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1225 New York Avenue, NW, Suite 450  
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September 13, 2012

**Dr. Joe Selby**  
Executive Director  
Patient-Centered Outcomes Research Institute  
1828 L St., NW, Suite 900  
Washington, DC 20036

**Dr. Sherine Gabriel**  
Chair  
Patient-Centered Outcomes Research Institute Methodology  
Committee

Dear Dr. Selby, Dr. Gabriel and members of the PCORI Methodology  
Committee:

The Personalized Medicine Coalition (PMC) appreciates the  
opportunity to comment on the draft methodology report recently  
published by the Patient-Centered Outcomes Research Institute's  
(PCORI) Methodology Committee.

We would like to state at the outset that we appreciate the  
considerable work done by the Methodology Committee. You have  
before you a one-time opportunity of critical importance to our  
nation's health system. How PCORI sets up its methodological  
framework will play an important role in determining the ultimate  
success or failure of Patient Centered Outcomes Research (PCOR) and  
thereby determine whether the Institute is able to ask and answer  
tough questions about how best to improve patient care. Congress  
tasked PCORI with not only funding research to answer tough  
questions, but also with finding the best ways to deliver outcomes  
information to providers, patients, and their caregivers.  
Unprecedented opportunities and unique challenges, like this one,  
require thoughtful deliberation and a commitment from all of us to  
ensure that the system put in place is able to meet Congress' challenge.

PCORI was designed to do something new and very different – to  
define how practical, feasible, and useful PCOR is to be conducted. As  
a 2009 Lewin Report, (available for free download here:  
<http://www.lewin.com/publications/publication/386/>) noted,  
comparative effectiveness research (CER) studies to date have rarely  
accommodated the collection and reporting of genomic, behavioral,

environmental, and other individual patient differences, such as adverse effects, and real-world issues of patient noncompliance and comorbidity. This omission stems, in part, from the inherent nature of various methodological approaches used to produce evidence of comparative effectiveness and the time, costs, and other hurdles associated with collecting and analyzing sufficient data at the subpopulation level to yield clinically and statistically significant findings. As directed by Congress, PCORI has the opportunity to create the methodological framework to address individual variation in CER.

In this letter, we highlight some opportunities for PCORI to shape the future of CER research and to address methodology standards, standards for understanding the heterogeneity of treatment effects (and for the study of diagnostics in particular). We also share reflections on stakeholder engagement, definitions and tone, and building PCORI's infrastructure. We include suggestions related to PCORI's infrastructure since we believe building a more robust infrastructure now is necessary for the Institute to develop its internal capabilities and to satisfy the statutory requirements of its mission, to be the unique institution that it was designed to be.

The Personalized Medicine Coalition (PMC) is an education and advocacy organization comprised of more than 220 academic, industry, patient, provider and payer communities, working to advance the understanding and adoption of personalized medicine to benefit patients and the health care system. We have strongly advocated for the alignment of comparative effectiveness research (CER) with personalized medicine, a paradigm which increasingly-enables clinical applications of treatment strategies based upon research-tested applications of individual variation.

Personalized medicine, the tailoring of medical treatments to patient characteristics, relies upon the ability to classify individuals into subpopulations that differ in disease susceptibility and treatment responses. It allows clinicians to target preventive or therapeutic interventions on those who will benefit, and thereby to spare the expense and side effects of treatment for those who will not, thus making medicine more efficient.

PMC is encouraged by the establishment of, and supports PCORI because the legislation creating it included a mandate to align personalized medicine and comparative effectiveness research (CER), and required procedures to assure that alignment. The methodology committee was charged by statute with, among other tasks, outlining standards for molecularly informed trials. We believe that research that considers differences in patient responses, including those based on genetic characteristics, will deliver evidence that can be used to improve the health care system and the quality of care for individual patients through personalized medicine.

PCORI was designed to address specific, practical questions of national importance and contract with researchers to answer these questions, yet the initial drafting of the

methodology report aligns greatly with traditional, investigator-driven approaches to research, which may (or may not) address the types of questions PCORI must answer. We believe that if research were to be funded as described in the draft methodology report, PCORI's work could be redundant with the work of existing research institutions within the federal government.

### **Methodology Standards**

We believe PCORI's Methodology Committee should take this opportunity to define a new methodological standard for health outcomes research. Congress designed PCORI to address some of the difficult questions that our health system needs answered; questions that have, so far, not been answered using traditional clinical research approaches and may not be answered by a randomized controlled trial (RCT). PCORI has the opportunity to explore alternative methods for PCOR including methodological standards for different types of real-world studies and appropriate statistical methods for them. We urge the Methodology Committee to tackle this challenging opportunity in future iterations of the report.

PCORI also has the opportunity to outline how traditional research methods may not be suitable for PCOR and to find more suitable methods for such research. For example, traditional Agency for Healthcare Research and Quality (AHRQ) systemic reviews often miss some caveats that might be of great importance to a group of patients and are thus relevant to PCOR. Similarly, subgroup variations may become apparent during the course of research. PCORI can guide researchers in how to best tackle study evolutions in a statistically and methodologically sound way. We suggest that the methodology committee develop a guide that supports real-world research such as the appropriate methods of gathering, using, and analyzing observational data and how to conduct scientifically robust, yet practical and efficient, clinical trials. We submit that by engaging a diverse breadth of researchers, including those outside of academia, the committee has the greatest chance of progressing PCOR and achieving its mission.

### Heterogeneity of Treatment Effectiveness Standards

We suggest that the standards for addressing heterogeneity of treatment effectiveness in observational and experimental PCOR should be revised to provide more effective guidance to researchers regarding biomarkers and genetic testing. Biomarker data, the hallmark of personalized medicine, is influencing how researchers address therapeutic development and disease management and is growing in its use by researchers across therapeutic disciplines. It is also redefining how drugs are labeled for use and how FDA regulates new products. Furthermore, the authorizing legislation directs the methodology committee to take into account genetic and molecular subtypes when examining individual variation. Therefore, we recommend that either a separate section on standards for biomarkers and genetic variables be added to the report or an additional section on heterogeneity of treatment effectiveness be developed to guide the use of biomarker data.

PCORI could provide researchers with guidance about how best to decide which subgroups to examine and how to analyze the data appropriately such as in the case of molecularly-defined subgroups that can, at times, be quite small. In explaining the role of heterogeneity of treatment effectiveness in PCOR methodology, it would be helpful for PCORI to elaborate on the role of CER in explaining what treatments works for whom. As written, the standards outlined in the draft methodology report are very comprehensive and give researchers rich information to consider when designing their studies. We are pleased that gaps in heterogeneity of treatment effects for alterative research studies were considered in the augmentation report that complements the larger methodology report. We would suggest, however, that some consideration be given to known subgroups where variation in treatment response is likely. For example, genetic variations can impact an individual's sensitivity to a pharmaceutical as well as how fast a person's body metabolizes it, thereby affecting drug efficacy. Since molecular medicine is a new and growing area of practice, we believe the research community would welcome additional guidance by the methodology committee for researchers conducting PCOR on these topics.

#### Diagnostic Test Study Standards:

Diagnostic tools offer the health care system ways to focus treatments on those who will benefit. Because new diagnostic tools are still emerging, we believe that PCORI has the opportunity to design and define new standards for diagnostics research. As currently outlined, however, the standards seem to focus on RCT-based studies that may not be suited for certain diagnostic tools.

Double-blinded, placebo-controlled RCTs are often infeasible for most new molecular diagnostic and genetic tests, for several reasons. First, most molecular diagnostic tests have populations of potential patients that are too small to recruit enough patients for a statistically-valid trial. Second, biomarker data are almost always discovered retrospectively, while analyzing results from trials that were not designed to test the relationship between the disease and a biomarker. Third, running a prospective, placebo-controlled trial of a molecular diagnostic test could be unethical, especially if the group receiving a placebo is known to have a gene that makes them a candidate for a potentially life-extending, life-saving treatment or helps them avoid adverse events. Fourth, reviewing molecular diagnostic tests will require a new paradigm for collecting and analyzing evidence. This may require using new methods such as variations in clinical trial design, using patient registries to identify respondents, analyzing archived biospecimens, and retrospective analysis of laboratory data. We believe guidance on these issues from PCORI will greatly advance the field.

### **Stakeholder Engagement**

The statute creating PCORI was very clear that public and stakeholder engagement in each step of PCORI's work is critical to the Institute's success. We are pleased that

PCORI makes the comments it receives from stakeholders publicly available and that meetings are held that allow for public comment and engagement. We are concerned, however, that public engagement is not as comprehensive as it needs to be and that some stakeholders are being overlooked by the process.

For example, the process regarding how PCORI uses the public comments it receives is unclear to us. Many of the public comments that were sent to PCORI and articulated during live meetings regarding the draft research agenda and priorities requested that the document's vague wording be replaced with specificity. Also, many stakeholders suggested changes to the PCOR definition yet little was done to explain the rationale for why certain suggestions were accepted and others were not. We believe the final version of the research agenda and priorities remains vague and think that transparency around the Institute's decisions would be helpful to ensure confidence in the integrity of the process. We request that PCORI develop, and release to the community, a table outlining the categories of specific comments that are received in all future public comment submission periods with an explanation of how PCORI addressed those comments (or why PCORI chose not to address them). We believe that such a process would give the community confidence that PCORI's policies are being developed with full consideration of stakeholder perspectives.

Regarding stakeholder engagement, while the board of governors has representation from nearly all stakeholder groups, the methodology committee does not. This construction may cause some innovations in PCOR methodology and statistical analysis used by non-represented groups to be overlooked. One easy solution is to diversify the methodology committee by including researchers from innovative life science companies.

### **Reflections on Definitions and Tone**

As we stated before, PMC is an education and advocacy organization comprised of academic, industry, patient, provider and payer communities, working to advance personalized medicine to benefit patients and the health care system. Our Coalition is made up of organizations committed to improving the quality of patient care by taking full advantage of the science behind personalized medicine.

We believe that PCORI should use the commonly-adopted definition of personalized medicine taken from the President's Council of Advisors on Science and Technology (PCAST) in their work, and include it in the glossary of this report. According to PCAST, personalized medicine "refers to the tailoring of medical treatment to the individual characteristics of each patient to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those will not."

We think the section of the report called “Problems that PCORI Hopes to Address” is beyond the intended scope of the methodological document, and thus suggest deleting the content of it. We suggest instead that PCORI focus on addressing the problems around generating useable, real-world comparative clinical effectiveness data.

Regarding language on conflict of interest in the report, we suggest that PCORI outline methods for transparency in research without barring large groups of stakeholders from participating in the process. PCORI could also highlight the contributions that industry-funded research makes to patient care and how that research could benefit future PCOR endeavors.

### **Infrastructure**

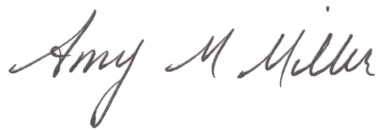
The statute creating PCORI contained some important directives that we believe should be incorporated into PCORI’s structure to comply with Congressional intent and support the science of personalized medicine. Many of the suggestions made above could be dealt with by addressing these infrastructure issues.

1. Personalized Medicine Expert Advisory Panel: PCORI has the statutory authority to create expert advisory panels, on any topic, to carry out its mission. To assist PCORI with assuring that their work supports personalized medicine, we encourage PCORI to develop an expert advisory panel devoted to personalized medicine. As an education organization dedicated to advancing the field, and populated by stakeholders from all sectors of the health care universe, we would like to offer our support and commitment to assisting and supporting these expert advisory panels, including offering our clinical science committee’s assistance in identifying potential members for this proposed expert advisory panel. Our clinical science committee is populated by personalized medicine researchers at major health centers, large and small diagnostics companies and within the research and development arms of pharmaceutical companies. They are eager to assist PCORI in any way that they can.
2. Update the Science: One of PCORI’s Congressionally-mandated tasks is to improve the quality of CER by incorporating new information and technological innovations into its studies by reviewing and updating the evidence as necessary and outlining what future research will be needed to address perceived information gaps. PMC suggests building this infrastructure within PCORI and the processes to achieve this goal now, proactively, as the foundations of the organization are being established.
3. Engaging Broad Scientific and Clinical Expertise: The mission of PCORI is unique and to carry it out, we suggest that PCORI have a unique set of individuals within PCORI to develop calls for research proposals, evaluate them, make awards, follow the progress of the research, and engage the public at steps along the way. Having this infrastructure “in-house” is a necessary step in the Institute’s development. We are willing to assist with this effort.

To conclude, we believe PCORI has an opportunity to improve the quality of patient care in the United States (and globally) through PCOR that incorporates personalized medicine. We specifically suggest developing standards for personalized medicine related PCOR and incorporating that into the heterogeneity of treatment effectiveness standards. We also suggest that more guidance be given to standards related to diagnostic test studies. Regarding stakeholder engagement, PMC would like to help PCORI engage stakeholders who might not currently be engaged. Finally, we suggest that PCORI develop internal infrastructure to achieve its goals.

If you have further questions, or if I can provide any resources or contacts for PCORI committees, please do not hesitate to contact me. Our membership stands ready to speak with you about this methodology and assist your efforts as much as possible.

Sincerely,

A handwritten signature in cursive script that reads "Amy M. Miller".

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