Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Ovarian Cancer Guidelines Panel consider the updates below and enclosed references, pertaining to the evaluation and management of patients with ovarian cancer.

Requested Update #1: Update footnote ‘e’ on pages OV-1, OV-2, and OV-3 to indicate that NGS-based testing to detect BRCA1 and BRCA2 alterations in tumor tissue is recommended as it may inform maintenance therapy. BRCA1/2 testing can be performed individually or as part of broad molecular profiling that also assesses NTRK gene fusions, TP53, MSI, HRD status, and tumor mutational burden (TMB). If a BRCA1/2 alteration is identified, the patient should be referred to genetic counseling and/or follow up with germline testing of the identified alteration.

Requested Update #2: Change foot note ‘w’ in algorithm for recurrent disease (pages OV-6, OV-7) to state that tumor molecular testing should include at least: BRCA1/2, MSI or DNA mismatch repair if not done previously, NTRK gene fusions, homologous recombination status, and tumor mutational burden. Tumor molecular testing can be performed as part of a single, NGS-based broad molecular profiling assay to inform the patient’s treatment options, including clinical trials.

Requested Update 3: In the Systemic Therapy section (pg OV-C 5 of 9), indicate that NGS-based tumor molecular testing should include at least: BRCA1/2, MSI or DNA mismatch repair if not done previously, NTRK gene fusions, homologous recombination status, and tumor mutational burden. Tumor molecular testing can be performed as part of a single, NGS-based broad tumor molecular profiling assay to inform the patient's treatment options, including clinical trials.

Requested Update 4: Under Tumor Molecular Analyses in the Principles of Pathology section (pg OV-B 1 of 3) indicate that MSI testing can be performed through a validated NGS panel, similarly to the NCCN® Colon and Rectal Cancer Guidelines (COL-B 4 of 6; REC-B 5 of 7). Also under Tumor Molecular Analysis in the Principles of Pathology section (pg OV-B 1 of 3), indicate that NGS-based testing for BRCA1/2, TP53, NTRK gene fusions, MSI status, HRD status, and tumor mutational burden could be performed as part of a single assay to inform the patient’s treatment options, including clinical trials.

Requested Update 5: Throughout the guideline (OV-1, OV-2, OV-3, OV-6, OV-7, OV-C 5 of 9, OV-B 1 of 3) change “evaluation of homologous recombination deficiency can be considered” to including HRD in the recommended tumor molecular testing (see language above in requests 1-4).

Rationale:

- **BRCA 1/BRCA 2**
  - In a study of 235 unselected ovarian cancer patients, somatic BRCA testing revealed 44 BRCA1/2 deleterious alterations. Germline DNA was available for analysis in 28 of the 44 BRCA alteration carriers and 11 of the 28 (39.3%) of the BRCA alterations were absent in the germline and determined to be somatic in origin. NGS-based comprehensive genomic profiling not only detects BRCA1/2 alterations that are somatic in origin but has also been shown to be highly concordant (97%) to Sanger sequencing in the identification of BRCA1/2 germline alterations. Therefore, somatic BRCA mutation testing should be offered to women with ovarian cancer as a first-line testing approach to help inform decisions about when to utilize PARPi to maximize clinical benefit.

- **NTRK**
  - Given that the current NCCN®Guidelines in Ovarian Cancer (v2.2019) list both larotrectinib and entrectinib as targeted treatment options in both platinum-sensitive and platinum-resistant disease, NTRK gene fusion testing should be clearly identified as part of the recommended tumor molecular testing strategy.

- **TP53**
  - Somatic alterations in the TP53 gene are associated with high grade epithelial ovarian cancers, mostly high grade serous. The absence of a TP53 mutation possibly in the presence of other mutations such as BRAF and KRAS, can reveal misclassified low grade serous tumors, certain other non-serous epithelial subtypes and sex-cord stromal tumors which have distinct treatment approaches from HGSC, and thus plays an important role as a diagnostic tool. In particular, trametinib extended PFS of low grade serous carcinoma to 13.0 months with a hazard ratio of 0.48 and KRAS
mutations predicted a higher response rate of 24% to binimetinib\(^4\). Additionally, TP53 loss has recently been shown to predict worse outcomes in patients with ovarian clear cell carcinoma\(^7\).

- **MSI and TMB**
  - NGS testing to detect high MSI has been validated across tumor types and is shown to be highly concordant (97%, 65/67 cases) with current standard methods for detecting mismatch repair deficiencies, such as MSI testing by PCR and MMR IHC\(^2\).
  - A meta-analyses of 22 studies of 1234 ovarian cancer cases showed that 8% of serous and 12-20% of nonserous ovarian cancers were MSI high\(^\)\(^8\). NGS-based CGP of ovarian cancers demonstrates that all MSI-H and some MSS ovarian cancers have an elevated TMB (Feinberg 2018). While more data is needed regarding the clinical utility of TMB in ovarian cancer patients, it has been shown to be an important genomic signature for immunotherapy response across other tumor types\(^18\) and, as an emerging biomarker, may play an important role in clinical trial eligibility regardless of tumor type. Comprehensive genomic profiling assays targeting ~1.1 Mb of coding genome can accurately assess TMB, showing high agreement to TMB calculations based on sequencing the whole exome (gold standard)\(^3\).

- **HRD**
  - High genomic loss of heterozygosity (LOH), related to deficiencies in DNA repair, serves as a marker for potential benefit from PARP inhibitors\(^4,5\).
  - HRD occurs in the setting of both germline and somatic loss of function mutations in BRCA1 or BRCA2, but can also occur through mutations of other HR pathway genes or epigenetic events causing loss of expression of these proteins. Testing for BRCA1/2 mutations identifies only a subset of patients with HRD ovarian cancer. Additional patients with HRD ovarian cancer who benefit from PARPi therapy can be identified by quantifying the proportion of the genome under loss of heterozygosity (LOH) resulting in a LOH score\(^5\).
  - Several recently published or presented trials demonstrate that HRD assays can enrich for PARPi sensitive patient populations, including demonstrating significant improvement in PFS in patients with HRD-deficient high-grade ovarian cancer, which may be useful in choosing between different 1st and later line treatment and maintenance regimens. Veliparib in addition to first-line carboplatin-paclitaxel chemotherapy was shown to significantly improve PFS in the HRD-deficient cohort compared to placebo (31.9 vs. 20.5 months; HR=0.57; 95 CI, 0.43 to 0.76, P<0.001)\(^4\). Niraparib significantly extended median PFS in HRD-deficient patients (21.9 vs. 10.4 months: HR=0.43; 95 CI, 0.31 to 0.59, P<0.001) when compared to placebo after response to first-line platinum chemotherapy\(^13\). Results from the PAOLA-1 trial show that maintenance olaparib plus bevacizumab after response to bevacizumab plus platinum-based chemotherapy showed the highest benefit in advanced ovarian cancer patients with tBRCA alterations or HRD-deficient/BRCAwt. However, in this trial, HRD-proficient/BRCAwt patients had equivalent PFS on bevacizumab alone compared to bevacizumab plus olaparib suggesting HRD evaluation may be used to define populations unlikely to benefit from this combination\(^6\).

- **Clinical Trials**
  - A comprehensive genomic profiling approach to tumor testing supports the NCCN\(^8\) recommendation for clinical trial participation for all cancer patients by increasing the number of advanced cancer patients who are identified as eligible and enroll in a clinical trial versus the national average\(^7,8\). In addition, a prospective study of patients with a wide variety of refractory tumors, found that comprehensive genomic profiling nearly doubled the rate of clinical trial enrollment versus a smaller hotspot panel (19% vs 11%)\(^19\).
  - Foundation Medicine has joined both the NCI-MATCH and ASCO TAPUR studies as an approved testing platform, and is accelerating accrual to these transformative trials using the combination of CGP and clinical trial matching capabilities.

Thank you for your review of this submission.

Sincerely

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Foundation Medicine
References


9. LBA2_PR Phase III PAOLA-1/ENGOT-ov25 trial: Olaparib plus bevacizumab (bev) as maintenance therapy in patients (pts) with newly diagnosed, advanced ovarian cancer (OC) treated with platinum-based chemotherapy (PCh) plus bev. *Annals of Oncology*, Volume 30, Supplement 5, October 2019

10. Murphy MA, Wentzensen N. Frequency of mismatch repair deficiency in ovarian cancer: a systematic review This article is a US Government work and, as such, is in the public domain of the United States of America. *Int J Cancer*. 2011;129(8):1914–1922. doi:10.1002/ijc.25835


15. LBA61 A randomized phase II/III study to assess the efficacy of trametinib in patients with recurrent or progressive low-grade serous ovarian or peritoneal cancer. *Annals of Oncology*, Volume 30, Issue Supplement_5, October 2019

