or secondary findings.[65] Diagnostic findings provide a clear explanation of the kidney disease in the patient, resulting in a diagnosis that explains their kidney disease. Incidental findings are unexpected genetic results unrelated to the kidney disease diagnosis. Secondary findings are variants in genes that are intentionally evaluated, as recommended by the genetics community.[54] Online public resources, such as online mendelian inheritance in man and GeneReviews, are often used to interpret the clinical effect of positive results. Disease-specific databases, including the Mayo Autosomal Dominant Polycystic Kidney Disease Variant Database for *PKD1* and *PKD2* and the *COL4A3*, *-4*, and *-5* pages on the Leiden Open Variation Database, are often used in nephrology to identify patients with clinical and genetic overlap.[66,67]

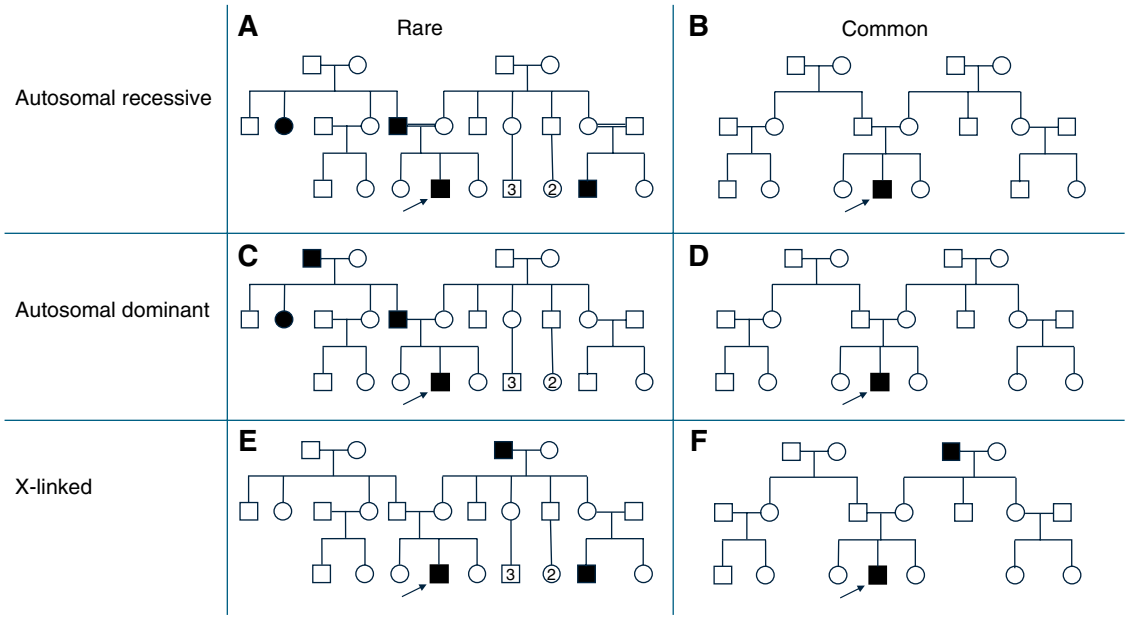

Figure 4. Inheritance patterns. (A and B) Representative pedigrees of anautosomal recessive disease. (C and D) Representative pedigrees of an autosomal dominant disease. (E and F) Representative pedigrees of a X-linked disease. (A, C and E) Only rarely such family history is reported by patients. (B, D and F) Common reports of family history. Squares represent male individuals, and circles represent female individuals. The filled shapes represent individuals affected with kidney disease, the arrow points to the proband, numbers inside the shapes represent the number of male or female individuals, and two parallel lines represent consanguinity. Common family history patterns (right column) are those that are commonly seen in families, due to lack of knowledge on family members' health, small family sizes, or in the absence of consanguinity.

Additional helpful resources used by genetic counselors for clinical interpretation are listed in Table 4.

The identification of VUS is a relatively frequent occurrence, especially in large panels.[68,69] VUS are often classified as such because of limited information in the literature, unknown effect on protein function, and prevalence in large control databases, such as the Genome Aggregation Database.[70] As a result, individuals from ancestries underrepresented in genetic research studies are more likely to carry VUS than individuals of European genetic ancestry.[71–73] However, because the significance of these variants cannot be determined at the time of reporting, no medical management should be based on VUS alone. Nevertheless, clinical assessment and reporting of these variants is recommended because they can be assessed and reclassified over time. Most VUS will eventually be reclassified as likely benign.[71] However, clinical laboratories are more likely to report upgrades of VUS to likely pathogenic, and such reclassifications can have significant effects on clinical management.[74]

Sometimes the genetic disease associated with the VUS matches the patient's clinical presentation and is a strong candidate for genetic diagnosis. In those cases, steps can be taken to reclassify the VUS as a likely pathogenic variant for clinical use; however, it depends on the number of pathogenic criteria already met for the specific variant.[70] When attempting to reclassify a VUS, collaboration between the nephrologist and a genetic counselor is highly recommended. The nephrologist can contact the GT laboratory or refer to a clinical genetic counselor. Nevertheless, the nephrologist's understanding of variant classification criteria is valuable, as ordering additional medical tests, gathering personal and familial medical information, or collecting familial biological samples might be requested to assist in reclassification.[70] VUS reclassification can be pursued through three major paths (Figure 6):[75]

1. Presence of pathognomonic features or significant overlap between the genetic disease and patient's clinical presentation; for example, an enzymatic test establishing a diagnosis of Fabry disease or immunofluorescence testing for *COL4A5* on kidney biopsy determining a diagnosis of X-linked Alport syndrome.
2. Genetic analysis of variant segregation among multiple or distantly related affected family members can demonstrate the linkage between the disease and the VUS.[76] Demonstrating that the variant is *de novo* in the patient (*i.e.*, absent in their unaffected parents) can also support pathogenicity.[70] For recessive disorders, if two variants are determined to be inherited separately (*i.e.*, one variant came from their mother and the other from their father), this provides evidence supporting the biallelic inheritance and may result in reclassification for one or both variants.
3. Functional analysis showing abnormal splicing at the RNA level or a deleterious or benign effect on protein function can be useful in variant reclassification but is typically performed in the research setting.[24,77,78] With the development of targeted therapies, pharmaceutical companies might offer functional testing to determine treatment eligibility.[12,13]

Because VUS resolution is not an immediate process, it is recommended to know whether the GT laboratory is

Table 2. Test explanation

Concept	Sample Wording	Question to Open the Conversation
What is the test and why is it being recommended	This test looks for differences in genes causing genetic kidney disease	Did you get GT in the past? Do you know someone who did? Tell me a little bit about their experience
Types of potential results	We all have genetic differences that make us unique. The genetics team's job is to check these differences to see if they cause kidney disease, don't cause it, or need more testing or follow-up Results can come back positive, meaning a genetic difference was found in a gene that causes disease and may explain or play a role in your kidney disease Results can be negative, meaning no genetic difference known to cause disease was found Sometimes, we get what's called an inconclusive result. This means a genetic difference was found, but we're not sure if it's causing the disease	Should I try to explain it in a different way? I Am not sure that I was clear What is your expectation about what this test will tell us?
To whom and how will results be returned	Results take about X weeks to complete from the moment the lab gets your sample. Results will be explained to you in detail and then added to your medical record	Does this time frame sound reasonable to you?
Potential impact on patient management and familial	Finding a genetic cause for your kidney disease could affect your care or treatment. We might suggest a different medication or recommend extra screenings or tests. Also, because genetics can run in families, this may affect other family members	Do you know if any of your family members have been tested? What was their experience like?
What are the test limitations	This testing is limited to the genes on the panel, and so that a difference a gene not included, or in part of the gene not tested could be missed. It's also possible your kidney disease is not genetic	Do you have any questions about what this test can or can't tell us?
Process for testing	The testing involves a cheek swab or blood draw Have you ever done a cheek swab before?	Do you know what a cheek swab is?
Cost and payment	United States: (For patients with health insurance) Testing is typically covered by most commercial insurance plans, but coverage does vary by policy	Are you worried about the test cost?
Testing is voluntary		This testing is your choice, would you like to proceed with it? Do you have any concerns or worries about testing?

GT, genetic testing.

taking the responsibility of contacting the patient and/or ordering clinician in cases of variant reclassification. Some laboratories offer free reanalysis a year or more after the first report and the clinician and the patient need to discuss whose responsibility it is to remember to request such reanalysis. One of the tools empowering patients to keep track of the classification of their variants is GenomeConnect, a registry of genetic and health information uploaded by patients and informing patients if a change in classification was made to their genetic variant (Table 4).

Most genetic tests in an unselected cohort of adults with kidney disease will yield a negative result.[11] This indicates that a disease-causing change in the genes or regions interrogated was not identified in that patient. Yet, the next steps and clinical implications depend on several factors. After receiving a negative result, the *a priori* suspicion of a genetic basis for disease and the patient's motivation to achieve a genetic diagnosis will guide the subsequent steps. The technical and clinical sensitivities of the test should be investigated (Figure 5).[24] If the selected genetic test has insufficient technical and clinical sensitivity for a condition of interest, additional GT should be considered. If technical and clinical sensitivities are sufficient, and there is a strong suspicion of a genetic etiology, broader or different clinical tests or referral to research studies might be recommended.

Clinical Integration and Planning Clinical Management

Regardless of the interpretation of the genetic test, the result should be integrated into the patient's clinical care (Figures 3B and 5). The clinician must consider whether the

Table 3. Structure of a genetic report

Part	Options	An Example
Test modality	Sanger, panel, exome, genome sequencing	Nephrotic syndrome panel
Result	Negative, positive, uncertain	Positive
Result details		
Gene name	*COL4A3*, *PKD1*, *etc.*	*NPHS2*
Disease name	ADPKD	*NPHS2*-associated nephrotic syndrome
Inheritance	Autosomal dominant, autosomal recessive, X-linked	Autosomal recessive
Variant	Coding DNA and protein change	c.413G>A (p.Arg138Gln; explanation rarely included in reports: Nucleotide adenine in cDNA location 413 changed into guanine. Amino acid arginine in location 138 of the protein changed into a glutamine.)
Zygosity	Heterozygote, homozygote, hemizygote	Homozygous
Classification	Pathogenic, likely pathogenic, variant of uncertain significance, risk allele	Pathogenic
Explanations		
Interpretation	Justification for variant classification criteria applied, clinical description of the associated genetic condition	This variant is in the dbSNP database: rs74315342. This variant is predicted to result in a single amino acid substitution (missense) of arg to gln at codon 138 in exon 3 of the *NPHS2* gene. This missense variant, p.Arg138Gln, has been reported in the compound heterozygous or homozygous state in multiple unrelated individuals with nephrotic syndrome and is considered a common pathogenic founder mutation in European populations (PubMed links). This variant has been observed at a frequency of 0.06% (163/282,690 alleles) in the broad gnomAD dataset. Its highest allele frequency in any subpopulation with available data is 0.11% in the European (Non-Finnish) population. There are no homozygous control individuals for this variant. In mice, a targeted knock-in study manifested severe proteinuria at birth and developed massive foot process effacement and ESKD within the first 5 wk of life
Recommendations	Referrals, family implications	Clinical correlation and genetic counseling are recommended. Test results should be interpreted in the context of the patient's clinical presentation and family history. Medical management should be based on the patient's clinical risk factors such as family history, lifestyle, and age. Individuals may wish to discuss these results with family members to allow them the option to be screened
Resources	ClinVar	This variant has one or more entries in ClinVar: RCV001003814.1, RCV000005691.13, RCV001171338.1, RCV001275640.1, RCV000414576.7, RCV001328321.1
Test explanation and limitations	Methodology and limitations, genes analyzed if panel, gene-specific limitations	VUS at the time of testing were not reported. This test is not designed to detect the presence of copy number–neutral gross chromosomal rearrangements such as translocations. DNA alterations in regulatory regions or deep intronic regions (>20 bp from an exon) are not detected by this test. There are technical limitations on the ability of DNA sequencing to detect small insertions and deletions

ADPKD, autosomal dominant polycystic kidney disease; dbSNP, single nucleotide polymorphism database; gnomAD, the Genome Aggregation Database; VUS, variants of uncertain significance.

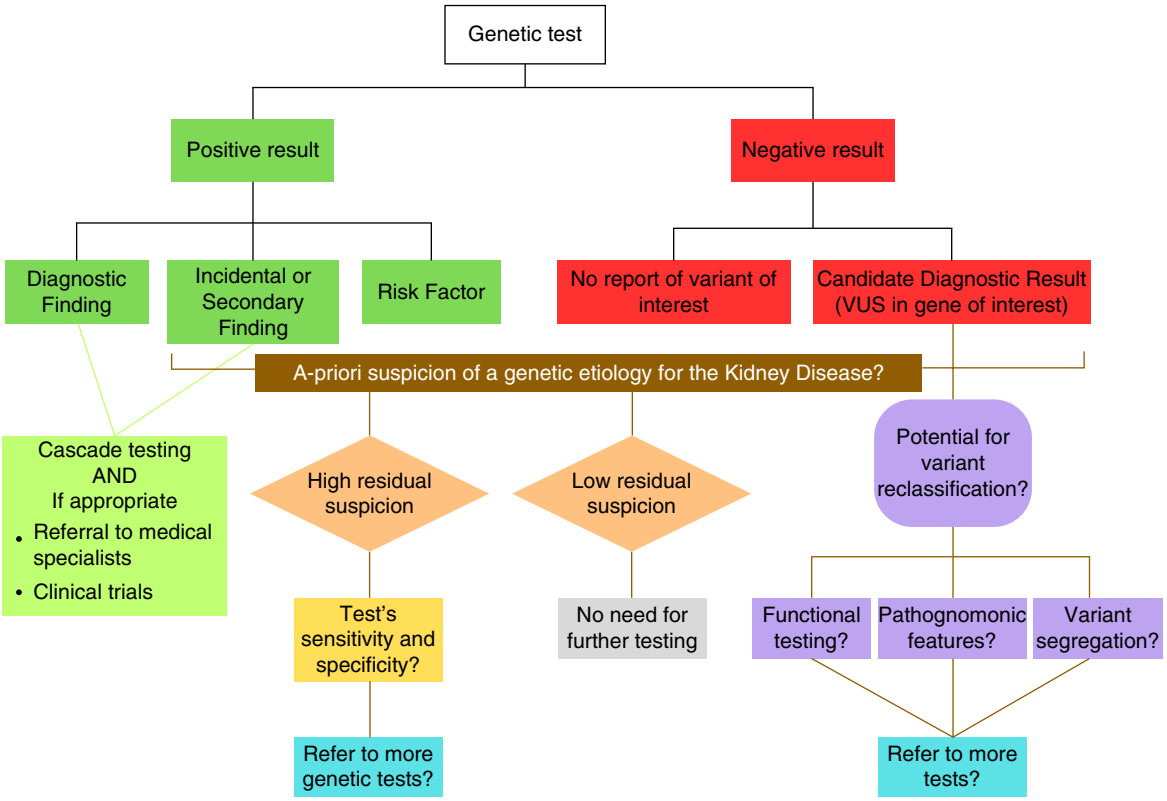

Figure 5. Planning the return of genetic test results. Genetic tests can have a positive result (green boxes) or a negative result (red boxes). Positive results include diagnostic results, incidental findings, or secondary findings and risk factors. In the case of diagnostic results, incidental or secondary findings, the recommendation is to refer to a genetic counselor for cascade testing and referral to other specialists or clinical trials if applicable (light green box). In the case of risk factors or reports without any variant of interest, the first question the clinician should ask themselves is about their *a priori* level of suspicion for a genetic etiology (brown box). If the residual suspicion is high, the test specificity and sensitivity should be assessed (yellow box) and if available additional genetic tests might be recommended (blue box). If the residual suspicion is low, no additional testing is required (gray box). If the negative result reports candidate diagnostic variants (VUS in a gene associated with a disease matching the patient's clinical presentation), the potential for variant reclassification should be assessed (purple boxes).

result provides information about prognosis or informs the care plan. This includes determining if additional procedures, such as a renal biopsy or referral to other specialists, are needed to clarify the results or guide management. Sometimes, GT results qualify patients to be eligible for clinical trials, so assessing available clinical trials for genetic conditions is warranted (Table 4).[79]

Referrals

When the genetic finding (diagnostic, incidental, or secondary) involves nonrenal features based on the extrarenal features reported with the condition in GeneReviews or online mendelian inheritance in man (Table 4), the patient should be referred to the appropriate specialist. For example, an individual with a molecular diagnosis of *INF2*-related FSGS should be referred to neurology for evaluation of Charcot-Marie-Tooth disease.[80] Depending on the condition, guidelines may recommend specific evaluations at diagnosis.[81] It may be advantageous for clinicians to establish a network of specialists for referrals. If available, referral to a center of expertise is recommended. In addition, referral to reproductive genetic counseling is warranted if the patient is planning for future children. Overall, patients with syndromic disorders (*i.e.*, with multiple affected organs) benefit from multidisciplinary care, which can be coordinated by a geneticist or a genetic counselor.[2]

Familial Implications

Unlike other medical tests, genetic diagnoses can have familial implications. It is the clinician's legal responsibility to encourage familial communication regarding any identified genetic risks.[82–84] Regardless of the clinical correlation, positive results should prompt referral to a genetic counselor to discuss cascade testing for at-risk family members and to explore family planning options, when applicable. Genetic counselors help facilitate familial communication, which is especially crucial when other family members do not know they are at increased risk of the genetic condition.[85]

Return of Genetic Results

Disclosing results involves assessing the patient's understanding of the result's effect on themselves and their families. Patients' emotional reactions to genetic results will vary based on the basis of their motivations for testing. For example, those motivated to pursue GT to understand their condition's etiology may welcome a positive result but feel frustrated by a negative or

Table 4. Table of resources

Topic	Questions	Tool Name	Website
Kidney genetics	When should I refer a patient to testing?	Australian-Melbourne Health Alliance	https://melbournegenomics.org.au/resources/genomic-testing-nephrologists/guide-funded-genomic-testing-nephrologists
		European Rare Kidney Diseases Reference Network	https://www.erknet.org/disease-information
General information and definitions	What does this term mean?	About Genomics	www.genome.gov/about-genomics
Genetic diseases information for clinicians	What is this disease?	GeneReviews	https://www.ncbi.nlm.nih.gov/books/NBK1116/
		OMIM	https://www.omim.org
	Is this gene definitively associated with disease?	ClinGen	https://clinicalgenome.org/curation-activities/gene-disease-validity/
Consent and disclosure discussions	How should I discuss GT with my patient?	CADRe	https://clinicalgenome.org/tools/cadre/#rich_media_2
	How can I enhance communication with my patient?	Four Evidence-Based Communication Strategies to Enhance Patient Care	https://www.aafp.org/pubs/fpm/issues/2018/0900/p13.html
Understanding genetic results	I need help understanding these results!	Guide to Interpreting Genetic Reports: A Genomics Toolkit	www.genome.gov/sites/default/files/media/files/2020-04/Guide_to_Interpreting_Genomic_Reports_Toolkit.pdf
	How are genetic variants interpreted?	ClinGen	https://clinicalgenome.org/working-groups/sequence-variant-interpretation/
Genetic diseases information for patients	What is this disease?	MEDLINE Plus Genetics	https://ghr.nlm.nih.gov/
Referral	Who can I refer my patient to?	Orphanet expert centers	https://www.orpha.net/en/expert-centres
		European Rare Kidney Diseases Reference Network	https://www.erknet.org/our-experts/the-european-reference-centers
		Find a Genetic Counselor (United States)	https://findageneticcounselor.nsgc.org/
		Clinical trial	https://www.clinicaltrials.gov
Patients' empowerment	Following up with VUS	GenomeConnect	www.genomeconnect.org/
	Connecting with individuals with the same disease	National Organization for Rare Disorders	https://rarediseases.org
		Orphanet patient organizations	https://www.orpha.net/en/patient-organisations

CADRe, ClinGen's Consent and Disclosure Recommendations; GT, genetic testing; OMIM, Online Mendelian Inheritance in Man; VUS, variants of uncertain significance.

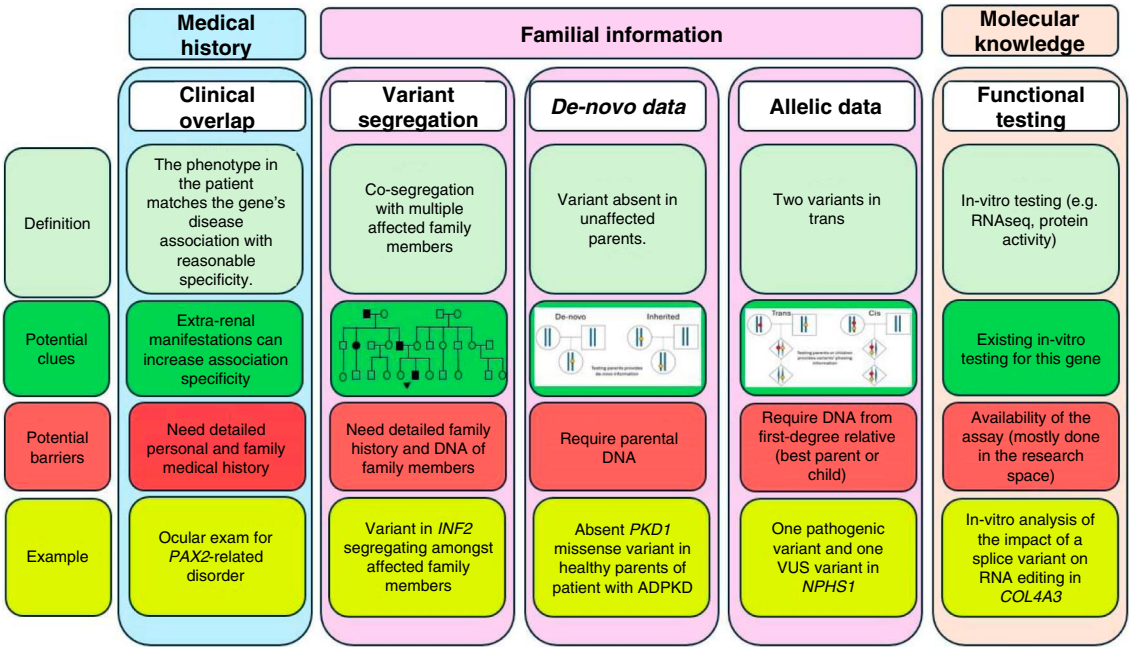

Figure 6. Potential for variant reclassification. Three general categories of information could lead to variant reclassification: medical history (blue), familial information (pink), and molecular knowledge (orange). The definition (light green), potential clues (dark green), potential barriers (red), and examples (yellow) are provided for each category. ADPKD, autosomal dominant polycystic kidney disease; RNAseq, sequencing of RNA.

inconclusive result. Conversely, those testing to assess family risks may view a positive result negatively, while considering a negative result as good news. It is important to avoid assuming a patient's reaction to the results and instead validate their emotional and verbal cues. Drawing from the informed consent conversation can help the patient better understand and contextualize the genetic results.

Genetic counselors are uniquely trained to gather information about the patient's motivations for testing, discuss perceptions about GT, respond to reactions to genetic results, and help develop healthy coping strategies to assess and address the psychological and social well-being of their patients. However, in the absence of their involvement in patient care, a variety of tools for psychosocial assessment and support have been developed. One such tool that has been incorporated into genetic counseling with positive outcomes is the Background, Affect, Trouble, Handling, and Empathy (BATHE) method. The technique can be used by clinicians to investigate many different aspects of a patient's current state by assessing their background issues, effect, and most troubling problem, with an emphasis on responding to with active empathy.

Takeaways

The first step to ensure access to GT for individuals with kidney diseases is to recognize patients who can most benefit from GT (Figures 1 and 4 and Table 1). The motivations to undergo GT can differ from those for other types of medical tests and must be considered when offering GT to patients (Figure 2). The different components of genetic counseling (Figure 3) may require more time than is currently available to nephrologists. While nephrologists should be given the time and support to offer GT to their patients independently, they can also refer patients to genetic counselors who can choose the right genetic tests, consent patients (Table 2), interpret results (Table 3), plan the return of the results (Figure 5), deliver the genetic results, and research the clinical relevance of VUS (Figure 6). There is a clear need for genetic counseling training programs worldwide to incorporate nephrogenetics into their curriculum because it is expected that more renal genetics clinics requiring genetic counselors will be needed in the future.[87] It is the hope that this review demystifies the genetic counseling process and will guide clinicians in either ordering genetic tests for their patients or referring them to genetic counselors.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/KN9/B48.

Funding

H. Milo Rasouly: National Institute of Diabetes and Digestive and Kidney Diseases (5K01DK132495).

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Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/B49.

Supplemental File 1. Assessing for and recognizing different inheritance patterns.

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