



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Proteomic Pattern Analysis of Blood for the Early Detection of Ovarian Cancer

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- Genetic Testing for Susceptibility to Breast and Ovarian Cancer (BRCA1 & BRCA2)
- Prophylactic Oophorectomy With or Without Hysterectomy
- Transvaginal Ultrasound for Ovarian and Endometrial Cancer Screening or Surveillance
- Tumor Markers for Diagnosis and Management of Cancer

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2010 CIGNA

Coverage Policy

CIGNA does not cover proteomic pattern analysis testing (e.g., OvaSure™, OvaCheck™) for screening, diagnosing or managing of ovarian cancer because it is considered experimental, investigational or unproven.

General Background

According to the American College of Obstetricians and Gynecologists (ACOG), there is no accurate screening test for the early detection of ovarian cancer (ACOG, 2007). Effective screening for a disease requires that the disease has a premalignant phase, a long preclinical phase, stage-dependent outcomes, curative treatments that are acceptable and readily available, and a cost-effective screening test that indicates consistent levels of sensitivity, specificity and positive predictive values. The premalignant condition that progresses to invasive ovarian cancer has not been well-defined. A decrease in mortality from ovarian cancer may occur if the detection of early-stage disease can be reliably determined (Zell and Meyskens, 2008).

Ovarian cancer is currently diagnosed using a combination of pelvic examination, ultrasound, computed tomography (CT) scans, and magnetic resonance imaging (MRI). When a mass is found or cancer is suspected,

then an invasive surgical biopsy is performed to confirm the diagnosis, the origin of the cancer and its stage. This information is then used to determine the course of treatment that will be recommended for each individual patient (ACS, 2010).

Researchers have suggested that an indicator for the presence and thus early screening of individuals for ovarian cancer could be determined by measuring the cancer antigen CA-125. However, other benign conditions can cause an elevation in CA-125 levels such as endometriosis, pelvic infection, pregnancy, menstruation, pancreatitis, renal failure, hepatitis, and congestive heart failure (Zell and Meyskens, 2008). Some ovarian cancers do not increase CA-125 levels. Normal CA-125 levels are found in about 50% of women with early stage ovarian cancers. About 20–25% of women with advanced ovarian cancers do not have higher CA-125 levels (ACOG, 2007).

In an effort to develop a screening test that could detect the presence of ovarian cancer in its earliest stages, rendering it amenable to curative measures, research is underway in the areas of proteomics. Proteomics is the systematic study of proteins in a particular cell, tissue, or organism. Researchers are currently applying proteomic technology in studies for the early detection of and ongoing surveillance of cancer (NCI, 2009). This approach does not search for specific known proteins but rather for differences in patterns of protein expression based on the use of mass spectroscopy which can be used to obtain sequence information on these proteins (Pincus, 2007).

A challenge with proteomics is that laboratories across the country collect, store, and study proteins in different ways. This lack of standardization makes it difficult to accurately compare results from one laboratory to another, and limits the number of cancer protein or biomarker tests that are available to the public. The National Cancer Institute (NCI) is working to standardize proteomics at laboratories across the country. In 2006, the NCI launched the Clinical Proteomic Technologies for Cancer (CPTC) initiative to coordinate the uniform collection, storage, and analysis of proteins (NCI, 2008).

Correlogics[®] Systems, Inc. (Bethesda, MD) has developed a serum-based test (OvaCheck[™]) for the early detection of ovarian cancer. According to the manufacturer's website, Correlogic's research is based on an approach that looks for subtle changes in protein and other serum molecule patterns, rather than an increase in an individual molecule. It employs patented computer technology (i.e., Proteome Quest[®]) to identify these hidden patterns. Once the initial processing is completed, spectral data is transmitted electronically to Correlogic, and analyzed remotely. Presently, Correlogic is conducting clinical trials on OvaCheck at numerous research sites in the United States and abroad. At this time, OvaCheck is not commercially available. Quest Diagnostics (Madison, NJ) references OvaCheck on their website as a proteomic test for ovarian cancer. According to the manufacturer website, OvaCheck has met European Union regulatory requirements and is cleared for distribution and sale in Europe.

U.S. Food and Drug Administration (FDA)

In 2008, the FDA issued a manufacturer letter to the Laboratory Corporation of America (Burlington, NC) stating they are reviewing the status of OvaSure[™] and whether it is subject to FDA oversight (FDA, 2008b).

Literature Review

Wang et al. (2008) evaluated the diagnostic value for ovarian cancer using proteomic pattern established by surface enhanced laser desorption/ionization (SELDI-TOF-MS) profiling of plasma proteins coupled with support vector machine (SVM) data analysis, and to investigate whether the proteomic pattern established by advanced ovarian cancer could be used for diagnosis of early-stage ovarian cancer patients. The study included 44 ovarian cancer patients (11 early-stage and 33 advanced ovarian cancer patients) and 31 age-matched noncancer controls. SELDI-TOF-MS coupled with SVM analysis was performed to establish a proteomic pattern to discriminate 33 advanced ovarian cancer patients from 31 non-cancer controls. A blind test, including 11 early-stage ovarian cancer cases, was performed to investigate whether proteomic pattern established by advanced ovarian cancer could be used for diagnosis of early-stage ovarian cancer patients. A seven-peak proteomic pattern was established which discriminated 33 advanced ovarian cancer patients from 31 non-cancer controls effectively. A sensitivity of 93.94% (31/33) and a specificity of 93.55% (29/31) were yielded from the proteomic pattern. After blind test, 9 of 11 early stage ovarian cancer patients were successfully diagnosed with the accuracy of 81.82%. The authors reported that although many studies have been done for ovarian cancer biomarker detection, results from different laboratories were different. In this study, the discriminate

protein peaks are not consistent with the previous studies. Additionally, in most of previous studies serum was used, however, in this study, plasma was used.

Helleman et al. (2008) reported on the use of surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS) to discover ovarian cancer biomarkers by comparing serum protein profiles of ovarian cancer patients (obtained before chemotherapy or at progression [n=51]) with those of healthy women (n=31). In addition, sera profiles from ovarian cancer patients after chemotherapy (n=12) were compared with those of ovarian cancer patients at progression (n=24). One of the discovered biomarkers was identified and subsequently confirmed and validated using enzyme-linked immunosorbent assay (ELISA). Eight primary (sensitivity=94%, specificity=97%, p<0.0001) and seven progression tumor biomarkers (sensitivity=91%, specificity=97%, p<0.0001) were discovered. In addition, eight potential progression monitoring biomarkers (sensitivity=75%, specificity=83%, p=0.0008) of which one, a biomarker of 11.7 kDa, was further identified as serum amyloid A1. Independent validation (ELISA) showed an elevated expression of this protein at relapse in four of the seven ovarian cancer patients tested. Combining the eight newly discovered progression monitoring biomarkers with CA125 resulted in an increase of the sensitivity (91–100%). The authors reported that these biomarkers, in combination with for instance CA125, should be validated in large ovarian cancer and control groups. This same technique to discover biomarkers was applied in the Petricoin et al. (2002) study.

Visintin et al. (2008) reported the characterization of a blood test, based on the quantitative analysis of six biomarkers using a multiplex platform. The study included a total of 362 healthy controls and 156 newly diagnosed ovarian cancer patients. Concentrations of leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor, and CA-125 were determined using a multiplex, bead-based, immunoassay system. The proteins identified in this study, with the exception of CA-125 and macrophage inhibitory factor, are all related to the normal physiology of the ovaries. All six markers were evaluated in a training set (181 samples from the control group and 113 samples from ovarian cancer patients) and a test set (181 sample control group and 43 ovarian cancer). The authors reported that multiplex and enzyme-linked immunosorbent assay (ELISA) exhibited the same pattern of expression for all the biomarkers. None of the biomarkers by themselves were good enough to differentiate healthy versus cancer cells. The combination of the six markers provided a better differentiation than CA-125. Four models with <2% classification error in training sets all had improvement (sensitivity 84%–98% at specificity 95%) over CA-125 (sensitivity 72% at specificity 95%) in the test set. The chosen model correctly classified 221 out of 224 specimens in the test set, with a classification accuracy of 98.7%. The PPV for the test sample is 99.3% and the negative predictive value is 99.2%.

Petricoin et al. (2002) reported the results from a combined diagnostic study conducted by the NCI and the FDA. The proteomic patterns from a database were compared to the serum protein markers of 116 serum samples using matrix-assisted laser desorption ionization (MALDI). Fifty of these samples were from women with known ovarian cancer, and 50 samples were used as a control from women without ovarian cancer. The researchers also included 16 additional samples taken from women with various medical conditions whose status in relation to ovarian cancer was unknown. The serum samples were then compared to the algorithm database of proteomic patterns. Of the 50 cancerous samples, all were confirmed as cancerous by the algorithmic reading. The system also identified 16 samples as ovarian cancer stage I. Of the 66 noncancerous samples, 63 were identified as cancer-free. This sample test produced results of 100% sensitivity and specificity of 95%, with a positive predictive value of 94% (84–99). The researchers concluded that these results justified the need for this type of testing to be conducted in a large population-based prospective study to validate their findings with patients with known cancer, suspected cancer, or as a basic population screening tool. During this study, the algorithmic technology used to identify the samples was MALDI, whereas the technology used for review of the OvaCheck samples was electrospray ionization (ESI) type mass spectrometry. Due to the variance of systems that was used to process each type of serum sample, it is difficult to draw conclusions from this study regarding the clinical utility of this test.

The Agency for Healthcare Research and Quality (AHRQ) published an evidence-based technology assessment for ovarian cancer detection and management. Within this report, the following conclusion was made: “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, serum testing using the tumor marker cancer antigen 125 (CA-125), and imaging using vaginal ultrasound have all proven ineffective.” The author indicates that additional studies are currently being conducted (Myers, 2006).

Professional Societies/Organizations

National Cancer Institute (NCI): The NCI PDQ® summary on ovarian cancer screening has indicated that there is insufficient evidence to determine whether routine screening for ovarian cancer with serum markers such as CA-125 levels, transvaginal ultrasound, or pelvic examinations would result in a decrease in mortality from ovarian cancer. The NCI has stated that “proteomics has been used to identify patterns or specific serum markers that may be used in place of, or in conjunction with, CA-125 measurements for the early detection of cancer. These studies have been small case-control studies that are limited by sample size and by the number of early-stage cancer cases included. Further evaluation is needed to determine whether any additional markers have clinical utility for the early detection of ovarian cancer” (NCI, 2009).

Society of Gynecologic Oncologists (SGO): In 2004, the SGO published their position concerning the use of OvaCheck as a “serum-based diagnostic test for ovarian cancer and that additional research is needed to validate the test’s effectiveness before it is offered to the public” (SGO, 2004). There has been no update to this guideline since 2004. Additionally, in 2008, the SGO published their position concerning the use of OvaSure stating that “after reviewing OvaSure’s materials, it is our opinion that additional research is needed to validate the test’s effectiveness before offering it to women outside of the context of a research study conducted with appropriate informed consent under the auspices of an institutional review board” (SGO, 2008).

American Academy of Family Physicians (AAFP): The AAFP summary of recommendations for clinical preventive services recommend against routine screening for ovarian cancer. This recommendation supports the U.S. Preventive Services Task Force (USPSTF) concerning ovarian cancer screening (AAFP, 2007).

U.S. Preventive Services Task Force (USPSTF): Guidance was published from the USPSTF, recommending against routine screening for ovarian cancer. This recommendation was based on fair evidence that screening with serum CA-125 level or transvaginal ultrasound can detect ovarian cancer at an earlier stage than it can be detected in the absence of screening; however, the task force found fair evidence that earlier detection would likely have a small effect, at best, on mortality from ovarian cancer. Because of the low prevalence of ovarian cancer and the invasive nature of diagnostic testing after a positive screening test, there is fair evidence that screening could likely lead to important harms. The USPSTF concluded that the potential harms outweigh the potential benefits (USPSTF, 2004). There has been no update to this guideline since 2004.

American College of Obstetrics and Gynecology (ACOG): The ACOG, the Committee on Gynecologic Practice and the Society of Gynecologic Oncologists indicated that although newer tumor markers and proteomics are undergoing investigation and appear promising, it is unclear whether they will help identify high-risk women or facilitate the early diagnosis of more women with ovarian cancer. Currently, there are no techniques that have proved to be effective in the routine screening of asymptomatic low-risk women for ovarian cancer (ACOG, 2002).

Summary

At this time, there is a lack of evidence through well-designed, large-population, randomized controlled clinical trials demonstrating the clinical utility of proteomic-based testing (e.g., OvaSure™, OvaCheck™) for the diagnosis, surveillance, or management of patient treatment protocols for ovarian cancer. Studies are needed to validate the sensitivity of this test in relation to patient outcomes, patient morbidity and mortality. Until these studies are conducted and published within the peer-reviewed literature, the role of proteomic-based testing (e.g., OvaSure™, OvaCheck™) in the screening, diagnosis and management of ovarian cancer remains unknown.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered:

CPT* Codes	Description
83788†	Mass spectrometry and tandem mass spectrometry (MS, MS/MS), analyte not elsewhere specified; qualitative, each specimen
83789†	Mass spectrometry and tandem mass spectrometry (MS, MS/MS), analyte not

	elsewhere specified; quantitative, each specimen
84999†	Unlisted chemistry procedure

ICD-9-CM Diagnosis Codes	Description
183.0	Malignant neoplasm of ovary
183.8	Malignant neoplasm of other specified sites of uterine adnexa Tubo-ovarian Utero-ovarian Malignant neoplasm of contiguous or overlapping sites of ovary and other uterine adnexa whose point of origin cannot be determined
795.82	Elevated cancer antigen 125 [CA 125]
V76.46	Special screening for malignant neoplasm of ovary
	Multiple/Varied

†**Note:** Experimental/investigational/unproven and not covered when used to report proteomic pattern analysis testing (e. g., OvaSure™, OvaCheck™).

*Current Procedural Terminology (CPT®) ©2010 American Medical Association: Chicago, IL.

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	9/15/2008	0171	Proteomic Pattern Analysis of Blood for the Early Detection of Ovarian Cancer (e.g., OvaCheck™)

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA's subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.