Genetic Testing in Peritoneal Dialysis: Applying International Recommendations to Identify Missed Diagnostic Opportunities

Lígia Catarina Ribeiro[1*], *Ana Rita Almeida*[2*], *Anabela Rodrigues*[3], *Luísa Lobato*[3]
*Joint first authors
1. Nephrology Department, ULS Castelo Branco, Castelo Branco, Portugal
2. Nephrology Department, ULS Loures, Odivelas, Portugal
3. Nephrology Department, ULS Santo António, Porto, Portugal

https://doi.org/10.71749/pkj.164

ABSTRACT

Introduction: Chronic kidney disease (CKD) of unknown etiology remains frequent and delays diagnosis and targeted therapy. International recommendations define when genetic testing should be offered, but their application has not been described in patients already established on kidney replacement therapy. Peritoneal dialysis (PD) patients are comparatively young, mostly transplant candidates and closely followed, and may particularly benefit from diagnostic reassessment.

Methods: Retrospective observational study including all patients enrolled in a hospital-based PD programme in January 2025. Demographics, comorbidities, CKD etiology, biopsy findings, family history, transplant status and prior genetic evaluation were extracted from source records. Criteria for genetic testing, based on international recommendations, were defined before record review.

Results: Sixty-six patients were included (62.1% male; mean age 54.5 ± 15.9 years), with a mean nephrology follow-up of 14.3 ± 9.6 years. Forty-two patients (63.6%) were actively listed for transplantation. Kidney biopsy was available in 21 patients (31.8%). In the remaining 45 (68.2%) the etiology had been attributed clinically and never revised. Family history was inconsistently documented. Twenty-four patients (36.4%; 95% CI 25.5–48.5) met at least one criterion for genetic testing, but only five (20.8% of those eligible; 7.6% of the cohort) had been evaluated, leaving 19 unmet indications.

Conclusion: One in three PD patients fulfilled criteria for genetic testing and four of five of these had never been tested, despite more than a decade of follow-up. Kidney replacement therapy should not be treated as the endpoint of etiological investigation: in PD, where most patients are transplant candidates, genetic evaluation remains clinically useful.

Keywords: Genetic Testing; Kidney Diseases, Cystic/genetics; Peritoneal Dialysis; Renal Insufficiency, Chronic/genetics

INTRODUCTION

Chronic kidney disease (CKD) is a major global public health challenge, imposing a growing burden on patients, healthcare systems and economies. Optimizing the diagnostic and therapeutic approach to CKD has a positive impact on outcomes and allows a reduction in costs associated with prolonged diagnostic odysseys and with the delayed initiation of targeted therapies.[1-3]

CKD of unknown etiology (CKDu) still accounts for an important part of CKD cases, which compromises disease management and long-term outcomes. Recent expert statements have called for a reconsideration of this concept, reframing it as a structured and standardized diagnostic category that is applied only after a comprehensive and systematic evaluation, including genetic testing and the revisiting of unconfirmed or historical diagnoses based on sources rather than on summaries. Such a comprehensive re-evaluation can reveal previously overlooked or misinterpreted findings and may lead directly to a definitive diagnosis or indicate a new diagnostic path.[4-6] Recent studies using genetic testing have demonstrated that Mendelian etiologies account for a meaningful proportion of cases of kidney disease of unknown etiology.[7,8]

Received: 12/08/2026 **Accepted:** 09/09/2026 **Published Online:** 19/09/2026 **Published:** -
* **Corresponding Author:** Lígia Catarina Ribeiro | ligia.catarina.r@gmail.com | ULS Castelo Branco, Avenida Pedro Álvares Cabral, 6000-085 Castelo Branco, Portugal

Although population-wide genetic testing may have potential benefits, the diagnostic yield is highest in selected clinical scenarios, which international recommendations now enumerate explicitly: cystic kidney or liver disease without family history, biopsy consistent with focal and segmental glomerulosclerosis without an obvious cause, biopsy consistent with tubulointerstitial nephropathy without vascular changes, biopsy showing alterations of the basement membrane, membranoproliferative or thrombotic microangiopathy patterns of unknown etiology, multiorgan syndromes, positive family history in first or second-degree relatives, CKDu with extrarenal manifestations, CKDu before 50 years of age, recipients of a living donor kidney, and atypical clinical presentations.[2,3,6,9]

In many clinical situations, genetic testing ends the diagnostic odyssey, alters management decisions, influences disease trajectory, and reduces the unnecessary use of healthcare resources. It allows clinicians to navigate a clearer roadmap for prevention, for the timely adoption of therapeutic interventions, for the avoidance of ineffective treatments, and for accurate counselling regarding individual and familial prognosis. In some cases, identification of a pathogenic variant may obviate the need for invasive procedures, that likely pathogenic variants (according to ACMG guidelines) may also be considered causal and actionable in terms of attributing etiology.[10-12] These benefits are frequently discussed in the context of early CKD, as though the opportunity to act upon them were confined to the period preceding kidney replacement therapy. This assumption deserves to be examined, because a substantial part of the value of an etiological diagnosis (its implications for transplantation and evaluation of related living donors, the anticipation of disease recurrence in the graft, surveillance of extrarenal manifestations, and for the counselling and testing of relatives) is realised precisely in patients who have already reached kidney failure.[10,12]

Genetic testing may therefore be particularly relevant in patients undergoing peritoneal dialysis, many of whom have long-standing CKD with uncertain or presumptive etiologies despite years of follow-up. This population is comparatively young, retains residual kidney function, is frequently accompanied by a small and stable multidisciplinary team, and is largely composed of active transplant candidates. Each of these characteristics increases, rather than diminishes, the potential yield and the potential usefulness of an etiological diagnosis. Despite the evolution of the CKD diagnostic landscape, however, a significant number of patients with CKD of undetermined cause persist in daily clinical practice.[4,5]

To the best of our knowledge, the frequency with which indications for genetic testing are present, and remain unacted upon, has not previously been described in a peritoneal dialysis population. The aim of this study was to characterize the etiological diagnoses of CKD in such a cohort, to determine how many patients fulfilled current criteria for genetic testing, and to establish in how many of those patients testing had actually been performed. Our purpose was not to estimate the prevalence of monogenic disease in dialysis, but to examine whether recommendations that are already established are being applied at a stage of the disease at which they remain clinically useful.

METHODS

A retrospective observational study was conducted in January 2025 in a cohort of patients enrolled in a hospital-based peritoneal dialysis program. All patients enrolled in the program at that date were included, and no exclusion criteria were applied.

Data was collected from electronic clinical records and covered the entire period from first nephrology referral to the index date. They included demographic characteristics, comorbidities, CKD etiology, clinical phenotype, renal biopsy findings, documented family history, previous kidney transplantation, active listing for transplantation, and information regarding prior genetic testing or genetic consultation. An etiological diagnosis was considered confirmed when supported by histology, by imaging meeting recognized diagnostic criteria, or by a molecular result; and presumptive when recorded in the absence of any of these. Family history was considered documented when the record contained an explicit statement regarding kidney disease, dialysis or transplantation in relatives, consanguinity, place of origin, or urinary abnormalities in first- or second-degree relatives; the absence of such a statement was recorded as not documented and was not taken to represent a negative family history.

Based on international guidelines and recommendations, we defined clinical criteria for genetic testing before beginning record review. These are presented in Table 1 together with their source, and included: positive family history in first and second-degree relatives, multiorgan syndromes of unknown origin, atypical clinical presentation, kidney biopsy suggestive of a genetic cause – chronic tubulointerstitial nephritis in the absence of significant vascular disease, focal and segmental glomerulosclerosis (FSGS) without secondary causes and with a pattern of corticorresistant FSGS, abnormalities of the glomerular basement membrane, idiopathic thrombotic microangiopathy, or a membranoproliferative pattern –, CKD or end-stage kidney disease of unknown etiology before 50 years of age, recipients of organs from living donors, specially patients who already have a suspected hereditary kidney disease, in which a molecular diagnosis may enable screening of the living donor –, presence of extra-renal manifestations, cystic kidney or liver disease without family history, and unexplained electrolyte abnormalities. Criteria referring to age relate to the onset of kidney failure rather than to age at the index date. Records were reviewed systematically using a standardized extraction form and working from original source documents, biopsy

and imaging reports, referral letters and previous hospital records, rather than from discharge summaries or the dialysis problem list. Each record was assessed against every criterion, and a patient was considered eligible for genetic testing when at least one criterion was fulfilled.

For each patient, age of presentation was determined at the first nephrology evaluation. We also report the age at the initiation of kidney replacement therapy. The date of onset of each comorbidity was not recorded in the clinical files. Clinical presentation refers to the abnormality that motivated the first nephrology evaluation, and not to the prevalence of that finding at any later point of follow-up.

Unfortunately, during the review, and despite every effort made, we were unable to describe the technology used to perform genetic testing in patients who underwent it, neither obtain the variant classification according to ACMG guidelines.

The analysis was descriptive. Continuous variables are presented as mean ± standard deviation with range, and categorical variables as absolute frequencies and percentages, calculated over the total cohort unless otherwise specified. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA).

Table 1. Criteria for genetic testing applied in this study, with source recommendation.

Domain	Criteria	Source recommendation
Family and personal history	Positive family history of kidney disease in first- or second-degree relatives	KDIGO Controversies Conference; ERA/ERKNet
	CKD or end-stage kidney disease of unknown etiology before 50 years of age	KDIGO Controversies Conference; ERA/ERKNet
	Recipient of, or candidate for, a kidney from a living related donor	KDIGO 2024 CKD guideline; KDIGO 2025 ADPKD guideline
Kidney biopsy findings	Focal and segmental glomerulosclerosis without secondary causes	ERA/ERKNet
	Chronic tubulointerstitial nephritis in the absence of significant vascular disease	ERA/ERKNet
	Abnormalities of the glomerular basement membrane	ERA/ERKNet
	Idiopathic thrombotic microangiopathy or membranoproliferative pattern	ERA/ERKNet; KDIGO Controversies Conference
Imaging findings	Cystic kidney or liver disease without family history	KDIGO 2025 ADPKD guideline
Extrarenal features	Multiorgan syndrome of unknown origin	KDIGO Controversies Conference
	Extra-renal manifestations accompanying kidney disease of unknown etiology	KDIGO Controversies Conference; ERA/ERKNet
Atypical clinical course	Atypical clinical presentation	ERA/ERKNet
	Unexplained electrolyte abnormalities	ERA/ERKNet

CKD, chronic kidney disease; ADPKD, autosomal dominant polycystic kidney disease.

RESULTS

A total of 66 patients were included. Most patients were of European ancestry (65 patients, 98.5%) and male (41 patients, 62.1%). Patients had been followed in nephrology outpatient consultation for a mean of 14.3 ± 9.6 years since their first referral.

Mean age at the first nephrology evaluation, taken as a proxy for the age at diagnosis of chronic kidney disease, was 36.2 ± 18.1 years (range 0–70). Mean age at the initiation of kidney replacement therapy was 46.7 ± 17.2 years (range 0–77), and 33 of these (52.4%) reached kidney failure before 50 years of age.

Regarding comorbidities, 58 patients (87.9%) had hypertension, 23 (34.8%) heart failure, 14 (21.2%) diabetes mellitus, 14 (21.2%) peripheral vascular disease and 10 (15.2%) cerebrovascular disease. Three patients (4.5%) had a history of renal malignancy and three (4.5%) had other neoplasms. Twelve patients (18.2%) had previously undergone kidney transplantation, one of whom had received two kidney transplants on separate occasions, with a mean time since transplantation of 19.3 ± 7.5 years. At the time of evaluation, 42 individuals (63.6%) were actively listed for kidney transplantation. Cohort characteristics are summarized in Table 2.

Table 2. Characteristics of the cohort.

	n (%) or mean ± SD
Demographics	
Male sex	41 (62.1)
European ancestry	65 (98.5)
Age, years (range)	54.5 ± 15.9 (21–80)
Nephrology follow-up since first referral, years	14.3 ± 9.6
Age at diagnosis of chronic kidney disease, years (range) †	36.2 ± 18.1 (0–70)
Age at initiation of kidney replacement therapy, years (range)	46.7 ± 17.2 (0–77)
Comorbidities	
Hypertension	58 (87.9)
Heart failure	23 (34.8)
Diabetes mellitus	14 (21.2)
Peripheral vascular disease	14 (21.2)
Cerebrovascular disease	10 (15.2)
History of renal malignancy	3 (4.5)
History of other malignancy	3 (4.5)
Transplant status	
Previous kidney transplantation	12 (18.2)
Time since transplantation, years	19.3 ± 7.5
Actively listed for transplantation	42 (63.6)
Clinical presentation *	
Proteinuria	35 (53.0)
Hematuria	18 (27.3)
Acute kidney injury	10 (15.2)
Hypertension	5 (7.6)
Kidney cysts	4 (6.1)
Other	5 (7.6)
Diagnostic evaluation	
Kidney biopsy available	21 (31.8)
Etiology presumptive (no histological confirmation)	45 (68.2)
Meeting ≥1 criterion for genetic testing	24 (36.4)
Genetic evaluation performed	5 (7.6)

* Presenting features were not mutually exclusive. † Age at diagnosis of chronic kidney disease corresponds to the age at the first nephrology evaluation.

Clinical presentation, in features that were not mutually exclusive, included proteinuria in 35 patients (53.0%), hematuria in 18 (27.3%), acute kidney injury in 10 (15.2%), hypertension in 5 (7.6%), kidney cysts in 4 (6.1%) and other presentations in 5 patients (7.6%). These proportions refer to the abnormality that motivated the first nephrology evaluation and not to the prevalence of each condition during follow-up. Hypertension is reported here only for the patients in whom it was the finding that prompted referral. As a comorbidity it was present in 58 patients (87.9%), as expected in a population with kidney failure.

Histological diagnosis based on kidney biopsy was available for 21 patients (31.8%). In the remaining 45 patients (68.2%) there was no histological confirmation, and the recorded etiology had been attributed on clinical grounds and was not subsequently revised. Family history was not consistently documented across medical records. In most cases there was no clear information regarding the patient's place of origin, consanguinity, familial history of CKD, or potentially asymptomatic urinary abnormalities in first or second-degree relatives, and no record was found of this information having been revisited at any point during follow-up.

Twenty-four patients (36.4%; 95% CI 25.5–48.5) met at least one criterion for genetic testing. Of these, 8 met only one criterion, 9 met two criteria simultaneously, 5 met

three criteria and 2 met more than three, as presented in Table 3.

Table 3. Number of criteria for genetic testing fulfilled per patient.

Number of criteria fulfilled	Patients, n	% of eligible patients (n = 24)	% of cohort (n = 66)
One	8	33.3	12.1
Two	9	37.5	13.6
Three	5	20.8	7.6
More than three	2	8.3	3.0
Total	24	100	36.4

Table 4 describes in detail, specific criteria fulfilled for each patient

Despite meeting testing criteria, only five patients in our cohort had undergone genetic evaluation, corresponding to 20.8% of the 24 eligible patients and to 7.6% of the whole cohort. The genetic tests performed and their indications are presented in Table 5. The methodology employed was heterogeneous, and in three of the five cases the type of study performed was not recorded in the clinical file. The variant identified in each patient tested and its classification according to the ACMG/AMP criteria are presented. Where the original laboratory report could not be retrieved from the clinical file, this is stated explicitly rather than inferred.

Table 4. Indication and methodology of the genetic tests performed.

Patient	Criteria fulfilled	Number of criteria
1	CKD or end-stage kidney disease of unknown etiology before 50 years of age Multiorgan syndrome of unknown origin	2
2	Positive family history of kidney disease in first- or second-degree relatives CKD or end-stage kidney disease of unknown etiology before 50 years of age Recipient of, or candidate for, a kidney from a living related donor Chronic tubulointerstitial nephritis in the absence of significant vascular disease	4
3	Positive family history of kidney disease in first- or second-degree relatives CKD or end-stage kidney disease of unknown etiology before 50 years of age	2
4	Multiorgan syndrome of unknown origin Extra-renal manifestations accompanying kidney disease of unknown etiology	2
5	CKD or end-stage kidney disease of unknown etiology before 50 years of age	1
6	Focal and segmental glomerulosclerosis without secondary causes	1
7	Positive family history of kidney disease in first- or second-degree relatives	1
8	Positive family history of kidney disease in first- or second-degree relatives	1
9	Positive family history of kidney disease in first- or second-degree relatives Atypical clinical presentation	2
10	CKD or end-stage kidney disease of unknown etiology before 50 years of age	1
11	Positive family history of kidney disease in first- or second-degree relatives CKD or end-stage kidney disease of unknown etiology before 50 years of age	2
12	CKD or end-stage kidney disease of unknown etiology before 50 years of age Focal and segmental glomerulosclerosis without secondary causes Atypical clinical presentation	3
13	Positive family history of kidney disease in first- or second-degree relatives CKD or end-stage kidney disease of unknown etiology before 50 years of age Extra-renal manifestations accompanying kidney disease of unknown etiology	3
14	CKD or end-stage kidney disease of unknown etiology before 50 years of age	1
15	Positive family history of kidney disease in first- or second-degree relatives Extra-renal manifestations accompanying kidney disease of unknown etiology Atypical clinical presentation	3
16	Positive family history of kidney disease in first- or second-degree relatives Cystic kidney or liver disease without family history	2
17	CKD or end-stage kidney disease of unknown etiology before 50 years of age Chronic tubulointerstitial nephritis in the absence of significant vascular disease Extra-renal manifestations accompanying kidney disease of unknown etiology	3
18	CKD or end-stage kidney disease of unknown etiology before 50 years of age Recipient of, or candidate for, a kidney from a living related donor Multiorgan syndrome of unknown origin Atypical clinical presentation	4
19	CKD or end-stage kidney disease of unknown etiology before 50 years of age Atypical clinical presentation	2
20	CKD or end-stage kidney disease of unknown etiology before 50 years of age Recipient of, or candidate for, a kidney from a living related donor	2
21	CKD or end-stage kidney disease of unknown etiology before 50 years of age	1
22	CKD or end-stage kidney disease of unknown etiology before 50 years of age Multiorgan syndrome of unknown origin Atypical clinical presentation	3
23	CKD or end-stage kidney disease of unknown etiology before 50 years of age Cystic kidney or liver disease without family history	2
24	CKD or end-stage kidney disease of unknown etiology before 50 years of age	1

CKD, chronic kidney disease.

Table 5. Indication and methodology of the genetic tests performed.

Patient	Indication for testing	Methodology	Variant identified	ACMG/AMP classification
1	Marfanoid habitus, for exclusion of Marfan, Ehlers–Danlos and Loeys–Dietz syndromes	Next-generation sequencing based on whole-exome sequencing of 77 genes, with copy-number variation analysis	Not recorded in the clinical file	Not applicable
2	Study of collagen IV nephropathy	Next-generation sequencing panel of genes associated with hereditary nephropathies	COL4A3	Not recorded in the clinical file
3	MELAS syndrome	Not recorded in the clinical file	*MT-ND5 m.13513G>A*	Not recorded in the clinical file
4	Nephrotic syndrome associated with *NPHS2*	Not recorded in the clinical file	Not recorded in the clinical file	Not applicable
5	Atypical haemolytic uraemic syndrome	Not recorded in the clinical file	*DGKE*, homozygous	Not recorded in the clinical file

MELAS, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; NPHS2, podocin gene. ACMG/AMP, American College of Medical Genetics and Genomics / Association for Molecular Pathology.

DISCUSSION

In this retrospective study of a peritoneal dialysis cohort with long-standing nephrological follow-up, one in three patients fulfilled current criteria for genetic testing, and four out of five of those patients had never been tested. To the best of our knowledge, this is the first description of the frequency of unmet indications for genetic testing in a peritoneal dialysis population, and it identifies a gap not of knowledge nor technical availability, but of application. These findings align with a growing body of evidence showing that, although genetic testing has become increasingly accessible and clinically relevant, its integration into routine nephrology practice remains limited and inconsistent.[10,14,16]

The central finding of this study is that these missed opportunities occurred despite ongoing clinical follow-up. Our patients had been followed in nephrology consultation for a mean of more than fourteen years before the index date, which corresponds to well over a decade of scheduled appointments in which a family history could have been taken, the original biopsy report reviewed, or a genetic study requested. The limited use of genetic testing, therefore, cannot be attributed to late referral or to lack of access to specialist care. It is worth noting that family history, the least costly element of the entire etiological evaluation, and the most predictive element of a monogenic cause, was the most consistently absent from the records we reviewed, which suggests that the diagnostic process fails at its earliest and simplest step rather than at the point of requesting a test.[14-16]

Our cohort reflects a population with a high burden of cardiovascular comorbidities and a long duration of renal disease, factors that frequently contribute to the attribution of CKD to presumed acquired causes such as hypertensive or vascular nephropathy, without a systematic reassessment of earlier diagnostic assumptions. This phenomenon has been well documented in recent literature, where convenience diagnoses have been identified as one of the leading factors preventing timely recognition of hereditary kidney diseases.[4] Hypertension, in particular, is as often a consequence of nephropathy as it is its cause, and its presence should not by itself close the etiological question.

These findings point to a broader assumption that we believe deserves to be challenged directly. The initiation of kidney replacement therapy appears, in practice, to function as the moment at which the etiological investigation is considered concluded. Clinical attention shifts, reasonably, towards dialysis adequacy, anemia, mineral and bone disorder and cardiovascular risk, and the question of why the kidneys failed is no longer asked. There is, however, no clinical justification for this. Reaching kidney failure removes neither the possibility nor the usefulness of establishing an etiological diagnosis. What changes is the way in which that diagnosis is used, not whether it is worth having.

This is particularly evident in peritoneal dialysis. Nearly two thirds of our cohort were actively listed for transplantation and a further 18.2% had already lost a first graft, so that for the great majority of these patients a molecular diagnosis bears on decisions that are still pending rather than on decisions already taken. A confirmed hereditary diagnosis may influence donor selection, help screen potential living related donors, estimate the risk of disease recurrence after transplantation, and in some conditions, guide the need for combined organ transplantation or for specific peri-transplant therapies. In addition, recognition of familial disease enables cascade testing and counselling of relatives, allowing early detection and preventive strategies that may delay or avoid kidney failure in family members, who are, in many cases, the same individuals being considered as living donors.[12,13] Beyond transplantation, identification of a pathogenic or likely pathogenic (ACMG/AMP classification) variant may clarify prognosis, inform the risk of extra-renal complications, guide surveillance, prevent unnecessary or repeated invasive procedures such as additional biopsies, and avoid

ineffective immunosuppressive therapies in patients with non-immune genetic conditions. In some conditions, it also carries implications for the dialysis prescription itself and for the type of transplant indicated. Even in advanced CKD or end-stage kidney disease, genetic testing remains clinically actionable rather than merely descriptive.[10,13]

Peritoneal dialysis programs are also a setting in which such a reassessment is practicable. The population is relatively small, patients are followed also by a small and stable team on a protocolized schedule that already includes periodic clinical review, and the clinical record is correspondingly complete.

The magnitude of the diagnostic opportunity forgone can be approximated. Reported diagnostic yields of panel or exome-based testing in adults selected by criteria comparable to those applied here range broadly from 15% to 40% and are higher in early-onset disease and in kidney failure of unknown etiology.[7,8,10,11] Applied to the 19 untested eligible patients in our cohort, this corresponds to an expected three to eight undiagnosed monogenic conditions within a single peritoneal dialysis program of 66 patients. This projection is illustrative rather than a result of our study, but it conveys the scale of what remains undiagnosed.

The limited use of genetic testing observed in our study mirrors barriers described in the literature: insufficient clinician genetic literacy, uncertainty regarding test selection and interpretation, resource limitations, time constraints on a holistic diagnostic approach, and fragmented collaboration between nephrologists and geneticists. Although the cost of genetic sequencing has decreased dramatically over recent years, the perception of high cost persists as a deterrent. Furthermore, the lack of standardized protocols and of structured training across nephrology curricula contributes to clinician hesitation, as extensively documented in international surveys.[14-16] The heterogeneity of the studies actually performed in our cohort, and the absence of any record of the methodology used in three of five cases, are consistent with an unstandardized pathway, and carry a practical implication: a patient recorded as having undergone a genetic study with an uninformative result cannot be assumed to have been adequately investigated.

These observations also raise the question of where in the clinical pathway the failure originates. The criteria fulfilled by our patients are not obscure: a first-degree relative with kidney disease, kidney failure before 50 years of age without a confirmed cause, kidney cysts without a family history, or a biopsy showing focal and segmental glomerulosclerosis with no evident secondary cause. Recognising them requires no genomic expertise, but it does require that they have been taught as red flags and that they be actively sought at the bedside. Specific training in hereditary kidney disease remains uneven across nephrology curricula, and surveys of practising nephrologists have shown consistently that formal genetic education is associated with a higher rate of referral for genetic evaluation, while its absence ranks among the most frequently cited barriers to testing.[9,14,15] Incorporating structured teaching of inherited kidney disease into residency programmes, and making the family history and the review of the original biopsy report an explicit and documented part of the first evaluation, is a low-cost intervention that would probably have captured most of the indications that went unrecognised in our cohort.

A second question is who should request a genetic study, as it is not a single act. It is a sequence of judgements: which patient should be tested, which test should be requested, what does the result mean, and what follows the result. Each of these fails when taken alone. In a survey of 149 nephrologists, a third had never ordered a genetic test, and among those who had, the most often reported difficulty was not access but knowing which test to choose.[14] Studies of tests ordered outside genetics services have found that a substantial proportion were not the appropriate ones, generating cost without reaching a diagnosis. Interpretation is no simpler, since nomenclature and reporting formats differ between laboratories, and a clinician without access to a clinical geneticist or a genetic counsellor is understandably reluctant to translate a report into a plan to present to the patient. The steps that determine the yield, however, are nephrological: the selection of candidates, the depth of phenotyping, the rereading of the original biopsy, and the matching of a variant against the clinical course. No specialty can carry the process alone, and the practical consequence is that the decision to test, the choice of test and the interpretation of the result should be taken and documented jointly.

What this requires is that the joint discussion be a standing feature of the centre rather than an occasional referral. In practice it means a scheduled nephrology–genetics meeting at which patients identified by the criteria in Table 1 are presented, the test is chosen with the geneticist before the sample is sent rather than after, the result is returned to the patient by whoever is best placed to explain it, and the testing of relatives is planned at the same time. Centers organized in this way have reported diagnostic yields approaching 40% in selected patients, revision of the clinical diagnosis in a substantial proportion of those diagnosed, and direct effects on management and on cascade testing.[18-20] From a health-system perspective, implementing structured genetic evaluation in peritoneal dialysis programs may be cost-effective. The relevant comparison is not the price of a genetic study against zero, but against an ineffective course of immunosuppression, an avoidable early graft loss from unanticipated recurrence, or the transplantation of a kidney from an affected related donor. By shortening the diagnostic odyssey, reducing redundant investigations and enabling precision management, genetic testing may optimize resource utilization while improving patient-centered outcomes.[2,10]

Our findings support a simple and practicable approach. Etiological reassessment should take place at defined moments in the peritoneal dialysis pathway, at entry into the program and at the annual review, rather than opportunistically. At each of these moments a structured family history should be recorded, the original biopsy and imaging reports retrieved, and an explicit statement made as to whether the etiological diagnosis is confirmed or presumptive. The criteria in Table 1 should then be applied and the outcome documented. Where capacity is limited, priority should be given to patients listed for transplantation with a potential related living donor, and to those who reached kidney failure before 50 years of age without a confirmed diagnosis. Referral should follow a defined route to a genetics consultation or to a joint nephrology–genetics meeting, and testing should be initiated before rather than during living-donor evaluation, so that the result is available when the decisions are actually made. The path to overcoming these constraints has been outlined by national and international societies, whose recommendations generally aim to improve reimbursement policies, increase clinician education, and simplify genetic data interpretation.[6,9] The barrier, therefore, appears to be conceptual rather than logistical.

This study has several limitations. It is a single-center study of 66 patients, and the precision of the estimates is correspondingly limited. The design is retrospective, and absence of documentation is not proof of absence of enquiry: a family history may have been taken and not recorded, which would overestimate eligibility for that particular criteria, although it would equally represent a documentation failure with the same practical consequence. Restriction to a peritoneal dialysis population introduces a selection bias operating in both directions, since these patients are younger and more often transplant candidates than the dialysis population as a whole, and our estimate is therefore not directly generalized to hemodialysis or to conservatively managed patients. The cohort was ethnically homogeneous, which precluded assessment of criteria and yields relating to ancestry-specific risk variants. Finally, genetic testing was not performed as part of this study, so the true diagnostic yield among untested eligible patients is inferred rather than observed. Taken together, our findings reinforce that CKD etiological evaluation is not a static process but should be dynamic and periodically re-examined, particularly in patients with atypical features, early-onset kidney failure, or non-informative biopsy results. The contemporary nephrology landscape, with the availability of next-generation sequencing, improved analytical tools and evolving consensus recommendations, provides the means to overcome long-standing diagnostic inertia. As demonstrated by our cohort, however, successful implementation depends on systematic approaches to clinical documentation, ongoing clinician education, and structured integration of genetic services into nephrology workflows.[1,6,13] Our study underscores that substantial room for improvement remains, and that aligning clinical practice with current evidence and international guidelines will be crucial to reducing the burden of CKD of unknown etiology.[2,9]

CONCLUSION

A substantial proportion of patients in our peritoneal dialysis program fulfilled current criteria for genetic testing, yet genetic evaluation had been performed in only one in five of them, despite a mean of more than fourteen years of nephrological follow-up. The key message of this work is that the initiation of kidney replacement therapy should not be understood as the endpoint of the etiological investigation. Being on dialysis, and specifically on peritoneal dialysis, neither prevents the establishment of an etiological diagnosis nor diminishes its usefulness: in a population that is comparatively young, largely composed of transplant candidates, and closely followed, the benefits of genetic evaluation are sufficient to sustain the continued pursuit of the cause of kidney disease.

Read in this light, our findings carry a message that goes beyond the timing of the investigation. If a large share of the patients in a closely followed dialysis programme fulfil criteria for genetic testing and most of them have never been tested, and if two thirds of the cohort carry an etiological label that was never confirmed, the reasonable inference is that a large proportion, and possibly the majority, of the patients we treat at the most advanced stage of kidney disease are living with an incomplete, unverified or simply incorrect diagnosis. This is not a limitation of the tools available but of their application. Establishing the cause of kidney disease in these patients is not an academic exercise appended to the end of the diagnostic pathway: it determines transplant strategy, the safety of related living donors, the surveillance of extrarenal disease, and the care of families who remain undiagnosed.

Awards and Previous Presentations

The present work was presented as oral communication at Encontro Renal 2025, 19-22nd November 2025, Estoril

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).
Provenance and Peer Review: Not commissioned; externally peer-reviewed.

Contributorship Statement

LCR and ARA: Writing the manuscript and data collection.
AR and LL: Revision.
All authors approved the final version of the manuscript for publication and assume responsibility for all aspects of the work, ensuring the accuracy and integrity of the data presented.

REFERENCES

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105:S117–S314.
2. Köttgen A, Cornec-Le Gall E, Halbritter J, Kiryluk K, Mallett AJ, Rasouly HM, et al. Genetics in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2022;101:1126–41. doi: 10.1016/j.kint.2022.03.019.
3. Kidney Disease: Improving Global Outcomes (KDIGO) ADPKD Work Group. KDIGO 2025 Clinical Practice Guideline for the Evaluation, Management, and Treatment of Autosomal Dominant Polycystic Kidney Disease (ADPKD). Kidney Int. 2025;107:S1–S239. doi: 10.1016/j.kint.2024.07.009.
4. Rao IR, Bangera A, Nagaraju SP, Shenoy SV, Prabhu RA, Rangaswamy D, et al. Chronic kidney disease of unknown aetiology: A comprehensive review of a global public health problem. Trop Med Int Health. 2023;28:588-600. doi: 10.1111/tmi.13913.
5. Bruck K, Stel VS, Fraser S, De Goeij MCM, Caskey F, Abu-Hanna A, et al. Chronic kidney disease of undetermined cause: a review. Diseases. 2023;31:52.
6. Knoers N, Antignac C, Bergmann C, Dahan K, Giglio S, Heidet L, et al. Genetic testing in the diagnosis of chronic kidney disease: recommendations for clinical practice. Nephrol Dial Transplant. 2022;37:239–54. doi: 10.1093/ndt/gfab218.
7. Groopman EE, Marasa M, Cameron-Christie S, Petrovski S, Aggarwal VS, Milo-Rasouly H, et al. Diagnostic utility of exome sequencing for kidney disease. N Engl J Med. 2019;380:142–51. doi: 10.1056/NEJMoa1806891.
8. Doreille A, Lombardi Y, Dancer M, Lamri R, Testard Q, Vanhoye X, et al. Exome-first strategy in adult patients with CKD: a cohort study. Kidney Int Rep. 2023;8:596–605. doi: 10.1016/j.ekir.2022.12.007.
9. Aron AW, Dahl NK. Clinical genetic testing in nephrology: core curriculum 2024. Am J Kidney Dis. 2024;84:632–45. doi: 10.1053/j.ajkd.2024.05.011.
10. Dahl NK, Bloom MS, Chebib FT, Clark D, Westemeyer M, Jandeska S, et al. The clinical utility of genetic testing in the diagnosis and management of adults with chronic kidney disease. J Am Soc Nephrol. 2023;34:2039–50. doi: 10.1681/ASN.0000000000000249.
11. Domingo-Gallego A, Pybus M, Bullich G, Furlano M, Ejarque-Vila L, Lorente-Grandoso L, et al. Clinical utility of genetic testing in early-onset kidney disease: seven genes are the main players. Nephrol Dial Transplant. 2022;37:687–96. doi: 10.1093/ndt/gfab019.
12. Connaughton DM, Hildebrandt F. Personalized medicine in chronic kidney disease by detection of monogenic mutations. Nephrol Dial Transplant. 2020;35:390–7. doi: 10.1093/ndt/gfz028.
13. Mallett AJ, McCarthy HJ, Ho G, Holman K, Farnsworth E, Patel C, et al. Massively parallel sequencing and targeted exomes in familial kidney disease can diagnose underlying genetic disorders. Kidney Int. 2017;92:1493–506. doi: 10.1016/j.kint.2017.06.013.
14. Mrug M, Bloom MS, Seto C, Malhotra M, Tabriziani H, Gauthier P, et al. Genetic testing for chronic kidney diseases: clinical utility and barriers perceived by nephrologists. Kidney Med. 2021;3:1050–6. doi: 10.1016/j.xkme.2021.08.006.
15. Rasouly HM, Balderes O, Marasa M, Fernandez H, Lipton M, Lin F, et al. The effect of genetic education on the referral of patients to genetic evaluation: findings from a national survey of nephrologists. Genet Med. 2023;25:100814. doi: 10.1016/j.gim.2023.100814.
16. Spigler M, Collins J, Paris M, Woolley R. Barriers to genetic testing for determining cause of kidney disease among healthcare providers. J Am Soc Nephrol. 2022;33:754. doi: 10.1681/ASN.20223311S1754a.
17. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. doi: 10.1038/gim.2015.30.
18. Mallett A, Fowles LF, McGaughran J, Healy H, Patel C. A multidisciplinary renal genetics clinic improves patient diagnosis. Med J Aust. 2016;204:58–9. doi: 10.5694/mja15.01157.
19. Jayasinghe K, Stark Z, Kerr PG, Gaff C, Martyn M, Whitlam J, et al. Clinical impact of genomic testing in patients with suspected monogenic kidney disease. Genet Med. 2021;23:183–91. doi: 10.1038/s41436-020-00963-4.
20. Alkanderi S, Yates LM, Johnson SA, Sayer JA. Lessons learned from a multidisciplinary renal genetics clinic. QJM. 2017;110:453–7. doi: 10.1093/qjmed/hcx030.