MEETING SUMMARY

Advisory Panel on Rare Disease

September 16, 2019

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OVERVIEW

On September 16, 2019, the PCORI Advisory Panel on Rare Disease (RDAP) held its fall meeting in Washington, DC.

RDAP's 14 members include patients, caregivers, representatives of patient advocacy organizations and industry, clinicians, payers, and researchers. The meeting was open to the public via webinar, and meeting materials were posted to the PCORI website in advance.

The meeting started with brief introductions of the panel members, welcomes to two new panelists, and a re-cap of the content of the June 2019 meeting. Two panel members shared their journeys from diagnosis to treatment as a rare disease patient and a parent of a child with a rare disease. Panel members also received an update on PCORI's Rare Disease Portfolio and discussed rare disease research opportunities for PCORnet's Rapid Cycle Research Program. RDAP members shared some of their current work outside of the advisory panel to help facilitate collaboration and a deeper understanding of panel members' connection to the issues. RDAP members discussed future plans for the advisory panel and recognized departing panel members, including Dr. Matt Cheung, MD, chair of the RDAP.

Introduction of New Panelists

Dr. Matt Cheung, Chair of the RDAP, welcomed the panelists, PCORI staff members, and public attending via webinar and introduced two new panelists: Saira Sultan, JD (stakeholder group: Policy Maker) and Doug Lindsay (stakeholder group: Patients/Caregivers and Patient Advocates).

Patient & Caregiver Journey: from Diagnosis to Treatment and Beyond

Julie Gortze, RN, panel member, and Cindy Luxhoj, MUP, co-chair of RDAP, shared their experiences as rare disease patient and caregiver of a rare disease patient.

Ms. Gortze told of her experience living with a rare disease that affects 1 in 30 million people. She has experienced a variety of symptoms from her rare disease nearly all her life, starting with hearing loss in the 2nd grade and progressing to full disability when she was in her 40s and 50s. Like many patients with rare diseases, she consulted with many physicians at ER visits, office consultations, and hospitalizations over the years only to receive misdiagnoses and unnecessary or ineffective treatments. Going to specialists at different locations and hospitals made it difficult to connect the dots between her symptoms and often led to repeated tests and missed opportunities. Forty-seven years after the first symptoms appeared, she finally received a diagnosis, which has led to more effective treatment. Even

though she was trained as a nurse, Ms. Gortze said she felt unprepared for the challenges of living with a rare disease and advocating for herself and had to learn along the way. She has started an advocacy group in the New England region for people with rare diseases in hopes of helping others struggling with rare diseases.

Ms. Luxhoj told the story of her daughter, Elena, who was born smaller than expected with a high bilirubin count and did not seem to respond to treatment. She also had difficulties eating and keeping food down. Unable to get effective diagnosis and treatment from her child's general practitioner, Ms. Luxhoj sought care at Children's Hospital in Seattle, where Elena was diagnosed with the rare disease, alagalle syndrome. Elena's symptoms included intense itching and inability to digest food properly to fuel growth. Surgery at age 11 to divert bile out of her body addressed these issues, improving her quality of life and allowing her to grow and develop more normally. At age 21, Elena started showing signs of jaundice again and her liver started declining. Before she could receive a liver transplant transplant, she developed c. diff and went into organ failure and died at age 24. Ms. Luxhoj described her difficulties accessing disease information, connecting with other families, her isolation and lack of support in caring for her child. To address these issues, Ms. Luxhoj founded a non-profit organization, the Alagalle Syndrome Alliance to look for answers, help other families, and not be so alone in the journey.

Discussion

Dr. Cheung thanked both presenters for their personal perspective on the days discussion topics: the definition of cross-cutting research when it comes to rare disease communities, and how to conduct comparative effectiveness research (CER) in the rare disease space.

RDAP members recommended the following topics for possible study:

- Delayed diagnosis and access to care (especially specialists), including applying predictive modeling or other big data solutions, facilitating sharing of medical records, and encouraging physicians to consult and work collaboratively to accelerate diagnosis.
- Transitions from pediatric/college/adult/end-of-life care, which are a common challenge across rare diseases and even more common diseases
- Financial burden/cost of care/insurance coverage, which are often complicated by missed diagnoses, duplicative testing, and difficulties getting insurance coverage
- Navigating the healthcare system and support for isolated patients
- Effective symptom management and using symptoms or clusters of symptoms to develop a phenotype for rare disease patients
- Research challenges in the rare disease space

Update on PCORI's Rare Disease Portfolio

Gyasi Moscou-Jackson, PhD, MHS, RN, Program Officer, Healthcare Delivery and Disparities Research, and Amanda Ruesch, MPH, Program Assistant, Office of Chief Science Officer, offered an update on PCORI's

Rare Disease Portfolio. PCORI uses NIH's definition of a rare disease: a condition that affects less than 200,000 in the United States.

Dr. Moscou-Jackson explained that since 2012 PCORI has invested 87 million for 32 studies in the rare disease space and funding in this area is directly influenced by RDAP. Funding for rare disease research spans PCORI's national funding priorities, with two-thirds of the research portfolio clinically focused on assessment of prevention, diagnosis, and treatment options and smaller amounts going to communication and dissemination research, addressing disparities, methods and improving health care systems. Two methods projects looked at rare disease in general, rather than specific conditions. One third compared active interventions, and two thirds were randomized controlled studies (RCTs) with sample sizes of more than 250 patients. About half of the studies use registries or some other network to recruit research subjects or as a data source. The studies looked at rare diseases in both adult and pediatric populations, and six studies focused on parents/caregivers. As of September 2019, 10 rare disease studies have been completed and an additional 6 are undergoing the PCORI peer-review process.

Fourteen studies have looked at topics considered crosscutting, including: shared decision making (tools and process), self-management interventions, healthcare service delivery models, and. transitional care models. Three method studies looked at self-phenotyping, patient and caregiver engagement in guideline development, and effective research designs for small samples.

Looking at primary outcomes in RDAPs priority areas, Dr. Moscou-Jackson reported that only three studies focused on quality of life (an RDAP priority) as a primary outcome, and just two studies that looked at a psychosocial outcome; she considered both areas are room to grow. She noted that caregiver outcomes (satisfaction and quality of life)—also a priority area mentioned by RDAP—are often included in studies, but as a secondary rather than primary outcome.

Dr. Nora McGhee, PhD, Senior Manager, Office of the Chief Science Officer, noted that other types of outcomes—especially quality of life indicators—are often included as secondary outcomes, which were not included in the analysis presented.

Ms. Ruesch reported on the lessons learned from 10 completed PCORI research studies. She based her presentation on information gleaned from structured conversations and surveys of PCORI program staff on barriers and facilitators to conducting comparative effectiveness research projects within the rare disease community. She noted that many of the issues identified by the program staff were similar if not the same as those that come up when researching common diseases, but solutions may require a different approach in rare diseases.

Some of the lessons learned included:

- Experienced investigators increase study success; familiarity with the field and clinicians helped facilitate study completion.
- Varying levels of engagement with the clinician and patient communities at study sites can influence success.
- Delays in developing interventions and slow recruitment that can affect the study's timeline.

- Incomplete adherence (especially in medication studies) or outside barriers (especially in internet interventions rural areas) and missing data challenge study completion.

Ms. Ruesch pointed out that the analysis so far has included only PCORI-funded research studies. PCORI has also made 50 engagement awards for rare diseases, including 8 projects and 42 conferences.

RDAP made the following recommendations:

- Consider alternatives to RCTs for ultra-rare diseases, given the challenges of randomization of small patient populations for which there are limited treatment options. Single-arm trials, natural history studies and leveraging data from multiple databases may help fill research gaps.
- Instead of looking at one disease, identify issues that crosscut multiple rare diseases to facilitate recruitment and faster results.
- Revisit past study proposals that might have good ideas but didn't get funded.
- Involve patients and caregivers early in study development to ensure that research questions and study structure address their concerns and keep them engaged throughout the study.
- Evaluate the impact of completed study care on delivery, insurance coverage and other factors to ensure that funded research is achieving the desired impact.
- Consider the impact of unique challenges of the placebo effect and defining endpoints and usual care for conditions that do not have clear treatment options.
- Consider longer study periods to ensure that outcomes important to patients can be measured in the allotted time.
- Review studies with well-identified patient-reported outcomes to detect best practices
- Partner with other organizations on investigations into the burden of illness and the cost of treatment with the goal of telling a compelling story that can influence payers on what treatments they cover.

PCORnet Rapid Cycle Research Opportunities

Maryan Zirkle, MD, MS, MA, Associate Director, Research Infrastructure at PCORI, gave an overview of PCORnet and outlined potential opportunities for studying rare diseases. PCORnet creates infrastructure, tools and policies to support rapid, efficient clinical research using multiple data sources, including electronic health records, insurance claims data, data reported by people, and other sources. The network includes more than 100 different health systems in total, 9 clinical research networks, two health plan research networks, and involves patient partners at all stages.

PCORnet's Rapid Cycle Research Program (RCRP) is a program within PCORnet designed to deliver rapid study results on prioritized, stakeholder-driven topics:

- Descriptive analysis of the data to determine cohorts and help assess study feasibility
- Small, rapid observations studies including analyses that take less than a year and a cost of less than $700,000 each.

Topics for the RCRP can arise from any PCORI stakeholders including staff, stakeholder groups, and strategy committees like RDAP, which go through an accelerated approval process with the goal to progress from idea to results within one year. Six projects have been funded during the past two years, and four have been completed.

Dr. Cheung asked the group to brainstorm ideas for rapid cycle research projects in the rare disease space. In previous panel meetings, the panel has decided the best approach is to ask the question, then determine if the dataset has the information needed to answer it.

Some of the ideas put forth by RDAP included:

- Track symptoms (such as muscle pain), clusters of symptoms or diagnoses, or patterns of usage (many different specialists, multiple ED visits) that may identify people with undiagnosed rare diseases. Consult with payers about how they identify patients for case management/care coordination services to see if their methods can be adapted to identify patients with rare diseases
- Identify patients diagnosed with rare diseases and look retrospectively at length of time and other patterns from presentation of RD symptoms to diagnosis
- Investigate best practices in transitions of care from pediatric to adult or primary care to specialist or specialists, perhaps by looking at how this is accomplished in successful patient-centered medical homes
- Determine if patients with that rare disease are being properly monitored and/or screened for common complications for their disease
- Investigate caregiver burden, which is often higher among those who care for patients with rare diseases
- Look at geographical differences in access to care to see how that compares in relation to population density (urban/rural), region of the country, and proximity to specialized care centers.

Panelist Work Outside the RDAP

To facilitate collaboration among the members of the RDAP, Dr. Cheung asked panel members to quickly explain their work outside of the panel's activities.

- Dr. Cheung has worked with PCORI since 2012 as a medical reviewer after his retirement from the pharmaceutical industry. He's working to form a group of PCORI ambassadors focused on helping to disseminate information about patient-centered outcomes research into rare diseases.
- Marcia Rupnow, MS. PhD, is involved in the research of rare diseases to support the generation of evidence—including patient-reported outcomes and burden of illness—for drugs developed by her company.
- Scott Berns, MD, MPH, a pediatrician, is co-founder of the Progeria Research Foundation which he founded with his wife (a basic scientist) in 1999 after his son was diagnosed with the condition.

Berns is also CEO for the National Institute of Children's Health Quality, an independent nonprofit has 17 grant-funded projects on complex issues in children's health.

- Stephen Mathai, MD, is a clinical researcher and has a clinical practice in pulmonary hypertension, focusing on a rare subtype called pulmonary arterial hypertension, a complication of several rare diseases including scleroderma and idiopathic pulmonary fibrosis.
- Tilicia Mayo-Gamble, PhD, MPH, MA, is a community engagement researcher whose husband has sickle cell beta thalassemia. Dr. Mayo-Gamble's worked on a PCORI engagement award and is now working on a project to train community health workers to increase access to sickle cell care for people in rural areas.
- Vanessa Boulanger, MSc, is Director of Scientific Research at the National Organization of Rare Disorders (NORD) and is currently working with the FDA to increase efficiencies in clinical trials and speed up the data collection and approval process for new drugs.
- Julie Abramson is a rare disease patient who has experience with Patient-Powered Research Networks (PPRNs), patient registries and clinical studies of rare diseases.
- Kathleen Gondek, MS, PhD, currently Vice President of Global Health Economics Outcomes Research and Epidemiology at Shire, has worked to develop treatment options for several different rare diseases.
- Sira Sultan, JD, is a lawyer by training and consultant to patient groups with a variety of conditions (including non-rare conditions) as well as founder of The Haystack Project, an organization that gives voice to the experiences of people with rare diseases.
- Julie Gortze, RN, is a rare disease patient who has built on her personal and professional experience (as a nurse) to create a rare disease nonprofit based in New England.
- Naomi Aronson, PhD, Executive Director of Clinical Evaluation, Innovation, and Policy at the Blue Cross Blue Shield Association, developed the clinical evaluation and assessment programs to review the evidence for policies that BCBS groups use to determine medical necessity.
- Sherene Shalhub, MD, MPH, is a vascular surgeon specializing in genetically triggered vascular diseases and the heritable dimensions of vascular diseases.
- Maureen Smith, MEd, volunteers for the Canadian Organization of Rare Diseases as well as other international organizations looking at rare diseases. Diagnosed with a rare disease when she was eight years old, she has been very involved in advocacy work for 20 years.
- Roxanna Bendixen, PhD, MS, is a researcher focused on Duchenne muscular dystrophy who serves on the Cooperative International Neuromuscular Research Group that has conducted clinical trials primarily focused on outcomes subject to change and has a special interest in sleep disorders.
- Cindy Luxhoj, MUP, left the Alagale Foundation in September 2018 but continues to follow their work which includes a comprehensive medical records review of Alagalle patients globally, a partnership to look at novel therapies, and a PCORI conference award to hold a research roundtable between families and researchers.

Future Planning

Dr. Cheung urged committee members to think about what would make the biggest difference in terms of cross-cutting research ideas and what the panel should focus on at the next meeting. Ideas generated by the panel included:

- **Outcome selection and measurement:** Organize a panel presentation of PCORI's work on outcome selections and measurement.
- **Issues of access:** Identify successful interventions to improve access and to explore how health plan research network representatives generate or evaluate evidence.
- **Common symptoms in rare diseases:** Look at common symptoms across rare diseases (itching, sleep disorders) that affect burden of disease, how to measure and identify effective approaches to diagnosis and treatment.
- **Challenges of CER in RD populations:** Look at successful studies and identify methods and approaches that work with PCORI's budget and time frame.

Conclusions

Co-chair Cindy Luxhoj recognized panel members whose terms expire with this meeting, including Dr. Cheung, chair of the panel, Maureen Smith, and Dr. Kathleen Gondek.

Dr. Chueng summarized the day's presentation and discussions. The main messages were:

- Although each patient and caregiver journey is unique, common themes emerge from telling individual stories and these can help identify crosscutting research ideas that can improve lives.
- The panel recognized but was not discouraged by the difficulty of research in the rare disease community and remined committed to impact more people even with a limited budget.
- By collaborating with other organizations—both those represented on the RDAP and beyond—RDAP can ensure that research remains focused on the needs of patients and caregivers and answers the questions of greatest interest to them.
- The next step will be to reconcile the panel's many ideas with existing efforts and rank them to continue the important work that has already begun.