June 20, 2019

To: Paul Gerrard, MD, Gabriel Bien-Willner MD PhD and Harry Feliciano, M.D., MPH
Medical Directors, Palmetto GBA MolDx Program

Re: Public Comment on Proposed/Draft Local Coverage Determination (LCD): **MolDX: Guardant360® Plasma-Based Comprehensive Genomic Profiling in Solid Tumors (DL38043)**

Dear Drs. Gerrard, Bien-Willner, and Feliciano:

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 submit our comments in response to the proposed Guardant360 Local Coverage Determination, which was first posted on March 28, 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 applauds Palmetto for providing a draft local coverage determination for the Guardant360 test that, if finalized as proposed, would ensure 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, such as those performed on a multi-analyte, next-generation sequencing (NGS) platform like the Guardant360 test, are a new development that identify biomarkers predictive of response to particular treatments for patients in a non-invasive manner that can return test results more quickly than other technologies.

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. This mutation can be rapidly detected using a liquid biopsy test such as the Guardant360 and the cobas EGFR Mutation Test v2.[13-15] 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 (e.g., cobas EGFR Mutation Test v2), sequentially and in real time.[16]

Current role of liquid biopsies in the clinical management of lung cancer:

The utility of liquid biopsies in the clinical management of lung cancer is unquestionable for several reasons. First, sample from a tissue biopsy may be inadequate to complete comprehensive biomarker testing. The Lung Cancer Mutation Consortium reports that only 48% of the starting 1542 subjects enrolled had comprehensive biomarker testing due to the issue of inadequate biopsy tissue.[17] Second, tissue acquisition for a lung biopsy comes with significant complications. In a claims analysis conducted by Karve et al, 63% of patients complained of at least one complication (difficulty breathing, chest pain, or pneumothorax) following a lung biopsy.[18] We applaud Palmetto's decision to propose coverage for 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.[19] As the science continues to evolve, the role of liquid biopsies in treatment decision-making for immunotherapies is also becoming evident. In a recent report, a positive correlation between co-occurring mutations in the KRAS and LKB1/STK11 genes and lack of response to immune checkpoint blockade in advanced-stage NSCLC was demonstrated.[20] Platforms such as Guardant360's liquid biopsy are able to detect such "exclusionary" changes. Furthermore, the utility of liquid biopsies to identify predictive biomarkers for immunotherapy, such as tumor mutational burden (TMB), is becoming increasingly established.[21] Therefore, the application of liquid biopsy-based 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.

A true comprehensive approach to biomarker testing:

Since the development of the first commercially available liquid biopsy approach (cobas EGFR Mutation Test v2), the science has considerably evolved. Current liquid biopsy technologies based on an NGS platform can detect multiple actionable mutations at the same time. In a recent study by Aggarwal and colleagues, in a sample of 323 NSCLC patients, 94 patients received a liquid biopsy test at the time of diagnosis (at the discretion of the treating physician). In this subset of patients, a targetable mutation was detected in 33%, suggesting that a comprehensive biopsy platform may be sufficient for treatment commencement.[22] Among the remaining 229 patients who had concurrent plasma and tissue NGS or were unable to have tissue NGS, a therapeutically targetable mutation was detected in tissue alone for 21% of patients, whereas the addition of plasma testing increased this number to 36%. The detection of targetable mutations using only a liquid biopsy platform did not impact the clinical course of the disease. Patients in plasma only and plasma + tissue groups had similar outcomes to targeted therapies.[22] These findings have been replicated in the recent Noninvasive vs. Invasive Lung Evaluation (NILE) study where the addition of a cell free DNA (cfDNA)-based NGS assay to tissue-based NGS increased the detection of an actionable mutation by 48% within a shorter turnaround time, including those with negative, not assessed, or insufficient tissue results.[23]

However, it is important to keep in mind that all NSCLCs do not shed enough DNA that would enable detection by cfDNA-based technologies.[19] Keeping this caveat in mind, we suggest that the optimal approach to receiving the most comprehensive picture of a patient's tumor at the time of diagnosis (before the start of first line treatment) may be a dual NGS panel, using both a tissue- and a liquid-based approach. This dual approach would mitigate the risk of missing actionable mutations and also for the treating physician to commence treatment with the "first available" results.

Expanding the one test per primary cancer limit for NGS:

Access to high-quality, timely NGS testing (at diagnosis and at recurrence or progression) is instrumental for matching patients to the appropriate targeted therapy and advancing precision medicine.

LUNGevity recognizes that Palmetto is bound by the limitations in the NCD to only cover one test per primary cancer, and we acknowledge that the language in the draft LCD indicates that Palmetto seems to recognize the importance of testing at different time points during the course of a tumor. We appreciate Palmetto's interpretation of the limitation under the NCD in a way that can benefit more Medicare beneficiaries, and we are

committed to continue to work with CMS to expand this limitation of the NCD to allow for multiple tests per primary cancer —consistent with clinical evidence and practice—to achieve appropriate access for Medicare beneficiaries.

New evidence clearly establishes the value of multiple NGS tests in the duration of a patient's treatment journey. An NGS panel at the **time of diagnosis** (**primary cancer before first-line treatment is initiated**) and subsequent NGS panels at **recurrence/progression** on first and subsequent lines of therapy fulfill similar and unique purposes.

NGS at diagnosis: An NGS panel at the time of diagnosis simultaneously checks for multiple clinically actionable mutations that help guide physicians to targeted therapies to treat NSCLC.[24] This, in turn, helps timely matching of the patient to the right targeted therapy should a targetable mutation be present. The National Comprehensive Cancer Network (NCCN) guidelines recommend multiplex testing such as NGS platforms for making treatment decisions.[25]

NGS at progression or recurrence: It is now well established that tumors evolve with time in response to targeted therapies.[26] 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. An 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 a C797S mutation in the EGFR gene and mutations in the PIK3CA and the MET genes.[27,28] 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. [27,29,30] This suggests that an NGS panel is ideal for determining the next line of treatment for an NSCLC patient who has progressed on a targeted agent and reiterates the importance of multiple NGS panels in a patient's lifetime.

As stated above, new mutations in NSCLC are being discovered very quickly and limiting access to one test per a patient's lifetime for a single primary cancer may be detrimental to their treatment and could both prevent their physicians from identifying the accurate first-line targeted therapy that may save their life and impede access to subsequent lines of therapy.

One of the crucial benefits of NGS testing is allowing a complete molecular profile of the patient's tumor before first-line treatment initiation and after treatment(s), and allowing

novel classes of drugs to be offered to the patient as their tumor evolves. Offering an NGS panel at the time of diagnosis and at recurrence or progression also allows for identifying driver mutations that have drugs in clinical development both as first-line treatment options and at progression or recurrence, thereby allowing patients to be enrolled rapidly in clinical trials. This is especially crucial since NCCN guidelines suggest that clinical trials may often offer the best treatment option in first- and subsequent-line settings.[25]

LUNGevity is grateful for the opportunity to comment on the above-captioned LCD and is eager to work with Palmetto to continue to ensure that patients have timely 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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