



ASPIRA

WOMEN'S HEALTH™

OVA1®

Instructions for Use

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Intended Use

OVA1® is a qualitative serum test that combines the results of five immunoassays into a single numerical result. 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. OVA1® 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.

PRECAUTION: OVA1® should not be used without an independent clinical/radiological evaluation and is **not** intended to be a screening test or to determine whether a patient should proceed to surgery. Incorrect use of OVA1® carries the risk of unnecessary testing, surgery, and/or delayed diagnosis.

Summary and Explanation of the Test

Ovarian tumors are being detected with increasing frequency in women of all ages. There are numerous recent publications clarifying the importance of a gynecologic oncologist in the care of subjects with ovarian cancer. The National Comprehensive Cancer Network (NCCN) [1] and the Society of Gynecologic Oncologists (SGO) [2] plus other studies have demonstrated the value of referring subjects with ovarian cancer to gynecologic oncologists for their surgery [3,4].

OVA1® should be used in conjunction with imaging studies and other clinical assessment in a woman for whom surgical intervention is planned. OVA1® can assist the decision-making process of whether to refer the subject to a gynecologic oncologist, when the referring physician's presurgical assessment does not indicate malignancy.

OVA1® is a device that incorporates the biomarker values from five immunoassays. The biomarker values used to generate the OVA1® result are Prealbumin – also called transthyretin (TT), Apolipoprotein A-1 (Apo A-1), β 2 Microglobulin (β 2M), Transferrin (Tfr), and Cancer Antigen 125 (CA 125 II) [5-7]. Biomarker values are determined using assays on the Roche cobas, an automated analyzer with electrochemiluminescence detection. The biomarker assays are conducted according to the manufacturer's directions as detailed in the Instructions for Use for each product and in this Instructions for Use. The assay values from the following systems are manually entered into a .csv file and evaluated by the OvaCalc software:

Roche cobas:

- CA 125 II (Roche)
- TT — Prealbumin (transthyretin) (Roche)
- Apo A-1 — Apolipoprotein A-1 (Roche)
- β 2M — Beta-2 Microglobulin (Roche)
- Tfr — Transferrin (Roche)

The OvaCalc software combines the results from these five biomarker assays and then uses a proprietary algorithm to generate an OVA1® result.

Principles of the Procedure

Principles of the individual assays for Prealbumin (TT), Apo A-1, β 2M, Transferrin (Tfr), and CA 125 II are as given in the respective Instructions for Use.

Patients are assigned a unitless result between 0.0 and 10.0 by the OvaCalc software; the result is called the OVA1[®] score. This result is given in the OVA1[®] report as written below:

Pre-menopausal

- Low probability of malignancy OVA1[®] < 5.0
- High probability of malignancy OVA1[®] ≥ 5.0

Post-menopausal

- Low probability of malignancy OVA1[®] < 4.4
- High probability of malignancy OVA1[®] ≥ 4.4

All reagent information for each individual assay that is run can be found in the following Instructions for Use.

- Tina-quant Apolipoprotein A-1 ver.2 (Roche)
- Tina-quant β2-Microglobulin (Roche)
- Prealbumin (Roche)
- Tina-quant Transferrin ver.2 (Roche)
- CA 125 II (Roche)
- CA 125 II CalSet II (Roche)
- Calibrator f.a.s. Lipids (Roche)
- β2-Microglobulin Calibrator (Roche)
- Calibrator f.a.s. PAC (Roche)
- Calibrator f.a.s. Proteins (Roche)

**Warnings and Precautions
For In Vitro Diagnostic Use**

- See PRECAUTION in box following the intended use statement.
- Only lot numbers for Prealbumin (transthyretin), Apolipoprotein A-1, β2 microglobulin, Transferrin, and CA 125 II provided by AWH, Inc. can be used for OVA1[®].
- You should notify AWH if you detect problems with any of the assays used in the OVA1[®] test. Users should heed the warnings and precautions listed in each of the Instructions for Use for the individual assays, in addition to those listed here.
- Only the reagents and systems specified in the Materials Required, Not Provided section are for use with OVA1[®]. The performance of OVA1[®] has not been evaluated with any other manufacturer’s reagents or systems.
- Use routine laboratory precautions. Do not eat, drink, or smoke in designated work areas.
- Do not use heat-inactivated samples or samples stabilized with azide.

IMPORTANT: It is critically important to have a second operator (reading from the Roche cobas source reports) verify all manually entered values and specimen IDs, after data entry into the .csv data file but prior to manually merging (importing) the data from the Excel data file into OvaCalc. (Please refer to Section 4 Running OvaCalc Software for a complete explanation of data importing and further verification.)

Specimens

- OVA1[®] is for use with serum only.
- Do not use plasma for OVA1[®].
- Do not use specimens that are heat-inactivated or stabilized with azide.
- As specified in the Instructions for Use of the individual biomarker assays:
 - Serum specimens must be completely coagulated and, after centrifugation, must not contain any particles or traces of fibrin.
 - Lipemic samples or frozen samples that are turbid after thawing must be clarified by centrifugation (10 minutes at ~15,000 x g) prior to testing. Lipemic samples that cannot be clarified should not be used. For testing, the clarified portion of the sample must be used, and must be drawn through the supernatant lipid layer.
 - Ensure serum specimens to be tested are at ambient temperature (20-25°C) before measurement.
 - Diluted samples must be used within 4 hours of dilution.

Storage

The storage and stability of the OVA1[®] individual assays is summarized below.

Table 1. Stability of OVA1[®] reagents.

	CA 125 (Roche)	β₂ micro- globulin (Roche)	Transferrin (Roche)
Storage	+2 to +8°C Do not freeze	+2 to +8°C Do not freeze	+2 to +8°C Do not freeze
Stability once opened	12 weeks at +2 to +8 °C	12 weeks at +2 to +8 °C	8 days at +2 to +8 °C
On-board Stability	6 weeks	12 weeks	8 weeks

	Prealbumin (Roche)	Apolipoprotein A-1 (Roche)
Storage	+2 to +8°C Do not freeze	+2 to +8°C Do not freeze
Stability once opened	3 days at +2 to +8°C	8 days at +2 to +8°C
On-board Stability	8 weeks	12 weeks

Table 2. Serum specimen stability.

<ul style="list-style-type: none"> ▪ Fresh serum stored at +2 to +8°C can be used up to 8 days.
<ul style="list-style-type: none"> ▪ Serum frozen within 24 hr at -20°C is stable up to 9 weeks.
<ul style="list-style-type: none"> ▪ Serum frozen within 24 hours and stored at -65 to -85° is stable up to 12 weeks.

Materials Provided

OvaCalc Software for download from the manufacturer.

Materials Required, Not Provided

Table 3. Materials required

Assay	Manufacturer
Tina-quant Apolipoprotein A-1 ver.2: 03032566122 •Calibrator f.a.s. Lipids:12172623160 •PreciControl ClinChem Multi 1: 05947626160 • PreciControl ClinChem Multi 2: 05947774160 •Diluent NaCl 9 %:04489357190	Roche
Tina-quant β 2-Microglobulin 140 tests: : 08047430190 • β 2-Microglobulin calibrator: 08047545190 • β 2-Microglobulin Control Set Serum: 08362785190 •Diluent NaCl 9 %: 04489357190	Roche
Prealbumin: 20764655322 • Calibrator f.a.s. PAC: 03555941190 •PreciControl ClinChem Multi 1: 05947626160 •PreciControl ClinChem Multi 2: 05947774160 •Diluent NaCl 9 %: 04489357190	Roche
Tina-quant Transferrin ver.2: 03015050122 • Calibrator f.a.s. Proteins: 11355279160 • Precinorm Protein: 10557897160 • Precipath Protein: 11333127160 • Precinorm U: 10171735122 • PreciControl ClinChem Multi 1:05947626160 • PreciControl ClinChem Multi 2: 05947774160 • Diluent NaCl 9 %: 04489357190	Roche
Cancer Antigen 125 (CA 125 II): 11776223161 •Calibrator:CA 125 II CalSet II: 07030207190 • PreciControl Tumor Marker: 11776452160	Roche
Non-reagent materials	
Excel software, version 2003 or later	Microsoft

Individual materials for each of the above listed assays are found in the respective Instructions for Use. Only AWH qualified lot numbers for Prealbumin, Apolipoprotein A-1, $\beta 2$ microglobulin, Transferrin, and CA 125 II provided by AWH, Inc. can be used for OVA1®.

The Roche cobas system is the required platform. All information on Use, Installation, Principles of Operation, Performance Characteristics, Operating Instructions, Precautions, and Limitations, Hazards, and Maintenance for the instruments can be found in the respective Instrument and/or Software Manuals for the cobas System.

Minimum computer requirements for OvaCalc Software:

- Operating System - Microsoft Windows XP
- Free disk space - 100 MB
- Processor - 1 GHz
- Memory - 512 MB RAM

Assay Characteristics and Components

Information on assay characteristics for each of the individual biomarker assays can be found in the respective Instructions for Use and Table 4 following.

Table 4. Performance characteristics of the individual biomarker assays in OVA1®.

Biomarker	Measuring Interval
$\beta 2$ M (Beta-2 microglobulin)	0.2-8.0 mg/L
Tfr (Transferrin)	10-520 mg/dL
TT (Prealbumin also known as transthyretin)	3-80 mg/dL
Apo A-1 (Apolipoprotein A1)	20-400 mg/dL
CA 125 II (Cancer antigen 125)	2.0-3000 IU/mL

Controls Required for Each Biomarker Assay

Each biomarker assay control must fall within the expected range for the controls used with the assays. Follow manufacturers' instructions for tracking the controls and instrument calibration data over time. Instrument calibration must be performed per the manufacturer's recommendations or when controls are out of specification.

Procedure

IMPORTANT: Only the specific assays listed in this Instructions for Use can be used to generate the OVA1® result.

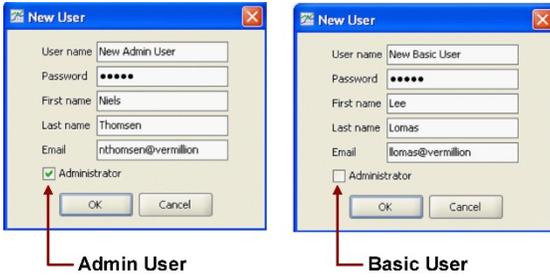
OvaCalc 3.0.3 runs on both Windows XP and Windows 7 operating systems.

1 Installing OvaCalc Software

Note: This procedure is done only the first time you use the software, and anytime you need to reload the software onto your computer.

- A. Verify that the date and time are correct on your computer system.
- B. To install OvaCalc, contact the manufacturer and follow instructions.
 - i. Click OvaCalc Software and log in by entering your Username and Password. (**Note:** Web site usernames and passwords are unique for OvaCalc Software operators and are obtained from AWH.)
 - ii. Double-click **Download OvaCalc Software**, then click **Run** in the File Download window to start downloading the software.
 - iii. Follow instructions on where to store OvaCalc on your computer (OvaCalc installs automatically onto your computer).
 - iv. To run OvaCalc, double-click the OvaCalc icon in Windows.
- C. Log in using the default OvaCalc Administrator account (username and password are case sensitive):
 - Username — **admin**
 - Password — **admin123**
- D. In the main toolbar, click **Manage Users** () and change the username and password of the OvaCalc Administrator account.
 - 1) Select **admin** and click **Edit**.
 - 2) Type new name and password, then click **OK**.
- E. Create one or more new user accounts at this time. Note that user accounts can be Administrative (full access) or Basic (restricted access).
 - 1) Click **New** in the Manage Users window.

2) Enter new user information, then click **OK**.



3) Repeat for as many users as needed. New users are listed in the Manage Users window. When done, click **OK**.

F. Exit the OvaCalc software.

2. *Activation*

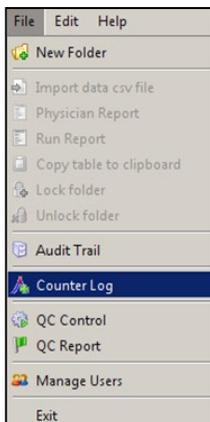
You must obtain an Activation Code for each computer for a defined number of OVA1® tests from AWH before you can run OvaCalc.

A. Open OvaCalc software and log in:

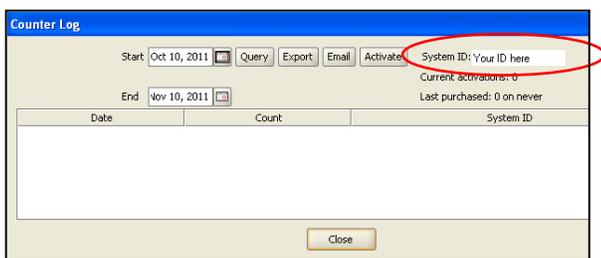
- User– **admin**
- Password – **admin123**



B. Select **File > Counter Log**.



C. In the Counter Log window, record your *System ID*, found in the upper right.

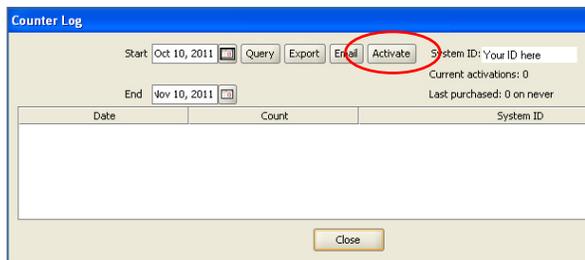


D. Send an email to OVA1data@aspirawh.com with the following:

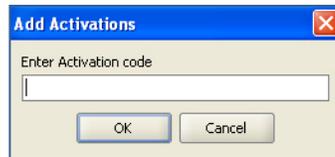
- Your System ID
- Your request for an Activation Code for a specific number of OVA1® tests (500, 1000, 2000, 5000, or 1 million tests).

E. When you receive your Activation Code, select **File > Counter Log**.

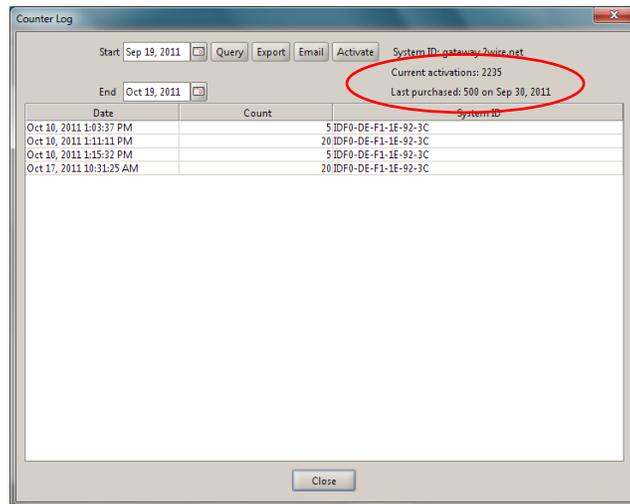
F. Click **Activate**.



G. In the Add Activations window, enter your Activation Code and click **OK**.



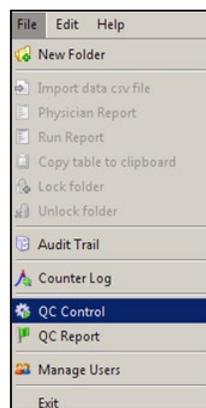
- The current activations and last purchased number and date are shown in the Counter Log window.



- Note that an Activation Code can be used only once. Activations are deducted after each data import and a new activation code must be obtained from AWH when all activations are used up.

3. *Automated QC Control*

A. Select **File > QC Control**.



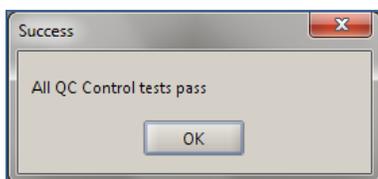
B. In the QC Control window, go to Processing Frequency and select **Daily or Weekly**, then click **OK** to close the

window or click **Process Files Now** to perform a QC check immediately.

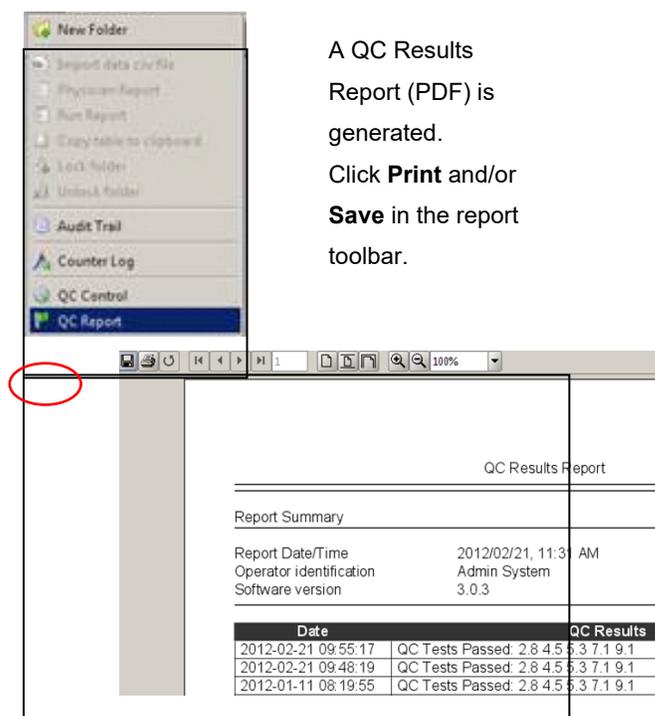


Note: Embedded data from the five QC Controls spanning the OVA1® range are automatically imported to calculate OVA1® scores based on your selected frequency.

C. When you open OvaCalc, a Success pop-up dialog box opens to indicate that QC Control has been performed according to the processing frequency and all QC control tests pass. Click **OK** to close.

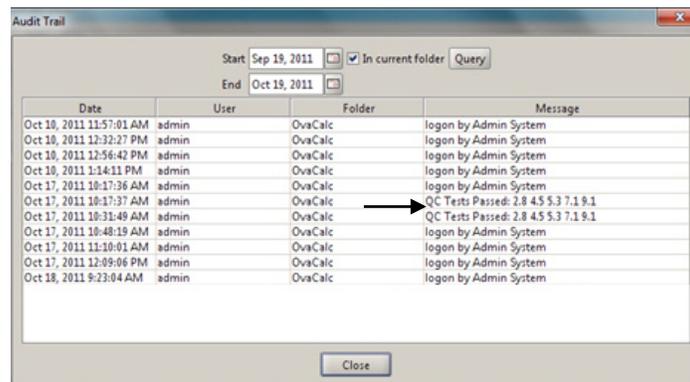


D. To view, print, and save the OVA1® scores of the five QC Controls and the accumulated record of performed QC, select **File > QC Report** (or click  in the tool bar).



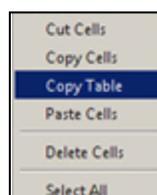
A QC Results Report (PDF) is generated. Click **Print** and/or **Save** in the report toolbar.

E. In the Audit Trail window, select the **Start** and **End** dates you want, then click **Query** to view the Audit Trail. The Audit Trail includes the date and time that QC was performed and the calculated OVA1® scores of the five embedded QC Controls.



F. Copy the Audit Trail to an Excel spreadsheet.

i) Right click over the entries to open the context menu.



- ii) Select **Copy Table**.
- iii) Paste the table into your Excel worksheet.

4. *Running the Biomarker Assays*

Run each of the following Biomarker Assays according to the manufacturer's instructions in the respective Instructions for Use. For Warnings and Precautions, Materials Required but Not Provided, and other detailed information, consult the appropriate Instructions for Use.

A. For all assays:

- 1) Set up your cobas instrument for the run following the analyzer-specific assay instructions in the appropriate Operator's Manual.
- 2) Bring reagents to approximately 20°C and place on reagent disk of analyzer.

IMPORTANT: Avoid the formation of foam.

Note: The system automatically regulates reagent temperature and opening/closing of bottles.

- 3) The analyzer automatically calculates the assay concentration of each specimen in the appropriate units.

B. Calibration and QC

- For assays run on the cobas, a QC screen includes displays of the distribution of the measured results around the target value of a QC test, as detailed in the Software Guide. The calibration information encoded in the reagent pack is used to update the master curve. This process is specific to the reagent lot and/or pack.

5. *Preparing Data for OvaCalc Software Analysis*

A. Prepare Data for Analysis

- i. Excel is used to manually enter specimen IDs and results from the Roche cobas assays, saving the data as a comma-separated values (.csv) data file.
- ii. **Note:** The biomarker values are manually entered into the.csv data file in the measurement units provided by the cobas.
- iii. **IMPORTANT:** It is critically important to have a second operator (reading from the Roche cobas source reports) verify all manually entered values and specimen IDs, after data entry into the .csv data file but prior to manually merging (importing) the data from the Excel data file into OvaCalc. (Please refer to Section 4

Running OvaCalc Software for a complete explanation of data importing and further verification.)

- B. Enter your data into a new Excel workbook created for OVA1® (only one sheet may be used in the workbook). Create columns with headings as follows:

- A. Specimen ID
- B. APO
- C. B2M
- D. TRF (TFR also accepted)
- E. TT
- F. CA125

- i. For columns B through F, use the Excel drop-down list **Format > Cells** to select two-decimal numeric display.

- C. Enter the Specimen ID and biomarker values for each specimen in rows under the column headers created in step 3 B.

Note: If any of the biomarker values are automatically flagged from the cobas they should not be entered into the Excel workbook sheet and used for OvaCalc. OVA1® results should be calculated only with valid results for all analytes from a single serum specimen.

- i. The operator must re-analyze any specimen that is flagged for any of the biomarker values from the cobas.
- ii. The specimen ID can be any unique character sequence less than 64 characters long. Biomarker readings are entered as numbers, without commas or other special characters. Each line in the .csv file must contain a specimen ID and five biomarker readings to obtain an OVA1® result. If a column is blank or a biomarker value is missing, OvaCalc will not produce an OVA1® result, and a processing error message will result. If the readings are not parsed as numbers they will not be read.
- iii. Operators can enter and save data from several specimen runs through Excel into a single .csv data file before the data are imported into the OvaCalc database. No specimen ID should appear more than once in a single .csv file. If a specimen is analyzed (i.e., on the cobas) more than once, and calculation of the OVA1® result is needed for each set of analyte values, then the separate sets of values should be entered into separate .csv files and imported into separate OvaCalc folders (see below).

- D. Select **File > Save As**.

- E. In the Save As dialog box, select **CSV** (Comma delimited)(* .csv) from the Save As Type drop-down list, enter a file name, then click **Save**.
- F. In the Excel dialog boxes that open, click **OK**, then click **Yes** to confirm .csv format.
- G. Perform a manual QC on the .csv data file.
 - 1) Have a second operator manually compare the Specimen IDs and values obtained from the cobas source reports with the data in the .csv data file. The second operator should correct any discrepancies, and confirm these corrections with the original operator.

IMPORTANT: If a sample ID appears more than once in a .csv file, an OvaCalc error message appears when the data file is being imported into the OvaCalc database, stating Duplicate Sample ID and displaying the ID number (e.g., Duplicate specimen id 4007-1 in line 6). You must cancel the import operation, then reopen the .csv file in Excel and edit it to correct the duplication. The resaved .csv file can then be re-imported into the OvaCalc database.

- 2) Save your QC'd .csv data file.

6. Running OvaCalc Software and Data Analysis

Note:

- A “file” refers to the .csv data file where the specimen (sample) ID and biomarker values are manually entered by the operator from the cobas
- An OvaCalc “folder” is a Windows file folder created or selected by the operator in OvaCalc. The data are imported from the .csv data file into the OvaCalc folder.
- Data can only be imported into the OvaCalc folder from the .csv data file. Data cannot be manually entered into the OvaCalc folder.

- A. Launch the OvaCalc software () from the desktop shortcut icon or from the Windows Start menu and log in. (Installing OvaCalc, above.)
- B. In the OvaCalc main toolbar, click **New Folder** ().
- C. Name the new folder and click **OK**.
 - i. The new folder is listed in the Explorer pane, toolbar icons become enabled, and an empty Specimen View pane opens.

- D. Click **Import Data** (), then click **Import from file** to open the navigation window, navigate to and select the .csv file(s) to import for the run, then click **Open**.
 - i. For every specimen ID that is identified during import, OvaCalc checks if the specimen ID is already in the OvaCalc database for the current OvaCalc folder. If a matching specimen ID is not found in the OvaCalc folder, a new record (for the specimen) is created in the OvaCalc folder. If a matching record (specimen ID) is found, the newly imported biomarker values are merged into the existing specimen ID record. New biomarker values will amend existing readings in the OvaCalc database for the current folder; therefore the operator must create a new folder when the same specimen ID has new biomarker value(s) and both records are to be retained.
 - ii. OvaCalc software over-writes biomarker values for specimen IDs that appear in more than one .csv file imported to a single OvaCalc folder. OvaCalc calculates the OVA1[®] result only after all five (5) biomarker values have been imported.
- E. In the Import dataset window, review the imported data and click **Next** to see the list of all specimens and values in the import. Continue clicking **Next** and follow prompts to confirm data. The import wizard prompts for data review before finalizing the import – this is a very important step to ensure that biomarker values are correct. If the operator detects any incorrect entries, the import operation must be cancelled, the value(s) amended and confirmed in the .csv data file (opened in Excel, edited and resaved), and the .csv file must be re-imported. The final page of the import wizard shows run dates.
- F. When done, click **Finish** and all data for the current OvaCalc folder are displayed in the Specimen Result View pane. In the Specimen Result View, a table with data for each Specimen ID and the OVA1[®] result is given. You can click and drag the margins of the columns to change viewing size. The run is automatically saved in OvaCalc for all OVA1[®] results and five (5) biomarkers for each specimen ID. Operator should confirm/release the entire “run” before processing/printing any final reports.

7. Printing Final Reports

- 1. Highlight the specimens for the report by clicking and dragging the mouse over the appropriate rows.

2. In the main toolbar, click **Physician Report** () to view, print and save the report.
3. To export the Run Report as a delimited .csv file, go to the main toolbar and click **Run Report** (). In the **Save** window, create a file name and save the Run Report as a .csv file (make sure that **.csv files** is selected for Files of Type). In the OvaCalc confirmation dialog box click **OK**. The Run Report opens after clicking OK.

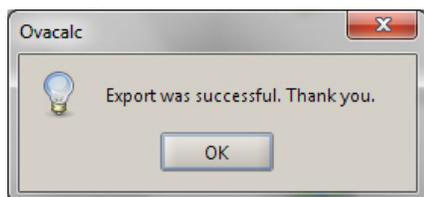


Note: If you do not want to export the Run Report as a .csv file, click **Cancel** in the **Save** window to open the Run Report without saving.

4. To save as a .pdf file, go to the report window, use the report toolbar to save.
5. You may also print or examine the report using the report toolbar. When done, click **OK** at the bottom of the report window.

8. Automatic sending of Counter Log to AWH

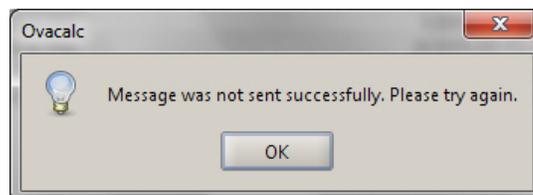
- A. OvaCalc automatically sends a counter log to ova1data@aspirawh.com once a week, starting from the date of installation. When OvaCalc is opened, a counter log is automatically exported and saved to the hard drive of computer with the default filename of UsageCount_mm_dd_yyyy, where mm_dd_yyyy represents the month, day and year of export.
- B. A dialog box confirms that counter log has been saved.



- C. A second dialog box confirms that counter log has been sent to AWH.



- D. In the event of email failure, the following dialog box opens.



Result Reporting

A run report is generated for operator verification and lists Specimen ID and OVA1[®] result. A flag is displayed in the Flag column if the value cannot be reported or there is no value.

The report to the Physician is patient specific and should be released only after all the results in the run report are verified by the operator. This report contains the same information as in the run report (the requesting physician's and laboratory director's information with the specimen information, e.g., Patient DOB and age, and report date can be written in by operator after printing).

The results for OVA1[®] are as follows:

Pre-menopausal

Low probability of malignancy	OVA1 [®] < 5.0
High probability of malignancy	OVA1 [®] ≥ 5.0

Post-menopausal

Low probability of malignancy	OVA1 [®] < 4.4
High probability of malignancy	OVA1 [®] ≥ 4.4

Refer to clinical study section below for information about determining menopausal status. Results of this test should always be interpreted in conjunction with the patient's medical history, clinical presentation and other findings. See PRECAUTION statement following the intended use at the beginning of the Instructions for Use.

Expected Values

The distribution of OVA1[®] results determined in specimens from healthy individuals and patients with nonmalignant or malignant diseases other than ovarian cancer is shown in the following tables. A total of 360 evaluable specimens were analyzed. The mean, standard deviation, median, and 5th to 95th percentile as observed in the data are shown for

each group. It is recommended that each laboratory establish its own reference range for the population of interest.

Expected OVA1[®] results for subjects with cancer conditions other than ovarian cancer are presented in Table 5 following.

Expected OVA1[®] results for subjects with non-cancer conditions are presented in Table 6 following.

Table 5. Expected OVA1[®] results for subjects with cancer conditions.

	Bladder Cancer	Breast Cancer	Cervical Cancer	Colon Cancer
	OVA1[®] result			
N	16	45	12	40
Mean (SD)	4.57 (1.109)	4.34 (1.151)	6.40 (1.979)	4.86 (1.259)
Median	4.4	4.1	6.6	4.8
5th to 95th percentile	2.9 to 6.5	2.9 to 6.0	3.4 to 9.8	3.0 to 7.0

	Endometrial Cancer	Leukemia	Lung Cancer	Lymphoma
	OVA1[®] result			
N	44	10	13	13
Mean (SD)	5.00 (1.467)	6.04 (0.651)	4.17 (0.884)	5.26 (1.669)
Median	4.6	6.1	4.0	4.6
5th to 95th percentile	3.5 to 8.3	4.6 to 7.0	3.0 to 5.5	3.0 to 8.6

Table 6. Expected OVA1[®] results for subjects with non-cancer conditions.

	Autoimmune Disease	Cardiac Disease	Diabetes
	OVA1[®] result		
N	10	12	40
Mean (SD)	5.23 (1.083)	5.28 (1.345)	4.39 (1.069)
Median	5.3	5.6	4.0
5th to 95th percentile	3.4 to 6.6	3.3 to 8.0	3.2 to 6.4

	Endometriosis	Hepatitis	Kidney Disease	Pregnant Women
	OVA1[®] result			
N	40	13	10	12
Mean (SD)	5.01 (1.189)	4.46 (0.832)	5.23 (1.083)	5.28 (1.345)
Median	4.7	4.2	5.3	5.6
5th to 95th percentile	3.4 to 7.1	3.5 to 6.0	3.4 to 6.6	3.3 to 8.0

	Anemia	Pelvic inflammatory disease	Malnutrition
	OVA1[®] result		
N	11	9	10
Mean (SD)	3.73 (0.673)	4.52 (1.072)	4.30 (0.948)
Median	4.0	4.4	4.4
5th to 95th percentile	2.7 to 4.7	3.2 to 6.3	2.8 to 5.7

Reference Values

OVA1[®] results in healthy women, 69 pre- and 78 post-menopausal were evaluated (total = 147 evaluable subjects). Ages ranged from 18 to 85 and represented whites (81.3%) Hispanic/Latino (8.7%) and African American (7.3%) subjects. Expected OVA1[®] results for healthy subjects are presented in Table 7.

Table 7. Summary of OVA1[®] results by menopausal status for evaluable women.

	All Healthy Subjects	Premenopausal Women	Postmenopausal Women
N	147	69	78
Mean (SD)	4.18 (0.858)	4.34 (0.871)	4.04 (0.827)
Median	4.10	4.30	3.95
Range (min, max)	2.7, 6.7	2.9, 6.7	2.7, 6.1
Reference interval (5th percentile, 95th percentile)	3.0, 5.8	3.0, 5.8	2.9, 5.9
OVA1[®] Result, n (%)			
Positive	46 (31.3%)	20 (29.0%)	26 (33.3%)
Negative	101 (68.7%)	49 (71.0%)	52 (66.7%)

Troubleshooting

Problem	Possible Cause and Solution
Error message – Imported data file cannot be read.	Possible corruption of .csv file. Review .csv data file. Re-enter Specimen IDs and/or results as needed. Import corrected file into OvaCalc software.
Error message – Duplicate Specimen ID in the Excel .csv data file. Eg: Duplicate specimen id 4007-1 in line 6	Review .csv data file and correct any duplications. Import corrected file into OvaCalc software.
Error message – Specimen missing one or more values.	1. Possible error in imported data file. Review cobas data output to ensure specimen ID has a marker result. Reconcile with .csv data file. Re-import into OvaCalc software.

Problem	Possible Cause and Solution
	2. Possible syntax error in data file. Review .csv file and correct column headings to match following: Specimen ID APO B2M TFR TT CA-125 Ensure Specimen ID and all values are entered correctly. Import corrected file into OvaCalc software.
Cannot print reports.	Printer-specific problem. Save report as a PDF and print the PDF.
Report printed with header missing.	Printer-specific problem. Save report as a PDF and print the PDF.
Specimen IDs in OvaCalc result table not in sequential order	Specimen IDs do not show in the same order as in the imported .csv file: Export and save Counter Log and send to AWH for record-keeping.** Open Counter Log window and record or take and save screen shot of: Current Activations Number, Last Purchased Date, and Purchased Number. Ensure all .csv data files, Run Run Repots, and QC Reports are backed up. Uninstall OvaCalc. Download the same version of OvaCalc from as provided. Install the downloaded OvaCalc to the same directory as previous installation on your computer. Run OvaCalc. Confirm transfer of data folders, Counter Log, QC Report, and Activations. <i>Note: Downloading to a different directory deletes the existing database, counter log, QC, and activation information.</i> **Must be done <i>before</i> uninstall. Existing database and counter log are not affected <i>only if</i> same version of OvaCalc is reinstalled.

Limitations of the Procedure

Information on the Limitations of the Procedure for each of the individual biomarker assays is detailed in the respective Instructions for Use.

- OVA1[®] is not a screening test. (See Tables 6 and 7)
- OVA1[®] is not a stand-alone diagnostic test. OVA1[®] should be used in conjunction with a complete and independent clinical patient evaluation.
- A negative OVA1[®] result, in the setting of a positive pre-surgical assessment, should not preclude oncology referral.
- Use of this assay is limited to personnel who have been trained by AWH, Inc. in the procedure. Failure to follow the instructions given in this insert may result in erroneous results.
- OVA1[®] is not indicated for patients with a diagnosis of malignancy within the last 5 years.
- All collected data from each of the individual five biomarkers must be manually transferred from the cobas printouts using the same units specified by the printouts into the .csv data file using Excel. Manual data entry verification must be performed before completing the import into OvaCalc software.
- Only reagents that have been qualified by AWH are acceptable for use with OVA1[®]. Users should verify manufacturer's lot numbers are qualified for individual biomarker assays and calibration reagents.
- Samples that have been heat-inactivated or stabilized with azide cannot be used.
- Samples that contain rheumatoid factor \geq 250 IU/mL cannot be used in the OVA1[®] test.
- Triglyceride levels above 4.5 g/L may interfere with the assay and should not be used in the OVA1[®] test.
- Follow manufacturers Instructions for Use for CA 125 II, Prealbumin (TT), and β_2 M for information about hook effects. There is no high dose Hook effect for Apo A-1 up to a concentration of 900 mg/dL or for Prealbumin up to a concentration of 300 mg/dL.
- Patient samples may contain heterophilic antibodies and anti-mouse antibodies that could cause false results in some of the immunoassays.

Refer to individual Instructions for Use (Apo A-1, β_2 M and CA 125 II) for further details.

Clinical Study Results

The information provided by OVA1[®] should be used by the physician as an adjunctive test to complement, not replace, other diagnostic and clinical procedures. To demonstrate that OVA1[®] provides additional information when used in combination with the physician's pre-surgical assessment, the ability of OVA1[®] to contribute to the physician's pre-surgical assessment was analyzed.

OVA1[®] was evaluated in a prospective, double-blind clinical study. OVA1[®] analysis was performed on 516 individual serum specimens collected prospectively from women who met the study inclusion criteria and proceeded to surgery for an ovarian mass. The clinical study population came from institutions with primary care physicians, gynecologists (non-GO), and/or gynecologic oncologists (GO). The clinical study subject enrollment centers are representative of institutions where ovarian tumor subjects potentially undergo a gynecologic examination. The specimens were collected at 27 demographically mixed sites that included large and small medical centers (universities/community hospitals), clinics that specialize in women's health, small gynecology/obstetrics groups, gynecology/oncology practices, and HMO groups).

Subject enrollment demographics and pathology diagnoses are given in Table 8.

Table 8. Demographic characteristics and pathology results or physician assessment results for all evaluable subjects.

	All Evaluable Subjects with Pre-surgical Assessment (N= 516)	Non-GO Physicians (N= 269)	GO Physicians (N= 247)
Age, years			
N	516	269	247
Mean (SD)	52.0 (13.9)	49.7 (13.6)	54.6 (13.8)
Range (min, max)	18 to 92	19 to 90	18 to 92
Menopausal Status, n (%)			
Pre	235 (45.5%)	144 (53.5%)	91 (36.8%)
Post	281 (54.5%)	125 (46.5%)	156 (63.2%)
Pathology Diagnosis, n (%)			
Benign ovarian conditions	355 (68.8%)	197 (73.2%)	158 (64.0%)

	All Evaluable Subjects with Pre-surgical Assessment (N= 516)	Non-GO Physicians (N= 269)	GO Physicians (N= 247)
Epithelial ovarian cancer (EOC)	96 (18.6%)	45 (16.7%)	51 (20.6%)
Other primary ovarian malignancies (non EOC)	9 (1.7%)	5 (1.9%)	4 (1.6%)
Ovarian tumors with low malignant potential (Borderline)	28 (5.4%)	12 (4.5%)	16 (6.5%)
Non-ovarian malignancies with involvement of the ovaries	18 (3.5%)	5 (1.9%)	13 (5.3%)
Non-ovarian malignancies with no involvement of ovaries	10 (1.9%)	5 (1.9%)	5 (2.0%)

Note: Menopausal status stated by patient. For 44 evaluable subjects, menopausal status assigned based on age: pre-menopausal assigned to women aged 50 or under, post-menopausal assigned to women over age 50.

Performance of OVA1[®] for Patients Evaluated by Physicians who are not Gynecologic Oncologists (non-GO)

A total of 269 patients (age range 19-90) were evaluated by non-GO (e.g., primary care physicians, gynecologists). Of the 269 patients, 144 subjects were identified as pre-menopausal and 125 as post-menopausal.

For each patient, the OVA1[®] result was compared to the pathology report from biopsied tissue. Malignancy included epithelial ovarian cancer (EOC), other primary ovarian malignancy, ovarian tumor with low malignant potential, malignancy extending to, or metastatic to ovaries, and malignancy that neither arose in nor involved the ovaries.

High probability of malignancy for premenopausal subjects was defined as OVA1[®] result of 5.0 or more; and for postmenopausal subjects OVA1[®] result of 4.4 or more.

Among 269 subjects, there were 72 subjects with malignancy by pathology and 197 subjects with no malignancy by pathology.

Table 9. All non-GO evaluated subjects – malignancy/no malignancy by pathology.

Malignancy by Pathology				
OVA1 [®] result		Pre-surgical assessment		
		Pos	Neg	Both
	Positive	49	14	63
Negative	3	6	9	
Both	52	20	72	
No Malignancy by Pathology				
OVA1 [®] result		Pre-surgical assessment		
		Pos	Neg	Both
	Positive	16	81	97
Negative	18	82	100	
Both	34	163	197	

The analysis examined whether patient referral to a gynecologic oncologist is supported when either the OVA1[®] result or the pre-surgical clinical assessment or both were determined to be positive.

Table 10 shows results for all subjects evaluated by non-GO, with “positive” results for likely malignancy either based on a positive pre-surgical assessment alone (single assessment), or based on a positive result from the pre-surgical assessment or from the OVA1[®] result or from both (dual assessment).

Table 10. All subjects evaluated by non-GO physicians.

Performance	Single assessment (pre-surgical assessment)	Dual assessment (pre-surgical assessment and OVA1 [®] Test result used)
Sensitivity 95% CI	72.2% (52/72) 61.0% to 81.2%	91.7% (66/72) 83.0% to 96.1%
Specificity 95% CI	82.7% (163/197) 76.9% to 87.4%	41.6% (82/197) 35.0% to 48.6%
Positive Predictive value (PPV) 95% CI	60.4% (52/86) 49.9% to 70.1%	36.5% (66/181) 29.8% to 43.7%
Negative Predictive Value (NPV) 95% CI	89.1% (163/183) 83.7% to 92.8%	93.2% (82/88) 85.9% to 96.8%
Prevalence	26.8% (72/269)	

With dual assessment, sensitivity for malignancy increased from 72% to 92%. That is, approximately two-thirds of the malignancies missed by pre-surgical assessment alone were called positive if a dual assessment was used. Specificity for malignant diagnoses decreased from 83% to 42% with dual assessment. The ratio of false positive results to true positive results for the study population increased from 34:52 (0.65:1) with single assessment to 115:66 (1.74:1) with dual assessment (PPV of the dual assessment decreased from 60% to 37%). However, NPV of the dual assessment increased from 89% to 93%, supporting improved performance by dual assessment. The confidence interval for the observed 4.1% increase was -0.5% to 8.7% (calculated by bootstrap). The statistical significance of the observed increase in NPV was borderline.

Performance characteristics of OVA1[®] with pre-surgical assessment for the 269 patients classified according to their menopausal status are presented separately in the tables below.

Pre-menopausal subjects

Among 144 pre-menopausal subjects with pre-surgical assessment by a non-GO, there were 26 subjects with malignancy by pathology and 118 subjects with no malignancy by pathology.

Table 11. Pre-menopausal non-GO evaluated subjects – malignancy/no malignancy by pathology.

Malignancy by Pathology				
		Pre-surgical assessment		
		Pos	Neg	
OVA1 [®] result	Positive	16	5	21
	Negative	1	4	5
		17	9	26
No Malignancy by Pathology				
		Pre-surgical assessment		
		Pos	Neg	
OVA1 [®] result	Positive	7	44	51
	Negative	13	54	67
		20	98	118

Table 12. Assessment of pre-menopausal subjects by non-GO and by non-GO plus OVA1[®].

Performance	Single assessment (pre-surgical assessment)	Dual assessment (pre-surgical assessment and OVA1 [®] Test result used)
Sensitivity	65.4% (17/26)	84.6% (22/26)
Specificity	83.1% (98/118)	45.8% (54/118)
PPV	45.9% (17/37)	25.6% (22/86)
NPV	91.6% (98/107)	93.1% (54/58)
Prevalence	18.1% (26/144)	

PPV of the dual assessment decreased from 46% to 26% and NPV of the dual assessment increased from 92% to 93%. The confidence interval for the observed 1.5% increase was -3.3% to 6.4% (calculated by bootstrap).

Post-menopausal subjects

Among 125 post-menopausal subjects with pre-surgical assessment by a non-GO, there were 46 subjects with malignancy by pathology and 79 subjects with no malignancy by pathology.

Table 13. Post-menopausal non-GO evaluated subjects – malignancy/no malignancy by pathology.

Malignancy by Pathology				
		Pre-surgical assessment		
		Pos	Neg	
OVA1 [®] result	Positive	33	9	42
	Negative	2	2	4
		35	11	46
No Malignancy by Pathology				
		Pre-surgical assessment		
		Pos	Neg	
OVA1 [®] result	Positive	9	37	46
	Negative	5	28	33
		14	65	79

Table 14. Assessment of post-menopausal subjects by non-GO and non-GO plus OVA1®.

Performance	Single assessment (pre-surgical assessment)	Dual assessment (pre-surgical assessment and OVA1® Test result used)
Sensitivity	76.1% (35/46)	95.7% (44/46)
Specificity	82.3% (65/79)	35.4% (28/79)
PPV	71.4% (35/49)	46.3% (44/95)
NPV	85.5% (65/76)	93.3% (28/30)
Prevalence	36.8% (46/125)	

PPV of the dual assessment decreased from 72% to 46% and NPV of the dual assessment increased from 86% to 93%. The confidence interval for the observed 7.8% increase was -1.6% to 17.2% (calculated by bootstrap).

Performance characteristics for OVA1®, without reference to the matched non-GO clinical/radiological assessments for malignancy

OVA1® is not for use as a stand alone test.

Clinical/radiological evaluation is needed in order to identify patients in the intended use population (women over age 18, ovarian adnexal mass present for which surgery is planned, and not yet referred to an oncologist), for whom the performance characteristics of the test are established.

OVA1® performance characteristics, without reference to the matched clinical/radiological assessments for malignancy, are summarized in Table 15.

Table 15 below shows performance of OVA1® alone for all clinical study subjects evaluated by non-GO, and separately by menopausal status for pre-menopausal and post-menopausal subjects.

Table 15. Performance of OVA1® alone^a compared to biopsy in patients evaluated by non-GO.

	All	Pre-	Post
N	269	144	125
Sensitivity	87.5% (63/72)	80.8% (21/26)	91.3% (42/46)
95% CI	77.9% - 93.3%	62.1% - 91.5%	79.7% - 96.6%
Specificity	50.8% (100/197)	56.8% (67/118)	41.8% (33/79)
95% CI	43.8% - 57.7%	47.8% - 65.4%	31.5% - 52.8%
NPV	91.7% (100/109)	93.1% (67/72)	89.2% (33/37)
PPV	39.4% (63/160)	29.2% (21/72)	47.7% (42/88)
Prevalence	26.8% (72/269)	18.1% (26/144)	36.8% (46/125)

^a OVA1® is not intended as a stand-alone diagnostic test.

A summary of OVA1® results by cancer stage for evaluable subjects with a primary ovarian malignancy (EOC and non-EOC combined) are summarized in the table below.

Table 16. OVA1® Results by Cancer Stage^a for primary ovarian malignancies in all evaluable subjects with a pre-surgical clinical assessment from non-GO.

	Stage I	Stage II	Stage III
No. of Subjects	14	11	25
OVA1® Mean (SD)	6.89 (2.313)	8.21 (1.600)	8.36 (1.289)
Median	6.55	8.60	8.70
Range (min, max)	3.6 to 10.0	5.1 to 10.0	5.5 to 10.0
OVA1® Positive	11	11	25
OVA1® Negative	3	0	0
OVA1® Sensitivity	78.6 %	100%	100%

^a No Stage IV Patients were evaluated by non-GO

The subjects identified with an ovarian malignancy were categorized by histologic subtype. Table 17 shows the sensitivity of the OVA1® result for each histologic subtype. 95.8% of subjects with epithelial ovarian cancer had a high risk OVA1® result (≥ 5.0).

Table 17. Performance by histological subtype.

Histological Subtype	Patients evaluated by Non-GO		
	OVA1 [®] Risk		
	Low Risk	High Risk ^b	Sensitivity %
Epithelial	1	44	97.8
Non-Epithelial	2	3	60.0
Low malignant potential	5	7	58.3
Metastatic ^a	0	5	100.0
Non-primary ovarian malignancies with no involvement of ovaries	1	4	80.0

a. Includes subjects with non-ovarian primary malignancy with involvement of the ovaries.

b. High risk cut-off: premenopausal subjects OVA1[®] result of 5.0 or more; postmenopausal subjects OVA1[®] result of 4.4 or more.

Performance of OVA1[®] for Patients Evaluated by Gynecologic-Oncologists (GO)

OVA1[®] results in patients evaluated by GO physicians were analyzed for comparison with results in patients evaluated by non-GO physicians.

The following table shows results for the 247 patients evaluated by gynecologic oncologists in the clinical study. There were 89 subjects with malignancy by pathology and 158 subjects with no malignancy by pathology. Compared to use of OVA1[®] in the non-GO evaluated patients, use of OVA1[®] increased sensitivity and decreased specificity in the GO-evaluated patients.

Table 18. GO evaluated subjects – malignancy/no malignancy by pathology. ^a

Malignancy by Pathology				
		Pre-surgical assessment		
		Pos	Neg	
		OVA1 [®] result	Positive	
Negative	2		1	3
		69	20	89
No Malignancy by Pathology				
		Pre-surgical assessment		
		Pos	Neg	
		OVA1 [®] result	Positive	
Negative	11		41	52
		40	118	158

^aThere were three Stage IV Patients evaluated by GO

Table 19 below shows results for all subjects evaluated by GO physicians, with "positive" results for likely malignancy either based on a positive pre-surgical assessment alone (single assessment), or based on a positive result from the pre-surgical assessment or from the OVA1[®] result or from both (dual assessment).

Table 19. GO evaluated subjects – assessments.

Performance	Single assessment (pre-surgical assessment)	Dual assessment (pre-surgical assessment and OVA1 [®] results used)
Sensitivity	77.5% (69/89)	98.9% (88/89)
Specificity	74.7% (118/158)	25.9% (41/158)
PPV	63.3% (69/109)	42.9% (88/205)
NPV	85.5% (118/138)	97.6% (41/42)
Prevalence	36.0% (89/247)	

With dual assessments within the GO-evaluated patients, sensitivity for malignancy increased from 78% to 99% and specificity for non-malignant diagnoses decreased from 75% to 26% with dual assessment. The PPV decreased from 63% to 43%. However, the NPV increased from 86% to 98%. The confidence interval for the observed 12.1% increase was 5.7% to 18.6% (calculated by bootstrap). The observed increase in NPV was statistically significant.

Analytical Performance

Precision

Precision performance of OVA1[®] was evaluated in accordance with CLSI guideline EP5-A2 "Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline." Five serum specimens spanning OVA1[®] result range (range of numerical results for OVA1[®]: 0.0 to 10.0) were tested over 20 days, two runs per day, and two replicates per run. Total percent coefficient of variation (%CV) was ≤ 5.2%.

Table 20. OVA1[®] Result Precision

Sample	n	OVA1 [®] (Mean)	Within-run		Between-run		Total	
			SD	%CV	SD	%CV	SD	%CV
1	80	2.74	0.065	2.4	0.011	0.4	0.091	3.3
2	80	3.39	0.101	3.0	0.099	2.9	0.159	4.7
3	80	3.74	0.149	4.0	0.097	2.6	0.192	5.1
4	80	4.69	0.290	6.2	0.000	0.0	0.349	7.4
5	80	9.94	0.061	0.6	0.051	0.5	0.098	1.0

Lot-to-Lot precision

Five serum specimens and a minimum of two control sera were analyzed at one site with three different reagent kit lots and three different calibrators over three different days by one operator. For each of the five specimens and the two controls, the mean and standard deviation (SD) for each sample were calculated. The %CV for between-lot imprecision was $\leq 2.8\%$.

Reproducibility

Five serum specimens spanning the OVA1[®] result range and a minimum of two controls per day were tested in duplicate, two runs each day, over 6 days, by two operators at each of three sites. For each of the five specimens, the mean, SD, %CV, median, and range of OVA1[®] results were calculated for an assessment of imprecision in the reproducibility study. The results for OVA1[®] are shown below:

Table 21. Assessment of imprecision from reproducibility study

		Serum Specimen				
		1	2	3	4	5
OVA1[®] result						
Mean		2.67	3.21	3.75	5.00	9.71
Repeatability	SD	0.069	0.094	0.157	0.364	0.157
	%CV	2.6	2.9	4.2	7.3	1.6
Between run	SD	0.034	0.087	0.091	0.000	0.129
	%CV	1.3	2.7	2.4	0.0	1.3
Between day	SD	0.000	0.000	0.146	0.032	0.045
	%CV	0.0	0.0	3.9	0.6	0.5
Between operator	SD	0.042	0.039	0.105	0.265	0.000
	%CV	1.6	1.2	2.8	5.3	0.0
Between sites	SD	0.057	0.141	0.000	0.103	0.212
	%CV	2.1	4.4	0.0	2.1	2.2
Reproducibility	SD	0.098	0.176	0.250	0.447	0.271
	%CV	3.7	5.5	6.7	8.9	2.8

Note: Contributions to variance from nested model for runs within days within operators within sites.

Interference

Three pooled serum samples with low (~3.0), medium (~4.4) and high (~7.3) OVA1[®] results were evaluated for interference by hemoglobin (9.0 g/L), conjugated bilirubin (0.9 g/L) and unconjugated bilirubin (0.9 g/L), triglycerides (4.6 g/L) and rheumatoid factor. No significant interference at the concentrations evaluated was observed on the OVA1[®] result for any of the interferents evaluated except for rheumatoid factor. Specimens with rheumatoid factor greater than 250 IU/mL are not appropriate for OVA1[®].

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Symbols

In Vitro Diagnostic



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OvaCalc Ver. 3.0.3 (OVA1[®] software)