Medical Policy Reference Manual
Medical Policy

11.01.028 Serum Proteomic Pattern Analysis Testing for Screening or Diagnosis of Ovarian Cancer

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Description

Ovarian cancer in its early stages is characterized by few, if any, symptoms, at the time when it is most treatable. When symptoms such as abdominal discomfort, nausea, or fatigue are present, they may be ambiguous or may imitate other, less serious disorders. For this reason, patients may not see their physicians until the disease has reached a more advanced stage, when the chances for long-term survival are unfavorable. An effective screening test for ovarian cancer in patients at risk for developing the disease is therefore highly desirable, but unfortunately, there has not been a screening test that is sensitive and specific enough to be used for this purpose.

Recent research has indicated that ovarian cancer leaves a characteristic pattern of protein structures in the serum, which can be detected using spectroscopic analysis. This "proteomic pattern" analysis is being developed as a possible screening test for the presence of ovarian cancer in the population at risk for the disease.

Policy

Proteomic pattern analysis as a screening or diagnostic test for ovarian cancer is considered **experimental / investigational**, as it does not meet TEC criteria # 1 - 5.

Policy Guidelines

Rationale:

1. The technology must have final approval from the appropriate U.S. government regulatory bodies:

The OvaCheck® test, developed by Correlogic Systems, Inc. of Bethesda, Maryland, is the current ovarian cancer biomarker product. It will in turn be offered through Quest Diagnostics® and LabCorp® as a screening test for ovarian cancer for those women whose physicians determine them to be in a high-risk classification.

In a letter from the FDA's Office of In Vitro Diagnostic Device Evaluation and Safety dated July 12, 2004, Correlogic Systems, Inc. was advised of the FDA's ruling that a Premarket Approval application would be required before Correlogic Systems could legally market the OvaCheck®. As of July 2006, it is unknown what the outcome of the FDA's ruling will be. In 2010, Correlogic filed for bankruptcy and in 2011 its assets including the OvaCheck® test were acquired by Vermillion®. The test has since been taken off the market on FDA recommendation.

2. The scientific evidence must permit conclusions concerning the effect on health outcomes:

At the present time there is no generally accepted screening tool for ovarian cancer, either in the high risk or general populations. The situation is complicated by the fact that there is no known premalignant lesion, which would limit screening patients to those with early-stage active disease. The tumor marker CA-125 has been used, but by itself it has rather poor sensitivity and specificity, given that CA-125 can be detected in a variety of situations, both malignant and benign. Because of its limitations, CA-125 is often used in conjunction with ultrasound to further improve diagnostic value, but even in combination the approach lacks acceptable specificity. The science of proteomics is viewed as a potentially superior screening tool because of its high sensitivity and specificity. Ovarian cancer is not a common disease, having an incidence of about 40 per 100,000 per year even in the most susceptible population. Because a positive ovarian cancer screening test would result in a surgical intervention of some kind, the screening test needs to be highly specific, both from a point of view of patient risk and health costs.

A review of evidence was undertaken to determine whether the OvaCheck® test may be considered an accepted diagnostic tool for early recognition of ovarian cancer in a susceptible population. Several researchers have already commented on the research thus far and the standards that must be met (Kohn, et al, and Stevens, et al, 2003). Petricoin, et al have reported the initial findings in a study group of 116 patients of whom 50 had been diagnosed with ovarian cancer. In this study, a reference data set was used that had been derived from 100 women, 50% affected by ovarian cancer and 50% unaffected. An algorithm was developed from the reference data set to analyze the samples of the study group. The algorithm identified all the 50 cases of cancer in the study sample, and correctly recognized 63 of the 66 non-malignant cases. The sensitivity therefore was 100%, and the specificity 95%. The authors' conclusion was that a prospective population-based screening study was justified. Zhu et al (2003) reported 100% sensitivity and 100% specificity in two independent data sets. On the other hand, Sorace and Zhan (2003) reported results of a detailed statistical analysis of the algorithm derived and found evidence of experimental bias which could confound the results initially reported.

The results of these initial studies, while promising, and indicative that proteomic serum testing may be sufficiently sensitive and specific to fulfill the requirements of a screening test for ovarian cancer, are not confirmatory. The issue of experimental bias pointed out by Sorace and Zhan must be addressed, and a prospective, population based study of rigorous design is needed to determine if acceptable sensitivity and specificity can be sustained in a target population.

3. The technology must improve the net health outcome:

There is insufficient evidence to date as to whether this test can improve net health outcomes. If the sensitivity is not adequate, use of the test could give false negative results, and early disease would not be detected. If, on the other hand, the specificity is too low, false positive results might lead to an inaccurate diagnosis. With the early results published to date, and the questions surrounding, it is not possible to conclude that this test could be used with confidence.

4. The technology must be as effective as any established alternatives:

At the present time, there is no effective screening test for ovarian cancer. The use of CA-125 as a screening test is not considered acceptable by the American College of Obstetrics and Gynecology because of low sensitivity and specificity. The use of ultrasound in conjunction, as explained by Jacobs and Menon (2004) improves the sensitivity and specificity somewhat, but not to acceptable levels for a screening tool. There is insufficient evidence to date whether serum proteomic testing allows conclusions as to its value as a screening tool.

5. The improvement must be attainable outside the investigational settings:

Whether serum proteomic testing for early-stage ovarian cancer improves health outcomes has not been established in the investigational settings.

In summary, serum proteomic testing for early-stage ovarian cancer has not been proven to be of benefit in the susceptible population. Two major laboratory corporations have nonetheless made a decision to offer this testing as of mid-2004, despite the statement issued in February 2004 by the Society of Gynecologic Oncologists (SGO). The SGO, in a published statement, opines that more research is needed to validate the test's effectiveness before offering it to the public.

Update 2006:

A search of the literature from March 2004 to June 2006 shows a lack of evidence-based literature recommending proteomic-based testing of serum as a definitive or adjunct diagnostic tool for ovarian cancer. As of July 2006, approval by FDA has not been granted for commercial use of this test.

Update 2008:

A search of the peer-reviewed literature was performed from June 2006 through June 2008. There is a lack of peer-reviewed literature regarding the use of proteomic-based testing of serum that demonstrated the impact on clinical outcomes for proteomic testing in the screening or detection of ovarian cancer. As of July 2008, the FDA has not granted the approval of the OvaCheck® test for commercial use. Therefore, the policy statement remains unchanged.

Update 2010:

A search of the peer-reviewed literature was performed from July 2008 through August 2010. Findings in the recent literature do not change the conclusions on Ovacheck® in the screening or diagnosis of ovarian cancer. As of August 2010, the FDA has not granted approval of the OvaCheck® test for commercial use. Therefore, the policy statement remains experimental / investigational.

Update 2012:

A search of the peer-reviewed literature was performed from September 2010 through September 2012. Findings in the recent literature do not change the conclusions on Ovacheck® in the screening or diagnosis of ovarian cancer. As of September 2012, the FDA has not granted approval of the Ovacheck® test for commercial use. Therefore, the policy statement is unchanged.

Update 2014:

A search of the peer-reviewed literature was performed from October 2012 through September 2014. In 2010, Correlogic filed for bankruptcy and in 2011 its assets including the OvaCheck® test were acquired by Vermillion®. The test has since been taken off the market on FDA recommendation. No new literature was found on the OvaCheck® test. The policy statement is unchanged.

Update 2016:

A search of the peer-reviewed literature was performed from October 2014 through November 2016. No new literature was found on the OvaCheck® test that is no longer marketed. However, there are several proteomic pattern analysis tests available, including but not limited to Ova1™, the ROMA assay, and the ROCA test. Vermillion® owns OVA1. According to the American Cancer Society, “Researchers continue to look for new tests to help diagnose ovarian cancer early but currently there are no reliable screening tests.” (ACS 2016) The American College of Oncologists and Gynecologists (ACOG) issued a statement in 2011 indicating that the utility of biomarkers for screening and diagnosis is not established. The National Comprehensive Cancer Network (NCCN) noted in 2014 that the Society of Gynecologic Oncologists do not recommend OVA1 as a screening tool. The NCCN Guidelines version 1.2016 reiterates that OVA1 should not be used for screening. On March 21, 2016, Vermillion Inc. announced FDA 510(k) clearance for Overa, successor to the OVA1 multivariate index assay. Overa was previously known as OVA2. Per the FDA 2016 safety communication, "Despite extensive research and published studies, there are currently no screening tests for ovarian cancer that are sensitive enough to reliably screen for ovarian cancer without a high number of inaccurate results." Therefore, the policy statement is unchanged.

Update 2019:

A search of the peer-reviewed literature was performed from December 2016 through April 2019. Findings in the recent literature do not change the conclusion proteomic pattern analysis as a screening or diagnostic test for ovarian cancer. Therefore, the policy statement is unchanged.

Update 2021:

A search of the peer-reviewed literature was performed from May 2019 through September 2021. Findings in the recent literature do not change the conclusion regarding proteomic pattern analysis as a screening or diagnostic test for ovarian cancer. Therefore, the policy statement is unchanged.

Cross References to Related Policies and Procedures

Proteomics-Based Testing for Evaluation of Ovarian Masses, Policy 11.01.045
Tumor Markers, 11.01.001

References

The following were among the resources reviewed and considered in developing this policy. By reviewing and considering the resources, CareFirst does not in any way endorse the contents thereof nor assume any liability or responsibility in connection therewith. The opinions and conclusions of the authors of these resources are their own and may or may not be in agreement with those of CareFirst.

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