U.PORTO

CICLO DE ESTUDOS
MEDICINA

Genetic testing before kidney transplantation

Leonor dos Santos Caetano Dias

M

2026

Genetic testing before kidney transplantation

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar - Universidade do Porto

Estudante:
Leonor dos Santos Caetano Dias
Estudante do 6º ano do Mestrado Integrado em Medicina
Instituto de Ciências Biomédicas Abel Salazar da Universidade do Porto
Endereço eletrónico: leonor.caetano.dias@gmail.com/up202009306@up.pt

Orientadora:
Doutora Luísa Maria Correia Lopes Lobato
Assistente Graduada Sénior de Nefrologia
Serviço de Nefrologia da Unidade Local de Saúde de Santo António, Porto, Portugal
Professora Catedrática Convidada do Instituto de Ciências Biomédicas Abel Salazar Universidade do Porto, Portugal
Investigadora da Unidade Multidisciplinar de Investigação Biomédica (UMIB)
Instituto de Ciências Biomédicas Abel Salazar e do Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional, Universidade do Porto, Portugal

Coorientador:
Dr. João Paulo Pimenta Fernandes
Assistente de Nefrologia da Unidade Local de Saúde de Santo António, Porto, Portugal
Docente Externo do Instituto de Ciências Biomédicas Abel Salazar
Universidade do Porto, Portugal

This dissertation contains results publicly presented at the following scientific meetings:

VI Oporto Biomedical Summit (OBS), March 20-22 2026
ICBAS in Super Bock Arena, Porto Portugal

Abstract title|Genetic testing previous to kidney transplantation in a cohort of European population: what are we missing?
Authors|Leonor Caetano Dias, João Fernandes, La Salete Martins, Luísa Lobato
Presentation|Oral
Distinction|Finalist for *Professor Corália Vicente Award*

63rd ERA Congress, June 3-6 2026
Annual Congress of European Renal Association
Glasgow, UK

Abstract title|Genetic testing before kidney transplantation and retransplantation applying KDIGO guidelines: the overlooked issues in a European Cohort
Authors|Leonor Caetano Dias, João Fernandes, La Salete Martins, Luísa Lobato
Presentation|Focussed oral

The author thanks the School of Medicine and Biomedical Sciences
the financial grant that enabled the presentation of her work and the participation
in the leading European Congress of Nephrology

A autora,

Assinado por: Leonor dos Santos Caetano Dias
Num. de Identificação: BI14584787
Data: 06-06-2026 13:14:41 +01:00

CHAVE MÓVEL

_____
Leonor dos Santos Caetano Dias

A orientadora,

Assinado por: Luísa Maria Correia Lopes Lobato
Identificação: BI05807791
Data: 2026-06-06 às 14:38:45

_____
Doutora Luísa Maria Correia Lopes Lobato

O coorientador,

Assinado por: João Paulo Pimenta Fernandes
Identificação: BI14586413
Data: 2026-06-06 às 15:07:08

_____
Dr. João Paulo Pimenta Fernandes

Porto, junho de 2026

Declaration of Scientific Integrity

I, Leonor dos Santos Caetano Dias (no. 202009306) a sixth-year student of the Integrated Master's Degree in Medicine at the School of Medicine and Biomedical Sciences - University of Porto, declare that this dissertation is my own work and has not been submitted for any other course or curricular units, at this or any other institution.

Porto, June 2026

Assinado por: Leonor dos Santos Caetano Dias
Num. de Identificação: BI14584787
Data: 06-06-2026 13:18:33 +01:00

CHAVE MÓVEL

_____

(Leonor dos Santos Caetano Dias)

Dedicatória

Aos meus pais, agradeço o apoio constante em todas as etapas do meu percurso, bem como a dedicação, o carinho e a confiança com que sempre me acompanharam. Agradeço por me permitirem abrir horizontes, crescer e acreditar.

Ao meu irmão, agradeço todo o apoio ao longo da minha vida e é um privilégio poder partilhá-la e crescermos juntos.

À minha tia Amália, agradeço a presença constante, o apoio incondicional e o carinho com que sempre me acompanhou ao longo da minha vida, mesmo perante a distância geográfica.

Aos meus amigos, agradeço todo o apoio e carinho ao longo deste percurso, bem como a motivação constante para abraçar novos desafios. Agradeço por terem tornado esta cidade, o Porto, uma verdadeira casa.

Acknowledgements

À Professora Doutora Luísa Lobato, agradeço o acompanhamento e o apoio essencial na elaboração deste trabalho, bem como a clareza com que orientou a interpretação dos resultados e a sua discussão. Agradeço ainda, como sempre me impulsionou a procurar formas externas de expor e valorizar cientificamente este trabalho.

Ao Dr. João Fernandes, agradeço o apoio e disponibilidade constante ao longo da elaboração deste trabalho. Agradeço a reflexão critica e científica essencial na definição metodológica e na análise dos resultados.

A ambos, o meu sincero agradecimento pela orientação idónea e dedicada.

Resumo

Introdução: A doença renal crónica (DRC) afeta aproximadamente 10% da população adulta e constitui um importante desafio de saúde pública. Os fatores genéticos contribuem para a etiologia da DRC, tendo sido identificadas causas monogénicas em até 20% dos casos.
De salientar que, em 2023, Portugal foi o terceiro pais na Europa com a maior incidência de início de terapêutica de substituição da função renal, o que comprova o substancial peso da DRC avançada no país.
Apesar da crescente evidência que demonstra a utilidade diagnóstica dos testes genéticos em Nefrologia, a sua integração na prática clínica diária na Europa continua a ser inconsistente. A realização de testes genéticos é particularmente relevante em doentes candidatos a transplante renal, nos quais um diagnóstico etiológico preciso pode ter implicações significativas na abordagem, nas decisões terapêuticas e no prognóstico.

Objetivos: Este estudo teve como objetivo avaliar a etiologia subjacente da DRC numa coorte de doentes referenciados à consulta de pré-transplante renal e determinar a relevância da incorporação de testes genéticos no seu processo de diagnóstico. A análise duma coorte num contexto de prática clínica real, previamente acompanhada e sujeita a investigação diagnóstica, visou obter uma caraterização da realidade da região do norte de Portugal.
A) Objetivo específico 1: avaliar ou reavaliar (revisitar) a etiologia subjacente da DRC na coorte de doentes em estudo. B) Objetivo específico 2: avaliar a relevância da integração dos testes genéticos no processo diagnóstico da DRC.

Métodos: Realizámos um estudo retrospetivo que incluiu doentes adultos referenciados para avaliação pré-transplante renal entre janeiro e junho de 2022, num Hospital Universitário português, o Hospital Santo António. Foram revistos os processos clínicos para recolha de dados demográficos e clínicos, idade de início dos sintomas, alterações laboratoriais no diagnóstico, biópsia renal, manifestações de patologia extrarrenal, modalidade e duração da terapêutica de substituição da função renal, testes genéticos prévios, história familiar e a elegibilidade para transplante renal com dador vivo.
Não foram realizados estudos ou testes genéticos adicionais para a concretização deste trabalho.
A elegibilidade para a realização de teste genético foi avaliada com base nos critérios aas recomendações da KDIGO; estas incluem marcadores clínicos de DRC de causa desconhecida, início antes dos 40 anos, história familiar de DRC, doença renal terminal ou diálise inexplicada,

manifestações sindrómicas, hematúria recorrente na infância, proteinúria persistente na ausência de diabetes, tubulopatias, doença renal quística sem padrão clássico de doença renal poliquística autossómica dominante e marcadores imagiológicos, rins pequenos e ecogénicos sem causa evidente, quistos renais bilaterais com distribuição atípica e anomalias congénitas do rim e trato urinário.
As análises estatísticas descritivas foram realizadas utilizando o software SPSS.

Resultados: Foram incluídos 278 doentes (186 do sexo masculino) com idade, em média, de 58 anos. A DRC de etiologia desconhecida representou 29.1% dos casos (81 doentes). Elementos-chave do diagnóstico estavam frequentemente em falta, com o resultado da biópsia renal não disponível em 56.8% (158 doentes) e história familiar não detalhada em 25.5% (71 casos).
Com base nos critérios da KDIGO, 124 doentes (44.6%) eram elegíveis para testes genéticos. No entanto, o teste foi integrado pelos nefrologistas só em 28 doentes (10.1%). Entre os doentes testados, foi identificada doença renal hereditária ou monogénica em 16 casos. Aplicando as indicações KDIGO, a indicação para teste genético nos candidatos a retransplante (49 para um segundo, 10 para um terceiro) subiu para 66,1% (n = 34), conferindo um *odds ratio* de 3,07 em comparação com os candidatos a primeiro transplante (n = 85, 38,8%); a iniciativa de realizar teste genético nos candidatos a retransplante foi verificada em 7 casos. Os candidatos a retransplante eram mais jovens relativamente aos outros candidatos (idade mediana de 55 versus 59) e tinham iniciado tratamento de substituição renal mais cedo (idade mediana de 35 versus 55 anos). Em 34 dos candidatos a retransplante (57,6%) o início da doença foi antes dos 40 anos e 11 relataram presença de história familiar de doença renal.

Conclusão: Este estudo revelou-se pioneiro em Portugal, avaliando a implementação das recomendações da KDIGO para realização de testes genéticos no contexto de uma coorte de candidatos a transplante renal. Identificamos uma lacuna diagnóstica, perspetivando a maior aplicabilidade nos candidatos a retransplante renal, com um risco três vezes superior de serem enquadrados nas indicações.
O estudo permite colocar a possibilidade de patologia recidivante nos transplantes prévios, particularizando a pertinência na avaliação futura de candidatos a receberem órgãos de dador vivo. Apesar das exigências em termos de recursos e tempo a investir, a implementação das recomendações KDIGO perspetiva elevada relevância em Portugal.

Palavras-chave: doença renal crónica; etiologia desconhecida; KDIGO, teste genético; história familiar; transplante renal.

Abstract

Introduction: Chronic kidney disease (CKD) affects approximately 10% of the adult population and represents a major public health challenge. Genetic factors contribute to the aetiology of CKD, with monogenic causes being identified in up to 20% of cases. Notably, in 2023, Portugal ranked as the third European country with the highest incidence of initiation of kidney replacement therapy, highlighting the substantial burden of advanced CKD in the country. Despite growing evidence demonstrating the diagnostic utility of genetic testing in Nephrology, its integration into routine clinical practice across Europe remains inconsistent. Genetic testing is particularly relevant in patients considered for kidney transplantation, in whom an accurate aetiological diagnosis may have significant implications for clinical management, therapeutic decision-making, and prognosis.

Objective: This study aimed to evaluate the underlying aetiology of CKD in a cohort of patients referred for pre-kidney transplant assessment and to determine the relevance of incorporating genetic testing into their diagnostic pathway. By analysing a cohort in a real-world clinical setting, previously followed and exposed to diagnostic investigation, the study sought to characterise the current situation in the northern region of Portugal.
A) Specific objective 1: To assess or reassess (revisit) the underlying aetiology of CKD in the study cohort. B) Specific objective 2: To evaluate the relevance of integrating genetic testing into the diagnostic work-up of CKD.

Methods: We conducted a retrospective study including adult patients referred for pre-kidney transplant assessment between January and June 2022 at a Portuguese university hospital, Hospital Santo António. Medical records were reviewed to collect demographic and clinical data, including age at symptom onset, laboratory abnormalities at diagnosis, kidney biopsy findings, manifestations of extrarenal disease, modality and duration of kidney replacement therapy, previous genetic testing, family history, and eligibility for living-donor kidney transplantation. No additional genetic studies or genetic tests were performed for the purposes of this work. Eligibility for genetic testing was assessed according to KDIGO recommendations. These include clinical indicators of CKD of unknown cause, disease onset before the age of 40 years, family history of CKD, end-stage kidney disease or unexplained dialysis, syndromic manifestations, recurrent haematuria during childhood, persistent proteinuria in the absence of diabetes, tubulopathies, cystic kidney without the classical pattern of autosomal dominant polycystic

kidney disease, and imaging findings such as small echogenic kidneys without an evident cause, bilateral renal cysts with atypical distribution, congenital anomalies of the kidney and urinary tract. Descriptive statistical analyses were performed using SPSS software.

Results: A total of 278 patients (186 male) were included, with a mean age of 58 years. CKD of unknown aetiology accounted for 29.1% of cases (81 patients). Key diagnostic information was frequently missing, with kidney biopsy results unavailable in 56.8% of patients (158 cases) and family history inadequately documented in 25.5% (71 cases).
Based on KDIGO criteria, 124 patients (44.6%) were eligible for genetic testing. However, nephrologists only in 28 patients (10.1%) had incorporated genetic testing. Among those tested, hereditary or monogenic kidney disease was identified in 16 cases.
Applying KDIGO indications, the proportion of retransplant candidates meeting criteria for genetic testing (49 awaiting a second transplant and 10 awaiting a third) increased to 66.1% (n = 34), corresponding to an odds ratio of 3.07 compared with first-transplant candidates (n = 85; 38.8%). The initiative to perform genetic testing in retransplant candidates was observed in only seven cases. Retransplant candidates were younger than first-transplant candidates (median age 55 versus 59 years) and had initiated kidney replacement therapy at an earlier age (median age 35 versus 55 years). Among retransplant candidates, 34 (57.6%) had disease onset before the age of 40 years, and 11 reported a family history of kidney disease.

Conclusion: This is the first study in Portugal to evaluate the implementation of KDIGO approach for genetic testing in a cohort of kidney transplant candidates. We identified a significant diagnostic gap and demonstrated that the recommendations may be particularly applicable to kidney retransplant candidates, who were three times more likely to meet testing criteria. The findings raise the possibility of recurrent disease contributing to previous graft failure and highlight the relevance of genetic evaluation in the future assessment of candidates for living-donor transplantation. Despite the demands of resources and time-consuming, putting KDIGO into practice appears highly relevant in the Portuguese population.

Keywords: chronic kidney disease; unknown aetiology; KDIGO; genetic testing; family history; kidney transplantation.

List of Abbreviations

CKD: Chronic kidney disease

ESKD: End-Stage kidney disease

MGKDs: Monogenic kidney diseases

CAKUT: Congenital Anomalies of the Kidneys and Urinary Tracts

eGFR: Estimated glomerular filtration rate

ACR: Albumin/creatinine ratio

KRT: Kidney replacement therapy

HD: Haemodialysis

PD: Peritoneal dialysis

KT: Kidney transplantation

DM: Diabetes Mellitus

HTN: Hypertension

CVD: Cardiovascular disease

MPS: Massively parallel sequencing

NGS: Next-Generation Sequencing

WGS: Whole-Genome Sequencing

ERA: European Renal Association

KDIGO: Kidney disease: Improving Global Outcomes

Index

List of Tables

List of Figures

1. Introduction

Chronic kidney disease (CKD) affects approximately 10% of the global adult population and represents a significant public health problem, affecting around 100 million people affected across Europe and incurring an estimated annual cost of €140 billion [1, 2]. It is projected that by 2040, CKD will become the fifth leading cause of death worldwide [2]. Accurate determination of CKD aetiology is extremely important for clinical management, risk stratification, therapeutic decision-making and transplant planning.

CKD is defined by abnormalities of kidney structure or function persisting for at least three months, characterized by a sustained glomerular filtration rate below 60 mL/min/1.73 m² and/or markers of kidney injury, such as persistent albuminuria, urinary sediment abnormalities, imaging or histological lesions, or a confirmed genetic kidney disease [3-5]. It should be noted that when a genetic disease is confirmed, it automatically meets the diagnostic criteria for CKD disease even when renal function is preserved [3, 5-7].

Current KDIGO recommendations and European Renal Association (ERA) guidelines emphasize classification according to Cause-GFR-Albuminuria (CGA) framework, which is based on etiology, kidney function and albuminuria.

Despite this well-defined diagnostic process, significant challenges remain in determining the underlying causes of CKD [3]. In Portugal, the impact of CKD is a major cause of concern, with a growing number of patients requiring kidney replacement therapies (KRT) [8]. In fact, is the third country with highest incidence of patients requiring KRT in Europe [9]. Among patients initiating KRT through hemodialysis, 14.9% have an indeterminate etiology. Early diagnosis is essential to widen the therapeutic window and reduce future complications. Kidney biopsy is used as a diagnostic tool to assess kidney damage, particularly in cases of renal dysfunction of unknown cause or in other scenarios indicating disease progression. However it often yields inconclusive results or fails to identify the underlying cause, especially in cases of advanced CKD [10]. In this context, genetic testing plays an increasingly important role. Genetic causes are estimated to account for 10–20% of CKD in adults and could potentially have avoided renal biopsy in 25% of cases [11-13], while massively parallel sequencing (MPS) provide diagnostic yields ranging from 6% to 30% in adults [14]. However, genetic testing remains underutilised in clinical practice as a diagnostic tool [15]. The identification of a genetic kidney disease has a significant impact on risk stratification, timely family counselling and kidney transplant outcomes [11].

This study aimed to evaluate the underlying aetiology of CKD in a cohort of patients referred for pre-kidney transplant assessment and to determine the relevance of incorporating

genetic testing into their diagnostic pathway. By analysing a cohort in a real-world clinical setting, previously followed and exposed to investigative track, it was pursued:

A) Specific objective 1: To assess or reassess (revisit) the underlying aetiology of CKD in the study cohort. We hypothesised that a proportion of cases with an indeterminate diagnosis might fulfil the criteria established by the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines for genetic testing;

B) Specific objective 2: To evaluate the relevance of integrating genetic testing into the diagnostic work-up of CKD. The aim was to understand the extent of inaccurate or incomplete diagnoses and to identify limitations of the current diagnostic paradigm. Systematic reassessment of diagnoses may support the future expansion of knowledge regarding the role of human genetics in the evaluation of kidney transplant candidates.

2. Methods

2.1 Study design and setting

We conducted single-centre retrospective study including adult patients with chronic kidney disease referred for pre-transplant appointments at the Department of Nephrology of Hospital de Santo António/Unidade Local de Saúde de Santo António, a University Hospital in Northern Portugal. Patients were included between January and June 2022. The study was based on an analysis of clinical records from the first pre-transplant nephrological evaluation performed during that period. CKD was defined and classified according to KDIGO guidelines, and all patients included were in stage G5.

No patients were specifically recruited for this study, and no diagnostic tests were ordered or performed for additional research purposes.

2.2 Study population

Eligible patients were adults aged 18 years or older with confirmed CKD referred for pre-transplant evaluation, including first transplant and re-transplant candidates.

Exclusion criteria included patients under 18 years of age, those who did not meet the CKD criteria, those not referred for transplant evaluation or those with insufficient clinical information to assess study outcomes.

A total of 286 patients were screened. Eight patients were excluded: four due to insufficient clinical information and four because they were paediatric patients. Overall, the study population included 278 adult pre-transplant candidates.

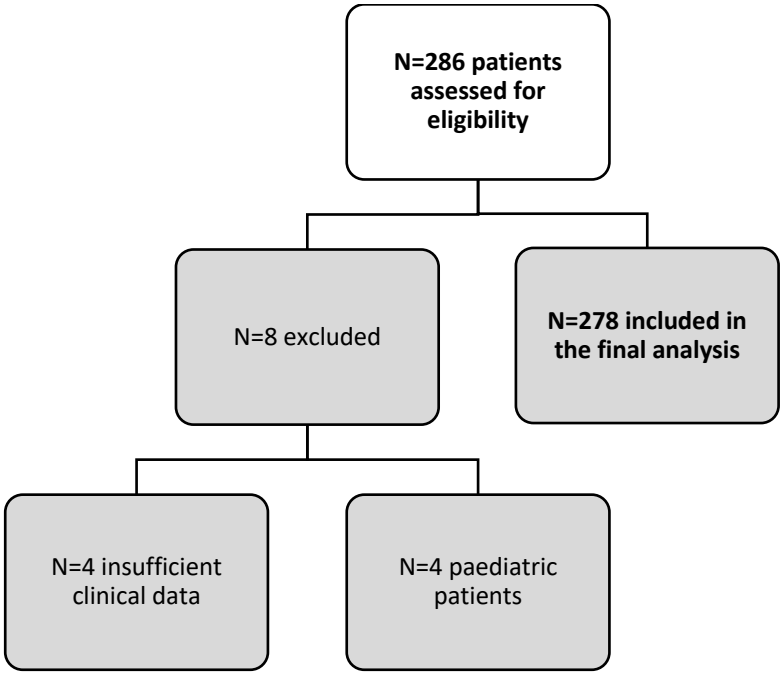


Figure 1. Flow chart of patient selection for the pre-transplant cohort (N: number of patients)

2.3 Data Collection

Clinical records were reviewed for demographic, clinical, laboratory, imaging, histological and genetic data. Collected variables included age, sex, demographic origin, age of onset of kidney disease, early clinical manifestations comorbidities, extrarenal manifestations, cardiovascular disease, family history of kidney disease or diabetes, type, duration and age at initiation of kidney replacement therapy, eligibility for living donor transplantation, previous kidney imaging, kidney biopsy status and histological diagnosis when available.

Previous genetic testing was recorded when performed, including their results. Absent family history data were documented as unavailable when not recorded in the clinical file.

2.4 Assessment of indication for genetic testing

Eligibility for genetic testing was assessed using a predefined set of clinical and imaging red flags for genetic kidney disease, based on criteria derived from KDIGO 2024 guidelines (KDIGO Controversies Conference on genetics in CKD). Patients were classified as fulfilling criteria for

genetic testing if at least one clinical or imaging red flag suggestive of hereditary or monogenic kidney disease was documented.

Clinical criteria included CKD of unknown cause; age at disease onset <40 years, positive family history of CKD, ESKD or unexplained dialysis, syndromic features, childhood-onset recurrent haematuria, persistent proteinuria without diabetes, suspected tubulopathy, or cystic disease without classic ADPKD pattern. Imaging criteria, including small echogenic kidneys without clear acquired cause, bilateral cysts with atypical distribution, CAKUT.

Patients in whom there was insufficient information in the clinical record to determine whether any criteria were met were classified as ineligible for genetic testing. Therefore, eligibility for genetic testing was assessed based on clinical records and ambiguous cases were reviewed by the study team. Patients who had previously undergone genetic testing were detailed separately and were not included in the indication for genetic testing category, as their indication had already resulted in testing. Consequently, the genetic testing indication variable was categorised as: had indication for genetic testing, no indication for genetic testing, or previously tested.

2.5 Endpoints

The primary outcome was the proportion of adult pre-transplant candidates fulfilling criteria for genetic testing.

Secondary outcomes included the proportion of patients who had previously undergone genetic testing, the proportion with a confirmed hereditary or monogenic diagnosis, among those tested the frequency of CKD of unknown aetiology, the availability of key diagnostic information, mainly kidney biopsy and family history.

2.6 Statistical analysis

Descriptive statistics were used to summarise the cohort. Continuous variables were presented as mean + standard deviation or median, according to distribution. Categorical variables were presented as absolute frequencies and percentages. Comparison between first transplant and re-transplant candidates were performed using the chi-square test for categorical variables and the Mann–Whitney U test for continuous variables. Odds ratios with 95% confidence intervals were calculated to estimate the association between re-transplant status and eligibility for genetic testing. Statistical analyses were conducted using SPSS, and a p-value <0.05 was considered statistically significant.

2.7 Ethics statement

Scientific and Ethical approvals were obtained according Institutional Clinical Academic Centre and Ethics Committee under the study number 261-25 (219-CAC-219-CE). All data were handled confidentially, anonymized prior to analysis, and processed in compliance with data protection and privacy regulations.

3. Results

3.1 Cohort Characteristics

Between January 2022 and June 2022, the clinical records of 278 patients from the Nephrology Department of Hospital Santo António, were retrospectively reviewed, based on their first pre-transplant appointment.

Baseline characteristics are shown in **Table 1**, most patients were male (n=186, 66.9%), and the median age was 58 years, ranging from 22 to 76 years. Most patients were Caucasian (n=276, 99.3%).

Regarding age at disease onset, the most prevalent group was 41-50 years (n=60, 21.6%), followed by 51-60 years (n=57, 20.5%) and 31-40 years (n=53, 19.1%). Age of onset was unavailable in 29 patients (10.4%). Initial renal manifestations were missing in 56 patients (20.1%), and 56 patients (20.1%) had non-specific findings. Among relevant findings, proteinuria was the most common initial manifestation (n=42,15.1%), followed by cystic/structural abnormalities (n=39, 14.0%) and nephrotic syndrome (n=25, 9.0%).

Concerning extrarenal manifestations, most patients had no documented extrarenal manifestations (n=130, 46.8%). When present, ocular involvement was the most frequent manifestation (n=27, 9.7%), followed by gastrointestinal (n=26, 9.4%) and genitourinary / CAKUT-related abnormalities (n=22, 7.9%). Diabetes mellitus was present in 74 patients (26.6%), and arterial hypertension in 228 patients (82.0%). A positive family history of CKD was reported in 85 patients (30.6%), whereas this information was missing in 71 patients (25.5%).

At the time of evaluation, most patients were receiving haemodialysis (n=208, 74.8%), followed by peritoneal dialysis (n=60, 21.6%), and six patients had kidney replacement therapy not yet indicated (2.2%).

Table I. Baseline demographic and clinical characteristics of the study cohort

	Whole Cohort n=278, (%)
Sex	**n (%)**
Female	92 (33.1)
Male	186 (66.9)
Age, years	
Median (range)	58.0 (22.0-76.0)
Ethnicity/Race, n (%)	
Caucasian	276 (99.3)
Black/African American	2 (0.7)
Age of onset of kidney disease (years)	**n (%)**
< 10	10 (3.6)
10-20	14 (5.0)
21-30	38 (13.7)
31-40	53 (19.1)
41-50	60 (21.6)
51-60	57 (20.5)
61-70	17 (6.1)
Unavailable	29 (10.4)
First clinical findings	**n (%)**
Haematuria	14 (5.0)
Proteinuria	42 (15.1)
Nephrotic Syndrome	25 (9.0)
Azotemia	21 (7.6)
Hypertensive crisis	16 (5.8)
AKI	4 (1.4)
Cystic/Structural	39 (14.0)
Infectious disease	1 (0.4)
Multisystemic phenotype	1 (0.4)
Non-specific findings	56 (20.1)
Asymptomatic	3 (1.1)
Unavailable	56 (20.1)
Extrarenal manifestations	**n (%)**
Auditory / hearing	3 (1.1)
Ocular	27 (9.7)
Neurologic	14 (5.0)
Cardiovascular	5 (1.8)
Dermatologic	7 (2.5)
Gastrointestinal	26 (9.4)
Respiratory	5 (1.8)
Endocrine / Metabolic	9 (3.2)
Hematologic	1 (0.4)
Genitourinary / CAKUT-related	22 (7.9)
Systemic autoimmune	14 (5.0)
Neoplastic predisposition	15 (5.4)

Table I. Baseline demographic and clinical characteristics of the study cohort (continued)

None	130 (46.8)
Diabetes	**n (%)**
Yes	74 (26.6)
No	203 (73.0)
Unavailable	1 (0.4)
HTN	**n (%)**
Yes	228 (82.0)
No	49 (17.6)
Unavailable	1 (0.4)
KRT type	**n (%)**
HD	208 (74.8)
PD	60 (21.6)
Unavailable	6 (2.2)
Family history of CKD	**n (%)**
Yes	85 (30.6)
No	115 (41.4)
Unknown	7 (2.5)
Unavailable	71 (25.5)

Abbreviations: HTN, Hypertension; AKI, Acute kidney injury; CAKUT, Congenital Anomalies of the kidney and urinary tract; KRT, Kidney replacement therapy; HD, Haemodialysis; PD, Peritoneal dialysis

3.2 Diagnostic workup and final CKD aetiology

The diagnostic evaluation based on kidney biopsy was limited by incomplete information in medical records. In 158 patients (56.8%), biopsy status was unavailable, which significantly restricts subsequent analyses and interpretation, 77 (27.7%) had undergone kidney biopsy and 43 (15.5%) had not. Among biopsied patients, the most frequent histopathological diagnosis was IgA nephropathy (n=18; 6.5%), followed by focal segmental glomerulosclerosis (n=13; 4.7%). An inconclusive histological result was reported in 14 patients (5.0%) due to advanced disease stages, or other reasons such as, sampling limitations, or etiologic heterogeneity. Other findings occurred included diabetic nephropathy (n=6; 2.2%), mesangial proliferative glomerulonephritis (n=5; 1.8%), glomerulosclerosis secondary to hypertension (n=4; 1.4%), chronic tubulointerstitial nephritis (n=4; 1.4%), ANCA-associated vasculities (n=3; 1.1%), amyloidosis (n=2; 0.7%), lupus nephritis (n=2; 0.7%).

Regarding final etiologic classification, the most common diagnosis was CKD of unknown cause, affecting 81 patients (29.1%), followed by acquired glomerular disease (n=60, 21.6%), hereditary or monogenic kidney disease (n=49, 17.6%), and diabetic kidney disease (n=39, 14.0%).

Table II. Diagnostic evaluation, genetic testing eligibility and final CKD aetiology

	Whole Cohort, n=278
Kidney biopsy	**n (%)**
Done	77 (27.7)
Not done	43 (15.5)
Unavailable	158 (56.8)
Kidney biopsy diagnosis	**n (%)**
IgA nephropathy	18 (6.5)
Diabetic nephropathy	6 (2.2)
ANCA-associated vasculitis	3 (1.1)
Focal segmental glomerulosclerosis	13 (4.7)
Nephronophthisis	1 (0.4)
Amyloidosis	2 (0.7)
Chronic tubulointerstitial nephritis	4 (1.4)
Acute tubular necrosis	1 (0.4)
Mesangial proliferative glomerulonephritis	5 (1.8)
Glomerulosclerosis secondary to hypertension	4 (1.4)
Polyomavirus nephropathy	1 (0.4)
Lupus nephritis	2 (0.7)
Anti-GBM crescentic glomerulonephritis	1 (0.4)
Granulomatous interstitial nephritis secondary to medications	1 (0.4)
Alport Syndrome	1 (0.4)
Inconclusive result	14 (5.0)
Indication for genetic testing	**n (%)**
Yes	124 (44.6)
No	126 (45.3)
Previously tested	28 (10.1)
Genetic testing performed	**n (%)**
Yes	28 (10.1)
Final diagnosis	**n (%)**
Diabetic kidney disease	39 (14.0)
Hypertensive / vascular kidney disease	15 (5.4)
Acquired glomerular disease	60 (21.6)
Hereditary / monogenic kidney disease	49 (17.6)
Non-genetic tubulointerstitial disease	12 (4.3)
Obstructive / urologic kidney disease	16 (5.8)
Systemic disease–related CKD	5 (1.8)
CKD of unknown cause	81 (29.1)
Kidney transplant–related diagnosis	1 (0.4)

3.3 Genetic Testing Eligibility and Uptake

Based on the indications for genetic testing previously described, according to international guidelines, 124 patients (44.6%) met the indications for genetic testing, and only 28 patients (10.1%) in the entire cohort had undergone it, highlighting a substantial gap between eligibility and test utilisation. Among tested patients, no monogenic or complement abnormality was identified in seven patients (25%), followed by no result available in five patients (17.9%), as well as ADPKD (PKD1/2), and with four patients (17.9%) COL4A-related disease.

Among patients fulfilling criteria for genetic testing, biopsy status was frequently unavailable. From 124 patients meeting criteria for genetic testing, 27 (21.8%) had undergone kidney biopsy, 19 (15.3%) had not and 78 (62.9%) had missing biopsy information.

Notably, CKD of unknown cause was the most prevalent diagnosis in eligible patients for genetic testing but without biopsy done (n=14, 73.7%) and among those with missing biopsy data (n=36, 46.2%).

3.4 Clinical profile according to genetic testing indication

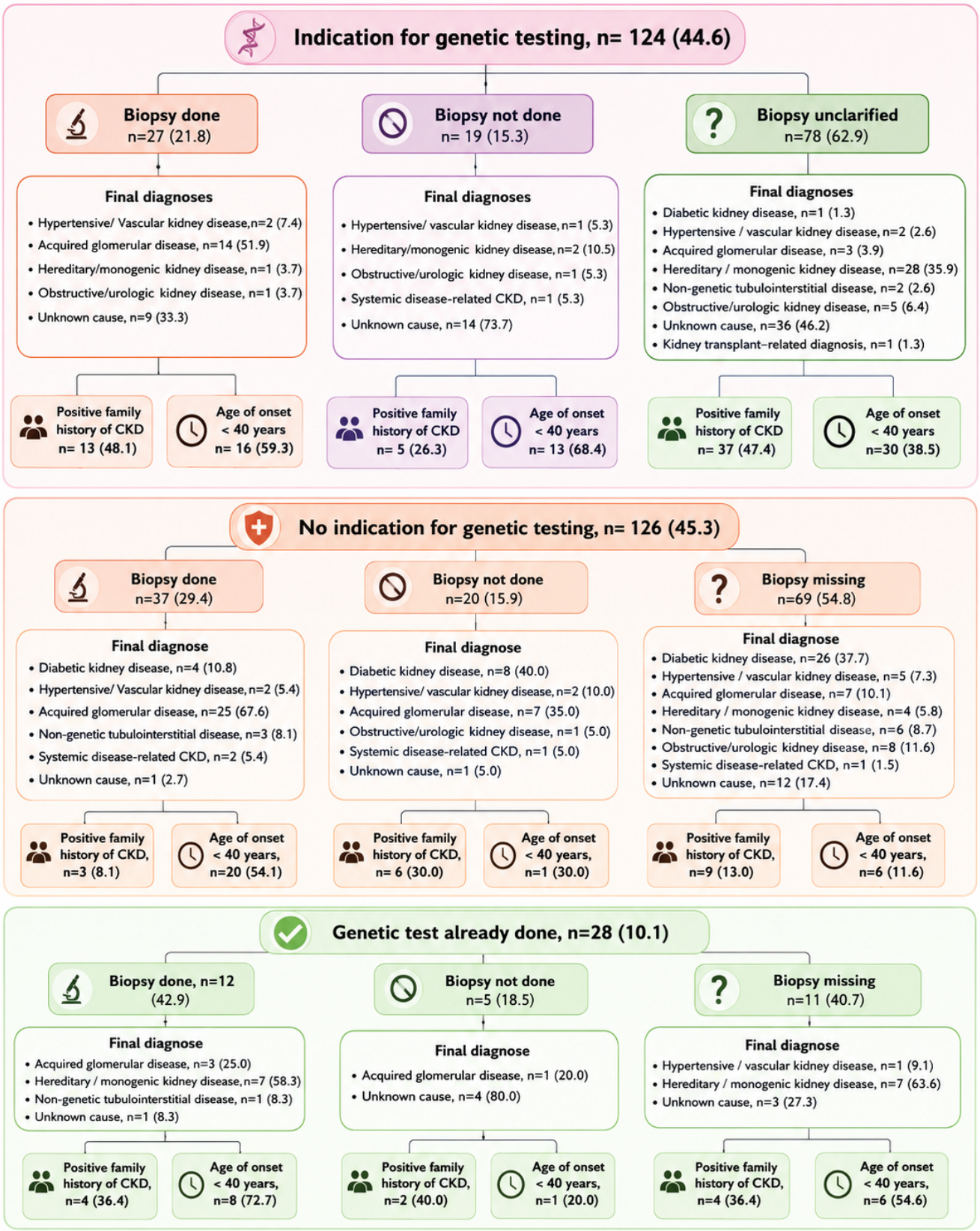
Among patients with an indication for genetic testing and available biopsy data, acquired glomerular disease (n=14, 51.9%) and unknown cause (n=9, 33.3%) were the most frequent final diagnoses.

In this group, clinical features supporting genetic evaluation were common, including positive family history of CKD (n=13, 48.1%) and age of onset below 40 years (n=16, 59.3%).

When considering patients without indication for genetic testing and biopsy done, acquired glomerular disease (n=25, 67.6%) and diabetic kidney disease (n=4, 10.8%) were the most frequent final diagnoses. Nevertheless, biopsy information was also frequently missing in this group (n=69, 54.8%).

3.5 Patients with prior genetic testing

Genetic testing had been performed in 28 patients (10.1%), among these 12 patients (42.9%) biopsy had been performed and was unavailable in 11 patients (40.7%). In patients who had undergone both biopsy and genetic testing the most frequent final diagnosis was hereditary or monogenic kidney disease (n=7, 58.3%), followed by acquired glomerular disease (n=3, 25.0%). Importantly, between patients with genetic testing but without biopsy, CKD of unknown cause remained the most frequent final diagnosis (n=4, 80.0%).


Indication for genetic testing, n= 124 (44.6)
Biopsy done
n=27 (21.8)
Biopsy not done
n= 19 (15.3)
Biopsy unclarified
n=78 (62.9)
Final diagnoses
• Hypertensive/ Vascular kidney disease,n=2 (7.4)
• Acquired glomerular disease, n=14 (51.9)
• Hereditary/monogenic kidney disease, n=1 (3.7)
• Obstructive/urologic kidney disease, n=1 (3.7)
• Unknown cause, n=9 (33.3)
Final diagnoses
• Hypertensive/ vascular kidney disease, n=1 (5.3)
• Hereditary/monogenic kidney disease, n=2 (10.5)
• Obstructive/urologic kidney disease, n=1 (5.3)
• Systemic disease-related CKD, n=1 (5.3)
• Unknown cause, n=14 (73.7)
Final diagnoses
• Diabetic kidney disease, n=1 (1.3)
• Hypertensive / vascular kidney disease, n=2 (2.6)
• Acquired glomerular disease, n=3 (3.9)
• Hereditary / monogenic kidney disease, n=28 (35.9)
• Non-genetic tubulointerstitial disease, n=2 (2.6)
• Obstructive/urologic kidney disease, n=5 (6.4)
• Unknown cause, n=36 (46.2)
• Kidney transplant-related diagnosis, n=1 (1.3)
Positive family history of CKD n= 13 (48.1)
Age of onset < 40 years n= 16 (59.3)
Positive family history of CKD n= 5 (26.3)
Age of onset < 40 years n= 13 (68.4)
Positive family history of CKD n= 37 (47.4)
Age of onset < 40 years n=30 (38.5)
No indication for genetic testing, n= 126 (45.3)
Biopsy done
n=37 (29.4)
Biopsy not done
n=20 (15.9)
Biopsy missing
n=69 (54.8)
Final diagnose
• Diabetic kidney disease, n=4 (10.8)
• Hypertensive/ Vascular kidney disease, n=2 (5.4)
• Acquired glomerular disease, n=25 (67.6)
• Non-genetic tubulointerstitial disease, n=3 (8.1)
• Systemic disease-related CKD, n=2 (5.4)
• Unknown cause, n=1 (2.7)
Final diagnose
• Diabetic kidney disease, n=8 (40.0)
• Hypertensive/ vascular kidney disease, n=2 (10.0)
• Acquired glomerular disease, n=7 (35.0)
• Obstructive/urologic kidney disease, n=1 (5.0)
• Systemic disease-related CKD, n=1 (5.0)
• Unknown cause, n=1 (5.0)
Final diagnose
• Diabetic kidney disease, n=26 (37.7)
• Hypertensive / vascular kidney disease, n=5 (7.3)
• Acquired glomerular disease, n=7 (10.1)
• Hereditary / monogenic kidney disease, n=4 (5.8)
• Non-genetic tubulointerstitial disease, n=6 (8.7)
• Obstructive/urologic kidney disease, n=8 (11.6)
• Systemic disease-related CKD, n=1 (1.5)
• Unknown cause, n=12 (17.4)
Positive family history of CKD, n=3 (8.1)
Age of onset < 40 years, n=20 (54.1)
Positive family history of CKD, n= 6 (30.0)
Age of onset < 40 years, n=1 (30.0)
Positive family history of CKD, n=9 (13.0)
Age of onset < 40 years, n=6 (11.6)
Genetic test already done, n=28 (10.1)
Biopsy done, n=12
(42.9)
Biopsy not done
n=5 (18.5)
Biopsy missing
n=11 (40.7)
Final diagnose
• Acquired glomerular disease, n=3 (25.0)
• Hereditary / monogenic kidney disease, n=7 (58.3)
• Non-genetic tubulointerstitial disease, n=1 (8.3)
• Unknown cause, n=1 (8.3)
Final diagnose
• Acquired glomerular disease, n=1 (20.0)
• Unknown cause, n=4 (80.0)
Final diagnose
• Hypertensive / vascular kidney disease, n=1 (9.1)
• Hereditary / monogenic kidney disease, n=7 (63.6)
• Unknown cause, n=3 (27.3)
Positive family history of CKD, n=4 (36.4)
Age of onset < 40 years, n=8 (72.7)
Positive family history of CKD, n=2 (40.0)
Age of onset < 40 years, n=1 (20.0)
Positive family history of CKD, n=4 (36.4)
Age of onset < 40 years, n=6 (54.6)

Genetic Result among those tested

- No monogenic or complement abnormality identified, n=7 (25.0)
- COL4A-related disease, n=4 (14.3)
- ADPKD (PKD1/PKD2), n=5 (17.9)
- APOL1 high-risk genotype, n=2 (7.1)
- ADTKD (UMOD/MUC1/REN/HNF1B), n=1 (3.6)
- Complement-mediated aHUS-CFHR3-1 homozygous deletion with anti-Factor H antibodies, n=1 (3.6)
- DGKE-related nephropathy (complement-independent TMA), n=1 (3.6)
- Other monogenic kidney disease, n=1 (3.6)
- Hereditary thrombophilia, n=1 (3.6)
- No result available, n=5 (17.9)

Figure 2. Diagnostic aetiology according to genetic testing eligibility and testing uptake

3.6 Subgroup analysis of re-transplant candidates

Of the 59 re-transplant candidates, 39 patients fulfilled criteria for genetic testing, corresponding to 66.1%. Comparing with first-transplant candidates, re-transplant candidates were more likely to met indication for genetic testing (66.1% versus 38.8%; Chi-square test, χ^2=14.01, p<0.001, OR 3.07, 95% CI 1.68-5.62). Re-transplant candidates were also younger at evaluation, with median age 55 versus 59 years, p=0.102 and started kidney replacement therapy earlier, with a median age 35 versus 55 years (p<0.001).

Regarding dialysis modality, 64.4% (n=38) of re-transplant candidates were on haemodialysis, compared with 80.0% (n=172) among first-transplant candidates (Chi-square test, χ^2=6.29, p=0.012).

In the re-transplant subgroup, the median age at disease onset was 27 years. A positive family history of kidney disease was reported in 11 patients (30.5%) while family history data were unavailable in 25 patients (42.4%).

Re-transplant candidates (n=59)
Genetic testing indicated: 39/59 (66.1%)
Median age at evaluation: 55 years
Median age at kidney disease onset: 27 years
Median age at KRT initiation: 35 years
Haemodialysis: 38 (64.4%)
Positive family history of CKD: 11 (30.5%)
Family history unavailable: 25 (42.4%)

	Re-transplant candidates (n=59)	First-transplant candidates (n=219)
Genetic testing indicated	39/59 (66.1%)	85/219 (38.8%)
Median age at evaluation	55 years	59 years
Median age at KRT initiation	35 years	55 years
Haemodialysis	38 (64.4%)	172 (80.0%)

Figure 3**.** Clinical profile of re-transplant candidates and comparison with first-transplant candidates

4. Discussion

4.1 Key findings

This retrospective pre-transplant cohort revealed a persistent diagnostic gap, based on the high burden of uncertain aetiology. In fact, CKD of unknown cause was the most frequent final classification, while key diagnostic elements were often unavailable (biopsy status in 56.8% and family history in 25.5%) and a marked mismatch between guideline-based eligibility for genetic testing (44.6%) and real-world test uptake. These findings are consistent with current guidelines and studies, which emphasize that genetic evaluation is increasingly central to etiologic clarification, prognostic stratification and transplant planning in CKD. It also reinforces the premise that CKD aetiology is often difficult to establish due to nonspecific and overlapping phenotypes and that genetic testing is increasingly positioned as an integral component of the diagnostic arsenal, especially when conventional approaches are limited [4, 7].

4.2 Genetic testing indication and the implementation gap

Based on KDIGO criteria, nearly half of patients met indications for genetic testing, highlighting the high prevalence of clinical features suggestive of hereditary or monogenic kidney disease in this population. However, only 10.1% of the entire cohort had undergone genetic

testing, revealing a marked discrepancy between eligibility for genetic testing and their utilisation. This gap may reflects a combination of factors, including limited access to genetic testing, lack of systemic referral pathways, incomplete phenotyping, and historical reliance on clinical or histopathologic diagnoses alone [16, 17]. Although this picture doesn't fit to our centre, the handicaps should be tracked.

The magnitude of missing diagnostic information in our cohort, mainly in kidney biopsy, is a direct contributor to the high rate of "unknown cause" classification and may reduce referral for genetic testing and counselling. In more than half of patients, biopsy status could not be established from available records and among those with biopsy performed, inconclusive results were not rare. This is of clinically relevant because advanced CKD can reduce biopsy yield due to chronic scarring and nonspecific changes, and biopsy is not always feasible in late-stage disease [4, 14].

4.3 Interrelationships among variables in the study cohort

The results indicate a complex interplay among kidney biopsy findings, indications for genetic testing, and final etiologic classification. Among patients with an indication for genetic testing who underwent biopsy, acquired glomerular disease was the most frequent diagnosis. This overlap is anticipated, as genetic kidney disease can mimic acquired conditions, and histopathology may reflect injury patterns rather than underlying aetiology [7, 14].

International guidelines emphasize that genetic heterogeneity and phenotypic overlap limit the effectiveness of phenotype- or biopsy-driven diagnoses and therefore support the use of broader kidney-focused gene panels in many clinical scenarios [7, 14].

In contrast, among patients who had already undergone genetic testing, hereditary or monogenic kidney disease was the predominant final diagnosis, mainly in cases with missing or inconclusive biopsy data. This finding supports the increasing recognition that genetic testing can resolve diagnostic uncertainty in cases labelled as CKD of unknown aetiology, particularly when combined with clinical features such as early disease onset or a positive family history.

Our findings are consistent with published cohorts, the proportion of our patients meeting guideline indications is consistent with a high underlying likelihood of genetic contributors in our selected cohort population. In adults with CKD of unknown origin, massively parallel sequencing based multigene panels provided a genetic diagnosis in 17% and led to at least one clinical consequence in 73% of patients [12]. The harmony between clinical in our cohort and the demonstrated yield in studies supports clinical plausibility that our region may be under-diagnosing monogenic disease [12].

Beyond single-cohort studies, broader evidence also supports meaningful diagnostic yield and clinical impact of genetic testing in adults with CKD. Diagnostic yield varies across adult CKD populations but is consistently higher in patients with family history and extrarenal features [18, 19]. Prospective real-world implementation studies using broad kidney gene panels have shown that positive findings frequently led to new or reclassified diagnoses and may change management, reinforcing the clinical actionability of genetic testing [20].

4.4 Clinical implications for pre-transplant evaluation

The transplant setting amplifies the importance of etiologic clarity. In our cohort, most patients were receiving kidney replacement therapy at this time, it is specifically the stage at which an uncertain aetiology can compromise future evaluation, such as recurrence-risk counselling, donor selection and targeted surveillance. This raises an important question: what are we missing when CKD reaches the transplant pathway?

In fact, monogenic diagnoses can inform transplant evaluation and support better therapeutic choices, but to do so, it is necessary to overcome barriers, including clinician education, test selection, and interpretation workflows [11]. Evidence from transplant-focused studies further shows that selective testing strategies in transplant candidates can yield clinically meaningful results and change evaluation steps [21].

The burden of missing key phenotypic elements in our records is itself a major result aligned with our second aim. This is highly relevant because both KDIGO and ERA consensus approaches systematically reassesses history (incorporating pedigree), extrarenal features and targeted imaging to maximize diagnostic yield and avoid false negatives or uninterpretable results [4, 7, 14].

In applied and clinical terms, our data explores standardized pre-test phenotyping checklists that could be implemented into transplant and advanced CKD workflows on a routine clinical practice, as shown in Figure 4.

Indeed, accurate etiologic diagnosis is particularly critical in the pre-transplant setting, where genetic findings may influence donor selection, recurrence risk, post-transplant management and family counselling [7, 21-23]. The high prevalence of undetermined aetiology observed in our cohort raises concerns regarding missed opportunities for personalized care and risk stratification [4, 24].

Additionally, the underutilization of kidney biopsy and genetic testing suggests that many patients progress to transplantation without a definitive diagnosis [7, 25]. Emerging as an opportunity to change this reality, implementing structured algorithms that integrate clinical features,

histopathology and genetic testing aligned with KDIGO and international recommendations, could substantially improve diagnostic precision and transplant planning [5, 11, 26]. In cohorts of patients who had undergone kidney biopsy, genetic testing resulted in a revised understanding of disease mechanism in 54% of cases and influenced treatment decisions in at least 26% [27].

In progressive CKD without distinctive imaging features, kidney biopsy may yield limited etiologic information, especially when performed late in the disease course, as nonspecific tubulointerstitial fibrosis and glomerulosclerosis may obscure pathognomonic findings [28]. In contrast, genetic testing can be performed at any disease stage, including pre-symptomatically, and offers a non-invasive and increasingly cost-effective diagnostic alternative [28]. A confirmed genetic diagnosis may also facilitate earlier recognition of extrarenal manifestations and enable preventive strategies to mitigate the risk of future severe complications [28]. In some instances, genetic testing may even reveal previously unrecognized genetic aetiologies of kidney disease. Notably, the underlying cause of end-stage renal disease (ESRD) remains unknown or presumed in a substantial proportion of patients on kidney transplant waiting lists [28].

Testing for genetic kidney diseases encompasses more than 150 rare monogenic disorders and has opened new avenues for diagnosis and management for patients and their families [29]. A clinical study demonstrated that implementing a structured referral workflow combined with multidisciplinary analyses significantly optimized the diagnosis of genetic kidney disorders, achieving a diagnostic yield of 67% and leading to changes in the initial clinical diagnosis in 19% of cases [30, 31]. In fact, many patients reach the pre-transplant pathway without a definitive aetiological diagnosis, suggesting the possibility that a monogenic kidney disease has been overlooked. Notably, in pre-transplant context is extremely important timely genetic testing, particularly when living donation is being considered. It is also essential this diagnostic gap in a specific group, women of reproductive age, as pregnancy may reveal previously unrecognized CKD through hypertension, proteinuria or decline kidney function.

From a clinician perspective, the highest perceived clinical utility of genetic testing has been reported for CKD of unknown aetiology, as well as for cystic and glomerular kidney diseases. These findings indicate that general nephrologists recognize the value of genetic testing, particularly in clinical contexts with a higher likelihood of identifying a genetic cause [32]. Consequently, broader adoption of genetic testing may be facilitated by an improved understanding of the genetic mechanisms underlying kidney function decline [32].

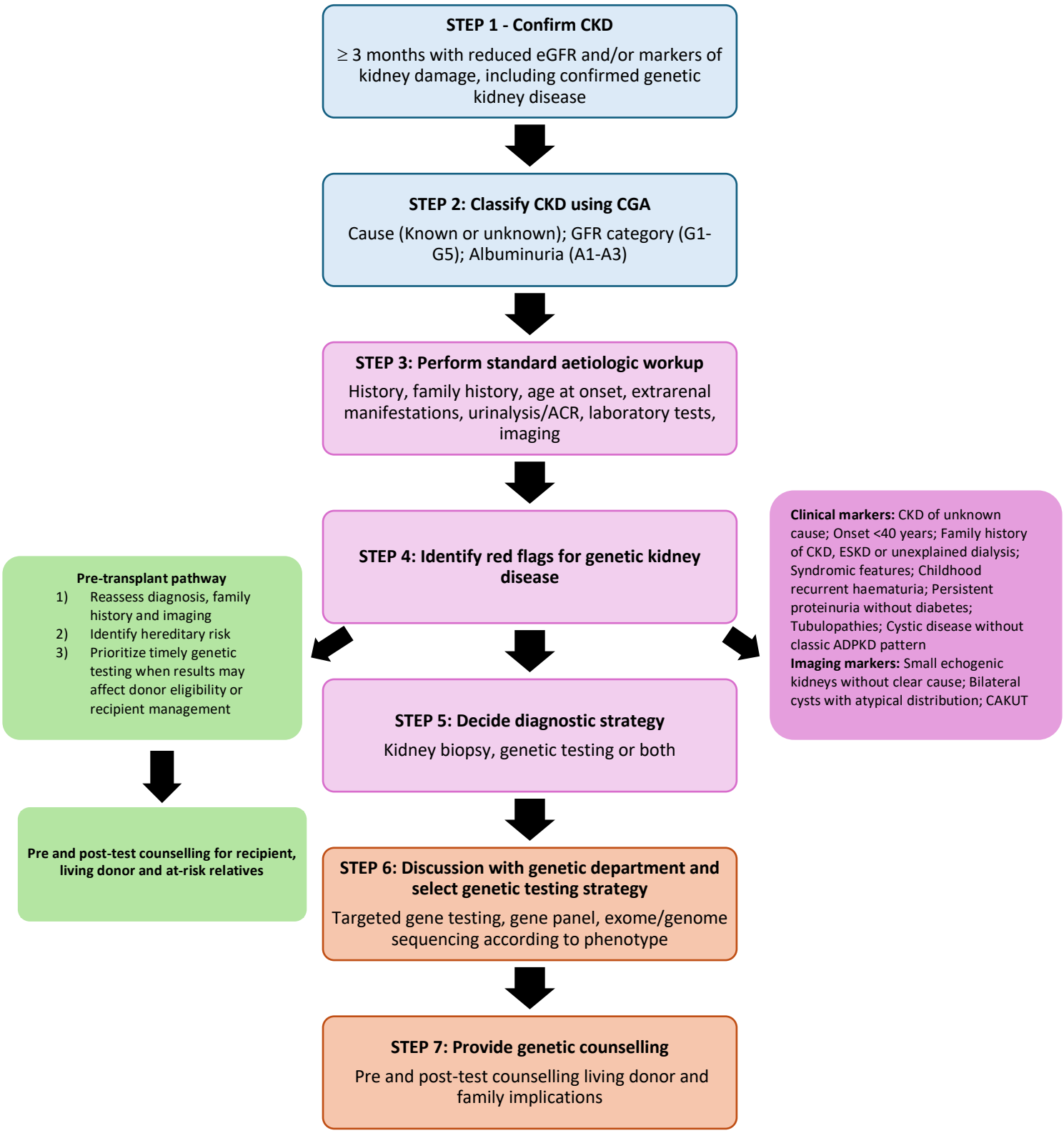


Figure. 4 Proposed diagnostic algorithm for CKD workup and genetic testing

Abbreviations: ACR, albumin-to-creatinine ratio; ADPKD, autosomal dominant polycystic kidney disease; CAKUT, congenital anomalies of the kidney and urinary tract; CGA, Cause-GFR-Albuminuria; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease.

4.5 Regional relevance and future directions

From a regional health-system perspective, our findings support the development of an integrated diagnostic pathway that explicitly associates structured phenotyping, decision-making on biopsy feasibility and yield, and early genetic testing when guideline indications are met or when biopsy is unavailable or uninformative. Recent framework efforts designed to standardize genetic testing eligibility and panel selection in CKD aim to promote equitable access and earlier diagnosis and emphasis on integrating genetics into routine nephrology care [11, 26].

Essentially, developing a more precise understanding of CKD aetiology in our region is essential for optimizing early detection strategies, refining referral pathways for genetic evaluation and aligning transplant practices with contemporary precision medicine approaches [4, 7]. Our findings provide a foundation for the development of region-specific protocols that incorporate genetic testing earlier in the disease course, particularly in patients with early onset, family history or atypical presentations [11, 26].

As a future perspective, the creation of an app-based clinical workflow could support nephrologists in rapidly and intuitively identifying CKD patients with indications for genetic testing. By integrating KDIGO-based red flags and ERA recommendations into a standardized decision-support tool, this approach could reduce heterogeneity in referral practices and stimulate earlier access to genetic evaluation.

This digital workflow could represent a step toward redefining the referral paradigm for genetic testing in nephrology, promoting earlier, more equitable and clinically driven access to genomic diagnosis, particularly important in a setting of living-donation.

4.6 Strengths and limitations

The main strength of this study is the analysis of a real-word cohort of adults with CKD referred for pre-transplant, reinforcing underrepresented information along patient path. The use of guideline-based criteria for eligibility for genetic testing verifies the clinical relevance and validity of the results.

Importantly, this work provides a practical framework that could be expanded to other clinical centres, be extended over time, including in different populations to estimate the global load of the genetic dimension of CKD.

Nevertheless, limitations arise, including the retrospective design and the missing data, mainly related to biopsy findings and family history of kidney disease; both may lead to an underestimation of the true prevalence of genetic kidney disease.

5. Conclusion

In conclusion, this is the first study in Portugal to investigate whether the high incidence of chronic kidney disease can be explained by underlying genetic causes. Importantly, this study represents one of the first efforts to characterize the phenotypic spectrum of patients referred for pre-transplant evaluation. By assessing these clinical features in a real-world national cohort, our results highlight the heterogeneity of inherited kidney disease presentation and reinforce that the diagnostic yield and phenotypic distribution of genetic kidney disorders may vary according to population background. Our study highlights a significant diagnostic gap facing kidney transplant candidates, with many of them fulfilling criteria for genetic testing but remaining untested. Notably, re-transplant candidates appear to represent a particularly high-risk group requiring a more refined systematic etiological clarification to better assess the risk of recurrence. This process is especially relevant in the context of living donation, where unidentified genetic disease may have direct implications for donor safety. Integrating Medical Genetics, genetic testing and genetic counselling into transplant pathways may therefore improve diagnosis, guide safer donor selection, and optimize transplant outcomes.

In Portuguese population, the CKD public health charge should motive a broader investment in genetic epidemiology.

6. References

1. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. Kidney Int Suppl (2011). 2022;12(1):7-11.
2. A systematic EU approach to chronic kidney disease [Internet]. European Parliament. 2022.
3. August P. Chronic Kidney Disease — Another Step Forward. New England Journal of Medicine. 2023;388(2):179-80.
4. Halbritter J, Figueres L, Van Eerde AM, et al. Chronic Kidney Disease of unexplained cause (CKDx): a consensus statement by the Genes & Kidney Working Group of the ERA. Nephrol Dial Transplant. 2025;40(12):2390-400.
5. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105(4s):S117-s314.
6. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179-84.
7. Köttgen A, Cornec-Le Gall E, Halbritter J, et al. Genetics in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney International. 2022;101(6):1126-41.
8. Registo Nacional de Doença Renal Crónica [Internet]. 2023.
9. Hoekstra MWF, Boenink R, Bonthuis M, et al. The ERA Registry Annual Report 2023: epidemiology of kidney replacement therapy in Europe, with a focus on age comparisons. Clinical Kidney Journal. 2026;19(5).
10. Biópsia Renal Percutânea- Indicações para o utente e Família [Internet]. 2022.
11. Franceschini N, Feldman DL, Berg JS, et al. Advancing Genetic Testing in Kidney Diseases: Report From a National Kidney Foundation Working Group. American Journal of Kidney Diseases. 2024;84(6):751-66.
12. de Haan A, Eijgelsheim M, Vogt L, et al. Genetic testing in a national cohort of adults with chronic kidney disease of unknown origin. Nephrol Dial Transplant. 2024.
13. Santos-Araújo C, Mendonça L, Carvalho DS, et al. Twenty years of real-world data to estimate chronic kidney disease prevalence and staging in an unselected population. Clin Kidney J. 2023;16(1):111-24.
14. Knoers N, Antignac C, Bergmann C, et al. Genetic testing in the diagnosis of chronic kidney disease: recommendations for clinical practice. Nephrol Dial Transplant. 2022;37(2):239-54.
15. Shen EC, Srinivasan S, Passero LE, et al. Barriers and Facilitators for Population Genetic Screening in Healthy Populations: A Systematic Review. Frontiers in Genetics. 2022;13.
16. Thomas CP, Freese ME, Ounda A, et al. Correction: Initial experience from a renal genetics clinic demonstrates a distinct role in patient management. Genetics in Medicine. 2021;23(10):2017-9.
17. Schott C, Arnaldi M, Baker C, et al. Implementation of a Kidney Genetic Service Into the Diagnostic Pathway for Patients With Chronic Kidney Disease in Canada. Kidney International Reports. 2025;10(2):574-90.

18. Schott C, Lebedeva V, Taylor C, et al. Utility of Genetic Testing in Adults with CKD: A Systematic Review and Meta-Analysis. Clinical Journal of the American Society of Nephrology. 2025;20(1):101-15.
19. Connaughton DM, Hildebrandt F, Groopman E, Gharavi AG, Mallett A. Supplementary Data for the Utility of Genetic Testing in Adults with Chronic Kidney Disease: Systematic Review and Meta-analysis. Clinical Journal of the American Society of Nephrology; 2024.
20. Dahl NK, Bloom MS, Chebib FT, et al. The Clinical Utility of Genetic Testing in the Diagnosis and Management of Adults with Chronic Kidney Disease. Journal of the American Society of Nephrology. 2023;34(12):2039-50.
21. Nissaisorakarn P, Fadakar PK, Safa K, et al. A pragmatic approach to selective genetic testing in kidney transplant candidates. Front Transplant. 2023;2:1342471.
22. Hays T, Groopman EE, Gharavi AG. Genetic testing for kidney disease of unknown etiology. Kidney Int. 2020;98(3):590-600.
23. Ottlewski I, Münch J, Wagner T, et al. Value of renal gene panel diagnostics in adults waiting for kidney transplantation due to undetermined end-stage renal disease. Kidney Int. 2019;96(1):222-30.
24. Mallawaarachchi AC, Fowles L, Wardrop L, et al. Genomic Testing in Patients with Kidney Failure of an Unknown Cause: A National Australian Study. Clin J Am Soc Nephrol. 2024;19(7):887-97.
25. Groopman EE, Marasa M, Cameron-Christie S, et al. Diagnostic Utility of Exome Sequencing for Kidney Disease. New England Journal of Medicine. 2019;380(2):142-51.
26. Du A, Lemay K, Bagga A, et al. Framework for standardized genetic testing recommendations for chronic kidney disease in Ontario. Genetics in Medicine Open. 2025;3:103442.
27. Snoek R, van Jaarsveld RH, Nguyen TQ, et al. Genetics-first approach improves diagnostics of ESKD patients <50 years old. Nephrol Dial Transplant. 2022;37(2):349-57.
28. Thomas CP, Freese ME, Ounda A, et al. Initial experience from a renal genetics clinic demonstrates a distinct role in patient management. Genet Med. 2020;22(6):1025-35.
29. Elhassan EAE, Murray SL, Connaughton DM, et al. The utility of a genetic kidney disease clinic employing a broad range of genomic testing platforms: experience of the Irish Kidney Gene Project. J Nephrol. 2022;35(6):1655-65.
30. Becherucci F, Landini S, Palazzo V, et al. A Clinical Workflow for Cost-Saving High-Rate Diagnosis of Genetic Kidney Diseases. Journal of the American Society of Nephrology. 2023;34(4):706-20.
31. Wu Y, Jayasinghe K, Stark Z, et al. Genomic testing for suspected monogenic kidney disease in children and adults: A health economic evaluation. Genetics in Medicine. 2023;25(11):100942.
32. Mrug M, Bloom MS, Seto C, et al. Genetic Testing for Chronic Kidney Diseases: Clinical Utility and Barriers Perceived by Nephrologists. Kidney Med. 2021;3(6):1050-6.