Clinical Review Criteria

Risk Prognosticator Tests

- BREVAGen™
- Fibroblast Growth Factor Receptor 3 (FGFR3)
- MammaPrint Test
- OVA1™ Test for the Assessment of Suspected Ovarian Cancer

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Criteria

For Medicare Members
See Genetic Testing (L34101).

For Non-Medicare Members

<table>
<thead>
<tr>
<th>Genetic Test</th>
<th>Criteria Used</th>
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<tbody>
<tr>
<td>BREVAGen™</td>
<td>There is insufficient evidence in the published medical literature to show that this service/therapy is as safe as standard services/therapies and/or provides better long-term outcomes than current standard services/therapies.</td>
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<tr>
<td>Fibroblast Growth Factor Receptor 3 (FGFR3)</td>
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<tr>
<td>OVA1™ Test for the Assessment of Suspected Ovarian Cancer</td>
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<tr>
<td>MammaPrint Test (Gene-Expression Profiling Test, 70-Gene Prognostic Signature)</td>
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The following information was used in the development of this document and is provided as background only. It is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

Evidence and Source Documents

- BREVAGen™
- Fibroblast growth factor receptor 3 (FGFR3)
- MammaPrint Test
- OVA1™ test for the assessment of suspected ovarian cancer

Medical Technology Assessment Committee (MTAC)

BREVAGen™

BACKGROUND

According to the American Cancer Society, breast cancer is the second leading cause of death in women in the United States after lung cancer. Current methods of assessing breast cancer risk include the Breast Cancer Risk Assessment Tool (BCRAT) otherwise known as the Gail model. This model incorporates individual risk factors such as basic demographic information, reproductive history and medical history. Recent genome wide association studies have identified several single nucleotide polymorphisms (SNPs) associated with an increased risk of breast cancer leading to an additional dimension and understanding of risk (Easton, Pooley et al. 2007; Stacey, Manolescu et al. 2007; Stacey, Manolescu et al. 2008). The BREVAGen™ (Phenogen Sciences, Inc., Charioette, NC) is a risk stratification test for sporadic breast cancer. Intended for use as an adjunct to the Gail model, the test consists of two parts, the first, a series of questions to determine clinical risk and the second, a buccal swab to analyze specific genetic markers. The latter part of the test, includes a panel of seven SNPs.
associated with breast cancer risk and does not include either of the BRCA mutations. Ultimately, a patient’s risk is calculated by multiplying the product of the individual SNP risks by the Gail model risk. According to the BREVAGen™ website, the test is only suitable for women of European descent aged 35 years or older. No test combining the results of SNP analysis with clinical factors to predict breast cancer risk has been approved or cleared by the U.S. Food and Drug Administration (FDA). BREVAGen™ is offered as a laboratory developed test and only requires oversight under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). The development and use of this laboratory developed test is restricted to laboratories certified as high complexity under CLIA. Under the current regulatory program, CLIA requires that laboratories demonstrate quality systems which includes validation and proficiency testing.

12/16/2013: MTAC REVIEW
BREVAGen
Evidence Conclusion: Analytic Validity Although the seven breast cancer associated SNPs were identified in genome wide association studies (Easton, Pooley et al. 2007; Stacey, Manolescu et al. 2007; Stacey, Manolescu et al. 2008), there are no publications that specifically report on the analytic validity of the BREVAGen™ panel. Clinical Validity The BREVAGen™ test was clinically validated in a nested case-control cohort study. The study included 1,664 women from the US Women’s Health Initiative (WHI) who developed breast cancer between randomization and study completion and 1,636 age-matched breast cancer-free controls (Mealiffe, Stokowski et al. 2010). Overall, the study suggests that the BREVAGen may add predictive accuracy to the Gail Model, however, the degree of improved risk prediction is modest and the clinical implications are not well established. The study is not generalizable as the included population was limited to postmenopausal white non-Hispanic women. In addition, four of the authors were employees of the developer of the BREVAGen™ during the time of publication and the analyses were relevant to the development of the product. Ideally, additional studies should be completed to further assess the clinical validity of the combined Gail and SNP risk model. Clinical Utility Theoretically, the BREVAGen™ test can provide information that can help guide physicians in making individualized patient management decisions, such as appropriate counseling, screening regimens and risk reduction strategies, however, there is no published literature to support the clinical utility. Conclusion: There is no evidence to determine the analytic validity of the BREVAGen™. There is some evidence to suggest that the addition of the BREVAGen™ panel is superior in determining breast cancer risk compared to Gail score alone. There is no evidence to determine the clinical utility of the BREVAGen™. Articles: A search of PubMed was completed for the period through November 2013 for studies on the accuracy of BREVAGen™ for detecting the absence or presence of certain common genetic variations associated with an increased risk for developing breast cancer. The search strategy used the terms BREVAGen, Breast Cancer Risk Tool, Gail Model, genetic risk, single nucleotide polymorphism, breast cancer, and sporadic with variations. To identify ongoing clinical trials, a search of the National Institute of Health Clinical Trials website was also conducted using the same methodology. Articles were limited to those published in the English language with human subject enrollment. The search was supplemented by an examination of article reference lists in addition to the PubMed related articles function. The literature search for BREVAGen™ revealed one publication that clinically validates the Breast Cancer Risk Model in combination with the genetic and clinical information. The following study was selected for review: Mealiffe ME, Stokowski RP, Rhee BK, et al. Assessment of clinical validity of a breast cancer risk model combining genetic and clinical information. Journal of the National Cancer Institute. 2010;102(21):1618-1627. See Evidence Table.

The use of BREVAGen does not meet the Kaiser Permanente Medical Technology Assessment Criteria.

Fibroblast Growth Factor Receptor 3 (FGFR3) for Urothelial Carcinoma
BACKGROUND
It is estimated that approximately 70,530 new cases of bladder cancer will be diagnosed in the United States in 2010, and 14,680 will die of the disease (Jemal 2010). The most commonly occurring form of bladder cancer in the United States is urothelial carcinoma (also known as transitional cell carcinoma). The clinical spectrum of urothelial carcinoma can be divided into 3 categories: non-muscle-invasive, muscle-invasive, and metastatic disease. This review will focus on non-muscle-invasive urothelial cancer (NMIUC), which makes up approximately 75-80% of urothelial carcinoma. NMIUC includes stage Ta (noninvasive papillary carcinoma), Tis (carcinoma in situ), and T1 (tumor invades subepithelial connective tissue) tumors. The standard treatment for stage Ta, Tis, and T1 tumors is transurethral resection of bladder tumor (TURBT). Depending on prognosis adjuvant intravesical chemotherapy or immunotherapy may also be considered. However, despite treatment a significant number of patients will develop recurrence within 1 to 2 years of the initial treatment. Because of the high risk of recurrence careful surveillance is required for patients with NMIUC (Chou 2010, Cheng 2011, NCCN 2011, Pollard 2010). Assessing the risk of progression and recurrence is important for planning therapy. The risk for tumor progression and recurrence is estimated using factors such as histological grade, stage, depth of invasion, and extent of
disease; however, the ability of these factors to predict clinical outcome is limited (Burger 2008, Cheng 2011, NCCN 2011). Recently, it has been suggested that molecular biomarkers such as fibroblast growth factor receptor 3 (FGFR3) may be useful for predicting clinical outcome and planning therapy. FGFR3 regulates cell growth, differentiation, and angiogenesis. More than 70% of low-grade noninvasive papillary urothelial carcinomas harbor FGFR3 mutations. Studies suggest that urothelial carcinomas that harbor FGFR3 mutations may be associated with improved prognosis (Cheng 2011). The CertNDx molecular grading assay (Predictive Biosciences, Inc.) was designed as a tool to be used in conjunction with clinical and histological parameters to aid in the clinical management of NMIUC. This test uses two biomarkers to determine molecular grade. The first biomarker is FGFR3 and the second is Ki-67, which is a marker of cell proliferation (Cheng 2011). Patients with molecular grade 1 (mG1) have FGFR3 mutations and low Ki-67 levels. Patients with molecular grade 2 (mG2) have FGFR3 mutations with high Ki-67 levels or wild-type FGFR3 and low Ki-67 levels. Patients with molecular grade 3 (mG3) are FGFR3 wild-type and have high Ki-67 levels. Patients with molecular grade 1 have favorable prognosis, patients with molecular grade 2 have intermediate prognosis, and patients with molecular grade 3 have poor prognosis.

10/17/2011: MTAC REVIEW
Fibroblast Growth Factor Receptor 3 (FGFR3) for Urothelial Carcinoma

Evidence Conclusion: Analytic validity- No studies were identified that addressed the analytic validity of the CertNDx molecular grading assay. Clinical validity - A recent prospective observational study evaluated the prognostic value of both WHO 1973 and 2004 grading systems, markers CK20, FGFR3, and Ki-67, and molecular grade (combination of FGFR3 and Ki-67) in 221 patients with urothelial carcinoma. In univariate analysis, WHO grade 1973, WHO grade 2004, pathological stage, FGFR3, Ki-67 status, and molecular grade were significantly associated with progression in stage; however, in a multivariate model, only WHO grade 1973 and 2004 remained significantly associated with progression in stage. None of the variables measured were significantly associated with recurrence-free survival (Burger 2008). Another study that included 255 patients with primary urothelial carcinoma also found that the combination of FGFR3 and Ki-67 status was not an independent predictor of recurrence-free or disease-specific survival (van Oers 2007). However, an observational study that included 286 patients with urothelial carcinoma found that in a multivariate analysis, the combination of FGFR3 and Ki-67 status predicted progression, recurrence rate, and disease-specific survival (van Rhijn 2003). Clinical utility - No studies were identified that addressed the clinical utility of the CertNDx molecular grading assay.

Conclusion: Analytic validity: No studies were identified that addressed the analytic validity of the CertNDx molecular grading assay. Clinical validity: Results from observational studies regarding the prognostic value of molecular grade (FGFR3/Ki-67) are mixed. Clinical utility: No studies were identified that addressed the clinical utility of the CertNDx molecular grading assay.

Articles: No studies were identified that addressed the analytic validity or clinical utility of the CertNDx molecular grading assay. Several studies were identified that evaluated the clinical validity of the CertNDx molecular grading assay. The most recent study was selected for review. The following study was critically appraised: Burger M, van der Aa MN, van Oers JM, et al. Prediction of progression of non-muscle-invasive bladder cancer by WHO 1973 and 2004 grading and by FGFR3 mutation status: a prospective study. Eur Urol. 2008;54:835-843. See Evidence Table.

The use of FGFR3 for urothelial carcinoma does not meet the Kaiser Permanente Medical Technology Assessment Criteria.

MammaPrint Test
BACKGROUND
Breast cancer affects almost 10% of women in western countries and is a major cause of morbidity and mortality. Most patients with lymph node negative disease may be successfully treated with surgery and local irradiation. Those with more aggressive disease may benefit from adjuvant chemotherapy and hormone therapy which could significantly improve their overall and disease-free survival. It is generally accepted that breast cancer patients with the poorer prognosis would gain the most benefits from systemic adjuvant therapy. The use of this adjuvant therapy is thus one of the most critical treatment decisions during the clinical management of breast cancer patients. Currently those with aggressive breast cancer are identified according to a combination of criteria including age, clinical stage and size of the tumor, histological type and grade of cancer, axillary node status, and hormone-receptor status. The ability of these criteria to predict outcome and disease progression is imperfect. Within a given patient population at a specified predicted risk of recurrence, there are some patients whose actual clinical outcome does not match that predicted by the indicators. As a result some of those who need adjuvant therapy do not receive it, while others may receive unnecessary toxic therapy (Kallioniemi 2002, DeVigier 2002). To overcome these issues, scientists are attempting to identify more accurate prognostic indicators. Microarray technology is revolutionizing researchers’ understanding of cancer biology through the simultaneous study of the
expression of tens of thousands of genes. Molecular profiling is the classification of tissue or other specimens for diagnostic, prognostic, and predictive purposes based on multiple gene expression. The potential value of gene expression profiling in assessing the risk of post-surgical breast cancer recurrence has been extensively investigated over the last few years. This has led to important insights in the molecular heterogeneity of cancers by revealing biologically and clinically relevant subtypes of tumors previously indistinguishable by the conventional approaches (Bertucci 2005). Due to the biological heterogeneity of breast cancers, women with the same stage of the disease may vary widely in their response to treatment and prognosis. Several gene expression-based predictors for breast cancer have been developed, but have not been used in routine clinical practice. According to researchers, this is mainly due to the limited validation and the limited clinical description of the molecular subtypes. Validation is a major challenge for microarray studies especially those with clinical implications as it requires a large sample size and because the results are influenced by the patient selection and by choice of the methods used to analyze gene expression data (Calza 2006, Hu 2006, Ioannidis 2007). The Amsterdam 70-gene profile (MammaPrint ®) was first developed using supervised gene expression profiling analysis of frozen tumor samples from two distinct patient populations. All were <55 years of age, and had lymph node negative disease. 44% had distant metastases within 5 years of completing treatment and 56% did not. By comparing the gene expression profile of patients with or without metastases, a signature 70-gene set that correlated with the outcome was identified and internally validated with the same group (van’t Veer 2002), and externally validated in two retrospective groups (Van De Vijver 2002 and Buyse 2006, see evidence tables). MammaPrint ® from Agenda is a qualitative in vitro diagnostic test service performed in a single laboratory using the gene expression profile of breast cancer tissue samples to assess a patient’s risk for distant metastases. The MammaPrint assay uses a panel of the Amsterdam 70-gene profile described above. It is a microarray based gene expression analysis of RNA extracted from breast tumor tissue. The MammaPrint ® analysis is designed to determine the activity of specific genes in a tissue sample compared to a reference standard. Its index ranges from -1.0 to +1.0. Tumor samples with an index above the threshold of +0.4 are classified as low risk, and those with an index equal to or less than the threshold are classified as high risk. The test requires fresh frozen samples which are shipped to the Agenda reference laboratory in the Netherlands. It is performed for breast cancer patients <61 years old, with Stage I invasive breast cancer or Stage II node negative invasive breast cancer, with tumor size <5 cm. It is indicated for use by physicians as a prognostic marker only, along with other clinicopathological factors. It is not intended for diagnosis, or for predicting or detecting response to therapy, or to help select the optimal therapy for patients (FDA).

08/06/2007: MTAC REVIEW
MammaPrint Test

Evidence Conclusion: The identification and validation of gene expression panels to improve risk prediction or treatment outcomes is a multistep process that starts by 1. Identifying the candidate genes (analytic validity), followed by 2. Evaluating the genetic panel associations with risk prediction or treatment outcomes in preliminary performance studies in relevant population (clinical validity), and 3. Determining whether the use of the multigenetic assay would direct the management of patients and improve outcomes (clinical utility). The most reliable method for validation is to derive a prognostic/predictive gene set from a training set and then apply it to a completely independent set, the test set, (Simon 2003, Ioannidis 2006, and Hu 2006). The MammaPrint test was developed based on research performed in the Netherlands Cancer Institute, The training set was derived from a study by van’t Veer and colleagues that included 98 women <55 years of age at diagnosis, with primary breast cancer (34 developed distant metastases within 5 years, 44 were disease free after at least 5 years). All patients were lymph node negative. 5 µg total RNA was isolated from frozen tumor material for each patient. The authors used inkjet-synthesized oligonucleotide microarrays that included 25,000 genes. Following several techniques 5000 genes were selected from the microarray, and then optimized to 70 genes with which a prognosis profile was established. The authors conducted a cross validation and concluded that a classification system based on these 70 genes outperformed all clinical variables in predicting the likelihood of distant metastases within five years. They noted however, that a selection of the patients based on the outcome (distant metastases or disease free in 5 years) was a limitation to the study. The same research team followed the initial study with a validation study (Van De Vijver, 2002) that included 295 women with either lymph node negative or lymph node positive breast cancer. The authors calculated the correlation coefficient of the level of expression of the 70- predictor genes identified in their initial study. They then classified the women with a correlation coefficient > 0.4 as having a good prognosis gene expression signature, and all the others as having a poor prognosis gene expression signature. In this validation set however the authors included 61 patients from the original training group used to derive the RNA expression signature, which could overestimate the relative risk and inflate the discriminating power of the test. The validation study included women < 55 years of age, with small tumors and at stage I or II of the disease which may not represent the entire spectrum of patients with breast cancer. Adjuvant hormone therapy or chemotherapy or both were given to most of the patients with lymph node positive disease. The Translational Research Network of the Breast International group (TRANSBIG) also conducted an independent validation study of the prognostic
signatures in a retrospective series of 302 untreated patients in five European countries. The study included only women node negative early stage breast cancer who had not received systemic adjuvant therapy, and thus may not represent the all patients with breast cancer. Its overall results showed that the 70-gene signature provided prognostic information on time to distant metastases and overall survival independent of the other clinical predictors. In conclusion, the selection of the 70-predictor genes was based on analyses of tumors from patients < 55 years of age with lymph node negative cancer who do not represent all women with breast cancer. The test proved to perform well as an independent prediction tool among the selected women studied. This however, does not necessarily indicate that it would predict treatment response. To date there are no published studies that show if modification of adjuvant therapy based on this test would improve disease free or overall survival. A large randomized controlled trial (Microarray for Node negative Disease may Avoid Chemotherapy [MINDACT]) that will evaluate the clinical utility of MammaPrint is underway. The trial will directly compare the use of prognostic information provided by the standard clinicopathological criteria vs. the MammaPrint test to decide whether to offer adjuvant chemotherapy to node-negative breast cancer patients. The MINDACT plans to prospectively include 6000 women, and follow-them up for a long duration in order to determine 5-year disease free-survival rate.

**Articles:** The literature search revealed multiple articles on molecular and gene-expression profiling in general. For the MammaPrint test in particular, there was a published study on the training set (to develop or derive the predictive classifier or model) by Van’t Veer and colleagues, and three validation studies to evaluate the predictive accuracy of the model (Van De Vijver 2002, Buyse 2006, and Glas 2006). All studies were reviewed but only the first two validation studies were critically appraised, Glas, et al’s study was not selected for critical appraisal due to patient overlap with the van De Vijver study. It is to be noted that Van De Vijver, van’t Veer, and several other principal authors are named inventors on a patent application for the 70-gene signature used in the studies. All studies also had financial ties to the manufacturer. The following studies were critically appraised: Van De Vijver MJ, He YD, van’t Veer LJ, et al. A gene expression signature as a predictor of survival in breast cancer. N Engl J Med 2002;347:1999-2009. See Evidence Table. Buyse M, van’t Veer, L, Viale G et al on behalf of the TRANSBIG Consortium. Validation and clinical utility of a 70-gene prognostic signature for women with node negative breast cancer. J Natl Cancer Inst 2006;98:1183-1192. See Evidence Table.

The use of the MammaPrint test in the treatment of recurring cancer does not meet the Kaiser Permanente Medical Technology Assessment Criteria.

**OVA1™ Test for the Assessment of Suspected Ovarian Cancer**

**BACKGROUND**

In the United States, ovarian cancer is the fifth leading cause of all cancer-related death among women. It is estimated that in 2010, there were 21,860 new cases of ovarian cancer and 13,850 deaths from ovarian cancer (Jemal 2010). The incidence of ovarian cancer increases with age with approximately two thirds of cases being diagnosed in women over the age of 55. Women with a family history of ovarian or breast cancer or who are carriers of the BRCA gene mutations are also at increased risk for ovarian cancer (Clarke-Pearson 2009). For patients with early stage disease, survival rates are greater than 90%; however, they are less than 30% for patients with advanced disease. Because of the lack of specific symptoms during the early stage approximately 70% of cases are diagnosed with advanced disease (Carter 2011). The most commonly used tests for the detection of ovarian cancer are transvaginal ultrasound (TVS) and serum CA-125. Recently, the FDA approved the OVA1™ test (Quest Diagnostics, Inc.) to be used as an adjunct to clinical/radiological evaluations for women planning surgery for an adnexal mass. This test measures the serum levels of 5 potential biochemical markers for ovarian cancer (transferritin, apolipoprotein A1, transferrin, CA-125, and β2-microglobulin). The results of the test are then interpreted using a proprietary algorithm to yield a single score ranging from 0 to 10 to indicate the likelihood that the adnexal mass is benign or malignant. A high probability for malignancy is defined as a score of at least 5.0 in premenopausal women or 4.4 in postmenopausal women. The goal of the OVA1™ test is to provide additional information to aid in indentifying patients who should be referred to a gynecologic oncologist for surgery (Carter 2011, Muller 2010). Studies suggest that women who receive their initial surgical care from an experienced gynecologic oncologist have improved outcomes and greater overall survival. Because of this the National Comprehensive Cancer Network (NCCN) recommends that all patients should undergo surgery by an experienced gynecologic oncologist (NCCN 2011). It is important to emphasize that this test is not approved for ovarian cancer screening and is not intended for use as a stand alone test. Another limitation of this test is that assay interference may occur in patients with rheumatoid factor levels of at least 250 IU/mL and triglyceride levels greater than 4.5 g/L (Muller 2010). In 2009, the FDA approved the use of this test for women over the age of 18 with an ovarian adnexal mass for which surgery is planned and have not yet been referred to an oncologist.

**10/17/2011: MTAC REVIEW**

**OVA1™ Test for the Assessment of Suspected Ovarian Cancer**

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**Evidence Conclusion:** Analytic validity - No studies were identified that evaluated the analytic validity of the OVA1™ test. Clinical validity - A recent observational study that included 524 women with ovarian tumors who were planning to undergo surgery compared the sensitivity and specificity of physician assessment alone (which included the use of CA 125) or combined with the OVA1™ test for identifying ovarian tumors at high risk for malignancy. Results from this study suggest that the addition of the OVA1™ test to physician assessment increased the sensitivity and the negative predictive value, but decreased the specificity and the positive predictive value (Ueland 2011). The performance of the American College of Obstetricians and Gynecologists (ACOG) referral guideline for women with a pelvic mass and the effect of replacing CA 125 with the OVA1™ test was also evaluated in this study population. The substitution of CA 125 for the OVA1™ test increased the sensitivity and the negative predictive value of the ACOG guidelines, but decreased the specificity and the positive predictive value (Miller 2011). Clinical utility - No studies were identified that evaluated the clinical utility of the OVA1™ test. Conclusion: Analytic validity: No studies were identified that evaluated analytic validity of the OVA1™ test. Clinical validity: Results from a recent observational study suggest that when added to physician assessment or substituted for CA 125, the OVA1™ test increased the sensitivity and the negative predictive value of these assessments, but decrease the specificity and positive predictive value. Clinical utility: No studies were identified that evaluated the clinical utility of the OVA1™ test.

**Articles:** No studies were identified that assessed the analytic validity or clinical utility of the OVA1™ test. Two studies were identified that addressed the clinical validity of the OVA1™ test. Both of these studies were selected for review. The following studies were selected for critical appraisal: Ueland FR, Desimone CP, Seamon LG, et al. Effectiveness of a multivariate index assay in the preoperative assessment of ovarian tumors. Obstet Gynecol 2011; 117:1289-1297. See Evidence Table. Ware Miller R, Smith A, DeSimone CP, et al. Performance of the American College of Obstetricians and Gynecologists’ ovarian tumor referral guidelines with a multivariate index assay. Obstet Gynecol. 2011;117:1298-1306. See Evidence Table.

The use of OVA1 for ovarian tumors does not meet the Kaiser Permanente Medical Technology Assessment Criteria.

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**Revision History**

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**Codes**

BrevaGen: No specific codes for this service
Fibroblast Growth Factor Receptor 3: No specific codes for this service
OVA1™: 81503
MammaPrint Test: S3854