Evaluation of Genetic Kidney Diseases in Living Donor Kidney Transplantation: Towards Precision Genomic Medicine in Donor Risk Assessment

Yasar Caliskan¹ · Brian Lee² · Adrian M. Whelan³ · Fadee Abualrub¹ · Krista L. Lentine¹ · Arksarapuk Jittirat⁴

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Abstract

Purpose of Review To provide a comprehensive update on the role of genetic testing for the evaluation of kidney transplant recipient and living donor candidates.

Recent Findings The evaluation of candidates for living donor transplantation and their potential donors occurs within an ever-changing landscape impacted by new evidence and risk assessment techniques. Criteria that were once considered contraindications to living kidney donation are now viewed as standard of care, while new tools identify novel risk markers that were unrecognized in past decades. Recent work suggests that nearly 10% of a cohort of patients with chronic/end-stage kidney disease had an identifiable genetic etiology, many whose original cause of renal disease was either unknown or misdiagnosed. Some also had an incidentally found genetic variant, unrelated to their nephropathy, but medically actionable. These patterns illustrate the substantial potential for genetic testing to better guide the selection of living donors and recipients, but guidance on the proper application and interpretation of novel technologies is in its infancy. In this review, we examine the utility of genetic testing in various kidney conditions, and discuss risks and unresolved challenges. Suggested algorithms in the context of related and unrelated donation are offered.

Summary Genetic testing is a rapidly evolving strategy for the evaluation of candidates for living donor transplantation and their potential donors that has potential to improve risk assessment and optimize the safety of donation.

Keywords Genetics · Genomic medicine · Kidney · Living donor · Transplantation

Introduction

Kidney transplantation is the best treatment modality of end-stage kidney disease (ESKD) and more transplants are needed as the incidence and prevalence rates of ESKD are increasing worldwide [1]. Multiple environmental and genetic factors play a role in these increased rates. The importance of genetics is better recognized with the recent explosive growth of knowledge in genetics of kidney diseases due to significant advances in sequencing technology [2–5]. Familial clustering of nephropathy has been repeatedly observed in between 10 and 29% of adults with chronic kidney disease (CKD) of various etiologies [3–6]. There is also evidence that physiological parameters of the kidney are at least partially heritable, e.g., glomerular filtration rate (GFR) with a heritability of 30–60% in the general population [7–9], albuminuria, and electrolyte excretion [10–12].

Living donor transplant recipients have lower risk of rejection, better allograft function, and significant graft and
patient survival advantages than deceased donor transplants [1, 13]. Donor nephrectomy however carries both short-term (i.e., perioperative complications) and long-term risks (hypertension, cardiovascular and metabolic diseases, and ESKD) [14•]. Compared with healthy non-donor controls, the risk of ESKD in kidney donors has been estimated as 8–11 times higher [15–17]. Therefore, donor candidates must undergo rigorous medical/surgical workup to ensure their safety [18]. Moreover, many living donors are first- or second-degree relatives of their recipients and are at higher risk of developing ESKD even in the absence of known monogenic diseases in the family [19, 20]. Approximately 15% of kidney transplant recipients have an unknown etiology of ESKD which can potentially be heritable [19, 20]. When a genetic cause is identified, it not only gives the transplant candidate a diagnosis (especially if post-transplant recurrence is a concern) but also allows for potential testing and counseling on the risks of living donation among donors. Therefore, genetic testing offers many benefits to recipient and living kidney donor candidates (Fig. 1). This review explores the ways in which genetic testing may improve and guide the care of recipients and living donor candidates of kidney transplantation.

**Benefits**

**Kidney Transplant Recipient Candidates**
- Confirm and characterize clinical diagnosis of ESKD etiology
- Provide diagnosis for ESKD of unknown etiology
- Inform family counseling and family planning
- Inform evaluation and management of possible extra-renal manifestations of identified genetic diagnosis
- Inform recurrence risk of primary kidney disease in the allograft

**Living Donor Candidates**
- Assess potential risk of inherited kidney disease, including risk of CKD/ESKD after donation
- Enhance safety of kidney donation based on comprehensive, precision-medicine testing

**Risks**
- Identify VUS with uncertain clinical implications
- Motivate need for additional testing
- Pose psychological stress to donor candidate and their families
- Reduce opportunities for living donation in individuals who may never develop CKD
- Increase cost of the evaluation
- Impact insurability – Genetic discrimination*

**Controversies**
- Optimal approach and interpretation of genetic testing results in recipient and donor candidates
  - When to pursue, and when to avoid unnecessary genetic testing
- Standardized diagnostic criteria for CKD/ESKD of unknown etiology
- Preferred genetic testing modality:
  - Sanger sequencing
  - Targetted panel sequencing (TPS)
  - Whole exome sequencing (WES) / Whole genome sequencing
- Interpretation of genetic variants in healthy donor candidates

* The Genetic Information Nondiscrimination Act (GINA) of 2008 prohibits denial of health insurance coverage or increased premiums based solely on a genetic predisposition to developing a disease, and bars using genetic information for employment decisions.
Principles of Genetic Testing in Living Donor Evaluation

The Kidney Disease Improving Global Outcomes (KDIGO) Guidelines for the Evaluation and Care of Living Kidney Donors recommend that transplant programs should have a strategy for assessment of inherited kidney disease in donor candidates when there is a family history of kidney failure and the recipient’s cause of kidney failure is unknown [18]. The US Organ Procurement and Transplantation Network (OPTN) policy requires that transplant centers in the USA must develop and comply with a written protocol for autosomal dominant polycystic kidney disease (ADPKD) or other inherited renal disease as indicated by family history [21].

Family history review during donor evaluation may identify conditions with increased prevalence within the donor candidate’s family. Further risk stratification with genetic testing could therefore be helpful in donor candidacy assessment and in the candidate’s decision to proceed. Published guidelines have advocated for judicious use of genetic testing in living kidney donor evaluations [22 23•• 24]. Testing should occur following genetic counseling and ideally should start with testing of the recipient candidate in most circumstances to identify a specific disease-causing variant which provides more reassurance if that variant is not identified within the donor candidate; ancestry-based testing related to apolipoprotein L1\textsuperscript{1} (\textit{APOL1}) is an exception. All donor candidates of sub-Saharan ancestry should be informed about \textit{APOL1} genetic variants and the risk of CKD [24]. The informed

Approach to Genetic Testing of Related Living Donor Candidates

![Genetic testing algorithm for evaluation of related living donor candidates. CKD, chronic kidney disease; CMA, chromosomal microarray; ESKD, end-stage kidney disease; TPS, targeted panel sequencing; VUS, variant of unknown significance; WES, whole exome sequencing](image-url)

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1. **Evaluate CKD Etiology in Recipient Candidate**
   - Known inherited kidney disease
   - Kidney disease of unknown etiology and/or early onset
   - Cystic kidney disease
   - Nephrolithiasis
   - Congenital disease with extrarenal signs
   - Consanguinity

2. **TPS or WES**
   - If congenital extrarenal manifestations:
     - CMA test of recipient candidate

3. **Diagnostic interpretation**
   - Positive result
   - VUS
   - Negative result

4. **TPS or CMA testing of the donor candidate**
   - Positive result
   - VUS
   - Negative result

5. **NOT a candidate for kidney donation**
   - Genetic counseling about ESKD risk
   - If risk acceptable to program and donor candidate, continue the evaluation

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Fig. 2 Genetic testing algorithm for evaluation of related living donor candidates. CKD, chronic kidney disease; CMA, chromosomal microarray; ESKD, end-stage kidney disease; TPS, targeted panel sequencing; VUS, variant of unknown significance; WES, whole exome sequencing
In recent years, there has been an increased interest in the use of genetic testing to improve the selection of kidney donors. This approach is especially relevant in the era of living related donor kidney transplants, where the risk of transmission of genetic kidney disease can be mitigated by identifying donors with a low risk of disease progression. Genetic testing can also provide valuable information for unrelated donor candidates, helping to identify those at higher risk of kidney disease or who may have a family history of kidney disease.

Donor candidates who are otherwise acceptable should be offered APOL1 genetic testing. In living related donor kidney transplants after genotyping of the recipient and interpretation of the data, further risk stratification with genetic testing could therefore be helpful in living related donor candidacy assessment and in the candidate’s decision to proceed [24]. Figure 2 displays a suggested genetic testing algorithm for the evaluation of living related donor candidates. In unrelated donor candidates with or without family history of kidney disease, our standard approach is summarized in Fig. 3. A suggested approach to ancestry-based genetic testing of Black living donor candidates (i.e., of sub-Saharan African ancestry) is shown in Fig. 4. Family history of cancer in the donor candidate is another emerging topic [25]; this review focuses on the evaluation of genetic kidney disease.

### Inherited Diseases and Genetic Testing in Kidney Transplantation

Inherited kidney diseases are classified as monogenic kidney diseases versus complex genetic kidney diseases (CGKD) such as low GFR (CKD) (Table 1). Conceptually, monogenic kidney diseases with very rare but very highly penetrant genetic variants in a single gene and CGKD with very common variants at multiple loci in the genome fall at opposite ends of the spectrum of inherited kidney diseases.

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**Approach to Genetic Testing of Unrelated Living Donor Candidates**

Evaluating family history of CKD in the donor candidate is crucial. Donor candidates with a family history of:

- Known inherited kidney disease
- Kidney disease of unknown etiology and/or early onset
- Cystic kidney disease
- Nephrolithiasis
- Congenital disease with extrarenal signs
- Consanguinity

- Disease-focused evaluation: TPS
- WES
- If congenital extrarenal manifestations:
  - CMA test of donor candidate

Diagnostic interpretation:

- Positive result: NOT a candidate for kidney donation
- VUS: Genetic counseling about ESKD risk
- Negative result: If risk acceptable to program and donor candidate, continue the evaluation

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**Fig. 3** Genetic testing algorithm for unrelated living donor candidates. CKD, chronic kidney disease; CMA, chromosomal microarray; ESKD, end-stage kidney disease; TPS, targeted panel sequencing; VUS, variant of unknown significance; WES, whole exome sequencing
Identification of a precise molecular diagnosis before transplantation will help to guide living donor candidate evaluation and the assessment of suitability of any living donor transplant based on anticipated donor’s renal prognosis and CKD risk after donation. Focused donor genetic testing should be considered when the recipient’s genetic diagnosis is clear, or the differential diagnosis is limited. If the differential diagnosis is large, broad base donor screening including whole exome sequencing (WES) or whole genome screening (WGS) should be considered.

**Monogenic Kidney Diseases**

In monogenic diseases (aka “single-gene disorders”), a pathogenic variant of a single gene (out of a total of ~25,000) is sufficient to cause the disease [26, 27]. The advent of next-generation sequencing (NGS), including WES, led to the discovery that a surprisingly high fraction of early-onset CKD is monogenic. A pathogenic variant in one of many alternative genes may also cause a similar-appearing disease in different patients which is known as “gene locus heterogeneity” [26, 27]. Most patients with inherited kidney diseases have causative monogenic variants, with more than 600 genes implicated and counting [28, 29]. A recent large cohort study evaluating the diagnostic utility of NGS in 3000 adult patients with CKD revealed diagnostic monogenic variants in 9.3% of CKD patients with various etiologies and detected 66 separate monogenic disorders [30••]. Genomic testing was particularly effective in diagnosing those with CKD of unknown origin, in which a diagnosis was reached in 18% [30••]. A family history of CKD, clinical diagnosis of congenital or cystic renal disease, and nephropathy of unknown origin were independent predictors of having a genetic cause [30••]. However, the frequency of monogenic conditions among kidney transplant recipients has not been extensively studied. In our previous studies of recipients with family history of ESKD, the major primary causes identified were focal segmental glomerulosclerosis (FSGS) (28%), ADPKD (21%), and Alport syndrome (12%) [31]. In patients with hereditary kidney diseases, kidney transplantation from a family member could be risky for both donor and recipient, and donors must be screened meticulously for the risk of having the same disease (Fig. 2). If a causal variant is identified in the recipient, genotyping should be offered to related donor candidates before living donor transplantation.

**Polycystic Kidney Disease (PKD)**

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of kidney disease in adults, with an estimated prevalence of 1 in 500–2500 individuals [32–34]. ADPKD is caused primarily by pathogenic variants of two genes, *PKD1* and *PKD2* [35, 36]. *PKD1* mutation screening is technically challenging due to its large size with presence of six pseudogenes with high levels of deoxyribonucleic acid (DNA) sequence similarity and extensive allelic heterogeneity. Despite these limitations, recent studies have delineated a strong genotype–phenotype correlation in ADPKD and begun to clarify the role of genetics underlying cases with atypical phenotypes. Kidney transplantation is the preferred treatment when ADPKD patients develop ESKD [32]. Currently, up to 90% of cases with ADPKD can now be diagnosed by genetic testing, which is
very helpful for clinical decision-making, especially regarding living related donation [37]. Furthermore, adoption of NGS provides a high-throughput, accurate, and comprehensive screen of multiple cystic disease and modifier genes at a reduced cost. The outcomes were similar in recipients with inherited kidney diseases regardless of donor origin (living vs. deceased). However, related living donor candidates for patients with ADKPD must be screened meticulously for a possibility of having the same disease [38]. Of note, kidney disease from PKD2 variants presents later in life than PKD1 variants, making the traditional radiologic/laboratory screening of donors less sensitive. Genetic tests can augment donor workup especially in asymptomatic younger donors as it can identify non-ADPKD cystic kidney diseases too. If potential living first-degree related donor is younger than 30 years old, genetic testing is recommended regardless of imaging [39]. Notably, for the ~10% of ADPKD patients without a currently identified mutation, PKD panel is not expected to be informative in the related donor candidate evaluation—emphasizing the critical importance of beginning genetic evaluation by testing the recipient candidate. If no known pathogenic mutation is identified in the recipient, the case should be discussed individually for limitations of PKD panel and other causes of recipient’s cystic kidney disease.

### Apolipoprotein L1 (APOL1)–Related Kidney Disease

Recipients of African ancestry are more likely to suffer from allograft failure than European American (EA) recipients [40, 41] and kidneys donated by African American (AA) donors fare worse after transplantation than organ from EA donors [42–44]. Ancestry-based studies showed that in individuals of recent African ancestry, variants in APOL1 gene are associated with certain forms of CKD. Carriers of two renal risk variants (RRVs—G1/G1 or G2/G2, or compound heterozygosity G1/G2) are at a heightened risk for FSGS, human immunodeficiency virus–associated nephropathy, and hypertension-associated ESKD [45–50]. Furthermore, AA kidney transplant recipients from deceased AA donors with two RRVs were found to have shorter allograft survival than AA donors with zero or one RRV [51–53]. Based on retrospective studies, presence of two APOL1 RRVs in

| Disease | Genes involved | % of ESKD cases | Clinical features | Recurs following transplant? |
|---------|----------------|-----------------|------------------|-----------------------------|
| ADPKD   | PKD1, PKD2     | 5               | Bilateral renal cysts, hepatic cysts, intracranial aneurysms | No |
| FSGS (genetic forms) and SRNS | NPHS1 (nephrin), NPHS2 (podocin), APOL1, ACTN4, IN2, COL4A3, COL4A4, COL4A5, TRPC6 | Unclear, all FSGS (genetic and non-genetic forms) accounts ~2.3% | Isolated proteinuria, nephrotic syndrome | Less likely than non-genetic forms of FSGS. Recurrence described in nephrin and podocin mutations |
| Alport syndrome | COL4A3, COL4A4, COL4A5 | 0.3–2.3% | Hematuria, ocular abnormalities, sensorineural hearing loss | No. Can develop anti-GBM nephritis |
| Thin basement membrane disease | COL4A3, COL4A4 | Unclear, rarely leading to ESKD | Asymptomatic hematuria, possible progression to CKD/ESKD | No |
| ADTKD   | UMOD, MUC1, REN, HNF1B, Sec61A1 | Unclear, likely underdiagnosed | Progressive CKD leading to ESKD, bland urine, renal biopsy often non-specific, some associated with maturity onset diabetes of young, gout arthritis | No |
| aHUS    | CFH, CFI, CFB, C3, MCP, DGKE, CFHR1-5, THBD | Unclear, likely underdiagnosed | MAHA, thrombocytopenia, TMA on kidney biopsy, kidney dysfunction | Yes, likely need ongoing anti-complement therapy |

**ADPKD**, autosomal dominant polycystic kidney disease; **ADTKD**, autosomal dominant tubulointerstitial kidney disease; **aHUS**, atypical hemolytic uremic syndrome; **ESKD**, end-stage kidney disease; **FSGS**, focal segmental glomerulosclerosis; **GBM**, glomerular basement membrane; **MAHA**, microangiopathic hemolytic anemia; **SRNS**, steroid-resistant nephrotic syndrome; **TMA**, thrombotic microangiopathy

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Table 1 Genetic kidney diseases and common genes involved
a donor is associated with lower pre- and post-donation estimated GFR (eGFR) and this may increase living kidney donors’ ESKD risk [54, 55]. Although up to 32% of individuals in selected populations have high-risk APOL1 genotypes, only a minority of these donors will eventually develop ESKD [56]. In the absence of prospective data, the role of APOL1 genotyping in living kidney donor candidate evaluation remains uncertain. However, all donor candidates of appropriate ancestry should be informed about APOL1 gene and the future risk of kidney disease [24]. Living kidney donor candidates who are otherwise acceptable should be offered APOL1 genotyping based on their ancestry (Fig. 4). Timing of genetic testing is also important, and it is recommended when candidates have passed preliminary medical and psychosocial evaluation. Genetic testing should only be offered after appropriate counseling [24]. APOL1 test results for RRVs should be shared with donor candidate. Currently, no data exist on the impact of the living donor APOL1 genotype on recipient outcomes and donor candidate and transplant provider should communicate in decision-making. In this process, donor candidates express their preferences and principles, and transplant providers disclose information about the transplantation, its benefits, risks, and alternatives, out of respect for donor autonomy [24]. Donor’s test result should not be shared with the recipient candidate to protect the donor’s privacy [24]. Counseling can be performed by transplant nephrologist or a member of the transplant team and should be offered before genetic testing and again after obtaining results. Taken together, two RRVs are often considered a contraindication to donation, best addressed with a thorough shared decision-making with the donor candidate (Fig. 4).

Focal Segmental Glomerulosclerosis

FSGS, an important cause of ESKD, covers a spectrum of clinicopathological syndromes sharing a common glomerular lesion, based on an injury of podocytes caused by diverse insults. Transplant candidates with primary FSGS have a significant risk of recurrence after transplantation, reported at an average rate of 30% [57–59]. Recurrence attributable graft loss is reported at 30–50%. Recently, The Post-Transplant Glomerular Disease (TANGO) study, an international observational cohort study, showed that idiopathic FSGS recurs post-transplant in one-third of cases and is associated with a five-fold higher risk of graft loss [60]. Response to treatment is associated with significantly better outcomes but is achieved in only half of cases. Despite living donation being an independent risk factor for disease recurrence, allograft survival is generally equivalent to or superior to deceased donor grafts [61]. Therefore, living donor kidney transplant in recipients with FSGS is not contraindicated and registry data suggests that outcome is best with 2-haplomatched living donor grafts [62]. Most reports suggest that genetic forms of the disease have a lower rate of recurrence although recurrence has been reported in recipients with nephrin (NPHS1) and podocin (NPHS2) pathogenic variants [63–65]. The differential risk of recurrence reported by most authors suggests a value for genetic screening in distinguishing genetic forms of FSGS pre-transplantation to prognosticate allograft outcomes in younger recipients with steroid-resistant nephrotic syndrome (SRNS). A genetic diagnosis can support personalized care, including informing targeted donor workup, post-transplant prognosis, and/or family counseling [30••, 66]. It may also help prioritize donor selection among several at-risk family members.

Alport Syndrome

Alport syndrome and thin basement membrane nephropathy are genetic diseases affecting the major type IV collagen network of the glomerular basement membrane (GBM) present in the kidney, lens, retina, and inner ear [67, 68]. This network contains a heterotrimer formed by the type IV collagen alpha3, alpha4, and alpha5 chains encoded, respectively, by the autosomal COL4A3 and COL4A4 genes and the X-linked COL4A5 gene [67–69]. Inheritance is X-linked in 75% of cases, with the remainder mostly in an autosomal recessive pattern. Alport patients who undergo kidney transplantation enjoy excellent patient and graft survival rates [70–72]. However, exposing the recipient’s immune system to “intact” GBM collagen antigens found in the donor kidney can lead rarely to post-transplantation de novo anti-GBM disease [70–74]. For living related donors, genotype–phenotype correlations for autosomal recessive Alport syndrome are less robust than those for X-linked Alport; clearly heterozygous females (mother and daughters of an X-linked patient) should be discouraged from donation due their future risk of hypertension and kidney disease [75].

Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)

ADTKD previously known by a number of names, most notably medullary cystic kidney disease, is a rare genetic cause of CKD and ESKD with an onset between the ages of 17 and 75 years [76–78]. The patient’s urinalysis is bland, with absent or mild proteinuria, and nocturia/enuresis is common in children as concentrating ability is lost. Histological features are equally non-specific and usual findings include interstitial fibrosis, tubular atrophy, microcyst formation, and thickening and lamellation of the tubular basement membranes. Affected patients do not have evidence of glomerular disease or deposition of immunoglobulins or complement factors [78, 79]. Five genes are known to
cause ADTKD: UMOD, MUC1, REN, HNF1B, and, more rarely, SEC61AI [78–80]. ADTKD due to UMOD, HNF1B, REN, and SEC61AI variants may have extrarenal features, while ADTKD due to MUC1 variants does not. Since kidney biopsy and clinical findings are non-specific, genetic testing may offer a more definitive diagnosis [80]. As most of these mutations are inherited in an autosomal dominant manner, all biologically related living donors should be genetically screened with donation deferred if testing positive [77, 81]. Moreover, since most HNF1B mutations are deletional, if first-line targeted exonic sequencing is negative, multiplex ligation-dependent probe amplification should be employed to detect large genomic rearrangements [82].

**Fabry Disease**

Fabry disease is an X-linked recessive monogenic disease caused by deficiency of the lysosomal hydrolase, α galactosidase A (α-Gal A), secondary to mutations in the galactosidase α (GLA) gene which results in systemic accumulation of trihexosylceramide (globotriaosylceramide [Gb3]) in the lysosomes of the vascular endothelium in multiple organs [83, 84]. Clinical features include neuropathic pain and angiokeratoma, proteinuria, CKD, left ventricular hypertrophy, arrhythmia, and stroke. Symptoms generally appear in childhood, although some go unrecognized until adulthood. Many affected males develop ESKD by age 35 to 45. Heterozygous females have a variable course, usually less severe, but can experience the full disease spectrum due to random X chromosome inactivation. The gold standard for diagnosis is the genetic analysis in search of causal variant, in addition to family history [83]. In homozygous patients, the enzyme activity can also be used. Once the diagnosis is confirmed, the patient and their family should receive genetic counseling. Specific treatments (enzymatic replacement or pharmacologic chaperones) should be initiated as soon as a diagnosis is obtained which can change the prognosis of the disease [83]. Despite a recurrence rate of Fabry disease after transplantation of 11.1%, allograft and patient survival are comparable among kidney transplant recipients with and without Fabry disease [85, 86], with continued enzyme replacement treatment in affected individuals post-transplantation. A detailed evaluation (slit lamp eye exam, leukocyte α-Gal A level) and genetic testing should be performed in living related donor candidates with a family history of Fabry disease due to the high risk of renal involvement. Daughters of an affected father most certainly are heterozygous and should be deferred.

**Atypical Hemolytic Uremic Syndrome (aHUS)**

Hemolytic uremic syndrome (HUS) is most commonly the result of infection with a Shiga toxin–producing *E. coli* (STEC-HUS, 90% of cases). STEC-HUS is a self-limiting illness that only rarely results in ESKD and very rarely recurs after transplantation (0–1%) [87]. Unlike STEC-HUS, the kidney prognosis of atypical HUS (aHUS) is poor [88]. However, eculizumab and the recently approved long-acting complement inhibitor ravulizumab have resulted in favorable outcomes in aHUS of both native and transplanted kidneys [89]. Recurrence of aHUS continues to be a major issue in the post-transplant period and risk factors include regulatory complement factor genetic variants, particularly complement factor H (CFH), and a previous history of recurrence in prior transplants. Historically, patients with a pathologic variant of CFH, Complement Factor I (CFI), C3, Complement Factor B, or high titer anti-CFH autoantibodies have an 80–90% risk of recurrence and without complement inhibitor treatment most grafts will fail [90, 91]. Patients with a variant membrane cofactor protein or low titer of historical anti-CFH antibodies have low risk of recurrence [90, 91]. However, candidates in whom no cause of aHUS is identified are at an intermediate risk of recurrence [92]. Candidates at risk of recurrent aHUS should be counseled about the preemptive use of a complement inhibitor or the need to start treatment perioperatively [93]. While the diagnosis of aHUS is made clinically, genetic testing bears great importance on the decision of timing and duration of complement inhibitor therapy. It is absolutely essential if a living related donor is considered, to protect the living donor and outcomes of the gift in the recipient [94]. Current genetic testing is imperfect in excluding the presence of aHUS in donor candidates even when the causal variant is known in the recipient, especially when 20–30% of causal variants are de novo and 10% have multiple pathogenic variants. If no causal variant is detected in the recipient candidate, the genetic evaluation of the living related donor candidates becomes more challenging. For these reasons, biologically related living kidney donors of recipient with aHUS should be evaluated cautiously by a team in conjunction with genetic counseling, with low threshold for not approving for donation.

**Complex Genetic Kidney Diseases**

Genetic variants in multiple different genes are necessary to culminate in renal disease. The degree of genetic causality varies with the mode of inheritance [26]. These usually manifest in adulthood and are much more frequent than monogenic diseases. As they show less heritability, environmental influences may play a larger role. Correlation between phenotype and genotype is weak, but genetic factors including variants in multiple genes may nevertheless play an important role in pathogenesis by conveying an increased relative risk. These polygenic variants leading to CKD are identified through genome-wide association studies (GWASs) [20, 26,
95–97] and exert weaker genetic causality on the phenotype and are usually referred to as “risk alleles.” GWASs are a tool used to look for associations between traits, including human disease and single-nucleotide variants (SNVs). These are observational studies and pool the results of many individuals to look for common links between SNVs and traits. Kottgen et al. identified a SNV, the polymorphism rs12917707, located near the UMOD gene, which if mutated causes autosomal dominant medullary cystic kidney disease type 2 leading to CKD [98]. These results were recently confirmed in a large worldwide cohort [99]. Most GWAS loci tend to explain only a relatively small proportion of overall risk and translation of these findings into concrete clinical benefit has proven a challenge. This has been compounded by other limits, including technological challenges, small sample size, and allelic heterogeneity. Genome-wide polygenic risk scores (GPSs) are designed to address the challenges by aggregating the effects of millions of genetic loci across the genome, including those that do not reach individual statistical significance. The approach to CGKDds and application of GPSs is currently undefined in transplantation, particularly vis-à-vis living donor evaluation.

Genetic Testing Modalities

The aim of diagnostic testing is not only to identify genetic variants but also to determine which among many possible variants detected are predicted to pose a risk to clinical outcomes [100]. Several genetic modalities are available: karyotyping, chromosomal microarray (CMA), Sanger sequencing, NGS including targeted gene panel sequencing, WES, and whole genome sequencing (WGS). Selection of the most appropriate diagnostic sequencing approach is made on the basis of various factors including diagnostic yield of the different sequencing modalities, the patient’s clinical picture, preferences for the types of results that may emerge with broader sequencing approaches, insurance coverage, and out-of-pocket costs to patients. Technical and clinical aspects of genetic testing modalities and their use in clinical transplant practice are summarized in Table 2 [101–126]. Table 3 summarizes some of the renally targeted gene panels available, differing in the number and kind of genes tested, and turnaround time.

Challenges in Genetic Testing

Genetic findings from NGS are increasingly being used to inform the clinical management of many kidney diseases, enabling clinical diagnosis and precise disease evaluation, guiding treatment choices, and informing family counseling [121]. Diagnostic genetic testing aims to identify the variants that cause disease in an individual patient; however, the large number of variations within the human genome makes this goal challenging [127]. As with any genetic study, questions arise as to whether the variants discovered in patients are actually pathogenic. The American College of Medical Genetics (ACMG) developed standards and guidelines for the classification and interpretation of sequence variants [113, 126–130]. The major challenge underlying this approach is that variants previously reported to cause related phenotypes in the existing databases were considered definitely or likely pathogenic according to guidelines [127]. However, recent reports suggested that existing databases include a significant proportion of incorrect disease attribution to variants when based on existing databases [121, 131]. The way to resolve this quandary is through a detailed review of existing clinical variant databases using newly available population genetic material [121]. Another area of uncertainty for patients and caregivers is indeterminate results, which are reported as variant of unknown significance (VUS). There are concerns regarding clinicians’ understanding of genetic test reports, particularly the limitations of our knowledge when a VUS is identified. The main concern is to misinterpret any variant as significant without a background understanding of normal human variation. There have been a number of high-profile legal cases where clinicians have misinterpreted DNA variants with serious consequences. The European Society of Human Genetics states that the utility of the test and the diagnostic yield should be considered before offering testing and whether testing will rule out or rule in a diagnosis. In contrast, the ACMG lists clinically actionable variants that should be reported, regardless of the initial indication for sequencing, and this policy is observed throughout the USA [132, 133]. Genetic counseling and periodic review of results will help reclassify such variants and initiatives such as ClinGen are now also developing kidney-specific workgroups to facilitate such efforts [134].

Return of Genetic Results and Clinical Implementation for Transplant Evaluation

Genetic testing is becoming an increasingly familiar tool in nephrology practice. However, there are scarce data regarding best practices for informing patients of results and clinical application of actionable genetic findings for kidney patients and donor candidates [135]. Broader utilization of genetic testing in routine transplant evaluation raises a number of technical, logistical, and ethical questions [135]. Interpretation of genetic data requires significant expertise from both geneticists and nephrologists. The list of kidney disease genes is evolving, as is the list of causative variants. Mutations previously identified as causative may need
| Primary aim                                           | CMA                                                                 | Sanger sequencing                                                                 | NGS                                                                 |
|------------------------------------------------------|---------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------|
| - Identification of translocations, CNVs, and chromosomal aneuploidies | - Targeted sequencing in identifying SNVs and INDELs < 10 bps in length | - Identification of variants in a specific set of curated genes                   | - Identification of SNVs/INDELs within coding regions of the genome |
| Advantages                                           | - CMA has higher resolution than standard karyotyping (50–100 kb)    | - Sequencing of specific genes or regions that are not attainable with NGS approaches | - Rapid and inexpensive sequencing at higher coverage than that achieved with WES or WGS |
| - Simple                                             | - Time-consuming for longer segment sequencing                       | - High diagnostic yield depending on the patient’s phenotype                       | - Reduces the number of SNVs needed to interpret                      |
| - Cost-effective                                     |                                                                     |                                                                                  | - Covers > 75% of pathogenic SNVs as they lie within the exome—Less expensive than WGS |
| Disadvantages                                        | - CMA has limitations with detecting SNVs, INDELs, balanced chromosomal rearrangements, and deletion/ duplications of < 50,000 bp | - Limited for large structural variants                                           | - Gene list in panel must be updated frequently to ensure that they remain current |
| - Time-consuming for longer segment sequencing       |                                                                     | - Error rate 0.5–2%                                                             | - Reanalysis efficacy is limited                                       |
| - Limited for large structural variants              |                                                                     |                                                                                  |                                                                      |
| - Gene list in panel must be updated frequently to ensure that they remain current |                                                                     |                                                                                  |                                                                      |
| - Error rate 0.5–2%                                  |                                                                     |                                                                                  |                                                                      |
| - Reanalysis efficacy is limited                     |                                                                     |                                                                                  |                                                                      |
| Use in clinical transplant practice                  | - Recipients with multiple congenital anomalies and developmental diseases | - Confirmatory testing in single-gene disorders detected by NGS                   | - First-line test for the molecular diagnosis of inherited kidney disease based on recipient’s phenotype |
| - Donor candidates with extrarenal congenital anomalies |                                                                     | - Screening at-risk family members including donor candidates for a known mutation in recipient | - Effective in evaluation of recipients with homogenous conditions such as Alport syndrome, and FSGS |
| - Screening of risk variants of APOL1 and LIMS1 genes in donors and recipients |                                                                     | - Screening of risk variants of APOL1 and LIMS1 genes in donors and recipients    | - Screening of recipients with undefined phenotype                     |
| - Screening of living donor candidates with family history of kidney disease |                                                                     |                                                                                  |                                                                      |
| - Recipients highly suspected of genetic diseases undiagnosed with more specific methodologies |                                                                     |                                                                                  |                                                                      |
| - Screening of living donor candidates with family history of kidney disease |                                                                     |                                                                                  |                                                                      |

CMA, chromosomal microarray; CNVs, copy number variations; NGS, next-generation sequencing; FSGS, focal segmental glomerulosclerosis; INDELs, insertions or deletions; SNVs, single-nucleotide variants; WES, whole exome sequencing; WGS, whole genome sequencing
to be reconsidered in light of evolving subsequent reports [136]. The significance of identified mutations is also more nuanced in healthy donor candidates. The significance of heterozygous mutations in asymptomatic family members of the affected recipient requires integration of clinical, familial, and genetic factors [137, 138].

Outstanding questions related to the widespread implementation of genetic testing in transplant practice include reimbursements for genetic testing and privacy concerns (e.g., sharing genetic results from a recipient with a prospective related donor and vice versa). Patients and donor candidates undergoing genetic testing require pre- and post-testing counseling to ensure they understand the risks as well as the benefits of diagnostics [139]. Informed consent for genetic testing preferably should cover all privacy concerns. Clinicians need to document the discussions conducted and that recipients and donors get coached on the possibility of unclear and/or unexpected genetic findings [139]. A multidisciplinary approach involving nephrologists, medical geneticists, and genetic counselors will help in safeguarding this process. Each recipient and donor should receive a standardized clinical consultation document that details the findings and management recommendations so they may share with outside providers, along with layperson communication to share with family members. The genetic findings should also be discussed with the referring nephrologist. The transplant team should not reveal the donor candidate’s genotyping findings to the recipient. The donor is free to discuss the results of genetic testing with the recipient.

Clinical genetic testing is rapidly moving towards genome-wide assessment [115, 140, 141]. These may yield results beyond the original diagnostic intent, revealing VUSs which may prompt additional investigations. Genome-wide sequencing approaches may uncover incidental or secondary findings of variants which can be medically actionable (e.g., detection of predisposition to hereditary cancers or cardiovascular disorders) and also have implications for nephrology care.

There have been reports of people experiencing genetic discrimination as a result of their genetic diagnosis [142]. In the USA, the Genetic Information Nondiscrimination Act (GINA) protects the right to health insurance and employment [143]. However, more subtle discrimination may still occur. As this is an emerging technology, there needs to be more education to the transplant community regarding the testing indications, tools available, counseling approaches and backup resources available, result interpretation, and avenues for specialist referral as unexpected information come to light along with family planning advice. The risk-to-benefits balance is summarized in Fig. 1 along with areas of controversies.

### Future Directions

Wider implementation of genetic testing in transplant practice will require maintaining an up-to-date list of nephropathy-associated genes, establishing best practice guidelines for periodic sequence reanalysis, elucidating VUSs still under investigation, developing efficient pipelines for rapid and iterative variant evaluation as emerging genes and variants are identified [103], and obtaining third-party payer coverage for the necessary follow-up care associated with detecting medically actionable genetic findings. Addressing physician knowledge gaps is also

| Table 3: Available panels for genetic kidney disease |
|-----------------------------------------------|
| **Organization** | **Test name (number of genes)** | **Pre-requisites** | **Estimated result turnaround time** |
| University of Iowa | KidneySeq™
- Comprehensive panel (312)
- Ciliopathy/TI (85)
- CAKUT (56)
- Glomerular (78)
- Tubular ion transport (72)
- Nephrolithiasis (35)
- APOL1 genotyping (1) | None | 45 days |
| Natera™ Renasight™ (382) | None | Suspected Alport/FSGS OR family h/o | 21-28 days |
| Invitae™ KIDNEYCODE™ (18) | | Alport/FSGS OR eGFR ≤ 90 ml/min/1.73 m² AND hematuria OR family h/o CKD | 10–21 days |

CAKUT, congenital anomalies of the kidney and urinary tract; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; h/o, history of; FSGS, focal segmental glomerulosclerosis; TI, tubulointerstitial
critical, and potentially met through strategies that include the introduction of algorithms alerting clinicians to a possible monogenic disease, development of decision support tools for electronic health records, and remote consultation options for centers lacking genetic expertise and/or the resources required for return of results. Future studies are needed to comprehensively evaluate the transplant clinicians’ thoughts and knowledge on relative diagnostic yields between different genetic sequencing modalities. The long-term effect of both primary and secondary genetic findings on nephrologic care, including on treatment decisions, preimplantation genetic diagnostics, transplantation eligibility, and third-party payer coverage (potentially incorporating these into the professional standards/fellowship training curriculum and board certification), should be further studied. Further systematic study is also needed to examine ethical and legal questions that may arise from result of results in addition to assessing the long-term effect of the genetic findings on transplant volume/rate, clinical outcomes, and healthcare utilization. Formation of multicenter interdisciplinary working groups and use of evidence-based frameworks to assess genotyping results in living donor candidates would greatly facilitate the use of state-of-the-art genotyping in transplant evaluation.

Conclusions

The nascent era of kidney genomics is on the cusp of emerging into mainstream practice across transplant centers. A concerted effort within the nephrology and transplant communities to disseminate information on the technologies, benefits, and potential risks can inform adoption of best practices, such that these technologies become assets added to the transplant nephrologist’s toolbox. When properly used, genetic testing should not pose unnecessary barriers to donation and transplantation, but rather can help guide recipient-donor evaluation using state-of-the-art precision medicine techniques to better ensure patient safety.

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Availability of the Data and Material Not applicable.

Code Availability Not applicable.

Declarations

Conflict of Interest K.L.L. is a consultant for CareDx, Inc. and serves on a Sanofi speakers’ bureau.

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