



This is a repository copy of *The diagnostic accuracy of ultrasound and genomic tests for the diagnosis of autosomal-dominant polycystic kidney disease: a systematic mapping review*.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/228710/>

Version: Accepted Version

Article:

Harnan, S., Gittus, M., Falzon, L. orcid.org/0000-0002-9449-6056 et al. (4 more authors) (2025) The diagnostic accuracy of ultrasound and genomic tests for the diagnosis of autosomal-dominant polycystic kidney disease: a systematic mapping review. *Clinical Kidney Journal*, 27 (12). sfaf187. ISSN 2048-8505

<https://doi.org/10.1093/ckj/sfaf187>

Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

The diagnostic accuracy of ultrasound and genomic tests for the diagnosis of autosomal-dominant polycystic kidney disease: a systematic mapping review

Sue Harnan, Sheffield Centre for Health and Related Research, University of Sheffield

Matt Gittus, Sheffield Centre for Health and Related Research, University of Sheffield

Louise Falzon, Sheffield Centre for Health and Related Research, University of Sheffield

Miranda Durkie, Sheffield Diagnostic Genetics Service, North East and Yorkshire Genomic Laboratory Hub, Sheffield Children's NHS Foundation Trust, Sheffield

Olena Mandrik, Sheffield Centre for Health and Related Research, University of Sheffield

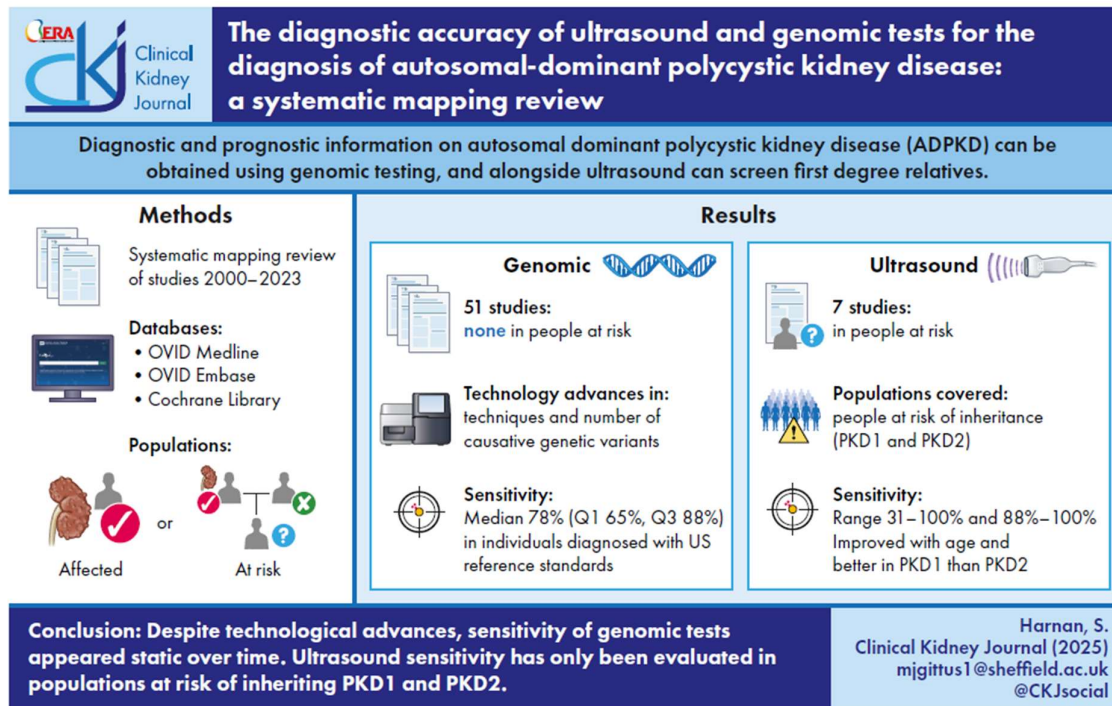
Albert Ong, Division of Clinical Medicine, University of Sheffield and Sheffield Kidney Institute

James Fotheringham, Sheffield Kidney Institute, University of Sheffield

Correspondence to:

Matt Gittus; E-mail: mjgittus1@sheffield.ac.uk

GRAPHICAL ABSTRACT



ABSTRACT

Background.

Genomic and ultrasound tests can provide diagnostic and prognostic information on autosomal dominant polycystic kidney disease (ADPKD), and can screen first degree relatives in whom early diagnosis can be advantageous. We conducted a systematic mapping review on test accuracy and characteristics over time.

Methods.

Medline, Embase and Cochrane were searched (August 2023) for studies in first-degree relatives/individuals clinically diagnosed with ADPKD receiving genomic or ultrasound tests. Acceptable reference standards for sensitivity/detection rate and specificity were definitive imaging or genomic confirmation. Genomic studies were categorised by technology and read length. Relationships between sensitivity, specificity, genomic technology, diagnostic criteria/reference standard and genes tested were compared.

Results.

From 1029 non-duplicate titles retrieved, 51 genomic and 7 ultrasound studies were included. There were no genomic studies in first degree relatives. Amongst studies in patients with clinical diagnoses, genomic sequencing methodologies were highly heterogeneous (next generation (short read (n=20), long read (n=1)), targeted sanger (n=19), whole exome (n=1) with additional multi-ligation probe analysis (n=13)). Median sensitivity was 78% (Interquartile range 65% to 88%). Ultrasound sensitivity and specificity generally improved with age and were worse in PKD2 patients compared to PKD1 (lowest reported 31% and 88%

respectively in polycystic kidney disease (*PKD*) 2 patients aged 5-14; highest 100% and 100% respectively in multiple gene/age categories).

Conclusions.

Despite technological advances, sensitivity of genomic tests appeared static between 2000 and 2023. Possible explanations include clinical diagnostic criteria (and hence populations recruited) widening from *PKD1* to include *PKD2* and atypical phenotypes, and small incremental gains of testing genes other than *PKD1* and *PKD2*. For people at risk of ADPKD in genetically unresolved families, the accuracy of ultrasound is uncertain. Unified genomic test taxonomies would facilitate future reviews.

Registration

PROSPERO CRD42023456727

Keywords: ADPKD, detection rate, diagnosis, genomic tests, mapping review, systematic review, ultrasonography

ORIGINAL UNEDITED MANUSCRIPT

KEY LEARNING POINTS

What was known:

- People at risk of inheriting ADPKD can be screened for the disease using ultrasound or genomic testing
- Genomic testing technologies have evolved rapidly over the last 20 years
- With the cost of genomic testing falling, some clinicians now have the choice between the two screening methods when the genomic variant in the affected individual is known.

This study adds:

- We found no genomic studies conducted in patients at risk of ADPKD, only in those already diagnosed using other methods
- Overall, despite improvements in genomic methods, the sensitivity of genomic tests reported in the studies does not appear to have improved over time; this may be due to the widening population being tested and small incremental gains in detection rate provided by testing genes other than PKD1 and PKD2
- We found no studies evaluating ultrasound in patients with genetic variants other than PKD1 and PKD2. Ultrasound test accuracy therefore remains unclear in these growing populations

Potential impact:

- Clinicians screening populations at risk of ADPKD should appreciate that the sensitivity and specificity of ultrasound in relatives of those with ADPKD not caused by PKD1 and PKD2 is unknown.
- Decision-makers considering investing in genomic technologies should be aware of the relatively small incremental value of broader genomic panels when individuals affected by these variants are few.

INTRODUCTION

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common hereditary kidney disease, affecting an estimated 12 million individuals worldwide.¹ Being dominantly inherited, first degree relatives have a 50% risk of developing the condition.² It is characterised by cystic expansion of the kidneys, progressing to bilateral kidney enlargement and subsequent chronic kidney disease (CKD).³ Symptoms typically begin around age 30.⁴ 50% of people with ADPKD require kidney replacement therapy by age 60.⁵ Although ADPKD is primarily caused by variants in *PKD1* and *PKD2* genes, ongoing discoveries of other causative genes have revealed greater genomic heterogeneity than previously understood.^{3,6} Even within *PKD1* and *PKD2* genes, there is significant allelic heterogeneity with over 1200 and almost 190 pathogenic/likely pathogenic variants identified for *PKD1* and *PKD2* respectively.⁷ Most identified families have unique variants, with fewer than 2% of unrelated ADPKD-affected families sharing the same variant.⁸

ADPKD diagnosis is mostly based on imaging and family history, and it can be difficult to differentiate from other cystic kidney diseases when imaging results are atypical or in young individuals with a negative family history.⁶ By age 40, a diagnosis of ADPKD can be ruled out in people who have no more than one kidney cyst.⁹ Genomic testing can provide a definitive diagnosis for patients, relatives at risk of inheriting the disease, and for individuals who are seeking genomic consultation prior to pre-implantation genomic diagnosis for reproduction or living kidney donor transplantation.⁶ If possible, genomic testing of a family member who has a clinical diagnosis of ADPKD using a full diagnostic genomic test, usually including *PKD1* and *PKD2* genes as a minimum, is the recommended first step when genomic testing individuals at risk of inheriting ADPKD is being performed. If a pathogenic variant is identified in this family member, then predictive testing in their relatives can be offered by targeted analysis of the familial pathogenic variant.

Historically, guidelines have hesitated to recommend genomic screening due to costs and limited accessibility.¹⁰ The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines state that an ultrasound diagnosis can be used even when the family is genetically resolved.¹¹ These guidelines have been designed to be applicable to healthcare systems worldwide and as costs associated with genomic tests drop, gene panels broaden and technology advances, a review of contemporary evidence to inform clinical practice guidelines is required. Earlier diagnosis has the potential to enable earlier management and improve

outcomes for people with ADPKD. This can occur through earlier access to lifestyle and medication interventions, family planning, and living donation information.^{12,13} This systematic mapping review aims to describe and characterise the available diagnostic accuracy literature relating to ultrasound and genomic tests for people at risk of ADPKD. We aim to look at the changes in technology and chart the sensitivity of genomic tests over time and the diagnostic accuracy of ultrasound tests, to provide an overview of this fast-paced and complex topic.

MATERIALS AND METHODS

This systematic mapping review is reported in line with recommendations made by PRISMA for scoping reviews,¹⁴ since there is no guidance for mapping reviews. We also considered relevant items from the PRISMA guidance for reporting diagnostic test accuracy reviews.¹⁵ There is no standard definition of a mapping review,¹⁶ but they are generally descriptive in nature, do not include statistical synthesis, but rather use graphical, tabular and narrative methodologies to characterise the literature.

The protocol was registered on the PROSPERO database (record number CRD42023456727), but some changes were made to the protocol as detailed in online supplement 1.

Search strategy

Potentially relevant articles were identified by searching Ovid Medline, Ovid Embase and the Cochrane Library from inception to August 2023. Relevant subject headings and free-text terms to represent 'Autosomal Dominant Polycystic Kidney Disease' AND 'ultrasound' OR 'genetic screening' were used. A validated search filter to identify diagnostic studies was applied,¹⁷ but the studies were not limited by year or language. Reference lists of relevant studies and reviews, and relevant articles in the Similar Articles feature in PubMed, and the Cited Reference Search in ISI Web of Science were also screened. The following relevant conferences were searched for the past 3 years: American Society of Nephrology Kidney Week, World Congress of Nephrology and European Renal Association Congress. Full details of the search dates and strategies are available in online supplement 2.

Study selection

The selection criteria for the review are reported in Table 1. Studies of ultrasound were included if they recruited first degree relatives of people with ADPKD (i.e. people with 50% risk of having ADPKD) and the reference standard was imaging after age 40 years according to published criteria (e.g., Pei *et al.*, 2009,¹⁸ Pei *et al.*, 2015,¹⁹ Torres *et al.*, 2012²⁰), or genomic confirmation by any genomic method (e.g. gene linkage analysis, sanger sequencing). Studies using high-resolution ultrasound were excluded because standard ultrasound remains the predominant method in clinical use.

Studies of genomic tests or diagnostic strategies including genomic tests were included if they recruited either first degree relatives of people with an ADPKD diagnosis, or people with or without a family history with a clinical ADPKD diagnosis according to published diagnostic criteria (e.g., Pei *et al.*, 2009,¹⁸ Pei *et al.*, 2015,¹⁹ Torres *et al.*, 2012²⁰), because these are the groups the tests would be used in. The reference standard could be a diagnosis using published criteria, or a genomic diagnosis. This was a change from the published protocol because no studies met the original criterion (see online supplement 1).

In both reviews, prenatal populations were excluded since short follow-up meant it was not clear if all the foetuses grew up to have the disease, and the pathogenic variant may have resulted in prenatal death such that testing in a child would never have been necessary.

We did not restrict inclusion to studies using the American College of Medical Genetics and Genomics guidance for the interpretation of sequence variants²¹, but attempted to standardise definitions where possible (see section *Sensitivity* below).

Two reviewers (SH and MG) separately used Covidence with AI-assisted study prioritisation to screen studies according to the inclusion criteria, considering first the title and abstract, then examining the full texts of the remaining articles. Any disagreements were resolved through discussion and involvement of a third reviewer (JF).

Data extraction and quality assessment

A data extraction form was created in Google Sheets, piloted on two articles and improved where necessary. Data extraction fields and methods are provided in online supplement 2 but briefly comprised data extraction, data coding and data double-checking by a second reviewer with resolution of disagreements through discussion.

As none of the studies of genomic tests were true diagnostic test accuracy studies and were therefore of generally low quality, QUADAS 2²² quality assessment was not performed.

Mapping analysis

The evidence map was primarily analysed according to two main criteria:

1. **Test type.** Ultrasound studies were grouped separately from genomic studies. Genomic studies were then categorised according to the sequencing technology used. These sequencing technology components are defined in Table 2 and categories described in online supplement 3. Studies were grouped by technology used (Sanger or next generation), the genomic target (targeted gene, whole exome or whole genome), and whether the read length was short (first and second generation) or long (third generation).
2. **Population.** The criteria used to recruit patients may affect the detection rate since early clinical definitions were largely based on *PKD1* (Ravine 1994) and then expanded to *PKD2* (Pei 2009 and Pei 2015). Studies were therefore grouped according to the criteria used to define the clinical diagnosis of ADPKD. Clinical criteria included Ravine 1994, Pei 2009 for ultrasound, and Pei 2015 for MRI or sometimes CT. Other criteria could be used for atypical presentations, such as Torres 2012. Studies could cite published criteria, or accurately describe the criteria which was then matched to the corresponding citation. Studies which recruited patients according to a genomic diagnosis were grouped separately.

A number of plots were then generated using R version 4.4 to show trends over time for factors including recruitment criteria, test types, gene targets and detection rate. Changes in longitudinal detection rate were estimated using the ggplot2 generalized linear model smoothed conditional mean function, weighted for study size, with a binomial link function.

RESULTS

The search strategy retrieved a total of 1078 titles, from which 27 duplicates were removed. Of the 1051 records remaining, 828 were excluded on the basis of their title or abstract. The full text of 223 studies were assessed for eligibility, and of these 165 were excluded (see Figure 1 for reasons). Seven studies^{18,23-28} of ultrasound and 50 studies^{6,8,29-76} of genomic tests were included in the review.

Studies of genomic tests

Location of studies: The country of origin of the included studies is mapped in **Figure 2**. The country contributing the most studies was China (n=10),^{42,46,49,51,52,71-75} followed by USA (n=6).^{35,63,64,67,68,77} The remainder were from across the globe, including Canadian, European Middle Eastern and Asian studies.

Recruitment criteria: Amongst the 51 genomic test studies (Table 3) patients were recruited according to Pei *et al.*, 2009¹⁸ and its extension Pei *et al.*, 2015¹⁹ (n=25 studies),^{6,8,30,31,34,35,37,38,41,43,44,46-49,53,55-57,62,65-67,71,72} most often. These criteria were derived in *PKD1* and *PKD2* patients. Ravine *et al.*, 1994²⁸ criteria, which targeted *PKD1* patients, were used in 16 studies.^{29,33,36,40,45,51,58-61,63,64,73-76} Other imaging criteria (Torres *et al.*, 2012, Torres *et al.*, 2017, KDIGO guideline criteria) were used in a further 5 studies,^{39,42,50,52,54} and these are likely to recruit a wider population than just *PKD1* and *PKD2*. Four studies recruited people using genomic tests: one⁶⁹ targeted people with *PKD1* and *PKD2* pathogenic variants and aimed to include as many different variants as possible, whilst the other three^{32,68,77} did not state which genes were targeted. One study used *PKD2* families previously analysed by linkage analysis.⁷⁰ Surprisingly, Ravine *et al.*, 1994²⁸ criteria were used to recruit patients in four studies^{29,58,61,74} published between 2018 to 2020. However, overall, due to the criteria used, the populations included in more recent studies were more heterogeneous and less phenotypically characteristic of *PKD1/PKD2* pathogenic variants (Figure 3A).

Reference standard: In nearly all cases, the reference standard was the same as the recruitment criteria. As already noted, these studies are only able to estimate detection rate (sensitivity) and cannot estimate specificity.

Test types: Amongst the 51 genomic test studies^{6,8,29-77} (Table 3), there was a similar number of studies of targeted Sanger sequencing (n=18)^{8,29,30,33,34,36,40,43,45,49,51,52,57-61,77} and targeted short read next generation sequencing (n=17).^{6,37,39,41,46,48,50,54,55,62,65,67,69,71,72,74,76} There was only one study of targeted long read next generation sequencing,³² one of WGS short read next generation sequencing,⁵³ two of WES short read next generation sequencing,^{35,38} eight tests used a combination of technologies,^{42,44,47,63,64,66,68,73} and four reported on other types of genomic tests.^{31,56,70,75} Studies were published from 2000 through to 2023 (date of searches).

Figure 3B charts the types of tests used over time. Sanger sequencing has been used consistently throughout the period, whilst the application of next generation technologies to ADPKD diagnosis was first reported in 2008 and use has increased over time. The one study of long read technology was published in 2017.³² Studies on tests used in combination started in 2002, with early studies focussing on DHPLC followed by Sanger sequencing,^{36,63,64,68,73} and later studies mostly using combinations of next generation sequencing, MLPA and Sanger but not always in the same order.^{42,44,47,66} Other test types encountered included high resolution melt (HRM)^{31,56,70} and single strand conformation polymorphism analysis (SSCP).⁷⁵

Gene targets: The genes targeted by genomic tests also broadened over time (Figure 3C). Four of the seven studies^{29,33,42,45,52,59,60} that only focussed on *PKD1* were among the five earliest studies conducted (2000 to 2002).^{33,45,59,60,63} Testing for genes beyond *PKD1* started with the inclusion of *PKD2* by Rossetti *et al.*, in 2002,⁶³ and expanded beyond *PKD1* and *PKD2* in 2017, when Iliuta *et al.*, 2017 included *GANAB* and *HNF1B*. Later tests^{6,38} broadened into *COL4A1*, *DNAJB11*, *REN*, and *UMOD*.

Sensitivity: Heterogeneity in the terminology used to categorise pathogenic variants supported grouping terminology erring towards the variant being pathogenic together. e.g., pathogenic, probably/likely/definitely/strong pathogenic, disease-causative, possibly damaging. To plot detection rate over time a subgroup of studies that reported both pathogenic/definitely pathogenic and likely/probably pathogenic (or similar terms) variants were selected. Studies were further grouped into three categories, to match the recruitment criteria to the genes tested (Ravine 1994 criteria, only genomic tests for *PKD1* or more were included; Pei 2009/2015, genomic tests for *PKD1* and *PKD2* or more were included; other criteria, only genomic tests for *PKD1*, *PKD2* and at least one other gene were included).

Figure 4 plots the sensitivity of the tests for these three subgroups. Across all three groups, the median detection rate was 78% (interquartile range 65% to 88%, total range 32% to 100%). Sensitivity remained fairly stable over the years (Ravine 1994 subgroup, range 32%⁵⁹ to 90%⁵¹ and Pei 2009/2015 subgroup, range 41%⁵⁵ to 100%)^{30,62} or had too few points for inference (Others subgroup).

Ultrasound studies

The characteristics of the seven studies^{18,23-28} are outlined in Table 4. The date of studies ranged from 1990²⁷ to 2009¹⁸ (*n.b.*, Pei *et al.*, 2015¹⁹ did not meet the inclusion criteria as it used high resolution ultrasound). All^{18,23-28} recruited people at 50% risk of ADPKD from families with. PKD1 (n=4),^{25,27,28 24} PKD2 (n=1)²³ or PKD1 and PKD2 (n=2)^{18,26} genotypes. All used a genomic reference standard.

Both sensitivity and specificity improved as age increased (see Figure 5 and Online Supplement 4), across both *PKD1* and *PKD2* populations, but accuracy was poorer in *PKD2* compared to *PKD1* populations. The lowest sensitivity and specificity were 31% and 88% respectively, reported in *PKD2* populations aged 5-14. The highest were 100% and 100% respectively in multiple gene/age categories.

DISCUSSION

Using 58 studies of genomic ($n = 51$) and ultrasound ($n = 7$) testing spanning over 30 years, this review charts the evolving methods available for screening first-degree relatives of people affected by ADPKD. Notably, none of the genomic studies we found recruited relatives at 50% risk of ADPKD, meaning the accuracy of the tests in this population is unclear. The available evidence suggests that, amongst people who have a clinical diagnosis of ADPKD but they or their family have not previously had genomic testing, the sensitivity of genomic tests is likely to be somewhere between 70 and 80%, depending on test methodology and the proportion of unknown variants within the population sample. Sensitivities lower than 50% and higher than 90% have also been reported.

Due to technological advances and increased sharing of known pathogenic variants we expected to see an increase in sensitivity over time, but instead the evidence suggests that the detection rate has not changed greatly. Possible explanations for these findings include a) the small impact that increased testing of a panel of cytogenic genes has when the vast majority of pathogenic variants are in *PKD1* and *PKD2*; b) pathogenic variants not detected by the methodology used e.g. deep intronic variants/structural variants/regulatory variants; c) unique variants detected with insufficient evidence to reach a (likely) pathogenic score (i.e. variant of uncertain significance); d) other cystogenic genes being responsible; e) other causes e.g. simple age-related cysts; and f) the observed widening recruitment criteria leading to more atypical cases being recruited, and an increase in the size of the population for which genomic testing has become relevant, owing to the identification of additional rare ADPKD genes such as *GANAB* and *HNF1B*, *COL4A1*, *DNAJB11*, *REN*, and *UMOD* (see Table 3). However, only one study in this review included the recently identified *IFT140* gene which has been shown to be the third most common gene associated with ADPKD after *PKD1* and *PKD2*⁷⁸. The extent and rate at which current gene panels have adopted these more recently identified variants was not the subject of our study, but it is possible laboratories may not wait for extensive publication on variants before incorporating them in their gene panels.

Meanwhile, no studies on the performance of ultrasound screening in first degree relatives of families with the more contemporary known pathogenic variants were identified. Consequently, the test accuracy of ultrasound outside populations with *PKD1* and *PKD2* is

currently unknown. The KDIGO guidelines¹¹ recommend that when making an initial diagnosis of ADPKD in an adult at risk, abdominal imaging by ultrasound can be used even when the family is genetically resolved. This is despite the lack of evidence in populations outside PKD1 and PKD2. Whilst genetically unresolved families are reliant on this screening modality and guidelines continue to recommend the use of ultrasound in families with other variants, further studies are required to establish the accuracy of the test in these populations. Clinicians may need to keep these uncertainties in mind when planning further monitoring and when considering alternative diagnoses.

In clinical practice, relatives of individuals who have no pathogenic variant identified by genomic testing may be receiving radiological screening tests derived and validated in populations who broadly speaking have different pathogenic variants, since our review found all ultrasound studies recruited patient with known PKD1 or PKD2. This may lead to uncertainty in clinical diagnoses, or incorrect exclusion of disease in relatives who are still in the early stages of a clinical disease with a more slowly progressing natural history.

This systematic mapping review has been conducted to the same standards as a systematic review in terms of the search methodology), study selection and data extraction. Data were organised according to several factors that may affect test metrics, including the recruitment criteria and reference standards used. Nevertheless, it does have some methodological limitations, often generated by the available evidence. The lack of data on diagnostic test accuracy of genomic tests in people at risk of ADPKD lead to protocol amendments including widening criteria to include studies reporting only sensitivity and in people with clinically confirmed ADPKD (removing the requirement for this to be confirmed after age 40). As a result, the included studies were not true diagnostic test accuracy studies. Critical appraisal using QUADAS-2²² was not performed because it is not designed for these studies and would have been uninformative. Heterogeneity in populations and test methodologies precluded meta-analysis. Since the genomic studies did not specify that included patients had to have a radiological diagnosis after a certain age, and since cysts tend to increase over time, the populations recruited according to these criteria may include more patients who presented at a young age and therefore have more progressive disease. Finally, there will inevitably remain some heterogeneity in how the pathogenic categories were defined, especially as new variants were identified and guidelines to determine variant pathogenicity have changed over time.⁷⁹

Policy makers should consider the generalisability of the patient populations recruited to the studies, which are broadening over time, to their own populations. The specifics of the test methodologies with respect to available expertise, equipment, and small incremental gains of the technologies and additional variants should also be considered.

In conclusion, this study demonstrates that whilst genomic testing methods have advanced, detection rates have not greatly improved, possibly due to wider inclusion criteria, and the small incremental gains of testing genes other than PKD1 and PKD2. For people at risk of ADPKD in genetically unresolved families, the accuracy of ultrasound is uncertain, and clinical communities should bear this in mind when screening for ADPKD.

FUNDING

This work was supported by the National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) programme (Grant Reference Number NIHR204357). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

CONFLICT OF INTEREST STATEMENT

None of the Authors have any conflicts to declare.

AUTHORS' CONTRIBUTIONS

Sue Harnan secured funding, planned, led and conducted the systematic mapping review, drafted the manuscript and co-ordinated authors contributions.

Matt Gittus conducted the systematic mapping review and contributed to drafting the manuscript.

Louise Falzon designed and ran the search strategy and contributed to drafting the manuscript.

Miranda Durkie provided expert advice in categorising the genomic tests and contributed to drafting the manuscript.

Olena Mandrik secured funding, contributed to data extraction and commented on the manuscript draft.

Albert Ong secured funding, provided expert advice and commented on the manuscript draft.

James Fotheringham conceptualised the overall project, secured funding, contributed to planning the systematic mapping review, contributed to data extraction, generated figures, and contributed to drafting the manuscript.

DATA AVAILABILITY STATEMENT

Data underpinning this review available from the authors upon request.

ORIGINAL UNEDITED MANUSCRIPT

REFERENCES

1. Chapman AB, Devuyst O, Eckardt K-U, et al. Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney international*. 2015;88(1):17-27.
 2. Chow CL, Ong AC. Autosomal dominant polycystic kidney disease. *Clinical medicine*. 2009;9(3):278.
 3. Choukroun G, Itakura Y, Albouze G, et al. Factors influencing progression of renal failure in autosomal dominant polycystic kidney disease. *Journal of the American Society of Nephrology*. 1995;6(6):1634-1642.
 4. Mahboob M, Rout P, Leslie SW, Bokhari SRA. Autosomal Dominant Polycystic Kidney Disease. Treasure Island (FL): StatPearls Publishing. Accessed 7/08/2024, <https://www.ncbi.nlm.nih.gov/books/NBK532934/>
 5. Brosnahan GM. Volume progression in polycystic kidney disease. *The New England journal of medicine*. 2006;355(7):733-734.
 6. Yu CC, Lee AF, Kohl S, et al. PKD2 founder mutation is the most common mutation of polycystic kidney disease in Taiwan. *npj Genomic Medicine*. 2022;7(1) (no pagination)doi:<https://dx.doi.org/10.1038/s41525-022-00309-w>
 7. Foundation P. PKD variant database. Accessed 07/08/2024, <http://pkdb.mayo.edu/>
 8. Audrezet MP, Cornec-Le Gall E, Chen JM, et al. Autosomal dominant polycystic kidney disease: Comprehensive mutation analysis of PKD1 and PKD2 in 700 unrelated patients. *Human Mutation*. 2012;33(8):1239-1250. doi:<https://dx.doi.org/10.1002/humu.22103>
 9. Pei Y, Watnick T. Diagnosis and screening of autosomal dominant polycystic kidney disease. *Advances in chronic kidney disease*. 2010;17(2):140-152.
 10. Dusic E, Theorin T, Wang C, Swisher EM, Bowen DJ, Team ES. Barriers, interventions, and recommendations: Improving the genetic testing landscape. *Frontiers in Digital Health*. 2022;4:961128.
 11. Torres VE, Ahn C, Barten TR, et al. KDIGO 2025 clinical practice guideline for the evaluation, management, and treatment of autosomal dominant polycystic kidney disease (ADPKD): executive summary. *Kidney International*. 2025;107(2):234-254.
 12. Genetic A, The New York-Mid-Atlantic Consortium for G, Newborn Screening S. Genetic Alliance Monographs and Guides. *Understanding Genetics: A New York, Mid-Atlantic Guide for Patients and Health Professionals*. Genetic Alliance
- Copyright © 2008, Genetic Alliance.; 2009.
13. 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. *Clinical Journal of the American Society of Nephrology*. 2021;16(5):671-673.
 14. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Annals of internal medicine*. 2018;169(7):467-473.
 15. McInnes MD, Moher D, Thombs BD, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. *Jama*. 2018;319(4):388-396.
 16. Campbell F, Tricco AC, Munn Z, et al. Mapping reviews, scoping reviews, and evidence and gap maps (EGMs): the same but different—the “Big Picture” review family. *Systematic reviews*. 2023;12(1):45.
 17. Haynes RB, Wilczynski NL. Optimal search strategies for retrieving scientifically strong studies of diagnosis from Medline: analytical survey. *Bmj*. 2004;328(7447):1040.

18. Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. *J Am Soc Nephrol*. 2009;20(1):205-12. doi:<https://dx.doi.org/10.1681/ASN.2008050507>
19. Pei Y, Hwang YH, Conklin J, et al. Imaging-based diagnosis of autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2015;26(3):746-53. doi:<https://dx.doi.org/10.1681/ASN.2014030297>
20. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *New England Journal of Medicine*. 2012;367(25):2407-2418.
21. Richards CS, Bale S, Bellissimo DB, et al. ACMG recommendations for standards for interpretation and reporting of sequence variations: Revisions 2007. *Genetics in Medicine*. 2008;10(4):294-300.
22. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of internal medicine*. 2011;155(8):529-536.
23. Demetriou K, Tziakouri C, Anninou K, et al. Autosomal dominant polycystic kidney disease - Type 2. Ultrasound, genetic and clinical correlations. *Nephrology Dialysis Transplantation*. 2000;15(2):205-211. doi:<https://dx.doi.org/10.1093/ndt/15.2.205>
24. Elles RG, Hodgkinson KA, Mallick NP, et al. Diagnosis of adult polycystic kidney disease by genetic markers and ultrasonographic imaging in a voluntary family register. *J Med Genet*. 1994;31(2):115-20.
25. Gabow PA, Kimberling WJ, Strain JD, Manco-Johnson ML, Johnson AM. Utility of ultrasonography in the diagnosis of autosomal dominant polycystic kidney disease in children. *J Am Soc Nephrol*. 1997;8(1):105-10.
26. Nicolau C, Torra R, Badenas C, et al. Autosomal dominant polycystic kidney disease types 1 and 2: assessment of US sensitivity for diagnosis. *Radiology*. 1999;213(1):273-6.
27. Parfrey PS, Bear JC, Morgan J, et al. The diagnosis and prognosis of autosomal dominant polycystic kidney disease. *N Engl J Med*. 1990;323(16):1085-90.
28. Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincaid-Smith P, Danks DM. Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. *Lancet*. 1994;343(8901):824-7.
29. Abdelwahed M, Hilbert P, Ahmed A, et al. Mutational analysis in patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD): Identification of five mutations in the PKD1 gene. *Gene*. 2018;671:28-35. doi:10.1016/j.gene.2018.05.112
30. Ali H, Al-Mulla F, Hussain N, et al. PKD1 Duplicated regions limit clinical Utility of Whole Exome Sequencing for Genetic Diagnosis of Autosomal Dominant Polycystic Kidney Disease. *Sci*. 2019;9(1):4141. doi:<https://dx.doi.org/10.1038/s41598-019-40761-w>
31. Bataille S, Berland Y, Fontes M, Burtsey S. High Resolution Melt analysis for mutation screening in PKD1 and PKD2. *BMC Nephrol*. 2011;12:57. doi:<https://dx.doi.org/10.1186/1471-2369-12-57>
32. Borrás DM, Vossen R, Liem M, et al. Detecting PKD1 variants in polycystic kidney disease patients by single-molecule long-read sequencing. *Hum Mutat*. 2017;38(7):870-879. doi:<https://dx.doi.org/10.1002/humu.23223>
33. Burtsey S, Lossi AM, Bayle J, Berland Y, Fontes M. Mutation screening of the PKD1 transcript by RT-PCR. *Journal of medical genetics*. 2002;39(6):422-429.
34. Carrera P, Calzavara S, Magistroni R, et al. Deciphering Variability of PKD1 and PKD2 in an Italian Cohort of 643 Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD). *Sci Rep*. 2016;6:30850. doi:10.1038/srep30850
35. Chang AR, Moore BS, Luo JZ, et al. Exome Sequencing of a Clinical Population for Autosomal Dominant Polycystic Kidney Disease. *Jama*. 2022;328(24):2412-2421. doi:10.1001/jama.2022.22847
36. Chang MY, Chen HM, Jenq CC, et al. Novel PKD1 and PKD2 mutations in Taiwanese patients with autosomal dominant polycystic kidney disease. *J Hum Genet*. 2013;58(11):720-7. doi:10.1038/jhg.2013.91

37. Choi R, Park HC, Lee K, et al. Identification of novel PKD1 and PKD2 mutations in Korean patients with autosomal dominant polycystic kidney disease. *BMC Med Genet.* 2014;15:129. doi:10.1186/s12881-014-0129-y
38. Elliott MD, James LC, Simms EL, et al. Mainstreaming Genetic Testing for Adult Patients With Autosomal Dominant Polycystic Kidney Disease. *Canadian Journal of Kidney Health and Disease.* 2021;8(no pagination)doi:<https://dx.doi.org/10.1177/20543581211055001>
39. Fujimaru T, Mori T, Sekine A, et al. Kidney enlargement and multiple liver cyst formation implicate mutations in PKD1/2 in adult sporadic polycystic kidney disease. *CLINICAL GENETICS.* 2018;94(1):125-131. doi:10.1111/cge.13249
40. Garcia-Gonzalez MA, Jones JG, Allen SK, et al. Evaluating the clinical utility of a molecular genetic test for polycystic kidney disease. *Mol Genet Metab.* 2007;92(1-2):160-7.
41. Hosseinpour M, Ardalani F, Mohseni M, et al. Targeted Next Generation Sequencing Revealed Novel Variants in the PKD1 and PKD2 Genes of Iranian Patients with Autosomal Dominant Polycystic Kidney Disease. *Arch Iran Med.* 2022;25(9):600-608. doi:<https://dx.doi.org/10.34172/aim.2022.95>
42. Hu HY, Zhang J, Qiu W, et al. Comprehensive strategy improves the genetic diagnosis of different polycystic kidney diseases. *Journal of Cellular and Molecular Medicine.* 2021;25(13):6318-6332. doi:<https://dx.doi.org/10.1111/jcmm.16608>
43. Hwang YH, Conklin J, Chan WN, et al. Refining Genotype-Phenotype Correlation in Autosomal Dominant Polycystic Kidney Disease. *JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY.* 2016;27(6):1861-1868. doi:10.1681/ASN.2015060648
44. Iliuta IA, Kalatharan V, Wang K, et al. Polycystic Kidney Disease without an Apparent Family History. *J Am Soc Nephrol.* 2017;28(9):2768-2776. doi:10.1681/asn.2016090938
45. Inoue S, Inoue K, Utsunomiya M, et al. Mutation analysis in PKD1 of Japanese autosomal dominant polycystic kidney disease patients. *Hum Mutat.* 2002;19(6):622-8. doi:10.1002/humu.10080
46. Jin M, Xie Y, Chen Z, et al. System analysis of gene mutations and clinical phenotype in Chinese patients with autosomal-dominant polycystic kidney disease. *Sci Rep.* 2016;6:35945. doi:10.1038/srep35945
47. Kim H, Park HC, Ryu H, et al. Genetic Characteristics of Korean Patients with Autosomal Dominant Polycystic Kidney Disease by Targeted Exome Sequencing. *Sci Rep.* 2019;9(1):16952. doi:10.1038/s41598-019-52474-1
48. Kinoshita M, Higashihara E, Kawano H, et al. Technical Evaluation: Identification of Pathogenic Mutations in PKD1 and PKD2 in Patients with Autosomal Dominant Polycystic Kidney Disease by Next-Generation Sequencing and Use of a Comprehensive New Classification System. *PLoS ONE.* 2016;11(11):e0166288. doi:<https://dx.doi.org/10.1371/journal.pone.0166288>
49. Li WN, Liu G, Zhao XG, et al. Genetic testing, ultrasonography and preimplantation genetic testing of men with autosomal dominant polycystic kidney disease in Hunan, China. *Andrologia.* 2022;54(1):12. doi:10.1111/and.14273
50. Lindemann CH, Wenzel A, Erger F, et al. A Low-Cost Sequencing Platform for Rapid Genotyping in ADPKD and its Impact on Clinical Care. *Kidney Int Rep.* 2023;8(3):455-466. doi:10.1016/j.ekir.2022.12.025
51. Liu B, Chen SC, Yang YM, et al. Identification of novel PKD1 and PKD2 mutations in a Chinese population with autosomal dominant polycystic kidney disease. *Sci Rep.* 2015;5:17468. doi:10.1038/srep17468
52. Liu W, Chen M, Wei J, et al. Modification of PCR conditions and design of exon-specific primers for the efficient molecular diagnosis of PKD1 mutations. *Kidney and Blood Pressure Research.* 2014;39(6):536-545. doi:<https://dx.doi.org/10.1159/000368464>
53. Mallawaarachchi AC, Lundie B, Hort Y, et al. Genomic diagnostics in polycystic kidney disease: an assessment of real-world use of whole-genome sequencing. *Eur J Hum Genet.* 2021;29(5):760-770. doi:<https://dx.doi.org/10.1038/s41431-020-00796-4>
54. Mantovani V, Bin S, Graziano C, et al. Gene Panel Analysis in a Large Cohort of Patients With Autosomal Dominant Polycystic Kidney Disease Allows the Identification of 80 Potentially Causative

- Novel Variants and the Characterization of a Complex Genetic Architecture in a Subset of Families. *Frontiers in Genetics*. 2020;11 (no pagination)doi:<https://dx.doi.org/10.3389/fgene.2020.00464>
55. Mochizuki T, Teraoka A, Akagawa H, et al. Mutation analyses by next-generation sequencing and multiplex ligation-dependent probe amplification in Japanese autosomal dominant polycystic kidney disease patients. *Clin Exp Nephrol*. 2019;23(8):1022-1030. doi:<https://dx.doi.org/10.1007/s10157-019-01736-3>
 56. Obeidova L, Elisakova V, Stekrova J, et al. Novel mutations of PKD genes in the Czech population with autosomal dominant polycystic kidney disease. *BMC Med Genet*. 2014;15:41. doi:10.1186/1471-2350-15-41
 57. Orisio S, Noris M, Rigoldi M, et al. Mutation Analysis of PKD1 and PKD2 Genes in a Large Italian Cohort Reveals Novel Pathogenic Variants Including A Novel Complex Rearrangement. *Nephron*. 2023;25doi:<https://dx.doi.org/10.1159/000530657>
 58. Pandita S, Ramachandran V, Balakrishnan P, et al. Identification of PKD1 and PKD2 gene variants in a cohort of 125 Asian Indian patients of ADPKD. *J Hum Genet*. 2019;64(5):409-419. doi:10.1038/s10038-019-0582-8
 59. Phakdeekitcharoen B, Watnick TJ, Ahn C, Whang DY, Burkhart B, Germino GG. Thirteen novel mutations of the replicated region of PKD1 in an Asian population. *Kidney Int*. 2000;58(4):1400-12. doi:10.1046/j.1523-1755.2000.00302.x
 60. Phakdeekitcharoen B, Watnick TJ, Germino GG. Mutation Analysis of the Entire Replicated Portion of PKD1 Using Genomic DNA Samples. *Journal of the American Society of Nephrology*. 2001;12(5):955-963.
 61. Raj S, Singh RG, Das P. Mutational screening of PKD1 and PKD2 in Indian ADPKD patients identified 95 genetic variants. *Mutat Res*. 2020;821:111718. doi:10.1016/j.mrfmmm.2020.111718
 62. Ranjzad F, Tara A, Basiri A, Aghdami N, Moghadasali R. Mutational screening of PKD1 and PKD2 Genes in Iranian population diagnosed with autosomal dominant polycystic kidney disease. *Clinical Laboratory*. 2017;63(7-8):1261-1267. doi:<https://dx.doi.org/10.7754/Clin.Lab.2017.170209>
 63. Rossetti S, Chauveau D, Walker D, et al. A complete mutation screen of the ADPKD genes by DHPLC. *Kidney Int*. 2002;61(5):1588-99.
 64. Rossetti S, Consugar MB, Chapman AB, et al. Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. *J Am Soc Nephrol*. 2007;18(7):2143-60. doi:10.1681/asn.2006121387
 65. Rossetti S, Hopp K, Sikkink RA, et al. Identification of gene mutations in autosomal dominant polycystic kidney disease through targeted resequencing. *J Am Soc Nephrol*. 2012;23(5):915-33. doi:10.1681/asn.2011101032
 66. Schonauer R, Baatz S, Nemitz-Kliemchen M, et al. Matching clinical and genetic diagnoses in autosomal dominant polycystic kidney disease reveals novel phenocopies and potential candidate genes. *Genetics in Medicine*. 2020;22(8):1374-1383. doi:<https://dx.doi.org/10.1038/s41436-020-0816-3>
 67. Tan AY, Michael A, Liu G, et al. Molecular diagnosis of autosomal dominant polycystic kidney disease using next-generation sequencing. *J Mol Diagn*. 2014;16(2):216-28. doi:<https://dx.doi.org/10.1016/j.jmoldx.2013.10.005>
 68. Tan YC, Blumenfeld JD, Anghel R, et al. Novel method for genomic analysis of PKD1 and PKD2 mutations in autosomal dominant polycystic kidney disease. *Hum Mutat*. 2009;30(2):264-73. doi:<https://dx.doi.org/10.1002/humu.20842>
 69. Trujillano D, Bullich G, Ossowski S, et al. Diagnosis of autosomal dominant polycystic kidney disease using efficient PKD1 and PKD2 targeted next-generation sequencing. *Molecular genetics & genomic medicine*. 2014;2(5):412-21. doi:10.1002/mgg3.82
 70. Virzi GM, Bruson A, Corradi V, et al. High-resolution melt as a screening method in autosomal dominant polycystic kidney disease (ADPKD). *J Clin Lab Anal*. 2014;28(4):328-34. doi:10.1002/jcla.21689

71. Xu D, Ma Y, Gu X, et al. Novel Mutations in the PKD1 and PKD2 Genes of Chinese Patients with Autosomal Dominant Polycystic Kidney Disease. *Kidney Blood Press Res.* 2018;43(2):297-309. doi:10.1159/000487899
72. Yang T, Meng Y, Wei X, et al. Identification of novel mutations of PKD1 gene in Chinese patients with autosomal dominant polycystic kidney disease by targeted next-generation sequencing. *Clin Chim Acta.* 2014;433:12-9. doi:10.1016/j.cca.2014.02.011
73. Yu CW, Yang YA, Zou L, et al. Identification of novel mutations in Chinese Hans with autosomal dominant polycystic kidney disease. *BMC Med Genet.* 2011;12:7. doi:10.1186/1471-2350-12-164
74. Zhang M, Liu S, Xia X, Cui Y, Li X. Identification of novel mutations and risk assessment of Han Chinese patients with autosomal dominant polycystic kidney disease. *Nephrology (Carlton).* 2019;24(5):504-510. doi:10.1111/nep.13270
75. Zhang S, Mei C, Zhang D, et al. Mutation analysis of autosomal dominant polycystic kidney disease genes in Han Chinese. *Nephron Exp Nephrol.* 2005;100(2):e63-76. doi:10.1159/000084572
76. Zhao X, Paterson AD, Zahirieh A, He N, Wang K, Pei Y. Molecular diagnostics in autosomal dominant polycystic kidney disease: utility and limitations. *Clinical journal of the American Society of Nephrology : CJASN.* 2008;3(1):146-152. doi:<https://dx.doi.org/10.2215/CJN.03430807>
77. Liu G, Tan AY, Michael A, et al. Development and validation of a whole genome amplification long-range PCR sequencing method for ADPKD genotyping of low-level DNA samples. *Gene.* 2014;550(1):131-135.
78. Senum SR, Li YSM, Benson KA, et al. Monoallelic IFT140 pathogenic variants are an important cause of the autosomal dominant polycystic kidney-spectrum phenotype. *The American Journal of Human Genetics.* 2022;109(1):136-156.
79. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genetics in medicine.* 2015;17(5):405-423.
80. Talking glossary of genomic and genetic terms. National Human Genome Research Institute. Accessed 26/09/2024, <https://www.genome.gov/genetics-glossary>
81. Genomics glossary. Genomics Education Programme. Updated 28/06/2019. Accessed 26/09/2024, <https://www.genomicseducation.hee.nhs.uk/glossary/>

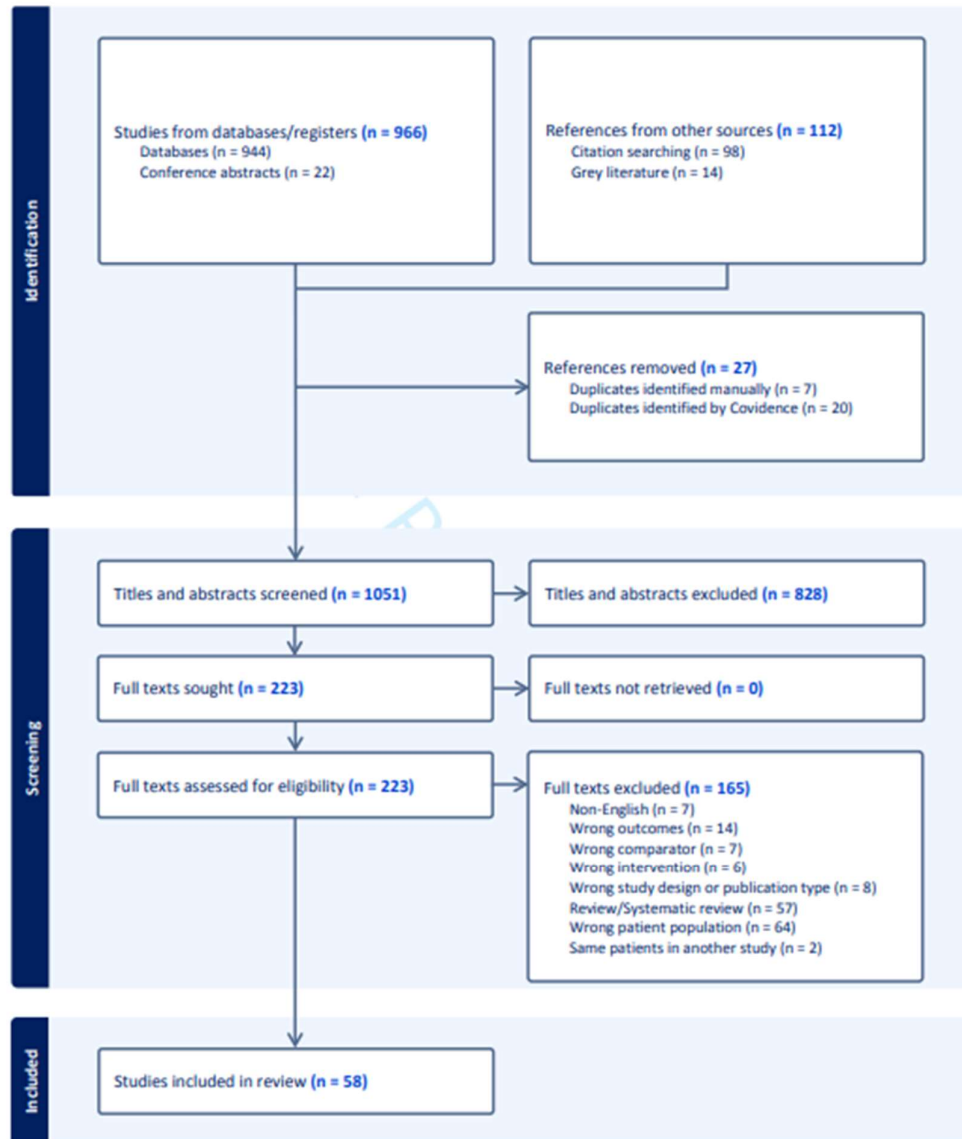


Figure 1 PRISMA flow chart showing the process of study selection for the review.

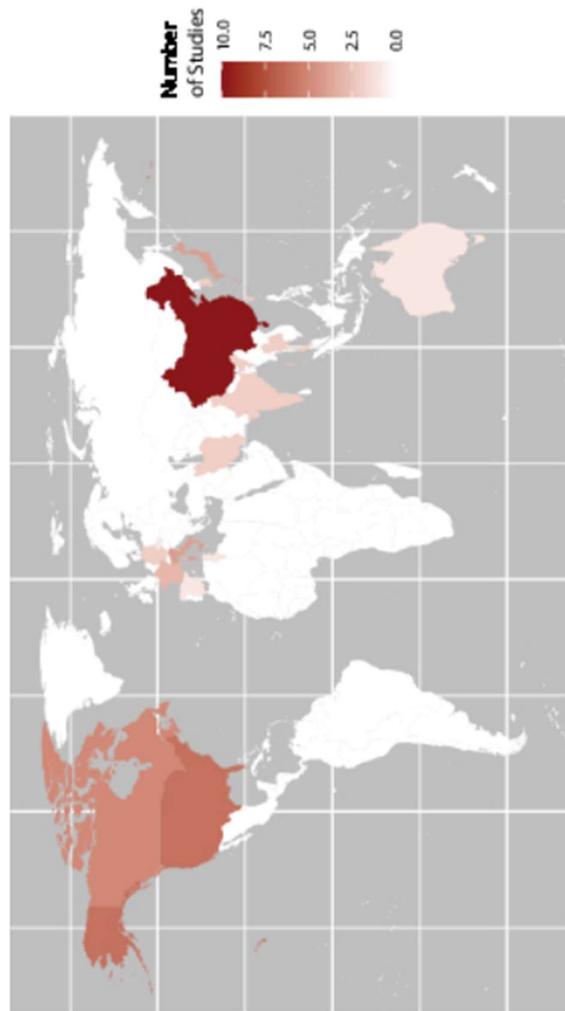


Figure 2 Map of origin of included studies

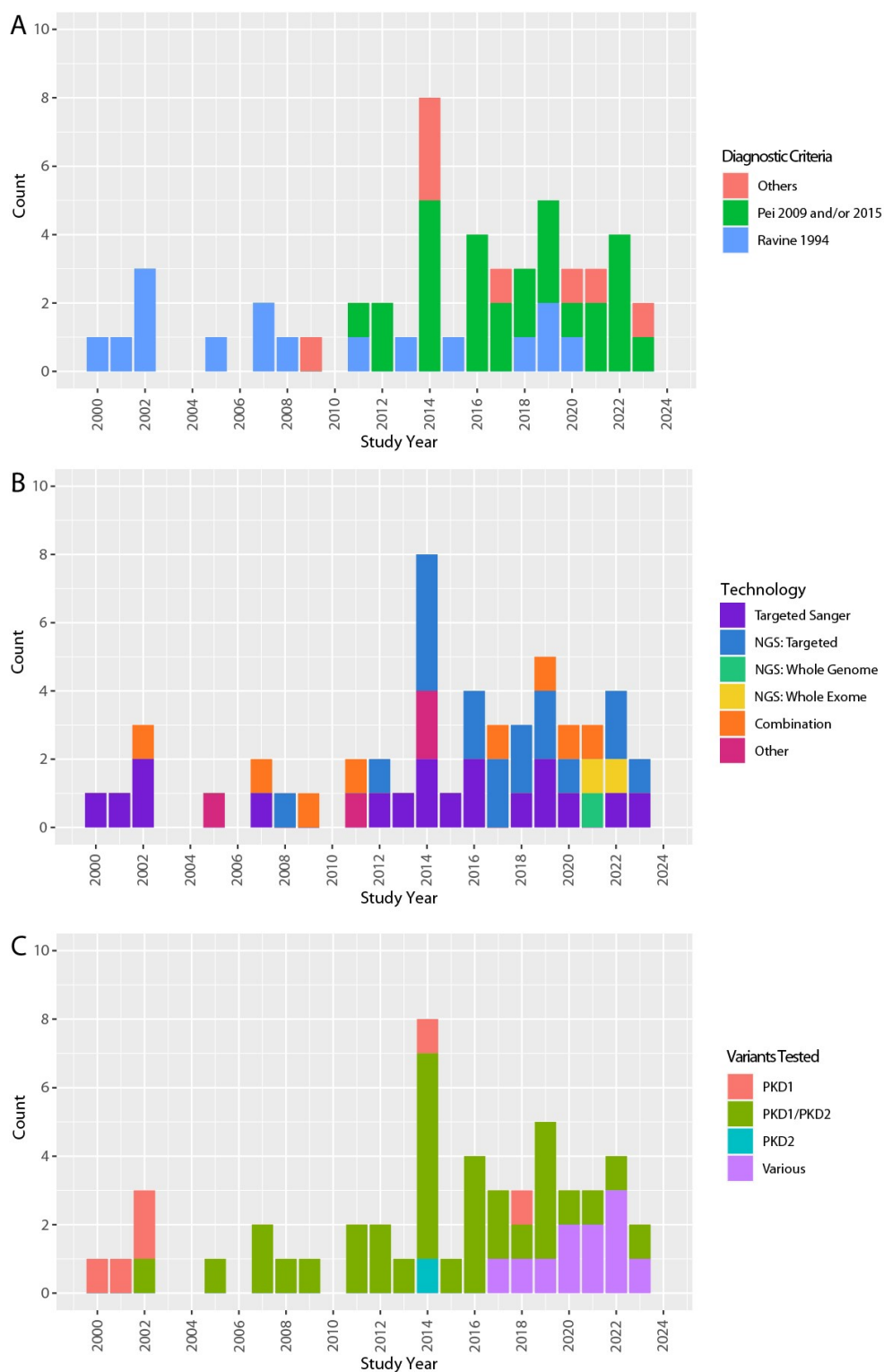


Figure 3: Charts of study characteristics over time. A) Diagnostic criteria/radiological reference standard for inclusion of individuals with clinical diagnosis of ADPKD by year of study publication; B) Genomic test technology by year of study publication; and C) Genes analysed by genomic tests by year of study publication.

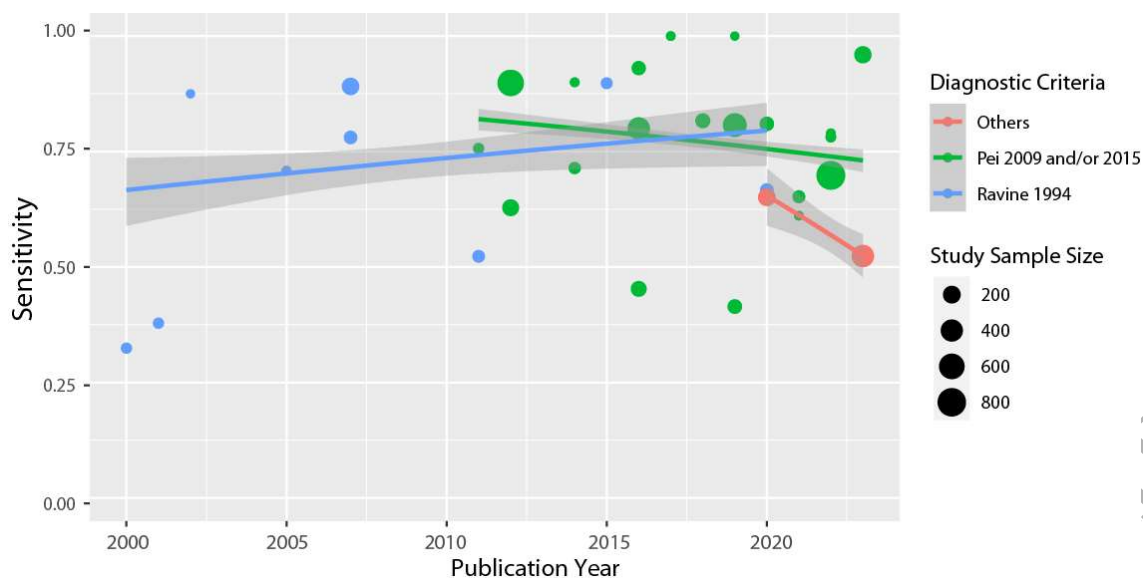


Figure 4 Diagnostic test accuracy (proportion with genomic variants classed as definitely pathogenic, pathogenic, likely pathogenic and probability pathogenic or similar terms), stratified by genes targeted and recruitment criteria, by study publication year. Blue line = studies recruiting according to Ravine 1994, with genomic testing for PKD1 or more; Green line = studies recruiting according to Pei 2009/2015, with genomic testing for PKD1 and PKD2 or more; Red line = studies recruiting according to other criteria, with genomic testing for more than PKD1 and PKD2. Studies weighted by size when estimating longitudinal changes and 95% confidence intervals (grey).

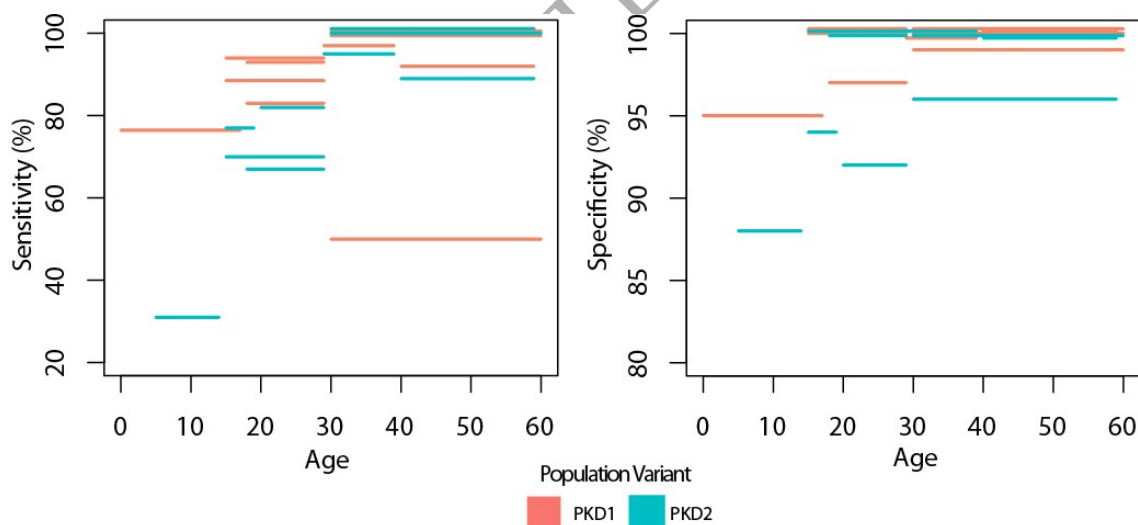


Figure 5 Sensitivity and specificity of ultrasound studies. Each bar represents the sensitivity or specificity for the age range spanned by the bar, as reported by individual studies included in this review.

Table 1. The selection criteria for the review

	Genomic test or strategy utilising genomic test(s)		Grey-scale ultrasound
Population	1st degree relatives of patients with an ADPKD diagnosis (clinical or genomic)	People with a clinical ADPKD diagnosis according to Pei <i>et al.</i> , 2009 ¹⁸ or Ravine <i>et al.</i> , 1994. ^{28*} With or without a family history, related or unrelated (preferred).***	1st degree relatives of patients with an ADPKD diagnosis (clinical or genomic) Studies in foetuses were excluded
Index test	Genomic test or diagnostic strategy utilising genomic tests		Grey-scale ultrasound
Reference standard	Imaging according to Pei <i>et al.</i> , 2009 ¹⁸ or Ravine <i>et al.</i> , 1994. ^{28*} or genomic confirmation**		Imaging according to Pei <i>et al.</i> , 2009 ¹⁸ or Ravine <i>et al.</i> , 1994. ^{28*} after age 40 or genomic confirmation**
Target condition	ADPKD		
Outcome	<ul style="list-style-type: none"> • Sensitivity and specificity; TP, FP, TN, FN. If not available, diagnostic rate (sensitivity)****. • Rates of pathogenic variants, variants of unknown significance, no pathogenic variants etc. 		
Study design	Diagnostic test accuracy studies. If none available, studies reporting sensitivity only were eligible.		

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; CT, computed tomography; FN, false negative; FP, false positive; MRI, magnetic resonance imaging; TN, true negative; TP, true positive

*studies which used alternative criteria, e.g. Torres *et al.*, 2012,²⁰ for atypical presentations were also included; Studies that considered negative scans in patients before 40 years of age as definitive were excluded; studies that applied Pei *et al.*, 2015¹⁹ criteria for CT and MRI imaging or Pei *et al.*, 2009¹⁸ or Ravine *et al.*, 1994²⁸ criteria for ultrasound were included. In cases of doubt about recruitment criteria, clinical experts were consulted.

**no limits were placed on the type of genomic confirmation. For genomic studies, only extracted data using a genomic reference standard if no data using an imaging reference standard were available from that study

*** where there was a choice, data for unrelated probands were extracted in preference to data for a mix of related and unrelated participants.

**** Diagnostic rate was only acceptable where studies recruited only patients with a clinical ADPKD diagnosis, and in this circumstance is equivalent to sensitivity of the test since all participants have clinical ADPKD (i.e. are reference-standard positive and therefore comprise all true positives and false negatives, but no true negatives or false positives).

Table 2. Sequencing technology component definitions^{80,81}

Components of genomic testing	Definition
Technology	The specific tools and platforms used to sequence and analyse DNA
Read length	The length of DNA sequence read by a sequencing machine in a single run, typically ranging from 50 to several thousand base pairs
Enrichment method	Techniques used to selectively capture and sequence specific regions of the genome
Analysis	Computational processes and algorithms used to interpret raw sequencing data including the examination of specific sets of genes
Genomic structural variation analysis	The identification of changes such as deletions, insertions, inversions, translocations, single nucleotide variations and copy number variations

Table 3 Characteristics of studies included in the review

Author, year, Country	N in study	Proband/per family?	Family history	Reference standard*	Genes targeted	Enrichment method	Small sequence variant analysis	Copy number variant analysis
Targeted Sanger Sequencing (n=18)								
Pei 2009 recruitment criteria (n=4)								
Ali 2019 ³⁰ Kuwait	6	Proband or per family	With family history	Pei 2009	<i>PKD1</i> ; <i>PKD2</i>	Amplicon	NA	None
Audrezet 2012 ⁸ France	528 (with FH) 172 (Without FH)	Proband or per family	With family history Without family history	Pei 2009	<i>PKD1</i> ; <i>PKD2</i>	Amplicon	NA	None
Hwang 2016 ⁴³ Canada	220	Proband or per family	Either with or without family history	Pei 2009	<i>PKD1</i> ; <i>PKD2</i>	Amplicon	NA	MLPA
Li 2022 ⁴⁹ China	19	Proband or per family	Either with or without family history	Pei 2009	<i>PKD1</i> ; <i>PKD2</i> ; <i>GANAB</i>	Amplicon	NA	MLPA
Pei 2009 and Torres 2012 recruitment criteria (n=1)								
Liu 2014a ⁵² China	10	Proband or per family	Either with or without family history	Family history: Pei 2009; no family history, Torres 2012	<i>PKD1</i>	Amplicon	NA	MLPA
Pei 2009/2015 recruitment criteria (n=2)								
Carrera 2016 ³⁴ Italy	440	Proband or per family	Either with or without family history	Pei 2009/2015	<i>PKD1</i> ; <i>PKD2</i>	Amplicon	NA	MLPA
Orisio 2023 ³⁷ Italy	198	Proband or per family	Either with or without family history	Pei 2009/2015	<i>PKD1</i> ; <i>PKD2</i>	Amplicon	NA	MLPA
Ravine 1994 recruitment criteria (n=10)								
Abdelwahed 2018 ²⁹ Tunisia	18	Some related	Either with or without family history	Ravine 1994	<i>PKD1</i>	Amplicon	NA	MLPA

Author, year, Country	N in study	Proband/per family?	Family history	Reference standard*	Genes targeted	Enrichment method	Small sequence variant analysis	Copy number variant analysis
Hosseinpour 2022 ⁴¹ Iran	32	Proband or per family	Either with or without family history	Pei 2015	<i>PKD1</i> ; <i>PKD2</i>	Hybridisation	Targeted panel	None
Ravine 1994 recruitment criteria (n=2)								
Zhang 2019 ⁷⁴ China	62	Proband or per family	Not reported	Ravine 1994	<i>PKD1</i> ; <i>PKD2</i> ; <i>PKHD1</i>	Hybridisation	Targeted panel	MLPA
Zhao 2008 ⁷⁶ Canada	3	Proband or per family	Either with or without family history	Ravine 1994 in Probands	<i>PKD1</i> ; <i>PKD2</i>	Amplicon	Targeted panel	None

ORIGINAL UNEDITED MANUSCRIPT

Author, year, Country	N in study	Proband/per family?	Family history	Reference standard*	Genes targeted	Enrichment method	Small sequence variant analysis	Copy number variant analysis
Pei 2009/Torres recruitment criteria (n=1)								
Fujimaru 2018 ³⁹ Japan	53	Proband or per family	Without family history	CT or MRI (>10 cysts in each kidney), Pei 2009, Torres 2012, Torres 2017	69 genes causing hereditary renal cystic disease	Hybridisation	Targeted panel	NGS CNV
Other imaging recruitment criteria*** (n=2)								
Lindemann 2023 ⁵⁰ Germany	441 123	Unclear	Either with or without family history	Imaging as per footnote***	<i>PKD1</i> ; <i>PKD2</i> ; <i>GANAB</i> ; <i>HNF1b</i>	Amplicon	Targeted panel	None
Mantovani 2020 ⁵⁴ Italy	191	Unclear	Either with or without family history	Pei 2009 criteria for US, MRI, CT if equivocal	<i>PKD1</i> ; <i>PKD2</i> ; 14 additional cystogenes (if negative)	Amplicon	Targeted panel	MLPA
Genomic criteria (<i>PKD1</i> or <i>PKD2</i> pathogenic variants) (n=1)								
Trujillano 2014 ⁶⁹ Spain	36	Unclear	Not reported	Sanger sequencing of <i>PKD1/2</i> exons, and if negative MLPA	<i>PKD1</i> ; <i>PKD2</i>	Amplicon	Targeted panel	None
Next Generation Sequencing: Targeted – Long read (n=1)								
Genomic recruitment criteria (n=1)								
Borras 2017 ³² Europe	19	Proband/per family	NR	Genomic (short read WGS or WES)	<i>PKD1</i> ; <i>PKD2</i>	SMRT	Panel	NGS breakpoint detection, MLPA

Author, year, Country	N in study	Proband/per family?	Family history	Reference standard*	Genes targeted	Enrichment method	Small sequence variant analysis	Copy number variant analysis
Next Generation Sequencing: WGS – Short read (n=1)								
Pei 2009 recruitment criteria (n=1)								
Mallawaarachchi 2021 ⁵³ Australia	42	Proband/per family	Either with or without family history	Pei 2009	<i>PKD1</i> ; <i>PKD2</i>	Hybridisation	Virtual panel	NGS CNV, MLPA
Next Generation Sequencing: WES – Short read (n=2)								
Pei 2009 and wider atypical disease recruitment criteria (n=2)								
Chang 2022 ³⁵ USA	235	Unclear	Either with or without family history	Pei 2009	<i>PKD1</i> , <i>PKD2</i> , and 11 atypical cystic genes (<i>ALG8</i> , <i>ALG9</i> , <i>DNAJB11</i> , <i>GANAB</i> , <i>HNF1B</i> , <i>IFT140</i> , <i>LRP5</i> , <i>PKHD</i> , <i>PRKCSH</i> , <i>SEC61B</i> , <i>SEC63</i>)	Hybridisation	Virtual panel	NGS CNV

Author, year, Country	N in study	Proband/per family?	Family history	Reference standard*	Genes targeted	Enrichment method	Small sequence variant analysis	Copy number variant analysis
Elliott 2021 ³⁸ Canada	18	Proband or per family	Either with or without family history	<p>Typical ADPKD: Pei 2009</p> <p>Atypical ADPKD: atypical kidney imaging (Mayo Class 2), no family history, atypical clinical presentation, suspicion for another genomic CKD</p>	<p>Typical ADPKD: <i>PKD1</i>; <i>PKD2</i></p> <p>Atypical ADPKD: <i>PKD1</i>, <i>PKD2</i>, <i>COL4A1</i>, <i>DNAJB11</i>, <i>GANAB</i>, <i>HNF1B</i>, <i>REN</i>, and <i>UMOD</i>.</p>	Hybridisation	Virtual panel	None

ORIGINAL UNEDITED MANUSCRIPT

Author, year, Country	N in study	Proband/per family?	Family history	Reference standard*	Genes targeted	Enrichment method	Small sequence variant analysis	Copy number variant analysis
Iliuta 2017 ⁴⁴ Not reported	205	Proband or per family	Either with or without family history (and reported separately)	Pei 2009 & Pei 2015	<i>PKD1</i> ; <i>PKD2</i> ; <i>GANAB</i> ; <i>HNF1B</i>	Hybridisation	NA/Targeted Panel	None
Targeted NGS then Sanger with MLPA then familial segregation analysis (n=1)								
Pei 2009 recruitment criteria (n=1)								
Kim 2019 ⁴⁷ Korea	524	Proband or per family	Either with or without family history	Pei 2009	<i>PKD1</i> ; <i>PKD2</i>	Hybridisation	Targeted Panel/NA	MLPA
Other types of tests (n=4)								
High Resolution Melt HRM(n=3)								
Pei 2009 recruitment criteria (n=2)								
Bataille 2011 ³¹ France	37	Proband or per family	Not reported	Pei 2009	<i>PKD1</i> ; <i>PKD2</i>	NA	NA	None
Obeidova 2014 ⁵⁶ Czech republic	56	Proband or per family	Either with or without family history	Pei 2009	<i>PKD1</i> ; <i>PKD2</i>	NA	NA	MLPA
PKD-2 linkage analysis recruitment criteria (n=1)								
Virzi 2014 ⁷⁰ Italy	16	Proband or per family	Not reported	<i>PKD2</i> linkage analysis	<i>PKD2</i>	NA	NA	None

Author, year, Country	N in study	Proband/per family?	Family history	Reference standard*	Genes targeted	Enrichment method	Small sequence variant analysis	Copy number variant analysis
Single-strand conformation polymorphism analysis (n=1)								
Ravine 1994 recruitment criteria (n=1)								
Zhang 2005 ⁷⁵ China	24	Proband or per family	Not reported	Ravine 1994	<i>PKD1</i> ; <i>PKD2</i>	NA	NA	None

* Reference standard: Terms such as “unified criteria”, “Ravine-Pei” and so on were assumed to be Pei *et al.*, 2009¹⁸

**Three cohorts were reported: Patient with ADPKD previously analysed by sanger sequencing (n=25); ADPKD cases that tested negative by Sanger sequencing (n=3); ADPKD not previously genomically tested (n=25)

*** Recruitment criteria: Lindeman *et al.*, 2023,⁵⁰ if family history, Pei *et al.*, 2009/2015,^{18,19} if no family history, at least 10 cysts per kidney, bilaterally enlarged kidneys, at least 1 classic extrarenal manifestation of ADPKD, and no extrarenal manifestations pointing toward differential diagnoses (e.g., hepatic fibrosis); Mantovani *et al.*, 2020,⁵⁴ Pei *et al.*, 2009¹⁸ for ultrasound, could use MRI or CT if equivocal.

ORIGINAL UNEDITED MANUSCRIPT

Table 4 **Characteristics of studies reporting test accuracy of ultrasound**

Author, year, Country	Population	N in study	Index test criteria for ADPKD	Ultrasound technology	Reference standard*	Age bands reported	Gene subgroups reported
Ultrasound							
1st degree relatives							
Parfrey 1990 ²⁷ (Bear 1992) Canada	1st degree family members of <i>PKD1</i> families (confirmed by gene linkage)	126 people from 10 <i>PKD1</i> families	1+ / 2+	NR	Gene linkage analysis	</> 30 years	All were <i>PKD1</i>
Elles 1994 ²⁴ UK	1st degree relatives of ADPKD (criteria for probands unclear)	80	Bear 1984 1+ / 2+	3.5-MHz scanner	Genomic markers	</> 30 years	Only reports results for <i>PKD1</i>
Ravine 1994 ²⁸ Australia	Undiagnosed 1st degree relatives of confirmed <i>PKD1</i> probands	204 (from 18 families)	1+ / 2+	3- or 5-MHZ	>95% or <5% probability of <i>PKD1</i> by DNA linkage analysis	15-29 ≥30	All were <i>PKD1</i>
Gabow 1997 ²⁵	Children 1st degree relatives of ADPKD1 families (genomically confirmed)	106 children (from 40 families)	Any cysts	NR	Gene linkage analysis	Children	All were <i>PKD1</i>

Author, year, Country	Population	N in study	Index test criteria for ADPKD	Ultrasound technology	Reference standard*	Age bands reported	Gene subgroups reported
Nicolau 1999 ²⁶ Spain	1st degree relatives of Type 1 or Type 2 ADPKD (genomically confirmed)	319 individuals from 54 families	Ravine 1994: <30: 2+ in total 30-59: 2+ / 2+ >60: 4+ / 4+	3.7 or 5-MHz	Genetic linkage study	</>30 years	<i>PKD1</i> <i>PKD2</i>
Demetriou 2000 ²³ Cyprus	1st degree relatives of ADPKD Type 2 families	211 alive people at risk from 3 families	Ravine 1994 (ADPKD-1) for adults and Gabow 1997 for children 5-14: 1+ Cysts 15-19: 1+ / 1+ Cysts Or 2+ / 0 20-29: 2+ / 1+ (3+ and bilateral involvement) 30-59: 2+ / 2+ 60>: 4+ / 4+	3.5 or 5-MHz	DNA linkage and direct mutation analyses	5-14 15-19 20-29 30-59 60>	All were <i>PKD2</i>
Pei 2009 ¹⁸ Australia, Europe, US	1st degree relatives at risk of PKD1 or PKD2 (proband diagnostic criteria unclear)	948	15-39: 3+ total 40-59: 2+ / 2+ >=60: 4+ / 4+	3- or 5-Mhz	Genomic testing (range of methods)	15-29 30-39 40-59 60+	<i>PKD1</i> <i>PKD2</i> Simulated cohort of mixed PKD1/2

ADPKD, autosomal-dominant polycystic kidney disease; DNA, deoxyribonucleic acid; PKD, polycystic kidney disease; NR, not reported.

[Click here for Prescribing Information](#)




This is a promotional advertisement intended for UK HCPs only, produced and funded by MEDICE UK

Vafseo® is indicated for the treatment of symptomatic anaemia associated with chronic kidney disease (CKD) in adults on chronic maintenance dialysis¹

A once-daily oral treatment for anaemia associated with CKD in patients receiving dialysis¹

Vafseo® is now recommended by NICE, within its marketing authorisation, as an option for treating symptomatic anaemia caused by CKD in adults having maintenance dialysis²



Contact MEDICE UK now to be put in touch with your regional Vafseo® Key Account Manager

Contact Us

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Adverse events should be reported. Reporting forms and information can be found at <https://yellowcard.mhra.gov.uk/> or search for MHRA Yellow Card in Google Play or Apple App Store. Adverse events should also be reported to Medice UK Ltd, 0204 582 2845, medicalinformation@medice.co.uk

MEDICE UK makes no warranties or representations of any kind as to the accuracy, completeness, reliability or usefulness of any information contained in third party sites and shall have no liability for any loss or damage of any kind that may arise from your use of such content or information. Inclusion of any third-party link does not imply an endorsement or recommendation by MEDICE UK.

Abbreviations: CKD, chronic kidney disease; HCP, healthcare professional; NICE, National Institute of Health and Care Excellence. **References:** 1. Vafseo 300 mg film-coated tablets Summary of Product Characteristics (SmPC). Available at: <https://www.medicines.org.uk/emc/product/15856/ampc> (Accessed March 2025). 2. NICE Guidance TA1035. Vadadustat for treating symptomatic anaemia in adults having dialysis for chronic kidney disease. Available at: <https://www.nice.org.uk/guidance/ta1035> (Accessed March 2025).



UK-VAF-2024-1983-v2
March 2025