KHA-CARI Autosomal Dominant Polycystic Kidney Disease Guideline: Imaging Approaches for Diagnosis

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GUIDELINE RECOMMENDATIONS*

a. We recommend ultrasound to be used as the first line imaging modality for diagnosis (1B)

b. We suggest using the age and genotype-dependent criterion listed below for diagnosis in at-risk individuals: (2B)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of cysts</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-39</td>
<td>At least 3 (unilateral or bilateral)</td>
</tr>
<tr>
<td>40-59</td>
<td>At least 2 in each kidney</td>
</tr>
<tr>
<td>&gt; 60</td>
<td>At least 4 in each kidney</td>
</tr>
</tbody>
</table>

Table 1. Diagnostic Criteria for At-Risk Individual With Positive Family History†

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of cysts</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40</td>
<td>No recommendation</td>
</tr>
<tr>
<td>≥ 40</td>
<td>Less than 2 cysts in each kidney</td>
</tr>
</tbody>
</table>

Table 2. Exclusion Criteria for At-Risk Individual With Positive Family History†

c. We recommend when ultrasound findings are equivocal and absolute disease exclusion is required, such as in the case of potential kidney donors, that molecular genotyping be performed as the diagnostic gold standard (1A)

Table 3. Suggested MRI Criterion for At-Risk Individual Older Than 15 Years With Positive Family History

<table>
<thead>
<tr>
<th>ADPKD</th>
<th>Number of renal cysts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>≥ 10 cysts in total</td>
</tr>
<tr>
<td>Exclusion</td>
<td>&lt; 5 cysts in total</td>
</tr>
</tbody>
</table>

For those with equivocal ultrasound findings not fitting into the guidelines above, and who do not require

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†Criteria used for recommendations and levels of evidence (1,2;A-D) are described in more detail in Tables 1 and 2 of Rangan G, Savige J. Introduction to the KHA-CARI Guidelines on ADPKD. Semin Nephrol. 2015;35:521-3 in this issue.

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UNGRADED SUGGESTIONS FOR CLINICAL CARE

Approach to Individuals With Equivocal Ultrasound Diagnosis

• Magnetic resonance imaging (MRI) can be considered as an alternative for disease exclusion in cases with an equivocal ultrasound diagnosis, or when molecular genotyping cannot be carried out. Gadolinium enhancement is preferable but not essential, and should be avoided in those with a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m² because of risk of nephrogenic systemic fibrosis (NSF). Greater than 10 cysts in total can be used as a cut-off for making a diagnosis using MRI, and a total of less than five cysts for disease exclusion. This is applicable for all individuals older than 15 years of age (Table 3).
immediate disease exclusion or confirmation, expert opinion suggests follow-up imaging with ultrasound in 5 to 10 years.

**Approach to Individuals With Renal Cysts Without Family History of Autosomal Dominant Polycystic Kidney Disease**

- Due to lack of evidence for diagnostic criteria for an individual with findings of cystic renal disease and with no family history, a number of factors should be considered when making a diagnosis:
  - Ultrasound imaging should be performed on the affected individual’s parents to assess for asymptomatic PKD2.
  - Ultrasound imaging for extra-renal cystic diseases including liver and pancreatic cysts can aid with diagnosis.
  - For less typical cases (borderline number of cysts and absence of frank kidney enlargement), serial imaging studies to track cyst growth or genetic testing may be necessary to make a diagnosis of autosomal dominant polycystic kidney disease (ADPKD).
  - If an arbitrary number for renal cyst count is to be enforced, then 10 cysts in total detectable on ultrasound seems to be the general consensus.

**IMPLEMENTATION AND AUDIT**

1. Audits should be conducted on the number of patients receiving screening as well as the number of diagnostic cases.
2. All positive cases should be flagged for medical follow-up to monitor disease progression and manage complications, either through the primary health provider or the nephrologist.
3. All equivocal cases should also be flagged for follow-up scanning in 5 to 10 years.

**BACKGROUND**

ADPKD is the most common hereditary disease that affects 1 in 500 to 1000 live births. The main feature of this disorder is the progressive development of renal and extrarenal cysts in an age-dependent manner, ultimately leading to parenchymal destruction and renal failure. There are two identified genes, polycystic kidney disease 1 (PKD1) and 2 (PKD2) that code for polycystin 1 and 2, respectively. The mutations for PKD1 and PKD2 genes account for approximately 85% and 15% of the cases, respectively. De novo mutations are uncommon but have been reported to constitute up to 3% of the total cases. Patients with PKD1 have much more severe renal disease compared with those with PKD2, with earlier onset of renal failure by approximately 10 to 15 years.4–6

ADPKD is relatively asymptomatic during the first 3 decades of life and renal impairment does not usually develop until the fourth decade.6 However, once renal function starts to decline, irreversible damage has already been established. Identification of affected patients is important for multiple reasons. First, anticipatory treatment such as stringent blood pressure control can be implemented. Second, with recent development in specific treatment for ADPKD, early detection of affected individuals will facilitate timely implementation of these treatments, and also assist with future family planning. Finally, disease exclusion is of paramount importance as part of the work-up for living-related kidney donors.

While molecular genotyping remains as the gold standard for confirming diagnosis, this test is costly, time consuming, and not always readily available.5,7 Imaging is an important approach to diagnosis, particularly in those who have not started to manifest complications of the disease. Here, we focus on the suitable modality for disease screening, disease confirmation and exclusion, the age group most appropriate to receive testing, and the recommended diagnostic criteria for the various modalities.

**SEARCH STRATEGY**

**Databases Searched**

Medical subject heading (MeSH) terms and text words for autosomal dominant polycystic kidney disease were combined with the MeSH terms and text words for ultrasonography, magnetic resonance imaging, imaging, and computed tomography (CT) scan. These were combined with MeSH terms and text words for diagnosis, diagnostic criteria, sensitivity, and specificity. Separate searches were conducted for prognosis, cost analysis, and adverse effects. The search was carried out in Ovid MEDLINE (1946-April 2014), Embase (1974-week 21, 2014), and the Cochrane Database of Systematic Reviews and Cochrane Registry of Clinical Trials (inception-June 2014).

**Date of searches:** April and June 2014.

**WHAT IS THE EVIDENCE?**

Supplementary evidence Tables are available online.

The diagnosis of overt ADPKD is generally straightforward. Affected patients typically present with enlarged kidneys with multiple cysts bilaterally and a positive family history of autosomal dominant inheritance. The difficult issues arise when making or excluding the diagnosis in individuals who are
asymptomatic. No randomized controlled trials are available that address this issue.

Overall, there is a broad consensus that while molecular genotyping remains the gold standard for diagnosis, conventional ultrasound should be the first-line diagnostic tool in screening at-risk individuals for ADPKD. This is based on the cost, accessibility, and noninvasive nature of ultrasound. This guideline group will focus on the imaging modality of choice and the appropriate diagnostic criterion under different circumstances and the patient group most appropriate for diagnostic screening.

1. Which Imaging Modality To Use?
Various modes of imaging have been examined in the literature. The earliest and most extensively tested was the conventional ultrasound, while historically it was the intravenous pyelogram. More recently, MRI, CT, and high-resolution ultrasound have all been examined as alternatives. Conventional ultrasound is operator dependent and can detect cysts larger than 1 cm. CT and MRI are operator independent with excellent interobserver reproducibility. With their increased image resolution, CT can detect cysts larger than 0.5 cm, while MRI can pick up cysts as small as 2 to 3 mm, significantly increasing the sensitivity (SEN). More recently, high-resolution ultrasound has been shown to rival the sensitivity of MRI.

i. Ultrasound
Ultrasound is inexpensive and noninvasive. It is considered the first-line modality across all age groups. Several large studies have examined the sensitivity and specificity (SPEC) of ultrasound diagnosis using genetic linkage studies as the gold standard.

Most notably, Ravine et al. conducted the earliest large-scale study examining this in 128 presymptomatic individuals with a 50% risk for PKD1 who were 15 years of age and above. Using the results from molecular genotyping, they tested the then widely accepted criteria that states the presence of at least two cysts in one kidney and one cyst in the other confirms the diagnosis (Table 4). The results revealed that although the sensitivity was excellent for individuals aged 30 and above (SEN, 100%), it was significantly lower for the younger subjects between 15 and 29 years old (SEN, 88.5%). Due to the slowly progressive nature of the disease, the higher cyst cut off in the younger population contributed to false-negative rates. Furthermore, Ravine et al. also noted that occurrence of simple cysts in younger adult life is extremely uncommon (0%-0.2%), unlike in their older counterparts. Therefore, applying the more stringent criteria of two cysts or more, in one or both kidneys, will increase sensitivity to 98% with an imperceptible change in the negative predictive value (NPV, 96%). Similarly, for a population older than 60 years of age in whom simple cystic lesions are a common finding, the criteria needs to be lifted to at least four cysts in each kidney to achieve the same results (positive predictive value, 96.7%; NPV, 100%). Other investigators yielding similar results specific to the PKD1 group have subsequently tested these criteria.

The main difference between PKD1 and PKD2 is the overall younger age of onset of end-stage renal disease in PKD1. The Ravine et al. criteria are only applicable for patients with a mutation due to PKD1. Nicolau et al. demonstrated that when the criterion of Ravine et al. is applied to PKD2 individuals, the sensitivity is markedly reduced. The greatest loss of sensitivity is in those younger than 30 years of age (SEN, 67%). However this study was confounded by the marked disparity in the group sizes (PKD1, n = 182; PKD2, n = 20), and, more importantly, in the small numbers of PKD2 cases included.

Subsequently, both Demetriou et al. and Pei et al. have demonstrated, in much larger cohorts, the loss of sensitivity using the Ravine et al. criterion on PKD2. Both studies used molecular genotyping as gold standard, and Pei et al. found that the loss of diagnostic sensitivity was most marked in the age group of 30 to 39, while Demetriou et al. found the difference to be maximal in those between 5 and 14 years of age. Through simulation studies, Pei et al. suggested a revised criterion, which is listed in Table 1. This revised criterion provided improved sensitivity and specificity in the younger age groups: 15 to 29 years (SEN, 0.81; SPEC, 1.00), 30 to 39 (SEN, 0.95; SPEC, 1.00), and 40 to 59 (SEN, 0.97; SPEC, 1.00). However, due to low sensitivity, the false-negative rate remains in excess of 14% for those under age 30. Thus, this criterion should not be used for disease exclusion, particularly in that age group.

The consensus demonstrated by all of the above studies is that the accuracy of ultrasound diagnosis is age dependent. Under the age of 15 years, ultrasound yields a high false-negative rate, but for those above 30 years of age with a 50% risk of ADPKD, ultrasound is extremely reliable for disease exclusion.

High-resolution (HR) ultrasound is emerging as a promising cost-effective alternative with precision rivaling that of MRI. Pei et al. conducted HR ultrasound and MRI using molecular genotyping as the gold standard in 126 at-risk patients for both PKD1 and PKD2. The HR ultrasound was also able to detect renal cysts as small as 2 to 3 mm. By using the unified criteria in Table 1, the sensitivity increased from 81% to 97.3% for the age group under 30 years, the age group with the lowest sensitivity. These figures closely matched that of...
MRI studies. However, HR ultrasound is not widely available, limiting its applicability at the moment.

ii. Other modalities

Both CT and MRI, with or without contrast, have been used for diagnosis of ADPKD, generally in cases where ultrasonography is equivocal.14,20 Both of these techniques have greater resolution and can detect cysts smaller than 1 cm, the limit at which most cysts are detectable on ultrasound. CT can detect cysts larger than 0.5 cm while MRI can detect those as small as 2 to 3 mm.21,22 The main issue with CT scanning is the associated radiation exposure. This is particularly problematic for the intended cohort of patients who yield ambiguous results on ultrasound, as they are generally younger in age. Several studies have examined CT results compared with ultrasound. They have found that CT scanning detected more renal cysts, possibly increasing diagnostic yield.20,23,24 However, those were retrospective studies, with small sample size and, most importantly, lacked confirmation with the gold standard of genetic testing. It remains unclear whether these additional cysts found on CT were diagnostic of ADPKD or represented benign renal cysts. The advantage of CT scanning was the ease of inclusion of liver and pancreatic views, which can detect extrarenal cystic disease, aiding in the diagnosis of ADPKD when renal findings are ambivalent.

The main concerns with CT scans are radiation exposure and potential nephrotoxicity of radiocontrast. MRI, by contrast, does not involve radiation exposure, and gadolinium is generally safe in patients with a near-normal glomerular filtration rate. For this reason, MRI may be a better option in patients with equivocal ultrasound findings and in disease monitoring. Heavy weighted T2 Single Shot Fast Spin-Echo sequence images permit detection of cysts 2 to 3 mm in diameter with great certainty.21

However, the use of MRI also has its safety issues and considerations. Movement artifact greatly affects quality of images. Almost all ADPKD MRI studies are performed in a single breath-hold with the patient remaining completely still. This is often not possible in children, or in some older patients. These cases may require sedation to achieve the desired outcome. Likewise, claustrophobia is a commonly encountered patient factor. These patients may also require sedation or even preclude the use of MRI. There are certain contraindications to MRI use including metallic foreign bodies and older prosthesis and implanted devices (newer devices are usually MRI compatible). Safety issues such as thermal burns from medication patches and hearing loss are uncommon but have been reported to be associated with MRI use.25

Finally, use of gadolinium in patients is problematic due to the increased risk of NSF. Patients on hemodialysis should not receive gadolinium-based contrast. Individuals with an estimated GFR of 30 to 60 mL/min/1.73 m² have a very low risk of NSF. The risk of NSF per injection rises from 0.1% in those with an estimated GFR of 15 to 30 mL/min/1.73 m² to 1% in stage 5 (<15 mL/min/1.73 m²).2

The accuracy of MRI imaging was demonstrated by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease group as part of their longitudinal observation of ADPKD individuals. Both large and small ADPKD kidney phantoms were constructed using water-filled balloons (cysts), agarose (kidney parenchyma), and vegetable oil (perinephric fat) to simulate the ADPKD kidney. The cysts ranged from 2 to 20 mL in volume. These phantoms were imaged with MRI in the absence of gadolinium in four different centers. Using volume displacement as the gold standard, the reliability coefficient for renal and cyst volumes were 99.9% and 89.2%, respectively. This demonstrates the accuracy and high reproducibility of the MRI scan in the context of ADPKD.11

With the high resolution, MRI will detect both simple cysts and those from ADPKD, potentially increasing the false-positive rate. Nascimento et al retrospectively examined 685 abdominal MRI scans performed for reasons other than screening for ADPKD, excluding those with obvious chronic kidney disease and renal atrophy. They found a much greater occurrence of simple renal cysts compared with figures reported in the literature using ultrasound. In this study, 62.5% of the patients were found to have at least one simple cyst.

The increased detection of cysts means that the diagnostic criteria needs to be formally validated. There is only one study attempting to validate MRI-based diagnosis against the gold standard of molecular genotyping. This study examined 126 subjects aged between 16 and 40 years, born with a 50% risk of either PKD1 or PKD2. Each study subject underwent MRI followed by genetic testing. Concurrently, 46 age-matched controls also underwent the same imaging protocol. For MRI results, using more than 10 cysts as a cut off for a positive diagnosis in the at-risk individuals of between 16 and 40 years of age, the sensitivity and positive predictive value reached 100%. They also noted that the genetically affected individuals typically had greater than 20 cysts on MRI. Thus, the total of fewer than 10 renal cysts as exclusion criteria also gave a specificity and NPV of 100%. The investigators, however, suggested reducing the cut off to be fewer than 5 cysts (with NPV of 100% and SPEC of 98.3%) for evaluation of living kidney donors among whom the clinical agenda is disease exclusion.
with high certainty. The main limitation is the lack of prespecified diagnostic criteria for this group. Ideally, further research using this criterion as a prespecified diagnostic protocol should be performed to validate these results.3

2. When Should We Be Screening for ADPKD in At-Risk Patients?

The criteria available are applicable to individuals over 15 years of age. Making a diagnosis based on imaging in the pediatric population is particularly problematic. The false-negative rate is highest among this population. False positives can also occur infrequently. This has been attributed to the misinterpretation of medullary pyramids as cysts.8 While false positives are much less common, they are more problematic due to the anxiety generated by these results. Studies have shown that in children under the age of 5 years, up to 50% of the imaging studies were inconclusive.5,14,26,27 There are a few studies examining disease screening in the pediatric population. Most notably, Mekahli et al28 conducted a retrospective review of 47 children with ADPKD between 1987 and 2007, who were either diagnosed by postnatal screening ultrasound or by presenting with symptoms. They found no difference in renal outcomes between the two groups, however, there were multiple confounders. First, it was a retrospective study with a short follow-up period (mean, 5.7 y; SD ± 3.6 y). The mean age of the children at final follow-up was 12.9 years (SD ± 5.1 y), which meant that many complications will not have yet developed or manifested. Since evidence is lacking in this area, no established criterion has been recommended on this issue.

Reed et al1 conducted a retrospective cohort study on 420 children under the age of 15 years with a family history of ADPKD. All subjects had been investigated with renal ultrasound. Renal cysts had been detected in 193 children, of these, 150 were bilateral and 43 were unilateral cysts. Of those with unilateral cysts, 26 received a follow-up ultrasound where 17 children had developed bilateral cysts. Similarly, of those with no cysts, 77 received follow-up ultrasound that revealed the development of bilateral cysts in 14 children and unilateral cysts in 4 others. This study was confounded by its retrospective nature and the absence of genetic confirmation of diagnosis. However, it demonstrated that childhood is a time of disease development and follow-up is essential during this period to confirm false negatives.

There is no clear age in the pediatric population for initial scanning or follow-up. Based on these studies, scan results for children under 15 years of age need to be interpreted with great caution. Between the ages of 15 and 30 years, there is still a false-negative rate in excess of 14%, with a sensitivity of only 81% when diagnosis is made by ultrasound, but this is much reduced if MRI is used, as it has a greater sensitivity of 97.3%. For those over 30 years of age, both ultrasound and MRI can diagnose and exclude disease with great certainty.1

3. How to Approach Diagnosing Individuals With Renal Cysts but No Family History?

Family history may be absent in 20% to 40% of new patients in whom the diagnosis of ADPKD is suspected from imaging scans performed to investigate hematuria, loin pain, or for unrelated reasons. In these individuals, disease can be the result of de novo mutation, due to PKD2 with mild disease undetectable in the parents,31 or unknown parentage. At present, there is a lack of evidence for diagnostic criteria for the individual with findings of cystic renal disease with no family history. It is beneficial to perform ultrasound on the parents to assess for asymptomatic PKD2 disease. The absence of cystic disease in family members could suggest a de novo mutation or, rarely, an alternative diagnosis (eg, autosomal-recessive PKD, particularly in younger children). Furthermore, the presence of cysts in extrarenal organs should also be sought to aid with the diagnosis.29 Finally, for less typical cases (borderline number of cysts, and absence of frank kidney enlargement), serial imaging studies to track cyst growth or genetic testing may be necessary to make a diagnosis of ADPKD.

If an arbitrary number for cyst count is to be enforced, then 10 cysts in total, detectable on ultrasound, seems to be the general consensus. A total of 10 cysts has been used as inclusion criteria in clinical trials for disease-modifying agents, such as the TEMPO 3:4 trial.30 This number is based on expert opinion for which there is no formal evidence. However, we acknowledge the significant interobserver variability in ultrasound-based cyst counts. Furthermore, for those individuals with fewer than 10 detectable cysts on ultrasound, expert opinion suggests follow-up ultrasound in 5 to 10 years. For those seeking a definitive diagnosis, either contrast-enhanced CT or non–gadolinium-enhanced MRI sequences can be used to clarify diagnosis. Molecular genetic testing should be considered if these imaging techniques also reveal ambiguous results.

In summary, in patients who seem to present as de novo cases, each case needs to be considered individually. We should take into account the parental ultrasound, presence of liver or pancreatic cysts, and the total number of cysts in the patient, taking greater than 10 cysts on ultrasound as a generally agreed cut-off point for the diagnosis of ADPKD.
4. What About Diagnosis of ADPKD in Children?

Although previously considered a disease of adults, it is now clear that ADPKD can be diagnosed as early as in utero, with significant clinical manifestations affecting a small proportion of patients in early childhood or adolescence. Affected children show enlarged kidneys and increased frequency of hypertension compared with unaffected children.\(^{28}\) When embarking on a diagnostic investigation, ultrasound is still the imaging modality of choice due to its noninvasive nature, while molecular genotyping remains the gold standard.\(^4\) As simple renal cysts are exceedingly rare in children, the presence of bilateral renal cysts in at-risk children are adequate for making a diagnosis of ADPKD. However, cystic disease in children, unlike in adults, have a long list of differentials that must be considered prior to making the diagnosis of ADPKD, as shown in Table 5 (Appendix).

A definite diagnosis of ADPKD in children is difficult to make. All diagnostic criteria have significantly reduced sensitivity when applied to children under the age of 15 years. The highest false-negative rate is greatest amongst children between 3 months and 5 years. False-positive renal ultrasounds, although less common, are possible due to misinterpretation of medullary pyramids as cysts.\(^4,8\) These may also have more serious connotations due to anxiety related to the diagnosis. The key question is whether children should be investigated in the first place, particularly when there is no targeted intervention available. One retrospective study examining this issue showed no difference in renal outcomes in children with ADPKD diagnosed by screening or presenting with symptoms.\(^{28}\)

In conclusion, based on the difficulty in accurately diagnosing and/or excluding disease, the paucity of data to support the benefits of early diagnosis and the possible anxiety generated by the diagnosis (as well as the lack of a readily available proven intervention to alter the natural history of renal disease), screening of disease in children less than 18 years of age is not supported by current evidence.

**SUMMARY OF THE EVIDENCE**

There were no randomized controlled trials on this topic but retrospective and prospective studies suggest that ultrasonography is the modality of choice. The unified age-specific ultrasound diagnostic criteria for ADPKD based on cyst count provide good sensitivity and specificity for at-risk individuals above the age of 15 years. Renal enlargement, although a key feature in ADPKD, is not incorporated into the diagnostic criteria. Figure 1 in the Appendix shows a suggested approach in conducting a diagnosis of ADPKD.

CT and MRI will detect simple cysts with high frequency. MRI is the preferred alternative due to safety and radiation-free profile. A proposed criteria based on cyst count provides some guidance in diagnosis and disease exclusion, but requires more rigorous testing and validation.

Imaging performed in infancy is of little diagnostic value as there is a higher probability of both false-negative and false-positive results. On the other hand, imaging diagnosis becomes less important with increasing age as the more affected individuals would have received a clinical diagnosis due to their marked symptoms (hypertension, hematuria, loin pain from cystic complications, and renal impairment). Imaging diagnosis in an otherwise asymptomatic at-risk individual may be of most importance between the ages of 20 to 30 years, when a positive diagnosis can be managed with potential prophylaxis. This is of increasing importance with the recent developments of promising disease-modifying agents.

When diagnosis is in doubt or disease exclusion is of paramount importance, such as in living-related kidney donors, genetic testing remains the gold standard, but MRI imaging using the proposed criteria may be an alternative when genetic testing is not readily available.

**WHAT DO THE OTHER GUIDELINES SAY?**

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

International Guidelines: No recommendation.

Spanish Guidelines\(^{31}\):

i) Ultrasonography is the recommended screening tool for relatives of an affected proband. Specific diagnostic criteria should be used for different clinical questions: either diagnosis of ADPKD in members of families with \(PKD1\) as the disease-causing gene or diagnosis of ADPKD in families with an unknown genetic defect (Supplementary Material, Table 6) (C).

ii) CT scanning should be used in uncertain cases or in those with suspicion of associated renal disease such as stones or tumor (D).

iii) MRI should be reserved for monitoring renal volume in clinical trials and in certain cases to distinguish a renal cyst from a tumor (D).

**SUGGESTIONS FOR FUTURE RESEARCH**

i) Further studies correlating imaging findings and molecular genotyping in de novo cases to establish diagnostic criteria.
ii) Further studies to determine the role of MRI in equivocal cases and MRI-diagnostic criteria.

iii) Whole-exome studies to determine causation in equivocal imaging cases without a family history of ADPKD.

APPENDIX A. SUPPLEMENTARY INFORMATION

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.semnephrol.2015.10.006.

REFERENCES


APPENDIX

APPENDICES

Table 4. Ravine's diagnostic criteria for at risk individuals with a family history of ADPKD type 1

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number of cysts</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30</td>
<td>At least 2 (unilateral or bilateral)</td>
</tr>
<tr>
<td>30-60</td>
<td>At least 2 in each kidney</td>
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<tr>
<td>&gt;60</td>
<td>At least 4 in each kidney</td>
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</table>

Table 5. Differential diagnosis of cystic and enlarged kidneys in children

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polycystic kidney diseases (PKD)</strong></td>
</tr>
<tr>
<td>- Autosomal recessive polycystic kidney disease (ARPKD)</td>
</tr>
<tr>
<td>- Autosomal dominant polycystic kidney disease (ADPKD)</td>
</tr>
<tr>
<td>- Glomerulocystic kidney disease</td>
</tr>
<tr>
<td>- Tuberous sclerosis complex (TSC)</td>
</tr>
<tr>
<td>- Von-Hippel-Lindau syndrome (VHL)</td>
</tr>
<tr>
<td><strong>Inherited disorders associated with polycystic kidneys</strong></td>
</tr>
<tr>
<td>- Bardet-Biedl syndrome</td>
</tr>
<tr>
<td>- Beckwith-Wiedemann syndrome</td>
</tr>
<tr>
<td>- Hajdu-Cheney syndrome</td>
</tr>
<tr>
<td>- Ivemark syndrome</td>
</tr>
<tr>
<td>- Jeune syndrome and other chondrodysplasia syndromes</td>
</tr>
<tr>
<td>- Juvenile nephronphthisis (JN) / medullary cystic disease (MCD) complex</td>
</tr>
<tr>
<td>- Meckel-Gruber syndrome</td>
</tr>
<tr>
<td>- Oro-facial-digital syndrome Type 1</td>
</tr>
<tr>
<td>- Trisomy 9 and 13</td>
</tr>
<tr>
<td>- Zellweger cerebrohepatorenal syndrome</td>
</tr>
<tr>
<td><strong>Sporadic disorders associated with cystic kidneys</strong></td>
</tr>
<tr>
<td>- Caliceal diverticula</td>
</tr>
<tr>
<td>- Isolated cystic dysplasia</td>
</tr>
<tr>
<td>- Multicystic dysplastic kidney (MCDK)</td>
</tr>
<tr>
<td>- Unilateral / localized cystic kidney disease</td>
</tr>
</tbody>
</table>

Figure 1. Suggested algorithm for patient presenting with renal cysts. 
Adapted from: Pei Y. Diagnostic approach in autosomal dominant polycystic kidney disease. 

Table 6. Spanish Guideline

Ultrasonography criteria (C)

Ravine's criteria (1994) for patients at risk of PKD1 mutation:
- At least two cysts in one kidney or one cyst in each kidney in patients younger than 30 years.
- At least two cysts in each kidney in patients aged 30–59 years.
- At least four cysts in each kidney in patients aged 60 years or older.

Pei's criteria (2009) for ADPKD patients with an unknown genotype and positive family history:
- Three or more (unilateral or bilateral) renal cysts in patients aged 15–39 years.
- Two or more cysts in each kidney in patients aged 40–59 years.
Presence of fewer than two renal cysts provides a negative predictive value of 100% and can be considered sufficient to rule out disease in at-risk individuals older than 40 years.

Source: Reprinted with Permission from Oxford University Press.
Doi:10.1093/ndt/gfu186
### Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>N</th>
<th>Study design</th>
<th>Setting</th>
<th>Participants</th>
<th>Group of interest/ experimental group</th>
<th>Comparison group/ control group</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Pei et al. (2015)[3]    | 172| Prospective cohort | Single center, Canada  | Participants with a 50% risk of ADPKD between 16 and 40 years of age.         | Participants underwent high resolution (HR) ultrasound and magnetic resonance imaging (MRI) as well as molecular genetic testing to define disease status (n = 126) | Healthy controls in the same age range without ADPKD underwent the same imaging tests (n = 46) | • Renal cyst counts  
• Sensitivity  
• Specificity |
| Reed et al. (2010)[4]   | 420| Longitudinal retrospective cohort study | Single center, USA | Children with a family history of ADPKD aged 15 years or younger.            | Renal ultrasonography was done for detection of renal cysts. 24-hour urine collection; blood pressure measurements and glomerular filtration rate were calculated. | N/A                                                                                                      | • Presence of renal cysts  
• Hypertension  
• Mean kidney volume |
| Chapman et al. (2003)[11]| 241| Prospective cohort | Multicenter, USA         | Patients with ADPKD, 15 to 45 years old with creatinine clearance > 70 ml/min | Patients underwent MR renal imaging, renal ischaemic clearance, comprehensive clinical evaluation and 24-hour urinary albumin and electrolyte excretion | N/A                                                                                                      | • Age at diagnosis  
• Family history  
• Hypertension  
• Renal volume  
• Cyst volume |
| Nascimento et al. (2001)[14]| 528| Retrospective review | Single center, USA         | MR imaging of the abdomen of patients between 18 and 59 years old.  | Consecutive MR imaging examinations.                                                                 | N/A                                                                                                      | • Reliability between the three radiologists  
• Number of cysts  
• Cyst size |
| Nicolau et al. (1999)[18]| 319| Diagnostic test study | Single center, Spain       | Patients at risk of ADPKD type 1 and 2, between the ages of 9 months and 72 years of age. | Renal ultrasonography and gene linkage analysis                                                                 | N/A                                                                                                      | • Diagnosis  
• Concordance  
• Sensitivity  
• Specificity  
• Accuracy |
| Gabow et al. (1997)[8]   | 106| Diagnostic test study | Single center, USA         | Children with a 50% risk for ADPKD from 40 ADPKD families. Only children who were in ADPKD 1 families were studied. | Abdominal ultrasonography (US) and gene linkage analysis (GLA) using markers for ADPKD 1 and ADPKD 2 genes. | N/A                                                                                                      | • Sensitivity of US  
• Specificity of US  
• Reliability  
• Renal volume |
<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>N</th>
<th>Study design</th>
<th>Setting</th>
<th>Participants</th>
<th>Group of interest/ experimental group</th>
<th>Comparison group/ control group</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Ravine et al. (1994)[17] | 381 | Diagnostic test study          | Multicenter, Australia   | Participants with a 50% risk of ADPKD between 15 and 70 years of age.        | Renal ultrasonography and genetic linkage studies (DNA polymorphic markers)                           | N/A                           | • Diagnosis of ADPKD by US  
  • Concordance  
  • Sensitivity  
  • Positive and negative predictive values                                                           |
| Dimitrakou et al. (1993)[20] | 40  | Diagnostic test study          | Single center, Bulgaria  | 26 children and 14 adults with clinic and echographic evidence of ADPKD     | Participants were subjected to a conventional non-contrast computer tomography (CT) of the kidneys    | N/A                           | • Age  
  • Detection rate  
  • Correlation                                                                                              |
| Kaariainen et al. (1988)[23] | 18 | Retrospective analysis         | Single center, Finland   | Children with genetically classified dominant and recessive polycystic kidney disease | Analysis of findings from intravenous pyelography (IVP), ultrasound (US) and computed tomography (CT). | N/A                           | • Classification for dominant and recessive polycystic kidney disease in children                  |
| Walker et al. (1984)     | 28 | Prospective cohort and retrospective analysis | Single center, USA | Family members of two generations affected with ADPKD                      | Sonograms, excretory urograms with nephrotomograms and clinical evaluation were compared for the diagnosis of adult PKD at an early age. | N/A                           | • Diagnosis (older and younger generation)  
  • Cyst size                                                                                           |
<p>| Segal et al. (1982)[24]  | 23 | Retrospective review           | Single center, USA       | Patients with polycystic kidney disease aged between 12 and 84 years.       | Computed tomography was used to detect polycystic kidney disease                                        | N/A                           | • Diagnosis                                                                                       |
| Hogewind et al. (1980)[5]  | 82 | Non-randomized controlled study | Single center, The Netherlands | Patients with ADPKD (group 1), healthy individuals (group 2) and possible carriers (group 3) with a 50% risk of being a carrier. Participants were aged between 7 and 56 years. | Ultrasound was conducted in all participants. Participants with a previous diagnosis of ADPKD had undergone intravenous pyelography. Potential carriers also had a tomographic intravenous pyelography done. | As per intervention group | • Diagnosis                                                                                       |
| Pei et al. (2009)[11]    | 948 | Observational study            | Multicenter, Australia, Europe, North America | Individuals with 50% risk for ADPKD, from 58 PKD1 and 39 PKD2 families | Participants were assessed with renal ultrasound and molecular genotyping                               | As per intervention group | • Diagnostic criteria                                                                             |</p>
<table>
<thead>
<tr>
<th>Study ID (author, year)</th>
<th>N</th>
<th>Study design</th>
<th>Setting</th>
<th>Participants</th>
<th>Group of interest/ experimental group</th>
<th>Comparison group/ control group</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Antiga et al. (2006)[22] | 13 | Pre and post observational study | Single center, Italy | Patients older than 18 years of age with advanced-stage ADPKD | Computed tomography was used to measure kidney, renal cyst, parenchyma (fully enhanced) and intermediate parenchyma (faintly contrast-enhanced) volumes before and after the placebo phase of the study. | N/A | - Glomerular filtration rate (GFR)  
- Total kidney volume (TKV)  
- Total cyst volume (TCV)  
- Intermediate parenchymal volume ($V_{IN}$)  
- Parenchymal volume ($V_{PAR}$)  
- Correlations with GFR  
- Correlation between percentage change in intermediate volume ($\Delta V_{IN}$ %) and percentage change in GFR ($\Delta$GFR %) |
| Avni et al. (2002) | 29 | Longitudinal study | Single center, Belgium | Children with ARPKD (16 cases) and ADPKD (13 cases) | Ultrasound imaging was conducted to assess the correlation between structural changes and onset of renal failure. | N/A | - ARPKD (16 cases)  
- ADPKD (13 cases) |
| Mekahli et al. (2010)[28] | 47 | Retrospective analysis of records | Single center, UK | Children with ADPKD diagnosed postnatally (group 1) or with presenting symptoms (group 2) | Children had blood pressure, albumin case notes and ultrasound results evaluated. | N/A | - Diagnosis  
- Kidney size  
- Cyst diameter  
- Blood pressure  
- Estimated glomerular filtration rate (eGFR) |
Table 2. Risk of bias- Controlled studies- quality appraisal tool EPOC

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Selection bias</th>
<th>Baseline similarities</th>
<th>Detection bias</th>
<th>Reporting bias</th>
<th>Other risks of bias</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Random sequence Allocation concealment</td>
<td>Measurements Characteristics</td>
<td>Incomplete data Assessor blinded Switching interventions</td>
<td>Unclear</td>
<td>Non-randomized controlled trial</td>
<td>Very low</td>
</tr>
<tr>
<td>Hogewind et al. (1980)[5]</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Unclear</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Risk of bias- Diagnostic studies - quality appraisal tool QUADAS 2

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Patient selection</th>
<th>Index test</th>
<th>Reference standard</th>
<th>Flow and timing</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Consecutive or random sample Case-control avoided Avoid inappropriate exclusion</td>
<td>Reference standard results unknown Pre-specified threshold Target condition Index test results unknown</td>
<td>Appropriate interval All patients reference standard All patients same reference standard All patients included in analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pei et al. (2015)[3]</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Nicolau et al. (1999)[18]</td>
<td>unclear</td>
<td>yes</td>
<td>unclear</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Gabow et al. (1997)[8]</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Ravine et al. (1994)[17]</td>
<td>no</td>
<td>yes</td>
<td>unclear</td>
<td>unclear</td>
<td>yes</td>
</tr>
<tr>
<td>Dimitrakoff et al. (1993)[20]</td>
<td>unclear</td>
<td>yes</td>
<td>no</td>
<td>no</td>
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<tr>
<td>Study ID</td>
<td>N</td>
<td>Study type</td>
<td>Quality</td>
<td>Comments</td>
<td></td>
</tr>
<tr>
<td>-----------------------</td>
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<td>---------------------------------------------------------------------------</td>
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<tr>
<td>Reed et al. (2010)</td>
<td>420</td>
<td>Longitudinal retrospective cohort study</td>
<td>Very low</td>
<td>No quality appraisal tool available</td>
<td></td>
</tr>
<tr>
<td>Chapman et al. (2003)</td>
<td>241</td>
<td>Prospective cohort</td>
<td>Very low</td>
<td>No quality appraisal tool available</td>
<td></td>
</tr>
<tr>
<td>Nascimento et al. (2001)</td>
<td>528</td>
<td>Retrospective review</td>
<td>Very low</td>
<td>No quality appraisal tools available; magnetic resonance abdominal imaging for a range of patients not specific for ADPKD</td>
<td></td>
</tr>
<tr>
<td>Kaariainen et al. (1988)</td>
<td>18</td>
<td>Retrospective analysis</td>
<td>Very low</td>
<td>No quality appraisal tools available; small sample size; pediatric study for autosomal dominant and autosomal recessive PKD.</td>
<td></td>
</tr>
<tr>
<td>Walker et al. (1984)</td>
<td>28</td>
<td>Prospective cohort and retrospective analysis</td>
<td>Very low</td>
<td>No quality appraisal tools available; small sample size</td>
<td></td>
</tr>
<tr>
<td>Segal et al. (1982)</td>
<td>23</td>
<td>Retrospective review</td>
<td>Very low</td>
<td>No quality appraisal tools available; small sample size</td>
<td></td>
</tr>
<tr>
<td>Mekahili et al. (2010)</td>
<td>47</td>
<td>Retrospective analysis of records</td>
<td>Very low</td>
<td>No quality appraisal tool available</td>
<td></td>
</tr>
<tr>
<td>Antiga et al. (2006)</td>
<td>13</td>
<td>Randomized cross over study</td>
<td>Very low</td>
<td>No quality appraisal tools available; small sample size</td>
<td></td>
</tr>
<tr>
<td>Avni et al. (2002)</td>
<td>29</td>
<td>Longitudinal study</td>
<td>Very low</td>
<td>No quality appraisal tools available; small sample size</td>
<td></td>
</tr>
<tr>
<td>Mosetti et al. (2003)</td>
<td>30</td>
<td>Retrospective analysis</td>
<td>Very low</td>
<td>No quality appraisal tools available; small sample size</td>
<td></td>
</tr>
<tr>
<td>Study ID</td>
<td>N</td>
<td>Study type</td>
<td>Intervention</td>
<td>Outcome</td>
<td>Results</td>
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<td>-------------------------------------------------------------------------------</td>
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</tr>
</tbody>
</table>
| Pei et al. (2015)[3] | 172  | Prospective cohort | Participants underwent high resolution (HR) ultrasound and magnetic resonance imaging (MRI) as well as molecular genetic testing to define disease status (n = 126) Healthy controls in the same age range without ADPKD underwent the same imaging tests (n = 46) | Sensitivity for ≥ 2 cysts in each kidney | • For subjects 16-29 years of age:  
  High resolution Ultra-sound = 97.3%  
  MRI = 100%  
  Sensitivity for ≥ 2 cysts in each kidney | Moderate |
|           |      |                    |                                                                              |                                                                                          | Sensitivity for ≥ 3 total renal cysts  
  For subjects 16-29 years of age:  
  High resolution Ultra-sound = 97.3%  
  MRI = 100%  
  Sensitivity for ≥ 3 total renal cysts  
  For subjects 30-40 years of age:  
  High resolution Ultra-sound = 100%  
  MRI = 100%  
  Sensitivity for a total of >10 renal cysts  
  For subject 16-29 years of age:  
  MRI = 100% | Very low  |
| Nicolau et al. (1999)[18] | 319  | Diagnostic test study | Renal ultrasonography and gene linkage analysis | US sensitivity (< 30 years old)  
  95% [80/84] individuals with the PKD1 mutation had positive findings (95%C.I: 88% to 99%)  
  67% [4/6] individuals who inherited the PKD2 mutation had positive findings (95%C.I: 22% to 96%)  
  US sensitivity (> 30 years old)  
  100% [98/98] individuals with a probability of >95% of having ADPKD type 1, had positive findings (95%C.I: 95% to 100%)  
  100% [14/14] individuals with a probability of >95% of having ADPKD type 2, had positive findings (95%C.I: 77% to 100%) | 97% [163/202] | Very low  |
| Nicolau et al. (1999)[18] |      |                    |                                                                              |                                                                                          | US sensitivity all age groups ADPKD type 1 and 2 | Very low  |
| Gabow et al. (1997)[8] | 106  | Diagnostic test study | Abdominal ultrasonography (US) and gene linkage analysis (GLA) using markers for ADPKD1 and ADPKD2 genes. | Sensitivity of US in childhood | 77% | Moderate  |
  At age 15-29 years, sensitivity = 88.3% [95%C.I: 66.4 to 97.2%] for ≥ 2 cysts in one kidney, ≥ 1 cyst in the other  
  At age >30 years, sensitivity = 100%, for ≥ 2 cysts in one kidney, ≥ 1 cyst in the other. | Low  |
<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Study type</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Quality</th>
</tr>
</thead>
</table>
| Pei et al.      | 172 | Prospective cohort | Participants underwent high resolution (HR) ultrasound and magnetic resonance imaging (MRI) as well as molecular genetic testing to define disease status (n = 126) Healthy controls in the same age range without ADPKD underwent the same imaging tests (n = 46) | Specificity for ≥ 2 cysts in each kidney | • For subjects 16-29 years of age:  
  • High resolution Ultra-sound = 100%  
  • MRI = 98.3%  
  Specificity for ≥ 2 cysts in each kidney | Moderate |
|                 |     |                  |                                                                              |                                | For subjects 30-40 years of age:  
  • High resolution Ultra-sound = 100%  
  • MRI = 100%  
  Specificity for ≥ 3 total renal cysts |                                | For subjects 16-29 years of age:  
  • High resolution Ultra-sound = 98.3%  
  • MRI = 96.6%  
  Specificity for ≥ 3 total renal cysts |                                | For subjects 30-40 years of age:  
  • High resolution Ultra-sound = 91.7%  
  • MRI = 95.8%  
  Specificity for a total of >10 renal cysts |                                | For subject 16-29 years of age:  
  • MRI = 100%  
  Conclusion: MRI is highly sensitive and specific for ADPKD diagnosis. High resolution ultrasound has the potential to rival the diagnostic performance of MRI but is both center and operator dependent. |
| Nicolau et al.  | 319 | Diagnostic test study | Renal ultrasonography and gene linkage analysis                               | US specificity all age groups ADPKD type 1 and 2 | 100% (117/117)  
  Accuracy of US for all age groups ADPKD type 1 and 2 | Very low |
| Nicolau et al.  |     |                  |                                                                              |                                | 98% (313/319)  
  Accuracy of US for all age groups ADPKD type 1 and 2 |                                |                                | Very low |
| Gabow et al.    | 106 | Diagnostic test study | Abdominal ultrasonography (US) and gene linkage analysis (GLA) using markers for ADPKD1 and ADPKD2 genes. | Specificity of US | 98%  
  Specificity of US |                                |                                | Moderate |
<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Study type</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Quality</th>
</tr>
</thead>
</table>
| Gabow et al. (1997)[8]| 106| Diagnostic test   | Abdominal ultrasonography (US) and gene linkage analysis (GLA) using markers for ADPKD1 and ADPKD2 genes. | Reliability (all ages)       | - False negative 25%  
- False negative rate was highest amongst children who were 3 months to 5 years old (38%)  
- False positive 2%  
- False positive rate was also highest for this age group: 3 months to 5 years of age (11%)                                                                 | Moderate |
| Ravine et al. (1994)[17] | 381| Diagnostic test   | Renal ultrasonography and genetic linkage studies (DNA polymorphic markers) | Positive and negative predictive values (PPV and NPV) for ≥ 2 cysts (unilateral or bilateral) | For individuals 15-29 years old:  
- PPV was 100%  
- NPV was 96.6%  

PPV and NPV for ≥ 2 cysts in each kidney  
For individuals 30-59 years old:  
- PPV was 100%  
- NPV was 100%  

PPV and NPV for ≥ 4 cysts in each kidney  
For individuals > 60 years old:  
- PPV was 96.9%  
- NPV was 100%  

Conclusion: Thus the presence of at least two renal cysts may be sufficient for diagnosis in individuals younger than 30 years;  
- at least two cysts in each kidney may be required for those aged 30-59 years;  
- and at least 4 cysts in each kidney for those above 60 years of age. | Low     |
Table 8. Cyst count, size and volume outcomes

<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Study type</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pei et al.</td>
<td>171</td>
<td>Prospective cohort</td>
<td>Participants underwent high resolution (HR) ultrasound and magnetic resonance imaging (MRI) as well as molecular genetic testing to define disease status (n = 126) Healthy controls in the same age range without ADPKD underwent the same imaging tests (n = 46)</td>
<td>Renal cyst counts</td>
<td>• 73 patients were affected, 72/73 had &gt; 20 cysts in both kidneys detected by MRI • 82 patients were unaffected, 81/82 had &lt; 3 cysts detected by MRI • Complete separation of the affected and unaffected subjects was not possible with ultrasound</td>
<td>Moderate</td>
</tr>
<tr>
<td>Nascimento et al.</td>
<td>528</td>
<td>Retrospective review</td>
<td>Consecutive MR imaging examinations.</td>
<td>Number of cysts</td>
<td>• These increased with age: • 0.71 cysts for 18-29 year old patients • 1.27 for 30-44 year old patients • 1.87 for 45-59 year old patients, P&lt;0.001</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Number of cysts: • 330/528 (62.5%) had at least one renal cyst • The total number of cysts was significantly greater in men 2.0 (95%CI: 1.5 – 2.5) than in women 1.2 (95%CI: 0.9 - 1.5), P &lt; 0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cyst size</td>
<td>• Cyst size of ≤ 10 mm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Conclusion: MR imaging depicted an increased number of simple renal cysts due to its increased sensitivity for cysts smaller than 1 cm. If cysts larger than 1cm are considered then US criteria for type 1 ADPKD can be applied to MR imaging.</td>
<td></td>
</tr>
<tr>
<td>Walker et al.</td>
<td>28</td>
<td>Prospective cohort and retrospective analysis</td>
<td>Sonograms, excretory urograms with nephrotomograms and clinical evaluation were compared for the diagnosis of adult PKD at an early age.</td>
<td>Cyst size (older generation)</td>
<td>• Cyst size for the adults ranged between 5 mm and 5 cm.</td>
<td>Very low</td>
</tr>
<tr>
<td>Chapman et al.</td>
<td>241</td>
<td>Prospective cohort</td>
<td>Patients underwent MR renal imaging, renal isothalamate clearance, comprehensive clinical evaluation and 24-</td>
<td>Cyst volume</td>
<td>• Age-adjusted cyst volume was inversely related to glomerular filtration rate r = −0.36, P &lt; 0.0001 • Age-adjusted cyst volume was directly related to urinary albumin excretion r = 0.39, P &lt; 0.0001</td>
<td>Very low</td>
</tr>
<tr>
<td>Study ID</td>
<td>N</td>
<td>Study type</td>
<td>Intervention</td>
<td>Outcome</td>
<td>Results</td>
<td>Quality</td>
</tr>
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<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>---------</td>
</tr>
</tbody>
</table>
| Chapman et al. (2003)[11] | 241 | Prospective cohort | hour urinary albumin and electrolyte excretion | % cyst volume | - Age-adjusted % cyst volume was inversely related to glomerular filtration rate $r = -0.35$, P < 0.0001  
- Age-adjusted % cyst volume was directly related to urinary albumin excretion $r = 0.41$, P < 0.0001 | Very low |
| Mekahli et al. (2010)[28] | 47 | Retrospective analysis of records | Children had blood pressure, albumin case notes and ultrasound results evaluated. | Kidney size | - 63% of children had normal sized kidneys with 16% unilateral nephromegaly  
- Patients had an increased kidney growth rate when compared to the normal population (P<0.001)  
At last follow-up:  
- 53% had enlarged kidneys  
- 26% had unilateral nephromegaly  
- 81% had multiple cysts | Very low |
| Cyst diameter (mean, SD) | | | | | - Diameter 2.2 (±1.2) cm  
- There was no difference between the groups in terms of uni- or bilateral nephromegaly or multiple cysts | |
| Antiga et al. (2006)[22] | 13 | Randomized cross over study | Computed tomography was used to measure kidney, renal cyst, parenchyma (fully enhanced) and intermediate parenchyma (faintly contrast-enhanced) volumes before and after the placebo phase of the study. | Total cyst volume (TCV) ml | - There was a significant increase in TCV volume from baseline 1592±825 compared to six months 1694±880  
- Percent change in TCV 6.2±5.9, P<0.05 | Very low |
Table 9. Kidney volume

<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Study type</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reed et al.</td>
<td>420</td>
<td>Longitudinal retrospective</td>
<td>Renal ultrasonography was done for detection of renal cysts. 24-hour urine</td>
<td>Mean kidney volume corrected by height (cm$^3$)</td>
<td>• Was significantly higher in children with bilateral cysts compared with children with unilateral or no cysts (0.97±0.59 versus 0.65±0.22 versus 0.59±0.21 respectively; P &lt; 0.001)</td>
<td>Very low</td>
</tr>
<tr>
<td>et al. (2010)</td>
<td></td>
<td>cohort study</td>
<td>collection; blood pressure measurements and glomerular filtration rate were</td>
<td></td>
<td>• At follow-up there was a significant difference between children who developed bilateral cysts compared to those with unilateral or no cysts (0.87±0.31 versus 0.64±0.13 versus 0.62±0.2 respectively; P &lt; 0.001)</td>
<td></td>
</tr>
<tr>
<td>Mosetti et al.</td>
<td>30</td>
<td>Retrospective analysis</td>
<td>Patients were examined with magnetic resonance imaging.</td>
<td>Mean kidney size</td>
<td>• Right kidney: length = 17.4 cm, 10.3 cm in transverse and 9.4 cm in antero-posterior diameter (AP)</td>
<td>Very low</td>
</tr>
<tr>
<td>et al. (2003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Left kidney: length = 15.9 cm, 9.3 cm in transverse and 9.3 cm in AP diameter.</td>
<td></td>
</tr>
<tr>
<td>Chapman et al.</td>
<td>241</td>
<td>Prospective cohort</td>
<td>Patients underwent MR renal imaging, renal iotahalate clearance, comprehensive</td>
<td>Renal volume</td>
<td>• Age-adjusted renal volume was inversely related to glomerular filtration rate r = -0.31, P &lt; 0.0001</td>
<td>Very low</td>
</tr>
<tr>
<td>et al. (2003)</td>
<td></td>
<td></td>
<td>clinical evaluation and 24-hour urinary albumin and electrolyte excretion</td>
<td></td>
<td>• Age-adjusted renal volume was directly related to urinary albumin excretion r = 0.42, P &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Gabow et al.</td>
<td>106</td>
<td>Diagnostic test study</td>
<td>Abdominal ultrasonography (US) and gene linkage analysis (GLA) using markers</td>
<td>Renal volume</td>
<td>• Total renal, cystic and non-cystic volume was significantly greater in the 25 - 34 and 35 - 45 year age groups compared to the 15 - 24 year age group.</td>
<td></td>
</tr>
<tr>
<td>(1997)</td>
<td></td>
<td></td>
<td>for ADPKD1 and ADPKD2 genes.</td>
<td></td>
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</tr>
<tr>
<td>Antiga et al.</td>
<td>13</td>
<td>Randomized cross over study</td>
<td>Computed tomography was used to measure kidney, renal cyst, parenchyma (fully</td>
<td>Total kidney volume (TKV) ml</td>
<td>• There was a significant increase in TKV volume from baseline 2412±935 compared to six months 2566±999</td>
<td>Very low</td>
</tr>
<tr>
<td>et al. (2006)</td>
<td></td>
<td></td>
<td>enhanced) and intermediate parenchyma (faintly contrast-enhanced) volumes</td>
<td></td>
<td>• Percent change in TKV 6.3±5.7%, P&lt;0.01</td>
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<td>before and after the placebo phase of the study.</td>
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</tbody>
</table>
Table 10. Diagnosis

<table>
<thead>
<tr>
<th>Study ID</th>
<th>N</th>
<th>Study type</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicolau et al. (1999)[18]</td>
<td>319</td>
<td>Diagnostic test study</td>
<td>Renal ultrasonography and gene linkage analysis</td>
<td>Diagnosis</td>
<td>• 182/319 (57%) participants had ADPKD type 1 and 20/319 (6%) had ADPKD type 2</td>
<td>Very low</td>
</tr>
<tr>
<td>Ravine et al. (1994)[17]</td>
<td>381</td>
<td>Diagnostic test study</td>
<td>Renal ultrasonography and genetic linkage studies (DNA polymorphic markers)</td>
<td>Diagnosis of ADPKD by US</td>
<td>• 183/381 (48%) had a positive diagnosis</td>
<td>Low</td>
</tr>
</tbody>
</table>
| Hogewind et al. (1980)[5] | 82  | Non-randomized controlled study      | Ultrasound was conducted in all participants. Participants with a previous diagnosis of ADPKD had undergone intravenous pyelography. Potential carriers also had a tomographic intravenous pyelography done. | Diagnosis                                         | • Group 1: ultrasonography correlated with the IVP results   
• Group 2: all volunteers were found to be healthy by US  
• Group 3: 17/52 (33%) of cases were found to be positive for APKD                                                                                       | Very low|
| Dimitrakos et al. (1993)[20] | 40  | Diagnostic test study                | Participants were subjected to a conventional non-contrast computer tomography (CT) of the kidneys | Detection rate (CT)                               | • 10/26 (38.5%) of children had a definitive diagnosis with CT  
• 13/26 (50%) of children had a suspected diagnosis with CT  
• 3/26 (11.5%) of children had a negative diagnosis with CT  
• 13/14 (93%) of adults had a definitive diagnosis with CT                                                                                      | Very low|
|                   |    |                                      |                                                                             | Diagnosis (older generation)                      | • 5/6 (83%) members of the older generation detected positive for the disease; participants' age ranged from 19 to 43 years  
• Results of the excretory urography/nephrotomography correlated with sonography;                                                                                     |         |
|                   |    |                                      |                                                                             | Diagnosis (younger generation)                    | • 11/22 (50%) patients were positive for the disease.  
• The age range was between 5.75 and 17 years (mean 9.8±1.9)  
• There was good correlation between the excretory urography/nephrotomography and sonography, however 6/11 (54.5%) patients had some discrepancies in findings  
• Most common findings were 3 - 20 mm lucent areas in the renal parenchyma;  
• Cysts were best seen by nephrotomography;  
• Usually one or two cysts were detected in only one kidney                                                                                                         |         |
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</table>
| Walker et al. (1984) | 28    | Prospective cohort and retrospective analysis | Sonograms, excretory urograms with nephrotomograms and clinical evaluation were compared for the diagnosis of adult PKD at an early age. | Diagnosis (older generation) | • 5/6 (83%) members of the older generation detected positive for the disease;  
• Participants’ ages ranged from 19 to 43 years  
• Results of the excretory urography/nephrotomography correlated with sonography  

Diagnosis (younger generation) |  
• 11/22 (50%) of patients were positive for the disease;  
• The age range was between 5.75 and 17 years (mean 9.8±1.9);  
• There was good correlation between the excretory urography/nephrotomography and sonography, however 6/11 (54.5%) patients had some discrepancies in findings  
• Most common findings were 3-20 mm lucent areas in the renal parenchyma;  
• Cysts were best seen by nephrotomography; usually one or two cysts were detected in only one kidney  

Conclusion: excretory urograms with nephrotomograms were slightly more sensitive especially for younger patients however sonography was sufficiently sensitive in the older child and was the preferred screening technique. | Very low |
| Segal et al. (1982)[24] | 23    | Retrospective review   | Computed tomography was used to detect polycystic kidney disease              | Diagnosis                                                               | • Diffuse, bilateral renal cystic disease was detected in all cases;  
• 74% (17/23) of patients had hepatic involvement;  
• 3/23 (13%) of patients had pancreatic cystic disease  

Conclusion: CT is more accurate than other conventional modalities in diagnosing renal cysts. | Very low |
| Mekahli et al. (2010)[16] | 47    | Retrospective analysis of records | Children had blood pressure, albumin case notes and ultrasound results evaluated. | Diagnosis                                                               | • 31/47 (66%) children were asymptomatic and diagnosed postnatally with ultrasound  
• 16/47 (34%) presented with symptoms:  
• 3/16 (19%) had antenatal enlarged, echobright kidneys;  
• 6/16 (38%) had urinary tract infection;  
• 5/16 (31%) presented with abdominal, back or loin pain;  
• 1/16 (6%) had macroscopic haematuria  
• and one (6%) other had enuresis  

Conclusion: excretory urograms with nephrotomograms were slightly more sensitive especially for younger patients however sonography was sufficiently sensitive in the older child and was the preferred screening technique. | Very low |
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<tr>
<td>Chapman et al. (2003)[11]</td>
<td>241</td>
<td>Prospective cohort</td>
<td>Patients underwent MR renal imaging, renal isothalamate clearance, comprehensive clinical evaluation and 24-hour urinary albumin and electrolyte excretion</td>
<td>Age at diagnosis</td>
<td>Mean age 24.5 ± 9.4 years</td>
<td>Very low</td>
</tr>
<tr>
<td>Dimitrakov et al. (1993)[20]</td>
<td>40</td>
<td>Diagnostic test study</td>
<td>Participants were subjected to a conventional non-contrast computer tomography (CT) of the kidneys</td>
<td>Age</td>
<td>Mean age for children was 11.0 ± 1.0 years</td>
<td>Very low</td>
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<td>Hogewind et al. (1980)[5]</td>
<td>82</td>
<td>Non-randomized controlled study</td>
<td>Ultrasound was conducted in all participants. Participants with a previous diagnosis of ADPKD had undergone intravenous pyelography. Potential carriers also had a tomographic intravenous pyelography done.</td>
<td>Diagnosis for potential carriers by age group</td>
<td>0/2 (0%) of children &lt; 10 years old were diagnosed positive; 3/20 (15%) of those between 11 and 20 years of age tested positive with US; 11/20 (55%) of participants aged between 21 and 30 years were diagnosed positive; 3/10 (30%) of participants aged &gt; 30 years old were positive for ADPKD Conclusion: the identification of about 50% of asymptomatic individuals at risk as gene carriers in the 21 - 30 years age group, both with US and IVP is promising for the early detection of the disease and for genetic counseling in the future.</td>
<td>Very low</td>
</tr>
<tr>
<td>Avni et al. (2002)</td>
<td>29</td>
<td>Longitudinal study</td>
<td>Ultrasound imaging was conducted to assess the correlation between structural changes and onset of renal failure.</td>
<td>ARPKD (16 cases)</td>
<td>Renal size was &gt; 4 standard deviations in 10/16 patients and remained stable throughout Kidneys appeared hyper-echogenic in 100% of patients, without cortico-medullary differentiation (CMD) in the majority (11/16) of patients Changes of CMD were observed in five patients Small cysts &lt; 1 cm were present in 7/16 patients at time of diagnosis, three patients had cysts &gt; 1 cm Diffuse hyper-echogenic foci developed in 14 patients, 13/14 had developed renal failure at the time of the examination or soon after (correlation P = 0.013)</td>
<td>Very low</td>
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<tr>
<td>Avni et al. (2002)</td>
<td></td>
<td>ADPKD (13 cases)</td>
<td></td>
<td></td>
<td>Renal size was between 0 to 2 standard deviations in 7/13 patients, and &gt;2 SD in the other six patients Renal echogenicity was normal in five; unable to assess in five others; and hyper-echogenic in three without cortico-medullary differentiation Cysts &gt;1 cm in 8/12 patients (with five patients having cysts &gt; 3 cm); &lt; 1 cm in four patients Size of cysts and of the kidneys remained stable and no renal failure occurred</td>
<td>Very low</td>
</tr>
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