Article:
Cornec-Le Gall, E. orcid.org/0000-0003-1958-4459 and Ong, A.C.M. orcid.org/0000-0002-7211-5400 (2025) Genetic testing in autosomal dominant polycystic kidney disease: why it matters in 2025. Clinical Kidney Journal, 18 (Supplement 2). ii17-ii25. ISSN: 2048-8505

https://doi.org/10.1093/ckj/sfaf331

Clinical Kidney Journal, 2025, vol. 18, Suppl 2, ii17–ii25

https://doi.org/10.1093/ckj/sfaf331
Advance Access Publication Date: 31 October 2025
CKJ Review

CKJ REVIEW

Genetic testing in autosomal dominant polycystic kidney disease: why it matters in 2025

Emilie Cornec-Le Gall [1,2] and Albert C.M. Ong [3,4]

[1]Service de Néphrologie, Hémodialyse et Transplantation Rénale, Centre de référence MARHEA, Filière ORKID, CHRU Brest, Brest, France, [2]University Brest, Inserm, UMR 1078, GGB, Brest, France, [3]Academic Nephrology, Department of Infection, Immunity and Cardiovascular Disease, Division of Clinical Medicine, School of Medicine and Population Health, Faculty of Health, University of Sheffield, Sheffield, UK and [4]Sheffield Kidney Institute, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK

Correspondence to: Emile Cornec-Le Gall; E-mail: emilie.cornec-legall@chu-brest.fr, Albert C.M. Ong; E-mail: a.ong@sheffield.ac.uk

ABSTRACT

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic cause of kidney failure globally, and a significant cause of morbidity and mortality. It is now recognized that it may result from both major and minor genes with associated differences in disease penetrance, symptom burden and clinical outcomes. Genetic testing is now readily available to discriminate between different genotypes and is being increasingly utilized for diagnostic and prognostic indications. In this short review, we summarize the reasons why testing should become part of standard care for ADPKD patients where available and highlight some current limitations and challenges to testing. Defining the genetic landscape in ADPKD for all ethnic groups will be key to the future development and deployment of individualized patient-centered management in this condition.

Keywords: ADPKD, genetic testing, precision nephrology, prognosis, variant-specific therapy

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) affects 1 in 1000 to 1 in 2500 individuals and is responsible for up to 10% of kidney failure cases in developed countries. Although the disease has long been associated with pathogenic variants in *PKD1* and *PKD2*, recent advances in molecular diagnostics have uncovered a broader genetic landscape, with now seven additional "minor genes" associated with the ADPKD spectrum. Moreover, the increasing use of genetic testing has enhanced the recognition of phenocopies—conditions mimicking ADPKD but caused by distinct genetic mechanisms. This expanded understanding has reshaped both the classification and management of ADPKD.

Despite the genetic basis of ADPKD, routine genetic testing has not yet been universally adopted in clinical nephrology. Concerns regarding cost, availability and interpretation persist. However, the context is changing. With improved sequencing platforms, decreasing costs and growing clinical utility, there is a strong case for broader implementation of genetic testing.

This review arises from a pro–con session on genetic testing in ADPKD at the 2025 European Renal Association meeting. The first author argues for systematic, judicious testing supported by 10 evidence-based points, whereas the last author emphasizes current limitations and practical challenges in cystic kidney diseases.

Received: 10.9.2025; accepted: 27.10.2025

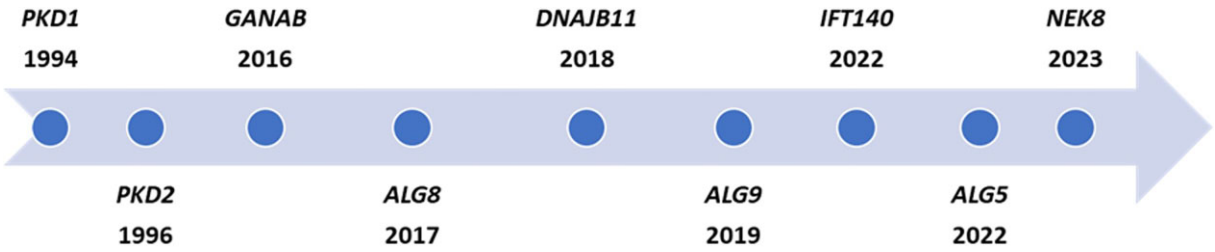

Figure 1: Chronological expansion of the ADPKD gene spectrum. Schematic timeline illustrating the progressive discovery of genes implicated in ADPKD.

GENETICS IN ALL ADULTS WITH ADPKD: YES!

Because ADPKD is a genetic disease

The name itself underscores the fundamental rationale for testing: ADPKD is a genetically defined disorder.

PKD1 and *PKD2* alone account for approximately 90% of genetically resolved cases, with *PKD1* pathogenic variants typically conferring a more severe clinical phenotype. *PKD1* is located on chromosome 16 and encodes polycystin-1 (PC1), a large N-linked glycoprotein expressed at the primary cilium [1]. *PKD2*, on chromosome 4, encodes polycystin-2 (PC2), a calcium-permeable channel that interacts with PC1 [2]. Both proteins function in the ciliary membrane and play key roles in mechanosensation and intracellular calcium signaling.

There is strong evidence that PC1 and PC2 interact to form a heterotetrameric complex composed of one PC1 and three PC2 subunits, as revealed by cryo-EM data [3]. This interaction is thought to be essential for proper maturation, trafficking and function of both proteins at the cilium [4]. ADPKD is classified as a ciliopathy, and several signaling pathways likely relevant to cystogenesis—including calcium, cAMP, G-protein, and possibly Wnt and planar cell polarity signaling—are linked to ciliary function. However, the precise physiological role of the polycystin complex in cilia remains incompletely understood. Evidence suggests that the polycystin complex may act as a mechanosensor, a receptor or a regulator of ciliary signaling [5].

Over the past decade, additional genes associated with ADPKD-like phenotypes have been identified (Fig. 1). These include *GANAB* and *DNAJB11*, involved in glycoprotein folding and endoplasmic reticulum quality control, as well as *ALG8*, *ALG9*, *ALG5* and others in the glycosylation machinery [6–10]. These genes are now recognized to contribute to the spectrum of atypical ADPKD or overlapping syndromes such as ADPLD and autosomal dominant tubulointerstitial kidney disease (ADTKD) [11]. In addition to these N-glycosylation–associated cystic genes, two genes previously associated with recessively inherited ciliopathies are now recognized as part of the ADPKD spectrum: monoallelic predicted loss-of-function variants in *IFT140* cause a mild form of ADPKD and account for ~2% of cases, whereas specific missense variants in the kinase domain of *NEK8* can cause a severe, early-onset form [12, 13].

This expanded genetic landscape has blurred the boundaries between cystic kidney diseases previously considered distinct.

Modern sequencing technologies have substantially improved the analysis of these genes; molecular testing now increasingly complements clinical criteria, shifting the diagnostic paradigm from clinical suspicion to molecular confirmation. The 2025 KDIGO guidelines explicitly recommend a nomenclature integrating gene identity, acknowledging the diversity within the ADPKD spectrum [14].

In clinical practice, testing can be performed using targeted next-generation sequencing panels, exome sequencing or genome sequencing depending on local resources [15]. Once a causal variant is defined within a family, Sanger analysis of just the pathogenic variant usually is sufficient to determine whether at-risk family members are affected. It should be noted, however, that *PKD1* poses specific technical challenges due to its large size, high GC content, and partial duplication (exons 1–33), which share >97% sequence identity with six pseudogenes on chromosome 16. These regions may not be fully captured or reliably mapped by exome sequencing, and targeted enrichment or complementary Sanger sequencing—particularly of exon 1—may be required to achieve complete coverage. These technical limitations should be carefully considered when interpreting a result in which no pathogenic or likely pathogenic variant is identified in *PKD1* [15].

To differentiate ADPKD from its phenocopies

Not all patients with bilateral renal cysts have a classical form of ADPKD. Genetic testing enables clinicians to distinguish ADPKD from phenocopies—conditions that mimic the phenotype but follow different inheritance patterns, prognoses and management implications. For example, patients with *OFD1*, *HNF1B* or *COL4A1* pathogenic variants may present with cystic kidneys yet have syndromic or systemic involvement requiring tailored care (Fig. 2) [15].

Data from the Genkyst cohort—a nationwide French registry of over 3900 individuals—highlight the frequency of phenocopies in real-world practice. More than 20 distinct genes have been identified in patients initially diagnosed with ADPKD based on clinical or radiological grounds [16]. These include genes associated with ADTKD, nephronophthisis or other ciliopathies.

Failure to recognize these entities can lead to mismanagement, misinform reproductive counseling and delay appropriate surveillance. Genetic confirmation enhances diagnostic precision, allowing tailored follow-up and counseling.

Because genetics helps stratify prognosis in ADPKD

Genotype is a key predictor of disease progression in ADPKD. It has long been recognized that patients with *PKD2* variants tend to experience a milder clinical course and reach kidney failure later than those with PKD1 variants [17]. Later research clarified that not only the gene but also the type of *PKD1* variant influences disease severity [18]. Truncating variants in *PKD1* are associated with a significantly earlier onset of kidney failure compared with non-truncating ones, a finding confirmed in multiple independent cohorts [19]. To provide individual prognosis information, the PROPKD score (predicting renal outcome

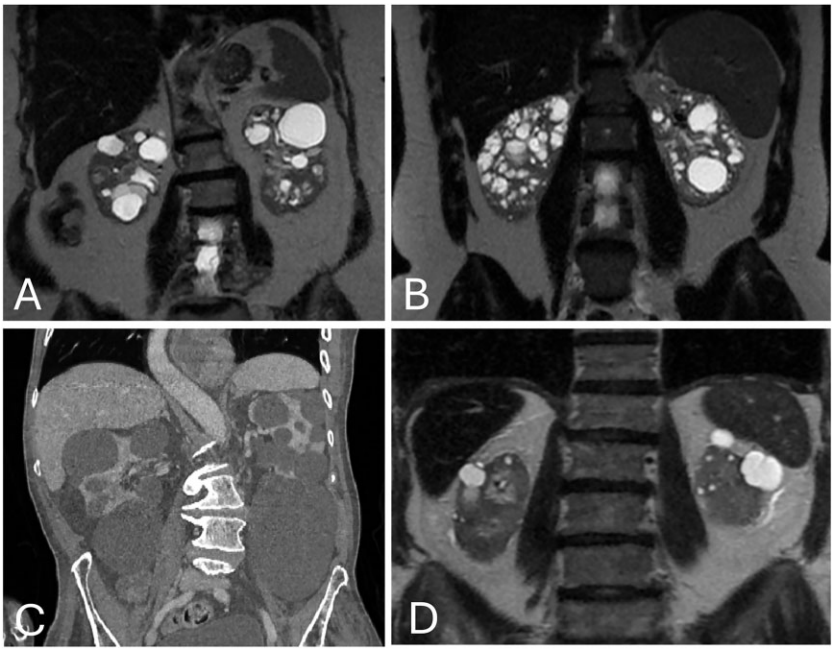

Figure 2: Examples of ADPKD phenocopies. (**A**) T2-weighted MRI of a 65-year-old woman (eGFR 45 mL/min/1.73 m²) with a large *HNF1B* deletion. (**B**) T2-weighted MRI of a 37-year-old woman (eGFR 69 mL/min/1.73 m²) with a frameshift variant in *OFD1* (c.710dup). (**C**) Contrast-enhanced computed tomography of a 68-year-old man (eGFR 56 mL/min/1.73 m²) with a frameshift variant in *COL4A1* (c.1462del). (**D**) T2-weighted MRI of a 78-year-old man (eGFR 10 mL/min/1.73 m²) with a missense variant in *UMOD* (c.184A>C; p.Thr62Pro).

in ADPKD) was subsequently developed [20]. This score combines genetic data with clinical information—onset of hypertension before age 35 years, urologic complications before age 35 years and sex—to stratify patients into low-, intermediate- or high-risk categories for disease progression. This stratification has practical clinical consequences: it informs the intensity of follow-up, eligibility and timing for therapeutic interventions, and anticipatory transplant planning. Notably, patients classified as low-risk by the PROPKD score did not show clear benefit from tolvaptan in a *post hoc* analysis of the TEMPO 3:4 randomized controlled trial [21]. This suggests that the PROPKD score can be a useful tool to enrich clinical trial cohorts with patients at higher risk of rapid progression, thereby maximizing the likelihood of demonstrating a treatment effect. It is also a valuable instrument for selecting appropriate candidates for therapeutic interventions in routine care.

Importantly, accurate prognostication in ADPKD ideally requires a holistic approach that takes advantage of all available elements. These include the Mayo imaging classification [Mayo Imaging Class (MIC)] relying on height-adjusted total kidney volume (TKV), genetic information and the PROPKD score, family history of kidney failure and estimated glomerular filtration rate (eGFR) [20, 22]. No single tool provides a complete picture; instead, their integration supports more precise risk stratification, therapeutic planning and timing of interventions [23].

Because it informs therapeutic decision-making

In some cases, genetic findings can alter therapeutic decisions entirely. For instance, pathogenic variants in *OFD1*, which can mimic ADPKD clinically (Fig. 2), are associated with a X-linked inherited ciliopathy without supportive evidence for tolvaptan efficacy. Similarly, patients with *ALG9*-related disease may have enlarged kidneys at a young age, yet there is currently no evidence supporting the benefit of tolvaptan or even the prognostic utility of TKV-based tools in these individuals. Individuals with *IFT140* variants may also present with kidney enlargement, but available data suggest a generally favorable prognosis, further underscoring the importance of accurate molecular diagnosis when considering disease-modifying therapies [24].

Because knowing the variant in one family member creates a diagnostic tool for others

Once a pathogenic variant has been identified in an affected family member, cascade testing can be performed rapidly and cost-effectively. In many cases, a single Sanger sequencing reaction is sufficient to confirm or exclude the presence of the familial variant in at-risk relatives. This facilitates early diagnosis in asymptomatic carriers and confidently rules out disease in unaffected individuals. The emotional and clinical impact of a clear molecular diagnosis is significant—it replaces uncertainty with clarity and informs both clinical surveillance and life planning. In countries with access to genetic testing, patients should be able to choose between imaging and genetic information, with decisions made through shared decision-making.

KDIGO 2025 acknowledges targeted familial testing as one of the approaches in genetically resolved families, reinforcing its practical value [15]. Importantly, exclusion of the diagnosis based on imaging alone is only possible after the age of 30 years in individuals at risk of ADPKD-*PKD1*, and after the age of 40 years in individuals at risk of ADPKD-*PKD2* [25]. Moreover, imaging-based diagnostic criteria—as well as imaging-based prognostic tools—are only validated in typical ADPKD due to *PKD1* or *PKD2* variants. In all other genetic contexts, molecular testing is the only reliable approach to confirm or exclude the disease.

To support selection of living kidney donors

The selection of living kidney donors from families affected by ADPKD is a frequent and challenging scenario. In younger individuals—particularly under 30 years of age, where no risk can be taken—genetic testing is indispensable. A second situation concerns equivocal imaging findings in mid-adulthood, such as the presence of multiple cysts in a potential donor. In this case, declining donation without further clarification risks losing a valuable opportunity, as the donor may in fact be unaffected. Genetic testing can resolve this uncertainty, and in the case of the identification of a small number of cysts in the candidate donor, a panel of PKD genes may be preferable to testing only for the known familial variant, to exclude other genetic forms of PKD. Importantly, this presupposes that a genetic diagnosis has already been established in the recipient, or another affected family member, which highlights the need to anticipate and organize testing early, ideally before the transplant evaluation process. KDIGO guidelines underscore the importance of excluding ADPKD in potential living-related donors and recognize the central role of genetic testing in both situations [14].

To enable informed genetic counseling and reproductive choices

Individuals with ADPKD who are of reproductive age face complex decisions regarding family planning. Genetic confirmation provides clarity that is essential for accurate counseling, including discussion of recurrence risks, inheritance patterns and available approaches to avoid transmission of the disease, such as preimplantation genetic testing (PG testing).

KDIGO 2025 highlights the need to offer appropriate counseling and all available options to affected individuals [15]. Importantly, a confirmed genetic diagnosis in the affected parent is a prerequisite for any intervention involving genetic selection. Anticipation is therefore critical: the familial variant must be identified in advance to make PGT feasible. While PGT is not yet accessible in all countries, its availability is steadily increasing [26]. Genetic testing thus may empower patients to make informed, autonomous decisions about their reproductive future.

To understand intrafamilial variability in disease severity

In clinical practice, significant phenotypic heterogeneity is often observed within families affected by ADPKD. While some individuals may remain asymptomatic for decades, others progress to kidney failure in early adulthood or before. Genetic testing can provide insights into the underlying causes of this variability.

One such mechanism is somatic mosaicism, in which only a subset of the individual's cells carries the pathogenic variant because a de novo mutation arose just after the formation of the egg at an early embryonic stage. Mosaicism can result in a milder or atypical phenotype in the proband and may go undetected using standard testing approaches. In ADPKD, low-level mosaicism has been reported in clinically affected individuals and can pose challenges in diagnosis and familial interpretation. A study of 20 ADPKD families with mosaicism, all involving PKD1, found that 5 had germline transmission while 15 were sporadic [27]. Disease severity was generally milder in mosaic individuals than in their affected offspring, though phenotypes varied.

Additionally, rare cases of biallelic inheritance involving pathogenic variants on both *PKD1* or *PKD2* alleles have been reported [11, 28–31]. These typically involve the co-inheritance of a hypomorphic allele from the unaffected parent and a pathogenic variant from the affected parent, leading to very early-onset ADPKD, which can be severe or even embryonically lethal. When such severe cases occur, identifying the underlying cause is essential to guide counseling for future pregnancies. Furthermore, rare cases of digenic disease have also been reported (e.g. co-inheritance of a *PKD1* and a *PKD2* variant) [32, 33].

Genetic testing helps elucidate these mechanisms and supports more accurate prognostication and genetic counselling.

Because it is increasingly available and affordable

Genetic testing is no longer a niche investigation or prohibitively expensive. In many healthcare systems, including several European countries, targeted gene panels and exome sequencing are reimbursed by health insurance. The reagent and sequencing costs for a cystic gene panel or virtual exome are now well below €200. The main contributor to the overall cost is the time and expertise required for interpretation. Even when this is taken into account, the cost remains reasonable and should not constitute a major barrier to implementation, except where disproportionately inflated pricing is applied in certain healthcare systems. In such circumstances, the solution is not to restrict access, but rather to advocate—through professional societies, key opinion leaders and the academic community—for more equitable access to testing.

Moreover, genetic testing is often performed once in a lifetime, with long-term utility for diagnosis, prognosis and familial cascade screening.

Although the interpretation of variants of uncertain significance (VUS) remains challenging, advances in population databases (e.g. gnomAD), *in silico* prediction tools and segregation studies are improving interpretative accuracy [34]. Resources such as ClinVar and, specifically for ADPKD, the Mayo ADPKD Variant Database are valuable, and international multidisciplinary collaboration remains essential [35, 36]. Looking ahead, broader access to systematic *in silico* evaluation is expected to further support variant interpretation [37].

Because variant-specific therapies are under development

Precision nephrology is moving rapidly towards genotype-guided therapies. Several experimental approaches are in development. One example is the small-molecule PC1 folding corrector VX-407, designed for certain missense variants in *PKD1*, with a Phase 2a trial underway (AGLOW, NCT07161037). A better understanding of genetic determinants of ADPKD may also provide clues for future therapeutic strategies: a recent study identified rare 5′-untranslated region variants in *PKD1* that reduce translation of polycystin-1 and suggest that modulation of upstream regulatory elements could be explored as a novel treatment approach [38].

Additional therapeutic strategies for polycystic kidney disease are under investigation and may ultimately depend on molecular stratification for patient selection. To prepare for this future, genetic characterization needs to be integrated into current practice. Identifying patients with relevant variants enables their participation in clinical trials and accelerates the translation of discoveries into clinical applications. Embedding molecular testing within standard care pathways today is essential to ensure timely access to emerging therapeutic options.

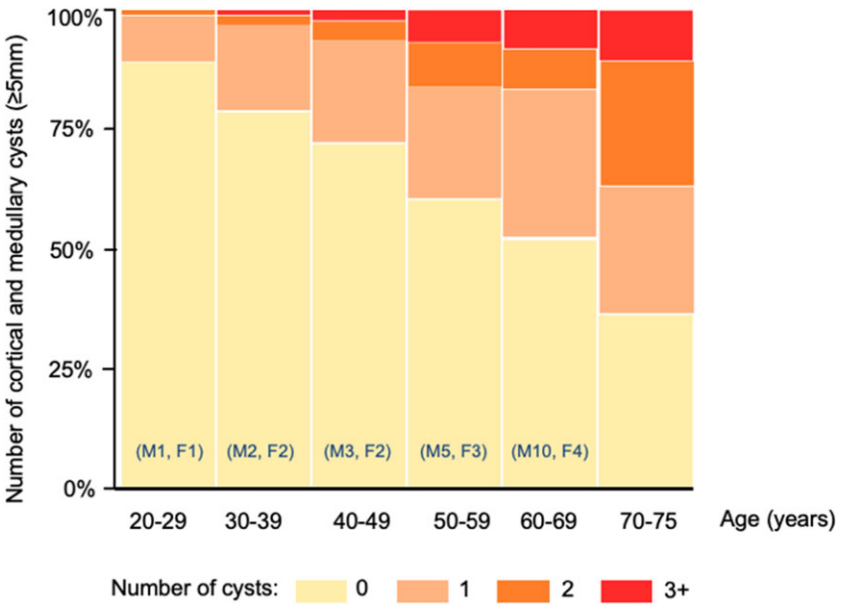

Figure 3: Age-related cyst formation in a population of healthy living kidney donors. Screening computed tomography scan data of a group of healthy living kidney donors ($n = 1948$) assessed between 2000 and 2008 at an expert center. The number of incidental cortical and medullary cysts (>5 mm) is indicated by color coding (0, 1, 2, 3 more more) according to age by decade. Based on size, these cysts should be detected by ultrasound. The numbering in each column by sex [male (M), female (F)] indicates the 97th centile for each age group. Figure adapted by permission of the author from Fig. 1 in Rule *et al.* (*AJKD* 2012 [42]).

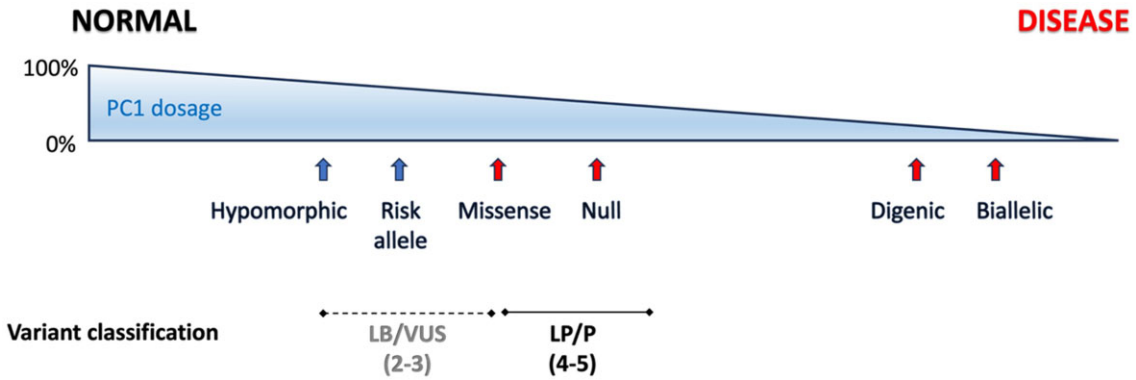

Figure 4: Variant classification, their predicted effects on gene dosage and relationship to disease. The predicted effect of different *PKD1* variants singly or in combination (digenic, biallelic) on PC1 dosage (0%–100%) and their relationship to disease displayed as a dosage-dependent mechanism. Variants are classified by the American College of Medical Genetics (ACMG) score of 1–5 [1 benign, 2 likely benign (LB), 3 VUS, 4 likely pathogenic (LP) and 5 pathogenic (P)]. The red arrowheads indicate disease-causing alleles while the blue arrowheads indicate low penetrance (hypomorphic) or susceptibility (risk) alleles which are often scored as ACMG 2–3. Missense variants may be classified as ACMG 3–5 depending on available evidence, leaving uncertainty in individual cases.

GENETICS IN ALL ADULTS WITH ADPKD: LIMITATIONS AND CHALLENGES

There are some limitations and challenges to current practice and the global implementation of genetic testing in ADPKD.

Patient selection and pre-test probability

There remains a high rate of genetically unresolved cases (no mutation detected in 20%–30%) in less selected populations even by whole-genome sequencing [39–41]. Since the pre-test probability of a positive result will depend strongly on patient selection, older individuals with atypical or mild disease who are increasingly being diagnosed on imaging are likely to be negative on testing, although some could carry minor gene or hypomorphic major gene variants. In some of these cases, testing may have little clinical significance for treatment but unselected testing on all patients will likely diagnose many patients who are well and asymptomatic with reduced kidney function but a negligible risk of kidney failure.

An informative study of 1948 potential kidney donors with normal kidney function at the Mayo Clinic between 2000 and 2008 reported the age-related prevalence of cysts (≥5 mm) detected on computed tomography scanning (Fig. 3) [42]. Although the population was not genotyped, it is likely that cyst formation can be part of normal ageing process with males more likely to develop cysts than females. In the 60–69 years age group, the 97th centile for males was 10 cysts, and for females it was 4 cysts. Current imaging ultrasound, criteria for diagnosis or disease exclusion have been derived from at-risk individuals in *PKD1* or *PKD2* pedigrees and do not apply to the minor genes [43]. With regard to magnetic resonance imaging (MRI), it should be noted

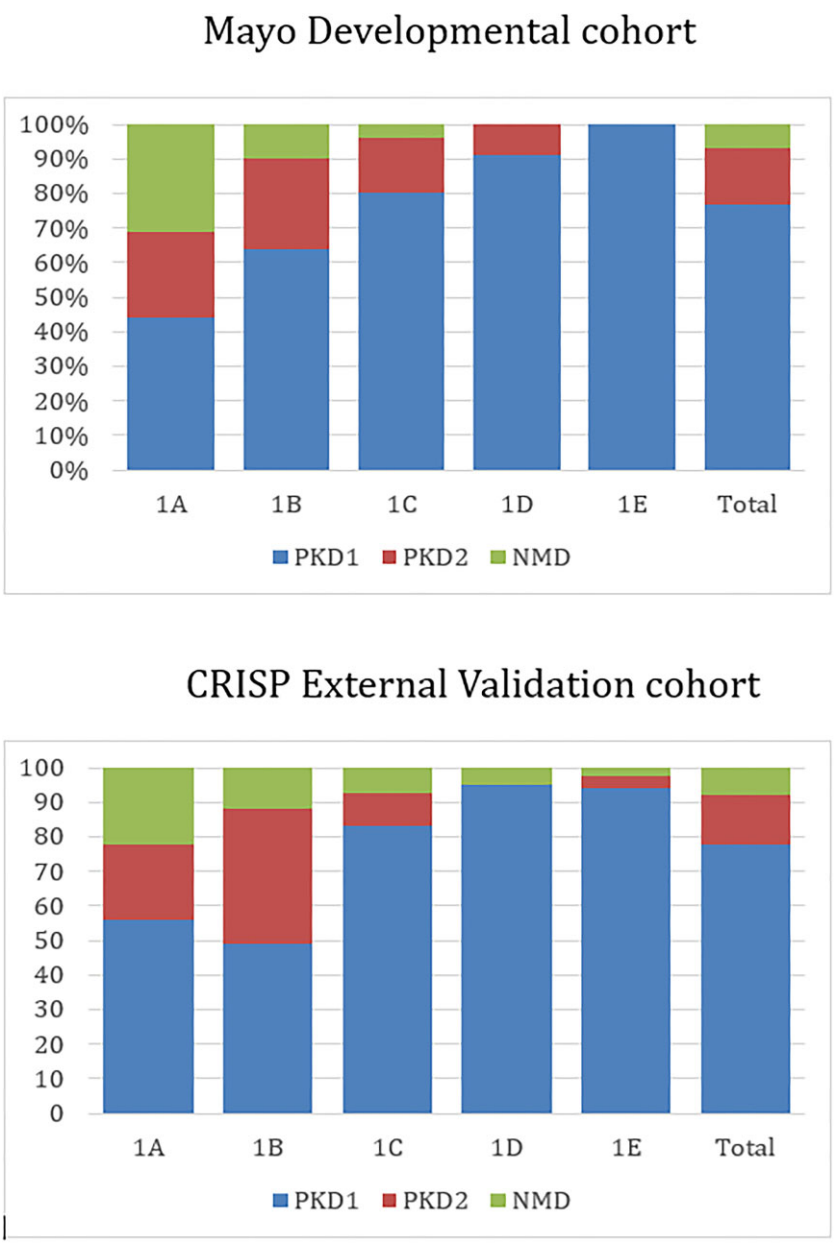

Figure 5: Genotype groups in MIC 1 (typical) patients from the Mayo Development ($n = 590$) and Consortium for Radiological Imaging Studies of Polycystic Kidney Disease (CRISP, $n = 177$) Validation Cohorts. The percentage of *PKD1* (blue), *PKD2* (red) and NMD (no mutation detected, green) variants in each MIC 1 subgroup is indicated. The final column denotes the overall percentage of each genotype class in the cohort. The percentage of *PKD1* variants increased from MIC 1A–E with a corresponding decrease in *PKD2* and NMD variants. The percentage of patients with non-*PKD1* or -*PKD2* variants (NMD group) was 6%–8% in patients with typical imaging morphology. Figure drawn from Table 2 reported in Irazabal *et al.* (*JASN* 2015 [22]).

that the diagnostic cut-off of 10 cysts in at-risk individuals only applies to those from *PKD1* and *PKD2* families between 16 and 40 years of age [43].

Variant interpretation especially for PKD1

A common issue that arises with more testing is the issue of variant interpretation. There is a significant though variable detection rate of VUS especially in *PKD1* (Fig. 4).

A genetic study in the Geisinger cohort in Pennsylvania demonstrated that a proportion of *PKD1* missense variants previously reported as likely pathogenic were, in fact, likely benign, since none of the carriers was shown to have cysts [40].

Alternatively, a variant might remain classified as a VUS (ACMG3) while it is in fact the cause of the disease simply because sufficient evidence for reclassification is lacking. The nephrologists and genetic counsellor have here a critical role to play to reach out to family members to perform co-segregation analysis to allow variant reclassification.

Since there are still no reliable functional assays accessible outside the research setting to define pathogenicity in cases of VUS, this could result in patient anxiety since the result neither disproves nor confirms the diagnosis and cannot be used for predictive testing, thus excluding screening options such as presymptomatic diagnosis, live related donation and PGD [44]. Pre-test counseling needs to explain the implications of an

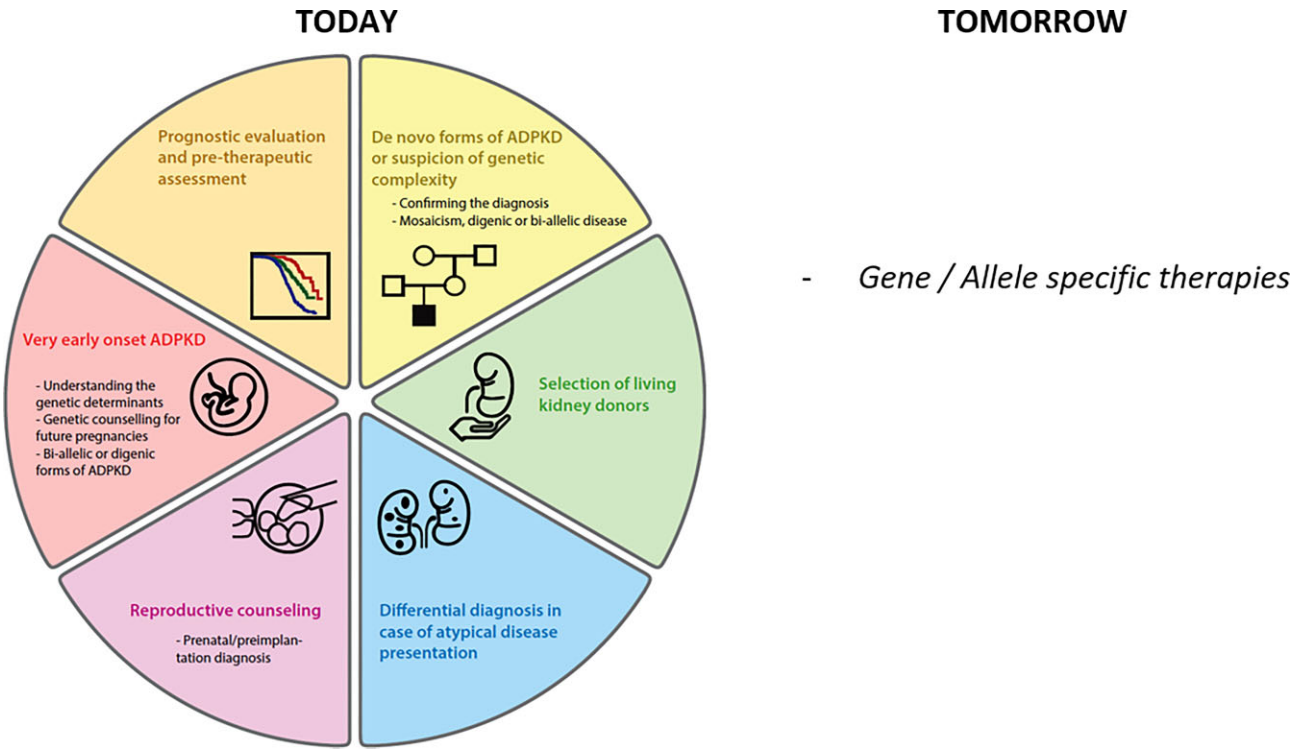

Figure 6: Actionability of genetic testing in ADPKD. Current and future applications of genetic testing in ADPKD, highlighting present-day clinical indications (today) and anticipated perspectives (tomorrow).

uncertain result as much as a negative or positive one [45]. It is worth noting however that the majority of *PKD1* and *PKD2* variants are predicted loss of function variants and hence classified as pathogenic with confidence.

The new KDIGO nomenclature for ADPKD includes both benign and severe phenotypes under a common disease label: pros and cons

The advantage of the new broader KDIGO nomenclature for ADPKD is to define a genetic basis for the observed phenotypic spectrum of ADPKD, defining major and minor genes that represent known population prevalence and disease incidence. Although useful for patient stratification, a disease label "ADPKD-gene" may still impact insurability and employability without offering any benefits such as improved access to treatment or healthcare. The careful education of all stakeholders will hence be essential, emphasizing the key importance of considering the gene suffix and not only the disease prefix.

Access to testing and patient selection for treatment

The cost of genome sequencing continues to fall and is becoming more accessible. However, few public health systems are currently funding genetic testing for ADPKD, and the cost must therefore be borne by the patient in many countries.

If testing is not accessible, a practical approach is to consider that the vast majority of ADPKD with typical diseases, i.e. positive family history, bilateral kidney involvement and enlargement (MIC 1) will have a major gene variant (*PKD1* or *PKD2*). Thus, obtaining an MIC by MRI measured TKV or ultrasound-measured mean kidney lengths may be sufficient for prognostic reasons, in the absence of historical eGFR information. This has been confirmed in a clinical diagnostic study using whole-genome sequencing [41].

Patients with minor gene variants tend to present with atypical kidney morphology (MIC 2) and a negative family history. In the developmental (Mayo Translational PKD Centre) and validation (Consortium for Radiological Imaging Studies of Polycystic Kidney Disease) cohorts used to derive the MIC, >90% of MIC Class 1 patients had *PKD1* or *PKD2* variants with only 6%–8% in the "no mutation detected" (i.e. no *PKD1* or *PKD2* variant which likely included untested minor gene variants) group (Fig. 5) [22]. Nonetheless, there was a low percentage of MIC Class 2 patients in both cohorts [8.8% MPTC, 2.2% Consortium for Radiological Imaging Studies of Polycystic Kidney Disease (CRISP)], likely based on inclusion criteria with limited genotyping especially in the former [22].

Although genotyping information was incomplete, it is likely that only *PKD1* or *PKD2* patients were included in the pivotal trial for tolvaptan (TEMPO 3:4, $n = 1445$) since 97% of those in the extension study (TEMPO 4:4, $n = 770$) with a positive test had *PKD1* or *PKD2* variants, with only 3% genetically unresolved [21]. If we considered only patients with MIC 1C–E for tolvaptan, there is a very small chance (<10%) of treating the occasional patient with a minor gene variant. Regardless of their genotype, patients with atypical disease (MIC Class 2) would not be eligible for tolvaptan, given that they would not fall into a "rapidly progressive" group.

CONCLUSION

In 2025, the rationale for genetic testing in ADPKD is stronger than ever. Genetic testing enables a definitive diagnosis, clarifies prognosis, informs therapeutic decisions, guides reproductive

planning, supports donor selection and prepares the field for emerging targeted therapies (Fig. 6).

While challenges remain—including interpretation of VUS and disparities in access—these are increasingly surmountable through collaborative care models. In parallel, attention must be paid to ensuring equitable access to genetic services across healthcare systems and geographies, as the benefits of testing should not be limited to specialized centers.

Genetic testing in ADPKD is no longer optional: it is a cornerstone of precision nephrology. Clinicians should advocate for its systematic but judicious use, prioritizing contexts where actionable insights are most likely. As the field continues to evolve, integrating genetic data will be essential for delivering optimal, equitable and forward-looking care to patients with ADPKD. Lastly, and most importantly, our approach must recognize and respect the patient's right to access genetic testing, as well as their perspective on its availability and timing [44–46].

ACKNOWLEDGEMENTS

A.C.M.O. acknowledges funding support from the PKD Foundation, Kidney Research UK, the PKD Charity UK, the Sheffield Hospitals Charity, Medical Research Council and the National Institute of Health and Care Research. We thank Andrew Rule for helpful discussion and permission to redraw Fig. 3, and Nikola Zagorec, Guillaume Buia, Hugo Lemoine and Matt Gittus for help in preparing the figures. The topic of this Review was also presented during the 62nd Congress of the European Renal Association in Vienna on 4–7 June 2025.

FUNDING

A .C .M .O .acknowledges funding support from the PKD Foundation, Kidney Research UK, the PKD Charity UK, the Sheffield Hospitals Charity, Medical Research Council and the National Institute of Health and Care Research. This paper is part of a Supplement that was financially supported by the ERA. The topic of this paper was also presented at the 62nd ERA Congress, Vienna & Virtual, June 4–7, 2025.

CONFLICT OF INTEREST STATEMENT

E.C.-L.G. has given talks, acted as consultant, participated on boards, or received travel support from Alexion, CSL Vifor, GSK, Vertex, Otsuka and Rhythm Pharmaceuticals. A.C.M.O. acknowledges consulting fees from Crinetics, GSK, Janssen, Mironid, Sanofi-Genzyme, Torque Bio, Travere and Vertex, paid to his institution.

REFERENCES

1. The European Polycystic Kidney Disease Consortium. The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16. The European Polycystic Kidney Disease Consortium. *Cell* 1994;**78**:725.
2. Mochizuki T, Wu G, Hayashi T *et al*. PKD2, a gene for polycystic kidney disease that encodes an integral membrane protein. *Science* 1996;**272**:1339–42. https://doi.org/10.1126/science.272.5266.1339
3. Su Q, Hu F, Ge X *et al*. Structure of the human PKD1-PKD2 complex. *Science* 2018;**361**:eaat9819. https://doi.org/10.1126/science.aat9819
4. Gainullin VG, Hopp K, Ward CJ *et al*. Polycystin-1 maturation requires polycystin-2 in a dose-dependent manner. *J Clin Invest* 2015;**125**:607–20. https://doi.org/10.1172/JCI76972
5. Boletta A, Caplan MJ. Physiologic mechanisms underlying polycystic kidney disease. *Physiol Rev* 2025;**105**:1553–607. https://doi.org/10.1152/physrev.00018.2024
6. Porath B, Gainullin VG, Cornec-Le Gall E *et al*. Mutations in GANAB, encoding the glucosidase IIα subunit, cause autosomal-dominant polycystic kidney and liver disease. *Am J Hum Genet* 2016;**98**:1193–207. https://doi.org/10.1016/j.ajhg.2016.05.004
7. Cornec-Le Gall E,Olson RJ, Besse W *et al*. Monoallelic mutations to DNAJB11 cause atypical autosomal-dominant polycystic kidney disease. *Am J Hum Genet* 2018;**102**:832–44.
8. Besse W, Chang AR, Luo JZ *et al*. ALG9 mutation carriers develop kidney and liver cysts. *J Am Soc Nephrol* 2019;**30**:2091–102. https://doi.org/10.1681/ASN.2019030298
9. Besse W, Dong K, Choi J *et al*. Isolated polycystic liver disease genes define effectors of polycystin-1 function. *J Clin Invest* 2017;**127**:1772–85. https://doi.org/10.1172/JCI90129
10. Lemoine H, Raud L, Foulquier F *et al*. Monoallelic pathogenic ALG5 variants cause atypical polycystic kidney disease and interstitial fibrosis. *Am J Hum Genet* 2022;**109**:1484–99. https://doi.org/10.1016/j.ajhg.2022.06.013
11. Cornec-Le Gall E, Torres VE, Harris PC. Genetic complexity of autosomal dominant polycystic kidney and liver diseases. *J Am Soc Nephrol* 2018;**29**:13–23.
12. Senum SR, Li YSM, Benson KA *et al*. Monoallelic IFT140 pathogenic variants are an important cause of the autosomal dominant polycystic kidney-spectrum phenotype. *Am J Hum Genet* 2022;**109**:136–56. https://doi.org/10.1016/j.ajhg.2021.11.016
13. Claus LR, Chen C, Stallworth J *et al*. Certain heterozygous variants in the kinase domain of the serine/threonine kinase NEK8 can cause an autosomal dominant form of polycystic kidney disease. *Kidney Int* 2023;**104**:995–1007. https://doi.org/10.1016/j.kint.2023.07.021
14. Torres VE, Ahn C, Barten TRM *et al*. KDIGO 2025 clinical practice guideline for the evaluation, management, and treatment of autosomal dominant polycystic kidney disease (ADPKD): executive summary. *Kidney Int* 2025;**107**:234–54. https://doi.org/10.1016/j.kint.2024.07.010
15. 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**:S1–239. https://doi.org/10.1016/j.kint.2024.07.009
16. Zagorec N, Audrézet M-P, Halimi JM *et al*. Genetic landscape in population-based adpkd cohort: beyond PKD Type 1 and PKD Type 2 [Internet]. San Diego, CA. 2024. *J Am Soc Nephrol* **35**:2024. Available from: https://www.asn-online.org/education/kidneyweek/archives/KW24Abstracts.pdf/ (23 November 2025, date last accessed).
17. Hateboer N, v Dijk MA, Bogdanova N *et al*. Comparison of phenotypes of polycystic kidney disease types 1 and 2. European PKD1-PKD2 Study Group. *Lancet* 1999;**353**:103–7. https://doi.org/10.1016/S0140-6736(98)03495-3
18. Cornec-Le Gall E, Audrezet MP, Chen JM *et al*. Type of PKD1 mutation influences renal outcome in ADPKD. *J Am Soc Nephrol* 2013;**24**:1006–13. https://doi.org/10.1681/ASN.2012070650
19. Heyer CM, Sundsbak JL, Abebe KZ *et al*. Predicted mutation strength of nontruncating PKD1 mutations aids genotype-phenotype correlations in autosomal dominant polycystic

kidney disease. *J Am Soc Nephrol* 2016;**27**:2872–84. https://doi.org/10.1681/ASN.2015050583 (23 November 2025, date last accessed).
20. Cornec-Le Gall E, Audrezet MP, Rousseau A *et al*. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2016;**27**:942–51. https://doi.org/10.1681/ASN.2015010016
21. Cornec-Le Gall E, Blais JD, Irazabal MV *et al*. Can we further enrich autosomal dominant polycystic kidney disease clinical trials for rapidly progressive patients? Application of the PROPKD score in the TEMPO trial. *Nephrol Dial Transplant* 2018;**33**:645–52.
22. Irazabal MV, Rangel LJ, Bergstralh EJ *et al*. Imaging classification of autosomal dominant polycystic kidney disease: a simple model for selecting patients for clinical trials. *J Am Soc Nephrol* 2015;**26**:160–72. https://doi.org/10.1681/ASN.2013101138
23. Wolff CA, Aiello V, Elhassan EAE *et al*. Integrated use of autosomal dominant polycystic kidney disease prediction tools for risk prognostication. *Clin J Am Soc Nephrol* 2025;**20**:397–409. https://doi.org/10.2215/CJN.0000000625
24. Zagorec N, Calamel A, Delaporte M *et al*. Clinical spectrum and prognosis of atypical autosomal dominant polycystic kidney disease caused by monoallelic pathogenic variants of IFT140. *Am J Kidney Dis* 2025;**85**:465–76.e1. https://doi.org/10.1053/j.ajkd.2024.10.009
25. Pei Y, Obaji J, Dupuis A *et al*. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol* 2009;**20**:205–12. https://doi.org/10.1681/ASN.2008050507
26. Snoek R, Stokman MF, Lichtenbelt KD *et al*. Preimplantation genetic testing for monogenic kidney disease. *Clin J Am Soc Nephrol* 2020;**15**:1279–86. https://doi.org/10.2215/CJN.03550320
27. Hopp K, Cornec-Le Gall E, Senum SR *et al*. Detection and characterization of mosaicism in autosomal dominant polycystic kidney disease. *Kidney Int* 2020;**97**:370–82. https://doi.org/10.1016/j.kint.2019.08.038
28. Audrezet MP, Corbiere C, Lebbah S *et al*. Comprehensive PKD1 and PKD2 mutation analysis in prenatal autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2016;**27**:722–9. https://doi.org/10.1681/ASN.2014101051
29. Losekoot M, Ruivenkamp CAL, Tholens AP *et al*. Neonatal onset autosomal dominant polycystic kidney disease (ADPKD) in a patient homozygous for a PKD2 missense mutation due to uniparental disomy. *J Med Genet* 2012;**49**:37–40. https://doi.org/10.1136/jmedgenet-2011-100452
30. Durkie M, Watson CM, Winship P *et al*. The common PKD1 p.(Ile3167Phe) variant is hypomorphic and associated with very early onset, biallelic polycystic kidney disease. *Hum Mutat* 2023;**2023**:5597005. https://doi.org/10.1155/2023/5597005
31. Durkie M, Chong J, Valluru MK *et al*. Biallelic inheritance of hypomorphic PKD1 variants is highly prevalent in very early onset polycystic kidney disease. *Genet Med* 2021;**23**:689–97. https://doi.org/10.1038/s41436-020-01026-4
32. Losekoot M, Meijer E, Hagen EC *et al*. Polycystic kidney disease caused by bilineal inheritance of truncating PKD1 as well as PKD2 mutations. *Kidney Int Rep* 2020;**5**:1828–32. https://doi.org/10.1016/j.ekir.2020.07.006
33. Graziani L, Zampatti S, Carriero ML *et al*. Co-inheritance of pathogenic variants in PKD1 and PKD2 genes determined by parental segregation and de novo origin: a case report. *Genes* 2023;**14**:1589. https://doi.org/10.3390/genes14081589
34. Karczewski KJ, Francioli LC, Tiao G *et al*. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature* 2020;**581**:434–43. https://doi.org/10.1038/s41586-020-2308-7
35. Landrum MJ, Lee JM, Benson M *et al*. ClinVar: improving access to variant interpretations and supporting evidence. *Nucleic Acids Res* 2018;**46**:D1062–D7. https://doi.org/10.1093/nar/gkx1153
36. Gout AM, Martin NC, Brown AF *et al*. PKDB: polycystic kidney disease mutation database—a gene variant database for autosomal dominant polycystic kidney disease. *Hum Mutat* 2007;**28**:654–9. https://doi.org/10.1002/humu.20474
37. Ha K, Loeb GB, Park M *et al*. ADPKD-causing missense variants in polycystin-1 disrupt cell surface localization or polycystin channel function. *bioRxiv* 2024; 2023.12.04.570035;not peer reviewed.
38. Wedd L, Hort Y, Patel C *et al*. PKD1 5'UTR variants are a rare cause of disease in ADPKD and suggest a new focus for therapeutic development. *Eur J Hum Genet* 2025. https://www.nature.com/articles/s41431-025-01949-z#citeas
39. Mallawaarachchi AC, Hort Y, Cowley MJ *et al*. Whole-genome sequencing overcomes pseudogene homology to diagnose autosomal dominant polycystic kidney disease. *Eur J Hum Genet* 2016;**24**:1584–90. https://doi.org/10.1038/ejhg.2016.48
40. Chang AR, Moore BS, Luo JZ *et al*. Exome sequencing of a clinical population for autosomal dominant polycystic kidney disease. *JAMA* 2022;**328**:2412–21. https://doi.org/10.1001/jama.2022.22847
41. Chen EWC, Chong J, Valluru MK *et al*. Combining genotype with height-adjusted kidney length predicts rapid progression of ADPKD. *Nephrol Dial Transplant* 2024;**39**:956–66. https://doi.org/10.1093/ndt/gfad270
42. Rule AD, Sasiwimonphan K, Lieske JC *et al*. Characteristics of renal cystic and solid lesions based on contrast-enhanced computed tomography of potential kidney donors. *Am J Kidney Dis* 2012;**59**:611–8. https://doi.org/10.1053/j.ajkd.2011.12.022
43. Pei Y, Hwang YH, Conklin J *et al*. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. *J Am Soc Nephrol* 2015;**26**:746–53. https://doi.org/10.1681/ASN.2014030297
44. Gittus M, Harris T, Ong AC. Patient Perspectives on ADPKD. *Adv Kidney Dis Health* 2023;**30**:294–302. https://doi.org/10.1053/j.akdh.2023.01.002
45. Logeman C, Cho Y, Sautenet B *et al*. "A sword of Damocles": patient and caregiver beliefs, attitudes and perspectives on presymptomatic testing for autosomal dominant polycystic kidney disease: a focus group study. *BMJ Open* 2020;**10**:e038005. https://doi.org/10.1136/bmjopen-2020-038005
46. Odland D. A patient perspective on genetic testing for ADPKD: the lack of complete genetic information, especially early in the course of the disease, is harming adult autosomal dominant polycystic kidney disease (ADPKD) patients. *Clin J Am Soc Nephrol* 2021;**16**:671–3. https://doi.org/10.2215/CJN.14051119

Received: 10.9.2025; accepted: 27.10.2025