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Multigene Expression Assays for Predicting Recurrence in Colon Cancer

Policy # 00257
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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers gene expression assays for determining the prognosis of stage II colon cancer following surgery to be **investigational.***

Background/Overview

Over a dozen different gene expression profile (GEP) tests have been developed and reported for use as prognostic markers in stage II colon cancer. These assays are intended to help identify patients with stage II colon cancer who are at high risk for recurrent disease and would be good candidates for adjuvant chemotherapy. Five assays are currently being marketed for clinical use in the United States: ColonPRS®‡, Signal Genetics, New York, NY; Coloprint®‡ Agendia NV, Amsterdam, Netherlands; Genefx Colon®‡, Precision Therapeutics, Pittsburgh, PA; OncoDefender-CRC®‡ (colon and rectal cancer), Everist Genomics, Ann Arbor, MI; and Oncotype DX®‡ colon cancer test; Genomic Health, Inc., Redwood City, CA. The gene signatures range from as small as 5 to as many as 634 genes. Independent validation studies ranging in size from 33 to 1,436 patients have been reported on these assays.

Of patients with stage II colon cancer, 75–80% are cured by surgery alone, and the absolute benefit of chemotherapy for the patient population is small. Those patients who are most likely to benefit from chemotherapy are difficult to identify by standard clinical and pathologic risk factors. Genomic tests are intended to be used as an aid in identifying those stage II patients most likely to experience recurrence after surgery. They are also intended to identify those patients most likely to benefit from additional treatment.

Colorectal cancer is classified stage II when it has spread outside the colon and/or rectum to nearby tissue but is not detectable in the lymph nodes and has not metastasized to distant sites (also called Dukes B). The primary treatment is surgical resection of the primary cancer and colonic anastomosis. After surgery the prognosis is good, with survival rates of 75% to 80% at 5 years. Meta-analysis of several trials of adjuvant therapy versus surgery alone in all stage II patients found statistically significant, although small, absolute benefit of chemotherapy for disease-free survival but not for overall survival. Therefore, adjuvant chemotherapy with 5-fluorouracil (5-FU) or capecitabine is recommended only as an option for resected patients with high-risk stage II disease (i.e. those. with poor prognostic features). However, the clinical and pathologic features used to identify high-risk disease are not well-established, and the patients for whom the benefits of adjuvant chemotherapy would most likely outweigh the harms cannot be identified with certainty. The current system relies on the use of a variety of factors including tumor sub-stage IIB (T4A tumors that invade the muscularis propria and extend into pericolorectal tissues) or IIC (T4B tumors that invade or are adherent to other organs or structures), obstruction or bowel perforation at initial diagnosis, inadequately low number of sampled lymph nodes at surgery (12 or less); histological features of

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aggressiveness, a high preoperative carcinoembryonic antigen level, and the presence of indeterminate or positive resection margins.

Of interest, a recent review has noted that microsatellite instability and mismatch repair (MMR) deficiency in colon cancer may represent confounding factors to be considered in treatment. The finding of these factors may identify a small population (15% to 20%) of the population with improved disease-free survival who may derive no benefit or may exhibit deleterious effects from adjuvant fluorouracil/leucovorin based treatments. The status of patients with regard to these findings may of critical important in how to study, interpret, and use a particular GEP test.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
To date, no gene expression test for evaluation of prognosis in stage II colon cancer has been cleared for marketing by the FDA. These tests are offered as laboratory-developed assays in clinical laboratory improvement amendment (CLIA)-licensed laboratories operated by each company and currently do not require FDA premarket review as a result of enforcement discretion.

Centers for Medicare and Medicaid Services (CMS)
No national coverage determination.

Rationale/Source

Introduction

Validation of genotyping to improve treatment outcomes is a multistep process. In general, important steps in the validation process address the following:

- **Analytic validity**: measures technical performance, i.e., whether the test accurately and reproducibly detects the gene markers of interest.
- **Clinical validity**: measures the strength of the associations between the selected genetic markers and clinical status.
- **Clinical utility:** determines whether the use of genotyping for specific genetic markers to guide treatment decisions improves patient outcomes such as survival or adverse event rate compared to standard treatment without genotyping.

Literature Review

Analytical Validity

Thirteen GEP assays have been developed and reported for use as a prognostic marker in stage II colon cancer since 2004. Five are currently offered commercially in the U.S. Information on basic elements of test performance including specimen type, sample handling, and technique used for GEP has been reported for many of these assays.

Clinical Validity

ColonPRS:
Van Laar in 2010 reported on a 163-gene expression test using data from 232 colon cancer patients across all stages (I to IV) of disease. Patients were stratified into high risk and low risk, and a second validation

performed in 33 stage II and 27 stage III patients. Gene expression classification was reported to show a statistically significant decrease in 5-year disease-free survival in low-risk stage II patients and a trend toward a statistically significant decrease in low-risk stage III patients. This assay ColonPRS is being marketed as a research use only test and has specific warnings against clinical use. However, the test has recently been acquired by Signal Genetics, L.L.C. It is unclear if the test is or will be marketed commercially for clinical use.

Coloprint:
Salazar et al. in 2010 described the development of an 18-gene expression test (the ColoPrint test). A total of 188 samples were prospectively collected from patients with colorectal cancers. Ribonucleic acid (RNA) was isolated from fresh tissue frozen in liquid nitrogen, labeled and hybridized to customized whole-genome oligonucleotide high-density microarrays. A cross-validation procedure was performed on 33,834 gene probes that showed variation across the training samples. These were scored for their association with 5-year distant metastasis-free survival. From this pool of genes, an optimal set of 18 nonredundant probes were identified. These were used to construct the classification scores used in the test. Results were dichotomized into a 2-category system identified as high-risk and low-risk scores.

In a small independent validation study using a patient cohort of 206 patients, 60% of patients were identified as low risk and 40% as high risk. The population studied, however, had a mixture of patients of different disease stages with only 56% representing stage II tumors. In the evaluation of patients with stage II disease, 63.2% were classified as low risk (with a 5-year recurrence-free survival of 90.9%) and 36.8% were classified as high risk (with 5-year recurrence-free survival of 73.9%).

A subsequent validation study was conducted in fresh frozen tumor samples from 135 patients who had undergone curative resection for stage II colon cancer. MMR status, clinical parameters, and follow-up data (median 8.4 years) were collected. Five-year distant metastasis-free survival was 95% for patients classified as low risk by ColoPrint and 80% for patients classified as high risk. Information about net reclassification and clinical utility was not provided. To date, larger validation studies have been published only in abstract form.

Genefx Colon:
Kennedy et al. in 2011 reported on the development of a 634-probe set signature. A training set of 215 patients (143 low risk and 73 high risk) was identified based on disease-free survival at 5 years. The assay was performed using deoxyribonucleic acid (DNA)-microarray analysis of formalin-fixed paraffin-embedded samples. Cross-validation studies were used to select an optimal transcript signature for prognostic classification.

Independent validation was performed on 144 patients enriched for recurrence (85 low-risk and 59 high-risk patients) using the threshold score identified in the training set. The signature in this convenience sample of patients predicted disease recurrence with a hazard ratio (HR) of 2.53 ($p < 0.001$) in the high-risk group. The signature also predicted cancer-related death with an HR of 2.21 ($p = 0.00084$) in the high-risk group. The authors noted a further retrospective validation of the test in a large cohort of stage II colon cancer

samples collected as part of a clinical trial is planned. As of July 2013, no additional information about this study was found.

OncoDefender:
Lenehan et al. in 2012 reported on their development of a 5-gene test, the OncoDefender. A total of 417 cancer-associated genes were preselected for study in archived formalin-fixed, paraffin-embedded primary adenocarcinoma tissues of 74 patients with colorectal cancer (15 with stage I disease and 59 with stage II disease; 60 with colon and 14 with rectal cancer). Patients were divided into a training set and a testing set. Cross validation was performed to estimate the ability of the classifier to generalize to unseen samples. The most important feature of gene fitness was the area under the receiver operating characteristics curve observed for each gene.

External validation was performed on 251 patients with stage I and II colon cancer obtained from an international study set. Patient drop-out from the archived sample banks used was substantial; only 264 (55%) of 484 patients with lymph-node negative colorectal carcinoma (CRC) satisfied the initial clinicopathologic screening. This included a mix of patients with both rectal and colon cancer (stage I and II). The test appeared to distinguish patients at high- versus low-risk of recurrence with a HR of 1.63, p = 0.031. Sensitivity and specificity of the OncoDefender was compared to National Comprehensive Cancer Network (NCCN) guidelines and showed similar sensitivity (69% vs. 73% with improved specificity 48% vs. 26%). However, isolated performance of the test in patients with stage II colon cancer was not reported, and several NCCN high-risk findings (bowel obstruction/perforation, and lymphovascular invasion) demonstrated higher HRs than observed using the molecular signature. The study alluded to but did not directly address clinical utility.

Oncotype DX:
O'Connell et al. in 2010 described the development of a 12-gene expression test (the Oncotype DX colon cancer test). A total of 761 candidate genes of possible prognostic value for recurrence or of possible predictive value for treatment were examined by correlating the genes in tumor samples with the clinical outcomes seen in 1,851 patients who had surgery with or without adjuvant 5-fluorouracil (5-FU)-based chemotherapy. Gene expression was quantitated from microdissected fixed paraffin-embedded primary colon cancer tissue. Of the 761 candidate genes surveyed, a multivariate analysis including disease severity, stage, and nodal involvement, reduced the genes to a 7-gene prognostic signature and a separate 6-gene predictive signature. Five reference genes are also included in the assay.

External validation of the algorithm in an independent study, the Quick and Simple and Reliable (QUASAR) study was reported in 2011. The relationship between the 7-gene test's recurrence score and risk of recurrence was found to be statistically significant with the 3-year risk of recurrence for predefined low-, intermediate-, and high-risk groups to be 12%, 18%, and 22%, respectively. No relationship was identified comparing the 6-gene treatment score results with benefit from chemotherapy.

Clinical Utility
No studies of a GEP for determining prognosis of patients with stage II colon cancer have been published demonstrating the effect of testing on overall reclassification of patients when compared to existing methods

of risk analysis. There is no published information on the impact from use of GEP results on patient outcomes. In the absence of information showing a direct effect on outcomes or establishing a strong chain of evidence that testing would be expected to have a positive net effect on outcomes, the clinical utility of testing remains unclear.

A Technical Brief published by the Agency for Healthcare Research and Quality (AHRQ) in December 2012 reviewed the clinical evidence for the use of gene expression profiling for predicting outcomes, including benefit from adjuvant chemotherapy, in patients with stage II colon cancer. The four commercially available assays reviewed above were included in the brief. No prospective studies were identified that assessed change in net health outcome with use of a GEP assay, and no studies were identified that used a net reclassification analysis and subsequently evaluated the impact of the reclassification on net health outcome. Additionally, evidence was limited regarding the reproducibility of test findings, indications for GEP testing in stage II patients, and whether or not results of GEP assays can stratify patients into clinically meaningful groups.

Ongoing Clinical Trials
The following relevant ongoing trials were identified from online site ClinicalTrials.gov:
NCT00903565. The ColoPrint Assay is being prospectively validated in patients with stage II colon cancer in the Prospective Analysis of Risk Stratification by Colo-Print (PARSC) study. Estimations of 3-year relapse rates by ColoPrint, ASCO criteria, and independent investigator risk assessment will be compared. The study was begun in September 2008 with estimated enrollment of 1,200 patients. However, the ClinicalTrials.gov record has not been updated since March 2012.

Summary
The available evidence indicates that GEP tests for colon cancer can improve risk prediction, particularly regarding the risk of recurrence in patients with stage II colon cancer. However, the evidence to date is insufficient to permit conclusions on how GEP classification compares with other approaches for identifying recurrence risk in stage II patients or on how GEP classification impacts patient outcomes (clinical utility). There is even less evidence to permit conclusions on how GEP classification compares with other approaches for management of other stages of colon cancer. Therefore, use of this test, including use to predict the likelihood of disease recurrence for patients with colon cancer, is considered investigational.

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Code Type	Code
CPT	84999
HCPCS	No codes
ICD-9 Diagnosis	All relative diagnoses
ICD-9 Procedure	No codes

Policy History

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04/24/2013 Medical Policy Implementation Committee approval. Changed investigational statement to include all gene expression assays, instead of only Oncotype Dx.
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*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
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