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EDUCATIONAL REVIEW

Looking at the (w)hole: magnet resonance imaging in polycystic kidney disease

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Abstract Inherited cystic kidney diseases, including autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD), are the most common monogenetic causes of end-stage renal disease (ESRD) in children and adults. While ARPKD is a rare and usually severe pediatric disease, the more common ADPKD typically shows a slowly progressive course leading to ESRD in adulthood. At the present time there is no established disease-modifying treatment for either ARPKD or ADPKD. Various therapeutic approaches are currently under investigation, such as V2 receptor antagonists, somatostatins, and mTOR inhibitors. Renal function remains stable for decades in ADPKD, and thus clinically meaningful surrogate markers to assess therapeutic efficacy are needed. Various studies have pointed out that total kidney volume (TKV) is a potential surrogate parameter for disease severity in ADPKD. Recent trials have therefore measured TKV by magnet resonance imaging (MRI) to monitor and to predict disease progression. Here, we discuss novel insights on polycystic kidney disease (PKD), the value of MRI, and the measurement of TKV in the diagnosis and follow-up of PKD, as well as novel emerging therapeutic strategies for ADPKD.

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Introduction

Inherited cystic kidney diseases are the most frequent monogenetic causes of end-stage renal disease (ESRD) worldwide. They form a genetically and phenotypically heterogeneous group of disorders with various degrees of extrarenal signs and symptoms. Making an accurate diagnosis may be challenging, especially in pediatric patients [1]. Despite the large heterogeneity of genetic cystic kidney diseases, all disease variants have been linked to the dysfunction of primary cilia—the membrane-bound cellular protuberances that sense the extracellular environment and control multiple intracellular signaling cascades, including mammalian target of rapamycin (mTOR) signaling. The proteins affected in genetic cystic kidney diseases localize to cilia or the ciliary base, and targeted deletion of crucial ciliary genes leads to cystic phenotypes in animal models [2–5]. Hereditary cystic kidney diseases are therefore nowadays thought to be a disorder of primary cilia—so-called "ciliopathies." Ciliary function and the pathogenesis of ciliopathies have recently been reviewed in various excellent articles [2–5].

Polycystic kidney diseases

The most important forms of inherited cystic kidney diseases are the autosomal recessive and the autosomal dominant variants of polycystic kidney diseases (PKDs). Recent reviews have summarized the PKDs from clinical and

pathophysiological angles [1, 5, 6]. We will therefore only briefly summarize some important aspects.

Autosomal recessive polycystic kidney disease

Autosomal recessive polycystic kidney disease (ARPKD) is a multi-system disease affecting kidneys, liver, pancreas, and lungs with an estimated incidence of 1:20,000 [7, 8]. This monogenic autosomal recessive disorder is caused by mutations in the *PKHD1* gene on chromosome 6p21 [1]. *PKHD1* encodes fibrocystin (FC), an approximately 450-kDa ciliary protein with a single transmembrane domain, a large extracellular part, and a short intracellular tail containing 18 amino acids which are sufficient for ciliary targeting of FC [9]. Recent data point to a role for FC in joint intracellular signaling pathways with the ADPKD proteins polycystin-1 (PC1) [10] and polycystin-2 (PC2) [11–14], but FC function remains poorly understood.

Kidney ultrasound in ARPKD patients at early disease stage or even in utero reveals the "salt and pepper" picture consisting of often enlarged, echoic, and polycystic kidneys [7, 8, 15], frequently with a sonolucent rim and absent corticomedullary differentiation [16, 17]. The cysts, deriving from the collecting duct [18], tend to be small and seldom reach more than 1–2 cm in diameter. Macrocysts are initially rarely seen. Cysts may even not be discernible in young children [17]. However, cysts can grow and resemble ADPKD at later stages of the disease.

In addition to altered kidneys, antenatal ultrasound often reveals oligohydramnios, which may be the cause of pulmonary hypoplasia, the major cause of mortality in the neonatal period [19]. Pulmonary hypoplasia, large kidneys compressing the lungs, and sepsis contribute to the perinatal mortality, which has been estimated to be as high as 30–50 % [7, 8]. Recent improvements in neonatal care and intensified antihypertensive treatment have improved the outcome [7]. According to a retrospective single-center study [20], infants surviving the perinatal period now have a survival rate of 87 and 80 % after 1 and 9 years, respectively. ARPKD children may present with or develop severe arterial hypertension, progressive renal disease, recurrent cholangitis, and hepatic fibrosis, leading to portal hypertension [20, 21]. Renal and hepatic functions can deteriorate, and approximately 50 % of the patients will require kidney transplantation before the age of 20 years [7, 22]. However, there is a high intra-familial and inter-familial variability concerning disease burden and progression [21, 23].

Autosomal dominant polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenetic kidney disease leading to dialysis-dependent chronic kidney disease in adulthood [24]. With an incidence of 1:500–1:1,000, it is one of the most common potentially lethal monogenetic diseases.

ADPKD is caused by mutations in either the *PKD1* or the *PKD2* gene. Mutations in *PKD1* are found in 85 % of patients [18]. The *PKD1* and *PKD2* genes encode PC1 and PC2, respectively, which among other sites both localize to the membrane of the cilium and have been implicated in various cellular events. While the very large transmembrane adhesion protein PC1 can regulate growth control pathways, PC2 is a nonselective cation channel from the family of transient receptor potential ion channels (TRPs) [18]. It has been proposed that PC1 and PC2 interact to form a chemo- and mechanosensing protein complex sensing fluid flow, such as in the renal tubule, with subsequent control of cell growth and differentiation [18, 25]. Bending of the primary cilia leads to an increase in intracellular calcium via a PC1-dependent mechanism [26, 27], and the ratio of PC1 to PC2 has been shown to regulate pressure sensing [28].

ADPKD is characterized by the development of multiple cysts in both kidneys and by potentially severe extrarenal complications [29]. Disease manifestations include hypertension, chronic back pain, cystic lesions in the liver, pancreas, and lung, cerebro-vascular hemorrhage, cardiac valve defects, abdominal hernias, hematuria, urinary tract infection, kidney stones, deregulated phosphate homeostasis, and an impaired quality of life [1, 6, 30, 31]. The formation of intracranial aneurysms can cluster in ADPKD families; therefore, the recording of a detailed family history helps to identify patients at risk. Only a few cases of ruptured intracranial aneurysms have been described in children affected by ADPKD [30].

Renal function is often preserved up to the age of 40 years, but thereafter the glomerular filtration rate (GFR) decreases and ESRD ensues in 50–70 % of patients by the fifth decade [32]. There is a high intra-familial and inter-familial variability in the rate of disease progression [23]. ESRD occurs approximately 20 years earlier in patients with underlying *PKD1* mutations than in patients with mutations in *PKD2* [23, 30, 32, 33], and the kidneys of the former have more, although not larger cysts. ADPKD results in bilateral renal changes; however, the phenotype may be asymmetric [17].

Being a classic dominant disease, the presence of ADPKD in parents and grandparents is often known, although a family history of the disease has been described to be inconspicuous in up to 40 % of the patients [30]. A small percentage of ADPKD patients present during childhood. It has been pointed out that given the high overall incidence of ADPKD, this small percentage still results in a significant number of pediatric ADPKD patients [34]. Pediatric patients with ADPKD are often detected by screening ultrasound, which shows a varying number of cysts in echoic normal-sized or enlarged kidneys [17]. Although the signs and symptoms of ADPKD are often mild and infrequent in pediatric patients, screening for and the

treatment of hypertension is recommended [30, 31, 35]. Extrarenal symptoms are rarely seen in children with ADPKD.

As ADPKD and ARPKD may show similar clinical and imaging manifestations in the early course of the disease, making the correct diagnosis can be challenging [35, 36]. A careful family history and the presence of congenital hepatic fibrosis may allow the clinician to distinguish between ARPKD and ADPKD [35, 37].

A diagnostic approach to cystic kidneys

The large variety of molecular causes of a cystic renal phenotype makes a structured clinical approach of particular importance. In addition to ARPKD and ADPKD, nephronophthisis (NPH), the most common genetic cause of ESRD during childhood and adolescence, may present with renal cysts [38]. As recently reviewed, there are also multiple syndromic disorders that display cystic kidneys [5, 39]. Six key questions seem to be decisive for the detection of and differentiation between the various kinds of genetic renal cystic diseases: (1) Kidney cysts or polycystic kidneys? (2) When did the first signs and symptoms appear? (3) Where are the cysts localized? (4) Where else and what else occurred? (5) What size are the kidneys and the cysts? (6) Who else in the family is affected by polycystic kidney disease? (Fig. 1). Kidney imaging and the family history are crucial for the diagnosis. Ultrasound is the first choice for diagnostic imaging in most clinical cases because it is a cost-effective, painless, and widely available technique that does not require radiation or sedation and can provide answers to the indicated questions with sufficient accuracy.

Kidney cysts or polycystic kidneys? It is important to distinguish between kidney cysts and polycystic kidneys. Isolated

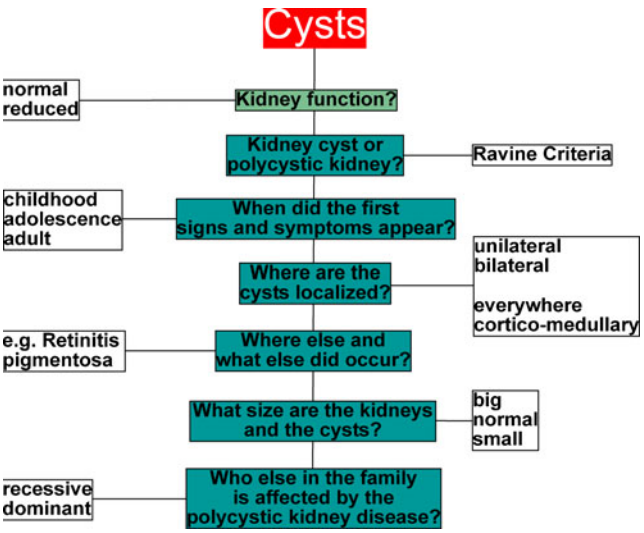

Fig. 1 A diagnostic approach to cystic kidneys: a few specific questions can help to identify an underlying genetic cystic kidney disease

simple kidney cysts in adult patients with normal renal function and absent extrarenal ADPKD manifestations are mostly of a benign nature [40], whereas even a single kidney cyst in a pediatric patient should raise suspicion and prompt a diagnostic work-up, including careful family and medical history-taking, physical examination and, where required, further abdominal imaging. Pediatric patients possibly affected by PKD have to be carefully followed; nephrotoxic substances should be avoided, and complications, such as hypertension and urinary tract infections, should be treated promptly. In adults aged ≤39 years with a positive family history of ADPKD, the presence of three kidney cysts uni- or bilaterally establishes the diagnosis of ADPKD with high sensitivity and specificity. According to the modified Ravine criteria, two cysts on each side for patients aged 40–59 years and four cysts on each side for patients aged >60 years make ADPKD the very likely diagnosis [41]. Fewer than two cysts in persons at risk aged >40 years excludes ADPKD. Of note, these criteria have been established for examination by ultrasound and for patients with a positive family history of ADPKD [41]. As magnetic resonance imaging (MRI) and computed tomography (CT) have higher detection rates, especially of small cysts, unmodified application of the Ravine criteria to MRI and CT data may result in false-positive results [42]. Novel, high-resolution ultrasound equipment may also be more sensitive in detecting small cysts. Standard values for MRI-based cyst detection have been established, revealing at least one cyst in 62.5 % of healthy adult individuals [43]. Early CT-based studies revealed simple renal cysts in 20 [44] and 24 % of patients[45]. Cyst size and cyst number increased with age, and men had more cysts than women. Importantly, MRI primarily increased the detection of cysts with a diameter of <1 cm [43] and may thus serve as a tool to discover, for example, affected persons prior to living kidney donation. In 420 children with a positive family history of ADPKD ultrasound screening detected renal cysts in 49 % of the individuals at the age of 15 years [46].

When did the first signs and symptoms appear? The age of clinical manifestation varies among different PKDs and provides hints to the underlying disease in pediatric patients. ARPKD may present antenatally, whereas ADPKD is often asymptomatic until early adulthood. Patients with juvenile NPH due to the common *NPHP1* mutations usually have first signs and symptoms after the sixth year of life, but NPH shows great clinical and genetic variability [38]. Exceptions occur for all forms of PKDs.

Where are the cysts located? The localization of cysts within the kidney and their lateralization may help the clinician to make the proper diagnosis in childhood. The cortico-medullary localization of cysts indicates NPH, and the occurrence of bilateral cysts points towards genetic disorders such as NPH, ARPKD, or ADPKD.

Where else and what else occurred? Many forms of inherited cystic kidney disease to some extent display extrarenal manifestations which can be indicative of a diagnosis. ADPKD may present with, for example, umbilical hernia, intracranial aneurysms, liver cysts, or arachnoidal cysts (Fig. 2). Hepatic manifestations in ARPKD can cause liver failure, whereas liver cysts in ADPKD rarely impair liver function. Furthermore, in syndromic disorders displaying cystic kidneys, multiple extrarenal manifestations do occur [2–5]. For example, retinitis pigmentosa in combination with NPH defines the Senior Løken syndrome, causing impairment of night and field vision. In the pleiotropic Bardet–Biedl syndrome, hexadactyly, anosmia, and obesity are among the symptoms that can be observed. Details of the symptoms observed in different syndromes have recently been reviewed [47]. In summary, the clinical suspicion of an underlying genetic cystic kidney disease requires a diligent clinical work-up to identify potential extrarenal signs and symptoms.

What size are the kidneys and cysts? Kidney size and cyst size provide critical information for diagnosis. Kidneys in patients suffering from NPH tend to be smaller than normal, but they keep their reniform contour; the cysts are often less than 2 cm in diameter. Kidneys from ARPKD patients grow in the early disease course and shrink with progressive disease in parallel with renal function decline; the majority of cysts are small (<2 mm in diameter). Kidneys from ADPKD patients are often enlarged, having multiple cysts in the cortex and medulla, and their size can greatly vary within the kidney, ranging from some millimeter to several centimeter in diameter. Ultrasound will give good information on kidney length, but may result in underestimation of kidney volume [42, 48]. Figure 3 shows the presentations of ARPKD and ADPKD kidneys.

Who else in the family is affected by PKD? Meticulous family history-taking is crucial to elucidate the mode of inheritance because it allows dissection of the forms of PKD with a similar phenotype but different hereditary transmission. As an example, differential diagnosis between ARPKD and ADPKD may be difficult in children. However, in ADPKD, the mutation of just one allele is sufficient to result in the cystic phenotype, while the recessive trait of ARPKD requires the mutation of both alleles. The family history is therefore more likely to reveal affected ancestors in ADPKD than in ARPKD.

The rational for kidney volume measurement in ADPKD—"big is bad"

The Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) has suggested that total kidney volume (TKV) in ADPKD predicts renal function

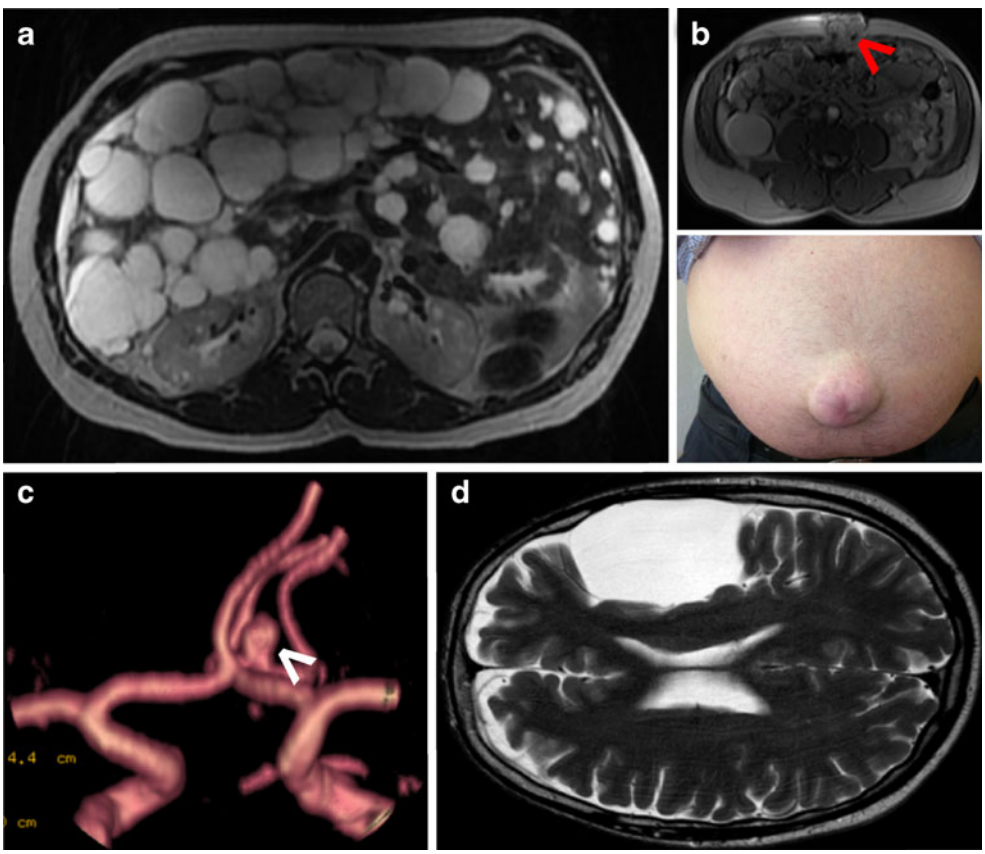

Fig. 2 Imaging panel displaying extra-renal manifestations of autosomal dominant polycystic kidney disease, such as liver cysts (**a**), umbilical hernia (**b**, *arrowhead*), aneurysm of A. cerebri media (**c**, *arrowhead*), and arachnoidal cyst (**d**)

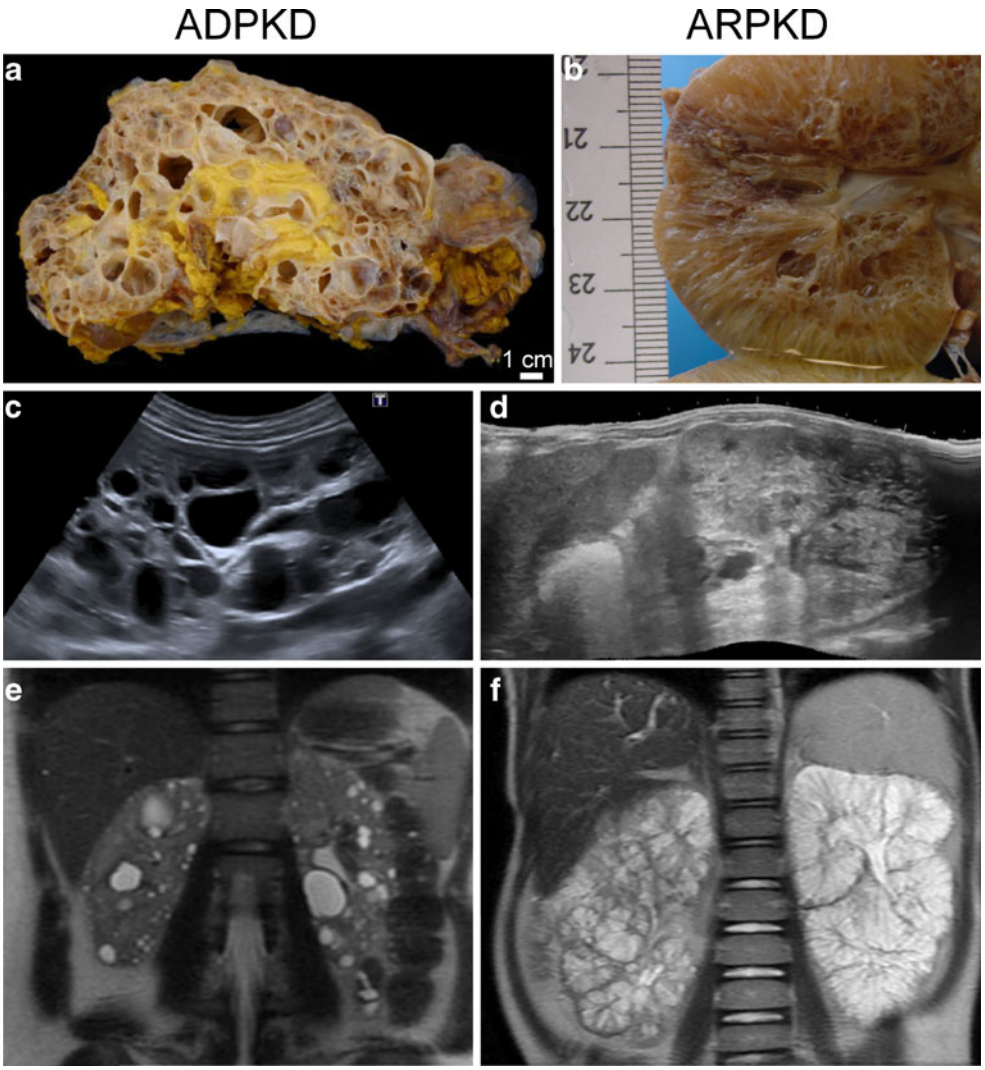

Fig. 3 Macroscopic pathological presentation of autosomal dominant polycystic kidney disease (*ADPKD*) (**a**) and autosomal recessive polycystic kidney disease (*ARPKD*) kidneys (**b**). Multiple renal cysts of different sizes can be recognized in the ADPKD kidney and are also detectable by ultrasound (**c**) and T2-weighted magnetic resonance imaging (MRI) (**e**). In ARPKD, cysts tend to be smaller. Ultrasound (**d**) and a T2-weighted MRI scan (**f**) show markedly enlarged kidneys with variable size cysts throughout renal parenchyma

decline and that TKV is therefore a surrogate parameter for disease severity in ADPKD, even before renal function declines [29, 49]. Other cystic kidney diseases were not studied initially. In ADPKD, cyst formation and growth start in utero, and cyst growth is accelerated during childhood and adolescence [29, 50–54]. ADPKD kidneys may attain absurd sizes at advanced disease stages, such as 1,500 cm^3 per kidney (normal 150–200 cm^3) [1]. However, kidney function is surprisingly well-preserved for decades, even in the presence of multiple cysts in both kidneys, until the 40th year of life when kidney function will start to deteriorate, and ESRD will occur in 50 % of ADPKD patients by the age of 50 years. At the late stage of the disease, when functional impairment becomes obvious, therapies may fail because large parts of normal renal parenchyma are replaced by cysts and accompanied fibrosis. An early intervention targeting cyst growth seems therefore to be more promising than late interventions when secondary changes may have rendered the polycystic kidney resistant to therapies. No disease-modifying treatment is currently available. As kidney growth in ADPKD is only due to cyst formation, and as kidney size has been associated with renal functional impairment, TKV has emerged as a surrogate parameter for disease severity in ADPKD [29]. Given the large variability in the kidney volume measurement associated with ultrasound and the exposure to ionizing radiation that would result from repetitive CT scans, MRI has become the preferred method to quantify TKV.

The value of TKV as a surrogate parameter for disease severity in ADPKD has been studied by several research groups. The CRISP study evaluated kidney and cyst volume by annual MRI as well as GFR measurements by iothalamate clearance in 232 young ADPKD patients with a GFR of >60 ml/min/1.72 m^2 over a period of 3 and 8 years [29]. Of these patients, 85 % had *PKD1* mutations and 15 % had *PKD2* mutations. The initial protocol included gadolinium enhancement for T1-weighted coronal images from which TKV was calculated by a stereological approach. Although no case of nephrogenic systemic fibrosis was reported, the consortium decided to perform the following studies without contrast material, a protocol change that did not impair the accuracy

of the TKV measurements [55]. The study showed that the expected progression of cyst growth and kidney volume occurred before functional impairment. The mean rate of kidney growth was 5.3 % per year. Total cyst growth and total kidney growth were closely correlated, indicating that kidney growth was due to cyst expansion only. Interestingly, PKD2 patients showed smaller kidney volumes and fewer cysts but did show the same rate of cyst expansion, suggesting that the milder clinical course in *PKD2* mutation is due to a lower number of cysts, hence lower rate of cyst formation, rather than a lower rate of cyst expansion. Rapid kidney growth was associated with a faster decline in kidney function. In 51 patients with a baseline kidney volume of >1,500 cm^3, GFR declined by 4.3 ml/min/year. Renal blood flow was measured in a subset of patients [56] and was found to be reciprocally associated with kidney volume: the larger the polycystic kidney, the lower the renal blood flow. Renal blood flow and age as well as gender, hypertension, and kidney volume predicted the loss of kidney function [49]. Kidney size was also associated with blood pressure: the larger the kidney, the more ADPKD patients suffered from hypertension [29].

CRISP data were confirmed and expanded in an ADPKD cohort in Switzerland with comparable patient baseline characteristics. The SUISSE ADPKD study imaging protocol included a T1- and T2-weighted acquisition without gadolinium. On T1-weighted images, kidney contour was manually tracked and then interpolated to measure individual kidney volume, and on T2-weighted images a semi-automated segmentation was applied to measure cyst volume. Kidney volume changes in 100 patients could be reliably evaluated by this protocol within a 6-month period. Volume regressions that were attributed to the asymptomatic rupture of large cysts were found in some of the patients. The researchers pointed out that kidney growth was solely due to an increase in cyst volume; however, kidney volume could be assessed more precisely than cyst volume [52].

The data from these two studies suggest that both cyst and renal growth directly underlie the functional renal impairment. Cyst and renal growth seem to follow patient-specific growth rates, which can be detected within 6 months. TKV is a reliable parameter to assess disease severity in ADPKD, although the method is technically demanding and time-consuming.

In children, a recent study that evaluated annual MRI scans of 77 ADPKD individuals aged between 4 and 21 years over a period of 5 years revealed that patients with high blood pressure (≥95th percentile) displayed larger TKVs and greater increases in fractional cyst volume than patients with normal blood pressure [48]. The body surface area-corrected fractional increase in cyst volume was 4.7±1.2 %/year in children with high blood pressure compared to 1.7±1.2 %/year in children with normal blood pressure. Kidney volume was calculated from T1-weighted images, whereas T2-weighted images were used for cyst volume quantification. Also, the number of recorded cysts grew faster in children with high blood pressure. Baseline and follow-up serum creatinine values were higher in children with elevated blood pressure [48].

These data confirm findings previously published by the same group, for which the authors used ultrasound imaging to detect and quantify the differences in renal volume between young hypertensive versus normotensive ADPKD patients [57].

For ARPKD, less data on the prediction of renal function by imaging is available. In a recent study, 73 ARPKD patients were prospectively studied by MRI and high-resolution ultrasonography [58]. There was a weak negative correlation between TKV and kidney function among children with enlarged kidneys. Corticomedullary involvement, as detected by high-resolution ultrasound, was associated with worse creatinine clearance when compared with isolated medullary involvement (61±32 vs. 131±46 ml/min/1.73 m^2). Importantly, in mild ARPKD, high-resolution ultrasonography was more efficient in detecting medullary cysts than normal ultrasonography [58]. The data confirmed previous findings that clinical variability in ARPKD could not be exclusively explained by the underlying *PKHD1* mutation [58–61]. As previously pointed out, and in contrast to ADPKD, TKV in ARPKD does not continue to increase during the course of the disease.

In summary, TKV measurement by MRI is precise, and TKV predicts renal function decline in ADPKD in adults. In this context, MRI may be a useful diagnostic tool to follow disease progression of ADPKD, such as within the context of clinical trials; for ARPKD, there is less evidence. However, the method is not yet practical for implementation in clinical routine and is usually not required for accurate ADPKD diagnosis. Furthermore, MRI in children obviously requires sedation in many cases, which is a substantial disadvantage compared to sonography. Ultrasound will allow a rough estimation of polycystic kidney size with sufficient precision to make a general risk assessment. Table 1 gives an overview of the advantages and disadvantages of different imaging modalities.

No matter which imaging method is chosen, future studies will also have to address the question of at what age a potential therapy is ideally initiated. This question is directly linked to diagnostic approaches for a not yet curable disease, as ethical concerns have been raised about diagnostic procedures in underage individuals who become symptomatic in adulthood. Early diagnosis or early detection of even small cysts by MRI may furthermore also directly affect the health care coverage (insurability) of the child.

Emerging treatment options in ADPKD

The insights into ciliary biology and dysregulated intracellular signaling pathways in different PKDs have laid the

Table 1 Advantages and disadvantages of different imaging modalities

Imaging modality	Advantages	Disadvantages
Sonography	Low costs	Operator-dependent
	Fast Painless	May miss small cysts
	Widely available	
	Reasonably accurate	
	Established diagnostic criteria for ADPKD	
Computed tomography	Sensitive for small cysts	Radiation
Magnetic resonance imaging	Sensitive for small cysts Precise volume measurements (e.g. TKV, cysts volume)	May require sedation (and intravenous access)

ADPKD, Autosomal dominant polycystic kidney disease; TKV, total kidney volume

groundwork for novel treatment approaches in ADPKD. First, using different rodent models, various research groups have published promising data on options for treating PKD. The mTOR inhibitors, the V2 receptor antagonists, the cyclin-dependent kinase (CDK) inhibitor (R-) roscovitine, the somatostatin analog octreotide, Src inhibitors, pioglitazone, etanercept, and the traditional Chinese medicine-derived natural product triptolide have all been found to reduce kidney volume in murine PKD models [62, 63]. These data have led to the establishment of various clinical trials for ADPKD in both Europe and the USA [62, 63]. An overview of some important trials is given in Table 2. The pathophysiological considerations underlying the novel treatment approaches have recently been summarized [32, 62, 63], and a detailed discussion is outside the scope of this manuscript. Briefly, for V2 receptor antagonists, evidence comes from the observation that tubular cells in ADPKD contain high levels of cAMP and that high levels of circulating vasopressin have been observed in PKD patients. Vasopressin induces intracellular increase of cAMP via the V2 receptor to increase fluid secretion into cysts via the CFTR channel [62, 63]. Vasopressin receptor antagonists reduce renal cyst growth in animal models [64]. The V2 receptor antagonist tolvaptan is currently under investigation in the TEMPO 3/4 trial (Tolvaptan Efficacy and Safety in Management of PKD and Outcomes), a large phase 3, placebo-controlled, double-blind study in 18 - to 50-year-old patients with a GFR of >60 ml/min but relatively large kidneys (>750 ml) as an indicator of progressive disease [65]. A recent study compared data from two 3-year studies on tolvaptan in 63 ADPKD patients in advanced disease stages with historical controls [baseline TKV: 1,635 (tolvaptan) vs. 1,422 ml (control); eGFR 62 ml/min/m^2 for both groups]. Tolvaptan reduced kidney growth [1.7 (tolvaptan) vs. 5.8 % (control)] and eGFR decline [−0.71 (tolvaptan) vs. −2.1 ml/min/1.73 m^2 (control)], but the tolvaptan treatment was associated with adverse events, in particular nycturia, in all patients [66].

Intracellular cAMP can also be reduced by a long-acting analog of somatostatin. Octreotide leads to reduced cyst growth and reduced hepatic cyst formation in the PCK rat, a model of ARPKD. However, there is no improvement in renal function. In line with this observation, a small randomized, crossover, placebo-controlled study found smaller kidney volume after treatment but did not show differences in renal function [67]. Another small randomized, double-blind, placebo-controlled trial on octreotide treatment for 1 year enrolled 42 patients with either ADPKD or autosomal dominant liver disease (ADPLD) with baseline iothalamate GFR of 70 ml/min or 71 ml/min, respectively [68]. The MRI-assessed mean TKV in the ADPKD patients was unchanged after 1 year on octreotide (1,143 vs. 1,129 ml) while there was an increase in the placebo group (803 vs. 874 ml). There was no significant difference in GFR change between the octreotide (−5.1 %) and the placebo group (−7.2 %). Octreotide was tolerated well [68].

A third study used subcutaneous lanreotide in a randomized, double-blind, placebo-controlled trial on patients with ADPLD or ADPKD [69]. CT-assessed mean TKV decreased from 1,000 to 983 ml with lanreotide, while TKV increased from 1,115 to 1,165 ml in the placebo group. Serum creatinine slightly decreased in the lanreotide group (83 to 80 μmol/l), while it slightly increased in the placebo group (91 to 96 μmol/l). The difference was not statistically significant. Lanreotide was well tolerated [69].

Blood pressure control, especially via inhibition of the renin–angiotensin–system (RAS), is currently being studied in the large HALT-PKD trials (Table 2). An activated intrarenal RAS has been observed in PKD patients [62], and hypertensive ADPKD patients display larger kidney volumes than age-matched normotensive control patients. A recent study, which tested the inhibition of angiotensin converting enzyme (ACE) in children with ADPKD, found no difference in the TKV growth rate assessed by ultrasonography [57] .

The two HALT-PKD trials will compare the combination of ACE inhibition (ACEI) with an angiotensin receptor blocker to ACEI alone in patients with an eGFR of either >60 (Study A) or 25–60 ml/min/1.73 m^2 (Study B). It will

Table 2 Overview of recent important clinical trials on pharmacological interventions for ADPKD

Name	Intervention	Study design	Eligibility	Enrollment target and primary endpoint	Follow-up time	Start-finish dates (status)	Sponsor
HALT-PKD (A), phase 3	Lisinopril/telmisartan vs. lisinopril/placebo; low vs. standard blood pressure target	Multicenter, randomized, double-blind, placebo-controlled	15–49 years, GFR >60, BP≥ 130/80 or under therapy	548, kidney volume change (MRI)	48 months	2006–2013 (trial active, recruitment completed)	NIDDK
HALT-PKD (B), phase 3	Lisinopril/telmisartan vs. lisinopril/placebo;	Multicenter, randomized, double-blind, placebo-controlled	18–64 years, GFR 25–60, BP≥ 130/80 or under therapy	470, time to 50 % reduction of eGFR, ESRD, death	60 months	2006–2013 (trial active recruitment completed)	NIDDK
Effect of statin on disease progression phase 3	Pravastatin	Randomized, double-blind, placebo-controlled	8–22 years, normal GFR	107, kidney volume, LVMI, urine albumin,	36 months	2006–2011 (trial active, recruitment completed)	University of Colorado
Tempo3/4, phase 3	V2 receptor antagonist (tolvaptan)	Multicenter, double-blind, placebo-controlled	18–50 years, GFR >60, kidney volume >750 ml	1500, kidney volume change (MRI)	36 months	2007–2011 (completed)	Otsuka Pharm.
Octreotide for ADPKD, phase 3	long-acting somatostatin (octreotide)	Randomized, single-blind placebo-controlled	18–75 years, GFR >40	78, kidney volume change (MRI)	36 months	2006–2011 (trial active, recruitment completed)	Mario Negri Institute, Bergamo
SUISSE study, phase 3	mTOR-inhibitor (sirolimus)	Randomized, open-label, placebo-controlled	18–40 years, GFR≥′70	100, kidney volume change (MRI)	12 months	2006–2010 (completed)	University of Zurich
SIRENA study, phase 2	mTOR-inhibitor (sirolimus)	Randomized, open-label, crossover	18–80 years GFR≥′70	16, kidney volume changed (CT)	6 months	2007–2009 (completed)	Mario Negri Institute, Bergamo
Sirolimus for ADPKD	mTOR-inhibitor (sirolimus)	Randomized, open-label, dose comparison	18–75 years, GFR >60 (I) GFR 25–59 (II)	45, change in iothalamate GFR	12 months	2006–2012 (trial active, not recruiting)	Cleveland Clinic
Everolimus for ADPKD	mTOR-Inhibitor (everolimus)	Multicenter, randomized, double-blind placebo-controlled	18–65 years GFR≥′30	433, kidney volume change (MRI)	24 months	2006–2009 (completed)	Novartis

mTOR, Mammalian target of rapamycin; eGFR, estimated glomerular filtration rate (units: ml/min/1.73 m^2); MRI, magnetic resonance imaging; ESRD, end-stage renal disease; LVMI, left ventricular mass index; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; BP, blood pressure

also compare standard blood pressure with low blood pressure targets in early-stage patients (Study A). Overall, more than 1,000 patients will be enrolled [70].

Finally, mTOR activation has been linked to the proliferative phenotype seen in ADPKD. The cyst epithelium of ADPKD kidneys shows activation of the mTOR pathway, and PC1 is a negative regulator of mTOR activation [71]. In animal models, mTOR inhibition reduced kidney volume and ameliorated renal function [71–78].

Four different trials have addressed the role of mTOR inhibition in ADPKD, and three of these chose kidney volume as a parameter to assess treatment efficacy. The SIRENA study was a randomized crossover study comparing a 6-month treatment with sirolimus to a 6-month treatment with conventional therapy and was completed by 15 patients [79]. Sirolimus did not halt kidney growth, whereas the non-cystic parenchymal volume was larger in the sirolimus-treated patients than in the controls. Sirolimus increased albuminuria and proteinuria. The GFR was unchanged [79].

Two large trials did not deliver the hoped-for therapeutic breakthrough of mTOR inhibition for ADPKD. The SUISSE ADPKD trial studied 100 patients between 18 and 40 years of age at an early disease stage with an estimated creatinine clearance of at least 70 ml/min in an 18-month, open-label, randomized, controlled trial. Mean initial TKV was 907 cm^3 for the treatment group and 1,003 cm^3 in the control group. Sirolimus was given at a target dose of 2 mg/day. The primary outcome was TKV after 18 months, which was blindly assessed on MRI scans. The trial did not find a difference in TKV after 18 months of sirolimus, but there was an increase in albuminuria; in contrast, the GFR was similar among patients receiving sirolimus or standard care [80].

In a parallel approach, Walz et al. [81] studied 433 patients with more advanced ADPKD in a 2-year, randomized, double-blinded, placebo-controlled trial. The patients had a mean eGFR of 53 ml/min/1.73 m^2 in the treatment group (56 ml/min/1.73 m^2 in the control group). The mean baseline TKV was 2,028 cm^3 and 1,911 cm^3 for the treatment and control group, respectively. The mTOR inhibitor everolimus was started at a dose of 2.5 mg, twice daily. The primary outcome was TKV assessed by MRI. While the trial observed a significant reduction of TKV after 1 year of everolimus treatment, this difference lost statistical significance after 2 years. Furthermore, patients receiving everolimus had a more rapid decline of eGFR compared to the placebo group after 2 years (8.9 ml/min in the everolimus group and 7.7 ml/min in the placebo group) [81].

mTOR inhibitors are not the magic bullets for ADPKD

Why did the studies fail to show the positive effects seen in animal models? As pointed out in an editorial by Terry Watnick and Gregory Germino [82], various possibilities should be considered. One is that the dosage of mTOR inhibitors may have been insufficient. The dosage used in some of the animal models was higher [74, 75], and a recent paper on a patient who received a kidney transplant from a previously undiagnosed ADPKD patient suggests that standard sirolimus dosage may decrease mTOR activity in mononucleated cells, but not in renal tubular epithelial cells lining cysts [83]. Still, limited tolerability led to a reduction of an initial high-dosage sirolimus regime in the SIRENA study [79] and to a high rate of withdrawals in the study by Walz et al. [81]. Thus, an increase of mTOR inhibitor dosage would most likely not be tolerated by a significant percentage of the patients. Strategies to deliver the mTOR inhibitor directly to renal tubular epithelial cells may circumvent this limitation.

Secondly, in particular in the SUISSE ADPKD trial, the follow-up of 18 months may not have been long enough to discriminate potentially beneficial effects. Longer follow-ups will be needed.

Thirdly, we may have to re-consider our animal models. Piontek et al. [84] demonstrated that the renal effects of *Pkd1* inactivation in the mouse depend on the time point of the event. Early inactivation, before terminal kidney development, leads to a far more dramatic phenotype than subsequent inactivation. This suggests a role of Pkd1 in both development and maintenance of renal morphology. Phenotypic effects, however, depend on the renal developmental status [84]. The late inactivation of *Pkd1* with a slowly progressive phenotype resembles human ADPKD better than most of the mouse models that were used in previous studies [84].

MRI to assess treatment efficacy in ADPKD—"big is bad, but does small equal good?"

The findings by Walz et al. [81] in addition to the findings of the somatostatin trials have also raised concerns about the value of TKV as a surrogate parameter in the assessment of ADPKD treatment. Various aspects need to be kept in mind when interpreting the results of the everolimus study. Everolimus slowed kidney growth in ADPKD patients after 1 year and may in this sense have reached its expected pharmacologic target. It has been speculated that this may point to a principal effectiveness and that an earlier intervention may be beneficial. While CRISP and the SUISSE ADPKD trial have shown that large TKVs are associated with lower GFR, it has been pointed out that this does not mean that a reduction of TKV is beneficial for kidney function in ADPKD [81]. mTOR inhibitors, somatostatin, and vaptanes may alter the function of the glomerulus directly and are thus independent of cyst growth; i.e., the increase in proteinuria indicates a glomerular effect of mTOR inhibition. Recent data have highlighted the importance of tightly regulated autophagy in the post-mitotic

glomerular podocytes [85–88]. mTOR inhibition has been shown to induce the accumulation of autophagosomes and autophagolysosomes in podocytes and to disrupt autophagic flux [85]. The specific knockout of mTOR in podocytes in animal models leads to early-onset proteinuria and focal and segmental glomerulosclerosis [85]. Further aspects of potential side effects of mTOR inhibitor treatment for ADPKD have been discussed in detail elsewhere [74, 89].

So what is the value of MRI for clinical trials? MRI may be a helpful and precise tool to measure TKV and thus to follow disease progression. However, recent results also suggest that TKV cannot be an exclusive parameter to assess the effectiveness and benefits of a therapeutic intervention in PKD. Continuous observation of renal function by conventional markers, such as serum creatinine, remains mandatory.

Concluding remarks

Insights into the pathogenesis of inherited cystic kidney diseases and ciliopathies in association with the possibilities of the genomic era have opened the doors for the establishment of novel treatment approaches for PKD. Kidney volume is a helpful tool for diagnosis, evaluation, and prognostic estimation of ADPKD, and MRI-based TKV measurements are precise and often applied in clinical studies, whereas ultrasound-based kidney size measurements are often sufficiently accurate for clinical routine.

Note while in press:

While this manuscript was in press Torres et al. published the results of the TEMPO 3:4 study: in this multicenter, double-blind, placebo-controlled, 3-year clinical trial on 1445 ADPKD patients (18-50 yrs, TKV >750 ml, estimated creatinine clearance 60 ml/min or more) Tolvaptan significantly reduced kidney growth rate and showed lower rates of renal function decline. There was however a higher discontinuation rate in the Tolvaptan group.

Multiple choice questions

1.) Common clinical complications of ARPKD include all of the following except:

   a. Hypertension
   b. Esophageal varices due to portal hypertension
   c. Cerebral aneurysm
   d. Pulmonary hypoplasia
   e. Recurrent cholangitis

2.) All of the following items of information can strongly contribute to the correct diagnosis of a cystic kidney disorder except:

   a. Kidney size
   b. Cyst localization
   c. Patient age
   d. Family history
   e. Sex

3.) Total kidney volume….

   a. Serves as a prognostic marker for cystic kidney diseases
   b. Is a valid follow-up parameter for ARPKD
   c. Equals total cyst volume in cystic kidney diseases
   d. Has been examined as a surrogate parameter for future decline of kidney function in early ADPKD
   e. Should be obtained by ultrasound in children.

4.) Ciliopathies….

   a. Always include cystic kidneys
   b. Are systemic disorders
   c. Require immediate treatment
   d. Cannot be diagnosed without genetic analysis
   e. Cannot be treated

5.) A single renal cyst in a child…

   a. Is normal
   b. Is pathognomonic for PKD
   c. Needs to be followed up and also requires looking carefully for extrarenal symptoms.
   d. Requires abdominal MRI
   e. Can be neglected as long as renal function is not impaired

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Answers

1) c
2) e
3) d
4) b
5) c