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Guidelines Panels: *Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer* (v. 1.2020)[1]

FDA status: Guardant Health's **Guardant360 CDx** is the first plasma-based comprehensive genomic profiling (CGP) test approved by the FDA to profile tumor mutations in all solid malignant neoplasms[2,3,4] (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 Ovarian 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. **Liquid biopsy as an alternative**. Please consider listing *liquid biopsy* using a well validated circulating tumor (ctDNA) assay (such as Guardant360) to assure that all patients with advanced or recurrent ovarian cancer are completely profiled for all Guideline-recommended biomarkers, including germline and somatic *BRCA1/2* mutations, microsatellite instability (MSI), and *NTRK* fusions. The goal is to give physicians greater autonomy in their choice of testing modality and provide patients with a non-invasive option. In patients whose diagnosis has already been histopathologically established, plasma-based testing may obviate the need for repeat invasive biopsy, as Guardant360 has been shown to identify targetable alterations at similar rates with similar matched-therapy outcomes as tissue-based profiling.[5,6,7]
2. ***Liquid biopsy specified***. Since not all ctDNA tests are technically equivalent, you may wish to add specific language to suggest using a FDA-approved ctDNA assay that has not only published analytical and clinical validation, [5,8,9,10] but has also achieved the gold standard for genomics tests: *published outcomes studies* based on ctDNA-identified germline and somatic *BRCA1/2* mutations and MSI in ovarian cancer (*e.g.*, Guardant360[5,11]).

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.[12]

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[1] NCCN Clinical Practice Guidelines in Oncology, Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer, Version 1.2020 – March 11, 2020.
[2] 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."
[3] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P200010, accessed August 25, 2020.
[4] https://www.fda.gov/news-events/press-announcements/fda-approves-first-liquid-biopsy-next-generation-sequencing-companion-diagnostic-test, accessed August 12, 2020.
[5] 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.
[6] Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med* 2018;378(8):731-739.
[7] 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.
[8] 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.
[9] 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.
[10] 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.
[11] 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.
[12] Liang W, Guan W, Chen,R, et al. Cancer Patients in SARS-CoV-2 Infection: A Nationwide Analysis in China. *Lancet Oncol* 2020;21:335-337.

Additionally, a growing number of therapies in cancer are *biomarker-dependent*, including PARP inhibitors for germline and somatic *BRCA1/2*,[1,13] pembrolizumab for MSI-high (MSI-H) disease,[7] and larotrectinib and entrectinib for *NTRK* fusions.[6] In the setting of genomic heterogeneity in ovarian cancer, plasma-based testing can provide a comprehensive profile of a patient's entire disease burden and capture treatment-induced tumor evolution.[11,13]

Many patients are not tested for MSI-H, mismatch repair deficiency, or other known oncogenic drivers that aid in therapy selection, despite being recommended for colorectal and lung cancers in Guidelines for years.[14,15] One would expect the problem of undergenotyping or incomplete genotyping to be similar in ovarian cancer, given the invasive nature of the biopsy required, and depletion of small biopsy tissue by serial individual biomarker testing.[16]

One in six (16%) with ovarian cancer have targetable germline *BRCA* mutations based on *The Cancer Genome Atlas*, and another 7% have targetable somatic *BRCA*1/2 mutations.[17,18] Despite multiple guidelines recommending testing for germline and somatic *BRCA*1/2 deleterious mutations, only 15-30% of women with ovarian cancer even receive germline testing,[19,20] and likely most are not tested for somatic *BRCA* mutations. Comprehensive genomic profiling, using targeted NGS of plasma with Guardant360, has been shown to detect deleterious germline *BRCA*1/2 mutations accurately in a prospective study.[11] ctDNA has an advantage over sequential germline *BRCA* testing followed by tumor testing for somatic *BRCA* mutations, as germline, somatic, and reversion mutations in *BRCA* are detected non-invasively in a single test (although ctDNA tests may miss larger deletions and structural arrangements in *BRCA*).[11,18] Guardant360-detected germline and somatic *BRCA* alterations have been shown to predict response to PARP inhibition in a prospective randomized controlled study.[11] Alternatively, reversion *BRCA* mutations (which restore gene function) detected by Guardant360 predict resistance to PARP inhibitors.[11]

Mismatch repair deficiency/MSI-H is present in up to 10% of epithelial ovarian cancers,[11] and has higher prevalence in nonserous histologies.[17] In cancer types (such as colorectal) in which MSI-H has been an established biomarker, the failure to test for MSI (undergenotyping) is widespread and serious,[14,15] largely due to tissue insufficiency related to serial individual biomarker testing.[21] It is expected that undergenotyping for MSI-H is also widespread in ovarian cancer, since Guidelines recommend using generally small biopsy samples to test for multiple biomarkers (PD-L1, germline and somatic *BRCA*1/2, *NTRK*). The undergenotyping problem for MSI-H may be addressed through the non-invasive, well validated, and FDA-approved Guardant360 assay.

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.

The Solution

A well validated plasma-based assay may overcome the challenges of heterogeneity and limited tissue availability; allow for the interrogation of the Guideline-recommended biomarkers *BRCA1/2*, MSI, and *NTRK*;[17] and help determine the outcome and individualize cancer therapy in patients with gynecologic cancer.[22]

ctDNA in peripheral blood is highly concordant with matched tissue testing for biomarkers of interest, including *BRCA1/2*,[5,6,11] 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.

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[13] Jacob SL, Kiedrowski LA, Young KC. The dynamic landscape of *BRCA1* reversion mutations from indel to SNV in a patient with ovarian cancer treated with PARP-inhibitors and immunotherapy. *Heliyon* 2020;6(5):e03841.
[14] 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.
[15] 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.
[16] Pennell NA, Mutebi A, Zhou Z et al. Economic Impact of Next-Generation Sequencing Versus Single-Gene Testing to Detect Genomic Alterations in Metastatic Non-Small-Cell Lung Cancer Using a Decision Analytic Model. *JCO Precis Oncol* 2019;3:1-9.
[17] Konstantinopolous PA, Norquist B, Lacchetti C et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. *J Clin Oncol* 2020;38:1222-1245.
[18] Vidula N, Rich T, Sartor O, et al. Routine Plasma-Based Genotyping to Comprehensively Detect Germline, Somatic and Reversion *BRCA* Mutations Among Patients with Advanced Solid Tumors. *Clin Canc Res* 2020, Figure 2.
[19] Kurian AW, Ward KC, Howlader N, et al. Genetic Testing and Results in a Population-Based Cohort of Breast Cancer Patients and Ovairan Cancer Patients. *J Clin Oncol* 2019;37:1305-1315.
[20] Childers C, Chilers K, Maggard-Gibbons M and Macinko J. National Estimates of Genetic Testing in Women with History of Breast or Ovarian Cancer. *J Clin Oncol* 2017;34:3800-3806.
[21] 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.
[22] Charo LM, Eskander RN, Okamura R. Clinical implications of plasma circulating tumor DNA in gynecologic cancer patients. *Molecular Oncology* 2020, in press.

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.

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 and FDA-approved plasma assay Guardant360[8,9,10] 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 as supported by FDA approval and published studies reporting on clinical utility and outcomes.

Suggested Revisions:

Page	**Specific revisions** (in ***blue***)
OV-3	[e] Germline and/or somatic *BRCA1/2* status, as ascertained through plasma- or tissue-based biopsy, informs maintenance therapy. [f] In the absence of a *BRCA1/2* mutation on liquid or tissue biopsy, HRD status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B).
OV-B 1 of 3	Tumor molecular analyses, whether performed on circulating tumor DNA (ctDNA) or tissue, as clinically indicated: ◊ Next-generation sequencing (NGS) performed on ctDNA or tissue for *BRCA1/2* somatic mutations ◊ Immunohistochemistry (IHC) for DNA mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2) or microsatellite instability (MSI) testing via polymerase chain reaction (PCR) or NGS on ctDNA or tissue ⋮
OV-C 3 of 10	Tumor molecular testing, whether through plasma or tissue, is recommended prior to initiation of therapy for persistent/recurrent disease. Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue or a current plasma sample if assessing circulating tumor DNA. Testing recommended to include at least: *BRCA1/2*, and MSI or dMMR if not previously done. Evaluation of homologous recombination deficiency can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.
OV-C 7 of 10 & 8 of 10	[p]For patients with deleterious germline *BRCA*-mutated (as detected by an FDA-approved plasma- or tissue-based test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy. [q]For patients with deleterious germline and/or somatic *BRCA* mutated (as detected by an FDA-approved plasma- or tissue-based test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy. ⋮ [t]Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue or a current plasma sample if assessing circulating tumor DNA. Testing recommended to include at least: *BRCA1/2*, and microsatellite instability or DNA mismatch repair if not previously done. Evaluation of homologous recombination deficiency can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.

Thank you for considering these suggestions.

Sincerely,

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[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.