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

Day 2 - December 14, 2021

Mat Edick, PhD
Chair, RDAP

Doug Lindsay, BS
Co-Chair, RDAP

RDAP PCORI Staff Team

- Carly Khan, PhD, MPH, RN
- Nora McGhee, PhD
- Fatou Ceesay, MPH
- Meghan Berman, MPH
- Rohini Mohanraj, MHA

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RDAP Chairs

Mat Edick, PhD
Chair, Advisory Panel on Rare Disease
Director of the Center for Strategic Health Partnerships, Michigan Public Health Institute

Doug Lindsay, BS
Co-Chair, Advisory Panel on Rare Disease
Personal Medical Consultant and
Founder of Doug Says LLC.

Housekeeping

- Please note that today's webinar is being recorded for posting on PCORI's website.
- Members of the public are invited to listen to the teleconference and view the webinar.
- Meeting materials can be found on the PCORI website. The recording of the webinar will also be made available to the public after this event.
- Anyone may submit a comment through the webinar chat function.
  - No public comment period is scheduled

Please visit www.pcori.org/events for more information.

COI Statement

Welcome to the Rare Disease Advisory Panel Winter 2021 virtual meeting.

I want to remind everyone that disclosures of conflicts of interest of members of the Advisory Panel are publicly available on PCORI's website. Members of the Rare Disease Advisory Panel are reminded to update your conflict-of-interest disclosures if the information has changed, in addition to completing your annual disclosure. You can do this by contacting your staff representative, Rohini Mohanraj.

Finally, if the Rare Disease Advisory Panel will deliberate or act on a matter that presents a conflict of interest for you, please inform one of the co-chairs so we can discuss how to best address the issue.

Day 2 Meeting Agenda

Start Time	Agenda Item	Presenters & Discussion Facilitator
1:00 PM	Welcome and Setting the Stage	Mat Edick, Doug Lindsay
1:05 PM	Monitoring Evidence in Rare Diseases: Health Care Horizon Scanning	Gowri Raman, Doug Lindsay
1:55 PM	BREAK	
2:05 PM	Critical Issues in the Rare Disease Community	Mat Edick
2:50 PM	Acknowledgments and Recap	Mat Edick, Doug Lindsay
3:00 PM	Adjourn	

Monitoring Evidence in Rare Diseases: Health Care Horizon Scanning

Gowri Raman, MBBS, MS

Senior Program Officer, Office of the Chief Engagement and Dissemination Officer

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Objectives

- Overall: To better understand New Technology products to monitor and assess evidence in rare diseases

- Monitor evidence: Health Care Horizon Scanning products
  - Cloud-based Online Database
  - High Potential Disruption Reports

- Assess evidence: Emerging Technologies and Therapeutics Reports

Evidence Monitoring – Balancing Evidentiary Needs

Horizon scanning reports
Emerging technology reports

Systematic reviews
Focused observational research

Phased trials (up to $22M)
Large pragmatic studies (up to $10M)
Broad research studies (up to $5M)

Time to Complete: Less than 1 year | 1-2 years | 3-7 years

D&I and engagement activities occur throughout timeline
Stakeholders provide input for report and research topics

Monitor and Assess Evidence – Short-term

Health Care Horizon Scanning

- Horizon Scanning of 5 Key Disease Topics
- COVID-19 Supplement

Emerging Technologies and Therapeutics Reports

- Gene Therapy in Cancer
- Artificial Intelligence in Clinical Care
- Proteomics in Cancer and Cardiovascular Diseases
- Next Generation Genomic Sequencing

Horizon Scan Products

Online Database
High Potential Disruption Reports

Overview of PCORI's Health Care Horizon Scanning System (HCHSS)

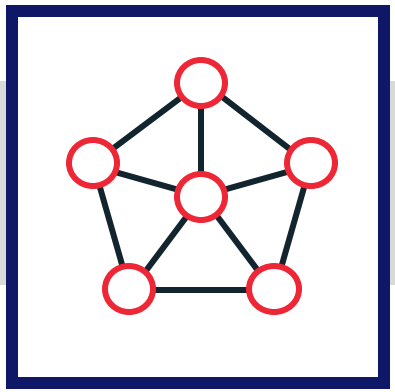
- Description: Early detection system identifying potentially disruptive health care innovations expected to be clinically available in the U.S. within three years
- Purpose: Helps PCORI make decisions about future research investments and serves as a resource for the public and research community
- Six Focus Areas
  - Cancer
  - Cardiovascular Diseases
  - Mental and Behavioral Health
  - Alzheimer's Disease and Other Dementias
  - Rare Diseases
  - COVID-19

What's Horizon Scanning

- Identify and monitor before entering the market.
- Highest potential for disruption to the current standard of care
- With an objective to help a range of stakeholders including PCORI, payers, patients, clinicians, researchers and others

Horizon Scanning

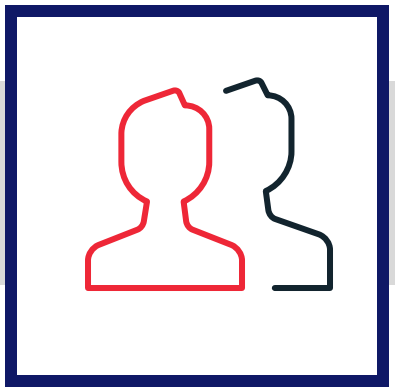
- **Overview of PCORI's HCHSS: Stakeholder Involvement**



Hallmark of HCHSS is the inclusion of patient and caregiver perspectives in addition to clinical, health systems, and research perspectives.

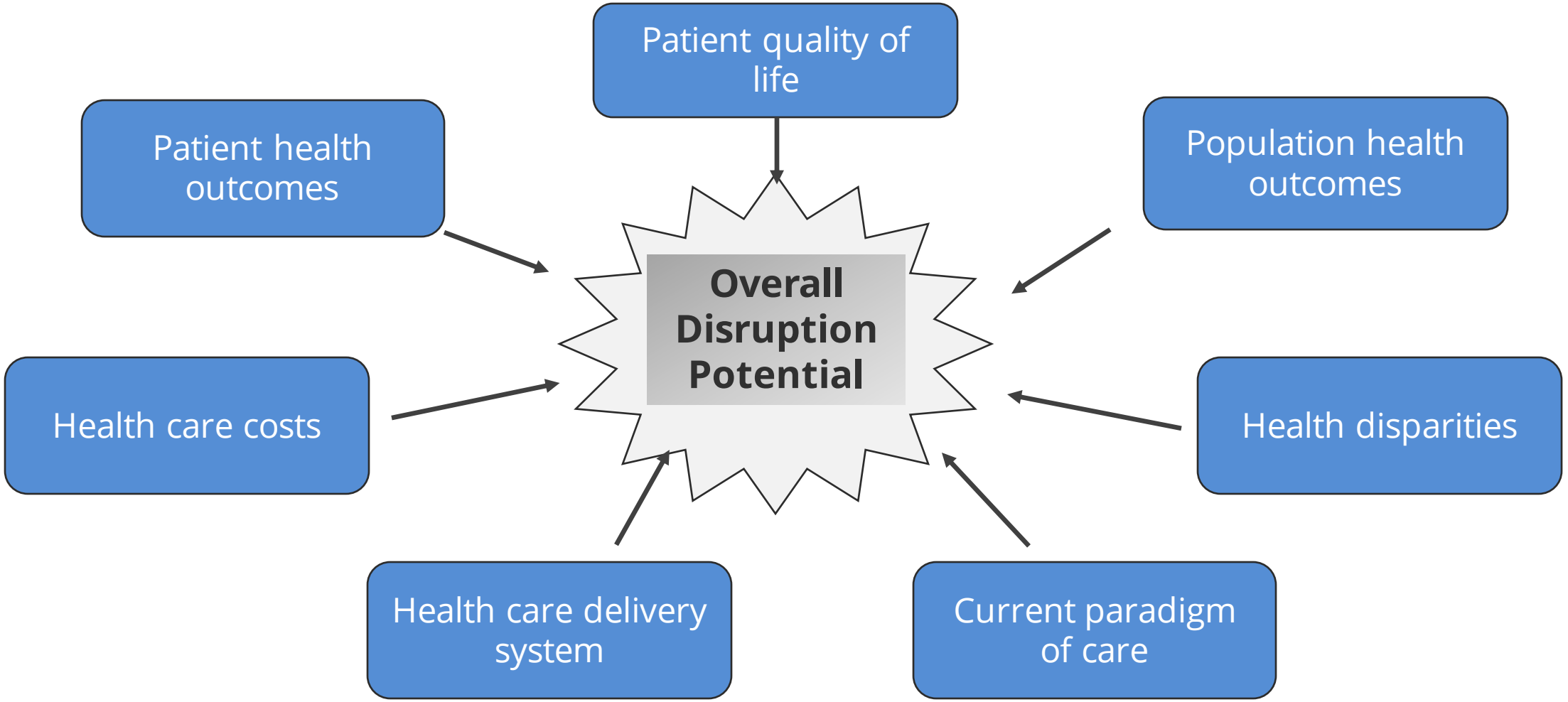
Stakeholders review brief reports and provide feedback based on personal experience and knowledge.

Comments help determine which health care innovations have the highest disruption potential and drive the selection of topics included in a report published twice a year.



Stakeholders also have aided with the design and testing of a searchable cloud-based, horizon scanning database.

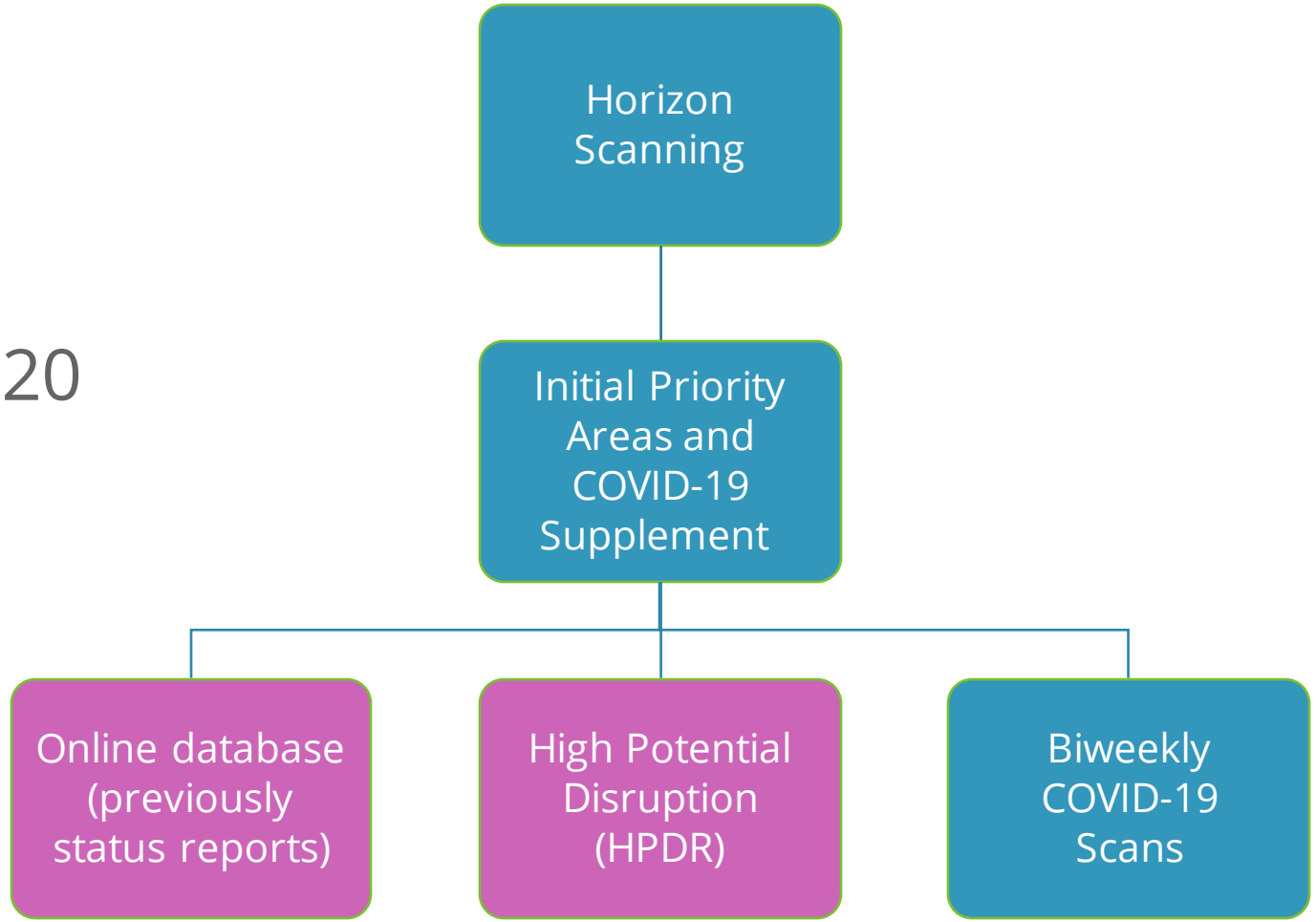
Horizon Scanning: Disruptive Interventions



Horizon Scanning Products

- *Cloud-based Database*
  Soft-launch completed!

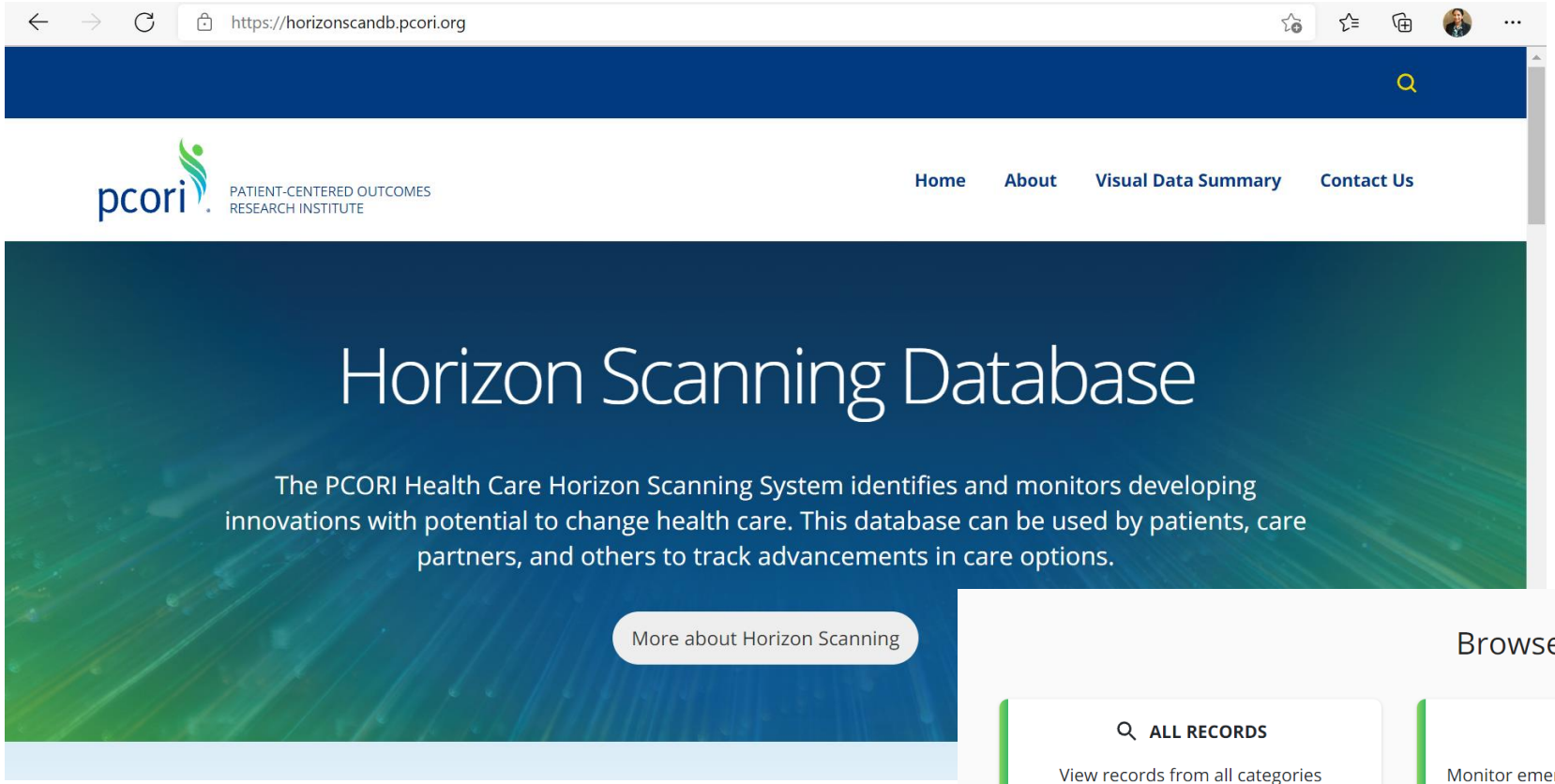
- COVID-19 Supplement – 2020 onwards



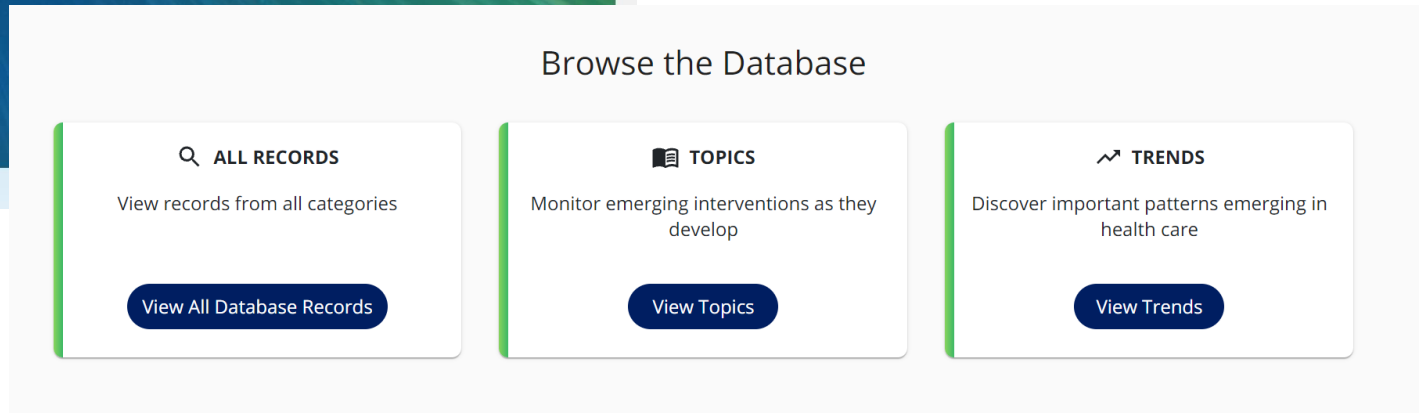
Horizon Scanning Database

From Rare Disease Context

Horizon Scanning Database



[PCORI Horizon Scanning Database]



Horizon Scanning Focus Areas

Alzheimer's Disease and Other Dementias

Cancer

Cardiovascular Diseases

COVID-19

Mental and Behavioral Health

Rare Diseases

Other

Browse the Database

ALL RECORDS

View records from all categories

View All Database Records

TOPICS

Monitor emerging interventions as they develop

View Topics

TRENDS

Discover important patterns emerging in health care

View Trends

Horizon Scanning Database – Rare Diseases

SELECT ALL FOR EXPORT	Title	Clinical Category	Record Type	Horizon Scanning Focus Areas	Updated	Record Status
☐	Fidanacogene elaparvovec (PF-06838435) to treat hemophilia B	Hematology	Topic	Rare Diseases	11/3/2021	Active
☐	Iptacopan (LNP023) to treat paroxysmal nocturnal hemoglobinuria	Hematology	Topic	Rare Diseases	10/7/2021	Active
☐	Bardoxolone methyl (bardoxolone) to treat Alport syndrome	Nephrology	Topic	Rare Diseases	10/5/2021	Active
☐	Leriglitazone (MIN-102) to treat Friedreich ataxia	Neurology	Topic	Rare Diseases	9/29/2021	Active
☐	Ibutamoren (LUM-201) to treat growth hormone deficiency	Endocrinology	Topic	Rare Diseases	9/29/2021	Active
☐	Verdiperstat (BHV-3241) to treat multiple system atrophy	Neurology	Topic	Rare Diseases	9/29/2021	Active

Horizon Scanning Database – Rare Disease Example

Bardoxolone methyl (bardoxolone) to treat Alport syndrome

Jump to Section: Patient | Intervention | Development | Possible Disruptions | Regulatory | Comparators | Outcomes

Patient

Patient Population
Children aged 12 years or older and adults aged up to 60 years with a genetically confirmed diagnosis of Alport syndrome and estimated glomerular filtration rate (eGFR) between 30 and 90 mL/min/1.73 m^2

Health Conditions
Alport syndrome

Health Conditions - Specific
Alport syndrome

Intervention

Intervention Name
Bardoxolone methyl (bardoxolone)

Date Posted
7/26/2021

Updated
10/5/2021

Focus Areas
Rare Diseases

Clinical Category
Nephrology

Key Theme
Treatment models

Horizon Scanning Database – Rare Disease Example (continued)

Intervention Use
Treatment

Intervention Class
Pharmaceutical

Rare Disease?
Yes

Search Tags
bardoxolone

Intervention Description
Bardoxolone methyl (bardoxolone) is an anti-inflammatory drug in development to treat Alport syndrome, a rare, inherited disease.

In Alport syndrome, mutations in genes encoding for type IV collagen change the structure and function of the glomerular basement membrane, the kidneys' filtration system. These mutations cause mitochondrial dysfunction and chronic inflammation, leading to scarring of the kidneys' blood vessels that ends in kidney failure.

No FDA-approved therapies exist for Alport syndrome. Kidney transplantation is potentially curative but is typically limited in availability. Disease management focuses on slowing the rate of kidney damage through diet, limiting fluid overload, and controlling high blood pressure to prevent overworking the damaged kidneys.

Bardoxolone purportedly could preserve kidney function and reduce the need for kidney transplantation. Bardoxolone is an activator of the Keap1/Nrf2 regulatory pathway, which helps resolve inflammation by normalizing mitochondrial function, restoring the oxidation-reduction balance, and suppressing cytokine production.

In clinical trials, bardoxolone is taken as oral capsules at doses of 5 to 30 mg, once daily.

Horizon Scanning Database – Rare Disease Example (continued)

Additional fields include:

- Development
  - Developers
  - Clinical Trial Phase
- Possible Disruptions
- Regulatory
  - Latest Regulatory Event
  - FDA Designations
  - Clinical Trials
  - Regulatory Notes
- Comparators
- Outcomes
- How to cite for that record

Horizon Scanning
High Potential Disruption Report

- Summary of potentially disruptive technologies (~4 pages). Covers the following sections:
  - **Highlights**
  - Patient Population
  - Evidence Development Summary
  - Mfr. And Regulatory Status
  - **Cost Information**
  - **Results and Discussion of Stakeholder Comments**

Tipton et al. Patient and Caregiver Engagement in the Patient-Centered Outcomes Research Institute (PCORI) Health Care Horizon Scanning System (HCHSS) Process. IJTAHC 2020 Dec 15;37:e13.

HPDR – Rare Disease Example

Arimoclomol (BRX-345) to Treat Niemann-Pick Disease Type C

Highlights

- Arimoclomol is an oral small-molecule drug intended to treat Niemann-Pick disease type C (NPC), a rare, progressive disease associated with mental and physical disability in infants and adults. The therapy is meant to amplify the production of heat shock proteins (HSPs) that purportedly rescue misfolded proteins and clear abnormal protein collections, which would improve liposome function and slow disease progression.
- FDA accepted the company's marketing application for the therapy in September 2020 and, in December 2020, updated a previously set decision date of March 17, 2021, to June 17, 2021.
- Stakeholders commenting on this topic thought that, as a disease-modifying drug, arimoclomol might improve patient health outcomes and improve quality of life for patients with NPC.
- Stakeholders thought that arimoclomol might become the standard of care if it becomes the first FDA-approved treatment for NPC.

HPDR – Rare Disease Example

Key Stakeholder Perspectives

Between September 8 and September 18, 2020, eight stakeholders, reflecting clinical, health systems, nursing, and research perspectives, provided comments and ratings on arimoclomol to treat NPC. The list below summarizes key stakeholder perspectives.

- Arimoclomol could meet a large unmet need in patients with NPC and, if the FDA approves it, to become the standard of care as the first approved treatment.
- The 74% reduction in disease progression reported from clinical trials with arimoclomol suggests it might significantly improve patient health outcomes and quality of life. The largest effect is likely to be in patients who begin this treatment early in their disease progression.
- More data are needed to assess whether arimoclomol will increase life expectancy in patients with NPC and how it might compare with off-label treatment with miglustat.
- The health care delivery system is unlikely to change dramatically because of arimoclomol, which would conveniently be taken by mouth at home. However, some health care use, such as hospitalizations, routine follow-up visits, and supportive treatment, might decrease in this patient population.
- Arimoclomol is likely to be expensive, although it might not differ much from the off-label comparator miglustat. Thus, it is unclear whether treatment cost will be significantly disrupted. Overall health care cost might be offset by less use of health care resources (see previous bullet point).

Evidence Assessment

Emerging Technologies and Therapeutics Reports

Emerging Technologies & Therapeutics Reports

Goal

- Provide timely information on new drugs or devices
- Emerging and limited evidence but are already in practice

Purpose

- Evidence summaries intended both to meet information needs and to inform more definitive research

Use

- Provide clarity about available evidence and areas of uncertainty for decision makers

Emerging Technologies & Therapeutics Reports

- Key Steps in the evaluation of a new therapeutics or technology

1. Broad overview of a new technology or therapeutics
2. Systematic search and selection of published studies and grey literature
3. Narrative description of regulatory approvals and uses of intervention
4. Mapping the evidence using interactive visual charts
5. Synthesis of stakeholder input on the issues of use, adoption, etc
6. Identify areas suitable/needing further evidence generation

Emerging Technologies & Therapeutics Reports: An Example

Landscape Review and Evidence Map of Gene Therapy, Part I: Adenovirus, Adeno-associated Virus, and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)

- History of gene therapies
- Description Adenoviral, AAV, and CRISPR Gene Therapy
  - FDA-approved therapies
  - Potential pipeline gene therapies
- Context in which gene therapy is used
- Ongoing premarket and post-market gene therapy studies
- Current evidence supporting gene therapy

Emerging Technologies & Therapeutics Reports: An Example (continued)

Important Issues Raised by Gene Therapy

- Implications of the current level of adoption and future diffusion
- Key issues pertaining to decisional uncertainty
- Potential areas of research focus for PCORI and others

Monitoring Evidence in Rare Diseases: Health Care Horizon Scanning

Thank you! Any Questions?

Gowri Raman, MBBS, MS
Senior Program Officer, OCEDO, PCORI
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For Horizon Scan-related queries, contact us at: horizonscan@pcori.org

BREAK (10 minutes)

We will return at 2:05 pm EST

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Critical Issues in the Rare Disease Community

Critical Issues in the Rare Disease Community

- Time for discussion.

- Prompts will be added on Day 2 of the meeting.

Acknowledgments and Recap

Thank You!

Adjourn