

March 15, 2012

Joe V. Selby, M.D., M.P.H.
Patient Centered Outcomes Institute
1701 Pennsylvania Ave., NW, Suite 300
Washington, DC 20006

Dear Dr. Selby:

The American Association for Cancer Research (AACR) is pleased to offer comments regarding the Patient-Centered Outcomes Research Institute's (PCORI's) draft National Priorities and Research Agenda (collectively referred to as the "draft document"). As the world's largest and oldest organization dedicated to cancer research, our 33,000 members span the range of researchers from basic scientists to clinical practitioners and include cancer survivors and advocates. The AACR is very supportive of PCORI's mission, which is quite closely aligned with the AACR's own mission to prevent and cure cancer through research, education, communication, and collaboration. Improved patient outcomes are a driving force behind both organizations, and our comments are intended to help strengthen the foundation of PCORI's vitally important work.

The AACR applauds PCORI's focus on evidence-based decision making, and stands ready to offer its continuing support for the organization's efforts. The AACR agrees with the selection of PCORI's five priority areas that seek not only to compare prevention, diagnosis and treatment options, but also to target them toward reducing disparities, while simultaneously working to develop a thriving patient-centered outcomes research (PCOR) ecosystem by fostering delivery system improvements, methodological improvements, and communications efforts.

The AACR's primary concern is the lack of specific guidance provided by the current draft document. In the draft document, PCORI "...encourages bold thinking about research projects," but the draft document does not by itself provide enough direction for researchers to put forth bold projects with any certainty that they are in alignment with PCORI's vision. PCORI has the challenging task of quickly changing the healthcare landscape by focusing research on missing evidence gaps that translate into immediate improvements in patient outcomes. To succeed in this task PCORI must instill a common vision into the entire research community by providing a roadmap showing which gaps need to be filled first and how to go about filling them. In the absence of a clear roadmap from PCORI, researchers will create their own visions and PCORI will lose the collaborative power that extends far beyond its influence due to its grant-making role. Below, we expand on this concern with the lack of specificity, along with concerns and recommendations with respect to funding allocation, funding mechanisms, disparities research, and rare diseases.

PCOR is integral component to realizing improvements in cancer care

As you know, cancer is the second-leading cause of death in the U.S., behind cardiovascular disease, and, with demographics shifting toward a significantly larger population of older Americans, cancer is expected to be the number one killer in a matter of years. Research has led to dramatic

improvements in cancer survival over the past decades. Last year, seven of the 35 newly-approved drugs in the U.S. were for the treatment of cancer, more than any other category. Even with this rapid growth of treatment options, a great deal of research remains to be done, as our understanding of genetics has begun to subdivide cancers that were once thought to be a single disease into smaller and smaller subtypes, each varying in responsiveness to different drugs and therapeutic approaches. Improving outcomes for cancer patients, therefore, relies increasingly on research to understand each individual patient and their unique disease.

Cancer research and biomedical science has also led to the ability to measure biomarkers that indicate either early stages of cancer or increased susceptibility for certain cancers. The technical ability to perform such tests, however, has not always been accompanied by a thorough understanding of how best to apply them for meaningful improvements in patient health. With so many new tools for detecting, preventing and fighting cancer, it is both an exciting time and a confusing time for patients, who, when confronted with a diagnosis of cancer, want to know what it means for them and what their options are for taking control of their future. Comparative effectiveness research (CER) provides an important opportunity to make sense of all the options and to apply the available tools in the ways that suit the patients' interests best.

Specific Points for Consideration

1. Lack of Specificity in the PCORI Research Agenda

The goals of PCORI's National Priorities and Research Agenda are to actively guide research toward filling critical evidence gaps around prevention, diagnosis, and treatment, and to create a sustainable ecosystem in which new evidence continually feeds into improved treatment. The guidance that PCORI is charged with providing is informed by the criteria defined by PCORI's authorizing statute, the Patient Protection and Affordable Care Act. It was generally expected by the patient and research advocacy community that those criteria would have been translated into a very clearly defined project agenda. A number of organizations have previously developed detailed prioritized CER agendas, addressing issues both across the spectrum of health care and within the organization's own disease of focus. A sampling of several cancer-specific priority lists can be found in Appendix A attached to this letter. What is notable about these other agendas is that they address PCORI's statutory criteria (e.g., populations and conditions), but they have done so through the specificity of the research agenda. PCORI, on the other hand, created a broadly-defined project agenda, but it has not defined clear guidelines for evaluating research proposals, which is, by default under such a broad agenda, where specific decisions about priorities will ultimately be made. Furthermore, PCORI has not indicated if such guidelines will be made available for public comment in advance of funding announcements. Under the proposed agenda, researchers would lack the critical elements needed to understand PCORI's vision.

In providing wide latitude for the research community to propose research projects, there is an implicit assumption that the research community is already well aligned with PCORI's vision for PCOR. In fact, the PCORI draft document states: "This approach recognizes the likelihood that as

PCORI begins its funding program, researchers partnered with stakeholders are well positioned to present a range of compelling questions.” Critics of an investigator-initiated approach to defining specific research projects are concerned that the current evidence gaps exist precisely because the research community has failed to focus its efforts on the questions that motivated Congress to establish PCORI. The questions that the research community identifies as important, and has interest and expertise in working on, are not by default matched to the evidence gaps identified by payers, patients and physicians.

The AACR agrees with PCORI’s stance that the research community is well equipped to formulate research questions, but we also argue that providing better defined targets for that research will improve the quality of submitted proposals. The AACR recognizes PCORI’s desire to avoid overly narrow research questions; however, PCORI has already shown an ability to extract broad general priorities from previous efforts at setting priorities and research agendas without directly emulating the same format or specificity of the source documents. The AACR therefore encourages PCORI to likewise build on these previous efforts to extract common but cross-cutting research agenda items that are more specific than the currently proposed agenda.

While PCORI has asked for feedback specifically on its draft document, it is ostensibly asking for feedback on the overall way it intends to shape the direction of PCOR. The AACR feels that the priorities in PCORI’s draft document identify the themes critical to moving the entire field of PCOR forward, but, because the research agenda portion of the document remains broad, the document as a whole does not provide guidance at a level of specificity that enables the research community to be true partners in advancing PCORI’s vision of PCOR.

While, as stated above, the AACR would prefer a more specific research agenda, it appears that PCORI is not currently prepared to take this approach. Instead, it appears that PCORI will express its specific vision of what it considers to be the future of PCOR through three separate steps: the draft National Priorities and Research Agenda, the Methodology Report, and the process of reviewing and rebalancing proposals for funding decisions. The draft National Priorities and Research Agenda outline the general themes of PCOR, in other words they address the question, “What is PCOR?” The Methodology Report will provide more detail by providing insight as to the types of desirable research approaches; in other words, it will explain the “how” of PCOR. Finally, the specific proposal review criteria and/or rebalancing criteria will be the practical filter for the final determination of which projects PCORI feels should be pursued based both on scientific rigor and the ability to impact priority questions; in other words it narrows the entire space of possible projects to those which best fit PCORI’s priorities by answering the question of “which”. The current draft National Priorities and Research Agenda document, therefore, represents only one piece of an incomplete mosaic that, only when assembled, will guide the future direction of PCOR. The AACR appreciates the opportunity to comment on the draft National Priorities and Research Agenda, and similarly looks forward to the opportunity to review the Methodology Report; however, without similar public and transparent opportunity to comment on the content and weighting of the review and/or rebalancing criteria prior to any funding announcements, the public process of discussing a shared vision for the future of PCOR will be both fractured and incomplete.

Both in the PCORI draft document and at the March 5th PCORI Board of Governors meeting, there was discussion about the use of a rebalancing process through which the submitted proposals that scored at the top of the peer-review process would be reordered on the basis of factors that in some cases were not explicitly listed in the funding announcement or in other cases represented either a second evaluation of a given factor or an added weighting of an already evaluated factor outside of the peer-review process. Eight factors identified at the March 5th meeting were: area of interest, population, methods, geography, research discipline of investigator, seniority of investigator, condition, and stakeholder/patient involvement. Some of these factors, including area of interest, population, or condition, are natural concerns that closely echo the criteria listed in statute. This rebalancing process, therefore, seems to be an attempt to incorporate statutory criteria into the selection of proposals, and therefore stands to play a major role in defining the direction of PCORI's research agenda. Given the importance of this step, the AACR strongly urges PCORI to make such decisions through a formalized and transparent process.

The AACR does not object to the principle of reviewing projects to ensure inclusion of specific conditions, methodologies, disciplines, etc., but we feel strongly that these review and rebalancing criteria need to be public and subject to community dialog **before** issuing a funding announcement. While the initial PCORI pilot projects were evaluated using a modified National Institutes of Health (NIH) review process, the exact review process by which future proposals are evaluated is still an open question. The review criteria must be made public before seeking proposals in order for researchers to be able to develop research proposals that are aligned with PCORI's goals and for patients to have faith that the research chosen for funding focuses on their needs. PCORI will obviously have a significant impact on the field through the work performed by grant awardees, but if the first full funding announcement elicits the same type of response as the PCORI pilot projects did, then there will easily be an order of magnitude more applicants than awardees. By explicitly defining its goals with respect to specific conditions, methodologies, populations, or disciplines, PCORI can provide a roadmap for conducting PCOR to the entire community of researchers, rather than simply rewarding those researchers who construct a proposal that happens to be aligned with review or rebalancing criteria that were not public.

Cancer researchers have a history of continually improving the standard of care, pitting new treatments against existing ones, finding novel therapeutic combinations, improving screening, and searching for biomarkers or genetic signatures that will enable targeted interventions to improve the outcomes of patient subpopulations. With this tradition, the AACR feels strongly that cancer researchers are well positioned to be lead contributors as the national efforts in PCOR are expanded. Our concern, therefore, is not whether the cancer research community is technically or philosophically prepared to embrace patient-centered research, but rather that, without unambiguous consensus criteria for determining project worthiness, PCORI will lose a critical window to focus the research community around a common patient-centered vision.

If PCORI intends to retain the broadly defined research agenda that has been proposed, the AACR urges that the complete process for proposal review and rebalancing, along with any weighting of criteria, be issued for public comment prior to initiating any funding announcements.

2. Allocation of Funding

While CER is often thought of primarily in terms of evaluating clinical interventions against each other, PCORI is also charged with looking at overall health system approaches, advancing the CER enterprise, addressing disparities, and better understanding how findings can be communicated. The “Comparative Assessment of Options for Prevention, Diagnosis, and Treatment” category is comprised of condition-specific research on prevention, diagnosis, and treatment and is the largest category, projected to receive 40% of the funding. While the “Disparities” category may fund investigations into issues of access and education, it is likely to also address specific disease conditions, bringing the study of conditions to approximately 50% of the total outlay.

While some investments in capacity and infrastructure may have large, long-term payouts, their effects are likely to be realized much later and harder to measure than individual clinical questions. Furthermore, the value of these allied investments is dependent on the quantity and quality of original research that they support, and the funding should reflect this dependency by placing primacy on specific clinical research questions. **The AACR therefore supports a funding breakdown that places a strong emphasis on clinical and preventive questions and feels that such a research-focused approach will provide the swiftest demonstration of the value of PCORI’s investment.**

3. Funding Mechanisms

The drafters of the statute envisioned a mixture of investigator-initiated and contract research, but the broad nature of the draft agenda makes it nearly impossible to conduct contract research. The draft document defers utilization of contract research to a later date, presumably once more specificity in the agenda is developed.

While not required by statute, the AACR feels PCORI should provide clearer guidance for its intent with respect to the timing and proportion of contract versus investigator-initiated research funding, along with the rationale for these plans. While the AACR supports using investigator-initiated research for the largest share of research, we acknowledge that contract research may offer benefits in terms of speed and specificity. While a transition toward contract research may be in PCORI’s plans, shifts without prior explanations may be misconstrued as a failure of investigator-initiated research to provide the needed results or as a less transparent way to allocate research funding. Awarding very specific contract research without a community discussion about a research agenda at a commensurate level of specificity fails to live up to PCORI’s mandate to provide information “... that comes from research guided by patients, caregivers and the broader health care community.” Clarity about the role and timing of contract research is needed at the outset to help avoid future misunderstandings.

4. Disparities

The AACR feels that the inclusion of a distinct agenda category aimed at addressing disparities is laudable; however, the descriptions of the agenda category “Addressing Disparities” is similar enough to the category “Comparative Assessment of Options for Prevention, Diagnosis, and

Treatment” that it is not clear how projects written for one category would differ greatly from projects written for the other. Patient-centered CER done rigorously would be expected to include subpopulations and should, by default, help alleviate disparities, although perhaps not as the primary goal of the research.

To address disparities in a more targeted and impactful way, the “Addressing Disparities” agenda category should be defined such that it specifically directs research aimed at diseases and conditions that are known to result in poorer outcomes in subpopulations subject to multiple health disparities. Selected examples of targeted conditions in cancer are prostate cancer incidence and death rate among African-American men, cervical cancer incidence in Hispanics and poorer treatment outcomes for African-American women with breast cancer.

5. Rare Diseases

We are aware that PCORI has noted the importance of studying rare diseases; however, it is primarily mentioned only in the draft document under the methodology priority. We urge continued consideration of this important aspect of disease, particularly with respect to cancer. Our understanding of the biology of cancer has taken us from the concept of cancer as one disease to the understanding that it is a group of perhaps several hundred related diseases. As genetic testing and the use of biomarkers have advanced, even diseases that were typically associated with the tissue of origin (e.g., lung, skin, breast, etc.) are being further divided into subtypes of cancers based on the presence or absence of specific biomarkers or genetic defects. This process of disease classification is known as nosology, and it is becoming increasingly useful as researchers are more often finding that the specific classification of a cancer by its component genetic defects, rather than the tissue of origin, determine the appropriate treatment modality. One practical outcome of this improved disease subclassification is that the many of these newly-defined cancer subtypes will meet the definition of rare diseases.

Some of the greatest treatment gains are made when specific subtypes of cancer are identified and targeted therapies are developed for a specific, and sometimes rare, genetic aberration. For this reason, the AACR strongly urges PCORI to exercise care when considering the size of the affected population when evaluating proposals. For cancer, the incidence of a disease subtyped by its genetic defect and the likelihood of research impacting treatment outcomes can often be inversely related.

Summary

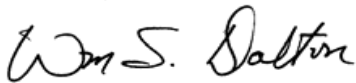
The cancer research community stands ready to contribute to the emerging domain of PCOR and support PCORI’s effort. We are excited about the enhanced focus on patient outcomes that PCORI brings to the research enterprise, but we caution that the ability of the research community to adapt to a PCOR mindset depends on a clear consensus roadmap of what well-designed and impactful PCOR looks like. While the National Priorities found in the draft document are a good first step, the Research Agenda portion of the document lacks the level of detail needed to convey a targeted vision of the field. We look forward to the opportunity to review the Methodology Report as an additional piece of the PCOR roadmap, but most importantly we hope that PCORI will provide

an opportunity for patient and stakeholder input on the process for proposal review and rebalancing, which will make up the final piece of the roadmap, assuming that more specificity is not included in the research agenda. All stakeholders are united in our desire to promote the best science possible to improve patient care, but different stakeholders may have different visions of what constitutes the “best science.” It is therefore PCORI’s duty to ensure clarity and consensus around a common vision. PCORI is charged with “...producing and promoting high integrity, evidence-based information – that comes from research guided by patients, caregivers and the broader health care community.” For patients and other stakeholders to feel truly engaged in providing meaningful input into the vision of PCOR, **all** of the processes that PCORI will use to direct research need to be open to input.

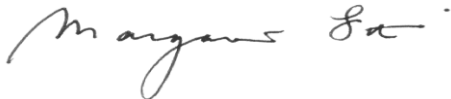
In addition to the comments offered above, the AACR stands ready to provide any further assistance to PCORI as additional guidance is developed. If you have questions, please feel free to contact the AACR through Mark Fleury, Ph.D., associate director for science policy, at 215-446-7147 or mark.fleury@aacr.org.

Thank you for your consideration of AACR’s comments.

Sincerely,



William S. Dalton, M.D.,
Chairperson, AACR Science Policy and Legislative Affairs Committee



Margaret Foti, Ph.D., M.D. (h.c.),
Chief Executive Officer, AACR

Appendix A: Research Agendas Focused on Cancer

A number of organizations have developed detailed CER prioritized agendas, addressing issues either across the spectrum of health care or within the organization's own disease of interest. The priority lists found in this appendix reflect the level of specificity in project agendas that the community expected to come from PCORI. Specific examples from these lists as well as from PCORI's agenda are shown below to illustrate the vastly different levels of specificity provided by PCORI and the rest of the advocacy and healthcare community followed by the full agendas listed.

Institute of Medicine (IOM):

- “Compare the effectiveness of imaging technologies in diagnosing, staging, and monitoring patients with cancer including positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT).”

Friends of Cancer Research (FOCR):

“Use of Proton Beam Therapy Compared to Intensity-Modulated Radiation Therapy (IMRT).”

Center for Medical Technology Policy (CMTP):

“Genetic Markers to Predict Tumor Behavior in Prostate Cancer”

PCORI:

- “Studies that compare situations in which the effectiveness of strategies for prevention, treatment, screening, diagnosis, or surveillance have not been adequately studied against alternative options and better evidence is needed to support decision-making by patients, caregivers, and healthcare professionals. Special emphasis is placed on studies conducted in typical clinical populations considering the full range of relevant patient-centered outcomes and possibilities that results may differ among patient groups based on patient characteristics (understood broadly as possibly including clinical, psychosocial, demographic, and other domains) or preferences. PCORI recognizes that a variety of study designs and approaches may contribute valid new knowledge about the comparative clinical effectiveness of specific strategies. There is a particular interest in comparisons for which new knowledge could address individual differences in patient values and preferences and support shared-decision making. (Criteria addressed: Current Gaps in Knowledge/Variations in Care, Potential to Influence Decision-Making, Inclusiveness of Different Populations, Patient-Centeredness)”

As seen from the four agenda items listed above, the more explicitly-defined IOM, FOCR, and CMTP agenda items would all fit within the broad PCORI agenda definition, as would a vast array of questions from other disease areas like Alzheimer's, diabetes, or developmental disabilities.

Institute of Medicine (IOM) Oncology CER Priorities

The IOM was specifically charged with developing a CER priority list as part of the America Recovery and Reinvestment Act (ARRA), which allocated over \$1 billion toward CER. Note that the 100 priorities were divided by quartile, and only those dealing with cancer are shown here.

First Quartile:

- Compare the effectiveness of management strategies for ductal carcinoma in situ (DCIS).
- Compare the effectiveness of imaging technologies in diagnosing, staging, and monitoring patients with cancer including positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT).
- Compare the effectiveness of genetic and biomarker testing and usual care in preventing and treating breast, colorectal, prostate, lung, and ovarian cancer, and possibly other clinical conditions for which promising biomarkers exist.
- Compare the effectiveness of interventions (e.g., community-based multilevel interventions, simple health education, usual care) to reduce health disparities in cardiovascular disease, diabetes, cancer, musculoskeletal diseases, and birth outcomes.

Second Quartile:

- Compare the effectiveness of film-screen or digital mammography alone and mammography plus magnetic resonance imaging (MRI) in community practice-based screening for breast cancer in high-risk women of different ages, risk factors, and race or ethnicity.
- Compare the effectiveness of new screening technologies (such as fecal immunochemical tests and computed tomography [CT] colonography) and usual care (fecal occult blood tests and colonoscopy) in preventing colorectal cancer.

Third Quartile:

- Compare the effectiveness of different strategies to engage and retain patients in care and to delineate barriers to care, especially for members of populations that experience health disparities.

Fourth Quartile:

- Compare the effectiveness of surgical resection, observation, or ablative techniques on disease-free and overall survival, tumor recurrence, quality of life, and toxicity in patients with liver metastases.

Center for Medical Technology Policy (CMTP) Oncology CER Priorities:

- Colorectal Cancer Screening Tests for Average Risk Patients
- HER2 Testing to Manage Patients with Non-Breast Solid Tumors
- Diagnostic Tests for Lung Cancer
- Stereotactic Body Radiotherapy for Lung Cancer
- Techniques for Assessing Metastatic Lymph Nodes
- Treatments for Unresectable Liver Cancer
- Treatments of Cancer Pain from Bone Metastases
- Genetic Markers to Predict Tumor Behavior in Prostate Cancer
- Therapies Following Breast-Conserving Surgery for Breast Cancer
- Circulating Tumor Cell Tests

Friends of Cancer Research (FOCR) CER Priorities:

- Use of Proton Beam Therapy Compared to Intensity-Modulated Radiation Therapy (IMRT)
- Use of Palliative Care versus Standard Treatment to Improve Survival
- Metastatic Cancer Registry to Compare Duration of Chemotherapy Treatment
- Imaging Surveillance Strategies (Frequency and/or Modality) for Cancer Survivors
- Effectiveness of Early Discussion of Advanced Directives and Resuscitation Choices on Quality of End-of-Life Care and Patient/Family Satisfaction
- Identifying Non-Responders to Approved Cancer Drugs by Using Data and Tools From the Human Genome Project
- Development of Standards for the Use of Patient Reported Outcomes in CER
- Comparative Studies of the Effectiveness of Strategies for Surveillance of Treated Cancer Patients
- Retrospective Analysis of Existing Trial Data to Determine How Health Outcome Trends Are Affected by Obesity
- Predicting and Preventing Thrombosis in Hematological Malignancies
- Use of Extensive or Limited Lymph Node Dissection to Prevent Recurrence of Melanoma
- Radiation Oncology Patient Registry
- Comparison of Different Tumor Ablation Techniques and Devices