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National Comprehensive Cancer Network® (NCCN) Guidelines Panel: Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer

On behalf of Illumina, I respectfully request the **NCCN Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer v3.2017** guideline panel to review the enclosed documents in support of including next-generation sequencing (NGS) when referring to various "molecular" related terminology and applications in the published guidelines as described in detail below.

Specific Requested Changes:
We propose changing *"FDA-approved test"* to *"FDA-approved NGS-based test"* and adjust *"or other validated tests"* to include "*or other validated NGS-based tests*".

FDA Clearance:

The FoundationFocus™ CDx$_{BRCA}$ is the first NGS-based companion *in vitro* diagnostic device approved by the FDA (PMA P160018[1]) for qualitative detection of *BRCA1* and *BRCA2* alterations in formalin-fixed paraffin-embedded (FFPE) ovarian tumor tissue. The FoundationFocus CDx$_{BRCA}$ assay detects sequence alterations in *BRCA1* and *BRCA2 (BRCA1/2)* genes. If an ovarian cancer patient is positive for any of the deleterious alterations specified in the *BRCA1/2* classification, the patient may be eligible for treatment with Rubraca™, (rucaparib), the second poly (ADP ribose) polymerase inhibitor (PARP inhibitor) to gain FDA approval for treating ovarian cancer.

Rationale:

As more data and techniques become available to evaluate patients' gene mutations and tumor mutational profiles, a more prescriptive approach is needed to direct laboratories to the most clinically relevant techniques. The FDA-approved NGS companion diagnostic test for rucaparib can detect both **germline and somatic** *BRCA1/2* mutations, which can help to identify up to twice as many patients[4,5,6,7] who may benefit from this targeted therapy, compared to Sanger sequencing. NGS can more accurately and sensitively detect, using less FFPE tumor tissue, a broader range of BRCA-related mutations[8].

The current Ovarian NCCN guidelines (figure OV-B (5 of 8) and (6 of 8) footnote "o") recommend for prescribing rucaparib, "*For patients with deleterious germline and/or somatic BRCA mutated (as detected by an FDA-approved 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.*" To make a distinction between the FDA approved BRCA 1/2 Sanger sequencing assay, approved for detecting **germline** alterations in blood or saliva prior to prescribing Lynparza™ (olaparib)[9-11], and the FDA approved NGS assay for detecting **germline** and **somatic** BRCA 1/2 mutations in FFPE tumor tissue, it would be accurate to specify an NGS-based test, as this type of test is required by the FDA.

Proposed Changes
Figure Changes: OV-B (5 of 8) and (6 of 8) Footnote o:

Current: *"For patients with deleterious germline and/or somatic BRCA mutated (as detected by an FDA-approved 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."*

Proposed: *"For patients with deleterious germline and/or somatic BRCA mutated (as detected by an FDA-approved NGS-based test or other validated NGS-based tests performed in a CLIA-approved facility) advanced ovarian cancer which have been treated with two or more lines of chemotherapy."*

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The following articles are submitted in support of using NGS as a technique to test molecular abnormalities. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

1) https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?ID=389050

2) https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209115s000lbl.pdf

3) Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. (2017) *Lancet Oncol*;18(1):75-87.

4) M. Moschetta, A. George, S. B. Kaye, S. Banerjee; BRCA somatic mutations and epigenetic BRCA modifications in serous ovarian cancer. (2016) *Ann Oncol.*;27(8):1449–1455.

5) Hennessy BT, Timms KM, Carey MS et al. Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. (2010) *J Clin Oncol.*;28(22):3570-3576.

6) Pennington KP, Walsh T, Harrell MI et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. (2014) *Clin Cancer Res.*;20(3):764-775.

7) Arts-de Jong M, de Bock GH, van Asperen CJ et al. Germline BRCA1/2 mutation testing is indicated in every patient with epithelial ovarian cancer: A systematic review. (2016) *Eur J Cancer.*;(61):137-145.

8) Schenkel, LC, Kerkhof J, Stuart A et al. Clinical Next-Generation Sequencing Pipeline Outperforms a Combined Approach Using Sanger Sequencing and Multiplex Ligation-Dependent Probe Amplification in Targeted Gene Panel Analysis. *J Mol Diagn.*:18(5):657–667.

9) Pujade-Lauraine E, Ledermann JA, Selle F et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double- blind, randomised, placebo-controlled, phase 3 trial. (2017) *Lancet Oncol.*;18(9):1274–1284.

10) Ledermann JA, Harter P, Gourley C et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomized, placebo-controlled, double-blind, phase 2 trial. (2016) *Lancet Oncol.*;17:1579-1589.

11) Gunderson CC and Moore KN BRACAnalysis CDx as a companion diagnostic tool for Lynparza. (2015) *Expert Rev Molecular Diagn.*; 15(9):1-6.

Sincerely,
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