



April 3, 2017

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

by electronic delivery

Re: Proposed Updates to the Value Assessment Framework

Dear Dr. Pearson:

The Personalized Medicine Coalition (PMC) appreciates the opportunity to submit comments regarding the proposed updates to the Institute for Clinical and Economic Review (ICER)'s Value Assessment Framework outlined in the *Overview of the ICER Value Framework and Proposals for an Update for 2017 - 2018*.

Comprised of some 250 member institutions from every sector of the health care ecosystem, PMC, an education 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.

In responding to the overview, PMC is interested exclusively in the extent to which proposed updates to the 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.

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

1. Considerations related to personalized medicine 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 efficacy and/or safety information can be obtained
3. Methods for assessing value must consider emerging or evolving value elements over time
4. All stakeholders must continue to be engaged, and multiple perspectives must be integrated throughout the value assessment process in order to truly encompass and reflect value 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 in general.

The Population Perspective and Intended Uses

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 how assessing the value of different therapies to individual patients could facilitate improvements and efficiencies at the population level by getting the right medicine to a patient as early as possible. 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 impact on a patient over the long term. Utilizing personalized medicine strategies, providers are able to identify individuals within larger populations that are more or less likely to respond to certain therapies. More precise treatments can reduce health care waste due to over- and/or under-treatment. Therefore, inclusion of these considerations should, on balance, lead to population-level efficacy, safety, and efficiency.

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. Proposed changes to the Framework involve “evaluation of diagnostic tests and delivery system interventions by taking into account their unique nature or circumstances,” but the Framework does not 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. This is particularly important considering that ICER’s updated Framework methods are set to be in place through 2019. Failure to explicitly address this important component of value at this time will undermine the usefulness and applicability of the Framework.

Process Updates Timeframe

The Framework’s proposed updates will impact ICER evidence reports for the two-year period beginning in April 2017. Personalized medicine considerations will affect many, if not all, of ICER’s value assessments going forward. ICER has already planned an assessment of, for example, ovarian cancer treatment, a disease state in which personalized medicine considerations will play a significant role.

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 when new evidence, particularly on diagnostic stratification or other contextual factors, may come to light.

Comments Regarding Specific Update Proposals

Although ICER’s proposed updates provide several incremental improvements toward consideration of personalized medicine practices and principles, further revision and refinement of the Framework is warranted to ensure the applicability and usefulness over the period in which the updated methodology will be implemented. Key areas are highlighted below.

Conceptual Structure of the ICER Framework

Inclusion of Evidence: 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 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. A Framework that considers clinical outcomes continuously would likely provide a more informative assessment. The Framework should consistently employ methods to assess value at interim time points over a longer term using practice-based evidence wherever possible.

Framework Perspective: The proposed changes to the Framework’s evaluation of “sustainable access to care” denote consideration of “long-term value” and “short-term affordability” for patients over discrete, predetermined time horizons. Instead, we recommend the Framework should 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 proposed change to evaluate sustainable access to high-value care falls short of a complete societal perspective of value. Elements such as systemic efficiency (i.e., getting the right treatment to a patient as early as possible), the contribution of innovation to further advancement of medicine, and the contribution of an innovation to an evolving care paradigm, etc., should be taken into consideration.

Comparative Clinical Effectiveness

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, real-world evidence (RWE) and grey literature. The extent to which these can and will pragmatically be incorporated, however, is yet to be determined. 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.

Incremental Cost-Effectiveness Analysis

ICER has proposed that it broaden its cost-effectiveness analyses, currently 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. ICER has also proposed utilization of a range of incremental cost-effectiveness thresholds (section 4.6), which are determined based on the average weighting of 10 pre-specified elements of other benefits and contextual considerations voted on and ranked by an independent committee.

Despite the newly proposed approach to dynamically set thresholds determined by the elements of other benefits and contextual considerations, ICER’s cost-effectiveness methods and thresholds do not adequately capture factors that are critical to demonstrating the value of personalized medicine, such as efficiency of treatment, avoidance of ineffective therapy, and reduction in adverse events. 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. The impact, value, and outcomes of each of these services rely on other steps within the continuum, as well as circumstances unique to each patient.

The consideration of services and treatments in silos does not recognize the complexity of individual patients, the reality of how personalized health care is delivered, or how these contribute to population health and well-being. Because health care is comprised of many, multifaceted interventions, 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 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.

Other Benefits or Disadvantages and Contextual Considerations

The Framework’s proposed update document states 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 stating that the Framework will continue to incorporate 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. The 10 elements listed as contextual considerations do not encompass many value elements that may be relevant to diagnostic testing. For example, the list does not include determination of clinical trial eligibility or the opportunity to predict resistance to avoid ineffective treatment initially or make an informed change in treatment when patients fail to respond, all of which are critical elements of the evolving treatment landscape and help build evidence of value of novel drugs.

ICER proposes a visual analog scale to rate the importance of each of the 10 elements relative to one another [Section 4.2]. The independent public appraisal committee will rate these elements. It is not clear how elements will be weighted with consideration of the value, or how each impacts the overall value metric. The valuation will be unknown prior to the public meeting and unavailable for critical evaluation, comment, agreement/disagreement, or discourse in advance.

The proposed methodology of ranking the relative contribution to the overall long-term value of these contextual considerations, and other benefits and disadvantages, is subjective. Therefore, transparency on how ICER will ensure calibration across appraisal committees (i.e., Northeast CEPAC, Midwest CEPAC, California CTAF) to ensure consistency within and across committees is warranted. Moreover, the approach risks applying false weight and a false sense of precision and accuracy to these subjective value elements. Furthermore, 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. PMC strongly advocates that ICER devise a method to formally account for these elements explicitly in the Framework to assure that specific value elements are appropriately considered in evaluations and that they account for emerging evidence.

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, 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.

Although patients and clinical experts will be permitted to attend and answer questions during appraisal committee meetings, they are still not voting members. This significantly undermines their voice in the process as the voting results are documented and reported in the final evidence report. Also, there is virtually no engagement with these stakeholders prior to formal meetings. Although efforts have been made to develop a patient engagement guide for participation and to partner with advocacy groups to conduct broad-based patient surveys to inform recent evaluations, participation remains largely ad hoc, and there is limited formal engagement in the 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.

While we appreciate that the timelines for responding to proposed process updates have been increased, it is unclear if the extended comment period will apply to comments regarding assessment reports. 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 seem to allow an adequate amount of time for their own review and reaction to stakeholder comments, particularly given the concurrent ongoing evaluations at any one time. 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 assessments.

Economic Model Transparency

While ICER provides open comment periods for proposed Framework updates and value assessment reports, it does not make the economic models on which the comparative value is determined available for peer review or review by stakeholders. PMC believes that ICER should make the economic models it relies upon available so that anyone in the public can validate ICER's methods, data sources, and assumptions.

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 as it impacts evaluations over the next two years. We hope this is the first step in public engagement on this topic, and 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 four overarching principles in mind, the Framework can better reflect and serve the needs of the health care community:

1. Considerations related to personalized medicine 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 efficacy and/or safety information can be obtained
3. Methods for assessing value must consider emerging or evolving value elements over time
4. All stakeholders must continue to be engaged, and multiple perspectives must be integrated throughout the value assessment process in order to truly encompass and reflect value 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, Ph.D.
Vice President, Science Policy