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\(^1\). 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 heading:

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

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,

Amy Mueller MD
Medical Director, Oncology
Illumina
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.


