Kidney Medicine

Genetic Counseling in Kidney Disease: A Perspective

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As genetic testing is increasingly integrated into nephrology practice there is a growing need for partnership with genetic experts. Genetic counselors are ideally suited to fill this role. The value of genetic counseling is born out of the clinical value of genetic test results against the backdrop of the complexity of genetic testing. Genetic counselors who specialize in nephrology are trained to understand and explain the potential effects of genes on kidney disease, which can enable patients to make informed decisions about proceeding with genetic testing, navigating variants of uncertain significance, educating on extrarenal features of hereditary kidney disease, facilitating cascade testing, providing post-test education about testing results, and assisting with family planning. Genetic counselors can partner with the nephrologist and provide the knowledge needed to maximize the use of genetic testing for patients for nephrology consultation. Genetic counseling is more than an element or extension of genetic testing; it is a dynamic, shared conversation between the patient and the genetic counselor where concerns, sentiments, information, and education are exchanged, and value-based decision making is facilitated.

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INTRODUCTION

The care for patients with kidney disease now often includes consideration of genetic testing.[1-3] As genetic testing becomes more commonplace in the nephrology specialty, there is an emerging need for partnership between the clinicians and genetics experts.[4-7] The clinician needs include help with the interpretation of genetic test results; resources to help facilitate patient discussions about the potential benefits, limitations, and risks of genetic testing; help in communicating test results to patients; and basic educational resources relating to the underlying genetic causes of chronic kidney disease (CKD).[4] Genetic counselors—health care professionals with training and expertise in hereditary conditions, genetic testing, risk assessment, counseling, communication, and education—are ideally suited to address these needs and provide support to the clinicians. Genetic counseling is an established health care field with a longstanding presence in specialties such as oncology, perinatology, and cardiology. Its introduction into the nephrology specialty is more recent.

Genetic testing can provide information on clinical management, prognosis, disease mitigation, transplant decision-making and reproductive planning.[1,6-9] However, there are associated complexities which arise from testing such as diagnostic versus predictive testing (testing at-risk individuals) and variant interpretation. This can lead to a lack of confidence about incorporating genomics into clinical practice. Genetic counselors fill the need for guidance related to testing by helping to clarify value while navigating complexity and uncertainty.

More than just an extension of genetic testing, genetic counseling is a dynamic, shared conversation between the patient and genetic counselor where information and sentiments are exchanged either as part of the genetic testing process or independent of testing. In genetic counseling sessions, there is a goal of promoting client-centered, informed, noncoercive and value-based decision making, thus enabling patients to make autonomous decisions regarding genetic testing. Genetic counselors help educate patients and clinicians on a wide range of genetic information based on their needs and circumstances.

Consider the following scenarios in which a genetic counselor specialized in nephrology may play a key role: (a) a family wants to know the best time to test their young children for autosomal dominant polycystic kidney disease (ADPKD); (b) a sibling group wants to determine who may be a suitable kidney donor for their father who has hereditary tubulointerstitial kidney disease; (c) a woman with hematuria wants to understand why her brother is more affected with Alport syndrome than she; (d) a grandmother feels guilty that a gene variant she carries could have been passed to her many grandchildren; and (e) parents want to understand the reproductive implications of a kidney disease-causing gene deletion identified in their child. In any of these scenarios, and many others, the genetic counselor can partner with the nephrology team to provide counseling, education, empathetic guidance, and care.

WHAT IS THE ROLE OF THE GENETIC COUNSELOR IN KIDNEY DISEASE?

The rapid growth of genetic testing over the last 3 decades has created a demand for genetic counseling services. In the United States and Canada there are currently 50-60 accredited training programs typically granting master's degrees in medical genetics or genetic counseling. Genetic counselors are certified by passing a board examination through the American Board of Genetic Counseling. The

Table 1. Examples of Genetic Conditions in Nephrology

Condition	Inheritance	Associated Genes	Genetic Phenomena Observed
APOL1 nephropathy	AR	*APOL1*	Variable expressivity, incomplete penetrance, and risk allele
Autosomal dominant polycystic kidney disease	AD	*PKD1, PKD2, GANAB, DNAJB11, IFT140*	Variable expressivity, pleiotropy, locus heterogeneity, incomplete penetrance, and some cases de novo
Autosomal dominant tubulointerstitial kidney disease—*UMOD* (ADTKD-*UMOD*)	AD	*UMOD*	Age related complete penetrance and portion of cases de novo
Bardet-Biedl syndrome	AR	>20 associated genes	Variable expressivity, pleiotropy, locus heterogeneity, and digenic inheritance
COL4A3- and *COL4A4*-related Alport syndrome	AD/AR	*COL4A3, COL4A4*	Variable expressivity, pleiotropy, locus heterogeneity, and digenic inheritance
COL4A5-related Alport syndrome	XL	*COL4A5*	Variable expressivity, pleiotropy, skewed X-inactivation, portion of cases de novo
Fabry disease	XL	*GLA*	Variable expressivity, pleiotropy, skewed X-inactivation, and portion of cases de novo
Familial hyperaldosteronism	AD	*CYP11B1/CYP11B2 CLCN2, KCNJ5, CACNA1H*	Variable expressivity, locus heterogeneity, and chimeric gene fusion
Gitelman syndrome	AR	*SLC12A3*	Variable expressivity
Autosomal dominant tubulointerstitial kidney disease—*HNF1B* (ADTKD-*HNF1B*)	AD	*HNF1B*	Variable expressivity, pleiotropy, and portion of cases de novo
Sickle cell trait (SCT) and sickle cell disease (SCD)	AR (SCD) AD (SCT)	*HBB*	Variable expressivity, pleiotropy, and incomplete dominance
WT1 Disorder	AD	*WT1*	Variable expressivity, pleiotropy, mostly de novo, and sex characteristic variation

Abbreviations and definitions: AD, autosomal dominant; AR, autosomal recessive; XL, X-linked; de novo, variant has arisen in an individual for the first time and is not inherited from a parent; Digenic inheritance, variants in 2 genes interacting to cause a genetic disease; Locus heterogeneity, presence of variants at different gene loci that cause the same or similar phenotypic expressions of a disease; Penetrance, the proportion of individuals with a particular genetic variant who show its effect; Pleiotropy, phenomenon of a single gene affecting seemingly unrelated organ systems; Skewed X-inactivation, nonrandom X-chromosome inactivation patterns in females often leading to symptoms in X-linked disorders; Variable Expressivity, the range of signs and symptoms that can occur in different people with the same genetic condition.

number of certified genetic counselors has risen from 495 in 1993, to 5629 in April 2021, and is expected to grow to 10,000 by 2030.[10]

In the practice of nephrology specialization, genetic counseling has come to play a critical role. The genetics of CKD can be complex. To date, over 600 monogenic causes of CKD have been identified, spanning cystic, glomerular, tubular, structural, nephrolithiasis and electrolyte disorders.[11] Hereditary kidney diseases display various inheritance patterns and may exhibit different penetrance, variable expressivity, genetic heterogeneity, digenic inheritance, and genotype-phenotype correlation. Variants in some genes are associated with conditions displaying both autosomal dominant and autosomal recessive inheritance (see Table 1 for further details and definitions). Genetic counselors specialized in nephrology are trained to assess these complex genetic phenomena and to understand the potential effect of the disease on the patient (ie, the proband who serves as the starting point for genetic investigation in a family) and their family members. They are uniquely skilled in facilitating the understanding of complex genetic information for both clinicians and patients—and can offer support to patients with different educational and cultural backgrounds and varying knowledge of genetics (Fig 1).

Genetic counselors practice in a variety of settings such as hospitals, clinics, laboratories, universities, government agencies, and telemedicine companies. Genetic counselors specialized in nephrology in both the clinic/hospital and laboratory settings perform hybrid roles wherein they counsel patients and field genetic inquiries from clinicians. Although there is an overlap in these settings, a clinic-based genetic counselor may provide direct patient counseling, deliver in-person provider consultations, and serve as a case management team member. A laboratory genetic counselor may provide abbreviated short-term counseling and insight into test sensitivity, residual risk, variant interpretation, and curation.

Genetic counselors specialized in nephrology can aid clinicians in identifying patients who may benefit from genetic testing, using clinical and family history information. They can also aid with genetic test selection. This process may include taking a 3 or 4 generation family history to gauge inheritance patterns, meeting with the proband and family to understand their goals in establishing a genetic diagnosis, reviewing genetic testing

Figure 1. Components of genetic counseling

results, facilitating informed consent, and in some instances navigating costs of genetic testing.[12]

There are other ways genetic counselors can work within the interdisciplinary team. Patients with complex multisystemic diseases may have extrarenal features. A genetic counselor can provide team education on the syndromic presentation and recommendations for further genetic specialized clinics or specialty referrals. For instance, should someone be diagnosed with Birt-Hogg-Dubé syndrome caused by *FLCN* gene variants, the associated kidney features and kidney screening will be managed by the nephrologist. However, associated extrarenal features such as cutaneous features (fibrofolliculomas/trichodiscomas), pulmonary features (lung cysts and risk of pneumothorax) and cancer risks (eg, bilateral or multifocal, early-onset renal cell carcinoma) may require additional referrals to appropriate specialists.

Genetic counselors provide both pretest and post-test counseling. Pretest counseling uses an informed consent process that ensures that the patients will have an in-depth discussion around risks (such as possible denial of life insurance), limitations and benefits, and possible outcomes of testing such as ambiguous results and unexpected findings (eg, extrarenal health problems). This discussion allows patients to make informed decisions regarding genetic testing and choose the best test or forgo testing altogether.

Pretest counseling can also include discussions of the risks of genetic testing on children for adult-onset conditions. For example, a family thinking about the best time to test their young healthy child for ADPKD should consider the implications for their child, alternatives to genetic testing, the child's involvement in the decision-making process, current status of treatment interventions, and availability of supportive services.

Post-test genetic counseling sessions provide time for patients to process the results of their genetic test and ask questions, and for the genetic counselor to provide support and guidance for next steps, regardless of the test result. For positive test results, genetic counseling may include test report interpretation, basic pathophysiology, information about clinical features and disease expression, current and future personal health risks, discussion of referral to additional specialists, and discussion about recurrence risk, familial risk, and family testing. In cases with negative results, genetic counseling can examine why

a hereditary cause was not identified. Limitations of the test may also be discussed, such as the possible relevance of negative test findings (eg, a combination of multiple genetic factors and/or environmental factors that could underlie the patient's kidney findings rather than a single gene disorder).

Post-test sessions also allow genetic counselors to support the patient through adaptation to a diagnosis or genetic risk. Genetic counselors are equipped to provide short-term psychosocial counseling when necessary. For example, the genetic counselor may need to employ empathetic listening and compassionate guidance to a grandmother who feels guilty that a gene variant she carries could have been passed to her many grandchildren. After a genetic diagnosis, the genetic counselor may also identify and provide information to the patient on local, regional, and national services and support groups.

HOW CAN GENETIC TESTING BE BENEFICIAL AND WHAT FURTHER VALUE CAN BE ADDED BY THE GENETIC COUNSELOR?

Genetic testing has been recommended for use as an early diagnostic tool for patient evaluation in CKD by multiple expert bodies.[13-15] Recent studies have demonstrated that monogenic causes can be identified in up to 10% of adults and 20%-50% of children with CKD.[13,16-18] Furthermore, diagnostic genetic findings have management implications for 26%-95% of patients.[16,18-20] Potential genetic test implications in patients with CKD includes the following: (a) changes to patient treatment/management because of diagnosis clarification/correction, (b) identification of potential extrarenal manifestations and enabling appropriate surveillance and management, (c) informing risk of kidney failure recurrence, (d) informing kidney transplant decisions, (e) identifying at-risk family members, and (f) providing reproductive testing options.

Genotype-specific testing for *PKD1* for patients with ADPKD provides an illustration of genetic testing benefits. For example, truncating (loss-of-function) *PKD1* variants are associated with earlier age of progression to kidney failure compared with those of nontruncating *PKD1* or *PKD2* variants.[21-23] A genetic diagnosis can be used as 1 component of modeling the disease progression followed by the application of targeted therapy.[21]

Additional value provided by genetic counselors to patients who received genetic testing can be illustrated in the following case of a positive *APOL1* gene test. Carrying 2 specific risk variants in *APOL1* (G1 and G2) is associated with high risk for development and progression of kidney disease.[24] Genetic counselors can help patients differentiate between low and high-risk test results. Further guidance will include informing the patient that 2 *APOL1* risk variants alone are not diagnostic for kidney disease, but rather a risk factor and that the risk of developing *APOL1*-related nephropathy is increased in individuals with certain health conditions such as hypertension-associated kidney failure, focal segmental glomerulosclerosis , HIV-associated nephropathy, and other forms of nondiabetic kidney disease.[24] Genetic counselors can identify and integrate relevant information about health conditions and environmental/lifestyle factors into the risk assessment to help individuals understand their likelihood of developing kidney disease.

Describing further illustrations, consider 2 siblings, where a brother has kidney failure and hearing loss, whereas his younger sister has microhematuria and mild kidney function decline. This scenario is suspicious for Alport syndrome. Hematuria or kidney disease may be the initial presenting feature in patients with Alport syndrome, however clarification of their diagnosis, by identifying which of the *COL4A* family of genes are implicated, can help determine whether there is an increased risk of sensorineural hearing loss and ocular findings. Should genetic testing reveal that each sibling has a *COL4A5* variant, the sister may wonder why her brother is more strongly affected. The genetic counselor's next action might include arranging for testing of all genes causative of Alport syndrome, then explaining about the X-linked inheritance, variable expressivity, prognosis and management guidelines, and X-linked inactivation.

CHALLENGES PRESENTED BY VARIANTS OF UNCERTAIN SIGNIFICANCE

A standardized classification scheme is applied to genetic test results based on the likelihood that a variant is disease causing.[25] Variants with pathogenic (P) and likely pathogenic (LP) classification are expected to affect gene function leading to disease. For many variants, however, the available information is inadequate or contradictory, and association with disease cannot be determined. These variants are designated as variants of uncertain significance (VUS) and are not recommended to be used to assign risk or guide medical management.[25] Over time, VUS may be reclassified as contributing or not contributing to disease as additional data offers clarification.

VUS results are often confusing to clinicians with less exposure to genetic testing.[26,27] Furthermore, patients have vastly different reactions to VUS identified during testing.[28] Genetic counselors are important in educating both patients and clinicians on VUS and their evolving nature.

Genetic counselors play a key role in assisting clinicians with VUS interpretation and determining their clinical relevance. Together, the genetic counselors and clinicians assess VUS relevance in relation to a patient's clinical presentation, family history, and inheritance pattern. Testing family members can help clarify VUS significance either by determining the segregation pattern of the disease in affected family members for autosomal dominant conditions, or by testing phase (the relationship of 2

variants in the same or opposite copies of a gene) for recessive conditions.

WHAT ARE THE RAMIFICATIONS OF GENETIC TESTING ON THE FAMILY?

Hereditary kidney disease diagnoses can affect the proband's children, siblings, and even distant relatives. When a diagnosis is confirmed by genetic testing, a patient may shift their focus to family effect. Genetic counselors can identify relatives that could be affected by using the tools of pedigree analysis and risk calculation. However, sharing results and implications of the test findings with family members can be arduous. Genetic counselors provide guidance to start these conversations and in locating resources for family members who could benefit from genetic testing or surveillance.

Cascade Testing

Cascade testing is a process by which at-risk relatives are tested after identification of a disease-causing variant in a proband is identified and is considered a standard practice in clinical genetics and is supported by kidney health organizations.[13,29] Cascade testing is performed through targeted testing, wherein the laboratory analyzes the specific disease-related gene variant(s) that were identified in the proband, but not other genes (which has obvious cost advantages). At-risk relatives who test positive for the familial variant(s) through the cascade testing can initiate appropriate surveillance and/or management changes, whereas those who test negative generally feel relief and can forego additional screening for the familial condition. Family variant testing may also reduce time to diagnosis and allow greater access to targeted therapies. This can be illustrated by familial aldosteronism, of which there are several subtypes and genes implicated. Confirming a specific diagnosis of familial hyperaldosteronism type 1 through genetic testing opens up the possibility of treatment with glucocorticoids and targeted family testing for this autosomal dominant condition.[30] In the cascade testing process, a genetic counselor will often collect a pedigree to identify at-risk relatives that could benefit from genetic testing, help with communication to the family members while accounting for family dynamics, and help ensure the correct family variant test is ordered.

Genetic Testing in Family Planning

A genetic diagnosis can also give individuals in the family planning process an opportunity to consider if their future children will be affected by the same condition. This may be a consideration for couples who have had a child considerably affected by an infantile condition or couples where at least 1 member is living with a condition likely to progress to kidney failure. For example, consider a couple whose first child developed renal cysts and diabetes syndrome as the result of a previously unknown paternally inherited *HNF1B* variant. Various reproductive options are available such as prenatal testing of a fetus to determine if they have the familial variant(s), or preimplantation genetic testing for monogenic kidney disease (PGT-M) where in vitro fertilization is combined with genetic testing to aid in embryo selection. The demand for PGT-M for hereditary kidney disease is growing.[31] PGT-M involves analysis of an embryo biopsy using a test customized to the familial variant. Embryos that do not harbor the familial variant(s) are preferentially selected for transfer. Genetic counselors can aid in educating families about these family planning options and in coordinating testing.

Genetic Testing in Transplant

Genetic testing in the context of potential living kidney donors (pLKD)s and related kidney transplant recipients (KTR)s is becoming ubiquitous because it can increase the chances of transplantation success and protect the long-term health of both the KTR and pLKD.[13,32] Genetic testing alone cannot predict the future kidney function of a pLKD or the outcomes after a transplantation; however, its consideration can initiate a conversation between the pLKDs, KTR, and genetic counselor about nuances of a genetic condition and the implications for the pLKD, KTR, and family members. When a pLKD is positive for variants associated with kidney disease, it is important to consider the following questions: what is the disease penetrance, what risk level is the recipient and their transplant team comfortable with, and is the likelihood of future kidney disease low enough to proceed with transplantation? For example, in individuals with ADPKD-*PKD1* or *PKD2* the lifetime risk of developing kidney cysts with other complications is fully penetrant (ie, 100%), although age-dependent. By contrast, the penetrance of having 2 risk alleles in *APOL1*, estimated to be present in 13% of African Americans, is considerably lower, and only a small proportion of these individuals (15%) will develop kidney disease.[24] Genetic counselors can help educate the patient and their family members about the nuances of a specific condition such as the mode of inheritance, age of onset of features, presence/type of extrarenal features, penetrance, and the availability of data for genotype-phenotype correlations. Moreover, genetic counseling can help balance the implications of a genetic test result and the pLKD's right to autonomy.[33]

When a genetic cause of kidney disease is known, family members can be evaluated to determine who in the family is at-risk versus who may be a potential candidate for kidney donation (Fig 2). In a scenario wherein a sibling group wants to determine who may be a suitable kidney donor to their father with a hereditary tubulointerstitial kidney disease, genetic testing should begin with the father. Imagine a pathogenic variant in *UMOD* was identified in the father. His children who inherited the dominant *UMOD* variant (50% chance) would be discouraged from proceeding with the transplantation

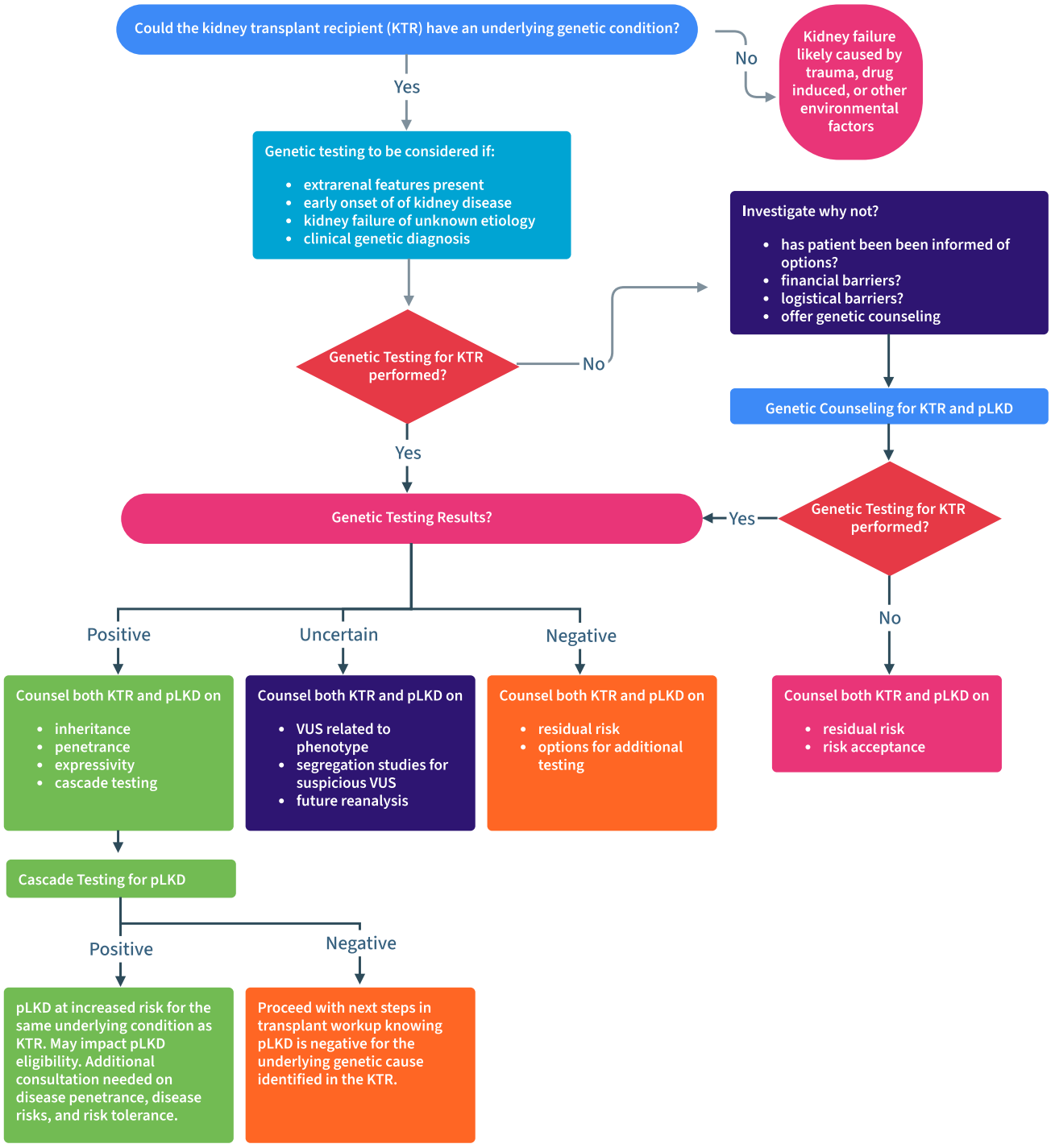

Figure 2. Flow chart of genetic counseling and genetic testing considerations for asymptomatic potential living kidney donor candidates who aim to donate to an affected family member. In this circumstance a family member refers to a blood relative (related by birth rather than through marriage or adoption). The affected family member's cause of kidney disease is an important factor in determining the future risk of kidney disease in the potential donor after transplantation if performed. VUS, variants of uncertain significance; KTR, kidney transplant recipients; pLKD, potential living kidney donor.

owing to their future kidney disease risk, which results from carrying this highly penetrant gene. Those children testing negative for the *UMOD* variant, however, could proceed with next steps. Although a genetic counselor cannot determine who can or cannot be a donor, they can empower patients/families and their clinicians with the knowledge to make informed decisions.

Both Kidney Disease Improving Global Outcomes (KDIGO) and the European Renal Association-Working Groups of Inherited Kidney Disorders (ERA-WGIKD)

emphasize the importance of testing at-risk relatives who are potential donors, particularly for disorders that demonstrate a dominant mode of inheritance, exhibit clinical variability, and/or reduced penetrance, for example, *PKD1/2*, *WT1* and *UMOD* (Table 1).[34] Although these broad recommendations exist, more disease-specific guidance may be warranted in the future to help clinicians balance minimizing the risks to donors while avoiding exacerbating organ shortage by reducing the pool of eligible donors.

Genetic testing can also provide important benefits to the KTR after transplantation. For example, atypical hemolytic-uremic syndrome (aHUS) is a condition that is linked to poor outcomes following kidney transplantation.[34] Tremendous genetic heterogeneity has been noted with aHUS, in that several different genes produce the same or similar phenotypes. Predisposition to aHUS is most often autosomal dominant with incomplete penetrance but can also be autosomal recessive. Treatment can be highly optimized by genetic testing. Evidence suggests that finding the causative gene is valuable in stratifying individuals into high (eg, *CFH*), moderate (eg, *CFI*), or low (eg, *DGKE*) risk of recurrence categories after kidney transplantation.[35] On contrary, pharmacological prophylaxis may be effective for people with variants in some genes (eg, *CFH*, *C3*, *CFB*, and *CFI*), but not beneficial for others (eg, *DGKE*).[35] Genetic counselors play an important part in the process of helping patients understand the repercussions of their test results.

CONCLUSION

Genetic counselors specialized in nephrology can assist the nephrologist and patient in interpreting genetic test results and provide ongoing support to patients with positive tests. They have extensive training and expertise in hereditary conditions, genetic testing, risk assessment, counseling, communication, and education. They provide both pretest and post-test genetic counseling for patients, ensuring that patients make informed decisions regarding genetic testing, help patients in understanding the results that are returned, and may provide and coordinate support for patients after the test results have been received.

The dynamic and continuing role of a genetic counselor specialized in nephrology in providing support to the patient is illustrated in the following scenario: an individual with a clinical diagnosis of polycystic kidney disease showed a previous negative result from genetic testing for *PKD1* and *PKD2*. The patient is referred to a genetic counselor by their nephrologist. In the genetic counseling session, the patient learns that some people may have a negative test result because the specific variant they have in *PKD1* or *PKD2* falls under the category of VUS. Fully informed about the drawbacks and benefits of receiving VUS results, the patient proceeds with getting their VUS results and a VUS in *PKD1* is identified. As the nephrologist and genetic counselor have high suspicion that the *PKD1* VUS may be disease causing, they work together to test various affected and unaffected relatives. The clinical information provided by the nephrologist and the family test results from the laboratory leads to the *PKD1* VUS being upgraded to LP and the patient now has a positive test result. The patient's 2 children decide to get tested after speaking with the genetic counselor. His oldest child tests negative and can discontinue ultrasound screening. His youngest child, newly married, is positive and can start the medication prescribed by his nephrologist and pursue genetic counseling with his wife to discuss reproductive options. In this scenario, the partnership between the nephrologist and genetic counselor positively affected the patient and his family members in providing a confirmed diagnosis, family counseling, and screening.

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