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Genomic Tests for Ovarian Cancer Detection and Management

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Prepared by:
Duke University Evidence-based Practice Center, Durham, NC

Investigators
Evan R. Myers, M.D., M.P.H. (Principal Investigator)
Laura J. Havrilesky, M.D.
Shalini L. Kulasingam, M.P.H., Ph.D.
Gillian D. Sanders, Ph.D.
Kathryn E. Cline, M.H.S. (Project Manager)
Rebecca N. Gray, D.Phil. (Editor)
Andrew Berchuck, M.D.
Douglas C. McCrory, M.D., M.H.S.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-Based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The Centers for Disease Control and Prevention (CDC) requested and provided funding for this report. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to **epc@ahrq.gov.**

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Julie Louise Gerberding, M.D., M.P.H.
Director
Centers for Disease Control and Prevention

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Beth A. Collins Sharp, Ph.D., R.N.
Director, EPC Program
Agency for Healthcare Research and Quality

Gurvaneet Randhawa, M.D., M.P.H.
EPC Program Task Order Officer
Agency for Healthcare Research and Quality

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Structured Abstract

Objective: To assess the evidence that the use of genomic tests for ovarian cancer screening, diagnosis, and treatment leads to improved outcomes.

Data Sources: MEDLINE® and reference lists of recent reviews.

Review Methods: We evaluated tests for: (a) single gene products; (b) genetic variations affecting risk of ovarian cancer; (c) gene expression; and (d) proteomics. For tests covered in recent evidence reports (cancer antigen 125 [CA-125] and breast cancer genes 1 and 2 [BRCA1/2]), we added studies published subsequent to the reports. We sought evidence on: (a) the analytic performance of tests in clinical laboratories; (b) the sensitivity and specificity of tests in different patient populations; (c) the clinical impact of testing in asymptomatic women, women with suspected ovarian cancer, and women with diagnosed ovarian cancer; (d) the harms of genomic testing; and (e) the impact of direct-to-consumer and direct-to-physician advertising on appropriate use of tests. We also constructed a computer simulation model to test the impact of different assumptions about ovarian cancer natural history on the relative effectiveness of different strategies.

Results: There are reasonable data on the clinical laboratory performance of most radioimmunoassays, but the majority of the data on other genomic tests comes from research laboratories. Genomic test sensitivity/specificity estimates are limited by small sample sizes, spectrum bias, and unrealistically large prevalences of ovarian cancer; in particular, estimates of positive predictive values derived from most of the studies are substantially higher than would be expected in most screening or diagnostic settings. We found no evidence relevant to the question of the impact of genomic tests on health outcomes in asymptomatic women. Although there is a relatively large literature on the association of test results and various clinical outcomes, the clinical utility of changing management based on these results has not been evaluated. We found no evidence that genomic tests for ovarian cancer have unique harms beyond those common to other tests for genetic susceptibility or other tests used in screening, diagnosis, and management of ovarian cancer. Studies of a direct-to-consumer campaign for BRCA1/2 testing suggest increased utilization, but the effect on "appropriateness" was unclear. Model simulations suggest that annual screening, even with a highly sensitive test, will not reduce ovarian cancer mortality by more than 50 percent; frequent screening has a very low positive predictive value, even with a highly specific test.

Conclusions: Although research remains promising, adaptation of genomic tests into clinical practice must await appropriately designed and powered studies in relevant clinical settings.

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Appendixes (including Evidence Tables) for this report are provided electronically at http://www.ahrq.gov/downloads/pub/evidence/pdf/genomicovc/genovc.pdf**.**

Executive Summary

Introduction

Ovarian cancer is the leading cause of cancer death from gynecologic malignancies in the United States, with an annual incidence of over 25,000 and an annual mortality of approximately 14,000. Cancer incidence increases dramatically with age.

The high case-fatality rate has largely been attributed to the fact that most ovarian cancers are diagnosed in advanced stages (Stage III, where the cancer has spread beyond the pelvis to the organs of the upper abdominal cavity, and Stage IV, where the cancer has spread outside the peritoneal cavity). Stage I cancer (limited to the ovaries) has a survival rate of over 90 percent.

There are five potential strategies for prevention of the morbidity and mortality from ovarian cancer. One is primary prevention through either medical or surgical therapy in the general population. Although observational studies suggest that the risk of developing ovarian cancer is reduced in women who used oral contraceptives or underwent tubal ligation, there are no prospective trials to allow estimation of the risks and benefits of these options specifically for ovarian cancer prevention. Although in theory prophylactic oophorectomy at the time of hysterectomy for other diseases should almost eliminate the chances of developing ovarian cancer, there are also no prospective studies of the benefits of this approach, and a recent decision analysis suggested that the harms in terms of other effects might outweigh the benefits. An alternative strategy for primary prevention is identifying groups of women at particularly high risk of developing ovarian cancer, and then using primary prevention strategies. Observational studies suggest that use of oral contraceptives reduces risk of ovarian cancer in women with inherited predisposition to ovarian cancer, but this has not been tested prospectively. Prophylactic oophorectomy does appear to reduce the risk of ovarian cancer in high-risk groups.

Another strategy for prevention of ovarian cancer mortality is screening to detect early stage cancers, either in the general population or in high-risk groups. To date, screening using the available technologies of physical examination, ultrasound, and/or cancer antigen 125 (CA-125) has not been shown to be effective in either situation.

Finally, use of targeted therapy based on the results of tests may identify subgroups of patients for whom specific therapies are likely to be effective; for example, identification of overexpression of human epidermal growth factor 2 (HER 2) in some breast cancers has led to improved survival with the use of a monoclonal antibody targeted against the receptor. To date, similar breakthroughs have not occurred in ovarian cancer.

Continued developments in technology have led to rapidly expanding knowledge about genes, gene expression, and protein patterns in a variety of disease processes. Because currently available strategies for the prevention of ovarian cancer have not proven as effective as interventions targeted against other cancers in women, there has been tremendous interest in using the tools of genomics and proteomics to identify potential new markers which can be used in any of the five classes of strategies. Although the term “genomics” has been used in many different ways, for the purposes of this report we define “genomic tests” as one of the following broad categories: (1) tests for the presence or quantity of the product of a single gene – the classic example of this is radioimmunoassay for CA-125; (2) tests for inherited or acquired mutations in genes which convey an increased risk of developing ovarian cancer, or which

predict differential responses to therapy – the classic example is testing for polymorphisms of breast cancer genes 1 and 2 (BRCA 1/2); (3) tests for quantitative expression of either single genes or multiple genes – differential patterns of expression between normal patients and ovarian cancer patients may aid in diagnosis and management, or help identify potential new single gene products for evaluation as screening and diagnostic tools; and (4) tests for protein expression, particularly in serum, which identify differential patterns between normal patients and patients with ovarian cancer.

This report focuses on the current evidence for the clinical utility of genomic tests, as defined above, in any of the five potential strategies for reducing ovarian cancer morbidity and mortality. Because evidence on the use of CA-125 for screening and diagnosis of ovarian cancer and the use of BRCA1/2 testing for identification of high-risk patients has been covered in recent evidence reports, we do not review that evidence directly; we do summarize the results of the earlier reports and discuss relevant studies subsequently published. The results of the present report are intended primarily to: (a) provide a resource for the Evaluation of Genomics Applications in Practice and Prevention (EGAPP) project of the Centers for Disease Control and Prevention (CDC); (b) provide a resource for other clinicians and policymakers developing guidelines on the use of genomic tests in ovarian cancer prevention; and (c) provide a resource for researchers and funding agencies in identifying gaps in our knowledge and research priorities.

Methods

Working with the Agency for Healthcare Research and Quality (AHRQ), the CDC, the EGAPP working group, and members of the technical expert panel, we refined six research questions to be addressed, using an analytic framework which incorporated probability of developing ovarian cancer, test results, and management based on those tests results.

We searched MEDLINE® (1966-May 2006). Searches of the databases were supplemented by reviews of reference lists of included articles, relevant review articles, and meta-analyses. We also searched the Food and Drug Administration web site for relevant documents. The searches yielded a total of 1,303 citations. Pairs of readers reviewed each abstract and selected 552 articles for full text review. Specific inclusion criteria were developed for each question, and both readers were required to agree on inclusion. After this review, a total of 113 articles were included for abstraction.

We developed tables to abstract each article, and quality criteria were adapted from the evidence report on omega-3 fatty acids for coronary heart disease prevention. For studies of diagnostic test performance, 2-by-2 tables were constructed for each included article, and sensitivity, specificity, and positive and negative predictive values, with 95 percent confidence intervals, were calculated.

We also further refined a Markov model of the natural history of ovarian cancer; the model is able to closely approximate age-specific incidence and mortality from ovarian cancer under two different assumptions about natural history – one that requires a stepwise progression through all four stages of the disease, and one which allows some cancers to spread directly from the ovaries (Stage I) to the upper abdomen (Stage III). The model is then used to estimate the implications of these different assumptions on the relative effectiveness of different prevention strategies.

Results

Literature on Key Questions

Question 1: What is the evidence that ovarian cancer genomic tests performed in a typical clinical laboratory actually measure what they are purported to measure? The published data on clinical laboratory performance suggests that currently available radioimmunoassays for single gene products have acceptable reproducibility and reliability, although even this level of variability may have some impact on clinical interpretation of results, especially when comparing relatively small serial changes, or levels close to the discriminatory threshold.

There is insufficient evidence to estimate how newer technologies such as microarrays or protein profiles would perform in a "typical clinical laboratory."

Question 2: What is the sensitivity and specificity of genomic tests in detecting ovarian cancer in asymptomatic and symptomatic women, including high-risk women? In general, single gene products other than CA-125 have not been shown to be useful in the diagnosis of ovarian cancer, either in symptomatic or asymptomatic women; the sensitivity of CA-125 in screening populations is approximately 80 percent. Small sample sizes, lack of detail on the prediagnosis history of patients, and an unrealistically high prevalence of ovarian cancer in the majority of studies make it difficult to assess how any of these tests would perform in clinical practice.

Estimating the clinical value of more complex tests, using multiple gene and/or protein markers, is even more difficult. Studies of protein expression, in particular, are limited by lack of consensus on appropriate statistical methods, small sample sizes with substantially higher prevalences of ovarian cancer than would be found in the general population, spectrum bias, lack of reproducibility, and uncertainty about the specificity of the biological processes resulting in the observed protein patterns.

Question 3: What is the evidence that genomic testing to detect ovarian cancer in asymptomatic women, including high-risk women, changes clinical management and leads to improved clinical outcomes? We did not identify any evidence on the value of tests other than CA-125 to detect ovarian cancer in asymptomatic women. CA-125 has not been shown to improve ovarian cancer mortality or quality of life; in series of women with mutations of BRCA1 and BRCA2, screening with CA-125 and transvaginal ultrasound does not appear to prevent development of advanced stage ovarian cancer.

Question 4: What is the evidence that genomic testing in women with clinical suspicion of ovarian cancer or with already-diagnosed ovarian cancer changes clinical management and leads to improved health outcomes? Although there is a reasonable amount of data on the association between genomic tests, particularly CA-125, and the likelihood of different clinical outcomes, we did not identify any studies which provided evidence for changes in management leading to improved outcomes based on the results of the tests, other than for CA-125. Based on the results of another evidence report, CA-125 is helpful in distinguishing malignant from benign masses in postmenopausal women.

Question 5: What are the harms of using genomic tests for ovarian cancer prevention and management? The majority of the available literature focuses on BRCA1/2 testing and rarely describes results specifically for ovarian cancer. In the few studies that did, concerns

about the risk of ovarian cancer were considerably less than for breast cancer; it is unclear whether testing for genetic markers of ovarian cancer susceptibility alone has different implications compared to testing for genes which affect both breast and ovarian cancer risk.

Conceptually, the harms of testing for genetic susceptibility for ovarian cancer should be no different than testing for genetic susceptibility of other cancers; the main issues are the effectiveness and potential risks of prevention strategies in those who are identified as high risk (primarily the risks of prophylactic oophorectomy), and issues related to reproduction. Similarly, the qualitative harms of the use of genomic tests for screening, diagnosis, and management – the psychological effect of a potential cancer diagnosis, the risks of diagnostic and therapeutic procedures including laparotomy, the harms of a false negative result leading to delayed or inappropriate management – are not conceptually different for genomic tests than for other types of tests, such as imaging; the main difference lies in the quantitative risks of these events, which in turn are determined by the sensitivity and specificity of the test and the pretest probability of disease.

Question 6: Has direct-to-consumer and direct-to-physician marketing of genomic tests for ovarian cancer increased the "appropriate" use of these tests? We identified two studies which compared utilization of BRCA1/2 tests for breast and ovarian cancer susceptibility before and after an advertising campaign; in both cases, utilization was compared in cities where the campaign was put in place to geographically distant cities where there was no formal campaign. The studies suggested increased utilization of testing, and one study found that the positive predictive value of testing declined after the campaign, but there was no way to judge whether the changes in testing were "appropriate."

Modeling Results

The model is able to approximate reported age-specific incidence and mortality from ovarian cancer under both assumptions about natural history. At a given value for test sensitivity, screening was less effective in reducing mortality in a model assuming direct transition from Stage I to Stage III than one assuming that all cancers progress to Stage II prior to Stage III. However, screening frequency was much more important than test sensitivity; even at a test sensitivity of 99 percent, screening frequencies of less than 12 months are needed to reduce ovarian cancer mortality by more than 50 percent. At these high screening frequencies, positive predictive values are less than three percent, even for a test with specificity of 99 percent.

Discussion

Limitations of the Report

The report did not include non-English publications. We did not formally attempt to estimate pooled sensitivity and specificity for tests because of heterogeneity of study design. Because many of the parameters in the natural history of ovarian cancer are unknown, any model will require assumptions and imputation of key parameters; calibrating a cohort model to cross-sectional data may result in errors in the imputation of these parameters because of unmeasured cohort effects in the cross-sectional data.

Limitations of the Literature

Common limitations of the literature included: failure to adequately describe relevant patient characteristics; small sample size with subsequent wide confidence intervals for estimates of sensitivity and specificity; unrealistically high prevalences of ovarian cancer; a spectrum of disease severity which does not reflect screening populations; lack of reproducibility for complex statistical algorithms; potentially inappropriate choices for cases and controls in initial developmental studies; and underlying assumptions about the natural history of ovarian cancer that may not reflect the actual biology of the disease.

Future Research

Research priorities include:

- A minimal consensus data set on key patient characteristics, with results presented with stratification by those characteristics as appropriate;
- Consensus reporting of key laboratory performance characteristics such as reproducibility, with estimates of the impact of reproducibility on test performance in practice;
- Documentation of the effect of any biological variability in test results within subjects on interpretation of results, especially for tests designed to be used in a serial fashion;
- Better characterization of true “negative” results, with documentation of followup;
- Evaluation of tests in realistic clinical situations, especially with regards to pretest probability;
- Explicit evaluation of the effect of management changes based on test results on patient outcomes; and
- Better understanding of the natural history of ovarian cancer in order to help prioritize research into better prevention strategies.

Conclusions

Despite intensive research efforts, ovarian cancer remains a leading cause of cancer death in women, and efforts at reducing its impact have been noticeably less successful than those for other cancers in women.

The prospect of new strategies for the prevention of ovarian cancer morbidity and mortality based on greater understanding of the molecular biology of the disease is exciting; unfortunately, we did not find any evidence that currently available tests have had a substantial impact on improving patient outcomes. Our modeling work suggests that the natural history of ovarian

cancer may make substantial mortality reductions difficult using a strategy based primarily on screening. Although research remains promising, adaptation of genomic tests into clinical practice must await appropriately designed and powered studies in relevant clinical settings.

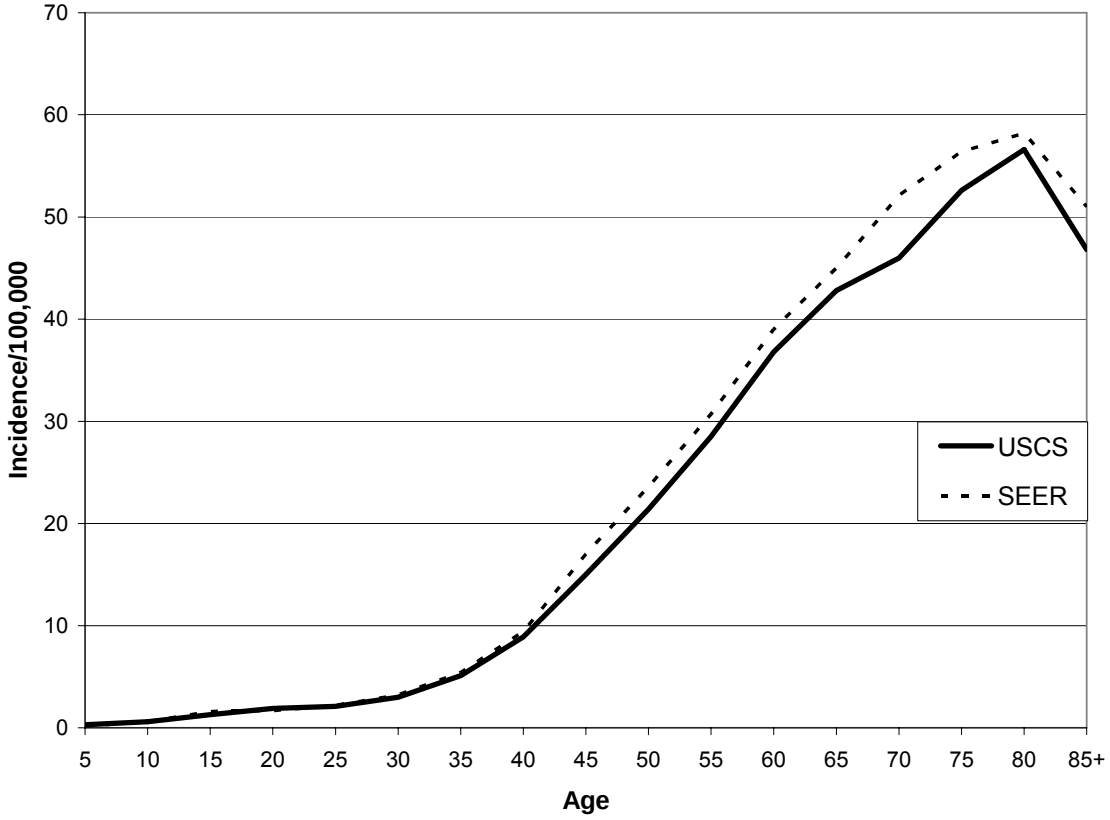
Evidence Report

Chapter 1. Introduction

Ovarian Cancer

Cancer of the ovaries is the leading cause of cancer death from gynecologic malignancies, with an annual incidence of over 25,000 and an annual mortality of approximately 14,000.[1] Cancer incidence increases dramatically with age, being relatively rare prior to age 50 (Figure 1).

Figure 1. U.S. ovarian cancer incidence by age, 1992-2003



Sources: Surveillance, Epidemiology, and End Results (SEER) Program[2] and United States Cancer Statistics (USCS).[3]

Ovarian cancer incidence varies by race and ethnicity. Both incidence and mortality are highest for white women (Table 1).

Table 1. Age-adjusted annual incidence and mortality per 100,000 women by race and ethnicity, 1992-2002*

	White	African-American	Asian/Pacific Islander	Native American	Hispanic
Incidence					
SEER	15.1	10.3	10.4	8.9	11.9

Table 1. Age-adjusted annual incidence and mortality per 100,000 women by race and ethnicity, 1992-2002* (continued)

	White	African-American	Asian/Pacific Islander	Native American	Hispanic
USCS	13.5	9.8	9.5	5.4	11.0
Mortality					
SEER	9.3	7.6	4.8	5.1	6.2
USCS	9.4	7.4	5.1	4.9	6.0

* Sources: Surveillance, Epidemiology, and End Results (SEER) Program[2] and United States Cancer Statistics (USCS).[3]

Malignant tumors of the ovary can either arise in the ovary (primary ovarian cancer) or be the result of metastasis from another site, such as the breast or colon. Primary ovarian tumors, whether benign or malignant, can arise from three broad types of cells: the cells on the surface (epithelial cells); the cells that form eggs (germ cells); and the cells surrounding the eggs, including the cells that produce ovarian hormones (sex cord-stromal cells). Epithelial tumors are the most common type, accounting for 60 percent of all ovarian tumors and up to 90 percent of primary cancers. Sex cord-stromal tumors account for 10 to 15 percent of all tumors, while germ cell tumors account for 25 percent of tumors. In general, sex cord-stromal tumors and germ cell tumors are relatively more common in younger premenopausal women. Thus, although ovarian cancer is relatively rare in younger women, when it does occur it is more likely to be a non-epithelial cancer than cancers in postmenopausal women.[4]

Within the broad classification of epithelial, sex cord-stromal, and germ cell tumors, tumors are further classified by the individual cell types from which the tumor is derived. For example, the most common epithelial tumors are serous and mucinous tumors, the most common sex-cord stromal tumors are fibromas (arising from the connective tissue surrounding eggs), and the most common germ cell tumors are teratomas. Within each histological class, tumors can be benign or malignant, based on their ability to metastasize.[4]

Some epithelial tumors are classified as "borderline" or "low malignant potential" (LMP) tumors. These are tumors in which there is no invasion into the ovarian stroma, but histologic evidence of proliferation (increased cell division, changes in the appearance of the cell nucleus). There is controversy over whether these tumors represent preinvasive cancer, and, if untreated, would go on to become a cancer, or whether they represent a subtype of tumor which has a relatively small chance of becoming a cancer.[4] In estimating the diagnostic accuracy of tests for determining whether a mass is benign or malignant, whether one classifies LMP tumors as benign or malignant can have an effect on the estimates of test performance, as we will discuss later in the report.

Ovarian cancer spreads primarily by dissemination throughout the peritoneal cavity; common sites of metastasis are the small and large bowel, the omentum, the liver, and the diaphragm. Spread to retroperitoneal lymph nodes is also common.

Treatment for ovarian cancer consists of surgical removal of the ovaries, fallopian tubes, and uterus (if present), along with as much metastatic disease as possible; if there is no obvious spread beyond the ovaries, the lymph nodes are sampled to determine if there has been lymphatic metastasis. Surgery is followed by chemotherapy, with responsiveness to chemotherapy

depending on the amount of tumor left after surgical removal and the cell type of tumor, among other factors.[4]

The high case-fatality rate observed in ovarian cancer has largely been attributed to the fact that most ovarian cancers are diagnosed in advanced stages (Stages III, where the cancer has spread beyond the pelvis to organs of the upper abdominal cavity, and IV, where the cancer has spread outside of the peritoneal cavity), when survival is poor. Stage I cancer (limited to the ovaries) has a survival rate of over 90 percent. Thus, there has long been a clinical and research emphasis on identifying methods for early detection of ovarian cancer, under the rationale that increasing the proportion of cancers detected in early stages will lead to decreases in morbidity and mortality.

Approaches to Reducing Ovarian Cancer Morbidity and Mortality

Conceptually, there are five basic strategies for reducing ovarian cancer morbidity and mortality; we briefly review the rationale for each below.

Primary Prevention in the Entire Population

Primary prevention can be achieved either through medical or surgical treatment which preserves the ovaries but reduces the incidence of ovarian cancer, or by removal of the ovaries themselves.

Although oral contraceptives and tubal ligation have consistently been associated with reduction in ovarian cancer in epidemiological studies,[5] the use of these measures as prophylaxis has never been prospectively tested in an adequately designed and powered trial; given the relative rarity of ovarian cancer, as well as the rarity of some of the serious side effects of oral contraceptives, such as an increased risk of deep vein thrombosis, such a trial may ultimately not be feasible.

Although primary peritoneal carcinomatosis, a condition which histologically and clinically is almost identical to ovarian cancer,[6] can occur after removal of the ovaries, it appears to be rare in average-risk women.[7] Bilateral oophorectomy in perimenopausal women undergoing hysterectomy for other causes has traditionally been recommended for prevention of ovarian cancer; however, this practice has also not been subjected to rigorous prospective study. A recent decision analysis suggests that, based on the available evidence, the potential harms from the other effects of oophorectomy may outweigh the benefits of ovarian cancer prevention.[8]

Primary Prevention in Women at Increased Risk for Developing Ovarian Cancer

This strategy depends on two things: the availability of a test for ascertainment of individuals at increased risk for developing ovarian cancer, and the availability of effective primary preventive treatment.

Although no randomized trials have been conducted, several observational studies suggest that women with an inherited predisposition to developing ovarian cancer who undergo

prophylactic oophorectomy are at reduced risk of developing ovarian cancer compared to the expected incidence in this population.[9-11] Observational data also suggests that oral contraceptive use reduces ovarian cancer incidence in high-risk groups.[12,13]

Secondary Prevention through Screening

Unlike cervical cancer, where screening has proven remarkably effective, no screening test has proven effective in reducing ovarian cancer mortality. Physical examination using the bimanual pelvic examination,[14] serum testing using the tumor marker cancer antigen 125 (CA-125), and imaging using vaginal ultrasound[15] have all proven ineffective; the U.S. Preventive Services Task Force (USPSTF) gives a D recommendation to current methods for screening for ovarian cancer (at least fair evidence that the practice is ineffective or that harms exceed benefits). Additional studies are currently being conducted.

Secondary Prevention through Screening in Women at High Risk

As with primary prevention, this strategy is dependent on both effective screening methods and the ability to accurately determine who is at "high risk." Screening, including more frequent screening, has not resulted in a reduced ovarian cancer incidence, or a substantial shift in stage distribution of detected cancers, in high-risk groups.[16-19]

Improved Therapy after Diagnosis of Ovarian Cancer

Identification of women who are particularly likely to respond to specific therapies, or identification of new targets for therapy, could lead to improved survival and quality of life in women with ovarian cancer. Although there is much ongoing research into possible targets for therapy, ovarian cancer therapy lags behind therapy for breast cancer, where identification of particular molecular targets appears to be effective.[20] This category could also include tests that help distinguish particular types of ovarian cancer from other types, and to distinguish primary ovarian cancer from cancer metastatic to the ovary from other sites, since misclassification could lead to relatively less effective therapy.

Genomic Tests

Advances in molecular biology, including the decoding of the human genome, have led to intensive research across the spectrum of human disease. The terms "genomics" or "genetic test" have been used differently in different settings. For the purposes of this report, we include the following types of tests based on the interests of the Agency for Healthcare Research and Quality (AHRQ), the Centers for Disease Control and Prevention (CDC), and the Evaluation of Genomics Applications in Practice and Prevention (EGAPP) program.

Tests Measuring Single Gene Products

These tests measure the concentration or presence/absence of proteins which are associated with the presence of ovarian cancer. The classic example of this type of test is CA-125, a protein for which several validated, commercially available assays are available. Levels of CA-125 are increased in patients with ovarian cancer compared to normal subjects, and the test is useful in discriminating benign from malignant masses in postmenopausal patients.[14] Typically, these tests are for proteins detectable in serum, although, in some cases, tests may be peformed in fluid aspirated from an ovarian mass or the peritoneal cavity, or immunohistochemistry stains may be performed on ovarian or tumor tissue.

Tests for Variations in DNA

Tests for inherited or acquired mutations (e.g., breast cancer genes 1 and 2 [BRCA1/2]) in single genes can potentially identify patients at higher risk for developing cancer. Alternatively, mutations in some genes in the cancer itself may indicate greater or lesser likelihood of responding to a given therapy, or of developing side effects with a given therapy. In addition, changes in the overall pattern of the genome, such as loss of heterozygosity, are characteristic of many cancers, and potentially have a role in diagnosis.[21] Finally, epigenetic changes (reversible changes to DNA and chromatin, such as the addition or subtraction of methyl groups), are currently under active investigation in a variety of cancers, including ovarian cancer.[22-24]

Gene Expression

Quantitative or semi-quantitive measurement of the expression (either higher or lower than normal) of particular genes in serum or tumor tissue has the potential for help in diagnosis (either as a screening tool or in discrminating particular subtypes of cancer), or potentially to aid in targeted therapy; for example, overexpression of human epidermal growth factor receptor 2 (HER-2) in breast cancer predicts responsiveness to therapy with an antibody against the receptor, trastuzimab.[20] Both single genes, and patterns of expression of multiple genes using technologies such as microarray, can be helpful. The introduction of high-throughput technology has facilitated the search for patterns of expression associated with specific outcomes, allowing simultaneous comparison of multiple genes in specimens from patients with and without the outcome. Studies of gene expression may also serve as the basis for identification of single gene products which can subsequently be evaluated as markers for screening, diagnosis, or management guidance.

Proteomics/Protein Characterization

Finally, quantification of protein patterns, typically in serum, can be performed using mass spectroscopy; one of the more common techniques is surfance-enhanced laser desorption inonization time-of-flight (SELDI-TOF).[25] As with multiple gene expression, protein patterns can be compared between patients with and without a given outcome of interest, or used to identify single markers.

Interest in Genomic Tests for Ovarian Cancer

Although there is widespread interest in genomic tests for prevention of morbidity and mortality for a wide range of conditions, ovarian cancer has been an area of particular interest on the part of the scientific community and lay public, largely because of the lack of an effective screening test. In particular, efforts to rapidly commercialize a proteomics-based test, OvaCheck™, prior to validation of the test in a large population, has led to a realization of the need for critical evaluation of the validity of these tests.[26,27]

Use of Genomic Tests in Prevention of Ovarian Cancer Morbidity and Mortality

Despite the broad definition of "genomic tests" used here, there are very few tests currently in clinical use for ovarian cancer (Table 2), based on a recent review of both the published and "grey" literature by the Tufts-New England Medical Center Evidence-based Practice Center.[28]

Table 2. Current usage of genomic tests in ovarian cancer[28]

Test	Type of test	Use of test			
		Increased risk	Screening	Diagnosis	Manage-ment
Commercially available					
Routine use in ovarian cancer					
Cancer antigen 125 (CA-125)	Single gene product			X	X
Beta human chorionic gonadotropin (β-hCG; germ cell tumors)	Single gene product			X	X
Breast cancer gene 1/2 (BRCA1/2)	Genetic variation	X			
Carcinoembryonic antigen (CEA)	Single gene product			X	
Investigational for ovarian cancer					
Cancer antigen 27-29 (CA-27-29)	Single gene product		X	X	
Lipid-associated sialic acid (LASA)	Single gene product		X	X	
Human epidermal growth factor receptor 2 (HER2)/neu	Gene expression				X
Investigational					
Chromosome 8q gain	Genetic variation				X
DNA methylation	Genetic variation		X	X	X
Epidermal growth factor receptor (EGFR)	Single gene product		X	X	

Table 2. Current usage of genomic tests in ovarian cancer[28] (continued)

Test	Type of test	Use of test			
		Increased risk	Screening	Diagnosis	Manage-ment
Genome-wide loss of heterozygosity	Genetic variation		X		
Lysophospholipids (LSA)	Single gene product		X		X
Matrix metalloproteinases (MMP)	Single gene product		X		
Protein expression profiles (OvaCheck, etc.)	Protein expression		X		
Urinary plasminogen activator	Single gene product		X		

Because the majority of applications for genomic tests are investigational, there are few formal guidelines for their use, other than recommendations for the use of CA-125 as an adjunct to diagnosis of ovarian cancer,[29] against the use of CA-125 for routine screening for ovarian cancer,[15,30] and for the use of BRCA1 and 2 testing in women with family histories suggestive of familial breast or ovarian cancer.[31]

Because the use of BRCA 1 and 2 testing for identifying women at high risk and the use of CA-125 for screening and as a diagnostic test in women with an adnexal mass have been recently covered by AHRQ evidence reports,[14,30,31] we have summarized the findings of these reports in the appropriate sections, incorporating any additional relevant evidence published subsequent to the reports.

In this review, and particularly in the discussion of the results and suggestions for future research, we will attempt to identify: (a) issues related to evaluation of specific strategies for ovarian cancer prevention; (b) issues related to evaluation of specific classes of "genomic tests;" and (c) where applicable, specific issues related to the evaluation of a given class of genomic test for a given prevention strategy.

Chapter 2. Methods

This section of the report describes the basic methodology used to develop the evidence report, including topic assessment and refinement, analytic framework, literature search strategies and results, literature screening, quality assessment, data abstraction methods, and quality control procedures.

Topic Assessment and Refinement

The Centers for Disease Control and Prevention (CDC) and the Agency for Healthcare Research and Quality (AHRQ) originally identified six key questions to be addressed by the report, which is intended to assess the evidence for the diagnostic accuracy, benefits, and harms of genomic tests in screening and management of ovarian cancer. The Duke research team clarified and refined the overall research objectives and key questions by first consulting with the two study sponsors, AHRQ and CDC, and then convening a national panel of technical experts to serve as advisors to the project. These experts were selected to represent relevant specialties. Members of the technical expert panel were:

Alfred O. Berg, M.D., M.P.H.; Department of Family Medicine, University of Washington; Seattle, WA (member of the CDC Evaluation of Genomic Applications in Practice and Prevention [EGAPP] Working Group)

Katrina Armstrong, M.D., M.S.C.E.; Leonard Davis Institute of Health Economics, University of Pennsylvania School of Medicine; Philadelphia, PA (EGAPP Working Group member)

Jeffrey Botkin, M.D., M.P.H.; Department of Pediatrics and Medical Ethics, University of Utah; Salt Lake City, UT (EGAPP Working Group member)

JoEllen Schildkraut, Ph.D.; Department of Prevention Research, Duke University; Durham, NC

As a result of an initial conference call with the technical experts, AHRQ, and CDC, the Duke research team finalized the key research questions to be included in the report and the approach that would be used to address them. The final key questions are as follows:

- *Question 1:* What is the evidence that ovarian cancer genomic tests performed in a typical clinical laboratory actually measure what they are purported to measure?

- *Question 2:* What is the sensitivity and specificity of genomic tests in detecting ovarian cancer in asymptomatic and symptomatic women, including high-risk women?

- *Question 3:* What is the evidence that genomic testing to detect ovarian cancer in asymptomatic women, including high-risk women, changes clinical management and leads to improved health outcomes?
- *Question 4:* What is the evidence that genomic testing in women with clinical suspicion of ovarian cancer or with already-diagnosed ovarian cancer changes clinical management and leads to improved health outcomes?

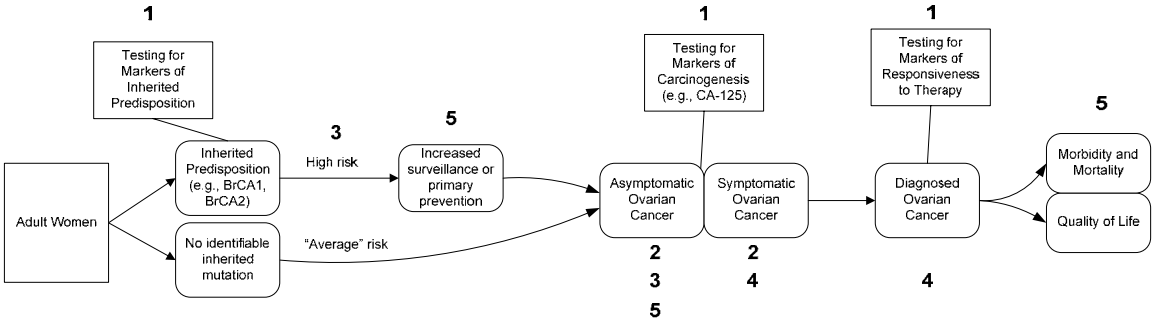
- *Question 5:* What are the harms of using genomic tests for ovarian cancer prevention and management?

- *Question 6:* Has direct-to-consumer and direct-to-physician marketing of genomic tests on ovarian cancer increased the "appropriate" use (as defined by study investigators) of these tests?

Analytic Framework

The methodological approach to this review was designed to inform the EGAPP Working Group's deliberations in formulating evidence-based recommendations for the use of genetic testing in the detection and management of ovarian cancer. We developed a project-specific analytic framework to address the key questions within the context of a standardized evidence report (Figure 2).

Figure 2. Analytic framework for evidence report



Note: Numbers refer to key questions

The analytic framework depicted above serves to clarify the relevant key questions as follows:

- Genomic tests can detect an inherited predisposition, genes and proteins that are associated with the presence of cancer, or genes and proteins that identify targets for therapy or predict response to therapy. Question 1 addresses whether available tests perform as intended at the level of the laboratory ("analytic validity").

- Genomic tests in the second category, above, may detect ovarian cancer either in women without symptoms (used as a screening test) or as part of the evaluation of women with symptoms (Question 2).

- Based on the results of genomic testing, women may have different strategies; women with a predisposition to ovarian cancer may undergo primary or secondary prevention strategies, while, ideally, asymptomatic women detected through genomic tests will have reduced ovarian cancer mortality, without unacceptable levels of harm from testing and diagnosis, than women who do not undergo genetic testing (Question 3).

- Genomic testing can potentially serve as a test to help discriminate cancer from benign conditions in women with symptoms, or lead to specific therapies with better outcomes in women who have already had a diagnosis of ovarian cancer (Question 4).

- As with any test, there are potential harms associated with genomic testing. These include anxiety about the risk of ovarian cancer and difficult decisions regarding reproduction and possible prophylactic surgery in women with inherited predispositions; additional diagnostic tests, including diagnostic surgery, or use of inappropriate therapy, in women with false-positive tests; and the failure to further evaluate, or appropriately treat, women with false-negative tests (Question 5).

- Although not in the formal pathway, marketing to consumers and physicians may make women more likely to undergo testing. Particularly in asymptomatic women, this testing may lead to (a) diagnosis of a predisposition in the absence of clear evidence on appropriate management strategies, or (b) diagnosis of "abnormality," leading to additional tests, including surgery (Question 6).

Literature Search and Review

Sources

The primary source of literature was MEDLINE® (1966-May 2006). Searches of this database were supplemented by reviews of reference lists contained in all included articles and in relevant review articles and meta-analyses.

Search Strategies

The basic search strategy used the National Library of Medicine's Medical Subject Headings (MeSH) key word nomenclature developed for MEDLINE.® Searches were limited to articles published in English. The exact search string used is given in Appendix A.* The three searches yielded a total of 1,303 citations, whose records were maintained in a ProCite (Thompson ISI ResearchSoft, Berkeley, CA) database.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/genovctp.htm.

Abstract and Full-text Screening

Paired researchers from the Duke research team independently reviewed abstracts and classified each as "include" or "exclude" according to study-specific criteria, which they also developed. Abstracts were included if at least one of the paired reviewers recommended that it be included. A total of 552 abstracts were included for the further full-text review stage. Interrater reliability for include/exclude decisions at the abstract screening stage was tested by having seven pairs of readers review 813 abstracts. Agreement was good to excellent (kappa 0.36 to 0.75).

At the full-text review stage, the paired researchers independently reviewed a set of the articles and indicated a decision to "include" or "exclude" the article for the data-abstraction stage. When a pair of reviewers arrived at different opinions about whether to include an article, they were asked to reconcile the difference. Detailed inclusion and exclusion screening criteria were developed by research question and are described immediately below.

Screening Criteria

Abstracts were included for full-text review if they met the criteria described below, or if insufficient information was provided to judge whether they met the criteria. Articles were included for abstraction if full-text review showed that all criteria were met.

An *article* was *included* if it pertained to:

(1) Epithelial ovarian cancer or primary peritoneal carcinomatosis; and

(2) Genomics as defined by AHRQ for this project to mean any gene-based test used for predicting risk of developing disease, screening, diagnosis of disease, disease management, or prognosis only in strategies for the prevention of ovarian cancer morbidity and mortality. These included single gene products (e.g., cancer antigen 125 [CA-125]); genetic variations (e.g., breast cancer genes 1/2 [BRCA1/2]); gene expression (e.g, human epidermal growth factor receptor 2 [HER2]/neu); and either single or multiple genes (e.g., microarrays) and protein expression (e.g., mass spectroscopy of multiple proteins in sera of patients with ovarian cancer compared with controls).

We *included tests* that:

(1) Detect the presence of inherited mutations or gene polymorphisms which increase the risk of development of ovarian cancer;

(2) Genes, RNA, or protein markers which are present or produced (or are present or produced in greater quantity) only in cells that have already undergone the transformation to cancer, and which can be used to detect asymptomatic or symptomatic cancers; and

(3) Genes or proteins which may help predict the response to specific types of therapy, or themselves be targets of specific therapies.

We *excluded* the following:

(1) Studies on BRCA1/2 screening and identification of risk covered in an earlier AHRQ evidence report;[31]

(2) Studies on CA-125 screening and diagnosis covered in earlier AHRQ evidence reports;[14,30]

(3) Studies involving only germ cell or stromal ovarian cancer, or non-ovarian primary;

(4) Studies where patients are not the denominator;

(5) Studies involving a cell line only;

(6) Studies where reported data do not allow construction of a 2-by-2 table.

Summaries of the results of the abstract screening and full-text review are provided in Tables 3 and 4. A list of excluded articles, with reasons for exclusion, is provided in Appendix B.*

Table 3. Results of abstract and full-text screening

Articles identified	1,303
Abstracts screened	1,303
Included	552
Excluded	751
Full-text articles screened	549†
Included	113
Excluded	436

† We were unable to obtain copies of 3 articles that passed the abstract screen.

Table 4. Included full-text articles by research question

Question	Number of articles
Question 1: Analytic validity of testing	32
Question 2: Sensitivity and specificity of tests	50
Question 3: Impact on clinical management of asymptomatic patients	0
Question 4: Impact on clinical management of diagnosed patients	29
Question 5: Harms of testing	4

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/genovctp.htm.

Question	Number of articles
Question 6: Impact of direct-to-consumer or physician marketing	2
Total number of included articles	113[†]

[†] Total does not equal sum of number of articles across questions because some articles were included for more than one question.

Table 5 depicts the specific tests and clinical application of the tests covered by the included articles.

Table 5. Tests and applications covered by articles included in this report

Category of genomic test	Clinical use of test			
	Predisposition	**Screening**	**Diagnosis**	**Management**
Single gene products		CA-125	Alpha-L-fucosidase CA-125, CA-72-4, CA-15-3, CA-19-9 CEA c-erb-2 CYFRA 21-1 Epithelial cell adhesion molecule FAS G-CSF hK6, hK10 IL-6, IL-8 M-CSF OVX1 p55, p75 (tumor necrosis factor receptors) Secretory leukocyte protease inhibitor Serum cadherin Soluble IL-2 alpha Soluble intracellular adhesion molecule TPS TATI Urinary gonadotropin peptide VEGF	Bcl-2 (anti-apoptosis protein) CA-125 CASA Cathespin-D CYFRA 21-1 c-erb-B2 hK6, hK10 IL-6 LRP Mdm2 MDR-1 MRP1/2 nm23 (metatstasis suppressor) Pgp p53 = TP53 (transcription factor) TN TPS
Genetic variations	BRCA1 BRCA2			p53 = TP53 (transcription factor)
Gene expression			CK19 Multiple genes: ascitic fluid Multiple genes: immunohisto-chemistry	c-erb-B2 Multiple genes: microarray
Proteomics		Ciphergen ProteinChips: SAX2, WCX2 Mass spectrometry using SELDI (statistical methods varied widely)		

Data Abstraction and Development of Evidence Tables

The Duke research team developed data abstraction forms/evidence table templates for abstracting data for the various key questions (Appendix C[*]). Based on clinical expertise, a pair of researchers was assigned to the research questions to abstract data from the eligible articles. One of the pair abstracted the data, and the second researcher over-read the article and the accompanying abstraction to check for accuracy and completeness. The completed evidence tables are provided in Appendix D.[*]

Quality Assessment Criteria

At the data abstraction stage, abstractors were asked to evaluate each included article for factors affecting internal and external validity. The quality assessment criteria used for this purpose were previously developed by the Tufts-New England Medical Center Evidence-based Practice Center for an evidence report on "Effects of Omega-3 Fatty Acids on Cardiovascular Disease."[32] Abstractors were instructed to assign a "+" or "-" to each item and provide a brief rationale for their decisions. Quality criteria assessed in this way were:

For Questions 1 and 2:

- Reference standard
- Verification bias
- Test reliability/variability
- Sample size
- Statistical tests
- Blinding
- Definition of +/- on screening test

For Questions 3-5 (randomized controlled trials [RCTs]):

- Randomization method
- Blinding
- Dropout rate < 20 percent
- Adequacy of randomization concealment

For Questions 3-5 (cohort studies):

- Unbiased selection of the cohort (prospective recruitment of subjects)
- Large sample size
- Adequate description of the cohort
- Use of validated method for genomic test (i.e., analytic validity established)
- Use of validated method for ascertaining clinical outcomes (e.g., surgical pathology, use of validated quality-of-life instrument, death)

[*] Appendixes cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/genovctp.htm.

- Adequate followup period
- Completeness of followup
- Analysis (multivariate adjustments) and reporting of results

For Questions 3-5 (case-control studies):

- Valid ascertainment of cases
- Unbiased selection of cases
- Appropriateness of the control population
- Verification that the control is free of cancer
- Comparability of cases and controls with respect to potential confounders
- Appropriateness of statistical analyses

After evaluating each study against its question- and design-specific quality criteria, abstractors applied a three-category (A, B, C) summary quality grading system that has been used in previous evidence reports by the Tufts-New England Medical Center Evidence-based Practice Center, including the report cited above.[32] This scheme defines a generic grading system for study quality that is applicable to each type of study design (i.e., RCT, cohort study, case-control study). The categories are defined as follows:

A Least bias; results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal randomized study; clear description of the population, setting, interventions, and comparison groups; appropriate measurement of outcomes; appropriate statistical and analytic methods and reporting; no reporting errors; less than 20 percent dropout; clear reporting of dropouts; and no obvious bias.

B Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria in category A. It has some deficiencies but none likely to cause major bias. Study may be missing information, making assessment of the limitations and potential problems difficult.

C Significant bias that may invalidate the results. A study with serious errors in design, analysis, or reporting. These studies may have large amounts of missing information or discrepancies in reporting.

Additional Analyses

Test Characteristics and Confidence Intervals

For test characteristics, a Microsoft Excel® spreadsheet was developed that calculated appropriate test characteristics (sensitivity, specificity, negative predictive value, positive predictive value) for individual studies if studies provided enough data to input (a) values for individual cells of a 2-by-2 table, (b) the prevalence of disease and values for sensitivity and

specificity, or (c) sufficient data to solve for two equations involving sensitivity, specificity, or predictive values. Ninety-five percent confidence intervals were automatically estimated using the approximate formula for proportions:

$p \pm 1.96 * \sqrt{p*(1-p)/N}$, where p = point estimate of proportion, N = total sample size.

Ovarian Cancer Model

Model description. We developed a Markov model to estimate the life expectancy for asymptomatic women who are considered candidates for potential prevention and screening strategies for ovarian cancer. The model tracks a hypothetical cohort of 40-year-old women over their lifetimes and compares the impact of one of six strategies for the prevention of ovarian cancer on cancer incidence, mortality, and overall life expectancy.

Simulation model. Women enter the Markov model (Figure 3), which follows the women's natural history of ovarian cancer; the probabilities of each event can be modified based on different strategies for primary prevention, screening, or targeted treatment (see below). Each month women are at risk for developing ovarian cancer. Over time, the cancer could progress through the different stages of ovarian cancer; we assumed that death from ovarian cancer was always preceded by diagnosis. Women with cancer could be detected either through a screening program or through clinical symptoms and diagnosis. Once detected, women undergo a laparotomy, and those who survive undergo treatment for their cancer. Cancer survival is based on the stage at diagnosis.

Historically, cancer progression has been modeled as a serial progression through clinical stages – Stage I is followed by Stage II, Stage II is followed by Stage III, and Stage IV follows Stage III. This conceptual model has worked well with cervical cancer, but it is not clear that using this overall "model" for ovarian cancer is appropriate for the following reasons:

- The main purpose of cancer staging is to identify groups of patients who have similar prognosis; this allows comparability in comparing treatment results in both prospective and retrospective studies. Although the concept that stages also represent biological progression is attractive, it is not necessarily true, and, at least in the case of the ovarian cancer staging system of the International Federation of Obstetrics and Gynecology (FIGO),[33] plays no role in the development and validation of a staging system.

- Cervical cancer is, in many ways, unique among human cancers: it has a single cause (persistent infection with certain types of human papilloma virus); exposure to this cause in most people occurs within a relatively narrow time frame (roughly ages 15 to 25, the times of highest sexual activity with multiple partners); and the most common type of cancer is a squamous type, which primarily spreads through direct extension. In contrast, the cause or causes of ovarian cancer are unclear, duration of exposure is unclear, and, most importantly, the pattern of spread and metastases is quite different.

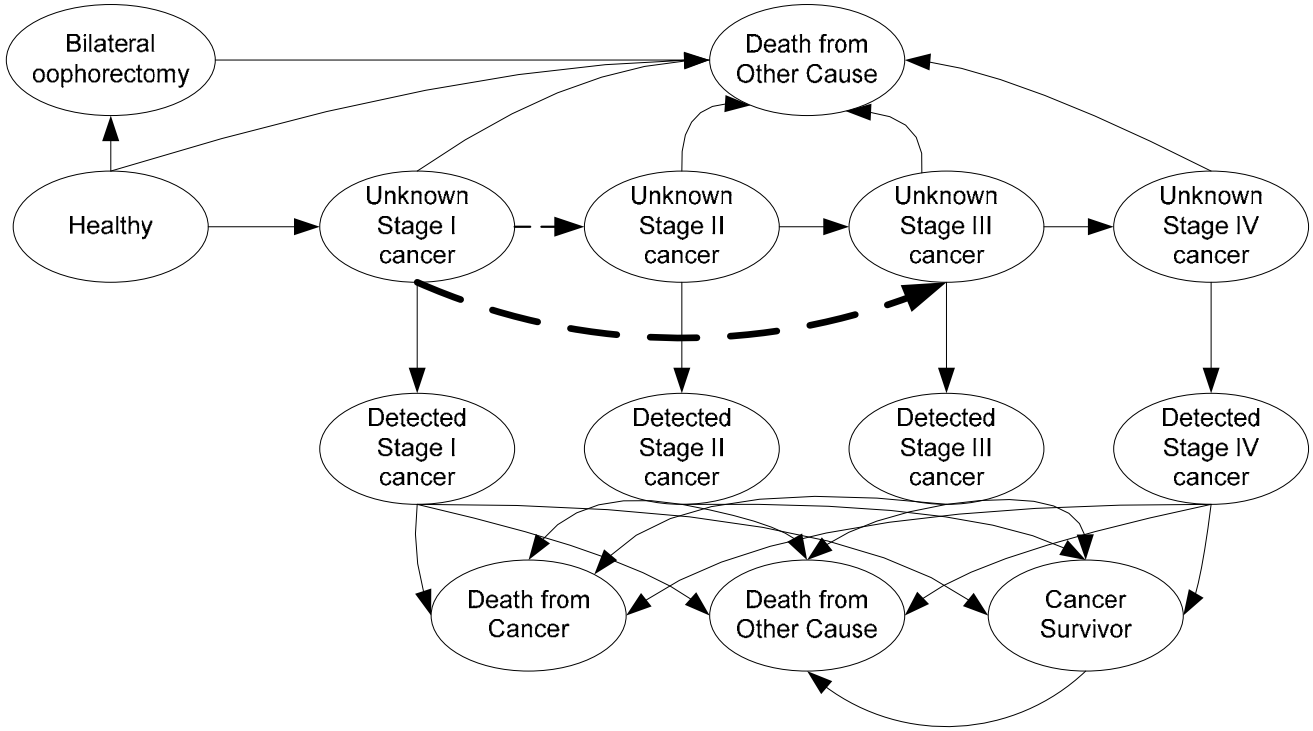
- By definition, Stage I ovarian cancer is limited to the ovary, Stage II involves the ovary and other organs in the pelvis, and Stage III, the most common stage at diagnosis, involves organs in the upper abdomen, including the large and small bowel, the

omentum, the diaphragm, and other peritoneal surfaces. Peritoneal fluid constantly circulates, and it is not uncommon for loops of small bowel to come in contact with the ovary. In order for the "conceptual model" requiring an intervening Stage II prior to development of Stage III to be correct, one has to assume that cancer cells on the surface of the ovary must necessarily spread to the uterus or other pelvic organs *before* they can spread to areas in the upper abdomen via transport in peritoneal fluid or via direct contact with small bowel. We postulate that a scenario where a certain unknown proportion of ovarian cancers progress directly from Stage I to Stage III is at least as plausible a scenario.

Given this uncertainty about the clinical progression of ovarian cancer, we therefore modeled the progression under two alternative assumptions: (1) that ovarian cancer needs to progress from Stage I to Stage II before progressing to Stage III; and (2) that a proportion of ovarian cancer progresses directly from Stage I to Stage III. We evaluated how these two competing assumptions about the natural history of ovarian cancer affect the required stage progression and mortality rates and the estimated life expectancies of the alternative prevention strategies.

We assumed that women who have survived their detected cancer for 5 years are to be considered disease-free and to have mortality equal to that of the general population. Each month, a woman may also choose to have a benign oophorectomy, reducing her risk of ovarian cancer. Throughout their lifetimes, all women are at risk for age-specific mortality unrelated to ovarian cancer. We also included age-specific rates for bilateral oophorectomy, under the assumption that women without ovaries are not at risk for developing ovarian cancer; we did not specifically model the possibility of primary peritoneal carcinomatosis in these women.

Figure 3. Schematic representation of Markov model of ovarian cancer



Arrows in Figure 3 depict possible transitions between states. Note that one version of the model allows transition directly from Stage I (confined to the ovaries) to Stage III (metastases to the upper abdomen).

Data sources. We obtained age-specific estimates of ovarian cancer incidence, mortality, stage distribution, and survival from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) online database Cancer Query System (http://seer.cancer.gov/canques).

Estimates for other-cause mortality were obtained by subtracting age-specific ovarian cancer mortality from age-specific all-cause mortality for women, using U.S. lifetables available from the National Center for Health Statistics (www.cdc.gov/nchs/deaths.htm).

Estimates for age-specific oophorectomy rates were obtained from AHRQ's Nationwide Inpatient Sample, using ICD-9 codes for bilateral oophorectomy, bilateral salpingoophorectomy, or removal of remaining ovary or remaining tube and ovary (http://hcup.ahrq.gov/HCUPnet.asp).

Software. We constructed the model and performed all analyses using DATA Pro 2006 (Williamstown, MA: TreeAge Software, Inc).

Prevention strategies. We modeled six clinical strategies of prevention for ovarian cancer (Figure 4):

(1) The baseline strategy of no screening or prevention (NoScreen) where women are identified with ovarian cancer only through development of clinical symptoms.

(2) A primary prevention strategy (PrimaryPrevention) where women undertake a hypothetical method of primary prevention which reduces their incidence of ovarian cancer.

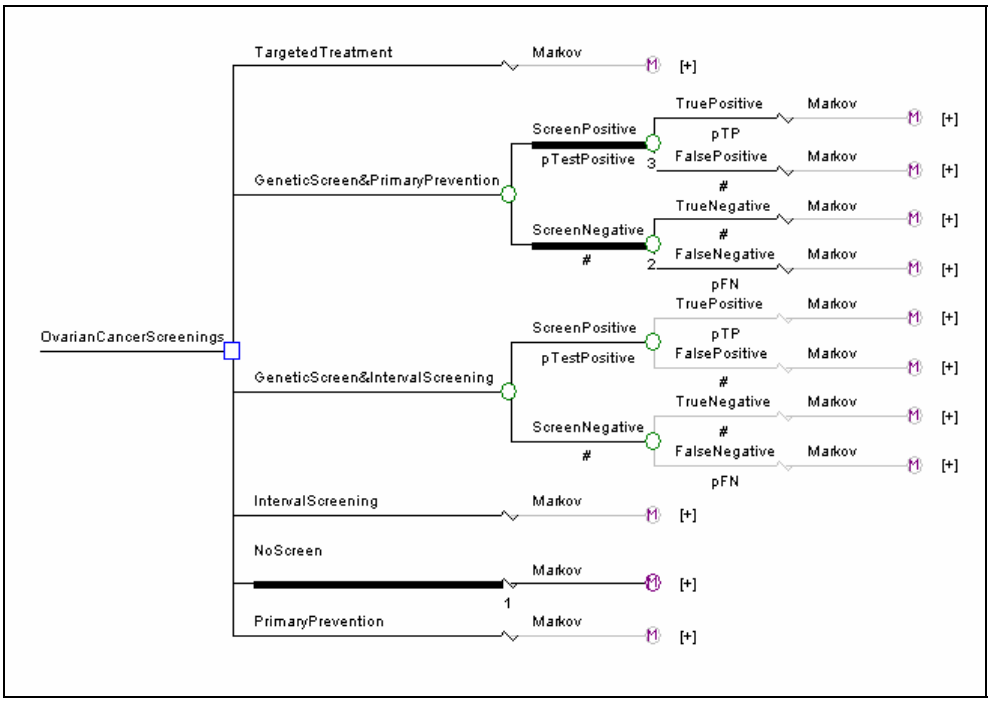
(3) An interval screening strategy (IntervalScreen) where women are screened at recurrent intervals for ovarian cancer using a hypothetical test. Women identified through screening could benefit from early treatment.

(4) A genetic screening strategy where women are tested for a specific genetic mutation and if positive undergo primary prevention for ovarian cancer (Genetic&PrimaryPrevention). The overall population risk for ovarian cancer is unchanged; we varied incidence in those with and without the putative mutation.

(5) A genetic screening strategy where women are tested for a specific genetic mutation and if positive they undergo screening for ovarian cancer at recurrent intervals (Genetic&IntervalScreen).

(6) A strategy where women once identified with ovarian cancer are tested for a hypothetical marker which allows targeted treatment for ovarian cancer (TargetTx). Women who are positive for the marker and undergo the targeted treatment experience greater survival.

Figure 4. Schematic representation of ovarian cancer prevention and treatment strategies



Approach. Because the majority of the literature on genomic testing does not allow definitive conclusions about the relative effectiveness of different strategies using different tests, we adapted a "generic" approach to comparison of different strategies.

We chose as a goal a 20 percent reduction in ovarian cancer death, similar to the reductions targed for other cancers in the Healthy People 2010 objectives. With this target, we used the calibrated models to explore the following clinical questions:

(1) How effective would a primary prevention intervention need to be to reduce ovarian cancer deaths by 20 percent?

(2) What combinations of test sensitivity and frequency result in at least a 20 percent reduction in mortality?

(3) What combinations of (a) prevalence of a genetic mutation in the population and (b) relative risk associated with that mutation would result in the target 20 percent reduction in ovarian cancer deaths with either primary prevention (at various levels of effectiveness) or interval screening (at varying levels of sensitivity and frequency)?

(4) How effective would a targeted treatment for ovarian cancer need to be (and in what proportion of the patient population would the marker for that treatment need to exist)? Note that we assume that targeted therapy would be equally effective across all stages of disease.

(5) How do the test characteristics for targeted treatment or genetic screening affect the results?

(6) How do the above results differ under the assumption that cancer must progress from Stage I to II and then III versus that assumption that ovarian cancer may progress directly from Stage I to Stage III?

(7) What effect does the assumption about natural history have on the relative efficacy of screening?

(8) What is the impact of attributable risk proportion on the potential efficacy of genetic risk factors?

Peer Review Process

We employed internal and external quality-monitoring checks through every phase of the study to reduce bias, enhance consistency, and verify accuracy. Examples of internal monitoring procedures include: three progressively stricter screening opportunities for each article (abstract screening, full-text article review, data abstraction review); involvement of three individuals (two clinicians and copy-editor) in each data abstraction; and agreement of at least two clinicians on all included studies.

Our principal external quality-monitoring device is the peer-review process. Nominations for peer reviewers were solicited from several sources, including the technical expert panel and interested federal agencies. The list of nominees was forwarded to AHRQ for vetting and approval. A list of peer reviewers submitting comments on this draft is provided in Appendix E.*

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/genovctp.htm.

Chapter 3. Results

Question 1: Analytic Validity of Testing

Question 1 is: What is the evidence that the ovarian cancer genomic tests performed in a typical clinical laboratory actually measure what they are purported to measure?

Approach

We sought to identify articles that provided details on the performance of genomic tests in a laboratory setting, with an emphasis on laboratories providing results for clinical care. Because data on sensitivity and specificity are covered under Question 2, our emphasis in this question was on evidence related to analytic performance, such as:

- Test reproducibility, as measured by inter- and intra-assay coefficients of variation for quantitative tests, or measurements of observer variability for tests that require human observation (such as immunohistochemistry).
- Measurements of correlation with other tests, including previous generations of other tests.
- Quantification of variability between laboratories.
- Analytic sensitivity and specificity in comparison to a recognized reference standard.

We included only articles that specifically addressed the laboratory performance of genomic tests for ovarian cancer. Although specific assays may have documented analytic validity when used for other cancers, or other conditions, our focus was on ovarian cancer.

Results

Articles included for Question 1 are summarized in Evidence Table 1 (Appendix D*).

Radioimmunoassays for single gene products – cancer antigen 125 (CA-125). We identified six articles that compared the performance of a next-generation radioimmunoassay (RIA) for CA-125 (CA-125 II) from various manufacturers to earlier generation tests or to other RIAs for other tumor markers.[34-39] All six studies reported high correlation coefficients with previous assays. All studies reported low inter- and intra-assay coefficients of variation (values generally less than 10 percent for inter-assay, less than 5 percent for intra-assay). Of note, two studies examined coefficients of variation at different levels of CA-125 and found changing variability with CA-125 levels. Fillela et al.,[38] using an automated analyzer, found coefficients of variation of 2.8 to 6.4 percent for "level 2" values of CA-125 (mean 47.1 U/mL), with values

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/genovctp.htm.

of 1.8 to 4 percent for "level 3" (mean 164.3 U/mL). Hubl et al.[34] reported slightly higher intra-assay coefficients of variation in mid-range (40 U/mL) compared to low-range values (10 to 20 U/mL). A third study[39] did not find an effect of concentration in the clinically relevant range. Because 35 U/mL is the most commonly used threshold for considering a CA-125 value suspicious for cancer, these results suggest that random variation in test results may have some impact on sensitivity and specificity at values close to the threshold. The clinical impact of this variability would ultimately depend on how values close to the threshold are managed.

Tuxen and colleagues performed serial measurements of CA-125 over the course of a year in 26 women with known ovarian cancer[40] and 31 healthy controls[41] to assess the relative effect of analytic variability and inter- and intra-individual biologic variation on CA-125 levels. In women with cancer, analytic imprecision accounted for 12 percent of the variability in levels, intra-individual variations 24.0 percent, and inter-individual variations 43.6 percent; after accounting for this imprecision, the investigators estimated that a change of greater than 62.6 percent in the reference value would be needed in order to be statistically significant. Similar values were found in healthy controls, with imprecision being greater in premenopausal women (69.5 percent) compared with postmenopausal women (35.7 percent) due to variability in levels over the course of the menstrual cycle. The change in reference value required for significance after accounting for variation in the entire group was 50 percent.

One study[37] compared sensitivity and specificity of the new generation and first generation assays using 138 stored samples and found slightly higher sensitivity with the new assay (89.8 vs. 84.7 percent), and lower specificity (83.5 vs. 84.7 percent). However, the prevalence of cancer in the samples was much higher than would be expected in a typical clinical population, and the confidence intervals for the sensitivity and specificity estimates overlapped.

Radioimmunoassays for other single gene products. Few studies of other markers were performed in clinical laboratories. Hasholzner and colleagues[36] evaluated clinical laboratory performance of an RIA for cancer antigen 72-4 (CA-72-4); intra-assay coefficients of variation were 3.5 to 4 percent, and inter-assay coefficients of variation were 5 to 7.4 percent. Correlation between CA-125 levels and CA-72-4 levels was good for healthy controls (-0.066), but poor for serous ovarian cancer patients (0.576).

Tuxen and colleagues[41] measured carcinoembryonic antigen (CEA) and tissue plasminogen activator (TPA) along with CA-125 in healthy controls in the study described above. For CEA, the change in reference values needed for significance after accounting for imprecision was 44.8 percent; for TPA, the value was 67.9 percent. Unlike with CA-125, menopausal status did not affect the degree of intra-individual variability.

Two studies reported research laboratory performance of two other single gene products and preliminary clinical validation. Riisbro and colleagues[42] reported an inter-assay coefficient of variation of 7.6 percent, and an intra-assay coefficient of variation of 4.6 percent for an RIA for soluble urokinase plasminogen activator receptor. Using 129 stored serum samples, levels were correlated with malignancy and stage of disease, but not after adjusting for other variables. Thougaard and colleagues[43] compared three different antibodies targeted against tetranectin, with similar performance in terms of assay variability, differences in absolute levels of 10 percent or less, and similar correlations in ovarian cancer patients (n = 43); levels were observed to decrease as cancer stage worsened.

Two studies[44,45] reported on the performance of RIAs developed after identification of candidate single gene products identified after using microarrays to identify overexpressed genes. These studies will be discussed below under "Microarrays."

Other assays. Sapi and colleagues[46] reported a method for removing peripheral lymphocytes from blood samples or ascitic fluid in order to measure telomerase activity. After this method, telomerase activity was observed in 8 of 8 patients with Stage IV ovarian cancer, 7 of 20 patients with Stage III, and 0 of 30 controls. CA-125 levels were higher in patients with positive telomerase assays.

Single gene mutation/polymorphism. Janatova and colleagues[47] evaluated the performance of Spreadex Polymer NAB (electrophoresis gels) in patients with known breast cancer gene 1/2 (BRCA1/2) mutations (n = 13) and 13 controls; the technique successfully identified mutations only in those subjects with known mutations; all patients with known mutations had mutations detected.

Wen and colleagues[48] compared microarray with gel-based DNA sequencing for identifying mutations in the p53 gene in 108 patients with ovarian cancer. Mutations were detected by both methods in 57 cancers, and no mutations by both methods, for a concordance of 81 percent.

Microarrays. Only one study specifically examined test performance in a clinical laboratory. Zarrinkar et al.[49] compared high-throughput microarray using parallel analysis to single sample assays in specimens from 31 patients with known ovarian cancer and found a high level of correlation (0.980).

Two studies reported preliminary data from research laboratories on candidate single-gene products identified initially through microarray studies.[44,45] Hellstrom and colleagues[45] compared the performance of an antibody to human epididymis protein 4 (HE4) to CA-125 in 121 subjects, of whom 37 (30.6 percent) had ovarian cancer. Reported sensitivities for HE4 were better for HE4 then for CA-125 at a fixed specificity of 96 percent, but confidence intervals were quite wide. Mok and colleagues[44] examined the performance of prostatin in 201 subjects, 64 (31.8 percent) of whom had ovarian cancer. Prostatin levels correlated poorly with CA-125 levels; sensitivity of prostatin was less than that of CA-125 at the same specificity of 94 percent, but the combination of the two markers had a sensitivity of 92 percent at the same level of specificity.

Proteomics. Although we identified 10 studies that looked at protein expression in serum as a potential biomarker for ovarian cancer,[50-59] all were performed in research laboratories. Because several of these studies have attracted wide attention in the media, we will discuss them in more detail here.

Petricoin et al.,[57] created a proteomics-based genetic algorithm with cluster analysis to distinguish between ovarian cancer and non-ovarian cancer serum samples using a training set of 50 ovarian cancers and 50 healthy controls from a high-risk population. The new algorithm was then tested using a validation set consisting of 50 ovarian cancers and 66 non-cancers, some with benign ovarian cysts, benign gynecologic disease, or benign non-gynecologic disease. The algorithm successfully classified 50/50 cancers (sensitivity = 100 percent) and 63/66 non-cancers (specificity = 95 percent) in the validation set. The study has two major limitations. First, the proteins used to distinguish cancers from non-cancers were not identified, leading to questions of whether proteins of interest were actually produced by tumor cells or by other inflammatory responses in the tumor's microenvironment. Although the reported positive predictive value is 94 percent in the study, the low prevalence of ovarian cancer (1 in 2,500) in the general population would reduce the positive predictive value of proteomic screening to less than one percent in a screening population.

These investigators subsequently published three datasets online as the Clinical Proteomics Program Databank (http://home.ccr.cancer.gov/ncifdaproteomics/ppatterns.asp). The first

dataset (2-16-02) consists of 100 control, 100 ovarian cancer, and 16 benign disease samples run on a Ciphergen H4 ProteinChip array. Ovarian Dataset 4-3-02 consists of the same samples run on Ciphergen WCX2 ProteinChip array. Ovarian Dataset 8-7-02 contains serum profiles run on Ciphergen WCX2 ProteinChip array of 162 ovarian cancer patients subdivided into stages and 91 non-cancer control subjects.

Sorace et al.[55] analyzed Ovarian Dataset 8-7-02 using a training set containing 45 controls and 80 cancers. A 2-sided Wilcoxon test was used to compare intensity between controls and cancers at different mass-to-charge (M/Z) values. A subset of M/Z values that resulted in the lowest Wilcoxon p-values was selected, and stepwise discriminant analysis was used to determine the subset of M/Z values that best discriminated cancers from controls. Classification rules were then used on the remainder of the patient data (test set). Three classification rules were developed, all with sensitivity > 90 percent and specificity > 90 percent when applied to the test set. The authors expressed concerns over the existence of highest discriminatory ability in the M/Z < 500 range, where data are traditionally discarded due to increased "noise." They hypothesized several explanations for these findings including very low molecular weight (MW) biomarkers such as LPA, low MW degradation products of higher MW macromolecules, and systematic processing error.

Li et al.[59] analyzed all three Clinical Proteomics Program Datasets using two different approaches: support vector machine statistical testing (SVM-ST) and support vector machine with genetic algorithm (SVM-GA). Datasets were not split into training and validation sets; instead, a leave-out-one cross validation was used. Sensitivity and specificity for analysis of Dataset 2-16-02 were lower than in the analysis by Petricoin et al.[57] of the same data (0.79 and 0.80 for SVM-ST, and 0.96 and 0.948 for SVM-GA, respectively). Sensitivity and specificity were improved with analysis of the other two datasets, achieving 100 percent sensitivity and 100 percent specificity using SVM-GA to analyze Dataset 8-7-02. The authors were unable to reproduce the sensitivity and specificity reported by Petricoin et al. when training an SVM with the discriminatory features identified in the latters' paper.

Zhang et al.[53] performed a multicenter study to analyze serum proteomic expression profiles using Ciphergen ProteinChip in 153 patients with epithelial ovarian cancers, 42 with other ovarian cancers, 166 with benign pelvic masses, and 142 healthy controls. Results were cross-validated against different subsets of the data to identify biomarkers. Three biomarkers (apolipoprotein A1, transthyretin, both down-regulated in ovarian cancers, and a fragment of human inter-alpha trypsin inhibitor, upregulated) were identified and immunoassays performed on serum from another subset of patients. Levels of these three biomarkers were included in a multivariate model to predict malignancy, and the model was tested on a validation set consisting of 138 ovarian cancers and 63 healthy controls. The resulting model had a sensitivity and specificity of 0.775 and 0.968, respectively, in distinguishing cancer from healthy controls. The authors also created a model incorporating CA-125 with the three markers, which improved on the specificity of CA-125 alone. The discovered biomarkers were all acute phase reactants deemed unlikely to be released by tumor cells. Controls were not age-matched and were significantly younger (median test and validation sets 39 and 44) compared to cancer patients (median 52 and 57).

Kozak et al.[60] analyzed serum from 109 ovarian cancers, 19 patients with benign disease, and 56 healthy donors using the Ciphergen ProteinChip SAX2. Samples were divided into training and test sets. Proteins differentially expressed were identified using t-test and Wilcoxon rank sum tests. Three biomarker protein panels were then developed: SBP (five markers), VBP I

(five markers), and VBP II (four markers). Multivariate logistic regression was used to develop panels with the best predictive value. Sensitivity and specificity were 0.957 and 0.826, respectively, for SBP; 0.815 and 0.949 for VBP I; and 0.728 and 0.949 for VBP II. Test sets were employed. Panels correctly identified early stage disease with variable sensitivity. Individual discriminatory proteins were not identified.

Although all studies reported good discrimination for the particular protein profile studied, there were several recurrent issues that limit the ability to draw inferences about potential clinical applicability:

- Technical issues with the assay. For example, Conrads and colleagues[58] noted that "comparisons…revealed that the variation in mass spectra (overall amplitude, total record count and deviation between ovarian cancer cases and control samples) was statistically indistinguishable from the variance within the process itself, as indicated by the serum reference standard." Sorace and Zahn,[55] in an analysis of a dataset used by several other groups, found sensitivity and specificity of 100 percent in a training set, but noted that much of the discrimination of the profile lies in the region of the spectroscopy results with low mass-to-charge ratios. They note that this region is problematic both because of technical issues of measurement and because differences in protein profiles in this region may result from processes independent of cancer.

- Varying analytic methods. No consistent methodology was used. Given the complexity of the data and the variety of methods used, it is difficult to draw consistent conclusions about performance. Li and colleagues[59] found marked variability in results using similar statistical methods on different datasets, as well as using different statistical methods on the same dataset.

- Unrealistically high prevalence of ovarian cancer. The majority of the studies compared serum samples from known ovarian cancer patients to healthy controls, using relatively small datasets of 100 to 200 subjects, with a prevalence of cancer of 30 to 50 percent. Although repeated sampling and resampling was performed in all of these studies, the prevalence of cancer was still substantially higher than it would be in a screening population (approximately 0.05 percent). Only one study[59] provided estimates for the positive predictive value within a screening population; these estimates were in general at least an order of magnitude lower than the results based on the original dataset.

Discussion

The majority of the literature we identified that specifically addressed issues of clinical laboratory performance in ovarian cancer dealt with radioimmunoassays of single gene products, with CA-125 being the most common product. Test reproducibility and validity is in general quite good for these assays, although a series of Danish studies by Tuxen and colleagues suggests that both inherent laboratory variation and biological variation should be considered when considering thresholds for determining clinically relevant changes in concentrations of these markers. In addition, coefficients of variation for CA-125 are generally greatest when levels are in the range of the most commonly used discriminatory threshold of 35 U/mL,

suggesting that this irreducible imprecision may have some impact on sensitivity and specificity in practice.

We did not identify any relevant literature on the clinical laboratory performance of other types of genomic tests. Although there were numerous articles describing research laboratory performance, the relevance of these studies to widespread clinical practice is uncertain. In particular, the prevalence of ovarian cancer in studies of potential proteomic patterns as predictors of early stage ovarian cancer is at least an order of magnitude higher than the likely prevalence in the general population.

Summary

The published data on clinical laboratory performance suggests that currently available radioimmunoassays for single gene products have acceptable reproducibility and reliability, although even this level of variability may have some impact on clinical interpretation of results, especially when comparing relatively small serial changes, or levels close to the discriminatory threshold.

There is insufficient evidence to estimate how newer technologies such as microarrays or protein profiles would perform in a "typical clinical laboratory."

Question 2: Sensitivity and Specificity of Tests

Question 2 is: What is the sensitivity and specificity of genomic tests in detecting ovarian cancer in asymptomatic and symptomatic women, including high-risk women?

Approach

We sought to identify articles that provided details on the sensitivity and specificity of genomic tests in a clinical setting. We separately reviewed studies intended for screening purposes, both in the general population and in women identified as high risk based on family history and/or BRCA testing, and studies used for diagnostic purposes, either in women with symptoms or women with a diagnosed mass.

Other Evidence Reports

Asymptomatic women – average risk. The systematic review conducted for the U.S. Preventive Services Task Force (USPSTF)[30] concluded that annual CA-125 screening had an estimated sensitivity of 80 percent, with false positive rates of 0.1 to 0.6 percent, based on three studies with small numbers of cancers and variable, relatively short, followup durations; the estimated positive predictive value for screening was 1 percent for women called for additional testing, and 15 percent for women undergoing surgery.

The evidence report on management of adnexal masses[14] found that the majority of studies did not report results separately for women with asymptomatic masses compared with those who had masses detected because of symptoms. Of note, the report also found an extremely low

sensitivity (less than 50 percent) of the bimanual pelvic examination as both a screening test and an initial diagnostic test.

Asymptomatic women – high risk. The BRCA1 and BRCA2 systematic review for the USPSTF[31] did not specifically address the sensitivity and specificity of genomic tests in this setting.

Symptomatic women – average risk. Again, the literature on the use of diagnostic tests, including genomic tests, does not provide useful information on differences in test performance in symptomatic versus asymptomatic women. The evidence report on management of adnexal masses[14] found an approximate sensitivity of 78 percent for CA-125 in the diagnosis of cancer in adnexal masses, with an approximate specificity of 78 percent; both sensitivity and specificity were higher in postmenopausal women. Other genomic tests (all single gene products) reviewed included TAG-92, cancer antigen 19.9 (CA-19.9), and CEA; all had sensitivities lower than the pooled estimates for CA-125. There were few studies examining combination testing; those that did failed to find improved discrimination compared to CA-125 alone.

Symptomatic women – high risk. The adnexal mass evidence report[14] did not identify any studies uniquely in high-risk populations.

Results

Articles included for Question 2 are summarized in Evidence Table 2 (Appendix D*).

Asymptomatic women. We did not identify any studies of genomic tests other than CA-125 that provided evidence of sensitivity and specificity as primary screening tests for ovarian cancer in asymptomatic women. The one major study published subsequent to the USPSTF review reported the initial baseline results of the National Cancer Institute Prostate, Lung, Colon, and Ovarian (PLCO) screening trial.[61] In this study, over 28,000 women aged 55 or older were screened with transvaginal ultrasound and CA-125; 402 women (1.4 percent) had an abnormal CA-125. Of the 19 invasive cancers, four had normal CA-125 levels for a sensitivity of 78.9 percent (95 percent confidence interval [CI], 60.6 to 97.3 percent), and a specificity of 98.7 percent (95 percent CI, 98.5 to 98.8 percent), consistent with previous studies in postmenopausal women.

Only one study[62] provided sufficient detail about patient characteristics to be able to ascertain test performance of a genomic test (in this case, vascular endothelial growth factor [VEGF]) as a diagnostic tool in asymptomatic women identified with a pelvic mass through screening; sensitivity was 55.9 percent, and specificity 55.3 percent, too low to be considered useful as a second line diagnostic test. All of the other studies that included women with a pelvic mass failed to report the proportion of women with a mass who had presented on the basis of symptoms, or on the basis of asymptomatic detection of a mass through a pelvic examination or imaging study; this limitation is shared by the majority of the literature on diagnosis of ovarian cancer in women with masses.[14]

Symptomatic women – single gene products. The majority of studies identified were retrospective studies that compared serum or, in some cases, tissue from women with known ovarian cancer to serum from women with benign adnexal masses and/or asymptomatic women. There were more than two studies identified for only two markers, CA-72-4 and VEGF.

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/genovctp.htm.

Table 6 shows results for CA-72-4. In general, sensitivity is poor. Although specificity is better (85 percent or higher), the high positive predictive values observed in these studies are a reflection of the high prevalence of cancer in the study populations. In a screening setting, where prevalence is likely to be less than one percent, positive predictive values would be much lower.

Table 7 shows results for VEGF. Although sensitivity was in general somewhat higher than for CA-72-4, specificity was somewhat lower.

Table 8 shows results for other single gene products. In general, there is a trade-off between sensitivity and specificity. Common limitations of these studies included failure to adequately characterize the study population (such as underlying risk factors, menopausal status, and how the patients presented to the health system); small numbers (as reflected in the wide confidence intervals of the sensitivity and specificity estimates); and prevalence of ovarian cancer much higher than would be expected in many clinical settings, especially screening settings. These limitations preclude meaningful synthesis or direct comparisons between tests.

Table 6. Studies of cancer antigen 72-4 (CA-72-4)

Study	Gene product	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence
Wakahara et al. 2001[63]	CA-72-4	20	20	18	108	50.0% (34.5 to 65.5%)	85.7% (79.6 to 91.8%)	52.6% (36.8 to 68.5%)	84.4% (78.1 to 90.7%)	24.3%
Schutter et al., 1998[64]	CA-72-4	28	15	6	86	65.0% (50.7 to 79.3%)	93.0% (87.8 to 98.2%)	82.4% (69.5 to 95.2%)	85.1% (78.2 to 92.1%)	31.9%
Fayed et al., 1998[65]	CA-72-4	21	9	3	57	70.0% (53.6 to 86.4%)	95.0% (89.5 to 100%)	87.5% (74.3 to 100%)	86.4% (78.1 to 94.6%)	33.3%
Zakrzewska et al., 1999[66]	CA-72-4	39	31	0	26	55.7% (44.1 to 67.4%)	100% (88.5 to 100%)	100% (92.3 to 100%)	45.6% (32.7 to 100%)	72.9%
Hasholzner et al., 1996[36]	CA-72-4 (benign vs. cancer)	66	57	1	36	54.0% (45.2 to 62.8%)	97.0% (91.5 to 100%)	98.5% (95.6 to 100%)	38.7% (28.8 to 48.6%)	76.9%
Hasholzner et al., 1996[36]	CA-72-4 (healthy vs. cancer)	66	57	1	29	54.0% (45.2 to 62.8%)	97.0% (90.9 to 100%)	98.5% (95.6 to 100%)	33.7% (23.7 to 43.7%)	80.4%

Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive

Table 7. Studies of vascular endothelial growth factor (VEGF)

Study	Gene product	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence
Tanir et al., 2003[67]	VEGF	11	1	6	44	91.7% (76.0 to 100%)	88.0% (79.0 to 97.0%)	64.7% (42.0 to 87.4%)	97.8% (93.5 to 100%)	19.4%
Gorelik et al., 2005[68]	VEGF	35	9	27	55	79.5% (67.6 to 91.4%)	67.4% (57.3 to 77.5%)	56.5% (44.1 to 68.8%)	85.9% (77.4 to 94.5%)	34.9%
Obermair et al., 1998[69]	VEGF	24	20	19	62	54.5% (39.8 to 69.3%)	76.5% (67.3 to 85.8%)	55.8% (41.0 to 70.7%)	75.6% (66.3 to 84.9%)	35.2%
Cooper et al., 2002[70]	VEGF	75	26	16	34	74.0% (65.4 to 82.6%)	68.0% (55.1 to 80.9%)	82.4% (74.6 to 90.2%)	56.7% (44.1 to 69.2%)	66.9%
Oehler and Caffier, 1999[71]	VEGF (benign mass controls)	29	12	7	13	70.7% (56.8 to 84.7%)	65.0% (44.1 to 85.9%)	80.6% (67.6 to 93.5%)	52.0% (32.4 to 71.6%)	67.2%
Oehler and Caffier, 1999[71]	VEGF (healthy controls)	30	11	6	14	73.2% (59.6 to 86.7%)	70.0% (49.9 to 90.1%)	83.3% (71.2 to 95.5%)	56.0% (36.5 to 75.5%)	67.2%

Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive

Table 8. Studies of other single gene products

Study	Gene product	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence
Abdel-Aleem et al., 1996[72]	Alpha-L-fucosidase	43	5	0	28	89.6% (80.9 to 98.2%)	100% (89.3 to 100%)	100% (93.0 to 100%)	84.8% (72.6 to 97.1%)	63.2%
Cherchi et al., 2002[73]	CA-15-3	10	10	6	38	50.0% (28.1 to 71.9%)	86.4% (76.2 to 96.5)	62.5% (38.8% to 86.2%)	79.2% (67.7 to 90.7%)	31.3%
Cherchi et al., 2002[73]	CA-19-9	13	7	2	42	65.0% (44.1 to 85.9%)	95.5% (89.3 to 100%)	86.7% (69.5 to 100%)	85.7% (75.9 to 95.5%)	31.3%
Wakahara et al., 2001[63]	CA-19-9	24	42	78	127	36.4% (24.8 to 48.0%)	62.0% (55.3 to 68.6%)	23.5% (15.3 to 31.8%)	75.1% (68.6 to 81.7%)	24.3%
Cherich et al., 2002[73]	CEA	8	12	0	44	40.0% (18.5 to 61.5%)	100% (93.2 to 100%)	100% (62.5 to 100%)	78.6% (67.8 to 89.3%)	31.3%
Zakrzewska et al., 1999[66]	CEA	7	63	0	26	10.0% (3.0 to 17.0%)	100% (88.5 to 100%)	100% (57.1 to 100%)	29.2% (19.8 to 38.7%)	72.9%
Mabrouk and Ali-Labib, 2003[74]	c-erb-2	4	16	4	16	20.0% (2.5 to 37.5%)	80.0% (62.5 to 97.5%)	50.0% (15.4 to 84.6%)	50.0% (32.7 to 67.3%)	50.0%
Inaba et al., 1995[75]	CYFRA 21-1	48	27	3	137	64.0% (53.1 to 74.9%)	97.9% (95.5 to 100%)	94.1% (87.7 to 100%)	83.5% (77.9 to 89.2%)	34.9%
Tempfer et al., 1998[76]	CYFRA 21-1	15	22	2	38	40.5% (24.7 to 56.4%)	95.0% (88.2 to 100%)	88.2% (72.9 to 100%)	63.3% (51.1 to 75.5%)	48.1%
Gorelik et al., 2005[68]	EGF	37	7	19	63	84.1% (73.3% to 94.9%)	76.7% (67.5 to 85.9%)	66.1% (53.7 to 78.5%)	90.0% (83.0 to 97.0%)	34.9%
Kim et al., 2003[77]	Epithelial cell adhesion molecule	22	30	2	50	42.3% (28.9 to 55.7%)	96.2% (90.9 to 100%)	91.7% (80.6 to 100%)	62.5% (51.9 to 73.1%)	50.0%
Hefler et al., 2000[78]	FAS	28	24	3	62	53.0% (39.4 to 66.6%)	95.0% (89.7 to 100%)	90.3% (79.9 to 100%)	72.1% (62.6 to 81.6%)	44.4%
Gorelik et al., 2005[68]	G-CSF	32	12	21	61	72.7% (59.5 to 85.9%)	74.4% (65.0 to 83.8%)	60.4% (47.2 to 73.5%)	83.6% (75.1 to 92.1%)	34.9%
Diamandis et al., 2003[79]	hK6	69	77	12	226	47.0% (38.9 to 55.1%)	95.0% (92.2 to 97.8%)	85.2% (77.4 to 92.9%)	74.6% (69.7 to 79.5%)	38.0%

Table 8. Studies of other single gene products (continued)

Study	Gene product	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence
Luo et al., 2001[80]	hK10	62	18	0	42	77.5% (68.3 to 86.7%)	100% (92.9 to 100%)	100% (95.2 to 100%)	70.0% (58.4 to 81.6%)	65.6%
Berek et al., 1991[81]	IL-6	18	18	2	10	50.0% (33.7 to 66.3%)	83.3% (62.2 to 100%)	90% (76.9 to 100%)	35.7% (18.0 to 53.5%)	75.0%
Gorelik et al., 2005[68]	IL-6	37	7	11	71	84.1% (73.3% to 94.9%)	86.0% (78.5 to 93.5.%)	77.1% (65.2 to 89.0%)	91.0% (84.7 to 97.4%)	34.9%
Gorelik et al., 2005[68]	IL-8	39	5	25	57	88.6% (79.2 to 98.0%)	69.8% (59.9 to 79.7%)	60.9% (49.0 to 72.9%)	91.9% (85.2 to 98.7%)	34.9%
Gorelik et al., 2005[68]	MCP	37	7	23	59	84.1% (73.3% to 94.9%)	72.1% (62.4 to 81.8%)	61.7% (49.4 to 74.0%)	89.4% (82.0 to 96.8%)	34.9%
van Haaften-Day et al., 2001[82]	M-CSF	69	134	28	166	34.0% (27.5 to 40.0%)	85.6% (80.6 to 90.5%)	71.1% (62.1 to 80.2%)	55.3% (49.7 to 61.0%)	51.1%
Bon et al., 1996[83]	Mucin-like carcinoma-associated antigen	29	47	0	70	38.2% (27.2 to 49.1%)	100% (95.7 to 100%)	100% (89.7 to 100%)	59.8% (50.9 to 68.7%)	52.1%
van Haaften-Day et al., 2001[82]	OVX1	38	165	16	178	18.7% (13.4 to 24.1%)	91.8% (87.9 to 95.6%)	70.4% (58.2 to 82.5%)	51.9% (46.6 to 57.2%)	51.1%
Onsrud et al., 1996[84]	p55	26	19	3	24	57.8% (43.3 to 72.2%)	88.9% (77.0 to 100%)	89.7% (78.6 to 100%)	55.8% (41.0 to 70.7%)	62.5%
Opala et al., 2005[85]	p55	28	23	1	15	54.9% (41.2 to 68.6%)	93.8% (81.9 to 100%)	96.6% (89.9 to 100%)	39.5% (23.9 to 55.0%)	76.1%
Onsrud et al., 1996[84]	p75	7	38	1	26	15.6% (5.0 to 26.1%)	96.3% (89.2 to 100%)	87.5% (64.6 to 100%)	40.6% (28.6 to 52.7%)	62.5%
Opala et al., 2005[85]	p75	22	29	3	13	43.1% (29.5 to 56.7%)	81.3% (62.1 to 100%)	88.0% (75.3 to 100%)	31.0% (17.0 to 44.9%)	76.1%
Tsukishiro et al., 2005 [86]	Secretory leukocyte protease inhibitor	42	13	5	20	76.0% (64.7 to 87.3%)	80.0% (64.3 to 95.7%)	89.4% (80.5 to 98.2%)	60.6% (43.9 to 77.3%)	68.8%

Table 8. Studies of other single gene products (continued)

Study	Gene product	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Prevalence
Darai et al., 1998[87]	Serum cadherin	11	5	0	52	68.8% (46.0 to 91.5%)	100% (94.2 to 100%)	100% (72.7 to 100%)	91.2% (83.9 to 98.6%)	23.5%
Baron et al., 2003[88]	Serum EGFR	125	100	8	136	55.6% (49.1 to 62.0%)	94.4% (90.7 to 98.2%)	94.0% (89.9 to 98.0%)	57.6% (51.3 to 63.9%)	60.9%
Baron et al., 2005[89]	Serum EGFR	141	84	86	160	62.7% (56.3 to 69.0%)	65.0% (59.1 to 71.0%)	62.1% (55.8 to 68.4%)	65.6% (59.6 to 71.5%)	47.8%
Udagawa et al., 1998[90]	Serum GAT	68	68	13	285	50.0% (41.6 to 58.4%)	95.6% (93.3 to 97.9%)	84.0% (76.0 to 91.9%)	80.7% (76.6 to 84.9%)	31.3%
Sedlaczek et al., 2002[91]	sIL to 2R	54	13	1	31	80.6% (71.1 to 90.1%)	96.9% (90.8 to 100%)	98.2% (94.7 to 100%)	70.5% (57.0 to 83.9%)	67.8%
Hurteau et al., 1995[92]	Soluble IL-2 receptor alpha	37	2	58	3	94.9% (87.9 to 100%)	4.9% (0 to 10.3%)	38.9% (29.1 to 48.8%)	60.0% (17.1 to 100%)	39.0%
Opala et al., 2003[93]	Soluble intra-cellular adhesion molecule 1	42	9	7	9	82.4% (71.9 to 92.8%)	56.3% (31.9 to 80.6%)	85.7% (75.9 to 95.5%)	50.0% (26.9 to 73.1%)	76.2%
McIntosh et al., 2004[94]	Soluble mesothelin-related marker (benign masses)	15	37	4	216	28.8% (16.5 to 41.2%)	98.2% (96.4 to 99.9%)	78.9% (60.6 to 97.3%)	85.4% (81.0 to 89.7%)	19.1%
Sedlaczek et al., 2002[91]	TPS	53	14	6	26	79.1% (69.4 to 88.8%)	81.3% (67.7 to 94.8%)	89.8% (82.1 to 97.5%)	65.0% (50.2 to 79.8%)	67.8%
Medl et al., 1995[95]	TATI	75	40	67	200	65.2% (56.5 to 73.9%)	74.9% (69.7 to 80.1%)	52.8% (44.6 to 61.0%)	83.3% (78.6 to 88.0%)	30.1%
Peters-Engl et al., 1995[96]	TATI	114	66	60	154	63.3% (56.3 to 70.4%)	72.0% (65.9 to 78.0%)	65.5% (58.5 to 72.6%)	70.0% (63.9 to 76.1%)	45.7%
Schutter et al., 1999[97]	Urinary gonadotropin peptide	7	2	7	14	78.0% (50.9 to 100%)	65.0% (44.6 to 85.4%)	50.0% (23.8 to 76.2%)	87.5% (71.3 to 100%)	30.0%

Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive

Symptomatic women – DNA variations. We did not identify any studies that allowed estimation of sensitivity and specificity of inherited or acquired mutations in detecting ovarian cancer.

Symptomatic women – gene expression. We identified one study that reported on the sensitivity of cytological tests of ascitic fluid for the presence of a series of genes believed to be activated in ovarian cancer;[98] although specificities were universally high, sensitivities ranged from 8 to 60 percent, with wide confidence intervals for both values. These low sensitivities were even more striking given the high prevalence of ovarian cancer in the samples (61 percent).

We identified one study that used immunohistochemistry for a range of gene products in the diagnosis of ovarian cancer in ovarian tissue;[99] performance for different markers ranged widely. Because there were only 20 ovarian cancer patients (out of a total of 70), confidence intervals were wide. In addition, no data were provided on the reproducibility of the assay or interpretation of results.

Another study measured cytokeratin 19 (CK19) expression in peripheral blood mononuclear cells;[100] false-positive rates were quite high in both discriminating cancer from benign ovarian tumors (specificity 28.6 percent) and cancer from normal controls (specificity 40.0 percent). Again, confidence intervals were very wide.

No other studies directly reported the sensitivity and specificity of gene expression patterns identified through the use of microarray technology.

Symptomatic women – proteomics. Studies of protein profiles as a potential tool for early diagnosis of ovarian cancer have attracted considerable attention recently. However, all of the identified studies examined test performance using databases; none have been tested in a clinical population.

Discussion

In general, single gene products other than CA-125 have not been shown to be useful in the diagnosis of ovarian cancer, either in symptomatic or asymptomatic women. Small sample sizes, lack of detail on the prediagnosis history of patients, and an unrealistically high prevalence of ovarian cancer in the majority of studies make it difficult to assess how any of these tests would perform in clinical practice.

Estimating the clinical value of more complex tests (those using multiple gene and/or protein markers) is even more difficult. Studies of protein expression, in particular, are limited by lack of consensus on appropriate statistical methods, small sample sizes with substantially higher prevalences of ovarian cancer than would be found in the general population, lack of reproducibility, and uncertainty about the specificity of the biological processes resulting in the observed protein patterns. Most importantly, none have been tested in clinical populations.

Question 3: Impact on Clinical Management of Asymptomatic Patients

Question 3 is: What is the evidence that genomic testing to detect ovarian cancer in asymptomatic women, including high-risk women, changes clinical management and leads to improved health outcomes?

Approach

We searched for articles related to the use of genomic tests in screening for ovarian cancer in asymptomatic women, including any studies that focused on screening in women previously identified as being at greater risk on the basis of family history or other genomic tests. We excluded studies of CA-125 that were previously reviewed in a report for the USPSTF;[30] we did, however, review studies published subsequent to the USPSTF review.

Other Evidence Reports

In the review of ovarian cancer screening for the USPSTF,[30] studies did consistently show a greater prevalence of Stage I ovarian cancer among women screened with CA-125 (based on small numbers of cancers), but there were no data on the impact of screening on mortality.

In the BRCA1 and BRCA2 review,[31] there were "limited" data on the efficacy of intensive screening among carriers, and no prospective studies of chemoprevention (especially oral contraceptives) or tubal ligation, although some suggestion from observational studies that both of those interventions might reduce ovarian cancer risk. In three retrospective studies and one cohort study, prophylactic oophorectomy reduced the risk of ovarian cancer by 85 to 100 percent, although the authors of the review noted that the confidence interval for risk reduction crossed 1.0 in the prospective study.

Results

We did not identify any studies of the use of genomic tests for screening asymptomatic women in any risk group that met our inclusion criteria.

Discussion

To date, no test has been shown to have acceptable sensitivity and specificity for screening for ovarian cancer, or to reduce the morbidity and mortality associated with ovarian cancer. Because definitive diagnosis of ovarian cancer requires surgery, a high level of specificity is needed in order to minimize the costs and potential complications of unnecessary surgery; although screening in high-risk groups could theoretically have better outcomes (because a higher pretest probability of cancer should result in better positive predictive values), this has not been demonstrated in adequately designed studies. One study of 1,610 women at increased risk because of family history found a positive predictive value for ovarian cancer of less than five percent (3 of 61 abnormal tests),[101] a value similar to that observed in the 28,000 average-risk women in the PLCO study (3.7 percent).[61] The ability to detect early cancer in these populations, even with intensive screening, may be limited; a study of 291 high-risk women who were screened every 6 months with ultrasound and CA-125 detected early stage ovarian cancer in only one of the eight women who developed ovarian or peritoneal cancer during 10 years of followup; five of the eight had had normal screening tests within 6 months of diagnosis.[18] Other studies in similar populations have reported similar findings.[16,19] The degree to which the lack of effectiveness of screening is due to insufficient test sensitivity rather than the inherent biology of ovarian cancer is discussed further in the section on modeling.

Summary

We found no articles on the use of genomic tests (other than CA-125) for detecting ovarian cancer in asymptomatic women, regardless of risk group.

Question 4: Impact on Clinical Management of Diagnosed Patients

Question 4 is: What is the evidence that genomic testing in women with clinical suspicion of ovarian cancer or with already-diagnosed ovarian cancer changes clinical management and leads to improved health outcomes?

Approach

Studies included in this section reported data on the association of genomic test results with either a change in clinical management or a health outcome related to a particular management strategy. For example, genomic tests whose results were associated with response to therapy are included here. We did not, however, include studies that related genomic tests strictly to prognosis, for example, describing survival differences based on genomic test results. Similarly, if genomic test results were associated with staging data, we did not include these studies here despite the fact that staging may in turn be used to select treatment. Our notion is that we were primarily interested in how genomic testing could inform clinical management beyond usual clinical staging, which is already routinely used to guide therapy.

Results

We found no studies that compare two groups of women, one of which underwent genomic testing and one of which did not. Ideally, such a study would be prospective with random allocation to the groups. In fact, we did not encounter any non-randomized comparative studies, either prospective or retrospective, that compare management or health outcomes in two such groups. Therefore, the following review considers only uncontrolled studies describing the association of test-positive and test-negative women with management and health outcomes. This design limits the certainty with which one might infer that applying the test in clinical practice could result in improved management decisions or health outcomes compared to not applying the test.

The description of evidence is divided first between studies of women with a clinical suspicion of ovarian cancer versus women with already diagnosed ovarian cancer. Within these groups, we will discuss the influence of genomic tests on specific management decisions or health outcomes. Summaries of all the included articles are provided in Evidence Table 3 (Appendix D*).

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/genovctp.htm.

Women with clinical suspicion of ovarian cancer. We found no studies that describe evidence regarding change in management or health outcome resulting from use of genomic testing in women with a clinical suspicion of ovarian cancer. A large number of studies discussed under Question 2 describe the diagnostic accuracy of genomic tests in women with a clinical suspicion of ovarian cancer (based on symptoms), but none of these studies, nor any others screened in the literature search, described clinical management changes or health outcomes resulting from these tests.

Women with already diagnosed ovarian cancer. The most studied use of genomic tests was for predicting or detecting response to treatment after debulking therapy and adjuvant chemotherapy. The studies were of two types. First, several studies sought to predict which patients would have a favorable response to chemotherapy (e.g., complete or partial response vs. stable or progressive disease). A second goal of studies was to predict, among women who appeared to have no evidence of disease on clinical evaluation, who would have evidence of disease on second-look laparotomy (SLL). Finally, several studies related genomic test results at the time of primary debulking surgery with the ability to achieve optimal cytoreduction.

Predicting favorable response to chemotherapy. We found six studies describing the association between CA-125 and favorable response to chemotherapy;[79,102-106] these studies used a wide range of threshold values, from 10 to 500 U/mL. In addition, the following tests were described in one study each: human kallikrein 6 (hK6);[79] low-density lipoprotein receptor-related protein (LRP), multidrug resistance protein (MRP), and P-glycoprotein (Pgp);[107] multidrug resistance gene 1 (MDR-1), MRP-1, and MRP-2;[108] TP53;[109] c-erb-B2;[110] and human kallikrein 10 (hK10).[111]

Table 9 and Figure 5 show the sensitivity and specificity of these tests for predicting response to chemotherapy. Estimates of sensitivity are widely scattered and range from 12 to 100 percent; specificity ranged from 0 to 84 percent. The only study to report diagnostic performance that exceeded that of the studies of change in CA-125[102,104-106] was one of MDR-1;[108] however, it is important to note that this relatively small study (n = 27) did not report estimates from the other markers assessed in the study (MRP-1 and MRP-2), but noted only that there was no association between those tests and response to chemotherapy.[108] No other studies have replicated this finding.

Table 9. Sensitivity and specificity of genomic tests for predicting response to chemotherapy

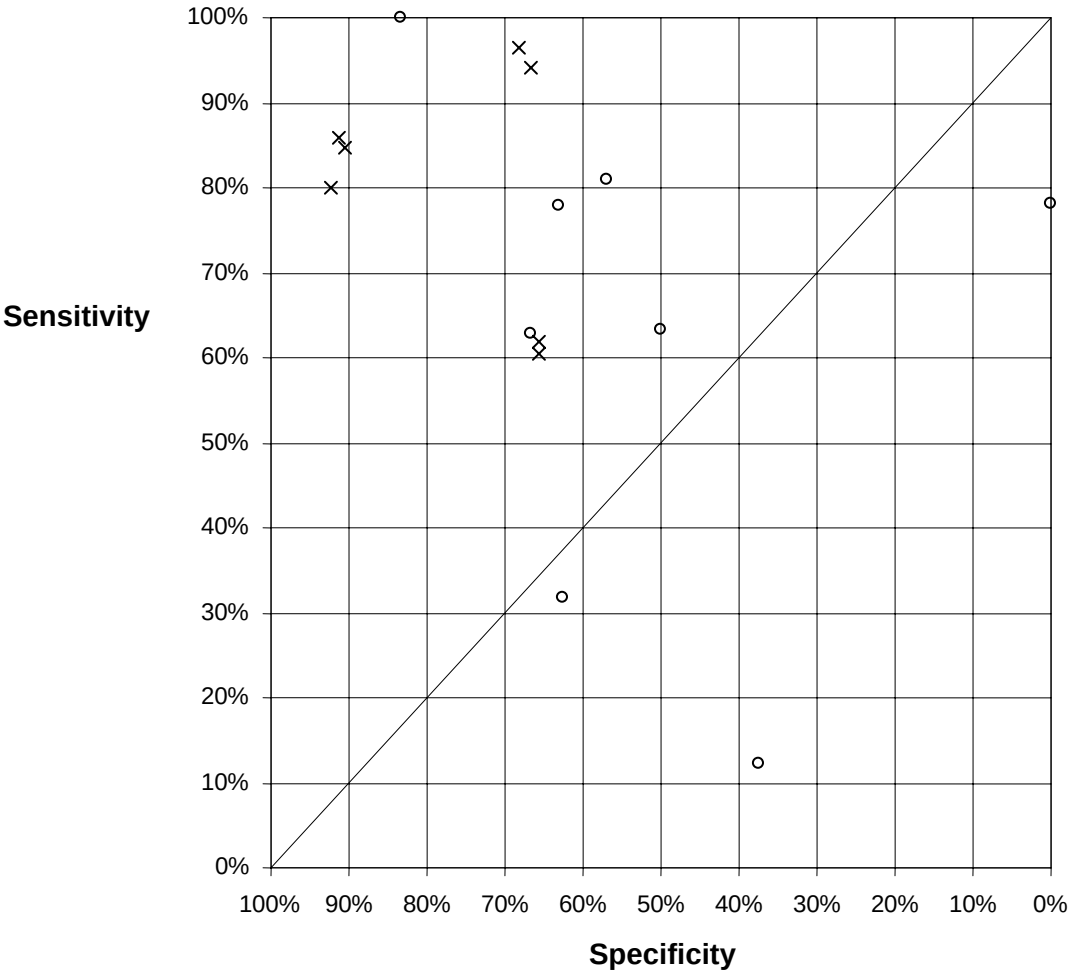
Test/Study	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Probability of response to chemotherapy
CA-125									
Balbi et al., 2005[102]	32	8	2	24	80.00% (65.2 to 89.5%)	92.30% (75.9 to 97.9%)	94.10% (80.9 to 98.4%)	75.00% (57.9 to 86.7%)	60.60%
Balbi et al., 2005[102]	22	4	2	19	84.60% (66.5 to 93.8%)	90.50% (71.1 to 97.3%)	91.70% (74.2 to 97.7%)	82.60% (62.9 to 93.0%)	55.30%
Rustin et al., 2001[104]	80	5	1	2	94.10% (87.0 to 97.5%)	66.70% (20.8 to 93.9%)	98.80% (93.3 to 99.8%)	28.60% (8.2 to 64.1%)	96.60%
Rustin et al., 1996[105]	73	12	4	42	85.90% (76.9 to 91.7%)	91.30% (79.7 to 96.6%)	94.80% (87.4 to 98.0%)	77.80% (65.1 to 86.8%)	64.90%
Gronlund et al., 2004[106]	27	1	14	30	96.40% (82.3 to 99.4%)	68.20% (53.4 to 80.0%)	65.90% (50.5 to 78.4%)	96.80% (83.8 to 99.4%)	38.90%
Gadducci et al., 2004[103] (CA-125 half life)	26	16	10	19	61.90% (46.8 to 75.0%)	65.50% (47.3 to 80.1%)	72.20% (56.0 to 84.2%)	54.30% (38.2 to 69.5%)	59.20%
Gadducci et al., 2004[103] (CA-125% reduction)	26	17	10	19	60.50% (45.6 to 73.6%)	65.50% (47.3 to 80.1%)	72.20% (56.0 to 84.2%)	52.80% (37.0 to 68.0%)	59.70%
hk6									
Diamandis et al., 2003[79]	17	4	46	61	81.00% (60.0 to 92.3%)	57.00% (47.5 to 66.0%)	27.00% (17.6 to 39.0%)	93.80% (85.2 to 97.6%)	16.40%
MDR-1									
Kamazawa et al., 2002[108]	21	0	1	5	100.00% (84.5 to 100.0%)	83.30% (43.6 to 97.0%)	95.50% (78.2 to 99.2%)	100.00% (56.6 to 100.0%)	77.80%
TP53									
Kupryjandzyk et al., 2003[109]	98	57	37	37	63.20% (55.4 to 70.4%)	50.00% (38.9 to 61.1%)	72.60% (64.5 to 79.4%)	39.40% (30.1 to 49.5%)	67.70%

Table 9. Sensitivity and specificity of genomic tests for predicting response to chemotherapy (continued)

Test/Study	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Probability of response to chemotherapy
c-erb-B2									
Lassus et al., 2004[110]	234	66	30	51	78.00% (73.0 to 82.3%)	63.00% (52.1 to 72.7%)	88.60% (84.2 to 91.9%)	43.60% (34.9 to 52.6%)	78.70%
hk10									
Luo et al., 2003[111]	74	44	7	14	62.70% (53.7 to 70.9%)	66.70% (45.4 to 82.8%)	91.40% (83.2 to 95.8%)	24.10% (15.0 to 36.5%)	84.90%
Pgp									
Izquierdo et al., 1995[107]	32	9	8	0	78.00% (63.3 to 88.0%)	0.00% (0.0 to 32.4%)	80.00% (65.2 to 89.5%)	0.00% (0.0 to 29.9%)	83.70%
MRP									
Izquierdo et al., 1995[107]	13	28	3	5	31.70% (19.6 to 47.0%)	62.50% (30.6 to 86.3%)	81.30% (57.0 to 93.4%)	15.20% (6.7 to 30.9%)	83.70%
LRP									
Izquierdo et al., 1995[107]	5	36	5	3	12.20% (5.3 to 25.5%)	37.50% (13.7 to 69.4%)	50.00% (23.7 to 76.3%)	7.70% (2.7 to 20.3%)	83.70%

Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive

Figure 5. Diagnostic performance of genomic tests to predict response to chemotherapy plotted in receiver operating characteristic (ROC) space



Key to Figure 5: Crosses indicate studies of CA-125; circles indicated other serum or immunohistochemical tests.

Predicting residual disease on SLL. A second goal of studies was to predict, among women who appeared to have no evidence of disease on clinical evaluation, who would have evidence of disease on SLL. A test might be clinically useful if it could predict with a high sensitivity which patients with clinically undetectable disease might have cancer progression on SLL. Such a test might obviate the need for SLL or at least improve the accuracy of clinical staging. CA-125 is one marker used to detect early recurrence.

We found five studies describing the association between CA-125 and positive disease on SLL.[112-116] Two studies described cancer-associated serum antigen (CASA).[113,114] In addition, the following markers were described in one study each: Cathespin-D and nm23;[117] p53, murine double minute protein (Mdm2), and Bcl-2;[118] interleukin 6 (IL-6);[81] cytokeratin fragment 21-1 (CYFRA 21-1);[119] tetranectin (TN);[113] and TPS.[115]

Three reports classified patients with microscopic disease as disease-negative,[81,117,118] while the remaining studies classified macroscopic or microscopic disease at SLL as disease-positive.

Table 10 shows the sensitivity of a positive test for identifying patients with positive SLL. The sensitivities for CA-125 range from 6.4 to 57.9 percent. Thresholds for a positive test vary from 10 U/mL to 35 U/mL, but there is no clear relationship between cut-point and sensitivity that explains the differences between studies. While most studies of CA-125 fell in the lower left quadrant of the receiver operating characteristic (ROC) space (Figure 6), representing low sensitivity but high specificity, the other genomic tests reported displayed greater variability, particularly in specificity. The higher average sensitivity was associated with lower specificity.

Studies also differ with regard to the separation in time between the time at which the marker was measured and the time of SLL. The immunohistochemical tests are based on surgical samples, while serum markers were measured after surgery, after adjuvant chemotherapy, and immediately prior to SLL.

Table 10. Sensitivity and specificity of genomic tests for identifying patients with residual disease at second-look laparotomy

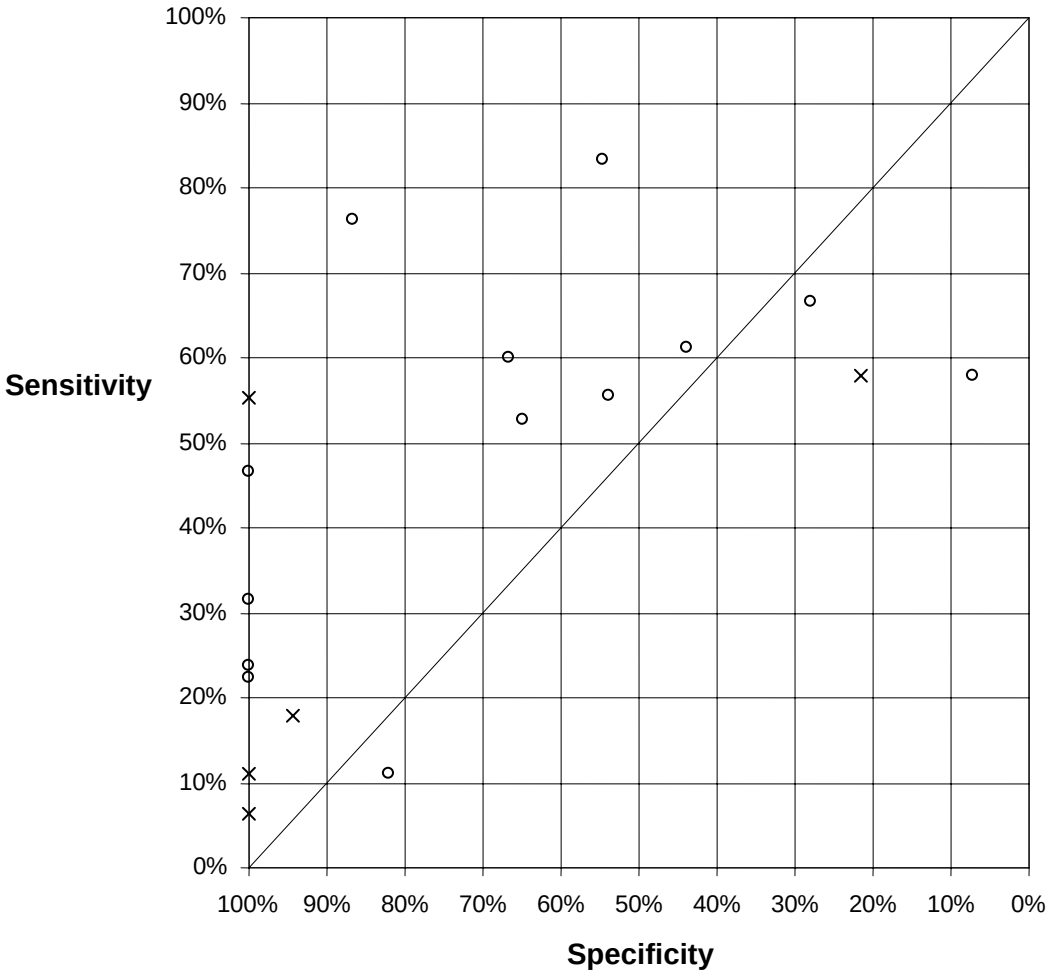
Test/Study	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Probabilty of residual disease
CA-125									
Folk et al., 1995[112]	3	24	0	18	11.1% (3.9 to 28.1%)	100.0% (82.4 to 100.0%)	100.0% (43.9 to 100.0%)	42.9% (29.1 to 57.8%)	60.0%
Hogdall et al., 1996[113]	21	17	0	30	55.3% (39.7 to 69.9%)	100.0% (88.6 to 100.0%)	100.0% (84.5 to 100.0%)	63.8% (49.5 to 76.0%)	55.9%
Senapad et al., 2000[115] CA-125 > 10	11	8	11	3	57.9% (36.3 to 76.9%)	21.4% (7.6 to 47.6%)	50.0% (30.7 to 69.3%)	27.3% (9.7 to 56.6%)	57.6%
Kierkegaard et al., 1995[114] CA-125 > 15	23	335	0	35	6.4% (4.3 to 9.5%)	100.0% (90.1 to 100.0%)	100.0% (85.7 to 100.0%)	9.5% (6.9 to 12.9%)	91.1%
Wong et al., 2000[116] CA-125 > 35	5	23	1	17	17.9% (7.9 to 35.6%)	94.4% (74.2 to 99.0%)	83.3% (43.6 to 97.0%)	42.5% (28.5 to 57.8%)	60.9%
CASA									
Hogdall et al., 1996[113]	12	26	0	29	31.6% (19.1 to 47.5%)	100.0% (88.3 to 100.0%)	100.0% (75.8 to 100.0%)	52.7% (39.8 to 65.3%)	56.7%
Kierkegaard et al., 1995[114]	13	45	0	35	22.4% (13.6 to 34.7%)	100.0% (90.1 to 100.0%)	100.0% (77.2 to 100.0%)	43.8% (33.4 to 54.7%)	62.4%
Cathepsin D									
Baekelandt et al., 1999[117]	22	14	78	61	61.1% (44.9 to 75.2%)	43.9% (35.9 to 52.2%)	22.0% (15.0 to 31.1%)	81.3% (71.1 to 88.5%)	20.6%
CYFRA 21-1									
Gadducci et al., 2001[119]	20	4	5	6	83.3% (64.1 to 93.3%)	54.5% (28.0 to 78.7%)	80.0% (60.9 to 91.1%)	60.0% (31.3 to 83.2%)	68.6%
p53									
Baekelandt et al., 1999[118]	20	16	64	75	55.6% (39.6 to 70.5%)	54.0% (45.7 to 62.0%)	23.8% (16.0 to 33.9%)	82.4% (73.3 to 88.9%)	20.6%
Ayhan et al., 1998[120]	9	6	5	10	60.0% (35.7 to 80.2%)	66.7% (41.7 to 84.8%)	64.3% (38.8 to 83.7%)	62.5% (38.6 to 81.5%)	50.0%

Table 10. Sensitivity and specificity of genomic tests for identifying patients with residual disease at second-look laparotomy (continued)

Test/Study	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Probability of residual disease
Other									
Baekelandt et al., 1999[117] nm23	24	12	100	39	66.7% (50.3 to 79.8%)	28.1% (21.3 to 36.0%)	19.4% (13.4 to 27.2%)	76.5% (63.2 to 86.0%)	20.6%
Baekelandt et al., 1999[118] Mdm2	4	32	25	114	11.1% (4.4 to 25.3%)	82.0% (74.8 to 87.5%)	13.8% (5.5 to 30.6%)	78.1% (70.7 to 84.0%)	20.6%
Baekelandt et al., 1999[118] Bcl-2	19	17	49	90	52.8% (37.0 to 68.0%)	64.7% (56.5 to 72.2%)	27.9% (18.7 to 39.6%)	84.1% (76.0 to 89.8%)	20.6%
Berek et al., 1991[81] IL-6	16	5	2	13	76.2% (54.9 to 89.4%)	86.7% (62.1 to 96.3%)	88.9% (67.2 to 96.9%)	72.2% (49.1 to 87.5%)	58.3%
Hogdall et al., 1996[113] TN	9	29	0	30	23.7% (13.0 to 39.2%)	100.0% (88.6 to 100.0%)	100.0% (70.1 to 100.0%)	50.8% (38.4 to 63.2%)	55.9%
Combination markers									
Kierkegaard et al., 1995[114]	27	31	0	35	46.6% (34.3 to 59.2%)	100.0% (90.1 to 100.0%)	100.0% (87.5 to 100.0%)	53.0% (41.2 to 64.6%)	62.4%
Senapad et al., 2000[115]	11	8	13	1	57.9% (36.3 to 76.9%)	7.1% (1.3 to 31.5%)	45.8% (27.9 to 64.9%)	11.1% (2.0 to 43.5%)	57.6%

Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive

Figure 6. Studies of the ability of serum markers to predict positive disease on second-look laparotomy following primary surgery and adjuvant chemotherapy plotted in ROC space



Key to Figure 6: Crosses indicated studies of CA-125; open circles indicate studies of other genomic tests.

Predicting ability to perform optimal cytoreduction. Several studies evaluated genomic tests for their ability to predict whether optimal cytoreduction (by surgical debulking) was possible. Definitions for optimal cytoreduction were identical between studies, based on the Gynecology Oncology Group criteria,[121] requiring no residual tumor masses > 1 cm at debulking surgery.

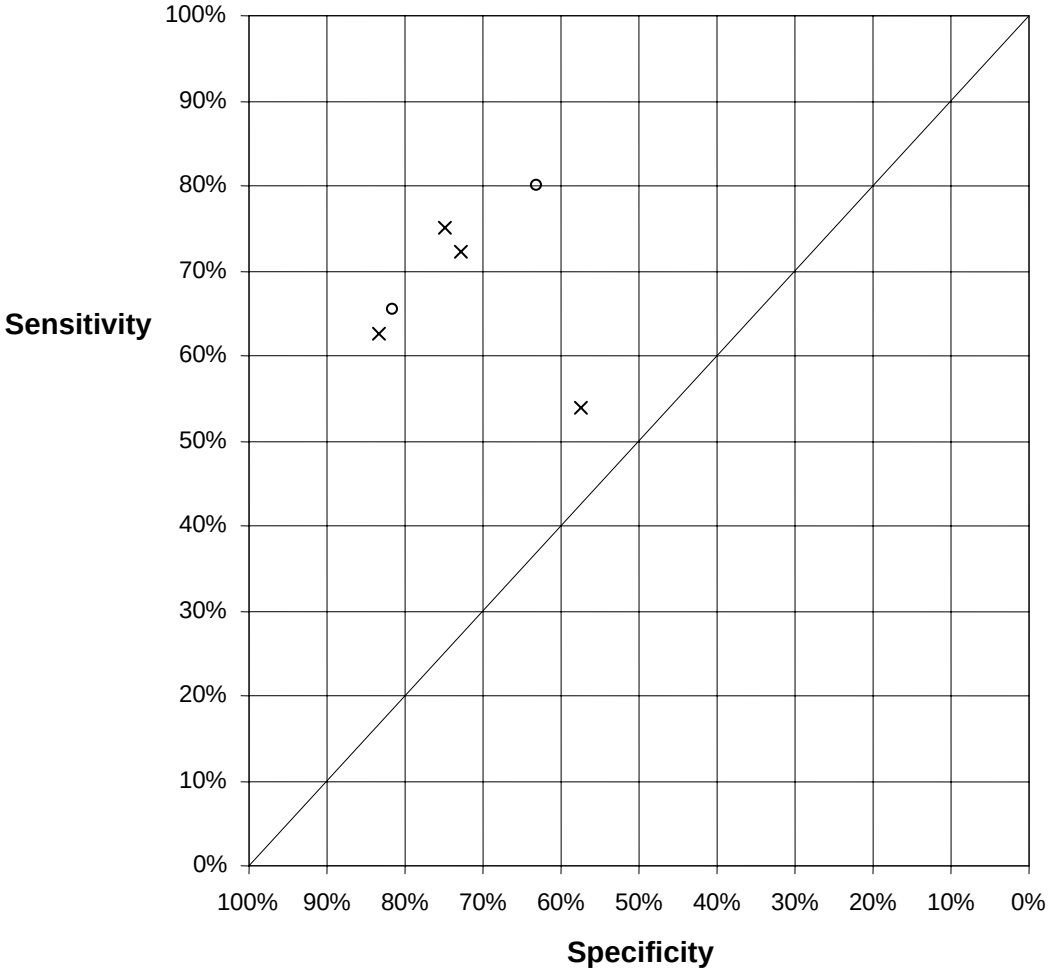
Table 11 and Figure 7 show the sensitivity and specificity of tests for predicting which patients will achieve optimal cytoreduction at primary surgical debulking.

Table 11. Sensitivity and specificity of tests for predicting which patients will achieve optimal cytoreduction at primary surgical debulking

Study/Test	TP	FN	FP	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Probability of optimal cytoreduction
Berchuck et al., 2004[122] Chip	20	5	7	12	80.0% (60.9 to 91.1%)	63.2% (41.0 to 80.9%)	74.1% (55.3 to 86.8%)	70.6% (46.9 to 86.7%)	56.8%
Diamandis et al., 2003[79] hK6	53	28	9	40	65.4% (54.6 to 74.9%)	81.6% (68.6 to 90.0%)	85.5% (74.7 to 92.2%)	58.8% (47.0 to 69.7%)	62.3%
Gemer et al., 2001[123] CA-125	10	6	4	20	62.5% (38.6 to 81.5%)	83.3% (64.1 to 93.3%)	71.4% (45.4 to 88.3%)	76.9% (57.9 to 89.0%)	40.0%
Memarzadeh et al., 2003[124] CA-125	14	12	31	42	53.8% (35.5 to 71.2%)	57.5% (46.1 to 68.2%)	31.1% (19.5 to 45.7%)	77.8% (65.1 to 86.8%)	26.3%
Obeidat et al., 2004[125] CA-125	13	5	6	16	72.2% (49.1 to 87.5%)	72.7% (51.8 to 86.8%)	68.4% (46.0 to 84.6%)	76.2% (54.9 to 89.4%)	45.0%
Saygili et al., 2002[126] CA-125	33	11	12	36	75.0% (60.6 to 85.4%)	75.0% (61.2 to 85.1%)	73.3% (59.0 to 84.0%)	76.6% (62.8 to 86.4%)	47.8%
Gemer et al., 2005[127] CA-125	126	56	138	104	69.2% (62.5 to 72.9%)	57.0% (50.8 to 63.2%)	54.8% (48.4 to 61.2%)	71.1% (64.8 to 77.5%)	42.9%

Abbreviations: CI = confidence interval; FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive

Figure 7. Diagnostic performance of studies of tests to predict suboptimal cytoreduction (surgical debulking with residual disease > 1 cm) plotted in ROC space



Key to Figure 7: Crosses indicate studies of CA-125; open circles indicate other tests.

Discussion

The vast majority of the available literature on the use of genomic tests in the management of patients with ovarian cancer consists of serum measurement of single-gene products, particularly CA-125, as predictors of (a) initial response to chemotherapy; (b) complete resolution of disease (i.e., negative SLL); or (c) the ability to perform optimal cytoreduction. There is also a substantial literature that reports on the association of various genomic tests with prognosis, but the majority of these studies were excluded because they did not describe patient management.

The studies that sought to predict initial response to chemotherapy were generally performed in unselected women with ovarian cancer, not just those with optimal debulking, for example. Although, in theory, there is significant benefit, both clinically and in the research setting, of being able to predict who will respond to chemotherapy, we did not identify any studies that demonstrated this; there were no studies, for example, that compared different chemotherapeutic regimens based on test results.

Studies evaluating the association of genomic test results with second-look surgery were commonly limited to women who had appeared to have a complete response to initial debulking and chemotherapy. In these studies serum markers were often measured close to the time of SLL (e.g., at the end of chemotherapy or immediately prior to SLL); however, immunohistochemical tests were usually based on tissue obtained at the time of primary surgery. SLL is sometimes used to evaluate women who appear clinically to have had a complete response, since other techniques, such as CA-125 and imaging, are fairly insensitive for very small disease. However, most of the data suggests that there is no substantial survival benefit to SLL, even if residual tumor is removed; a Gynecologic Oncology Group non-randomized study reported a difference in median survival of only 1 month.[128] Thus, the SLL might be more properly though of as a test for monitoring disease or the outcome of treatment (a reference standard) rather than as a therapeutic option itself; the potential benefit of better sensitivity at detecting residual disease would be the ability to avoid the need for SLL altogether (and its concomitant cost and morbidity).

Finally, the prediction of optimal debulking is potentially helpful; for example, patients might benefit by referral to particularly expert surgeons, or to research protocols. Patients unlikely to obtain optimal debulking could be selected for neoadjuvant chemotherapy to improve the likelihood of debulking success; however, this strategy has not been tested.[129] As with tests for response to chemotherapy, there are, as yet, no studies prospectively demonstrating improved patient outcomes from such a strategy.

Summary

Although there is a reasonable amount of data on the association between genomic tests, particularly CA-125, and the likelihood of different clinical outcomes, we did not identify any studies that provided evidence for changes in management leading to improved outcomes based on the results of the tests.

Question 5: Harms of Using Genomic Tests

Question 5 is: What are the harms of using genomic tests for ovarian cancer prevention and management?

Approach

The nature of the potential harms associated with genomic testing in ovarian cancer varies depending on the potential application of the test:

Testing for increased risk of ovarian cancer. Potential harms associated with testing for inherited or acquired genetic changes that are associated with increased risk of ovarian cancer include:

- The harms associated with the management of women who have positive results. These include complications of primary preventive therapy (for example, surgical complications from prophylactic oophorectomy) and sequelae of the therapy (loss of fertility, premature

menopause). For strategies involving more frequent screening, the impact on time and any discomforts associated with the screening test need to be considered.

- The effects on quality of life and other psychological measures of a diagnosis that provides knowledge of an increased risk of disease, with little direct evidence for the benefit of management strategies.

- The potential impact on decisions about childbearing for inherited mutation.

Screening for early ovarian cancer, diagnosis of ovarian cancer. The main potential harm associated with the use of genomic tests for screening for ovarian cancer or for the diagnosis of ovarian cancer is the risk of a false-positive test result, with potential for anxiety about the diagnosis, as well as the risks of definitive diagnostic surgery.[14]

Testing for targets for specific therapy. The main potential harm associated with testing for specific targets is a false-positive result, which would lead to inappropriately exposing a patient to the risks of the targeted treatment, provision of ineffective treatment, and delayed start of potentially more effective therapy.

We searched for studies that described these classes of adverse outcomes for any type of genomic testing, excluding studies covered in previous reviews of the potential harms of screening using CA-125 and BRCA1/2 conducted for the USPSTF,[14,30,31] but including articles published after the inclusion dates for these reviews.

Other Evidence Reports

The review of ovarian cancer screening for the USPSF did not identify any specific articles describing harms of screening, but pointed out the low positive predictive value of available tests and the large number of unnecessary surgeries.[30] The adnexal mass evidence report was unable to draw any conclusions about the potential harms of false-positive surgeries because of limitations in the literature, primarily a failure to distinguish the preoperative indication for surgery from the postoperative findings.[14]

The review of BRCA1/2 testing identified relatively few studies addressing the harms of testing.[31] Only one study reported complications of prophylactic oophorectomy in carriers (4 of 80 women). Quality-of-life studies which involved only prophylactic oophorectomy (as opposed to prophylactic mastectomy with or without oophorectomy) were inconclusive.[31]

Results

We did not identify any articles that specifically described the harms associated with genomic testing for ovarian cancer. In the PLCO study, 62 of 402 women with an elevated CA-125 underwent surgical biopsy; of these, 16 had any neoplasm, with 13 (3.7 percent) having an invasive cancer.[61] The paper did not report whether there were any complications from these surgeries.

We identified four studies of BRCA1/2 testing published since the USPSTF review (see Evidence Table 4, Appendix D*).

McInerney-Leo and colleagues published two papers from the same large study. In the first paper,[130] they reported data on a variety of psychological measures, including depression, self-esteem, and cancer-related distress, in 212 adult members of families with documented BRCA1/2 mutations before and after counseling and possible testing. Intrusive thoughts, depressive symptoms, and breast and ovarian cancer worries improved in subjects with negative test results, but there was no change in those with positive results, or in those who declined testing.

In the second paper, McInerney-Leo and colleagues[131] measured the impact of BRCA1/2 testing on family relationships using a validated index in the same study population. Interestingly, subjects who declined testing had more positive changes than those who accepted testing. In those who accepted testing, there was a non-significant trend towards decreased expressiveness among family members in those who had an abnormal test result.

Two studies reported measures separately for ovarian and breast cancer in women at risk for BRCA1 and BRCA2 mutations. In the first, Bish and colleagues[132] collected data on a variety of quality-of-life measures in 203 subjects undergoing counseling regarding BRCA1 and 2 mutation testing because of family histories, and found that (1) worry about ovarian cancer was significantly less than worry for breast cancer; (2) worry about ovarian cancer was highest in women with a personal history of cancer, independent of the degree of risk or results of testing and (3) there was no overall change in worry about ovarian cancer in response to testing.

Claes and colleagues[133] performed a similar study in 71 similar subjects. As in the Bish study, there were differences in responses by cancer type: risk perception and distress were higher for breast cancer than for ovarian cancer. After testing, distress related to ovarian cancer was higher in carriers then in non-carriers, but was not signficiantly different from baseline levels by 12 months posttesting. Women who underwent prophylactic oophorectomy had decreased levels of concern, but higher levels of somatic symptoms.

Discussion

Only two articles specifically reported outcomes relevant to ovarian cancer. The majority of the available literature focuses on BRCA1/2 testing, but does not report results separately for ovarian and breast cancer outcomes. The differences observed in the studies we did identify suggest that testing for genetic markers of ovarian cancer susceptibility alone may have different implications compared to testing for genes that affect both breast and ovarian cancer risk.

For the most part, the potential harms associated with the use of genomic tests in screening, diagnosis, and management of ovarian cancer are no different than those of other tests, such as imaging: the risks of false-positive results leading to unnecessary and potentially dangerous treatment, as well as the psychological effects of a cancer diagnosis; and the risks of false-negative results leading to delayed diagnosis and therapy, with a potential for a poorer prognosis. The types of risks are similar – the only potential difference between genomic tests and other modalities lies in the quantitative risk of false-negative and false-positive results, which in turn depends on test sensitivity, specificity, and the pretest probability of disease. Higher quality evidence about the test characteristics of genomic tests for ovarian cancer should allow better

* Appendixes cited in this report are provided electronically at http://www.ahrq.gov/clinic/tp/genovctp.htm.

estimation of these types of harms. The one type of test that might have implications similar to those for markers of increased risk would be a test for an inherited polymorphism that affected the likelihood of response to therapy; if such a polymorphism also affected the likelihood of responses or side effects for therapies for other conditions, the longer term implications for the patient and her family would have to be considered.

For tests of markers of increased risk, such as inherited mutations, there are some additional potential harms, namely, the impact of knowledge of increased risk when optimal options for reducing that risk, either through primary or secondary prevention, are unclear. Specifically, in the case of ovarian cancer, bilateral oophorectomy in premenopausal women affects childbearing potential and induces premature menopause; given the uncertainty about optimal methods for hormone replacement, this option may be even more confusing for some women. Because of varying degrees of penetrance, even the estimate of increased risk associated with a given mutation is subject to a fairly wide degree of uncertainty. Issues surrounding heritability in subsequent generations may also be important to some women. In this case, although the literature on BRCA testing is helpful in identifying some of these issues, there is a greater need for providing results specifically for ovarian cancer-related issues in studies of markers which affect the risk of several types of cancers. The available literature suggests that, for most women with BRCA mutations, breast cancer is a greater concern than ovarian cancer. Given the differences in both quantitative risk and the types of risks associated with testing, diagnosis, and prophylaxis, results need to be provided specifically for ovarian cancer-related outcomes in studies of BRCA testing.

Summary

The literature on the harms of genomic tests for ovarian cancer is sparse, with the majority of the available literature on psychological impacts of testing consisting of studies of women tested for susceptibility to both breast and ovarian cancer. Future studies will need not only to identify the short-term psychological impact of different test results, but also provide data on the outcomes of strategies used to reduce the risk of ovarian cancer in patients who undergo testing for susceptibility. The theoretical harms of genomic tests in the setting of screening, diagnosis, and management of ovarian cancer are similar to those for other types of tests and should ultimately be estimated based on better evidence for test characteristics and the effectiveness of management strategies based on test results.

Question 6: Direct-to-Consumer and Direct-to-Physician Marketing

Question 6 is: Has direct-to-consumer and direct-to-physician marketing of genomic tests on ovarian cancer increased the “appropriate” use (as defined by study investigators) of these tests?

Approach

We searched for articles that specifically measured responses by providers and/or patients to direct advertising campaigns. We also considered alternative sources of data on the nature and

volume of direct-to-consumer and direct-to-provider marketing and identified methodological issues involved with utilizing these alternative sources.

Results

We did not identify any articles specifically targeting ovarian cancer genomic testing. We identified two articles that investigated the impact of a single advertising campaign for BRCA1/2 testing, targeted at women at high risk for breast or ovarian cancer.[134,135]

From September 2002 through February 2003, the U.S. manufacturer of BRCA1/2 testing conducted a pilot direct-to-consumer marketing campaign in Atlanta, Georgia, and Denver, Colorado. The campaign was targeted at women aged 25 to 54 with personal or family histories of breast and/or ovarian cancer, along with their healthcare providers. Television, radio, and print advertisements were generated to raise awareness about BRCA1/2 testing and to motivate women to ask their providers about how testing might help assess risk and change management. Providers received information and patient support materials prior to the beginning of the campaign. Although this marketing campaign was not designed as a research study, two groups were able to take advantage of the campaign and design studies to assess the impact of the campaign on test utilization.

In a study conducted by the Centers for Disease Control and Prevention (CDC) and the state health departments of Colorado, Georgia, North Carolina, and Washington,[134] investigators conducted a survey of providers and consumers in the two pilot cities and two comparison metropolitan areas (Raleigh-Durham, NC, and Seattle, WA). From April 21 through May 20, 2004, a 51-question consumer telephone survey was conducted using random telephone numbers, with a target response of 1,600 women. Questions included family history; campaign awareness; interest in genetic testing for BRCA1/2; cancer concerns; and interactions with providers, family, and friends. A 35-question survey and monetary survey were mailed to providers (randomly selected to be proportionately representative of family practice, internal medicine, obstetrics/gynecology, and oncology) on May 1, 2003; the target response was approximately 1,600.

One thousand and six hundred and thirty-five (1,635) women completed the survey, for a response rate of 45 percent; most were non-Hispanic white women with more than high school education and a median age of 40 years. Women in the pilot cities were significantly more likely to have heard of the test, but no significant differences were observed in stated knowledge about genetic testing, concern about risk for breast and ovarian cancer, or proportion of women who had talked with someone about genetic testing. Family histories were similar among those who expressed an increased interest compared to those who did not.

One thousand and fifty-four (1,054) providers completed the survey (66 percent response rate). Providers in pilot cities were significantly more likely to report that they and their patients had been exposed to an advertisement about genetic testing and to report an increase in the number of patients asking about testing, asking for genetic counseling, and requesting testing. The number of tests ordered increased significantly in the pilot cities as well, although the number of referrals for counseling did not increase. Provider knowledge about testing did not differ between cities, but knowledge did differ between specialists, with obstetricians/gynecologists and oncologists having higher levels of knowledge.

Limitations noted by study investigators included lack of data on non-responders; the potential for bias because of the low response rate among consumers; a relatively short lag time

between the advertising campaign and the survey, which might have been insufficient to allow all those interested in testing to undertake and complete the process; lack of availability of data on the number of tests actually performed and the appropriateness of those tests because of the proprietary nature of the tests; and lack of data on the appropriateness of education, counseling, and testing ordered by providers.

A separate study conducted by investigators at Kaiser Permanente Colorado compared utilization of testing before and after the advertising campaign to similar time periods using data from the Henry Ford Health System in Detroit, Michigan.[135] Utilization assessment was through electronic records. The investigators noted a 240 percent increase in the number of referrals for genetic testing in Colorado during the advertising campaign compared to a similar time period 1 year prior to the campaign (from 144 referrals per average membership to 499 referrals per average membership), while no change was seen in Detroit (53 and 52 referrals per average membership during the two time periods).

Interestingly, although the absolute number of women with 10 percent or greater pretest probability of a mutation increased during the advertising campaign, the proportion of all referrals with a high pretest probability decreased from 69 percent to 48 percent in Denver, while no change was seen in Detroit. An increase in referrals from non-physician providers was noted.

The authors noted the difference between self-reported patient behavior in the CDC report and their observations; possible explanations included inaccurate self-report, differences in interest in testing between the general population and women with prepaid access to healthcare, concurrent education efforts by Kaiser Permanente, and discussion among women at workplaces or other settings with common insurance coverage.

Discussion

We identified only two relevant articles on the impact of direct-to-consumer advertising on utilization of genomic tests, both involving the same advertising campaign. One study found evidence of increased awareness of the test covered in the advertising campaign among consumers, but no self-reported increase in knowledge or intention to get tested. Conversely, providers reported the perception of an increased number of patients discussing and requesting testing and reported ordering more tests. The second study used administrative data to measure test utilization within a managed care organization before and after the campaign and found an increase in the number of tests ordered, with a decrease in the proportion of women with a high pretest probability of a mutation.

There are a number of methodological issues involved in assessing the impact of advertising on genetic test utilization:

Definition of "appropriate" use of testing. Possible definitions include:

- Use of the test only in those women with characteristics similar to those for whom the benefit of the test has been conclusively demonstrated, preferably through a randomized trial.

- Use of the test only in those women with characteristics that meet criteria agreed upon by expert consensus.

- Use of the test only in women who receive unbiased counseling on the state of knowledge regarding the benefits and harms of the test and who, based on their personal preferences, wish to have the test.

- Use of the test only in women for whom use of the test is estimated to result in an acceptable cost-effectiveness ratio.

Given the state of the literature on genomic tests in ovarian cancer, consensus opinions on appropriateness are likely to be the only criteria available for the near future.

Measuring test utilization. There are several challenges to measuring test utilization:

- As the CDC researchers noted, data on tests performed in private laboratories may not be publicly available; companies may view these data as proprietary information which, if available, would put them at a disadvantage in a competitive marketplace.

- Test utilization data could be obtained through administrative data, such as from a managed care organization. The ability to link to clinical data could help in estimating "appropriateness" – estimation of pretest probability of BRCA1/2 mutations by the Kaiser researchers is an example of this. However, this type of data is also often proprietary and not readily accessible to outside researchers. In addition, depending on the data source, there may be issues about the generalizability of results, since presumably utilization of tests and other resources would be more tightly constrained within a managed care organization. Also, as the Kaiser researchers point out, women enrolled in managed care plans may be different in many respects from the general population.

Quantifying direct-to-consumer advertising. Challenges to measuring and quantifying direct-to-consumer advertising include:

- Estimating exposure to various advertising in various types of media requires complex survey methodology.

- Measurement of the impact of non-advertising coverage in the media, such as coverage in news reports of scientific meetings, journal publications, or other forums (such as congressional hearings), needs to be considered.

- It is possible that other publicly available information could provide some insight into advertising; for example, annual reports of publicly traded companies might provide a breakdown of marketing expenses, although the extent to which specific inferences could be drawn about the nature of these marketing expenses is unclear.

Quantifying direct-to-physician advertising. Methdological challenges in measuring direct-to-physician advertising include:

- Quantifying advertising in journals would require either hand searches or access to records from a specific journal. This would be particularly difficult for non-peer-reviewed journals, which are frequently not maintained in medical libraries, but which may represent a significant portion of the literature.

- Quantifying other types of "advertising," such as sponsorship of symposia at meetings, exhibits at meetings, sponsorship of continuing education activities at local hospitals, etc.

Study design. Even with a clear definition of "appropriate use" and methods for measuring utilization and advertising, there remain additional methodological issues. For example, although randomized trials would be ideal, it is difficult to imagine how one would be feasible. Before-and-after studies, with "exposed" and control populations, as were done with BRCA1/2 testing, appear to be the most practical, but require considerable planning, including, ideally, advance notice about the advertising campaign.

Summary

There are considerable methodological issues involved in determining the effect of direct-to-consumer and direct-to-physician marketing on the appropriate or inappropriate use of tests. We identified two studies of a single advertising campaign which suggested increased utilization of testing in the near term after a direct-to-consumer campaign, but provided little information on the appropriateness of the testing. The decrease in pretest probability observed after the advertising campaign suggests that, for some types of genomic tests, there may be a decrease in positive predictive value in response to advertising.

Modeling Results

The results presented below represent initial calibration of the natural history models (one assuming that all cancers progress through Stage II, and one allowing direct progression to Stage III from Stage I).

Model Validation

Lifetime cancer incidence and mortality. Figures 8-11 and Table 12 show the results of these calibrations under our two natural history assumptions of disease progression.

Figure 8. Age-specific probability of developing ovarian cancer (assuming Stage II is necessary transition)

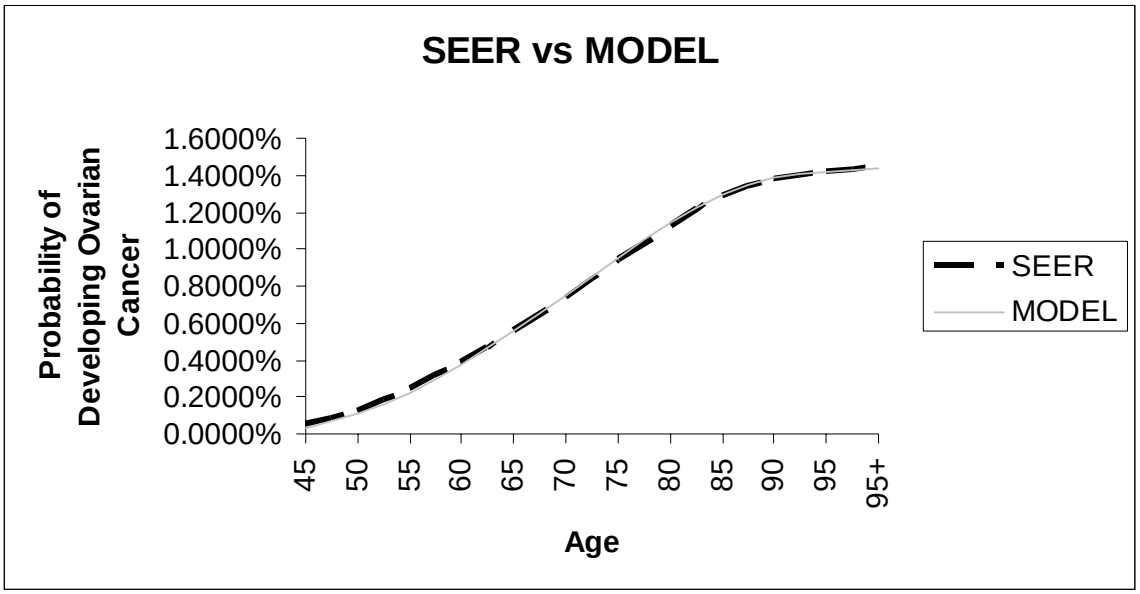


Figure 9. Age-specific probability of dying from ovarian cancer (assuming Stage II is necessary transition)

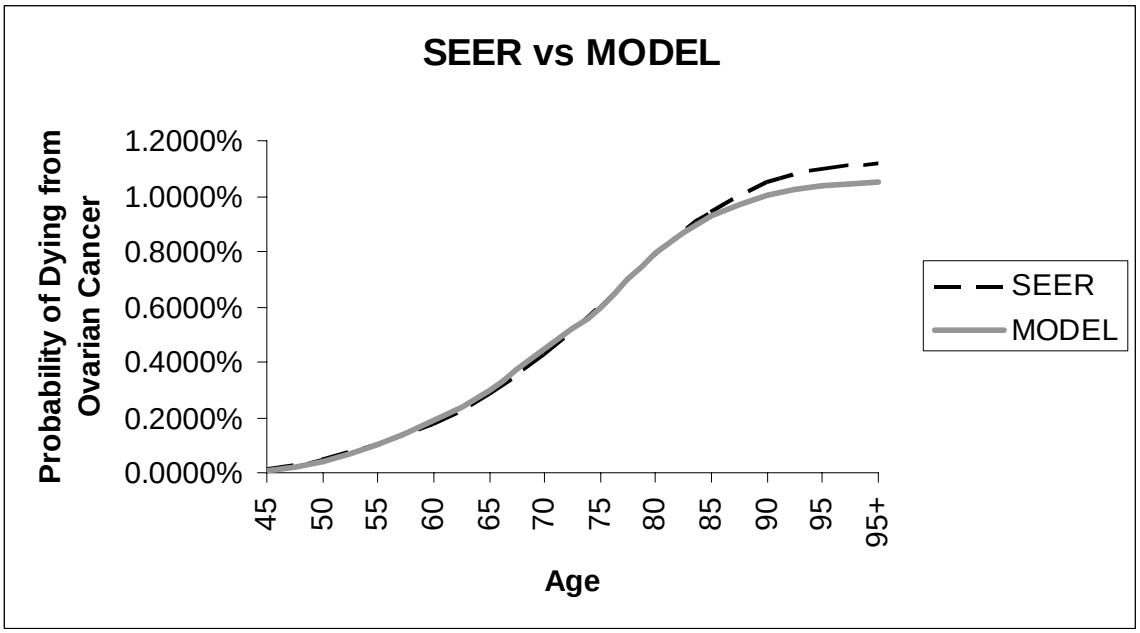


Figure 10. Age-specific probability of developing ovarian cancer (assuming Stage I can transition directly to Stage III)

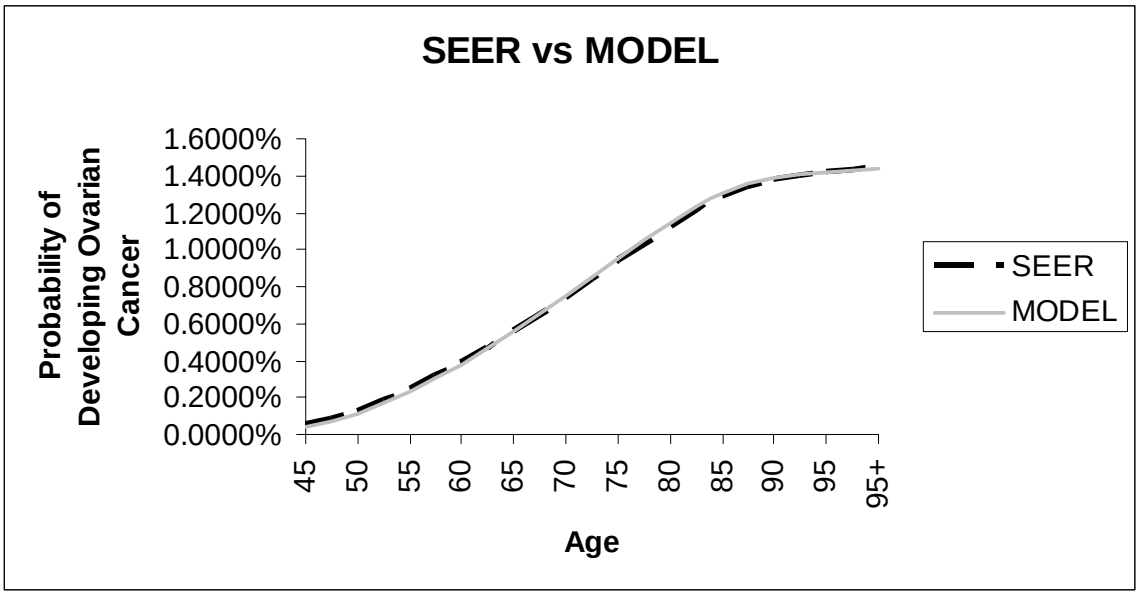
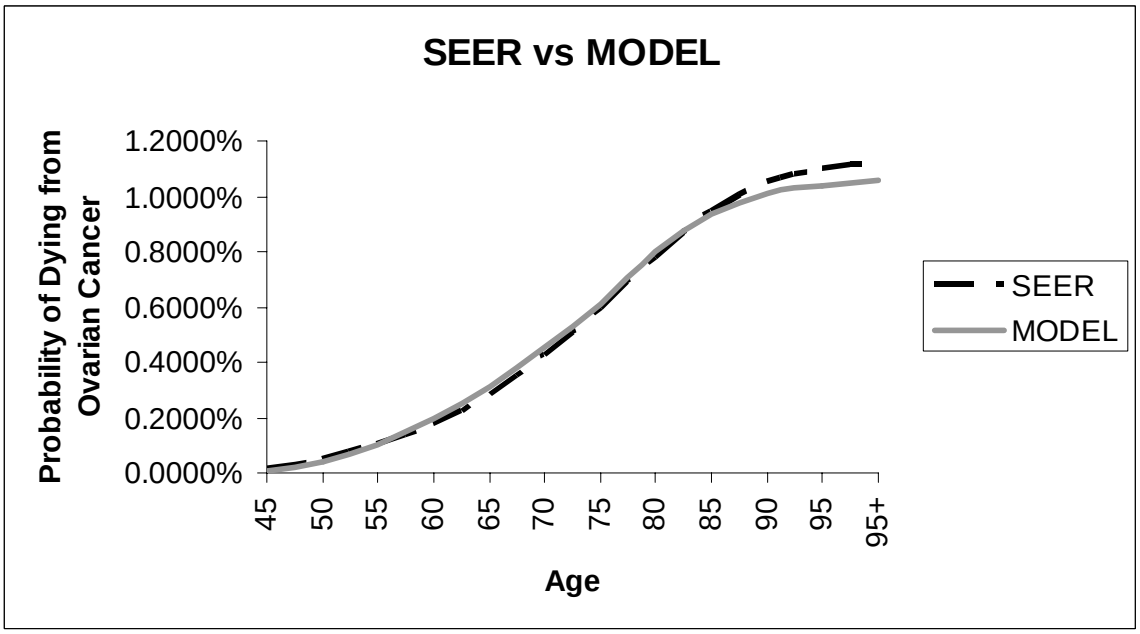


Figure 11. Age-specific probability of dying from ovarian cancer (assuming Stage I can transition directly to Stage III)



Both models closely approximate the Surveillance, Epidemiology, and End Results (SEER) lifetime risk for women at age 40 of 1.44 percent; there is a slight underestimation of mortality risk, primarily for women 85 and older (which is likely due to the assumption of constant stage-specific probability of diagnosis; because of age-specific variations in access to care, prevalence of conditions mimicking ovarian cancer, etc., this assumption may be incorrect). Lifetime risk of

dying from ovarian cancer within the SEER data is 1.13 percent; model predictions are 1.06 percent.

Stage distribution. Table 12 illustrates overall and age-specific stage distributions from SEER and the two models.

Table 12. Overall and age-specific stage distribution of ovarian cancer at diagnosis

Age	Stage I			Stage II			Stage III/IV		
	SEER	Model 1*	Model 2*	SEER	Model 1*	Model 2*	SEER	Model 1*	Model 2*
45-54	25.77%	20.66%	21.18%	8.25%	9.71%	5.81%	65.98%	69.63%	73.02%
55-64	17.71%	19.57%	20.33%	7.29%	9.45%	5.79%	75.00%	70.98%	73.88%
65-74	12.63%	19.14%	19.98%	6.32%	9.34%	5.78%	81.05%	71.53%	74.24%
75+	9.20%	18.83%	19.74%	5.75%	9.26%	5.78%	85.06%	71.91%	74.49%
All ages	16.33%	19.55%	20.31%	6.90%	9.44%	5.79%	76.77%	71.01%	73.91%

* Model 1 assumes that patients must transition from Stage I ovarian cancer through Stage II before progressing to Stage III. Model 2 assumes that some proportion of patients proceed directly to Stage III ovarian cancer from Stage I.

Although many of the parameters of the model are known (stage-specific mortality, age-specific mortality from other causes, etc.), there are several parameters which are "unknowable unknowns." In particular, we can never know with any degree of precision two key variables: (1) the rate at which an ovarian cancer at a given stage will proceed to the next stage; and (2) the probability that, within a given time period, a woman with a given stage of ovarian cancer will have her cancer detected and thus become an incident case. These probabilities must be imputed from available data – we know what the cancer incidence and stage distribution should be, and the values for these "unknowable" parameters are adjusted until a reasonable approximation is achieved. Table 13 shows the current values for these imputed probabilities.

Table 13. Baseline estimates for annual probability of progressing between stages and stage-specific probability of progression

Parameter	Value: Model 1	Value: Model 2
Annual probability of progression		
Stage I to Stage II or III	0.75	0.725
Stage II to Stage III	0.925	0.75
Stage III to Stage IV	0.35	0.35
Proportion of Stage I tumors progressing directly to Stage III	0	0.75
Annual probability of detection		
Stage I	0.25	0.25
Stage II	0.25	0.4
Stage III	0.7	0.7
Stage IV	1	1

The wider variation in stage distribution observed between age groups within the SEER data compared to model predictions may be due to any of several factors:

(1) There may be age-specific variations in the rates of progression between stages; for example, age-related changes in hormonal status or immune function may affect the likelihood of metastasis.

(2) There may be age-specific variations in the rates of detection within stages; for example, older women may have their cancer detected at later stages because of less access to physicians, different thresholds for seeking care for symptoms, or delayed diagnosis because the non-specific symptoms of ovarian cancer frequently mimic other conditions common in older women.

(3) SEER data is cross-sectional, and the model is simulating a cohort. There may be unmeasured cohort effects in exposure to risk factors for ovarian cancer, competing risks, etc., which are not captured.

Future versions of the model will explore these possibilities by allowing the probabilities of progression and detection to vary with age. Allowing either more rapid progression to Stage III/IV or lower probability of detection among older women, in particular, would result in a greater proportion of advanced stage disease and higher mortality rates, and result in a closer match to SEER data. However, the greater "precision" of such an approach must be balanced against the risks of introducing inaccuracies by "overfitting" a cohort model which does not incorporate potential cohort effects into cross-sectional data.

Impact of Different Strategies

In order to compare the relative impact of different strategies and the conditions under which they would be effective, sensitivity analyses were conducted to determine the values for specific parameters that would result in a 20 percent reduction in ovarian cancer mortality. Table 14 summarizes these results.

Table 14. Parameter estimates resulting in 20% reduction in ovarian cancer mortality under different strategies

Strategy	Model 1	Model 2
Primary prevention	Efficacy of primary prevention must be greater than 20%	
Interval screening	Screening (with 95% specific and 90% sensitive test) should be every 33 months or less	Screening (with 95% specific and 90% sensitive test) should be every 31 months or less
Interval screening	Assuming every 2-year screening, sensitivity must be greater than 67%	Assuming every 2-year screening, sensitivity must be greater than 69%
Genetic screening and interval screening of women with the mutation	Assuming every 2-year screening for positive patients, a genetic mutation needs to confer at least a 30x risk increase	Assuming every 2-year screening for positive patients, a genetic mutation needs to confer at least a 32x risk increase

Table 14. Parameter estimates resulting in 20% reduction in ovarian cancer mortality under different strategies (continued)

Strategy	Model 1	Model 2
Genetic screening and interval screening	Assuming every 2-year screening for positive patients, the genetic mutation needs to be prevalent in 60% of the population	Assuming every 2-year screening for positive patients, the genetic mutation needs to be prevalent in 64% of the population
Genetic screening and primary prevention in women with the mutation (effectiveness of primary prevention = 20%)	A genetic mutation needs to confer at least a 30x risk increase	A genetic mutation needs to confer at least a 30x risk increase
Genetic screening and primary prevention in women with the mutation (effectiveness of primary prevention = 20%)	The genetic mutation needs to be prevalent in 51% of the population	The genetic mutation needs to be prevalent in 52% of the population
Targeted treatment	If the targeted treatment reduces cancer mortality by 67% then the targeted risk factor needs to be prevalent in approximately 80% of the population. An 89% reduction would require 35% prevalence of the targeted risk factor.	If the targeted treatment reduces cancer mortality by 67% then the targeted risk factor needs to be prevalent in approximately 89% of the population. An 89% reduction would require 35% prevalence of the targeted risk factor.

Addressing the original questions:

(1) How effective would a primary prevention intervention need to be to reduce ovarian cancer deaths by 20 percent?

Not surprisingly, a primary intervention in the entire population that reduces ovarian cancer incidence by 20 percent should reduce mortality by 20 percent. This level of reduction could be achieved either by an intervention with 20 percent reduction used in 100 percent of the population, or by an intervention with higher efficacy used in a smaller proportion (for example, a 20 percent overall reduction would be achieved by an intervention with 40 percent efficacy used in 50 percent of the population).

(2) What combinations of test sensitivity and frequency result in at least a 20 percent reduction in mortality?

At a sensitivity of 90 percent, screening could be done relatively infrequently (every 33 months) and still result in a predicted decrease of 20 percent in mortality. For biannual screening, sensitivity could be as low as 67 percent.

(3) What combinations of (a) prevalence of a genetic mutation in the population and (b) relative risk associated with that mutation would result in the target 20 percent reduction in ovarian cancer deaths with either primary prevention (at various levels of effectiveness) or interval screening (at varying levels of sensitivity and specificity)?

At a population level, very high relative risks and prevalences are required to have a substantial impact on overall ovarian cancer mortality; primary prevention or screening could, in theory, be highly effective for individuals with the genetic predisposition, but this would have a relatively small impact on overall population mortality.

(4) How effective would a targeted treatment for ovarian cancer need to be (and in what proportion of the population would the marker for that treatment need to exist)? Note that we assume that targeted therapy would be equally effective across all stages of disease.

If the targeted treatment reduces cancer mortality by 67 percent, then the targeted risk factor needs to be prevalent in approximately 80 percent of the population. An 89 percent reduction would require 35 percent prevalence of the targeted risk factor.

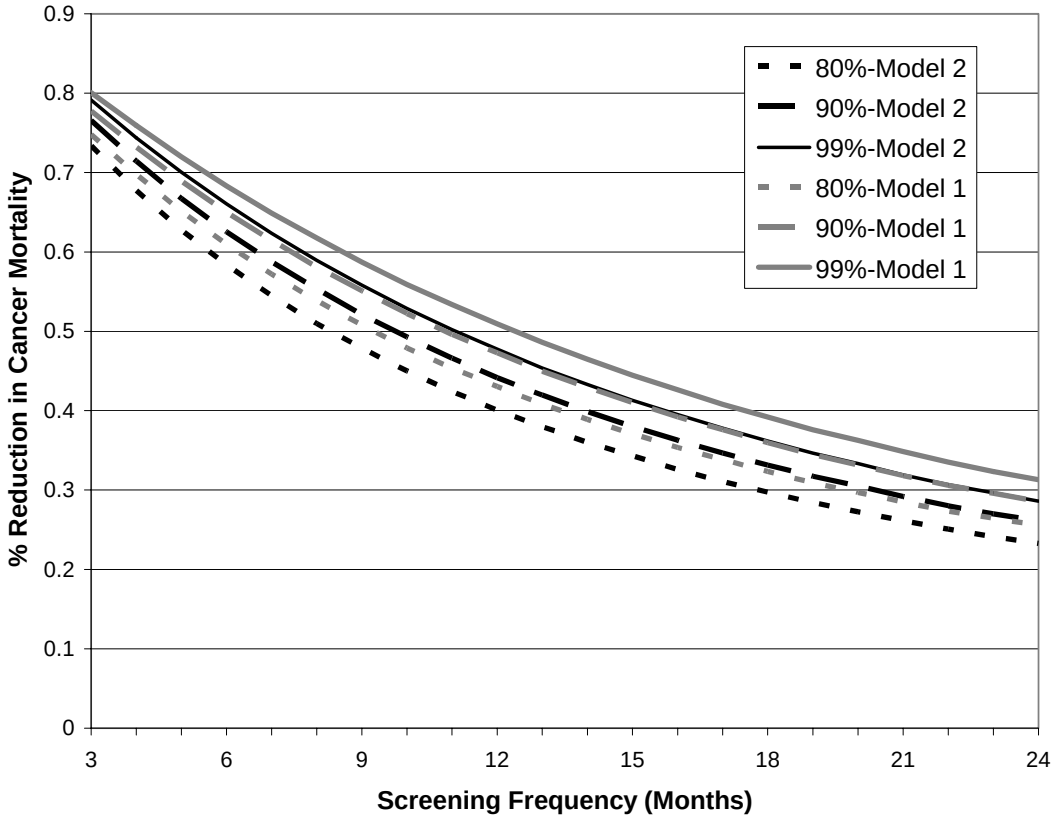
(5) How do the test characteristics for targeted treatment or genetic screening affect the results?

(6) How do the above results differ under the assumption that cancer must progress from Stage I to II (Model 1) and then III versus that assumption that ovarian cancer may progress directly from Stage I to Stage III (Model 2)?

(7) What effect does the assumption about natural history have on the relative efficacy of screening?

Figure 12 illustrates the effect of varying screening intervals at three different levels of test sensitivity, and for the two different models. Reductions of less than 20 percent occur at intervals greater than 30 months.

Figure 12. Effect of screening frequency on reduction in cancer mortality at different levels of test sensitivity



Of note:

- At any given level of sensitivity, Model 1 (which assumes that Stage II is required prior to development of Stage III) results in greater relative reduction in cancer mortality than Model 2, where cancer can progress directly from Stage I to Stage III.

- This difference is relatively small, largely because the duration of Stage II in Model 1 needed to result in stage distributions similar to observed data is short.

- This effect is somewhat ameliorated by decreasing the screening interval (allowing more opportunities to detect the Stage I cancer prior to progression to Stage III).

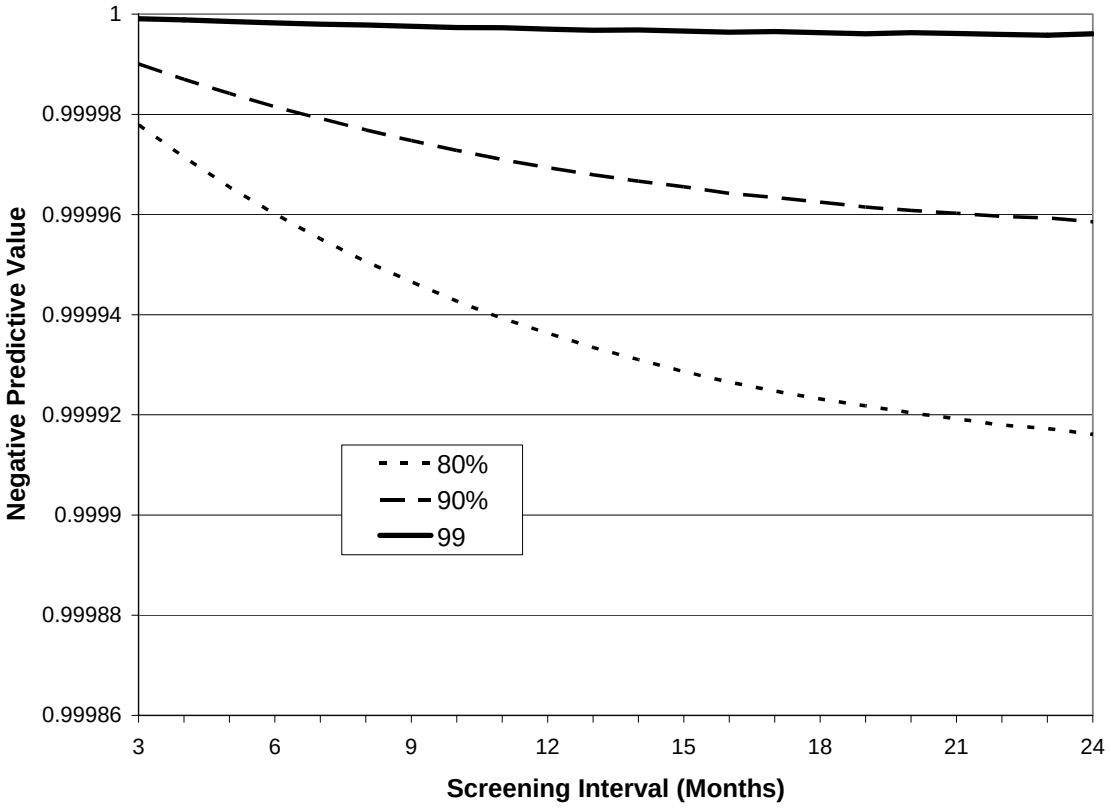
- Under both models, the difference in relative cancer reduction at a screening interval at 12 months between a test with a sensitivity of 80 percent and one with a sensitivity of 99 percent is approximately 7 percent. At any given level of sensitivity, this difference can also be achieved by reducing the screening interval by 3 months.

- Reductions in mortality greater than 50 percent require screening at most every 12 months; at sensitivities below 99 percent, screening needs to be at less than annual intervals.

- The finding that mortality reduction is highly sensitive to screening intervals of less than 12 months, but relatively insensitive to screening intervals between 12 and 30 months, suggests that screening at less frequent intervals is detecting a population of tumors which are relatively indolent (length bias).

Figure 13 illustrates the impact of screening frequency and test sensitivity under the assumptions of Model 2 (some cancers progress directly to Stage III from Stage I) on the lifetime negative predictive value of screening.

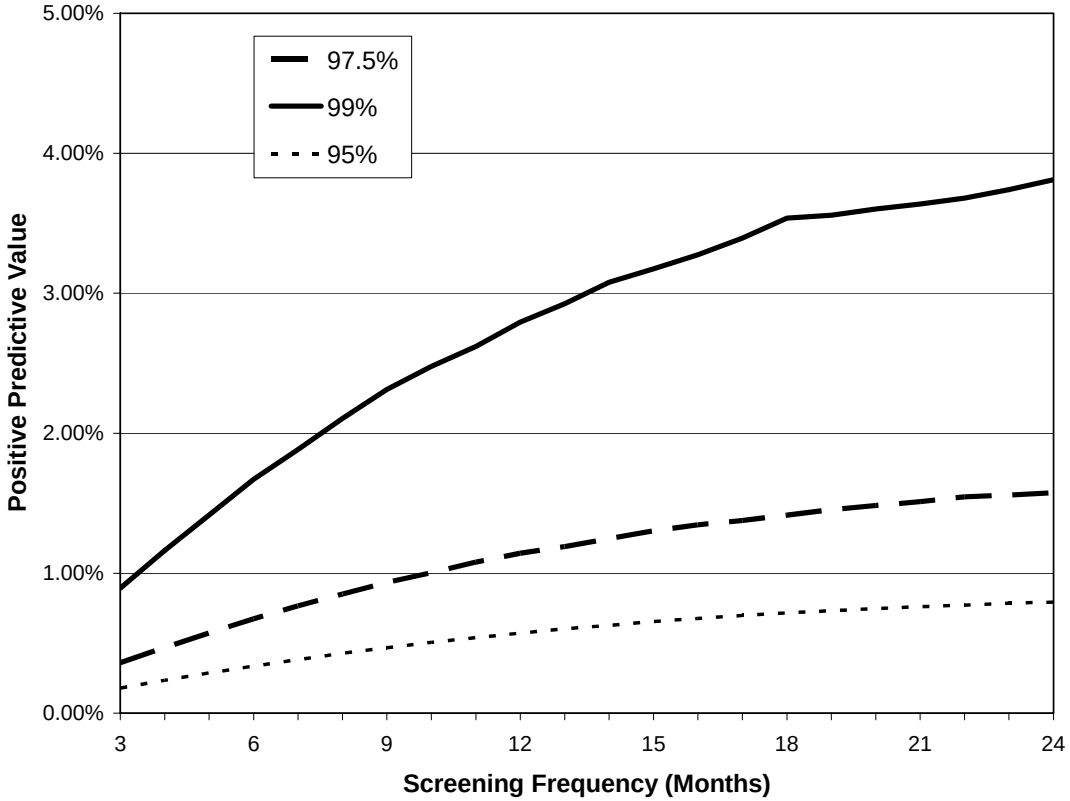
Figure 13. Effect of screening frequency on population negative predictive value at different levels of test sensitivity (specificity fixed at 99%)



Note that, although the relationship between negative predictive value and screening interval increases as test sensitivity decreases, the negative predictive value is still greater than 99.99 percent at a sensitivity of 80 percent with biennial screening; this is due to the relatively rarity of ovarian cancer.

Conversely, positive predictive value over the lifetime of the cohort is quite sensitive to screening frequency (Figure 14).

Figure 14. Effect of screening frequency on population positive predictive value at different levels of test specificity (sensitivity fixed at 99%)



Even at high levels of specificity, the positive predictive value remains below four percent. At the screening frequencies required for 50 percent reduction in mortality, the positive predictive value is less than three percent. Although this does not have a substantial impact on overall mortality, because of the relatively low mortality associated with laparotomy, it does have a substantial impact on the efficiency of screening (Table 15). At intervals of 12 months or less, and specificities less than 97.5 percent, the average woman is guaranteed to have at least one false positive test result over her lifetime. Given the above findings regarding sensitivity and screening frequency, and that there is an almost inevitable tradeoff between sensitivity and specificity, it seems likely that screening with the frequency required to have a substantial impact on mortality will result in a very high number of false-positive results.

Table 15. Estimated lifetime number of false positive results at different screening frequencies and test specificities

Screening interval (months)	Test specificity		
	95%	97.50%	99%
3	8.11	4.05	1.62
6	4.07	2.03	0.81
9	2.72	1.36	0.54
12	2.05	1.02	0.41

Table 15. Estimated lifetime number of false positive results at different screening frequencies and test specificities (continued)

Screening interval (months)	Test specificity		
	95%	97.50%	99%
15	1.64	0.82	0.33
18	1.37	0.69	0.27
21	1.18	0.59	0.24
24	1.04	0.52	0.21

Summary

- The current model closely approximates lifetime cancer incidence, mortality, and stage distribution. Differences between observed and predicted values for age-specific stage distribution and mortality will require further imputation of values for stage-specific progression and detection probabilities.

- Strategies which seek to identify high-risk groups are likely to have relatively small impact on overall ovarian cancer mortality, even if they are highly successful in reducing mortality in the risk group.

- Therapies after diagnosis which are based on genomic targets may reduce mortality substantially, but only if the targets are common and treatment highly effective.

- Reductions in ovarian cancer mortality of greater than 50 percent through screening require testing at intervals of 12 months or less, and are relatively independent of test sensitivity. Conversely, the number of false-positive results is quite high at these screening intervals unless test specificity is quite high.

- These findings suggest that the failure to identify effective strategies for ovarian cancer screening may be due at least in part to the natural history of the disease, rather than the failure of the tests evaluated.

Chapter 4. Discussion

Limitations of the Report

There are several limitations to this evidence report:

- We did not review articles published in languages other than English because of a lack of resources for translation. It is possible that this led to failure to include some relevant studies.

- We did not attempt to perform meta-analysis of specific tests, because of the considerable heterogeneity in design and patient populations.

- Although we attempted to provide some sense of study quality, the validity and reproducibility of measures of study quality is uncertain.

- Many of the key parameters used in modeling ovarian cancer incidence and mortality are unknown, and, in some cases, unknowable. In particular, this is true for the probability of progression between stages, and the probability that a woman with ovarian cancer at a given stage will have her cancer detected on the basis of symptoms. Although the model can be calibrated to provide a good fit to current data, it is possible that choices about the imputed values used for these parameters are incorrect in ways that affect the validity of the model.

- The model is calibrated against reported age-specific incidence. Because the model simulates a cohort but is calibrated against cross-sectional age-specific data, it is possible that cohort effects in important variables, such as exposure to causes of ovarian cancer, exposure to risk modifiers such as pregnancy or contraceptive use, or competing risks such as other cause mortality or oophorectomy rates, play important roles in the observed incidence in specific age groups. Failure to take these into account during calibration may result in errors in the model (this is a common but rarely discussed issue with almost all cohort models of cancer incidence).

Methodological Issues in the Literature

Description of the Patient Population

Many of the issues identified in the evidence report on adnexal mass[14] were found in this literature as well. The majority of the papers reviewed failed to adequately describe the patient population; in particular, for those studies that included women with both benign and malignant ovarian disease, the manner in which the mass was originally detected and the subsequent evaluation can affect the probability of underlying disease, and thus predictive values. Depending on study design, prevalence may also indirectly affect estimates of sensitivity and

specificity, especially in cases where women who have a negative test do not undergo the reference standard evaluation. Thus, even though the performance of a given test may vary depending on whether the patient is symptomatic or asymptomatic, the failure of studies to describe this aspect of their population makes drawing inference about applicability in specific clinical settings difficult.

Another common shortcoming was the failure of many studies to describe potential differences in results stratified by age or menopausal status. Given the clear and widely recognized relationship between age and ovarian cancer risk, as well as the effect of menopausal status on the prevalence of biological processes that may affect the levels of some tumor markers such as cancer antigen 125 (CA-125), we believe that this should be standard in all studies of potential ovarian cancer tests. This is especially true for studies of complex phenomena such as multiple gene or protein expression patterns, where the discovery process is based on identifying differences in patterns between populations; if some of the identified differences between cancer patients and controls in gene expression or protein profiles are in fact differences related to aging, menopausal status, or other processes unrelated to ovarian cancer, the ultimate sensitivity and specificity of tests based on these pattern recognitions may be substantially worse than in preliminary reports.

Sample Size

Few of the studies we reviewed included *a priori* sample size calculations, and use of confidence intervals for parameter estimates was uncommon. Our calculated confidence intervals were, for the most part, quite wide.

Prevalence of Ovarian Cancer in Samples

The majority of the studies we reviewed included prevalence of ovarian cancer of 30 to 60 percent. In a screening setting, this is several orders of magnitude higher than the observed prevalence in screening studies in the U.S. of 0.05 to 0.2 percent.[14] This higher prevalence leads to falsely decreased confidence intervals for the estimates of sensitivity. Even more importantly, as only one author[59] pointed out, this prevalence lowers the positive predictive value of tests to substantially less than 5 percent.

The prevalence in studies of the diagnostic use of a test would be expected to be higher, but, as discussed above, how much higher is dependent on the age, menopausal status, symptom status, etc., of the patient. Failure to describe these characteristics prevents assessment of how closely the study population reflects a likely clinical population.

Stage Distribution within Samples

Given that most ovarian cancer presents in later stages, the stage distribution of samples used for test development and validation is likely to be skewed towards later stages. Any abnormalities identified may be more common in advanced cancers than early cancers; since the goal of screening is to identify early stage (or even preinvasive cancers), the sensitivity for tests derived from these types of samples may be quite lower in real-world settings. This is especially true for tests which identify simultaneous multiple changes in a variety of markers (such as gene

arrays or studies of protein patterns) without a clear understanding of the underlying biological significance of the changes. Changes associated with late stage cancer may not be seen in early cancers.

Biological and Observer Variability in Test Results

Many studies, especially of tests for single gene products, reported measures of assay reproducibility. However, we identified only one series of studies[40,41] that reported on the impact of both test and biological variability on interpretation of test results, in this case the significance of changes in CA-125 levels. Since both test reproducibility and biological variations may affect test characteristics (especially in applications where serial measurements are used to make clinical decisions), documentation of these effects for other tests should be required.

Similarly, for studies of multiple gene or protein expression, demonstration of reproducibility of results by different groups using similar analytic approaches is necessary; the available evidence suggests that reproducibility is still an issue.[55,59]

Use of Tests for Decisionmaking in Management

The majority of the studies we identified on the use of genomic tests in patients already diagnosed with ovarian cancer reported on associations between test results and certain clinical outcomes, such as lack of response to chemotherapy, positive second look laparotomy, or length of overall or disease-free survival. We did not identify any studies which explicitly discussed how these results could be used, let alone any studies which formally tested the impact of use of the tests on patient outcomes. For example, if the results of a genomic test indicate a greater likelihood of failure to respond to standard chemotherapy, should that patient be offered only experimental therapies, or comfort care, rather than undergoing the effects of therapy which is unlikely to work? There are obvious ethical and feasibility issues involved in designing studies of such an approach, but if a patient will undergo the same therapy regardless of the results of the genomic tests, there seems to be little clinical value to performing the test. It is possible that there is some value to the patient and her family in having greater information about the probability of various outcomes, even if therapy is not affected, but this should be demonstrated using appropriate study designs and instruments.

Selection of Cases and Controls in Initial Test Development

The most common approach to initial test development in the studies we reviewed was to use serum or tissue from patients with cancer and compare results to a comparison group with no disease, or with non-ovarian cancer disease. In some cases, an attempt was made to discriminate between normal women, women with early stage ovarian cancer, and women with late stage ovarian cancer, in the hopes of identifying markers of early stage disease.

There are several implicit assumptions involved with this type of study design:

- If attempts are not made to discriminate between stages, then the assumption is that all cancers, regardless of stage, exhibit a similar pattern. However, if there are changes in

gene and/or protein patterns which are associated with advancing stage, failure to examine differences between stages may affect test accuracy.

- If stages are examined differently, then the assumption is that all of the advanced stage cancers must have "looked" like the early stage cancers at some point. However, if "early" stage cancers represent cancers which are biologically different, rather than an early, necessary step in the development of ovarian cancer,[136] then identification of markers of early stage cancer may not result in substantial reductions in mortality.

- There are no other factors other than ovarian cancer itself which can explain observed differences between cancers and controls. The effect of potential confounders such as age, menopausal status, or other factors on gene or protein patterns would affect test specificity substantially.

Ultimately, the ideal approach is to use prospectively collected sera to attempt to identify markers for those patients who subsequently developed advanced stage ovarian cancer, an approach which may be achievable in some of the large ongoing studies of ovarian cancer screening.[137]

Natural History of Ovarian Cancer

The search for better screening tests for ovarian cancer has been based on the implicit assumption that ovarian cancer progresses through a series of stages in a fashion analogous to that of cervical cancer. Alternative models are biologically plausible, and, as demonstrated by our simulation models, mathematical models can be "fitted" to match reported data under both alternatives. Our modeling suggests that, even under a model that assumes that all cancers progress through Stage II, screening at intervals more frequent than every 12 months is needed to reduce mortality by greater than 50 percent, even with a highly sensitive test, and that such screening would have a very low positive predictive value, even with a highly specific test.

If this is the case, then alternative methods for reducing ovarian cancer morbidity and mortality, such as improved methods for primary prevention and improved therapies, may ultimately offer more promise than the search for the Pap test equivalent in ovarian cancer.

Implications of Findings

Question 1 (Analytic Validity)

With the exception of studies of radioimmunoassay, there is little available literature on the analytic validity of genomic tests for ovarian cancer, especially for use in commercial or clinical laboratories.

Question 2 (Sensitivity and Specificity)

Sensitivity and specificity of genomic tests in clinical practice are difficult to estimate, since there have been few well-designed studies in typical clinical situations, and estimates for available tests have wide confidence intervals. In particular, studies of proteomic tests have not been performed in realistic clinical scenarios; even with high specificity, positive predictive values in a screening setting are likely to be very low.

Question 3 (Clinical Management of Asymptomatic Women)

We did not identify any articles which provided evidence on the use of genomic tests in asymptomatic women.

Question 4 (Clinical Management of Diagnosed Women)

Although we identified articles reporting an association with various genomic test results and different clinical outcomes, we did not identify any studies which evaluated any change in management based on those test results.

Question 5 (Potential Harms)

The potential harms of genomic testing fall into two categories: (1) those related to identification of inherited susceptibility to ovarian cancer, which include the psychological impact of test results, decisionmaking regarding reproduction, and decisionmaking regarding prophylaxis; and (2) those related to test results in a screening, diagnostic, or clinical setting, which primarily include the risks of diagnosis for false-positive results and the risks of delayed or inappropriate treatment of false-negative results. We did not identify any studies of the potential harms of testing for genetic susceptibility for genes uniquely associated with ovarian cancer; data from two small studies suggest that, among women at risk for breast cancer gene 1/2 (BRCA1/2) mutations, psychosocial/quality-of-life implications of testing are different for ovarian cancer compared with breast cancer. We also did not identify any literature on the harms of the use of genomic testing in screening, diagnosis, and treatment. Conceptually, there is no reason to think that these harms would be qualitatively any different for genomic tests than for other modalities such as pelvic examination, CA-125, or ultrasound; any differences between genomics-based tests and other would lie in the quantitative risks of false-positive and false-negative results.

Question 6 (Direct Marketing)

We identified two studies on the impact of direct-to-consumer advertising for BRCA1 and 2 testing for susceptibility to both breast and ovarian cancer, which suggested increased utilization by both physicians and patients. Although one of the studies suggested that there was an increased use of the test among lower-risk women (as evidenced by a decrease in test positive predictive value), it is unclear whether this was truly “inappropriate.”

Modeling

We were able to closely approximate reported ovarian cancer incidence and mortality using a simulation model. This model can be used to identify test and treatment characteristics that would result in substantial reductions in ovarian cancer mortality. The most striking finding of the model is that the effect of screening frequency in achieving large-scale reductions in ovarian cancer mortality is greater than that of test sensitivity; achieving mortality reductions greater than 50 percent requires screening frequencies of less than 12 months. This is problematic for several reasons. First, a pilot study suggests that women are unlikely to be compliant with more frequent screening intervals.[138] Second, more frequent screening results in lower overall positive predictive value, even with a highly specific test. Finally, if effective primary prevention strategies are identified which lower the incidence of ovarian cancer, the positive predictive value of screening will be lowered to an even larger extent.

Chapter 5. Future Research

This chapter outlines research priorities identified through the review, both in terms of fundamental gaps in knowledge and in addressing methodological issues in existing studies.

Minimal Data Reporting

We suggest that future studies relevant to screening and diagnosis provide data on, and present results stratified by, the following minimal subject characteristics:

- Subject age and/or menopausal status;
- Subject race and ethnicity;
- Presence or absence of known risk factors for ovarian cancer, particularly family history;
- For subjects with cancer or adnexal masses, the means by which the mass was initially diagnosed;
- For subjects with cancer or adnexal masses, the reason for the initial examination which led to diagnosis of a mass: symptoms referable to a mass or ovarian cancer, evaluation for other symptoms, asymptomatic screening for ovarian cancer, or asymptomatic screening for other conditions.

We recognize that, when using large databases for initial analysis, such as those used in many early proteomics studies, such detail may not be available; however, researchers should recognize and discuss the potential biases introduced by these factors.

Test Reproducibility

- Data on test reproducibility – such as coefficients of variation, inter- and intra-observer agreement, or concordance of results across laboratories – should be consistently reported or referenced.
- Whenever possible, the potential impact of this reproducibility on test characteristics should be estimated. For example, given a coefficient of variation of some percent, what proportion of test results will fall on the other side of the threshold between positive and negative due to chance alone?
- The potential impact of reproducibility on interpretation of serial test results should also be estimated where appropriate.

Biological Variability

- The effect of variation with time, either randomly or in relation to cyclic changes such as the menstrual cycle, should also be reported for tests which have potential use as serial markers.

- Any variability due to age, menopausal status, or other biological processes should be tested for and noted.

Test-Negative Subjects

- Since in many studies "control" patients never undergo the reference standard (histological examination of the ovaries), there is the potential for verification bias. Although, given the relatively low incidence of ovarian cancer, the probability of misclassification is fairly low, studies should ideally have some followup on test-negative subjects to ensure that ovarian cancer has not developed within a short time after the test was performed.

Evaluation of Tests

- Ultimately, tests need to be evaluated based on their intended use and at the stage in the clinical pathway where they will be used. Therefore, potential screening tests must be evaluated in screening settings, with a realistic underlying prevalence of cancer. Similarly, potential diagnostic tests must be tested in settings where there is uncertainty about the diagnosis of ovarian cancer.

- Ideally, test characteristics for a variety of tests will be compared within the same study population, in order to avoid the inherent difficulties of comparing results across studies. At a minimum, given that the performance characteristics of cancer antigen 125 (CA-125) are well established, new tests should be directly compared to CA-125.

- Although retrospective studies based on sera or other tissues are useful for establishing estimates of test performance for sample size considerations, new screening and diagnostic tests need to be evaluated prospectively. For example:

    - For screening tests, prospective demonstration of at least one important outcome, such as (a) reduced ovarian cancer-specific mortality, or (b) improved quality of life as documented by a validated instrument. Ideally, this would be done via randomized trials; however, alternative study designs (such as prospective cohort studies with appropriate adjustment for potential confounders) are reasonable for rarer primary outcomes (such as ovarian cancer mortality). In the screening context, given the relatively low positive predictive value of any screening test, documenting the effect of the test on overall quality of life at the population level should be easily demonstrated within the context of a randomized trial.

- Evaluation of the use of tests in predicting outcomes must ultimately be linked to some change in patient outcomes; at the least, there should be some measure of the value of the information gained from the test result is helpful in some way to the patient. Ideally, the effect of changes in management based on test results should be evaluated in properly designed studies. For example:

    - For tests which appear to reliably predict failure to respond to conventional therapies, studies should prospectively document improved patient outcomes based on this knowledge (such as improved quality of life based on more precise prognosis, or improved quality of life due to avoidance of side effects from ineffective therapy). Ideally, this would be based on randomized trials – patients could be randomized to testing with treatment based on test results, versus no testing; alternatively, testing could be done, with randomized allocation to usual care versus no care for those with test results predicting poor response.

    - For tests which predict greater response to specific agents, improved survival and quality of life need to be documented using randomized trials of those agents in those with specific test results.

Natural History of Ovarian Cancer

- Underlying assumptions about the natural history of ovarian cancer can have a large effect on the estimated impact of screening compared to other strategies for prevention of ovarian cancer morbidity and mortality. Every effort should be made towards a better understanding of whether ovarian cancer "behaves" like cervical cancer in the sense of progressing through different stages, or whether rapid progression is the most common biological behavior.

- The implications of these assumptions on the relative efficacy of screening compared to other strategies needs to be evaluated by more sophisticated simulation models.

Chapter 6. Conclusions

Ovarian cancer remains a significant cause of morbidity and mortality in women, and efforts at reducing its toll have been relatively unsuccessful, especially when compared with other causes of cancer death in women. Unlike lung cancer or cervical cancer, there does not appear to be a common causal exposure which can be addressed through various public health interventions; unlike cervical, breast, or colorectal cancer, effective screening methods have not yet been identified; unlike breast cancer, markers of response to specific treatments have not yet been discovered and proven to improve patient outcomes.

The ever-increasing knowledge of the role of genes in health and disease offers the promise of greater understanding of the biology of ovarian cancer, and evidence-based strategies for prevention based on that understanding. Understanding of the causal mechanisms could potentially lead to population-based primary prevention strategies which preserve ovarian function, while identification of markers of increased risk in addition to breast cancer genes 1/2 (BRCA 1/2) offers the potential for more radical preventive measures such as prophylactic oophorectomy. Improved understanding of the molecular changes leading to cancer may lead to screening tests of very high sensitivity and specificity. Identification of markers of response to therapy could lead to improved survival, or reduced side effects from current treatment.

Unfortunately, our review found that there is limited evidence for the utility of genomic tests other than cancer antigen 125 (CA-125) or BRCA1/2 in the prevention of ovarian cancer. Other than commercially approved radioimmunoassay tests for single gene products, there is little available literature on the analytic validity of potential genomic tests in typical clinical laboratories. There are almost no data on the sensitivity and specificity of genomic tests for screening or diagnosis in clinically realistic settings. Although results of some genomic tests have been shown to be associated with certain outcomes of treatment, there are no data on how changes in management based on those test results would lead to improved patient outcomes.

New genomic tests do not appear to have any qualitative risks beyond those of other tests for inherited susceptibility for cancer, or other tests used in screening, management, and treatment. Depending on the ultimate sensitivity and specificity of the tests in typical practice, the quantitative probability of these harms may differ from existing tests.

The use of direct-to-consumer advertising has the potential to increase utilization of these tests, but, in the absence of criteria for “appropriate use,” it is unclear how to evaluate this increased utilization.

Ultimately, the clinical utility of genomic tests in the prevention of morbidity and mortality from ovarian cancer will depend not only on the sensitivity and specificity of a given test in a specific clinical situation, but on the underlying natural history of ovarian cancer. If the biological features of ovarian cancer predispose most cancers to rapid dissemination within the abdominal cavity, then strategies which emphasize primary prevention and/or improved treatment efficacy may ultimately be more effective than the most sensitive and specific test.

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List of Acronyms/Abbreviations

AHRQ	Agency for Healthcare Research and Quality
β-hCG	Beta human chorionic gonadotropin
Bcl-2	(Anti-apoptosis protein)
BRCA1/2	Breast cancer gene 1/2
CA-125	Cancer antigen 125
CA-15-3	Cancer antigen 15-3
CA-19-9	Cancer antigen 19-9
CA-27-29	Cancer antigen 27-29
CA-72-4	Cancer antigen 72-4
CASA	Cancer-associated serum antigen
CDC	Centers for Disease Control and Prevention
CEA	Carcinoembryonic antigen
c-erb-B2	(Same as HER-2)
c-erb-2	(Same as HER-2)
CI	Confidence interval
CK19	Cytokeratin 19
CYFRA 21-1	Cytokeratin fragment 21
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
EGFR	Epidermal growth factor receptor
FAS	Fatty acid synthase
FIGO	International Federation of Obstetrics and Gynecology
GAT	Galactosyltransferase associated with tumor
G-CSF	Granulocyte-colony stimulating factor
HE4	Human epididymis protein 4
HER-2	Human epidermal growth factor receptor 2
hK6	Human kallikrein 6
hK10	Human kallikrein 10
IL-2	Interleukin 2
IL-6	Interleukin 6
IL-8	Interleukin 8
LASA	Lipid-associated sialic acid
LMP	Low malignant potential
LRP	Low-density lipoprotein receptor-related protein
LSA	Lysophospholipids
M-CSF	Macrophage colony stimulating factor
Mdm2	Murine double minute protein
MDR-1	Multidrug resistance gene 1
MeSH	Medical Subject Headings
MMP	Matrix metalloproteinases
MRP1/2	Multidrug resistance protein 1/2
MW	Molecular weight
M/Z	Mass-to-charge
nm23	(Metastasis suppressor)
OVX1	(Monoclonal antibody raised against a human ovarian carcinoma cell line)

p53	(Transcription factor)
p55, p75	(Tumor necrosis factor receptors)
Pgp	P-glycoprotein
PLCO	Prostate, Lung, Colon, and Ovarian screening trial (National Cancer Institute)
RCT	Randomized controlled trial
RIA	Radioimmunoassay
ROC	Receiver operating characteristic
SAX2	Strong anionic exchanger
SEER	Surveillance, Epidemiology, and End Results
SELDI-TOF	Surfance-enhanced laser desorption inonization time-of-flight
SLL	Second-look laparotomy
SVM-GA	Support vector machine with genetic algorithm
SVM-ST	Support vector machine statistical testing
TATI	Tumor-associated trypsin inhibitor
TN	Tetranectin
TP53	(Same as p53)
TPA	Tissue plasminogen activator
TPS	Tissue polypeptide-specific antigen
USCS	United States Cancer Statistics
USPSTF	U.S. Preventive Services Task Force
VEGF	Vascular endothelial growth factor
WCX2	Weak cationic exchanger

APPENDIXES

Appendix A: Exact Search String

Database: Ovid MEDLINE® <1966 to May Week 2 2006>
Search Strategy:
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1. liotta l$.au.
2. Ovarian Neoplasms/
3. 1 and 2
4. exp Ovarian Neoplasms/
5. exp Genomics/
6. exp Genetic Phenomena/
7. ovacheck.mp.
8. myriad.mp.
9. Chorionic Gonadotropin, beta Subunit, Human/
10. GENES, BRCA1/ or BRCA1 PROTEIN/
11. GENES, BRCA2/ or BRCA2 PROTEIN/
12. CA-125 Antigen/
13. Antigens, Tumor-Associated, Carbohydrate/
14. Carcinoembryonic Antigen/
15. Receptor, erbB-2/
16. Tumor Markers, Biological/
17. Antigens, Neoplasm/
18. 4 and (or/5-17)
19. correlogic.mp.
20. 4 and (or/5,7-17)
21. 18 not 20
22. limit 20 to (humans and english language and abstracts)
23. exp Diagnosis/
24. exp "Sensitivity and Specificity"/
25. di.fs.
26. 22 and (or/24-25)
27. 3 and 26
28. 3 and 22
29. 3 not 28
30. 28 not 27
31. *"Proteome"/
32. oligonucleotide array sequence analysis/ or protein array analysis/
33. 4 and (or/5,7-17,32)
34. 33 not 20
35. 3 and 34
36. 2 and (or/5,7-17,32)
37. *ovarian neoplasms/
38. 37 and (or/5,7-17,32)
39. 2 and (or/7-8,19,32)

40. 3 and 39
41. 39 not 26
42. 3 not 26
43. 41 or 42
44. limit 43 to (humans and english language)
45. limit 44 to abstracts
46. from 45 keep 1-10
47. from 45 keep 1-167
48. "Reproducibility of Results"/
49. reference standards/
50. quality control/
51. reference values/
52. or/48-51
53. 52 and (or/5,7-17,19,32) and 4
54. 52 and (or/5,7-17,19,32) and 4
55. 52 and (or/5,7-17,19,32)
56. Genetic Screening/
57. Genetic Counseling/
58. 4 and (or/56-57)
59. limit 58 to (humans and english language and abstracts)
60. 59 not (26 or 45)
61. 54 not (26 or 45)
62. limit 61 to (humans and abstracts)
63. genes, brca1/ or genes, brca2/
64. 60 not 63
65. 60 not 64
66. from 64 keep 1-155
67. from 62 keep 1-76

Appendix B: List of Excluded Studies

All excluded studies listed below were reviewed in their full-text version. Following each reference, in italics, is the reason for exclusion. Reasons for exclusion signify only the usefulness of the articles for this study and are not intended as criticisms of the articles.

Abendstein B, Daxenbichler G, Windbichler G, et al. Predictive value of uPA, PAI-1, HER-2 and VEGF in the serum of ovarian cancer patients. Anticancer Res 2000;20(1B):569-72. *Exclude: non-specific general prognosis.*

Adib TR, Henderson S, Perrett C, et al. Predicting biomarkers for ovarian cancer using gene-expression microarrays. Br J Cancer 2004;90(3):686-92. *Exclude: cell line only.*

Afify AM, al-Khafaji BM. Diagnostic utility of thyroid transcription factor-1 expression in adenocarcinomas presenting in serous fluids. Acta Cytol 2002;46(4):675-8. *Exclude: no 2x2 table.*

Afify AM, Ferguson AW, Davila RM, et al. Expression of CD44S and CD44v5 is more common in stage III than in stage I serous ovarian carcinomas. Appl Immunohistochem Mol Morphol 2001;9(4):309-14. *Exclude: denominator NOT patients.*

Ahmed N, Oliva KT, Barker G, et al. Proteomic tracking of serum protein isoforms as screening biomarkers of ovarian cancer. Proteomics 2005;5(17):4625-36. *Exclude: no 2x2 table.*

Ahmed N, Riley C, Rice GE, et al. Alpha(v)beta(6) integrin-A marker for the malignant potential of epithelial ovarian cancer. J Histochem Cytochem 2002;50(10):1371-80. *Exclude: denominator NOT patients.*

Akahiro J, Konno R, Ito K, et al. Impact of serum interleukin-18 level as a prognostic indicator in patients with epithelial ovarian carcinoma. Int J Clin Oncol 2004;9(1):42-6. *Exclude: no 2x2 table.*

Ala-Fossi SL, Aine R, Punnonen R, et al. Is potential to produce inhibins related to prognosis in ovarian granulosa cell tumors? Eur J Gynaecol Oncol 2000;21(2):187-9. *Exclude: only germ cell or stromal.*

Alexe G, Alexe S, Liotta LA, et al. Ovarian cancer detection by logical analysis of proteomic data. Proteomics 2004;4(3):766-83. *Exclude: mathematical model.*

Ali-Fehmi R, Che M, Khalifeh I, et al. The effect of cyclooxygenase-2 expression on tumor vascularity in advanced stage ovarian serous carcinoma. Cancer 2003;98(7):1423-9. *Exclude: no 2x2 table.*

Altavilla G, Marchetti M, Padovan P, et al. Predictive value of proliferative cellular nuclear antigen (PCNA) and Ki-67 antigen in advanced stage serous papilliferous ovarian cancer. Eur J Gynaecol Oncol 1996;17(6):524-8. *Exclude: prognosis only, no link to mgmt or outcomes.*

Altevogt P, Fogel M. The role of L1 in the progression of ovarian carcinomas. Zentralbl Gynakol 2004;126(5):323-5. *Exclude: relevant review.*

Alvarez Secord A, Sayer R, Snyder SA, et al. The relationship between serum vascular endothelial growth factor, persistent disease, and survival at second-look laparotomy in ovarian cancer. Gynecol Oncol 2004;94(1):74-9. *Exclude: no 2x2 table.*

Andersen MR, Nelson J, Peacock S, et al. Worry about ovarian cancer risk and use of screening by high-risk women: how you recruit affects what you find. Am J Med Genet A 2004;129(2):130-5. *Exclude: Background only.*

Antonic J, Rakar S. Validity of colour and pulsed Doppler US and tumour marker CA 125 in differentiation between benign and malignant ovarian masses. Eur J Gynaecol Oncol 1996;17(1):29-35. *Exclude: no 2x2 table.*

Aranganathan S, Senthil K, Nalini N. A case control study of glycoprotein status in ovarian carcinoma. Clin Biochem 2005;38(6):535-9. *Exclude: no 2x2 table.*

Aris VM, Cody MJ, Cheng J, et al. Noise filtering and nonparametric analysis of microarray data underscores discriminating markers of oral, prostate, lung, ovarian and breast cancer. BMC Bioinformatics 2004;5(1):185. *Exclude: denominator NOT patients.*

Arnold JM, Cummings M, Purdie D, et al. Reduced expression of intercellular adhesion molecule-1 in ovarian adenocarcinomas. Br J Cancer 2001;85(9):1351-8. *Exclude: cell line only.*

Arslan AA, Zeleniuch-Jacquotte A, Lundin E, et al. Serum follicle-stimulating hormone and risk of epithelial ovarian cancer in postmenopausal women. Cancer Epidemiol Biomarkers Prev 2003;12(12):1531-5. *Exclude: not diagnostic test.*

Attanoos RL, Webb R, Dojcinov SD, et al. Value of mesothelial and epithelial antibodies in distinguishing diffuse peritoneal mesothelioma in females from serous

papillary carcinoma of the ovary and peritoneum. Histopathology 2002;40(3):237-44. *Exclude: pathology study.*

Auranen A, Grenman S, Kleml PJ. Immunohistochemically detected p53 and HER-2/neu expression and nuclear DNA content in familial epithelial ovarian carcinomas. Cancer 1997;79(11):2147-53. *Exclude: no 2x2 table.*

Ayhan A, Ertunc D, Tok EC, et al. Expression of the c-Met in advanced epithelial ovarian cancer and its prognostic significance. Int J Gynecol Cancer 2005;15(4):618-23. *Exclude: no 2x2 table.*

Baekelandt M, Holm R, Nesland JM, et al. Expression of apoptosis-related proteins is an independent determinant of patient prognosis in advanced ovarian cancer. J Clin Oncol 2000;18(22):3775-81. *Exclude: non-specific general prognosis.*

Baekelandt MM, Holm R, Nesland JM, et al. P-glycoprotein expression is a marker for chemotherapy resistance and prognosis in advanced ovarian cancer. Anticancer Res 2000;20(2B):1061-7. *Exclude: non-specific general prognosis.*

Bajetta E, Di Leo A, Biganzoli L, et al. Phase II study of vinorelbine in patients with pretreated advanced ovarian cancer: activity in platinum-resistant disease. J Clin Oncol 1996;14(9):2546-51. *Exclude: unrelated.*

Bandopadhyay M, Ganguly AK. Putrescine, DNA, RNA and protein contents in human uterine, breast and rectal cancer. J Postgrad Med 2000;46(3):172-5. *Exclude: denominator NOT patients.*

Banks RE, Gearing AJ, Hemingway IK, et al. Circulating intercellular adhesion molecule-1 (ICAM-1), E-selectin and vascular cell adhesion molecule-1 (VCAM-1) in human malignancies. Br J Cancer 1993;68(1):122-4. *Exclude: no OVCA-specific data.*

Barbati A, Mariani L, Porpora MG, et al. Serum evaluation of P53 protein in patients with gynaecological cancer. Anticancer Res 2000;20(2A):1033-5. *Exclude: no 2x2 table.*

Barbieri F, Lorenzi P, Ragni N, et al. Overexpression of cyclin D1 is associated with poor survival in epithelial ovarian cancer. Oncology 2004;66(4):310-5. *Exclude: prognosis only, no link to mgmt or outcomes.*

Bard MP, Hegmans JP, Hemmes A, et al. Proteomic analysis of exosomes isolated from human malignant pleural effusions. Am J Respir Cell Mol Biol 2004;31(1):114-21. *Exclude: N=1 case report.*

Baron AT, Lafky JM, Boardman CH, et al. Serum sErbB1 and epidermal growth factor levels as tumor biomarkers in women with stage III or IV epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev 1999;8(2):129-37. *Exclude: prognosis only, no link to mgmt or outcomes.*

Baron-Hay S, Boyle F, Ferrier A, et al. Elevated serum insulin-like growth factor binding protein-2 as a prognostic marker in patients with ovarian cancer. Clin Cancer Res 2004;10(5):1796-806. *Exclude: no 2x2 table.*

Barton DP, Blanchard DK, Michelini-Norris B, et al. High serum and ascitic soluble interleukin-2 receptor alpha levels in advanced epithelial ovarian cancer. Blood 1993;81(2):424-9. *Exclude: no 2x2 table.*

Bayani J, Brenton JD, Macgregor PF, et al. Parallel analysis of sporadic primary ovarian carcinomas by spectral karyotyping, comparative genomic hybridization, and expression microarrays. Cancer Res 2002;62(12):3466-76. *Exclude: cell line only.*

Bellotti T, Luo Z, Gammerman A, et al. Qualified predictions for microarray and proteomics pattern diagnostics with confidence machines. Int J Neural Syst 2005;15(4):247-58. *Exclude: no 2x2 table.*

Ben-Arie A, Hagay Z, Ben-Hur H, et al. Elevated serum alkaline phosphatase may enable early diagnosis of ovarian cancer. Eur J Obstet Gynecol Reprod Biol 1999;86(1):69-71. *Exclude: N=1 case report.*

Ben-Hur H, Gurevich P, Ben-Arie A, et al. Apoptosis and apoptosis-related proteins (Fas, Fas ligand, bcl-2, p53) in macrophages of human ovarian epithelial tumors. Eur J Gynaecol Oncol 2000;21(2):141-5. *Exclude: cell line only.*

Berchuck A, Iversen ES, Lancaster JM, et al. Patterns of gene expression that characterize long-term survival in advanced stage serous ovarian cancers. Clin Cancer Res 2005;11(10):3686-96. *Exclude: no 2x2 table.*

Bergen HR 3rd, Vasmatzis G, Cliby WA, et al. Discovery of ovarian cancer biomarkers in serum using NanoLC electrospray ionization TOF and FT-ICR mass spectrometry. Dis Markers 2003-2004;19(4-5):239-49. *Exclude: no quantification of reproducibility.*

Berker B, Dunder I, Ensari A, et al. Prognostic significance of apoptotic index and bcl-2 and p53 expression in epithelial ovarian carcinoma. Eur J Gynaecol Oncol 2002;23(6):505-10. *Exclude: prognosis only, no link to mgmt or outcomes.*

Berker B, Dunder I, Ensari A, et al. Prognostic value of p53 accumulation in epithelial ovarian carcinomas. Arch Gynecol Obstet 2002;266(4):205-9. *Exclude: prognosis only, no link to mgmt or outcomes.*

Bernardini M, Lee CH, Beheshti B, et al. High-resolution mapping of genomic imbalance and identification of gene expression profiles associated with differential chemotherapy response in serous epithelial ovarian cancer.

Neoplasia 2005;7(6):603-13. *Exclude: no 2x2 table.*

Bese T, Nomir SK. The importance of serum insulin-like growth factor-I level determination in the follow-up of patients with epithelial ovarian cancer. Eur J Gynaecol Oncol 2001;22(5):372-6. *Exclude: prognosis only, no link to mgmt or outcomes.*

Bild AH, Yao G, Chang JT, et al. Oncogenic pathway signatures in human cancers as a guide to targeted therapies. Nature 2006;439(7074):353-7. *Exclude: no 2x2 table.*

Bildrici K, Tel N, Ozalp SS, et al. Prognostic significance of DNA topoisomerase II-alpha (Ki-S1) immunoexpression in endometrial carcinoma. Eur J Gynaecol Oncol 2002;23(6):540-4. *Exclude: not OVCA.*

Blandy C, Chabal F, Stoppa-Lyonnet D, et al. Testing participation in BRCA1/2-positive families: initiator role of index cases. Genet Test 2003;7(3):225-33. *Exclude: BRCA-Q5.*

Bluman LG, Rimer BK, Regan Sterba K, et al. Attitudes, knowledge, risk perceptions and decision-making among women with breast and/or ovarian cancer considering testing for BRCA1 and BRCA2 and their spouses. Psychooncology 2003;12(5):410-27. *Exclude: BRCA-Q5.*

Boente MP, Berchuck A, Rodriguez GC, et al. The effect of interferon gamma on epidermal growth factor receptor expression in normal and malignant ovarian epithelial cells. Am J Obstet Gynecol 1992;167(6):1877-82. *Exclude: cell line only.*

Bon GG, Kenemans P, Verstraeten R, et al. Serum tumor marker immunoassays in gynecologic oncology: establishment of reference values. Am J Obstet Gynecol 1996;174(1 Pt 1):107-14. *Exclude: no 2x2 table.*

Bonadona V, Saltel P, Desseigne F, et al. Cancer patients who experienced diagnostic genetic testing for cancer susceptibility: reactions and behavior after the disclosure of a positive test result. Cancer Epidemiol Biomarkers Prev 2002;11(1):97-104. *Exclude: Q5 pre-10-2004.*

Bonome T, Lee JY, Park DC, et al. Expression profiling of serous low malignant potential, low-grade, and high-grade tumors of the ovary. Cancer Res 2005;65(22):10602-12. *Exclude: no 2x2 table.*

Boran N, Kayikcioglu F, Yalvac S, et al. Significance of serum and peritoneal fluid lactate dehydrogenase levels in ovarian cancer. Gynecol Obstet Invest 2000;49(4):272-4. *Exclude: no 2x2 table.*

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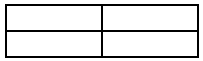
Appendix C: Sample Data Abstraction Forms

Question 1: *What is the evidence that ovarian cancer genomic tests performed in a typical clinical laboratory actually measure what they are purported to measure?*

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
StudyID	**Geographical location** [city & state (U.S.) or city & country (foreign)]: **Study dates** [month & year]: **Size of population** [give num/denom for screening studies]: **Type of laboratory** [delete all that do not apply]: Clinical lab Commercial lab Hospital-based clinical samples Research lab Not reported	**Genomic test(s) used:** **Type(s) of samples** [delete all that do not apply]: Blood or tissue Cyst fluid Ascites	**Age:** Mean (SD): Median: Range: **Race/ethnicity (n [%]):** **Diagnoses (n [%]):** Ovarian cancer: Borderline: Benign ovarian mass: Other (specify): Healthy controls: **Inclusion criteria:** **Exclusion criteria:**	[For each test reported, please provide a 2x2 table and report or calculate sensitivity, specificity, NPV, and PPV (all with confidence intervals); alternatively, for continuous variables, report the correlation coefficient or other measure of association. Also include data on reproducibility (inter- and intra-assay coefficient of variation, kappa, etc.).] 1) [2x2 table – use this header space to provide information needed for reader to interpret "Test +," "Test -," "Ref stand +," and "Ref stand -" headings in following table.] 2) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.)	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE] [COMMENT ON BIASES, ETC. AFFECTING CLINICAL INTERPRETATION] **Quality assessment:** [+ if appropriate quality, - if not; add text to describe] Reference standard: Verification bias: Test reliability/variability: Sample size: Statistical tests: Blinding: Definition of +/- on screening test: Grade: **This article is also relevant to:** [delete all that do not apply] Question 2 Question 3 Question 4 Question 5 Question 6

Question 2: *What is the sensitivity and specificity of genomic tests in detecting ovarian cancer in asymptomatic and symptomatic women, including high-risk women?*

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
StudyID	**Geographical location** [city & state (U.S.) or city & country (foreign)]: **Study dates** [month & year]: **Size of population** [give num/denom for screening studies]: **Type of population** [delete all that do not apply]: Screening Adnexal mass Other (specify) **Genomic test(s) used:** **Reference standard** [delete all that do not apply]: Surgical pathology Clinical outcome (specify) **Reference standard applied to all test negatives?:** **Test reliability established?:** **Statistical tests used:** **Blinding:** **Definition of positive and negative on screening test:**	**Age:** Mean (SD): Median: Range: **Menopausal status (n [%]):** Pre (< 45): Peri (45-55): Post (> 55): **Race/ethnicity (n [%]):** **Risk factors (n [%]):** Family history: Genotype: Other (specify): **Diagnoses (n [%]):** Ovarian cancer: Borderline: Benign ovarian mass: Other (specify): Healthy controls: **Inclusion criteria:** **Exclusion criteria:**	**Screening only (n [%]):** **Diagnosis of mass:** - Symptomatic (n [%]): - Asymptomatic, detected by exam (n [%]): - Asymptomatic, detected by imaging (n [%]): **Additional data used for diagnosis:**	[For each test reported, please provide a 2x2 table and report or calculate sensitivity, specificity, NPV, and PPV (all with confidence intervals). Also include data on reproducibility (inter- and intra-assay coefficient of variation, kappa, etc.).] 1) [2x2 table – use this header space to provide information needed for reader to interpret Test +, Test -, Disease +, and Disease - headings in following table.]  2) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.)	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE] [COMMENT ON BIASES, ETC. AFFECTING CLINICAL INTERPRETATION] **Quality assessment:** [+ if appropriate quality, - if not; add text to describe] Reference standard: Verification bias: Test reliability/variability: Sample size: Statistical tests: Blinding: Definition of +/- on screening test: Grade: **This article is also relevant to:** [delete all that do not apply] Question 1 Question 3 Question 4 Question 5 Question 6

Question 3: *What is the evidence that genomic testing to detect ovarian cancer in asymptomatic women, including high-risk women, changes clinical management and leads to improved health outcomes?*

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
StudyID	**Geographical location** [city & state (U.S.) or city & country (foreign)]: **Study dates** [month & year]: **Study type** [delete all but one]: RCT Cohort Case-control Other (specify) **Size of population:** **Genomic test(s) used:** **Reference standard:** [delete all that do not apply] Surgical pathology Clinical outcome (specify) **Test reliability established?:** **Statistical tests used:** **Definition of positive and negative on screening test:**	**Age:** Mean (SD): Median: Range: **Menopausal status (n [%]):** Pre (< 45): Peri (45-55): Post (> 55): **Race/ethnicity (n [%]):** **Risk factors (n [%]):** Family history: Genotype: Other (specify): **Inclusion criteria:** **Exclusion criteria:**	**Use of test results:** [e.g., change in screening test or frequency] **Outcomes measured:** [delete all that do not apply] Cancer incidence Cancer mortality Quality of life Other (specify)	For each outcome measured, report outcomes based on test result; include 95% confidence intervals if available.	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE] [COMMENT ON BIASES, ETC. AFFECTING CLINICAL INTERPRETATION] **Quality assessment:** [+ if appropriate quality, - if not; add text to describe] *For RCT:* Randomization method: Blinding: Dropout rate < 20%: Adequacy of randomization concealment: *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): Large sample size: Adequate description of the cohort: Use of validated method for genomic test: Use of validated method for ascertaining clinical outcomes: Adequate follow-up period: Completeness of follow-up: Analysis (multivariate adjustments) and reporting of results: *For case-control study:* Valid ascertainment of cases: Unbiased selection of cases: Appropriateness of the control

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
					population: Verification that the control is free of cancer: Comparability of cases and controls with respect to potential confounders: Validated dietary assessment method: Appropriateness of statistical analyses: Grade: **This article is also relevant to:** [delete all that do not apply] Question 1 Question 2 Question 4 Question 5 Question 6

Question 4: *What is the evidence that genomic testing in women with clinical suspicion of ovarian cancer or with already-diagnosed ovarian cancer changes clinical management and leads to improved health outcomes?*

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
StudyID	**Geographical location** [city & state (U.S.) or city & country (foreign)]:	**Age:** Mean (SD): Median: Range:	**Use of test results:** [e.g., change in screening test or frequency]	[For each outcome measured, report outcomes based on test result. Note that you should only abstract data when 2x2 tables can be constructed. Articles that report only Kaplan Meier curves or Hazard Ratios should not be abstracted.]	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE]
	Study dates [month & year]:	**Menopausal status (n [%]):** Pre (< 45): Peri (45-55):	**Outcomes measured:** [delete all that do not apply] Cancer incidence Cancer mortality	1) [2x2 table - use this space to provide information needed for reader to interpret Test +, Test -, Outcome +, and Outcome - headings in following table.]	[COMMENT ON BIASES, ETC. AFFECTING CLINICAL INTERPRETATION]
	Study type [delete all but one]: RCT Cohort Case-control Other (specify)	Post (> 55): **Race/ethnicity (n [%]):**	Quality of life Other (specify)		**Quality assessment:** [+ if appropriate quality, - if not; add text to describe]
	Size of population:	**Risk factors (n [%]):** Family history: Genotype: Other (specify):			*For RCT:* Randomization method: Blinding: Dropout rate < 20%: Adequacy of randomization concealment:
	Genomic test(s) used: **Reference standard:** [delete all that do not apply] Surgical pathology Clinical outcome (specify)	**Diagnoses (n [%]):** Ovarian cancer: Borderline: Benign ovarian mass: Other (specify): Healthy controls:		2) [2x2 table - use this space to provide information needed for reader to interpret Test +, Test -, Outcome +, and Outcome - headings in following table.]	*For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): Large sample size: Adequate description of the cohort: Use of validated method for genomic test:
	Test reliability established?: **Statistical tests used:**	**Treatment (n [%]):** Surgery: Chemotherapy: Platinum: Taxol: Other (specify): Other (specify):			Use of validated method for ascertaining clinical outcomes: Adequate follow-up period: Completeness of follow-up: Analysis (multivariate adjustments) and reporting of results:
	Definition of positive and negative on screening test:	**Inclusion criteria:** **Exclusion criteria:**			*For case-control study:* Valid ascertainment of cases: Unbiased selection of cases: Appropriateness of the control

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
				3) Hazard Ratio or other relevant information:	population: Verification that the control is free of cancer: Comparability of cases and controls with respect to potential confounders: Validated dietary assessment method: Appropriateness of statistical analyses: Grade: **This article is also relevant to:** [delete all that do not apply] Question 1 Question 2 Question 3 Question 5 Question 6

Question 5: *What are the harms of using genomic tests for ovarian cancer prevention and management?*

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
StudyID	**Geographical location** [city & state (U.S.) or city & country (foreign)]:	**Age:** Mean (SD): Median: Range:	**Use of test results:** [e.g., change in screening test or frequency]	For each outcome measured, report outcomes based on test result. 1)	[IF ARTICLE SHOULD BE EXCLUDED, PLEASE EXPLAIN WHY HERE]
	Study dates [month & year]:	**Menopausal status (n [%]):** Pre (< 45): Peri (45-55): Post (> 55):	**Outcomes measured:** [delete all that do not apply] Complications Quality of life Other (specify)	2)	[COMMENT ON BIASES, ETC. AFFECTING CLINICAL INTERPRETATION]
	Study type [delete all but one]: RCT Cohort Case-control Other (specify)	**Race/ethnicity (n [%]):**		3) 4)	**Quality assessment:** [+ if appropriate quality, - if not; add text to describe] *For RCT:* Randomization method: Blinding:
	Size of population:	**Risk factors (n [%]):** Family history: Genotype: Other (specify):		5)	Dropout rate < 20%: Adequacy of randomization concealment:
	Genomic test(s) used: **Reference standard:** [delete all that do not apply] Surgical pathology Clinical outcome (specify)	**Diagnoses (n [%]):** Ovarian cancer: Borderline: Benign ovarian mass: Other (specify): Healthy controls: **Inclusion criteria:**		6) 7)	*For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): Large sample size: Adequate description of the cohort: Use of validated method for genomic test:
	Test reliability established?:	**Exclusion criteria:**			Use of validated method for ascertaining clinical outcomes: Adequate follow-up period: Completeness of follow-up: Analysis (multivariate adjustments) and reporting of results:
	Statistical tests used:				*For case-control study:*
	Definition of positive and negative on screening test:				Valid ascertainment of cases: Unbiased selection of cases: Appropriateness of the control population: Verification that the control is free of

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
					cancer: Comparability of cases and controls with respect to potential confounders: Validated dietary assessment method: Appropriateness of statistical analyses: Grade: **This article is also relevant to:** [delete all that do not apply] Question 1 Question 2 Question 3 Question 4 Question 6

Appendix D: Evidence Tables

Evidence Table 1 – Question 1: *What is the evidence that ovarian cancer genomic tests performed in a typical clinical laboratory actually measure what they are purported to measure?*

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Benet-kiewicz, Wang, Schaner, et al., 2005 **#8570**	**Geographical location:** Uppsala, Sweden; Oslo, Norway; Palo Alto, CA **Study dates:** NR **Size of population:** 18 **Type of laboratory:** Hospital-based clinical samples Research lab	**Genomic test(s) used:** Microarray of chromosome 22 Two methods used: DNA copy number counted, mRNA expression measured **Type(s) of samples:** Blood or tissue Cyst fluid Ascites	**Age:** NR, but referenced **Race/ethnicity (n [%]):** All Norwegian **Diagnoses (n [%]):** Ovarian cancer: 18 (100%) Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 0 **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Abnormalities detected in 12 of 18 tumors. 21 frequently deleted genes with low mRNA expression, 12 amplified genes with elevated mRNA.	**Comments:** - Cancers only - Small sample **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: - Statistical tests: - Blinding: - Definition of +/- on screening test:+ Grade: B
Brinkmann, Ryan, Ayhan, et al., 2004 **#1400**	**Geographical location:** London, UK; Belfast, Northern Ireland; Berlin, Germany **Study dates:** NR **Size of population:** 62 **Type of laboratory:** Hospital-based clinical samples Research lab	**Genomic test(s) used:** DNA: loss of heterozygosity, microsatellite instability Based on findings, odds that two tumors represented either single primary with metastasis or dual primary calculated. Classified as single primary if odds > 1, dual primary if odds < 1. **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 69 (100%) - 38 synchronous endometrial/ovarian - 15 bilateral ovarian - 9 synchronous endometrial/bilateral ovarian **Inclusion criteria:** Diagnosis of synchronous tumors **Exclusion criteria:** **NR**	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Concordance between genetic and histo-pathologic diagnosis: Endometrial/ovarian: 42% Bilateral ovarian: 67%	**Comments:** - No linkage with clinical outcomes - The poor agreement between pathologist opinion and genetic testing suggests that pathologists are not very good at detecting primary tumors with metastases vs. asynchronous primary tumors. **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: - Statistical tests:+ Blinding: - Definition of +/- on screening test: - Grade: C

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Conrads, Fusaro, Ross, et al., 2004 **#1150**	**Geographical location:** Frederick and Bethesda, MD; Chicago, IL **Study dates:** NR **Size of population:** 248 **Type of laboratory** Hospital-based clinical samples Research lab	**Genomic test(s) used:** Mass spectroscopy of protein expression using ProteinChip arrays 1) High vs. low resolution spectrometers compared 2) Candidate patterns determined using Proteome Quest software; algorithm combines elements of genetic algorithms and self-organizing adaptive pattern-recognition 3) Candidates selected in training set evaluated in blinded training set 4) Variances between assays compared to a reference standard **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR for entire study; for training set, 28 healthy, 49 cancer; two testing sets 37 healthy, 63 cancer; 37 healthy, 40 cancer Of total 103 cancer, 22 (20%) stage I **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Low resolution spectrometer, cancer vs. healthy: Ref+ / Ref- / Tot T+: 103 / 0 / 103 T-: 0 / 67 / 67 Tot: 103 / 67 / 170 Value / Lower 95% CI / Upper 95% CI Se: 100.0% / 97.1% / 100.0% Sp: 100.0% / 95.5% / 100.0% PPV: 100.0% / 97.1% / 100.0% NPV: 100.0% / 95.5% / 100.0% 2) High resolution spectrometer, cancer vs. healthy: Ref+ / Ref- / Tot T+: 68 / 0 / 68 T-: 0 / 43 / 43 Tot: 68 / 43 / 111 Value / Lower 95% CI / Upper 95% CI Se: 100.0% / 95.6% / 100.0% Sp: 100.0% / 93.0% / 100.0% PPV: 100.0% / 95.6% / 100.0% NPV: 100.0% / 93.0% / 100.0% 3) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): "Comparisons…revealed that the variation in the mass spectra (overall amplitude, total record count and deviation in mean amplitudes) between ovarian cancer cases and control samples was statistically indistinguishable from the variance within the process itself, as indicated by the serum reference standard."	**Comments:** - Full spectrum of clinical disease not reported - Prevalence of disease 50% or greater – much higher than in screening or even most diagnostic situations - Confidence intervals for sensitivity/specificity estimates not presented **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + (reported, but low) Sample size: - Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Filella, Ballesta, Fox, et al., 1996 **#7620**	**Geographical location:** Barcelona, Spain; London, UK; Graz, Austria; Chambery, France **Study dates:** NR **Size of population:** 239 normal, 167 cancers **Type of laboratory:** Clinical lab	**Genomic test(s) used:** COBAS CORE automated immunoassay analyzer **Type(s) of samples:** Blood or tissue	**Age:** Range: 17-89 for controls **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 167 (41.1%) Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 239 (58.9%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Coefficent of variation: level 1 (mean 17.2) 3.8 to 6.1%, level 2 (mean 47.1) 2.8 to 6.4%, level 3 (mean 164.3) 1.8 to 4%. 97.5 percentile for CA-125 assay: 36.7; median 8.8. CA-125 levels correlated with disease stage in ovarian cancer, show response to treatment.	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability:+ Sample size: + Statistical tests:+ Blinding: - Definition of +/- on screening test:+ Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Hasholzner, Baumgartner, Steiber, et al., 1996 **#7520**	**Geographical location:** Munich, Germany **Study dates:** NR **Size of population:** 426 **Type of laboratory:** Clinical lab Hospital-based specimens	**Genomic test(s) used:** CA 72-4, CA-125 II using COBAS-CORE EIA kit **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: At time of primary diagnosis: 123 (28.9%); during follow-up: 236 (55.4%) Borderline: 0 Benign ovarian mass: 37 (8.7%) Other: 0 Healthy controls: 30 (7.0%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) CA-125, 31 U/mL threshold, specificity fixed at for healthy controls; controls and benign masses vs. cancer: Ref+ / Ref- / Tot T+: 105 / 16 / 121 T-: 18 / 51 / 69 Tot: 123 / 67 / 190 Value (Lower 95% CI – Upper 95% CI) Se: 85.0% (78.7% – 91.3%) Sp: 76.8% (66.7% – 86.9%) PPV: 86.8% (80.7% – 92.8%) NPV: 73.9% (63.6% – 84.3%) 2) CA-72.4, threshold 2.9 U/mL, specificity fixed at 95% for healthy controls; healthy controls plus benign masses vs. cancer: Ref+ / Ref- / Tot T+: 66 / 4 / 70 T-: 57 / 63 / 120 Tot: 123 / 67 / 190 Value (Lower 95% CI – Upper 95% CI) Se: 54.0% (45.2% – 62.8%) Sp: 94.5% (89.0% – 100.0%) PPV: 94.3% (88.8% – 99.7%) NPV: 52.5% (43.6% – 61.4%) 3) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Intra-assay coefficient of variation: CA 72.4: 3.5 to 4% CA-125 II: 3.4% Inter-assay coefficient of variation: CA 72.4: 5 to 7.4%	**Comments:** - Prevalence of cancer in sample higher than in normal population **Quality assessment:** Reference standard: + Verification bias:- Test reliability/variability: + Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
				CA-125 II: 8.4% Correlation between markers: -0.066 (controls) 0.576 (serous ovarian cancer)	
Heinzel-mann-Schwarz, Gardiner-Garden, Henshall, et al., 2004 **#8650**	**Geographical location:** Randwick, Australia **Study dates:** NR **Size of population:** 158 **Type of laboratory:** Hospital-based clinical samples Research lab	**Genomic test(s) used:** Microarray and immunohistochemistry 3 cell adhesion molecules identified **Type(s) of samples:** Blood or tissue	**Age:** 23 (20%) < 50 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 158 (100%) Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 0 **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): In univariate analysis, no marker was significantly associated with either relapse-free survival or disease-specific survival. Closest was CLDN3 (HR 0.63, 95% CI 0.4 to 1.0, p = 0.068). Scoring of expression by 2 independent readers, discrepancies resolved by consensus.	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Hellström, Raycraft, Hayden-Ledbetter, et al., 2003 **#2560**	**Geographical location:** Seattle, WA **Study dates:** NR **Size of population:** 121 **Type of laboratory:** Research lab	**Genomic test(s) used:** HE4: Gene identified through microarray as overexpressed in ovarian cancer; monoclonal antibody and ELISA generated **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 37 (30.6%) Borderline: 0 Benign ovarian mass: 19 (15.7%) Other: 0 Healthy controls: 65 (53.7%) **Inclusion criteria:** Stored sera at NCI **Exclusion criteria:** NR	1) HE4 for early stage cancer vs. normal at specificity of 96% (sensitivity of CA-125 71% at this level of specificity): Ref+ / Ref- / Tot T+: 6 / 3 / 9 T-: 1 / 62 / 63 Tot: 7 / 65 / 72 Value (Lower 95% CI – Upper 95% CI) Se: 85.7% (59.8% – 100.0%) Sp: 95.4% (90.3% – 100.0%) PPV: 66.7% (35.9% – 97.5%) NPV: 98.4% (95.3% – 100.0%) 2) HE4 for late stage cancer vs normal at specificity of 96% (sensitivity of CA-125 at same specificity = 80%): Ref+ / Ref- / Tot T+: 24 / 3 / 27 T-: 6 / 62 / 68 Tot: 30 / 65 / 95 Value (Lower 95% CI – Upper 95% CI) Se: 80.0% (65.7% – 94.3%) Sp: 95.4% (90.3% – 100.0%) PPV: 88.9% (77.0% – 100.0%) NPV: 91.2% (84.4% – 97.9%) 3) HE4 for all cancer cases vs. all benign diseases at specificity of 96% (sensitivity of CA-125 at same specificity = 40%): Ref+ / Ref- / Tot T+: 20 / 1 / 21 T-: 17 / 18 / 35 Tot: 37 / 19 / 56 Lower / Upper	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: - Statistical tests: - Blinding: - Definition of +/- on screening test: + Grade: C

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
				Value 95% CI 95% CI Se 54.1% 38.0% 70.1% Sp 94.7% 84.7% 100.0% PPV 95.2% 86.1% 100.0% NPV 51.4% 34.9% 68.0% 4) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Sensitivity/specificity compared to CA-125 reported for fixed levels of specificity for each marker; in general, similar performance.	
Hubl, Chan, Van Ingen, et al., 1999 **#5520**	**Geographical location:** Dresden, Göttingen, and Mannheim, Germany; Baltimore, MD; Tokai, Japan; Rotterdam, The Netherlands; Barcelona and Asturias, Spain; Creteil, France **Study dates:** NR **Size of population:** NR (593 controls, N for other diseases not specified) **Type of laboratory:** Clinical lab Hospital-based clinical samples	**Genomic test(s) used:** Elecsys® CA-125 II Assay **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: NR Borderline: NR Benign ovarian mass: NR Other: 0 Healthy controls: 593; % not calculable **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Low range (10 to 20 U/mL): Intra-assay CV: 1.0 to 3.0% Interassay CV: 3.0 to 10.9% Mid-range (40 U/mL): Intra-assay CV: 0.8 to 4.6% Interassay CV: 2.4 to 8.7% Correlation with other immunoassays: 0.932 to 0.989 95 percentile for healthy subjects: 35 U/mL	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: - Statistical tests:+ Blinding: - Definition of +/- on screening test: = Grade: C

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Janatova, Pohlreich, and Matous, 2003 **#2410**	**Geographical location:** Prague, Czech Republic **Study dates:** NR **Size of population:** 26 **Type of laboratory:** Research lab	**Genomic test(s) used:** Spreadex Polymer NAB (electrophoresis gels) **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** NR: 13 (50%) with known BrCA1/2 mutations, 13 controls **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Mutations detected using technique in subjects with known mutations; none in controls	**Comments:** - Small sample size - No formal measure of agreement **Quality assessment:** Reference standard: + Verification bias:- Test reliability/variability:+ Sample size: - Statistical tests: - Blinding: - Definition of +/- on screening test: - Grade: C
Kenemans, Vestraeten, van Kamp, et al., 1995 **#8200**	**Geographical location:** Amsterdam, The Netherlands **Study dates:** NR **Size of population:** 417 samples, from 285 patients **Type of laboratory:** Clinical lab Hospital-based clinical samples	**Genomic test(s) used:** 2nd generation CA-125 Centocor CA-125 II BYK LIamat Boehriner Mannheim (use mouse monoclonal antibody as capture) **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 216 (51.8%) Borderline: 0 Benign ovarian mass: 111 (26.6%) Other: - Endometrial CA: 24 (5.8%) - Colon CA: 22 (5.3%) - Pregnant: 44 (10.6%) Healthy controls: 0 **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Regression coefficients from 0.88 to 1.17. Centocor CA-125 II: intra-assay CV 5%, inter-assay CV 7%. No differences in ROC curves.	**Comments:** - High prevalence of cancer **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Li, Tang, Wu, et al., 2004 **#1160**	**Geographical location:** Tampa, FL **Study dates:** NR **Size of population:** 3 public access data bases: I: 216 II: 216 III: 253 **Type of laboratory:** Research lab	**Genomic test(s) used:** SELDI proteomics, analyzed using - Filtered approach with statistical testing - Wapper approach using genetic algorithms **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** *Datasets I and II:* Ovarian cancer: 100 (46.3%) Benign ovarian mass: 7.4% Healthy controls: 100 (46.3%) *Dataset III:* Ovarian cancer: 162 (64.0%) Healthy controls: 91 (36.0%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Filter approach (all 3 datasets pooled): Dis+ / Dis- / Tot T+: 337 / 32 / 369 T-: 25 / 291 / 316 Tot: 362 / 323 / 685 Value (Lower 95% CI – Upper 95% CI) Se: 93.1% (90.5% – 95.7%) Sp: 90.1% (86.8% – 93.4%) PPV: 91.3% (88.5% – 94.2%) NPV: 92.1% (89.1% – 95.1%) Individual datasets specificity ranged from 80.1 to 96.7%; estimated PPV based on prevalence of 0.05% ranged from 0.2 to 1.48% 2) Genetic algorithm approach (all 3 datasets pooled): Dis+ / Dis- / Tot T+: 356 / 7 / 363 T-: 6 / 316 / 322 Tot: 362 / 323 / 685 Value (Lower 95% CI – Upper 95% CI) Se: 98.3% (97.0% – 99.7%) Sp: 97.8% (96.2% – 99.4%) PPV: 98.1% (96.7% – 99.5%) NPV: 98.1% (96.7% – 99.6%) Individual data sets specificity ranged from 95.4 to 100%; estimated PPV based on prevalence of 0.05% ranged from 0.92 to 100%	**Comments:** - Appropriate discussion of effect of low prevalence of ovarian cancer on PPV; estimation of test performance based on real-world prevalence - Reporting of variability in results across methods, using same datasets **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: + Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: A

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Liu, 2006 **#12810**	**Geographical location:** Dallas, TX **Study dates:** NR **Size of population:** 253 **Type of laboratory:** Research lab	**Genomic test(s) used:** **Type(s) of samples:** Blood or tissue (reanalysis of data from Clinical Proteomic Program Databank)	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 162 (64%) Healthy controls: 91 (36%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Support Vector Machine (SVM) – Linear kernel: 2) SVM – Polynomial kernel: 3) SVM – Radial kernel:	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: - Statistical tests: + Blinding: Definition of +/- on screening test: Grade: B

1) Support Vector Machine (SVM) – Linear kernel:

	Dis+	Dis-	Tot
T+	160	7	167
T-	2	84	86
Tot	**162**	**91**	253

	Value	Lower 95% CI	Upper 95% CI
Se	**99.0%**	97.5%	100.0%
Sp	**92.0%**	86.4%	97.6%
PPV	95.8%	92.8%	98.8%
NPV	97.7%	94.5%	100.0%

2) SVM – Polynomial kernel:

	Dis+	Dis-	Tot
T+	162	19	181
T-	0	72	72
Tot	**162**	**91**	253

	Value	Lower 95% CI	Upper 95% CI
Se	**100.0%**	98.1%	100.0%
Sp	**79.0%**	70.6%	87.4%
PPV	89.5%	85.0%	94.0%
NPV	100.0%	95.8%	100.0%

3) SVM – Radial kernel:

	Dis+	Dis-	Tot
T+	162	91	253
T-	0	0	0
Tot	**162**	**91**	253

	Value	Lower 95% CI	Upper 95% CI
Se	**100.0%**	98.1%	100.0%
Sp	**0.0%**	0.0%	0.0%
PPV	64.0%	58.1%	69.9%
NPV	-	-	-

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Meinhold-Heerlein, Bauer-schlag, Hilpert, et al., 2005 **#8710**	**Geographical location:** Kiel, Frieburg, Bonn, and Berlin, Germany; San Diego, CA **Study dates:** NR **Size of population:** 57 **Type of laboratory:** Hospital-based clinical samples Research lab	**Genomic test(s) used:** Microarray **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 49 (86.0%) Borderline: 8 (14.0%) Benign ovarian mass: 0 Other: 0 Healthy controls: 0 **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Sensitivity/specificity not reported; predictive model based on gene expression correctly discriminated between low malignant potential/grade 1 invasive vs. grade 2 or 3 invasive 54/57 (95%).	**Comments:** - Survival data not available for all patients - Survival not analyzed by microarray results **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: - Statistical tests:- Blinding: - Definition of +/- on screening test: + Grade: C
Mok, Chao, Skates, et al., 2001 **#4140**	**Geographical location:** Boston, MA; Charleston, SC **Study dates:** NR **Size of population:** 201 **Type of laboratory:** Hospital-based clinical samples Research lab	**Genomic test(s) used:** Microarray used to identify prostatin (secreted protein); antibody/ELISA developed **Type(s) of samples:** Blood or tissue	**Age:** < 55: 102 (55.7%) ≥ 55: 89 (44.3%) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 64 (31.8%) Borderline: 0 Benign ovarian mass: 42 (20.9%) Other (other GYN cancers): 24 (11.9%) Healthy controls: 71(35.3%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Correlation with CA-125 0.217 (p = 0.2) in nonmucinous cancers, -0.004 (p = -0.97) in controls; markers together had better sensitivity (92%) at specificity of 94% than either alone (CA-125 sensitivity 64.9%; prostatin 51.4% at 94% specificity).	**Comments:** - Small sample size - Enriched for ovarian cancer compared to population **Quality assessment:** Reference standard:+ Verification bias:- Test reliability/variability: + Sample size: - Statistical tests:- Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Mor, Visintin, Lai, et al., 2005 **#240**	**Geographical location:** New Haven, CT; Washington, DC; Las Vegas, NV **Study dates:** NR **Size of population:** Validation set: 206 **Type of laboratory:** Hospital-based clinical samples Research lab Commercial lab	**Genomic test(s) used:** Microarray (cytokine rolling circle) EIA Classification by Support vector machine k-nearest neighbors classification tree Validation run 1000 times Score based classification method also used Markers selected: Leptin Prolactin OPN IGF-II **Type(s) of samples:** Blood or tissue	**Age:** Mean ages of groups in validation set 58.4-63 years **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 100 (48.5%) Borderline: 0 Benign ovarian mass: 0 Other (family history): 40 (19.4%) Healthy controls: 66 (32.0%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Scoring rule based on leptin, prolactin, OPN, and IGF-II for diagnosis of ovarian cancer (cut points empirically derived): Ref+ / Ref- / Tot T+: **96** / **6** / 102 T-: **4** / **100** / 104 Tot: 100 / 106 / 206 Value (Lower 95% CI – Upper 95% CI) Se: 96.0% (92.2% – 99.8%) Sp: 94.3% (89.9% – 98.7%) PPV: 94.1% (89.6% – 98.7%) NPV: 96.2% (92.5% – 99.8%)	**Comments:** - High prevalence of cancer **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: - Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Petricoin, Ardekani, Hitt, et al., 2002 **#3870**	**Geographical location:** Bethesda, MD; Houston, TX; Lawrenceville, NJ; Chicago, IL **Study dates:** NR **Size of population:** 117 **Type of laboratory:** Hospital-based clinical samples Research lab	**Genomic test(s) used:** Protein profiling using mass spectroscopy Patterns identified through genetic algorithm, closer analysis **Type(s) of samples:** Blood or tissue	**Age:** *Development set:* Median: 49 Range: 21-75 *Validation set:* Median: 48 Range: 25-73 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** *Development set:* Ovarian cancer: 50 (50%) Borderline: 0 Benign ovarian mass: 13 (13%) Other: 0 Healthy controls: 37 (37%) *Validation set:* Ovarian cancer: 50 (43.1%) Borderline: 0 Benign ovarian mass: 25 (21.6%) Other (non-gyn inflammatory disease): 7 (6.0%) Healthy controls: 24 (20.7%) **Inclusion criteria:** Controls: 5 years follow-up without cancer **Exclusion criteria:** NR	1) Cancer vs. benign disease, peak identified: |	Ref+	Ref-	Tot
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T+	50	3	53
T-	0	63	63
Tot	50	66	116 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	100.0%	94.0%	100.0%
Sp	95.5%	90.4%	100.0%
PPV	94.3%	88.1%	100.0%
NPV	100.0%	95.2%	100.0%	 2) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Coefficient of variation < 10% if specimens not frozen and thawed more than twice, and, once thawed, kept at 4°C for < 24 hours. Sera from one unaffected, one Stage III cancer run 100 times; 100% concordance.	**Comments:** - Population well-characterized - Prevalence of ovarian cancer much higher than in general population **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: + Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: A

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Rai, Zhang, Rosen-zweig, et al., 2002 **#3180**	**Geographical location:** Baltimore, MD; Fremont, CA **Study dates:** NR **Size of population:** 81 **Type of laboratory:** Hospital-based clinical samples Research lab	**Genomic test(s) used:** Protein profile using ProteinChip Patterns selected by classification and regression tree (CART) and unified maximum separability analysis (UMSA) **Type(s) of samples:** Blood or tissue	**Age:** *Cancer cases:* Median: 53 Range: 36-84 *Controls:* Median: 57 Range: 45-75 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 43 (53%) Borderline: 0 Benign ovarian mass: 0 Other ("nongynecologic diseases"): 38 (47%) Healthy controls: 0 **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Logistic regression using 60, 79 kd peaks: |	Ref+	Ref-	Tot
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T+	25	2	27
T-	17	36	53
Tot	42	38	80 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	59.5%	44.7%	74.3%
Sp	94.7%	87.6%	100.0%
PPV	92.6%	82.7%	100.0%
NPV	67.9%	55.4%	80.5% | 2) Logistic regression model using biomarkers at 60, 79 kD plus CA-125 (>35 U/mL cutoff): |	Ref+	Ref-	Tot
---	---	---	---
T+	30	2	32
T-	2	34	36
Tot	32	36	68 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	93.8%	85.4%	100.0%
Sp	94.4%	86.9%	100.0%
PPV	93.8%	85.4%	100.0%
NPV	94.4%	87.0%	100.0%	 Sensitivity of CA-125 alone 65.6% (95% CI 49.2 to 82.1%), specificity 97.2% (91.9 to 100%).	**Comments:** - Very high prevalence of cancer relative to general population - Reproduciblity not reported **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: - Sample size: + (confidence intervals reported) Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Riisbro, Stephens, Brunner, et al., 2001 **#4190**	**Geographical location:** Copenhagen and Hvidovre, Denmark; Russelsheim, Germany **Study dates:** NR **Size of population:** 129 **Type of laboratory:** Hospital-based clinical samples Research lab	**Genomic test(s) used:** RIA for soluble urokinase plasminogen activator receptor **Type(s) of samples:** Blood or tissue	**Age:** Median (range) for: Healthy controls: 36 (29-84) Benign gyn disease: 50 (22-73) Ovarian cancer: 63 (22-82) **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 53 (41.1%) Borderline: 0 Benign ovarian mass: 17 (13.2%) Other (benign endometrial conditions): 28 (21.0%) Healthy controls: 31 (24.0%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Interassay CV: 7.6% Intra-assay CV: 4.6% Levels correlated with malignancy, stage of disease, but not significantly in multivariate analysis.	**Comments:** - High prevalence of malignancy **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability:+ Sample size: - Statistical tests:+ Blinding: + Definition of +/- on screening test: + Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Sapi, Okpo-kwasili, and Rutherford, 2002 **#3630**	**Geographical location:** New Haven, CT **Study dates:** NR **Size of population:** 58 **Type of laboratory:** Research lab Hospital-based clinical samples	**Genomic test(s) used:** Telomerase activity in peripheral cells (blood or ascites) after methods to remove peripheral leukocytes **Type(s) of samples:** Blood or tissue Ascites	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 28 (48.3%) Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 30 (51.7%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Telomerase activity in 8/8 Stage IV, 7/20 Stage III, 0/30 controls (after purification). CA-125 levels higher in patients with positive telomerase.	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability:+ Sample size: - Statistical tests:+ Blinding: - Definition of +/- on screening test:+ Grade: B
Sorace and Zahn, 2003 **#9210**	**Geographical location:** Baltimore, MD **Study dates:** NR **Size of population:** 253 **Type of laboratory:** Research lab	**Genomic test(s) used:** Analysis of serum mass spectrometry data from Clinical Proteomics Program Databank Training set of 45 spectra from 91 controls, 80 spectra from 162 cases Test set consisted of those not selected for training set Two-sided Wilcoxon tests used to compare intensity between cancer, controls Varying decision rules applied to data **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 162 (64%) Controls: 91 (36%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Sensitivity/specificity 100% in training set with different rules, but varied in test sets. Much of discrimination lies in low mass to charge (M/Z) region, which is problematic because of potential for experimental bias, technical issues.	**Comments:** - Prevalence of cancer in sample higher than in normal population **Quality assessment:** Reference standard: + Verification bias:+ Test reliability/variability: + Sample size: - Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Tamakoshi, Kikkawa, Hasegawa, et al., 1995 **#8210**	**Geographical location:** Nagoya, Japan **Study dates:** NR **Size of population:** NR (593 controls, N for other diseases not specified) **Type of laboratory:** Clinical lab Hospital-based clinical samples	**Genomic test(s) used:** Centocore CA-125 II Assay **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 59 (39.6%) Borderline: 0 Benign ovarian mass: 49 (30.9%) Other: - Endometrial ca: 10 (6.7%) - Cervical ca: 14 (9.4%) Healthy controls: 20 (13.4%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) CA-125 II: Ovarian cancer vs. benign and normal (other cancers not included): Ref+ / Ref- / Tot T+: 53 / 13 / 66 T-: 6 / 66 / 72 Tot: 59 / 79 / 138 Value (Lower 95% CI – Upper 95% CI) Se: 89.8% (82.1% – 97.5%) Sp: 83.5% (75.4% – 91.7%) PPV: 80.3% (70.7% – 89.9%) NPV: 91.7% (85.3% – 98.1%) 2) CA-125 I: Ovarian cancer vs. benign and normal (other cancers not included): Ref+ / Ref- / Tot T+: 50 / 9 / 59 T-: 9 / 70 / 79 Tot: 59 / 79 / 138 Value (Lower 95% CI – Upper 95% CI) Se: 84.7% (75.6% – 93.9%) Sp: 88.6% (81.6% – 95.6%) PPV: 84.7% (75.6% – 93.9%) NPV: 88.6% (81.6% – 95.6%) Difference in tests: more positives with CA-125 II in endometrial cyst (?endometriosis), fewer in non-serous cancers. 3) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Correlation coefficient: 0.86. Coefficient of variation of CA-125 II smaller, especially at lower concentrations.	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability:- + Sample size: - Statistical tests:+ Blinding: - Definition of +/- on screening test: = Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Thougaard, Hogdall, Kjaer, et al., 1998 **#6610**	**Geographical location:** Frederiksberg, Copenhagen, and Aarhus, Denmark **Study dates:** NR **Size of population:** 153 (67 men) **Type of laboratory:** Research lab	**Genomic test(s) used:** Three different antibody (2 monoclonal, 1 polyclonal) for tetranectin **Type(s) of samples:** Blood or tissue	**Age:** *Controls (women):* Median: 36 Range: 20-59 *Cancer:* Median: 57.5 Range: 35-76 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 43 (28% of total study pop; 50% of women) Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 110 (67 men, 43 women) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Coefficient of variation by level of tetranectin: Intra-assay Hyb 130-13 Hby 130-14 A371 Low 5.6% 2.9% 7.5% Med 3.3% 2.4% 5.5% High 3.2% 1.9% 8.3% Inter-assay Hyb 130-13 Hby 130-14 A371 Low 11.1% 12.1% 6.2% Med 8.3% 5.4% 4.9% High 8.2% 4.4% 7.9% Difference between assays 10% or less. Similar performance in ovarian cancer patients—with decreasing levels with increasing FIGO stage.	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: NA Test reliability/variability: + Sample size: - Statistical tests: + Blinding: + Definition of +/- on screening test: NA Grade: A

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Tuxen, Soletormos, Peterson, et al., 2001 **#4200**	**Geographical location:** Copenhagen, Hillerod, and Odense, Denmark **Study dates:** NR **Size of population:** 31 **Type of laboratory:** Clinical lab	**Genomic test(s) used:** CA-125, CEA, TPA 16 samples obtained over course of 1 year; 4 samples within 2-3 week time period x 4 Median interval between series 12 weeks (range 9-15 weeks) Each sample run in duplicate, assays by same analyst Commercial kits used Values transformed to natural logarithm **Type(s) of samples:** Blood or tissue	**Age:** Median: 55 Range: 32-71 **Other (menopausal status):** 11 (35.5%) premenopausal 20 (64.5%) postmenopausal **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 0 Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 31 (100%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): CA-125 II – contribution of different components to imprecision: Mean analytic imprecision: 7.8% Mean intraindividual variability: Short term: 11.8% Long term: 16.0% Combined: 20% Change in reference value needed to be significant after accounting for imprecision: 50% Imprecision greatest in premenopausal women (69.5% compared to 35.7% in postmenopausal women), due to larger intra-individual biological variability. CEA – change in reference value needed to be significant after accounting for imprecision: 44.8% TPA – change in reference value needed to be significant after accounting for imprecision: 67.9% Differences by menopausal status not seen with CEA and TPA.	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability:+ Sample size: - Statistical tests: + Blinding: + Definition of +/- on screening test:+ Grade: A

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Tuxen, Soletormos, Rustin, et al., 2000 **#4670**	**Geographical location:** Copenhagen and Hvidovre, Denmark; Middlesex, UK **Study dates:** Dec 1989-Apr 1994 **Size of population:** 26 subjects (225 samples) **Type of laboratory:** Clinical lab	**Genomic test(s) used:** Cobas Core CA-125 II Collected from 3 months post-chemotherapy to 12 months before last clinical evaluation Natural logarithm transformed **Type(s) of samples:** Blood or tissue	**Age:** Median: 64 Range: 24-75 **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 26 (100%) Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 0 **Inclusion criteria:** No evidence of progression of disease using radiological or surgical follow-up **Exclusion criteria:** Early death Secondary cancer Treatment with monoclonal antibody Rising CA-125 levels Less than 5 available samples Continuously falling levels	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Contribution to variability in values: Analytic imprecison: 12% Intra-individual variation: 32.0% (24.0% after exclusion of one outlier) Inter-individual variation: 43.6% Change in reference value needed to be significant after accounting for imprecision: 79.7% (62.6% after excluding one patient with outlier values).	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: - Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: A

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
van Ingen, Chan, Hubl, et al., 1998 **#6490**	**Geographical location** Rotterdam,Tthe Netherlands; Baltimore, MD; Dresden, Göttingen, and Mannheim, Germany; Isehara, Japan; Barcelona and Madrid, Spain; Creteil Cedex, France **Study dates:** NR **Size of population:** 1879 **Type of laboratory:** Clinical lab Commercial lab	**Genomic test(s) used:** Automated CA-125 II assay using Elecsys 2010 (Boehringer Mannheim) **Type(s) of samples:** Blood or tissue	**Age:** NR: all greater than 18; of normal women, 49.4% postmenopausal **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 150 (7.9%) Benign ovarian mass: NR; 80 (4.2%) had benign gynecologic diseases, including cervical and endometrial conditions Other: - Benign disease (including non-gynecologic): 342 (18.2%) - Other cancers: 505 (26.9%) Healthy controls: - Women: 593 (31.6%) - Men: 289 (15.4%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Intra-assay CVs: 0.8 to 3.3% Inter-assay CVs: 2.4 to 10.9% Correlations with other assays: 0.932 to 0.989 No interference observed with high levels of bilirubin, hemoglobin, or triglycerides.	**Comments:** - Population reasonably well-characterized - Considerable detail provided on analytic validity in multiple clinical labs **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: + Statistical tests: + Blinding: NR Definition of +/- on screening test: + Grade: A

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Wen, Bernstein, Lescallett, et al., 2000 **#9830**	**Geographical location:** Los Angeles, CA **Study dates:** NR **Size of population:** 108 **Type of laboratory:** Hospital-based clinical samples Research lab	**Genomic test(s) used:** Microarray and gel-based DNA sequencing for p53 mutations **Type(s) of samples:** Blood or tissue	**Age:** NR, but referenced **Race/ethnicity (n [%]):** NR, but ?referenced **Diagnoses (n [%]):** Ovarian cancer: 108 (100%) Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 0 **Inclusion criteria:** NR, but referenced **Exclusion criteria:** NR	1) Microarray, mutation or no mutation: Ref+ / Ref- / Tot T+: **71** / **0** / 71 T-: **6** / **31** / 37 Tot: 77 / 31 / 108 Value (Lower 95% CI – Upper 95% CI) Se: 92.2% (86.2% – 98.2%) Sp: 100.0% (90.3% – 100.0%) PPV: 100.0% (95.8% – 100.0%) NPV: 83.8% (71.9% – 95.7%) 2) Conventional sequence analysis, mutation or no mutation: Dis+ / Dis- / Tot T+: **63** / **0** / 63 T-: **14** / **31** / 45 Tot: 77 / 31 / 108 Value (Lower 95% CI – Upper 95% CI) Se: 81.8% (73.2% – 90.4%) Sp: 100.0% (90.3% – 100.0%) PPV: 100.0% (95.2% – 100.0%) NPV: 68.9% (55.4% – 82.4%) 3) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Mutations detected by both methods in 57 cancers, no mutations in 31, concordance 81%.	**Comments:** - Direct comparison between microarray versus sequencing ; discussion of mechanisms for differences presented **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: - Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Wu, Abbott, Fishman, et al., 2003 **#2360**	**Geographical location:** New Haven, CT; Chicago, IL **Study dates:** NR **Size of population:** 91 (2 specimens not used in final analysis) **Type of laboratory:** Hospital-based clinical samples Research lab	**Genomic test(s) used:** Mass spectroscopy for protein profiles Several different methods for selecting variables compared: 1) Random forest algorithm (bootstrap aggregation with random feature selection) 2) Classification trees (CART) 3) Linear discriminant analysis and quadratic discriminant analysis **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 47 (51.6%) Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 44 (47.4%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Error rate using random forest algorithm is lower, more stable compared to CART or linear discriminant analysis. Other methods not stable using large number of variables.	**Comments:** - High prevalence of ovarian cancer - Small sample, multiple simulations **Quality assessment:** Reference standard:+ Verification bias: + Test reliability/variability: + Sample size: - Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: B
Yu, Ongarello, Fiedler, et al., 2005 **#190**	**Geographical location** Peking, China; Graz, Austria; Lawrence, Kansas **Study dates:** NR **Size of population:** 216 **Type of laboratory:** Hospital-based clinical samples Research lab	**Genomic test(s) used:** Mass spectrometry of proteins 4 step statistical procedure: 1) Binning, using CART 2) Kolmogorov-Smirnov (KS)-test based feature selection (comparing distribution of values) 3) Restriction of coefficient of variation 4) Wavelet transformation of data **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 121 (56%) Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 95 (44%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Cancer vs. control, based on classification results of described procedure: Ref+ / Ref- / Tot T+: 119 / 9 / 128 T-: 2 / 86 / 88 Tot: 121 / 95 / 216 Value / Lower 95% CI / Upper 95% CI Se: 98.3% / 96.1% / 100.0% Sp: 90.5% / 84.6% / 96.4% PPV: 93.0% / 88.5% / 97.4% NPV: 97.7% / 94.6% / 100.0%	**Comments:** - Small sample, multiple simulations - Prevalence of ovarian cancer very high **Quality assessment:** Reference standard:+ Verification bias: + Test reliability/variability: - Sample size: - Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Yu, Zheng, Tang, et al., 2005 **#310**	**Geographical location:** Hangzhou, China **Study dates:** NR **Size of population:** 61 **Type of laboratory:** Hospital-based clinical samples Research lab	**Genomic test(s) used:** SELDI protein profiling SVM classification used to identify candidates 90% of samples blinded training set, 10% test set; procedure repeated 10 times **Type(s) of samples:** Blood or tissue	**Age:** *Cancer:* Median: 57 Range: 14-68 *Control:* "Age and sex matched" **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 31 (50.8%) Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 29 (49.2%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Results for test set (60 iterations, but only 6 cases): Ref+ / Ref- / Tot T+: 29 / 1 / 30 T-: 1 / 29 / 30 Tot: 30 / 30 / 60 Value (Lower 95% CI – Upper 95% CI) Se: 96.7% (90.2% – 100.0%) Sp: 96.7% (90.2% – 100.0%) PPV: 96.7% (90.2% – 100.0%) NPV: 96.7% (90.2% – 100.0%)	**Comments:** - Histologic type not described - High prevalence of cancer in data set - Only 6 subjects in each test set **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: - Sample size: - Statistical tests: + Blinding: + Definition of +/- on screening test: - Grade: C
Zarrinkar, Mainquist, Zamora, et al., 2001 **#9750**	**Geographical location:** San Diego and Santa Clara, CA **Study dates:** NR **Size of population:** 31 patients Ovarian cancer, normal prostate, and fibroblast cell lines **Type of laboratory:** Commercial lab Hospital-based clinical samples Research lab	**Genomic test(s) used:** High-throughput microarray using parallel analysis Results compared to single sample processing **Type(s) of samples:** Tissue Cell lines	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 27 (87.1%) Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 4 (12.9%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Correlation between wafer vs. individual chips 0.980 (CAOV-3). Similar correlation (0.982) for a mixture of breast and prostate cell lines. False positives 31 of approximately 6800 in ovarian cell line validation.	**Comments:** - Few normals - Tissue, not serum **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring
Zhang, Bast, Yu, et al., 2004 **#790**	**Geographical location:** Baltimore, MD; Houston, Tex; Fremont, CA; Durham, NC; Randwick, Australia; Groningen, the Netherlands; London, UK **Study dates:** NR **Size of population:** Development set: 503 **Type of laboratory:** Hospital-based clinical samples Research lab	**Genomic test(s) used:** ProteinChip Biomarker System Unified maximum separability analysis used to select peaks Identified proteins purified Testing and validation sets used **Type(s) of samples:** Blood or tissue	**Age:** NR **Race/ethnicity (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 167 (33.2%) Borderline: 28 (2.8%) Benign ovarian mass: 166 (33.0%) Other: 0 Healthy controls: 142 (28.2%) **Inclusion criteria:** NR **Exclusion criteria:** NR	1) Results of validation set, CA-125 alone, specificity fixed at 97% for healthy controls (disease – includes benign pelvic mass): Ref+ / Ref- / Tot T+: 106 / 42 / 148 T-: 32 / 187 / 219 Tot: 138 / 229 / 367 Value / Lower 95% CI / Upper 95% CI Se: 76.8% / 69.8% / 83.9% Sp: 81.7% / 76.6% / 86.7% PPV: 71.6% / 64.4% / 78.9% NPV: 85.4% / 80.7% / 90.1% 2) Results of validation set, logistic model with 3 biomarkers identified in study, specificity fixed at 97% for healthy controls (disease – includes benign pelvic mass): Ref+ / Ref- / Tot T+: 107 / 82 / 189 T-: 31 / 147 / 178 Tot: 138 / 229 / 367 Value / Lower 95% CI / Upper 95% CI Se: 77.5% / 70.6% / 84.5% Sp: 64.2% / 58.0% / 70.4% PPV: 56.6% / 49.5% / 63.7% NPV: 82.6% / 77.0% / 88.2% 3) Results of validation set, logistic model with 3 biomarkers identified in study plus CA-125, specificity fixed at 97% for healthy controls (disease – includes benign pelvic mass): Ref+ / Ref- / Tot T+: 108 / 93 / 201 T-: 30 / 136 / 166 Tot: 138 / 229 / 367	**Comments:** - High prevalence of ovarian cancer - Population well-characterized **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: + Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: A

Evidence Table 1 – Question 1 (continued)

Study	Study Design	Description of Test(s)	Patient Characteristics	Results	Comments/Quality Scoring

	Value	Lower 95% CI	Upper 95% CI
Se	78.3%	71.4%	85.1%
Sp	59.4%	53.0%	65.7%
PPV	53.7%	46.8%	60.6%
NPV	81.9%	76.1%	87.8%

Zhu, Wang, Ma, et al., 2003

#2100

Geographical location:
Stony Brook and Upton, NY

Study dates:
NR

Size of population:
Test set: 216
Validation: 253

Type of laboratory:
Research lab

Genomic test(s) used:
Mass spectrometry (SELDI) from FDA/NCI database

Random field selection of markers

Type(s) of samples :
Blood or tissue

Age: NR

Race/ethnicity (n [%]):
NR

Diagnoses (n [%]):
Test set:
Ovarian cancer: 100 (46.3%)
Borderline: 0
Benign ovarian mass: 0
Other: 0
Healthy controls: 116 (53.7%)

Validation set:
Ovarian cancer: 162 (64.0%)
Borderline: 0
Benign ovarian mass: 0
Other: 0
Healthy controls: 91 (36.0%)

Inclusion criteria:
NR

Exclusion criteria:
NR

1) Validation set:

	Ref+	Ref-	Tot
T+	162	0	162
T-	0	91	91
Tot	162	91	253

	Value	Lower 95% CI	Upper 95% CI
Se	100.0%	98.1%	100.0%
Sp	100.0%	96.7%	100.0%
PPV	100.0%	98.1%	100.0%
NPV	100.0%	96.7%	100.0%

Using different training set to identify markers and 50 iterations, 50 perfect classifications, although best subset of markers differed between iterations.

Comments:
- High prevalence of cancer

Quality assessment:
Reference standard: +
Verification bias: -
Test reliability/variability: -
Sample size: -
Statistical tests: +
Blinding: +
Definition of +/- on screening test: +

Grade: B

Evidence Table 2 – Question 2: *What is the sensitivity and specificity of genomic tests in detecting ovarian cancer in asymptomatic and symptomatic women, including high-risk women?*

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Abdel-Aleem, Ahmed, Sabra, et al., 1996 **#7330**	**Geographical location:** Assiut, Egypt **Study dates:** Jun 1994-Dec 1995 **Size of population:** 151 total, including 101 patients (48 with ovarian carcinoma; 26 with epithelial ovarian cancer) and 50 healthy controls **Type of population:** Adnexal mass **Genomic test(s) used:** Alpha-L-fucosidase **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** 2 references to assay methods **Statistical tests used:** Se, Sp, PPV, NPV **Blinding:** No **Definition of positive and negative on screening test:** ≤ 275 U/mL	**Age:** Mean (SD): 46.9 ± 1.6 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** Family history: 3 (6%) Genotype: NR **Diagnoses (n [%]):** Ovarian cancer: 48 (32%) Benign ovarian mass: 28 (18.5%) Healthy controls: 50 (33%) **Inclusion criteria:** - Women with genital tract tumors - Controls: women admitted for genital prolapse or dysfunctional uterine bleeding **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** None	1) alpha-L-fucosidase ≤ 275 U/mL for diagnosis of ovarian cancer (all women with tumors): |	Dis+	Dis-	Tot
---	---	---	---
T+	43	0	43
T-	5	28	33
Tot	48	28	76 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	89.6%	80.9%	98.2%
Sp	100.0%	89.3%	100.0%
PPV	100.0%	93.0%	100.0%
NPV	84.8%	72.6%	97.1% | 2) alpha-L-fucosidase ≤ 275 U/mL for diagnosis of ovarian cancer (Dis- are healthy controls): |	Dis+	Dis-	Tot
---	---	---	---
T+	43	1	44
T-	5	49	54
Tot	48	50	98 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	89.6%	80.9%	98.2%
Sp	98.0%	94.1%	100.0%
PPV	97.7%	93.3%	100.0%
NPV	90.7%	83.0%	98.5%		**Comments:** - Study uses healthy control comparison group **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Baron, Boardman, Lafky, et al., 2005 **#450**	**Geographical location:** Multiple sites in U.S. **Study dates:** 1985-94 **Size of population:** - Serum samples from 225 women with incident epithelial ovarian cancer - 246 benign ovarian neoplasm - 253 benign gynecologic condition **Type of population:** Screening Adnexal mass **Genomic test(s) used:** sEGFR/sErbB1 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** No **Test reliability established?:** Yes **Statistical tests used:** Se, Sp **Blinding:** No **Definition of positive and negative on screening test:** sEGFR < 1000 fmol/mL	**Age:** Ovarian cancer: Median: 61 Range: 24-87 Benign ovarian neoplasm: Median: 51 Range: 18-88 Benign gynecological conditions: Median: 42 Range: 18-84 **Menopausal status (n [%]):** Ovarian cancer: Pre (< 45): 35 Post (> 55): 183 Indeterminate: 7 Benign ovarian neoplasm: Pre (< 45): 108 Post (> 55): 123 Indeterminate: 15 Benign gynecological condition: Pre (< 45): 187 Post (> 55): 53 Indeterminate: 13 **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 225 Benign ovarian mass: 246 Benign gynecologic condition: 253	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) sEGFR < 1000 fmol/mL for diagnosis of ovarian cancer vs. patients with benign ovarian neoplasms: |	Dis+	Dis-	Tot
---	---	---	---
T+	141	86	227
T-	84	160	244
Tot	225	246	471 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	62.7%	56.3%	69.0%
Sp	65.0%	59.1%	71.0%
PPV	62.1%	55.8%	68.4%
NPV	65.6%	59.6%	71.5% | 2) sEGFR < 1000 fmol/mL OR CA-125 ≥ 50 U/mL for diagnosis of ovarian cancer vs. patients with benign ovarian neoplasms: |	Dis+	Dis-	Tot
---	---	---	---
T+	190	90	280
T-	34	156	190
Tot	224	246	470 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	84.8%	80.1%	89.5%
Sp	63.4%	57.4%	69.4%
PPV	67.9%	62.4%	73.3%
NPV	82.1%	76.7%	87.6% | 3) sEGFR < 1000 fmol/mL AND CA-125 ≥ 50 U/mL for diagnosis of ovarian cancer vs. patients with benign ovarian neoplasms: |	Dis+	Dis-	Tot
---	---	---	---
T+	113	0	113
T-	109	246	355
Tot	222	246	468		**Comments:** None **Quality assessment:** Reference standard: + Verification bias: +/- Test reliability/variability: +/- Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

Inclusion criteria:
- Incident EOC and serum sample in repository
- Controls having surgery at Mayo for benign ovarian neoplasm or other benign gynecologic condition

Exclusion criteria:
NR

	Value	Lower 95% CI	Upper 95% CI
Se	50.9%	44.3%	57.5%
Sp	100.0%	98.8%	100.0%
PPV	100.0%	97.3%	100.0%
NPV	69.3%	64.5%	74.1%

4) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.):

"Interassay biological detection limit (4.5 SD above the zero calibrator) for the ALISA done in this study was 7.5 fmol/mL sEGFR."

Not abstracted
2x2 tables also reported for:
CA-125 ≥ 33 U/L
CA-125 ≥ 50 U/mL
CA-125 ≥ 135 U/mL

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Baron, Cora, Lafky, et al., 2003 **#2960**	**Geographical location:** Multiple sites in U.S. (tissue banks) **Study dates:** 1985-2001; date ranges varied by site **Size of population:** 144 healthy women 225 epithelial ovarian cancer (EOC) cases **Type of population:** Known cancer cases and healthy controls **Genomic test(s) used:** sEGFR/sErbB1 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** No **Test reliability established?:** No **Statistical tests used:** Se, Sp, ROC, regression modelling **Blinding:** No **Definition of positive and negative on screening test:** Cut-off is 95% lower limit in healthy women for each group (not fixed)	**Age:** NR **Menopausal status (n [%]):** EOC cases: Pre (< 45): 35 Post (> 55): 183 Healthy controls: Pre (< 45): 81 Post (> 55): 59 **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 225 Healthy controls: 144 **Inclusion criteria:** Serum in tissue bank collected from women within 30 days of primary cytoreductive surgery for EOC **Exclusion criteria:** Previous cytoreductive surgery, radiation, or chemotherapy	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) p110 sEGFR < 624 fmol/mL for diagnosis of EOC (all stages, all women): |	Dis+	Dis-	Tot
---	---	---	---
T+	125	8	133
T-	100	136	236
Tot	225	144	369 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	55.6%	49.1%	62.0%
Sp	94.4%	90.7%	98.2%
PPV	94.0%	89.9%	98.0%
NPV	57.6%	51.3%	63.9% | 2) p110 sEGFR < 1185 fmol/mL for diagnosis of EOC (all stages, premenopausal women): |	Dis+	Dis-	Tot
---	---	---	---
T+	26	5	31
T-	9	76	85
Tot	35	81	116 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	74.3%	59.8%	88.8%
Sp	93.8%	88.6%	99.1%
PPV	83.9%	70.9%	96.8%
NPV	89.4%	82.9%	96.0%	 Additional tables reported for D+ = Stage I/II or Stage III/IV and for postmenopausal women, women ages 20-40, ages 41-60 and ages 61-87 years.	**Comments:** - Healthy controls were younger, more often premenopausal than EOC cases - Cut-off value changed for each analysis **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: - Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Berek, Chung, Kaldi, et al., 1991 **#12230**	**Geographical location:** Los Angeles, CA **Study dates:** NR **Size of population:** 36 women with EOC 12 controls **Type of population:** Adnexal mass Histologically proven cancer **Genomic test(s) used:** IL-6 CA-125 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Yes (references) **Statistical tests used:** Se **Blinding:** Yes **Definition of positive and negative on screening test:** "On the basis of IL-6 value of 0.12 ± 0.03 in healthy adult women." Threshold used is unclear.	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 36 Healthy controls: 12 **Inclusion criteria:** Histologically documented epithelial ovarian cancer **Exclusion criteria:** NR	**Screening only (n [%]):** 0 **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) Elevated IL-6 for diagnosis of macroscopic EOC (microscopic EOC and control patients = Dis-): |	Dis+	Dis-	Tot
---	---	---	---
T+	16	4	20
T-	5	23	28
Tot	21	27	48 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	76.2%	58.0%	94.4%
Sp	85.2%	71.8%	98.6%
PPV	80.0%	62.5%	97.5%
NPV	82.1%	68.0%	96.3% | 2) Elevated IL-6 for diagnosis of EOC (microscopic or macroscopic EOC = Dis+ and control patients = Dis-): |	Dis+	Dis-	Tot
---	---	---	---
T+	18	2	20
T-	18	10	28
Tot	36	12	48 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	50.0%	33.7%	66.3%
Sp	83.3%	62.2%	100.0%
PPV	90.0%	76.9%	100.0%
NPV	35.7%	18.0%	53.5%	 3) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Interassay variation 20%. Correlation of serum IL-6 levels and CA-125 levels in pts with EOC = 0.84.	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: +/- Test reliability/variability: +/- Sample size: - Statistical tests: - Blinding: + Definition of +/- on screening test: - Grade: C

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Bon, Verheijen, Zueten-horst, et al., 1996 **#7470**	**Geographical location:** Amsterdam, The Netherlands **Study dates:** NR **Size of population:** 76 malignant ovarian tumor 70 benign ovarian tumor 962 healthy controls **Type of population:** Screening **Genomic test(s) used:** Mucin-like Carcinoma-associated antigen **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** No **Test reliability established?:** NR **Statistical tests used:** ROC. Se, Sp **Blinding:** NR **Definition of positive and negative on screening test:** 14 U/mL, based on 95% in healthy controls of 19.2 U/mL	**Age:** Median: 45-49 **Menopausal status (n [%]):** Controls n = 962 Pre (< 45): 279 Peri (45-55): 503 Post (> 55): 180 **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 76 Benign ovarian mass: 70 Healthy controls: 962 **Inclusion criteria:** - Controls – asymptomatic volunteers participating in a screening study for early detection of ovarian cancer - Known benign ovarian tumor or ovarian carcinoma **Exclusion criteria:** Abnormal pelvic exam	**Screening only (n [%]):** 962 (86.8%); used only to define cut-off value **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) CA > 14 U/mL for diagnosis of ovarian cancer (vs. benign ovarian tumors): |	Dis+	Dis-	Tot
---	---	---	---
T+	29	0	29
T-	47	70	117
Tot	76	70	146 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	38.2%	27.2%	49.1%
Sp	100.0%	95.7%	100.0%
PPV	100.0%	89.7%	100.0%
NPV	59.8%	50.9%	68.7% | 2) CA-125 > 35 U/mL for diagnosis of ovarian cancer (vs. benign ovarian tumors): |	Dis+	Dis-	Tot
---	---	---	---
T+	61	54	115
T-	15	16	31
Tot	76	70	146 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	80.3%	71.4%	89.2%
Sp	23.2%	13.3%	33.1%
PPV	53.0%	43.9%	62.2%
NPV	51.6%	34.0%	69.2%		**Comments:** - Prevalence of cancer high in diagnostic population **Quality assessment:** Reference standard: +/- Verification bias: - Test reliability/variability: - Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: +/- Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Chang, Lee, Goodman, et al., 2002 **#3230**	**Geographical location:** Baltimore, MD **Study dates:** NR (tumor bank) **Size of population:** 54 ovarian tumor **Type of population:** Adnexal mass **Genomic test(s) used:** Allelic Imbalance (AI) Plasma DNA levels CA-125 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** No **Test reliability established?:** No **Statistical tests used:** ROC curves, logistic regression models **Blinding:** No **Definition of positive and negative on screening test:** No	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 41 Borderline: 6 Other: 3 - 3 endometrioid - 2 clear cell - 1 granulosa cell - 1 immature teratoma Healthy controls: 44 164 patients with non-neoplastic diseases **Inclusion criteria:** Sample in tumor bank **Exclusion criteria:** None specified	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) Allelic imbalance for diagnosis of ovarian cancer: |	Dis+	Dis-	Tot
---	---	---	---
T+	50	0	50
T-	4	31	35
Tot	54	31	85 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	92.6%	85.6%	99.6%
Sp	100.0%	90.3%	100.0%
PPV	100.0%	94.0%	100.0%
NPV	88.6%	78.0%	99.1% | 2) Plasma DNA concentration for diagnosis of ovarian cancer (cut off set to achieve 100% specificity): |	Dis+	Dis-	Tot
---	---	---	---
T+	29	0	29
T-	25	31	56
Tot	54	31	85 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	54.0%	40.7%	67.3%
Sp	100.0%	90.3%	100.0%
PPV	100.0%	89.7%	100.0%
NPV	55.4%	42.3%	68.4% | 3) CA-125 > 35 U/mL for diagnosis of ovarian cancer: |	Dis+	Dis-	Tot
---	---	---	---
T+	30	2	32
T-	15	16	31
Tot	45	18	63 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	67.0%	53.3%	80.7%		**Comments:** - This study included patients with a wide range of neoplasm, but ovarian was the largest group and it reported data on ovarian subgroup separately. **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: + Statistical tests: - Blinding: - Definition of +/- on screening test: - Grade: C

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Sp 89.0% 74.5% 100.0% PPV 93.8% 85.4% 100.0% NPV 51.6% 34.0% 69.2%	
Cherchi, Capo-bianco, Ambrosini, et al., 2002 **#3780**	**Geographical location:** Sassari, Italy **Study dates:** NR **Size of population:** 44 women benign 20 women malignant **Type of population:** Adnexal mass **Genomic test(s) used:** CA-125 CA-19.9 CEA TPA CA-15.3 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Referenced **Statistical tests used:** Se **Blinding:** No **Definition of positive and negative on screening test:** Yes, provided (see	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Cystic ovarian tumors **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) CA-125 (serum) > 35 IU/mL for diagnosis of ovarian cancer (vs. benign ovarian tumor or functional ovarian cyst): Dis+ Dis- Tot T+ 16 4 20 T- 4 40 44 Tot 20 44 64 Value Lower 95% CI Upper 95% CI Se 80.0% 62.5% 97.5% Sp 90.9% 82.4% 99.4% PPV 80.0% 62.5% 97.5% NPV 90.9% 82.4% 99.4% 2) CA 15.3 (serum) > 30 IU/mL for diagnosis of ovarian cancer (vs. benign ovarian tumor or functional ovarian cyst): Dis+ Dis- Tot T+ 10 6 16 T- 10 38 48 Tot 20 44 64 Value Lower 95% CI Upper 95% CI Se 50.0% 28.1% 71.9% Sp 86.4% 76.2% 96.5% PPV 62.5% 38.8% 86.2% NPV 79.2% 67.7% 90.7% 3) TPA (serum) > 70 IU/mL for diagnosis of ovarian cancer (vs. benign ovarian tumor or functional ovarian cyst):	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: - Sample size: - Statistical tests: - Blinding: - Definition of +/- on screening test: + Grade: C

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

Results)

	Dis+	Dis-	Tot
T+	10	8	18
T-	10	36	46
Tot	20	44	64

	Value	Lower 95% CI	Upper 95% CI
Se	50.0%	28.1%	71.9%
Sp	81.8%	70.4%	93.2%
PPV	55.6%	32.6%	78.5%
NPV	78.3%	66.3%	90.2%

4) CA 19.9 (serum) > 35 IU/mL for diagnosis of ovarian cancer (vs. benign ovarian tumor or functional ovarian cyst):

	Dis+	Dis-	Tot
T+	13	2	15
T-	7	42	49
Tot	20	44	64

	Value	Lower 95% CI	Upper 95% CI
Se	65.0%	44.1%	85.9%
Sp	95.5%	89.3%	100.0%
PPV	86.7%	69.5%	100.0%
NPV	85.7%	75.9%	95.5%

5) CEA (serum) > 5 ng/mL for diagnosis of ovarian cancer (vs. benign ovarian tumor or functional ovarian cyst):

	Dis+	Dis-	Tot
T+	8	0	8
T-	12	44	56
Tot	20	44	64

	Value	Lower 95% CI	Upper 95% CI
Se	40.0%	18.5%	61.5%
Sp	100.0%	93.2%	100.0%
PPV	100.0%	62.5%	100.0%
NPV	78.6%	67.8%	89.3%

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Data also reported for same markers in intracyst fluid.	
Cooper, Ritchie, Brog-hammer, et al., 2002 **#3360**	**Geographical location:** Iowa City, IA **Study dates:** 1995-2000 **Size of population:** 151 **Type of population:** Adnexal mass **Genomic test(s) used:** Serum VEGF **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Commercial test Quantikine HVEGF, R&D Systems , no references provided **Statistical tests used:** ROC **Blinding:** No **Definition of positive and negative on screening test:** No	**Age:** Ovarian cancer: Mean (SD): 64 Range: 20-78 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 81 Borderline: 16 Benign ovarian mass: 34 Other: - 13 peritoneal cancer - 7 fallopian tube cancer **Inclusion criteria:** Treated on gynecologic oncology service with preoperative serum samples available **Exclusion criteria:** None specified	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) VEGF > 246 pg/mL for diagnosis of invasive cancer (vs. LMP tumors or benign disease): |	Dis+	Dis-	Tot
---	---	---	---
T+	75	16	91
T-	26	34	60
Tot	101	50	151 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	74.0%	65.4%	82.6%
Sp	68.0%	55.1%	80.9%
PPV	82.4%	74.6%	90.2%
NPV	56.7%	44.1%	69.2%	 Additional data reported for CA-125 but 2x2 tables could not be determined: Se 93% Sp 71% PPV 93% NPV 68%	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: - Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: - Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Czekierdowski, 2002 **#3020**	**Geographical location:** Lublin, Poland **Study dates:** 1994-99 **Size of population:** 451 women with persistent adnexal mass from among 4876 women screened with TVUS **Type of population:** Screening **Genomic test(s) used:** VEGF (also measured CA-19.9; CA-72.4; CA-125) **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** No **Test reliability established?:** No **Statistical tests used:** ROC, LR **Blinding:** No **Definition of positive and negative on screening test:** No, 350 pg/mL was optimal cut-off	**Age:** Mean (SD): 38 Median: 39 Range: 13-76 **Menopausal status (n [%]):** Post (> 55): 88 (19.5%) (47% of cancers) **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 47 Benign ovarian mass: 404 **Inclusion criteria:** Adnexal mass on screening TVUS **Exclusion criteria:** NR	**Screening only (n [%]):** 100% **Diagnosis of mass:** - Symptomatic (n [%]): 0 - Asymptomatic, detected by exam (n [%]): 0 - Asymptomatic, detected by imaging (n [%]): 100% **Additional data used for diagnosis:** NR	1) VEGF > 350 pg/mL for diagnosis of ovarian cancer: |	Dis+	Dis-	Tot
---	---	---	---
T+	13	42	55
T-	9	52	61
Tot	22	94	116 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	59.1%	38.5%	79.6%
Sp	55.3%	45.3%	65.4%
PPV	23.6%	12.4%	34.9%
NPV	85.2%	76.3%	94.1% | 2x2 provided for 6 other cut-offs including 100, 150, 200, 300, 450 and 600 pg/mL. AUC = 0.5895 (95% CI, 0.4505 to 0.7285). 2) Logistic regression including Doppler US and tumor markers: |	Dis+	Dis-	Tot
---	---	---	---
T+	16	8	24
T-	6	86	92
Tot	22	94	116 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	72.0%	53.2%	90.8%
Sp	91.9%	86.4%	97.4%
PPV	66.7%	47.8%	85.5%
NPV	93.5%	88.4%	98.5%	 3) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.) VGEF: Sensitivity of the assay was 9 pg/mL. Inter-assay variability was less than 10%.	**Comments:** - Menopausal status different between cancers and benign masses **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: - Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Darai, Bringuier, Walker-Combrouze, et al., 1998 **#6520**	**Geographical location:** Paris, France **Study dates:** Sep 95 - Apr 96 **Size of population:** 77 women **Type of population:** Adnexal mass **Genomic test(s) used:** sICAM-1 sCD44std sE-cadherin **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Yes **Statistical tests used:** Se, Sp **Blinding:** No **Definition of positive and negative on screening test:** No	**Age:** Range: 18-75 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 11 Borderline: 5 Benign ovarian mass: Other: 61 - 23 luteal cyst - 9 dermoid cysts - 29 cystadenoma **Inclusion criteria:** Presenting with cystic ovarian mass **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) sE-cadherin >10,000 ng/mL for diagnosis of ovarian cancer (vs. benign cystadenomas and luteal cysts): |	Dis+	Dis-	Tot
---	---	---	---
T+	11	0	11
T-	5	52	57
Tot	16	52	68 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	68.8%	46.0%	91.5%
Sp	100.0%	94.2%	100.0%
PPV	100.0%	72.7%	100.0%
NPV	91.2%	83.9%	98.6%	 No 2x2 data for sICAM-1 or sCD44std 2) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Interassay coefficient of variation for samples of cyst fluid assayed in duplicate by two operators was 8% to 14.5% (these figures compared well with those provided by the manufacturers for serum samples).	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: - Grade: C

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Diamandis, Scorilas, Fracchioli, et al., 2003 **#2850**	**Geographical location:** Turin, Italy; Groningen, The Netherlands; Leuven, Belgium; Helsinki, Finland **Study dates:** NR **Size of population:** 384 **Type of population:** Adnexal mass **Genomic test(s) used:** Human kallikrein 6 (hK6) CA-125 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** No, only benign ovarian disease group (not apparently healthy controls) **Test reliability established?:** Yes **Statistical tests used:** Se, Sp **Blinding:** No **Definition of positive and negative on screening test:** hK6 > 4.2 µg/L (90% Sp) hK6 > 4.4 µg/L (95% Sp)	**Age:** Ovarian cancer: Mean: 56 Median: 57 Range: 28-78 Benign disease: Mean: 46 Median: 45 Range: 21-76 Healthy controls: Mean: 52 Median: 49 Range: 26-72 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 146 Benign ovarian mass: 141 Healthy controls: 97 **Inclusion criteria:** Known ovarian mass, undergoing surgery **Exclusion criteria:** None specified	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) hK6 > 4.2 µg/L for diagnosis of ovarian cancer (vs. benigns and controls): |	Dis+	Dis-	Tot
---	---	---	---
T+	76	24	100
T-	70	214	284
Tot	146	238	384 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	52.0%	43.9%	60.1%
Sp	90.0%	86.2%	93.8%
PPV	76.0%	67.6%	84.4%
NPV	75.4%	70.3%	80.4% | 2) hK6 > 4.4 µg/L for diagnosis of ovarian cancer (vs. benigns and controls): |	Dis+	Dis-	Tot
---	---	---	---
T+	69	12	81
T-	77	226	303
Tot	146	238	384 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	47.0%	38.9%	55.1%
Sp	95.0%	92.2%	97.8%
PPV	85.2%	77.4%	92.9%
NPV	74.6%	69.7%	79.5%	 3) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): hK6 detection limit is 0.1 ug/L; dynamic range up to 50 ug/L; precision less than 10% within the measurement range.	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: - Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Fayed, Ahmad, Kassim, et al., 1998 **#6350**	**Geographical location:** Cairo, Egypt **Study dates:** Mar 94 - Apr 96 **Size of population:** 30 women ovarian cancer 30 benign pelvic disease 30 healthy controls **Type of population:** Adnexal mass **Genomic test(s) used:** CA-125 CA-72-4 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes, benign pelvic diseases No, healthy controls **Test reliability established?:** No **Statistical tests used:** Se, Sp **Blinding:** No **Definition of positive and negative on screening test:** No	**Age:** Ovarian cancer: Range: 19-65 Benign pelvic disease: Range: 20-60 Healthy controls: Range: 22-63 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 30 Benign ovarian mass: 30 Healthy controls: 30 **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) CA-125 ≥ 85 U/mL for diagnosis of ovarian cancer (vs. benign disease and healthy controls): Dis+ / Dis- / Tot T+: 23 / 3 / 26 T-: 7 / 57 / 64 Tot: 30 / 60 / 90 Value / Lower 95% CI / Upper 95% CI Se: 76.7% / 61.6% / 91.8% Sp: 95.0% / 89.5% / 100.0% PPV: 88.5% / 76.2% / 100.0% NPV: 89.1% / 81.4% / 96.7% 2) CA 72-4 ≥ 8.5 U/mL for diagnosis of ovarian cancer (vs. benign disease and healthy controls): Dis+ / Dis- / Tot T+: 21 / 3 / 24 T-: 9 / 57 / 66 Tot: 30 / 60 / 90 Value / Lower 95% CI / Upper 95% CI Se: 70.0% / 53.6% / 86.4% Sp: 95.0% / 89.5% / 100.0% PPV: 87.5% / 74.3% / 100.0% NPV: 86.4% / 78.1% / 94.6% 3) CA-125 ≥ 85 U/mL OR CA 72-4 ≥ 8.5 U/mL for diagnosis of ovarian cancer (vs. benign disease and healthy controls): Dis+ / Dis- / Tot T+: 29 / 3 / 32 T-: 2 / 57 / 59 Tot: 30 / 60 / 91 Lower / Upper	**Comments:** None **Quality assessment:** Reference standard: +/- Verification bias: - Test reliability/variability: - Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: - Grade: C

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Value 95% CI 95% CI Se **95.0%** 87.2% 100.0% Sp **95.0%** 89.5% 100.0% PPV 90.6% 80.5% 100.0% NPV 96.6% 92.0% 100.0%	
Gadducci, Baicchi, Marrai, et al., 1996 **#7770**	**Geographical location:** Pisa, Italy **Study dates:** NR **Size of population:** 121 **Type of population:** Adnexal mass **Genomic test(s) used:** D-dimer CA-125 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** NR **Test reliability established?:** NR **Statistical tests used:** Mann-Whitney U test, Spearman rank correlation, logistic regression, p < 0.05 **Blinding:** NR **Definition of positive and negative on**	**Age:** Cancer: Median: 62 Range: 28-81 Benign: Median: 42 Range: 17-73 **Menopausal status (n [%]):** Pre (< 45): 57 (47%) Post (> 55): 64 (53%) **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** Clinical diagnosis of ovarian mass **Diagnoses (n [%]):** Ovarian cancer: 56 (46%) Benign ovarian mass: 65 (54%) **Inclusion criteria:** Consecutive patients with clinical diagnosis of ovarian mass **Exclusion criteria:** Patients with cardiovascular disease, diabetes, acute or chronic inflammatory disease, previous malignancy, or	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR Does not indicate how mass was diagnosed – just that they were going to laparotomy **Additional data used for diagnosis:** NR	1) CA-125 (> 65 U/mL): Dis+ Dis- Tot T+ 43 4 47 T- 13 61 74 Tot **56** **65** 121 Value Lower 95% CI Upper 95% CI Se **76.8%** 65.7% 87.9% Sp **93.8%** 87.9% 99.7% PPV 91.5% 83.5% 99.5% NPV 82.4% 73.8% 91.1% 2) D-Dimer (> 416 ng/mL): Dis+ Dis- Tot T+ 51 11 62 T- 5 54 59 Tot **56** **65** 121 Value Lower 95% CI Upper 95% CI Se **91.1%** 83.6% 98.6% Sp **83.1%** 74.0% 92.2% PPV 82.3% 72.7% 91.8% NPV 91.5% 84.4% 98.6% 3) Premenopause (CA-125): Dis+ Dis- Tot T+ 8 4 12 T- 4 41 45 Tot **12** **45** 57	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: A

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

screening test:
D-dimer = 416 ng/mL
CA-125 = 65 U/mL

previous episodes of thrombophlebitis or thromboembolia

	Value	Lower 95% CI	Upper 95% CI
Se	**66.7%**	40.0%	93.4%
Sp	**91.1%**	82.8%	99.4%
PPV	66.7%	40.0%	93.3%
NPV	91.1%	82.8%	99.4%

4) Premenopause D-Dimer:

	Dis+	Dis-	Tot
T+	12	4	16
T-	0	41	41
Tot	**12**	**45**	57

	Value	Lower 95% CI	Upper 95% CI
Se	**100.0%**	75.0%	100.0%
Sp	**91.1%**	82.8%	99.4%
PPV	75.0%	53.8%	96.2%
NPV	100.0%	92.7%	100.0%

5) Postmenopause CA-125:

	Dis+	Dis-	Tot
T+	35	0	35
T-	9	20	29
Tot	**44**	**20**	64

	Value	Lower 95% CI	Upper 95% CI
Se	**79.5%**	67.6%	91.4%
Sp	**100.0%**	85.0%	100.0%
PPV	100.0%	91.4%	100.0%
NPV	69.0%	52.1%	85.8%

6) Postmenopause D-Dimer:

	Dis+	Dis-	Tot
T+	39	7	46
T-	5	13	18
Tot	**44**	**20**	64

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Value / Lower 95% CI / Upper 95% CI Se 88.6% 79.2% 98.0% Sp 65.0% 44.1% 85.9% PPV 84.8% 74.4% 95.2% NPV 72.2% 51.5% 92.9%	
Gorelik, Landsittel, Marrangoni, et al., 2005 **#350**	**Geographical location:** Cleveland, OH **Study dates:** NR **Size of population:** 126 **Type of population:** Screening **Genomic test(s) used:** Cytokines CA-125 **Reference standard:** NR **Reference standard applied to all test negatives?:** NR **Test reliability established?:** Yes **Statistical tests used:** Wilcoxon rank sum Spearman CART **Blinding:** NR **Definition of positive and negative on**	**Age:** Control: Median: 46 Range: 36-76 Early cancer: Median: 46 Range: 34-88 Benign: Median: 44.5 Range: 28-87 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 44 (35%) Benign ovarian mass: 37 (29%) Healthy controls: 45 (36%) **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) CA-125: Dis+ / Dis- / Tot T+ 42 21 63 T- 2 61 63 Tot 44 82 126 Value / Lower 95% CI / Upper 95% CI Se 95.5% 89.4% 100.0% Sp 74.4% 65.0% 83.8% PPV 66.7% 55.0% 78.3% NPV 96.8% 92.5% 100.0% 2) IL-6: Dis+ / Dis- / Tot T+ 37 11 48 T- 7 71 78 Tot 44 82 126 Value / Lower 95% CI / Upper 95% CI Se 84.1% 73.3% 94.9% Sp 86.0% 78.5% 93.5% PPV 77.1% 65.2% 89.0% NPV 91.0% 84.7% 97.4% 3) EGF: Dis+ / Dis- / Tot T+ 37 19 56 T- 7 63 70 Tot 44 82 126	**Comments:** - Cannot determine if cut points were used to determine sensitivity and specificity as listed in Table 3. **Quality assessment:** Reference standard: - Verification bias: - Test reliability/variability: + Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: - Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

screening test:
CA-125 < 28
Il-6 < 0.4
IL-8 < 5.2
EGF < 149.3
VEGF < 126.5

	Value	Lower 95% CI	Upper 95% CI
Se	**84.1%**	73.3%	94.9%
Sp	**76.7%**	67.5%	85.9%
PPV	66.1%	53.7%	78.5%
NPV	90.0%	83.0%	97.0%

4) IL-8:

	Dis+	Dis-	Tot
T+	39	25	64
T-	5	57	62
Tot	**44**	**82**	126

	Value	Lower 95% CI	Upper 95% CI
Se	**88.6%**	79.2%	98.0%
Sp	**69.8%**	59.9%	79.7%
PPV	60.9%	49.0%	72.9%
NPV	91.9%	85.2%	98.7%

5) MCP:

	Dis+	Dis-	Tot
T+	37	23	60
T-	7	59	66
Tot	**44**	**82**	126

	Value	Lower 95% CI	Upper 95% CI
Se	**84.1%**	73.3%	94.9%
Sp	**72.1%**	62.4%	81.8%
PPV	61.7%	49.4%	74.0%
NPV	89.4%	82.0%	96.8%

6) VEGF:

	Dis+	Dis-	Tot
T+	35	27	62
T-	9	55	64
Tot	**44**	**82**	126

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	Value	Lower 95% CI	Upper 95% CI
Se	**79.5%**	67.6%	91.4%
Sp	**67.4%**	57.3%	77.5%
PPV	56.5%	44.1%	68.8%
NPV	85.9%	77.4%	94.5%

7) G-CSF:

	Dis+	Dis-	Tot
T+	32	21	53
T-	12	61	73
Tot	**44**	**82**	126

	Value	Lower 95% CI	Upper 95% CI
Se	**72.7%**	59.5%	85.9%
Sp	**74.4%**	65.0%	83.8%
PPV	60.4%	47.2%	73.5%
NPV	83.6%	75.1%	92.1%

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Hasholzner, Baum-gartner, Stieber, et al., 1996 **#7520**	**Geographical location:** Munich, Germany **Study dates:** NR **Size of population:** 426 **Type of population:** Screening **Genomic test(s) used:** CA-125 CA-72-4 **Reference standard:** Surgical pathology Clinical outcome **Reference standard applied to all test negatives?:** NR **Test reliability established?:** NR **Statistical tests used:** NR **Blinding:** NR **Definition of positive and negative on screening test:** CA-125: 160 U/mL CA-72-4: 3 U/mL	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 359 (84%) Benign ovarian mass: 37 (8.6%) Healthy controls: 30 (7%) **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) CA-125 for healthy vs. cancer: |	Dis+	Dis-	Tot
---	---	---	---
T+	64	0	64
T-	59	30	89
Tot	123	30	153 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	52.0%	43.2%	60.8%
Sp	100.0%	90.0%	100.0%
PPV	100.0%	95.3%	100.0%
NPV	33.7%	23.9%	43.5% | 2) CA-125 for benign vs. cancer: |	Dis+	Dis-	Tot
---	---	---	---
T+	64	1	65
T-	59	36	95
Tot	123	37	160 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	52.0%	43.2%	60.8%
Sp	97.0%	91.5%	100.0%
PPV	98.5%	95.5%	100.0%
NPV	37.9%	28.1%	47.7% | 3) CA 72-4 for healthy vs. cancer: |	Dis+	Dis-	Tot
---	---	---	---
T+	66	1	67
T-	57	29	86
Tot	123	30	153 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	54.0%	45.2%	62.8%
Sp	97.0%	90.9%	100.0%
PPV	98.5%	95.6%	100.0%
NPV	33.7%	23.7%	43.7%		**Comments:** None **Quality assessment:** Reference standard: - Verification bias: + Test reliability/variability: + Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

4) CA 72-4 for benign vs. cancer:

	Dis+	Dis-	Tot
T+	66	1	67
T-	57	36	93
Tot	123	37	160

	Value	Lower 95% CI	Upper 95% CI
Se	54.0%	45.2%	62.8%
Sp	97.0%	91.5%	100.0%
PPV	98.5%	95.6%	100.0%
NPV	38.7%	28.8%	48.6%

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Hefler, Mayerhofer, Nardi, et al., 2000 **#5050**	**Geographical location:** Vienna, Austria **Study dates:** Dec 1992-Mar 1999 **Size of population:** 117 **Type of population:** Screening **Genomic test(s) used:** Serum soluble Fas levels **Reference standard:** Surgical pathology Clinical outcome **Reference standard applied to all test negatives?:** NR **Test reliability established?:** Yes **Statistical tests used:** Fas levels CA-125 **Blinding:** NR **Definition of positive and negative on screening test:** Fas: 3.69 ng/mL CA-125: 409 U/mL	**Age:** Cancer: Median: 57 Range: 29-87 Benign: Median: 50 Range: 24-79 Healthy: Median: 39 Range: 23-58 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 52 (44%) Benign ovarian mass: 30 (26%) Healthy controls: 35 (30%) **Inclusion criteria:** Consecutive women with stage I, II, or III ovarian cancer **Exclusion criteria:** Borderline ovarian cancer	**Screening only (n [%]):** NR **Diagnosis of mass:NR** - Symptomatic (n [%]): - Asymptomatic, detected by exam (n [%]): - Asymptomatic, detected by imaging (n [%]): **Additional data used for diagnosis:** Follow-up of women with cancer	1) Fas: |	Dis+	Dis-	Tot
---	---	---	---
T+	28	3	31
T-	24	62	86
Tot	52	65	117 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	53.0%	39.4%	66.6%
Sp	95.0%	89.7%	100.0%
PPV	90.3%	79.9%	100.0%
NPV	72.1%	62.6%	81.6% | 2) CA-125: |	Dis+	Dis-	Tot
---	---	---	---
T+	37	3	40
T-	15	62	77
Tot	52	65	117 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	71.0%	58.7%	83.3%
Sp	95.0%	89.7%	100.0%
PPV	92.5%	84.3%	100.0%
NPV	80.5%	71.7%	89.4% | 3) CA-125 and Fas combined: |	Dis+	Dis-	Tot
---	---	---	---
T+	42	3	45
T-	10	62	72
Tot	52	65	117 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	81.0%	70.3%	91.7%
Sp	95.0%	89.7%	100.0%
PPV	93.3%	86.0%	100.0%
NPV	86.1%	78.1%	94.1%		**Comments:** None **Quality assessment:** Reference standard: - Verification bias: + Test reliability/variability: + Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Hibbs, Skubitz, Pambuccian, et al., 2004 **#9030**	**Geographical location:** Minneapolis, MN **Study dates:** NR **Size of population:** 87 **Type of population:** Screening **Genomic test(s) used:** Gene expression B8 integrin BMP-7 Claudin-4 Col ix a2 CRABp-1 FOX J1 S100A1 **Reference standard:** Surgical pathology Clinical outcome **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Yes **Statistical tests used:** Youden's misclassification; pair-wise tissue comparisons; Wilcoxon-Mann-Whitney; linear logistic regression **Blinding:** Yes **Definition of positive and negative on**	**Age:** Healthy: Mean: 51 Range: 32-79 Serous papillary ovarian cancer: Mean: 57.6 Range: 29-79 Serous papillary ovarian cancer to the omentum: Mean: 59.7 Range: 29-79 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 37 (43%) Healthy controls: 50 (57%) **Inclusion criteria:** None had been treated with chemotherapy before resection **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) B8 integrin (normal vs. ovarian carcinoma): |	Dis+	Dis-	Tot
---	---	---	---
T+	16	7	23
T-	4	43	47
Tot	20	50	70 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	80.0%	62.5%	97.5%
Sp	86.7%	77.3%	96.1%
PPV	69.6%	50.8%	88.4%
NPV	91.5%	83.5%	99.5% | 2) B8 integrin (normal vs. metastatic ovarian carcinoma): |	Dis+	Dis-	Tot
---	---	---	---
T+	14	7	21
T-	3	43	46
Tot	17	50	67 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	80.0%	61.0%	99.0%
Sp	86.7%	77.3%	96.1%
PPV	66.7%	46.5%	86.8%
NPV	93.5%	86.3%	100.0% | 3) BMP-7 (normal vs. ovarian carcinoma): |	Dis+	Dis-	Tot
---	---	---	---
T+	12	17	29
T-	8	33	41
Tot	20	50	70 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	60.0%	38.5%	81.5%
Sp	66.7%	53.6%	79.8%
PPV	41.4%	23.5%	59.3%		**Comments:** None **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: - Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: A

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

screening test:
+++ maximum positive
++ moderate
+ weak
+/- faint or questionable
- lack of staining

	Value	Lower 95% CI	Upper 95% CI
NPV	80.5%	68.4%	92.6%

4) BMP-7 (normal vs. metastatic ovarian carcinoma):

	Dis+	Dis-	Tot
T+	10	17	27
T-	7	33	40
Tot	17	50	67

	Value	Lower 95% CI	Upper 95% CI
Se	60.0%	36.7%	83.3%
Sp	66.7%	53.6%	79.8%
PPV	37.0%	18.8%	55.3%
NPV	82.5%	70.7%	94.3%

5) Claudin-4 (normal vs. ovarian carcinoma):

	Dis+	Dis-	Tot
T+	20	3	23
T-	0	47	47
Tot	20	50	70

	Value	Lower 95% CI	Upper 95% CI
Se	99.3%	85.0%	100.0%
Sp	93.3%	86.4%	100.0%
PPV	87.0%	73.2%	100.0%
NPV	100.0%	93.6%	100.0%

6) Claudin-4 (normal vs. metastatic ovarian carcinoma):

	Dis+	Dis-	Tot
T+	17	3	20
T-	0	47	47
Tot	17	50	67

	Value	Lower 95% CI	Upper 95% CI

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

Se	**100.0%**	82.4%	100.0%
Sp	**93.3%**	86.4%	100.0%
PPV	85.0%	69.4%	100.0%
NPV	100.0%	93.6%	100.0%

7) COL Ix a2 (normal vs. ovarian carcinoma):

	Dis+	Dis-	Tot
T+	4	0	4
T-	16	50	66
Tot	**20**	**50**	70

	Value	Lower 95% CI	Upper 95% CI
Se	**20.0%**	2.5%	37.5%
Sp	**100.0%**	94.0%	100.0%
PPV	100.0%	25.0%	100.0%
NPV	75.8%	65.4%	86.1%

8) COL Ix a2 (normal vs. metastatic ovarian carcinoma):

	Dis+	Dis-	Tot
T+	3	0	3
T-	14	50	64
Tot	**17**	**50**	67

	Value	Lower 95% CI	Upper 95% CI
Se	**20.0%**	1.0%	39.0%
Sp	**100.0%**	94.0%	100.0%
PPV	100.0%	0.0%	100.0%
NPV	78.1%	68.0%	88.3%

9) CRABP-1 (normal vs. ovarian carcinoma):

	Dis+	Dis-	Tot
T+	11	23	34
T-	9	27	36
Tot	**20**	**50**	70

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

	Value	Lower 95% CI	Upper 95% CI
Se	**53.3%**	31.4%	75.2%
Sp	**53.3%**	39.5%	67.1%
PPV	32.4%	16.6%	48.1%
NPV	75.0%	60.9%	89.1%

10) CRABP-1 (normal vs. metastatic ovarian carcinoma):

	Dis+	Dis-	Tot
T+	2	0	2
T-	15	50	65
Tot	**17**	**50**	67

	Value	Lower 95% CI	Upper 95% CI
Se	**13.3%**	0.0%	29.4%
Sp	**100.0%**	94.0%	100.0%
PPV	100.0%	0%	100.0%
NPV	76.9%	66.7%	87.2%

11) FOX J1 (normal vs. ovarian carcinoma):

	Dis+	Dis-	Tot
T+	19	33	52
T-	1	17	18
Tot	**20**	**50**	70

	Value	Lower 95% CI	Upper 95% CI
Se	**93.3%**	82.3%	100.0%
Sp	**33.3%**	20.2%	46.4%
PPV	36.5%	23.5%	49.6%
NPV	94.4%	83.9%	100.0%

12) FOX J1 (normal vs. metastatic ovarian carcinoma):

	Dis+	Dis-	Tot
T+	17	33	50

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

T-	0	17	17
Tot	17	50	67

	Value	Lower 95% CI	Upper 95% CI
Se	100.0%	82.4%	100.0%
Sp	33.3%	20.2%	46.4%
PPV	34.0%	20.9%	47.1%
NPV	100.0%	82.4%	100.0%

13) S100A1 (normal vs. ovarian carcinoma):

	Dis+	Dis-	Tot
T+	20	20	40
T-	0	30	30
Tot	20	50	70

	Value	Lower 95% CI	Upper 95% CI
Se	100.0%	85.0%	100.0%
Sp	60.0%	46.4%	73.6%
PPV	50.0%	34.5%	65.5%
NPV	100.0%	90.0%	100.0%

14) S100A1 (normal vs. metastatic ovarian carcinoma):

	Dis+	Dis-	Tot
T+	16	20	36
T-	1	30	31
Tot	17	50	67

	Value	Lower 95% CI	Upper 95% CI
Se	93.3%	81.4%	100.0%
Sp	60.0%	46.4%	73.6%
PPV	44.4%	28.2%	60.7%
NPV	96.8%	90.6%	100.0%

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Hofmann and Ruschen-burg, 2002 **#3610**	**Geographical location:** Göttingen Germany **Study dates:** NR **Size of population:** 44 **Type of population:** Screening **Genomic test(s) used:** BAGE MAGE-1 MAGE-3 GAGE-1/2 **Reference standard:** Surgical pathology Clinical outcome **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Yes **Statistical tests used:** Sensitivity, specificity **Blinding:** NR **Definition of positive and negative on screening test:** Presence or absence of gene	**Age:** Median: 68 Range: 36-82 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 27 (61%) Healthy controls: 17 (39%) **Inclusion criteria:** Samples sent to department of cytology for routine diagnosis; clinically suspected ovarian carcinoma **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) BAGE: |	Dis+	Dis-	Tot
---	---	---	---
T+	16	1	17
T-	11	16	27
Tot	27	17	44 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	60.0%	41.5%	78.5%
Sp	94.0%	82.7%	100.0%
PPV	94.1%	82.9%	100.0%
NPV	59.3%	40.7%	77.8% | 2) MAGE-1: |	Dis+	Dis-	Tot
---	---	---	---
T+	2	0	2
T-	25	17	42
Tot	27	17	44 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	8.0%	0.0%	18.2%
Sp	100.0%	82.4%	100.0%
PPV	100.0%	0%	100.0%
NPV	40.5%	25.6%	55.3% | 3) MAGE-3: |	Dis+	Dis-	Tot
---	---	---	---
T+	9	0	9
T-	18	17	35
Tot	27	17	44 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	32.0%	14.4%	49.6%
Sp	100.0%	82.4%	100.0%
PPV	100.0%	66.7%	100.0%
NPV	48.6%	32.0%	65.1%		**Comments:** None **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

4) GAGE-1/2:

	Dis+	Dis-	Tot
T+	9	0	9
T-	18	17	35
Tot	27	17	44

	Value	Lower 95% CI	Upper 95% CI
Se	32.0%	14.4%	49.6%
Sp	100.0%	82.4%	100.0%
PPV	100.0%	66.7%	100.0%
NPV	48.6%	32.0%	65.1%

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Hurteau, Woolas, Jacobs, et al., 1995 **#7890**	**Geographical location:** London, England **Study dates:** NR **Size of population:** 192 **Type of population:** Screening **Genomic test(s) used:** sIL-2Rα CA-125 **Reference standard:** Surgical pathology Clinical outcome **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Yes **Statistical tests used:** Student's t test, p<0.05 **Blinding:** NR **Definition of positive and negative on screening test:** sIL-2Rα = 650 U/mL CA-125 = 35 U/mL	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR: **Diagnoses (n [%]):** Ovarian cancer: 39 (20%) Benign ovarian mass: 61 (32%) Healthy controls: 92 (48%) **Inclusion criteria:** Gynecologic masses and healthy controls **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) sIL-2Rα: Dis+ / Dis- / Tot T+: 37 / 58 / 95 T-: 2 / 3 / 5 Tot: 39 / 61 / 100 Value (Lower 95% CI – Upper 95% CI) Se: 94.9% (87.9% – 100.0%) Sp: 4.9% (0.0% – 10.3%) PPV: 38.9% (29.1% – 48.8%) NPV: 60.0% (17.1% – 100.0%) 2) sIL-2Rα +CA-125: Dis+ / Dis- / Tot T+: 34 / 44 / 78 T-: 5 / 17 / 22 Tot: 39 / 61 / 100 Value (Lower 95% CI – Upper 95% CI) Se: 87.2% (76.7% – 97.7%) Sp: 27.9% (16.6% – 39.1%) PPV: 43.6% (32.6% – 54.6%) NPV: 77.3% (59.8% – 94.8%) Values were reversed in table. Unable to duplicate sensitivity value.	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Inaba, Negishi, Fukasawa, et al., 1995 **#7960**	**Geographical location:** Tokyo, Japan **Study dates:** NR **Size of population:** 215 **Type of population:** Screening **Genomic test(s) used:** Cytokeratin fragment 21 (CYFRA 21-1) CA-125 SCC **Reference standard:** Surgical pathology Clinical outcome **Reference standard applied to all test negatives?:** NR **Test reliability established?:** Yes **Statistical tests used:** X^2 test with Yates correction, t test, p<0.05 **Blinding:** NR **Definition of positive and negative on screening test:** CYFRA 21-1 = 1.9 ng/mL CA-125 = 35 U/mL SCC = 1.5 ng/mL	**Age:** Healthy: Range: 18-53 Benign: Range: 19-55 Cancer: Range: 23-69 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 75 (35%) Benign ovarian mass: 38 (18%) Healthy controls: 102 (47%) **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) CYFRA 21-1: |	Dis+	Dis-	Tot
---	---	---	---
T+	48	3	51
T-	27	137	164
Tot	75	140	215 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	64.0%	53.1%	74.9%
Sp	97.9%	95.5%	100.0%
PPV	94.1%	87.7%	100.0%
NPV	83.5%	77.9%	89.2% | 2) CA-125: |	Dis+	Dis-	Tot
---	---	---	---
T+	44	20	64
T-	31	120	151
Tot	75	140	215 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	58.7%	47.5%	69.8%
Sp	85.7%	79.9%	91.5%
PPV	68.8%	57.4%	80.1%
NPV	79.5%	73.0%	85.9%		**Comments:** None **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: A

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Kim, Herlyn, Wong, et al., 2003 **#9230**	**Geographical location:** Boston, MA **Study dates:** 1992-2000 **Size of population:** 104 **Type of population:** Screening **Genomic test(s) used:** Ep-CAM **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Yes **Statistical tests used:** Mean, SD, 95% CI; Mann-Whitney U test **Blinding:** Yes – to clinical data **Definition of positive and negative on screening test:** 0.140 cutoff	**Age:** Mean (SD): 58 Range: 45-76 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 52 (50%) Benign ovarian mass: 26 (25%) Healthy controls: 26 (25%) **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) EP-CAM cutoff 0.140: |	Dis+	Dis-	Tot
---	---	---	---
T+	22	2	24
T-	30	50	80
Tot	52	52	104 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	42.3%	28.9%	55.7%
Sp	96.2%	90.9%	100.0%
PPV	91.7%	80.6%	100.0%
NPV	62.5%	51.9%	73.1% | 2) EP-CAM cutoff 0.115: |	Dis+	Dis-	Tot
---	---	---	---
T+	38	11	49
T-	14	41	55
Tot	52	52	104 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	73.1%	61.0%	85.1%
Sp	78.8%	67.7%	89.9%
PPV	77.6%	65.9%	89.2%
NPV	74.5%	63.0%	86.1% | 3) CA-125 cutoff 35 U/mL: |	Dis+	Dis-	Tot
---	---	---	---
T+	45	6	51
T-	7	46	53
Tot	52	52	104 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	86.5%	77.2%	95.8%
Sp	88.5%	79.8%	97.2%
PPV	88.2%	79.4%	97.1%
NPV	86.8%	77.7%	95.9%		**Comments:** None **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				4) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): A patient with positive EP-CAM has 11.4-fold risk of normal women in the diagnosis of ovarian cancer (odds ratio = 11.4, CI = 3.6 to 36.1, relative risk = 3.8) in comparison with CA-125 (OR = 49.3, CI = 11.6 to 208.6, RR = 7.5).	

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Kozak, Amneus, Pusey, et al., 2003 **#2220**	**Geographical location:** Los Angeles, CA **Study dates:** NR **Size of population:** 184 **Type of population:** Screening **Genomic test(s) used:** Biomarker panels **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Yes **Statistical tests used:** Proteinchip data analysis software **Blinding:** NR **Definition of positive and negative on screening test:** NR	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 109 (59%) Benign ovarian mass: 19 (10%) Healthy controls: 56 (30%) **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) Screening panel #1 (when Se equals Sp): Dis+ / Dis- / Tot T+: 94 / 10 / 104 T-: 15 / 65 / 80 Tot: 109 / 75 / 184 Value (Lower 95% CI – Upper 95% CI) Se: 86.2% (79.7% – 92.7%) Sp: 87.0% (79.4% – 94.6%) PPV: 90.4% (84.7% – 96.1%) NPV: 81.3% (72.7% – 89.8%) 2) Screening panel #1 (highest accuracy): Dis+ / Dis- / Tot T+: 104 / 13 / 117 T-: 5 / 62 / 67 Tot: 109 / 75 / 184 Value (Lower 95% CI – Upper 95% CI) Se: 95.7% (91.9% – 99.5%) Sp: 82.6% (74.0% – 91.2%) PPV: 88.9% (83.2% – 94.6%) NPV: 92.5% (86.2% – 98.8%) 3) Validation panel #1 (when Se equals Sp): Dis+ / Dis- / Tot T+: 93 / 11 / 104 T-: 16 / 64 / 80 Tot: 109 / 75 / 184 Value (Lower 95% CI – Upper 95% CI) Se: 85.2% (78.5% – 91.9%) Sp: 84.7% (76.6% – 92.8%) PPV: 89.4% (83.5% – 95.3%) NPV: 80.0% (71.2% – 88.8%)	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

4) Validation panel #1 (highest accuracy):

	Dis+	Dis-	Tot
T+	89	4	93
T-	20	71	91
Tot	109	75	184

	Value	Lower 95% CI	Upper 95% CI
Se	81.5%	74.2%	88.8%
Sp	94.9%	89.9%	99.9%
PPV	95.7%	91.6%	99.8%
NPV	78.0%	69.5%	86.5%

5) Validation panel #2 (when Se equals Sp):

	Dis+	Dis-	Tot
T+	89	14	103
T-	20	61	81
Tot	109	75	184

	Value	Lower 95% CI	Upper 95% CI
Se	81.5%	74.2%	88.8%
Sp	81.4%	72.6%	90.2%
PPV	86.4%	79.8%	93.0%
NPV	75.3%	65.9%	84.7%

6) Validation panel #2 (highest accuracy):

	Dis+	Dis-	Tot
T+	79	4	83
T-	30	71	101
Tot	109	75	184

	Value	Lower 95% CI	Upper 95% CI
Se	72.8%	64.4%	81.2%
Sp	94.9%	89.9%	99.9%
PPV	95.2%	90.6%	99.8%
NPV	70.3%	61.4%	79.2%

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Lee, Park, Jung, et al., 2005 **#270**	**Geographical location:** Seoul, South Korea **Study dates:** 1994-2002 **Size of population:** 201 **Type of population:** Screening **Genomic test(s) used:** P53 P21 Bax Bcl-2 GADD45 Cyclin E CDK2 PCNA MDM2 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** NR **Test reliability established?:** NR **Statistical tests used:** Cochran-Mantel-Haenszel chi-square test and Cochran-Armitage trend test **Blinding:** Yes **Definition of positive and negative on**	**Age:** Median: 51 Range: 16-86 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 104 Borderline: 37 Benign ovarian mass: 60 **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	Using > 50% positivity: 1) P53: |	Dis+	Dis-	Tot
---	---	---	---
T+	30	0	30
T-	74	97	171
Tot	104	97	201 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	28.8%	20.1%	37.6%
Sp	100.0%	96.9%	100.0%
PPV	100.0%	90.0%	100.0%
NPV	56.7%	49.3%	64.2% | 2) P21: |	Dis+	Dis-	Tot
---	---	---	---
T+	7	5	12
T-	97	92	189
Tot	104	97	201 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	6.7%	1.9%	11.5%
Sp	94.8%	90.4%	99.2%
PPV	58.3%	30.4%	86.2%
NPV	48.7%	41.6%	55.8% | 3) Bax: |	Dis+	Dis-	Tot
---	---	---	---
T+	34	10	44
T-	70	87	157
Tot	104	97	201 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	32.7%	23.7%	41.7%
Sp	89.7%	83.6%	95.7%
PPV	77.3%	64.9%	89.7%		**Comments:** None **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: + Statistical tests: + Blinding: + Definition of +/- on screening test: - Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

screening test:
0-5% positivity
6-49% positivity
≥ 50% positivity

NPV	55.4%	47.6%	63.2%

4) Bcl-2:

	Dis+	Dis-	Tot
T+	13	15	28
T-	91	82	173
Tot	104	97	201

	Value	Lower 95% CI	Upper 95% CI
Se	12.5%	6.1%	18.9%
Sp	84.5%	77.3%	91.7%
PPV	46.4%	28.0%	64.9%
NPV	47.4%	40.0%	54.8%

5) GADD45:

	Dis+	Dis-	Tot
T+	9	21	30
T-	95	76	171
Tot	104	97	201

	Value	Lower 95% CI	Upper 95% CI
Se	8.7%	3.3%	14.1%
Sp	78.4%	70.2%	86.5%
PPV	30.0%	13.6%	46.4%
NPV	44.4%	37.0%	51.9%

6) Cyclin E:

	Dis+	Dis-	Tot
T+	12	0	12
T-	92	97	189
Tot	104	97	201

	Value	Lower 95% CI	Upper 95% CI
Se	11.5%	5.4%	17.7%
Sp	100.0%	96.9%	100.0%
PPV	100.0%	75.0%	100.0%

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

NPV	51.3%	44.2%	58.4%

7) CDK2:

	Dis+	Dis-	Tot
T+	9	0	9
T-	95	97	192
Tot	104	97	201

	Value	Lower 95% CI	Upper 95% CI
Se	8.7%	3.3%	14.1%
Sp	100.0%	96.9%	100.0%
PPV	100.0%	66.7%	100.0%
NPV	50.5%	43.4%	57.6%

8) MDM2:

	Dis+	Dis-	Tot
T+	11	34	45
T-	93	63	156
Tot	104	97	201

	Value	Lower 95% CI	Upper 95% CI
Se	10.6%	4.7%	16.5%
Sp	64.9%	55.5%	74.4%
PPV	24.4%	11.9%	37.0%
NPV	40.4%	32.7%	48.1%

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Luo, Bunting, Scorilas, et al., 2001 **#4490**	**Geographical location:** Toronto, Ontario, Canada **Study dates:** NR **Size of population:** 122 **Type of population:** Screening **Genomic test(s) used:** Hk10 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** NR **Test reliability established?:** Yes **Statistical tests used:** Pearson correlation coefficient, Mann-Whitney test, ROC, AUC **Blinding:** NR **Definition of positive and negative on screening test:** Hk10 > 1.5 µg/L Hk10 > 0.8 µg/L	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 80 (66%) Healthy controls: 42 (34%) **Inclusion criteria:** CA-125 > 372 Ku/l for patients with cancer **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) hk10 > 1.5 µg/L: Dis+ / Dis- / Tot T+: 45 / 0 / 45 T-: 35 / 42 / 77 Tot: 80 / 42 / 122 Value (Lower 95% CI – Upper 95% CI) Se: 56.3% (45.4% – 67.1%) Sp: 100.0% (92.9% – 100.0%) PPV: 100.0% (93.3% – 100.0%) NPV: 54.5% (43.4% – 65.7%) 2) hk10 > 0.8 µg/L: Dis+ / Dis- / Tot T+: 62 / 0 / 62 T-: 18 / 42 / 60 Tot: 80 / 42 / 122 Value (Lower 95% CI – Upper 95% CI) Se: 77.5% (68.3% – 86.7%) Sp: 100.0% (92.9% – 100.0%) PPV: 100.0% (95.2% – 100.0%) NPV: 70.0% (58.4% – 81.6%) 3) ROC curve analysis (AUC 0.92,0.88-0.96): Weak correlation between serum hk10 and CA-125 in ovarian cancer patients (r = 0.23, p = 0.04).	**Comments:** None **Quality assessment:** Reference standard: - Verification bias: + Test reliability/variability: + Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Mabrouk and Ali-Labib, 2003 **#2200**	**Geographical location:** Cairo, Egypt **Study dates:** NR **Size of population:** 60 **Type of population:** Ad hoc **Genomic test(s) used:** uPAR c-erbB-2 CA-125 CA-15.3 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** No **Test reliability established?:** Yes **Statistical tests used:** Pearson correlation Fisher's exact test **Blinding:** NR **Definition of positive and negative on screening test:** Negatives defined as: uPAR: 0.1 ng/mL c-erbB-2: +/1 CA-15.3: < 25 U/mL CA-125: < 35 U/mL	**Age:** Ovarian cancer: Mean (SD): 46 (11.97) Benign ovarian mass: Mean (SD): 45.7 (12.95) Healthy controls: Mean (SD): 46 (15.21) **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** Egyptian 100% **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 20 (33.3%) Benign ovarian mass: 20 (33.3%) Healthy controls: 20 (33.3%) **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** Not applicable **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** Histopathology for diagnosis	1) c-erbB-2: |	Dis+	Dis-	Tot
---	---	---	---
T+	4	4	8
T-	16	16	32
Tot	20	20	40 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	20.0%	2.5%	37.5%
Sp	80.0%	62.5%	97.5%
PPV	50.0%	15.4%	84.6%
NPV	50.0%	32.7%	67.3% | 2) uPAR: |	Dis+	Dis-	Tot
---	---	---	---
T+	20	9	29
T-	0	11	11
Tot	20	20	40 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	100.0%	85.0%	100.0%
Sp	55.0%	33.2%	76.8%
PPV	69.0%	52.1%	85.8%
NPV	100.0%	72.7%	100.0%		**Comments:** - Ad hoc population - Estimates will be higher than in real screening population **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: C

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Makhlouf, Fathalla, Zakhary, et al., 2004 **#1980**	**Geographical location:** Assiut, Egypt **Study dates:** Mar 1998 - Apr 2000 **Size of population:** Ad hoc population 46 malignant 16 benign 30 normal/controls **Type of population:** Ad hoc **Genomic test(s) used:** Sulfatides **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** NR **Statistical tests used:** Mann Whitney U Kruskall Wallis Chi square Firshers **Blinding:** NR **Definition of positive and negative on screening test:** 57 µg/mg	**Age:** Malignant: Mean: 50 Range: 44.5-55 Benign: Mean: 27.5 Range: 20-44 Control: Mean: 45 Range: 40-49 **Menopausal status (n [%]):** 41/92 (44%) **Race/ethnicity (n [%]):** Egyptian 100% **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 46 Benign ovarian mass: 16 Healthy controls: 30 **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** Not applicable **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) Sulfatides for predicting malignancy at cutoff of 57 µg/mg: |	Dis+	Dis-	Tot
---	---	---	---
T+	**42**	**2**	44
T-	**4**	**28**	32
Tot	46	30	76 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	91.3%	83.2%	99.4%
Sp	93.3%	84.4%	100.0%
PPV	95.5%	89.3%	100.0%
NPV	87.5%	76.0%	99.0% | 2) Sulfatides for predicting malignancy at cutoff of 91.3 µg/mg: |	Dis+	Dis-	Tot
---	---	---	---
T+	45	0	45
T-	1	30	31
Tot	**46**	**30**	76 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	**97.0%**	92.1%	100.0%
Sp	**100.0%**	90.0%	100.0%
PPV	100.0%	93.3%	100.0%
NPV	96.8%	90.6%	100.0%		**Comments:** None **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: - Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
McIntosh, Drescher, Karlan, et al., 2004 **#1410**	**Geographical location:** Seattle WA; Los Angeles, CA **Study dates:** NR **Size of population:** 52 ovarian cancer 43 benign 220 healthy **Type of population:** Ad hoc **Genomic test(s) used:** CA-125 Soluble mesothelin-related marker **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** No **Statistical tests used:** Logistic Regression ROC analysis Mann Witney U Wilcoxin **Blinding:** NR **Definition of positive and negative on screening test:** Based on a fixed specificity of 98%	**Age:** NR **Menopausal status (n [%]):** 225/315 (71%) **Race/ethnicity (n [%]):** 3 Native American 8 Asian 1 Black 4 Hispanic 268 White **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 52 Benign ovarian mass: 43 Healthy controls: 220 **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** Not applicable **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) CA-125 – healthy controls: |	Dis+	Dis-	Tot
---	---	---	---
T+	41	4	45
T-	11	216	227
Tot	52	220	272 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	78.8%	67.7%	89.9%
Sp	98.2%	96.4%	99.9%
PPV	91.1%	82.8%	99.4%
NPV	95.2%	92.4%	97.9% | 2) CA-125 – benign controls: |	Dis+	Dis-	Tot
---	---	---	---
T+	20	4	24
T-	32	216	248
Tot	52	220	272 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	38.5%	25.2%	51.7%
Sp	98.2%	96.4%	99.9%
PPV	83.3%	68.4%	98.2%
NPV	87.1%	82.9%	91.3% | 3) SMR – healthy controls: |	Dis+	Dis-	Tot
---	---	---	---
T+	31	4	35
T-	21	216	237
Tot	52	220	272 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	59.6%	46.3%	73.0%
Sp	98.2%	96.4%	99.9%
PPV	88.6%	78.0%	99.1%
NPV	91.1%	87.5%	94.8%		**Comments:** - Ad hoc population – sensitivity and specificity are artificial **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: - Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

4) SMR – benign controls:

	Dis+	Dis-	Tot
T+	15	4	19
T-	37	216	253
Tot	52	220	272

	Value	Lower 95% CI	Upper 95% CI
Se	28.8%	16.5%	41.2%
Sp	98.2%	96.4%	99.9%
PPV	78.9%	60.6%	97.3%
NPV	85.4%	81.0%	89.7%

5) Combined SMR + CA-125 – healthy controls:

	Dis+	Dis-	Tot
T+	45	4	49
T-	7	216	223
Tot	52	220	272

	Value	Lower 95% CI	Upper 95% CI
Se	86.5%	77.3%	95.8%
Sp	98.2%	96.4%	99.9%
PPV	91.8%	84.2%	99.5%
NPV	96.9%	94.6%	99.1%

6) Combined SMR + CA-125 – benign controls:

	Dis+	Dis-	Tot
T+	17	4	21
T-	22	216	238
Tot	39	220	259

	Value	Lower 95% CI	Upper 95% CI
Se	43.6%	28.0%	59.2%
Sp	98.2%	96.4%	99.9%
PPV	81.0%	64.2%	97.7%

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				NPV 90.8% 87.1% 94.4%	
Medl, Ogris, Peters-Engl, et al., 1995 **#8220**	**Geographical location:** Austria **Study dates:** May 1988 - Jun 1993 **Size of population:** 419 **Type of population:** Screening **Genomic test(s) used:** CA-125 Tumor-associated trypsin inhibitor (TATI) **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** NR **Test reliability established?:** Yes **Statistical tests used:** Se, Sp, PPV, NPV, ROC curves; Kruskal-Wallis test used for statistical analysis **Blinding:** Yes **Definition of positive and negative on screening test:** TATI > 21 ng/mL CA-125 > 35 U/mL	**Age:** Mean: 62.4 Range: 23-87 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** Austrian 100% **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 152 Benign ovarian mass: 267 **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) TATI > 21 ng/mL: |	Dis+	Dis-	Tot
---	---	---	---
T+	75	67	142
T-	40	200	240
Tot	115	267	382 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	65.2%	56.5%	73.9%
Sp	74.9%	69.7%	80.1%
PPV	52.8%	44.6%	61.0%
NPV	83.3%	78.6%	88.0% | 2) CA-125 > 35 U/mL: |	Dis+	Dis-	Tot
---	---	---	---
T+	90	59	149
T-	25	208	233
Tot	115	267	382 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	78.3%	70.7%	85.8%
Sp	77.9%	72.9%	82.9%
PPV	60.4%	52.5%	68.3%
NPV	89.3%	85.3%	93.2% | 3) CA-125 > 65 U/mL: |	Dis+	Dis-	Tot
---	---	---	---
T+	79	23	102
T-	36	244	280
Tot	115	267	382 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	68.7%	60.2%	77.2%
Sp	91.4%	88.0%	94.8%		**Comments:** - Consecutive patients enrolled but not all had either disease or benign tumors; may not be true screening population **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: + Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

PPV	77.5%	69.3%	85.6%
NPV	87.1%	83.2%	91.1%

4) TATI > 21 ng/mL or CA-125 > 35 U/mL:

	Dis+	Dis-	Tot
T+	**105**	**105**	210
T-	**10**	**162**	172
Tot	115	267	382

	Value	Lower 95% CI	Upper 95% CI
Se	91.3%	86.2%	96.5%
Sp	60.7%	54.8%	66.5%
PPV	50.0%	43.2%	56.8%
NPV	94.2%	90.7%	97.7%

5) TATI > 21 ng/mL or CA-125 > 65 U/mL:

	Dis+	Dis-	Tot
T+	**98**	**85**	183
T-	**17**	**182**	199
Tot	115	267	382

	Value	Lower 95% CI	Upper 95% CI
Se	85.2%	78.7%	91.7%
Sp	68.2%	62.6%	73.8%
PPV	53.6%	46.3%	60.8%
NPV	91.5%	87.6%	95.3%

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Obermair, Tempfer, Hefler, et al., 1998 **#6690**	**Geographical location:** Austria **Study dates:** NR **Size of population:** 256 **Type of population:** Ad hoc **Genomic test(s) used:** Vascular endothelial growth factor CA-125 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Unable to determine **Test reliability established?:** Yes **Statistical tests used:** Logistic Regression ROC curves **Blinding:** NR **Definition of positive and negative on screening test:** VEGF – 363.7 pg/ml CA-125 – 74.9 U/ml	**Age:** Median: 47 Range: 21-79 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 44 Benign ovarian mass: 81 Healthy controls: 131 **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) VEGF – healthy/cancer: |	Dis+	Dis-	Tot
---	---	---	---
T+	24	19	43
T-	20	62	82
Tot	44	81	125 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	54.5%	39.8%	69.3%
Sp	76.5%	67.3%	85.8%
PPV	55.8%	41.0%	70.7%
NPV	75.6%	66.3%	84.9% | 2) CA-125: |	Dis+	Dis-	Tot
---	---	---	---
T+	37	6	43
T-	7	75	82
Tot	44	81	125 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	84.1%	73.3%	94.9%
Sp	92.6%	86.9%	98.3%
PPV	86.0%	75.7%	96.4%
NPV	91.5%	85.4%	97.5%		**Comments:** None **Quality assessment:** Reference standard: - Verification bias: - Test reliability/variability: + Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Oehler and Caffier, 1999 **#5560**	**Geographical location:** Wurzburg, Germany; Houston, TX **Study dates:** NR **Size of population:** 41 cancers 20 benign tumors 20 normal controls **Type of population:** Ad hoc **Genomic test(s) used:** VEGF **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** No **Test reliability established?:** Yes **Statistical tests used:** Kruskal-Wallis Mann-Whitney U ROC curve **Blinding:** NR **Definition of positive and negative on screening test:** 300 pg/mL	**Ovarian CA patients** **Age:** Mean: 60 Range: 32-83 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 41 Benign ovarian mass: 20 Healthy controls: 20 **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) VEGF – ovarian cancer and normal controls: |	Dis+	Dis-	Tot
---	---	---	---
T+	30	6	36
T-	11	14	25
Tot	41	20	61 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	73.2%	59.6%	86.7%
Sp	70.0%	49.9%	90.1%
PPV	83.3%	71.2%	95.5%
NPV	56.0%	36.5%	75.5% | 2) VEGF – ovarian cancer and benign tumors: |	Dis+	Dis-	Tot
---	---	---	---
T+	29	7	36
T-	12	13	25
Tot	41	20	61 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	70.7%	56.8%	84.7%
Sp	65.0%	44.1%	85.9%
PPV	80.6%	67.6%	93.5%
NPV	52.0%	32.4%	71.6%		**Comments:** - Ad hoc population **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Onsrud, Shabana, and Austgulen, 1996 **#7710**	**Geographical location:** Trondhiem, Norway **Study dates:** NR **Size of population:** 45 - cancer 27 - benign pelvic masses 26 - controls **Type of population:** Ad hoc **Genomic test(s) used:** p55 p75 CA-125 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** No **Statistical tests used:** Wilcoxin rank sum **Blinding:** NR **Definition of positive and negative on screening test:** Mean + 2 SD of the control women for all three tests: p55 = 2.0 ng/mL p75 = 4.3 ng/mL CA-125 = 20 U/mL	**Age:** Ovarian cancer: Median: 58 Range: 21-80 Benign tumors: Median: 45 Range: 19-67 Normal controls: Median: 39 Range: 27-76 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 45 Benign ovarian mass: 27 Healthy controls: 26 **Inclusion criteria:** Patients undergoing laparotomy surgery **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	Note: All tables are for ovarian cancer versus benign tumors. 1) p55: Dis+ / Dis- / Tot T+: **26** / **3** / 29 T-: **19** / **24** / 43 Tot: 45 / 27 / 72 Value / Lower 95% CI / Upper 95% CI Se: 57.8% / 43.3% / 72.2% Sp: 88.9% / 77.0% / 100.0% PPV: 89.7% / 78.6% / 100.0% NPV: 55.8% / 41.0% / 70.7% 2) p75: Dis+ / Dis- / Tot T+: **7** / **1** / 8 T-: **38** / **26** / 64 Tot: 45 / 27 / 72 Value / Lower 95% CI / Upper 95% CI Se: 15.6% / 5.0% / 26.1% Sp: 96.3% / 89.2% / 100.0% PPV: 87.5% / 64.6% / 100.0% NPV: 40.6% / 28.6% / 52.7% 3) CA-125: Dis+ / Dis- / Tot T+: **37** / **4** / 41 T-: **8** / **23** / 31 Tot: 45 / 27 / 72 Value / Lower 95% CI / Upper 95% CI Se: 82.2% / 71.1% / 93.4% Sp: 85.2% / 71.8% / 98.6%	**Comments:** None **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

PPV	90.2%	81.2%	99.3%
NPV	74.2%	58.8%	89.6%

Note: NPV calculated here does not match the 72% reported in the paper.

4) p55 + CA-125:

	Dis+	Dis-	Tot
T+	**38**	**6**	44
T-	**7**	**21**	28
Tot	45	27	72

	Value	Lower 95% CI	Upper 95% CI
Se	84.4%	73.9%	95.0%
Sp	77.8%	62.1%	93.5%
PPV	86.4%	76.2%	96.5%
NPV	74.2%	58.8%	89.6%

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Opala, Drews, Rzymski, et al., 2003 **#2650**	**Geographical location:** Poznan, Poland **Study dates:** Jun 2000 – Nov 2002 **Size of population:** 101 with suspicious tumors 16 healthy women **Type of population:** Ad hoc **Genomic test(s) used:** Soluble intracellular adhesion molecule-1 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** NR **Test reliability established?:** Yes **Statistical tests used:** Mann Witney U Spearman Pearson **Blinding:** NR **Definition of positive and negative on screening test:** CA-125 = 35 U/mL sICAM-1 = 250 ng/mL	**Age:** Cancer: Mean (SD): 51.5 (11.5) Range: 23-80 Borderline: Mean (SD): 46.0 (15.8) Range: 25-62 Benign: Mean (SD): 39.4 (14.3) Range: 13-71 Normal: Mean (SD): 27.8 (12.6) Range: 20-63 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 51 Borderline: 5 Benign ovarian mass: 45 Healthy controls: 16 **Inclusion criteria:** Women treated surgically b/c of suspicious pelvic tumors **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	Note: All tables are for ovarian cancer vs. healthy controls. 1) sICAM-1: |	Dis+	Dis-	Tot
---	---	---	---
T+	42	7	49
T-	9	9	18
Tot	51	16	67 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	82.4%	71.9%	92.8%
Sp	56.3%	31.9%	80.6%
PPV	85.7%	75.9%	95.5%
NPV	50.0%	26.9%	73.1% | Note: Numbers do not match those reported in the article. 2) CA-125: |	Dis+	Dis-	Tot
---	---	---	---
T+	48	4	52
T-	3	12	15
Tot	**51**	**16**	67 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	**93.8%**	87.2%	100.0%
Sp	**74.5%**	53.1%	95.9%
PPV	92.3%	85.1%	99.6%
NPV	80.0%	59.8%	100.0% | Note: Numbers do not match those reported in the article. (3) sICAM-I + CA-125: |	Dis+	Dis-	Tot
---	---	---	---
T+	48	2	50
T-	3	14	17		**Comments:** - Majority of analyses applied to women with malignancies - Unable to determine specificity for CA-125 - Same patient population as Opala et al., 2005 (#480) **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: C

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

Tot **51** **16** 67

	Value	Lower 95% CI	Upper 95% CI
Se	**93.8%**	87.2%	100.0%
Sp	**86.3%**	69.5%	100.0%
PPV	96.0%	90.6%	100.0%
NPV	82.4%	64.2%	100.0%

Note: Numbers do not match those reported in the article.

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Opala, Rzymski, Wildzak, et al., 2005 **#480**	**Geographical location:** Poznan, Poland **Study dates:** Jun 2000 – Nov 2002 **Size of population:** 101 with suspicious tumors 16 healthy women **Type of population:** Ad hoc **Genomic test(s) used:** p55 p75 CA-125 **Reference standard applied to all test negatives?:** No **Test reliability established?:** Yes **Statistical tests used:** Mann Withney U ROC curves Correlation coefficients **Blinding:** NR **Definition of positive and negative on screening test:** p55: 1663 pg/mL p75: 2837 pg/mL CA-125: 35 U/mL	**Age:** Cancer: Mean (SD): 51.5 (11.5) Range: 23-80 Borderline: Mean (SD): 46.0 (15.8) Range: 25-62 Benign: Mean (SD): 39.4 (14.3) Range: 13-71 Normal: Mean (SD): 27.8 (12.6) Range: 20-63 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 51 Borderline: 5 Benign ovarian mass: 45 Healthy controls: 16 **Inclusion criteria:** Women treated surgically b/c of suspicious pelvic tumors **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) p55: |	Dis+	Dis-	Tot
---	---	---	---
T+	28	1	29
T-	23	15	38
Tot	51	16	67 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	54.9%	41.2%	68.6%
Sp	93.8%	81.9%	100.0%
PPV	96.6%	89.9%	100.0%
NPV	39.5%	23.9%	55.0% | 2) p75: |	Dis+	Dis-	Tot
---	---	---	---
T+	22	3	25
T-	29	13	42
Tot	51	16	67 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	43.1%	29.5%	56.7%
Sp	81.3%	62.1%	100.0%
PPV	88.0%	75.3%	100.0%
NPV	31.0%	17.0%	44.9% | 3) CA-125: |	Dis+	Dis-	Tot
---	---	---	---
T+	38	1	39
T-	13	15	28
Tot	51	16	67 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	74.5%	62.5%	86.5%
Sp	93.8%	81.9%	100.0%
PPV	97.4%	92.5%	100.0%
NPV	53.6%	35.1%	72.0%		**Comments:** - Cutpoint established using cancer versus controls - Ad hoc population - Same patient population as Opala et al., 2003 (#2650) **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: C

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Peters-Engl, Medl, Ogris, et al., 1995 **#7840**	**Geographical location:** Vienna, Austria **Study dates:** NR **Size of population:** 180 ovarian cancer 214 with benign pelvic disease **Type of population:** Ad hoc **Genomic test(s) used:** TATI CA-125 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Yes **Statistical tests used:** "Non parametric test" **Blinding:** Yes **Definition of positive and negative on screening test:** TATI: 21 ng/ml CA-125: 35 U/ml	**Age:** Mean: 62.4 Range: 23-87 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** Austrian 100% **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 180 Benign ovarian mass: 214 Healthy controls: 149 – used for determination of cutpoint only **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) TATI: |	Dis+	Dis-	Tot
---	---	---	---
T+	114	60	174
T-	66	154	220
Tot	180	214	394 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	63.3%	56.3%	70.4%
Sp	72.0%	65.9%	78.0%
PPV	65.5%	58.5%	72.6%
NPV	70.0%	63.9%	76.1% | 2) CA-125: |	Dis+	Dis-	Tot
---	---	---	---
T+	144	39	183
T-	36	175	211
Tot	180	214	394 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	80.0%	74.2%	85.8%
Sp	81.8%	76.6%	86.9%
PPV	78.7%	72.8%	84.6%
NPV	82.9%	77.9%	88.0% | 3) CA-125 + TATI: |	Dis+	Dis-	Tot
---	---	---	---
T+	164	75	239
T-	16	139	155
Tot	180	214	394 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	91.1%	87.0%	95.3%
Sp	65.0%	58.6%	71.3%
PPV	68.6%	62.7%	74.5%
NPV	89.7%	84.9%	94.5%		**Comments:** None **Quality assessment:** Reference standard: + Verification bias: : + Test reliability/variability: : + Sample size: : + Statistical tests: : + Blinding: : + Definition of +/- on screening test: + Grade: A

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Schutter, Mijatovic, Kok, et al., 1999 **#5950**	**Geographical location:** Amsterdam, The Netherlands **Study dates:** NR **Size of population:** 31 **Type of population:** Malignant and non-malignant disease **Genomic test(s) used:** UGP (urinary gonadotropin peptide) UGP/Cr CA-125 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** No (except CA-125) **Statistical tests used:** Se, Se, ROC **Blinding:** NR **Definition of positive and negative on screening test:** UGP > 1 fmol/L is positive UGP/creat > 1.33 fmol/mg positive CA-125 > 100 U/mL positive	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 9 Benign ovarian or uterine mass: 10 Other benign controls: 12 - Sterilization: 3 - Refertilization (?): 2 - Prolapse: 2 - DUB: 2 - Endometriosis: 2 - Sterility: 1 **Inclusion criteria:** Scheduled for surgery due to a gynecologic condition **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) Ability of UGP >1 fmol/L to discriminate ovarian carcinoma from all benign gynecologic conditions (both benign masses and controls): Dis+ / Dis- / Tot T+: 7 / 7 / 14 T-: 2 / 14 / 16 Tot: 9 / 21 / 30 Value (Lower 95% CI – Upper 95% CI) Se: 78.0% (50.9% – 100.0%) Sp: 65.0% (44.6% – 85.4%) PPV: 50.0% (23.8% – 76.2%) NPV: 87.5% (71.3% – 100.0%) 2) Ability of UGP/creat > 1.33 fmol/mg to discriminate ovarian arcinoma from all benign gynecologic conditions (both benign masses and controls). Note: same numbers as first table: Dis+ / Dis- / Tot T+: 7 / 7 / 14 T-: 2 / 14 / 16 Tot: 9 / 21 / 30 Value (Lower 95% CI – Upper 95% CI) Se: 78.0% (50.9% – 100.0%) Sp: 65.0% (44.6% – 85.4%) PPV: 50.0% (23.8% – 76.2%) NPV: 87.5% (71.3% – 100.0%)	**Comments:** - Only 9 cancers. - For purposes of deciding whether this marker is better as a screening test or a diagnostic test it would be preferable to see the performance for discriminating cancers from other masses or cancers versus healthy controls, instead of mixing them together. Would also be preferable to differentiate ovarian benign masses from uterine benign masses. **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: - Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Schutter, Sohn, Kristen, et al., 1998 **#6850**	**Geographical location:** Amsterdam, The Netherlands **Study dates:** NR **Size of population:** 155 **Type of population:** Adnexal mass **Genomic test(s) used:** CA 72-4 CA-125 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Yes **Statistical tests used:** Se, Sp, PPV, NPV, ROC, logistic regression (incorporating ultrasound score) **Blinding:** NR **Definition of positive and negative on screening test:** CA-125 < 35 u/mL normal CA-72-4 < 3 normal	**Age:** Mean: 63 Median: 61 Range: 45-88 **Menopausal status (n [%]):** Post (> 55): 155 (100%) **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 43 (27%) Borderline: 4 (3%) Benign ovarian mass: 92 (59%) Other (non-ovarian malignancies): 16 (10%) **Inclusion criteria:** Plan to undergo surgery for a pelvic mass, postmenopausal **Exclusion criteria:** Exclusion criteria not defined in this paper, reader is referred to Reference #1.	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) CA-72-4, ovarian cancer versus benign masses, cutoff 2 U/mL: Dis+ / Dis- / Tot T+: 36 / 42 / 78 T-: 7 / 50 / 57 Tot: 43 / 92 / 135 Value (Lower 95% CI – Upper 95% CI) Se: 84.0% (73.0% – 95.0%) Sp: 54.0% (43.8% – 64.2%) PPV: 46.2% (35.1% – 57.2%) NPV: 87.7% (79.2% – 96.2%) 2) CA-72-4, ovarian cancer versus benign masses, cutoff 3 U/mL: Dis+ / Dis- / Tot T+: 28 / 6 / 34 T-: 15 / 86 / 101 Tot: 43 / 92 / 135 Value (Lower 95% CI – Upper 95% CI) Se: 65.0% (50.7% – 79.3%) Sp: 93.0% (87.8% – 98.2%) PPV: 82.4% (69.5% – 95.2%) NPV: 85.1% (78.2% – 92.1%) For CA-72-4 with cutoff 3.2 U/mL, Se = 65, Sp = 95, PPV = 85, NPV = 85.	**Comments:** - No healthy controls – all patients had either malignant or non-malignant pathology **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: + Statistical tests: + Blinding: NR Definition of +/- on screening test: + Grade: A

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Sedlaczek, Frydecka, Gabrys, et al., 2002 **#3310**	**Geographical location:** Wroclaw, Poland **Study dates:** NR **Size of population:** 99 **Type of population:** Adnexal mass **Genomic test(s) used:** TPS, sIL-2R, CA-125 **Reference standard** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Yes **Statistical tests used:** Mann-Whitney U, Wilcoxon **Blinding:** NR **Definition of positive and negative on screening test:** CA-125 < 35 U/mL normal TPS < 80 U/mL normal sIL-2R < 2140 pg/nl normal	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 67 (67%) Benign ovarian mass: 32 (32%) **Inclusion criteria:** Planned surgery for ovarian mass **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) TPS serum – ovarian cancer vs. benign ovarian mass: |	Dis+	Dis-	Tot
---	---	---	---
T+	53	6	59
T-	14	26	40
Tot	67	32	99 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	79.1%	69.4%	88.8%
Sp	81.3%	67.7%	94.8%
PPV	89.8%	82.1%	97.5%
NPV	65.0%	50.2%	79.8% | 2) sIL-2R serum – ovarian cancer vs. benign ovarian mass: |	Dis+	Dis-	Tot
---	---	---	---
T+	54	1	55
T-	13	31	44
Tot	67	32	99 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	80.6%	71.1%	90.1%
Sp	96.9%	90.8%	100.0%
PPV	98.2%	94.7%	100.0%
NPV	70.5%	57.0%	83.9% | 3) TPS cyst fluid – ovarian cancer vs. benign ovarian mass: |	Dis+	Dis-	Tot
---	---	---	---
T+	26	32	58
T-	0	0	0
Tot	26	32	58 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	100.0%	88.5%	100.0%
Sp	0.0%	0.0%	0.0%		**Comments:** - TPS levels are elevated in cyst fluid of all patients with benign disease (Sp = 0) - No data on levels in ascites of patients with benign disease (cant calculate specificity) **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: Unclear Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

PPV	44.8%	32.0%	57.6%
NPV	#DIV/0!	#DIV/0!	#DIV/0!

4) sIL-2R cyst fluid – ovarian cancer vs. benign ovarian mass:

	Dis+	Dis-	Tot
T+	21	4	25
T-	5	28	33
Tot	26	32	58

	Value	Lower 95% CI	Upper 95% CI
Se	80.8%	65.6%	95.9%
Sp	87.5%	76.0%	99.0%
PPV	84.0%	69.6%	98.4%
NPV	84.8%	72.6%	97.1%

5) TPS ascites – ovarian cancer vs. benign ovarian mass:

	Dis+	Dis-	Tot
T+	45	0	45
T-	0	0	0
Tot	45	0	45

	Value	Lower 95% CI	Upper 95% CI
Se	100.0%	93.3%	100.0%
Sp	#DIV/0!	#DIV/0!	#DIV/0!
PPV	100.0%	93.3%	100.0%
NPV	#DIV/0!	#DIV/0!	#DIV/0!

6) sIL-2R ascites – ovarian cancer vs. benign ovarian mass:

	Dis+	Dis-	Tot
T+	44	0	44
T-	1	0	1
Tot	45	0	45

		Lower	Upper

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Value 95% CI 95% CI Se 97.8% 93.5% 100.0% Sp #DIV/0! #DIV/0! #DIV/0! PPV 100.0% 93.2% 100.0% NPV 0.0% 0.0% 0.0%	
Skates, Horick, Yu, et al., 2004 **#1380**	**Geographical location:** Boston, MA; Houston, TX; Durham, NC; Baltimore, MD; Groningen, The Netherlands; London, UK **Study dates:** NR **Size of population:** 189 (training set); 158 (validation set) **Type of population** Known cases of cancer, healthy controls **Genomic test(s) used:** CA-125 II CA-15-3 CA-72-4 Macrophage colony-stimulating factor (M-CSF) **Reference standard** Surgical pathology for cancer; not specified for controls **Reference standard applied to all test negatives?:** Unclear **Test reliability established?:**	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 60 (38.0%) Healthy controls: 98 (62.0%) **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	Models including all 4 markers. 1) Logistic regression, cancer vs. control. Note: 95% CIs may not reflect 95% CI estimates based on statistical model; CIs not reported: Dis+ Dis- Tot T+ 41 2 43 T- 19 96 115 Tot 60 98 158 Value Lower 95% CI Upper 95% CI Se 68.0% 56.2% 79.8% Sp 98.0% 95.2% 100.0% PPV 95.3% 89.1% 100.0% NPV 83.5% 76.7% 90.3% 2) CART, cancer vs. control. Note: 95% CIs may not reflect 95% CI estimates based on statistical model; CIs not reported: Dis+ Dis- Tot T+ 21 2 23 T- 39 96 135 Tot 60 98 158 Value Lower 95% CI Upper 95% CI Se 35.0% 22.9% 47.1% Sp 98.0% 95.2% 100.0% PPV 91.3% 79.8% 100.0% NPV 71.1% 63.5% 78.8%	**Comments:** - Very high prevalence of cancer in both test and validation sets - 95% CIs for estimates of sensitivity/specificity with each statistical method not presented uniformly **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: - Statistical tests: + Blinding: + Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Referenced **Statistical tests used:** Logistic regression using results from multiple markers; CART trees; mixture discriminant analysis **Blinding:** NR **Definition of positive and negative on screening test:**			3) MDA, cancer vs. control. Note: 95% CIs may not reflect 95% CI estimates based on statistical model; CIs not reported: Dis+ / Dis- / Tot T+: 41 / 2 / 43 T-: 19 / 96 / 115 Tot: 60 / 98 / 158 Value / Lower 95% CI / Upper 95% CI Se: 68.0% / 56.2% / 79.8% Sp: 98.0% / 95.2% / 100.0% PPV: 95.3% / 89.1% / 100.0% NPV: 83.5% / 76.7% / 90.3% 4) Possible additional 2x2 tables: Combinations of markers at 98% specificity: CA-125 II + CA-72.4: Se 67% CA-125 II + CA-72-4 +M-CSF: Se 70% CA-125 II + CA-72-4 +M-CSF + CA-15-3: Se 68% Additional 2x2 tables possible for some models, but at specificity fixed at 95%. 5) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Single marker sensitivities all lower at fixed specificity.	

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Takano, Okamoto, Fukushima, et al., 2000 **#4960**	**Geographical location:** Tokyo, Japan **Study dates:** NR **Size of population:** 59 **Type of population:** Ovarian cancer, benign ovarian tumor, or healthy control **Genomic test(s) used:** CK19 expression in peripheral blood mononuclear cells (PBMCs) **Reference standard:** Surgical pathology (not specified but assumed) **Reference standard applied to all test negatives?:** No **Test reliability established?:** No **Statistical tests used:** Not applicable **Blinding:** NR **Definition of positive and negative on screening test:** Not given (any present versus none present is assumed based on reading paper)	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 25 (42%) Benign ovarian mass: 14 (24%) Healthy controls: 20 (34%) **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) CK19 expression in PBMCs – ovarian cancer vs. benign ovarian tumors: Dis+ / Dis- / Tot T+: 21 / 10 / 31 T-: 4 / 4 / 8 Tot: 25 / 14 / 39 Value (Lower 95% CI – Upper 95% CI) Se: 84.0% (69.6% – 98.4%) Sp: 28.6% (4.9% – 52.2%) PPV: 67.7% (51.3% – 84.2%) NPV: 50.0% (15.4% – 84.6%) 2) CK19 expression in PBMCs – ovarian cancer vs. healthy controls: Dis+ / Dis- / Tot T+: 21 / 12 / 33 T-: 4 / 8 / 12 Tot: 25 / 20 / 45 Value (Lower 95% CI – Upper 95% CI) Se: 84.0% (69.6% – 98.4%) Sp: 40.0% (18.5% – 61.5%) PPV: 63.6% (47.2% – 80.0%) NPV: 66.7% (40.0% – 93.3%)	**Comments:** - No definition of positive or negative expression provided; must assume the ability to detect any expression with PCR is the cutoff. - Authors note poor performance of this test to distinguish cancers from controls or benign tumors. **Quality assessment:** Reference standard: - Verification bias: - Test reliability/variability: - Sample size: - Statistical tests: - Blinding: - Definition of +/- on screening test: - Grade: C

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Tanir, Ozalp, Yalcin, et al., 2003 **#2630**	**Geographical location:** Eskisehir, Turkey **Study dates:** Aug 2001-Sep 2002 **Size of population:** 63 **Type of population:** Adnexal mass **Genomic test(s) used:** Serum VEGF **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** No **Statistical tests used:** Se, Sp, ROC, positive and negative likelihood ratios **Blinding:** NR **Definition of positive and negative on screening test:** 68.7 pg/mL was proposed, as it had best Se, Sp (different cutoffs were examined)	**Age:** Non-neoplastic: Mean (SD): 39 (± 2) Neoplastic: Mean (SD): 56.9 (± 4.2) **Menopausal status (n [%]):** Pre (< 45): 40 (63%) Post (> 55): 23 (37%) **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer (group III): 12 (19.3%) Non-neoplastic benign (group I): 40 (64.5%) Neoplastic benign (group II): 10 (16.1%) **Inclusion criteria:** Pelvic mass, planned surgery **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** Among post-menopausal women, used tumor volume, solid/cystic appearance, presence and thickness of septa, uni-or bilaterality, intratumoral papillary excrescences to determine malignancy of mass	1) Serum VEGF cutoff 68.7 pg/mL – benign and non-neoplastic versus malignant ovarian masses. Se 92, Sp 88, LR(+) 3.3, LR(-) 0.11 |	Dis+	Dis-	Tot
---	---	---	---
T+	11	6	17
T-	1	44	45
Tot	12	50	62 | |	Value	Lower 95% CI	Upper 95% CI
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Se	91.7%	76.0%	100.0%
Sp	88.0%	79.0%	97.0%
PPV	64.7%	42.0%	87.4%
NPV	97.8%	93.5%	100.0%	 2) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): AUC for VEGF = 0.938 (95% CI 0.81 to 0.96). AUC for VEGF (postmenopausal only) = 0.902 (0.70 to 0.98).	**Comments:** - Small n limits clinical interpretation of results **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: - Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: C

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Tempfer, Hefler, Heinzl, et al., 1998 **#6560**	**Geographical location:** Vienna, Austria **Study dates:** NR **Size of population:** 175 **Type of population:** Adnexal mass Other benign conditions **Genomic test(s) used:** CYFRA 21-1 **Reference standard:** Surgical pathology Clinical outcome (some patients had known benign conditions and were not operative candidates) **Reference standard applied to all test negatives?:** N/A **Test reliability established?:** No **Statistical tests used:** Se, Sp, ROC curves **Blinding:** NR **Definition of positive and negative on screening test:** CYFRA 21-1 level of 4.7 mcg/L was used to report Se, Sp	**Age:** Median: 57.9 (cancer patients), 31.3 (healthy controls) **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 37 (21%) Other: - Benign cyst: 90 (51%) - Endometriosis: 10 (6%) - PID: 38 (22%) - Healthy controls: 40 (23%) - Inflammatory bowel disease: 10 (6%) - Cirrhosis: 20 (11%) **Inclusion criteria:** Surgery for a pelvic mass, healthy controls, and controls with non-malignant diseases **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) CYFRA 21-1 cutoff 4.7 mcg/L – ovarian cancer vs. healthy controls: Se 41%, Sp 95%. Dis+ / Dis- / Tot T+: 15 / 2 / 17 T-: 22 / 38 / 60 Tot: 37 / 40 / 77 Value (Lower 95% CI, Upper 95% CI) Se: 40.5% (24.7%, 56.4%) Sp: 95.0% (88.2%, 100.0%) PPV: 88.2% (72.9%, 100.0%) NPV: 63.3% (51.1%, 75.5%) 2) CYFRA 21-1 – ovarian cancer vs. benign ovarian cyst: AUC = 0.86. Individual cutoffs not given. 3) Data on other test accuracy measures (correlation coefficient, interclass correlation, etc.): Intra-assay correlation coefficient is 6.5% at a concentration of 3 mcg/L CYFRA 21-1.	**Comments:** - Cancers and controls were not age-matched. - No cutoffs were established for CYFRA 21-1 and not enough data given to re-create the Se and Sp. **Quality assessment:** Reference standard: - Verification bias: - (apparently healthy controls didn't have surgery to check for ovarian cancer, and no follow up was specified for them) Test reliability/variability: + Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: - Grade: C

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Tsukishiro, Suzumori, Nishikawa, et al., 2005 **#870**	**Geographical location:** Nagoya, Japan **Study dates:** 1997-2004 **Size of population:** 118 **Type of population:** Adnexal mass Healthy controls **Genomic test(s) used:** Secretory leukocyte protease inhibitor (SLPI) **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** All except healthy controls **Test reliability established?:** No **Statistical tests used:** Se,Sp, ROC **Blinding:** No **Definition of positive and negative on screening test:** SLPI > 50 ng/mL CA-125 > 30 U/mL	**Age:** Malignant: Mean (SD): 54 (1.8) Benign: Mean (SD): 50 (4.3) Control: Mean (SD): 49 (4.8) **Menopausal status (n [%]):** Pre (< 50): 14 Post (> 50): 41 **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 55 (47%) Benign ovarian mass: 25 (21%) Healthy controls: 38 (32%) **Inclusion criteria:** Pre-operative for assessment of ovarian mass, healthy controls **Exclusion criteria:** "Inflammatory states", positive blood cultures, CRP > 5 mg/dl, peripheral leukocyte counts >10,000, borderline tumors	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) SLPI cutoff 50 ng/mL – ovarian cancer vs. benign cysts: |	Dis+	Dis-	Tot
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T+	42	5	47
T-	13	20	33
Tot	**55**	**25**	80 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	**76.0%**	64.7%	87.3%
Sp	**80.0%**	64.3%	95.7%
PPV	89.4%	80.5%	98.2%
NPV	60.6%	43.9%	77.3% | 2) SLPI > 50 ng/mL and CA-125 > 30 U/mL – ovarian cancer vs. benign ovarian cysts: |	Dis+	Dis-	Tot
---	---	---	---
T+	52	0	52
T-	3	25	28
Tot	**55**	**25**	80 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	**95.0%**	89.2%	100.0%
Sp	**100.0%**	88.0%	100.0%
PPV	100.0%	94.2%	100.0%
NPV	89.3%	77.8%	100.0% | 3) CA-125 > 30U/mL – ovarian cancer vs. benign ovarian cysts: |	Dis+	Dis-	Tot
---	---	---	---
T+	48	4	52
T-	7	21	28
Tot	**55**	**25**	80 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	**87.0%**	78.1%	95.9%
Sp	**84.0%**	69.6%	98.4%		**Comments:** **Quality assessment:** Reference standard: + (except healthy controls) Verification bias: + (except healthy controls) Test reliability/variability: - no info Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				PPV 92.3% 85.1% 99.6% NPV 75.0% 59.0% 91.0%	
Udagawa, Aoki, Ito, et al., 1998 **#6640**	**Geographical location:** Tokyo, Japan **Study dates:** NR **Size of population:** 860 **Type of population:** Multiple clinical groups, some with cancer (see Diagnoses) **Genomic test(s) used:** Serum GAT (galactosyltransferase associated with tumor) **Reference standard:** NR **Reference standard applied to all test negatives?:** No **Test reliability established?:** No **Statistical tests used:** Se, Sp, ROC **Blinding:** NR **Definition of positive and negative on screening test:** GAT > 16 U/mL (2 SDs over the mean) CA-602 > 63 U/mL	**Age:** Range: 10-89 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 134 (16%) Benign ovarian mass: 193 (22%) Healthy controls: 294 (34%) Pregnant: 32 (4%) Endometriosis: 110 (13%) Cervical cancer: 40 (5%) Endometrial cancer: 48 (6%) Cancer metastatic to ovary: 9 (1%) **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** 0 **Diagnosis of mass: NR** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) GAT cutoff 16 U/mL – ovarian cancer vs. benign ovarian tumors: Dis+ Dis- Tot T+ 68 13 81 T- 68 285 353 Tot 136 298 434 Value Lower 95% CI Upper 95% CI Se 50.0% 41.6% 58.4% Sp 95.6% 93.3% 97.9% PPV 84.0% 76.0% 91.9% NPV 80.7% 76.6% 84.9% AUC of GAT = 0.791 2) GAT/CA602/CA546 – ovarian malignancy vs. benign ovarian mass: The second and third markers each have one reference to their discovery as putative ovarian cancer markers. Dis+ Dis- Tot T+ 115 112 227 T- 21 186 207 Tot 136 298 434 Value Lower 95% CI Upper 95% CI Se 84.6% 78.5% 90.7% Sp 62.4% 56.9% 67.9% PPV 50.7% 44.2% 57.2% NPV 89.9% 85.7% 94.0% 3) Data on other test accuracy measures (correlation coefficient, interclass correlation,	**Comments:** - Did not separate ovarian cancer from malignancy metastatic to the ovary in analysis for Se/Sp - Menopausal status not specified - No age comparison between groups reported **Quality assessment:** Reference standard: - Verification bias: - Test reliability/variability: - Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: C

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	CA-546 > 12U/mL			etc.): Coefficient of variation < 5%.	
van Haaften-Day, Shen, Xu, et al., 2001 **#4010**	**Geographical location:** Sydney, Australia; Houston, TX; Durham, NC; Groningen, The Netherlands **Study dates:** May 1989-Oct 1993 for some subjects (not reported for all) **Size of population:** 398 **Type of population:** Adnexal mass; 87 healthy subjects **Genomic test(s) used:** CA-125-II M-CSF OVX1 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** No **Test reliability established?:** Referenced **Statistical tests used:** Logistic regression **Blinding:** NR **Definition of positive**	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 175 (44.1%) Borderline: 28 (7.1%) Benign ovarian mass: 77 (19.4%) Healthy controls: 117 (29.5%) **Inclusion criteria:** NR **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) CA-125 > 35 U/mL, including borderline as Dis+: |	Dis+	Dis-	Tot
---	---	---	---
T+	153	27	180
T-	50	167	217
Tot	203	194	397 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	75.4%	69.4%	81.3%
Sp	86.1%	81.2%	91.0%
PPV	85.0%	79.8%	90.2%
NPV	77.0%	71.4%	82.6% | 2) OVX1 > 7.2 U/mL, cancer + borderline vs. benign and control: |	Dis+	Dis-	Tot
---	---	---	---
T+	38	16	54
T-	165	178	343
Tot	203	194	397 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	18.7%	13.4%	24.1%
Sp	91.8%	87.9%	95.6%
PPV	70.4%	58.2%	82.5%
NPV	51.9%	46.6%	57.2% | 3) M-CSF > 3.5 ng/mL, cancer + borderline vs. benign and control: |	Dis+	Dis-	Tot
---	---	---	---
T+	69	28	97
T-	134	166	300
Tot	203	194	397		**Comments:** - Benign masses not included in reported false positive rates - 95% CIs not universally reported - Sensitivity generally better for invasive than for borderline **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring

and negative on screening test:
Positive if:
CA-125 II > 35 U/mL
OVX1 > 7.2
M-CSF > 3.5

	Value	Lower 95% CI	Upper 95% CI
Se	34.0%	27.5%	40.5%
Sp	85.6%	80.6%	90.5%
PPV	71.1%	62.1%	80.2%
NPV	55.3%	49.7%	61.0%

4) All 3 markers, any test above threshold = positive, cancer + borderline vs. benign + healthy control:

	Dis+	Dis-	Tot
T+	**155**	**52**	207
T-	**48**	**142**	190
Tot	203	194	397

	Value	Lower 95% CI	Upper 95% CI
Se	76.4%	70.5%	82.2%
Sp	73.2%	67.0%	79.4%
PPV	74.9%	69.0%	80.8%
NPV	74.7%	68.6%	80.9%

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Wakahara, Kikkawa, Nawa, et al., 2001 **#4120**	**Geographical location:** Toyohashi, Japan **Study dates:** 1994-1999 **Size of population:** 292 **Type of population:** Adnexal mass **Genomic test(s) used:** CA 19-9, CA 72-4, CA-125 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Yes **Statistical tests used:** Se, Sp, ROC **Blinding:** NR **Definition of positive and negative on screening test:** Abnormal defined as: CA-125 > 35U/mL CA-19-9 > 37U/mL CA-72-4 > 4 U/mL	**Age:** Mean (SD): 40.3 - Benign: 37.5 (13.1) - LMP: 41 (19.9) - Cancer: 48.8 (14.7) Range: 11-79 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 66 (23%) Borderline: 18 (6.1%) Benign ovarian mass: 208 (71%) **Inclusion criteria:** Surgery for an adnexal mass **Exclusion criteria:** NR	**Screening only (n [%]):** 292 (assumed) **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** Transvaginal sonography; 4 patterns used to determine/describe malignancy	1) CA-19-9 cutoff 37 U/mL, ovarian cancer versus benign ovarian mass: AUC for CA-19-9 = 0.475 |	Dis+	Dis-	Tot
---	---	---	---
T+	24	78	102
T-	42	127	169
Tot	66	205	271 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	36.4%	24.8%	48.0%
Sp	62.0%	55.3%	68.6%
PPV	23.5%	15.3%	31.8%
NPV	75.1%	68.6%	81.7% | 2) CA-72-4 cutoff 4 U/mL, ovarian cancer versus benign ovarian mass. AUC for CA-72-4 = 0.645 |	Dis+	Dis-	Tot
---	---	---	---
T+	20	18	38
T-	20	108	128
Tot	40	126	166 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	50.0%	34.5%	65.5%
Sp	85.7%	79.6%	91.8%
PPV	52.6%	36.8%	68.5%
NPV	84.4%	78.1%	90.7%		**Comments:** - The study demonstrates that the tumor markers in question are no better than age as a discriminator of benign versus malignant ovarian masses (AUC for age = 0.685). **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: + Statistical tests: + Blinding: - (NR) Definition of +/- on screening test: + Grade: A

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Warwas, Haczynska, Gerber, 1997 **#7160**	**Geographical location:** Wroclaw, Poland **Study dates:** 1989-1994 **Size of population:** 127 **Type of population:** Ovarian cancers, benign ovarian cysts, 2 control groups **Genomic test(s) used:** Cathepsin B-like activity Antipapain activity **Reference standard:** Surgical pathology None for healthy controls **Reference standard applied to all test negatives?:** No **Test reliability established?:** No **Statistical tests used:** Se **Blinding:** NR **Definition of positive and negative on screening test:** The mean value for benign ovarian cysts plus 2 SDs = 102.3 mIU/L (cathepsin b); 117.9 nU/L (anti-papain activity)	**Age:** Cancer: Median: 51 Range: 14-82 Benign cyst: Median: 48 Range: 35-60 Healthy controls: Median: 39 Range: 28-46 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 75 (59%) Benign ovarian mass: 17 (13%) Healthy controls: 15 (12%) Uterine fibroids: 20 (16%) **Inclusion criteria:** Surgery for ovarian mass, uterine fibroids, or control group (no surgery) **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) Cathepsin B, cutoff 102.3 – ovarian cancer vs. benign ovarian cysts: Se: All stages 78.6 %; stage I 60% |	Dis+	Dis-	Tot
---	---	---	---
T+	59	0	59
T-	16	17	33
Tot	75	17	92 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	78.6%	69.3%	87.9%
Sp	100.0%	82.4%	100.0%
PPV	100.0%	94.9%	100.0%
NPV	51.5%	34.5%	68.6% | 2) Antipapain activity, cutoff 117.9 mU/L – ovarian cancers vs. benign cysts: Se: All stages 22.6%, stage I 50% |	Dis+	Dis-	Tot
---	---	---	---
T+	17	0	17
T-	58	17	75
Tot	75	17	92 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	22.6%	13.1%	32.1%
Sp	100.0%	82.4%	100.0%
PPV	100.0%	82.4%	100.0%
NPV	22.7%	13.2%	32.1%		**Comments:** - Controls were not age-matched. **Quality assessment:** Reference standard: + Verification bias: - (controls did not have surgery) Test reliability/variability: - Sample size: - (only 17 with benign cysts) Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: C

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Weitzel, Ding, Larson, et al., 2000 **#11800**	**Geographical location:** Duarte, CA **Study dates:** NR **Size of population:** 244 **Type of population:** Ovarian cancer or control **Genomic test(s) used:** Rare HRAS1 allele polymorphisms **Reference standard:** Surgical pathology or clinical status (controls) **Reference standard applied to all test negatives?:** No (controls did not have follow up or surgery) **Test reliability established?:** No **Statistical tests used:** Odds ratios **Blinding:** NR **Definition of positive and negative on screening test:** Presence or absence of HRAS1 polymorphism as determined by PCR; a number of techniques are described depending on the type of sample obtained (blood, tissue, or both)	**Age:** Ovarian cancer: Mean (SD): 53.2 (13.3) Controls: Mean (SD): 52.5 (15.4) **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** Caucasian 244 (100%) **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 136 (56%) Healthy controls: 108 (44%) **Inclusion criteria:** - Cases: epithelial ovarian cancer - Controls: age and race matched, no history of cancer and ovaries intact **Exclusion criteria:** Prior oophorectomy, history of cancer (for control group)	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) Existence of a rare HRAS1 allele; ovarian cancer vs. healthy controls; OR for having cancer with a rare allele is 1.76 (95%CI 1.08 to 2.87). Risk appears to increase with the presence of 2 rare alleles (OR 2.86, 0.75 to 10.94). Dis+ / Dis- / Tot T+: 29 / 14 / 43 T-: 107 / 94 / 201 Tot: 136 / 108 / 244 Value / Lower 95% CI / Upper 95% CI Se: 21.5% / 14.6% / 28.4% Sp: 86.6% / 80.2% / 93.0% PPV: 67.4% / 53.4% / 81.4% NPV: 46.8% / 39.9% / 53.7%	**Comments:** - Some cancer patient samples were blood; others were tissue (controls were all blood) which could introduce error if there was a somatic allelic deletion in the cancer tissue only. The authors performed extra testing on 24 samples for which both blood and tissue were available and concluded that the results were concordant. - Authors conclude that HRAS allele status may modify ovarian cancer risk. **Quality assessment:** Reference standard: + Verification bias: - (controls did not have surgery) Test reliability/variability: - Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Yuce, Baykal, Genc, et al., 2001 **#4220**	**Geographical location:** Ankara, Turkey **Study dates:** Dec 1998-Jun 1999 **Size of population:** 65 **Type of population:** Adnexal mass **Genomic test(s) used:** LDH – serum and peritoneal fluid **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Yes **Statistical tests used:** Se, Sp, PPV, NPV **Blinding:** NR **Definition of positive and negative on screening test:** Serum LDH: 512.28 U/mL Peritoneal LDH: 650 U/mL Serum CA-125: 129 U/mL	**Age:** Benign masses: Mean: 45.3 Range: 22-77 Ovarian cancer: Mean: 58.6 Range: 20-78 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 27 (41.5%) Benign ovarian mass: 38 (58.5%) **Inclusion criteria:** Ovarian mass for surgery **Exclusion criteria:** NR	**Screening only (n [%]):** None **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) Serum LDH cutoff 512.28 U/mL – ovarian cancer vs. benign ovarian mass: |	Dis+	Dis-	Tot
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T+	5	2	7
T-	22	36	58
Tot	27	38	65 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	18.5%	3.9%	33.1%
Sp	94.7%	87.6%	100.0%
PPV	71.4%	38.0%	100.0%
NPV	62.1%	49.6%	74.6% | 2) Peritoneal LDH cutoff 650 U/mL – ovarian cancer vs. benign ovarian mass: |	Dis+	Dis-	Tot
---	---	---	---
T+	13	3	16
T-	14	35	49
Tot	27	38	65 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	48.1%	29.3%	66.9%
Sp	92.1%	83.5%	100.0%
PPV	81.3%	62.1%	100.0%
NPV	71.4%	58.8%	84.1% | 3) Peritoneal LDH cutoff 650 U/mL and serum cA125 cutoff 129 U/mL – ovarian cancer vs. benign ovarian mass: |	Dis+	Dis-	Tot
---	---	---	---
T+	20	4	24
T-	7	34	41
Tot	27	38	65 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	74.1%	57.6%	90.6%		**Comments:** - Cutoffs were determined "statistically" but exact method of determination not specified. - N is fairly low. - Peritoneal fluid was not always available in benign cases and washings were obtained in these cases. This would introduce a variable dilution effect on the samples and possibly lead to a false lower LDH level in the benign controls, subsequently falsely enhancing the calculated Se for cancers. - Authors claim LDH adds to the Se of CA-125 without detracting significantly from Sp. **Quality assessment:** Reference standard: + Verification bias: + Test reliability/variability: + Sample size: - Statistical tests: + Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
				Sp 89.9% 80.3% 99.5% PPV 83.3% 68.4% 98.2% NPV 82.9% 71.4% 94.4%	
Zakrzewska, Borawska, Poznanski, et al., 1999 **#5960**	**Geographical location:** Bialystok, Poland **Study dates:** NR **Size of population:** 96 **Type of population:** Patients with ovarian neoplasms **Genomic test(s) used:** CEA, CA-72-4, CA-125 **Reference standard:** Surgical pathology **Reference standard applied to all test negatives?:** Yes **Test reliability established?:** Yes **Statistical tests used:** Wilcoxin test for significance **Blinding:** NR **Definition of positive and negative on screening test:** CA-125: < 35 U/mL CA72-4: < 9.8 U/mL CEA: < 5 ng/mL	**Age:** Cancer: Mean: 47 Range: 38-72 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 70 (73%) Benign ovarian neoplasm: 26 (27%) **Inclusion criteria:** Ovarian cancer or benign ovarian neoplasm **Exclusion criteria:** NR	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) CA72-4 cutoff 9.8 U/mL – ovarian cancer vs. benign ovarian neoplasm: Dis+ Dis- Tot T+ **39** **0** 39 T- **31** **26** 57 Tot 70 26 96 Value Lower 95% CI Upper 95% CI Se 55.7% 44.1% 67.4% Sp 100.0% 88.5% 100.0% PPV 100.0% 92.3% 100.0% NPV 45.6% 32.7% 58.5% 2) CEA cutoff 5 ng/mL – ovarian cancer vs. benign ovarian neoplasm: Dis+ Dis- Tot T+ **7** **0** 7 T- **63** **26** 89 Tot 70 26 96 Value Lower 95% CI Upper 95% CI Se 10.0% 3.0% 17.0% Sp 100.0% 88.5% 100.0% PPV 100.0% 57.1% 100.0% NPV 29.2% 19.8% 38.7%	**Comments:** - Authors also present data on sensitivity of each marker for detecting various histologic subtypes of ovarian cancer, which does not have relevance for clinical management. **Quality assessment:** Reference standard: + Verification bias: - Test reliability/variability: + Sample size: + Statistical tests: - Blinding: - Definition of +/- on screening test: + Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
Zhang, Bast, Yu, et al., 2004 **#790**	**Geographical location:** Baltimore, MD **Study dates:** NR **Size of population:** 503 for proteomic profiling (discovery set) + 142 for testing identified markers (validation set) = 645 **Type of population:** Ovarian cancers versus various clinical groups **Genomic test(s) used:** **Proteomics:** SELDI mass spectrometry (Ciphergen ProteinChip Biomarker System) **Reference standard:** NR **Reference standard applied to all test negatives?:** NR **Test reliability established?:** No **Statistical tests used:** After identification of 3 biomarkers using proteomics platform, a multivariate model was constructed using the 3 biomarkers to predict malignancy, with or without incorporation of CA-125 information.	**Age:** Ovarian cancer, test set: Mean (SD): 52 (16) Median: 54 Menopausal: 57.9% Healthy control, test set: Mean (SD): 39 (11) Median: 38 Menopausal: 20.5% Ovarian cancer, validation set: Mean (SD): 57 (13) Median: 57 Menopausal: 74.6% Healthy control, validation set: Mean (SD): 44 (10) Median: 45 Menopausal: 34.9% Benign mass, validation set: Mean (SD): 53 (16) Median: 51 Menopausal: 55.5% **Menopausal status (n [%]):** See above **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 194 (30%) Borderline: 28 (4%) Recurrent ovarian cancer: 14 (2%)	**Screening only (n [%]):** NR **Diagnosis of mass:** - Symptomatic (n [%]): NR - Asymptomatic, detected by exam (n [%]): NR - Asymptomatic, detected by imaging (n [%]): NR **Additional data used for diagnosis:** NR	1) Three-biomarker multivariate model: ovarian cancer vs. healthy controls (validation set): |	Dis+	Dis-	Tot
---	---	---	---
T+	107	2	109
T-	31	61	92
Tot	138	63	201 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	77.5%	70.6%	84.5%
Sp	96.8%	92.5%	100.0%
PPV	98.2%	95.6%	100.0%
NPV	66.3%	56.6%	76.0%		**Comments:** - Age different between cases and healthy controls - The 3 biomarkers identified were all "acute phase reactants" not likely to be secreted by tumor cells. **Quality assessment:** Reference standard: - Verification bias: + Test reliability/variability: + (a validation set was used) Sample size: + Statistical tests: + Blinding: - Definition of +/- on screening test: - (a predictive model was used, no cutoffs given in text) Grade: B

Evidence Table 2 – Question 2 (continued)

Study	Study Design	Patients	Clinical Presentation	Results	Comments/Quality Scoring
	Models were evaluated using Se, Sp, ROC **Blinding:** NR **Definition of positive and negative on screening test:** Used a combination of variables identified from multiple logistic regression based on mass spectroscopy. Peaks occurring at m/z 12,828; 28043 and 3,272 were used.	Benign pelvic mass: 166 (26%) Healthy controls: 183 (28%) Other: - Breast cancer: 20 (3%) - Colon cancer: 20 (3%) - Prostate cancer: 20 (3%) **Inclusion criteria:** Clinical groups listed above **Exclusion criteria:** NR			

Evidence Table 3 – Question 4: *What is the evidence that genomic testing in women with clinical suspicion of ovarian cancer or with already-diagnosed ovarian cancer changes clinical management and leads to improved health outcomes?*

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Ayhan, Tuncer, and Ayhan, 1998 **#6460**	**Geographical location:** Ankara, Turkey **Study dates:** 1988-1994 **Study type:** Cohort **Size of population:** 48 **Genomic test(s) used:** p53 - immunohistochemistry **Reference standard:** Surgical pathology **Test reliability established?:** Yes **Statistical tests used:** Chi square **Definition of positive and negative on screening test:** NR	**Age:** Mean: 52.8 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 48 (100%) **Treatment (n [%]):** Surgery: 48 (100%) Chemotherapy (platinum): 48 (100%) **Inclusion criteria:** Ovarian carcinoma subjected to primary surgery and cisplatinum-based chemotherapy followed by second-look laparotomy **Exclusion criteria:** NR	**Use of test results:** No change in management (prediction only) **Outcomes measured:** Cancer progression on second-look laparotomy (SLL)	1) p53 expression to predict residual disease at SLL – all patients: Out+ = positive SLL Out- = negative SLL T+ = p53 overexpressed T- = p53 not overexpressed |	Out+	Out-	Tot
---	---	---	---
T+	12	8	20
T-	10	18	28
Tot	22	26	48 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	54.5%	33.7%	75.4%
Sp	69.2%	51.5%	87.0%
PPV	60.0%	38.5%	81.5%
NPV	64.3%	46.5%	82.0% | 2) p53 expression to predict residual disease at SLL – serous stage III only (T/Out as described above): |	Out+	Out-	Tot
---	---	---	---
T+	9	5	14
T-	6	10	16
Tot	15	15	30 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	60.0%	35.2%	84.8%
Sp	66.7%	42.8%	90.5%
PPV	64.3%	39.2%	89.4%
NPV	62.5%	38.8%	86.2%		**Comments:** Cohort was non-uniform in terms of stage of disease (5 pts Stage I-II; 43 pts Stage III) **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): Unknown Large sample size: - Adequate description of the cohort: - Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: - Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Baekelandt, Holm, Trope, et al., 1999 **#6000**	**Geographical location:** Oslo, Norway **Study dates:** 1988-1993 **Study type:** Cohort **Size of population:** 185 **Genomic test(s) used:** Cathepsin-D nm23 Immunohistochemistry (IHC) **Reference standard:** Surgical pathology **Test reliability established?:** Yes **Statistical tests used:** Differences in proportions were evaluated by the chi-square or Fisher's exact test. Disease-free and corrected survival rates using Kaplan-Meier, log-rank test, and Cox proportional hazards regression model. **Definition of positive and negative on screening test:** Positive > 10% moderate or strong staining	**Age:** Median: 54 Range: 21-70 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 185 (100%) **Treatment (n [%]):** Surgery: First surgery, 185 (100%) Chemotherapy (platinum): 185 (100%) Other (epirubicin): 185 (100%) **Inclusion criteria:** Consecutive patients in a multicenter trial on consolidation treatment after second-look laparotomy in stage III ovarian cancer patients. Patient age < 71 years, Karnofsky index ≥ 60, histologically verified and previously untreated stage III epithelial ovarian cancer and s-creatinin < 115 µmol/L. **Exclusion criteria:** NR	**Use of test results:** No change in management (prediction only) **Outcomes measured:** Cancer mortality Cancer progression or regression with primary chemotherapy as assessed at time of second-look laparotomy (SLL)	1) Cathespin-D levels to predict residual disease after to primary chemotherapy: Out+ = macroscopic residual or no response to chemo Out- = complete pathologic response or microscopic residual disease only T+ = cathepsin D positive IHC T- = cathepsin D negative IHC |	Dis+	Dis-	Tot
---	---	---	---
T+	78	22	100
T-	61	14	75
Tot	139	36	175 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	56.1%	47.9%	64.4%
Sp	38.9%	23.0%	54.8%
PPV	78.0%	69.9%	86.1%
NPV	18.7%	9.8%	27.5% | 2) nm23 levels to predict residual disease after primary chemotherapy (T/Out as described above): |	Dis+	Dis-	Tot
---	---	---	---
T+	100	24	124
T-	39	12	51
Tot	139	36	175 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	71.9%	64.5%	79.4%
Sp	33.3%	17.9%	48.7%
PPV	80.6%	73.7%	87.6%
NPV	23.5%	11.9%	35.2%		**Comments:** - Same population as Baekelandt et al., 1999 (#830) - Lumping together "complete pathologic response" and "microscopic disease only" is somewhat arbitrary. Would be more appropriate to assess complete pathologic responders (negative SLL) versus anyone with detectable disease (positive SLL). **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: + Grade: A

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Baekelandt, Kristensen, Nesland, et al., 1999 **#830**	**Geographical location:** Oslo, Norway **Study dates:** 1988-1993 **Study type:** Cohort **Size of population:** 185 **Genomic test(s) used:** P53, mdm2, bcl-2 by Immunohistochemistry (IHC) **Reference standard:** Surgical pathology **Test reliability established?:** Yes **Statistical tests used:** Differences in proportions were evaluated by the chi-square or Fisher's exact test. Disease-free and corrected survival rates using Kaplan-Meier, log-rank test, and Cox proportional hazards regression model. **Definition of positive and negative on screening test:** For p53 and bcl-2: immunostaining of at least 5% of tumor cells For mdm2: not specified	**Age:** Median: 54 Range: 21-70 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 185 (100%) **Treatment (n [%]):** Surgery: First surgery 185 (100%) Chemotherapy (platinum): 185 (100%) Other (epirubicin): 185 (100%) **Inclusion criteria:** Consecutive patients in a multicenter trial on consolidation treatment after second-look laparotomy (SLL) in stage III ovarian cancer patients. Patient age < 71 years, Karnofsky index ≥ 60, histologically verified and previously untreated stage III epithelial ovarian cancer and s-creatinin < 115 µmol/L. **Exclusion criteria:** NR	**Use of test results:** No change in management (prediction only) **Outcomes measured:** Cancer mortality Cancer progression or regression Findings at SLL (complete pathologic response, microscopic or macroscopic disease)	1) p53 expression to predict residual disease at SLL: Out+ = macroscopic disease at SLL Out- = complete pathologic response or microscopic residual only T+ = p53 expression ≥ 5% tumor cells T- = p53 negative or < 5% staining Dis+ / Dis- / Tot T+: 64 / 20 / 84 T-: 75 / 16 / 91 Tot: 139 / 36 / 175 Value (Lower 95% CI – Upper 95% CI) Se: 46.0% (37.8% – 54.3%) Sp: 44.4% (28.2% – 60.7%) PPV: 76.2% (67.1% – 85.3%) NPV: 17.6% (9.8% – 25.4%) 2) mdm2 expression to predict residual disease at SLL: Out+/Out- = see above T+ = mdm2 staining (percentage of cells not specified) T- = mdm2 negative (percentage not specified) Dis+ / Dis- / Tot T+: 25 / 4 / 29 T-: 114 / 32 / 146 Tot: 139 / 36 / 175 Value (Lower 95% CI – Upper 95% CI) Se: 18.0% (11.6% – 24.4%) Sp: 88.9% (78.6% – 99.2%) PPV: 86.2% (73.7% – 98.8%) NPV: 21.9% (15.2% – 28.6%)	**Comments:** - Same population as Baekelandt et al., 1999 (#6000) - Cutoffs for defining positive or negative immunostaining are rather arbitrary and were not defined for mdm2. - Lumping together "complete pathologic response" and "microscopic disease only" is somewhat arbitrary. Would be more appropriate to assess complete pathologic responders (negative SLL) versus anyone with detectable disease (positive SLL). **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: +/- (cutoffs indistinct) Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: + Grade: A

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring

3) bcl-2 expression to predict residual disease at SLL:

Out+/Out- = see above
T+ = ≥ 5% of tumor cells stain positive for bcl-2
T- = < 5% tumor cells stain positive for bcl-2

	Dis+	Dis-	Tot
T+	**49**	**19**	68
T-	**90**	**17**	107
Tot	139	36	175

	Value	Lower 95% CI	Upper 95% CI
Se	35.3%	27.3%	43.2%
Sp	47.2%	30.9%	63.5%
PPV	72.1%	61.4%	82.7%
NPV	15.9%	9.0%	22.8%

4) Hazard Ratio or other relevant information:

Overall survival was lower in patients with p53 expression and loss of bcl-2 expression using Kaplan Meier analysis.

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Balbi, Cardone, Passaro, et al., 2005 **#90**	**Geographical location:** Naples, Italy **Study dates:** 1992-2002 **Study type:** Cohort **Size of population:** 150 **Genomic test(s) used:** CA-125 **Reference standard:** Radiographic imaging: size of measurable lesions on CT, MRI, ultrasound, or physical examination. Response, stable disease, or disease progression as determined by WHO criteria. **Test reliability established?:** Yes **Statistical tests used:** Chi-square test **Definition of positive and negative on screening test:** CA-125 < 30 U/mL considered normal Response to therapy by CA-125 criteria: "50% response" = 50% decrease in CA-125 from pre-treatment level after	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 150 (100%) **Treatment (n [%]):** Surgery: 150 (100%) Chemotherapy: - Single agent Platinum: 96 (64%) - Single agent Taxol: 54 (46%) **Inclusion criteria:** Treated with adjuvant chemo after optimal surgery for epithelial carcinoma of the ovary. Had to have CA-125 measurements performed on at least three serum samples, with at least one sample having a level more than 40 U/mL at the start of therapy. Maximum period during which a response may occur is the first 6 months after the start of treatment. The final sample had to be at least 28 days after the previous sample. Also needed to have at least one bidimensionally measurable	**Use of test results:** No change in management (prediction only) **Outcomes measured:** Response to treatment where response was defined as two samples where there was a 50% decrease, confirmed by a 4th sample or a serial decrease over three sample of greater than 75%	1) Ability of CA-125 criteria to measure response to platinum when compared to conventional criteria: Out+ = response to chemo by standard criteria Dis -= no response by standard criteria T+ = response by CA-125 criteria T- = no response by CA-125 criteria |	Out+	Out-	Tot
---	---	---	---
T+	32	2	34
T-	8	24	32
Tot	40	26	66 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	80.0%	67.6%	92.4%
Sp	92.3%	82.1%	100.0%
PPV	94.1%	86.2%	100.0%
NPV	75.0%	60.0%	90.0% | 2) Ability of CA-125 criteria to measure response to paclitaxel when compared to conventional criteria (T/Out defined as above): |	Out+	Out-	Tot
---	---	---	---
T+	22	2	24
T-	4	19	23
Tot	26	21	47 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	84.6%	70.7%	98.5%
Sp	90.5%	77.9%	100.0%
PPV	91.7%	80.6%	100.0%
NPV	82.6%	67.1%	98.1%		**Comments:** - This study validates the use of CA-125 to follow patients in clinical trials. Many patients with ovarian cancer have no measurable disease and are not eligible for clinical trials. This paper lends some evidence to support following patients for response to chemo with CA-125 alone. **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): Unknown Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: - Grade: A

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
	2 samples "75% response" = 75% drop in CA-125 from pre-treatment level after 3 samples	lesion as evidenced by CT, MRI, US or physical exam. **Exclusion criteria:** NR			
Berchuck, Iversen, Lancaster, et al., 2004 **#1740**	**Geographical location:** Durham, NC **Study dates:** 1988-2001 **Study type:** Cohort **Size of population:** 49 **Genomic test(s) used:** Microarray analysis using Affymetrix U133A GeneChip **Reference standard:** Degree of surgical cytoreduction (optimal = all residual tumor nodules are < 1 cm in diameter; suboptimal = at least one tumor nodule > 2 cm) **Test reliability established?:** NR **Statistical tests used:** Multivariable predictive modelling; within-sample validation **Definition of positive and negative on**	**Age:** Median: 63 (optimal debulked), 57 (suboptimally debulked) **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** White: 17 (89%) of optimal and 18 (72%) of suboptimal Black: 2 (11%) of optimal, and 3 (12%) or suboptimal **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 49 (100%) **Treatment (n [%]):** Surgery: 49 (100%) Chemotherapy (platinum): 49 (100%) **Inclusion criteria:** Treated for serous ovarian cancer, all patients were < 75 years, and none had died of causes other than ovarian cancer **Exclusion criteria:** NR	**Use of test results:** No change in management (prediction only) **Outcomes measured:** Optimal or suboptimal debulking	1) Microarray for prediction of ability to debulk stage III/IV cancer (n = 44): Out+ = optimal debulking performed Out- = suboptimal debulking performed T+ = chip predicts optimal debulking T- = chip predicts suboptimal debulking |	Out+	Out-	Tot
---	---	---	---
T+	12	5	17
T-	7	20	27
Tot	19	25	44 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	63.2%	41.5%	84.8%
Sp	80.0%	64.3%	95.7%
PPV	70.6%	48.9%	92.2%
NPV	74.1%	57.5%	90.6%		**Comments:** - No separate validation set; leave-one-out cross validation used. **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: - Use of validated method for genomic test: - (no validation set) Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: + Grade: A

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
	screening test: Optimal debulking prediction				
Berek, Chung, Kaldi, et al., 1991 **#12230**	**Geographical location:** Los Angeles, CA **Study dates:** NR **Study type:** Cohort **Size of population:** 48 **Genomic test(s) used:** IL-6 **Reference standard:** Surgical pathology **Test reliability established?:** Yes **Statistical tests used:** Student's t-test **Definition of positive and negative on screening test:** IL-6 > 0.20 U/mL elevated	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 36 (66%) Healthy controls: 12 (34%) **Treatment (n [%]):** NR **Inclusion criteria:** Histologically documented epithelial ovarian cancer; plan to undergo surgery **Exclusion criteria:** NR	**Use of test results:** No change in management (prediction only) **Outcomes measured:** Cancer mortality Quality of life Quantity of measurable disease at laparotomy	1) IL-6 to predict macroscopic versus microscopic disease: Out+ = macroscopic disease present Out- = microscopic disease present T+ = IL6 positive T- = IL6 negative |	Out+	Out-	Tot
---	---	---	---
T+	16	2	18
T-	5	13	18
Tot	21	15	36 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	76.2%	58.0%	94.4%
Sp	86.7%	69.5%	100.0%
PPV	88.9%	74.4%	100.0%
NPV	72.2%	51.5%	92.9% | 2) IL-6 to predict degree of macroscopic disease: Out+ = > 2 cm disease Out- = < 2 cm T+ = IL6 positive T- = IL6 negative |	Out+	Out-	Tot
---	---	---	---
T+	8	8	16
T-	1	4	5
Tot	9	12	21 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	88.9%	68.4%	100.0%
Sp	33.3%	6.7%	60.0%
PPV	50.0%	25.5%	74.5%
NPV	80.0%	44.9%	100.0%		**Comments:** - Unclear whether surgery was primary exploration or a second-look laparotomy. Because the clinical situation is not well defined it is unclear how management would be changed with this test. - Reasons/reference for choosing a cutoff level of 0.2 U/mL not given. - Used case-control method, with subjects drawn from different known disease status categories (macro, micro, control) **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: - Use of validated method for genomic test: - (not clear there is an established level for cutoff) Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: - Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Diamandis, Scorilas, Fracchioli, et al., 2003 **#2850**	**Geographical location:** Toronto, Canada **Study dates:** NR **Study type:** Case-control **Size of population:** 97 healthy controls 141 benign disease 146 ovarian cancer **Genomic test(s) used:** Human kallikrien 6 (hK6) CA-125 **Reference standard:** Surgical pathology **Test reliability established?:** Yes **Statistical tests used:** ROC curve, paired t-tests, Kaplan Meier, Cox proportional hazards **Definition of positive and negative on screening test:** hK6 - 4.2 µg/L hK6- 4.4 µg/L CA-125 > 23KU/L low CA-125 23-60 slightly elevated CA-125 > 60KU/L elevated	**Age:** Healthy: Mean (SD): 52 Median: 49 Range: 26-72 Benign disease: Mean (SD): 46 Median: 45 Range: 21-76 Ovarian Cancer: Mean (SD): 56 Median: 57 Range: 28-78 **Menopausal status Ovarian cancer only (n [%]):** 103/146 (71%) **Race/ethnicity (n [%]):** NR (pooled cases from Italy, Netherlands, Belgium, Finland) **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 146 Benign ovarian mass: 141 Healthy controls: 97 **Treatment (n [%]):** Chemotherapy: Platinum: 146 **Inclusion criteria:** None stated **Exclusion criteria:** None stated	**Use of test results:** No change in management (prediction only) **Outcomes measured:** Residual tumor Recurrence Response to chemotherapy Response to chemotherapy was assessed as follows: complete response was defined as a resolution of all evidence of disease for at least 1 month; a decrease (lasting at least 1 month) of at least 50% in the diameters of all measurable lesions without the development of new lesions was termed partial response. Stable disease was defined as a decrease of <25% in the product of the diameters of all measurable lesions, an increase of ≥25% was termed as a progressive disease.	1) hK6 > 4.4 µg/L for predicting presence of residual tumor Dis + / Dis - / Tot T + : 43 / 24 / 67 T - : 9 / 52 / 61 Tot : 52 / 76 / 128 Value (Lower 95% CI – Upper 95% CI) Se: 82.7% (72.4% – 93.0%) Sp: 68.4% (58.0% – 78.9%) PPV: 64.2% (52.7% – 75.7%) NPV: 85.2% (76.3% – 94.1%) 2) hK6 > 4.4 µg/L for predicting debulking success – optimal debulking defined residual disease < 1cm diameter Dis+ / Dis- / Tot T+ : 40 / 28 / 68 T- : 9 / 53 / 62 Tot : 49 / 81 / 130 Value (Lower 95% CI – Upper 95% CI) Se: 81.6% (70.8% – 92.5%) Sp: 65.4% (55.1% – 75.8%) PPV: 58.8% (47.1% – 70.5%) NPV: 85.5% (76.7% – 94.3%) 3) hK6 > 4.4 µg/L for predicting response to chemotherapy – complete/partial remission defined as no disease Dis+ / Dis- / Tot T+ : 17 / 46 / 63 T- : 4 / 61 / 65 Tot : 21 / 107 / 128 Value (Lower 95% CI – Upper 95% CI)	**Comments:** Includes women with different stages of ovarian cancer (St I – 32; St II 11; St III 73; St IV 8; St unknown 22). **Quality assessment:** *For case-control study:* Valid ascertainment of cases: + Unbiased selection of cases: - Appropriateness of the control population: - Verification that the control is free of cancer: - Comparability of cases and controls with respect to potential confounders: - Appropriateness of statistical analyses: + Study is based on case series with normal patients/benign disease as controls. Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
				Se 81.0% 64.2% 97.7% Sp 57.0% 47.6% 66.4% PPV 27.0% 16.0% 37.9% NPV 93.8% 88.0% 99.7% 4) Hazard Ratio or other relevant information: hK6 positive – 4.10 (2.28 to 7.36)	
Folk, Botsford, and Musa, 1995 **#8260**	**Geographical location:** Syracuse, NY **Study dates:** 1989-93 **Study type:** Not specified – ad hoc **Size of population:** 60 **Genomic test(s) used:** CA-125 **Reference standard:** Surgical pathology Clinical outcome **Test reliability established?:** Not stated **Statistical tests used:** t-test **Definition of positive and negative on screening test:** CA-125 < 35IU/ml CA-125 < 20IU/ml for response to therapy	**Age:** Mean (SD): 55.2 Range: 25-85 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 60 (100%) **Treatment (n [%]):** Surgery: 60 Chemotherapy: 60 Variable regimens **Inclusion criteria:** None specified **Exclusion criteria:** None specified	**Use of test results:** No change in management (prediction only) **Outcomes measured:** Cancer progression on second-look laparotomy (SLL)	1) CA-125 (after 3rd course of Chemo) ≥ 35 to predict residual disease at SLL Dis+ Dis- Tot T+ 3 0 3 T- 24 18 42 Tot 27 18 45 Value Lower 95% CI Upper 95% CI Se 11.1% 0.0% 23.0% Sp 100.0% 83.3% 100.0% PPV 100.0% 0.0% 100.0% NPV 42.9% 27.9% 57.8% 2) CA-125 (after 3rd course of Chemo) ≥ 20 U/ml Dis+ Dis- Tot T+ 6 5 11 T- 21 13 34 Tot 27 18 45 Value Lower 95% CI Upper 95% CI Se 22.2% 6.5% 37.9% Sp 72.2% 51.5% 92.9% PPV 54.5% 25.1% 84.0% NPV 38.2% 21.9% 54.6% 3) CA-125 (immediately prior to SLL) ≥ 35 U/ml; SLL positive or negative	**Comments:** None **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: + Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: + Selection of patients not described – case series. Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring

	Dis+	Dis-	Tot
T+	9	0	9
T-	18	18	36
Tot	27	18	45

	Value	Lower 95% CI	Upper 95% CI
Se	33.3%	15.6%	51.1%
Sp	100.0%	83.3%	100.0%
PPV	100.0%	66.7%	100.0%
NPV	50.0%	33.7%	66.3%

4) CA-125 (immediately prior to SLL) ≥ 20 U/ml

	Dis+	Dis-	Tot
T+	7	2	9
T-	18	18	36
Tot	25	20	45

	Value	Lower 95% CI	Upper 95% CI
Se	28.0%	10.4%	45.6%
Sp	90.0%	76.9%	100.0%
PPV	77.8%	50.6%	100.0%
NPV	50.0%	33.7%	66.3%

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Gadducci, Cosio, Fanucchi, et al., 2004 **#1810**	**Geographical location:** Pisa, Italy **Study dates:** 1996-2000 **Study type:** Other (retrospective series) **Size of population:** 71 **Genomic test(s) used:** CA-125 **Reference standard:** Surgical pathology Clinical outcome (based on exam, sonography, and radiology) **Test reliability established?:** Not stated **Statistical tests used:** Chi square, logistic regression **Definition of positive and negative on screening test:** CA-125 half life ≤ 14 days CA-125 % reduction after 1st cycle of chemo ≤ 71%	**Age:** Mean (SD): 58 Range: 27-73 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** Italian **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 71 (100%) **Treatment (n [%]):** Surgery: 71 (100%) Chemotherapy: 71 Platinum: 71 Paclitaxel: 71 **Inclusion criteria:** Patients with Stage IIc-IV cancer **Exclusion criteria:** None stated	**Use of test results:** Prediction of outcome of chemotherapy **Outcomes measured:** Response to treatment Progression-free survival Overall survival	1) CA-125 half-life ≤ 14 days to predict complete response to treatment Dis+ / Dis- / Tot T+: 26 / 10 / 36 T-: 16 / 19 / 35 Tot: 42 / 29 / 71 Value (Lower 95% CI – Upper 95% CI) Se: 61.9% (47.2% – 76.6%) Sp: 65.5% (48.2% – 82.8%) PPV: 72.2% (57.6% – 86.9%) NPV: 54.3% (37.8% – 70.8%) 2) CA-125 percentage reduction after first cycle of chemotherapy > 71% to predict complete response to treatment Dis+ / Dis- / Tot T+: 25 / 10 / 35 T-: 17 / 19 / 36 Tot: 42 / 29 / 71 Value (Lower 95% CI – Upper 95% CI) Se: 59.5% (44.7% – 74.4%) Sp: 65.5% (48.2% – 82.8%) PPV: 71.4% (56.5% – 86.4%) NPV: 52.8% (36.5% – 69.1%) 3) Hazard Ratio or other relevant information: Serum 125 half life Complete response to treatment OR 3.362 (1.178-9.594) Progression free survival HR 2.739 (1.425-6.262) Overall survival HR 3.113 (1.214-7.980)	**Comments:** Case series – not sure how selected Study population includes women at different stages (II-II n=60; IV n=11) Study combines women with no response by clinical evaluation (who were not considered for SLL) with women who required SLL for evaluation of response. **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: + Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: + Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Gadducci, Ferdeghini, Cosio, et al., 2001 **#4180**	**Geographical location:** Pisa Italy **Study dates:** NR **Study type:** Other (ad hoc) **Size of population:** 60 with cancer 59 with benign disease used to determine cutpoints **Genomic test(s) used:** CYFRA 21-1 CA-125 **Reference standard:** Surgical pathology Clinical outcome **Test reliability established?:** Not stated **Statistical tests used:** Fisher's exact tests, Mann Whitney U, Spearman rank, logistic regression **Definition of positive and negative on screening test:** Used the 25,50 and 75 quantiles of pre-operative CYFRA 21-1 – 1.9, 4.8 and 14.4 ng/ml	**Age:** Cases: Median: 58.5 Range: 23-80 Benign disease: Median: 39 Range: 20-82 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 60 Borderline: 59 Info. limited to 39 patients with advanced ovarian cancer **Treatment (n [%]):** Surgery: 0? Chemotherapy: 39 Platinum: 34 **Inclusion criteria:** 60 consecutive patients with untreated ovarian cancer **Exclusion criteria:** None stated	**Use of test results:** Not used **Outcomes measured:** Complete responders	1) No disease – defined as complete responders. Of 39 with advanced (III-IV) disease. 4 did not have SLL so data not presented in paper). CYFRA 21-1 - < 1.9 is negative Dis+ / Dis- / Tot T+: **20** / **5** / 25 T-: **4** / **6** / 10 Tot: 24 / 11 / 35 Value / Lower 95% CI / Upper 95% CI Se: 83.3% / 68.4% / 98.2% Sp: 54.5% / 25.1% / 84.0% PPV: 80.0% / 64.3% / 95.7% NPV: 60.0% / 29.6% / 90.4% 2) CYFRA 21-1 < 4.8 is negative Dis+ / Dis- / Tot T+: **16** / **2** / 18 T-: **8** / **9** / 17 Tot: 24 / 11 / 35 Value / Lower 95% CI / Upper 95% CI Se: 66.7% / 47.8% / 85.5% Sp: 81.8% / 59.0% / 100.0% PPV: 88.9% / 74.4% / 100.0% NPV: 52.9% / 29.2% / 76.7% 3) CYFRA 21-1<14.4 is negative Dis+ / Dis- / Tot T+: **8** / **0** / 8 T-: **16** / **11** / 27 Tot: 24 / 11 / 35 Value / Lower 95% CI / Upper 95% CI	**Comments:** - Unclear as to how cases detected. Of 60 cases, data presented for only 35 cases stage II-IV disease. **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: + Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: - Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: - Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
				Se 33.3% 14.5% 52.2% Sp 100.0% 72.7% 100.0% PPV 100.0% 62.5% 100.0% NPV 40.7% 22.2% 59.3%	
Gemer, Lurian, Gdalevich, et al., 2005 **#13320**	**Geographical location:** Ashkelon, Beer Sheva, Tzrifin, Haifa, Kfar Saba, Rehovot, Petah Tikva, and Jerusalem, Israel **Study dates:** NR **Study type:** Cohort **Size of population:** 424 **Genomic test(s) used:** CA-125 **Reference standard:** Clinical outcome (suboptimal debulking) **Test reliability established?:** Yes **Statistical tests used:** Sensitivity, specificity, ROC curve **Definition of positive and negative on screening test:** CA-125 at different cutpoints	**Age:** Median: 62 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: - Stage IIIA 25 (5.9%) - Stage IIIB 75 (17.7%) - Stage IIIC 296 (69.8%) - Stage IV 28 (6.6%) **Treatment (n [%]):** Cytoreductive surgery 100% **Inclusion criteria:** Stage III and IV ovarian cancer undergoing primary cytoreductive surgery (diameter of largest residual nodule ≤ 1 cm) **Exclusion criteria:** None specified	**Use of test results:** Prediction of debulking (theoretical - retrospective study, no change in management) **Outcomes measured:** Suboptimal debulking	1) Test characteristics of CA-125 > 400 to predict suboptimal debulking: Dis+ Dis- Tot T+ 126 104 230 T- 56 138 194 Tot **182** **242** 424 Value Lower 95% CI Upper 95% CI Se **69.2%** 62.5% 75.9% Sp **57.0%** 50.8% 63.2% PPV 54.8% 48.4% 61.2% NPV 71.1% 64.8% 77.5% Area under ROC: 0.65	**Comments:** None **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: - Grade: A (but no linkage to change in management)

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Gemer, Segal, and Kopmar, 2001 **#4430**	**Geographical location:** Ashkelon, Israel **Study dates:** NR **Study type:** Other (retrospective case series) **Size of population:** 40 stage III patients **Genomic test(s) used:** CA-125 **Reference standard:** Pathology **Test reliability established?:** Not stated **Statistical tests used:** ANOVA, t-test, chi-square **Definition of positive and negative on screening test:** CA-125 > 500 U/mL CA-125 > 1500 U/mL	**Age:** Median: 65 Range: 42-78 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** Israeli **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 40 (100%) **Treatment (n [%]):** Surgery: 40 **Inclusion criteria:** Stage III **Exclusion criteria:** None stated	**Use of test results:** Not used for management **Outcomes measured:** Optimal cytoreduction, defined by the Gynecology Oncology Group as the diameter of the largest residual nodule measure < 1cm.	1) CA-125 < 500 U/mL to predict optimal cytoreduction: Dis+ / Dis- / Tot T+: 20 / 6 / 26 T-: 4 / 10 / 14 Tot: 24 / 16 / 40 Value (Lower 95% CI – Upper 95% CI) Se: 83.3% (68.4% – 98.2%) Sp: 62.5% (38.8% – 86.2%) PPV: 76.9% (60.7% – 93.1%) NPV: 71.4% (47.8% – 95.1%) 2) CA-125 < 1500 U/mL to predict optimal cytoreduction: Dis+ / Dis- / Tot T+: 24 / 8 / 32 T-: 0 / 8 / 8 Tot: 24 / 16 / 40 Value (Lower 95% CI – Upper 95% CI) Se: 100.0% (87.5% – 100.0%) Sp: 50.0% (25.5% – 74.5%) PPV: 75.0% (60.0% – 90.0%) NPV: 100.0% (62.5% – 100.0%)	**Comments:** - Case series restricted to Stage III **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: + Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: - Grade: C

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Gronlund, Hansen, Hogdall, et al., 2004 **#11660**	**Geographical location:** Copenhagen, Denmark **Study dates:** Aug 1994-Jan 2001 **Study type:** Case series **Size of population:** 124 **Genomic test(s) used:** CA-125 change, using 2 criteria: **Reference standard:** Clinical outcome using US or CT for ascertainment of tumor volume **Test reliability established?:** Yes **Statistical tests used:** Sensitivity, specificity, Fisher's exact **Definition of positive and negative on screening test:** 1) GCIG: 2 pretreatment samples at least 70 u/mL, with at least 2 additional samples after start of treatment; Response=≥ 50% decrease by 4th sample 2) CA-125 ratio: Pretreatment level at least 70 u/mL; ratio of	**Age:** Median: 59.4 Range: 34.8-77.2 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 124 (100%, all recurrent) **Treatment (n [%]):** Surgery: 124 Chemotherapy: 124 Platinum: 60 Taxol: 60 Topotecan: 64 **Inclusion criteria:** Recurrent disease after primary surgery/chemotherapy **Exclusion criteria:** NR	**Use of test results:** Prediction of response to second-line chemotherapy with topotecan (n = 64) or platinum/paclitaxel (n = 60) **Outcomes measured:** Tumor volume	1) GCIG criteria (at least 50% decrease = response), complete and partial response vs. no change or progression (sensitivity for detecting response); only 72 subjects evaluable: |	Out+	Out-	Tot
---	---	---	---
T+	27	14	41
T-	1	30	31
Tot	28	44	72 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	96.4%	89.6%	100.0%
Sp	68.2%	54.4%	81.9%
PPV	65.9%	51.3%	80.4%
NPV	96.8%	90.6%	100.0%	 2) Hazard Ratio or other relevant information: Unable to do 2x2 table for ratio; performance was best when measured after 3rd cycle of chemotherapy (n = 73); reported sensitivity 91% (95% CI, specificity 61% (95% CI 43 to 76%).	**Comments:** None **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: + Use of validated method for genomic test:- Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: + Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
	posttreatment to pretreatment value ≤ 0.5				
Heinrich, Bottcher-Luiz, Andrade, et al., 2004 **#780**	**Geographical location:** Campinas, Sao Paulo, Brazil, and Denver, CO **Study dates:** NR **Study type:** Cohort (retrospective) **Size of population:** 74 women **Genomic test(s) used:** HER-2 CA-125 **Reference standard:** Surgical pathology Clinical outcome (tumor progression) **Test reliability established?:** NR **Statistical tests used:** None **Definition of positive and negative on screening test:** Yes	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Borderline: 45 (100%) **Treatment (n [%]):** Surgery: 45 (100%) **Inclusion criteria:** Patients with borderline ovarian tumors and samples available in tissue bank **Exclusion criteria:** "Inadequate follow-up information"	**Use of test results:** Potential for herceptin therapy Staging **Outcomes measured:** Stage Tumor progression	1) CA-125 expression (mod-strong homogeneous cytoplasmic staining) for staging of borderline Ov tumors (FIGO stage II or III vs stage I): Dis+ / Dis- / Tot T+: 10 / 12 / 22 T-: 6 / 17 / 23 Tot: 16 / 29 / 45 Value / Lower 95% CI / Upper 95% CI Se: 62.5% / 38.8% / 86.2% Sp: 58.6% / 40.7% / 76.5% PPV: 45.5% / 24.6% / 66.3% NPV: 73.9% / 56.0% / 91.9% 2) None of the 45 tumors showed HER-2 overexpression.	**Comments:** - Abnormal FISH results (HER-2) were found in only 7 patients, thus no association reported with FIGO stage. - No association of CA-125 or HER-2 with FIGO stage in borderline ovarian tumors. **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: - Use of validated method for genomic test: - Use of validated method for ascertaining clinical outcomes: - Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: - Grade: C

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Hogdall, Hogdall, Hording, et al., 1996 **#7730**	**Geographical location:** Copenhagen, Denmark **Study dates:** Sep 94 – Jun 87 **Study type:** Cohort **Size of population:** 63 second-look; 5 third-look in 65 patients **Genomic test(s) used:** Tetranectin (TN) CA-125 CASA **Reference standard:** Surgical pathology **Test reliability established?:** Tetranectin - yes **Statistical tests used:** Sensitivity, specificity **Definition of positive and negative on screening test:** TN ≤ 9.3 mg/l CASA ≥ 10 U/ml CA-125 ≥ 35 U/ml	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 100% **Treatment (n [%]):** Chemotherapy: Platinum: 50% Other (Cyclo-phosphamide, Adriamycin and 5-FU [CAF]): 50% **Inclusion criteria:** Participants in a RCT comparing chemo regimens after primary surgery for ovarian cancer **Exclusion criteria:** NR	**Use of test results:** Prediction of residual tumor **Outcomes measured:** Presence of residual tumor after adjuvant chemotherapy at second-look laparotomy (SLL)	1) TN ≤ 9.3 mg/l to predict presence of residual tumor at SLL after primary resection and chemotherapy for ovarian cancer: |	Dis+	Dis-	Tot
---	---	---	---
T+	9	0	9
T-	29	30	59
Tot	38	30	68 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	23.7%	10.2%	37.2%
Sp	100.0%	90.0%	100.0%
PPV	100.0%	66.7%	100.0%
NPV	50.8%	38.1%	63.6% | 2) CASA ≥ 10 U/ml to predict presence of residual tumor at SLL after primary resection and chemotherapy for ovarian cancer: |	Dis+	Dis-	Tot
---	---	---	---
T+	12	0	12
T-	26	29	55
Tot	38	29	67 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	31.6%	16.8%	46.4%
Sp	100.0%	89.7%	100.0%
PPV	100.0%	75.0%	100.0%
NPV	52.7%	39.5%	65.9%	 Additional tables reported for CA-125 ≥ 10 U/ml CA-125 ≥ 35 U/ml CASA ≥ 10 or CA-125 ≥ 35 CASA ≥ 10 or CA-125 ≥ 10 CASA ≥ 10 or CA-125 ≥ 35 or TN ≤ 9.3 CASA ≥ 10 or CA-125 ≥ 10 or TN ≤ 9.3	**Comments:** - This study provides reliable data for use of tumor markers to detect residual tumor – possibly obviating the need for second-look surgery. It is evaluated as a diagnostic test. - This study did not estimate the impact of testing on clinical management. **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + (outcome data collected as part of RCT comparing two chemo regimens) Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: - Grade: A

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Izquierdo, van der Zee, Vermorken, et al., 1995 **#8010**	**Geographical location:** Amsterdam and Groningen, The Netherlands **Study dates:** 1984-1993 **Study type:** Cohort/retrospective case series **Size of population:** 57 women/tumors **Genomic test(s) used:** Markers Lrp, Mrp, and Pgp **Reference standard:** Surgical pathology **Test reliability established?:** Yes **Statistical tests used:** Sensitivity, specificity, survival analysis **Definition of positive and negative on screening test:** Yes, more than 10% of cells stained; kappa test of reliability 0.553 -0.854 (blind interpretation)	**Age:** Mean (SD): 66 Range: 29-84 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 57 (100%) **Treatment (n [%]):** Surgery: 57 (100%) Chemotherapy: Platinum: 50 (88%) **Inclusion criteria:** Banked frozen specimens from women who underwent initial surgery for stage II or IV Ov Ca **Exclusion criteria:** None specified	**Use of test results:** Prediction of response to chemotherapy **Outcomes measured:** Cancer mortality Response by second-look surgery (SLL) or clinical and/or radiographic evaluation (WHO criteria)	1) Pgp expression negative to predict response (partial or none vs complete) to induction chemotherapy: Dis+ / Dis- / Tot T+: 32 / 8 / 40 T-: 9 / 0 / 9 Tot: 41 / 8 / 49 Value / Lower 95% CI / Upper 95% CI Se: 78.0% / 65.4% / 90.7% Sp: 0.0% / 0.0% / 0.0% PPV: 80.0% / 67.6% / 92.4% NPV: 0.0% / 0.0% / 0.0% 2) Mrp expression negative to predict response (partial or none vs complete) to induction chemotherapy: Dis+ / Dis- / Tot T+: 13 / 3 / 16 T-: 28 / 5 / 33 Tot: 41 / 8 / 49 Value / Lower 95% CI / Upper 95% CI Se: 31.7% / 17.5% / 46.0% Sp: 62.5% / 29.0% / 96.0% PPV: 81.3% / 62.1% / 100.0% NPV: 15.2% / 2.9% / 27.4% 3) Lrp expression negative to predict response (partial or none vs complete) to induction chemotherapy Dis+ / Dis- / Tot T+: 5 / 5 / 10 T-: 36 / 3 / 39 Tot: 41 / 8 / 49 Lower / Upper	**Comments:** Study combines women with no response by clinical evaluation (who were not considered for SLL) with women who required SLL for evaluation of response. **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: + Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: + Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring

	Value	95% CI	95% CI
Se	12.2%	2.2%	22.2%
Sp	37.5%	4.0%	71.0%
PPV	50.0%	19.0%	81.0%
NPV	7.7%	0.0%	16.1%

4) Hazard Ratio or other relevant information:
No association between Pgp or Mrp and either progression-free survival or overall survival in univariate survival analysis.

Lrp-positive tumors had shorter progression-free (9 mo vs 28 mo; p = 0.003) and overall survival (median 15 mo vs 42 mo; p = 0.007) than Lrp-negative tumors.

Lrp remained a significant predictor (p = 0.009) of survival in a multivariable survival analysis controlling for FIGO stage, residual tumor after initial surgery, tumor grade, and presence of ascites.

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Kamazawa, Kigawa, Kanamori, et al., 2002 **#3550**	**Geographical location:** Yonago, Japan **Study dates:** 2000-2001 **Study type:** Cohort/case series **Size of population:** 27 women **Genomic test(s) used:** MDR-1 MRP-1 MRP-2 by RT-PCR **Reference standard:** Surgical pathology Clinical outcome (response, CR, PR, NC) **Test reliability established?:** No **Statistical tests used:** t-test, sensitivity, specificity **Definition of positive and negative on screening test:** MDR-1 gene expression of 100	**Age:** Mean (SD): 55.2 Range: 21-72 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 27 (100%) **Treatment (n [%]):** Surgery: 27 (100%) Chemotherapy: Platinum: 27 (100%) **Inclusion criteria:** Residual disease after primary surgery **Exclusion criteria:** Borderline malignancy	**Use of test results:** Predictor of response to paclitaxel-based chemotherapy **Outcomes measured:** Complete or partial response to chemotherapy as measured by CT/MR/US	1) MDR-1 expression < 100 to predict response to chemotherapy: Dis+ / Dis- / Tot T+: 21 / 1 / 22 T-: 0 / 5 / 5 Tot: 21 / 6 / 27 Value / Lower 95% CI / Upper 95% CI Se: 100.0% / 85.7% / 100.0% Sp: 80.0% / 48.0% / 100.0% PPV: 95.5% / 86.8% / 100.0% NPV: 100.0% / 40.0% / 100.0% Tests of MRP-1 and MRP-2 did not differ between responders and non-responders (Figure; 2x2 not provided)	**Comments:** - Cut-off was selected post hoc to obtain 100% sensitivity. - Note there is an error in the text of the article in reported specificity for MDR. We chose the value of 80% to be consistent with the description of data and Figure 4; Se and PPV were reported correctly according to this interpretation. **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: - Use of validated method for genomic test: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: - Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Kierkegaard, Mogensen, Mogensen, et al., 1995 **#7940**	**Geographical location:** Aarhus, Denmark **Study dates:** Sep 1987 – Dec 1992 **Study type:** Cohort **Size of population:** 93 women from 265 consecutive patients **Genomic test(s) used:** CASA CA-125 **Reference standard:** Surgical pathology **Test reliability established?:** No **Statistical tests used:** Sensitivity, specificity, Cox **Definition of positive and negative on screening test:** Yes	**Age:** Median: 54.6 Range: 27-70 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 93 (100%) **Treatment (n [%]):** Surgery: 93 (100%) Chemotherapy: Platinum: 93 (100%) **Inclusion criteria:** Epithelial ovarian cancer FIGO stage II, III or IV, with no residual tumor at primary surgery **Exclusion criteria:** NR	**Use of test results:** Prediction of positive second-look laparotomy **Outcomes measured:** Presence of residual disease at second-look	1) CASA > 8 U/ml for diagnosis of tumor at SLL: |	Dis+	Dis-	Tot
---	---	---	---
T+	13	0	13
T-	45	35	80
Tot	58	35	93 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	22.4%	11.7%	33.1%
Sp	100.0%	91.4%	100.0%
PPV	100.0%	76.9%	100.0%
NPV	43.8%	32.9%	54.6% | 2) CA-125 > 15 U/ml for diagnosis of tumor at SLL: |	Dis+	Dis-	Tot
---	---	---	---
T+	23	0	23
T-	35	35	70
Tot	58	35	93 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	39.7%	27.1%	52.2%
Sp	100.0%	91.4%	100.0%
PPV	100.0%	87.0%	100.0%
NPV	50.0%	38.3%	61.7% | 3) CASA > 8 U/ml OR CA-125 > 15 U/ml for diagnosis of tumor at SLL: |	Dis+	Dis-	Tot
---	---	---	---
T+	27	0	27
T-	31	35	66
Tot	58	35	93 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	46.6%	33.7%	59.4%
Sp	100.0%	91.4%	100.0%		**Comments:** - There was a difference between patient with macroscopic and microscopic tumor at SLL. Markers were more sensitive for macroscopic tumor, and less sensitive for microscopic tumor (28% vs 11% for CASA; 51% vs 16% for CA-125). **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: + Use of validated method for genomic test: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: + Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
				PPV 100.0% 88.9% 100.0% NPV 53.0% 41.0% 65.1% 4) Hazard Ratio or other relevant information: In multivariable model for survival (controlling for age, histopathology, FIGO stage and grade): RR CA-125 > 35 U/ml = 2.9 (2.1 to 3.7; p = 0.007) RR for CASA > 8 U.ml = 2.2 (1.5 to 3.0; p = 0.043)	

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Kupry-janczyk, Szymanska, Madry, et al., 2003 **#2830**	**Geographical location:** Krakow, Poland **Study dates:** NR **Study type:** Cohort/retrospective series **Size of population:** 229 patients from 548 cases submitted **Genomic test(s) used:** TP53 **Reference standard:** Clinical outcome (tumor response by WHO clinical criteria) **Test reliability established?:** No **Statistical tests used:** 2x2, CPH model **Definition of positive and negative on screening test:** Yes	**Age:** Median: 53.2 Range: 24-77 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 229 (100%) **Treatment (n [%]):** Surgery: 229 (100%) Chemotherapy (platinum): 229 (100%) **Inclusion criteria:** Ov Ca FIGO IIB-IV, platinum chemotherapy and available tumor tissue in bank **Exclusion criteria:** Chemo before staging laparotomy	**Use of test results:** Prediction of tumor response to platinum-based chemotherapy **Outcomes measured:** Cancer mortality Tumor response (WHO criteria)	1) TP53 expression positive to predict response to chemotherapy (CR or PR vs. NC or PD): Dis+ / Dis- / Tot T+: 98 / 37 / 135 T-: 57 / 37 / 94 Tot: 155 / 74 / 229 Value (Lower 95% CI – Upper 95% CI) Se: 63.2% (55.6% – 70.8%) Sp: 50.0% (38.6% – 61.4%) PPV: 72.6% (65.1% – 80.1%) NPV: 39.4% (29.5% – 49.2%)	**Comments:** - This is more of a pilot study than one suggesting a clinical use for this marker. **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: + Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Lassus, Leminen, Vayrynen, et al., 2004 **#1360**	**Geographical location:** Helsinki, Finland **Study dates:** 1980-2000 **Study type:** Cohort **Size of population:** 401 women **Genomic test(s) used:** ERBB2 Tissue protein microarray **Reference standard:** Surgical pathology CT/MR Death **Test reliability established?:** No **Statistical tests used:** Survival analysis **Definition of positive and negative on screening test:** No	**Age:** < 57 years: 38% ≥ 57 years: 62% **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** 98% white/Finnish **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 401 (100%) **Treatment (n [%]):** Surgery: 401 (100%) Chemotherapy: Platinum: 345 (96%) Taxol: Other (not specified): 13 (3%) No chemotherapy: 42 (10%) **Inclusion criteria:** Ov Ca treated at Helsinki Univ, with data for both primary treatment and survival status. **Exclusion criteria:** Non-serous tumors	**Use of test results:** Prediction of response **Outcomes measured:** Cancer mortality Response to chemotherapy	1) ERBB2 gene copy number = 2 (vs. 3-5 or > 5) to predict response to chemotherapy (CR or PR vs. NR or PD): Dis+ / Dis- / Tot T+: 234 / 30 / 264 T-: 66 / 51 / 117 Tot: 300 / 81 / 381 Value / Lower 95% CI / Upper 95% CI Se: 78.0% / 73.3% / 82.7% Sp: 63.0% / 52.5% / 73.5% PPV: 88.6% / 84.8% / 92.5% NPV: 43.6% / 34.6% / 52.6% 2) Hazard Ratio or other relevant information: In multivariable survival analysis ERBB2 copy number status was an independent prognostic factor (HR 2.14 [1.34 to 3.42] for > 5 gene copies, and HR 1.70 [1.17 to 2.46] for 3-5 gene copies compared to 2 copies). Other independent prognostic factors included: Grade (1, 2 or 3) Residual tumor > 1cm Age ≥ 57 years FIGO stage (I, II, II IV)	**Comments:** None **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: + Adequate description of the cohort: - Use of validated method for genomic test: - Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: + Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Luo, Katsaros, Scorilas, et al., 2003 **#2930**	**Geographical location:** Turin, Italy; Groningen, The Netherlands; Leuven, Belgium; Helsinki, Finland **Study dates:** NR **Study type:** Cohort/case series **Size of population:** 146 Ov Ca **Genomic test(s) used:** hK10 **Reference standard:** Surgical pathology **Test reliability established?:** Referenced **Statistical tests used:** Survival analysis **Definition of positive and negative on screening test:** No	**Age:** Ovarian Ca Mean (SD): 52 Median: 49 Range: 26-72 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 146 (100%) Benign ovarian mass: 141 Healthy controls: 97 **Treatment (n [%]):** Surgery: 146 (100%) Chemotherapy: NR **Inclusion criteria:** Not described **Exclusion criteria:** NR	**Use of test results:** Prediction of response to chemotherapy **Outcomes measured:** Cancer mortality Tumor response to chemotherapy	1) hK10 < 843 ng/L to predict response to chemotherapy (CR/PR vs NC/PD): Dis+ / Dis- / Tot T+: 74 / 7 / 81 T-: 44 / 14 / 58 Tot: 118 / 21 / 139 Value (Lower 95% CI – Upper 95% CI) Se: 62.7% (54.0% – 71.4%) Sp: 66.7% (46.5% – 86.8%) PPV: 91.4% (85.2% – 97.5%) NPV: 24.1% (13.1% – 35.2%) 2) Hazard Ratio or other relevant information: hK10 positive (> 843 ng/L) was NOT associated with PFS, HR = 1.31 (0.65 to 2.62; p = 0.45). hK10 positive was associated with OS, HR = 3.43 (1.23 to 5.54; p = 0.018).	**Comments:** None **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: - Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: - Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Memar-zadeh, Lee, Berek, et al., 2003 **#2790**	**Geographical location:** Los Angeles, CA **Study dates:** 1989-2001 **Study type:** Case-control Cases = optimally cytoreduced Controls = suboptimally cytoreduced **Size of population:** 99 **Genomic test(s) used:** CA-125 **Reference standard:** Clinical outcome: optimal versus suboptimal cytoreduction. Optimal is defined as all residual tumor nodules less than 1 cm. **Test reliability established?:** Yes **Statistical tests used:** Sensitivity, specificity, ROC **Definition of positive and negative on screening test:** Cutoff CA-125 912 U/ml determined using ROC	**Age:** Median: 59 Range: 23-83 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 99 (100%) **Treatment (n [%]):** Surgery: 99 (100%) **Inclusion criteria:** Stage IIIC-IV ovarian cancer who had primary cytoreductive surgery **Exclusion criteria:** Borderline tumors	**Use of test results:** Predicting optimal cytoreduction **Outcomes measured:** Ability to perform optimal cytoreductive surgery	1) CA-125 > 912 U/mL to predict suboptimal cytoreduction Out+ = suboptimal Out- = Optimal T+ = above cutoff T- = below cutoff Dis+ / Dis- / Tot T+: 14 / 31 / 45 T-: 12 / 42 / 54 Tot: 26 / 73 / 99 Value (Lower 95% CI – Upper 95% CI) Se: 53.8% (34.7% – 73.0%) Sp: 57.5% (46.2% – 68.9%) PPV: 31.1% (17.6% – 44.6%) NPV: 77.8% (66.7% – 88.9%)	**Comments:** - Retrospective. Unclear whether any patients were excluded (data not given). - No validation set to confirm their cutoff level as valid. - No determination of other predictors of optimal debulking other than CA-125 or confounding variables. **Quality assessment:** *For case-control study:* Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: N/A Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment method: N/A Appropriateness of statistical analyses: + Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Obeidat, Latimer, and Crawford, 2004 **#1800**	**Geographical location:** Irbid, Jordan **Study dates:** 1/00-12/01 **Study type:** Case-control **Size of population:** 40 **Genomic test(s) used:** CA-125 **Reference standard:** Clinical outcome: optimal surgical cytoreduction, GOG criteria, largest remaining tumor nodule ≤ 1 cm **Test reliability established?:** Yes **Statistical tests used:** Sensitivity, specificity, ROC curves **Definition of positive and negative on screening test:** CA-125 > 500 U/mL	**Age:** Median: Optimal debulking: 57 Suboptimal: 63.5 Range: Optimal: 30-79 Suboptimal: 49-78 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 40 (100%) **Treatment (n [%]):** Surgery: 40 (100%) **Inclusion criteria:** Stage III ovarian cancer **Exclusion criteria:** Borderline malignancy	**Use of test results:** Predicting optimal cytoreduction **Outcomes measured:** Optimal surgical cytoreduction	1) CA-125 ≥ 500U/ml to predict sub-optimal cytoreduction: Out+ = suboptimal cytoreduction Out- = optimal cytoreduction T+ = CA-125 > 500 T- = CA-125 < 500 |	Out+	Out-	Tot
---	---	---	---
T+	13	6	19
T-	5	16	21
Tot	18	22	40 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	72.0%	51.3%	92.7%
Sp	73.0%	54.4%	91.6%
PPV	68.4%	47.5%	89.3%
NPV	76.2%	58.0%	94.4%		**Comments:** - Not able to reproduce the 95% CIs reported in paper. **Quality assessment:** *For case-control study:* Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: N/A Comparability of cases and controls with respect to potential confounders:+ Validated dietary assessment method: N/A Appropriateness of statistical analyses: + Grade: A

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Rustin, Marples, Nelstrop, et al., 2001 **#4110**	**Geographical location:** Northwood, UK **Study dates:** 1981-1999 **Study type:** Case-control **Size of population:** 300 → 88 who had persistent elevation of CA-125 following primary chemotherapy were the basis for this paper's analysis **Genomic test(s) used:** CA-125 **Reference standard:** Clinical outcome: radiographic evidence of disease progression or clinical evidence of progression **Test reliability established?:** Yes **Statistical tests used:** Sensitivity **Definition of positive and negative on screening test:** Elevation of CA-125 to twice the nadir level	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 300 (100%) **Treatment (n [%]):** Chemotherapy (type not specified): 300 (100%) **Inclusion criteria:** Treatment with first line chemotherapy for ovarian cancer; at least one CA-125 available; CA-125 elevated above normal range persistently post-treatment **Exclusion criteria:** Normal CA-125 at conclusion of primary chemotherapy	**Use of test results:** Change/delay in treatment **Outcomes measured:** Cancer progression based on clinical criteria	1) Ability of CA-125 doubling to diagnose ovarian cancer progression as measured by clinical signs or radiography: Out+ = patients whose disease progressed Out- = patients whose disease did not progress T+ = CA-125 doubled T- = CA-125 did not double |	Out+	Out-	Tot
---	---	---	---
T+	80	1	81
T-	5	2	7
Tot	85	3	88 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	94.1%	89.1%	99.1%
Sp	66.7%	13.3%	100.0%
PPV	98.8%	96.4%	100.0%
NPV	28.6%	0.0%	62.0%		**Comments:** - No specific measurement criteria were used as gold standard (eg, RECIST criteria for target lesion size) - Few outcome negatives (patients who did not progress) limits ability to calculate SP and NPV **Quality assessment:** *For case-control study:* Valid ascertainment of cases: + Unbiased selection of cases: - Appropriateness of the control population: + Verification that the control is free of cancer: - (no minimum follow up specified to confirm lack of progression) Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment method: NA Appropriateness of statistical analyses: + Grade: C

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Rustin, Nelstrop, Tuxen, et al., 1996 **#7510**	**Geographical location:** Northwood, UK **Study dates:** 12/89-4/94 **Study type:** Case-control **Size of population:** 255 **Genomic test(s) used:** CA-125 **Reference standard:** Clinical outcome: clinical evidence of ovarian cancer progression with follow up at least 12 months **Test reliability established?:** Yes **Statistical tests used:** Sensitivity, specificity, PPV, NPV **Definition of positive and negative on screening test:** Upper limit of normal CA-125 is 30 U/ml. Definition of progression is a doubling of the CA15 from a baseline level ≤ 30.	**Age:** NR **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 255 (100%) **Treatment (n [%]):** Chemotherapy (carboplatin or cisplatin): 100% **Inclusion criteria:** Patients with ovarian cancer enrolled on a large trial of 5 versus 8 cycles of carboplatin or cisplatin. **Exclusion criteria:** - Very few (< 4) CA-125 samples available; - Patients who received treatment with a monoclonal antibody; - Patients with secondary malignancy; follow up less than 12 months, persistent CA-125 elevation following primary treatment	**Use of test results:** Treat relapse disease early **Outcomes measured:** Cancer progression	1) Ability of CA-125 to detect progression Out+ = progression of cancer Out- = no progression T+ = CA-125 double the normal cutoff (30u/ml) T- = CA-125 never doubled the normal cutoff |	Out+	Out-	Tot
---	---	---	---
T+	73	4	77
T-	12	42	54
Tot	85	46	131 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	85.9%	78.5%	93.3%
Sp	91.3%	83.2%	99.4%
PPV	94.8%	89.8%	99.8%
NPV	77.8%	66.7%	88.9% | 2) Ability of CA-125 to predict early progression: Out+ = progression of cancer Out- = no progression T+ = 2 consecutive CA-125 more than double the normal cutoff (30u/ml) T- = did not meet T+ criteria above |	Out+	Out-	Tot
---	---	---	---
T+	73	1	74
T-	14	42	56
Tot	87	43	130 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	83.9%	76.2%	91.6%
Sp	97.7%	93.2%	100.0%
PPV	98.6%	96.0%	100.0%
NPV	75.0%	63.7%	86.3%		**Comments:** - Several possible definitions of CA-125 criteria for progression of cancer were explored (Table2). Authors chose their “best” definition but no validation set to confirm predictive value. **Quality assessment:** *For case-control study:* Valid ascertainment of cases: + Unbiased selection of cases: + Appropriateness of the control population: + Verification that the control is free of cancer: + follow up at least 12 months Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment method: NA Appropriateness of statistical analyses: + Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Santillan, Garg, Zahurak, et al., 2005 **#13220**	**Geographical location:** Baltimore, MD **Study dates:** Sep 1997-Mar 2003 **Study type:** Cohort **Size of population:** 39 **Genomic test(s) used:** CA-125 **Reference standard:** Clinical outcome: Recurrent disease (pathology or radiologic evidence of recurrence) **Test reliability established?:** Yes **Statistical tests used:** Fisher's exact test, t-test **Definition of positive and negative on screening test:** Absolute change in CA-125 post-treatment ≥ 5	**Age:** Mean: 55 Range: 43-71 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 39 (100%) **Treatment (n [%]):** NR **Inclusion criteria:** - CA-125 > 35 at diagnosis - Complete response to initial therapy with CA-125 < 35 - At least 3 serial serum CA-125 measurements - Clinical or radiologic determination of disease status at last visit **Exclusion criteria:** None specified	**Use of test results:** Prediction of recurrence **Outcomes measured:** Cancer recurrence	1) Recurrence; positive test = absolute change in CA-125 ≥ 5 |	Dis+	Dis-	Tot
---	---	---	---
T+	22	1	23
T-	0	16	16
Tot	22	17	39 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	100.0%	86.4%	100.0%
Sp	94.1%	82.9%	100.0%
PPV	95.7%	87.3%	100.0%
NPV	100.0%	81.3%	100.0%		**Comments:** None **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): + Large sample size: - Adequate description of the cohort: + Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: - Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: - Grade: C

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Saygili, Guclu, Uslu, et al., 2002 **#3680**	**Geographical location:** Izmir, Turkey **Study dates:** 1994-2001 **Study type:** Case-control **Size of population:** 92 **Genomic test(s) used:** CA-125 **Reference standard:** Surgical pathology Clinical outcome: Surgical cytoreduction of all tumor nodules to less than 1 cm (optimal cytoreduction) **Test reliability established?:** Yes **Statistical tests used:** Sensitivity, specificity, ROC **Definition of positive and negative on screening test:** CA-125 cutoff 500 U/ml established using ROC curve	**Age:** Mean (SD): 56 Range: 46-64 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 92 (100%) **Treatment (n [%]):** Surgery: 92 (100%) Chemotherapy: NR **Inclusion criteria:** Stage IIIC ovarian cancer, patient undergoing primary surgery **Exclusion criteria:** Pre-operative chemotherapy	**Use of test results:** Determine whether patients will be resectable **Outcomes measured:** Ability to optimally cytoreduce ovarian cancer	1) CA-125 > 500 U/mL to predict sub-optimal surgical cytoreduction: Out+ = suboptimal Out- = optimal T+ = CA-125>500 T- = CA-125<500 |	Dis+	Dis-	Tot
---	---	---	---
T+	33	12	45
T-	11	36	47
Tot	44	48	92 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	75.0%	62.2%	87.8%
Sp	75.0%	62.8%	87.3%
PPV	73.3%	60.4%	86.3%
NPV	76.6%	64.5%	88.7%		**Comments:** - No comment on confounding variables/other predictors of optimal debulking between the groups **Quality assessment:** *For case-control study:* Valid ascertainment of cases:+ Unbiased selection of cases: - (unclear whether consecutive) Appropriateness of the control population: + Verification that the control is free of cancer: N/A Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment method: N/A Appropriateness of statistical analyses: + Grade: C

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Senapad, Neungton, Thirapaka-wong, et al., 2000 **#5170**	**Geographical location:** Bangkok, Thailand **Study dates:** 5/95-12/98 **Study type:** Cohort **Size of population:** 33 **Genomic test(s) used:** CA-125, TPS **Reference standard:**] Surgical pathology at second-look laparotomy **Test reliability established?:** CA-125 – yes TPS – no **Statistical tests used:** Sensitivity, specificity, PPV, NPV **Definition of positive and negative on screening test:** For prediction of negative second-look laparotomy: CA-125 < 10 u/ml TPS < 50 U/ml	**Age:** Median: 45 Range: 27-72 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 33 (100%) **Treatment (n [%]):** Chemotherapy (cis-platinum, paraplatin, or the paclitaxel combination regime): 33 (100%) **Inclusion criteria:** - Non-mucinous epithelial ovarian cancer, stage III-IV - All achieved a complete response with primary chemotherapy (no physical exam or radiographic evidence of disease) - All underwent second-look laparotomy following completion of 6 cycles of chemotherapy **Exclusion criteria:** - Non complete responders - Patients who did not receive second-look laparotomy	**Use of test results:** Potential use of authors' criteria to predict negative second-look laparotomy (and therefore avoid surgery) **Outcomes measured:** Pathology results at second-look laparotomy	1) CA-125 > 10 U/mL to predict positive second-look laparotomy Out+ = positive second-look Out- = negative second-look T+ = CA-125 > 10 T- = CA-125 < 10 |	Dis+	Dis-	Tot
---	---	---	---
T+	11	11	22
T-	8	3	11
Tot	19	14	33 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	57.9%	35.7%	80.1%
Sp	21.4%	0.0%	42.9%
PPV	50.0%	29.1%	70.9%
NPV	27.3%	1.0%	53.6% | 2) Combination of CA-125 > 10 and TPS>50 to predict positive SLL Out+ = positive SLL Out- = negative SLL T+ = CA-125 > 10 and TPS > 50 T- = doesn't meet T+ criteria above |	Dis+	Dis-	Tot
---	---	---	---
T+	11	13	24
T-	8	1	9
Tot	19	14	33 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	57.9%	35.7%	80.1%
Sp	7.1%	0.0%	20.6%
PPV	45.8%	25.9%	65.8%
NPV	11.1%	0.0%	31.6%		**Comments:** - Authors suggest a subset of patients with low levels of CA-125 and TPS could forgo second-look due to the NPV of 88.9 achieved with a combination of the 2 markers. - Second-look laparotomy is no longer standard of care in United States, making this less relevant **Quality assessment:** *For case-control study:* Valid ascertainment of cases: + Unbiased selection of cases: - not specified Appropriateness of the control population: + Verification that the control is free of cancer: + Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment method: N/A Appropriateness of statistical analyses: + Grade: B

Evidence Table 3 – Question 4 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Wong, Dai, Lele, et al., 2000 **#5400**	**Geographical location:** Buffalo, NY **Study dates:** 1/90-12/96 **Study type:** Case-control **Size of population:** 72 **Genomic test(s) used:** CA-125 **Reference standard:** Surgical pathology **Test reliability established?:** Yes **Statistical tests used:** Sensitivity, specificity, NPV **Definition of positive and negative on screening test:** CA-125 < 35U/ml normal	**Age:** Mean: 58.9 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** Ovarian cancer: 72 (100%) **Treatment (n [%]):** Primary surgery: 72 (100%) Second-look surgery: 46 (64%) Chemotherapy (platinum-based): 70 (97%) - Cisplatin/cytoxan: 43 (60%) - Cisplatin/taxol: 15 (21%) - Cisplatin/Adria/Cytoxan: 12 (17%) - Methotrexate/Cytoxan: 2 (3%) **Inclusion criteria:** Patients with epithelial ovarian cancer who under-went initial optimal surgical cytoreduction followed by 6 cycles of platinum-based chemotherapy **Exclusion criteria:** Non-epithelial ovarian cancer	**Use of test results:** No use in the current study **Outcomes measured:** Pathology results at second-look laparotomy/laparoscopy, if performed Overall survival	1) Ability of CA-125 performed after 3 cycles chemotherapy to predict positive second-look laparotomy performed after 6 cycles chemotherapy: Out+ = positive pathology at second-look Out- = negative pathology at second-look T+ = CA-125 > 35U/ml T- = CA-125 < 35U/ml |	Out+	Out-	Tot
---	---	---	---
T+	5	1	6
T-	23	17	40
Tot	**28**	**18**	46 | |	Value	Lower 95% CI	Upper 95% CI
---	---	---	---
Se	**17.9%**	3.7%	32.1%
Sp	**94.7%**	84.4%	100.0%
PPV	83.3%	53.5%	100.0%
NPV	42.5%	27.2%	57.8%	 2) Other relevant information: CA-125 in normal range after 3 cycles chemotherapy predicted better median survival (30 months vs. 17 months, P < 0.0001 log rank test).	**Comments:** - Study demonstrates that early normalization of CA-125 after only 3 cycles chemo does not accurately predict who will have a negative second-look laparotomy, does predict improved overall survival. **Quality assessment:** *For case-control study:* Valid ascertainment of cases: + Unbiased selection of cases:+ Appropriateness of the control population: + Verification that the control is free of cancer: + Comparability of cases and controls with respect to potential confounders: - Validated dietary assessment method: N/A Appropriateness of statistical analyses+: Grade: B

Evidence Table 4 – Question 5: *What are the harms of using genomic tests for ovarian cancer prevention and management?*

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
Bish, Sutton, Jacobs, et al., 2002 **#10530**	**Geographical location:** London, UK **Study dates:** May 1997-May 1999 **Study type:** Cohort **Size of population:** 203 **Genomic test(s) used:** BRCA1/BRCA2 **Reference standard:** Clinical outcome (psychological distress) **Test reliability established?:** Yes – validated scale for measuring outcome **Statistical tests used:** ANOVA, t-tests **Definition of positive and negative on screening test:** Positive BRCA1/BRCA2	**Age:** Mean (SD): 42.3 (12.6) Range: 18-73 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** 97% White 3% Other **Definition of "high risk":** Estimated lifetime cancer risk of 1 in 3 or higher **Diagnoses (n [%]):** 46 (24%) with previous history of breast and/or ovarian cancer (1 with ovarian cancer, 4 with both, rest with breast cancer) 26 (13.4%) low risk 76 (39.2%) moderate 46 (23.7%) high risk **Inclusion criteria:** Referral criteria (any of the following): - Breast cancer < 40 years - More than 1 primary - Breast and ovary as 2 primary tumors - 3 close relatives with breast or ovarian cancer - 2 close relatives with breast or ovarian cancer if 1 < 50 - 1 1st degree relative with cancer < 40 - 1 1st degree relative with bilateral breast cancer or 2 primaries	**Use of test results:** Counseling regarding BRCA1/BRCA2 testing, options for screening and surveillance **Outcomes measured:** Quality of life - Hospital Anxiety and Depression Scale - General Health Questionnaire - Cancer Worry Scale - Perceived risk of cancer - Perceived risk of mutation Timing of outcome measurement: - Pre-consultation - 2 weeks post-consultation (83% response) - 6 months (85% response) - 12 months (91%) Only those with data at all 4 time points (n = 203, 35% of initial cohort scheduled for genetic consultation during time period) were included in the analysis	1) At baseline, significantly less worry about ovarian cancer compared to breast cancer (7% vs. 34% reported worry often or almost all the time). 2) Worry about ovarian cancer increased significantly among those with history of breast or ovarian cancer compared to unaffected women, no matter what risk group. 3) Overall no change in worry in response to counseling.	**Comments:** None **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: + Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: - (high dropout rate) Analysis (multivariate adjustments) and reporting of results: + Grade: B

Evidence Table 4 – Question 5 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
		- "Very worried about family history" **Exclusion criteria:** None specified			
Claes, Evers-Kiebooms, Denayer, et al., 2005 **#13010**	**Geographical location** Leuven, Belgium **Study dates:** 1999-July 2003 **Study type:** Cohort **Size of population:** 71 (68 [96%] completed follow-up) **Genomic test(s) used:** BRCA1/BRCA2 **Reference standard:** Clinical outcome (quality of life measured using validated instruments) **Test reliability established?:** Yes **Statistical tests used:** Fisher's exact test, t-tests **Definition of positive and negative on screening test:** Positive BRCA1 or BRCA2	**Age:** Carriers (n = 34) Mean (SD): 38.4 (11.4) Range: 19-61 Non-carriers (n = 34) Mean (SD): 35.24 (10.6) Range: 19-64 **Menopausal status (n [%]):** NR **Race/ethnicity (n [%]):** NR **Risk factors (n [%]):** NR **Diagnoses (n [%]):** NR **Inclusion criteria:** Family members of patients with identified BRCA1/BRCA2 mutations **Exclusion criteria:** None specified	**Use of test results:** Counseled about risk, prophylactic surgery **Outcomes measured:** Quality of life - Coping strategies (Utrecht Coping List) - Perceived impact of test result - Risk perception - Sense of control - Cancer-specific distress (Impact of Event Scale) - General distress (Spielberger STAI)	1) Intrusive thoughts, depressive symptoms, and breast and ovarian cancer worries improved for those with negative result. 2) No change from baseline in those with positive test results or those who refused testing. 3) Problem-solving training results in greater improvement than client-based counseling. 4) Sex not significant factor in multivariate analysis.	**Comments:** None **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: - Adequate description of the cohort: + Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: - Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: + Grade: B

Evidence Table 4 – Question 5 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
McInerney-Leo, Biesecker, Hadley, et al., 2004 **#10100**	**Geographical location** Bethesda, Rockville, and Baltimore, MD; Philadelphia, PA **Study dates:** NR **Study type:** Cohort **Size of population:** 212 (559 invited, 262 agreed and completed baseline, 212 completed baseline and follow-up) **Genomic test(s) used:** BRCA1/BRCA2 **Reference standard:** Clinical outcome (measures of family relationships [conflict, cohesiveness, expressiveness], using Family Relationship Index) **Test reliability established?:** Yes **Statistical tests used:** Paired t-tests, ANOVAs; linear regression **Definition of positive and negative on screening test:** NA	**Age:** Range: 95 (45%) under 40 (not reported by sex) **Menopausal status (n [%]):** NR; 35% male **Race/ethnicity (n [%]):** "Primarily Caucasian" **Risk factors (n [%]):** Family history: 212 (100%) **Diagnoses (n [%]):** Ovarian cancer: 0 Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 100% **Inclusion criteria:** Age > 18, family members with at least one BRCA1 or 2 mutation identified **Exclusion criteria:** None specified	**Use of test results:** Not specified; subjects randomized to problem-solving training or client-centered counseling **Outcomes measured:** - Depression (Center for Epidemiologic Studies Depression Scale) - Self-esteem (Rosenberg Self-Esteem Scale) - Cancer-related distress (Impact of Events Scale, Breast Cancer Worries Scale, Ovarian Cancer Worries Scale)	1) Intrusive thoughts, depressive symptoms, and breast and ovarian cancer worries improved for those with negative result. 2) No change from baseline in those with positive test results or those who refused testing. 3) Problem-solving training results in greater improvement than client-based counseling. 4) Sex not significant factor in multivariate analysis.	**Comments:** - Same study population as in McInerney-Leo et al., 2005 (#520) - Families in study had participated in previous study necessitating communication between relatives - Baseline levels of cohesion higher than average, conflict lower than average - 212 subjects came from only 13 families – thus, many subjects in this study are from the same families, possibly a source of bias **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: - Completeness of follow-up: + Analysis (multivariate adjustments) and reporting of results: + Grade: B

Evidence Table 4 – Question 5 (continued)

Study	Study Design	Patients	Outcome Measures	Results	Comments/Quality Scoring
McInerney-Leo, Biesecker, Hadley, et al., 2005 **#520**	**Geographical location:** Bethesda, Rockville, and Baltimore, MD; Philadelphia, PA **Study dates:** NR **Study type:** Cohort of adult members of families with identified BRCA1/2 mutations **Size of population:** 212 (559 invited, 262 agreed and completed baseline, 212 completed baseline and follow-up) **Genomic test(s) used:** BRCA1/BRCA2 **Reference standard:** Clinical outcome (measures of family relationships [conflict, cohesiveness, expressiveness] using Family Relationship Index) **Test reliability established?:** Yes **Statistical tests used:** Paired t-tests, ANOVAs; linear regression **Definition of positive and negative on screening test:** NA	**Age:** Range: "over half over age of 40" **Menopausal status (n [%]):** NR; 35% male **Race/ethnicity (n [%]):** "Primarily Caucasian" **Risk factors (n [%]):** Family history: 212 (100%) **Diagnoses (n [%]):** Ovarian cancer: 0 Borderline: 0 Benign ovarian mass: 0 Other: 0 Healthy controls: 100% **Inclusion criteria:** Age > 18, family members with at least one BRCA1 or 2 mutation identified **Exclusion criteria:** None specified	**Use of test results:** Offered genetic testing **Outcomes measured:** Measures of family relationships	1) Subjects who declined genetic testing had positive changes in family relationships; expressiveness and cohesiveness increased compared to those who chose testing. 2) Abnormal test result was associated with decreased expressiveness compared to negative test result (trend, but not significant at $p < 0.05$). 3) Sex not significant factor in multivariate analysis.	**Comments:** - Same study population as in McInerney-Leo et al., 2004 (#10100) - Families in study had participated in previous study necessitating communication between relatives - Baseline levels of cohesion higher than average, conflict lower than average - 212 subjects came from only 13 families – thus, many subjects in this study are from the same families, possibly a source of bias **Quality assessment:** *For cohort study:* Unbiased selection of the cohort (prospective recruitment of subjects): - Large sample size: + Adequate description of the cohort: + (referenced) Use of validated method for genomic test: + Use of validated method for ascertaining clinical outcomes: + Adequate follow-up period: + Completeness of follow-up: - Analysis (multivariate adjustments) and reporting of results: + Grade: B

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Appendix E: Peer Reviewers

The Duke Evidence-based Practice Center is grateful to the following peer reviewers who read and commented on a draft version of this report:

Ralph J. Coates, PhD, Associate Director for Science, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, Atlanta, Georgia

Tracy G. Lively, PhD, Associate Chief, Diagnostics Evaluation Branch, Cancer Diagnosis Program, National Cancer Institute, Rockville, Maryland

Edward E. Partridge, MD, Professor, Obstetrics and Gynecology, and Interim Director, UAB Comprehensive Cancer Center, Birmingham, Alabama

Gurvaneet Randhawa, MD, MPH, Center for Outcomes and Evidence, Agency for Healthcare Research and Quality, Rockville, Maryland

Edward (Ted) Trimble, MD, MPH, Head of Gynecologic Cancer Therapeutics and Quality of Cancer Care Therapeutics, National Cancer Institute, Rockville, Maryland

Combined comments from the Evaluation of Genomics Applications in Practice and Prevention (EGAPP)/Centers for Disease Control and Prevention (CDC) Discussion Group

Nominations for peer reviewers were solicited from several sources, including the project's technical expert panel and interested federal agencies. The list of nominees was vetted and approved by the Agency for Healthcare Research and Quality (AHRQ).