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NCCN Guidelines Panel: *Breast Cancer* (version 5.2020)

FDA status: Guardant Health's **Guardant360** plasma-based comprehensive genomic profiling (CGP) 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).

On behalf of Guardant Health, I thank the Breast Cancer Panel and staff for their rapid and thorough updates to the Guidelines, which incorporate the best and latest science pertaining to treatment selection.

Requests:

1. ***Tissue or liquid.*** Please consider suggesting that a well validated *plasma-based* next-generation sequencing (NGS) assay be used in advanced (recurrent or stage IV) breast cancer to support current Guideline-recommended testing in any cancer subtype for *BRCA1/2*, *NTRK* fusions, and MSI-H when (a) these predictive biomarkers have not been evaluated, or (b) tissue biopsy is infeasible or yields an insufficient sample. Such a suggestion is aligned with the current recommendation to use "tumor or liquid biopsy" to assess for *PIK3CA* mutations for HR+/HER2- breast cancer, with the admonition "if liquid biopsy is negative, tumor tissue testing is recommended."[1]
2. ***Liquid as a noninvasive alternative.*** Elsewhere, the Guidelines recommend repeat biopsy to assess for changes in ER/PR/HER2 status in the metastatic tumor,[2] but often doing so is infeasible, especially when the metastases are predominantly bony. Therefore, please consider suggesting that when repeat tissue biopsy "cannot safely be obtained" liquid biopsy be considered to assess for any change in HER2 (*ERBB2* gene amplification) status before commencing treatment otherwise based solely (and suboptimally) on the historical status of the primary tumor. Liquid biopsy (as a safer, less invasive alternative) has been recommended in similar scenarios for lung and pancreatic cancers for some time,[3,4] and recently so for gastric and esophageal and esophagogastric junction cancers.[5,6]

Rationale*:*

The Problem. While tissue biopsy has been the historical standard for biomarker development and clinical trial enrollment, routine biopsy of breast cancer metastases may be infeasible due to cost, morbidity, and low yield related to the bone-predominant metastasis from this type of cancer, with such metastasis occurring in 70% of patients with metastatic breast cancer.[7] The coronavirus crisis has also raised concern about patients being placed at higher risk of exposure from hospital visits, obviated through mobile phlebotomy employed in liquid testing.[8,9] Additionally, a growing number of therapies in breast cancer are *biomarker-dependent*, including alpelisib in HR+/HER2- patients with activating *PIK3CA* alterations, pembrolizumab for MSI-H disease, and larotrectinib and entrectinib for *NTRK* fusions.[10,11,12] The Guidelines recommend re-biopsy of the tumor at first recurrence;[2] however, clear evidence suggests that tumors continue to evolve with time and treatment, leading to both spatial and temporal heterogeneity.[13,14,15,16,17] Thus, tissue biopsies may *not* provide a comprehensive profile of a patient's entire disease burden and may not capture treatment-induced tumor evolution (*e.g.*, the development of acquired resistance alterations like *ESR1* in response to aromatase inhibitor therapy). Lastly, as more and more genomic targets are recommended for testing, the problem of tissue sufficiency (and attendant untimeliness of results from tissue biopsy) will become increasingly challenging, particularly when considering that repeated biopsies may be required to obtain an up-to-date picture of the molecular alterations within the tumor.

The Solution. A well validated plasma-based circulating tumor DNA (ctDNA) NGS assay may overcome the challenge of limited tissue availability, especially in patients with bone-only metastases, and allow for the interrogation of Guideline-recommended biomarkers. In this examination, ctDNA in peripheral blood ("liquid biopsy") is highly concordant with matched tissue NGS[18,19] and captures the evolution of the cancer genomic landscape associated with subsequent

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[1] NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, Version 5.2020 – July 15, 2020, page BINV-R 1 of 3, footnote b.
[2] NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, Version 5.2020 – July 15, 2020, page BINV 17.
[3] 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.
[4] NCCN Clinical Practice Guidelines in Oncology, Pancreatic Cancer, Version 1.2020 – November 26, 2019, page PANC-7.
[5] NCCN Clinical Practice Guidelines in Oncology, Gastric Cancer, Version 2.2020 – May 13, 2020, page GAST-B 5 of 6.
[6] NCCN Clinical Practice Guidelines in Oncology, Esophageal and Esophagogastric Junction Cancers, Version 3.2020 – July 7, 2020, page ESOPH-B 5 of 6.
[7] Manders K, van de Poll-Franse LV, Creemers GJ, et al. Clinical management of women with metastatic breast cancer: A descriptive study according to age group. *BMC Cancer*. 2006;6:179.
[8] Liang W, Guan W, Chen,R, et al. Cancer Patients in SARS-CoV-2 Infection: A Nationwide Analysis in China. *Lancet Oncology*. 2020;21:335-337.
[9] Dietz JR, Moran MS, Isakoff SJ, et al. Recommendations for Prioritization, Treatment, and Triage of Breast Cancer Patients during the COVID-19 Pandemic. The COVID-19 Pandemic Breast Cancer Consortium. *Breast Cancer Res Treat*. 2020;181(3):487-497.
[10] André F, Ciruelos E, Rubovszky G, et al. Alpelisib for *PIK3CA*-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med*. 2019;380(20):1929-1940.
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[12] Marcus L, Lemery SJ, Keegan P, Pazdur R. FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors. *Clin Cancer Res*. 2019;25(13):3753-3758.
[13] Litton JK, Burstein HJ, Turner NC. Molecular Testing in Breast Cancer. *Am Soc Clin Oncol Educ Book*. 2019;39:e1-e7.
[14] 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.
[15] O'Leary B, Cutts RJ, Liu Y, et al. The Genetic Landscape and Clonal Evolution of Breast Cancer Resistance to Palbociclib plus Fulvestrant in the PALOMA-3 Trial. *Cancer Discov*. 2018;8(11):1390-1403.
[16] Lin KK, Harrell MI, Oza AM, et al. *BRCA* Reversion Mutations in Circulating Tumor DNA Predict Primary and Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma. *Cancer Discov*. 2019;9(2):210-219.
[17] Razavi P, Dickler MN, Shah PD, et al. Alterations in *PTEN* and *ESR1* promote clinical resistance to alpelisib plus aromatase inhibitors. *Nat Cancer*. 2020;1:382-393.
[18] 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.
[19] The manuscript reporting on the concordance between ctDNA and tissue in plasmaMATCH is in press and can be provided upon publication. In the meantime, please refer to presentations delivered at the San Antonio Breast Cancer Symposium in December 2019 from Turner et al. (Results from the plasmaMATCH trial: A multiple parallel cohort, multi-centre clinical trial of circulating tumour DNA testing to direct targeted therapies in patients with advanced breast cancer) and Kingston et al. (The genomic landscape of breast cancer based on ctDNA analysis: Data from the plasmaMATCH trial) published in *Cancer Research* in February 2020.

therapies and disease progression, including resistance mechanisms to endocrine therapy and PARP inhibitors.[13,15,16,17,20,21] Plasma-based detection of HER2 copy number gain predicts response to later-line HER2-targeted therapy better than does historical HER2 amplification detected via tissue in patients who had received intervening HER2-targeted therapy, which may be especially important to assess in patients receiving several sequential lines of HER2-targeted treatment.[22] *Plasma-based* CGP by a well validated NGS assay provides a non-invasive means of reliably detecting the growing numbers of biomarkers currently recommended in the Guidelines. Such testing, particularly when tissue is unavailable, may *increase Guideline-recommended genotyping* (and return results more quickly).

A Note on Naming. The Breast Panel 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, the Panel may wish to *name* the well validated plasma assay Guardant360[14,23,24] in *delineating what should be covered*, as it has done (along with its prostate counterpart) in mentioning RNA expression assays, noting the level of evidence for these tests.[25,26] In a similar vein, the Molecular Diagnostic Services Program has named Guardant360 as useful in ascertaining the alterations driving breast cancer in Medicare patients.[27] 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 published studies reporting on clinical utility and outcomes.

Suggested Revisions:

<table>
<tr><th>Page</th><th>Specific revisions (in blue)</th></tr>
<tr><td>BINV-17</td><td>RECURRENT/STAGE IV (M1) DISEASE
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• First recurrence of disease should be biopsied[x]
[x] In cases in which tissue biopsy is infeasible or unavailable, biomarker testing via a well validated plasma-based NGS assay (liquid biopsy) such as Guardant360 may be used to evaluate molecular alterations and MSI-H status to identify candidates for additional targeted therapies.
[fff] In clinical situations where a biopsy cannot safely be obtained, a well validated plasma-based NGS assay (liquid biopsy) such as Guardant360 may be used to detect HER2 copy number gain, but if liquid biopsy is uninformative and the clinical evidence is strongly supportive of recurrence, treatment may then commence based on the ER/PR/HER2 status of the primary tumor.</td></tr>
<tr><td>BINV-A
1 OF 2</td><td>PRINCIPLES OF BIOMARKER TESTING
HER2 TESTING[a,b]
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• After a negative HER2 test result on initial biopsy sample, consider retesting on subsequent surgical or other additional sample if the initial sample was suboptimal (eg, minimal invasive cancer was present, cold ischemic time or fixation was suboptimal), testing error is expected, additional samples contain higher grade morphologically distinct cancer from the biopsy, to rule out heterogeneity in a high grade cancer, or if it will otherwise aid in clinical decision-making.[a] If retesting of an additional tissue sample is infeasible, testing via a liquid biopsy assay validated for detection of HER2 copy number gain may be considered.</td></tr>
<tr><td>BINV-R
1 OF 3</td><td>ADDITIONAL TARGETED THERAPIES AND ASSOCIATED BIOMARKER TESTING
FOR RECURRENT OR STAGE IV (M1) DISEASE
<table>
<tr><th>Breast Cancer Subtype</th><th>Biomarker</th><th>Detection</th></tr>
<tr><td>.
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HR-positive/
HER2-negative[b]</td><td>.
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PIK3CA mutation</td><td>.
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PCR (blood or tissue block if blood negative), NGS molecular panel testing (from blood or tissue)</td></tr>
<tr><td>Any[x]</td><td>NTRK fusion</td><td>FISH, NGS (from blood or tissue), PCR (tissue block)</td></tr>
<tr><td>Any[x]</td><td>MSI-H/dMMR</td><td>IHC, PCR (tissue block), NGS (from blood or tissue)</td></tr>
</table>
[b] For HR-positive/HER2-negative breast cancer, assess for PIK3CA mutations with tumor or well validated liquid biopsy to identify candidates for alpelisib plus fulvestrant. PIK3CA mutation testing can be done on tumor tissue or ctDNA in peripheral blood (liquid biopsy). If liquid biopsy is negative, tumor tissue testing is recommended.
[x] In cases in which tissue biopsy is infeasible or unavailable, biomarker testing via a well validated plasma-based NGS assay (liquid biopsy) such as Guardant360 may be used to evaluate molecular alterations and MSI-H status to identify candidates for additional targeted therapies.</td></tr>
</table>

Thank you for considering these suggestions.

Sincerely,

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

[20] Fribbens C, O'Leary B, Kilburn L, et al. Plasma ESR1 Mutations and the Treatment of Estrogen Receptor-Positive Advanced Breast Cancer. *J Clin Oncol*. 2016;34(25):2961-2968.
[21] Vidula N, Rich TA, Sartor O, et al. Routine Plasma-Based Genotyping to Comprehensively Detect Germline, Somatic, and Reversion *BRCA* Mutations among Patients with Advanced Solid Tumors. *Clin Cancer Res*. 2020;26(11):2546-2555.
[22] Abraham J, Montero AJ, Jankowitz RC, et al. Safety and Efficacy of T-DM1 Plus Neratinib in Patients With Metastatic HER2-Positive Breast Cancer: NSABP Foundation Trial FB-10. *J Clin Oncol*. 2019;37(29):2601-2609.
[23] 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.
[24] 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.
[25] NCCN Clinical Practice Guidelines in Oncology, Breast Cancer, Version 5.2020 – July 15, 2020, page BINV-N 1 of 4.
[26] NCCN Clinical Practice Guidelines in Oncology, Prostate Cancer, Version 2.2020 – May 21, 2020, page PROS-2A.
[27] Palmetto GBA Medicare Administrative Contractor, "Local Coverage Determination (LCD): MolDX: Plasma-Based Genomic Profiling in Solid Tumors (L38043)," effective March 5, 2020.