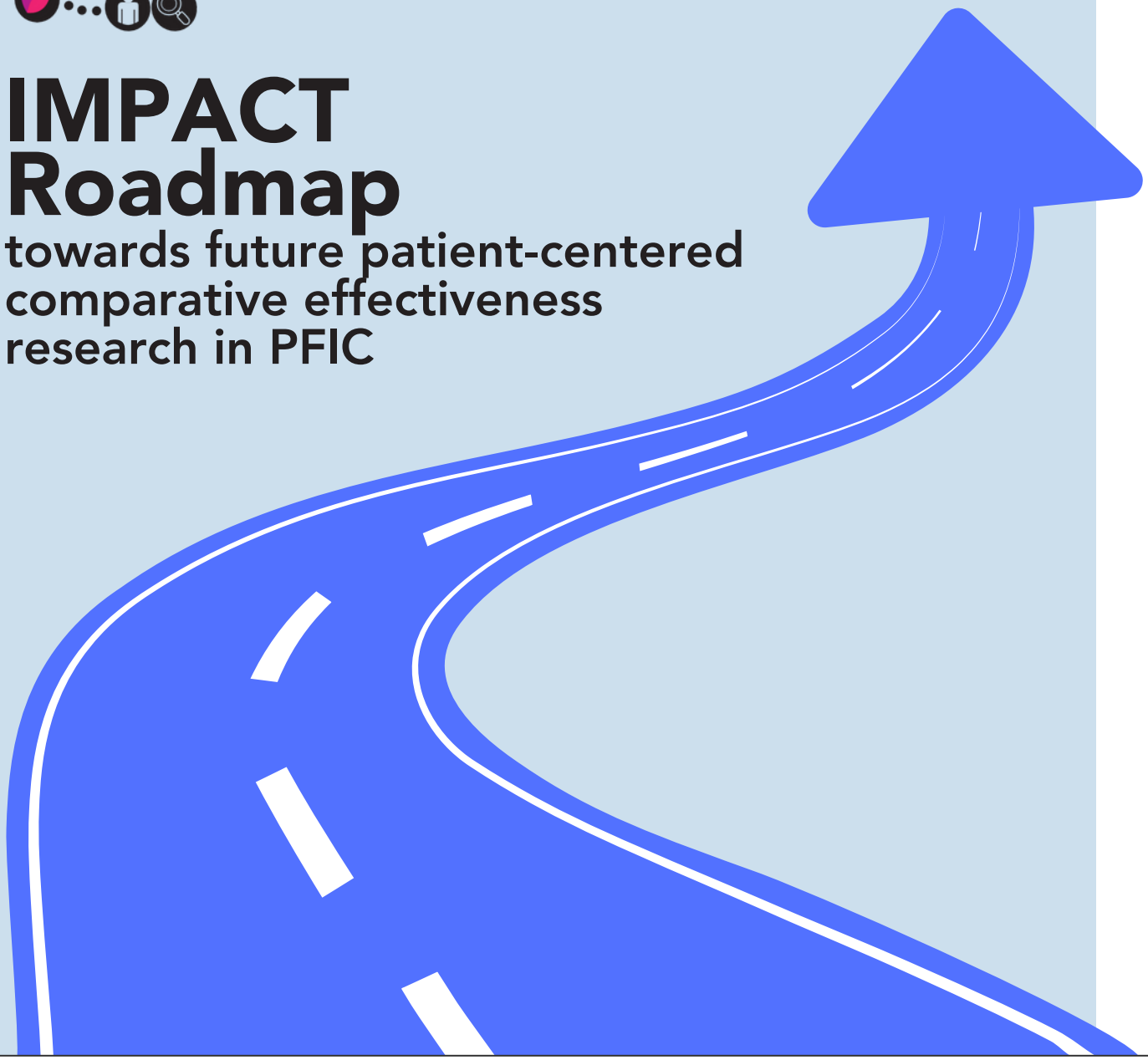
IMPACT Roadmap

towards future patient-centered comparative effectiveness research in PFIC



pfic Advocacy & Resource Network , Inc.

June 2025

Table of Contents

Executive Summary 3

About this Roadmap 4

Acknowledgements 5

Creating the Roadmap 6

Motivation 6

Project IMPACT Overview 7

Goal & Objectives 7

Methods 7

Participation 9

Evaluation Strategy 9

Roadmap 11

Overview 11

Engagement Guidance 12

Barriers & Solutions to PFIC Patient-Researcher Partnerships 12

Guidance for Forming Successful Multistakeholder Research Teams 13

Communication & Dissemination Strategies 16

Future Directions for PFIC CER 17

Guiding Principles for PFIC Patient-Centered CER Projects 17

Considerations for Variability in Care Common in Rare Diseases 17

Considerations for Variability in Care Across PFIC Subtypes 18

PFIC Patient-Centered CER Targets 19

Strategies to Reduce the Burden of Study Participation 23

Next Steps & Sustainability 23

Closing Remarks 27

Executive Summary

The IMPACT Roadmap toward patient-centered comparative effectiveness research (CER) is the result of Project IMPACT, a two-year, PCORI-funded engagement project led by PFIC Network. Developed through extensive collaboration with patients, caregivers, clinicians, and researchers, the roadmap outlines strategies, tools, and priorities for PFIC-specific CER that reflects the real-world priorities of PFIC patients and their families as well as the considerations of clinicians and researchers.

Project IMPACT engaged stakeholders through six learning modules, a series of ten multi-stakeholder focus groups, and the development of the PFIC Treatment Experience App (TEA) - a web-based tool that collects and displays patients' real-world treatment experiences. Across these activities, participants helped define the core components needed to initiate and sustain future patient-centered CER projects in PFIC, including:

- principles for meaningful, sustainable stakeholder engagement
- PFIC-specific CER research targets that reflect real-world decisional dilemmas and patient priorities
- strategies to reduce the burden of study participation
- guidance for successful multistakeholder research partnerships
- a long-term plan to build and scale patient-driven research infrastructure for PFIC CER.

This roadmap is designed for use by PFIC Network community leaders, clinicians, researchers, and funders. It serves as both a call to action and a practical guide for building PFIC patient-centered CER teams and studies that reflect the voices and values of those most impacted while being scientifically sound.

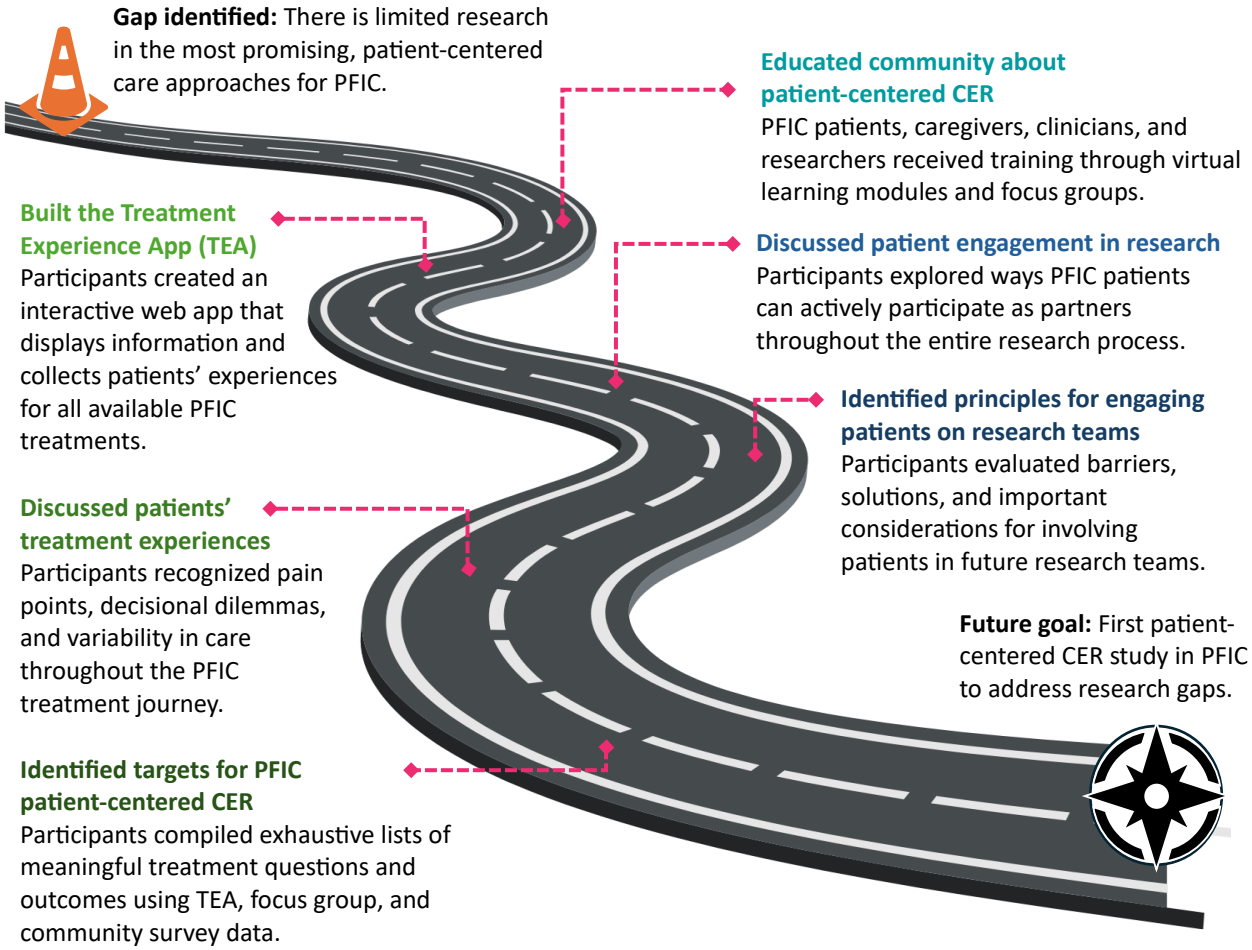
This project was funded through a Patient- Centered Outcomes Research Institute® (PCORI®) Eugene Washington PCORI Engagement Award (Contract #30455). The statements presented in this work are solely the responsibility of the author(s) and do not necessarily represent the views of PCORI®.

About this Roadmap

PFIC Network developed this roadmap in collaboration with patients, caregivers, clinicians, and researchers to guide future patient-centered comparative effectiveness research (CER) in progressive familial intrahepatic cholestasis (PFIC). Drawing from insights gathered through the two-year PCORI-funded Project IMPACT, the roadmap highlights shared priorities, actionable strategies, and infrastructure needs for launching meaningful PFIC CER studies.

Figure 1 below summarizes the process used to develop this roadmap and the integrated engagement activities that informed its content. The sections that follow describe the motivation behind this work, how it was carried out, and the strategies and priorities that emerged.

Figure 1. Creating the IMPACT Roadmap for PFIC Patient-Centered CER



Acknowledgements

We extend our heartfelt thanks to everyone who made the development of this roadmap possible. Project IMPACT was a truly collaborative effort—grounded in shared learning, mutual respect, and a deep commitment to improving research and care for people living with PFIC.

We are especially grateful to our Project IMPACT team—Melissa Kochanowsky, Gitta Lubke, Alexandra Perez, Jim Squires, Emily Ventura, Emily Perito, and Sarah Brengosz—for your leadership, insight, and steadfast support throughout every phase of project IMPACT.

To all the patients, parents, clinicians, and researchers who participated in the learning modules, focus groups, and Treatment Experience App: we could not have accomplished this project without you. Your experiences, ideas, and feedback shaped every part of this work. Thank you for diving into this effort with honesty, courage, and generosity. Your voices are at the heart of this roadmap and will continue to guide PFIC research for years to come.

We also thank Paolo Catalla and his team from Semi:Formal for their creativity, thoughtful design work, and ability to translate complex ideas into clear, accessible visuals that brought the IMPACT Treatment Experience App to life.

This project was supported by a Eugene Washington PCORI Engagement Award from the Patient-Centered Outcomes Research Institute (PCORI). We are deeply grateful for PCORI's support and their commitment to building infrastructure for patient-centered comparative effectiveness research in rare diseases.

Thank you to everyone involved—for your time, your trust, and your partnership in shaping the future of research in PFIC.

Creating the Roadmap

Motivation

Progressive familial intrahepatic cholestasis (PFIC) is a group of rare genetic disorders related to defects in bile transport that can lead to liver failure during childhood. PFIC diseases exhibit considerable intra- and inter-subtype variability in both severity and prognosis. While new treatments are emerging, patients and families face difficult care decisions - often with limited information about how those treatments will impact their or their child's quality of life, long-term health outcomes, or day-to-day functioning. For many, the journey through PFIC care is filled with uncertainty, tradeoffs, and an overwhelming lack of patient-centered data.

These realities were brought into sharp focus during PFIC Network's 2022 Family & Scientific Conference, where patients, caregivers, clinicians, and researchers came together to discuss the most pressing challenges facing the PFIC community. In roundtable discussions, parents shared stories of navigating high-risk surgeries like biliary diversion and liver transplant, often without clear or consistent guidance. Many expressed feeling isolated in their decision-making, unable to find real-world data that could help them understand the benefits, burdens, and likely outcomes of each treatment option.

> **"Transplant is not a treatment; it's changing one disease into another."**
> – PFIC Caregiver, 2022 Family & Scientific Conference Roundtable

These conversations revealed an urgent need for patient-centered evidence on the real-world benefits and burdens of PFIC treatments to better support care decisions. Yet at the time, PFIC lacked the infrastructure to make this possible:

- no mechanisms for patients to help shape research questions or define meaningful outcomes
- no process to identify or prioritize research grounded in lived experience
- no tools or training to support patient involvement in the research process

PFIC Network launched Project IMPACT to begin addressing these gaps and chart a path toward patient-centered CER in PFIC. Our long-term vision is to enable the first patient-centered CER study in PFIC - generating real-world evidence that addresses the decisional dilemmas facing patients and their families and ultimately improves the lives of those affected by the disease.

Project IMPACT Overview

Goal & Objectives

Funded by a Eugene Washington Engagement Award from the Patient-Centered Outcomes Research Institute (PCORI), Project IMPACT was launched in 2023 to build capacity for patient-centered comparative effectiveness research (CER) in PFIC. Rather than conducting a research study, IMPACT focused on preparing the PFIC community - patients, families, clinicians, and researchers - to engage as partners in future research efforts.

The project was grounded in multistakeholder engagement at every stage. Patients and caregivers worked alongside clinicians and researchers to co-design tools, define CER targets, and explore what it means to build equitable, collaborative research teams in the context of PFIC.

Project IMPACT centered on four key objectives:

1. **establish a shared understanding** of patient-centered CER across stakeholder groups
2. **gather community input** on how to form and sustain multistakeholder research partnerships
3. **develop a web-based Treatment Experience App (TEA)** to collect and share patients' real-world treatment experiences
4. **co-create a roadmap** to guide the design of future PFIC patient-centered CER studies

Through these efforts, IMPACT created not only a roadmap, but a network of informed, empowered stakeholders ready to lead the next phase of capacity building for patient-centered CER in PFIC.

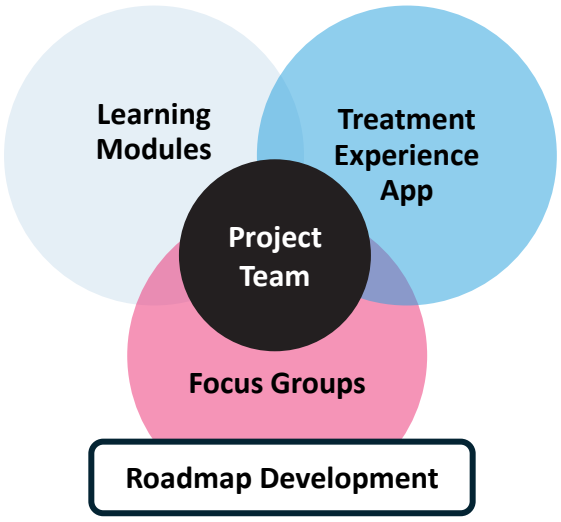
Methods

To accomplish our objectives, Project IMPACT was organized around four interconnected engagement pathways. Each pathway offered opportunities for patients, caregivers, clinicians, and researchers to contribute their expertise—and together, they formed the backbone of this roadmap.

Project Team

A seven-member project team—composed of PFIC parents, PFIC Network staff, clinician-researchers, and a statistician—provided strategic oversight and synthesis across all activities. The team met regularly to:

Figure 2. IMPACT Engagement Pathways



- design project activities and oversee development of the Treatment Experience App
- evaluate engagement in project activities and guide ongoing improvements
- share emerging findings with the community through summary reports, updated modules, and focus group discussions.

Learning Modules

To build a shared foundation of knowledge among patients, parents, clinicians, and researchers, the IMPACT Project Team developed six virtual learning modules covering key topics in patient-centered CER. The learning modules included content adapted from the PCORI-funded PARTNER project, PCORI's Research Fundamentals, and Building Effective Multistakeholder Research Teams. The modules were delivered asynchronously through REDCap and paired with brief feedback surveys. While most modules focused on education and capacity building, two were specifically designed to gather stakeholder input—one on the design of the Treatment Experience App (TEA), and another on the draft list of PFIC CER targets. Survey responses informed module refinement, guided focus group discussions, and directly contributed to the development of key project deliverables. A brief overview of each IMPACT module is shown in the table below:

Table 1. IMPACT Learning Modules

Module 1: What is Patient-Centered Outcomes Research (PCOR)?
Introduced the core principles of patient-centered comparative effectiveness research (previously known as PCOR).
Module 2: How Can I Contribute to PCOR?
Explained the various roles patients, parents, and other stakeholders can play in shaping and conducting CER.
Module 3: How Do We Develop Research Questions That Matter?
Provided guidance on framing research questions that reflect the priorities and of patients and families.
Module 4: Virtual Tour of the Treatment Experience App (TEA)
Offered a walkthrough of the TEA platform and invited participants to give feedback on its design and usability.
Module 5: Review of Draft PFIC Patient-Centered CER Targets
Collected input from participants on the draft list of PFIC patient-centered CER targets.
Module 6: Multistakeholder Research Teams
Examined how to build successful multistakeholder teams capable of planning and carrying out CER projects.

Focus Groups

Ten multi-stakeholder focus groups were held over the course of the project, including two in-person sessions at the 2024 PFIC Family & Scientific Conference and 2025 Cholestatic Liver Disease Summit. Co-facilitated by PFIC parent Alexandra Perez and clinician-researcher Jim Squires, each session followed a structured agenda focused on key topics such as designing the Treatment Experience App (TEA), building patient-researcher partnerships, and identifying PFIC patient-centered CER targets. These sessions were central to Project IMPACT's success—grounding all project outputs in the lived experiences and priorities of the PFIC community and laying a strong foundation for future patient-centered CER.

To read focus group summaries, visit: https://www.pfic.org/project-impact/project-impact-feed/

Treatment Experience App (TEA)

The Treatment Experience App (TEA is a web-based platform designed to collect and publicly share patients' treatment experiences. The app allows users to submit structured entries about medications, surgeries, and nutrition interventions, which are summarized by IMPACT staff in regular intervals and displayed alongside plain-language clinical summaries. During the project, so far 92 entries have been submitted, helping identify treatment patterns, sources of variability in care, and outcomes that matter most to families. The TEA directly informed the development of the PFIC Patient-Centered CER targets and will remain active beyond the project to support ongoing engagement and research planning as well as providing a valuable information resource for PFIC families.

Participation

IMPACT engaged a diverse mix of patients, caregivers, clinicians, and researchers across all major activities. The figure below summarizes participation rates by stakeholder type across the project team, learning modules, focus groups, and the Treatment Experience App.

Figure 3. IMPACT Participation by Stakeholder Role and Activity

Project Team	Modules & Focus Groups	Treatment Experience App
•**2** parents/caregivers •**2** clinician-researchers •**2** PFIC Network staff •**1** statistician	•**50** patients & parents •**10** clinicians & researchers •from **7** unique centers	•**92** total entries across medications, surgeries, and vitamins.

Evaluation Strategy

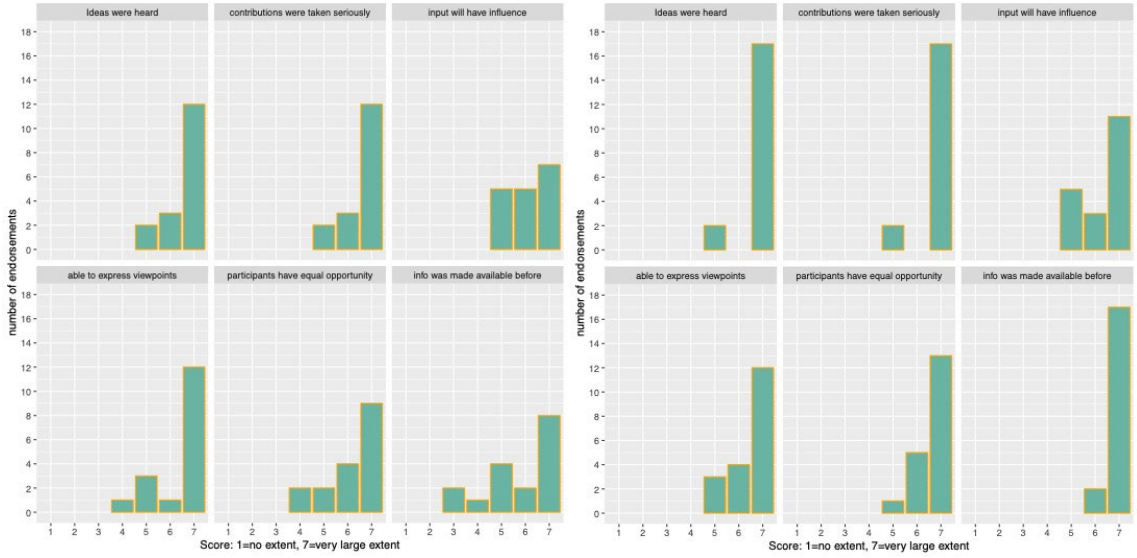
The project team continuously evaluated activities across all four pathways to refine engagement strategies and improve overall participant experience. As part of this process, we used the Patient Engagement Evaluation Tool (PEET; Moore et al., 2022), a validated short questionnaire targeting different aspects of patient engagement. The PEET was administered after each bi-monthly project team meeting to assess team dynamics and strengthen internal collaboration. The PEET was also used following each focus group to evaluate the quality of engagement and inform adjustments to facilitation and implementation.

Open-ended responses to the PEET surveys offered actionable insights, particularly regarding focus group facilitation. Initial data highlighted that participants appreciated providing more information about the focus group discussion topics in advance, using a more structured

facilitation style, and encouraging time limits on individual responses to ensure equitable participation. The project team reviewed this feedback and implemented changes in subsequent sessions to promote more inclusive and productive discussions.

A comparison of PEET results from the start of the project in November 2023 to those collected at the end in May 2025 (Figure 4) revealed a consistently strong and steadily improving level of engagement. Notable gains were observed in areas such as participants feeling their ideas were heard, having equal opportunity to contribute, and receiving relevant information before meetings. These improvements were likely driven by iterative adaptations made in response to the constructive feedback gathered through the PEET's open-ended responses.

Figure 4. PEET Results – November 2023 (left) & May 2025 (right)



Note: Participants completed the PEET after each project team and focus group meeting. Bars in the graph represent the number of participant endorsements for a given answer category, scored on a 7-point Likert scale (1 = "to no extent," 7 = "to a very large extent"). The left graph shows data from November 2023 whereas the right shows the results from March 2025. Improvements were observed across all domains, particularly in participant perceptions of influence, equal opportunity to contribute, and availability of information prior to activities.

Roadmap

Overview

The previous sections described the motivation, process, and participants that shaped Project IMPACT. What follows is the roadmap itself—a forward-looking guide to support (a) building a dedicated PFIC patient-centered CER infrastructure and (b) designing future studies that reflect the priorities of people living with PFIC.

This roadmap serves as both a **planning tool** and a **resource library** to strengthen long-term capacity for patient-centered CER. Developed through Project IMPACT, it reflects the shared insights and contributions of patients, parents, clinicians, and researchers. PFIC Network will use this roadmap to foster sustainable multi-stakeholder collaboration and guide the development of future patient-centered CER projects.

To support these goals, the roadmap is organized into three key sections:

1. **Engagement Guidance**
   Tools and recommendations for supporting meaningful, sustained involvement of patients and partners in research, including:
   - Barriers & Solutions to PFIC Patient-Researcher Partnerships
   - Guidance for Forming Successful Multistakeholder Research Teams
   - Communication & Dissemination Strategies

2. **Future Directions for PFIC CER**
   Content to inform the design of CER studies grounded in patient priorities, including:
   - Guiding Principles for PFIC Patient-Centered CER Projects
   - Considerations for Variability in Care Common in Rare Diseases
   - Considerations for Variability in Care Across PFIC Subtypes
   - PFIC Patient-Centered CER Targets
   - Strategies to Reduce the Burden of Study Participation

3. **Next Steps & Sustainability**
   Guidance for continuing this work beyond IMPACT, including:
   - Remaining Capacity Needs
   - 5-Year Plan
   - Sustainability

Together, these components offer a practical, community-informed framework to guide both immediate planning and longer-term progress toward launching the first patient-centered CER study in PFIC.

Engagement Guidance

A core principle of patient-centered CER is the meaningful and active involvement of patients as equal partners at every stage of research, from study design to the dissemination of findings. This approach ensures that research methods and the resulting evidence directly reflect patient priorities, needs, and lived experiences. Through discussions on patient engagement in research, IMPACT participants contributed insights that can be used by future PFIC patients, caregivers, clinicians, and researchers when forming patient-centered CER project teams.

Barriers & Solutions to PFIC Patient-Researcher Partnerships

Participants identified barriers and proposed solutions for partnering in future patient-centered CER projects. The resulting figure (Figure 5 below) can be used as a guide when organizing PFIC patient-centered CER project teams.

Figure 5. Barriers & Solutions to PFIC Patient-Researcher Partnerships

BARRIER	DESCRIPTION	SOLUTION
Time Constraints	Partners in patient-centered CER projects must navigate busy schedules between work, school, and hospital visits.	Schedule project activities in alignment with availability; send materials in advance; keep activities short, efficient, and output-driven.
Logistics	Partners in patient-centered CER projects may navigate logistic challenges in order to participate (e.g., childcare, travel to meetings or site visits).	Obtain sufficient project funding to provide compensation to partners and accommodate logistical support needs.
Knowledge	Partners may have a lack of knowledge and/or experience with patient-centered CER and the research process.	Provide comprehensive patient-centered CER education in lay language; provide opportunities for live Q&A.
Confidence about contributions, value of patient-centered CER	Partners are concerned whether their opinion and contributions will be valued, if the patient-centered CER project will truly help patients, and/or result in a publication or idea to pursue in future research.	Engage all partners on the research project team in shared decision-making; ensure study endpoints are relevant to the community.
Cultural & Systemic	Historical mistrust of healthcare institutions, language, and systemic economic barriers impact diverse partner engagement.	Engage targeted efforts to reach more of the PFIC community through inclusive patient-centered CER awareness and education campaigns.

Pediatric Inclusion	Many PFIC patients are children, posing unique communication and scheduling challenges - but it is important to include their voices in patient-centered CER design.		Provide child assent and parental consent forms; schedule activities around school hours; create engagement opportunities and material for children's education level.

Note: A framework for addressing barriers in patient-researcher partnerships, providing solutions to enhance inclusivity, efficiency, and representativeness in PFIC patient-centered CER project teams.

Guidance for Forming Successful Multistakeholder Research Teams

Forming successful multistakeholder research teams will be essential to ensure that patient-centered comparative effectiveness research (CER) in PFIC reflects the real-world needs, priorities, and experiences of patients and families. Through IMPACT Module 6 and the April 2025 Focus Group, participants identified key stakeholder partners who should be involved, the types of support needed for successful collaboration, and strategies to sustain partner engagement across the lifespan of a research project. Survey results from Module 6 showed strong interest from PFIC patients, parents, clinicians, and researchers participating in IMPACT to join future multistakeholder research teams.

Key Stakeholder Partners for Patient-Centered CER in PFIC

Participants emphasized the importance of including a wide range of voices in the research team to ensure the full spectrum of experience, expertise, and needs are represented throughout the research process.

They recommended forming a consistent core team that includes:

- **Patients** to represent diverse lived experiences across ages, disease stages, and geographies, including adolescents, adults, and post-transplant individuals. Younger patients could be engaged through Child Life Specialist-led sessions or teen advisory boards.
- **Parents** to provide critical caregiver perspectives on the daily impacts of PFIC and experiences with clinical care.
- **Clinicians** from both specialty centers and general hospitals to offer insights into diagnosis, treatment practices, and care delivery challenges.
- **Researchers (clinical and lab):** Clinical researchers have the experience to carry out studies with patient participants and can help ensure that research questions are clinically feasible and meaningful. Lab researchers have the experience to study biological phenomena in a controlled setting and can use patient-centered CER results to identify new biological questions or mechanisms to investigate through lab research.
- **Statistician** to ensure rigorous study design, data collection and analysis, and reporting to support credible, high-quality findings.

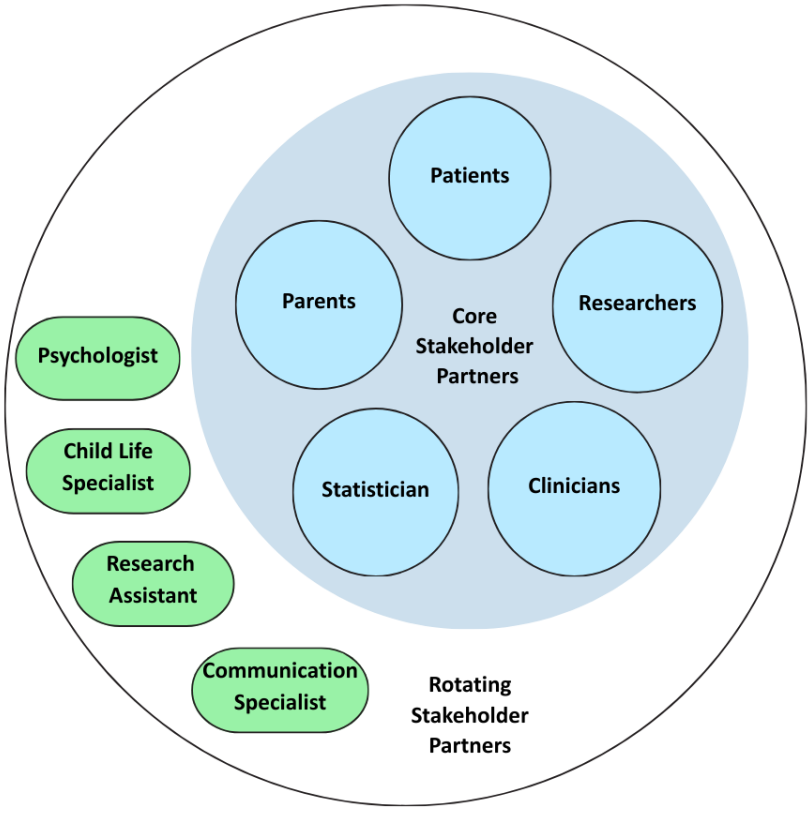
Participants agreed that maintaining a consistent core team - supported by rotating members based on project needs - can help balance continuity with the diverse expertise required across

all stages of a research project. Participants recommended involving rotating members whose expertise is relevant to specific stages of the project, including:

- **Psychologist** to support patient-centered engagement and address emotional or behavioral aspects of research participation.
- **Child Life Specialist** to help capture pediatric patient voices through developmentally appropriate methods such as art, play, or storytelling.
- **Research Assistant** to assist with study coordination, participant communication, and logistics as well as to support data collection.
- **Communications Specialist** to support dissemination of research findings through accessible formats, creative outreach, and broader public engagement beyond traditional academic channels.

These responses were used to develop Figure 6 below.

Figure 6. Key Stakeholders for Patient-Centered CER in PFIC



Note: Core and rotating stakeholder partners identified to support different stages of multistakeholder patient-centered CER teams in PFIC.

Support for Multistakeholder Research Teams

Participants identified several types of support needed to ensure that all stakeholders can work together as equal partners:

- **Flexible participation options**
  - offer multiple ways to engage - such as core team roles, short-term advisory roles, or rotating participation
  - allow input asynchronously and schedule meetings at times that accommodate multiple time zones
- **Clear expectations and structured tasks**
  - define roles, responsibilities, and timelines early
  - break tasks into manageable parts to support participation
- **Training on research processes and terms**
  - provide plain-language written guides
  - share brief (under 10 minute) explainer videos
  - offer 1:1 mentorship if possible
- **Opportunities to meet in person**
  - plan at least one in-person meeting early to build trust, strengthen communication, and support collaboration
- **Support for pediatric engagement**
  - given that a significant proportion of PFIC research participants will be children and adolescents, use pediatric-specific strategies to ensure meaningful input from younger patients, including:
    - child life specialist-led sessions
    - play-based methods
    - teen advisory boards
- **Compensation for time and effort**
  - offer financial compensation to recognize time contributions and reduce barriers to participation

Strategies to Sustain Partner Engagement

Participants emphasized that building flexibility into the engagement structure is critical, as some studies may span several years, and participants' availability and capacity may change over time. To sustain engagement, participants recommended:

- **maintaining a consistent core group** of committed members to provide continuity across all research stages
- **creating flexible committees or advisory groups** comprising patients, families, clinicians, and other stakeholders to bring in new voices as needed based on the phase of the project
- **providing ongoing onboarding and clear communication** to support both core members and new contributors, making participation approachable at every stage
- **fostering connection and community:** feeling connected to others throughout the research project helps create a sense of support and belonging, which encourages ongoing engagement over time.

Motivations for Participation in Multistakeholder Research Teams

Most participants expressed a desire for varying levels of involvement in future multistakeholder research teams, ranging from providing occasional advisory input to co-investigator roles. Participants identified several key motivations for participating in research teams:

- ensuring focus on patient and caregiver priorities
- improving care outcomes
- contributing to community building
- contributing to efficient, feasible, and patient-engaged research

Communication & Dissemination Strategies

Participants described a consistent experience of being asked to enroll in research studies without receiving updates or results afterward unless they actively searched for them. This lack of follow-up was seen as a major gap in how research is communicated back to patients and their families. They expressed a strong desire for more accessible, timely, and understandable communication. Suggestions included:

- receiving study results in plain language with limited medical jargon
- using formats like visual abstracts, pictograms, or short explainer videos (ideally under 10 minutes, with chapters or segments)
- having a consistent point of contact from the research team to follow up with results and be available to answer any questions
- offering a centralized location - such as a section on the PFIC Network website - where updates and results could be posted in an easy-to-read format

When surveyed on preferences for receiving communications about research activities and findings, participants provided the following responses listed in Table 2 below.

Table 2. IMPACT Participant Communication Preferences (N=19)

Response	Count
Email Newsletters	16
Website	12
Social Media	8
Live Webinars	6
Print Mail	5
Academic Publications	4
Blog Posts	2

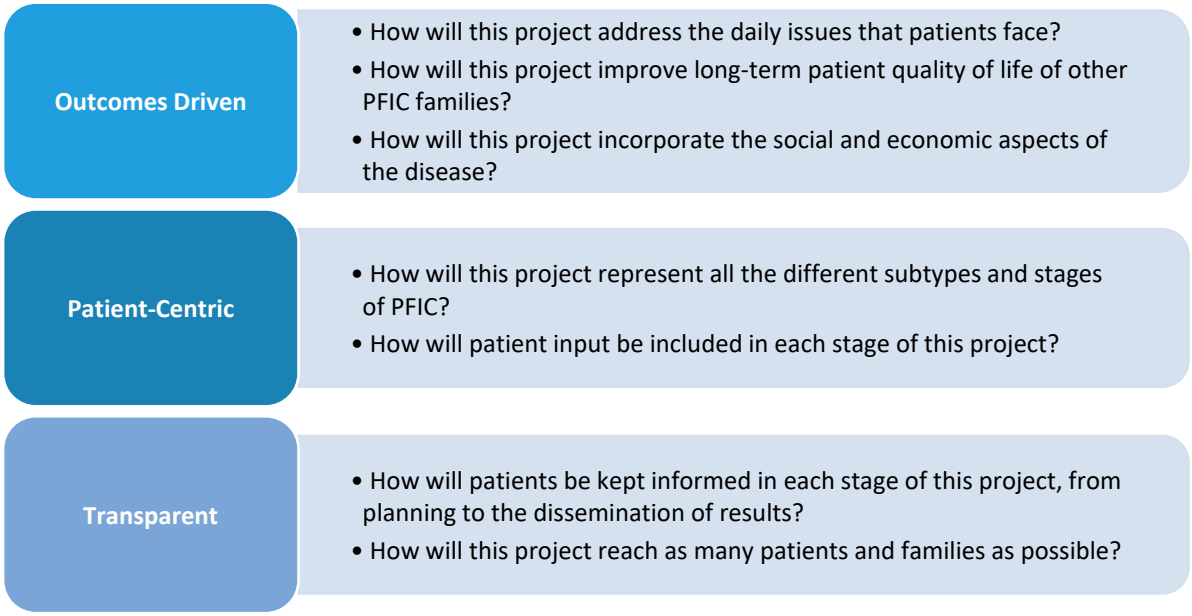
Note: Participant feedback indicated a strong preference for receiving information via email newsletters and websites.

Future Directions for PFIC CER

Guiding Principles for PFIC Patient-Centered CER Projects

IMPACT participants explored questions such as "What would research look like that is truly centered on patients and families?" Their answers were used to develop guiding principles (see Figure 7 below), which may be used in as a "checklist" when designing patient-centered CER projects.

Figure 7. IMPACT Guiding Principles for PFIC Patient-Centered CER Projects



Note: PFIC patient-centered CER projects should be outcomes-driven, patient-centric, and transparent by aligning with patient priorities, integrating ongoing patient input into methods, and ensuring clear communication at every stage.

Considerations for Variability in Care Common in Rare Diseases

PFIC patients consistently reported experiencing differences in care between PFIC treatment centers and worry whether they are receiving the "right" treatment. Patient-centered CER has the potential to help reduce this variability by:

- Identifying the most effective treatments to reduce reliance on less effective options
- Supporting the development of clinical guidelines, which can help standardize care, and help patients and their providers to make more informed treatment decisions

Initial participant discussions in project IMPACT underscored the need to start by identifying systemic barriers to reduce care variability in PFIC. Understanding these barriers is a crucial first step toward understanding how patient-centered CER *specifically* can address these challenges and lead to better care outcomes for the PFIC community. Participants identified the following barriers and associated solutions to reducing variability in care for PFIC (see Figure 8 below).

Figure 8. Stakeholder-Identified Barriers & Solutions to Reducing Variability in Care in PFIC

Barriers		Solutions
Cost and accessibility of treatments and surgeries	→	Patient treatment and self-advocacy education
Lack of standard care practices for PFIC	→	Develop consensus treatment plans
Lack of designated "centers of excellence"	→	Establish PFIC centers of excellence
Variability in provider knowledge of PFIC subtypes	→	Facilitate provider education on the different PFIC diseases and respective treatment choices
Lack of communication between providers at different centers	→	Develop realistic treatment guidance for under-resourced care centers
Clinicians not involving patients as partners in care decisions	→	Develop guidance for patient-centered care decision-making
Lack of comprehensive evidence regarding patient-centered treatment outcomes	→	Patient-centered comparative effectiveness research

Note: Participants identified several systemic barriers to PFIC care variability, with patient-centered CER as one solution to improve consistency in care amid broader challenges.

Considerations for Variability in Care Across PFIC Subtypes

PFIC is a group of similar yet unique rare genetic diseases, and treatment choices vary considerably across the different diagnoses and stages of disease (e.g., PFIC1/FIC 1 vs. PFIC 2/BSEP, pre- vs. post-transplant). Treatment variability is therefore one of the challenges that needs to be addressed when evaluating which treatments and outcomes would be most relevant to investigate in a patient-centered CER study. Participants explored how we can adapt patient-centered CER to PFIC given this variability in treatment choices. They identified the following considerations for designing PFIC CER studies, and specifically, for evaluating which treatments and outcomes to investigate (see Table 3 below):

Table 3. Evaluating Treatment Comparators & Outcomes for PFIC Patient-Centered CER

Is there specific variability in PFIC care approaches that we can investigate with CER?
• Variability in care can be due to the uniqueness of each PFIC patient but can also be due to lack of sufficient systematic knowledge related to treatment success. Treatment variability can therefore help to reveal which treatments would be insightful to compare. IMPACT members discussed how PFIC patients' care has varied between centers, including differences in nutritional interventions and the combination of treatments used to manage itch.
Which treatments are feasible to compare?

• Not all treatments are feasible to compare. For example, IMPACT members would like to know which of the two available IBAT inhibitors, maralixibat and odevixibat, work better to treat itch. However, clinical trials conducted separately for the two medications have shown very similar effects and effect sizes, and it would be very challenging if not practically impossible to recruit enough study participants to detect reliable differences between the two treatments.
Can the outcomes be measured reliably?
• To identify treatment outcomes that are important to patients and their families we designed the IMPACT Treatment Experience App (TEA), which is a web app hosted on PFIC Network's website. The TEA showed that itch, sleep, and different aspects of quality-of-life rank among the most important treatment-related outcomes in PFIC. These outcomes can be measured reliably by using validated questionnaires such as the PROMIS scales used in the PFIC Network Patient Registry. In addition, both the TEA data and the focus group discussions revealed the importance of growth, malnutrition, and diarrhea. These outcomes can be reliably captured with established clinical measures.
Can the outcomes be measured in a reasonable timeframe?
• When designing a study, it's important to check if outcomes can be measured within a reasonable timeframe that fits the study's goals, budget, and participant availability. For example, changes in itch levels or growth can be assessed in a reasonable timeframe whereas native liver survival (while being a crucial clinical outcome), can take years to measure.
How many PFIC patients and families are affected by these treatments and outcomes?
• Which treatments and outcomes are meaningful to investigate can vary depending on diagnosis and transplant status. As a community, we must decide whether to prioritize studies that focus on specific PFIC subtypes or whether to address treatments and outcomes that are relevant across all subtypes and stages of the disease. For example, interventions such as nutrition support and itch medications, along with the respective outcomes revealed by the TEA and focus group discussions can be relevant across different subtype diagnoses.

Note: IBAT = Ileal Bile Acid Transporter. PROMIS = Patient-Reported Outcomes Measurement Information System; PROMIS scales, developed through an NIH-funded program, are standardized measures designed to assess patient-reported outcomes across various domains, such as physical, mental, and social health.

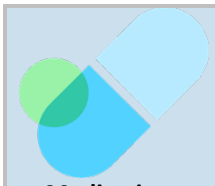
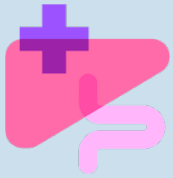
PFIC Patient-Centered CER Targets

Community-Identified Questions

Using data from the Treatment Experience App (TEA), focus groups, and surveys conducted as part of IMPACT, participants compiled an exhaustive list of treatment questions (see Table 4 below). These questions are grouped into four main categories: Medications, Surgeries, Nutrition, and Diagnosis, Delivery of Care & Other Support.

Table 4. PFIC Treatment Questions

TOPIC	QUESTIONS
	<u>IBAT-related medications</u> • How do the different non-IBAT medications compare in reducing itch? • How does combining IBAT inhibitors with other medications compare to using IBAT inhibitors alone for reducing itch, gastrointestinal symptoms, and improving quality of life? • What are the short and long-term side effects of IBAT inhibitors versus external and/or internal biliary diversion surgery?

 **Medications**	<u>Non-IBAT medications</u> • How do alternative therapies like cold baths or massage impact itching and quality of life? • What is the best medication to reduce PFIC-related fatigue? • What is the best way to manage the psychological effects of PFIC on patients and families during any stage of the disease? • How does the mental health of PFIC patients receiving psychological intervention compare with those who receive none? <u>Liver transplant & post-transplant medications</u> • Which is more effective at reducing post-transplant pruritus: IBAT inhibitors, non-IBAT medications, or other treatments? • What is the comparative effectiveness of antidiarrheals, IBAT inhibitors, external and internal biliary diversion surgery in reducing post-transplant diarrhea? • How do the short and long-term side effects of post- liver transplant medications compare to pre- liver transplant medications?
 **Surgeries**	<u>Biliary diversion</u> • How does the likelihood of benefit from internal versus external biliary diversion vary among different PFIC types? • What will work better to relieve itch – external or internal biliary diversion? • What ostomy supplies have worked best with an external biliary diversion? <u>Surgeries and IBATs</u> • Which delays the need for liver transplant longer: diversion surgery or IBAT inhibitors? • How does the financial burden of surgical biliary diversion or liver transplant compare to the financial burden of being prescribed an IBAT inhibitor long-term? • How and when do you most effectively reverse an external or internal biliary diversion to solely using IBAT inhibitor? <u>Liver transplant</u> • What are the best criteria to determine the necessity and urgency of liver transplant? • When is the optimal time to pursue liver transplantation? • How does a live donor liver transplant compare to a deceased donor liver transplant when it comes to care, longevity, and quality of life after transplant? • How do growth and quality of life compare pre- and post- liver transplant? <u>Surgeries - general</u> • How do different surgeries (external/internal biliary diversion and liver transplant) compare in improving the quality of life for PFIC patients and their families?
 Nutrition	<u>Vitamins & Supplements</u> • What types of OTC supplements best support growth and development? • How do aggressive nutritional treatments (such as NG tubes or TPN) compare to more passive approaches (like oral formulas) in terms of tolerability, as well as their impact on weight, growth, and quality of life? • How does regular versus infrequent monitoring of vitamin levels impact health and quality of life outcomes related to vitamin deficiencies? <u>Diet</u>

	• Which is better: formula or blended food? • How does an MCT-enhanced diet impact growth versus a non- MCT enhanced diet? • How does a diet high in processed foods, sugars, fats, and starches compare with one containing fewer of these elements in terms of its impact on pruritus, gastrointestinal symptoms, quality of life, and liver health? <u>Post-transplant</u> • How do antidiarrheal medications (like loperamide) compare to external/internal biliary diversion surgery in reducing diarrhea after liver transplant?
Diagnosis, delivery of care, & other support	<u>Diagnosis</u> • What is the best approach to reduce the time to diagnosis for PFIC? • How does one measure of itch compare to another (e.g. inpatient surveys, patient-reported outcomes, monitoring with a daily app, wearables)? <u>Delivery of care</u> • What is the comparative effectiveness of pain management intervention (e.g., EMLA cream or gas protocol for needle insertion) versus no pain management intervention in improving patients' mental health? • What is the comparative effectiveness of having a dietician in the care team versus no dietician in improving nutrition and quality of life outcomes for PFIC patients? • What is comparative effectiveness of mental health support in addition to itch treatments versus itch treatments alone (i.e., usual care) in improving patient and caregiver mental health, itch severity, and quality of life? <u>Other support</u> • What is the best way to make the process of insurance approvals for medications easier and faster? • What is the best way to educate my providers and specialists about PFIC? • What is the best way to educate my child's school personnel about PFIC? • What is the best way to improve the transition from pediatric to adult care? • What is the best supplemental insurance to help cover costs associated with PFIC?

Note: IBAT = Ileal Bile Acid Transporter. OTC = Over the Counter. NG = Nasogastric. TPN = Total Parenteral Nutrition. MCT = Medium Chain Triglyceride. EMLA = Eutectic Mixture of Local Anesthetics.

Community-Identified Outcomes

Participants also identified key outcomes to assess treatment effectiveness in the proposed questions (Table 4), categorized into two types: patient-reported and clinical (see Table 5 below).

Table 5. PFIC Treatment Outcomes to Measure

OUTCOME TYPE	OUTCOMES
Patient-Reported	<u>Medications-specific</u> • Itch relief, skin health, sleep quality, reduction of pain, reduction of fatigue, reduction of diarrhea, reduced frequency and severity of episodes <u>Surgeries-specific</u> • Itch relief, reduced abdominal pain/discomfort, improved social acceptance (e.g., concerning ostomy bags, growth delays), reduction of diarrhea, improved toilet training

	Nutrition-specific • Improved palatability (e.g. treatment taste, ease of consuming quantity) Cross-intervention • Improved patient quality of life, improved quality of life for caregivers/family/siblings, improved mental health (reduced anxiety/depression/irritability), improved focus and school performance, improved ability to enjoy major life events, play and swim Care Delivery & Support-specific • Reduced number of workdays missed for care, lowered financial burden of the disease and treatments, impact of delayed insurance approvals on quality of life, impact of switching insurance companies on treatment access, improved ease of acquiring compounded medications, trust in provider/healthcare system, improved testing for cancers
Clinical	Medications-specific • Slowed/halted disease progression, native liver survival Surgeries-specific • Native liver survival, reduced post-transplant complications Nutrition-specific • Improved vitamin levels, weight gain, improved growth (height), improved strength, reduction/prevention of hearing loss

Note: Participants identified key patient-reported and clinical outcomes within and across the four categories of treatments/interventions from Table 2 (medications, surgeries, nutrition, care delivery and other support).

Emergent Priority Areas

We held the final IMPACT focus group as an in-person breakout session at the 2025 Cholestatic Liver Disease Summit in Denver (https://www.myast.org/events/cholestatic-liver-disease-summit). This conference was a joint multi-disease event focusing on PFIC, Alagille Syndrome, Biliary Atresia, and Primary Sclerosing Cholangitis. The meeting was attended by patients, parents, clinicians, researchers, regulators, and industry representatives focused on rare cholestatic liver diseases. A total of 16 PFIC patients and parents and 11 clinicians and researchers attended the IMPACT breakout session. The group reviewed the list of patient-centered CER targets and discussed priority areas for future CER based on these targets. Through IMPACT activities, including the Treatment Experience App (TEA), patients had identified itch and quality of life as important outcomes for future CER. During the conference discussion, mental health interventions to address itch and quality of life emerged as a primary area of shared interest. Notably, evaluating the efficacy of mental health interventions alongside existing medications to address itch and quality of life were also identified as a common priority during the conference cross-disease research roundtable. A structured prioritization and feasibility assessment is planned as part of our proposed follow-up work. Based on findings

from the cross-disease roundtables, we have decided to include the Alagille and Biliary Atresia communities in these follow-up efforts to inform potential cross-disease CER opportunities.

Strategies to Reduce the Burden of Study Participation

Participants also brainstormed a list of ways to design a patient-centered CER study that would motivate and reduce the burden for PFIC patients and families to participate in a study comparing PFIC treatments. We grouped these recommendations into four categories:

1. Create a trusted and welcoming environment
   - ✓ A strong recommendation from a trusted physician
   - ✓ Mental health/psychological support if needed
   - ✓ A dedicated case manager/care coordinator
   - ✓ A communication specialist trained to answer questions for the trial
   - ✓ Warm, welcoming, and patient research staff
   - ✓ Personalized reminders
   - ✓ Toys or presents for child participants

2. Time and compensation
   - ✓ Limited time required away from family
   - ✓ Services offered at home or through local clinics if possible
   - ✓ Minimal number of hospital visits required
   - ✓ Financial compensation
   - ✓ Flexible timing of visits
   - ✓ Scheduling visits during breaks from school to minimize disruption
   - ✓ Shorter visits

3. Medical considerations
   - ✓ Minimal medical trauma anticipated
   - ✓ Avoiding invasive procedures (e.g. by using surveys)
   - ✓ No blood samples in addition to routine draws

4. Other considerations
   - ✓ Frequent updates on study progress, changes, and results
   - ✓ A transparent plan for dissemination of study results
   - ✓ Setting clear expectations
   - ✓ Support for smaller centers to enroll study participants

Sustainability & Next Steps

Looking Ahead: Building Further Capacity for Patient-Centered CER in PFIC

PFIC Network launched project IMPACT to build a foundation for patient-centered CER in PFIC. IMPACT brought together patients, parents, clinicians, and researchers to:

- learn principles of patient-centered CER and multi-stakeholder research engagement
- develop tools to support long-term collaboration, including the Treatment Experience App (TEA) - which captures patient-reported treatment experiences to inform meaningful outcomes to investigate in CER - and the IMPACT roadmap, which includes guidance for building multi-stakeholder PFIC research teams
- identify CER targets informed by PFIC patients' lived experiences and clinical insights.

Through educational modules, focus groups, and project team meetings, IMPACT fostered shared knowledge and trust among patients and researchers while producing tools and research priorities that will support future patient-centered CER in PFIC.

Remaining Capacity Needs Post-IMPACT

Despite the progress made through IMPACT, two critical gaps must be addressed before we can pursue the first patient-centered CER study in PFIC:

1. Currently, no **dedicated infrastructure** exists to support sustainable, PFIC-specific patient-centered CER. Existing pediatric liver disease consortia mostly aim to advance clinical PFIC research. They do not focus on patient-centered comparative effectiveness research (CER), nor do they engage patients and families as active partners in governance or research design.
2. Research targets identified through IMPACT still need to be **refined and prioritized** through a structured, collaborative process that considers both scientific feasibility and patient-perceived importance.

To address these gaps, PFIC Network has applied for a second PCORI Eugene Washington Engagement Award to support the PATH project (Patient-driven engagement for Advancing Treatment Research). PATH will establish the remaining infrastructure needed to launch patient-centered CER in PFIC by forming a multi-stakeholder consortium, creating a governance charter, and finalizing a prioritized research agenda.

Five Year Plan: Short, Medium-, & Long-Term Objectives

Building on the momentum of project IMPACT, PFIC Network has developed a five-year plan to establish the remaining infrastructure, governance, and partnerships needed to initiate and sustain patient-centered CER in PFIC. This plan is organized across three phases—short-, medium-, and long-term—each with defined objectives that build upon one another. Together, these efforts will create a durable, patient-led research infrastructure capable of designing and conducting meaningful CER aligned with the priorities of PFIC patients.

Short Term (2025–2027) – PATH Project – Building Capacity

- form a steering committee of 4–6 PFIC research centers, 4–6 patient family representatives, and 2–3 nursing professionals
- develop a Patient-Centered Research Consortium governance charter that embeds equitable decision-making across all stakeholders
- finalize a prioritized research agenda based on IMPACT findings and additional

community input
- publish a consortium development framework for replication by other rare disease groups

  Outcomes: A functioning, patient-centered research consortium with the infrastructure and tools to co-lead future patient-centered CER studies.

Medium Term (2027-2029) – Putting Capacity into Practice

- evaluate and refine consortium processes using member feedback
- transition the Steering Committee into a formal Patient-Centered Research Consortium
- institute additional committees and rotating stakeholder partners as needed
- use the governance charter and research agenda to design and prepare for the first PFIC-specific patient-centered CER study
- disseminate tools and lessons learned to other rare disease patient advocacy groups

  Outcomes: The Patient-Centered Research Consortium launches the first multi-center CER study in PFIC aligned with patient priorities and shares its approach as a model for other rare diseases.

Long Term (2029 and beyond) – Sustaining and Scaling the Work

- maintain ongoing Patient-Centered Research Consortium involvement across the full research lifecycle (i.e. review, dissemination, and implementation of study findings)
- update the research agenda every two years using structured community input
- integrate study results into the IMPACT Treatment Experience App and clinical care guidelines to support real-world treatment decision-making
- onboard new consortium members using PATH-developed tools and training

  Outcomes: A sustainable, scalable research infrastructure led by patients and embedded in PFIC Network's operations, advancing patient-centered CER in PFIC and inspiring similar models across the rare disease research landscape.

Five Year Plan: Resources & Engagement Strategy

To achieve our short-, medium-, and long-term objectives, PFIC Network will leverage the capacity, tools, and partnerships developed through IMPACT and expanded through PATH.

Capacity & Tools

- IMPACT Treatment Experience App (TEA)
  - The TEA will inform the development of the research agenda. The TEA features an ongoing data collection tool where patients can input their treatment experiences. The TEA will be updated in the long term with findings from patient-centered CER studies.
- IMPACT Roadmap
  - The roadmap provides immediate guidance for forming multi-stakeholder research teams within the consortium and will remain a reference for engagement and training for consortium members over time. We plan to also

publish a visual and interactive version of the roadmap as well as tools that translate roadmap items into practical checklists for researchers pursuing patient-centered CER in PFIC.

- IMPACT Engagement Evaluation tools (e.g., PEET):
    - The Patient Engagement Evaluation Tool (PEET) will be used throughout our ongoing activities to assess the quality of engagement and support continuous improvement.
- New capacity and resources to be developed in PATH:
    - Learning Modules
        - We will adapt and expand virtual learning modules from IMPACT to prepare consortium members for their roles in patient-centered CER.
    - Consortium Governance Charter
        - The governance charter will support consortium formation, guide operations and study planning, and define structures for member onboarding and sustainability.
    - Research Administrator
        - We will hire a research administrator during PATH to manage operations, logistics, and coordination for the consortium.
    - Consortium Development Framework
        - During PATH, we will document the process of forming a multi-stakeholder, patient-centered research consortium. The resulting framework will be made public in order to increase the accessibility for patient advocacy groups to pursue formation of research consortia and patient-centered CER.

Stakeholder Partnerships

PFIC Network will engage stakeholder partners who participated in IMPACT, including patients, parents, clinicians, and researchers already familiar with patient-centered CER to form the Patient-Centered Research Consortium. Additional recruitment will target patients and parents from the PFIC Network community, as well as clinicians, nurses, individual researchers, and research centers with experience in treating PFIC. All consortium members will receive shared training and compensation, supporting equitable, long-term collaboration.

This strategy enables our

- **short-term objectives** by recruiting and training a diverse Consortium Steering Committee to co-develop the governance charter and research agenda.
- **medium-term objectives** by equipping consortium members to lead study planning and launch the first PFIC patient-centered CER project
- **long-term objectives** by sustaining engagement, onboarding new members, and adapting the model for other rare disease communities.

Together, these resources and partnerships will support a durable, patient-led research infrastructure that drives meaningful CER in PFIC and contributes to a scalable model for other

rare disease patient organizations.

Sustainability

By the end of the five-year plan, the PFIC Patient-Centered Research Consortium will be fully integrated into PFIC Network's operations, with trained stakeholder partners, governance and multi-center research infrastructure in place to plan and execute patient-centered CER. The consortium will have initiated its first PFIC patient-centered CER study, coordinated by a dedicated Research Administrator, using funding pursued through PCORI, NIH, and/or private sources.

Closing Remarks

Project IMPACT introduced the PFIC community to patient-centered comparative effectiveness research (CER) and served as the first structured effort to map available PFIC treatments alongside both clinical and patient-reported outcomes. Using the Treatment Experience App (TEA), interactive learning modules, and focus groups, the project provided foundational knowledge to guide future patient-centered CER efforts in PFIC.

While this work established a strong starting point, there is still much to be done to advance patient-centered research and improve clinical management of PFIC. We will work to ensure that the insights gained from this project will help shape future studies and foster ongoing collaboration among patients, caregivers, clinicians, and researchers to address the most pressing treatment questions in PFIC.