

Performance of the American College of Obstetricians and Gynecologists' Ovarian Tumor Referral Guidelines With a Multivariate Index Assay

Rachel Ware Miller, MD, Alan Smith, MS, Christopher P. DeSimone, MD, Leigh Seamon, DO, MPH, Scott Goodrich, MD, Iwona Podzielinski, MD, Lori Sokoll, PhD, John R. van Nagell Jr, MD, Zhen Zhang, PhD, and Frederick R. Ueland, MD

OBJECTIVE: The American College of Obstetricians and Gynecologists (the College) published referral guidelines for women with a pelvic mass that incorporate CA 125. A new multivariate index assay assesses the malignant risk of ovarian tumors before surgery. Our objective was to estimate the performance of the College guidelines with this new multivariate index assay.

METHODS: This prospective, multi-institutional trial included 27 primary care and specialty sites throughout the United States. The College guidelines were evaluated in women scheduled for surgery for an ovarian mass. Clin-

ical criteria and blood for biomarkers were collected before surgery. A standard CA 125-II assay was used and the value applied to the multivariate index assay algorithm and the CA 125 analysis. Study results were correlated with surgical pathology.

RESULTS: Of the 590 women enrolled with ovarian mass on pelvic imaging, 516 were evaluable. There were 161 malignancies (45 premenopausal and 116 postmenopausal). The College referral criteria had a modest sensitivity in detecting malignancy. Replacing CA 125 with the multivariate index assay increased the sensitivity (77–94%) and negative predictive value (87–93%) while decreasing specificity (68–35%) and positive predictive value (52–40%). Similar trends were noted for premenopausal women and early-stage disease.

CONCLUSION: Replacing CA 125 with the multivariate index assay improves the sensitivity and negative predictive value of the College referral guidelines while decreasing specificity and positive predictive value. The high sensitivity is maintained in premenopausal women and early-stage disease.

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The National Institutes of Health released a consensus statement in 1994 declaring “women with ovarian masses who have been identified preoperatively as having a significant risk of ovarian cancer should be given the option of having their surgery performed by a gynecologic oncologist.”¹ There have been numerous publications and guidelines recommending that women with ovarian cancer be under the care of a gynecologic oncologist.^{2–8} Reports indicate that only one third of women with malignant

For a list of OVA1 trial sites and each primary investigator specialty, see the Appendix online at <http://links.lww.com/AOG/A243>.

From the Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Kentucky Markey Cancer Center, Lexington, Kentucky; Applied Clinical Intelligence, Bala Cynwyd, Pennsylvania; and the Department of Pathology, Center for Biomarker Discovery, Johns Hopkins Medical Institutions, Baltimore, Maryland.

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Corresponding author: Rachel Ware Miller, MD, Assistant Professor of Gynecologic Oncology, University of Kentucky Markey Cancer Center, 800 Rose Street, Lexington, KY 40536-0298; e-mail: raware00@uky.edu.

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ovarian tumors are referred to gynecologic oncologists for primary surgery.^{9,10}

The American College of Obstetricians and Gynecologists (the College) published referral guidelines incorporating menopausal status, physical examination, family history, imaging, and CA 125.⁶ These guidelines are useful in predicting advanced-stage ovarian cancer^{11,12} but “perform poorly in identifying early-stage disease, especially in premenopausal women, primarily due to lack of early markers and signs of ovarian cancer.”¹² An effective preoperative test, particularly for younger women and early-stage cancers, can have a favorable effect on women’s health as survival is better in these populations.¹³ This is relevant because only 10% of women with early-stage ovarian cancer receive the recommended staging and treatment.¹⁴

The OVA1 test (multivariate index assay) is a new multivariate diagnostic biomarker assay approved by the U.S. Food and Drug Administration for use in conjunction with physician evaluation to determine whether an ovarian tumor warrants referral to a gynecologic oncologist. Our study objective was to estimate the performance of the College referral guidelines and the effect of replacing CA 125 with the multivariate index assay.

MATERIALS AND METHODS

This multi-institutional trial enrolled patients from 27 primary care and specialty sites across the United States (see the Appendix, available online at <http://links.lww.com/AOG/A243>). The sites included women’s health clinics, obstetrics and gynecology groups, community and university hospitals, gynecologic oncology practices, and health maintenance organization groups. Institutional review board approval was obtained from each site. Participants were recruited by medical staff at each participating institution and represent a consecutive series of patients who met inclusion criteria and agreed to participate in the study. Inclusion criteria included: female patients age 18 years or older, a level of understanding sufficient to give informed consent, agreeable to phlebotomy, an ovarian tumor with planned surgical intervention within 3 months of imaging, and signed informed consent. All ovarian tumors were confirmed with an imaging study (ultrasonography, computed tomography scan, magnetic resonance imaging) before enrollment. Patients were excluded from the study if: age younger than 18, surgical intervention was not planned, declined phlebotomy, or had a malignancy diagnosis in the last 10 years (excepting nonmelanoma skin cancer). Menopause was defined

as the absence of menses for at least 12 months or age 50 or older in those patients who were unclear about their menopausal status.

Before surgery, 30 to 50 mL of venous blood was collected into BD plastic vacutainer tubes with clot activators and centrifuged after sitting at 18–25°C for a minimum of 1 hour and a maximum of 6 hours postphlebotomy. The serum specimens for each patient were pooled and aliquots stored at –65°C to –85°C. The specimens were shipped frozen for storage to PrecisionMed International. Biomarker measurements were performed at Quest Diagnostics, Inc. and validated at Johns Hopkins Medical Institutions and Specialty Laboratories. Validation results were submitted to the U.S. Food and Drug Administration. All testing sites were blinded to the clinical and pathologic data. Data analysis was performed by Applied Clinical Intelligence.

The multivariate index assay consists of five immunoassays combined into a single numerical result, including: CA 125-II, transthyretin (prealbumin), apolipoprotein A1, beta 2 microglobulin, and transferrin. Many of these individual biomarkers have been previously reported.^{15–17} The multivariate index assay algorithm cutoffs were derived and validated from two independent serum training sets. The premenopausal and postmenopausal cutoffs were selected to maximize the utility of the composite index over its individual component markers while maintaining a high level of sensitivity and negative predictive value. CA 125-II was measured on the Elecsys 2010 (Roche Diagnostics) and the other four markers were measured on the BN II System (Siemens Healthcare Diagnostics). The OvaCalc software imports, reconciles, and numerically combines the values for each assay and uses the multivariate index assay algorithm to generate an ovarian malignancy risk index score for each individual specimen. The output of the multivariate index assay algorithm is a numeric index between 0.0 and 10.0, with the following clinical report:

- Premenopausal
 - Low probability of malignancy (multivariate index assay less than 5.0)
 - High probability of malignancy (multivariate index assay 5.0 or higher)
- Postmenopausal
 - Low probability of malignancy (multivariate index assay less than 4.4)
 - High probability of malignancy (multivariate index assay 4.4 or higher)



A standard CA 125-II assay (Roche Elecsys) was performed for each patient and the value used in the multivariate index assay algorithm and the CA 125 analysis. The CA 125 clinical cutoff values were chosen in accordance with the College referral criteria^{5,11} as more than 200 units/mL for premenopausal women and more than 35 units/mL for postmenopausal women. Additionally, we evaluated the modified College criteria proposed by Dearking (more than 67 units/mL for premenopausal women).¹²

The College criteria recommend preoperative consultation with a gynecologic oncologist for one or more of following criteria:

Premenopausal women

1. Very elevated CA 125 (more than 200 units/mL)
2. Ascites
3. Evidence of abdominal or distant metastasis
4. Family history of one or more first-degree relatives with ovarian or breast cancer.

Postmenopausal women

1. Any elevated CA 125 (more than 35 units/mL)
2. Nodular or fixed pelvic mass
3. Ascites
4. Evidence of abdominal or distant metastasis
5. Family history of one or more first-degree relatives with ovarian or breast cancer.

The revisions to the College guidelines proposed by Dearking include: 1) eliminating the family history of one or more first-degree relatives with ovarian or breast cancer, and 2) lowering the CA 125 threshold in premenopausal women to 67 units/mL.¹²

The statistical analysis was stratified based on menopausal status, stage, and pathology diagnosis. Clinically relevant criteria such as sensitivity, specificity, and predictive values were calculated to evaluate the performance of the College and modified College referral criteria. McNemar's χ^2 test was used to compare the performance of the College guidelines with and without the multivariate index assay. Test performance was calculated for all pelvic malignancies (including epithelial ovarian cancer, nonepithelial ovarian cancer, borderline ovarian tumors, metastases to the ovary, and other nonovarian pelvic malignancies), with respect to menopausal status. Subanalysis was performed in patients with primary ovarian malignancies (epithelial and nonepithelial ovarian cancers) with respect to menopausal status and stage. Ninety-five percent confidence intervals were constructed, and *P* values were calculated from *t* tests and Fisher exact test

where appropriate. Statistical analysis was performed with SAS 9.1 (SAS Institute Inc.).

RESULTS

Between 2007 and 2008, the study enrolled 590 women with an ovarian mass verified by an imaging study. Of these, 516 were evaluable. Women were excluded from analysis if surgery was either not performed²⁷ or delayed more than 3 months,³ pathology report was not available (*n*=26),²⁶ blood specimen was unusable (*n*=9),⁹ physician assessment was not available (*n*=8),⁸ or imaging study did not confirm an adnexal tumor (*n*=1).¹ The clinical and pathologic characteristics of all evaluable patients are summarized in Table 1. More than half of the patients (52%) were enrolled by physicians who were not specialty trained in gynecologic oncology. There were 161 pelvic malignancies in women with a documented ovarian tumor on preoperative imaging. One hundred and fifty one had ovarian malignancies (29%), nine patients had a pelvic malignancy but normal ovarian histology, and one patient had an ovarian tumor of low malignant potential and a synchronous endometrial cancer. There were 355 patients with benign ovarian conditions.

The performance of the College and modified College referral guidelines in all pelvic malignancies are reported in Table 2. Evaluating all 516 patients, the performance of the Dearking modifications did not differ statistically from the College criteria. When separated by menopausal status, the modified College guidelines were associated with an increase in sensitivity (58–76%) and decrease in specificity (77–70%) for premenopausal women, and increase in specificity (56–71%) for postmenopausal women. On univariate analysis, CA 125, ascites, and radiographic evidence of metastatic disease had the highest odds ratio for predicting ovarian cancer (Table 3).

The multivariate index assay was substituted for CA 125 in the College guidelines and the results are summarized in Tables 4, 5, and 6. Using McNemar's test, the sensitivity of the College guidelines with the multivariate index assay was significantly higher than the College guidelines (χ^2 of 21.5 [df=1], *P*<.001). Compared with the College guidelines, the calculated negative predictive value for the College guidelines with the multivariate index assay also increased, whereas the specificity and positive predictive value decreased (Table 4). The improvement in sensitivity and negative predictive value was most notable for premenopausal women. When a subanalysis for primary ovarian malignancy was performed, the College guidelines with



Table 1. Summary of Evaluable Patients

Characteristic	All Patients (N=516)	Premenopausal Patients (n=235)	Postmenopausal Patients (n=281)	P
Age (y)				
n	516	235	281	
Mean (SD)	52.0 (13.9)	40.9 (8.3)	61.4 (10.3)	<.001
Range (min–max)	18–92	18–58	37–92	
Ethnicity or race				<.001
Hispanic or Latina	40 (7.8)	25 (10.6)	15 (5.3)	
Asian	10 (1.9)	6 (2.6)	4 (1.4)	
African American	56 (10.9)	40 (17.0)	16 (5.7)	
White	407 (78.9)	163 (69.4)	244 (86.8)	
Other	3 (0.6)	1 (0.4)	2 (0.7)	
No. of pregnancies				<.001
None	96 (18.6)	56 (23.8)	40 (7.8)	
1	68 (13.2)	37 (15.7)	31 (11.0)	
2	117 (22.7)	58 (24.7)	59 (21.0)	
3	113 (21.9)	51 (21.7)	62 (22.1)	
4 or more	120 (23.3)	33 (14.0)	87 (31.0)	
Not specified	2 (0.4)	0	2 (0.7)	
Pathology diagnosis				<.001
Benign ovarian conditions	355 (68.8)	190 (80.9)	165 (58.7)	
Epithelial ovarian cancer	94 (18.2)	25 (10.6)	69 (24.6)	
Stage*				.142
Stage I	23 (24.5)	7 (28.0)	16 (23.2)	
Stage II	17 (18.1)	7 (28.0)	10 (14.5)	
Stage III	50 (53.2)	10 (40.0)	40 (58.0)	
Stage IV	3 (3.2)		3 (4.3)	
Not given	1 (1.1)	1 (4.0)		
Pathology*				.032
Serous	55 (58.5)	11 (44.0)	44 (63.8)	
Mucinous	8 (8.5)	4 (16.0)	4 (5.8)	
Endometrioid	10 (10.6)	6 (24.0)	4 (5.8)	
Clear cell	8 (8.5)	3 (12.0)	5 (7.2)	
Transitional	2 (2.1)		2 (2.9)	
Carcinosarcoma	5 (5.3)		5 (7.2)	
Mixed	1 (1.1)	1 (4.0)		
Undifferentiated	2 (2.1)		2 (2.9)	
Other	3 (3.2)		3 (4.3)	
Primary nonepithelial ovarian malignancy	11 (2.1)	3 (1.3)	8 (2.8)	
Pathology†				.491
Sarcoma	2 (18.2)		2 (25.0)	
Sex cord stromal	7 (63.6)	3 (100.0)	4 (50.0)	
Germ cell	2 (18.2)		2 (25.0)	
Borderline ovarian tumor	28 (5.4)	8 (3.4)	20 (7.1)	
Metastatic malignancies to the ovaries	18 (3.5)	6 (2.6)	12 (4.3)	
Nonprimary ovarian malignancies with no involvement of ovaries	10 (1.9)	3 (1.3)	7 (2.5)	
CA 125-II (international units/mL)				
n	516	235	281	
Mean (SD)	312.9 (1,565.0)	153.2 (447.8)	446.4 (2,073.2)	.022
Range (min–max)	0.6–28,733	0.6–3,885	1.9–28,733	
Multivariate index assay value				
n	516	235	281	
Mean (SD)	5.8 (1.88)	5.5 (1.77)	6.0 (1.95)	.004
Range (min–max)	2.7–10.0	2.8–10.0	2.7–10.0	
Ascites on imaging	50 (10)	20 (8)	30 (11)	.457
Metastatic implants on imaging	23 (4)	3 (1)	20 (7)	.001
Nodular or fixed pelvic mass on exam	75 (15)	33 (14)	42 (15)	.803

(continued)

Table 1. Summary of Evaluable Patients (continued)

Characteristic	All Patients (N=516)	Premenopausal Patients (n=235)	Postmenopausal Patients (n=281)	P
Family history of breast cancer	59 (11)	24 (10)	35 (12)	.488
Family history of ovarian cancer	33 (6)	15 (6)	18 (6)	1.000
Family history of cancer	84 (16)	35 (15)	49 (17)	.474

SD, standard deviation; min, minimum; max, maximum.

Data are n (%) unless otherwise specified.

Menopausal status imputed when not stated from patient's age. Premenopausal imputed when age 50 or younger, postmenopausal when age older than 50.

CA 125-II as assayed from blood draw used for the multivariate index assay score.

P values calculated from *t* tests for age, CA 125-II, and multivariate index assay values and from Fisher's exact test for the categorical variables, except no. of pregnancies, where a Mantel-Haenszel test of ordinal association was used.

* For stage and detailed pathology, the percentage is of the number of epithelial ovarian cancers.

† For detailed pathology, the percentage is of the number of nonepithelial ovarian cancers.

the multivariate index assay were more sensitive but less specific for early-stage disease than the original College criteria for premenopausal (Table 5) and postmenopausal (Table 6) women. When all 161 malignancies are evaluated, the College guidelines with the multivariate index assay identified 79% (15/19) of missed malignancies in premenopausal, and 67% (12/18) of malignancies missed in postmenopausal women compared with the College criteria. Furthermore, for primary ovarian malignancies (epithelial and nonepithelial ovarian malignancies), the College guidelines with the multivariate index assay correctly identified 78% (7/9) of missed early-stage premenopausal malignancies, and all five missed malignancies in postmenopausal women. The College guidelines with the multivar-

iate index assay detected 93% (25/27) of premenopausal and all (76/76) postmenopausal primary ovarian malignancies.

DISCUSSION

There is agreement on the importance of early involvement of a gynecologic oncologist in the care of women with ovarian cancer.²⁻¹⁰ The challenge is how best to identify tumors at risk for malignancy, particularly in premenopausal women who account for up to 20% of all ovarian cancers.^{18,19} Examination alone is often unreliable.^{20,21} Although several algorithms have been proposed,^{5,6,22-28} they either are used infrequently or are ineffective given that only 30-40% of women with ovarian cancer initially are treated by a gynecologic oncologist.^{9,10} Sensible referral guidelines are important

Table 2. Summary Statistics for American College of Obstetricians and Gynecologists and Modified American College of Obstetricians and Gynecologists Criteria

	All Patients (N=516)		Premenopausal Patients (n=235)		Postmenopausal Patients (n=281)	
	College Criteria	Modified College Criteria*	College Criteria	Modified College Criteria*	College Criteria	Modified College Criteria*
Sensitivity (%)	77	80	58	76	84	81
n/N	124/161	128/161	26/45	34/45	98/116	94/116
95% CI	70-83	73-85	43-71	61-86	77-90	73-87
Specificity (%)	68	71	77	70	56	71
n/N	240/355	251/355	147/190	134/190	93/165	117/165
95% CI	63-72	66-75	71-83	64-77	49-64	64-77
PPV (%)	52	55	38	38	58	66
n/N	124/239	128/232	26/69	34/90	98/170	94/142
95% CI	46-58	49-61	27-50	28-48	50-65	58-74
NPV (%)	87	88	89	92	84	84
n/N	240/277	251/284	147/166	134/145	93/111	117/139
95% CI	82-90	84-92	83-92	87-96	76-90	77-89

College, American College of Obstetricians and Gynecologists; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

* Modified College criteria as defined by Dearking AC, Aletti GD, McGree ME, Weaver AL, Sommerfield MK, Cliby WA. How relevant are ACOG and SGO guidelines for referral of adnexal mass? *Obstet Gynecol* 2007;110:841-8.



Table 3. Univariate Comparison for Individual College Algorithms for Ovarian Cancer Risk

Variable	College Criteria		Modified College Criteria*		College-MIA Criteria	
	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
Premenopausal vs postmenopausal	3.0 (2.0–4.4)	<.001	3.0 (2.0–4.4)	<.001	—	—
CA 125-II level higher than referral guideline vs lower than guideline	11.6 (7.5–18.0)	<.001	9.3 (6.0–14.4)	<.001	—	—
Multivariate index assay positive vs negative	—	—	—	—	9.30 (5.0–17.4)	<.001
Absence vs presence of ascites	7.8 (4.0–15.3)	<.001	7.8 (4.0–15.3)	<.001	7.8 (4.0–15.3)	<.001
Evidence of metastasis vs no evidence of metastasis	11.7 (3.9–35.1)	<.001	11.7 (3.9–35.1)	<.001	11.7 (3.9–35.1)	<.001
Normal pelvic exam vs presence of nodular mass, fixed mass, or both	3.3 (1.7–6.2)	<.001	—	—	3.3 (1.7–6.2)	<.001
Family history of breast cancer vs no family history of breast cancer	1.9 (1.1–3.3)	0.036	—	—	—	—
Family history of ovarian cancer vs no family history of ovarian cancer	1.5 (0.7–3.0)	0.332	—	—	—	—

College, American College of Obstetricians and Gynecologists; MIA, multivariate index assay.

* Modified College Criteria as defined by Dearing AC, Aletti GD, McGree ME, Weaver AL, Sommerfield MK, Cliby WA. How relevant are ACOG and SGO guidelines for referral of adnexal mass? *Obstet Gynecol* 2007;110:841–8.

to help concentrate ovarian cancer care at centers where surgical expertise improves outcomes.²⁹

In this multicenter trial, the College guidelines were evaluated in a diverse group of primary care and specialty centers. The sensitivity of the College referral criteria was lower than previously published.^{11,12} The predictive values were also lower in this study, which may be a consequence of lower overall cancer prevalence (31% compared with 37%). Considering the Dearing modifications, eliminating family his-

tory and lowering the CA 125 threshold for premenopausal women further emphasized the significance of the CA 125 result. In our trial, most patients did not show signs of advanced disease on imaging (8% ascites; 1% metastatic implants). So for all remaining premenopausal women, CA 125 was the only criterion left to determine the risk of malignancy.

The multivariate index assay is approved for use in women scheduled for surgery for an ovarian tumor. This assay combines CA 125 with four additional biomarkers, enhancing its ability to detect malignancy, particularly early-stage cancers. When the multivariate index assay replaces CA 125 in the College guidelines, the new guidelines detect almost 80% of all missed malignancies and more than 90% of missed epithelial ovarian cancers. The high sensitivity in premenopausal women and early-stage cancers is where CA 125 and the College guidelines have underperformed. Identifying these patients for referral is valuable because many are not receiving appropriate surgical staging and treatment.^{13,14} The College guidelines with the multivariate index assay are also effective at detecting advanced disease, where aggressive cytoreductive surgery and chemotherapy improve overall survival.^{7–10,29} In addition, the College guidelines with the multivariate index assay permit a simplified algorithm for evaluating a pelvic mass. Because menopausal status is incorporated into the multivariate index assay result and family history appears to be of marginal significance, the referral criteria can be simplified (Box

Table 4. Summary Statistics for College Criteria With Multivariate Index Assay Replacing CA 125

	College-MIA		
	All Patients (N = 516)	Premenopausal Patients (n = 235)	Postmenopausal Patients (n = 281)
Sensitivity (%)	94	91	95
n/N	151/161	41/45	110/116
95% CI	89–97	79–97	89–98
Specificity (%)	35	43	26
n/N	124/355	82/190	42/165
95% CI	30–40	36–50	19–33
PPV (%)	40	28	47
n/N	151/382	41/149	110/233
95% CI	35–45	21–35	41–54
NPV (%)	93	95	88
n/N	124/134	82/86	42/48
95% CI	87–96	89–98	75–94

College, American College of Obstetricians and Gynecologists; MIA, multivariate index assay; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.



Table 5. Performance of College and College–Multivariate Index Assay Criteria in Identifying Ovarian Malignancy in Premenopausal Women by Cancer Stage

Premenopausal Patients	College Criteria Primary Cancer* Stage		College–MIA Criteria Primary Cancer* Stage	
	Early	Late	Early	Late
Sensitivity (%)	47	100	88	100
n/N	8/17	10/10	15/17	10/10
95% CI	26–69	72–100	66–97	72–100
Specificity (%)	77	77	43	43
n/N	147/190	147/190	82/190	82/190
95% CI	71–83	71–83	36–50	36–50
PPV (%)	16	19	12	9
n/N	8/51	10/53	15/123	10/118
95% CI	8–28	11–31	8–19	5–15
NPV (%)	94	100	98	100
n/N	147/156	147/147	82/84	82/82
95% CI	89–97	98–100	92–99	96–100

College, American College of Obstetricians and Gynecologists. MIA, multivariate index assay; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

“Early” cancer stage is defined as Stages I or II, and “Late” cancer stage is defined as stages III or IV. For one premenopausal patient with an epithelial ovarian cancer, no stage information was recorded.

* Includes all primary epithelial ovarian cancers and nonepithelial ovarian malignancies (excludes malignancies that were not staged: borderline ovarian tumors, metastases to ovaries and other nonovarian malignancies) and performance measures calculated based on considering all primary ovarian cancers (epithelial ovarian cancers and nonepithelial ovarian malignancies) compared with all patients with benign masses.

Table 6. Performance of College and College–Multivariate Index Assay Criteria in Identifying Ovarian Malignancy in Postmenopausal Women by Cancer Stage

Postmenopausal Patients	College Criteria Primary Cancer* Stage		College–MIA Criteria Primary Cancer* Stage	
	Early	Late	Early	Late
Sensitivity (%)	88	98	100	100
n/N	28/32	43/44	32/32	44/44
95% CI	72–95	88–100	89–100	92–100
Specificity (%)	56	56	26	26
n/N	93/165	93/165	42/165	42/165
95% CI	49–64	49–64	19–33	19–33
PPV (%)	28	37	21	26
n/N	28/100	43/115	32/155	44/167
95% CI	20–38	29–46	15–28	20–34
NPV (%)	96	99	100	100
n/N	93/97	93/94	42/42	42/42
95% CI	90–98	94–100	92–100	92–100

College, American College of Obstetricians and Gynecologists. MIA, multivariate index assay; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

“Early” cancer stage is defined as Stages I or II, and “Late” cancer stage is defined as stages III or IV. For one postmenopausal patient with a nonepithelial ovarian cancer, no stage information was recorded.

* Includes all primary epithelial ovarian cancers and non-epithelial ovarian malignancies (excludes malignancies that were not staged: borderline ovarian tumors, metastases to ovaries and other nonovarian malignancies) and performance measures calculated based on considering all primary ovarian cancers (epithelial ovarian cancers and nonepithelial ovarian malignancies) compared to all patients with benign masses.

1). The clinical performance of this simplified algorithm is similar to Table 4, with sensitivity 93%, specificity 40%, positive predictive value 41%, and negative predictive value 93%.

Beyond identifying more malignancies, it is not known precisely how the multivariate index assay will affect the referral of patients. Adding the multivariate index assay to the College criteria resulted in a decrease in specificity, which implies

that women with nonmalignant tumors may be referred to gynecologic oncologists. In actual practice, lower specificity does not necessarily translate into more benign tumor referrals. The decision to refer a patient is an individualized integration of medical and nonmedical variables. Historically, 12% to 40% of women referred to a gynecologic oncologist have an ovarian malignancy^{11,12,23}; thus, current practice demonstrates that more than 60–80% of referrals are for benign disease. In this trial, the calculated specificity of the College criteria was 68%, yet the number of nonmalignant tumors referred to the gynecologic oncologist was very high. Of the 355 benign ovarian tumors in the study, 72% were referred to a gynecologic oncologist for surgery, including 45% of patients referred despite the belief by the enrolling physician that the tumor was benign. It is possible that the higher negative predictive value of the College guidelines with the multivariate index assay may add enough reassur-

Box 1. College–Multivariate Index Assay Criteria for Referral of an Ovarian Tumor*

- Nodular or fixed pelvic mass on examination
- Ascites
- Evidence of abdominal or distant metastasis on imaging
- Multivariate index assay test positive

College, American College of Obstetricians and Gynecologists. * Any one of these warrants referral to a gynecologic oncologist.



ance to deter referral in situations where the clinician is uncertain.

One of the strengths of this study is the multicenter design, enrolling a diverse patient population from numerous geographic sites. All study information was collected prospectively and recorded before surgery, including blood, imaging studies, physical examination, and family history. Also, internal biomarker validation was performed at two independent laboratories. A potential limitation of this study is the use of the newer CA 125-II assay rather than the original assay. Today, there are numerous CA 125 and CA 125-II assays which are available and used interchangeably for preoperative evaluations with very similar diagnostic accuracy.³⁰ The cancer prevalence in this study is similar to previous reports.^{11,12} In a population with lower cancer prevalence, the test performance will have a lower positive predictive value and higher negative predictive value, although sensitivity and specificity will be unaffected.

In conclusion, replacing CA 125 with the multivariate index assay improves the sensitivity and negative predictive value of the College referral guidelines while decreasing specificity and positive predictive value. Using the multivariate index assay in the College guidelines will identify more malignancies before surgery, but further study is needed to determine the effect on patient referral.

REFERENCES

1. NIH consensus conference. Ovarian cancer. Screening, treatment, and follow-up. NIH Consensus Development Panel on Ovarian Cancer. *JAMA* 1995;273:491-7.
2. Morgan RJ Jr, Copeland L, Gershenson D, Locker G, McIntosh D, Ozols R, et al. NCCN Ovarian Cancer Practice Guidelines. The National Comprehensive Cancer Network. *Oncology* 1996;10:293-310.
3. Hoskins W, Rice L, Rubin S. Ovarian cancer surgical practice guidelines. *Oncology* 1997;11:896-900, 903-4.
4. Elit L, Plante M, Bessette P, DePetrillo A. Surgical management of an adnexal mass suspicious for malignancy. *SOGC Clinical Practice Guidelines* 2000;97:1-5.
5. The role of the generalist obstetrician-gynecologist in the early detection of ovarian cancer. ACOG Committee Opinion No. 280. The American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2002;100:1413-6.
6. Myers E, Bastian L, Havrilesky L, Kulasingam S, Terplan M, Cline K, et al. Management of adnexal mass. Rockville (MD): U.S. Department of Health and Human Services; 2006.
7. Engelen MJ, Kos HE, Willemse PH, Aalders JG, de Vries EG, Schaapveld M, et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. *Cancer* 2006;106:589-98.
8. Giede KC, Kieser K, Dodge J, Rosen B. Who should operate on patients with ovarian cancer? An evidence-based review. *Gynecol Oncol* 2005;99:447-61.
9. Earle CC, Schrag D, Neville BA, Yabroff KR, Topor M, Fahey A, et al. Effect of surgeon specialty on processes of care and outcomes for ovarian cancer patients. *J Natl Cancer Inst* 2006;98:172-80.
10. Carney ME, Lancaster JM, Ford C, Tsodikov A, Wiggins CL. A population-based study of patterns of care for ovarian cancer: who is seen by a gynecologic oncologist and who is not? *Gynecol Oncol* 2002;84:36-42.
11. Im SS, Gordon AN, Buttin BM, Leath CA 3rd, Gostout BS, Shah C, et al. Validation of referral guidelines for women with pelvic masses. *Obstet Gynecol* 2005;105:35-41.
12. Dearing AC, Aletti GD, McGree ME, Weaver AL, Sommerfield MK, Cliby WA. How relevant are ACOG and SGO guidelines for referral of adnexal mass? *Obstet Gynecol* 2007;110:841-8.
13. Lee CK, Pires de Miranda M, Ledermann J, Ruiz de Elvira M, Nelstrop A, Lambert H, et al. Outcome of epithelial ovarian cancer in women under 40 years of age treated with platinum-based chemotherapy. *European J of Cancer* 1999;35:727-32.
14. Munoz K, Harlan L, Tribble E. Patterns of care for women with ovarian cancer in the United States. *J Clin Oncol* 1997;15:3408-15.
15. Bast RC Jr, Klug TL, St John E, Jenison E, Niloff JM, Lazarus H, et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. *N Engl J Med* 1983;309:883-7.
16. Jacobs I, Bast RC Jr. The CA 125 tumour-associated antigen: a review of the literature. *Hum Reprod* 1989;4:1-12.
17. Zhang Z, Bast R, Yu Y, Li J, Sokoll L, Rai AJ, et al. Three biomarkers identified from serum proteomic analysis for the detection of early stage ovarian cancer. *Cancer Res* 2004;64:5882-90.
18. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun M. Cancer statistics, 2009. *CA Cancer J Clin* 2009;59:225-49.
19. Bristow R, Zahurak M, del Carmen M, Gordon T, Fox H, Trimble E, et al. Ovarian cancer surgery in Maryland: volume-based access to care. *Gynecol Oncol* 2004;93:353-60.
20. Ueland FR, Depriest PD, Desimone CP, Pavlik EJ, Lele SM, Kryscio RJ, et al. The accuracy of examination under anesthesia and transvaginal sonography in evaluating ovarian size. *Gynecol Oncol* 2005;99:400-3.
21. Buys S, Partidge E, Greene M, Prorok PC, Reding D, Riley TL, et al. Ovarian cancer screening in the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial: findings from the initial screen of a randomized trial. *Am J Obstet Gynecol* 2005;193:1630-9.
22. DePriest PD, Shenson D, Fried A, Hunter JE, Andrews SJ, Gallion HH, et al. A morphology index based on sonographic findings in ovarian cancer. *Gynecol Oncol* 1993;51:7-11.
23. Ueland F, DePriest P, Pavlik E, Kryscio R, van Nagell J Jr. Preoperative differentiation of malignant from benign ovarian tumors: the efficacy of morphology indexing and Doppler flow sonography. *Gynecol Oncol* 2003;91:46-50.
24. Gostout BS, Brewer MA. Guidelines for referral of the patient with an adnexal mass. *Clinical Obstet Gynecol* 2006;49:448-58.
25. Tingulstad S, Skjeldestad FE, Halvorsen T, Nustad K, Onsrud M. The risk-of-malignancy index to evaluate poten-



- tial ovarian cancers in local hospitals. *Obstet Gynecol* 1999;93:448–52.
26. Maggina T, Gadducci A, D'Addario V, Pecorelli S, Lissoni A, Stella M, et al. Prospective multicenter study on CA 125 in postmenopausal pelvic masses. *Gynecol Oncol* 1994;54:117–23.
27. Schutter E, Kenemans P, Sohn C, Kristen P, Crombach G, Westermann R, et al. Diagnostic value of pelvic examination, ultrasound, and serum CA 125 in postmenopausal women with a pelvic mass. An international multicenter study. *Cancer* 1994;74:1398–406.
28. Jacobs I, Oram D, Fairbanks J, Turner J, Frost C, Grudzinskas J. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynecol* 1990;97:922–9.
29. Tingulstad S, Skjeldestad F, Hagen B. The effect of centralization of primary surgery on survival in ovarian cancer patients. *Obstet Gynecol* 2003;102:499–505.
30. Davelaar E, van Kamp G, Verstraeten R, Kenemans P. Comparison of seven immunoassays for the quantification of CA 125 antigen in serum. *Clin Chem* 1998;44:1417–22.

