

Update on PCORI

Personalized Medicine Coalition Policy Committee

Joe Selby, Executive Director

February 21, 2019



Overview of Today's Presentation



- PCOR and Personalized Medicine – new directions
- New Evidence Products from PCORI
- Update on PCORI re-authorization efforts
- Q&A

New Directions in Personalized (Patient-Centered) Research and Care at PCORI

Getting More from the Data: One size does not fit all!

(From the Patient-Protection and Affordable Care Act, 2010)



Research shall be designed, as appropriate, to take into account the **potential for differences in the effectiveness of health care treatments, services, and items as used with various subpopulations**, such as racial and ethnic minorities, women, age, and groups of individuals with different comorbidities, genetic and molecular sub-types, or quality of life preferences and include members of such subpopulations as subjects in the research as feasible and appropriate.

What do we mean by Heterogeneity of Treatment Effect?

The variation in how individuals respond to a treatment. This is a vital and yet underexplored concept of importance to regulators, manufacturers, payors, healthcare providers, academic researchers, and patient and consumer advocacy groups.”

Two closely related approaches:

1. Subgroup Differences – analyses in existing datasets (e.g., RCTs may be used for refining clinical guidelines, product development, marketing
2. Predictive Models – require large, heterogeneous populations and may be used to guide individual treatment decisions

PCORI Has Focused on Needs for Subpopulation Evidence Since Inception



- **2011** PCORI-commissioned paper suggested **two main roles for HTE analyses**:
 - (1) to estimate treatment effects in clinically relevant subgroups (subgroup analysis);
 - (2) to predict whether an individual might benefit from a treatment (predictive learning)
- **2012** Three initial cross-cutting HTE methodology standards emphasized pre-specification, rigorous analysis, and transparent reporting
 - Little existing guidance was found for individual treatment prediction.
 - Approaches to determining relevant subgroups were not further examined.
- **2012** PFAs from beginning emphasize addressing HTE in proposed studies

Early PCORI Pilot Project: Reanalysis of the Diabetes Prevention Project (DPP)

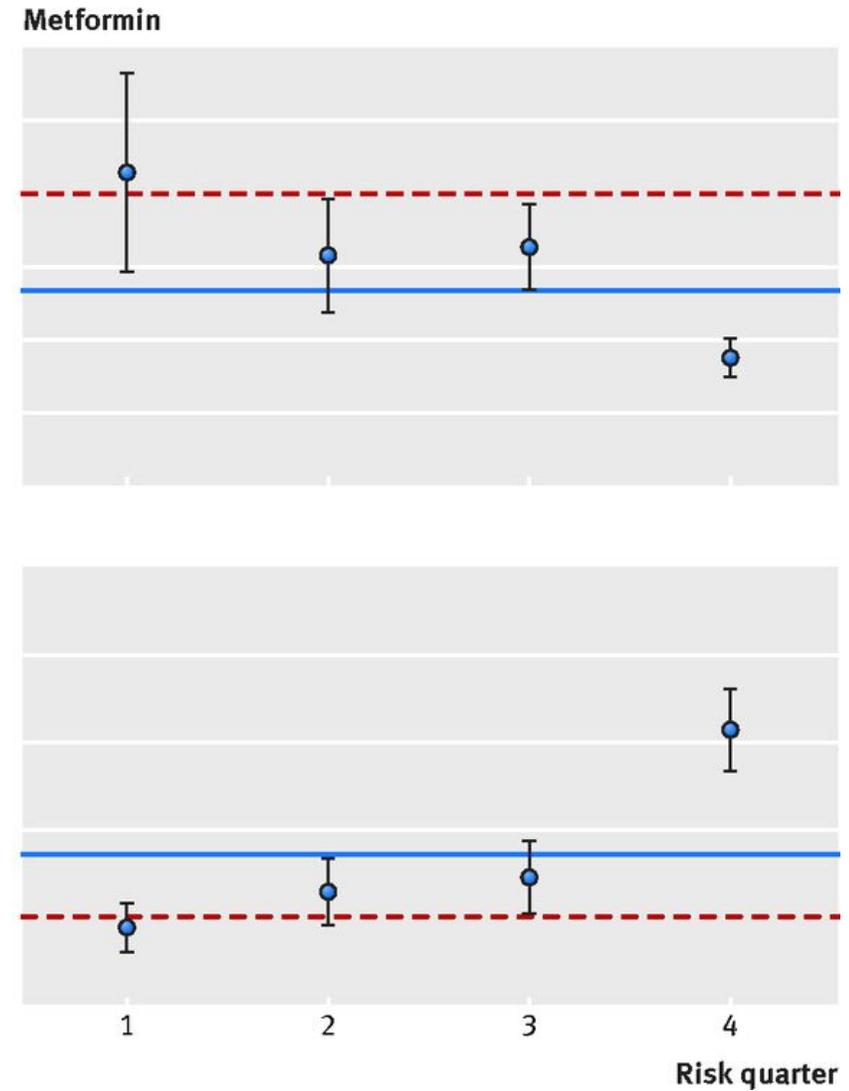
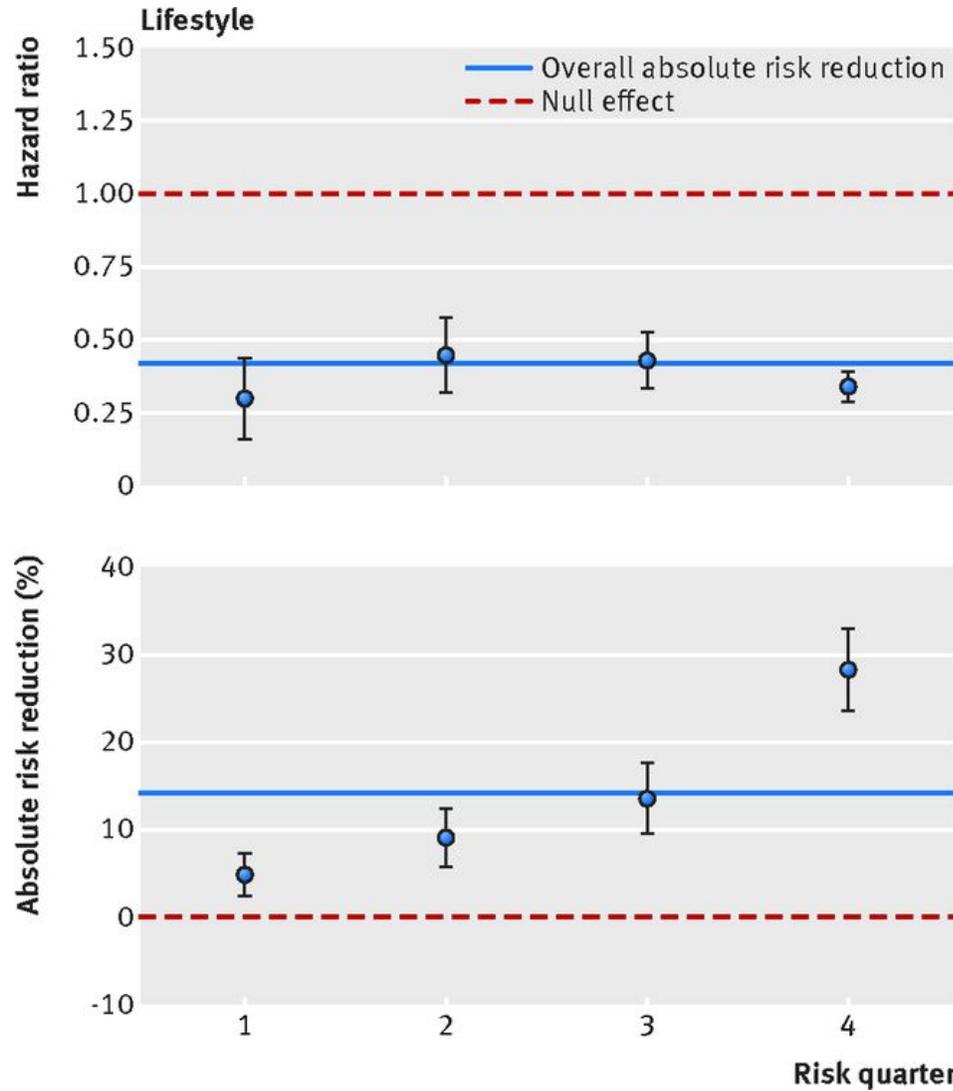


- 3-arm RCT of metformin or lifestyle intervention (vs placebo) in 3,000+ participants with impaired glucose metabolism (NEJM, 2001)
 - Lifestyle intervention reduced incidence of diabetes by 58 percent compared to 31 percent reduction in metformin group
- Re-analysis asked: Does everyone benefit equally from each type of intervention?
 - Multivariable diabetes risk prediction model used to divide participants into 4 pre-intervention risk quartiles
 - Absolute risk reductions from each treatment analyzed after stratifying by risk of developing diabetes



Sussman JB, Kent DM, Nelson JP, & Hayward RA. Improving diabetes prevention with benefit based tailored treatment: risk based reanalysis of Diabetes Prevention Program. *BMJ* 2015;350:h454. doi:10.1136/bmj.h454.

Risk of Developing Diabetes: DPP Re-Analysis



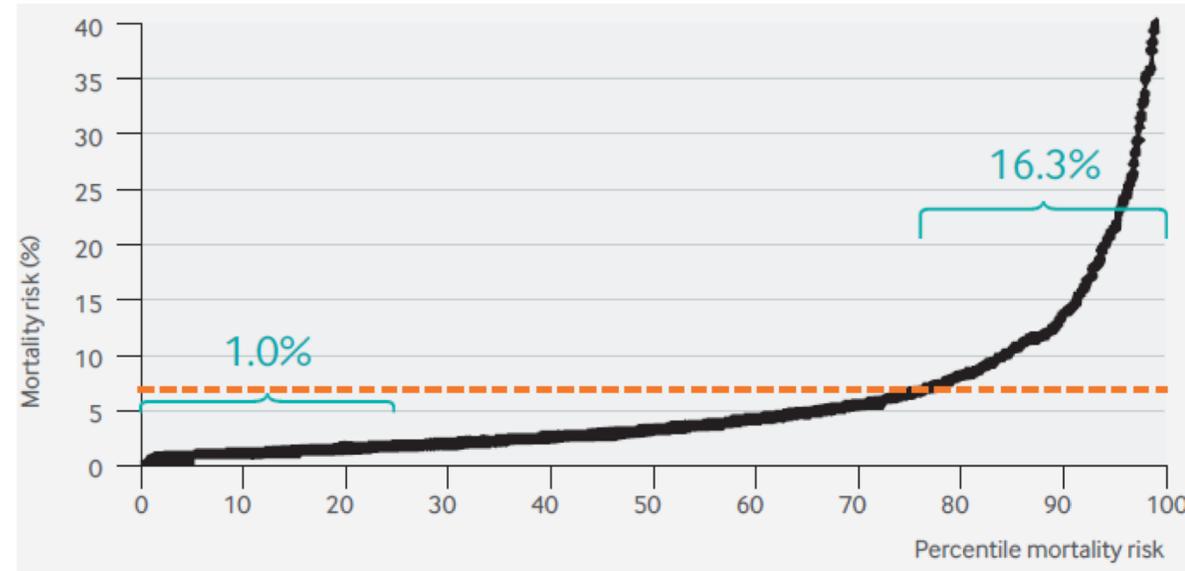
Subsequent HTE Findings from Other Early PCORI Investments



- Even in phase 3 efficacy trials, trial participants often vary substantially in their baseline risk for the primary outcome and this variation can be clinically meaningful
 - *Kent et al. Risk and treatment effect heterogeneity: re-analysis of individual participant data from 32 large clinical trials. Int J Epidemiol 2016;45(6):2075-2088.*
- Analyzing trial data stratified on outcome risk is not a new concept, is well understood and accepted, but is underapplied
 - *Dahabreh IJ, Hayward RA, & Kent DM. Using group data to treat individuals: understanding heterogeneous treatment effects in the age of precision medicine and patient-centered evidence. Int J Epidemiol 2016; 45(6):2184-2193.*
- Heterogeneity of outcomes using the absolute (risk difference) or relative (RR) scales may differ; the most relevant scale depends on the research purpose
 - *Lesko CR, Henderson NC, & Varadhan, R. Considerations when assessing heterogeneity of treatment effect in patient-centered outcomes research. J Clin Epidemiol 2018;100:22-31.*

Outcome Risk Variability in 38 trials

- Substantial variability in outcome risk among trial participants that could be clinically meaningful is not uncommon
- 14/38 publicly available datasets from large sample phase III trial datasets had statistically significant treatment effects (18 unique comparisons)
- When results were stratified into quartiles based on predicted outcome risk, absolute risk reduction usually showed significant meaningful heterogeneity while relative measures generally did not
- Among 25% of trials, differences in treatment effect between participants in lowest and highest risk quartiles were judged clinically meaningful



Kent, Steyerberg, & van Klaveren. *Personalized evidence based medicine: predictive approaches to heterogenous treatment effects*. *BMJ* 2018; 363:k4245

Building from Initial PCORI HTE work



- A more robust, useful, consistent framework for HTE analysis supports PCORI's overall mandate
- Within such a framework, more routinely analyzing trial data to consider how treatment results may vary across differences in baseline risk and more routinely looking at absolute as well as relative treatment differences is a good first start
- Outcome risk prediction/prognostic models are well accepted, understood, and applied already in clinical practice, and thus ready for more widespread use than other developing approaches
- Appropriate re-analysis of research data will be easier in the future of Open Science

Progress to Date on Supporting Personalized Decision-making

- **Predictive Approaches to Treatment Heterogeneity (PATH) Resource Center**
 - Awarded May 2017 (Tufts University, Kent, PI)—two year initial contract with two option years
- **May 2018 NAM meeting** Proceedings: in preparation
 - Blog: Statistical Thinking. *Viewpoints*
 - *on Heterogeneity of Treatment Effect and Precision Medicine.*
<http://www.fharrell.com/post/hteview/>



“The simple idea of risk magnification has more potential to improve medical decision making and cut costs than "omics" precision medicine approaches. Risk magnification uses standard statistical tools and standard clinical variables. Maybe it's not sexy enough or expensive enough to catch on.”

Next Steps: How PCORI Can Continue to Address Needs for Subpopulation Evidence



- MC may update its cross-cutting heterogeneity of treatment **effect methodology standards** to reflect recent Resource Center work
- PATH Resource Center helping develop approaches to add study aims and funds for analyzing results using risk-based approaches **within PCORI-funded trials**
- Integrate **IPD MA** opportunities with other means to support research data re-use for examining HTE
- Invest in **additional methodological studies** to consolidate the field and address heterogeneity of treatment effect, particularly using predictive models as opposed to prognostic models
- **Continue to partner** with others (e.g., FDA, NAM, guideline developers like USPSTF, Ensuring Value in Research Funders Forum) to pilot and responsibly champion the production, understanding, and use of evidence about treatment heterogeneity

Progress to Date on Supporting Personalized Decision-making

- IPD MA
 - Commissioned EPPPIC (Evaluating Progesterone for Prevention of Pre-term Birth International Consortium) to examine subpopulation and regimen exploration of more than 40 RCTs worldwide
 - New methodology standards for IPD MA being finalized
 - Developed funding mechanism for collaborative trialist conference as the first step within overall trialist-methodologist consortium model that addresses conflicts of interest and meets IOM/WHO requirements for trustworthy evidence
 - **IPD MA can be required for adequate power to explore treatment variation and to avoid ecologic bias in regression approaches**

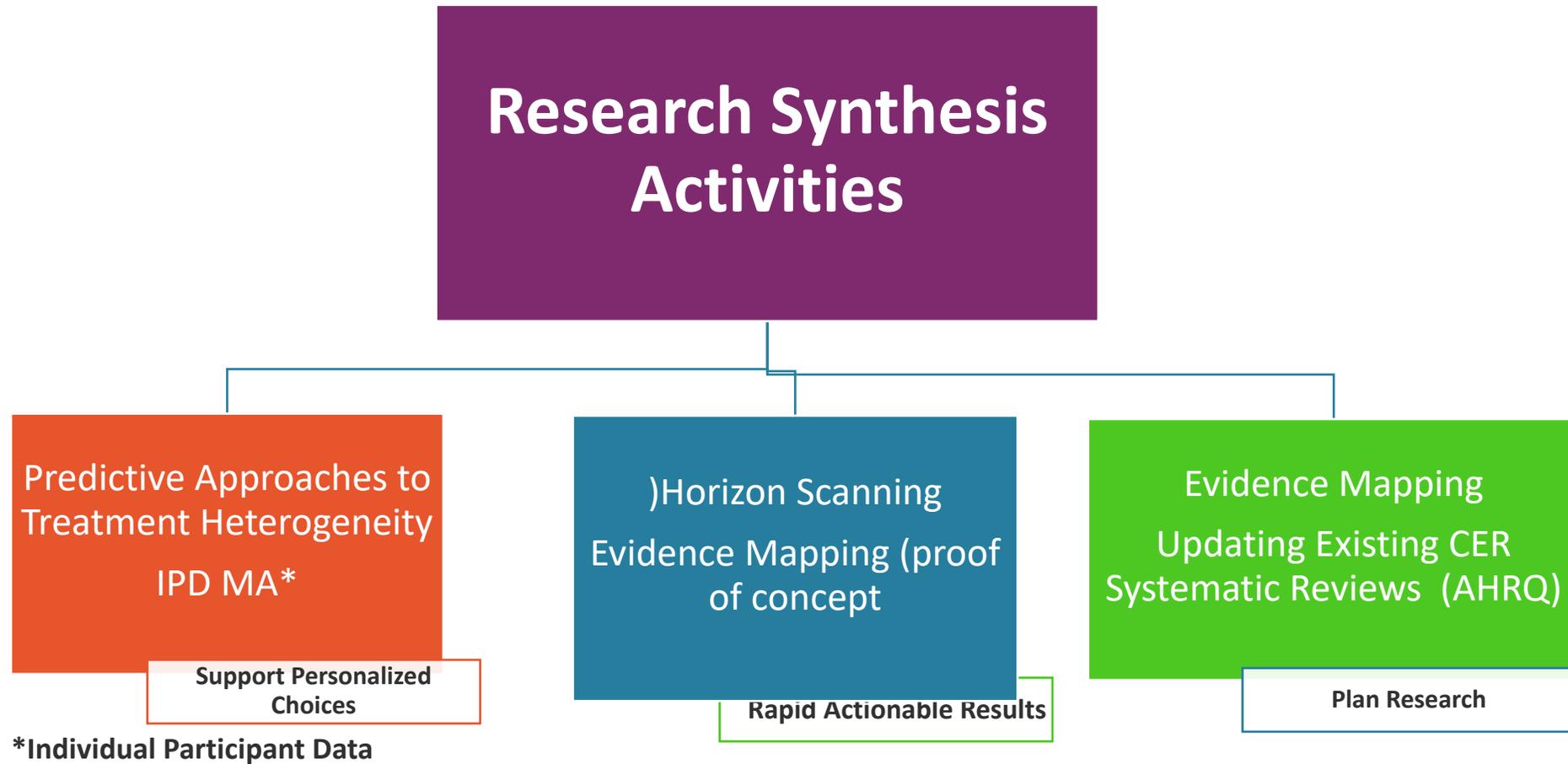
Demand for Valid Personalized Evidence is Widespread across PCORI Stakeholders

- **Patients** clearly want all health care to be as personalized as possible
- **Clinicians** are encouraged to utilize shared decision making and apply the logic of personalization to individual clinical decisions without always having the evidence to support them
- **Health care systems and payers** seek to parse those most likely to benefit from treatments and “predictive analytic” methods are proliferating, e.g. through machine-learning and “big data”
- Evidence-based **guideline developers** are increasingly using multivariate risk models to target subpopulation recommendations traditionally based only on age and sex



PCORI Evidence Products Update

Overview of Research Synthesis Initiative (Launched in 2016)



An Expanded Range of Evidence Products

New efforts:

- **Healthcare horizon scanning** identifies and monitors target technologies and therapeutics in healthcare and serves to identify key research questions
- **Emerging technology and therapeutics reports** are intended to meet information needs and inform more definitive research on new and/or innovative interventions

Ongoing and evolving opportunities:

- **Evidence maps** visually depict the state of available evidence surrounding emerging areas in the field based on existing systematic reviews
- **Updated and novel systematic reviews** provide a more comprehensive approach to synthesizing the current state of evidence in the field on a given topic

Horizon Scanning

Early Alert for Important Emerging Technologies



- **Goal:** Identify and monitor target technologies and therapeutics in healthcare
 - Forecast which target technologies:
 - Will be high impact (e.g., clinical care, care delivery, outcomes, costs)?
 - Will be disruptive?
- **Purpose:** Help identify and monitor important new therapeutics and technologies before they enter the market (ideally about 3 years before market entry)
- **Use:** Identify key research questions that PCORI can address as the technologies enter the market, in collaboration with stakeholders: industry, patients, payers, clinicians

Track a Wide Range of Potential Innovations

Example: New Off-Label Use for Methotrexate



Topic Title	Potential Patient Population	Intervention Developer/Manufacturer(s) Phase of Development	Potential Comparators	Potential Health or Other Impacts
Off-label methotrexate for treatment of diabetes-associated cardiovascular disease	Patients with type 2 diabetes mellitus (T2DM) or metabolic syndrome who have had a heart attack	<p>Inflammation is thought to play an important role in cardiovascular disease; however, it is not known whether treating inflammation will decrease the risk of cardiovascular disease. Conditions such as T2DM and metabolic syndrome are associated with an enhanced proinflammatory response, and patients with these conditions are at increased risk of experiencing myocardial infarction (MI) and stroke. The anti-inflammatory agent methotrexate is being investigated to prevent stroke, MI recurrence, and cardiovascular death in patients with T2DM or metabolic syndrome who have a history of MI. In a clinical trial, methotrexate is being administered orally, 15–20 mg, weekly, plus 1.0 mg folic acid 6 days per week.</p> <p>National Heart, Lung, and Blood Institute, Bethesda, MD Brigham and Women’s Hospital, Boston, MA 389 other institutions and physician practices in U.S. and Canada</p> <p>Phase III trial ongoing</p>	<p>Anticoagulants Antidiabetes agents Antihypertensives Antiplatelets Cholesterol-lowering agents Lifestyle changes</p>	<p>Decreased risk of stroke Decreased risk of MI recurrence Decreased risk of cardiovascular death Improved quality of life</p>

Source: Agency for Healthcare Research and Quality Status Update Report

Leverage Detailed Reporting on Potential High Impact Interventions

Example: Cologuard for Colorectal Cancer Screening



Stool DNA Molecular Test (Cologuard) for Colorectal Cancer Screening

Unmet need: Colorectal cancer (CRC) is the third most common cancer diagnosed in the United States. It tends to develop slowly, and precancerous lesions and early stage CRCs can typically be successfully treated by surgical resection. Successful CRC screening programs could mitigate much of the morbidity and mortality associated with this condition; however, the U.S. Centers for Disease Control and Prevention estimated that in 2012, 34.9% of screening-eligible individuals were not up to date with screening recommendations and 27.7% of screening-eligible individuals had never undergone screening.³⁵ Therefore, new screening methods are highly desired that could increase the percentage of the population that undergoes recommended CRC screening.

Intervention: Cologuard is an in vitro diagnostic test intended to detect genetic signatures of colorectal precancers and cancers in cells shed from the intestinal walls and excreted with stool.³⁶ To undergo screening, patients provide a stool sample of at least 36 g, which is analyzed for the presence of the three following markers associated with CRC and precancerous lesions:

- Hypermethylated DNA derived from two genes known to be methylated in CRCs and adenomas (*NDRG4* and *BMP3*)
- Alleles of the *KRAS* gene known to be acquired as somatic mutations in CRCs and adenomas
- Hemoglobin using a highly sensitive fecal immunoassay

Integrating the methylation marker, mutation marker, and hemoglobin results using a logistic-regression algorithm generates a positive or negative result based on cutoffs established by prior

Source: AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report: Cancer.

Emerging Technologies and Therapeutics Reports

- **Goal:** Provide timely information on new drugs or devices (such as those identified by horizon scan reports, evidence summaries, evidence mapping, and more in-depth evidence syntheses, as appropriate)
- **Purpose:** “Pre-PCORI research” evidence summaries intended both to meet information needs and to inform more definitive research
 - Develop with stakeholder input
 - Include patient-centered outcomes, healthcare delivery disruptions, and comparisons that need to be addressed in order to measure value
 - Identify on-going studies, including patient populations, settings, etc.
 - Discuss regulatory and policy environment
- **Use:** Provide clarity about available evidence and areas of uncertainty for decision makers

Inaugural Emerging Technology Report

Gene Therapies

- **Deliverable: Evidence Map and Landscape Review of Gene Therapies**
 - CRISPR and other DNA editing technologies
 - Adenovirus, adeno-associated virus therapies (AAV)
 - CAR-T and other modified autologous cell products
 - RNA Inhibitors
 - Plasmid-Based Therapies
 - Antisense Therapies
 - Other viral-based therapies

Evidence Maps

- **Goal:** Inform clinical and research decision making through systematically searching research evidence, and displaying the findings in an accessible, usually visual, format
- **Purpose:** Develop an easily understandable visual representation of the availability of research evidence
 - How much research has been done (and sometimes what that research shows)
 - What questions research HASN'T answered (evidence gaps)
- **Use:** To help with evidence-informed decision making, and to highlight and prioritize evidence gaps for future research

- Two completed:
 - mHealth for self-management of chronic disease
 - Interventions for fatigue in multiple sclerosis
- Two underway:
 - Localized prostate cancer
 - Pelvic floor muscle training for urinary incontinence
- More under discussion and we are seeking your input on topics to consider for the future

PCORI Evidence Map

Interventions for Fatigue in Multiple Sclerosis



- First round: Stakeholder-driven updates of prior AHRQ reviews
 - Stroke Prevention in Atrial Fibrillation Patients
 - Drug Therapy for Early Rheumatoid Arthritis
 - Nonsurgical Treatments for Urinary Incontinence in Women
 - Psychological and Pharmacological Treatments for Adults with Posttraumatic Stress Disorder
- Upcoming: Nominations from professional societies for reviews to aid in guideline development
 - Finalizing first round of topics

Progress Toward PCORI Re-authorization

Summary on Reauthorization



- A set of bipartisan Senators have agreed to lead efforts and introduce legislation reauthorizing PCORI in 2019.
 - Goal is to work with stakeholder community to develop a consensus legislative proposal
 - Expect the proposed legislation will likely include minor changes/tweaks
 - Similar bipartisan efforts building in the House
- Third-party advocates are also building an independent, proactive effort to support PCORI.
 - There is an effort to coordinate among various stakeholder organizations/communities to support a unified effort to support PCORI reauthorization
 - Allies held a *Friends of PCORI Reauthorization* launch event in January

Ongoing Activity in Congress

Senate Champions



Mark Warner (D-VA)



Bill Cassidy (R-LA)



Chris Van Hollen (D-MD)



Shelly Moore Capito (R-WV)

The Senate staff have scheduled meetings with key stakeholder communities through March to solicit their input and feedback on what PCORI's reauthorization language should include.

While we have identified Democratic Champions, we are still working to secure Republican Champions.

House Champions



Diana DeGette (D-CO)



Don Beyer (D-VA)

Preferred Republican Champions



Tom Reed (R-NY)



Fred Upton (R-MI)

PCORI will continue to showcase and demonstrate the value of our research.

Need for Information

- There is continued need for trustworthy, evidence-based information
- Increasing focus on individual patient preferences and values

Real Impact

- PCORI research results are showing potential for clinical impact and savings to individuals and health system
- Investment in high priority topics – opioids, heart disease, diabetes, etc.

Unique Role

- PCORI is funding research that answers real-world questions from patients and providers
- This is research that is unique to PCORI's mission and would likely not be funded by NIH or AHRQ

Highlights of Patient-Centered PCORI-Funded Research Results

Patient-centered outcomes research results can reveal underutilized and overutilized care.

High-Impact, Underutilized

Blood Thinner Keeps Stroke Survivors in Their Homes

Using the blood thinner warfarin helped stroke survivors reduce future hospitalizations and stay in their homes—on average 46 more days at home over two years — compared with those who didn't take the drug after being discharged from the hospital. The drug also lowered the rates of stroke recurrence and heart attack, but staying at home rather than having to go to a nursing home or hospital was the outcome that mattered most to patients.

Xian Y et al. *BMJ*. 2015; 351

O'Brien EC et al. *Circulation*. 2015 Oct 13; 132 (15)

Over five years
in the United States,
466
strokes could
be avoided

Low-Impact, overutilized

For Many with Type 2 Diabetes, Daily Finger Sticks Offer Little Health Benefit

People with type 2 diabetes who are not using insulin are often advised to check their blood sugar levels using daily finger sticks, which can be painful and inconvenient, as well as run up out-of-pocket costs for test strips. This study suggests that for these patients, daily self-monitoring does not help control diabetes or delay the need to start insulin compared with not doing so.

Young L et al. *JAMA Intern Med*. 2017 Jul 1; 177(7)

 Over five years,
10 BILLION
finger sticks could
be avoided

Trending in the Right Direction

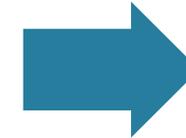
3 Years Ago

- Very little awareness about PCORI among policymakers
- No results yet to show impact and value of PCORI
- Lots of questions about our research prioritization
- Not much engagement from key stakeholders
- Little interest in reauthorization



PCORI Reactions

- Increased focus on targeted, high-priority topics
- Growing number of results and impact analyses
- Ongoing education of policymakers and engagement of key stakeholders
- Delivering on stakeholder requests (i.e., forums, new initiatives, products)



Today

- Identification of bipartisan Congressional champions
- Support for reauthorization from key stakeholders, including payers
- Continued release of impactful research findings
- Increasing awareness on the role and value of PCORI