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NCCN Guidelines Panel: Non-Small Cell Lung Cancer (NSCLC), as pertaining to version 3.2020

FDA status: Guardant Health's **Guardant360** plasma-based comprehensive genomic profiling laboratory test has been designated for *Breakthrough Review* by the FDA (and is Clinical Laboratory Improvement Act-certified, College of American Pathologists-accredited, and New York State Department of Health-approved).

On behalf of Guardant Health, I thank the NSCLC Guidelines Panel and staff for their rapid and thorough updates to the Guidelines, which incorporate the best and latest science pertaining to treatment selection in advanced cancer. To improve the understanding of these invaluable Guidelines, I respectfully request that the Panel consider the following suggestion to clarify the language used to describe the recommended expanded molecular testing.

Request: I recommend that the term *comprehensive genomic profiling* (CGP) replace *broad molecular profiling* to align with the naming convention used by Medicare and other payers.

Rationale: *Comprehensive genomic profiling* is the term used by Medicare's Molecular Diagnostics (MolDX) Program for next-generation sequencing (NGS) of all NCCN-recommended genomic targets.[1] It implies that a test thus defined evaluates *all four* major types of alterations (single nucleotide variants, indels, fusions, and copy number amplifications),[2] and that *whole exons* are sequenced, not necessarily all exons, but the *critical exons* defined as those known to harbor less common but activating and targetable mutations, such as *EGFR* G719A (which may lead to selecting afatinib over erlotinib). Multiple Blues and other private plans have also changed their naming convention to *comprehensive genomic profiling*.[3] Using this consistent nomenclature will provide more clarity for clinicians following the Guidelines and help them differentiate hotspot testing (generally IHC or qPCR-

[1] In its Local Coverage Article on "Targeted and Comprehensive Genomic Profile Next-Generation Sequencing Testing in Cancer" (attached), MolDX defines *CGP* as follows:

> "CGP refers to NGS-based molecular assays that provide additional insight beyond individual gene hotspots; these assays seek to describe the genomic makeup of a tumor and can help identify underlying mechanisms of disease to guide clinical decision making. These tests include not only mutations in individual relevant genes, but also patterns of mutations across related genes in established cancer pathways and often include an assessment of overall mutational burden. These tests typically involve sequencing of entire exonic regions of genes of interest (within a comprehensive gene panel or whole exome sequencing), and may also include selected intronic regions. CGP can detect multiple types of molecular alterations (i.e., SNVs, small and large INDELs, copy number alterations (CNAs), structural variants (SVs), and splice-site variants) in a single assay. Patterns of mutations seen across multiple genes may be used to infer clinically relevant etiologies, such as DNA mismatch repair deficiency and microsatellite instability, and total mutational load/burden (TMB) may be determined. CGP testing may also include RNA sequencing to detect structural variations, such as translocations or large deletions, and to detect functional splicing mutations. CGP is not defined as a targeted panel by MolDX."

MolDX consistently applies this terminology elsewhere in its determinations, such as in its Local Coverage Determination on "Plasma-Based Genomic Profiling in Solid Tumors" (attached).

[2] In the case of *copy number amplifications* for NSCLC, *HER2* and *MET* focal amplifications may be important.

[3] As an example, Blue Shield of California's related policy (attached) is entitled "Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies." Similar use of *CGP* may be found in the policies of other Blues, including of South Carolina and Tennessee (both attached), as well as in the review the BCBS Association's Evidence Street (attached).

based) from more comprehensive testing (generally NGS-based). As Medicare and many other payers now cover CGP whether tissue- or blood-based,[4] oncologists and their patients may benefit from NCCN guidance in delineating the difference between hotspot and broader testing.

Specific revisions: To harmonize the language in the Guidelines with that increasingly used by payers, I recommend the following revisions (in ***blue***):

Page NSCL-18

Current language under "TESTING[ii]" (which occurs twice):	Proposed change under "TESTING[ii]" (which occurs twice, with the suggested revision below applying to each instance):
Testing should be conducted as part of broad molecular profiling[kk,ll]	Testing should be conducted as part of **comprehensive genomic** profiling[kk,ll] **that includes *EGFR, ALK, ROS1,* and *BRAF***
Current language under *ii* footnote:	Proposed change under *ii* footnote:
If there is insufficient tissue to allow testing for all of *EGFR*, *ALK*, *ROS1*, and *BRAF*, repeat biopsy and/or plasma testing should be done.	If there is insufficient tissue to allow testing for all of *EGFR*, *ALK*, *ROS1*, and *BRAF*, repeat biopsy and/or plasma**-based comprehensive genomic profiling that is well validated and performed in a CLIA-approved laboratory** should be done. **Also, for patients who are unable to undergo a traditional biopsy, testing using a plasma-based assay as defined in the preceding sentence that includes *EGFR, ALK, ROS1,* and *BRAF* may be considered.**
Current language under *kk* footnote:	Proposed change under *kk* footnote:
The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations….Broad molecular profiling is a key component of improvement of care of patients with NSCLC.	The NCCN NSCLC Guidelines Panel strongly advises **testing with a well validated NGS-based comprehensive genomic profiling assay performed in a CLIA-approved laboratory** with the goal of identifying rare driver mutations….**Comprehensive genomic profiling** is a key component of improvement of care of patients with NSCLC. **If there is insufficient tissue to allow for such profiling, repeat biopsy and/or plasma-based comprehensive genomic profiling that is well validated and performed in a CLIA-approved laboratory may be considered. Also, for patients who are unable to undergo a traditional biopsy, plasma-based profiling as defined in the preceding sentence may be considered.**

Page NSCL-G 1 of 5: Fifth line under "Testing Methodologies"

Current language:	Proposed change:
…testing be performed via a broad, panel-based approach, most typically performed by next generation sequencing (NGS).	…testing be performed via **comprehensive genomic profiling**, most typically performed by next generation sequencing (NGS) **covering all NCCN-recommended molecular markers**.

Page MS-13: Last sentence under "Molecular Testing for Biomarkers"

Current language:	Proposed change:
Broad molecular profiling systems may be used to simultaneously test for multiple biomarkers.	**Comprehensive genomic** profiling systems may be used to simultaneously test for multiple biomarkers.

To harmonize the Guidelines with payer policies as well as the robust literature supporting Guardant360, I respectfully request that the Panel consider these clarifications.

Sincerely,

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Vice President, Medical Affairs | Guardant Health

[4] Most of these positive policies for blood-based CGP, by the way, *specifically name* Guardant360.