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NCCN Guidelines Panel: Non-Small Cell Lung Cancer

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Non-Small Cell Lung Cancer (NSCLC) to review the enclosed information on plasma or cell-free/circulating tumor DNA (ctDNA) next-generation sequencing (NGS) testing for the appropriate identification of patients eligible for targeted therapy.

Specific change #1:

We respectfully request that the language for plasma-based NGS testing be updated to reflect the latest advances in plasma testing as an appropriate initial option for genomic testing at diagnosis in metastatic NSCLC. Suggest the proposed language below to allow health care providers the choice of either ctDNA or tissue testing depending on the clinical situation, with a recommendation that plasma-based testing be followed by reflex tissue testing if no ctDNA alterations are detected. Additionally, we respectfully request to update the language around ctDNA testing to be considered in specific clinical circumstances as proposed below.

NCCN NSCLC v4.2021	Current Language in the Guidelines	Proposed Language
NSCL-18	Establish histologic subtype[a] with adequate tissue for molecular testing (consider rebiopsy[kk] if appropriate)	Establish histologic subtype[a] with adequate tissue for molecular testing (consider plasma testing or rebiopsy[kk] if appropriate)
NSCL-18 and NSCL-19 Footnote kk	If there is insufficient tissue to allow testing for all of *EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET, and RET*, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.	If there is insufficient tissue to allow testing for all of *EGFR, ALK, ROS1, BRAF, NTRK1/2/3, MET, and RET*, plasma testing should be done. Reflex to tissue biopsy if no ctDNA alterations are detected. If neither plasma or tissue testing is feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.

NSCL-H (5 of 5)	The use of cell-free/circulating tumor DNA testing can be considered in specific clinical circumstances, most notably: • If a patient is medically unfit for invasive tissue sampling • In the initial diagnostic setting, if following pathologic confirmation of a NSCLC diagnosis there is insufficient material for molecular analysis, cell-free/circulating tumor DNA should be used only if follow-up tissue-based analysis is planned for all patients in which an oncogenic driver is not identified.	Some clinical circumstances may warrant special consideration of cell-free/ctDNA testing, most notably: • When a tissue biopsy is not feasible • If tissue is insufficient or of uncertain adequacy • When a faster turnaround time is critical to inform optimal treatment decisions.
MS-13	However, cfDNA testing can be used in specific circumstances if 1) the patient is not medically fit for invasive tissue sampling, or 2) there is insufficient tissue for molecular analysis and follow-up tissue-based analysis will be done if an oncogenic driver is not identified.	The availability of validated, FDA-approved NGS assays supports use of plasma-based biomarker testing as an appropriate initial testing option at diagnosis, provided every effort is made to reflex to tissue testing if no circulating tumor DNA alterations are identified. However, some clinical circumstances may warrant special consideration of cell-free/ctDNA testing. Most notably, when a tissue biopsy is not feasible, if tissue is insufficient or of uncertain adequacy, or when a faster turnaround time is critical to inform optimal treatment decisions.

<u>Rationale:</u>
Data has shown non-inferiority of plasma testing to tissue testing for the identification of metastatic NSCLC patients for targeted therapy. The high specificity or positive predictive value (PPV) for targetable driver mutations means that positive ctDNA-based results are clinically actionable and tissue-based testing can be avoided in some patients.[1] Additionally, ctDNA based testing may allow for more patients with actionable biomarkers to be identified in comparison to tissue.

In a recently published report which prospectively compared tissue genotyping to ctDNA plasma genotyping, 0/186 patients were genotyped for eight biomarkers (*ALK, EGFR, ROS1, BRAF*

V600E, RET, MET exon 14 skipping variants, ERBB2 (HER2), and KRAS) evaluated utilizing SOC tissue genotyping per physicians choice, compared with 90.8% of patients tested using a cell-free DNA-based NGS assay. Additionally, the authors reported that if the primary modality for molecular testing was tissue-based genotyping, 68 of the 119 patients (57.1%) with an actionable biomarker would have been identified by tissue, with an additional 42.9% of patients identified on reflex ctDNA testing. In contrast, using ctDNA genotyping as the initial test, 80.7% of patients with an actionable biomarker would have been identified, with the remaining 19.3% of patients identified on reflex tissue testing.[2]

Plasma-based testing offers an alternative to tissue testing in that it is more readily accessible, less invasive, can provide results faster, and is associated with clinical responses and outcomes similar to those for tissue. Incorporation of plasma-based NGS testing for genotyping patients at diagnosis may, therefore, allow more NSCLC patients with driver mutations to be identified and treated appropriately.[1,3,4]

Specific change #2:

We respectfully request to update the guideline language to clarify that ctDNA testing standards and guidelines *are* established since there are now established analytical validation protocols in place.

NCCN NSCLC v4.2021	Current Language in the Guidelines	Proposed Language
MS-13 NSCL-H (5 of 5)	Standards and guidelines for cell-free DNA (cfDNA)/circulating tumor DNA testing for genetic variants have not been established.	Standards and guidelines for cell-free DNA (cfDNA)/circulating tumor DNA testing for genetic variants are established.

Rationale:

A standardized approach to developing accurate ctDNA tests was an identified gap in guaranteeing the legitimacy of results used to guide treatment decisions. The Blood Profiling Atlas in Cancer Consortium developed analytical protocols to validate NGS-based ctDNA testing with guidance on aspects of validation studies that include: limits of detection, accuracy, and sample functional characterization.[5] Additionally, the FDA has set the standards for evaluating both analytic and clinical performance. The recent FDA approvals of Guardant360® CDx and FoundationOne® Liquid CDx demonstrate that these tests have met the rigor of the FDA standards and are validated plasma-based tests.[6,7]

Specific change #3: We respectfully request that the recommendation for "broader molecular profiling" be clarified and more specifically defined.

NCCN NSCLC v4.2021	Current Language in the Guidelines	Proposed Language
NSCL-18 Footnote mm NSCL-H (1 of 5) MS-13 MS-14	The NCCN NSCLC Guidelines Panel strongly advises 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.	The NCCN NSCLC Guidelines Panel strongly advises comprehensive genomic profiling utilizing either cell-free/ctDNA or tissue next-generation sequencing tests, 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. Comprehensive genomic profiling is a key component of the improvement of care of patients with NSCLC.

Rationale:
There have been reports of healthcare payors considering large multi-gene panels as experimental and investigational. The rationale may likely be correlated to the low number of actionable genes compared to the large gene panels that are sequenced as part of NGS testing. Payors are skeptical that large multi-gene panels meet the clinical utility threshold and without more specific language some payors have determined an arbitrary number of genes (e.g. 50) to be acceptable for coverage.[8] The two plasma-based NGS tests recently approved by the FDA report alterations in 55 genes (Guardant360®) and 324 genes (FoundationOne® Liquid CDx).[6,7] Given the wide variation in panel size for the various FDA-approved assays and LDTs, a more definitive recommendation for comprehensive genomic profiling would help make testing for biomarkers accessible and allow more patients with rare driver mutations to be identified and treated appropriately.

Sincerely,
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[3] Aggarwal C, Thompson JC, Black TA, et al. Clinical Implications of Plasma-Based Genotyping With the Delivery of Personalized Therapy in Metastatic Non-Small Cell Lung Cancer. *JAMA Oncol*. 2019;5(2):173-180.
[4] Leighl NB, Page RD, Raymond, VM, et al. Clinical Utility of Comprehensive Cell-Free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non-Small Cell Lung Cancer. *Clin Cancer Res*. 2019. http://dx.doi.org/10.1158/1078-0432.CCR-19-0624.
[5] Godsey JH, Silvestro A, Barrett JC, et al. Generic Protocols for the Analytical Validation of Next-Generation Sequencing-Based ctDNA Assays: A Joint Consensus Recommendation of the BloodPAC's Analytical Variables Working Group. *Clin Chemistry.* 2020; 66(9): 1156-1166.
[6] Guardant360® CDx Summary of Safety and Effectiveness Data (SSED)
[7] FoundationOne® Liquid CDx Summary of Safety and Effectiveness Data (SSED)
[8] American Cancer Society (ACS) Cancer Action Network (CAN) and LUNGevity Foundation. Payer Coverage Policies of Tumor Biomarker Testing. https://www.fightcancer.org/sites/default/files/ACS%20CAN%20and%20LUNGevityPayer%20Coverage%20Policies%20of%20Tumor%20Biomarker%20Testing.pdf. Published September 2020. Accessed March, 10, 2021.