Kidney Medicine

Polycystic Kidney Disease Drug Development: A Conference Report

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Autosomal dominant polycystic kidney disease (ADPKD) is part of a spectrum of inherited diseases that also includes autosomal recessive polycystic kidney disease, autosomal dominant polycystic liver disease, and an expanding group of recessively inherited disorders collectively termed hepatorenal fibrocystic disorders. ADPKD is the most common monogenic disorder frequently leading to chronic kidney failure with an estimated prevalence of 12 million people worldwide. Currently, only one drug (tolvaptan) has been approved by regulatory agencies as disease-modifying therapy for ADPKD, but, given its mechanism of action and side effect profile, the need for an improved therapy for ADPKD remains a priority. Although significant regulatory progress has been made, with qualification of total kidney volume as a prognostic enrichment biomarker and its later designation as a reasonably likely surrogate endpoint for progression of ADPKD within clinical trials, further work is needed to accelerate drug development efforts for all forms of PKD. In May 2021, the PKD Outcomes Consortium at the Critical Path Institute and the PKD Foundation organized a PKD Regulatory Summit to spur conversations among patients, industry, academic, and regulatory stakeholders regarding future development of tools and drugs for ADPKD and autosomal recessive polycystic kidney disease. This Special Report reviews the key points discussed during the summit and provides future direction related to PKD drug development tools.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is part of a spectrum of inherited diseases that also includes autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic liver disease, and an expanding group of rare recessively inherited disorders collectively termed hepatorenal fibrocystic disorders. ADPKD is the most common monogenic disorder that typically leads to kidney failure with an incidence of 1 in 500-1000 live births and affecting 600,000 people in the United States and 12 million people worldwide.[1] ADPKD mainly manifests with clinical symptoms during adult life and is characterized by extensive cystic enlargement and fibrosis of both kidneys, which progressively destroy the kidney architecture and lead to 50% incidence of kidney failure by the sixth decade of life.[1] In addition to PKD, multiple extrarenal manifestations are part of ADPKD.[2]

The clinical course of kidney disease in ADPKD is typically marked by a long period of stable glomerular filtration rate (GFR) due to hyperfiltration despite the continuous expansion of height-adjusted total kidney volume (htTKV) due to the growth of cysts. Disease courses may vary. Because of the observed stability or slow decrease of GFR even in the presence of ~5-fold change in kidney volume in many patients, clinical trial design in ADPKD is challenging, particularly when using established regulatory endpoints such as doubling of serum creatinine levels or achievement of kidney failure, which would require earlier intervention and decade(s)-long trials. That being said, regulatory precedent based on the loss of kidney function may also be acceptable as a surrogate endpoint.[3] Functional kidney impairment in ARPKD is frequently present already in childhood and adolescence,

but there is pronounced clinical variability with limited data on GFR courses. Tolvaptan, a vasopressin V2 receptor antagonist, is the only approved disease-modifying therapy for ADPKD and is available in multiple countries.[2] There is, however, a strong need for additional and alternative therapeutic approaches for ADPKD, ARPKD, and beyond. To this end, previous efforts by the Critical Path Institute's (C-Path) Polycystic Kidney Disease Outcomes Consortium (PKDOC), in conjunction with the PKD Foundation, academic, industry, and regulatory stakeholders have led to qualification of total kidney volume (TKV) as a prognostic enrichment biomarker for ADPKD by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Furthermore, the FDA designated TKV as a reasonably likely surrogate marker for disease progression in ADPKD, which could serve as an endpoint under an accelerated approval pathway followed by a post-marketing confirmation trial showing an effect on the loss of kidney function.

Nevertheless, because of the continued significant unmet need and challenges in the ADPKD/ARPKD drug development space, C-Path/PKDOC in conjunction with the PKD Foundation organized a Regulatory Summit (May 19-20, 2021) convening representatives from academia, industry, regulatory agencies (FDA and EMA), and the patient community (a list of the workshop participants are included in the acknowledgments). This diverse set of voices from across the PKD ecosystem was critical to generating a holistic output of perspectives, which can then be shared with the wider community and distilled into actionable, focused milestones.

The topics discussed during the Summit addressed: development of novel biomarkers for ADPKD/ARPKD

disease progression and drug response, challenges in patient-level data sharing, and development of clinical outcome assessment tools (Box 1). Other topics are covered in a series of *Clinical Journal of the American Society of Nephrology* perspective articles recently published that included perspectives for drug development for ARPKD and early ADPKD[4,5] and the importance of standardization of the key elements of an ADPKD pivotal trial template.[6]

C-Path is an independent nonprofit public–private partnership with the FDA, developed to catalyze the advancement of medical innovation and regulatory science. C-Path has been involved in the establishment of various consortia of stakeholders from government, industry, academia, and patient organizations to share expertise and develop tools and approaches for speeding up advancement of therapies. The PKD Foundation is the largest PKD patient advocacy organization in the world and the only organization in the United States solely dedicated to finding treatments and a cure for PKD.

CURRENT USE OF BIOMARKERS IN ADPKD

The traditional endpoints to study progression of kidney disease rely on measures or estimates of GFR including doubling of serum creatinine or kidney survival.[7] A 30%-40% GFR decline as a surrogate endpoint for kidney failure may also be considered by the FDA and EMA under certain conditions.[8] Importantly, the basis for tolvaptan approval in the United States relied on its effect on the rate of loss of kidney function; this has also been indicated as an acceptable endpoint in the last PKDOC Regulatory Summit publication.[3]

The phase of stable kidney function with progressive structural cystic kidney disease is followed by a phase of more rapid loss of kidney function in many patients. It is important to note that measurable declines in GFR have been found even for patients with GFR levels higher than $60 \text{ mL/min/1.73 m}^2$ and that linear rather than the depicted curvilinear eGFR trajectories of eGFR decline have been described for the most severely affected subgroups according to imaging or genetic stratification.[9,10]

Defining the right inclusion criteria for a clinical trial and enriching the study population for patients at comparable disease stage and with comparable risk for progression is of particular importance in ADPKD. Prognostic biomarkers are critical in identifying and stratifying patients with rapid disease progression at risk of kidney failure. htTKV emerged as a potential biomarker associated with decline in kidney function.[11] Based on efforts from stakeholders in the field, the initial FDA/EMA qualification for the use of baseline htTKV was as a prognostic enrichment biomarker to select patients with ADPKD at high risk for a progressive decline in kidney function (defined as a confirmed 30% decline in the patient's estimated GFR [eGFR]). htTKV as a prognostic biomarker—along with the patient's age and baseline eGFR—can help to find appropriate candidates, potentially leading to smaller, shorter and less expensive trials.[12,13] Furthermore, a reasonably likely surrogate endpoint designation (initially mentioned in the PKDOC Regulatory Summit

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Box 1. Salient points from the Summit

- Development of novel biomarkers for disease progression and drug response for ADPKD and ARPKD
  - ◇ The measurement of the currently qualified prognostic enrichment biomarker ie, TKV, is resource-intensive
  - ◇ Additional prognostic tools include the PROPKD score and historical fast decline of eGFR; information on the genotype may be relevant
  - ◇ Further potential prognostic fluid-based biomarkers are not FDA-endorsed and still require further validation
  - ◇ Early-onset hypertension may be a potential marker to consider for pediatric ADPKD
  - ◇ Alternative measurements for TKV outside of CT or MRI are needed for the pediatric population to minimize radiation exposure and the potential need for sedation
  - ◇ Antenatal nephromegaly, oligo-/anhydramnios and the presence kidney cysts in ARPKD patients gradually increased the risk of dialysis dependency in the first year of life and may serve as first risk markers for severe kidney disease in ARPKD
- Importance of developing clinical outcome assessment tools for both ADPKD and ARPKD
  - ◇ Chronic pain significantly impacts quality of life in ADPKD yet there is no validated ADPKD-related chronic pain assessment tool
  - ◇ Quality of life should be considered as another regularly measured clinical outcome
  - ◇ Patient-focused drug development is another important opportunity to incorporate the patient experience into the drug development process
- Overcoming challenges in patient-level data sharing
  - ◇ Lack of common standardized data elements and differing policies regarding data safety and privacy complicate data sharing
  - ◇ Harmonization of local and regional datasets may be one approach to data sharing, as has been done in other fields
- A series of perspective articles in *CJASN* cover the other points discussed during the summit including perspectives on drug development for ARPKD and pediatric ADPKD[4,5] and the importance of standardization of the key elements of an ADPKD pivotal trial template to hasten the development of therapies.[6]

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; *CJASN, Clinical Journal of the American Society of Nephrology*; CT, computed tomography; eGFR, estimated glomerular filtration rate; FDA, Food and Drug Administration; MRI, magnetic resonance imaging; TKV, total kidney volume.

publication[3]) by the FDA followed in 2018. In the last few years, htTKV in concert with age, as part of the Mayo Imaging Classification, emerged as a practical method for identifying patients at risk of rapid ADPKD progression (Mayo class 1C-1E).[14,15] Furthermore, the PROPKD[16] score, a kidney failure prognostic model incorporating the type of genetic and allelic variant, sex, and occurrence of hypertension or a urological event before the age of 35 years, has also been employed to stratify patients at risk of rapid progression. The individual history of eGFR decline has also been suggested as a marker of rapid progression (muller et al., NDT 2022-ADD).[17]

Matching the extent of cyst burden to the degree of abnormal kidney function requires further refinement. That is where imaging, genetic, epigenetic, molecular, and biochemical biomarkers would add an extra level of predictive power to the current risk assessment models.

EMERGING BIOMARKERS

ADPKD

Although htTKV combined with eGFR provide a starting step to assess disease progression and likely therapy responders, additional tools are needed to refine the current models. One significant rate limiting step is the fact that assessment of htTKV and genotype are resource intensive and their associations with rate of disease progression are limited at an individual patient level.[18] Furthermore, htTKV poorly predicts eGFR decline for the 5%–10% of patients with atypical morphology (class 2).[19] A plethora of biomarkers have been shown to display associations with ADPKD disease progression, suggesting prognostic potential (Table 1).[20-28] From an association standpoint, prognostic biomarkers should display a link with baseline eGFR and/or htTKV but also predict longitudinal growth in htTKV, decline in GFR, or time to kidney failure. Recent approaches to identify novel prognostic biomarkers have ranged from assessing disease severity based on the urine concentrating ability in patients after water deprivation[29] to looking at serum and urinary proteins, peptides, and metabolites. Increased levels of plasma copeptin, a stable precursor of arginine vasopressin, has been linked with an increased risk of ADPKD progression.[20-23] Furthermore, tolvaptan-treated individuals with a larger percentage increase in copeptin from baseline to week 3 had a better disease outcome, with less kidney growth and eGFR decline after 3 years, implying a potential promise for copeptin as both a prognostic and pharmacodynamic/drug response biomarker for use of tolvaptan in ADPKD.[30] Other biomarkers that have shown potential as prognostic indicators of disease progression are kidney injury molecule 1, β2 microglobulin, neutrophil gelatinase-associated lipocalin, monocyte chemoattractant protein 1, fibroblast growth factor 23 (FGF-23), and microRNAs, among others.[18,24-26,31,32] Furthermore, urine-to-plasma urea ratio reflecting the kidney concentrating ability has been shown to decrease with increased disease severity.[28]

A combined risk score incorporating the urine-to-plasma urea ratio, genetic variant, and Mayo classification predicted rapidly progressive disease better than each of the predictors separately.[28]

Mass spectrometry-based approaches have been employed to assess the composition of the urinary peptidome where markers such as thrombin III, fibrinogen, and α1 antitrypsin (previously shown to reside in the cystic fluid) were found as well as extracellular matrix components associated with cyst cell plasticity, eg, collagen degradation products, cathepsin, and matrix metalloproteinases.[33] More recently, urinary exosomes from ADPKD patients were shown to display reduced levels of polycystin-1 and polycystin-2 and an increase in desmosome components (periplakin and envoplakin), villin 1, and complement proteins compared with healthy controls.[27,34]

Finally, combining panels of urinary peptidome biomarker signatures and applying a machine-learning classifier, a diagnosis and risk stratification of relatively early ADPKD was obtained.[35]

On the imaging side, fast, automatic segmentations using machine learning/artificial intelligence for segmenting polycystic kidneys (cyst size, cyst number, etc) have been developed.[36] Magnetic resonance imaging (MRI)-detected height-adjusted total cyst number and height-adjusted total cyst volume both increased exponentially in early ADPKD in a study by the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP)[37] consortium and were correlated to the underlying genotype.

Additionally, texture analysis, diffusion tensor imaging, and T2 mapping can potentially be used to ascertain dynamic cystic structural changes with better sensitivity than visual detection. Combining htTKV with other imaging markers may enhance our understanding of the changes occurring within the non-cystic parenchyma and lead to improvement in prognostic algorithms.[14]

Conventional techniques such as ultrasound, computed tomography, and MRI have so far been unable to image kidney fibrosis successfully. Technological advances have recently enhanced the capabilities, suggesting the exciting potential to noninvasively image fibrosis in the kidney. In particular, elastography-based techniques may have a role in assessing kidney fibrosis. Elastography has been successfully employed to measure liver stiffness. However, the kidney is structurally more complex, which leads to technical limitations for kidney elastography.[38,39]

In summary, extensive research has already been done in the biomarker field with a focus on ADPKD. It is clear that fluid (serum and urine) biomarkers may hold promise from a prognostic and potentially therapeutic response perspective. That being said, further systematic confirmation in larger ADPKD cohorts at different stages of severity coupled with longer longitudinal evaluation is necessary to improve the correlation/association strength to build a case for potential regulatory acceptance as future prognostic ADPKD biomarkers.

Table 1. Emerging Fluid Biomarkers for ADPKD

Identity	Type	Biological Compartment	Mechanism	Patient Sample Features	ADPKD Correlation
Copeptin[20-23]	Prognostic, PD/drug response	Urine, serum	Portion of AVP precursor peptide, a surrogate marker of AVP	**Urine:** 50 patients; Age 49.3 ± 4.1 y; TKV 1138.1 (814-2065) mL; eGFR 53.2 (29.4-68.4) mL/min/1.73 m² **Serum:** 129 patients; TKV 1500 (940-2180) mL; eGFR 77 ± 31 mL/min/1.73 m²	**Urine**: positively with TKV ($R = 0.351$, $P = 0.014$), htTKV ($R = 0.383$, $P = 0.008$) and negatively with eGFR ($R = -0.304$, p = 0.036 **Serum**: positively with TKV ($R = 0.47$) and albuminuria ($R = 0.39$) and negatively with eGFR ($R = -0.58$) and effective renal blood flow ($R = -0.52$), all $P < 0.001$
Fibroblast growth factor 23 (FGF-23)[24]	Prognostic	Serum	Bone derived phosphaturic hormone	192 patients; Age 32.4 ± 8.9 y; htTKV 615 ± 364 mL/m; eGFR 91.7 ± 21.9 mL/min/1.73 m²	Patients in highest quartile for baseline FGF-23 level had higher rate of increase in htTKV (0.95% per y, $P = 0.0016$), and faster rate of decline in GFR (difference of -1.03 mL/min/1.73 m² per y, $P = 0.005$) compared with lowest quartile, after adjusting for other covariates, including htTKV and genotype; highest quartile of FGF-23 was also associated with substantial increase in risk for the composite endpoint of kidney failure, death, or doubling of serum creatinine (hazard ratio of 2.45 in the fully adjusted model, $P = 0.03$)
Monocyte chemoattractant protein 1 (MCP-1)[25]	Prognostic	Urine	Chemokine that modulates monocyte behavior	102 patients; Age 40 ± 11 y; TKV 1500 (990-2200) mL; eGFR 68 ± 27 ml/min/1.73 m²	MCP-1 was associated positively with TKV independent of albuminuria $R = 0.58$; $P < 0.001$
Kidney injury molecule 1 (KIM-1)[26]	Prognostic	Urine	KIM-1 is processed and the ectodomain is released in the urine after tubular injury	Study A and study B HALT population	High urinary (u)KIM-1/Cr (above the median) correlated with an annual decline in eGFR that was 0.47 mL/min greater than low uKIM-1/Cr ($P = 0.0015$); high baseline uKIM-1/Cr was associated with higher htTKV compared to low uKIM-1/Cr ($P = 0.02$)
Neutrophil gelatinase-associated lipocalin [25]	Prognostic	Urine	Elevated in AKI settings, part of the innate immune response	102 patients; Age 40 ± 11 y; TKV 1500 (900-2200) mL; eGFR 68 +± 27 mL/min/1.73 m²	NGAL excretion was positively associated with TKV. $R = 0.22$, $P < 0.001$ (TKV)
N-acetyl-β-glucosaminidase (NAG)[27]	Prognostic	Urine	Marker of proximal tubule injury	102 patients; Age 40 ± 11 y; TKV 1500 (900-2200) mL; eGFR 68 ± 27 mL/min/1.73 m²	$R = -0.30$; $P = 0.002$ (eGFR); $R = 0.27$; $P = 0.007$ (TKV)

(Continued)

Table 1 (Cont'd). Emerging Fluid Biomarkers for ADPKD

Identity	Type	Biological Compartment	Mechanism	Patient Sample Features	ADPKD Correlation
β2 microglobulin[18]	Prognostic	Urine	Tubular injury marker	130 patients; Age 49 ± 21 y; htTKV 764 ± 390 mL/m; eGFR 87 ± 13 mL/min/1.73 m²	R= -0.45 ($P < 0.01$)—eGFR slope; R = 0.40 ($P < 0.01$) TKV
Villin-1, envoplakin, periplakin[27]	Prognostic	Urinary extracellular vesicles	Cytoskeleton-binding proteins modulating cell motility and morphology	34 patients; Age 45 ± 3.4 y; htTKV 1350 ± 325 mL; eGFR 47.2 ± 3.5 mL/min/1.73 m²	R= 0.51, 0.69, 0.71, respectively; $P < 0.01$, htTKV
Urine: plasma urea ratio[28]	Prognostic	Urine, plasma	Urine concentrating defects are linked with a lower urine: plasma urea ratio	583 patients; Age 47 ± 11 y; htTKV 898 (549-1364) mL/m; eGFR 64 ± 24 mL/min/1.73 m²	β= 0.57; P = 0.02; eGFR slope (corrected for eGFR, sex, baseline age, htTKV, and PKD mutation)

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; AKI, acute kidney injury; AVP, arginine vasopressin; Cr, creatinine; eGFR, estimated glomerular filtration rate, FGF-23, fibroblast growth factor 23; htTKV, height-adjusted total kidney volume; KIM-1, kidney injury molecule 1; NAG, N-acetyl-β-glucosaminidase; NGAL, Neutrophil gelatinase-associated lipocalin; PD, peritoneal dialysis.

Specific Considerations for Early ADPKD and Pediatric ADPKD

ADPKD begins at conception, but 2%-5% may clinically present in childhood as severe forms with very early-onset ADPKD.[40] There is a wide phenotypic spectrum ranging from severe neonatal presentations to the incidental sonographic finding of kidney cysts.[41] Moreover, hypertension and cardiovascular morbidity, which often precede loss of kidney function, represent the leading cause of mortality in adults with ADPKD. Indeed, the onset of hypertension or first urological events before 35 years of age is associated with faster progression to kidney failure, making this as an important sign of disease progression.[16] Hypertension occurs with increased frequency in children with ADPKD, with an overall prevalence of 20%-40%.[42] Children with ADPKD who have hypertension have larger kidneys and a faster kidney growth rate than those with normal blood pressure.[43,44] These data may open the field for early-onset hypertension as an important marker in clinical trials.

The lack of large studies in pediatric ADPKD is associated with a need to validate endpoints for clinical trials as the known data for adults are not systematically transferable to children. The precise measurement of htTKV with computed tomography or MRI is not clinically practical in children due to radiation exposure and a potential need of sedation for MRI in young children. Novel alternative methods are being studied and require validation for this population such as 3-dimensional ultrasound.[45]

Exploration of other biomarkers for ADPKD progression demonstrated that urinary monocyte chemoattractant protein 1 level was significantly higher in pediatric ADPKD patients compared to controls. This finding was more pronounced in patients with PKD1 variants and in patients with very early-onset ADPKD or early symptomatic ADPKD.[46]

The early ADPKD stage is becoming an interesting target for therapies as the kidney parenchyma may be preserved. The first interventional study using tolvaptan in children and adolescents with ADPKD (phase 3b, two-part study; EudraCT number: 2016-000187-42; ClinicalTrials.gov identifier: NCT02964273) has been performed[47] and first results are expected soon. Given the side effects of tolvaptan, additional therapies may be of particular interest for the pediatric and young adult age-group for long-term treatment.

ARPKD

First data on emerging potential prognostic biomarkers in ARPKD have recently been published (studies summarized in Table 2).[48-51] It was found that the antenatal sonographic findings of nephromegaly, oligo-/anhydramnios and detection of kidney cysts gradually increased the risk of dialysis dependency in the first year of life in a model based on a study of 385 clinically diagnosed ARPKD cases.[48] Fitting to this data, early postnatal htTKV has been

Table 2. Potential Future Biomarkers for Assessment of Kidney Disease in ARPKD

Prenatal Ultrasound[48]	
Prenatal symptom combination	*Probability of dialysis within 12 months after birth (95% confidence interval)*
No prenatal anomalies	0.015 (0.005-0.041)
Enlarged kidneys	0.033 (0.006-0.155)
Renal cysts	0.034 (0.008-0.135)
Enlarged kidneys and renal cysts	0.071 (0.021-0.215)
Oligo-/anhydramnios (OAH)	0.087 (0.032-0.214)
OAH and enlarged kidneys	0.174 (0.055-0.431)
OAH and renal cysts	0.178 (0.047-0.486)
OAH and enlarged kidneys and renal cysts	0.323 (0.222-0.445)
Height-adjusted total kidney volume in the first 18 mo of life [49]	
Subgroups	*Ten-year kidney survival rates*
Highest quartile (>597 mL/m)	20%
Middle quartiles (>192-597 mL/min)	75%
Lower quartile (≤192 mL/min)	94%
Need for postnatal ventilation[48,50]	
Subgroups/studies	*Finding*
Multivariate Cox model for predictors of the need for KRT in the first year of life	Hazard ratio of 6.994 for patients with ventilation or assisted breathing
Age at onset of eGFR below 75% normal adjusted for age	Ventilated: 1 d; Not ventilated: 335 d
Genetic findings[51]	
Subgroups	*Findings*
Two truncating variants	Small numbers, risk of perinatal mortality; 5-y kidney survival in one study with 13 patients: ~35%
Missense variants in 709-1837	15-y kidney survival in one study: ~93% when combined with a null variant or 100% in patients with 2 missense variants

Abbreviations: ARPKD, autosomal recessive polycystic kidney disease; eGFR, estimated glomerular filtration rate; KRT, kidney replacement therapy; OAH, oligo-/anhydramnios

shown to be associated with worse kidney survival in ARPKD patients.[49] Previous studies had already described a weak inverse correlation of htTKV and kidney function in children with ARPKD.[52] Independently, postnatal ventilation has repetitively been suggested as a marker for severe kidney disease.[48,50] Genetically, biallelic null variants are associated with worse kidney survival while patients with either 2 missense variants affecting the fibrocystin amino acids 709-1837 or a null variant and 1 missense variant in that region of the *PKHD1* gene showed better kidney survival in an analysis from a large European cohort.[48] For the liver, in addition to biallelic null variants, missense variants affecting amino acids 2625-4074 were associated with worse outcome.[51,53]. MRI or ultrasound-based elastography of the liver and the spleen may become useful markers to assess hepatic fibrosis.[54,55] A previous report described platelet count as the best predictor for the severity of portal hypertension in ARPKD.[56] Much additional work will be required to obtain a deeper understanding of potential prognostic and predictive biomarkers in ARPKD.

CLINICAL OUTCOME ASSESSMENT TOOLS FOR ADPKD AND ARPKD

Beyond the classic endpoints of clinical trials on kidney diseases, clinical outcome assessment tools such as patient-reported outcome measures have received much interest over the last years. Given the described challenges in ADPKD and the rareness and the multi-organ disease complexity in ARPKD, clinical outcome assessments may become of particular interest for the PKD field.

ADPKD

Chronic pain is a common feature of ADPKD.[57] Kidney cyst expansion can lead to capsule distension and compression of surrounding organs. Yet, pain was shown to occur early in the disease, often before kidney enlargement.[58] In spite of the significant impact of chronic pain on the quality of life in ADPKD, no streamlined process of collecting patient pain-related data is currently established. The Standardized Outcomes in Nephrology-Polycystic Kidney Disease initiative was started to achieve standardized core outcomes for PKD trials.[59] It led to the identification of ADPKD-related chronic pain as a core patient-reported outcome, but the absence of validated ADPKD-specific pain assessment tools is a major limitation, eg, disease-related pain is reported in only 22% of ADPKD clinical trials.[60]

Pain assessment requires a holistic strategy of evaluating intensity, affective–motivational unpleasantness, and suffering components.[61] The IMMPACT[62] group underlined 6 outcome measures for pain assessment in clinical trials including the nature of pain, impact on physical and emotional functioning and, where an intervention is

administered, participant's improvement rating, satisfaction, and adverse events.

To date, the only pain assessment tool in ADPKD, ie, ADPKD Pain & Discomfort Scale, was developed by Otsuka Pharmaceutical Co Ltd.[63] Here, the authors identified 3 distinct pain patterns (chronic dull kidney pain, acute severe kidney pain, fullness/discomfort) from patient focus groups across Europe and the United States. The Otsuka Pain & Discomfort Scale has limitations via its restriction to pain perceived to originate from the kidneys.

Recently, El-Damanawi and colleagues[60] designed an ADPKD pain assessment tool incorporating salient pain features and IMMPACT[62] domains drawn from questionnaires validated in other pain conditions and applied it in the context of ADPKD patients with chronic kidney disease stage 1-4. The ADPKD impact scale generated covered 3 conceptual domains (physical, emotional, and fatigue) and although the reliability and validity were supported, the impact of ADPKD-related pain on a patients' health-related quality of life (HRQoL) needs further evaluation.

Finally, another ADPKD clinical outcome assessment measure to consider is the HRQoL. A study from Eriksson and colleagues[64] used various questionnaires to define metrics (including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), which showed that HRQoL was highest in those with earlier versus later stages of chronic kidney disease; a significant loss in HRQoL was seen as chronic kidney disease progressed. Further studies will be needed to better define the quality of life concepts of interest for future development of patient reported outcome tools.

ARPKD

Patient-reported outcome measures have not yet been established in ARPKD. Most previous studies focused on the description of clinical endpoints such as patient or organ survival.[42] Patient- and family-centered outcome measures could, in the future, be of major importance for this early onset severe disorder that can impose a major psychosocial burden on patients and their families and caregivers. Clearly, much more work is needed in this field.

One avenue of potential interest are patient-focused drug development meetings, which have started in 2013 and have allowed empowering opportunities for patients to inform medical product development by sharing their journey and experiences. This approach has been part of an FDA-supported transition toward patient-centric drug development and care. Since 2014, the FDA expanded the patient-focused drug development initiative to allow stakeholders to organize externally led patient-focused drug development meetings, eg, on Alport Syndrome. Understanding what is most important to ARPKD patients and families can help develop tailored clinical outcome assessments to efficiently collect meaningful patient experience data. Patient input can drive the process to identify unmet medical needs and critical clinical outcomes to be pursued in clinical trials. Furthermore, it can ensure clarity with respect to disease features (including severity and progression) of the patient cohort to be included. Collection of the data can ensure that any clinical outcome assessment instruments to be developed are fit-for-purpose in the context of ARPKD.

IMPORTANCE OF DATA SHARING FOR ADVANCING PKD DRUG DEVELOPMENT

Data sharing is in theory a straightforward process, yet in the context of biomedical pre-clinical and clinical research, it becomes challenging and mired with roadblocks. At the heart of data sharing lays the commitment from stakeholders to collaborate and work together to achieve meaningful and actionable data sharing outcomes. When that occurs, the impact is unequivocal in terms of development of tools that optimize and speed up drug development and the advancement of therapies to patients. The coronavirus disease 2019 pandemic provided a lot of lessons that can be applied to other fields to accelerate data sharing initiatives and support progress across medical product development.

For successful patient-level data sharing and to achieve impact, stakeholders will need to cooperate and expand the precompetitive space. This involves the use of standards and common data elements in the collection of data in conjunction with the right resources to ingest, curate, and map those data. The places where data sharing occurs (as part of public–private partnerships, for example) must ensure cooperative interactions and be able to address concerns regarding data safety and privacy. Beyond the International Conference on Harmonisation rules of Good Clinical Practice, national and supranational legislation and rules differ between countries and continents and are strongly influenced by cultural and historical backgrounds. Such rules have to be followed, and this may impose a substantial obstacle for data transfer. Harmonization of local and regional datasets may be a feasible approach as established for pediatric academic PKD natural history studies for both ARPKD and ADPKD (ARegPKD; The Hepato/Renal Fibrocystic Diseases Translational Resource; ADPedKD)[65-67] (described in Table 3). When combined with regulatory agency involvement, a profound impact of utilizing patient-level data to better public health can be achieved.

Many examples of successful data sharing efforts have been described, eg, in oncology.[68,69] C-Path in conjunction with the National Organization for Rare Disorders and the FDA, have launched a major initiative to encourage similar advances in data sharing, ie, Rare Disease Cures Accelerator-Data and Analytics Platform, which is being developed to improve product development across all rare diseases. The Rare Disease Cures Accelerator-Data and Analytics Platform promotes the sharing of existing patient-level data and encourages standardization for collection of new data.

Within the European Union, the European Joint Program on Rare Diseases coordinates access to multiple data

Table 3. Clinical Data Resources for PKD Research

ARPKD

Study or data resource	Type of study
ARegPKD (www.aregpkd.org)	International longitudinal cohort study of patients with clinical diagnosis of ARPKD with a focus on Europe.
The Hepato/Renal Fibrocystic Diseases Translational Resource (www.arpkdb.org)	Longitudinal cohort study of patients with ARPKD or other hepatorenal fibrocystic diseases (HRFD) with a focus on USA.
Renal RaDaR – ARPKD (https://rarerenal.renalreg.org/radar-registry/)	Longitudinal cohort study by UK Kidney Association for patients with rare diseases - chapter on ARPKD.

ADPKD

Study or data resource	Type of study
ADPedKD (www.adpedkd.org)	International longitudinal cohort study of pediatric ADPKD patients. Subchapter covering Europe, Asia, Africa and South America, a subchapter covering UK, a subchapter covering North America, and a subchapter covering Australia.
AD(H)PKD (www.adpkd.org)	The German ADPKD Tolvaptan Treatment Registry is a multicentric national cohort study of patients suffering from ADPKD that are considered for tolvaptan treatment.
ADPKD registry (https://connect.pkdcure.org/adpkd-registry/)	National, online collection of patient-reported data in the United States, launched by the PKD Foundation.
Analysis of Clinical and Molecular Genetic Data Influencing the Evolution and Response to Therapy of ADPKD patients (GENKYST) (https://www.girci-go.org/reseaux/reseau-genkyst/)	Genkyst is a multicentric regional longitudinal cohort study in the West of France.
ERKReg (www.erknet.org)	International European longitudinal cohort study of patients with rare kidney diseases in Europe, including PKD.
Kansas PKD RTCC | Clinical and Translational Core | Early PKD Observational Cohort Study (EPOC) (https://www.kumc.edu/research/pkd-research-and-translation-core-center.html)	Multicentric longitudinal cohort study in the United States for patients aged 4-35 y and eGFR >80 mL/min/1.73 m^2.
Maryland PKD RTCC | Clinical and Translational Core | Adult ADPKD Cohort https://www.baltimorepkdcenter.org/	Longitudinal cohort study in the United States for adult ADPKD patients without kidney failure and eGFR>15 ml/min/1.73m^2
UAB PKD RTCC | Clinical and Translational Core | ADPedKD-US Cohort | Pediatric ADPKD (https://adpedkd-us.org/)	Longitudinal cohort study of patients (< 18 years of age) with ADPKD. US node of ADPedKD international database.
Renal RaDaR – ADPKD (https://rarerenal.renalreg.org/radar-registry/)	National longitudinal cohort study by UK Kidney Association for patients with rare diseases - chapter on ADPKD; includes UK node of ADPedKD international database.
Multiple studies	Data obtained for specific therapeutic approaches, specific diagnostic approaches or specific biosample collections.
	Data and samples obtained during interventional clinical trials.

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; eGFR, estimated glomerular filtration rate; HRFD, hepatorenal fibrocystic disease; PKD, polycystic kidney disease.

sources and services. The European Joint Program on Rare Diseases aims to improve the integration, efficacy, production, and social impact of research on rare diseases. This includes registries and cohorts, biobanks, animal models and cell lines, analysis of experimental and phenotypic human data, and identification of clinical experts, joint standards, recognized guidelines, knowledge bases, and tools, eg, for translational and clinical research and development. For clinical care and international research the European Reference Networks have been established as virtual international European networks dedicated to complex or rare diseases. This includes the European Rare Kidney Disease Reference Network.

For PKD data sharing, it is critical to continue to combine updated, longitudinal or randomized controlled trial placebo data for refining the current disease progression modeling tools. Previous data sharing and collaboration efforts led by PKDOC in conjunction with academic, industry, and regulatory stakeholders led to the creation of a Clinical Data Interchange Standards Consortium Study Data Tabulation Model standard for common ADPKD data elements, which allowed the mapping of patient registry and CRISP data as the basis of modeling efforts for regulatory endorsement of TKV as a prognostic biomarker.

Going beyond Clinical Data Interchange Standards Consortium standards and potentially standardizing clinical report forms would be important for better capturing clinical data. Combining that with lab data sharing via electronic health records, would enhance the overall breadth of disease data points and significantly enhance current modeling efforts.

Clinical trial data sharing can enhance scientific progress and ultimately lead to an improvement in public health. Effective data sharing can mitigate duplication of efforts, reduce patient exposure to unnecessary interventions, and serve to modulate the design of trials in the development phase. Finally, it behooves all of the stakeholders operating in this field to support data sharing as an ethical imperative as study participants are putting themselves at risk to contribute to science; therefore, utilization of their contribution via sensible and effective data sharing becomes paramount.

CONCLUSION

Much unmet need remains in PKD, both on the biomarker and therapeutic side. Continued collaboration and data sharing efforts in the field among relevant stakeholders are warranted to lead to enhanced prognostic and therapeutic biomarkers, endpoints, and a feasible regulatory pathway (for all forms of PKD including ARPKD), which hopefully will lead to more therapies reaching the market. Community-wide initiatives such as the PKD Regulatory Summit are critical in spurring conversations and collaborations and continuing those efforts will enable the efficient tackling of cross-cutting issues and will spur the ongoing development of treatments for ADPKD.

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