PERSONALIZED MEDICINE COALITION

June 10, 2019

ATTN: Steven D. Pearson, M.D., M.Sc.
Founder and President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

by electronic delivery

Re: Comments on the 2020 Value Assessment Framework

Dear Dr. Pearson:

The Personalized Medicine Coalition (PMC) appreciates the opportunity to submit comments regarding the forthcoming draft revisions to the Institute for Clinical and Economic Review (ICER)'s value assessment framework, to be published in August of 2019.

Comprised of over 200 member institutions from every sector of the health care ecosystem, PMC, an educational and advocacy organization representing patients, providers, payers, innovators, and scientists from around the world, promotes the understanding and adoption of personalized medicine concepts, services, and products to benefit patients and the health system.

Personalized medicine is an emerging field that uses diagnostic tools to identify specific biological markers, often genetic, that help determine which medical treatments and procedures will work best for each patient. By combining this information with an individual's medical records, circumstances, and values, personalized medicine allows doctors and patients to develop targeted prevention and treatment plans.

PMC's primary interest is in the extent to which proposed updates to ICER's value assessment framework, herein called the framework, reflect a consideration of the value of personalized medicine products, services, and concepts. Considerations related to personalized medicine can significantly impact the assessment of comparative clinical effectiveness and comparative value. Treatments that are targeted for use based on a patient's molecular characteristics and individual circumstances improve outcomes by allowing physicians to provide the most effective and safest treatment to each patient as early as possible. Doing so may in turn bring down costs by helping to avoid ineffective or harmful treatment options and reducing the downstream expenses associated with rapid disease progression and/or adverse events.

Personalized Medicine Coalition
personalizedmedicinecoalition.org
1710 Rhode Island Ave., NW, Suite 700
Washington, DC 20036
P: 202.589.1770
F: 202.589.1778

To this end, PMC recommends that ICER recognize five principles as it continues to consider concepts related to personalized medicine within the framework:

1. Considerations related to personalized medicine, such as heterogeneity of treatment effect, treatment efficiency (i.e., potential cost savings by avoiding less effective treatment or adverse side effects), and individual values and circumstances can significantly impact comparative clinical effectiveness and value assessment.
2. Diagnostic testing must be considered an integral part of the assessment of the value of treatment options where heterogeneity of treatment effect can be assessed, or efficacy and/or safety information can be obtained.
3. Methods for assessing value must consider real-world evidence (RWE) that can provide insight on emerging or evolving value elements over time.
4. Valuation approaches should be transparent and consistent and include a broad array of benefits that are important to patients and society.
5. All stakeholders must be engaged, and multiple perspectives must be integrated throughout the value assessment process in order to encompass all value elements that need to be considered in the assessment of various treatments to the health care system.

Statement of Neutrality

Many of PMC's members will present their own responses to ICER and will actively advocate for those positions. PMC's comments are designed to provide feedback so that the general concept of personalized medicine can advance, and are not intended to impact adversely the ability of individual PMC members, alone or in combination, to pursue separate comments with respect to the proposed updates to the value assessment framework or related issues.

General Comments Regarding the Framework

We offer these comments about how the scope of the framework may affect the field of personalized medicine.

<u>The Population Perspective, Heterogeneity, and Intended Uses</u>

The framework is intended to inform medical policies through a population-level perspective. ICER should not conflate, however, the impact of a therapy on patient health outcomes with the potential budget impact to any individual stakeholder or stakeholder group. We acknowledge ICER's statement that stakeholders focused on population-level decision-making, including payers and policymakers, are the intended audience of its value assessments. This does not discount or diminish, however, other key perspectives of value.

ICER should consider, for example, how assessing the value of different therapies to individual patients could facilitate improvements and efficiencies at the population level by ensuring that only those patients

who are most likely to benefit from new therapies actually receive them. The final decision of which therapy, or combination of therapies, is most appropriate for a patient must (1) be left to the patient working with his or her provider; (2) involve consideration of the patient's clinical circumstances; and (3) involve consideration of a therapy's long-term impact on a patient. Utilizing personalized medicine strategies, providers are able to identify individuals within larger populations that are more or less likely to respond to certain therapies. Therefore, inclusion of these considerations should, on balance, lead to population-level efficacy, safety, and efficiency.

Value Factors

We recommend that the framework examine a broad range of factors specific to each evidence review within the appropriate context to inform and support determination of high-value care. This may include short-term
affordability and long-term value, but these factors alone are insufficient. Furthermore, the valuation of sustainable access to high-value care falls short of a complete societal perspective of value (Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, Kuntz KM, Meltzer DO, Owens DK, Prosser LA, Salomon JA. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA*. 2016 Sep 13;316(10):1093-103). The societal perspective may often incorporate factors such as productivity and caregiver burden. A societal perspective will ensure that all patient- and societal-focused benefits are included, not just those that will be accrued by the payer. Elements such as systemic efficiency (i.e., getting the right treatment to a patient as early as possible), the contribution of innovation to the further advancement of medicine, and the contribution of an innovation to an evolving care paradigm should be taken into consideration.

Length of Time for Review

While we appreciate that the timelines for responding to proposed process updates have been increased, they are often still insufficient for the purpose of soliciting feedback from multi-stakeholder coalitions like PMC. PMC and its members can support ICER by providing in-depth, technical insights on the subject matter of ICER's evaluations. As a coalition, any insights we offer must represent the interests of a range of disciplines and balance the perspectives and needs of our many members. Meanwhile, the field of personalized medicine is moving at an incredibly rapid pace. In this context, it is impractical for many stakeholders, particularly coalitions like PMC, to fully react to and respond to ICER's complex and lengthy reports in a short period of time. The length of open comment periods should reflect the importance, length, and complexity of the items to which the community is responding.

Furthermore, ICER does not allocate an adequate amount of time to its own review and reaction to stakeholder comments. PMC reiterates its recommendation that all comments submitted to ICER and their disposition should be publicly available. ICER should give its rationale for issues that it has chosen not to incorporate or address. Longer timelines for ICER's review and consideration of stakeholder input, and unlimited length requirements related to stakeholder feedback, will allow for greater community acceptance of ICER's assessments.

Comments Regarding Specific Areas for which ICER is Requesting Input

We appreciate ICER's call for comments on how to improve the framework and efforts through prior framework revisions that have provided greater alignment with personalized medicine practices and principles; however, further revision and refinement of the framework in this area is warranted to ensure the applicability and usefulness over the period during which the updated methodology will be implemented. Key recommendations related to ICER's specific requests for input are highlighted below.

Cost-effectiveness thresholds

ICER has implemented a range of incremental cost-effectiveness thresholds, which are determined based on the average weighting of pre-specified elements or other benefits and contextual considerations voted on and ranked by an independent committee. It should be recognized that no single metric threshold can or should be universally applicable, as thresholds are likely to vary by decision-maker, population, and disease. Furthermore, ICER's current approach of setting a uniform budget impact threshold based on a fixed portion of drug expenditures creates an artificial affordability threshold that could have negative, unintended consequences such as shifting spending toward lower cost care that is less efficient, thereby moving away from personalized medicine and reducing the value of our health care dollar.

The approach ICER takes to evaluate the magnitude and certainty of net health benefit

Inclusion of Evidence and Process Updates

The next iteration of the framework will impact ICER evidence reports for all assessments initiated in 2020 and beyond. Personalized medicine considerations will affect many, if not all, of ICER's value assessments going forward, as evidenced by the fact that over the last four years (2015 – 2018), personalized medicines have accounted for more that 25 percent of all new drug approvals, and the number of newly approved personalized medicines is expected to continue to grow (Personalized Medicine Coalition, *Personalized Medicine at FDA: A Progress and Outlook Report*: http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM_at_FDA_A_Progress_and_Outlook_Report.pdf).

Evidence review of clinical outcomes within the framework is mostly limited to data accumulated for a product up to its market launch. This does not take into account emerging value factors and evidence accumulated after product launch. New and emerging technologies are disadvantaged in assessments where the framework compares the value of established products vs. that of emerging products (e.g., pre-launch, new to market) since only early indicators of efficacy, safety, and value are acknowledged.

The personalized medicine field is evolving too rapidly to accurately maintain a current assessment of treatment value with a two-year period between assessment reviews and updates. For example, shortly after ICER published its report on the value of non-small cell lung cancer treatments, technology advancements related to the use of biomarkers to help guide treatment decisions altered the value proposition for some treatments. For a value assessment framework to remain useful over time, evidence reports

need to be updated more routinely. ICER should provide criteria for when evidence reviews will be updated based on new evidence, particularly as it relates to diagnostic stratification or other contextual factors. The framework should consistently employ methods to assess value at interim time points over a longer term using practice-based evidence wherever possible.

Randomized Clinical Trials and Real-World Evidence

We appreciate the steps ICER has taken to open the framework to the inclusion of a broader range of data sources for assessments, extending beyond randomized clinical trials (RCTs) to include, for example, RWE and grey literature. RCTs have great value in determining clinical safety and efficacy of therapies, but value can differ when viewed through the lens of actual practice in the real-world situation. It is unclear how these data will be incorporated into ICER evaluations, models, and value metrics, but it is important that RWE carry an appropriate amount of weight in evaluations and that this is defined *a priori* in the framework. Furthermore, conducting RCTs for some personalized medicines is not feasible because it would be impossible to develop a large enough cohort of patients with a rare genetic variant necessary to demonstrate clinical significance. In these cases, RWE is instrumental to the personalized medicine value assessment. The evidence landscape is evolving away from the traditional RCT. With the growing focus on personalized medicine, smaller patient populations make them harder and more expensive to conduct. Finally, RWE can also provide information on how patients who may often be excluded from RCTs due to co-morbidities or other criteria may benefit from a therapeutic in routine clinical practice.

Report Development and Stakeholder Engagement

PMC commends ICER on efforts to further engage stakeholders on policy development, both in recent value
assessment reports and in the proposed revisions to the framework. Consideration of perspectives of all personalized medicine community stakeholders, especially patients and caregivers, is critical to getting the right treatment to each patient as early in their care as possible. However, we respectfully note room for greater engagement that can more completely integrate patients and other critical stakeholders into the value assessment process. In order to truly encompass and reflect clinical real-world experience and value to patients, these stakeholders' perspectives must be integrated throughout the process.

To encourage continued high-quality input, PMC recommends that ICER make the process for communication with patients and caregivers clear. We are pleased that ICER increasingly provides opportunities for patients to engage throughout a value assessment and to submit data. To complement ICER's Patient Open Input Questionnaire, ICER should clearly emphasize and describe the patient-provided information that would be valuable for patient groups to collect. The earlier that patient groups are aware of a call for feedback and what types of input/data collection will be useful, the better they can accommodate these requests. Data quality may also be improved.

The use of QALY and the evLYG

We appreciate that ICER has made efforts to broaden its cost-effectiveness analyses, focused on cost per life year

gained and cost per quality-adjusted life year (QALY), to permit consideration of alternate, or additional, cost-effectiveness and cost-utility measures, which may capture important disease-specific outcomes such as cost per consequence, when relevant.

While the QALY's ability to provide a single measure of the "value" of a treatment makes it a commonly used metric for quantifying health benefits, patients do not receive treatments in isolation. Personalized medicine is a complex, multifaceted process with patients receiving care along a continuum — from diagnostic testing, clinician and genetic counselor consultation, disease management and monitoring, to medication therapy and hospitalization when necessary.

A single measure cannot adequately capture true patient-centered value and the broad heterogeneity of clinically relevant characteristics and preferences across patients and diseases. PMC therefore recommends disaggregating the single-value metric and considering a more comprehensive set of value elements that is inclusive and reflects personalized medicine services and concepts as well as individual patient circumstances.

Methods by which to integrate potential benefits, contextual considerations, and other factors

Contextual Considerations

ICER maintains that "Evaluations of long-term cost-effectiveness are made challenging because of the potential for evolution of devices/diagnostics and the attendant changes in cost, effectiveness, and the types of patients that will be treated." ICER answers this challenge by incorporating specific unique approaches to evidence evaluation and use of diagnostic interventions as contextual considerations. While we appreciate that ICER recognizes the potential for these elements to impact value, and the potential for the evolution of treatment value due to devices/diagnostics, the consideration of "contextual considerations" falls short of adequately capturing the value factors that may be realized due to diagnostic tests. For example, the framework does not explicitly include value factors related to predictive testing to (1) avoid ineffective treatment initially; (2) make an informed change in treatment when patients fail to respond; or (3) determine clinical trial eligibility — all of which are critical elements of the evolving treatment landscape and help build evidence of value of novel drugs.

Appropriate Consideration of Diagnostic Tests

The framework does not have a formal, consistent approach for the consideration of diagnostics intended to help guide treatment decisions where appropriate. The framework considers "evaluation of diagnostic tests and delivery system interventions by taking into account their unique nature or circumstances," but the framework does not specifically call on assessments to consider validation, utility, and economic impact of diagnostic tests. Guidelines for a consistent approach should consider (1) when diagnostics should/should not be included in assessment processes, (2) how (methodologically) diagnostics are included in the evidence review and economic evaluations, and (3) implications and standards for analyzing and reporting on patient subgroups.

Diagnostic testing in personalized medicine is a key step on the path to getting the right medicine to a patient as

early as possible. It is imperative that the framework considers testing an integral part of clinical decision-making by which efficacy and safety information of treatments can be obtained. The detection or measurement of biomarkers plays an important role in determining value across numerous clinical scenarios, many of which are subject to rapidly advancing scientific knowledge. The context of biomarkers within clinical scenarios must therefore be figured into the framework's methodology. Failure to explicitly address this important component of value at this time will undermine the usefulness and applicability of the framework going forward.

Valuation Approaches

The relative contribution to the overall long-term value of these contextual considerations, and other benefits and disadvantages, is subjective. Relying on contextual considerations thereby risks applying false weight and a false sense of precision and accuracy to these subjective value elements. The subjective relative ranking scale proposed by ICER may unfairly undervalue innovative personalized medicines, as it may be particularly problematic for newer treatments and therapies where evidence of societal and contextual benefits may be lacking at the time of assessment. ICER's current approach leaves the consideration of these factors up to the discretion of the voting panel, which may not have the expertise or appropriate context to meaningfully evaluate them. Because it is heavily dependent upon the perspectives and decisions of a small group, this valuation approach is not transparent or consistent. Furthermore, the approach may be insufficient to incorporate the impact of important patient-centered factors.

PMC strongly advocates that ICER devise a method to formally account for these elements with a fully transparent valuation approach that incorporates viewpoints from all stakeholders to assure that specific value elements are appropriately considered in evaluations and that they account for emerging evidence.

Conclusions/Recommendations

Personalized medicine has a profound impact on the comparative value of treatments, and now is the time for ICER to formally address, take into consideration, and clearly delineate the methods for integrating personalized medicine products, services, and concepts into the framework. We look forward to working with you to improve ICER's process so that the principles of personalized medicine (getting the right treatment to a patient as early in their care as possible) are incorporated into its work.

With these five principles in mind, the framework can better reflect and serve the needs of the health care community:

1. Considerations related to personalized medicine, such as heterogeneity of treatment effect, treatment efficiency (i.e., potential cost savings by avoiding less effective treatment or adverse side effects), and individual values and circumstances can significantly impact comparative clinical effectiveness and value assessment.
2. Diagnostic testing must be considered an integral part of the assessment of the value of treatment options where heterogeneity of treatment effect can be assessed or efficacy and/or safety information can be obtained.

3. Methods for assessing value must consider RWE that can provide insight on emerging or evolving value elements over time.
4. Valuation approaches should be transparent and consistent and include a broad array of benefits that are important to patients and society.
5. All stakeholders must be engaged, and multiple perspectives must be integrated throughout the value assessment process in order to encompass all value elements that need to be considered in the assessment of various treatments to the health care system.

PMC appreciates the opportunity to provide these comments. PMC and ICER are united by a shared goal of providing patients and health care providers with safe and effective technologies that will best serve the needs of patients and the health care system. If you have any questions about the content of this letter, please contact me at dpritchard@personalizedmedicinecoalition.org or (202) 787-5912. We look forward to further opportunities to provide feedback.

Sincerely yours,

Daryl Pritchard
Senior Vice President, Science Policy
Personalized Medicine Coalition