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NCCN Guidelines Panel: Non-Small Cell Lung Cancer

On behalf of Illumina, I respectfully request the NCCN Non-Small Cell Lung Cancer guideline panel to review the enclosed recommended guideline changes to support the use of next-generation sequencing (NGS)-based multi-gene testing in preference to single-gene testing.

Specific Requested Changes:

Below are recommended changes for the NCCN NSCLC 3.2018 Guidelines. We recommend NGS assays be used as the preferred method for molecular testing as suggested by Guideline footnote ii (pg. NSCL-17): “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.”

FDA Clearance:

The recommendation of the NGS technique does not have any one specific product associated with it and, therefore, is not FDA cleared.

Rationale:

Our recommendation to use an NGS-based technique as the preferred method for NSCLC-related biomarker assessment is based on growing evidence to support the usage of NGS in a clinical setting^{1,2}. There are multiple NGS biomarker panel assays that have been validated and proven to detect mutations, indels, gene rearrangements (i.e. fusions), as well as copy number variations (CNVs) in NSCLC tumor tissue^{3,4,5,6,7}. NGS meets the current NCCN NSCLC 3.2018 recommendations for broad molecular profiling across multiple clinically significant biomarker targets, including, but not limited to EGFR, BRAF, ALK and ROS1. We propose that NGS-based broad molecular profiling be recommended as the preferable way to begin tumor testing. Using one consolidated test with multiple clinically relevant markers can help preserve tissue and identify additional driver or resistance mutations, better guiding therapeutic decision making. Numerous NGS assays are validated to identify patients whose tumors contain most, if not all, of the genetic alterations targeted by approved therapies (eg, EGFR, BRAF, ALK or ROS1 alterations)^{6,7,8,9}.

Additionally, in the case of initial resistance or acquired resistance leading to disease progression, NGS is most capable of identifying those resistance mutations.^{10,11} Comprehensive molecular screening by NGS can facilitate and expedite access to clinical trials, thus enabling broader testing of novel therapies.^{1,12} Consistent with the NCCN recommendation to steer patients to therapeutic clinical trials, NGS-based broad molecular profiling finds alterations that indeed provide a match to targeted therapies in >65% of patients with NSCLC.¹³

Additional information supporting this will be found in NSCL-G (footnote hh) and footnote ii suggesting broad molecular testing for finding driver mutations to recommend targeted therapies or clinical trials.

Proposed Changes:

NSCL-17: pg30

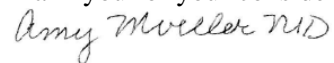
Current Language: under **TESTING^{hh}** heading:

- Molecular Testing
 - EGFR Mutation testing
 - ALK Testing
 - ROS Testing
 - BRAF Testing
 - Testing should be conducted as part of a broad molecular profilingⁱⁱ

Bullet point should be changed to:

- Molecular Testing
 - EGFR Mutation testing
 - ALK Testing
 - ROS Testing
 - BRAF Testing
 - Consider NGS-based assays that include EGFR, ALK, ROS1, and BRAF as part of a broad molecular profiling strategy.

Thank you for your consideration,



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The following articles are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also authors of some of these publications.

1. Cheng, Donovan T., Talia N. Mitchell, Ahmet Zehir, Ronak H. Shah, Ryma Benayed, Aijazuddin Syed, Raghu Chandramohan, et al. "Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A Hybridization Capture-Based Next-Generation Sequencing Clinical Assay for Solid Tumor Molecular Oncology." *The Journal of Molecular Diagnostics* 17, no. 3 (May 1, 2015): 251–64. <https://doi.org/10.1016/j.jmoldx.2014.12.006>.
2. Lih, Chih-Jian, Robin D. Harrington, David J. Sims, Kneshay N. Harper, Courtney H. Bouk, Vivekananda Datta, Jonathan Yau, et al. "Analytical Validation of the Next-Generation Sequencing Assay for a Nationwide Signal-Finding Clinical Trial: Molecular Analysis for Therapy Choice Clinical Trial." *The Journal of Molecular Diagnostics: JMD* 19, no. 2 (2017): 313–27. <https://doi.org/10.1016/j.jmoldx.2016.10.007>.
3. Foundation Medicine PreMarket Approval(PMA) Foundation One CDx Panel [package insert]. Cambridge, MA : 2017
4. Zehir A, Benayed R, Shah RH, et al. Mutational Landscape of Metastatic Cancer Revealed from Prospective Clinical Sequencing of 10,000 Patients. *Nature medicine*. 2017;23(6):703-713. doi:10.1038/nm.4333.
5. Li, Marilyn M., Michael Datto, Eric J. Duncavage, Shashikant Kulkarni, Neal I. Lindeman, Somak Roy, Apostolia M. Tsimberidou, et al. "Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists." *The Journal of Molecular Diagnostics: JMD* 19, no. 1 (2017): 4–23. <https://doi.org/10.1016/j.jmoldx.2016.10.002>.
6. Hovelson, Daniel H., Andrew S. McDaniel, Andi K. Cani, Bryan Johnson, Kate Rhodes, Paul D. Williams, Santhoshi Bandla, et al. "Development and Validation of a Scalable Next-Generation Sequencing System for Assessing Relevant Somatic Variants in Solid Tumors." *Neoplasia (New York, N.Y.)* 17, no. 4 (April 2015): 385–99. <https://doi.org/10.1016/j.neo.2015.03.004>.
7. Pekar-Zlotin, Marina, Fred R. Hirsch, Lior Soussan-Gutman, Maya Ilouze, Addie Dvir, Theresa Boyle, Murry Wynes, et al. "Fluorescence in Situ Hybridization, Immunohistochemistry, and next-Generation Sequencing for Detection of EML4-ALK Rearrangement in Lung Cancer." *The Oncologist* 20, no. 3 (March 2015): 316–22. <https://doi.org/10.1634/theoncologist.2014-0389>.
8. Han, Ji-Youn, Sun Hye Kim, Yeon-Su Lee, Seung-Youn Lee, Jung-Ah Hwang, Jin Young Kim, Sung Jin Yoon, and Geon Kook Lee. "Comparison of Targeted Next-Generation Sequencing with Conventional Sequencing for Predicting the Responsiveness to Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor (EGFR-TKI) Therapy in Never-Smokers with Lung Adenocarcinoma." *Lung Cancer (Amsterdam, Netherlands)* 85, no. 2 (August 2014): 161–67. <https://doi.org/10.1016/j.lungcan.2014.04.009>.
9. Tuononen, Katja, Satu Mäki-Nevala, Virinder Kaur Sarhadi, Aino Wirtanen, Mikko Rönty, Kaisa Salmenkivi, Jenny M. Andrews, et al. "Comparison of Targeted Next-Generation Sequencing (NGS) and Real-Time PCR in the Detection of EGFR, KRAS, and BRAF Mutations on Formalin-Fixed, Paraffin-Embedded Tumor Material of Non-Small Cell Lung Carcinoma-Superiority of NGS." *Genes, Chromosomes & Cancer* 52, no. 5 (May 2013): 503–11. <https://doi.org/10.1002/gcc.22047>.
10. Lindeman, Neal I., Philip T. Cagle, Dara L. Aisner, Maria E. Arcila, Mary Beth Beasley, Eric Bernicker, Carol Colasacco, et al. "Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors: Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology." *The Journal of Molecular Diagnostics: JMD*, January 23, 2018. <https://doi.org/10.1016/j.jmoldx.2017.11.004>.
11. Kalemkerian, Gregory P., Navneet Narula, Erin B. Kennedy, William A. Biermann, Jessica Donington, Natasha B. Leighl, Madelyn Lew, et al. "Molecular Testing Guideline for the Selection of Patients With Lung Cancer for Treatment With Targeted Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update." *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, February 5, 2018, JCO2017767293. <https://doi.org/10.1200/JCO.2017.76.7293>.
12. Garcia, Elizabeth P., Alissa Minkovsky, Yonghui Jia, Matthew D. Ducar, Priyanka Shivdasani, Xin Gong, Azra H. Ligon, et al. "Validation of OncoPanel: A Targeted Next-Generation Sequencing Assay for the Detection of Somatic Variants in Cancer." *Archives of Pathology & Laboratory Medicine* 141, no. 6 (June 2017): 751–58. <https://doi.org/10.5858/arpa.2016-0527-OA>.
13. Drilon, Alexander, Lu Wang, Maria E. Arcila, Sohail Balasubramanian, Joel R. Greenbowe, Jeffrey S. Ross, Phil Stephens, et al. "Broad, Hybrid Capture-Based Next-Generation Sequencing Identifies Actionable Genomic Alterations in Lung Adenocarcinomas Otherwise Negative for Such Alterations by Other Genomic Testing Approaches." *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research* 21, no. 16 (August 15, 2015): 3631–39. <https://doi.org/10.1158/1078-0432.CCR-14-2683>.