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# Monogenic Kidney Diseases in Kidney Transplantation

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## Abstract

Monogenic kidney diseases are involved in up to 15% of end-stage kidney diseases in adults, and in 70 % of pediatric patients. When these disorders lead to kidney failure, kidney transplantation is the preferred mode of replacement therapy. Kidney transplantation requires specific considerations depending on the nature of the genetic disorder, the potential oncological risk, the risk of recurrence in the graft, the possibility of specific complications of immunosuppression, and the issue of living donation. The availability of genetic testing should play an increasing role in the evaluation of patients or related living donor candidates before transplantation, relevant for the pre- and post-transplantation management.

**Keywords:** Genetic testing, Mendelian diseases, living donation, immunosuppression, oncological transformation, recurrence risk

## 1. Introduction

At least 10-15% of adults and 70 % of children with end-stage kidney diseases (ESKD) have an inherited kidney disease. [1,2] Early age of onset, familial history of kidney diseases, congenital or cystic disease, and association with syndromic and extra-renal features are classically associated with a higher probability of genetic kidney diseases (GKD). [3,4] The increasing availability of genetic testing and reference databases implies that a molecular diagnosis can be obtained more readily, usually before patients are considered for kidney transplantation (KT).

Since KT is the preferred option for most patients with GKD and kidney failure, important issues should be considered both before and after transplantation. Genetic testing has a direct clinical utility, by influencing disease surveillance and management, and guiding specific therapies. Some kidney diseases of genetic origin may recur on the kidney graft or present an increased risk of cancer or systemic manifestations, requiring early diagnosis and specific management in terms of immunosuppression and follow-up. The availability of genetic testing has also practical implications for the selection of related living donor candidates. [5-7]

Here, we address the specificities of genetic testing in KT; discuss the risk of recurrence in the transplant and of oncological transformation associated with certain GKD; review specific features of the most frequent inherited disorders and those with multisystemic complications; discuss the influence of immunosuppression on disease courses and living donation; and list unmet needs and perspectives in the field.

## 2. Genetic testing in kidney transplant candidates

### A. Diagnostic yield of genetic testing in kidney transplant candidates

In daily practice, about 15% of chronic kidney diseases (CKD) are of unknown origin.[3] Currently, there is no strong recommendation for the systematic use of genetic testing in such cases. An increased likelihood of a genetic diagnosis is associated with positive family history, young age of onset, structural or cystic abnormalities of the kidneys, unknown etiology of CKD, and extrarenal manifestations (Figure 1). The studies of Groopman et al. demonstrated that exome sequencing yielded a genetic diagnosis in approximately 10% of cases in two cohorts totaling 3315 adult patients with advanced CKD (and among them 2144 with ESKD) reaching 17 % in patients with CKD of unknown origin. [5] A recent extensive literature survey of diagnostic yield across and within kidney phenotype groups reviewed five studies reporting on ESKD populations that were waitlisted for transplant surgery or had received a kidney

transplant. A diagnostic yield was extrapolated ranging from 12.5 to 24.6%. [8] The authors report that positive family history, consanguinity, extrarenal features, and young age of onset of ESKD positively influenced the diagnostic yield. [8] However, it is important to state that ESKD onset at adult age should not prevent from pursuing a genetic diagnosis as typical childhood-onset diseases can be diagnosed at adult age. A prominent example is the rather common recurrent 290kb *NPHP1* deletion that was detected in homozygous state in 0.5% of an adult cohort of 5606 ESKD patients. The authors concluded that nephronophtisis is a relatively frequent monogenic cause of adult-onset kidney ESKD. [9]

B. Impact of identifying a genetic origin to kidney failure

Identifying the genetic origin of kidney failure has important clinical implications for the patient including pre- and post-transplant management, as some GKD have extra-renal metabolic, vascular or oncologic manifestations, and for living donation (Table 1). However, genetic tests are expensive, and the cost-effectiveness of a systematic genetic testing strategy is not established.[1] In particular, the identification of multiple variants of unknown significance (VUS) raises the issue of specificity and the need for filtering parameters. Social, professional and psychological consequences of a genetic diagnosis for the patient and relatives deserve careful management (Figure 1). In any case, patients and families must be carefully informed about the implications of genetic testing. [3]

Genetic testing in the context of kidney transplantation has the capacity to identify genetic kidney disease at risk of recurrence in the kidney graft or associated with a risk that could be modified by the transplant management. In line, both KDIGO [10] and KDOQI [11] recommend performing genetic testing in patients with a clinical course consistent with genetic focal segmental glomerulosclerosis (FSGS), C3 glomerulopathy, atypical hemolytic and uremic syndrome (aHUS) and primary hyperoxaluria (Tables 1 and 2).

C. Genetic testing techniques

The modalities for genetic testing have been reviewed in detail recently. [3,6,12] Table 3 summarizes the commercially available methods, with their indications, limits, advantages and examples where the tests are most appropriate. Most genetic laboratories currently use massive parallel sequencing-based exome sequencing with data analysis restricted to virtual panels

based on genes known to be linked to a given phenotype or group of diseases (Figure 1). Panels have the benefit of excluding incidental findings in genes not linked to the observed phenotype; if targeted panels are used (i.e., only genes of interest sequenced as opposed to WES) they need however to be updated frequently due to the discovery of new genes. Whole exome sequencing (WES) allows retrospective expansion of analysis when no pathogenic variants are found in the initial panel, for instance when new genes have been associated with the phenotype. Yet, WES has in general less deep sequence coverage than targeted gene panels and some genes need to be evaluated with specific techniques - including long-range PCR or capture-based panels (e.g. *PKD1*) or variable number tandem repeat (VNTR) sequencing approach coupled with a spectrometry-based probe extension assay (e.g. *MUC1*). Coverage of WES is limited to exonic regions and misses deep intronic variants, variants in regulatory regions and variants in intergenic regions as recently described in Gitelman disease [13], or Alport syndrome. [14] These variants can be captured by whole genome sequencing (WGS).

Another caveat of MPS techniques (especially for WES) is the difficulties in identifying large copy number variant (CNV). Chromosome microarrays or multiplex ligation-dependent probe amplification (MLPA) can be used to identify large CNVs or multi- or single-exon CNVs (e.g. *HNF1B*), respectively. In cases of suspected mosaicism or mitochondrial diseases, genetic testing can be made on leucocytes but also in kidney cells collected from the urine. [15,16] In addition, clinicians need to make sure that targeted panels are regularly updated to include novel gene-disease relationships. This also stresses the importance of working with a clinical genetics team and /or genetic counsellors to provide optimal clinical care and to follow guidelines for molecular diagnosis. [17]

D. VUS interpretation

Finding a variant of unknown significance is always challenging. The clinical nephrologist can help the genetic team and can contribute to provide additional arguments for the pathogenicity of a detected genetic variant of unknown significance: e.g. provide extensive and detailed clinical information that helps in variant interpretation, perform segregation analysis in the family, help with functional testing by carefully preserving kidney tissue/biopsies or extracting cDNA from urinary cells.

E. Polygenic risk score and pharmacogenomics

Large genome-wide association studies (GWAS) identifying hundreds of single nucletodie polymorphisms (SNPs) influencing the risk of CKD and other kidney related traits[18,19] are instrumental to develop polygenic risk scores (PRS) that can be used to test the combined association of these SNPs with a given outcome and to stratify populations at risk for the development of common diseases. More specifically in the transplant setting, the impact of donor and recipient (n total= 10844) eGFR-derived PRS on posttransplant eGFR at different time-points has been assessed in a European renal transplant population. [20] PRS using recipient genotype alone, as well as combined donor and recipient genotypes were significantly associated with eGFR at 1-year posttransplant. 32% of the variability in eGFR at 1-year posttransplant was explained by a model containing clinical covariates and combined donor-recipient PRS. Compared to kidneys from European American deceased-donors, kidneys from African American deceased-donors have shorter allograft survival and African American living-kidney donors more often develop kidney failure and it is believed that much of this difference is due to APOL1 risk genotypes in AA individuals. To get better insights into this clinically relevant topic, the National Institutes of Health (NIH)-sponsored APOLLO study is prospectively assessing kidney allograft survival from donors with recent African ancestry based on donor and recipient APOL1 genotypes. [21] Future studies will need to assess the combined/additive value of determining polygenic risk score in addition to monogenic risks such as APOL1 to allow precision medicine in the transplant setting. With respect to monogenic kidney disease, an exciting study was able to show that variable penetrance of kidney disease in autosomal dominant polycystic kidney disease (ADPKD) and in carriers of deleterious variants in *COL4A3, COL4A4, or COL4A5* genes is partially explained by differences in polygenic risk profiles. These findings could be taken into consideration in the future to plan pretranplantation workup in carriers of such variants or even to evaluate family members as potential kidney donors. [22] With respect to transplant complications and post transplant management, it has been shown that recipient type 2 diabetes mellitus (T2D) PRS was significantly associated with the development of post kidney transplantation diabetes mellitus. [23] Another example for transplant complications comes from the European ancestry renal transplant cohorts (n = 889), where PRS derived from nontransplant non-melanoma skin cancer is predictive of occurrence and timing of non-melanoma skin cancer in posttransplant patients. [24]

Drug pharmacokinetics is influenced by variations in genes involved in drug metabolism and transport while drug pharmacodynamics is affected by variants in genes encoding for drug-target proteins. Therefore, pharmacogenomics approaches in kidney transplant recipients could allow personalized immunosuppression regiments or other tailored drug adaptations. Indeed, it has been suggested that, among a cohort of 853 kidney allograft recipients, each recipient had at least one actionable pharmacogenomic diplotype (i.e., a specific combination of two haplotypes) and the majority carried three or four actionable diplotypes among the 12 genes that would require dose modifications or medication changes if they were prescribed these medications (including tacrolimus, azathioprine, clopidogrel, warfarin, simvastatin, voriconazole, antidepressants and proton-pump inhibitors). [25] For tacrolimus in particular, the inter-individual differences in pharmacokinetics are in large part determined genetically and SNPs in the *CYP3A4* and *CYP3A5* genes have been linked to an individual's drug metabolizing phenotype. Currently, several prospective intervention trials, investigating the efficacy of initial algorithm-based dosing using polygenic and clinical factors in adult renal allograft recipients are ongoing (https://www.trialregister.nl/trial/7360; NCT03465410; NCT03020589; NCT03527238 see clinicaltrials.gov) (doi.org/10.1080/23808993.2020.1776107)."

## 3. Genetic kidney diseases with risk of recurrence

### A. Complement mediated diseases

#### 1. Atypical hemolytic and uremic syndrome

Atypical hemolytic and uremic syndrome (aHUS) (MIM #235400) manifests with thombotic microangiopathy (TMA) associated with very poor kidney outcome if untreated. Pathogenic variants in alternative complement pathway genes account for approximatively 50 % of the predisposition to develop aHUS and lead typically to a dominant pattern of inheritance with reduced penetrance. In contrast, atypical HUS associated with pathogenic variants in *DGKE* (complete penetrance) and deletions of *CFHR3/CFHR1* and *CFHR1/CFHR4* are typically inherited in an autosomal recessive manner. Acquired autoantibodies against complement regulatory proteins have also been described. [26]

The risk of aHUS recurence after transplantation is driven by genetic findings. This risk is particularly high in patients with abnormalities in genes encoding for complement circulating proteins (complement factor H [CFH], factor I [CFI], factor B [CFB], and C3) while isolated genetic abnormalities in the transmembrane and intracellular proteins membrane cofactor

protein and diacyl-glycerol kinase confer low risk of recurrence because allografts express normal proteins. [27, 28]

Screening for variants in complement genes usually includes at least five complement genes (*CFH*, *C3*, *CFI*, *CFB* and *MCP*) and MLPA to identify potential *CFHR1−CFH* hybrid genes, which are caused by nonallelic homologous recombination. To date, more than 500 variants in these genes have been identified in patients with aHUS. [26] For individuals presenting early (eg. before 1 year) or if there is evidence for autosomal recessive inheritance, single gene testing for *DGKE* could be considered. Otherwise, multigene panels are widely available and need to be complemented by appropriate testing for hybrid genes or copy number variants (eg MLPA). Before availability of eculizumab (anti-C5 monoclonal antibody), te outocome after kidneytransplantation was poor, with a 60-80% risk of recurrence that was strongly associated with transplant failure. [29] The use of eculizumab as prophylaxis for aHUS recurrence after KT has profoundly modified kidney graft outcome. [29.30] The KDIGO guidelines [31] recommend life-long prophylaxis with eculizumab in aHUS patients at moderate- and high-risk of recurrence after KT (Table 2).

Challenges for genetic kidney diseases and kidney transplantation (Table 4) include the absence of identification of a pathogenic variant in complement genes in 40-60 % of patients with aHUS.[27,32] Other biochemical markers of complement system dysregulation, for instance related to C5b-9, are currently investigated. [27,33] Some patients with secondary HUS may also have genetic defects in complement pathway [34,35] raising the issue whether systemic screening of complement genetic abnormalities in secondary HUS is required. The optimal period of prophylaxis with eculizumab after KT is also debatable. The recommendation for a lifelong prophylaxis after KT, especially in cases of high-risk mutations, is not supported by randomized data. Some studies have suggested that eculizumab could be stopped in patients with aHUS in native kidneys, with cases of relapse responding to prompt resumption of anti-C5 therapy. [36,37] These issues are important, considering the cost of the drug and the increased risk of meningococcal infection.

### 2. C3 glomerulopathy

C3 glomerulopathy (C3G) (MIM #614809) is caused by the dysregulation of the alternative complement pathway with glomerular deposition of complement factors. The diagnosis relies on kidney biopsy showing intense C3 staining with no/minimal immunoglobulin staining.[38] Pathogenic variants in the alternative complement pathway, the same genes implicated in

aHUS, are detected in about one third of patients and lead to a dominant pattern of inheritance.[38] Recurrence rates of C3G after KT range from 67% to 84% (Table 2) with a median time to recurrence of 14-28 months in the two largest reported case series.[39] However, unlike aHUS, there are currently no data supporting a direct relationship between genetic defects and recurrent disease after transplantation.[39] Moreover, the use of eculizumab is rather disappointing for the treatment of C3G, when compared to aHUS.[40] In patients with C3G, post-transplantation use of eculizumab seemed to reduce allograft loss compared to plasma exchanges or rituximab, [41] but its use as prophylactic treatment is not currently recommended (Table 4). Other strategies, including the complement C3 inhibitor pegcetacoplan, are currently tested in C3G (NCT04572854).

## B. Crystalline nephropathies

### 1. Primary hyperoxaluria

Primary hyperoxalurias (PH) are a group of rare autosomal recessive diseases, characterized by the excessive production of oxalate in the liver. PH is more prevalent in countries with consanguinity (with a prevalence of 10% or higher in some North African and Middle Eastern nations).[42] Since the kidney is the sole organ that excretes oxalate, the constant high oxalate calcium load in PH leads to nephrocalcinosis, recurrent kidney stones, oxalate nephropathy, CKD and kidney failure. As CKD progresses, systemic accumulation of oxalate occurs, predominantly in bones, eyes, heart, skin, and central nervous system. [43,44] PH1 (MIM #259900) is the most frequent (+/- 80%) and severe form of PH, caused by a deficient peroxisomal alanine glyoxylate aminotransferase (AGT) encoded by the *AGXT* gene. [44] The molecular pathogenesis behind PH1 is relatively complex. A "minor allele" (20% frequency in individuals of European origin), characterized by a cryptic mitochondrial targeting sequence acts synergistically with some pathogenic variants in cis and drives mislocalization to mitochondria. Overall, >200 *AGXT* pathogenic variants have been documented, but a handful among them are common pathogenic variants, sometimes enriched in specific ethnicities, and accounting for the majority of PH1-causing alleles. Missense variants lead to loss of enzyme catalytic activity, loss of immunoreactivity, or mistargeting to mitochondria instead of peroxisomes. In addition, large deletions or intragenic deletions are described that require dedicated techniques (e.g. MLPA). [44] Most patients with PH1 reach kidney failure in the first two-three decades of life.[42] Current treatments are mostly conservative, including hyperhydration, vitamin B6, and sodium/potassium citrate. Patients harbouring pathogenic variants resulting in mistargeting of

AGT are most likely to respond to vitamin B6 treatment. Innovative therapeutic strategies are currently investigated, including RNA interference (RNAi) drugs that may correct the liver metabolic defect (and potentially replace liver transplantation).

Solid organ transplantation strategies for PH include liver transplantation (combined with KT or performed before KT-sequential approach) to cure the metabolic defect. [42,43]However, solid organ transplantation is challenging for PH patients with kidney failure, because of the high-risk of recurrence of oxalate nephropathy in the transplanted kidney, with risk of graft loss [42-46] Isolated kidney transplantation may be considered in very selected patients who are vitamin B6-sensitive. [47] A more accurate assessment of systemic oxalosis using 18-Fluoro-D glucose positron emission tomography imaging may help to decide the right timing of kidney transplantation. [48,49]

### 2. Adenine phosphoribosyltransferase deficiency

Adenine phosphoribosyltransferase (APRT) deficiency (MIM #614723) is an autosomal recessive disorder of purine metabolism, causing the oxidization of adenine by xanthine oxydase (XO) into 2,8-dihydroxyadenine (2,8-DHA). DHA is poorly soluble in the urine leading to the formation of kidney stones and crystalline nephropathy. [50,51] APRT deficiency is diagnosed by the absence of APRT activity in red blood cells or the identification of pathogenic mutations in the *APRT* gene. Treatment relies on XO inhibitors (allopurinol and febuxostat) reducing DHA production, along with high fluid intake and low-purine diet. [51] The largest series have been mainly described in Iceland, Japan and France. [52,53] Unfortunately, APRT deficiency is often diagnosed in the setting of recurrence following KT, ranging from 10 days to more than 20 years after KT. [50,52] Improvement in allograft outcomes among patients who received treatment with xanthine oxydase inhibitor before or at the time of kidney transplantation was recently suggested. [50] Large doses of allopurinol (400mg/day or greater) may be needed to adequately prevent recurrence of APRT deficiency nephropathy. Consequently, XO inhibitors should not be stopped in dialyzed patients on waiting list for KT. After transplantation, azathioprine is contra-indicated with xanthine oxydase inhibitors given the well-known risk of agranulocytosis. [54]

### 4. Genetic kidney diseases with oncological risk

Routine cancer screening should be performed for evaluation of candidates for kidney transplantation. [10] For patient with a history of cancer, the timing of KT after successful

treatment depends on the type of cancer and stage at initial diagnosis. Some genetic kidney diseases confer an increased oncological risk that may be increased by immunosuppressive regimen - thus influencing post- kidney transplantation monitoring. Conversely, kidney failure can also be the consequence of cancer treatment eg chimiotherapy. For patients (and their affected relatives) meeting any of the cancer genetics referral criteria, the American College of Medical Genetics (ACMG) guidelines recommend referring patients to a cancer genetics specialist [56] for work up and testing for monogenic cancer predisposition syndromes.

### A. Tuberous sclerosis complex

Tuberous sclerosis complex (TSC) (MIM #191100) is an autosomal dominant disorder with variable penetrance caused by mutations in either *TSC1* or *TSC2* genes coding for hamartin and tuberin, respectively. *De novo* mutations may occur in 1/3 of patients. [57] Diagnostic work up needs to exclude single nucleotide variant, as well as intragenic or whole gene deletions. It is also important to exclude *TSC1/2* somatic mosaicism in cases where a clinical diagnosis is established but germline/blood genetic testing is negative. The clinical manifestations are related to benign tumors that develop in multiple organs mainly the skin, brain and kidney- but also the lungs, eyes, heart and liver. Kidney lesions include angiomyolipoma (AML), renal cysts, oncocytoma and a higher risk to develop renal cell carcinoma (RCC) than in the general population. [57,58] In patients with enlarged cystic kidneys, a TSC2/PKD1 contiguous gene deletion should be excluded. Kidney AMLs and cysts are common features in mosaic TSC. [59] TSC-associated angiomyolipomas can be treated with mTOR inhibitors as recommended first line therapy. The incidence of RCC in TSC is reported in 2-4% patients, often in children and young adults, with a female predominance. [60] Patients with TSC2 mutations seem to be at greater risk for kidney cysts, AML and kidney malignany (and other advers outcomes such as intellectual disability and infantile spasms) compared to patients with TSC1 mutations. [61,62] Preemptive bilateral nephrectomy in patients reaching kidney failure may avoid neoplasm development and AML bleeding although it requires confirmation. [63] If removal of native kidneys is not performed before kidney transplantation, it seems reasonable to propose annual magnetic resonance imaging (MRI) surveillance**.**

### B. Von Hippel-Lindau disease

Von Hippel-Lindau (VHL) disease (MIM #193300) is a dominantly inherited syndrome, caused by mutations in the *VHL* gene, and which predisposes to the development of various tumors, including RCC and pancreatic neuroendocrine tumors. RCC develops in 70% of patients at a younger age (45 years at diagnosis) [64] and more frequently multifocal and bilateral than in sporadic cases. [65] Diagnostic work-up needs to exclude both SNVs and intragenic or larger CNVs. It has been suggested that risk of RCC is lower in individuals with *VHL* deletions, especially deletions that extend 5' and include *BRK1*. [66] Nephron-sparing surgery techniques such as partial nephrectomy are indicated in tumors larger than 3 cm and may reduce the risk of metastasis while preserving kidney function. [64] Although a prior cancer is not an absolute contraindication for kidney transplantation, the recent KDIGO guidelines [10] suggest waiting 2 to 5 years before KT depending on the localization, size and invasive nature of the malignancy. There are no specific recommendations for other organic malignancy, e.g. pancreatic neuroendocrine tumors. Patients with VHL on dialysis and awaiting for KT must be evaluated for RCC at least every 2 years, preferably using MRI. [67] Pancreas imaging should be monitored every 2 years preferably with gadolinium-enhanced MRI. [68] We suggest continuing oncological screening after kidney transplantation

### C. WT1 pathogenic variants

Wilms tumour (WT, or nephroblastoma) is one of the most frequent kidney cancer in children. It can occur with rare syndromes that are associated with heterozygous variants in the *WT1* gene with a dominant pattern of inheritance. [69]

The WAGR syndrome (Wilms tumour, Aniridia, Genitourinary anomalies and Range of developmental delays; MIM #194072) is caused by a deletion in chromosome 11p13 including *WT1* and *PAX6* genes. [70] Patients may experience WT but also isolated proteinuria and focal and segmental glomerular sclerosis and have higher risk of CKD. [70] Current recommendations for WT screening in WAGR syndrome include kidney ultrasound (US) every 3 months from birth or diagnosis until 8 years of age, followed by 6-month screens until the age of 18 years. [71] It seems reasonable to continue the annual oncological screening after KT, based on US or MRI in adults for more accuracy.

Denys Drash syndrome (DDS) (MIM #194080) is caused by mutations in exons 8 and 9 of *WT1* and is characterized by the association of early onset steroid-resistant nephrotic syndrome (SRNS) with mesangial sclerosis, WT and, in some patients, pseudohermaphrodism and increasing risk of gonadoblastoma. [72] It is recommended to wait at least 1-2 years after

completion of chemotherapy for WT before kidney transplantation. [73] Furthermore, total nephrectomy is recommended for DDS at the time of KT because of the high risk of recurrence of WT. [73]

Frasier syndrome (MIM #136680) is due to intron splicing variants in intron 9 of *WT1* gene [74] and is associated with SRNS, gonadal tumors, and male pseudohermaphrodism. Prophylactic gonadectomy at time of diagnosis has been suggested, as the risk of gonadal tumor is up to 60%. [75]

### D. Birt-Hogg-Dube syndrome

Birt-Hogg-Dube syndrome (BHD, MIM #135150) is an autosomal dominant condition characterized by benign skin hamartomas, pulmonary cysts leading to spontaneous pneumothorax, and an increased risk of RCC. This syndrome is caused by pathogenic variants in the *FLCN* gene encoding for the protein folliculin, a putative tumor suppressor gene. [76] Renal cancers occur in 12-34 % of patients around age 50 years, with variable histology (chromophobe and mixed chomophobe-oncocytic pattern mostly). Tumors <3 cm require active surveillance whereas larger tumors require nephron-sparing surgery. Some patients may develop colorectal cancer, which may justify performing colonoscopy screening at least 10 years earlier than in the general population. [77]

Other ultra-rare, syndromes associated with a higher risk of RCC include hereditary papillary renal carcinoma (MIM #605074); hereditary leiomyomatosis and renal cell cancer (MIM #150800); hereditary BAP-1-associated renal cell carcinoma (MIM #614327); and succinate dehydrogenase deficiency (MIM #614145). [64]

### E. Beckwith-Wiedemann spectrum

Beckwith-Wiedemann syndrome (BWS, MIM #130650) is a congenital condition with a variable clinical manifestation of overgrowth, hyperinsulinism and which confers a high risk, up to 30 %, of embryonal cancers (Wilms tumor, neuroblastoma and hepatoblastoma). [78,79] BWS is linked to molecular alterations in imprinted genes located on chromosome 11 (11p15) such as *CDKN1C* or *IGF2*. Genomic imprinting is an epigenetic condition by which only one copy of a gene is expressed depending on whether they are inherited from the father or the mother. Gene sequence is not modified but gene expression is silenced by epigenetic modifications (usually methylation) of DNA in a germ cell. These changes are frequentely

mosaic - complicating genetic testing. Most commonly, BWS is caused by loss or gain ofmethylation at imprinting center 2 or 1, respectively. Paternal uniparental disomy at the BWS critical locus is seen in 20%-30% of the cases, sometimes in mosaic forms. Maternally-inherited pathogenic variants in *CDKN1C* are frequently encountered in familial forms of BWS. Rarely CNV involving the 11p15.5 locus are encountered. Molecular diagnosis algorithms usually start by performing DNA methylation tests at the 11p15 differentially methylated regions. [79] Patients with BWS also have an increased risk of hypercalciuria and nephrocalcinosis. [79] The recent guidelines suggest performing regular screening for embryonal tumors with ultrasound every 3 months until 7 years. Patients with IC1 gain of methylation are at highest risk for Wilms tumors and patients with IC2 loss of methylation at lowest risk and it has been suggested that the latter do not require regular ultrasound screening. [79] There is no consensus for the oncological screening after 7 years old.

## 5. Genetic kidney diseases with special considerations regarding kidney transplantation

### A. Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD; MIM #173900; #613095) accounts for up to 10% of patients requiring KRT. [80] The vast majority of patients with ADPKD will end up with kidney failure, with KT being the preferred modality of KRT. [81] ADPKD, which involving all populations, is thus the most common monogenic disease encountered in KT patients.

ADPKD is essentially caused by mutations in either *PKD1* or *PKD2* accounting for about 80% and 15% of the cases, respectively. These genes encode membrane proteins (polycystin-1 and polycystin-2) which play multiple roles in kidney tubular cells and other cell types. The remaining cases are associated with mutations in genes that modulate the expression or maturation of the polycystins, including *IFT140, GANAB, PRKCSH, ALG8, SEC61B,* and *SEC63*, that cause a mild form of ADPKD with variable cystic liver disease severity. [82]

Atypical cystic kidney diseases associated with tubulointerstitial damage have also been linked to mutations in *DNAJB11*, coding for a cofactor involved in the proper folding and assembly of membrane or secretory proteins, and *HNF1B*, coding for a transcription factor. Mutations in HNF1Bcan result in various kidney and extra-renal disorders.[83] In 50% of patients with *HNF1B*-related disease, a whole *HNF1B* gene deletion is detected, occurring in the context of the 1.4-megabase (Mb) recurrent deletion flanked on each side by segmental

duplications at position 17q12 and encompassing *HNF1B* along with 14 other genes. The 17q12 recurrent deletion syndrome combines structural or functional abnormalities of the kidney and urinary tract (~90%), MODY5 (~40%), and neurodevelopmental or neuropsychiatric disorders (~50%). As mentioned in table 3, chromosomal microarray or another technique capable to detect copy number variants is required to make this diagnosis.

ADPKD-like phenotypes have also been associated with mutations in *COL4A1* in the HANAC syndrome (MIM #611773) and with mutations in the X-linked *OFD1* gene causing the ciliopathy named oral-facial-digital syndrome type 1 (MIM #311200). [82]

The diagnosis of ADPKD is typically based on a positive family history and the evidence of multiple kidney cysts by kidney imaging. Genetic testing for ADPKD is useful in patients with early and severe manifestations, marked intrafamilial disease variability, lack of apparent family history, atypical kidney imaging, syndromic presentation, and in at-risk subjects for potential kidney donation. [12] The genetic testing for *PKD1* requires specific approaches, reviewed recently. [82] Patients harboring a mutation in *PKD1* have larger kidneys and, on average, reach kidney failure 20 years faster than those harboring a *PKD2* mutation. Among *PKD1* mutations, protein-truncating mutations (nonsense, frameshift) or large deletions are associated with a more severe kidney phenotype than nontruncating mutations. [82]

The pre-transplant work-up of patients with ADPKD should address the main complications of the disease. [81] Prophylactic native nephrectomy is recommended only in patients with intractable kidney pain, recurrent and/or severe bleeding, infections or nephrolithiasis, suspicion of RCC, or when space is required for graft implantation. [81,82] The timing of prophylactic nephrectomy, pre- or during-KT, remains debated. [84,85] Pre-transplant nephrectomy is usually restricted for patients who are highly symptomatic and/or oligoanuric with extremely large kidneys. [81] Alternatively, transcatheter arterial embolization may reduce kidney volume by about 50% at 12 months. [86,87] The above decisions should also consider that the volume of native PKD kidneys decreases significantly after transplantation. [88] Importantly, RCC does not appear to occur more frequently in ADPKD than in other renal diseases. [89,90]

Hepatomegaly caused by liver cysts can severely affect patient's quality of life, with potential for fatigue, malnutrition and secondary sarcopenia that may drive prioritization for liver transplantation. [91] Indeed, experts suggest using skeletal muscle index < 38,5$cm^2/m^2$ in females and 52,4$cm^2/m^2$ in males as an additional criteria to consider liver transplantation in patients with polycystic liver diseases. These parameters are considered more objective than the symptoms of discomfort or mid-arm circumference.

The prevalence of intracranial aneurysms (ICA) is four times higher in patients with ADPKD than in the general population (9-12% vs 2-3%), further enhanced (>20%) in case of positive family history of ICA. [81,82] The rupture rate of ICA in patients with ADPKD is much larger than in the general population, as also reflected by a much younger mean age of rupture. [82] Pre-transplant screening for intracranial aneurysms using cerebral MRI is reasonable in ADPKD transplant candidates who have a family history of ICA and/or intracranial hemorrhage, or a personal history of ICA. [80] Universal screening has also been advocated by some, depending on the local situation and cost-utility analyses. [92]

### B. Alport syndrome

Alport syndrome (AS) is caused by pathogenic variants in three genes *COL4A3, COL4A4,* and *COL4A5* and is the second most frequent cause of monogenic kidney disease after ADPKD. [93] Indeed, in the study of Groopman et al. [5], 92/3315 (0.27%) patients had a pathogenic variant in a *COL4A* genes. Although patients with AS who undergo KT have an excellent patient and graft survival, they may rarely (0.4 to 2%) develop anti-glomerular basement membrane (GBM) nephritis after transplantation. [94,95] Males with X-linked AS (MIM #301050) and truncating *COL4A5* mutations are mostly at risk to develop de novo anti-GBM nephritis [96,97] with antibodies against the α5 (IV) chain- not detected by routine ELISA assay for anti-GBM directed to α3 (IV) chain. [98] Therefore, the diagnosis relies on kidney graft biopsy showing linear IgG staining along the glomerular basal membrane together with glomerular necrosis or crescentic lesions. [99] Plasmapheresis combined with cyclophosphamide administration and steroids, like in anti-GBM nephritis and Goodpasture syndrome, often fail to rescue graft function. [99] Patients with autosomal recessive Alport (MIM #203780) may also develop anti-GBM antibodies against α3 or α4 (IV) chains. [100]

### C. Cystinosis

Cystinosis (MIM #219800 and #219900) is a lysosomal storage disease (LSD) caused by recessive mutations in the *CTNS* gene coding for the proton-driven transporter cystinosin that exports cystine out of lysosomes. The accumulation of cystine leads to multi-systemic complications including proximal tubular dysfunction (renal Fanconi syndrome) and most often, kidney failure. [101] Half of affected individuals of Northern European descent are homozygous for a 57kb deletion at 17p13 and arising apparently through a founder effect. [102]

CTNS diagnosis can be established by detecting cystine crystals in the cornea, elevated cystine levels in leukocytes or the identification of biallelic pathogenic variants in *CTNS* on molecular genetic testing including modalities able to detect the 57kb deletion (or other deletions, e.g. MLPA). Therapy with cysteamine, which allows cystine to exit lysosomes, has improved the prognosis of cystinosis, with a 9.1-year increase in the median age at dialysis from the 1970s to the 1990s. [103] Cysteamine must be continued after KT to prevent multiorganic complications resulting from the systemic LSD. [103,104] There is no risk of recurrence of the LSD in the kidney graft, as wild-type cystinosin is operating in the kidney. Of note, protocol biopsies have shown cystine crystals within the interstitial tissue and glomeruli of the transplanted kidney, without any apparent manifestations. [102]

### D. Fabry disease

Fabry disease (FD; MIM #301500) is an X-linked, lysosomal storage disease due to inactivating mutations in the *GLA* gene coding for the lysosomal enzyme alpha-galactosidase A. The enzymatic defect leads to the multi-systemic accumulation of glycosphingolipids, especially globotriaosylceramide (Gb3), causing chronic kidney disease, hypohydrosis, skin lesions (angiokeratomas), cardiomyopathy with arrythmias, strokes, and small-fiber peripheral neuropathy, which shortens the life expectancy. [105] Patients with FD can be treated with i.v. infusion of recombinant alpha-galactosidase or with oral chaperone therapy which corrects the misfolding of the enzyme and rescues the trafficking to lysosomes. [106] These therapies enable cellular Gb3 clearance and may stabilize or slow decline in kidney function. [107] However, ERT can lead to the formation of neutralizing antidrug antibodies, reducing the efficacy of therapy.[108] Fabry disease account for 0.2 % of patients on hemodialysis [109]. Kidney transplantation is safe in Fabry disease, as recently confirmed by a meta-analysis pooling 424 patients. [108] Decreased plasma Gb3 levels, stable kidney function, decreased left ventricular mass and improved cardiac contractility were reported among transplanted patients on ERT. [110] To protect against the systemic accumulation of glycosphingolipids, ERT should be continued on dialysis and after KT. [108] The development of ERT antibodies seems to be rarer in patients with FD on immunosuppressive medications for KT. [111] Finding Gb3 deposits in the graft does not seem to impact on the outcome of the transplant. [110] The effect of the oral chaperone migalastat in patients with KT has not been investigated so far. (Table 4)

## 6. Influence of immunosuppression: post-transplant diabetes, HNF1B, mitochondrial diseases and TSC

The commonly used immunosuppressive regimen after KT is the association of tacrolimus, mycophenolate mofetil and steroids, associated with a lower acute rejection risk compared to cyclosporine- or mTORi- based combinations. [112] The choice of the immunosuppressive regimen influences the risk for developing metabolic, oncologic, and infectious side effects after KT. For instance, tacrolimus may be more associated with new-onset post transplant diabetes (NODAT) that cyclosporine. [113]

NODAT is a common and severe complication after kidney transplantation. Genetic variants have been identified as risk factors for development of post transplant diabetes. The Swiss Transplant Cohort Study [114] showed that patients carrying the *SP110 rs2114592C>T* single nucleotid polymorphism have 10-fold higher risk to develop post-transplant diabetes. Shaked et al recently reported a significant association between type 2 diabetes polygenic risk scores in kidney transplant recipients and the development of NODAT. [115]

Patients harboring a pathogenic variant in *HNF1B* are at high risk to develop diabetes and NODAT [116,117] as well as patients with mitochondrial diseases or cystinosis. [103,118] In case of NODAT, the use of metformine should be avoided in mitochondrial diseases because of the increased risk of lactic acidosis. [118] The impact of a tacrolimus-free regimen in these patients needs to be explored**.** In line, the indications for inhibitors of mammalian target of rapamycin (mTOR) after transplantation may be discussed in particular diseases such as mitochondrial disorders or TSC. Mitochondrial diseases are clinically heterogeneous and can manifest with a wide range of clinical symptoms affecting the nervous system and muscles, but also the kidneys and the heart. mtDNA mutations are typically inherited from the mother but can also occur *de novo*. [119] Pathogenic mtDNA mutations are characterized by heteroplasmy, i.e. a condition in which wild-type and mutated mtDNA molecules can coexist in the same cell. The expression of different clinical phenotypes is likely related to variable heteroplasmy levels within the affected tissues and the detection of heteroplasmy in urinary cells can be used to diagnose mitochondrial disease. [120] In addition, it has been shown that for the single most common cause of mitochondrial disease, the m.3243A>G point mutation in the mitochondrial-encoded MTTL1 gene, the mutation load in urinary epithelium cells provided the best predictor of clinical outcome [121] Currently, few treatment options for mitochondrial diseases are available

and management is mainly supportive. [122] Experimental studies have shown that reduced mTOR signaling attenuates the disease in a mouse model of Leigh syndrome, a mitochondrial disease. [123] Rapamycin has been used in 4 KT patients in replacement of CNI and has shown to improve their quality of life.[124] Further studies are needed to assess mTOR inhibitors in mitochondrial diseases with or without KT. (Table 4)

In TSC, AMLs increase with age and can complicate with acute bleeding, which can necessitate arterial embolization or nephrectomy - further reducing kidney function. [125,126] Since the hamartin-tuberin complex normally inhibits the mTOR pathway involved in cell growth and proliferation, mTOR inhibitors have been proposed to reduce AML at risk of bleeding. [127,128] This treatment should lower the prevalence of KF among patients with TSC, even if mTOR inhibitors may induce proteinuria. [57] Series of KT patients with TSC are rare [63,126,129] and little is known about the course of AMLs in native kidneys after transplantation. The potential benefit of using mTOR inhibitors for AMLs after KT needs to be evaluated. Conversely, it is well described that mTOR inhibitors have beneficial effects on extra-renal features such as lymphangioleiomymatosis (LAM) and subependymal giant cell astocytoma (SEGA) but also in refractory epilepsia. [130] This treatment should most likely be continued after KT to control further organ damage.

## 7. Living donation and genetic kidney disease

### A. General considerations

Kidney donors related to a recipient with a known genetic condition should be tested early during the donor-evaluation process. [131] There is consensus that donor candidates with a GKD that can cause kidney failure should not donate, particularly in dominantly inherited diseases such as ADPKD (Figure 2).

For ADPKD, candidate related living donors should be evaluated for kidney cysts, using age-dependent criteria for ultrasound imaging [132] or MRI for higher sensitivity to detect subcentimeter kidney cysts. [133] Finding more than 10 kidney cysts in patients with familial history of ADPKD aged 16–40 years can make the diagnosis of ADPKD. The increased availability of genetic testing in ADPKD (see above) will facilitate the screen for potential

kidney donors. In patients aged < 30 years with normal MRI findings and in those with equivocal MRI findings, genetic testing is indicated. [82]

Whether familial living donation is allowed in aHUS is controversial, considering that genetic mutations are not found after regular screening in 40-60% of cases. [26] It is currently recommended to consider living related donation in aHUS if the genetic factors are identified in the recipient and the related donor does not share the pathogenic variant(s). [131]

In diseases with an autosomal recessive mode of inheritance, first-degree relatives may harbour a heterozygous mutation and related living donation is considered suitable. [134] Alport syndrome is an exception to this statement. In 2022, the revised guidelines [93] considered the risk of kidney donation in *COL4A3* or *COL4A4* carriers unacceptable in most cases even when donors are older than 40 years with a normal renal function and without proteinuria. For the X-linked AS (XLAS), women previously called "carrier" are now preferentially called heterozygous female subjects of *COL4A5* pathogenic variants. [135] Indeed, some studies recognized a substantial risk of proteinuria and progressive kidney disease and also sensorineural hearing loss in these female patients. [136,138] The most recent consensus is that XLAS women should be excluded from living donation. [93,135] This statement can be extended in other X-linked diseases such as Fabry disease or Dent disease. [2]

In mitochondrial diseases, due to maternal transmission and mitochondrial heteroplasmy, the mother of the affected proband should not be candidate for living donation and siblings should be discouraged.

### B. Apolipoprotein 1

Risk variants in the *APOL1* gene (namely G1 and G2) coding for the apolipoprotein L1 are prevalent in populations with ancestors from sub-saharian Africa because they confer protection against *Trypasonoma* infection. [139] Patients carrying two risk variants (G1/G1, G1/G2, G2/G2) are at increased susceptibilty to develop various kidney diseases (hypertension-associated KF, FSGS, and HIV nephropathy) and CKD. [140] The high prevalence of *APOL1* variants in Black individuals of recent African ancestry [141] and the strong association with CKD development have raised important questions in kidney transplantation setting. [142] In the context of living donation, whether *APOL1* genotyping should be routinely performed in candidates with African ancestry and whether donor candidates carrying high-risk mutations should be excluded from donation are controversial issues. In favour of a systematic screening approach are the slightly increased rates of kidney failure after nephrectomy in high-risk *APOL1* donors compared to

others. [143-145] Moreover, Santoriello et al. [146] found that Afro-American donors, especially those harboring *APOL1* high-risk genotypes, may predispose recipients to collapsing focal and segmental glomerulosclerosis when exposed to second hits, such as acute rejection or viral infection that could activate podocyte innate immune pathways. In addition, Zhang et al. [147] reported the association of recipient APOL1 risk alleles with allograft survival and cellular rejection events. Conversely, Lee et al. found no difference in allograft survival at 5 years post-transplant for recipients with high-risk APOL1 genotypes.[148] Systematic screening of all deceased and living donors for *APOL1* might allow better risk assessment information for the donor and better allocation of organs. [142,149] Yet, this approach may exclude patients from the survival benefit of KT (even if transplanted with a high-risk grafts) compared to the poor survival associated with prolonged dialysis. In addition, there is a lack of evidence for identifing high-risk *APOL1* donors who are truly at risk of developing rapidly progressing CKD vs those who will not. Further studies are ongoing to address this issue. (Table 4)

**8. Kidney graft harbouring a genetic disease: contraindication?**

The potential use of kidney grafts from a donor with a known GKD has been poorly studied. Individual reports and case-series suggest that kidneys from deceased donors with ADPKD may be suitable for KT. [150-155] For instance, Shamali et al [155] identified 16 cases of donors with ADPKD (median age 24 years) with normal kidney function at donation. Recipients had a mean age of 46 years old. After KT, one recipient had a primary non-function, 2 had a transplantectomy because of infection and pain due to the size of the transplanted kidney. After a median follow-up of 36 months, 13 had a functioning graft with a median serum creatinine of 124 μmol/L. Thus, although all grafts from ADPKD donors should not be considered for KT, some might be a good option, especially in old recipients with limited life expectancy or in case of marked intrafamilial heterogeneity.

The use of living donors with a GKD has also been reported. Some patients with pauci-symptomatic genetic tubulopathy, such Gitelman syndrome [156-160] might be suitable for organ donation with good mid-term outcomes for both the donor and the recipient.

In extremely rare situations, the possible indication of pre-emptive bilateral native nephrectomy followed by kidney transplantation *prior to kidney failure* has been raised. Such situations may include patients presenting invalidating manifestations of a genetic tubular disorder, e.g. in children with Bartter syndrome presenting with life-threatening electrolyte disorders that cannot be compensated by supplementation. [161]

## 9. Conclusion

Through access to genetic testing, a growing number of patients with CKD or kidney failure have a molecular diagnosis of GKD. Implementing genetic testing in the context of KT and ensuring an optimal use of the genetic information requires specific measures (Table 5), which will need the involvement of multidisciplinary teams often operating in highly specialized tertiary care centers. [6]

An understanding of the different modalities of genetic testing, of the different types of variants, and their classification, needs to be integrated with detailed clinical and pathological insights to ensure the best interpretation of results – both for recipients and candidate-donors. Cost of the testing, turnaround time, and continuous pace of discovery regarding the genetic architecture of disease represent additional challenges (Table 4). Once validated, the genetic diagnosis offers immediate benefits in terms of clinical management of the patient and at-risk family members – highly relevant for KT (Figure 1).

Clinicians dealing with kidney diseases should devise practical ways to implement multidisciplinary teams to use molecular testing in KT clinics. [162] The evolving perception of genetic testing in many countries, together with patient empowerment and more active roles for patient organisations, best practice guidelines, education and delivery of the genetic information on physicians, patients, and society, and support from networks and national organisations such as National Organizations of Rare Disorders (NORD) in the USA and Orphanet in Europe will facilitate such implementation. [2]

Mounting evidence suggests that variants in important genes are involved in a spectrum of kidney diseases, ranging from large- to small-effect sizes responsible for monogenic diseases or complex disorders including CKD, respectively. [163,164] Based on their prevalence, these variants can be identified by MPS and other modalities of genetic testing or by genome-wide association studies (GWAS). As described above, genetic testing has a tremendous potential for impacting both the pre- and post-kidney transplantation phases. At the other extreme of the spectrum, polygenic risk scores, based on common variants identified by GWAS, may be helpful to identify individuals at high risk of CKD or other types of complications potentially relevant for KT. The use of such genetic information, which can be obtained before the onset of symptoms, would then be particularly useful to implement screening and prevention measures relevant for KT recipients and potential donors. [165,166]

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**Table 1. Screening for genetic kidney diseases with implications for kidney transplantation.**

| Type of disease | Clinical features |
|---|---|
| Complement mediated diseases | • Atypical HUS<br>• GNC3<br>• KFUO suggesting TMA (preeclampsia, malignant hypertension, secondary TMA) |
| Crystalline nephropathies | • Primary hyperoxaluria<br>• KFUO with a history of lithiasis and/or nephrocalcinosis<br>• KFUO with an interstitial nephritis pattern (bland sediment, low proteinuria)<br>• KFUO with a proximal tubulopathy pattern |
| Glomerular diseases | • Steroid-resistant nephrotic syndrome<br>• FSGS lesions on kidney biopsy<br>• KFUO with a glomerular pattern (hematuria, glomerular proteinuria) |
| Cystic diseases | • ADPKD (family history, enlarged kidneys, liver cysts)<br>• ADTKD (bland sediment, normal-sized kidneys, early hyperuricemia/gout) |

**Abbreviations:** ADPKD, Autosomal dominant polycystic kidney disease; ADTKD, Autosomal dominant tubulointerstitial kidney disease; HUS, Hemolytic and uremic syndrome; KFUO, Kidney failure of unknown origin; TMA, Thrombotic microangiopathy; GNC3, C3 glomerulopathy

**Table 2. Genetic kidney diseases at risk of recurrence after kidney transplantation.**

| Disease (Inheritance) | Risk of recurrence | Management |
|---|---|---|
| Atypical HUS (AD/AR) | High-, moderate-, low- risk stratification* | Eculizumab prophylaxis in high- and moderate-risk |
| C3 glomerulopathy (AD) | 67-84 % independent of the type of mutations | Consider eculizumab in early and severe case of recurrence. |
| Primary hyperoxaluria (AR) | Not quantified | **Before transplantation**<br>-Early initiation of conservative measures after diagnosis (hyperhydration, potassium-sodium citrate, vitamin B6)<br>-Consider early initiation of RNAi (if available)<br><br>**During and after transplantation**<br>-Consider isolated kidney transplantation combined with RNAi**<br>-Consider isolated kidney transplantation in highly-selected vitamine B6 responders<br>-Consider dual liver-kidney transplantation***<br><br>-In patients not on chronic dialysis : consider early transplantation (before occurrence of systemic oxalosis)<br>-In patients on chronic dialysis : consider transplantation when pre-dialysis POx <30-35 mmol/L**** |
| APRT deficiency (AR) | Not quantified | XO inhibitors at high doses to initiate early after diagnosis and continue after transplantation. |

*High risk: history of recurrence with a previous allograft and/or pathogenic variant of the CFH/C3/CFB genes; moderate risk: negative complement screening result or pathogenic variant in the CFI gene or detectable circulating anti-CFH antibody; low risk: isolated pathogenic variants in MCP or DGKE genes or anti-CFH antibodies no longer detected at the time of transplantation. **Under investigation, only in countries where RNAi are available. ***If RNAi not available or have demonstrated their inefficacy in decreasing hepatic oxalate production. ****Or if demonstration of the absence of systemic oxalosis.

**Abbreviations:** AD, Autosomal dominant; APRT, Adenosine phosphoribosyl transferase; AR, Autosomal recessive; HUS, Hemolytic and uremic syndrome; KT, Kidney transplantation;; PH, Primary hyperoxaluria; Pox, Plasma oxalate; RNAi, RNA interference agents; XO, Xanthine oxidase.

**Table 3. Different genetic testing modalities and their indications, advantages and limitations**

| Test | Application | Indications | Advantages | Limitations | Examples |
|---|---|---|---|---|---|
| ***Sanger sequencing*** | Detection of SNVs and small indels | - Validation of MPS results<br>- Targeted specific gene(s), e.g. phenotypes with little genetic heterogeneity<br>- MPS-refractory regions | - Fast and cost effective for low number of genes<br>- No incidental findings | - Limited number of genes analysable<br>- No detection of large structural variants<br>- Low sensitivity for low-level mosaicism | - APOL1 genotyping<br>- Specific phenotypes (Fabry disease, Tuberous Sclerosis) |
| ***Chromosomal microarray*** | Copy number variants (unbalanced genomic rearrangements) | - Multiple congenital anomalies<br>- recognizable phenotypes associated with CNV (e.g. del 17q12) | - Good resolution (~200kb)<br>- Untargeted/genome-wide<br>- SNP array able to detect uniparental disomy | - No detection of SNVs, small indels and CNV under the resolution threshold<br>- No detection of balanced chromosomal rearrangements<br>- Limited detection of low-grade mosaicism<br>- Inaccuracies in some chromosomic regions (e.g. telomeres) | - 17q12 recurrent deletion syndrome<br>- 22q11.2 deletion syndrome |
| ***Multiplex ligation-dependent probe amplification*** | Small copy number variants (e.g. exon-level CNV) and/or assessment of methylation status | - Analysis of genes where exon deletions/duplications or aberrant methylation are a known mechanism of disease<br>- Confirm/refine deletions/duplications suspected on MPS analysis | - Fast and cost effective<br>- High troughput (multiplex)<br>- Sensible to methylation | - No detection of unknown SNVs, may miss small indels<br>- Not readily available for all targets<br>- Limited detection of low-grade mosaicism<br>- Susceptible to polymorphisms | Suspicion of kidney disease linked to HNF1B (prenatal hyperechogenic kidneys or a multisystemic presentation with e.g. MODY, hypoMg2+ and GU abnormalities) |
| ***Targeted MPS gene panel*** | Phenotype driven detection of SNV and indels in genes of interest (Targeted panel sequencing or virtual panels from Exome/Genome sequencing) | Phenotype(s) or group of disorders with defined spectrum of genes involved | - No incidental findings<br>- Can be optimized to reach high coverage for CNV calling (incl. Exon-level) and detection of mosaicism (targeted panels)<br>- Analysis can be extended to exome/genome (virtual panels) | - Frequent update with redesign and validation of the assay may be necessary (Targeted panels)<br>- No detection of large CNV and structural variants | - Cystic kidney disease gene panel<br>- Gene panel for for COL4A3, COL4A4, and COL4A5 for suspected Alport syndrome |

| | | | | | |
|---|---|---|---|---|---|
| ***Exome sequencing*** | Detection of SNVs and indels within coding regions of the genome | - Genetically heterogeneous or nonspecific phenotypes, e.g. CKD of unknown aetiology<br>- Syndromic diseases without "spot diagnosis" and/or after negative targeted panel | - Unbiased analysis of coding region<br>- Cost-efficient because most patients with monogenic disease harbour variants in coding regions<br>- Discovery of novel genes<br>- Allows incidental findings in actionable genes | - Lower per-base coverage and limited coverage of certain regions<br>- Limitations in CNV calling<br>- Incidental findings | - CKD of unknown aetiology after routine clinical workup<br>- Multiple congenital anomalies with normal chromosomal microarray |
| ***Genome sequencing*** | Detection of SNVs, indels and CNV within coding and non-coding regions | - Idem Exome sequencing<br>- Soon first line test due to genome-wide detection of SNV, indels, CNV and balanced rearrangements? | - Coding and non-coding region, i.e. deep intronic variants<br>- Improved sensibility of CNV detection (uniform coverage)<br>- Detection of balanced rearrangements<br>-Superior to overcomes pseudogene homology | - Challenges in interpreting non-coding variants<br>- Interpretation bottleneck due to large amounts of data, increased turnaround time<br>- Incidental findings | - Detection of second intronic variant in recessive diseases (eg. Gitelman or Alport syndromes)<br>- Complex genes with pseudogenes (eg. PKD1) |

APOL1: Apolipoprotein 1; CKD : chronic kidney disease; GU : genitourinary; indels : insertion/deletions ; MLPA : Multiplex Ligation-dependent Probe Amplification; MPS : Massive parallel sequencing; SNV : single nucleotide variant; VUS : variant of unknown significance

Adapted from Knoers et al. [3]

**Table 4. Genetic kidney diseases and kidney transplantation: Key questions and ongoing trials.**

| Disease | Key questions | Ongoing clinical trials |
|---|---|---|
| Atypical hemolytic and uremic syndrome | • Duration of Eculizumab after transplantation<br>• Clinical relevance of sC5b-9 in plasma, C5b-9 depositions in kidney biopsies, and ex-vivo test for C5b-9 endothelial deposition for diagnosis-monitoring of aHUS<br>• Utility of aHUS genetic screening in patients with secondary TMA<br>• Availability of eculizumab, especially in developing countries | |
| C3 glomerulopathy | • Biomarkers to stratify the risk of recurrence after kidney transplantation<br>• Curative and/or prophylactic treatment for recurrence | Phase 2 study assessing safety and efficacy of pegcetacoplan in post-transplant recurrence of C3 glomerulopathy (***NCT04572854***)<br>Managed Access Program with Iptacopan for C3 glomerulopathy ***(NCT05222412)*** |
| Primary hyperoxaluria | • RNAi alone to treat the hepatic metabolic defect (and replace liver transplantation)<br>• Accurate assessment of systemic oxalosis to help physician decide on the right timing for kidney transplantation.<br>• Availability of RNAi, especially in developing countries | Phase 3 trial investigating lumasiran in PH1 patients with advanced CKD including patients who undergo isolated kidney transplantation (***NCT04152200***) |
| Tuberous sclerosis complex | • Safety and efficacy of preemptive nephrectomy<br>• Safety and efficacy of mTORi after transplantation | |
| Fabry disease | • Safety and efficacy of long-term use of ERT (especially migalastat) after transplantation | |
| Mitochondrial diseases | • Safety and efficacy of mTORi after transplantation | |
| apolipoprotein L1 (APOL1) | • Impact of *APOL1* variant on donor and recipient outcome after transplantation | Prospective observational study assessing the effects of renal-risk variants in the APOL1 gene on outcomes for kidneys from donors with recent African ancestry and the recipients of their kidneys, after deceased- and living-donor renal transplantation (***NCT03615235***) |
| Severe tubulopathy | • Risk-benefit balance in considering kidney transplantation in patients with severe tubulopathy impacting quality of life without kidney failure | |
| Kidney graft with genetic disease | • Risk/benefits balance of using a graft with known mild genetic kidney diseases. Potential indications? Long-term outcome in case of living donation? | |

**Abbreviations:** aHUS, Atypical hemolytic and uremic syndrome; mTORi, Inhibitors of mechanistic target of rapamycine; KT, Kidney transplantation; RNAi, RNA interference; CKD, chronic kidney disease; ERT : enzyme replacement therapy; TMA, Thrombotic microangiopathy.

**Table 5. Key steps for implementation of genetic testing in kidney transplantation.**

| |
|---|
| Obtain detailed family history in all patients with CKD |
| Document the age of onset of kidney disease manifestations |
| Encourage standardized phenotyping and multisystem evaluation |
| Increase genetic literacy in healthcare professionals, and in patients and their families |
| Define algorithms for genetic testing in case of CKD of unknown etiology |
| Plan periodic reanalysis of genetically unsolved cases |
| Ensure adequate return of genetic results to the patient, with appropriate genetic counseling |
| Ensure pretest genetic counseling and information on the medical and potential economic and psychosocial consequences of genetic testing |
| Promote multidisciplinary KT teams including genetic counsellors |
| Develop and implement decision tools to guide genetic testing before KT |
| Take advantage of expert centers and international reference networks (e.g. ERNs) |
| Encourage participation in expert panels or case reviews |
| Encourage exchange of data and inclusion in large cohorts of genotyped patients |
| Interact with patient organisations |
| Use appropriate reference sets for patients from underrepresented populations with CKD |
| Encourage participation in research genomics protocols |

**Legends to Figures**

**Figure 1. Genetic testing in kidney transplantation: Predictive factors, modalities, actionable genes and impact.**

Abbreviations: aHUS : atypical hemolytic and uremic syndrome ; CGH: comparative genomic hybridization; CKD : chronic kidney disease; CNV : copy number variation; ERT : enzyme replacement therapy; GNC3 : C3 glomerulopathy; iARN : interference RNA; MLPA : multiplex ligation-dependant probe amplification; MPS : massive parallel sequencing; PH1 : primary hyperoxaluria; SNP : small nucleotide polymorphism; WES: whole exome sequencing; WGS : whole genome sequencing

**Figure 2. Genetic kidney diseases: Types of inheritance and related living donation.**
Representative pedigrees and typical diseases are provided for each modality of inheritance. Depending on the mode of transmission, the related living donation may be allowed (V), contra-indicated (X) or discouraged (±).

Figure 1



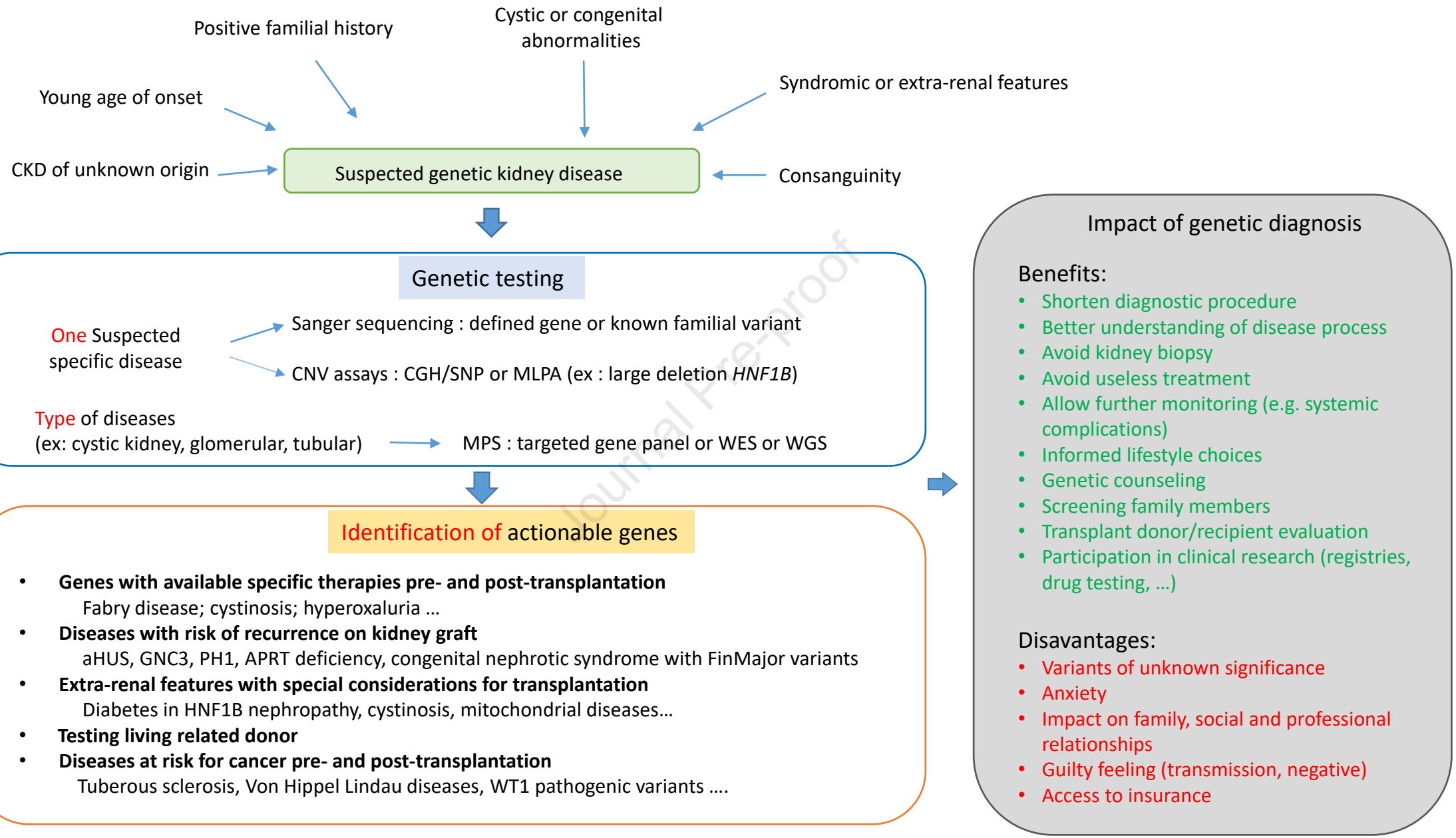
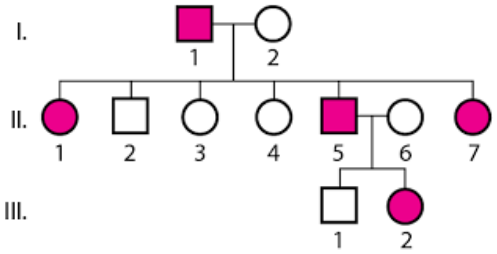


Figure 2

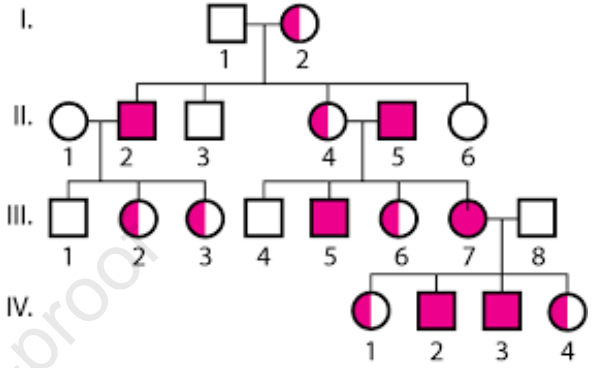





## Dominant diseases

(ADPKD, ADTKD, aHUS, TSC, VHL,…)

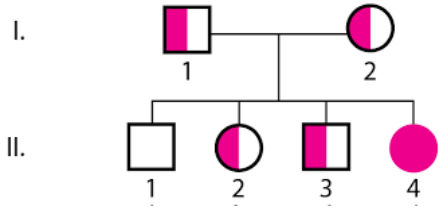
Related donors
Affected: X
Non-affected: V




## X-linked diseases

(Alport, Fabry, …)

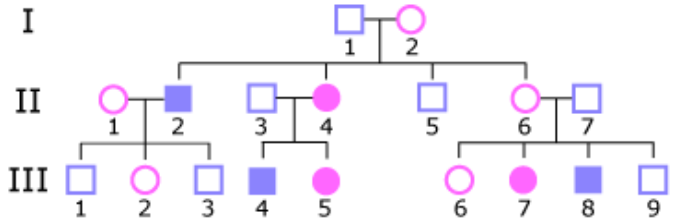
Hemizygous male: X
Heterozygous female: X




## Recessive diseases

(Cystinosis, PH1, …)

Heterozygous subjects: V
Heterozygous COL4A3/A4 subjects: X




## Mitochondrial diseases

(MELAS, …)

Mother: X
Siblings: ±