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**Date of request**: July 20, 2020

**NCCN Guidelines Panels**: *Colon Cancer* (version 4.2020) and *Rectal Cancer* (version 6.2020)

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

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On behalf of Guardant Health, I thank the Colon and Rectal Cancer Panels and staff for their rapid and thorough updates to the Guidelines, which incorporate the best and latest science pertaining to treatment selection. In our common interest in updating these Guidelines, I hope you will consider the following request in addition to the ones conveyed in my correspondence dated January 30, 2020.

**Request**: I respectfully request that the Panel consider encouraging comprehensive genomic profiling by a well validated tissue- *or plasma-based*[1,2,3] next-generation sequencing (NGS) assay when patients with colorectal cancer (CRC) have not undergone comprehensive testing. (A similar recommendation to complete comprehenisive genomic assessment through tissue, or ctDNA using *plasma* if tissue is unavailable, is in the Guidelines for breast, lung, and pancreatic cancers[4,5,6] and was recently added for gastric and esophageal and esophagogastric junction cancers.[7,8])

**Rationale***:*

***The Problem.*** A recent multicenter study found that *only* 40% of patients with advanced colon cancer receive guideline-recommended comprehensive genomic profiling (with only 41% tested for expanded *RAS*, 43% for *BRAF* V600E, and 51% for microsatellite instability/mismatch repair (MSI/dMMR)),[9] consistent with previous studies reporting that the majority of patients are receiving neither expanded *RAS* nor MSI/dMMR testing. In a national survey, 48% of physicians reported that the reason for their not testing was insufficient tissue.[10] Incomplete testing may be an even greater problem in underserved and poor populations, as more than 31% of physicians in the same study stated that concern about cost led to incomplete testing.[10] Lastly, as more and more genomic targets are recommended for testing (with both the Colon and Rectal Cancer Guidelines[11] adding HER2 amplification and *NTRK* fusion testing), the problem of tissue sufficiency (and attendant untimeliness of results form tissue biopsy) will become increasingly challenging.

***The Solution.*** *Plasma-based* comprehensive genomic profiling by a validated NGS assay provides a non-invasive means of reliably detecting biomarkers currently recommended in the Guidelines. Such testing, particularly when tissue is unavailable, may *increase guideline-recommended genotyping* (and return results more quickly).

***Concordance?*** As for the concordance between plasma- and tissue-based testing, these methods are similar in detecting guideline-recommended biomarkers in newly diagnosed CRC,[12] and plasma-based testing may even be *superior* in patients with CRC at progression due to tumor heterogeneity,[13] with a sensitivity of 97.9% for the plasma assay Guardant360 in detecting *ERBB2* (HER2) amplifications in tissue-positive patients with CRC.[14]

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[1] Odegaard JI, Vincent JJ, Mortimer S, et al. Validation of a Plasma-Based Comprehensive Cancer Genotyping Assay Utilizing Orthogonal Tissue- and Plasma-Based Methodologies. *Clin Cancer Res Off J Am Assoc Cancer Res* 2018;24:3539-3549.
[2] Willis J, Lefterova MI, Artyomenko A, et al. Validation of Microsatellite Instability Detection Using a Comprehensive Plasma-Based Genotyping Panel. *Clin Cancer Res Off J Am Assoc Cancer Res* 2019;19:1324.
[3] Lanman RB, Mortimer SA, Zill OA, et al. Analytical and Clinical Validation of a Digital Sequencing Panel for Quantitative, Highly Accurate Evaluation of Cell-Free Circulating Tumor DNA. *PloS One* 2015;10:e0140712.
[4] NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, Version 4.2020 – May 8, 2020, page BINV-R 1 of 3.
[5] NCCN Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer, Version 6.2020 – June 15, 2020, pages NSCL-18, NSCL-18A, NSCL-G 5 of 5.
[6] NCCN Clinical Practice Guidelines in Oncology, Pancreatic Cancer, Version 1.2020 – November 26, 2019, page PANC-7.
[7] NCCN Clinical Practice Guidelines in Oncology, Gastric Cancer, Version 2.2020 – May 13, 2020, page GAST-B 5 of 6.
[8] NCCN Clinical Practice Guidelines in Oncology, Esophageal and Esophagogastric Junction Cancers, Version 3.2020 – July 7, 2020, page ESOPH-B 5 of 6.
[9] Gutierrez ME et al. Genomic Profiling for *KRAS*, *NRAS*, *BRAF*, Microsatellite Instability, and Mismatch Repair Deficiency Among Patients With Metastatic Colon Cancer. *JCO Precis Oncol* 2019;1-9.
[10] Eriksson J, Amonkar M, Al-Jassar G, et al. Mismatch Repair/Microsatellite Instability Testing Practices among US Physicians Treating Patients with Advanced/Metastatic Colorectal Cancer. *J Clin Med* 2019;8(4):558-566.
[11] In versions 2.2019.
[12] Gupta R, Othman T, Chen C, et al. Guardant360 Circulating Tumor DNA Assay Is Concordant with FoundationOne Next-Generation Sequencing in Detecting Actionable Driver Mutations in Anti-EGFR Naive Metastatic Colorectal Cancer. *The Oncologist* 2020;25(3):235-243.
[13] Parikh AR et al. Liquid versus tissue biopsy for detecting acquired resistance and tumor heterogeneity in gastrointestinal cancers. *Nat Med 2019;*25,1415-1421. (The primary reason to test CRC patients *at progression* is because they were incompletely tested *when newly diagnosed*.)
[14] Siravegna G et al. Plasma HER2 (ERBB2) Copy Number Predicts Response to HER2-targeted Therapy in Metastatic Colorectal Cancer. *Clin Cancer Res Off J Am Assoc Cancer Res 2019;*25,3046-3053.

***A note on naming.*** NCCN may wish to categorize types of testing based upon evidence, classifying specific tests that meet evidence thresholds (*i.e.*, 2A, 2B), with validation and outcomes studies demonstrating utility. I understand and respect that NCCN may not routinely recommend specific tests, but suggest that the Colon and Rectal Panels may wish to reconsider naming Guardant360 in *delineating what should and should not be covered*, as the Molecular Diagnostic Services Program[15] and the NCCN panels for both prostate and breast cancers (in mentioning several RNA expression assays, noting the level of evidence for these tests)[16,17] have done. Oncologists would benefit from clearer guidance on *which tests* are well validated and supported by published studies reporting on clinical utility and outcomes.

**Suggested Revisions**:

| Page | **Specific revisions** (in ***blue***) |
|---|---|
| COL-B 4 of 8 | The comprehensive genomic profiling ~~testing~~ can be performed on formalin-fixed paraffin-embedded tissue~~.~~ or circulating tumor DNA (sometimes referred to as "liquid biopsy") using a well validated plasma-based next-generation sequencing assay such as Guardant360 or other similarly well validated test (irrespective of panel size as long as evidence thresholds have been surpassed). The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the *KRAS*, *NRAS*, and *BRAF* mutations are similar in both specimen types. |
| | Testing for MSI may be accomplished by polymerase chain reaction (PCR) or a validated tissue or plasma NGS panel,[2] the latter especially in patients with metastatic disease who require comprehensive genomic profiling ~~genotyping~~ of *RAS* and *BRAF*. |
| COL-B 5 of 8 | NGS on tissue or plasma is another methodology for testing for HER2 amplification.[13] |

Thank you for considering these suggested revisions.

Sincerely,

Mark D. Hiatt, MD, MBA, MS
Vice President, Medical Affairs | Guardant Health

[15] Palmetto GBA Medicare Administrative Contractor, "Local Coverage Determination (LCD): MolDX: Plasma-Based Genomic Profiling in Solid Tumors (L38043)," effective March 5, 2020.
[16] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Prostate Cancer, Version 2.2020 – May 21, 2020, page PROS-2A.
[17] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), Breast Cancer, Version 4.2020 – May 8, 2020, page BINV-N 1 of 4.