Autosomal Recessive Polycystic Kidney Disease (ARPKD)

Adjunct EL-PFDD Scientific Workshop Report

Workshop held virtually on January 23, 2023, 2:00– 4:00 p.m. ET

Report date: May 28, 2024

Meeting Organizers

PKD FOUNDATION
Polycystic kidney disease

PKD
POLYCYSTIC KIDNEY DISEASE OUTCOMES CONSORTIUM
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Executive Summary

The mission of the Polycystic Kidney Disease (PKD) Foundation is to fund research, advocate for patients, and ultimately to end PKD. On August 29, 2023, the PKD Foundation hosted the *Autosomal Recessive Polycystic Kidney Disease (ARPKD) Externally-Led Patient-Focused Drug Development (EL-PFDD) Meeting*. As a critical follow up to this meeting, the ARPKD Adjunct EL-PFDD Scientific Workshop was held on January 23, 2024. This workshop gave ARPKD clinical and research experts an opportunity to first reflect on what was shared by the ARPKD community, then to identify important scientific priorities and data needed to move the field forward.

ARPKD is a rare genetic disease, characterized by progressive decline in kidney function and progressive changes in liver/bile duct structure and function. ARPKD's rare disease status and clinical variability have limited the development of targeted therapies for this disease. As a result, the burden of ARPKD is profound, not only for those living with the disease but for their entire families.

Discussion insights and action items that emerged from the workshop included:

- Better accommodate the needs of ARPKD patients and families during clinical trials.
- Optimize supportive care to reduce ARPKD symptoms and improve patient quality of life on a day-to-day basis.
- Develop ARPKD-specific clinical, biochemical, genetic, and imaging biomarkers to track disease progression and measure improvement.
- Develop more accurate ways to measure blood pressure in infants and small children.
- Enroll ARPKD patients into registries and databases to ensure research-ready patient cohorts.
- Ultimately the ARPKD research and clinical communities should aim to enable clinical trials and develop new treatments for ARPKD.

Each insight includes several expert recommendations and suggestions for advancing ARPKD care and research. A Roadmap for ARPKD Therapy Development is presented which includes objectives and goals for moving forward. As a result of this workshop, the ARPKD community hopes for better treatments for themselves and their affected family members.

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Brief Clinical Summary

Autosomal Recessive Polycystic Kidney Disease (ARPKD) is a rare genetic disease that affects approximately 1,500 children and young adults in the United States. Most ARPKD patients have variations in the *PKHD1* gene, which encodes the fibrocystin protein. However, ARPKD can also result from variants in the *DZIP1L* and *CYS1* genes.

ARPKD is progressive and can affect both the kidneys as well as the liver. The disease is clinically heterogenous, with the severity of kidney and liver manifestations and disease outcomes varying from one patient to the next. Although ARPKD can be diagnosed anytime from before birth to later in life, an earlier presentation is a risk factor for more severe disease.

ARPKD is characterized by the development of microscopic kidney cysts resulting in kidney enlargement and progressive chronic kidney disease. Individuals with ARPKD experience declining kidney function, often leading to the need for dialysis and eventual transplant. Enlarged kidneys and antenatal impairment of kidney function leading to decreased amniotic fluid can impact lung development. Those experiencing diminished kidney function can suffer from anemia, bone health impacts, and issues with growth or learning. High blood pressure is a common symptom.

Many living with ARKPD often also experience congenital hepatic fibrosis (CHF), resulting from scarring around the bile ducts and the portal vein. Portal hypertension impedes the blood flowing from internal organs such as the spleen, esophagus, and stomach. This causes high blood pressure in those organs and damage to those organs. Esophageal varices can bleed. An enlarged spleen causes low platelet and white blood cell counts. Patients will experience progressive changes in the structure and function of the liver/bile ducts, and some will need a liver transplant.

Current ARPKD treatments only manage disease symptoms but cannot prevent or stop kidney and liver/bile duct disease. ARPKD's rare disease status and clinical variability have limited the development of targeted therapies for this disease. As a result, the burden of ARPKD is profound, not only for those living with the disease but for their entire families.

Patient Focused Drug Development

The United States Food and Drug Administration (FDA) first launched the patient focused drug development initiative in 2012. This program recognizes that "*patients who live with a disease have a direct stake in the outcome of FDA's decisions and are in a unique position to contribute to the understanding of their disease*" (78 Fed. Reg 21,613 (April 11, 2013).

The FDA is interested in two particular categories of the patient experience: (1) **Analysis of Condition** includes the burden of disease and impacts on activities of daily living; (2) **Current Treatment Options** includes patients' perspectives on the adequacy of available therapies to help understand unmet medical needs and prospects for future treatments. This information is considered within a structured risk-benefit decision making framework, and helps the FDA calibrate exactly how much risk a patient population will tolerate for a given set of benefits. The patient voice can also be used to inform the selection or development of meaningful clinical outcome assessments (COAs) to be used as clinical trial endpoints. Additional patient-focused drug development resources are provided in Appendix 1.

The *ARPKDEL-PFDD Meeting* was held on August 29, 2023. During this meeting, individuals living with ARPKD shared their experiences with the FDA, clinicians, researchers, industry, and advocacy organizations to help them to understand the profound burden of ARPKD and the urgent need for better treatments. This is especially vital for the ARPKD community as there are no available disease-specific therapies for this disease.

The key insights from the ARPKD EL-PFDD meeting are presented in a benefit-risk framework as a foundation for the FDA's Benefit-Risk Assessment (see **Table 1**). Note that the information in this sample framework is likely to evolve over time.

TABLE 1: Benefit-Risk Table for ARPKD

	EVIDENCE AND UNCERTAINTIES	CONCLUSIONS AND REASONS
ANALYSIS OF CONDITION	**ARPKD is a rare genetic disorder.** The clinical course of ARPKD is highly variable and can present any time from before birth to adulthood. An ARPKD diagnosis is traumatic, and consequences can be tragic. The disease is progressive and affects the kidneys as well as the liver. **Most individuals living with ARPKD experience a large number of disease-related health concerns.** Kidney failure and high blood pressure are the most bothersome, followed by liver problems including congenital hepatic fibrosis (CHF). Many patients also experience enlarged kidneys, gastrointestinal problems, fatigue, anxiety/depression, enlarged spleen, growth failure, breathing issues, immunosuppression, pain, and premature death. Signs and symptoms worsen as kidney and liver disease in ARPKD progress.	**ARKPD has an incredible disease burden. The disease is progressive, and new symptoms are likely to appear.** Most children cannot fully participate in, school and social activities due to fatigue and their participation in sports may be restricted due to concerns about the risk of kidney injury. Many miss out on school because of illness and frequent care appointments. Some who are living with the disease have a sense of being different and do not want to draw attention to their needs. Many find it hard to make longer term plans as their future is uncertain. **ARPKD families have many worries: disease progression leading to premature death, needing a kidney and/or liver transplant or dialysis, and worsening symptoms**. Many parents worry about their child's uncertain future and some feel like their child is living on borrowed time.

CURRENT TREATMENT OPTIONS	**There are no FDA-approved treatments to stop ARPKD disease progression**. Patients rely on many medications and medical procedures for symptom management: blood pressure medications, growth hormone, dialysis, splenectomies, prescription of iron supplements, and others. Other approaches include a low salt diet, other dietary modifications, and hydration. Most patients will do everything they can do to spare their organs. **Ultimately, many patients will require a kidney transplant, a liver transplant or even a combined liver-kidney transplant. The ARPKD community emphasized that transplants are not curative but a trade off of one chronic condition for another.** Many children have received kidney and liver transplants from their parents; donated organs have a finite lifespan and eventually need to be replaced.	**ARPKD families are frustrated by the lack of treatment options**. Treatments only help somewhat, only treat some of the symptoms, and it can be challenging to tell that they are working. Most treatments have many side effects, and the amount of monitoring is excessive. **The ARPKD community needs treatments that prevent progression of kidney and liver disease, to delay dialysis and transplantation**. The community needs symptom-reducing treatments, better treatments, more information and more research, especially more clinical trials.
	See the Voice of the Patient report for a more detailed narrative: [ARPKD PFDD 2023 | PKD Foundation (pkdcure.org/el-pfdd)]	

Adjunct Scientific Workshop Summary

ARPKD Adjunct EL-PFDD Scientific Workshop, held on January 23, 2024, was a critical follow up to the EL-PFDD meeting. This workshop gave ARPKD clinical and research experts an opportunity to reflect on what was shared by ARPKD patients and families, and to identify important scientific priorities and data needed to move the field forward. The workshop was cohosted by **Matt Becka,** MBA, DNP, RN, the Chief Research Officer at the PKD Foundation, and by **James Valentine**, JD, MHS, Hyman Phelps, & MacNamara, P.C. (HPM).

Matt Becka provided a summary of the meeting agenda, in Appendix 2. **Larry Bauer**, RN, MA, Senior Regulatory Drug Expert, HPM., summarized key points from the ARPKD EL-PFDD meeting. He described the most significant ARPKD symptoms, impacts, and top unmet medical needs identified by families. He highlighted the findings with powerful quotes from patients and caregivers. **James Valentine** provided a general framework for integrating the patient voice in drug development to set the context for the workshop discussions.

The meeting included two short presentations. **Dr. Lisa M. Guay-Woodford**, Director of the Inherited Kidney Diseases Program at the Children's Hospital of Philadelphia (CHOP), discussed the opportunities and challenges of conducting ARPKD-specific clinical trials. **Dr. Katherine Dell,** pediatric nephrologist and Professor of Pediatrics at Case Western Reserve University and Director of Clinical and Translational Research for Cleveland Clinic Children's, provided a landscape analysis of tools to evaluate what's most important to ARPKD patients and an overview of emerging biomarker that could be used in clinical trials in the future. Each presentation was followed by a panel discussion with key opinion leaders and expert physician scientists, moderated by **James Valentine**. In addition to Drs. Guay-Woodford and Dell, the discussion sessions also included **Dr. Erum Hartung**, pediatric nephrologist at CHOP and an Assistant Professor of Pediatrics at the University of Pennsylvania, and **Dr. Max C. Liebau**, Head of Translational Pediatric Nephrology at the University Hospital Cologne, Germany. Brief biographies of these experts are included in Appendix 3.

Following the panel discussions, **Matt Becka** closed the workshop by thanking the clinical experts and all others in attendance.

A video recording of the January 23, 2024 ARPKD Adjunct Scientific Workshop is available here. This website also includes links to the ARPKD Adjunct EL-PFDD Scientific Workshop and the ARPKD Voice of the Patient report, as well as a recording of the August 29, 2023 ARPKD EL-PFDD Meeting.

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Expert Discussion and Recommendations

After reflecting on what they heard from the ARPKD community at the EL-PFDD meeting, experts discussed strategies to overcome some of the challenges, to create new knowledge, and to translate current knowledge into clinically meaningful trials for ARPKD. Their discussion points and recommendations are summarized below. A Roadmap for ARPKD Therapy Development is presented, which includes objectives, goals, strategies, outcomes and next steps for the way forward.

Discussion insight: Better accommodate the needs of ARPKD patients and families during clinical trials.

Expert reflections and discussion: Experts clearly heard that ARPKD families are highly motivated to participate in clinical trials and this is consistent in their clinical practices. Experts identified some of the barriers that prevent their patients from enrolling in clinical trials and discussed practical ways to make clinical trials more accessible to patients and families. Note that some of these suggestions may be limited by US regulatory or jurisdictional issues.

Expert recommendation 1: Reduce the burden of clinical trial procedures and testing for patients.

Experts described how arduous testing procedures and lengthy clinic visits discourage clinical trial enrollment. For example, collecting multiple 24-hour urine samples is particularly burdensome for children who attend school and other activities.

Include patient/family voices and perspectives in the planning stages of clinical trials. Highly motivated families need to be involved at the earliest stages of clinical trial planning to assess what members of their community are able to tolerate in terms of travel, testing, duration, and clinical risk.

Consider ways to reduce the testing burden without compromising safety. With any clinical trial, a fine balance must be established between safety (the need to see patients frequently, monitor blood values etc.), versus how much testing and examination time is tolerable for patients to endure.

Consider liaising with the FDA and other regulatory agencies to discuss these approaches at the earliest point of a clinical trial. Experts provided this advice based on their own learnings and experience with patient studies.

Expert recommendation 2: Bring clinical trials closer to patients or make participating through local labs and clinics more accessible.

Long distance travel is particularly impactful for ARPKD families, especially for those whose children have g-tubes or who frequently vomit. It is also disruptive for families with multiple children, and whose other children attend school or participate in activities. Many clinical trials only cover the travel expenses of one parent, yet two are often needed to assist on a plane or drive if in a car if an ARPKD child needs extra medical care.

Build collaborative networks to leverage local resources. This may include local pediatricians at local hospitals where samples and data can be collected.

Contract with local labs who can send results to the central lab. Patients can have blood and other data collected much closer to home. Experts noted that this approach is already successful used by their transplant patients.

Home visits with clinical research nurses/clinical research organizations. Nurses can obtain much of the necessary data, however experts stated that some of the more difficult nephrology assessments, such as obtaining accurate blood pressure from infants, requires specialized training.

Medication delivery and virtual medication accounting. Delivering the medication supply to the home saves families from having to travel to a central site. In addition, medication accounting and other study related procedures may be able to be done virtually.

Discussion insight: Optimize supportive care to reduce ARPKD symptoms and improve patient quality of life on a day-to-day basis.

Expert reflections and discussion: Experts were impacted by hearing how profoundly ARPKD can alter a child's quality of life. They were particularly surprised by the prominence and frequency of gastrointestinal (GI) symptoms and how greatly they impact quality of life. While experts were familiar with feeding issues and GI intolerance, they felt that the degree and severity that some of the ARPKD families reported was striking. Experts discussed the wide range of symptoms and heterogeneity that see from one patient to the next.

Expert recommendation 3: Improve symptom management for each of the ARPKD manifestations experienced by patients.

Optimizing supportive management could lead to significant quality of life improvements including better hypertension control, less vomiting, stronger growth, less pain. A series of incremental refinements in the ways that

symptoms are managed – for example, without adverse drug effects - may lead to improvements in quality of life and lifespan. Experts cited the example of cystic fibrosis, where incremental improvements to symptom management have led to extended lifespans for these patients.

Rather than try to solve all issues at once, focus on improving life for those living with ARPKD one symptom at a time. One expert remarked, *"If ARPKD is an elephant, we shouldn't try to swallow the whole elephant with the way we're going to design trial. Maybe let's start with the trunk."*

Seek multidisciplinary input for ways to minimize symptoms. Related disease groups may have best practices to share, such as recommendations for how to improve outcomes for children who frequently vomit (regardless of diagnosis).

Expert recommendation 4: Focus on hybrid clinical trial outcomes, including how new interventions make patients feel.

In addition to hard clinical outcomes such as delaying time to dialysis or reducing the need for a kidney or liver transplant, clinical trials need to also focus on improving how patients feel every day.

Reducing patient fatigue and/or pain is important. Kidney and liver dysfunction cause children to feel incredibly tired and miserable. A new medication that only minimally reduces glomerular filtration rate (GFR) decline but helps to alleviate fatigue may be worth pursing. Conversely, if a treatment slows GFR decline but makes patients feel terrible, then patients won't want to take the medication or stay in the trial. As an example, in autosomal dominant polycystic kidney disease (ADPKD) trials, tolvaptan not only demonstrated a GFR change but very rapidly improved patient pain.[1]

Patient reported outcome measures are likely to be important to evaluate GI and other symptoms. Few validated clinical tools exist to measure vomiting or GI issues, so patient reported outcome measures (PROMs) will likely be extremely important.

Adopt or adapt instruments that other studies and registries have used to record the patient experience and measure quality-of-life. Experts described how tools used by CORES or the Chronic Kidney Disease in Children (CKiD) Cohort could be adapted for ARPKD. They also noted that the

[1] Casteleijn NF, et al.. *Tolvaptan and Kidney Pain in Patients With Autosomal Dominant Polycystic Kidney Disease: Secondary Analysis From a Randomized Controlled Trial*. Am J Kidney Dis. 2017 Feb;69(2):210-219. doi: 10.1053/j.ajkd.2016.08.028. Epub 2016 Nov 14. PMID: 27856088; PMCID: PMC5497700.

PROMIS (Patient-Reported Outcomes Measurement Information System), which include nausea and vomiting, could be extremely important.

Discussion insight: Develop ARPKD-specific clinical, biochemical, genetic, and imaging biomarkers to track disease progression and measure improvement.

Expert reflections and discussion: Experts heard families describe how challenging it can be to determine if treatments are working. Assessing kidney and liver disease progression in clinical care and during clinical trials is impossible to do without ARPKD-specific biomarkers. The clinical variability in ARPKD manifestations makes measuring change even more challenging. Unfortunately, many the FDA-approved surrogate endpoints of kidney and liver disease severity and progression that are used for drug approvals for other kidney and liver diseases are not applicable to ARPKD/CHF.

Expert recommendation 5: Develop biomarkers to identify patients at the highest risk for progression.

Experts discussed novel imaging methods that - in combination with other biomarkers - may be used to study new interventions in clinical trials or to determine which patients may benefit most from an existing FDA-approved medication for another indication. A few of these promising imaging biomarkers described by experts are listed below. More information is provided in Appendix 1.

Height corrected total kidney volume (TKV) may be used to identify the likelihood of fast progression in very young children. Recent data from the ARegPKD registry suggests that this metric may help to identify the youngest ARPKD patients, under eighteen months of age, who generally have a more severe ARPKD course.

Novel quantitative MRI techniques in development may be useful for the assessment of ARPKD kidney disease severity as well as progression. A specific method, magnetic resonance fingerprinting (MRF) is resistant to motion artifact, highly reproducible, rapid, and may eliminate the need for sedation. These features are very important for studies in young children.

Ultrasound elastography to detect and measure portal hypertension in liver disease. This can be used to identify patients who are experiencing stiffness in their left liver, versus those without.

Expert recommendation 6: Consider using patient reported outcomes in combination with biomarkers for clinical trial endpoints.

Clinical outcome assessments (COAs) are ways to measure the impact of different clinical trial interventions on the patient and the family. COAs are measures of how a patient feels or functions, outside of survival measures or biomarkers. These can include measures of performance, clinician-reported scales, observer-reported metrics, as well as PROMs.

Discussion insight: Develop more accurate ways to measure blood pressure in infants and small children .

Expert reflection and discussion: Throughout the EL-PFDD meeting, parents asked for improved methods to monitor blood pressure in children. Experts acknowledged that obtaining blood pressure from an infant or a small child is challenge that creates barriers for effective day-to-day patient management, research, and evaluating ARPKD clinical trial endpoints.

Expert recommendation 7: Lead and leverage other patient groups to inspire technology innovation.

ARPKD patient numbers are small. However, child blood pressure is a challenge in other pediatric kidney, cardiac and rare diseases as well. Working with other pediatric patient groups will enable us to create a much larger and more visible group of families who need a solution.

Make a strong case to medical device developers to refine blood pressure machines that are more accurate in infants and small children.

Consider a worldwide clinical trial on hypertension management. Experts are enthusiastic about further exploring this idea, as hypertension is one of the most impactful ARPKD health effects and can even impact children's cognition. Additionally, this symptom is not limited to the ARPKD rare disease community and could encompass many pediatric kidney disease communities. Experts noted that obtaining accurate blood pressure from infants and young children requires experience and specialized training.

Discussion Insight: Enroll ARPKD patients into registries and databases to ensure research-ready patient cohorts.

Expert reflection and discussion: Experts estimate that in the United States, there are 1,500 individuals with ARPKD between the ages of 0-29 years. Knowing exactly who these patients are, what subgroups they fall into, and where these patients are located, provides a tremendous opportunity to create adequately sized subgroups to power clinical trials. Also, by knowing

who the patients are and where they are located before trials are launched, researchers can target trial locations and trial procedures closer to where the patients are located. This requires infrastructure and research networks as described in expert recommendation #2.

Expert recommendation 8: Collect the same core data elements from each patient enrolled in international databases and registries.

By harmonizing the data collected, ARPKD databases can capture the largest possible cohort of patients and patient subgroups. Experts described several of the different registries already in existence and acknowledged the work that Dr. Liebau has already done to build the ARegPKD registry, Dr. Guay-Woodford's work with the Hepato-Renal Fibrocystic Disease Research and Translational Core Center, and the work of Drs. Liebau and Guay-Woodford to harmonize data points between their databases.

Experts also discussed collecting PROMs in registries to help researchers understand the true ARPKD disease burden and better inform patient-reported outcomes to be prioritized in clinical trials.

Expert recommendation 9: Collaborate with and learn from other patient registries and databases.

A question asked by a meeting attendee highlighted an area for future collaboration. The attendee asked, *"Should the PKD foundation establish a patient powered registry similar to what was done for ADPKD? This could allow patients and families to self-identify and bring in some of those who may not already be connected with the expert academic centers."* Matt Becka responded by informing meeting attendees that the Foundation was already looking for opportunities to collaborate with Dr. Guay-Woodford's database and, instead of overlapping, find ways to strengthen her existing resource through enrollment or site participation incentives.

Experts discussed opportunities to potentially collaborate with PEDSnet, a pediatric learning health system that draws data from electronic health records (EHR) and includes over 13 million children across the United States, to obtain EHR data from hundreds of children with ARPKD.

Discussion insight: Ultimately the ARPKD research and clinical communities should aim to enable clinical trials and develop new treatments for ARPKD.

Expert reflections and discussion: At the EL-PFDD meeting, experts heard that patients need new treatments: to prevent kidney or liver disease progression and delay time to kidney and or liver transplant; to avoid the

need for dialysis; to effectively target symptoms such as high blood pressure; that have fewer side effects; that are easier to administer, especially for younger children. Experts discussed some of the ARPKD clinical trial challenges, including small numbers of patients and the significant variation in disease severity and the rates of progression for both the liver and the kidney disease.

Throughout the workshop, experts brainstormed about opportunities to learn from others, build on what has already been created and to create change for those with ARPKD. They emphasized how the remarkable level of medical collegiality in the cystic disease field is an asset for the ARPKD community.

Expert recommendation 10: Create ARPKD patient subgroups to allow clinical trials to target different disease issues.

Creating specific subgroups of patients with ARPKD based on unique clinical features, imaging biomarkers (described in expert recommendation #5), age of diagnoses, or even different treatment goals may lead to more specific and effective clinical trials. It is possible that some subgroups may be more amenable to specific therapies. Ideally, improvements for one subgroup could be examined in subsequent subgroups.

Defining very specific ARPKD patient subgroups would enrich clinical trials. Clinical trials would require fewer patients to be adequately powered to measure significant change. This is an important point in a population such as ARPKD, which has such small patient numbers.

Experts described the two most obvious ARPKD patient subgroups: those at the highest risk of progression and those who have less severe or slower progression. The first subgroup consists of the children who come to medical attention early in life, with rapidly progressive kidney failure. These children require targeted therapies to target PKD specific pathways to slow the rate of disease progression with a focus on kidney disease. The second consists of slightly older individuals who progress relatively slowly and are often diagnosed with an incidental finding on an ultrasound. These children require an approach that optimizes symptom management.

Define smaller graduated subgroups within these two cohorts. Ideally, each of these smaller subgroups may eventually have more refined treatment and monitoring recommendations.

Expert recommendation 11: Broaden inclusion criteria to increase eligibility for kidney and liver clinical trials.

Many medications are metabolized by the kidney and liver; often patients below a certain kidney function level or with evidence of liver disease (such as portal hypertension) are excluded from participating in clinical trials. Much more consideration must go into meaningful and realistic inclusion and exclusion criteria with respect to including greater numbers of ARPKD patients, but without compromising safety. Again, experts emphasized liaising with the FDA to discuss these approaches in the earliest point of a clinical trial, and to include patient perspectives in protocol design to understand the highest risk trade-off they'll accept.

Focus on finding treatments for the subgroup with the highest risk of rapid kidney and liver disease progression. This group of patients is at high risk of very early kidney or liver failure and would derive the greatest benefit from a potential pharmacological intervention. The clinical trial could measure for example, longer time to kidney/liver failure or maybe even avoidance of kidney/liver failure.

Find ways to better measure clinical change in the subgroup of patients with liver dysfunction. Experts suggested targeting this population later in childhood, as opposed to kidney disease in ARPKD, liver disease may not show progression until adulthood. There are gaps in knowledge about why some patients with ARPKD develop a more pronounced form of liver disease than others and if there are early clinical markers or disease patterns that could inform risk of progression.

Expert recommendation 12: Leverage pathobiological insights from related disorders.

Examine the similarities and differences of diseases that are genetically distinct from ARPKD but share some overlapping clinical presentations and may share some common pathways. Examples presented and discussed include hepato-renal fibrocystic diseases (autosomal dominant PKD (ADPKD), nephronophthisis (NPHP), Bardet-Biedel syndrome (BBS) and Meckel-Gruber syndrome (MKS) or glomerulocystic kidney disease) which may share common pathways with ARPKD.

Look for opportunities to repurpose drugs. Novel treatments for other diseases may be candidates for further study in ARPKD. As an example, clinical trials for tolvaptan, which was first approved in ADPKD, are now underway for ARPKD.

Identify novel agents. Consider obtaining multi-disciplinary input, preliminary data from patient registries and prospective observational studies as starting points to identify novel agents. For example, early signals from surgical or GI clinical trials may reveal novel approaches to reducing vomiting or potential methods for blood pressure management.

Roadmap for ARPKD Therapy Development

OBJECTIVES:

1. **Develop biomarkers to enable clinical trials and advancement of new treatments for ARPKD**
2. **Optimize clinical trial participation**
3. **Provide supportive care to reduce symptoms and improve QOL**

	1	1	2	2	3	3	3
GOAL	Better accommodate ARPKD patients and families during clinical trials		Improve supportive care and QOL	Enroll patients into registries and databases		Develop ARPKD-specific biomarkers to track disease progression and measure improvement		Leverage insights from related disorders to repurpose drugs and identify novel agents
STRATEGIES	Reduce clinical trial procedures and testing burdens	Decentralize trials to bring clinical trials closer to the patients	Focus on symptom management for each ARPKD manifestation experienced by patients	Collaborate with other patient registries and database	Create specific ARPKD patient subgroups from the fastest to slowest progressor	Find biomarkers that identify patients at the highest risk for progression	Find ways to better measure clinical change in the subgroup of patients with liver dysfunction	Lead and leverage patients from pediatric kidney disease communities to address hypertension
OUTCOMES	Patient perspectives and FDA input in early clinical trial planning	Increased patient access to clinical trial opportunities	Reduce patient pain and fatigue	Collect consistent core data elements Capture PROs measures in registries	Find treatments for the fastest progressing patient subgroups	Investment into therapeutic development by multiple stakeholders	Hybrid clinical trial outcomes: biomarkers + PROs measure how patients feel	Accurate blood pressure measures in infants and small children
NEXT STEPS	Partner with patient advocacy groups to create formal patient feedback processes	Agree on study procedures that can be done off-site at local clinics or laboratories	Develop and implement PROs to evaluate patients' symptoms in clinical care and clinical trials	Create consortium of ARPKD databases and registries	Broaden clinical trial inclusion criteria to increase eligibility	Publish white paper on appropriate clinical trial endpoints	Solicit and fund proposals on this topic	Worldwide hypertension management clinical trial

ACKNOWLEDGEMENTS

The PKD Foundation and the PKD Outcomes Consortium of the Critical Path Institute thank all of those who helped to organize and to participate in the ARPKD Adjunct EL-PFDD Scientific Workshop.

Thank you to our ARPKD experts, Dr. Lisa Guay-Woodford, Dr. Katherine Dell, Dr. Erum Hartung, and Dr. Max Liebau for sharing their time as well as their wealth of knowledge and experience.

Thank you to Larry Bauer and James Valentine, our partners in planning and facilitation. Thank you to the Dudley Digital Works media team for the production planning and for all the behind-the-scenes work.

We are so grateful to the participants of the August 29, 2023 ARPKD Externally-Led Patient Focused Drug Development meeting for providing the patient voice. Thank you for sharing your stories, and testimonies and valuable insights which we hope will inform clinical trial design and the development of therapies targeting the outcomes that matter most to you.

Finally, we wish to express our deep appreciation to the researchers working in labs and clinics around the world, striving towards a better understanding of basic and translational ARPKD science and moving us closer to future clinical trials and therapies. We hope this meeting will encourage future research and successful new therapy development for people living with ARPKD who urgently need treatment options.

About this report

Support for the ARPKD Adjuvant EL-PFDD Scientific Workshop and report was provided by the PKD Foundation and the Stolper family.

This report was prepared and submitted on behalf of the PKD Foundation by: Elise Hoover, Vice President of Research Programs, PKD Foundation; Sorin Fedeles, PhD, MBA, Executive Director, Rare and Orphan Diseases, Polycystic Kidney Disease Outcomes Consortium (PKDOC); Wendy Vanasco, Senior Project Manager, Rare and Orphan Diseases, PKDOC; and by Chrystal Palaty, medical writer. Consulting Partners include Larry Bauer, RN, MA, and James Valentine, JD, MHS, from Hyman Phelps, & MacNamara, P.C. Technical services for the workshop were Provided by Dudley Digital Works.

Please contact PKD Foundation, at research@pkdcure.org for questions related to this report.

Appendix 1: Additional Resources for Next Steps

Additional patient-focused drug development resources:

- FDA's PFDD Guidance series: https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical
- FDA's Draft Guidance on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products - Guidance for Industry https://www.fda.gov/media/133660/download

ARPKD registry resources:

- ARPKD Database (ARPKDB)- https://arpkdb.org/.

  Children's National Hospital has established a NIDDK-funded interdisciplinary center of excellence in PKD-related research, with specific emphasis on ARPKD. A resource developed at this center of excellence is, Core A: Hepato/Renal Fibrocystic Disease Translational Resource, also called the ARPKD Database. This Core resource was designed to develop a unique set of clinical, genetic, and educational resources for autosomal recessive polycystic kidney disease (ARPKD and other recessive forms of renal cystic disease).

- ARegPKD - https://www.escapenet.eu/achievements/aregpkd/

  International Registry Study on Autosomal Recessive Polycystic Kidney Disease. In this project the ESCAPE Network and the German Pediatric Nephrology Association (GPN) have joined forces with renowned translational researchers interested in Autosomal Recessive Polycystic Kidney Disease (ARPKD) to:

  - advance the pathophysiological understanding,
  - provide an observational evidence base for unified clinical management concepts,
  - establish clinical and biomarkers predicting the risk of early and progressive disease,
  - lay the foundation for innovative translational research toward novel therapeutic targets, and

- pave the way for clinical trials in children with ARPKD.

Biomarker resources.

- Height corrected total kidney volume (TKV)
- Quantitative MRI/MR Fingerprinting (MRF) for the assessment of ARPKD kidney disease severity as well as progression.[2][3]
- Ultrasound elastography to detect and measure portal hypertension in liver disease.

[2] MacAskill CJ, Markley M, Farr S, Parsons A, Perino JR, McBennett K, et al. Rapid B(1)-Insensitive MR Fingerprinting for Quantitative Kidney Imaging. Radiology. 2021;300(2):380-7.

[3] MacAskill CJ, Erokwu BO, Markley M, Parsons A, Farr S, Zhang Y, et al. Multi-parametric MRI of kidney disease progression for autosomal recessive polycystic kidney disease: mouse model and initial patient results. Pediatr Res. 2021;89(1):157-62.

Appendix 2: Adjunct Scientific Workshop Agenda

Meeting date and time: January 23, 2024, 2:00– 4:00 p.m. Eastern Time

1:00-1:05 p.m.	**Opening Remarks** *Matt Becka, MBA, DNP, RN, Chief Research Officer at the PKD Foundation*
1:05-1:20 p.m.	**Recap of EL-PFDD: What's Important to ARPKD Patients/Caregivers** *Larry Bauer, RN, MA, HPM*
1:20-1:30 p.m.	**Framework for Integrating the Patient Voice into Drug Development** *James Valentine, JD, MHS, (HPM)*
1:30-1:40 p.m.	**Opportunities to Conduct Clinical Trials in ARPKD** *Lisa M. Guay-Woodford, MD, Children's Hospital of Philadelphia*
1:40-2:15 p.m.	**Panel Discussion: Perspectives on Facilitating Clinical Trials in ARPKD** *Moderated by James Valentine, JD, MHS, HPM* *Panelists:* *– Lisa Guay-Woodford, MD, CHOP* *– Katherine Dell, MD, Cleveland Clinic Children's* *– Erum Hartung, MD, CHOP* *– Max Liebau, MD, University of Cologne*
2:15-2:25 p.m.	**Landscape Analysis of Tools to Evaluate What's Important to ARPKD Patients** *Katherine Dell, MD, Cleveland Clinic Children's*
2:25-2:55 p.m.	**Panel Discussion: Setting a Patient-Focused Research Agenda for Drug Development Tools** *Moderated by James Valentine, JD, MHS, HPM* *Panelists:* *– Lisa Guay-Woodford, MD, CHOP* *– Katherine Dell, MD, Cleveland Clinic Children's* *– Erum Hartung, MD, CHOP* *– Max Liebau, MD, University of Cologne*
2:55-3:00 p.m.	**Closing Remarks** *Matt Becka, MBA, DNP, RN, Chief Research Officer at the PKD Foundation*

Appendix 3: ARPKD Expert Biographies

Katherine Dell, MD, is a pediatric nephrologist and clinician scientist with over 25 years of experience in research and care of children with ARPKD. She received her medical degree from Harvard Medical School and completed training in Pediatrics and Pediatric Nephrology at The Children's Hospital of Philadelphia. She is currently Professor of Pediatrics at Case Western Reserve University and Director of Clinical and Translational Research for Cleveland Clinic Children's. The major focus of her NIH and PKD Foundation-funded research is development of magnetic resonance imaging (MRI) biomarkers of ARPKD kidney and liver disease progression. She is a two-time recipient of the Dr. Vincent H. Gattone Research Award from the PKD Foundation. She currently serves as a member of the Board of Directors of the PKD Foundation.

Lisa M. Guay-Woodford, MD, is an internationally recognized pediatric nephrologist whose work focuses on identifying clinical and genetic factors involved in the pathogenesis of inherited renal disorders, most notably autosomal recessive polycystic kidney disease (ARPKD). Her laboratory participated in the identification of the human ARPKD gene as part of an international consortium and her group was the first to identify a candidate modifier gene for ARPKD. She has directed the NIDDK-funded Hepato-Renal Fibrocystic Disease Research and Translational Core Center, initially established when she was at the University of Alabama at Birmingham (UAB), and she continues to serve as co-Director of the UAB Childhood Cystic Kidney Disease Core Center. Her research program has been funded by the NIH, the Burroughs Wellcome Fund Clinical Scientist Award in Translational Research, and the Polycystic Kidney Disease Foundation. In 2009, Dr. Guay-Woodford was awarded the Lillian Jean Kaplan International Prize for Advancement in the Understanding of Polycystic Kidney Disease, given by the PKD Foundation and the International Society of Nephrology.

Dr. Guay-Woodford has recently assumed the role of Senior Advisor for Clinical and Translational Research Initiatives and Director of the Inherited Kidney Diseases Program at the Children's Hospital of Philadelphia (CHOP). She holds the Presidential Scholar Endowed Chair for Clinical and Translational Science and serves as Professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania.

Erum Hartung, MD, MTR is a pediatric nephrologist at Children's Hospital of Philadelphia (CHOP) and an Assistant Professor of Pediatrics at the University

of Pennsylvania. Her clinical and research focus is in polycystic kidney disease, particularly autosomal recessive polycystic kidney disease (ARPKD). She co-directs the Combined Kidney/Liver Program at CHOP, which specializes in the care of children with ARPKD and other genetic kidney/liver diseases and ciliopathies. Her research aims to accelerate the development of new treatments for ARPKD through observational and database studies to better define the natural history and complications of ARPKD, and through imaging studies to develop new biomarkers of kidney and liver disease progression.

Max C. Liebau, MD, is a clinical consultant pediatric nephrologist and transplant physician at the Department of Pediatrics at the University Hospital Cologne, Germany, where he holds positions as Head of the Social Pediatric Center for Chronically Ill Children and Head of Translational Pediatric Nephrology. Prof. Liebau combines his clinical training as a pediatric nephrologist with his experience in cellular and molecular biology obtained in the Nephrology Research Laboratories in Freiburg and Cologne, Germany and at the University of California, Santa Barbara. His group follows a translational research approach to study genetic kidney diseases with a special focus on Autosomal Recessive Polycystic Kidney Disease (ARPKD). The group aims to understand the molecular function of the ARPKD protein fibrocystin and to characterize clinical long-term courses of ARPKD as a basis for the identification of clinical and/or biochemical risk markers of disease progression. Prof. Liebau's research is funded by the German Research Council and the German Federal Ministry for Education and Research amongst others.