October 31, 2019

To: Premera Blue Cross
Sent via email

Re: Public Comment on Premera Blue Cross' Clinical Appropriateness Guidelines: Molecular Testing, Effective December 16, 2019

Dear Premara Blue Cross:

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 the 538,243 Americans living with the disease,[1] we appreciate the opportunity to comment on Premera's Clinical Appropriateness Guidelines on Molecular Testing that will go into effect on December 16, 2019.

As a leading patient advocacy group that represents the voice and interest of the national lung cancer survivor community by accelerating research to patients that is meaningful to them, empowering patients to be active participants in their care and care decisions, and helping remove barriers to access to high quality care, LUNGevity is well positioned to comment on Premera's Clinical Appropriateness Guidelines on Molecular Testing.

Timely access to diagnostics that inform treatment decisions is critical for all patients, especially cancer patients. In this era of unprecedented scientific advancements for the treatment of lung cancer, lung cancer patients diagnosed today have the advantage, opportunity, and right to learn about the unique biomarker profile (including genetic alterations and PD-L1 protein levels) of their cancer to help them identify the most appropriate treatment option. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, diagnosed in about 85 percent of people with lung cancer.[2,3] The complex nature of this disease requires personalized management plans for patients.[3] 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.[4-8] Now at least 10 driver mutations in adenocarcinoma have been identified (EGFR, ALK, ROS, RET, ERB2/HER2 mutations, ERB2/HER2 amplifications, MET amplifications, MET mutations, TRK, BRAF, KRAS).[7-10] In concert with the identification of an increasing number of targetable mutations is the development of novel, potent, and specifically targeted therapies. For example, at present, third generation EGFR[11] tyrosine

kinase inhibitors (TKIs) and anaplastic lymphoma kinase (ALK) TKIs[12] are used in clinical practice. With the increased use of targeted agents has come the problem of acquired resistance, where cancer cells inevitably develop resistance to the targeted agent. The EGFR T790M is an excellent example of a resistance mutation that develops in patients treated with first- and second-generation EGFR TKIs and that has a treatment option, osimertinib.[13] Lung cancer is now leading the field of precision medicine where research is rapidly progressing to (1) develop better targeted therapies that combat mechanisms of resistance, and (2) noninvasive sampling processes – such as liquid biopsies – that can monitor status of the resistance mutations, sequentially and in real time.[14]

Before implementing the proposed Clinical Appropriateness Guidelines on Molecular Testing, we encourage Premara to broaden the coverage policy to consider the clinical utility and analytical validity of a test platform rather than determine coverage based on arbitrary factors such as the number of genes on a panel. Currently, several NGS panels, varying in their range and depth of coverage, are utilized by clinicians in the United States (For example, Oncomine Dx - 23 genes, MSK-IMPACT - 468 genes, and FoundationOne - 324 genes).[15] The coverage of these panels are determined by factors such as their gene enrichment approach. Furthermore, the range of coverage also determines whether new biomarkers are present on the panel.

Presently, there is no scientific evidence that suggest that the **number of genes** included in a NGS panel clearly predict treatment decision-making and consequently patient outcomes. Rather, the quality of the NGS panel, as judged by its range of gene coverage, clinical utility and analytical validity, is what impacts patient outcomes.

We strongly urge Premera, Blue Cross to consider evidence from panels that clearly demonstrate utility and need of an NGS panel under the following circumstances:

Comprehensive NGS panel at diagnosis: Traditionally, **before a first-line treatment decision** was made for treating lung cancer patients, sequential testing for single mutations was performed. Now, the National Comprehensive Cancer Network (NCCN) guidelines recommend multiplex testing such as NGS platforms for making treatment decisions.[16] This multi-analyte testing approach is tissue-sparing when compared with sequential single-analyte testing where each negative result leads to rapid depletion of biopsy tissue. The NCCN guidelines also clearly state that a panel covering genes that have an appropriate FDA-approved targeted therapy as well as genes that have promising ongoing clinical trials should be used, again attesting to the fact that range and depth of coverage is more important than an arbitrary number.[16]

Comprehensive NGS panel at progression or recurrence: It is now well established that tumors evolve with time in response to targeted therapies.[17] These new molecular alterations confer acquired resistance to targeted therapies and are responsible for progression or recurrence after a patient has received first-line targeted treatments. A comprehensive NGS panel at the time of progression or recurrence helps identify these new mechanisms of resistance or tumor heterogeneity after treatment with a targeted agent, **often independent of the original driver mutation detected at the time of diagnosis**. In the recent FLAURA trial of first-line osimertinib in EGFR-positive NSCLC, NGS assays at the time of progression helped identify additional mechanisms of resistance such as mutations in the PIK3CA and the MET genes.[18,19] Currently, drugs targeting the PIK3CA and the MET genes are in clinical development, suggesting that an NGS panel is ideal for determining the next line of treatment for an NSCLC patient who has progressed on a targeted agent. Given the incredible pace at which lung cancer research and drug development is advancing, a fixed-number gene panel will not only impede access to new targeted therapies when a patient progresses on their first- or subsequent line of therapy, but also inhibit overall scientific innovation and drug development.

Immunotherapy biomarker-compatible panels: Currently, three immune checkpoint inhibitors (ICIs)[20-22], either as single agents or in combination, are approved for use in advanced-stage NSCLC, with another ICI's approval on the horizon[23]. Given these advances, patient selection for ICI use continues to be an area of intense investigation. Pembrolizumab is currently the only ICI with a requirement for PD-L1 immunohistochemistry.[20] However, PD-L1 expression is an imperfect biomarker for predicting ICI response, given that variability across PD-LI immunohistochemistry platforms and the heterogenous expression of PD-L1 protein. Recent evidence points toward the clinical utility of tumor mutational burden (TMB) as a predictive biomarker for ICIs[24] and suggests that TMB levels may, in fact, predict a unique subset of responders, independent of PD-L1 expression[25]. Based on these findings, the NCCN guidelines now recommends measurement of TMB as part of a patient's treatment decision-making process.[16] Given that small gene panels do not capture TMB, it is in the best interest of patients to receive comprehensive NGS panels that can help their treating physicians decide whether they may benefit from ICI.

As discussed above, access to high-quality, timely NGS testing is instrumental for matching patients to the appropriate targeted therapy or immunotherapy and advancing precision medicine. This access should be determined by the quality of scientific evidence available and not arbitrary parameters such as number of genes included in a panel.

LUNGevity is grateful for the opportunity to comment on Premera Blue Cross' Clinical Appropriateness Guidelines on Molecular Testing and we offer ourselves as a resource to partner with Premara to ensure that patients have access to high-quality biomarker testing. The recommendations outlined above can be discussed with me, my staff, 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 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 Chief Executive Officer
LUNGevity Foundation

ABOUT LUNGEVITY:

LUNGevity's mission is to improve outcomes for people diagnosed with lung cancer. Our goals are three-fold: (1) to accelerate research to patients that is meaningful to them; (2) to empower patients to be active participants in their 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. Additionally, we collaborate with other lung cancer patient advocacy groups and organizations, such as the American Lung Association and CHEST, who serve the lung cancer community.

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