Name of Policy:
Serum Biomarker Human Epididymis Protein 4 (HE4)

Policy #: 445  Latest Review Date: March 2014
Category: Laboratory  Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:

Human epididymis protein 4 (HE4) is a potential new biomarker that has been cleared by the U.S. Food and Drug Administration (FDA) for monitoring patients with epithelial ovarian cancer. HE4 is proposed as a replacement for or a complement to CA-125 for monitoring disease progression and recurrence. HE4 has also been proposed as a test to evaluate women with ovarian masses and to screen for ovarian cancer in asymptomatic women.

Ovarian cancer is the fifth most common cause of cancer mortality in U.S. women. According to Surveillance Epidemiology and End Results (SEER) data, in 2013, an estimated 22,240 women will be diagnosed with ovarian cancer and 14,030 women will die of the disease. Stage at diagnosis is an important predictor of survival; however, most women are not diagnosed until the disease has spread. According to Surveillance Epidemiology and End Results (SEER) data, for the period 1999-2006, 62% of women with ovarian cancer were diagnosed when the disease had distant metastases (Stage IV) and this was associated with a 27.6% five-year survival rate. In contrast, the 15% of women diagnosed with localized cancer (Stage I) had a 93.5% five-year survival rate. Epithelial ovarian tumors account for 85 to 90% of ovarian cancers.

The standard treatment for epithelial ovarian cancer is surgical staging and primary cytoreductive surgery followed by chemotherapy in most cases. There is a lack of consensus about an optimal approach to follow-up patients with ovarian cancer following primary treatment. Patients undergo regular physical examinations. In addition, managing patients with serial measurement of the biomarker CA-125 to detect early recurrence of disease is common. A rising CA-125 level has been found to correlate with disease recurrence and has been found to detect recurrent ovarian cancer earlier than clinical detection. However, a survival advantage of initiating treatment based on early detection with CA-125 has not been demonstrated to date. For example, a randomized controlled trial (RCT) with women in ovarian cancer that was in complete remission did not find a significant difference in overall survival when treatment for remission was initiated when CA-125 concentration exceeded twice the limit of normal compared to delaying treatment initiation until symptom onset.

Another serum biomarker, cleared by the FDA for monitoring patients with epithelial ovarian cancer, is human epididymis protein 4 (HE4). HE4 is made up of two whey acidic proteins with a four disulfide core domain. It has been found to be overexpressed by epithelial ovarian cancer tumors and to circulate in the serum of patients with epithelial ovarian cancer. Levels of HE4 may be less likely to be elevated due to benign conditions, as is the case with CA-125, which would make HE4 a candidate to replace or complement CA-125. Tests for HE4 are FDA-approved for monitoring women known to have epithelial ovarian cancer. Another possible application of HE4 testing is screening asymptomatic women for ovarian cancer; screening is not an accepted use of the CA-125 test.

The policy also addresses use of the HE4 as a stand-alone test for evaluating women with ovarian masses who have not been diagnosed with ovarian cancer. The Risk of Ovarian Malignancy Algorithm (ROMA) combines HE4, CA-125 and menopausal status into a numeric score. ROMA has been cleared by FDA for predicting risk that an adnexal mass is malignant; this test is considered separately in policy #426, Proteomics-based Testing for the Evaluation of Ovarian (Adnexal) Masses.
Policy:
Measurement of human epididymis protein 4 (HE4) for any and all indications does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
Assessment of a diagnostic technology typically focuses on three parameters: 1) technical performance; 2) diagnostic performance (sensitivity, specificity, and positive and negative predictive value) in appropriate populations of patients; and 3) demonstration that the diagnostic information can be used to improve patient outcomes (clinical utility).

Technical performance of a device is typically assessed with two types of studies, those that compare test measurements with a gold standard, and those that compare results taken with the same device on different occasions (test-retest).

Diagnostic performance is evaluated by the ability of a test to accurately diagnose a clinical condition in comparison with the gold standard. The sensitivity of a test is the ability to detect a disease when the condition is present (true positive), while specificity indicates the ability to detect patients who are suspected of disease but who do not have the condition (true negative). Evaluation of diagnostic performance, therefore, requires independent assessment by the two methods in a population of patients who are suspected of disease but who do not all have the disease.

Evidence related to improvement of clinical outcomes with use of this testing assesses the data linking use of a test to changes in health outcomes (clinical utility). While in some cases, tests can be evaluated adequately using technical and diagnostic performance, when a test identifies a new or different group of patients with a disease; randomized trials are needed to demonstrate impact of the test on the net health outcome.

Technical Performance
The FDA substantial equivalence determination decision summary documents for the HE4 EIA and ARCHITECT HE4 include data on technical performance. For example, the precision of the ARCHITECT HE4 test was assessed at three sites; samples were tested in two replicates using two lots of reagents in two separate runs per day for 20 days. Samples included three panels of pooled human serum and three controls. Total imprecision of the panels ranged from 3.4% to 5.4%. The upper limit of the 95% confidence interval for total imprecision for all samples was 6.1% or lower; this met the predetermined acceptance criteria for imprecision which was 10% or
less. Moreover, the test met acceptance criteria for linearity and stability of samples, as well as observed interference from common endogenous substances (i.e., bilirubin, hemoglobin, and high and low protein concentrations).

Diagnostic Performance
Monitoring Disease Progression and Recurrence in Women with Epithelial Ovarian Cancer
Since CA-125 is considered standard of care for assessing risk of ovarian cancer in women presenting with a pelvic mass and managing patients with ovarian cancer, the literature review addressed the questions of whether the diagnostic performance of HE4 was superior to CA-125 and whether combined testing HE4 and CA-125 was superior to CA0125 alone.

FDA documents included information on the diagnostic performance of HE4 for monitoring the progression and recurrence of ovarian cancer. FDA materials addressed the noninferiority rather than the superiority of HE4 tests to CA-125. A study reported in the 510(k) substantial equivalence determination decision summary for the HE4 EIA assay evaluated whether this test was noninferior to the CA-125 test. The study included samples from 80 women with epithelial ovarian cancer who were undergoing serial surveillance of cancer progression. Blood samples were obtained from a large cancer center in the United States; they were not drawn specifically for this study. A total of 354 samples were obtained for the 80 women (women had multiple visits over time). Receiver operating curve (ROC) analysis was used to compare the two assays, and clinical evidence of progression was used as the reference standard. When a positive change in HE4 level (i.e., to indicate disease progression) was defined as a value at least 25% higher than the previous value of the test, the sensitivity of the test was 76/126 (60.3%), and the specificity was 171/228 (75%). (Note that the unit of analysis was the number of samples rather than the number of women.) The area under the curve (AUC) in the ROC curves was found to be similar (0.725 for HE4 and 0.709 for CA-125, respectively) with overlap in the confidence intervals; according to the authors, this indicated that the HE4 assay was not inferior to the CA-125 assay for detecting cancer progression.

Another analysis estimated the cutoff values and specificity for the HE4 and CA-125 assays at a fixed sensitivity. The specificity values for CA-125 and HE4 were not statistically different at the respective cutoffs and sensitivities; for example, using a cutoff of 15.4% above the previous value for the HE4 test, the sensitivity of the HE4 was 64.3% and the specificity was 69.3%. The specificity of CA-125 at a matching sensitivity was 70.2%; this used a cut-off for the CA-125 level of an increase of at least 32.8%. These data were also said to confirm that HE4 EIA test is not inferior to the CA-125 test for detecting ovarian cancer progression.

The 510(k) substantial equivalence determination decision summary for the ARCHITECT HE4 assay reports data from a retrospective study using remnant serial samples from 76 women diagnosed with epithelial ovarian cancer that were being monitored after completion of chemotherapy. The eligibility criteria included availability of at least three serial specimens; samples could have been drawn during and/or after treatment. Clinical determination of disease progression was used as the reference standard. A positive test was defined an HE4 level that was 14% higher than the previous reading. Using this cut-off, the sensitivity of the assay for detecting progressive disease was 53/99 events (53.5%). The specificity of the assay was 260/331 (78.5%). Of note, the sensitivity is lower than that reported above for the HE4 EIA at a
similar specificity, when a cutoff of a 25% increase was used (sensitivity=60.3% and specificity=75%).

FDA documents noted that there is no clinically accepted cut-off for use in monitoring cancer progression in epithelial ovarian cancer patients using the HE4 assays. As previously mentioned, a study included in the HE4 EIA assay materials defined a positive test as a level that is 25% higher than a previous measurement, and a study on the ARCHITECT HE4 test defined a positive test as an increase of at least 14% in the level of HE4. The FDA documents further state that clinicians may decide whether to use the cut-offs in the studies or another cut-off that reflects their own preferences in the tradeoff between sensitivity and specificity.

Representative studies other than FDA documents on the diagnostic performance of HE4 for monitoring progression and/or recurrence of epithelial cancer are described next:

A 2013 study by Braicu et al evaluated 275 patients with advanced primary ovarian cancer who underwent cytoreductive surgery and adjuvant platinum-based chemotherapy at a specialized clinic. In 221 of 275 (80.4%), preoperative HE4 and CA-125 values, as well as data on residual tumor mass after debulking were available. For HE4 levels, the AUC for residual tumor mass was 0.634. At an HE4 cut-off value of 235 pM, the sensitivity was 76.6% and specificity was 47.4%. When the cut-off for HE4 was 500 pM, the sensitivity was 51.9% and the specificity was 70.4%. For CA-125, the AUC for residual tumor mass was 0.643, nearly the same as for HE4. At a cut-off of 500 IU/mL, the sensitivity of CA-125 for predicting complete tumor resection was 69.4% and the specificity was 52.3%. Using the most accurate cut-offs for HE4 (235 pM) and CA-125 (500 IU/mL), the combined combination of the two markers had sensitivity of 64.8% and specificity of 73.5%. Median follow-up was 25 months (range, 1-49 months) In multivariate analysis, neither HE4 nor CA-125 levels significantly predicted overall survival or progression-free survival.

In 2012, a study was published by Plotti and colleagues in Italy evaluating the ability of HE4 to predict ovarian cancer recurrence. The study included 34 women with radiological suspicion of ovarian cancer recurrence and a comparison group of 34 women with benign adnexal conditions. Serum samples were obtained 24 hours before surgery. All women with suspected ovarian cancer had recurrent disease confirmed at surgery. HE4 tests were evaluated at two cutoffs, greater than 70 pmol/L and greater than 150 pmol/L. The sensitivity of HE4 at the 70 pmol/L cut-off was 74% (25 of 34 cases were identified) and sensitivity of HE4 at the 150 pmol/L cut-off was 26% (9 of 34). The specificity was 100% at both cut-offs. In contrast, the sensitivity and specificity of CA-125 were 35% (12 of 34) and 59%, respectively. Using a combination of HE4 at a cut-off of 70 pmol/L and CA-125, the sensitivity to detect recurrent ovarian cancer was 76% and the specificity was 100%.

Section summary
There are few studies evaluating the diagnostic accuracy of HE4 for monitoring ovarian cancer progression or recurrence. There is insufficient evidence that the diagnostic accuracy of HE4, alone or in combination with CA-125, is superior to CA-125 alone. Moreover, there is a lack of clarity about the cut-off of HE4 to use for disease progression/recurrence.
Diagnosing ovarian cancer

Because CA-125 is the marker most often recommended for evaluation of adnexal masses, the literature review addressed the question of whether the diagnostic performance of HE4 was superior to CA-125 and whether combined HE4 and CA-125 was superior to CA-125 alone.

Several meta-analyses of studies on the accuracy of HE4 for diagnosing ovarian cancer were published in 2012 and 2013. Table 1 presents the pooled sensitivities and specificities of HE4 from meta-analyses that conducted quality assessments of individual studies and that limited their reviews to studies using pathologic findings as the reference standard for ovarian cancer diagnosis.

Table 1: Meta-analyses of studies on HE4 for diagnosing ovarian cancer

<table>
<thead>
<tr>
<th>Citation</th>
<th>No studies</th>
<th>Sens (95% CI)</th>
<th>Spec (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al, 2013</td>
<td>31</td>
<td>0.73 (0.71 to 0.75)</td>
<td>0.89 (0.88 to 0.90)</td>
</tr>
<tr>
<td>Ferraro et al, 2013</td>
<td>14</td>
<td>0.79 (0.76 to 0.81)</td>
<td>0.93 (0.92 to 0.94)</td>
</tr>
<tr>
<td>Yu et al, 2012</td>
<td>12</td>
<td>0.80 (0.77 to 0.83)</td>
<td>0.92 (0.90 to 0.93)</td>
</tr>
<tr>
<td>Wu et al, 2012*</td>
<td>7</td>
<td>0.74 (0.69 to 0.78)</td>
<td>0.90 (0.87 to 0.92)</td>
</tr>
</tbody>
</table>

Sens: sensitivity; Spec: specificity; CI: confidence interval

*Studies using HE4 to distinguish between ovarian cancer and benign disease

Meta-analyses differed somewhat in their study inclusion criteria, search dates and other factors but, as shown in Table 1, had similar results in terms of diagnostic value of HE4; pooled sensitivities ranged from 0.73 to 0.80, and pooled specificities ranged from 0.89 to 0.93.

Two of the meta-analyses also pooled studies on the diagnostic accuracy of CA-125. In the Ferraro et al meta-analysis (13 studies), pooled sensitivity was 0.79 (95% CI, 0.77 to 0.82) and pooled specificity was 0.78 (95% CI, 0.76 to 0.80). In an additional analysis by Ferraro et al, a meta-analysis of four studies on the combination of HE4 and CA-125 found a sensitivity of 0.82 (95% CI, 0.78 to 0.86) and specificity of 0.76 (95% CI, 0.72 to 0.80). The overall diagnostic performance of HE4 alone, or in combination with CA-125 was not statistically significantly better than CA-125 alone.

Yu et al conducted a meta-analysis of 10 studies on CA-125 and found a pooled sensitivity of 0.66 (95% CI, 0.62 to 0.70) and a pooled specificity of 0.87 (95% CI, 0.85 to 0.89) The diagnostic performance did not differ significantly from the performance of HE4 (as shown in Table 1). However, in a subanalysis of the studies in which the control groups consisted of women with benign disease, the specificity but not sensitivity of HE4 was significantly higher than CA-125. In this subgroup, the pooled sensitivity was 0.77 (95% CI, 0.74 to 0.81) for HE4 and 0.73 (95% CI, 0.68 to 0.77) for CA-125, and the pooled specificity was 0.91 (95% CI, 0.89 to 0.92) for HE4 and 0.79 (95% CI, 0.77 to 0.82).

Studies published on 2013 evaluated the diagnostic performance of HE4 as a second-line test after subjective assessment of transvaginal ultrasound. Final histologic diagnosis was used as the reference standard. Kaijser et al enrolled 389 patients with a suspicious pelvic mass who were scheduled for surgery. Data on 360 (93%) patients were available for analysis. Experienced ultrasonographers categorized each mass as benign, borderline or invasive malignant. Serum samples were obtained before surgery and HE4 levels were measured, using a cut-off of at least
70 pmol/L to indicate malignancy. Overall, subjective ultrasound evaluation by an experienced examiner had higher sensitivity and specificity than serum HE4. Sensitivity was 97% with subjective assessment ultrasound and 74% with HE4, and specificity was 90% and 85%, respectively. The additional consideration of HE4 values after sonographers categorized a mass as benign resulted in a slight increase in sensitivity and a large increase in the number of false-positives. Moreover, sequential use of serum HE4 after sonographers categorized a mass as malignant resulted in lower sensitivity and an increase in specificity.

Moszynski et al retrospectively reviewed records on 253 women with adnexal masses. Women were examined with transvaginal ultrasound by an experienced examiner before surgery. The sonographer categorized masses as certainly benign, probably benign, uncertain, probably malignant and certainly malignant. Tumors in the certainly benign and certainly malignant categories were excluded from further analysis, and the remainder (n=145) were considered suspicious tumors. HE4 and CA-125 levels were measured in serum, a cut-off of 65 pmol/L was used for HE4. The sensitivity and specificity of ultrasound evaluation for diagnosing the suspicious tumors was 93.3% and 90.6%, respectively. Neither HE4 nor CA-125 improved diagnostic accuracy for suspicious tumors. Sensitivity and specificity of HE4 was 80.0% and 91.7%, respectively, and the sensitivity and specificity of CA-125 was 85.8% and 74.7%, respectively. A logistic regression analysis confirmed that neither HE4 nor CA-125 improved diagnostic accuracy beyond that of subjective assessment of ultrasonography.

Section summary
A number of studies evaluating the diagnostic accuracy of HE4 for evaluating adnexal masses have been published and there are several meta-analyses of these studies. Two meta-analyses compared the diagnostic accuracy of HE4 and CA-125. One of these did not find a statistically significant difference in diagnostic performance, and the other did not find a significant difference overall and found a significantly higher specificity but not sensitivity in the subgroup of studies in which women with benign disease were included in the control group. In addition, studies have not found that HE4 improves diagnostic accuracy beyond that of subjective assessment of transvaginal ultrasound. The evidence is insufficient to conclude that HE4 alone or in combination with CA-125 has significantly better diagnostic performance than CA-125 alone.

Screening Asymptomatic Women
No published studies were identified that evaluated the diagnostic performance of the HE4 biomarker for screening asymptomatic women for ovarian cancer compared to a reference standard.

A retrospective study published in 2010 by Anderson et al aimed to determine the potential value of using HE4 and other biomarkers in early identification of ovarian cancer in asymptomatic women. The study included 34 women with ovarian cancer and 70 matched controls, all of whom were participating in an unrelated randomized controlled trial including smokers at increased risk of lung cancer. Blood samples were available for the women between 0 and 18 years before ovarian cancer diagnosis. In descriptive analyses, individual serum markers, including HE4, CA-125, and mesothelin, showed increasing accuracy over time approaching the diagnosis of ovarian cancer. Mean concentrations of these markers, which were measured by visually-read immunoassays, began to increase approximately three years before diagnosis but
attained detectable levels only within the final year before diagnosis. The study has a small sample size limiting the ability to conduct quantitative analysis and included only heavy smokers so may not be representative of the population of women at risk of ovarian cancer. The National Comprehensive Cancer Network (NCCN) 2011 ovarian cancer guideline cited the Anderson study in support of their statement that HE4 and other biomarkers do not appear to increase early enough to be useful in detecting early-state ovarian cancer.

In 2011, Urban and colleagues retrospectively reviewed preclinical samples to evaluate the potential utility of HE4 and other markers as a secondary screening test in women found to have epithelial ovarian cancer. There were samples from 112 ovarian cancer patients and 706 matched controls. Individuals participated in the Prostate, Lung, Colorectal and Ovarian (PLCO) trial and had been screened annually for six years with CA-125. Serum samples to evaluate potential markers were taken from the year proximate to the one in which women were diagnosed with ovarian cancer. (Serum samples were not available for the fourth screen so they were taken from the third year for the women diagnosed with ovarian cancer between the third and fourth screens.) The investigators evaluated the associations between CA-125, HE4, and levels of five other markers with malignancy, accounting for increasing CA-125 levels and adjusting for demographic characteristics. Increase in CA-125 levels was associated with statistically significant increases in all of the markers. Levels of HE4 were most elevated, compared to controls (i.e. the highest average HE4 level was 4.26 standard deviations above the mean HE4 level in control samples). The utility of HE4 as a biomarker to screen for ovarian cancer along with CA-125 needs to be further evaluated in prospective studies and confirmed in RCTs that evaluate the impact of screening on health outcomes.

Section summary
There is insufficient evidence from prospective or controlled studies that HE4 is an effective screening tool for identifying ovarian cancer in asymptomatic women.

Clinical Utility
No prospective studies were identified that compared health outcomes in patients managed with and without HE4 testing, alone or in combination with other disease markers. In addition, no randomized controlled trials evaluating the clinical utility of screening asymptomatic women with HE4 were identified.

Summary
There are limited data on the diagnostic test performance of the human epididymis protein 4 (HE4) test used to diagnose ovarian cancer or to monitor disease progression and recurrence in women after initial treatment for epithelial ovarian cancer. There is no established cut-off for determining when an HE4 test is positive, when used for identifying disease progression or recurrence. Available studies have used different cut-offs for identifying a recurrence. Moreover, a survival advantage of early detection of ovarian cancer recurrence using HE4 levels or other biomarkers has not been established. No published studies were identified evaluating use of the HE4 test to screen asymptomatic women for ovarian cancer. Thus, the HE4 test is considered investigational for all indications.
Practice Guidelines and Position Statements
In December 2012, the U.S. Preventive Services Task Force (USPSTF) published an updated recommendation statement on screening for ovarian cancer. The USPSTF recommended against screening for ovarian cancer in asymptomatic women (D recommendation). HE4 was not specifically discussed.

The 2013 National Comprehensive Cancer Network (NCCN) ovarian cancer guideline states that, for monitoring/follow-up of patients with Stage I-IV ovarian cancer with a complete response to initial treatment, “CA-125 or other tumor marker” should be used at every visit if initially elevated. The guideline does not specify any marker other than CA-125 for monitoring patients after treatment.

The NCCN guideline states the following on evaluating undiagnosed pelvic masses:
“The primary workup should include an ultrasound and/or abdominal/pelvic CT [computed tomography] scan…and appropriate laboratory studies…” The guideline mentions that CA-125 and several other markers can be measured if clinically indicated; HE4 is not listed as one of the markers.

The NCCN guideline states the following on screening for ovarian cancer:
“Randomized data do not yet support routine screening for ovarian cancer in the general population, and routine screening is not currently recommended by any professional society. Some physicians follow women with high-risk factors (e.g., those with BRCA mutations, those with a family history) using CA-125 monitoring and endovaginal ultrasound; however, prospective validation of these tests remains elusive.”

The National Institute for Health and Clinical Excellence (NICE) issued guidance in 2011 on the recognition and initial management of ovarian cancer. The guideline includes the following recommendations:
• Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer.
• If serum CA125 is 35 IU/ml or greater, arrange an ultrasound scan of the abdomen and pelvis.
• If the ultrasound suggests ovarian cancer, refer the woman urgently for further investigation.
• For any woman who has normal serum CA125 (less than 35 IU/ml), or CA125 of 35 IU/ml or greater but a normal ultrasound: 1) assess her carefully for other clinical causes of her symptoms and investigate if appropriate; 2) if no other clinical cause is apparent, advise.
• Calculate a risk of malignancy index I (RMI I) score (after performing an ultrasound). (The RMI I combines CA-125, menopausal status and the ultrasound score).

The NICE guidance does not mention HE4.
Key Words:
Human epididymis protein 4, HE4, HE4 EIA test, ARCHITECT HE4

Approved by Governing Bodies:
In June 2008, the HE4 EIA test kit (Fujirebio Diagnostics, Sweden) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The FDA determined that this device was substantially equivalent to a CA-125 assay kit for use as an aid in monitoring disease progression or recurrence in patients with epithelial ovarian cancer. The FDA-cleared indication states that serial testing for HE4 should be done in conjunction with other clinical methods used for monitoring ovarian cancer and that the HE4 test is not intended to assess the risk of disease outcomes.

In March 2010, the ARCHITECT™ HE4 (Abbott Diagnostics, co-developed with Fujirebio Diagnostics), an automated version of the HE4 EIA test, was cleared by the FDA for the same indications. The ARCHITECT HE4 test is being distributed in the United States by Quest Diagnostics (Madison, NJ).

Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:
CPT Codes:
86305 Human epididymis protein 4 (HE4)

References:

Policy History:
Medical Policy Group, September 2009 (2)
Medical Policy Group, August 2010 (2)
Medical Policy Panel, August 2010
Medical Policy Administration Committee, August 2010
Available for comment September 4-October 18, 2010
Medical Policy Group, October 2010
Medical Policy Panel, August 2011
Medical Policy Group, September 2011 (2): Description, Key Points, Reference updated
Medical Policy Panel, August 2012
Medical Policy Group, April 2013 (1): Update to Key Points and References; Material on evaluation of ovarian (adnexal) masses removed as this is addressed in policy 426; no change to policy statement
Medical Policy Panel, August 2013
Medical Policy Group, September 2013 (1): Update to Descriptions, Key Points and References; no change to policy statement
Medical Policy Panel, March 2014
Medical Policy Group, March 2014 (1): Update to Key Points and References; no change to policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.