



BONNIE J. ADDARIO
LUNG CANCER
FOUNDATION



SAVING LIVES AND ADVANCING
RESEARCH BY EMPOWERING
THOSE LIVING WITH AND
AT RISK FOR LUNG CANCER.

LungCancerAlliance.org

1700 K Street NW, Ste 660
Washington, DC 20006

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Health Evidence Review Commission
500 Summer St. NE, E-65
Salem OR 97301
HERC.Info@state.or.us (503) 373-1985

Submitted electronically: HERC.Info@state.or.us

Re: Draft Coverage Guidance: FDA-approved Next Generation Sequencing Tests for Tumors of Diverse Histology

Dear Health Evidence Review Commission Members,

Lung Cancer Alliance (LCA) and the Bonnie J. Addario Lung Cancer Foundation (ALCF) appreciate the opportunity to provide comments on the Oregon Health Evidence Review Commission's (HERC) draft Coverage Guidance document on *FDA-Approved Next Generation Sequencing (NGS) Tests for Tumors of Diverse Histology*. LCA and ALCF are national and international patient advocacy groups, representing lung cancer patients, survivors and caregivers, improving care, education, and research to help save lives and address the leading cause of cancer death - nearly a third of this nation's total cancer mortality burden. Our joint societies strongly disagree with the HERC evidence summary that is based solely on three published papers in 2015, with a primary justification from one France paper. There are other supporting papers establishing the positive clinical utility of NGS testing and its impact on clinical outcomes and decision making and the reason why Medicare and the FDA have approved NGS coverage.

Our joint societies urge the Oregon HERC to revise their draft NGS coverage guidance document and caution against the proposed two-tiered coverage recommendation that is in direct conflict with the NGS National Medicare coverage decision as well as the Food and Drug Administration (FDA) approval. The draft HERC NGS coverage guidance will prevent advanced cancer patients (Medicaid Oregon patients etc.) from obtaining medically reasonable and necessary NGS testing. This testing helps diagnose and match patients with the right targeted therapies and clinical trials earlier in the treatment paradigm that can have life-changing results, increase survival rates, and potentially lead to less overall system costs by prevention of advanced disease.

The Medicare and FDA processes are both scientific and evidence-based and have a high benchmark in making a favorable coverage recommendation. It is alarming that Oregon HERC has deemed "insufficient evidence" for all NGS testing which is in direct opposition to the Medicare and the FDA coverage approvals for NGS. CMS concluded:

"Based on the evidence reviewed we believe that FDA-approved and FDA-cleared laboratory in vitro diagnostic tests using NGS as a companion diagnostic is sufficient for patients with

recurrent, relapsed, refractory, metastatic, or advanced stage III, or stage IV cancer to expect meaningful improvement in their health outcomes, such as PFS. These FDA-approved or cleared companion diagnostics using NGS have demonstrated improvements in patient health outcomes when used by the treating physician and the patient to guide the selection of proven treatments. Therefore, we are covering such a test..."

CMS NGS NCD

In March 2018, the first next-generation sequencing (NGS)-based (FoundationOne CDx™), broad companion diagnostic for all solid tumors was approved for national Medicare coverage by the Centers for Medicare and Medicaid Services (CMS) via their National Coverage Determination (NCD) Process and FDA parallel review. The CMS' evidence review process included 280 relevant articles that were the basis for their positive national coverage decision for all Medicare beneficiaries. See below CMS review process and press release.

During the NCD process, CMS evaluated relevant clinical evidence to determine whether or not the NGS evidence was of sufficient quality to support a finding that an item or service falling within one or more benefit categories is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§ 1862 (a)(1)(A)). This appraisal of evidence during a national coverage Medicare analysis enables CMS to determine to what degree they are confident that: 1) the specific assessment of a clinical question relevant to the coverage request can be answered conclusively; 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS Press Release: CMS finalized a National Coverage Determination that covers diagnostic laboratory tests using Next Generation Sequencing (NGS) for patients with advanced cancer (i.e., recurrent, metastatic, relapsed, refractory, or stages III or IV cancer). CMS believes when these tests are used as a companion diagnostic to identify patients with certain genetic mutations that may benefit from U.S. Food and Drug Administration (FDA)-approved treatments, these tests can assist patients and their oncologists in making more informed treatment decisions. Additionally, when a known cancer mutation cannot be matched to a treatment then results from the diagnostic lab test using NGS can help determine a patient's candidacy for cancer clinical trials.

This NCD recognizes the importance of analytical and clinical validation of the diagnostic laboratory test that is part of FDA approval or clearance and provides national coverage after demonstration that use of the diagnostic laboratory test guides the management and treatment of the patient improves health outcomes. Tests that gain FDA approval or clearance as an in vitro companion diagnostic will automatically receive full coverage under this final NCD, provided other coverage criteria are also met. Coverage determinations for other diagnostic laboratory tests using NGS for Medicare patients with advanced cancer will be made by local Medicare Administrative Contractors. In addition, after considering all public comments, this final decision expanded coverage to patients with relapsed, refractory or stage III cancers. The final decision also extends coverage to repeat testing when the patient has a new primary diagnosis of cancer.

Relevant Studies

In addition to the 280 papers and articles reviewed by CMS, we also point the HERC to several articles that support the use of NGS testing and linkage to prolonged survival rates in metastatic lung adenocarcinoma patients. The [Lung Cancer Mutation Consortium](#) (Kris et al.), the median overall survival was extended by more than one year in patients with an oncogenic driver who received genotype-directed therapy versus those who did not. The [IMPACT](#) study concluded that the median progression-free survival in those who received matched versus nonmatched therapy was 4.0 months and 2.8 months, respectively (hazard ratio, 0.67), and median overall survival was 9.3 and 7.3 months, respectively (HR, 0.72). The 3-year overall survival rate was 15% versus 7%, respectively, and 10-year survival was 6% and 1%, respectively. In Hematology and Oncology, an [impact study](#) addresses targeted therapy and survival rates in lung cancer versus chemotherapy. See below for the relevant excerpt.

*Over the last few years, the use of molecular profiling to direct patients to specific targeted therapies has irrevocably changed how we treat lung cancer. Despite this, many randomized trials have failed to show an apparent survival advantage from this approach in stage IV disease. Are we using targeted therapy for no real benefit, lulled into a false sense of security by impressive radiographic responses—only to shorten the patient’s life later? Of course not, as anyone who treats lung cancer patients can tell by how the quality and quantity of our patients’ lives have improved in the last few years. **Profound and durable responses now can be achieved in an increasing proportion of patients across a range of actionable abnormalities; historical trends and meta-analyses of trials all suggest the overall survival benefit is really there; and, when large populations are explored, key subsets of patients, who are likely to be the ones harboring the most actionable molecular markers, are now living longer than they did before targeted therapies were available.** Is it easy to point to a single irrefutable piece of evidence proving the survival benefit of targeted therapy in lung cancer? No, but it is also impossible to ignore.*

Also, there have been updates to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]), supporting broad or expanded molecular profiling to match patients for available therapies or clinical trials. In particular, the NSCLC Panel strongly advised "broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC."

Our joint societies recommend that the HERC at minimum use a similar if not the same evidence review process as CMS and FDA as previously described above. We disagree with the HERC report that states "randomized clinical trials utilizing next-generation sequencing are certainly feasible and appropriate and would not need to be of long duration for the most prevalent types of cancer." Use of RCTs while often considered the gold standard for robust studies, also have limitations and should be utilized with thoughtful consideration regarding duration, medical appropriateness, medical ethics, and patient need. Patients with metastatic cancer are very ill, without time, and in need of NGS testing for targeted therapies. Due to advanced metastatic cancer complications and low patient enrollments, it is unlikely and uncertain how an RCT is feasible or ethical.

Regarding companion diagnostic indication of FoundationOne CDx, an RCT is inappropriate, as you cannot randomize these patients (i.e., no-test control). For the companion diagnostic indications of FoundationOne CDx, relevant biomarkers included in the assay are medically reasonable and necessary to identify patients who are candidates for the companion therapies. Multiple biomarkers are

appropriate to identify for targeted therapies with patients that have several tumor types, and the use of the NGS panels can help with limited tissue scenarios for testing. These patients cannot be randomized to a control arm with sequential testing with single marker tests. For example, the FDA allows single-arm studies when approving new therapeutics in these patient groups (e.g., biomarker status).

We have concerns about the draft NGS HERC coverage guidance document that will limit access to this potentially life-saving testing. Notably, many patients with lung cancer find they have a mutational profile (for example an EGFR mutation in exon 19) that suggests treatment with an FDA-approved targeted therapy, and at the point of recurrence they may have new mutations (such as EGFR-T790M or an additional MEK mutation) that could point to a different FDA-approved therapeutic or an appropriate clinical trial. As the current draft NGS HERC coverage guidance language stands, it will impose significant patient access issues. We know from our own experiences that many lung cancer patients are unable to have tissue-based NGS testing because there is insufficient biopsy material due to complications such as collapsed lungs.

Many of the newer agents are beginning to be studied in non-metastatic cancer. We believe that coverage should be available to those who need it including advanced, and non-metastatic disease. This point is particularly critical with the recent advance of lung cancer screening, where we will now be able to find lung cancers at an earlier, more treatable stage. Having patients matched to appropriately targeted treatments and clinical trials earlier in the treatment paradigm is more patient-centric and can lead to cost-effectiveness by preventing advanced disease.

Summary

In summary, careful consideration of the CMS and FDA NGS coverage decision and respective evidence reviews, as well as public comments and additional relevant studies should be closely evaluated. We recommend that the HERC replace their draft recommendation with at minimum the CMS NCD NGS coverage language.

We believe there is sufficient data to support coverage for next-generation sequencing tests which help patients and their physicians identify the best treatment options based on the molecular makeup of their cancer. LCA has direct experience with these tests through our LungMATCH program that provides testing to help identify a patient's personalized treatment options. Based on our experience, we believe that appropriate, high-quality testing is helping patients with lung cancer survive longer and with a better quality of life.

Our joint societies thank you for this opportunity to comment on this important coverage guidance. If you have any questions, please contact Anita McGlothlin at amcglathlin@lungcanceralliance.org.

Sincerely,



Laurie Fenton Ambrose
President & CEO
Lung Cancer Alliance



David M. LeDuc
Executive Director
Bonnie J. Addario Lung Cancer Foundation