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Imaging of kidney cysts and cystic kidney diseases in children:

An International Working Group Consensus Statement

Supplementary Materials

Content

Appendix E1 Supplementary Methods

For systematic literature reviews MEDLINE and the Cochrane library were searched for relevant literature up to September 2017. The literature summary on contrast enhanced ultrasound (CEUS) was updated prior to submission in May 2018. The searches were restricted to original articles (excluding case reports) published in English, German and French. Search strategies, inclusion and exclusion criteria are listed in Table E7. Each study was assessed for validity according to criteria proposed by the Grading of Recommendations Assessment, Development and Evaluation working group (GRADE) (1). This includes ranking each study with respect to risk of bias (limitations in study design or execution), indirectness (how directly the purpose of the study was related to the question of the literature review), inconsistency (whether results were consistent across studies), and imprecision (whether study results were precise enough to draw adequate conclusions) on a scale of “not serious”, “serious” and “very serious”. The categories “serious” or “very serious” indicates that concerns in this domain led to downgrading of the evidence. Reviewers could also list other considerations (e.g. suspicion of publication bias, influence of plausible residual confounding) and rated the study for overall level of importance in answering the health question (on a scale of 1-9, where 9 is most important).

Table E1 - Consensus group members

Name	Area of expertise	Working group
Avni, E. Fred	Pediatric and prenatal Radiology, pediatric genitourinary imaging	Technical issues, tumors & TSC
Breysem, Luc	Pediatric radiology, ADPKD	ADPKD & ARPKD
Burgmaier, Kathrin	Pediatric nephrology, ARPKD	ADPKD & ARPKD
Caroli, Anna	Renal magnetic resonance imaging, ADPKD	Technical issues, tumors & TSC
Cetiner, Metin	Pediatric nephrology, renal ultrasound, Bardet-Biedl Syndrome	Other cystic nephropathies
Franke, Doris	Pediatric ultrasound, pediatric nephrologist	Technical issues, tumors & TSC
Gimpel, Charlotte	Pediatric nephrology, guideline preparation	Other cystic nephropathies
Haffner, Dieter	Pediatric nephrology, inherited kidney disease, guideline	Other cystic nephropathies
Hartung, Erum A.	Pediatric Nephrology, polycystic kidney disease	Other cystic nephropathies
König, Jens	Pediatric nephrology, nephronophthisis	Other cystic nephropathies
Liebau, Max C.	Pediatric nephrology, polycystic kidney disease	ADPKD & ARPKD
Mekahli, Djalila	Pediatric nephrology, polycystic kidney disease	ADPKD & ARPKD
Ong, Albert C.M.	Adult nephrology, ADPKD	ADPKD & ARPKD
Pape, Lars	Pediatric nephrology, renal ultrasound	Technical issues, tumors & TSC
Schaefer, Franz	Pediatric nephrology, inherited kidney diseases, guideline	ADPKD & ARPKD
Titieni, Andrea	Pediatric nephrology	Other cystic nephropathies
Torra, Roser	Adult nephrology, ADPKD, TSC	Technical issues, tumors & TSC
Winyard, Paul J.D.	Pediatric nephrology, prenatal cystic kidney disease	Other cystic nephropathies

Table E2 - Literature review on contrast enhanced ultrasound (CEUS) for complex renal cysts in adults

Title	First Author	Journal	Year	Study design	Nº & type of patients (Bosniak category on CT)	Findings	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[1]
Studies examining CEUS for diagnosing benign vs malignant disease in (only) complex cystic renal lesions												
Comparison of contrast-enhanced ultrasound with MRI in the diagnosis of complex cystic renal masses: a meta-analysis. PMID: 29363321	Zhou, L.	Acta Radiol. 59(10):1254-1263	2018	Metaanalysis of studies comparing diagnostic efficacy of CEUS or MRI (using CT or follow-up > 1 year)	17 studies with 1142 lesions (10 for CEUS, 9 for MRI)	Pooled values for CEUS: sensitivity:95%, specificity 84% positive likelihood ratio 5.62, negative likelihood ratio 0.09 AUCs-SROC curves 95.66% Subgroup analysis including only studies using histopathological reference standard decreased the sensitivity and specificity of CEUS (94% vs. 95% and 73% vs. 84%) Pooled values for MRI: sensitivity: 92%, specificity 91% positive likelihood ratio 6.74, negative likelihood ratio 0.13 AUCs-SROC curves 94.65%. The subgroup analysis indicated that the scanning slice thickness may influence the diagnostic efficacy of MRI.	Not serious	Not serious	Not serious	Not serious	Includes non-peer-reviewed studies.	8
Diagnostic performance of contrast-enhanced ultrasonography and magnetic resonance imaging for the assessment of complex renal cysts: A prospective study. PMID: 28147450	Defortescu, G.	Int J Urol. 24(3):184-189.	2017	Prospective comparative study of CT, MRI and CEUS	47 patients (age 37-76 years) with 47 Bosniak 2F or 3 cysts on CT (18-58 mm). 19 had histological confirmation, others followed-up for 17-48 months	CEUS: sensitivity 100%, specificity 97%, negative predictive value 100%, positive predictive value 93%, kappa = 0.95, upgraded Bosniak compared to CT in 9. CT: sensitivity 36%, specificity 76%; Cohen's kappa (to final diagnosis) = 0.11 MRI: sensitivity 71%, specificity 91%, kappa = 0.64, upgraded Bosniak compared to CT in 5.	Not serious	Not serious	Not serious	Adults only	14/47 malignant lesions	7

[1] Where 9 is highest and 1 is lowest

Title	First Author	Journal	Year	Study design	Nº & type of patients (Bosniak category on CT)	Findings	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[1]
Prospective comparison of use of contrast-enhanced ultrasound and contrast-enhanced computed tomography in the Bosniak classification of complex renal cysts. PMID: 27433270	Ragel, M.	Ultrasound 24(1):6-16.	2016	Prospective comparison of contrast enhanced CT and CEUS	46 patients (36-94 years) with 51 complex renal cysts (Bosniak I to IV, 11-107 mm). 3 had histological confirmation, others followed-up for 6-24 months.	All malignant lesions were classified as such simultaneously on both modalities by at least one observer. CEUS gave a higher Bosniak classification than CT in 31 % of cysts by both observers. There was complete agreement in Bosniak classification between both modalities and both observers in six cysts (11.8%). There was agreement of Bosniak classification on both modalities in 21 of 51 cysts (41.2%) for observer 1 and in 17 of 51 cysts (33.3%) for observer 2.	Not serious	Not serious	Not serious	Adults only	3/51 malignant lesions	7
Bosniak classification system: a prospective comparison of CT, contrast-enhanced US, and MR for categorizing complex renal cystic masses. PMID: 26019242	Graumann, O.	Acta Radiol. 57(11):1409-1417	2016	Prospective comparative study of CT, MRI and CEUS	44 patients (aged 42-80 years) with 46 complex renal cysts (Bosniak II – IV). Histological confirmation in 6 lesions. CT as gold standard.	CEUS (n=43): 79% were in agreement with CT (κ = 0.86). Five BII lesions were upgraded to BIIF and four lesions were categorized lower with CEUS. MRI (n=41): 78% were in agreement with CT (κ = 0.91). Three BII lesions were upgraded to BIIF and six lesions were categorized one category lower.	Not serious	Not serious	Not serious	Adults only	4/46 malignant	7
Renal Complex Cystic Masses: Usefulness of Contrast-Enhanced Ultrasound (CEUS) in Their Assessment and Its Agreement with Computed Tomography. PMID: 27787749	Sanz, E.	Curr Urol Rep. 17(12):89.	2016	Prospective comparison of CT and CEUS	66 patients (median age 68 years) with 67 complex renal cysts (Bosniak II-IV). CT as gold standard.	CEUS: sensitivity 100 %, specificity 81 %, positive predictive value 70 %, and negative predictive value 100 %. Kappa index shows good agreement to CT (0.71; 95 % CI 0.57-0.85), both overall and stratified by categories according to Bosniak classification. A total of 8 lesions were discordant, and seven of eight classified as malignant by CEUS and not by CT. Of those seven lesions classified as malignant by CEUS, six (six of seven, 86 %) were malignant in the pathological exam. ROC curves show the superiority of CEUS [0.91 (0.83–0.98) p = 0.000] compared to CT [0.79 (0.65–0.92) p = 0.000]	Not serious	Not serious	Not serious	Adults only	21/66 malignant (on CT)	7

Title	First Author	Journal	Year	Study design	Nº & type of patients (Bosniak category on CT)	Findings	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[1]
Comparison of contrast-enhanced sonography with MRI in the diagnosis of complex cystic renal masses. PMID: 25179487	Chen, Y.	J Clin Ultrasound 43(4):203-209	2015	Prospective comparison of MRI and CEUS	59 patients (21–78 years) with 71 complex cystic renal masses (Bosniak II-IV, 8-98 mm). 43 confirmed by histology (36 malignant), others followed-up 12-40 months	CEUS: sensitivity 97%, specificity 71%, overall accuracy 85% The agreement between the classification using CEUS and the final diagnoses was fair to good (kappa = 0.51). MRI: sensitivity 81%, specificity 77%, overall accuracy 79% The agreement between MRI and the final diagnoses was also fair to good (kappa = 0.51). The areas below the receiver operating characteristic curves of CEUS and MRI were 0.84 and 0.79, respectively.	Not serious	Not serious	Not serious	Adults only	36/71 malignant lesions. No CT	7
Contrast-enhanced ultrasonography for evaluation of cystic renal mass: in comparison to contrast-enhanced CT and conventional ultrasound. PMID: 24929667	Xue, L.Y.	Abdom Imaging. 39(6):1274-83	2014	Retrospective comparison of CEUS to histology	103 patients (aged years) compared to histopathology. CT available in 70.	CEUS: The phenomenon that solid-like component by US did not enhance by CEUS was a strong predictor of benign disease, with a positive predictive value (PPV) of 100%. Enhancement of solid, soft tissue by CEUS was highly predictive of malignancy, with a PPV of 100%. The diagnostic performance of CEUS was better than US for benign cystic lesions. In malignancies, CEUS demonstrated more septa, thicker wall or septa, and more solid components than US and CECT. CEUS permitted categorization of 51.7% (30/58) and 28.6% (10/35) of malignant tumors in higher grade than by US and CECT, respectively. In benign lesions, CEUS detected more septa than CECT and correctly diagnosed benign cysts which appeared as solid lesions in US. CEUS permitted downgrading of 71.1% (32/45) and 17.1% (6/35) of benign lesions compared to US and CECT.	Not serious	Not serious	Not serious	Adults only	58/103 malignant lesions.	7

Title	First Author	Journal	Year	Study design	Nº & type of patients (Bosniak category on CT)	Findings	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[1]
Comparison of contrast-enhanced sonography with unenhanced sonography and contrast-enhanced CT in the diagnosis of malignancy in complex cystic renal masses. PMID: 18806171	Quaia, E.	AJR Am J Roentgenol. 191(4):1239-49	2008	Retrospective comparative study of CT and CEUS	41 patients (29-84 years) with 41 complex cystic lesions on CT (20-80 mm). 30 histologically confirmed others followed-up for 12-24 months.	CEUS: sensitivity: reader 1: 86%, reader 2: 86%, reader 3: 95% Specificity: reader 1: 79%, reader 2: 79%, reader 3: 63% overall diagnostic accuracy: reader 1: 83%, reader 2: 83%, reader 3: 80% CT: sensitivity: reader 1: 81%, reader 2: 81%, reader 3: 95% Specificity: reader 1: 68%, reader 2: 42%, reader 3: 42% overall diagnostic accuracy: reader 1: 75%, reader 2: 63%, reader 3: 70% US: sensitivity: reader 1: 48%, reader 2: 48%, reader 3: 43% Specificity: reader 1: 11%, reader 2: 11%, reader 3: 16% overall diagnostic accuracy: reader 1: 30%, reader 2: 30%, reader 3: 30% CEUS was better than US in diagnostic performance and confidence ($p<0.05$) for all readers. CEUS was better than CT in diagnostic performance (sensitivity, specificity, positive and negative predictive value and accuracy for all readers except reader 3, were sensitivity was equal.	Not serious	Not serious	Not serious	Adults only	21/40 malignant lesions	7
Complex cystic renal masses: characterization with contrast-enhanced US. PMID: 17392251	Ascenti, G.	Radiology. 243(1):158-65.	2007	Prospective comparative study of US and CEUS	40 patients (31-77 years) with 44 complex cystic renal masses (Bosniak II-IV). Confirmation on histology (n=9), or follow-up (n=31, 12-24 months)	CEUS: Complete concordance between contrast-enhanced US and CT was observed in the differentiation of surgical and nonsurgical complex cysts. Complete concordance among the three readers in the assessment of vascularity with CEUS was found. Concordance between CEUS and CT in the evaluation of vascularization was high (kappa = 0.77, $P < 0.001$). CT: complete concordance between the readers was found for classification with CT. Inter-observer agreement in the evaluation of enhancement on CT images was high (kappa = 0.88, $P < .001$). US: high inter-observer agreement was high (kappa = 0.86, $P < 0.001$) for classification	Not serious	Not serious	Not serious	Adults only	5/44 malignant lesions	7

Title	First Author	Journal	Year	Study design	Nº & type of patients (Bosniak category on CT)	Findings	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[1]
Assessment of cystic renal masses based on Bosniak classification: comparison of CT and contrast-enhanced US. PMID: 17097844	Park, B.K.	Eur J Radiol. 61(2):310-4	2007	Retrospective study comparing CT and CEUS	31 patients (26-68 years) with 31 cystic renal masses (Bosniak I-III, 8-97mm). All histologically confirmed.	CEUS: diagnostic accuracy 90% CT: diagnostic accuracy 71% (P>0.05 for difference to CEUS). CEUS and CT images showed same Bosniak classification in 23 (74%) lesions and there were differences in 8 (26%) lesions, all of which were upgraded by CEUS. CEUS images depicted more septa in 10 (32%) lesions, more thickened wall and/or septa in 4 (13%) lesions, and stronger enhancement in 19 (61%) lesions. For six lesions, solid component was detected by CEUS but not by CT.	Not serious	Not serious	Not serious	Adults only	Only 3/31 lesions are not malignant	5
Studies examining CEUS for diagnosing benign vs malignant disease in complex and solid cystic renal lesions												
Diagnostic accuracy of contrast-enhanced ultrasound for characterization of kidney lesions in patients with and without chronic kidney disease. PMID: 28793871	Chang, E.H.	BMC Nephrol. 18(1):266	2017	Prospective comparison of CEUS with histology (n=23) or follow-up imaging (n=21)	44 Patients (n=25 with chronic kidney disease, n=19 without) with cystic and solid indeterminate or suspicious kidney lesions.	CEUS: sensitivity 96% (95% CI: 84%, 99%) specificity of 50% (95% CI: 32%, 68%) Among patients with chronic kidney disease, CEUS sensitivity 90% (95% CI: 56%, 98%), specificity 55% (95% CI: 36%, 73%)	Not serious	Not serious	Not serious	Not serious	21/44 malignancies. Much lower rate of histology in CKD + group.	4
Contrast-Enhanced Ultrasound Classification of Previously Indeterminate Renal Lesions. PMID: 28429490	Zarzour, J.G.	J Ultrasound Med. 36(9):1819-1827	2017	Retrospective comparison of CEUS to final diagnosis by histologic examination or follow-up	41 out of 134 patients with 41 indeterminate lesions, who either had histological confirmation (n=16) or follow-up > 1 year	CEUS: sensitivity 100% (20 of 20; 95% CI, 83%–100%; P<0.0001); specificity 86% (18 of 21; 95% CI,62%–97%; P5.0026); positive predictive value 87% (20 of 23; 95% CI, 66%–97%; P5.0005), negative predictive value 100% (18 of 18; 95% CI, 81%–100%, p<0.001) accuracy 90% (37 of 41; 95% CI, 80%-98%, p<0.001)	Short minimum follow-up	Not serious	Not serious	Adults only, mix of cystic and solid lesions.	15 / 94 malignancies	4

Title	First Author	Journal	Year	Study design	Nº & type of patients (Bosniak category on CT)	Findings	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[1]
Minimally Complex Renal Cysts: Outcomes and Ultrasound Evaluation Compared with Contrast-Enhanced Cross-Sectional Imaging Bosniak Classification. PMID: 28755789	Destefani, M.H.	Ultrasound Med Biol. 43(10):2167-2173.	2017	Retrospective comparison of CEUS to CT/MRI or histology	51 minimally complex cysts and 47 complex cysts.	No sensitivity and specificity values given. All minimally complex cysts on US were benign. The inter-observer agreement on use of a k-test for US classification of complex/MC was 0.704 (95% confidence interval [CI] 0.517–0.892, p<0.001). For CT/MRI classification, inter-observer agreement was 0.745 (95% CI 0.631–0859, p < 0.001).	Not serious	Not serious	Not serious	Not serious	Not serious	3
Contrast-enhanced ultrasound of the kidney: a single-institution experience. PMID: 29218489	Oon, S.F.	Ir J Med Sci. 187(3):795-802	2017	Retrospective comparison of CEUS to CT/MRI or histology	31 patients (7 solid renal lesions, 21 cystic renal lesions and 3 'indeterminate' renal lesions)	No sensitivity and specificity values given.	Not serious	Not serious	Not serious	Not serious	16/31 malignant lesions	3
Diagnostic performance of contrast-enhanced ultrasound in the evaluation of renal masses in patients with renal impairment. PMID: 27770118	Yong, C.	Med J Malaysia. 71(4):193-198.	2016	Retrospective comparison of CEUS to final diagnosis by histologic examination or follow-up	63 patients (aged 28-92 years) with 74 indeterminate renal lesions (4-79mm) and reduced GFR	CEUS: sensitivity 96% (95% CI 77.2-99.9) specificity 94% (95% CI 84.1-98.8%) PPV 88% (95% CI 68-97%) NPV 98% (95% CI 89-100%) 1 false negative case was a small carcinoma.	Not serious	Not serious	Not serious	Adults only, mix of cystic and solid lesions.	22/74 malignant lesions	4
The role of contrast-enhanced ultrasound in the classification of CT-indeterminate renal lesions. PMID: 27609413	Edenberg, J.	Scand J Urol. 50(6):445-451	2016	Comparison of CEUS to CT	140 patients (mean age 64 years) with 148 indeterminate renal lesions (5-166 mm)	CEUS: Sensitivity 100%, specificity 94% positive predictive value 87% negative predictive value 100% Bosniak category III: 4 malignant, 3 benign on surgery Bosniak category IV: 7 malignant, 0 benign on surgery Problem: category II not followed up.	Not serious	Not serious	Not serious	Adults only	18/140 malignant lesions	4

Title	First Author	Journal	Year	Study design	Nº & type of patients (Bosniak category on CT)	Findings	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[1]
Renal Masses With Equivocal Enhancement at CT: Characterization With Contrast-Enhanced Ultrasound. PMID: 25905962	Bertolotto, M.	AJR Am J Roentgenol. 204(5): W557-65	2015	Retrospective characterization of equivocal CT lesions on CEUS	47 patients (age 38-88 years) with 47 renal lesions (8-77mm), with histology in 30 and follow up (> 3 years) in others.	CEUS: The diagnostic performance of contrast-enhanced ultrasound to characterize the lesions as benign or malignant was high for both readers (AUC, 0.958 and 0.966, respectively). Interreader agreement for cystic/solid classification was complete. 12 likely complex cystic lesions at US were cystic also on CEUS and reference procedures. Eleven of 34 lesions that appeared solid at US were cystic on CEUS and reference procedures. One lesion considered likely solid by one radiologist and possibly cystic by the other was a solid tumor at CEUS and histologic analysis.	Not serious	Not serious	Not serious	Adults only, mix of cystic and solid lesions.	30/47 malignant lesions	4
Prospective evaluation of CT indeterminate renal masses using US and contrast-enhanced ultrasound. PMID: 25209216	Nicolau, C.	Abdom Imaging. 40(3):542-51.	2015	Prospecitve comparison of CT, US and CEUS	72 patients (aged 34-92 years) with 83 indeterminate renal lesions (Bosniak I-IV or solid). Final diagnosis by histology or follow-up > 23 months with a conclusive imaging study.	CEUS: sensitivity of 96%, specificity of 94%, and overall accuracy of 95%. US: sensitivity of 36%, specificity of 52%, and overall accuracy of 42%.	Not serious	Not serious	Not serious	Adults only, mix of cystic and solid lesions.	28/83 (34%) malignant lesions	6

Title	First Author	Journal	Year	Study design	Nº & type of patients (Bosniak category on CT)	Findings	Risk of bias	Indirectness	Inconsistency	Imprecision	Other con-siderations	Importance[1]
Evaluation of indeterminate renal masses with contrast-enhanced US: a diagnostic performance study. PMID: 24475802	Barr, R.G.	Radiology. 271(1):133-42	2014	Retrospective comparison of CT, MRI and CEUS.	721 patients (17-95 years) with 1018 indeterminate renal masses (2-161 mm) on CT, MRI or conventional US. 265 patients (306 lesions) have a confirmed diagnosis, of which only 10 patients (10 lesions) have benign cystic lesions and 37 patients (61 lesions) are AML.	<u>per-patient analysis in cases with confirmed diagnosis:</u> sensitivity 100% (126 of 126; 95% CI: 97%, 100%) specificity 95% (132 of 139; 95% CI: 99%, 98%) PPV 95% (126 of 133), NPV 100% (132 of 132). <u>per-patient analysis in cases with confirmed diagnosis:</u> sensitivity 100% (139 of 139; 95% CI: 97%,100%) specificity 95% (159 of167; 95% CI: 918%, 98%), positive predictive value 95% (139 of 147), negative predictive value 100% (159 of 159). Visualization of occasional bubbles or a constant flow of bubbles without nodularity within a fine septation of a cystic mass is a benign finding (16 of 16, 100%). Angiomyolipomas (61 of 61, 100%) enhance less than normal renal cortex does, often with a peripheral distribution, while echogenic renal cell carcinoma (7 of 7, 100%) have diffuse intense enhancement with washout.	Not serious	Not serious	Not serious	Adults only, but starting at 17 years, mix of cystic and solid lesions.	139/306 (45%) malignant lesions. Large series	5
Diagnostic accuracy of contrast-enhanced ultrasound for renal cell carcinoma: a meta-analysis. PMID: 24659450	Wang, C.	Tumour Biol. 35(7):6343-50.	2014	Meta-Analysis of 11 studies	567 patients with RCC and 313 with benign renal tumors	Pooled sensitivity for diagnosing RCC: 88% (95% CI 85-90%) Pooled specificity for diagnosing RCC: 80% (95% CI 75-85%)	Mainly Asian cohort (10/11 papers).	Not serious	Not serious	Adults only. 5/11 studies published in Chinese only. Mix of cystic and solid lesions.	567/880 (64%) malignant lesions. Ghost-written paper?	6

Title	First Author	Journal	Year	Study design	Nº & type of patients (Bosniak category on CT)	Findings	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[1]
Studies examining CEUS for diagnosing benign vs malignant disease in acquired cystic kidney disease in ESRD / after renal transplantation												
Contrast-enhanced ultrasound (CEUS) as a new technique to characterize suspected renal transplant malignancies in renal transplant patients in comparison to standard imaging modalities. PMID: 29630539	Mueller-Peltzer, K	Clin Hemorheol Microcirc. 69(1-2):69-75	2018	Prospective comparison of CEUS to CT (n=15) or MRI (n=7) as gold standard	22 renal transplant patients with suspected renal transplant malignancies. Age 28.2 years to 74.6 (mean age 55.7 years; SD±13.0 years)	sensitivity 100%, specificity 94% positive predictive value (PPV) 80% negative predictive value (NPV) of 100%	Not serious	Not serious	Not serious	Adults only.	Not only ACDK, i.e. Cystic and solid lesions (unclear how many of each).	5
Contrast-enhanced ultrasound assessment of complex cystic lesions in renal transplant recipients with acquired cystic kidney disease: preliminary experience. PMID: 22974874	Paudice, N.	Transplant Proc. 44(7):1928-9	2012	Prospective comparison of US and CEUS (CT only in some cases!)	15 patients with 34 indeterminate lesions on US.	CEUS revealed Bosniak category III or above in 4 patients, all of whom had histologically confirmed malignancy. However, the others were only followed by CEUS (length of time not given), without further CT or histological evaluation	CEUS category II were not confirmed by CT or pathology.	Not serious	Not serious	Small study.		4

AUCs-SROC curve: area under the curve in the summary receiver operating characteristic curve
CECT: contrast enhanced CT
CEUS: contrast enhanced ultrasound
CT: computer tomography
MRI: magnetic resonance imaging
US: ultrasound

Table E3 - Literature summary on Malignancy in children with a multicystic dysplastic kidney (MCDK)

No of Studies & Reference	Study designs	Incidence of malignancy	Follow up	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations
Malignancy								
41 (Refs 2–17)	15 cohort studies after 2005 and 1 systematic review of 26 cohort studies before 2005	0/ 2335 = 0%	Not given in 7. Shortest median follow up: 23 months. Longest median follow up: 10.1 years.	Serious	Not serious	Not serious	Not serious	Majority do not have follow-up > 10 years

Table E4 - Literature summary on HNF1B disease (manifestations seen on medical imaging)

No of studies & references	Study design	Nº of events	Nº of patients	Event rate (range)	Risk of bias	Indirectness	Inconsistency	Imprecision
prenatal radiological findings in patients with HNF1ß – disease								
abnormal renal ultrasound								
9 (18–26)	retrospective analysis of prenatal ultrasound in patients with HNF1B including TOP	230	386	60% (31-100%)	very serious [2]	not serious	Serious	not serious
renal cysts								
6 (18,20–22,25,27)	prenatal ultrasound in patients with HNF1B alteration including TOP	66	120	55% (34-100%)	Serious [2]	not serious	Serious	not serious
hyperechoic kidneys								
5 (18,20,22,24,25)	retrospective analysis of prenatal ultrasound in patients with HNF1B including TOP	73	125	58% (25-77%)	very serious [2]	not serious	Serious	not serious
normal renal size								
4 (20,22,25,27)	prenatal ultrasound in patients with HNF1B including TOP	67	105	64% (40-89%)	Serious [3]	not serious	Serious	serious
increased renal size								
4 (20,22,25,27)	prenatal ultrasound in patients with HNF1B including TOP	20	105	19% (0-60%)	Serious [3]	not serious	Serious	serious
unilateral renal agenesis								
6 (18,20,22,24,25,27)	prenatal ultrasound in patients with HNF1B including TOP	7	126	6% (0-13%)	not serious	not serious	not serious	not serious
unilateral renal hypoplasia/dysplasia/MCDK								
7 (18,20–22,24,25,27)	prenatal ultrasound in patients with HNF1B including TOP	19	150	13 % (0-50%)	Serious [4]	not serious	Serious	not serious
bilateral renal hypoplasia/dysplasia/MCDK								
7 (18,20–22,24,25,27)	prenatal ultrasound in patients with HNF1B including TOP	9	150	6 % (0-33%)	Serious [2]	not serious	not serious	not serious

[2] Selected cohorts (i.e. suspicion of HNF1b often based on abnormal renal ultrasound findings)
[3] Variable definitions of increased kidney size
[4] Different unilateral findings grouped together

No of studies & references	Study design	Nº of events	Nº of patients	Event rate (range)	Risk of bias	Indirectness	Inconsistency	Imprecision
radiological findings in patients with HNF1ß – disease from 0-16 years								
abnormal renal ultrasound								
5 (20,24,28–30)	retrospective analysis of patients with HNF1B	104	109	95% (50-100%)	very serious [2]	not serious	not serious	not serious
renal cysts								
11 (20,23,24,26,28–34)	renal ultrasound in patients with HNF1B	237	312	76% (50-84%)	Serious [2]	not serious	not serious	not serious
hyperechoic kidneys								
6 (20,23,24,31,26,29)	renal ultrasound in patients with HNF1B	137	258	53% (18-97%)	Serious [2]	not serious	Very serious	not serious
normal renal size								
3 (19,24,35)	renal ultrasound in patients with HNF1B	105 (kidneys)	132 (kidneys)	62% (44-80%)	Serious [2]	not serious	Serious	not serious
increased renal size								
3 (19,24,35)	renal ultrasound in patients with HNF1B	4 (kidneys)	132 (kidneys)	7% (7-80%)	Serious [3,5]	not serious	Very serious	not serious
unilateral renal agenesis								
8 (19,23,24,26,28,29,35,36)	renal ultrasound in patients with HNF1B	30	319	9% (0-75%)	Serious [2]	not serious	Very serious	not serious
unilateral renal hypoplasia/dysplasia/MCDK								
7 (20,23,29,31–34)	renal ultrasound in patients with HNF1B	37	143	26% (12-50%)	very serious [4]	not serious	not serious	very serious
bilateral renal hypoplasia/dysplasia/MCDK								
7 (20,23,29,31–34)	renal ultrasound in patients with HNF1B	21	143	15% (0-40%)	very serious [4]	not serious	not serious	very serious
radiological findings in patients with HNF1ß – disease in adulthood								
abnormal renal ultrasound								
6 (20,21,30,37–39)	renal ultrasound in patients with HNF1B	52	62	84% (50-91%)	very serious [2]	not serious	not serious	not serious
renal cysts								
9 (20,21,23,26,30,34,37–39)	renal ultrasound in patients with HNF1B	97	146	66% (38-86%)	Serious [2]	not serious	not serious	not serious
hyperechoic kidneys								
3 (20,23,26)	renal ultrasound in patients with HNF1B	9	87	10% (3-56%)	Serious	not serious	Serious	serious
normal renal size								

[5] Small studies; percent of kidneys, not patients

No of studies & references	Study design	Nº of events	Nº of patients	Event rate (range)	Risk of bias	Indirectness	Inconsistency	Imprecision
2 (20,21)	renal ultrasound in patients with HNF1B	42 (kidneys)	59 (kidneys)	71% (63-89%)	very serious [3]	not serious	not serious	serious
increased renal size								
2 (20,21)	renal ultrasound in patients with HNF1B	4 (kidneys)	59 (kidneys)	7% (0-10%)	very serious [3]	not serious	not serious	serious
unilateral renal agenesis								
6 (20,21,21,23,26,34,38)	renal ultrasound in patients with HNF1B	17	124	14% (12-18%)	Serious [2]	not serious	not serious	serious
unilateral renal hypoplasia/dysplasia/MCDK								
4 (20,21,23,34)	renal ultrasound in patients with HNF1B	5	57	9% (0-18%)	very serious [4]	not serious	not serious	very serious
bilateral renal hypoplasia/dysplasia/MCDK								
4 (20,21,23,34)	renal ultrasound in patients with HNF1B	10	57	16% (1-22%)	very serious [4]	not serious	not serious	very serious
extrarenal radiological findings in patients with HNF1ß – disease								
urinary tract anomalies								
11 (18–20,22–27,34,38)	analysis of patients with HNF1B	76	490	16% (6-50%)	not serious	not serious	Serious	serious
genital malformations								
15 (18,20–23,25,26,29,30,33,34,40–43)	analysis of patients with HNF1B	67	428	16% (0-71%)	not serious	not serious	Serious	serious
pancreatic anomalies								
10 (18,21–23,25,26,29,39,42,44)	analysis of patients with HNF1B	67	333	20% (1-100%)	not serious	not serious	Serious	serious

TOP: termination of pregnancy, HNF1B: hepatocyte nuclear factor 1 beta (=transcription factor 2)

Table E5 - Literature review on imaging diagnosis of ADPKD in children and young adults

Title	First Author	Journal	Year	Study design	N° & type of patients	Methodological details	Prediction of genetic diagnosis	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[6]
Studies in at-risk children and young adults determining sensitivity and specificity compared to genetic analysis													
Ultrasound													
PKD 1 only													
Unified criteria for ultrasonographic diagnosis of ADPKD	Pei, Y.	J Am Soc Nephrol. 20(1):205-12	2009	Diagnostic study in at-risk individuals	113 patients with *PKD1* mutations aged 15-29 years + similar number of unaffected siblings (*n* aged <18 years unspecified).	Ultrasound with 3 or 5 MHz sector probe. Simulated data set of 1000 patients bootstrapped from the original dataset	≥1 renal cyst: sensitivity 99% (97 to 100%) specificity 98% (95 to 100%) ≥2 renal cysts (uni- or bilateral): sensitivity 98% (95 to 100%) specificity 99% (96 to 100%) ≥3 renal cysts (uni- or bilateral): Sensitivity 94% (89 to 98%) Specificity 100%	Serious[7]	Not serious	Not serious	Not serious	Partial overlap with Ravine et al and Parfrey et al	7
Autosomal dominant polycystic kidney disease types 1 and 2: assessment of US sensitivity for diagnosis	Nicolau, C.	Radiology. 213(1):273-6	1999	Diagnostic study in at-risk individuals	146 individuals at risk of *PKD1* aged between 9 months-30 years (*n* aged <18 years unspecified). 84 affected and 62 unaffected.	Ultrasound with 3.7 or 5 MHz	≥ 2 (uni-or bilateral) renal cyst: sensitivity: 95% Specificity: 100% False negative results: 4/84 (aged 2,3, 5 and 26 years) False positive results: 0/62	Serious [7]	Not serious	Not serious	Not serious		7

[6] Where 9 is highest and 1 is lowest

[7] No separate analysis for pediatric patients

Title	First Author	Journal	Year	Study design	Nº & type of patients	Methodological details	Prediction of genetic diagnosis	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[6]
The use of ultrasonography and linkage studies for early diagnosis of autosomal dominant polycystic kidney disease (ADPKD).	Papadopoulou, D.	Ren Fail. 21(1):67-84	1999	Diagnostic study in at-risk individuals	33 children with *PKD1* (n=13 < 12 years and n=23 of 12-19 years)	Ultrasound, not further specified.	≥ 2 cysts in one kidney plus ≥ 1 in the other: < 12 years: sensitivity 23% 12-19 years: sensitivity 87% (unaffected children also examined, but as *n* not given, specificity, NPV and PPV analysis not possible)	Not serious	Not serious	Not serious	Not serious	Small sample size. Strict diagnostic criterion.	8
Utility of ultrasonography in the diagnosis of autosomal dominant polycystic kidney disease in children	Gabow, P.A.	Am Soc Nephrol. 8(1):105-10	1997	Diagnostic study in at-risk individuals	105 children with risk of *PKD1* mutation.	Ultrasound, not further specified.	≥1 renal cyst (sensitivity, specificity, false negative rate, false positive rate): all children: 77%, 98%, 25%, 2% 3 mths-5 years: 62%, 89%, 38%, 11% 5-10 years: 82%, 100%, 19%, 0% 10-15 years: 86%, 100%, 23%, 0% 15-17.5 years: 67%, 100%, 22%, 0%	Not serious	Not serious	Not serious	Not serious		8
Diagnosis of adult polycystic kidney disease by genetic markers and ultrasonographic imaging in a voluntary family register	Elles, R.G.	J Med Genet. 31(2):115-20.	1994	Diagnostic study in at-risk individuals	56 persons at risk for *PKD1* aged < 30 years.	Ultrasound with 3.5 MHz linear or sector probe.	Age group < 30 years: ≥ 2 cysts in one kidney plus ≥ 1 in the other: Sensitivity 96% Specificity 100% PPV 100%, NPV 97% Age class 0-9 years: Observed frequency of positive ultrasound 23.5 ± 20% vs predicted frequency of 49%. I.e. evidence for significant rate of false negatives. Age class 10-19 years: Observed frequency of positive ultrasound 60 ± 13% vs predicted frequency of 43%. I.e. no evidence for significant rate of false negatives.	Not serious	Not serious	Not serious	Not serious	Separate analysis for 0-9 year olds (but n not given for this group)	8

Title	First Author	Journal	Year	Study design	Nº & type of patients	Methodological details	Prediction of genetic diagnosis	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[6]
Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1	Ravine, D.	Lancet 343(8901):824-7.	1994	Diagnostic study in at-risk individuals	204 previously not examined at-risk individuals of *PKD1* (of which 37 were aged 15-19 years)	Ultrasound with 3 or 5 MHz sector probe.	Age 15-29 years ("similar in 15-19 and 20-29yr olds"): ≥ 1 renal cyst: sensitivity 96% ≥ 2 (uni-or bilateral) renal cyst: sensitivity 96% ≥ 2 cysts in one kidney plus ≥ 1 in the other: Sensitivity 89% ≥ 2 cysts in each kidney: sensitivity 8%5 ≥ 4 cysts in each kidney: sensitivity 81% At age 20 years: (PPV and NPV) ≥ 1 renal cyst: 100%, 97% ≥ 2 (uni-or bilateral) renal cyst: 100%, 97% ≥ 2 cysts in one kidney plus ≥ 1 in the other: 100%, 91% ≥ 2 cysts in each kidney: 100%, 88% ≥ 4 cysts in each kidney: 100%, 85%	Serious [7]	Not serious	Not serious	Not serious		8
Autosomal dominant polycystic kidney disease: new information for genetic counselling.	Bear, J.C.	Am J Med Genet. 43(3):548-53.	1992	Diagnostic study in at-risk individuals	125 children and young adults at risk of *PKD1* (n=19 0-9 years, n=52 10-19 years, n=54 20-29 years) (overlap with Parfrey et al).	Ultrasound, not further specified.	≥ 2 cysts in one kidney plus ≥ 1 in the other: Calculated rate of false negative ultrasounds: 0-9 years: 36% 10-19 years: 8% 20-29 years: 0%	Not serious	Not serious	Not serious	Not serious	Separate analysis for 0-9 and 10-19 year olds. Overlap with Parfrey et al.	8
The diagnosis and prognosis of autosomal dominant polycystic kidney disease	Parfrey, P.S.	N Engl J Med. 323(16):1085-90	1990	Diagnostic study in at-risk individuals	Individuals at risk of *PKD1* mutation aged < 30 years. 48 affected and 23 unaffected	Ultrasound, not further specified.	≥ 2 cysts in one kidney plus ≥ 1 in the other: 40/48 affected and 0/23 unaffected Equivocal: 1/48 affected and 1/23 unaffected No cysts: 7/48 and 22/23 unaffected	Serious [7]	Not serious	Not serious	Not serious		7

Title	First Author	Journal	Year	Study design	Nº & type of patients	Methodological details	Prediction of genetic diagnosis	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[6]
PKD 2 only													
Unified criteria for ultrasonographic diagnosis of ADPKD	Pei, Y.	J Am Soc Nephrol. 20(1):205-12	2009	Diagnostic study in at-risk individuals	41 patients with *PKD2* mutations aged 15-29 years + similar number of unaffected siblings (*n* aged <18 years unspecified).	Ultrasound with 3 or 5 MHz sector probe. Simulated data set of 1000 patients bootstrapped from the original dataset	≥1 renal cyst: sensitivity 79% (67% to 90%) specificity 97% (91% to 100%) ≥2 renal cysts (uni- or bilateral): Sensitivity 72% (59% to 83%) Specificity 100% ≥3 renal cysts (uni- or bilateral): Sensitivity 70% (57% to 81%) Specificity 100% 3 truly pediatric patients (aged 16 and 17) are affected by *PKD2* but have NO cysts.	Serious[7]	Not serious	Not serious	Not serious	Partial overlap with Ravine et al and Parfrey et al	7
Autosomal dominant polycystic kidney disease types 1 and 2: assessment of US sensitivity for diagnosis	Nicolau, C.	Radiology. 213(1):273-6.	1999	Diagnostic study in at-risk individuals	15 individuals at risk of *PKD2* aged between 9 months-30 years (*n* aged <18 years unspecified). 6 affected and 9 unaffected.	Ultrasound with 3.7 or 5 MHz	≥ 2 (uni-or bilateral) renal cyst: sensitivity: 67% Specificity: 100% False negative results: 2/16 (aged 5 and 10 years) False positive results: 0/9	Serious[7]	Not serious	Not serious	Not serious		7

Title	First Author	Journal	Year	Study design	Nº & type of patients	Methodological details	Prediction of genetic diagnosis	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[6]
Known familial ADPKD but unknown genotype													
Unified criteria for ultrasonographic diagnosis of ADPKD	Pei, Y.	J Am Soc Nephrol. 20(1):205-12	2009	Diagnostic study in at-risk individuals	15-29 year olds out of 577 *PKD1* and 371 *PKD2*-at-risk individuals (*n* aged <18yr unspecified).	Ultrasound with 3 or 5 MHz sector probe. Simulated data set of 1000 patients bootstrapped from the original dataset. Case-mix: 85% *PKD1*, 15% *PKD2*	≥1 renal cyst: sensitivity 89% (84% to 94%) specificity 97% (94% to 99%) ≥2 renal cysts (uni- or bilateral): Sensitivity 85% (79% to 91%) Specificity 99% (98% to 100%) ≥3 renal cysts (uni- or bilateral): Sensitivity 82% (75% to 88%) Specificity 100%	Serious Error! Bookmark not defined.	Not serious	Not serious	Not serious	Partial overlap with Ravine et al and Parfrey et al	7
Autosomal dominant polycystic kidney disease types 1 and 2: assessment of US sensitivity for diagnosis	Nicolau, C.	Radiology. 213(1):273-6.	1999	Diagnostic study in at-risk individuals	161 individuals at risk of *PKD1* (91%) of *PKD2* (9%) aged 9 months - 30 years (*37* aged <16 years). 90 affected and 71 unaffected.	Ultrasound with 3.7 or 5 MHz	≥ 2 (uni-or bilateral) renal cyst: sensitivity: 93% Specificity: 100% False negative results: 6/90 False positive results: 0/71	Serious [7]	Not serious	Not serious	Not serious		7
High-resolution ultrasound													
Imaging-based diagnosis of autosomal dominant polycystic kidney disease	Pei, Y.	J Am Soc Nephrol. 26(3):746-53	2015	Diagnostic study in at-risk individuals and healthy controls	37 patients with ADPKD and 58 unaffected (healthy siblings and controls), aged 16-29 years. 56% have truncating *PKD1*, 22% non-truncating *PKD1* and 22% *PKD2* mutations.	High resolution ultrasound with 3.8 to 8 MHz probes	Sensitivity, specificity, PPV and NPV: ≥ 1 renal cyst: 97%, 85%, 80%, 98% ≥ 2 (uni-or bilateral) renal cysts: 97%, 95%, 92%, 98% ≥ 3 (uni-or bilateral) renal cysts: 97%, 98%, 97%, 98% ≥ 4 (uni-or bilateral) renal cysts: 97%, 98%, 97%, 98% ≥ 2 cysts in each kidney: 97%, 100%, 100%, 98% Compared to conventional ultrasound (Pei 2009): better sensitivity, but slightly lower specificity.	Serious [7]	Not serious	Not serious	Not serious	Exact n < 18 years not mentioned	7

Title	First Author	Journal	Year	Study design	Nº & type of patients	Methodological details	Prediction of genetic diagnosis	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[6]
MRI													
Imaging-based diagnosis of autosomal dominant polycystic kidney disease	Pei, Y.	J Am Soc Nephrol. 26(3):746-53	2015	Diagnostic study in at-risk individuals and healthy controls	37 patients with ADPKD and 58 unaffected (healthy siblings and controls), aged 16-29 years. 56% have truncating *PKD1*, 22% non-truncating *PKD1* and 22% *PKD2* mutations.	T2 weighted, fast-spin echo sequence without gadolinium on 1.5 Tesla scanner	Sensitivity, specificity, PPV and NPV: ≥ 5 (uni-or bilateral) renal cysts: 100%, 98%, 97%, 100% > 10 (uni-or bilateral) renal cysts: 100%, 100%, 100%, 100% ≥ 2 cysts in each kidney: 100%, 98%, 97%, 100% Suggest to use >10 cysts as diagnostic criterion in individuals at risk of ADPKD, and stricter <5 criterion for exclusion of ADPKD in potential living related kidney donors.	Serious[7]	Not serious	Not serious	Not serious	Exact n < 18 years not mentioned	7
Studies in at-risk children without genetic diagnostics but follow-up ultrasound													
Renal ultrasonographic evaluation in children at risk of autosomal dominant polycystic kidney disease.	Reed, B.	Am J Kidney Dis. 56(1):50-6	2010	Cohort study of at-risk children	420 children (mean age 8.3 ± 4.2 years)	No genetic diagnostics. 3 groups: no cysts/ unilateral cysts/ bilateral cysts	Initially 227/420 children did not have cysts, but 10/43 (23%) with follow-up at age > 15 years and 14/77 (18%) with follow-up at age ≤ 15 years later developed bilateral cysts. Initially 43/420 children only had unilateral cysts. Of these 2/8 (25%) with follow-up at age > 15 years and 17/26 (65%) with follow-up at age ≤ 15 years later developed bilateral cysts. However, 3/34 (7%) did not have any cysts on follow-up.	Selected group	Not serious	Not serious	No genetic diagnostics.		5
The spectrum of autosomal dominant polycystic kidney disease in children.	Fick, G.M.	J Am Soc Nephrol. 4(9):1654-60.	1994	Cohort study of at-risk children	39 children with follow-up out of 154 children from families with clinical ADPKD	No genetic diagnostics. Diagnostic criterion ≥ 1 cyst.	Of 17 children without cysts, none developed cysts on follow–up. Of 4 children with only 1 cyst, 3 developed bilateral cysts on follow-up (mean 4 years later). Of 22 with ≥ 1 cyst, none had no cysts on follow-up.	Probably biased towards more severe cases.	Not serious	Not serious	No genetic diagnostics.		5

Title	First Author	Journal	Year	Study design	Nº & type of patients	Methodological details	Prediction of genetic diagnosis	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations	Importance[6]
Autosomal dominant polycystic kidney disease in childhood: a longitudinal study.	Sedman, A.	Kidney Int. 31(4):1000-5	1987	Cohort study of at-risk children	68 children with follow-up out of 154 children from families with clinical ADPKD	No genetic diagnostics. Diagnostic criterion > 5 cysts.	Of 37 children without cysts, 3 developed < 5 cysts and 4 developed > 5 cysts after age 18 years. Of 12 children with < 5 cysts, 2 were classified normal and 4 developed > 5 cysts after age 18 years. Of 19 children with > 5 cysts, none were reclassified later.	Unusually severely affected cohort (3 with ESRD)	Not serious	Very strict diagnostic criterion	No genetic diagnostics.	Very strict diagnostic criterion	5
Studies in affected children													
PKD 1													
Genotype-phenotype correlation in children with autosomal dominant polycystic kidney disease.	Fencl, F.	Pediatr Nephrol. 24(5):983-9	2009	Cohort study in patients	50 Patients with *PKD1* (and positive family history)	mean age at diagnosis 5.4 ± 4.3 years	Total number of cysts: mean 13.39 ± 12.53 Bilateral renal cysts: n=43 (86%) Enlarged kidneys: n= 16 (32%) Diameter of the biggest cyst: 16.79 ± 10.65 mm	Selected group	Not serious	Not serious	Not serious		3
PKD 2													
Genotype-phenotype correlation in children with autosomal dominant polycystic kidney disease.	Fencl, F.	Pediatr Nephrol. 24(5):983-9	2009	Cohort study in patients	10 patients with *PKD2* (and positive family history)	mean age at diagnosis 7.9 ± 5.0 years	Total number of cysts: mean 3.00 ± 2.10 Bilateral renal cysts: n= 3 (30%) Enlarged kidneys: n= 0 (0%) Diameter of the biggest cyst: mean 5.08 ± 1.53 mm	Small study	Not serious	Not serious	Not serious		3

ADPKD: autosomal dominant polycystic kidney disease.
ESRD: end stage renal disease
NPV: negative predictive value
PPV: positive predictive value

Table E6 - Literature summary on cysts in children with tuberous sclerosis complex

No of Studies & References	Study designs	Incidence of cysts (range across studies)	Incidence of AML (range across studies)	Risk of bias	Indirectness	Inconsistency	Imprecision	Other considerations
Exclusively pediatric cohorts								
7 (45–51)	Mainly retrospective cohort studies, 1 cross sectional study	70/313 = 22% (5 – 30%)	114/255 = 45% (26 – 62%)	Not serious [8]	Not serious	Not serious	Serious [9]	2 older ultrasound studies have similar rates to MRI studies
Mixed pediatric and adult cohorts								
9 (48,51–58)	1 prospective registry (65% of patients), 8 cohort studies.	879/3198 = 27% (25 – 47%)	1585/3166 = 50% (40 – 87%)	Not serious	Not serious	Not serious	Not serious	Children mostly not reported separately
Children with TSC2/PKD1 contiguous gene deletion syndrome								
5 (47,50,59–61)	Cohort studies, mostly in selected populations	29/30 = 97% (67 – 100%)	9/27 = 33 % (0 – 86%)	Very serious [10]	Not serious	Serious	Serious [11]	

[8] Despite fact that mostly small cohorts from referral centers

[9] Increase of incidence across childhood years in most studies

[10] Very small patient numbers. Single patient without cysts only followed up to age 4.5 years. Early studies only perform genetics in those with early severe cysts.

[11] Very small patient numbers. AMLs hard to visualize among multiple cysts (therefore incidence depends on quality of imaging)

Table E7 – search strategies and number of papers screened for systematic literature reviews

Table No	MEDLINE search terms	No of items screened	Inclusion criteria	Exclusion criteria	Going back to	No of studies included [12]
S2 – CEUS in cystic kidney disease	(((((((ultrasound) OR sonography)) AND contrast)) AND ((kidney) OR renal))) AND cyst*	334	Studies with at least some cystic and some benign renal lesions (i.e. not only solid or only malignant)	case reports, conference abstracts, non-English	Up to and including meta-analysis by Wang et al in 2014	22
	Bosniak AND child*	16				
S3 – diagnosis of ADPKD in children and young adults	("ADPKD" or "dominant AND polycystic") AND "screening"	764	Geneticall y confirmed diagnosis of ADPKD	Studies with purely histological diagnosis of ADPKD	No age limit	17
	Papers before June 2014 extracted from the systematic literature review in Rangan, G.K. et al. "KHA-CARI Autosomal Dominant Polycystic Kidney Disease Guideline: Screening for Polycystic Kidney Disease" Seminars in Nephrology 2015; 35(6), 557-564					
S4 – manifesta	*((((HNF1βeta) OR hnf1 beta) OR TCF2) OR TCF 2) AND imag**	37	Studies in humans. At least 5-	Case reports < 5 patients. No human data. No radiological findings.	No age limit (HNF1β discovered in	28

[12] Systematic review counts as single study

tions of HNF1B disease on medical imaging	(((((((HNF1βeta) OR hnf1 beta) OR HNF1β) OR tcf2) OR tcf 2) AND ("1997/08/01"[PDat] : "2017/08/01"[PDat]) AND Humans[Mesh])) AND ren*	186	10 patients for major feature (renal phenotype). Aat least 2 patients for extrarenal phenotypes	Incidence of diabetes, liver function test abnormalities, hypomagnesemia and hyperuricemia not listed, because they are not imaging findings. Early onset gout and malignancy not included because not relevant in pediatrics.	1997).	
	Relevant papers from references					
S6 – malignancy in MCDK	"Multicystic dysplastic kidney" or "MCDK"	833		Case reports	Up to and including systematic review by Narchi et al in 2005	16

Suggestions for further research

Simple and complex cysts

- Examine prevalence of simple and complex cysts at different ages in different populations
- Evaluate long-term outcome of children with simple / single cysts
- Examine the role of CEUS in the diagnostic workup of pediatric cystic kidney tumors

Cystic dysplasia

- Examine the correlation of renal size and volume to long-term functional outcome in renal hypo/dysplasia

ARPKD and ADPKD:

- Establish prognostically relevant disease classification for children with ARPKD and ADPKD
- Establish diagnostic imaging criteria for ADPKD in children
- Evaluate the utility of high-resolution US and/or MRI for more sensitive evaluation of cyst progression in children with ADPKD and ARPKD
- Explore the role of liver (and kidney) elastography in ARPKD
- Explore the role of 3D volumetric US to monitor progression of ADPKD
- Establish the natural history of kidney growth and function in ARPKD and ADPKD in unbiased populations

TSC

- Investigate the pathogenesis of renal failure in *TSC2/PKD1* CGS aside from renal cysts; explain discordant radiological findings compared to ADPKD.
- Describe/follow the growth of cysts in *TSC2/PKD1* CGS in a multinational cohort

Nephronophthisis

- Examine the prevalence of liver disease in children with nephronophthisis
- Explore the role of liver elastography in nephronophthisis

Bardet-Biedl syndrome

- Investigate the pathogenesis of the variable kidney phenotypes

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