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Guidelines Panels: *Gastric Cancer* (v. 3.2020)[1] and *Esophageal and Esophagogastric Junction (EGJ) Cancers* (v. 4.2020)[2]

FDA status: Guardant Health's **Guardant360 CDx** is the first (and only) plasma-based comprehensive genomic profiling (CGP) test approved by the FDA to profile tumor mutations in all solid malignant neoplasms[3,4,5] (and is also certified, accredited, and approved by the Clinical Laboratory Improvement Act, College of American Pathologists, and New York State Department of Health, respectively).

On behalf of Guardant Health, I thank the Gastric and Esophageal and EGJ Cancers Panels and staff for their rapid and thorough updates to the Guidelines, which incorporate the best and latest science pertaining to treatment selection. I was gladdened to see the incorporation of our suggestions (in correspondence dated January 30, 2020) to

- suggest that clinicians consider the use of a plasma-based circulating tumor DNA (ctDNA) next-generation sequencing (NGS) assay ("liquid biopsy"), as the "detection of mutations/alterations in DNA shed from" gastric, esophageal, and EGJ "carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles," and
- use the clarifying language of "comprehensive genomic profiling via a validated NGS assay."[1,2]

Requests:

1. ***Liquid as a tool to profile more patients***. Please consider expanding this use of a well validated ctDNA assay beyond "patients who are unable to undergo a traditional biopsy" to give physicians greater autonomy in their choice of testing modality. In patients whose diagnosis is already established by histopathology, plasma-based testing may obviate the need for a repeat invasive biopsy *even for patients who are able to undergo one*, as Guardant360 has been shown to identify targetable alterations at similar rates with similar matched therapy outcomes as tissue-based profiling.[6,7,8,9,10,11] In this setting, tissue can be saved for testing that requires it (like PD-L1 or diagnostic stains).
2. ***Liquid as a noninvasive means to capture tumor heterogeneity***. Since gastric and esophageal cancers exhibit a high degree of spatial and temporal heterogeneity,[8,12] ctDNA may be a comparable, if not preferred, means to identify the most important targets for a given patient without exposing him or her to invasive biopsies of multiple metastatic lesions. Please also consider suggesting that plasma-based CGP be used in the respective guidelines when MSI and *ERBB2* (HER2) testing on tissue has not been completed or is uninformative, regardless of the patient's ability to undergo additional invasive biopsy.[8,11,12,13]
3. ***Liquid defined***. I also concur with the caveat regarding cautious interpretation of a negative result from liquid biopsy, as *not all ctDNA tests are technically equivalent* and the particular alterations of greatest interest in these cancers (MSI and amplifications) are, indeed, difficult to detect. Therefore, you may wish to add specific language to suggest using a FDA-approved ctDNA assay that has not only *published analytical and clinical validation*,[14,15,16] but also *published outcomes studies* based on ctDNA-identified *ERBB2* (HER2)[7,9,11,12,13] and MSI[6] in detecting alterations in gastric and esophageal cancers (*e.g.*, Guardant360).

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[1] NCCN Clinical Practice Guidelines in Oncology, Gastric Cancer, Version 3.2020 – August 14, 2020, page GAST-B 5 of 6.
[2] NCCN Clinical Practice Guidelines in Oncology, Esophageal and Esophagogastric Junction Cancers, Version 4.2020 – August 14, 2020, page ESOPH-B 5 of 6.
[3] Correspondence dated August 7, 2020, to Guardant Health from the FDA, which notes that Guardant360 "is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with any solid malignant neoplasms."
[4] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P200010, accessed August 25, 2020.
[5] https://www.fda.gov/news-events/press-announcements/fda-approves-first-liquid-biopsy-next-generation-sequencing-companion-diagnostic-test, accessed August 12, 2020.
[6] Willis J, Lefterova MI, Artyomenko A, et al. Validation of Microsatellite Instability Detection Using a Comprehensive Plasma-Based Genotyping Panel. *Clin Cancer Res*. 2019;25(23):7035-7045.
[7] Kim ST, Banks KC, Pectasides E, et al. Impact of genomic alterations on lapatinib treatment outcome and cell-free genomic landscape during HER2 therapy in HER2+ gastric cancer patients. *Ann Oncol* 2018;29:1037-1048.
[8] Pectasides E, Stachler MD, Derks S, et al. Genomic heterogeneity as a barrier to precision medicine in gastroesophageal adenocarcinoma. *Cancer Discov* 2018;8:37-48.
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[11] Maron SB, Chase LM, Lomnicki S, et al. Circulating Tumor DNA Sequencing Analysis of Gastroesophageal Adenocarcinoma. *Clin Cancer Res* 2019;25(23):7098-7112.
[12] Catenacci DVT, Kang Y-K, Park H, et al. Margetuximab plus pembrolizumab in patients with previously treated, HER2-positive gastro-oesophageal adenocarcinoma (CP-MGAH22–05): a single-arm, phase 1b–2 trial. *Lancet Oncol* 2020;21:1066-1076.
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[15] Zill OA, Banks KC, Fairclough SR, et al. The Landscape of Actionable Genomic Alterations in Cell-Free Circulating Tumor DNA from 21,807 Advanced Cancer Patients. *Clin Cancer Res* 2018;24(15):3528-3538.
[16] 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* 2018;24:3539-3549.

Rationale*:*

The Problem

While tissue analysis has been the historical standard for biomarker development and clinical trial enrollment, routine biopsy or re-biopsy of tumors and their metastases may be infeasible due to cost, morbidity, and low yield. The coronavirus crisis has also raised concern about patients being placed at higher risk of exposure from hospital visits needed for the conventional biopsies, obviated through mobile phlebotomy at home employed in liquid testing.[17]

Additionally, a growing number of therapies in cancer are *biomarker-dependent*, including trastuzumab in patients with HER2+ disease, pembrolizumab for MSI-H and TMB-high disease, and larotrectinib and entrectinib for *NTRK* fusions.[1,2,18,19] Despite high rates of genomic heterogeneity in gastric and esophageal cancers, even at initial presentation of metastatic disease, response to HER2 amplifications as identified by ctDNA has been remarkable, providing through plasma a comprehensive profile of a patient's entire disease burden and capturing treatment-induced tumor evolution.[7,9,12,13]

Lastly, as more and more genomic targets are recommended for testing, the problems of accessibility and/or sufficiency of tissue specimens and attendant delay of results from tissue biopsy will become increasingly challenging, particularly when considering that repeated biopsies over time and/or multiple lesions may be required to obtain a complete and up-to-date picture of the molecular alterations within the patient's disease. Even now, many patients are not tested for MSI-H, mismatch repair deficiency, or other known oncogenic drivers that aid in therapy selection in cancer, despite being recommended in Guidelines for years.[20,21]

The Solution

A well validated plasma-based ctDNA NGS assay may overcome the challenges of the heterogeneity in these cancers as well as concerns regarding limited tissue availability and allow for the interrogation of the Guideline-recommended biomarkers MSI, HER2, and *NTRK*.

ctDNA in peripheral blood is highly concordant with matched tissue testing for biomarkers of interest in gastric and esophageal cancers, including MSI and targetable amplifications like *ERBB2* (HER2),[6,7,8,9] and can non-invasively capture additional targetable biomarkers due to heterogeneity as well as the evolution of the cancer genomic landscape associated with subsequent therapies and disease progression. In one recent study, the presence of HER2 amplification as detected by ctDNA was the only biomarker significantly associated with progression-free survival after first-line pembrolizumab and trastuzumab.[9]

Such testing, particularly when tissue is unavailable, may *increase rates of complete testing for all Guideline-recommended genomic targets*, return results more quickly, and identify more patients likely to benefit from biomarker-matched therapies.[22]

A Note on Naming

NCCN may wish to categorize types of testing based on *evidence*, classifying specific tests that meet evidence thresholds (*i.e.*, 2A, 2B), with validation and outcomes studies demonstrating utility. To this end, NCCN may wish to *name* the well validated plasma assay Guardant360[14,15,16] (whose validation studies have outcomes specifically in gastrointestinal cancer) in *delineating what should be covered*, as its panels for breast and prostate cancers have done in mentioning other FDA-approved assays, noting the level of evidence for these tests.[23,24]

In a similar vein, the Molecular Diagnostic Services Program relied upon by the Centers for Medicare & Medicaid Services has named Guardant360 as useful in ascertaining the alterations driving solid tumors in Medicare patients.[25]

Oncologists, particularly those in the community who may be seeing a wide variety of cancer types, may benefit from such clearer guidance on *which tests* are well validated and supported by FDA approval and published studies reporting on clinical utility and outcomes.

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[20] Gutierrez ME, Choi K, Lanman RB et al. Genomic Profiling of Advanced Non-Small Cell Lung Cancer in Community Settings: Gaps and Opportunities. *Clin Lung Cancer* 2017;18(6):651-659.
[21] Gutierrez ME, Price KS, Lanman RB, et al. Genomic Profiling for *KRAS*, *NRAS*, *BRAF*, Microsatellite Instability, and Mismatch Repair Deficiency Among Patients with Metastatic Colon Cancer. *JCO Precis Oncol* 2019;3:1-9.
[22] Nakamura Y, Taniguchi H, Ikeda M, et al. Clinical utility of circulating tumor DNA sequencing in advanced gastrointestinal cancer: SCRUM-Japan, GI-SCREEN and GOZILA studies. *Nat Med* 2020, in press (accepted
[23] NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, Version 5.2020 – July 15, 2020, page BINV-N 1 of 4.
[24] NCCN Clinical Practice Guidelines in Oncology, Prostate Cancer, Version 2.2020 – May 21, 2020, page PROS-2A.
[25] Palmetto GBA Medicare Administrative Contractor, "Local Coverage Determination (LCD): MolDX: Plasma-Based Genomic Profiling in Solid Tumors (L38043)," effective March 5, 2020.

Suggested Revisions:

Page	**Specific revisions** (in ***blue***)
GAST-9	Perform HER2 by IHC, FISH, or plasma or tissue NGS~~,~~; PD-L1 by IHC~~,~~; MSI by PCR~~/~~ or plasma or tissue NGS; MMR by IHC testing (if not done previously) if metastatic adenocarcinoma is documented or suspected[d]
GAST-B 3 of 6	Assessment of Overexpression or Amplification of HER2 in Gastric Cancer For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach for whom trastuzumab[e] therapy is being considered, assessment for tumor HER2 overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization (ISH) method is recommended. Next-generation sequencing (NGS), whether it be through plasma ("liquid biopsy") or tissue, offers the opportunity to assess numerous mutations simultaneously, along with other molecular events such as amplification, deletions, tumor mutation burden, and microsatellite instability status. Comparable outcomes for HER2 amplifications detected by NGS performed on plasma (as in "liquid biopsy") have been reported. ~~When limited diagnostic tissue is available for testing and the patient is unable to undergo additional procedures,~~ NGS can be considered instead of sequential testing for single biomarkers, especially by means of a test that has been specifically validated in gastric cancer. It should be noted that NGS has several inherent limitations and thus whenever possible, the use of gold-standard assays (IHC/ISH) should be performed.
GAST-B 4 of 6	The testing is performed on formalin-fixed, paraffin-embedded (FFPE) tissue and results are interpreted as MSI-high (MSI-H) or mismatch repair-deficient (dMMR) in accordance with CAP DNA Mismatch Repair Biomarker Reporting Guidelines. MSI may be determined by plasma or tissue NGS using a well validated test. MMR or MSI testing should be performed only in CLIA-approved laboratories. Patients with MSI-H or dMMR tumors should be referred to a genetics counselor for further assessment.
GAST-B 5 of 6	Liquid Biopsy • The genomic alterations of solid cancers may be identified by evaluating circulating tumor DNA (ctDNA) in the blood, hence a form of "liquid biopsy." Liquid biopsy is being used more frequently in patients with advanced disease who are unable to have a clinical biopsy for disease surveillance and management. The detection of mutations/alterations in DNA shed from gastric carcinomas can identify targetable alterations or the evolution of clones with altered treatment response profiles. Excellent outcomes for some alterations, especially MSI and HER2 amplifications, detected by NGS performed on plasma have been reported. Therefore, ~~for patients who are unable to undergo a traditional biopsy,~~ testing using a validated NGS-based comprehensive genomic profiling assay performed on plasma in a CLIA-approved laboratory may be considered. A negative result should be interpreted with caution, as this does not exclude the presence of tumor mutations or amplifications.
ESOPH-10	Perform HER2 by IHC, FISH, or plasma or tissue NGS; MSI by PCR~~/~~ or plasma or tissue NGS; MMR by IHC; and PD-L1 testing by IHC (if not done previously) if metastatic squamous cell carcinoma is suspected[c]
ESOPH-B 3 of 6	Assessment of Overexpression or Amplification of HER2 in Esophageal and Esophagogastric Junction Cancers For patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the esophagus or EGJ for whom trastuzumab[i] therapy is being considered, assessment for tumor HER2 overexpression using immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) or other in situ hybridization (ISH) method is recommended. Next-generation sequencing (NGS), whether it be through plasma ("liquid biopsy") or tissue, offers the opportunity to assess numerous mutations simultaneously, along with other molecular events such as amplification, deletions, tumor mutation burden, and microsatellite instability status. Comparable outcomes for HER2 amplifications detected by NGS performed on plasma (as in "liquid biopsy") have been reported. ~~When limited diagnostic tissue is available for testing and the patient is unable to undergo additional procedures,~~ NGS can be considered instead of sequential testing for single biomarkers, especially by means of a test that has been specifically validated in esophageal and EGJ cancers. It should be noted that NGS has several inherent limitations and thus whenever possible, the use of gold-standard assays (IHC/ISH) should be performed.
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Thank you for considering these suggestions.

Sincerely,

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