Internal Thematic Meeting Summary

Advisory Panel on Rare Disease (RDAP) Virtual Meeting: Winter 2021

December 13 & 14, 2021

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Overview

The Patient-Centered Outcomes Research Institute (PCORI) hosted a virtual two-day winter meeting for the Rare Disease Advisory Panel (RDAP). On Day 1, two panel members shared their diagnostic odysseys and experience in rare disease multi-stakeholder research. PCORI shared an update on its rare disease portfolio and proposed research agenda, in alignment with the strategic plan. The day concluded with a round-robin brainstorming session around the changes the panel members would like to see in rare disease research. On Day 2, PCORI presented its new horizon scanning tool and database. The panel members then discussed critical issues in the rare disease community for PCORI's consideration. Finally, the RDAP Chair and Co-Chair thanked the panel members and adjourned.

Day 1

Welcome, Introductions, and Setting the Stage

- Mat Edick, PhD, Chair, Advisory Panel on Rare Disease
- Doug Lindsay, BS, Co-Chair, Advisory Panel on Rare Disease
- Carly Khan, PhD, MPH, RN, Associate Director, Healthcare Delivery and Disparities Research

Mat Edick and Doug Lindsay introduced themselves and welcomed the panel to the meeting. They reviewed housekeeping items and provided an overview of the meeting agenda. Following the welcome, each PCORI Rare Disease Advisory Panel member introduced themselves. Next, Carly Khan, Associate Director of Healthcare Delivery and Disparities Research at PCORI, gave a brief summary of program updates. Three new engagement awards had been funded since the last RDAP meeting, two focused on osteogenesis imperfecta and one on capacity building for the rare disease community. Khan noted nominations for new RDAP members is open through March 2022. Additionally, the next PCORI Annual Meeting is scheduled for October 26-28, 2022.

RDAP Speakers: Experience with the Patient and Caregiver Journey from Diagnosis to Treatment and Beyond

- Sarah Bacon, MS
- Danielle Boyce, MPH
- Doug Lindsay, BS, Co-Chair, Advisory Panel on Rare Disease

Lindsay introduced the two RDAP speakers, Sarah Bacon and Danielle Boyce, who were invited to share their rare disease journey as a patient or caregiver, from diagnosis to treatment, and the impact it has had on them.

Bacon gave a presentation titled, “Living with Zebras” which described her odyssey as a rare disease patient with lymphangioleiomyomatosis, or LAM. LAM is a progressive, estrogen sensitive disease found in women and often diagnosed during pregnancy or labor. Bacon’s primary care provider (PCP) had missed the signs of LAM for many years, noting that her symptoms were initially misdiagnosed as pleurisy, before a pulmonologist correctly identified them as LAM.

Bacon became an advocate for herself and for research into novel LAM treatments, and in doing so, encountered tension between two LAM advocacy groups. These politics meant that certain doctors were not recommended if they were not part of an advocacy network which may negatively impact treatment accessibility for patients with LAM.

When Bacon began working with Dr. Jeanine D’Armentio, who was conducting research into a new treatment for LAM, she discovered she could raise funds for early-stage research that could open the door for additional grants. As a champion for herself and the rare disease community, Bacon also published articles speaking out about the ramifications of National Institutes of Health (NIH) budgets cuts that had been proposed in 2013. The NIH is the largest funder of rare disease research, since biotech and pharmaceutical companies focus on diseases with larger patient populations; budget reductions would undercut progress in the NIH rare disease research portfolio.

Bacon also engaged in advocacy efforts with Congress, participating in Rare Disease Week in Washington, DC, and lobbying lawmakers to pass bills that support the rare disease community such as the Open Act and 21st Century Cures Act. She also noted her participation in global conferences, bringing a patient perspective to these conversations.

Next, Boyce presented on her rare disease odyssey as a caregiver to her son Charlie, who was diagnosed with infantile spasms when he was ten months old. She connected with other parents experiencing similar journeys through the Infantile Spasms Community Forum and continues to be involved with this community to share information about symptoms, diagnoses, and treatments, as well as for support. Boyce became involved in the rare disease advocacy space as a researcher and Principal Investigator (PI), as well as a speaker. She shared advice for people engaged in multi-stakeholder research, drawing from her experience as a researcher and parent, on how to engage with patients and families in the research process. As a caregiver, her advice to researchers and clinicians centered on the following points:

- Patients, caregivers, and advocacy group staff bring different perspectives
- Engage early, often, and meaningfully
- Consider our lifestyle and accommodate accordingly
- Don’t assume we won’t be interested in scientific programming
- Support the un- and under-diagnosed
- Develop patient reported outcomes (PROs) for people with intellectual and developmental disabilities

- Include caregivers and siblings when evaluating outcomes

Boyce notes her son is doing well and shared her email, encouraging panel members to contact her if they have questions.

Discussion

Lindsay thanked the presenters for their compelling presentations and opened the discussion to the panel. Below, the panel members' comments are summarized by them:

COVID-19

Lindsay asked the panelists if they would like to give an update on their odyssey. Bacon shared that her health has improved during the COVID-19 pandemic. She attributes her progress to the lack of travel and minimal exposure to more common illnesses such as the common cold and the flu.

Another panel member underscored the importance of studying the effects, positive and negative, of COVID-19 on rare diseases, and collecting these stories to inform telehealth decisions as the pandemic continues.

Diagnosis and treatment

Bacon shared that in her search for therapies and treatments, she experienced some benefit using MDMA guided therapy to treat her trauma and anxiety. Bacon is training to become a guided therapist herself to help others reframe and overcome their anxiety.

Boyce shared that throughout her odyssey with her son, she experienced conflicting opinions and treatment plans from different doctors, even within the same hospital. She now confides in her community more than in researchers and physicians.

One panel member asked to hear the presenters discuss the moment they received their diagnosis, and how diagnoses can be shared more optimally. Boyce noted that Charlie's diagnosis was shared very casually, and that until a formal conversation with the medical team could occur, she began her own research online which was detrimental to her mental state. Bacon shared that her primary care provider and first pulmonologist missed LAM because they had never seen it before, and thus weren't expecting it, and didn't know where to look. She proposed the creation of a digital network for frontline providers, including PCPs and pediatricians, to query to improve the diagnosis timeline.

Boyce shared that due to the prolonged time to diagnosis and diagnostic uncertainty of rare diseases, research and treatment should be trauma informed.

Genetic testing

One panel member shared their experience being a person with sickle cell anemia and the difficulty finding treatments and therapies for certain genotypes. They noted they are unable to use most drugs developed to treat sickle cell anemia due to their specific disease genotype and that studies focused on rare genotypes within rare diseases are needed.

Another panel member asked how physicians can better communicate with insurance providers to provide rationale for something like genetic testing for a rare condition should be covered. Boyce offered that genetic testing is important because certain medications can be contraindicated for specific mutations. She has found success working directly with a testing company to explore coverage options and also noted many research studies include genetic testing, so study participation may also be a way to access and or finance testing.

Family

A panel member emphasized Boyce's point about including siblings in outcomes-based research projects. Boyce shared in response that she wrote a children's book titled, *Charlie's Teacher* that helps explain to young siblings why children with rare diseases receive special treatment. Boyce also shared a resource called the Sibling Support Project that focuses on this population.

Insurance

Bacon shared that her biggest insurance headache is around medical devices. Her strategy has been to publish complaints and stories on social media, and to report them to the Better Business Bureau and to Department of Commerce.

Another panel member shared they would like to see more insurance companies included in multi-stakeholder conversations around rare disease. Communicating with these companies could help patients understand what requirements and documentation are needed for insurance to cover the cost of a treatment or test.

Discussion: PCORI-Funded Rare Disease Portfolio Update

- Nora McGhee, PhD, Senior Program Officer, Clinical Effectiveness and Decision Science
- Carly Khan, PhD, MPH, RN, Associate Director, Healthcare Delivery and Disparities Research
- Rohini Mohanraj, MHA, Program Associate, Research Infrastructure
- Doug Lindsay, BS, Co-Chair, Advisory Panel on Rare Disease

Nora McGhee and Rohini Mohanraj gave an update on PCORI's Rare Disease portfolio. PCORI has awarded $108 million in funding across 34 rare disease studies and another $4 million for four methods studies. Mohanraj shared a slide listing the different rare disease studies that had

been funded noting several addressed sickle cell disease, acute myeloid leukemia (AML), and cerebral palsy, while 19 others each addressed a different rare disease. Finally, Mohanraj noted nine studies focused on cross-cutting research topics to include shared decision making, patient self-directed care, and health service delivery models.

Next, Khan shared a few study profiles to provide examples of the CER studies focused on rare diseases. The first study developed tools and information to guide patients' choice of therapies in older and medically frail patients with AML. The second study profile compared the effectiveness of different treatment strategies for polyarticular idiopathic arthritis. McGhee closed their presentation by posing the following three questions to the advisory panel members for discussion:

- What are your reactions to the balance of the portfolio? What would an ideal balance look like to you?
- Are there other aspects of PCORI's CER and Methods research portfolio that you would like further information on?
- What topics (excluding specific diseases) can be addressed by CER that are not being covered?

Discussion

Application process and assistance

One member asked PCORI to share the rate of rare disease projects funded and how that rate compares to PCORI's overall funding rate. Khan was not sure and noted they would get back to the panel about this.

A panelist suggested creating an opportunity for investigators to discuss potential research projects with program officers to understand if their study would be appropriate for a PCORI funding opportunity. Further, this member noted a question could be added to the funding application which asks if the investigator has met with a program office to discuss the project. They cited this would not only benefit investigators but could yield more promising proposals for rare disease research funded by PCORI. Khan and McGee discussed the PCORI funding announcements, both investigator-initiated and targeted, are carefully written to include details of what PCORI wants to see in a given project.

One panelist asked if PCORI has a process to guide applicants in engaging patients throughout the research process.

Portfolio balance and additional topics of interest

Citing the portfolio of PCORI-funded rare disease projects discussed earlier in the presentation, one member requested more information about how PCORI groups various rare diseases into

broad categories and further, if there are certain categories that need more attention or research. McGhee shared that PCORI is open to a variety of disease areas and more broad groups. McGhee understands that many people have particular diseases they would like to see research in, and PCORI is looking for more general advice. Khan elaborated that PCORI is also open to hearing other ways of thinking about the portfolio in ways that would be the most informative to the community.

Adding on to the question of rare disease categories, another member asked if there are gaps in the rare disease portfolio where PCORI has not received enough applicants or strong enough applications that should be the focus moving forward. A PCORI staff thanked the panelist for their question and noted an interest in not only focusing on single rare diseases, but perhaps more on cross-cutting issues that impact the rare disease community more broadly.

Another panel member suggested that PCORI fund research on resource utilization management and engaging the payer perspective in rare disease treatment. They added that research on telehealth, comparing healthcare experiences before and during the pandemic, can inform telehealth policy and coverage moving forward.

A second panel member also underscored the need to better understand how to leverage telehealth to improve access to treatments and therapies.

One panel member suggested that PCORI might look at the impact of delayed diagnosis or misdiagnosis. They also suggested ophthalmology as a disease group that could be highlighted, citing that the FDA approved the first gene therapy for retinal disease in 2021.

A panel member suggested that PCORI could fund the evaluation of methods used to conduct research among children and adults with intellectual and developmental disabilities. They noted it's difficult to conduct traditional research with these populations because the methodological tools aren't suitable for them.

Another panel member described an opportunity to expand disparities research to rural populations, citing the example that many clinical trials for rare diseases occur in major cities. They also shared that there is an opportunity to examine health care cost and access disparities based on state Medicaid waiver status.

A panel member also highlighted funding research that examines the effectiveness of newborn screening, which is currently underfunded in the United States and could create opportunities to identify rare diseases before any symptoms present. They also mentioned funding research in healthcare access disparities focused on vulnerable populations.

A panel member suggested that PCORI look for ways to support existing rare disease community groups as a way of balancing the disease portfolio.

Another panel member expressed a need to fund natural history studies for rare diseases, which PCORI doesn't currently fund. They suggested PCORI partner with other organizations to

create this knowledge base. They pointed out that many of PCORI's funded projects were for diseases where there is known natural history, which is not the case for most rare diseases.

Strategic Planning: Proposed Research Agenda

- Marina Broitman, PhD, Associate Director for Peer Review, PCORI

Marina Broitman provided an overview of PCORI's proposed research agenda and framework for achieving the National Priorities for Health. The National Priorities for Health serve as ambitious long-term goals to guide PCORI's funding of patient centered CER and other engagement infrastructure initiatives. There are five priorities that contribute to improving patient-centered health:

- Increase evidence for existing interventions and emerging innovations in health.
- Enhance infrastructure to accelerate Patient Centered Outcomes Research (PCOR).
- Advance the science of dissemination, implementation, and health communication.
- Achieve health equity.
- Accelerate progress toward an integrated learning health system.

The PCORI Research Agenda provides a framework for achieving progress on the National Priorities for Health. The agenda is comprised of six statements that all begin with "fund research that," to emphasize the connection to funding CER specifically. Those statements are:

- Fund research that fills patient- and stakeholder-prioritized evidence gaps and is representative of diverse patient populations and settings.
- Fund research that aims to achieve health equity and eliminate health and healthcare disparities.
- Fund research that builds the evidence base for emerging interventions by leveraging the full range of data resources and partnerships.
- Fund research that examines the diverse burdens and clinical and economic impacts important to patients and other stakeholders.
- Fund research that focuses on health promotion and illness prevention by addressing health drivers that occur where people live, work, learn, and play.
- Fund research that integrates implementation science and that advances approaches for communicating evidence so the public can access, understand, and act on research findings.

Broitman concluded the presentation by sharing illustrative examples for each of the Research Agenda statements to provide further context.

Discussion

Broitman opened the dialogue for panelists to respond to four discussion questions:

1. How might the proposed Research Agenda meet future needs for PCORI's strategy of funding CER?
2. How could the proposed Research Agenda support a research portfolio that is inclusive of this panel's topics of interest?
3. Is there an important research area that you would like to see better reflected in the proposed Research Agenda?
4. What kinds of research portfolios will be important to support the specific Statements?

Current funding and data sources

A panel member expressed confusion by the statement, "fund research that builds the evidence base for emerging interventions by leveraging the full range of data resources and partnerships" noting it felt counterintuitive to leverage data resources and partnerships if there is no existing evidence base for emerging and novel interventions.

Supporting rare disease research

One panel member suggested the Research Agenda can support rare disease research by funding the development of an infrastructure, or a structured mentorship program, to support rare disease organizations in submitting grant proposals. They noted that many of these organizations are small and thus do not have the capacity to engage in the PCORI grant process. Another panel member expanded on this idea by suggesting that there should also be an infrastructure to foster training for researchers who want to participate in rare disease research and engage with rare communities.

A couple panel members agreed that a related issue is the lack of continuity in rare disease research and engagement funding. One member noted that this is currently happening with the ISAAC study, which is scheduled to lose funding and be disbanded in six months.

One panel member recommended that PCORI consider identifying the rare disease community as an equity group, noting the diagnostic odysseys and barriers to finding effective treatments as health disparities.

Round Robin: Brainstorming Session

- Mat Edick, PhD, Chair, Advisory Panel on Rare Disease

Edick introduced the round robin brainstorming session and reminded participants that the discussion would be used to inform the discussions in Day 2. He asked each panelist to describe the changes they wished to see in rare disease research. Below is a summary of RDAP members' discussion by theme.

Improving availability of rare disease data

A panelist expressed that electronic health records (EHRs) should regularly capture data elements specific to rare disease (e.g., genetic variants) so that this data can be easily

integrated into natural history studies and other rare disease research projects. They noted that improving the data interoperability has a lot of potential benefits and could lead to cost savings.

Genetic Testing

A panel member suggested advocating for genetic testing in rare disease patients because it can facilitate earlier interventions. They stated that with the advances in gene therapy, it is unacceptable for patients to endure incorrect or delayed diagnoses when a clinical trial or treatment options may be available.

Another panel member echoed this idea and added that physicians may not be aware of the different tests available to diagnose rare diseases. They suggested using EHR technologies to prompt these tests.

One panel member noted that awareness of rare disease testing should be spread by companies that sponsor genetic testing because they have a commercial interest in diagnosing rare diseases and selling gene therapies. They suggested that PCORI, or another institution, fund a database that allows providers to search symptoms of rare diseases and off-label uses for prescription drugs.

A panel member agreed with the above ideas. They noted that it is important to continue building the groundwork of rare disease research.

Another panel member agreed and suggested that the rare disease community spend more time and energy making connections with payers.

Funding other rare disease research designs

One panel member expressed confusion about why PCORI does not fund natural history research, because it has a direct bearing on the methodologic and CER missions of the Institute. They noted that many patients who participate in natural history studies are the same rare disease patients who also participate in effectiveness trials and infrastructure projects. They shared that this could lead to burnout of the patient population, and therefore, researchers should maximize the overlap between these research stages, as well as improve information sharing amongst researchers and projects.

Another panel member expanded on this idea and recommended studying the change in natural histories of patients.

A panel member suggested spending efforts in developing better CER trial designs, at least for diseases that are chronic. They noted that many rare diseases cannot get research funding for effectiveness studies because they are statistically underpowered.

Another panel member added that the lack of research funding leads to a dearth of rare disease data, which then further contributes to a lack of funding.

An additional panel member added that there is also a lack of data in the transition period for rare disease patients because the system does not follow them after receiving a treatment.

Health Literacy

One panel member encouraged more investment in health literacy because it is critically important to accessing health care.

Acknowledgements and Recap

- Mat Edick, PhD, Chair, Advisory Panel on Rare Disease
- Doug Lindsay, BS, Co-Chair, Advisory Panel on Rare Disease

Edick thanked the panel and presenters for a productive meeting and made special mention of the PCORI staff who assisted with the planning and execution of the meeting. He noted that PCORI is very willing to support rare disease research and is looking to the RDAP to help them decide how.

Day 2

Welcome and Setting the Stage

- Mat Edick, PhD, Chair, Advisory Panel on Rare Disease
- Doug Lindsay, BS, Co-Chair, Advisory Panel on Rare Disease

Edick and Lindsay welcomed the RDAP members to Day 2 of the Winter Virtual Meeting. They reviewed housekeeping items and introduced speakers for the first presentation.

Monitoring Evidence in Rare Diseases: Health Care Horizon Scanning

- Gowri Raman, MBBS, MS, Senior Program Officer, Office of the Chief Engagement and Dissemination Officer
- Doug Lindsay, BS, Co-Chair, Advisory Panel on Rare Disease

Gowri Raman presented on the new technology program and products that are used to monitor and assess evidence in rare disease research. Raman described products used for short-term, medium-term, and long-term monitoring. For short-term monitoring, PCORI produces emerging technologies and therapeutics reports which focus on five key disease topics, including rare diseases.

Raman then described PCORI's new healthcare horizon scanning system, launched in November of 2021, which is used to identify and monitor healthcare innovations before they enter the market and then flag those which have the highest potential for disruption to the current standard of care. These activities are intended to guide PCORI's future research investment

decisions. PCORI's horizon scanning system includes patient and caregiver perspectives in addition to clinical, healthcare system, and research perspectives. Once an initial list is produced based on a scan of the published literature, stakeholder comments are solicited to rank each topic which are incorporated into a database. Reports of high potential disruption are published twice a year.

This database appears on the front page of the PCORI website and is searchable by topic area and key word; an archive will be created as interventions are withdrawn or fail during the pre-market stage. Individual topics and searches are exportable to a CSV file. Raman then shared an example of how to navigate the database.

Finally, Raman presented PCORI's emerging technologies and therapeutics report. This report combines published studies and grey literature to examine interventions in the development pipeline, and findings are presented in visual charts. Raman then concluded their presentation and opened the floor for panelist questions and discussion.

Discussion

One panelist opened the discussion by asking for clarification on what was considered "grey literature." Raman noted they define grey literature as information from sources such as the FDA website, clinicaltrials.gov, and investment and marketing websites that aren't in traditional journals and noted that specific lists are included in the methodology report.

Intended Use and Audience

One panel member asked Raman to clarify how this horizon scanning tool is linked to PCORI's typical funding mechanisms. Raman responded that this database could assist in comparative effectiveness research by identifying early clinical trial results. Raman's colleague, William Lawrence, elaborated that horizon scanning can impact decisions PCORI makes regarding future research by identifying emerging areas of focus and where there may be evidence gaps. Raman shared that the purpose of horizon scanning is to improve evidence generation.

A panel member asked how often the database is updated. Raman clarified that PCORI's vendor is continuously updating the database, noting that the updates are reviewed by an internal PCORI team before being made live within the searchable database. PCORI does monitor site analytics to understand which reports receive the most traffic, and where users are based.

Another panel member commented that they believe this will be a useful tool and clearinghouse for information that organizations and providers who do not have the resources to complete this level of horizon scanning can use.

One panel member asked PCORI to clarify the intended audience for this tool. Raman described that the database is evolving and is currently being shared through advisory panel meetings, however there are newsletter articles, presentations, press releases, and social media outreach efforts planned for the near future. Raman noted the target audience is PCORI staff as well as

patients and caregivers. The panelist reiterated the importance of defining an audience at the outset to use resources most effectively and efficiently. Lawrence agreed that this is a point for PCORI to focus on. McGee added that the panel members could share this resource with their circles as another dissemination route. The database can be used on a mobile platform, so it is accessible to people across platforms and devices.

Critical Issues in the Rare Disease Community

- Mat Edick, PhD, Chair, Advisory Panel on Rare Disease

Edick introduced the following two prompts used to inform the discussion of critical issues in the rare disease community and reminded participants that this session should be used to generate questions for PCORI from the rare disease community.

- What else can PCORI do to meet the needs of the rare disease community and what aspects of foundational work might not be addressable within the existing engagement funding mechanisms?
- Are there any ideas or thoughts on partnering with outside agencies and organizations, to bridge gaps, to get ready for CER?

Additional research needs and topics

A panel member suggested developing a "PCORI Boot Camp" that would educate non-profits and other organizations about submitting grant proposals. Another panel member agreed with this idea and added that there could also be a mentorship component or direct program training that validates rare disease research as a career. An additional panel member also expressed support for a boot camp and noted that PCORI needs to work with people who regularly engage the rare disease patients that the Institute is trying to reach. They noted that a boot camp could shed light on where the disconnect is between PCORI engagement awards and the stakeholder community. Karen Martin, Director of PCORI's Engagement Awards, introduced herself and asked clarifying questions about the boot camp recommendation: would it be a boot camp for performing research, about strictly engagement, or both? The panelist shared that they envisioned a training that would prepare organizations to submit a PCORI grant application. Another panel member expanded on this vision to include a walkthrough of successful and failed grant applications. A third panel member had a slightly different vision of the boot camp which involved career mentorship opportunities. An additional panel member supported their vision and noted that it would be important to make space for investigators that want to learn more about engagement at PCORI.

A panel member suggested that PCORI uses the Institute's existing framework to engage payers with the rare disease community. Another panel member agreed and provided anecdotal support that payers are often confused about why they are asked to participate in discussions

with rare disease populations. An additional panel member noted that the medical policy services staff at Blue Cross and Blue Shield Association are making efforts to educate their plans on particular issues with respect to rare disease research.

A panel member recommended developing a database or online resource that would be constantly updated which helps rare disease patients to locate experts that are doing research or treating the rare disease of interest.

Several panelists expressed interest in more regular meetings to discuss the topics presented during this Winter Meeting.

Partnerships with agencies and organizations

One panelist noted that the National Center for Advancing Translational Sciences (NCATS) seems to be a natural collaborator with PCORI.

Another panel member explained that their organization has a collaborative of institutions that primarily focus on research, and they partner together and then try to partner with larger funders, like NIH or PCORI. They suggested looking for different models within groups of researchers that are trying to bring their studies to larger populations and then create collaboration there.

A panel member asked existing partnerships with PCORI. McGhee and Khan noted that PCORI currently partners with the Association for Medical Imaging Management, the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Critical Path Institute (CPATH).

A panel member asked what PCORI envisions these new partnerships will look like. McGhee noted that PCORI wants to identify how they can help research areas that are not necessarily ready for CER. They also stated that new partnerships could be either independent or joint funding ventures for new projects.

Acknowledgments and Recap

- Mat Edick, PhD, Chair, Advisory Panel on Rare Disease
- Doug Lindsay, BS, Co-Chair, Advisory Panel on Rare Disease

Edick, Lindsay, and PCORI staff thanked the panelists for a productive discussion over the last two days. They reminded attendees they would be receiving an email with a post-meeting survey and concluded the meeting.