LUNGEVITY
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November 15, 2018

Dr. James Almas
Medical Director
MolDX
17 Technology Circle
AG-315
Columbia, SC 29202
Submitted Electronically

Re: Proposed Local Coverage Determination: Inivata, InVisionFirst (DL37870)

Dear Dr. Almas:

On behalf of LUNGevity Foundation, the nation's preeminent lung cancer nonprofit that funds research, provides education and support, and builds communities for the 234,030 Americans diagnosed with lung cancer each year and the 541,035 Americans living with the disease, we appreciate the opportunity to submit our comments in response to the proposed Local Coverage Determination (LCD) for Inivata's InVisionFirst liquid biopsy for patients with lung cancer (DL37870).

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 applauds MolDX for providing a local coverage determination for the Inivata test and ensuring new testing options are available for lung cancer patients. In this era of unprecedented scientific advancements for the treatment of lung cancer, particularly in the field of biomarker testing, liquid biopsy tests, like Inivata's, are a promising new development that identify markers predictive of response to particular treatments for patients in a convenient, low cost, and quickly-responsive manner.

Non-small cell lung cancer (NSCLC) is the more common type of lung cancer, diagnosed in about 85 percent of people with lung cancer.[1,2] The complex nature of this disease requires personalized management plans for patients.[2] 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 patient.[3-7] 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).[6-9] 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[10] tyrosine kinase inhibitors (TKIs) and anaplastic lymphoma kinase (ALK) TKIs[11] 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. This mutation can be rapidly detected using a liquid biopsy test such as the cobas EGFR Mutation Test v2.[12] 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 assays – such as liquid biopsies – that can monitor status of the resistance mutations (e.g., cobas EGFR Mutation Test v2), sequentially and in real time.[13]

The utility of liquid biopsies in the clinical management of lung cancer is unquestionable, because 1 out of 4 NCSLC patients may be ineligible for a solid tissue biopsy.[14] We applaud MolDx's decision to cover liquid biopsy-based testing for such patients. In her ASCO 2017 presentation on biomarker testing for lung cancer, LUNGevity Scientific Advisory Board (SAB) member, Dr. Alice Shaw from Massachusetts General Hospital, pointed out that liquid biopsies may help in (1) initial detection of targetable mutations in advanced-stage NSCLC at the time of diagnosis, (2) identification of acquired resistance mutations in patients who have relapsed on targeted therapies, and (3) monitoring response to targeted therapies and predicting outcome in advanced-stage NSCLC patient.[15] As the science continues to evolve, the role of liquid biopsies in treatment decision-making for immunotherapies is becoming evident. In a recent report, a positive correlation between co-occuring mutations in the KRAS and LKB1/STK11 genes and lack of response to immune checkpoint blockade in advanced-stage NSCLC was demonstrated.[16] Furthermore, the utility of liquid biopsies to identify predictive biomarkers for immunotherapy, such as tumor mutational burden (TMB), is becoming increasingly established.[17] Therefore, the application of liquid biopsy-based multi-analyte NGS testing will become increasingly important, especially in the lung cancer space, where biomarker testing will have to keep pace with the development of newer targeted therapies and immunotherapies.

Given the utility of liquid biopsy and monitoring importance, we request that you reconsider the "patient is progressing on EGFR TKIs other than osimertinib" of the coverage guidance to include patients who have been treated with front-line osimertinib. The use of osimertinib in the first-line setting (FLAURA trial) offers a far superior median progression-free survival of 18.9 months versus 10.2 months median PFS offered by first- and second-generation EGFR TKIs.[18] With this progress has come the need to understand mechanisms of resistance to osimertinib in the first-line setting. In the FLAURA trial, mechanisms of resistance observed in nine patients studied includes a variety of genomic alterations (such as MET amplifications, PIK3CA mutations, or C797S mutations, for example) in the absence of an acquired T790M mutation. Despite the small sample size, this provocative data suggests that detection of resistance mutations such as PIK3CA or EGFR C797S in patients who have progressed on first-line osimertinib, using non-invasive approaches, may help determine second-line treatment options. Currently, drugs targeting MET amplification or PIK3CA are in clinical development and there is evidence suggesting that EGFR C797S is sensitive to first-generation EGFR inhibitors such as erlotinib. [19-21] Using a non-invasive test at the time of progression would not only be beneficial to the patient but also expedite the selection of second-line treatment options.

As a leading patient advocacy group that represents the voice and interest of the national lung cancer survivor community, we are excited about the role of liquid biopsies in clinical management of NSCLC. The discussion outlined above can be discussed with my staff, myself, and LUNGevity's SAB, 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 dialog.

LUNGevity is grateful for the opportunity to comment on this determination. 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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