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NCCN Guidelines Panel: Non-Small Cell Lung Cancer Version 1.2018, National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

First of all, we would like to commend the NCCN NSCLC Committee and staff for providing the latest expert guidance available to oncologists treating non-small cell lung cancer (NSCLC), such as the recent inclusion of *BRAF* V600E as a biomarker for targeted therapy as well as a negative predictor of immunotherapy response.¹ In view of recent decisions by insurance payers to cover Guardant360 in NSCLC,² including the draft CMS Molecular Diagnostics (MoDx) local coverage decision (LCD),³ we respectfully request the *NCCN (Non-Small Cell Lung Cancer Panel)* to review the following three proposed changes to NSCLC guideline v. 1.2018.⁴

Specific Changes and Rationale for each:

1. **Change:** We request that footnote gg in NSCL-17 be changed from "If repeat biopsy is not feasible, plasma biopsy should be considered" to "If broad molecular profiling for the seven genes with FDA-approved targeted drugs [*EGFR*, *ALK*, *ROS1*, *BRAF*, *RET*, *MET* (amplification and exon 14 skipping mutation), and *ERBB2* (HER2) alterations] is incomplete, then broad molecular profiling utilizing either tissue- or plasma-based comprehensive genomic profiling (CGP) is recommended. However, if plasma-based CGP testing does not identify any known oncogenic driver alteration in NSCLC then a repeat tissue biopsy is indicated." We additionally request that you define "plasma-based comprehensive genomic profiling (CGP) as a plasma-based next-generation sequencing (NGS) test covering all four major classes of genomic alterations (point mutations, indels, fusions, and copy number amplifications), complete sequencing of the exons harboring targetable mutations, and inclusion of the mutually exclusive driver oncogenes in NSCLC."

Rationale: To require a repeat tissue biopsy before plasma-based CGP puts patients in harm's way, with a pneumothorax risk as high as 19% in community- and population-based studies.^{5,6} This is one reason why many advanced NSCLC patients are not fully genotyped for guideline-recommended genomic targets. Recent studies reveal that 1/3 of patients are not tested for *EGFR* mutations and *ALK* fusions, 75% are not tested for *ROS1* fusions, and 80%-85% are not tested for *BRAF*, *MET*, *RET* or *ERBB2* (HER2) alterations.⁷ In another large study of almost 7,000 advanced NSCLC patients in 166 clinics, 25% were not tested for *EGFR* or *ALK*.⁸ Increasing demands on the tissue biopsy sample (e.g. PD-L1 testing) are exacerbating the tissue insufficiency problem. Almost half of biopsies required for biomarker-directed clinical trials failed or could not be conducted in a recent study, with poor performance status responsible for the majority of failures.⁹ In addition, the time-to-results for tissue-based genotyping in that study was 35 days, versus the current 7 day turnaround time for Guardant360. Plasma-based CGP will increase genotyping rates, reduce complications, and produce results faster than repeat biopsies.

2. **Change:** On NSCL-26 change "PD-L1 expression ($\geq 50\%$) and *EGFR*, *ALK*, *ROS1*, *BRAF*, negative or unknown" by replacing "or unknown" with "by tissue- and/or plasma-based CGP," and adding *MET* as a target.

Rationale: When patients with these 5 targetable oncogenes are treated with FDA-approved drugs their response rates are two to three-fold better than with immunotherapy (IO). More importantly, these five genomic biomarkers identify patients who respond very poorly to IO.^{1,10-12} As above, a

significant number of patients are undergenotyped for *EGFR*, *ALK*, *ROS1*, *BRAF* and *MET* – all robust negative predictors of response to immunotherapy. ASCO guidelines (2017) do not recommend IO in *EGFR*-mutated patients, even in the third line of treatment following an *EGFR* TKI and chemotherapy.¹³ Because patients are incompletely tested for alterations in these five genes when repeat biopsy is infeasible or of insufficient in quantity, they may be placed on ineffective and expensive immunotherapy if “or unknown” is permitted. Considering the expense of IO agents, recommending plasma-based CGP when tissue CGP is infeasible is essential to avoid IO in likely first-line non-responders as well as to identify every possible targeted therapy candidate.

3. **Change:** On NSCL-19 after progression on *EGFR* TKIs, change footnote pp “If tissue biopsy is not feasible, plasma biopsy should be considered” to “Plasma- or tissue-based genotyping should be considered at progression on TKIs for *EGFR*, *ALK*, *ROS1*, *RET* or *MET*.” Then keep “Consider reflex to tissue-based testing, if plasma-based CGP is negative.”

Rationale: At progression, knowledge of which *ALK* or *ROS1* alterations are driving resistance to earlier generation *ALK*/*ROS1* inhibitors can aid in the selection of the next generation TKI.^{14,15} For example, the presence of *ALK* G1202R means that alectinib will not be an effective choice at progression versus brigatinib or lorlatinib. Similarly, the presence of gatekeeper mutations in *MET* (Y1230 and D1228) will require Type II *MET* inhibitors (e.g. cabozantinib or a clinical trial on a next-generation *MET* inhibitor) in patients progressing on crizotinib for *MET* exon 14 skipping mutation.^{16,17} Thus, testing at progression with plasma-based CGP should not be limited to looking for *EGFR* T790M in patients progressing on *EGFR* TKIs. Plasma-based CGP with Guardant360 tests for the targetable resistance alterations in all five of these genes without subjecting patients to a repeat tissue biopsy or delays obtaining FFPE slides from referring hospitals. In addition, when osimertinib moves to the first line, testing at progression with Guardant360 has demonstrated a need to identify *EGFR* C797S and a host of other alterations, as T790M does not drive resistance to this *EGFR* TKI.¹⁸

FDA Status: The Guardant360 plasma-based CGP test is not FDA-approved but is a Clinical Laboratory Improvement Act-certified, College of American Pathologists–accredited, and New York State Department of Health-approved laboratory test. Recently, insurance company payers, including the Center for Medicare and Medicaid Services (CMS) Molecular Diagnostics Program (MoIDX) have recommended coverage for only one plasma-based comprehensive genomic profiling (CGP) test in advanced NSCLC: Guardant360. These payers have recognized the now 45 peer-reviewed publications utility on Guardant360, including a dozen clinical utility studies in NSCLC (see **Appendix I**). We thank the NCCN panel members who have been co-authors on many of these publications. Lastly, **Appendix II** provides language explaining why NSCLC panel design must be comprehensive in order to effectively reduce repeat tissue biopsies. We would appreciate hearing your thoughts on this proposal and would be happy to discuss any and all items individually if needed.

Sincerely,



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APPENDIX I

Summary of Guardant360 NSCLC Outcome Studies:

Guardant360: 45 Peer-reviewed Publications

Extensively validated and the only comprehensive liquid biopsy with prospective outcome studies

Criteria	Guardant360	References
Number of peer-reviewed publications	43	1-43
All NCCN Guideline Somatic Genomic Targets (point mutations, indels, fusions, amplifications)	Yes	
Published analytical and clinical validation	Yes	4
Published blinded external validation (outside academic centers compare their tissue NGS to ctDNA test)	Yes (24)	1-3, 6-7, 10-12, 14, 17-19, 21-23, 27-32, 37-38, 40, 42-43
Published outcomes (excludes single patient case reports)	Yes (18)	6-7, 9-13, 16, 18-19, 23, 27, 29, 31, 35, 39-41
Validation of copy number amplification with outcomes	Yes (4)	6,13, 23, 40
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Guardant360: Outcome Studies by Cancer Type

All outcomes studies for NCCN Guideline-Recommended Targets demonstrate expected response rates

Cancer	# Guardant360 Publications	References
All published outcomes studies (excludes single patient case reports)	18	1-18
NSCLC (<i>EGFR</i> , <i>ALK</i> , <i>ROS1</i> , <i>MET</i> exon 14, <i>RET</i>)	12	1-12
Colorectal cancer (<i>BRAF</i> V600E, overall utility)	2	13-14
Gastric cancer (<i>ERBB2</i> (HER2) amp)	2	15-16
Breast cancer (<i>ERBB2</i> (HER2) amp, <i>ERBB2</i> mutation)	2	17-18

NSCLC

- Villalón (Salgia) 2016 *Oncotarget*
- Thompson (Carpenter) 2016 *Clin Canc Res*
- Rozenblum (Peled) 2016 *J Thor Onc*
- Santos (Hunis) 2016 *Clinics in Oncology*
- Peled (Elkabetz) 2017 *J of Thor Onc*
- Lu (Collisson) 2017 *Cancer Research*
- Kim (Lee) 2017 *JCO Precision Oncology*
- Gutierrez (Goldberg) 2017 *Clin Lung Canc*
- Schwaederlé (Kurzrock) 2017 *Canc Res*
- Schwaederlé (Kurzrock) 2017 *Clin Canc Res*
- Engstrom (Christiansen) 2017 *Clin Canc Res*
- Sarfaty (Peled) 2017 *Clinic Lung Cancer*

Colorectal Cancer

- Hong (Kopetz) 2016 *Canc Disc*
- Lima (Pereira) 2017 *PLoS One*

Gastroesophageal Cancer

- Kim (Lee) 2017 *JCO Prec Oncol*
- Pectasides (Catenacci) 2017 *Canc Disc*

Breast Cancer

- Liang 2015 *Breast Cancer Res Treat*
- Ma (Ellis) 2017 *Clin Canc Res*

APPENDIX II

Suggested background relevant to plasma-based broad molecular profiling or NGS for consideration in the Principles of Molecular and Biomarker Analysis:

Traditionally, tumor genotyping has been conducted by direct interrogation of tumor tissue obtained through invasive tissue sampling procedures. This diagnostic approach, however, is limited by the availability of sufficient tumor tissue and the ability of patients to undergo invasive procedures. In a recent study of community based oncologists, nearly one third of NSCLC patients were not tested for *EGFR* or *ALK*, over 75% were not tested for *ROS1* fusions, and fewer than 10% were tested for all guideline recommended alterations.⁷ These results were similar to a study in a single academic center where only 58% of non-squamous NSCLC were tested for *EGFR* and 40% for *ALK* fusions, despite 13% of patients undergoing repeat invasive biopsies to obtain sufficient tissue for genomic testing.⁸ Tissue availability was similarly limited in several recent series, some of which reported that more than 50% of NSCLC patients had insufficient or unobtainable material for tissue-based comprehensive genomic profiling (CGP).

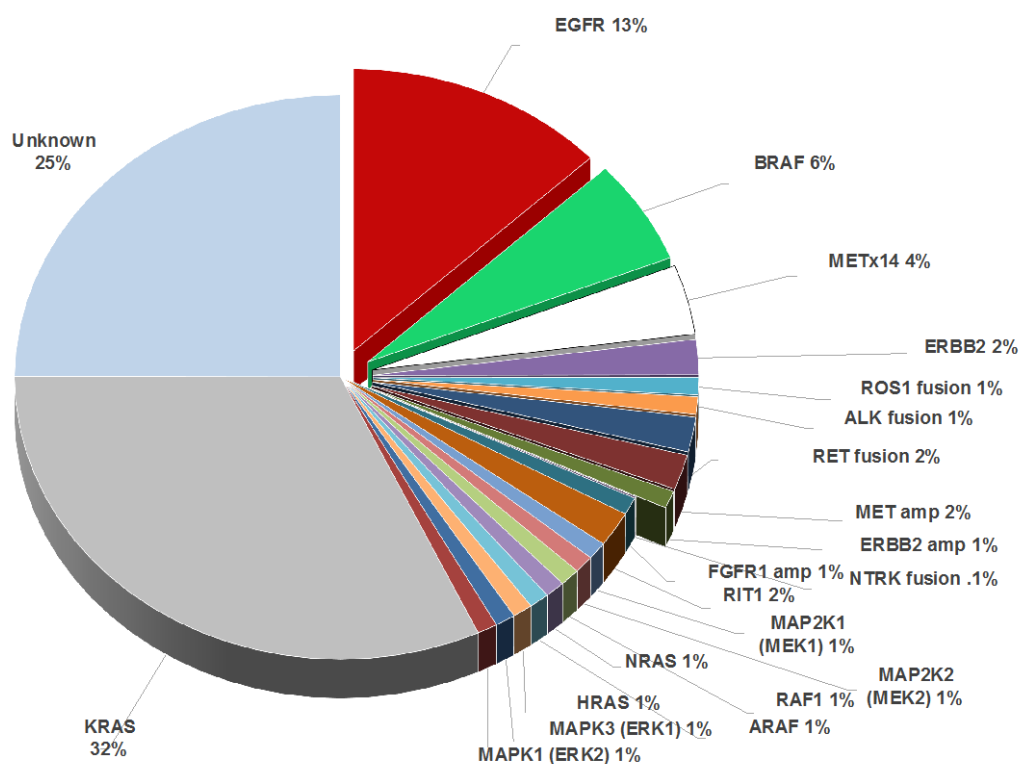
Even when successful, tissue acquisition procedures pose a significant morbidity and mortality risk to patients. In a recent report, 19% of all lung tissue acquisition procedures resulted in a serious adverse event in Medicare patients,⁵ while the National Lung Cancer Screening Trial reported 1-2% mortality rates in their cohorts.¹⁹ Given the high rates of inadequate genotyping described above, plasma-based CGP can provide an opportunity for incompletely or under-genotyped patients to benefit from matched therapy. Preliminary studies suggest that plasma-based CGP can identify potential genomic targets in both the first and second lines, with response rates similar to those of patients identified using tissue-based CGP and tissue-based companion diagnostics.^{20–26}

Currently, a variety of techniques are used to test for these genomic alterations in plasma specimens to determine if a patient is a candidate for targeted therapy, including the FDA-approved cobas® *EGFR* Mutation Test (tissue or plasma samples) for erlotinib and osimertinib, which interrogates specific regions in *EGFR* to determine whether the genomic alteration of interest is present. For multiple reasons, these FDA-approved companion liquid biopsy tests and other existing LDT techniques may miss deleterious *EGFR* mutations and other targetable genomic alterations that can be identified with next-generation sequencing (NGS). First, some FDA-approved tests have low sensitivity, such as the Roche cobas plasma *EGFR* T790M test, which only has 51% sensitivity for tissue-detected *EGFR* T790M.²⁷ Second, genomic alterations may occur outside the sequenced region in liquid biopsy tests that only evaluate “hotspots” or those loci of the most common mutations.²⁸ Thirdly, targetable genomic alterations are found across all four major classes of alterations (single nucleotide variants or point mutations, indels, copy number amplifications, and fusions/rearrangements) but some classes are not detectable by certain tests.²⁹ Lastly, NGS may have overall higher sensitivity than PCR, IHC, or FISH-based methods for targetable alterations.^{23,30–32}

The clinical utility of liquid biopsies rests upon its use to obviate repeat invasive tissue biopsies. However, the Achilles Heel of liquid biopsies is that they have imperfect sensitivity, so when negative, a repeat tissue biopsy should still be considered. Careful NSCLC test panel design can mitigate this problem if either a valid treatment target (e.g., *EGFR* L858R) or a mutually exclusive driver (e.g., *KRAS* G12V) is identified. Even though the *KRAS* mutation is not targetable, it is informative, as a patient with a plasma-detected oncogenic mutation in *KRAS* need not undergo a subsequent tissue biopsy to look further for an *EGFR* mutation.³³ These oncogenic driver genes are mutually exclusive in the upfront setting. Because there are at least 20 known, mutually exclusive oncogenic driver genes comprising 75% of the drivers in lung adenocarcinoma,³⁴ including these enables a liquid biopsy test to obviate the need for invasive tissue biopsies dramatically even when one of the seven targetable alterations is found.³⁵

75% of Lung Adenocarcinoma Driver Alterations are Known and Mutually Exclusive

Finding any one of them ends the Diagnostic Odyssey, Preventing a Repeat Biopsy



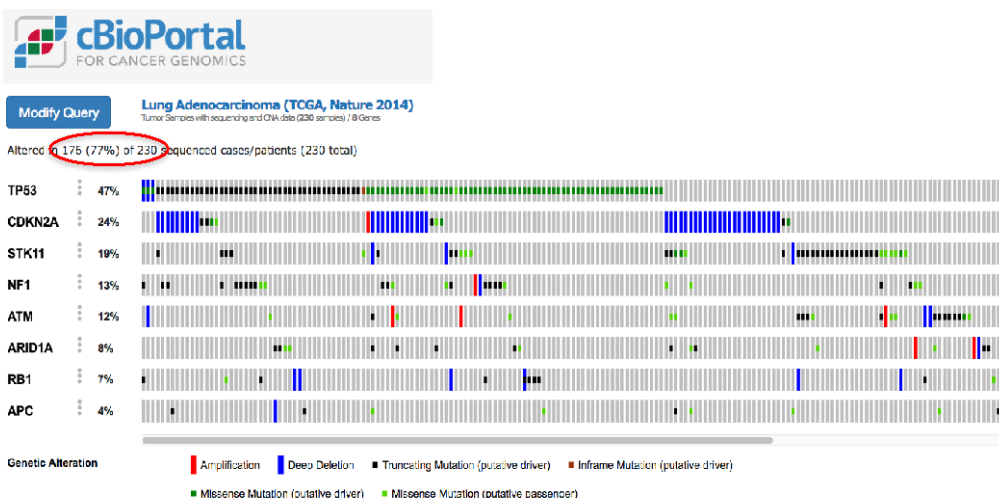
Campbell (Meyerson) and TCGA 2016 *Nature Genetics*

Inactivating mutations in tumor suppressor genes are the “first hit” in carcinogenesis and occur before a “second hit” activating mutation in an oncogene. As the “first hit”, inactivating mutations in tumor suppressor genes are generally present at the highest allele fraction and may be optimal genomic markers of tumor DNA shedding. The detection of any one of these may serve as an informative marker of tumor DNA shedding and help to avoid a repeat invasive biopsy when no *EGFR/ALK/ROS1/BRAF* mutations are found. When a tumor suppressor gene such as *TP53* is

inactivated and at high variant allele fraction, then the tumor is likely shedding adequate amounts of DNA and any oncogenic driver mutations likely would have been detectable. Conversely, if an inactivating mutation in *TP53* is present at low allele fraction, and no oncogene alteration is present, a repeat tissue biopsy would be recommended to ascertain whether a targetable *EGFR/ALK/ROS1/BRAF* alteration was present in the tumor tissue but not shed into the bloodstream. One or more of eight tumor suppressor genes are inactivated in 77% of lung adenocarcinoma cases.

First Hit” Inactivating Mutations Occur in 8 Tumor Suppressor Genes in 77% of Non-Squamous NSCLC

Guardant360 Uses These as Markers of Tumor Shedding When Mutations in Oncogenes are not Detected



Thus, plasma-based CGP in NSCLC requires a more extensive list of genes than just the seven targetable oncogenes targeted with tissue biopsy. Guardant360 appropriately includes all 20 known oncogenes and the eight most common tumor suppressor genes, with complete coverage of all exons in *TP53*, *CDKN2A*, etc. Without this comprehensive NSCLC panel design of 28 genes, a liquid biopsy test cannot obviate the majority of repeat tissue biopsies.

Therefore, we define plasma-based comprehensive genomic profiling (CGP) as:

1. Able to detect all four major classes of genomic alterations.
2. Complete sequencing of the critical exons in targetable genes, defining critical exons as those that harbor sensitizing mutations.
3. Inclusion of all 20 known mutually exclusive oncogenes, and the 8 most common tumor suppressor genes in NSCLC.