Submitted by:
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NCCN Guidelines Panel: Ovarian cancer

On behalf of Vermillion, Inc., I respectfully request the NCCN review the enclosed data for inclusion of a five-biomarker cancer risk assay in the pre-surgical work-up of undiagnosed adnexal masses.

Specific Changes: Under MS-6 and MS-7 (under undiagnosed pelvic masses), recommend the use of OVA1, or a five biomarker assay with equivalent sensitivity, to all ovarian masses as a routine component of the generalist's pre-surgical workup for equivocal adnexal masses with no obvious indication of metastatic disease, to augment the detection of and gynecologic oncologist referral rate for hard-to-diagnose and benign-appearing malignancies, including early stage and pre-menopausal ovarian cancers.

FDA Clearance: The OVA1 test is a qualitative five-biomarker blood test that helps assess the likelihood of malignancy in adnexal masses prior to surgery when the physician's independent clinical and radiological evaluation does not indicate malignancy. It is indicated for women who meet the following criteria: over age 18, ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist.

Rationale: In support of the proposed change, the Society of Gynecologic Oncology published a position statement for a five-biomarker cancer risk assay as a component of the physician work-up to improve the detection and referral of pelvic masses planned for surgery that are at elevated risk of malignancy. (https://www.sgo.org/newsroom/position-statements-2/multiplex-serum-testing-for-women-with-pelvic-mass/).

The following clinical validation publications (in chronological order) are submitted in support of this proposed change. New study data on **health economics and the validation of a second generation assay** to improve specificity (#6 and #7 respectively) have been included to further demonstrate the value and application of a five-biomarker cancer risk assay.

Studies:

1. Ueland FR, et al. Effectiveness of a multivariate index assay in the preoperative assessment of ovarian tumors. Obstet Gynecol. 2011 Jun;117(6):1289-97.

- 524 prospective patient cases, which included 161 malignancies, were evaluated and the results validated OVA1's 96% sensitivity when used with clinical impression and OVA1's standalone sensitivity of 93%, which was a significant improvement compared to CA-125II alone (69%).

2. Ware Miller R, et al. Performance of the American College of Obstetricians and Gynecologists' ovarian tumor referral guidelines with a multivariate index assay. Obstet Gynecol. 2011 Jun;117(6):1298-306.

- The 516 patient cohort study demonstrated that replacing CA-125II with OVA1 in the ACOG guidelines for referral to a gynecologic oncologist increased the sensitivity for ovarian malignancies from 77 to 94% and, as a result, increased overall referrals.

3. Bristow RE, et al., Ovarian malignancy risk stratification of the adnexal mass using a multivariate index assay. Gynecol Oncol. 2013;128:252-259.

- The multi-institutional prospective trial validated OVA1's intended use performance by demonstrating that 94% (29/31) of pre-menopausal ovarian cancers and 97% of (59/61) post-menopausal ovarian cancers were identified across all subtypes.

4. Longoria TC, et al., Clinical performance of a multivariate index assay for detecting early-stage ovarian cancer. Am J Obstet Gynecol. 2014 Jan;210(1):78. e1-9.

- 1,016 prospective patient cases, which included 86 early-stage ovarian cancers, were assessed and the results determined that adding OVA1 to clinical impression reduced the percent of early-stage cancers missed or undetected from 31% to 5%.

5. Goodrich ST, et al., The effect of ovarian imaging on the clinical interpretation of a multivariate index assay. Am J Obstet Gynecol. 2014 Jul;211(1):65.e1-65.e11.

- 1,024 prospective patient cases, which included 255 malignancies across menopausal status, stages and subtypes, were assessed and the results determined that adding OVA1 to imaging reduced the percent of cancers missed or undetected from 23% to 2%.

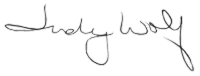
6. Forde GK, et al. Cost Effectiveness Analysis of a Multivariate Index Assay compared to Modified ACOG Criteria and CA-125 in the Triage of Women with Adnexal Masses. Abstract published at ACMQ 2015, Alexandria, VA

- The study demonstrated cost effectiveness of OVA1 in comparison to modified ACOG referral guidelines ($35,094/QALY) and CA-125 testing alone ($12,189/QALY); this was mainly attributed to fewer projected reoperations and pre-treatment CT scans compared to the other modalities.

7. Wolf JK et al. Validation of a Second-generation MIA (MIA2G) for Triage of Adnexal Masses. Abstract published at ASCO 2015, Chicago, IL

- An algorithm using three MIA markers (CA125-II, transferrin and Apo A-1) and two new biomarkers (FSH and HE4) showed improved specificity (69.1%) and PPV (40.4%) over the biomarkers used for OVA1 (53.6% and 31.4%, respectively). Sensitivity and NPV were not significantly different.

Sincerely,



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