Submitted by:
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Date of request: October 18, 2016
NCCN Guidelines Panel:

On behalf of Vermillion/ASPiRA Laboratories, I respectfully request the NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer to review the enclosed data for inclusion of the Multivariate Index Assay test OVA1 in both the Ovarian Cancer TOC Discussion and the Table of Contents Discussion.

Specific Changes:
1. Recommend on page M-5 that you change the wording to "Based on data documenting an increased survival, NCCN Guidelines Panel Members recommend that all patients *with an elevated OVA1 result* should undergo surgery by an experienced gynecologic oncologist"
2. Recommend on page OV-1 that "CA125" is removed from the "Work Up" section and "OVA1 and/or MIA or other tumor markers as clinically indicated" is replaced.
3. Recommend on page OV-1 under the "Primary Treatment" section you add "Establish baseline CA125 as clinically indicated either from OVA1 and/or MIA result or separately."

FDA Clearance: The OVA1 Test is a qualitative serum test that combines the results of five immunoassays into a single numerical score. 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. The OVA1 Test is an aid to further assess the likelihood that malignancy is present when the physician's independent clinical and radiological evaluation does not indicate malignancy. The test is not intended as a screening or stand-alone diagnostic assay.

Rationale: In light of the recent FDA statement on ovarian cancer screening tests causing increased confusion in the Gynecological world and providers now not wanting to order any biomarkers on pelvic masses, we feel it is important for practitioners to know that the OVA1 FDA Cleared test is the only test proven to determine risk of malignancy across all histologic subtypes and menopausal statuses prior to operating, thus avoiding any missed malignancies being operated on by a generalist and patients suffering worse prognoses. Furthermore, with just under 1400 board certified Gynecological Oncologists in this country, a refer all recommendation will lead to delayed diagnosis and treatment.

The following articles are submitted in support of these proposed changes. We would like to acknowledge the tireless work of the NCCN Panel Members who are trying to improve the outcomes for women with ovarian cancer just as we are.
1. Ueland, et. al. Effectiveness of a Multivariate Index Assay in the Preoperative Assessment of Ovarian Tumors. *Obstet Gynecol*. 2011; Vol 117:1289-1297. This paper was the initial OVA1 Clinical Validation study. It showed that OVA1 detected 76% of malignancies missed by CA125 alone and OVA1 in conjunction with physician assessment detected 86% of malignancies missed by CA125. This was a prospective, multi-institutional trial involving 27 primary care and specialty sites in the US.
2. Bristow, et al., Impact of a Multivariate Index Assay on Referral Patterns for Surgical Management of Adnexal Mass. *AJOG* 2013; 209: 581.e1-8. This paper demonstrated that OVA1 had a statistically significant higher sensitivity (90.2%) for detecting ovarian malignancy compared to clinical assessment (73.2%), CA125 (68.3%), and mACOG guidelines (79.3%); however, use of OVA1 does not lead to over-referral.
3. Bristow, et. al. Ovarian Malignancy Risk Stratification of the Adnexal Mass using a Multivariate Index Assay. *Gynecologic Oncology* 2013; 128:252-259. This paper was a second clinical validation study that showed how the use of OVA1 can detect 95.7% of ovarian malignancies with 91.4% of cases being found in early stage versus only 65.7% being found early stage by CA125. Additionally, 43.1% of malignancies were FIGO Stage 1.
4. Goodrich, et. al. The Effect of Ovarian Imaging on the Clinical Interpretation of a Multivariate Index Assay. *AJOG* 2014; N=1024. Using OVA1 in conjunction with Ultrasound findings reduces missing ovarian cancer to just 2% (ultrasound alone missed 23% of malignancies and CT scan missed 20%).

Sincerely,

Marra S. Francis, MD, FACOG, Chief Medical Officer Vermillion, Inc.