October 18, 2019

Steven, D. Pearson, MD MSc, FRCP
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson,

On behalf of LUNGevity Foundation, the nation's preeminent lung cancer nonprofit that funds research, provides education and support, and builds communities for the approximately 230,000 Americans diagnosed with lung cancer each year and 540,000 Americans living with the disease,[1] we appreciate the opportunity to provide comments on ICER's proposed changes for its 2020 Value Assessment Framework. The following comments align very closely with the comments submitted by LUNGevity Foundation in June 2019, and while they are specific to lung cancer, we believe that the same concerns and principles should apply to other disease areas as well.

LUNGevity's mission is to improve outcomes for people diagnosed with lung cancer. Our goals are threefold: (1) to accelerate research to patients that is meaningful to them; (2) to empower patients to be active participants in their own care and care decisions; and (3) to help remove barriers to access to high-quality care. We have the largest lung cancer survivor network in the country and actively engage with them to identify, understand, and address unmet patient needs. We also have a world-class Scientific Advisory Board that guides the programs and initiatives of the organization and contributes to public comment letters such as this one.

We appreciate the work and the desire to create tools to facilitate the conversation between healthcare providers and patients around treatment options. We also recognize the incredible responsibility of ensuring that ALL stakeholders–***especially patients***–are fully represented in developing these tools, as well as the utmost importance of including robust data that represent how the therapies are used in practice.

As we have touched on in previous comments, lung cancer, like many other diseases, is a heterogeneous set of diseases, both in terms of the biology of the diseases and in the experiences of patients living with lung cancer, and as such, any model or framework attempting to make assessments about the disease or treatments for the disease must be flexible enough to accommodate this heterogeneity. We do not believe that the proposed Value Assessment Framework adequately addresses the heterogeneity of lung cancer or the personalized nature of the treatments that are often driven by the presence or lack of biomarkers. Additionally, as stated in earlier comment letters, models based on population-level data or assessments will fall short of accurately reflecting the value of drugs in the lung cancer space. Given these shortcomings, we offer suggestions in our comments as to how ICER can make its model more flexible, comprehensive, and patient-centric to better assess the value of treatments for heterogeneous diseases that impact diverse patient populations.

In summary, we recommend the following to make the ICER model more rigorous and patient-centric:

A. Provide transparency to model development and a clear pathway for incorporating methodological input and key stakeholder feedback
B. Include the patient experience in determining the value of a treatment approach.
C. Incorporate patient-reported outcome/Quality-of-Life metrics along with aggregate metrics, such as QALYs and evLYGs, to quantify the economic impact of precision therapeutics
D. Incorporate real-world data and real-world evidence about clinical practice
E. Expand the framework to include the role of precision diagnostics
F. Allow flexibility in the calculation of budget impact in the Value Assessment Framework

These are discussed in greater detail below.

A. Provide transparency to model development and a clear pathway for incorporating methodological input and key stakeholder feedback

Transparency is an important component of making a value framework model robust and reproducible.

Methodological input: Oncology value frameworks such as the ASCO Value Framework[2] and Memorial Sloan Kettering Drug Abacus[3] have made their methodology transparent. We understand and appreciate the effort ICER has put in toward building a robust cost-effectiveness model and respect the proprietary nature of the effort. While ICER has already made strides in making their models transparent to manufacturers, we recommend that ICER make its models publicly available to all users. This will ensure that ICER models are accessible to methodological experts in the field who can use and attest to the credibility of the ICER models, thereby increasing acceptability. Furthermore, models should be customizable by stakeholders for use outside of review purposes.

Key stakeholder feedback: Key stakeholders of value frameworks are patients and clinicians.[4] We commend ICER for providing an opportunity to gather feedback from patients and patient advocacy groups. However, it is unclear how these comments are incorporated into the final model. In addition to the three areas of feedback described in the guidelines document from ICER,[5] we recommend that ICER provide a mechanism of feedback at the inception of and during the development of a framework. Having patient feedback throughout the development process rather than after the creation of a framework will ensure that both the process and the product are patient-centric.

Clinician input during the model development is also essential to ensuring that predictions of treatment choice made by a value framework are clinically meaningful and take into account the choice of drugs available. Given the rapid evolution of lung cancer therapies (there have been more than 15 new FDA approvals for lung cancer since 2015),[6] we encourage ICER to include expert clinicians who are advising on the real-world use of the therapies as part of both model development and feedback on the final model. To this end, ICER should be open to revising models based on clinician input.

Recommendation: We suggest that ICER incorporate key stakeholder feedback throughout the model development process and make models publicly available for methodological review and validation.

B. **Include the patient experience in determining the value of a treatment approach**

With progress in lung cancer treatment, survivors are living longer. It is imperative to incorporate the survivor perspective directly rather than make generalized statements about all people with lung cancer as the patient/survivor populations can be very different. Contrary to popular belief, lung cancer is also becoming a disease of the young and the non-smoker.[7] A young, 30-year-old, stage IV survivor may value benefits from a treatment regimen very differently than a 70-year-old survivor. These nuances can be captured through **patient preference** studies and quality-of-life metrics, which are often not included in existing clinical trial data.

LUNGevity Foundation has spearheaded the first lung cancer advocacy-driven patient preference initiative. The initiative, *Project Transform*, is a multi-year, multi-stakeholder collaborative endeavor between LUNGevity and The Ohio State University. It encompasses core principles of patient-centered outcomes research (PCOR), in line with LUNGevity's mission of providing a voice to the lung cancer patient. Currently in its third year, the project built its quantitative phase through a rigorous patient engagement model in which lung cancer patients provided direct feedback and input on the project implementation.[8,9] An important finding from the quantitative component showed that patients who had received 2 or more lines of therapies had different preferences than those patients who were on their first treatment. Specifically, patients who had been on more than one line of therapy were willing to give up only 2.2 health month equivalents (additional months of progression-free survival a new treatment would need to provide for participants to accept additional side effects) for a drug that caused increased long-term side effects, as compared to 3.7 months by patients on their first treatment.[10] Age is an additional determinant of patient preference. Younger (less than 60 years of age) and older ($\geq$ 60 years of age) patients value different aspects of their cancer treatment: younger patients are willing to undergo more aggressive treatments with a higher incidence of side effects as long as those treatments provide a longer PFS.[11] Taken together, these results demonstrate that patient experience is very heterogeneous and should be taken into account in value assessment frameworks.

Recommendation: We recommend that ICER incorporate patient experience data (for example, patient preference research) that provides contextual information of the value of the quality and quantity of life a specific treatment provides. Particularly, patient experience data will be of paramount importance in determining the true value of care for a patient, where standard of care may evolve or multiple treatment options exist (such as multiple tyrosine kinase inhibitors for a specific targetable mutation).

C. **Incorporate patient-reported outcome/Quality-of-Life metrics into aggregate metrics, such as QALYs and evLYGs, to quantify the economic impact of precision therapeutics**

The lung cancer treatment landscape has rapidly evolved over the past five years, with the US Food and Drug Administration approving more than 15 new treatments for advanced-stage non-small cell lung cancer (NSCLC)—more than in the prior 15 years combined. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, diagnosed in about 85% of people with lung cancer.[12,13] The complex nature of this disease requires personalized management plans for patients.[13] Since the discovery of the first epidermal growth factor receptor (EGFR) mutation in lung cancer in 2004, targeted therapies have become a major component of the treatment arsenal of NSCLC

patients.[14-16] Now, more than 20 driver mutations in adenocarcinoma have been identified, among them EGFR, ALK, ROS1, RET, ERB2/HER2 mutations, ERB2/HER2 amplifications, MET amplifications, MET mutations, TRK, BRAF, and KRAS.[17,18] In concert with the identification of an increasing number of targetable mutations is the development of novel, potent, and more specific targeted therapies. For example, the first-line treatment options for EGFR- and ALK-positive lung cancer have changed in the last year. Furthermore, even for those NSCLC patients without a driver mutation, first-line immunotherapy with or without chemotherapy has become the standard of care.[19,20] This rapid evolution of care has increased the need to rethink the thoracic oncology treatment paradigm, including how to combine or sequence drugs. Lung cancer patients are now living longer, higher-quality lives.

QALYs or quality-adjusted life-years have long been used by economists to forecast healthcare financial decisions. While the QALY is easy to use, Neumann and colleagues, in their *New England Journal of Medicine* article, point out that the QALY value typically used by healthcare economists in fact underestimates the impact of a drug.[21] In addition, QALYs are not appropriate for measuring complex health interventions (such as lung cancer treatment) where "gain of health" is not the only measure.[22] Also, QALY is an aggregate metric and does not capture patient-level data in making economic predictions. An ideal model is one that includes patient-level metrics that can customize a prediction to an individual patient, in line with the tenets of precision medicine. In her *New York Times* blog, ovarian cancer survivor Susan Gubar poignantly captures the inadequacies of QALYs in treatment decisions.[23] She writes, "[w]hatever the estimate, a crude ratio of cost effectiveness, like the QALY, seems presumptuous. How can qualitative factors (nausea, fatigue) be converted into quantitative numbers? How can general calculations account for individual variations (my preference for fatigue over nausea) or overriding personal beliefs and principles about what constitutes a valuable existence?" Furthermore, unlike other diseases where QALYs may have some applicability, lung cancer is not a singular disease. Rather, it is a continuum where stage of diagnosis, presence or absence of actionable mutations, recurrence, and end-of-life care would impact a patient's decision about a treatment option. Using QALYs may not adequately capture what different patients value along the lung cancer continuum.[24] In summary, QALYs neither capture the heterogeneity of lung cancer biology nor the breadth of patient experience along the lung cancer continuum.

In the current model, ICER attempts to address these shortcomings by developing and utilizing a new metric, Equal Value of Life Years Gained (evLYG), to complement QALYs. While the addition of evLYGs is a step in the right direction and adds another dimension of measurement to QALYs, it continues to be an aggregate metric and completely misses the mark on capturing patient heterogeneity both from a precision medicine and a patient experience perspective. A life extension-based metric such as evLYG is based on a short-sighted assumption that quantity of life is the main determinant of treatment choice. As discussed in Section B, cost-effectiveness analysis should take into consideration values patients place on the balance between the quality and quantity of life a drug provides. Also, other data sources such as patient-reported outcomes (PROs) can provide highly rich contextual information on how a patient feels and functions on different treatments.[25] Following the guidance issued by the FDA on both the collection and the use of PRO data, there has been a steady increase in PRO data collection in clinical trials confirming both the importance and the availability of such data.[25]

Recommendation: To increase the sensitivity of QALYs and evLYGs, we strongly recommend that ICER incorporate patient-reported outcomes (PROs) and quality-of-life metrics into their framework.

Doing so will help accurately capture the differences in patient perspective along the lung cancer continuum. PROs and QoL measure are quantitative metrics that are captured using validated instruments and in a scientifically rigorous manner. Including these metrics will help make the ICER framework more patient-centric[26] and compatible with the tenets of precision medicine. ASCO in their value framework discussion—"[p]atient self-reporting affords the opportunity to understand better the impact of care processes on how patients feel (and can optimize) good clinical practice"—points out the value and role of PRO data in increasing both the patient-centricity and robustness of their value framework model.[2]

D. Incorporate real-world data and real-world evidence about clinical practice

LUNGevity Foundation supports the use of real-world data in value frameworks. Despite an expansion of clinical trials in global sites, an overwhelming proportion of trial participants are Caucasian (86% in 2014 vs. 92% in 1997).[27] While beneficial for registrational purposes, the disproportionate number of Caucasians in clinical trials makes clinical trials a missed opportunity for truly capturing the patient experience in a real-world setting, as the participant composition does not reflect the true prevalence of the disease in a real-world setting in different racial and ethnic communities.[28] Furthermore, lung cancer clinical trials often exclude patients with brain metastases and low performance status.[29] Given that a majority of advanced-stage patients present with brain metastasis at the time of diagnosis or are very sick due to the high symptom burden of lung cancer, a pristine clinical trial cohort does not capture the lived experience of a lung cancer patient outside of a trial setting. A recent study demonstrates that real-world evidence can replicate only about 15% of interventional clinical trials, reiterating that clinical trial data and real-world data should be viewed as complementary rather than interchangeable.[30]

As real-world data traditionally comes from four sources (clinical data from electronic health records, administrative/claims data, patient-generated/reported data, and third-party data sources through cross-industry data collaborations, such as Project Data Sphere), it is important to develop strict evidentiary standards for the use of such data. Given the FDA's recent commitment to develop guidelines for the use of real-world evidence for post-marketing surveillance,[31] we see ICER's efforts to incorporate real-world data in value frameworks as timely and complementary.

Recommendation: We encourage ICER to reassess evidence once a drug has been used in clinical practice for a sufficient amount of time to accurately capture the impact a drug has made on the survivor community. At a minimum, we recommend that ICER revisit the assumptions of their model when adequate post-marketing surveillance information is available through real-world data.

E. Expand the framework to include the role of precision diagnostics

Drugs are one component of the larger healthcare system; therefore, focusing value frameworks solely on the cost of medications will likely underestimate the true value of a personalized therapeutic that is effected in a selected patient population. The use of high-quality diagnostic tests with well-established clinical and analytical validity to identify appropriate therapies is tied to better outcomes for patients and prevents harm by avoiding therapies that will not provide benefit to patients.

In this era of unprecedented scientific advancements for the treatment of lung cancer, particularly as we identify new biomarkers and biomarker-driven therapies, the value of a personalized therapeutic is highly contingent on the following assumptions:

1. Availability of a high-quality diagnostic test
2. Use of the test in the selection of the right biomarker-segmented patient population
3. Matching the patient to the right biomarker-driven treatment and, conversely, ensuring that the wrong patient doesn't get treated with the incorrect treatment

The importance of assumptions 2 and 3 can be demonstrated through recent research published in the field of targeted therapeutics. There is a clear survival benefit from access to a companion diagnostic for advanced-stage NSCLC patients before commencing first-line treatment, ensuring that patients get matched to the right therapy.[32] In addition, diagnostic biomarker testing may not only impact the right treatment selection, but in fact may also prevent a patient from getting matched to the wrong treatment. It is now well-documented that NSCLC patients with a driver mutation who receive an immune checkpoint inhibitor (ICI) before they receive a targeted therapy show a much higher incidence of severe immune-related adverse events that require hospitalization. This has been reported in patients with EGFR mutations receiving osimertinib after an ICI[33] and in patients with oncogenic alterations in ALK, ROS1, or MET receiving crizotinib after an ICI.[34]

Recommendation: To appropriately integrate the use of diagnostics into the ICER Value Assessment Framework, we recommend ICER provide guidance on the standards that diagnostic tests should meet in order to be incorporated into an evaluation of a therapy, or at a minimum provide information on the clinical and analytical validity of the diagnostics that were used for the therapy selection in the ICER model.

F. Allow flexibility in the calculation of budget impact in the Value Assessment Framework

Budget impact (a population-level measure) is not a measure of whether a treatment is of good value or not. While the median age of a lung cancer diagnosis is 70 years,[1] there is a significant and growing population of younger patients. In this younger patient population, there is a 59% increased chance of detecting a targetable alteration, as compared to patients above the age of 50.[35] Compared to traditional chemotherapies, targeted therapies provide a far superior survival profile with fewer side effects. Therefore, use of these targeted drugs will determine whether the population of young lung cancer patients is healthy enough to resume employment and reclaim years of economic productivity. The budget impact analysis conducted by ICER is unlikely to capture these complex nuances of lung cancer epidemiology and treatment (along with patient preferences and disease heterogeneity as described above). While the Department of Labor has not analyzed these statistics, as this population of younger lung cancer patients continues to grow, the true economic impact of a lung cancer diagnosis on this younger population will become evident. Furthermore, ICER's current methodology of budget impact analysis relies on threshold calculations that not only erroneously inflate the budget impact of lung cancer precision therapeutics but also underestimate the value component of these drugs.

Recommendation: We strongly urge that ICER make their model publicly available and not use the ICER-calculated $815 million/per drug threshold criterion. This will enable stakeholders to utilize their

own criteria of price, uptake, and time horizon, and derive their own budget impact. In addition, we recommend that ICER continue to iterate on its existing model as data on the epidemiology and genetics of the younger lung cancer population continue to evolve.

Conclusion

We urge the audience and users of ICER models to recognize that the Value Framework is static and estimates the price of a treatment at a singular point in time based on clinical trial data, a best-case situation analysis of access of diagnostics and therapeutics, and mathematical assumptions. The framework needs to be contextualized with the clinical reality of patients, such as clinical and patient heterogeneity of lung cancer and the line of treatment a patient is receiving.

LUNGevity sincerely thanks you for the opportunity to comment on ICER's Value Assessment Framework and offer suggestions on how to improve its accuracy and to reflect the patient voice. We look forward to additional opportunities to contribute to ICER's ongoing work and encourage the institute to provide more opportunities for stakeholder input into its process for developing and refining its framework.

As stated, the areas of concern that we have outlined above can be actively discussed with my staff, me, and LUNGevity's Scientific Advisory Board, which is made up of some of the world's leading experts in lung cancer biology, practice management, access to innovative medicines, and overall patient care. I encourage you and ICER to access our expertise.

I can be reached at 240-454-3100 or aeferris@lungevity.org if you have any questions or would like to engage in further dialogue.

Thank you for your attention to this very important matter.

Sincerely,

Andrea Stern Ferris
President and Chairman
LUNGevity Foundation

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