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NCCN Guidelines Panel: Gastric Cancer Version 3.2019, and Esophageal and Esophagogastric Junction Cancers Version 3.2019, National Comprehensive Cancer Network, <https://www.nccn.org>

We commend the NCCN Gastric and Esophageal/Esophagogastric Junction Cancer Committees and staff for providing the latest expert guidance available to oncologists treating advanced gastrointestinal cancers, and request that plasma-based comprehensive genomic profiling (CGP) be recommended in the respective guidelines when MSI testing has not been completed or when ERBB2 (HER2) testing on primary gastroesophageal tissue is negative.

FDA status: The Guardant360 plasma-based CGP test has been designated for *Breakthrough Review* by the FDA. This laboratory test is Clinical Laboratory Improvement Act-certified, College of American Pathologists–accredited, and New York State Department of Health-approved.

Comprehensive genomic profiling (CGP) is the Medicare Molecular Diagnostics (MoIDX) Program’s term for targeted next-generation sequencing (NGS) covering all NCCN-guideline-recommended genomic targets, and all four major classes of alteration types.¹ Yesterday, MoIDX issued a new local coverage decision covering Guardant360, and naming it specifically, in nearly all advanced solid tumor cancer types, including gastric, esophageal, and esophagogastric junction cancers.²

Testing for microsatellite instability high (MSI-H) with a non-invasive blood test has been validated with Guardant360 and outcomes from immune checkpoint inhibition for Guardant360-detected MSI-H patients have been shown to be as expected with tissue-detected MSI-H.³ However, many patients are not tested for MSI-H or mismatch repair deficiency germline testing in gastrointestinal cancer patients, despite being recommended in NCCN guidelines for years.⁴

Testing primary gastric cancer for *ERBB2* (HER2) amplification may miss HER2 positivity in one-third of cases detectable with Guardant360 with plasma.⁵ In that study, nearly 90% of the metastatic lesions were concordant with Guardant360, underscoring the high degree of intra- and inter-tumor heterogeneity for HER2 in advanced gastric cancer.

To harmonize the NCCN guidelines with the expanded coverage of Guardant360 in nearly all advanced solid tumor cancers, including gastric and esophageal cancers, as well as the robust literature supporting Guardant360, we respectfully request that the NCCN Gastric and Esophageal/Esophagogastric Panels consider two changes to their guidelines:

1. Plasma-based comprehensive genomic profiling (CGP) should be recommended in patients with newly diagnosed metastatic or unresectable recurrent stage III/IV Gastric and Esophageal/Esophagogastric Cancers, when patients have not been tested for MSI/dMMR or when primary gastric tissue has been tested on tissue but negative for *ERBB2* (HER2) amplification.
2. Guardant360 should be named in the guidelines. There are currently 150 publications utilizing Guardant360. No other liquid biopsy assay has been validated by literally dozens of external clinical validity studies. In addition eight clinical outcomes studies for Guardant360 in advanced gastric/esophagogastric cancers have been published.^{3, 5-11} Other tests also do not have the testing volumes enabling a 7-day turnaround time, which is critical for patients with rapidly declining performance status. However, despite the extensive and differentiating publication record related to Guardant360, several **private payers use the lack of reference to Guardant360 in NCCN guidelines as an excuse to maintain the assay as *experimental* and thus not covered by insurance.** In addition to naming our test, we propose that you could help payers infer that Guardant360 is well validated by referencing studies that used the test. Please also consider including a statement such as the following: **“Well validated plasma-based comprehensive genomic profiling tests should be used.”^{3, 12, 13} In addition to clinical validation, assays with substantial published outcomes studies demonstrating clinical utility are recommended.**^{3, 5-11} This statement would enable payers to review the references selected and conclude that Guardant360 is considered by the NCCN panelists to be well validated, and that one may reliably treat mutations found in plasma with this methodology. Several large payers will not grant coverage in advanced gastrointestinal cancers until they see such language, because they claim that they do not have the capability to distinguish one liquid biopsy from another without NCCN guidance. These payers sometimes tell oncologists they are responsible for Guardant360 costs, or worse, require advanced cancer patients to pay for testing out of their own pockets.

We thank the NCCN panel members for their careful review of this considerable body of published literature on Guardant360.

Sincerely,




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