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Genetic kidney diseases as an underrecognized cause of chronic kidney disease: the key role of international registry reports

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ABSTRACT

Inherited kidney diseases (IKDs) are among the leading causes of early-onset chronic kidney disease (CKD) and are responsible for at least 10–15% of cases of kidney replacement therapy (KRT) in adults. Paediatric nephrologists are very aware of the high prevalence of IKDs among their patients, but this is not the case for adult nephrologists. Recent publications have demonstrated that monogenic diseases account for a significant percentage of adult cases of CKD. A substantial number of these patients have received a non-specific/incorrect diagnosis or a diagnosis of CKD of unknown aetiology, which precludes correct treatment, follow-up and genetic counselling. There are a number of reasons why genetic kidney diseases are difficult to diagnose in adulthood: (i) adult nephrologists, in general, are not knowledgeable about IKDs; (ii) existence of atypical phenotypes; (iii) genetic testing is not universally available; (iv) family history is not always available or may be negative; (v) lack of knowledge of various genotype–phenotype relationships and (vi) conflicting interpretation of the pathogenicity of many sequence variants. Registries can contribute to visualize the burden of IKDs by regularly grouping all IKDs in their annual reports, as is done for glomerulonephritis or interstitial diseases, rather than reporting only cystic disease and hiding other IKDs under labels such as 'miscellaneous' or 'other'. Any effort to reduce the percentage of patients needing KRT with a diagnosis of 'nephropathy of unknown etiology' or an unspecific/incorrect diagnosis should be encouraged as a step towards precision nephrology. Genetic testing may be of value in this context but should not be used indiscriminately, but rather on the basis of a deep knowledge of IKDs.

Keywords: chronic kidney disease, familial, genetic, genetic testing, inherited kidney disease, registries

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INTRODUCTION

Chronic kidney disease (CKD) affects an increasing percentage of the population, reducing the quality of life and also having a very significant socio-economic impact [1]. Kidney biopsy has long been the fundamental diagnostic tool for identifying the cause of CKD. However, in recent years the aetiological diagnosis of kidney diseases has been enhanced by the advent of biomarkers such as anti-phospholipase A2 receptor antibodies, which facilitate the diagnosis of primary membranous nephropathy even in the absence of a kidney biopsy. Despite these advances, a significant percentage of patients without a diagnosis still reach CKD category G5. The latest published European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) registry data [2, 3] indicate that this percentage is as high as 27% among patients who are on kidney replacement therapy (KRT) (Figure 1A). According to the US Renal Data System (USRDS) Annual Report 2017 (https://www.usrds.org/), 22% of paediatric patients and 18% of adult patients who start KRT do so without a certain diagnosis (Figure 1B).

It also needs to be emphasized that apart from the alarmingly high and ever-increasing percentage of adult patients who start KRT without a precise diagnosis, some of those diagnosed as having hypertensive nephropathy, diabetic nephropathy or unspecified glomerulopathy subsequently prove to have an incorrect diagnosis [4]. Hypertensive nephropathy is the second most common cause of KRT in both Europe, where it ties with glomerulonephritis [2], and the USA [5]. The incidence of KRT due to hypertensive nephropathy is related to the incidence of other causes of end-stage kidney disease but not to the burden of hypertension per country [6]; consequently, a diagnosis of hypertensive nephropathy essentially equates to CKD of unknown aetiology in a patient with hypertension. Something similar occurs in some cases of diabetic nephropathy in patients with mild diabetes and in those labelled as having unspecific glomerulopathy.

Despite the rarity of each individual inherited kidney disease (IKD), taken together the IKDs account for ~10–15% of adult patients and most paediatric patients on KRT [7–10]. The only IKD clearly reflected in national and international registries is autosomal dominant polycystic kidney disease (ADPKD). While ADPKD has a similar prevalence in different regions of the world, its relative frequency among the causes of CKD varies depending on the prevalence of other nephropathies such as diabetic and hypertensive kidney disease, which are more closely related to lifestyle. The other IKDs are grouped in the 'miscellaneous' category of the ERA-EDTA registry and in the unknown/other sections in the USRDS. This generates a problem of invisibility: out of sight, out of mind.

A key point to note is that a non-negligible percentage of patients who need KRT without a specific diagnosis suffer undiagnosed genetic kidney conditions, as has been

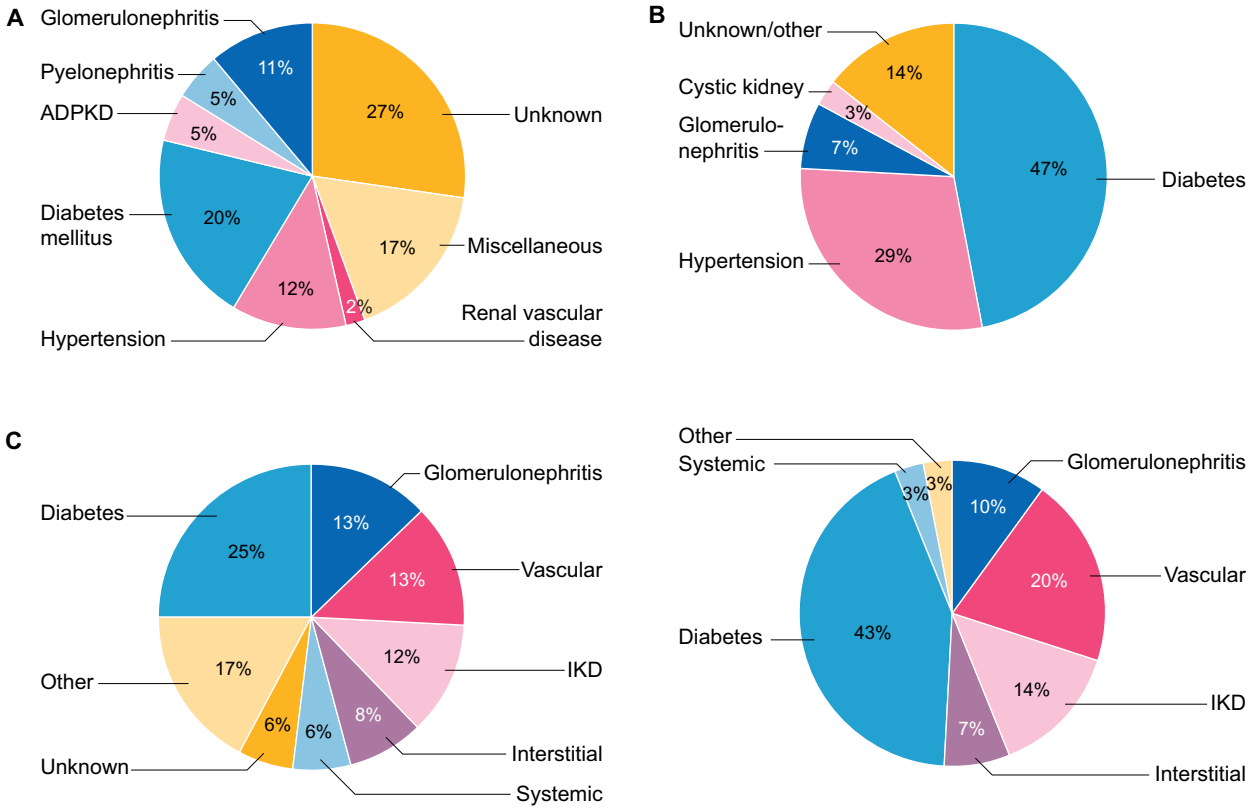

FIGURE 1: (**A**) Percentage of incident patients receiving KRT according to the primary cause of kidney disease: ERA-EDTA registry 2018 as presented in the annual report [2, 3]. (**B**) Percentage of incident patients receiving KRT according to the primary cause of kidney disease: USRDS 2017, as presented in the annual report [5]. (**C**) Percentage of incident patients receiving KRT according to the primary cause of kidney disease when IKDs (cystic and non-cystic) are presented as a single category: left panel, data from Madrid renal registry, right panel: data from Catalan renal registry (Manuel Aparicio, personal communication for Registro Madrileño de Enfermedades Renales and http://trasplantaments.gencat.cat/web/.content/minisite/trasplantament/registres_activitat/registre_de_malalts_renals/arxius/Informe-RMRC-2018.pdf for the Catalan Society of Nephrology).

demonstrated in a large cohort of adult patients with CKD [4]. In this study, genomic analysis using whole-exome sequencing (WES) revealed that among 3315 adult patients with CKD, 9.1% had a monogenic kidney disease. It is particularly noteworthy that a precise diagnosis was achieved in 17.1% of the 281 patients labelled as having kidney disease of unknown aetiology. In another study, Connaughton *et al.* [11] identified the genetic cause of 34% of kidney diseases of unknown aetiology. These data highlight the prevalence of IKDs among CKD cases as a whole. In addition, the fact that ∼30% of patients with CKD have a family member with kidney disease suggests that genetic variants can explain a significant proportion of CKD cases [12]. Alport syndrome is now considered to be almost as frequent as ADPKD [4], the latter being a difficult-to-miss diagnosis that accounts for ∼5% of patients on KRT. Genetic forms of interstitial kidney diseases, including autosomal dominant tubulointerstitial kidney disease (ADTKD) and nephronophthisis, may also be more frequent than anticipated among patients with CKD of unknown aetiology or misdiagnosed [4, 13].

In many cases, inaccurate diagnoses serve to disguise a suboptimal diagnostic workup. As part of that workup, genetic testing should be considered to rule out an IKD. There are two fundamental ways in which genetics can explain the family aggregation of CKD. Pathogenic variants in Mendelian genes are rare, but they exert an enormous disease-causing effect; examples include IKDs such as ADPKD, Alport syndrome, ADTKD and tubulopathies. On the other hand, common genetic variants exert a very slight effect on the phenotype but are very frequent. The CKDgen consortium attempts to discover genetic loci associated with CKD-classifying quantitative traits that influence the evolution and even the presentation of many kidney diseases [14]. The heritability of the estimated glomerular filtration rate has been suggested to be somewhere between 6% and 30% in the general population [15–17], and several loci have been reported to be associated with kidney function [18, 19]. Genetic variants related to the presence and degree of microalbuminuria and proteinuria have also been identified [20] and a meta-analysis revealed variants of significance for rapid decline in kidney function [21]. DNA variants in *APOL1* have been shown to be associated with non-diabetic CKD in individuals of African origin [22]. In addition, genome-wide association studies (GWASs) have led to the discovery of a significant number of loci that cause small to moderate effects in immunoglobulin A nephropathy, membranous nephropathy and steroid-sensitive nephrotic syndrome [23]. All of these GWAS findings reveal a genetic background in non-commonly IKDs. The utility of these findings lies above all in the development of prognostic scores for these nephropathies. GWAS findings have less direct impact, at least individually, than the pathogenic variants found in genes causing Mendelian diseases, which are the leading cause of a given phenotype. The present article focuses on the latter. It is of great importance that nephrologists can access the tools to diagnose IKDs. It has been estimated that across a wide spectrum of disorders, up to 50% of individuals with rare genetic conditions remain undiagnosed, and IKDs are no exception [24].

AVAILABLE TECHNIQUES FOR THE DIAGNOSIS OF IKDS

The implementation of next-generation sequencing (NGS) technologies (also known as massively parallel sequencing) in routine genetic testing has hugely improved the diagnostic yield in patients with IKDs. NGS technologies process millions of sequencing reactions in parallel and at the same time. They enable the detection of all types of genetic variants, from single-nucleotide variants to large structural variants [copy number variations (CNVs)], although the sensitivity for CNV detection is lower. There are three NGS approaches, applied for different purposes: targeted gene panels, in which a panel of genes specific for a disease is examined simultaneously; WES, which targets all protein-coding genes in the human genome; and whole-genome sequencing, which is used to determine the complete DNA sequence of the genome. All three approaches have their advantages and disadvantages, as well summarized elsewhere [25, 26]. The clinical interpretation of the thousands of variants identified in each individual with respect to the reference sequence genome represents a bottleneck in all NGS approaches. While the number of gene–disease relationships reported within the field of nephrology has rapidly expanded, the evidence to support these relationships is frequently very limited, which precludes precise evaluation of genomic variation in clinical settings. The National Institutes of Health–funded Clinical Genome Resource has developed a framework for the definition and evaluation of the clinical validity of gene–disease pairs across a wide range of Mendelian disorders [27]. Moreover, in recent years, laboratories across the world have implemented standardized guidelines for the clinical interpretation of sequence variants associated with Mendelian diseases [28]. These guidelines allow the classification of sequence variants according to a five-tier nomenclature system: pathogenic, likely pathogenic, uncertain significance, likely benign and benign. The largest category is variants of unknown significance, which makes genetic testing difficult in many patients.

The availability of larger and more diverse reference datasets has shown that many previously reported pathogenic variants in fact have an allele frequency that exceeds the disease prevalence and can be reclassified as benign. As a general rule, clinicians should only act on variants that are classified as either pathogenic or likely pathogenic and should also consider reassessing old genetic results in the light of newly available data. It is evident that post-sequencing data analysis is becoming the key step in NGS. While the cost of sequencing has been declining rapidly, the amount of sequence data generated is expanding, as a consequence of which data analysis and storage are accounting for larger fractions of the real cost of sequencing [29].

NGS has facilitated identification of the genetic basis of several IKDs and improved the diagnosis and management of patients with these nephropathies. It should be noted that other genetic techniques must be used for the diagnosis of ADTKD-*MUC1*, which is not possible on the basis of NGS [30–32]. Thus comprehensive exclusion of other nephropathies requires both NGS and a search for specific genetic variants that are known to be relatively common but are missed by NGS. In addition to variants in a single gene, chromosomal abnormalities contribute to IKDs, and this is especially true in children with neurodevelopmental and/or multiorgan syndromes [33, 34]. Such chromosomal anomalies can be identified by karyotyping or by 'comparative genomic hybridization', which is a molecular cytogenetic method for the analysis of CNVs.

Clinicians should be aware of the potential psychosocial implications that a genetic diagnosis has for patients. There is a need for a multidisciplinary approach to genetic testing for IKDs. It does not seem feasible that all nephrologists requesting a genetic test will be sufficiently proficient to interpret any kind of genetic report appropriately. For example, many nephrologists do not know about the very common finding of variant of unknown significance. A multidisciplinary team comprising molecular geneticists,

nephrologists, psychologists and genetic counselors should help in delivering this kind of genetic result to patients.

OBSTACLES TO SUSPECTING AN IKD

Patients often spend years visiting multiple healthcare providers before they receive an accurate diagnosis of an IKD. For some diseases, such as ADPKD, clinical suspicion of the disease combined with information acquired by means of clinical imaging studies is usually sufficient for diagnosis; however, this does not hold true for the vast majority of IKDs. Genetic testing has led to the reclassification of IKDs and has also broadened the phenotypic spectrum of many classic IKDs.

There are several reasons why a nephrologist may never suspect a genetic disease in a patient with a kidney condition. Among these, lack of knowledge on IKDs in conjunction with the presence of an unexpected phenotype is probably the main obstacle to diagnosis. A family history of kidney disease is frequently not obtained in adults with kidney disease. Questions on the existence of kidney disease among family members should be asked periodically, as individuals may not initially be aware of health issues in family members but may become interested in them when asked. Additionally, the family history may evolve over time, as subclinically affected individuals may eventually develop manifestations of kidney disease. On the other hand, patients may display a phenotype very different from that described initially for the disease in question, making it very unlikely that the nephrologist will consider this disease. There are a number of explanations for the existence of phenotypes that differ greatly from those classically described.

i. Allelic heterogeneity: Different pathogenic variants in a particular gene give rise to different phenotypes [35–37]. For example, some missense variants in Fabry patients allow the production of a certain amount of -galactosidase and give rise to a late and predominantly cardiac phenotype [38].
ii. Incomplete penetrance: Some individuals who carry a given pathogenic variant do not develop the disease phenotype [39–41]. This has been shown to occur for certain IKDs, including ADTKD, in which intrafamilial variability may be so pronounced that the nephrologist will not suspect an IKD [31].
iii. Oligogenic inheritance and modifier genes: The disease phenotype is determined by pathogenic variants in more than one gene. For example, patients with mutations in a steroid-resistant nephrotic syndrome/focal segmental glomerulosclerosis (FSGS) gene and *COL4A3* present a more severe phenotype than family members with a mutation in only one of these genes [42]. On the other hand, a sequence variant in a modifier gene that is not a disease-causing variant acts as a genetic modifier of the disease phenotype. For example, it has been suggested that heterozygous deleterious *TTC21B* variants act as genetic modifiers of the severity of glomerular and cystic kidney diseases [43]. Also, hypomorphic alleles, which are sequence variants that by themselves give rise to no phenotype or only a very mild one, together with another hypomorphic allele or a pathogenic variant in *trans*, worsen the phenotype [44]. This has been shown in, for exxample, ADPKD, where almost asymptomatic parents who carry a hypomorphic allele have severely affected children [45].
iv. Mosaicism: The coexistence of mutated and wild-type cells in a patient who is a *de novo* case for an IKD can explain milder clinical presentations. This is a frequent finding in mildly affected tuberous sclerosis patients. These patients have limited organ involvement, as most cells in their body do not carry the pathogenic tuberous sclerosis complex variant. However, they may have extremely severely affected offspring, as in the progeny without mosaicism, where all cells throughout the body harbour the pathogenic variant [46].
v. Epigenetic regulation: These are modifications to the genome that are not encoded in the DNA sequence but do form a part of the cellular memory and impact on the phenotype. Environmental insults such as hyperglycaemia or uraemia can lead to an altered metabolic situation, which in turn can trigger changes in chromatin modifications and gene expression.
vi. X inactivation: This is a physiologic process in which one of the copies of the two X chromosomes present in every female cell is inactivated. The inactive X chromosome is silenced through epigenetic modifications and is transcriptionally inactive. In humans, X chromosome inactivation is a random process, but in certain cases it is skewed towards the wild-type or the mutated allele. When a very high percentage of cells with the wild-type allele is inactivated, the disease will be much more severe than would normally be expected in a female [45, 47, 48]. This phenomenon is very important for certain IKDs, including X-linked Alport syndrome and Fabry disease. While one would expect females to be much less severely affected than males with these diseases, the skewed X inactivation means that in these pedigrees some females will be affected to the same extent, impeding identification of an X-linked pattern of inheritance [49].
vii. Environmental factors: Both during embryonic development and throughout life, phenotype is influenced by environmental factors. For exxample, a lifestyle not in accord with cardiovascular health will worsen the course of almost any IKD.

TIPS ON HOW TO SUSPECT AN IKD

Although, as previously pointed out, a significant percentage of patients with kidney disease of unknown aetiology may have an IKD and genetic testing allows a diagnosis to be made, one must not make the mistake of requesting unsubstantiated genetic studies. While the cost of NGS has decreased, it is still sufficiently high that it must not be used in a non-cost-effective way.

The following circumstances may arouse suspicion of an IKD, in descending order of importance (Figure 2):

i. a family history of kidney disease or a patient from an area with a high level of inbreeding, which may make one think of an autosomal recessive disease
ii. patients with cystic kidney diseases, tubulopathies or suspected monogenic glomerulopathies have a likely monogenic cause of the disease [50]
iii. a syndromic disease in which organs besides the kidney are affected
iv. congenital kidney anomalies
v. kidney disease of unknown aetiology in patients <25–30 years of age; at least 20% of CKD patients under the age of 25 years have an IKD [9, 50]
vi. haematuric (and proteinuric) kidney disease without a definitive diagnosis by kidney biopsy or with a diagnosis of

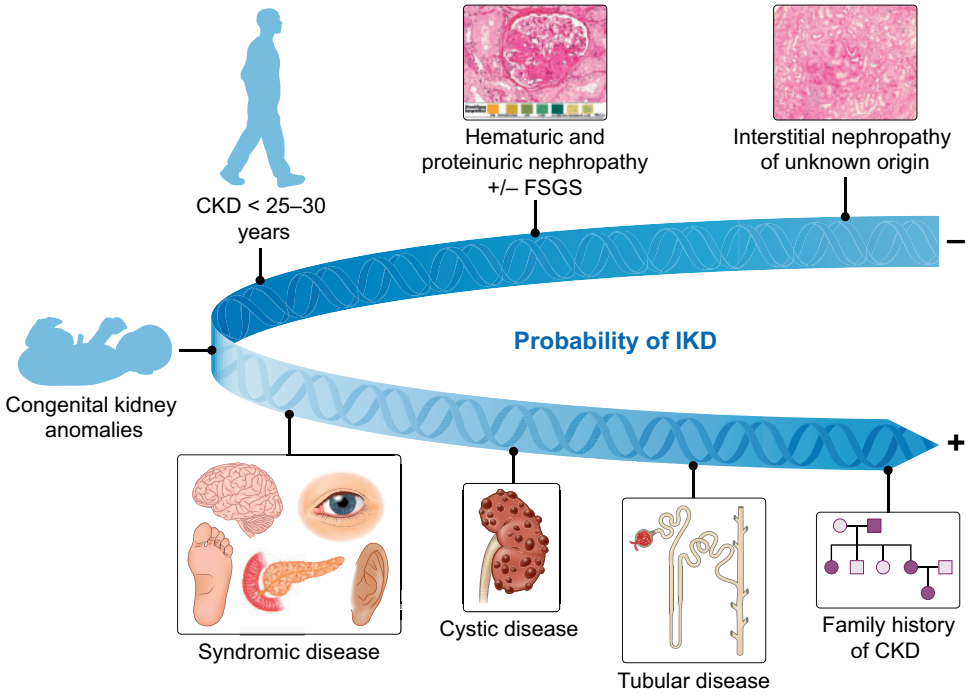

FIGURE 2: Situations warranting suspicion of an IKD.

FSGS; such disease may be due to mutations in the *COL4A3* or *COL4A4* genes, giving rise to the so-called autosomal dominant Alport syndrome with highly variable clinical expression [51–53]

vii. interstitial nephropathy without an apparent cause, even in the absence of a family history, as it may show incomplete penetrance or be a sporadic case.

BENEFITS OF DIAGNOSING AN IKD IN CKD PATIENTS

The diagnosis of an IKD in a patient with CKD not only implies the end of a diagnostic odyssey for many patients, but also has clear repercussions for prognosis, management and treatment. Actionable findings will greatly benefit the patient's outcome. For example, when faced with FSGS, the expectations after a kidney transplant will be very different depending on whether the origin is immunological or genetic. In the latter case, the likelihood of recurrence is non-existent. In the case of a proteinuric kidney disease of genetic origin, corticosteroid therapy or immunosuppression will not be administered. Once a precise diagnosis has been established, e.g. Alport syndrome, the patient will be able to take part in clinical trials and to benefit from future treatments. In the case of IKDs with systemic or syndromic involvement, study of the patient will extend beyond the renal involvement to encompass other organs. Also, in the context of living donor transplantation, the fact that an IKD has been diagnosed will have repercussions, since there will be relatives in whom nephropathy must be ruled out before they can be considered as donors.

When an IKD is suspected, it seems reasonable not to perform a kidney biopsy but to order a genetic test, which may facilitate a precise diagnosis and prevent unnecessary use of an invasive procedure such as a kidney biopsy.

One of the most relevant consequences of reaching a diagnosis of an IKD is the possibility of offering genetic counselling, including pre-symptomatic testing that may provide strategies and reproductive options to prevent passage of the disease to new generations, e.g. prenatal diagnosis or pre-implantation genetic testing [54]. The diagnosis of a rare IKD also allows patients to access reference centres that are used to manage their disease and can provide up-to-date information and management. This is one of the aims of the European Reference Network for Rare Kidney Diseases (ERKnet; https://www.erknet.org/index.php?id=home). Genetic testing of IKDs has also allowed the reclassification of many conditions and improved disease ontology [55]. One of the drawbacks of genetic testing is that, in some countries, it may have consequences for insurance coverage. In addition, legal, social and ethical difficulties need to be addressed in some cases.

CONCLUSION

Achieving a precise diagnosis is a fundamental goal of medical practice. Genetic testing has emerged as a powerful diagnostic tool in nephrology. The evidence that at least 10% of adult patients and most children with CKD [7, 9] suffer from an IKD together with the accessibility of new genetic diagnostic tools should allow the diagnosis of a high percentage of undiagnosed IKDs and thus assist in reducing the number of patients who need KRT without a certain diagnosis or with an incorrect one. It is important to determine which patients will benefit from genetic studies, and certain medical and family history data are helpful in deciding whether to order a genetic test. As indications for genetic testing continue to expand, better education will be required for both patients and nephrologists regarding topics such as genomic medicine, informed consent, the potential benefits and implications of genetic results and current limitations in the interpretation of genetic results. National and international registries may promote awareness of IKDs by reporting them as a separate category encompassing all IKDs instead of splicing the IKD category and dumping non-cystic

IKDs into the invisible 'other' or 'miscellaneous' categories (Figure 1C). Any effort to reduce the percentage of patients reaching the need for KRT with a diagnosis of nephropathy of unknown etiology or an unspecific/incorrect diagnosis should be encouraged. Genetic testing may be of value in this context but should not be used indiscriminately, but rather on the basis of a deep knowledge of IKDs.

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CONFLICT OF INTEREST STATEMENT

The results presented herein have not been presented in whole or part. The authors declare no conflicts of interest.

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