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NCCN Guidelines Panel: Ovarian Cancer

Dear Panel Members,

On behalf of Foundation Medicine, I respectfully request the NCCN® Ovarian Cancer Guidelines Panel review the enclosed data, which supports comprehensive genomic profiling (CGP) of a tumor specimen as part of the standard of care management for patients with advanced ovarian cancer. CGP assays include FoundationOne®, currently available, and FoundationOne *CDx*™, currently under parallel and expedited review by FDA and CMS with anticipated approval later this year. We hope that the data accompanying this letter will encourage the NCCN Ovarian Cancer Panel to consider including in its guidelines a recommendation favoring CGP for assessing molecular biomarkers to guide therapy.

Specific Changes: We request that the Panel consider adding CGP to the NCCN Ovarian Cancer Guidelines as part of the work-up for patients experiencing relapse or recurrent disease. CGP is an effective molecular diagnostic tool for the evaluation of a patient with advanced ovarian cancer to identify predictive genomic alterations, including alterations across all exons of *BRCA1* and *BRCA2*, other genes in the homologous recombination repair (HR) pathway, and a phenotype of HR-deficiency (HRD, high levels of genomic loss of heterozygosity; LOH) for potential sensitivity[1–3] or resistance[4,5] to the use of poly (ADP-ribose) polymerase (PARP) inhibitors. CGP also provides a simultaneous assessment of microsatellite instability (MSI), mismatch repair gene alterations that underlie Lynch Syndrome (*MLH1*, *MLH2*, *MLH6*, *PMS2*), and tumor mutational burden (TMB) to guide therapy using immune checkpoint inhibitors such as pembrolizumab[4]. We request that the panel add guidance for the applicability of CGP to support and enhance[5] the identification of patients with ovarian cancer meeting the NCCN® guidelines for Genetic/Familial High-Risk Assessment[6]. Finally, we request that the panel indicate that CGP may facilitate more rational selection of clinical trials, when appropriate, as it can identify targets for treatment using agents FDA-approved for other indications (e.g. as in the ASCO TAPUR study[7,8]) or can detect known driver alterations that are rare in a given tumor type and not routinely tested for with disease specific panels, but which confer eligibility for genomically matched clinical trials (e.g. NCI MATCH).

FDA Clearance: FoundationOne is a laboratory developed test (LDT) currently available for clinical use. FoundationOne *CDx™* is currently under parallel and expedited review by FDA and CMS with anticipated FDA approval in late 2017. Unlike conventional bridging studies for a single biomarker in one tumor type, achieving an anticipated broad approval involved submitting an analysis across all four classes of genomic alterations (base substitutions, indels, copy number variations and rearrangements) for a dataset comprising more than 6,000 samples. Validation and concordance was demonstrated for more than 36 distinct tumor types and a variety of specimen types (e.g., tumor resections, core biopsies, and fine needle aspirates). The FoundationOne *CDx*™ assay will both identify patients whose tumors contain alterations associated with FDA-approved therapies and serve as a molecular screen to facilitate access to clinical trials, permitting more rapid testing overall and reducing the time and cost of drug development. This anticipated FDA approved product includes variant calling across 324 genes, genomic signatures for MSI and TMB, and clinical claims in the intended use for diseases with current companion diagnostics, including breast cancer, NSCLC, melanoma, colorectal and ovarian cancers. As such, we continue to submit analogous requests to respective NCCN disease panels for these additional cancers. It is anticipated that this FDA approval across solid tumors will be accompanied by a CMS NCD (National Coverage Determination).

Rationale for Preferring Comprehensive Genomic Profiling: Advanced, metastatic ovarian cancer remains an incurable disease with minimal improvement in mortality over the past decade; prevention within inherited ovarian cancer syndrome families and development of improved treatments are high priorities[9]. Many genes have been shown to be important for the development of ovarian tumors. The use of a broad genomic assay able to detect both specific clinically relevant alterations (e.g., in HR or MMR genes) and complex genomic signatures (i.e., MSI-high or LOH-high) is needed to effectively characterize and categorize ovarian tumors[10]. Inherited alterations in several genes predispose women to ovarian cancer, and somatic alterations in many of the same genes also underlie sensitivity to targeted treatments, chemotherapies, and immunotherapies. CGP of a tumor sample using hybrid capture can simultaneously detect both inherited and somatic alterations in *BRCA1, BRCA2,* other HR deficiency-related genes[11] such as *RAD51C, ATM,* or *PALB2*, as well as the

genomic signature of HRD[3]. Any of these can underlie or predict sensitivity to treatment with inhibitors of PARP[1–3] and prompt a genetic/familial high-risk assessment if one had not previously been completed.

A recent analysis shows that only a small fraction of patients with ovarian cancer have undergone (≤11.6%) or discussed the NCCN recommended testing (15.1%) for inherited alterations, despite evidence-based guideline support as the standard of care for at least the past 5 years[5]. In addition to helping select effective therapies, CGP may be one method to improve identification of individuals at highest risk for carrying inherited predisposition alleles amongst the estimated 400,000 currently unscreened ovarian cancer patients[6]. Similarly, a fraction of ovarian cancers are related to Lynch Syndrome[12,13]. Alterations in MMR genes and the phenotypic effects, measured as high levels of MSI and TMB, are detectable using only a sufficiently expansive genomic assay[4], and may identify both individuals eligible for immunotherapy and additional families with inherited cancer predispositions. Furthermore, unbiased sequencing approaches, such as hybrid capture-based next-generation sequencing, can detect combinations of inherited and acquired genomic alterations (including rearrangements, copy number loss, and insertions or deletions) in HR genes, which may be associated with, depending on their co-occurrence, either sensitivity or resistance to platinum-based chemotherapy or PARP inhibitors[14–17].

For patients with ovarian subtypes or signatures consistent with decreased sensitivity to PARPi, alterations in signaling pathways may prompt exploration of alternative treatment approaches within clinical trials, including combinations, such as olaparib and cediranib[18], or therapies targeting pathways less commonly activated. mTOR/PI3K pathway alterations are found in ~41% of *BRCA*-wildtype/LOH-low (HR proficient) ovarian serous carcinomas[19], 70% of clear cell ovarian cancers[7], and at high rates in other non-serous subtypes[10]. Responses to genomically matched therapies targeting the mTOR/PI3K pathway have been reported, particularly for clear cell carcinomas[7,8]. The RAS/RAF/MEK pathway is also frequently mutated, especially in low grade serous carcinomas, and may indicate sensitivity to MEK or RAF inhibitors[8]. In addition, several genes are of prognostic significance in ovarian cancer, including *TP53*, *CCNE1, KRAS*, *BRAF,* and *NF1*[20].

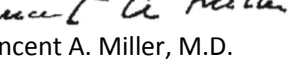
Numerous promising therapeutic approaches are based upon an understanding of cancer genomics and therefore many clinical trials require specified genomic alterations for patient enrollment, including trials offered by the NCI (NCI-MATCH) and ASCO (TAPUR). Consistent with the NCCN® recommendation to provide patients with opportunities to participate in clinical trials, multiplex CGP assays, such as FoundationOne® and FoundationOne *CDx*™, can potentially match > 80% of patients with ovarian cancer to single agent or combination clinical trials. CGP can direct to trials for PARPi and immune modulating therapies[19] by detecting DNA repair pathway alterations[11] (affecting *BRCA1, BRCA2*, *PALB2, BRIP1, BARD1*, *ATM*, *POLE*, *POLD1*, *MLH1*, *MSH2*, *MSH6*, and *PMS2*) or complex genomic signatures[19] (LOH-high, MSI-high, or TMB-high). Similarly, mechanistically driven clinical trials may be indicated when alterations affecting other genes: *PIK3CA*, *PTEN*, and *AKT*[8] (mutation or amplification); *ERBB2* (HER2)*, ERBB3, EGFR*, *FGFR1*, and *FGFR2* (amplification or mutation)*; TP53*[21]*; RAS, RAF,* or *NF1* alterations are detected[9,10,22]. 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. Studies evaluating the use of molecular profiles to direct treatment strategies for patient with gynecological malignancies have shown responses or clinical benefit for 64% of patients[22], and CGP has been successfully used to direct patients to clinical trials[23,24].

CGP can also inform treatment by refining tumor histology through identification of common, distinguishing, or pathognomonic alterations, such as *FOXL2* (C134W) which distinguishes adult granulosa cell tumors from other sex-cord stromal tumors, or *SMARCA4* alterations that characterize small cell carcinoma of the ovary, hypercalcemic type[25] and predict sensitivity to EZH2 inhibitors in clinical development[26].

Taken together, these data indicate CGP is an essential addition to clinical care for patients with this deadly malignancy.

Thank you for your review of this submission.

Sincerely,



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