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Risk Stratification of the Persistent Ovarian Mass with OVA1
CA 125 Alone is not Enough for Surgical Planning

Encountering an undiagnosed malignancy during an anticipated benign surgical intervention is stressful for the surgeon—and devastating for the unprepared patient.

More than 21,000 women are diagnosed with ovarian cancer in the United States annually, and more than 14,000 die each year.[1] Leading medical associations, including the American College of Obstetrics and Gynecology (ACOG), recommend that women with suspected ovarian cancer be referred to a gynecologic oncologist for surgery for the best potential outcomes. However, only an estimated one-third of women who have a malignant tumor are operated on by a gynecologic oncologist for that initial surgery.[2] In order to help healthcare providers find these missed cancer diagnoses, they need a highly sensitive tool which compliments both clinical impression and radiology findings. The need is especially great for premenopausal women, for whom preserving fertility is a concern—new biomarkers are essential to help assess if a consultation or referral is an appropriate step.

When deciding on the type of surgery for a patient with an adnexal mass, estimating the risk of malignancy is essential for the general gynecologist or sub-specialist. If a diagnosis of ovarian cancer is confirmed, it is well recognized and accepted that the patient's best prognosis and survival benefit lies in having an optimal debulking with proper staging at the index procedure. It is therefore critically important to have a tool that better stratifies who may or may not be at a higher risk of an ovarian malignancy so the most appropriate physician specialist may perform the surgery.

The ability to detect ovarian cancer at an early stage is likewise crucial to better survivability. Of note, are recent findings published in the March 25, 2013 issue of Gynecologic Oncology that "geographic proximity to a high-volume hospital and travel distance are associated with treatment guidance adherence for advanced-stage ovarian cancer." This research also revealed important health disparities, "Geographic barriers to standard ovarian cancer treatment disproportionately affect racial minorities and women of low-SES."[3] The lead author was Robert E. Bristow, M.D., director of Gynecologic Oncology Services at UC Irvine Healthcare and former director of gynecologic oncology at Johns Hopkins.

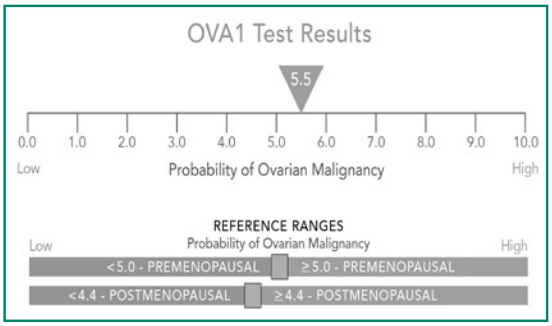
Multivariate Biomarker Advantage with OVA1

CA 125 has been used off label for many years to predict malignancy before surgery; however, the performance of CA 125 for pre-surgical assessment for malignancy is inadequate (50% missed cancer for early stage ovarian cancers; greater than 25% missed cancers for late stage cancers).[4] Additionally, CA 125 may not be elevated across all histology types of ovarian malignancy. For the pre-surgical assessment of the adnexal mass, CA 125 alone is *not* enough.

"CA 125 became entrenched in gynecological ovarian mass evaluation due to lack of a validated and better alternative previously. That's remarkable considering CA 125 was never FDA approved for pre-surgical use, has limited specificity, and poor sensitivity in early ovarian cancer stages. It also performs poorly in premenopausal patients." said Hector O. Chapa M.D., F.A.C.O.G. Dr. Chapa is medical director for the Dallas-based Women's Specialty Center, clinical faculty at Methodist Medical Center Dallas, and a published author for women's health.

Aid in Pre-Surgical Rule Out Protocol

OVA1 is the first FDA-cleared, protein based, in vitro diagnostic multivariate index assay (MIA) indicated for the evaluation of an ovarian mass prior to surgery. The clearance of OVA1 by the FDA came in September of 2009. OVA1 is a qualitative serum test that combines the results of five immunoassays—β2 microglobulin, CA 125II, apolipoprotein A-1, prealbumin and transferrin—into a single numerical result. The test result is reported on a scale from 0-10 taking into account menopausal status. "OVA1 provides a clinically superior alternative regardless of menopausal status or mass histology." Dr. Chapa said.



High Sensitivity for Cancer Detection

The purpose of the OVA1 blood test is to NOT miss cancer prior to surgery of the adnexal mass. With 96% sensitivity prior to surgery, OVA1 may help refer cancers to gynecologic oncology specialists, while the 98% negative predictive value, helps ensure that the gynecologist can treat the patient with confidence that the ovarian mass is not malignant. OVA1 is effective in detecting ovarian malignancies in premenopausal and postmenopausal women with adnexal masses scheduled for surgery, including early stage disease. OVA1's sensitivity provides full coverage for picking up epithelial as well as non-epithelial ovarian cancers.

OVA1® and CA125II Performance by Stage

Subtype	OVA1	CA125II
Stage I	89.3	64.3
Stage II	100	71.4
Early Stage	91.4	65.7
Premenopausal Early Stage	90.9	45.5
Postmenopausal Early Stage	91.7	75

Source: Bristow, Robert et al. Ovarian Malignancy Risk Stratification of the Adnexal Mass Using a Multivariate Index Assay, Gynecologic Oncology, Vol 128, Issue 2, Feb 2013, p252-259.

During the last year, new research was published in three peer-reviewed publications concluding that in more than 1,000 women studied using OVA1 prior to planned surgery, OVA1 consistently helped the OB/GYN formulate the careplan.[3-6] Earlier studies, published in 2011, also confirmed these findings.[7-10]

"There are two reasons that a general OB/GYN would want to order an OVA1 test. The first is to be able to evaluate an ovarian mass for cancer before surgery and ideally have the patient triaged to a GYN oncologist if the test suggests cancer. The second reason is with the high negative predictive value of 98%—it allows an OB/GYN to feel confident a mass is most likely not malignant so there are no surprises at the time of surgery. I operate on a lot of women with ovarian masses so this is peace of mind for me and my patients," Atlanta-based gynecologist Michael D. Randell, M.D., F.A.C.O.G. explained. "The OVA1 test result doesn't change the plan for surgery—it just helps decide whether a general OB/GYN or a GYN oncologist is going to perform the surgery. So, if a patient has an ovarian mass and surgery is planned, order the test."

Dr. Bristow published another study looking at the impact on referral patterns when OVA1 was used in the pelvic mass work-up. He found that the use of OVA1 as a risk stratification test was associated with referral patterns comparable to actual clinical practice and had higher sensitivity than any other pelvic mass triage algorithm.

"As a general OB/GYN, I don't treat ovarian cancers but I do see a large number of patients with ovarian cysts and or masses that need to be evaluated. In the past all we had was physical exam and sonography as tools to diagnose cancer as well as surgery, if needed. OVA1 has allowed us to reassure patients or refer them to the right surgeon more often than not. The sensitivity of the test has made a big impact on how we treat these patients." San-Antonio-based obstetrician-gynecologist (OB/GYN) Valentin Almendarez, M.D., F.A.C.O.G. said.

OVA1 is the first MIA to provide a result reflective of both HOST response and TUMOR behavior:

The OVA500 results were published in the February 2013 *Gynecologic Oncology* in the article, "Ovarian Malignancy Risk Stratification of the Adnexal Mass Using a Multivariate Index Assay."

OVA500 Study Summary

Results (N=494)	Clinical Impression (CI)	CA125II	OVA1	OVA1 & CI
Sensitivity %	73.9	73.9	**92.4**	**95.7**
Specificity %	92.5	94.5	53.5	50.7
PPV %	69.4	75.6	31.3	30.8
NPV %	93.9	94.1	**96.8**	**98.1**
% Cancers Missed	26.1	26.1	**7.6**	**4.3**

This multi-center study investigated OVA1 performance in the pre-surgical detection of malignancy among 494 women prospectively enrolled from non-gynecologic oncology practices. Sensitivity across all types of ovarian cancers was 96% when OVA1 was added to routine clinical assessment. Importantly, OVA1 identified 83% of cancers missed by clinical assessment and 71% of cancers missed by CA 125.

The American College of Obstetricians and Gynecologists (ACOG) referral guidelines for women with a pelvic mass incorporate CA 125; however, a study by Miller et al. (2011, Obstet Gynecol) concluded that "replacing CA 125 with the multivariate index assay improved the sensitivity and negative predictive value of the College referral guidelines while it decreased specificity and positive predictive value. This high sensitivity was maintained in premenopausal women as well as early-stage disease."[9]

Citing the FDA clearance of OVA1, ACOG and the Society of Gynecologic Oncologists (SGO), released a joint committee opinion stating that OVA1 "appears to improve the predictability of ovarian cancer in women with pelvic masses."[10]

OVA1 is offered through Vermillion's new CLIA Certified Laboratory, ASPiRA LABS, as well as through Quest Diagnostics. ASPiRA LABS is led by Herbert Fritsche, PhD, formerly clinical chemistry section chief in the Department of Pathology and Laboratory Medicine at MD Anderson Cancer Center. ASPiRA LABS offers a personalized patient report for OVA1 to the ordering physician, to facilitate better consultation with the patient and her family as she faces a planned surgery. OVA1 is covered by Medicare and other insurance plans.

VERMILLION AND ASPIRA LABS

Vermillion develops and commercializes high-value, multi-marker, diagnostic tests which address unmet needs in gynecologic oncology and women's health. ASPiRA LABS is a resource for personalized tests including OVA1 prior to surgery and Longitudinal CA 125 to monitor ovarian cancer once treated.

For more about OVA1® and ASPiRA LABS, visit www.OVA-1.com and www.aspiralab.com. Customer service can be reached at 1.844.ASPiRA1.

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