Kansas City

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Multigene Expression Assay for Predicting Recurrence in Colon Cancer

Policy Number: 2.04.61
Origination: 8/2010
Last Review: 10/2014
Next Review: 10/2015

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will not provide coverage for multigene expression assay for predicting recurrence in colon cancer. This is considered investigational.

When Policy Topic is covered

Not Applicable

When Policy Topic is not covered

Gene expression assays for determining the prognosis of stage II colon cancer following surgery are considered **investigational.**

Considerations

There is no specific code for this laboratory test.

Description of Procedure or Service

Over a dozen different gene expression profile (GEP) tests have been developed and reported for use as prognostic markers in stage 2 colon cancer. These assays are intended to help identify patients with stage 2 colon cancer who are at high risk for recurrent disease and would be good candidates for adjuvant chemotherapy. Five assays are currently marketed for clinical use in the United States: ColonPRS® (ChipDX, New York, NY), Coloprint® (Agendia NV, Amsterdam, the Netherlands), GeneFx Colon® (Precision Therapeutics, Pittsburgh, PA), OncoDefender™-CRC for colon and rectal cancer (Everist Genomics, Ann Arbor, MI), and Oncotype DX® colon cancer test (Genomic Health Inc., Redwood City, CA). Gene signatures range from as small as 5 to as many as 634 genes. Independent validation studies ranging in size from 33 to 1436 patients have been reported on these assays.

Available evidence indicates that GEP tests for colon cancer can improve risk prediction, particularly the risk of recurrence in patients with stage 2 colon cancer. However, evidence to date is insufficient to permit conclusions on how GEP classification compares with other approaches for identifying recurrence risk in stage 2 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.

Background

Of patients with stage 2 colon cancer, 75-80% are cured by surgery alone, and the absolute benefit of chemotherapy for the overall patient population is small. Patients most likely to benefit from chemotherapy are difficult to identify by standard clinical and pathological risk factors. Genomic tests are intended to be used as an aid for identifying stage 2 patients most likely to experience recurrence after surgery and most likely to benefit from additional treatment.

Colorectal cancer is classified as stage 2 when it has spread outside the colon and/or rectum to nearby tissue but is not detectable in lymph nodes and has not metastasized to distant sites (also called Dukes B). Primary treatment is surgical resection of the primary cancer and colonic anastomosis. After surgery prognosis is good, with survival rates of 75% to 80% at 5 years.[1] A 2008 meta-analysis of 50 studies of adjuvant therapy versus surgery alone in stage 2 patients found statistically significant, although small, absolute benefit of chemotherapy for disease-free survival but not for overall survival.[1] Therefore, adjuvant chemotherapy with 5-fluorouracil (5-FU) or capecitabine is recommended only as an option for resected patients with high-risk stage 2 disease (ie those with poor prognostic features).[2] However, clinical and pathological features used to identify high-risk disease are not well-established, and patients for whom benefits of adjuvant chemotherapy would most likely outweigh harms cannot be identified with certainty. The current system relies on a variety of factors including tumor sub-stage 2B (T4A tumors that invade the muscularis propria and extend into pericolorectal tissues) or 2C (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 aggressiveness, a high preoperative carcinoembryonic antigen level, and indeterminate or positive resection margins.[2]

Of interest, a recent review has noted that microsatellite instability (MSI) and mismatch repair (MMR) deficiency in colon cancer may represent confounding factors to be considered in treatment.[3] These factors may identify a small proportion (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. Patient MSI and MMR status may be critically important in how to study, interpret, and use a particular gene expression profile (GEP) test.

Regulatory Status

To date, no gene expression test for evaluation of prognosis in stage 2 colon cancer has been cleared for marketing by the U.S. Food and Drug Administration (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.

Rationale

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, ie, whether the test accurately and reproducibly detects gene markers of interest.
- **Clinical validity**: measures the strength of associations between 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 with standard treatment without genotyping.

Literature Review

An updated literature search was performed using the MEDLINE database for the period through July 9, 2014.

Analytical Validity

Many gene expression profile (GEP) assays have been developed and reported for use as a prognostic marker in stage 2 colon cancer since 2004.4-19 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 et al (2010) reported on a 163-gene expression test using data from 232 colon cancer patients across all stages (1 to 4) of disease (training set).10 Patients were stratified into high- and low-risk groups, and a second validation was performed in 33 stage 2 and 27 stage 3 patients (test set). Among stage 2 patients, 5-year disease-free survival was statistically significantly prolonged in low-risk compared with high-risk patients, but among stage 3 patients, 5-year disease-free survival did not differ statistically between low- and high-risk groups. ColonPRS® is marketed for research use only. The test was originally marketed by Signal Genetics, but now is available through its subsidiary, ChipDX. A telephone call to the company confirmed that ColonPRS® was for internal research use only.

ColoPrint®

Salazar et al (2011) 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. 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 was identified and used to construct classification scores for the test. Results were dichotomized into a 2-category, low- and high-risk scoring system.

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 2 tumors. In the evaluation of patients with stage 2 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 2 colon cancer.20 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 (2011) reported on the development of a 634-probe set signature.15 A training set of 215 patients (143 low-risk and 73 high-risk) was identified based on 5-year disease-free survival. The assay was performed using 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 ($p<0.001$) in the high-risk group. The authors noted that additional retrospective validation of the test in a large cohort of stage 2 colon cancer samples collected as part of a clinical trial was planned. As of July 2014, no additional information about this study was found.

OncoDefender®

Lenehan et al (2012) reported on their development of a 5-gene test, OncoDefender®.22 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 1 disease and 59 with stage 2 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 for each gene.

External validation was performed on 251 patients with stage 1 and 2 colon cancer obtained from an international study set. Patient drop-out from the set of archived samples used was substantial; only 264 (55%) of 484 patients with lymph-node negative colorectal carcinoma (CRC) satisfied the initial clinicopathological screening. This included a mix of patients with both rectal and colon cancer (stage 1 and 2). The test appeared to distinguish patients at high- versus low-risk of recurrence with an HR of 1.63 (p=0.031). Sensitivity and specificity of OncoDefender® was compared with 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 2 colon cancer was not reported, and several NCCN high-risk findings (bowel obstruction/perforation and lymphovascular invasion) demonstrated higher hazard ratios than observed with the molecular signature. The study alluded to but did not directly address clinical utility.

Oncotype DX®

O'Connell et al (2010) described the development of a 12-gene expression test, Oncotype DX® colon cancer test.[9] 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 clinical outcomes in 1851 patients who had surgery with or without adjuvant 5-fluorouracil (5-FU)-based chemotherapy. Gene expression was quantified from microdissected fixed paraffin-embedded primary colon cancer tissue. Of 761 candidate genes, multivariate analysis including disease severity, stage, and nodal involvement reduced the gene set to a 7-gene prognostic signature and a separate 6-gene predictive signature. Five reference genes also are included in the assay.

External validation of the algorithm was reported in 2011 in an independent study using fixed paraffin-embedded primary tumor samples from patients with stage 2 colon cancer who had participated in the Quick and Simple and Reliable (QUASAR) study of adjuvant chemotherapy versus surgery alone.[23] The relationship between the 7-gene recurrence score and risk of recurrence was found to be statistically significant, with 3-year risk of recurrence for predefined low-, intermediate-, and high-risk groups of 12%, 18%, and 22%, respectively. No relationship between a 6-gene treatment score and benefit from chemotherapy was identified.

Venook et al (2013) conducted a validation study using tumor tissue from 690 patients with stage 2 colon cancer who had participated in the Cancer and Leukemia Group B (CALGB) 9581 trial.[24] CALGB 9581 randomized 1713 patients with stage 2 colon cancer to treatment with edrecolomab, an experimental monoclonal antibody, or observation; disease-free and overall survival did not differ between treatment groups. Venook et al selected samples stratified by treatment group from those who had tumor tissue available (40% of the original patient sample). The authors used recurrence score cut points of 29 and 39 to determine low-, intermediate-, and high-risk groups; these values differ from the cut points of 30 and 41 validated in the QUASAR study described above. Estimated 5-year recurrence risk was 12% (95% CI, 10 to 15), 15% (95% CI, 12 to 17), and 18% (95% CI, 14 to 22) in the low-, intermediate-, and high-risk groups, respectively. In multivariate analysis, every 25 unit change in recurrence score was associated with recurrence independently of tumor stage, tumor grade, mismatch repair (MMR) status, presence or absence of lymphovascular invasion, and number of nodes assessed.

Yothers et al (2013) conducted a validation study using tumor tissue from 264 patients with stage 2 colon cancer who had participated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trial.[25] NSABP C-07 randomized 2409 patients with stage 2 (28%) or stage 3 (72%) colon cancer to adjuvant chemotherapy with 5-fluorouracil plus leucovorin (FULV) or oxaliplatin plus FULV (FLOX). Yothers et al randomly selected 50% of patients who had tissue available, for a total of 892 tissue samples, 264 of whom (30%) had stage 2 cancer. For these patients, estimated 5-year recurrence risks adjusted for treatment (FULV vs FLOX) were 9% (95% CI, 6 to 13) in the Oncotype-defined low-risk group, 13% (95% CI, 8 to 17) in the intermediate-risk group, and 18% (95% CI, 12 to 25) in the high risk

group. Five-year recurrence risk was reduced in high-risk patients who received oxaliplatin compared with those who did not (Kaplan-Meier estimated 5-year recurrence risk, 9% [95% CI, 3 to 25] FLOX vs 23% [95% CI, 12 to 42] FULV), but this difference was not observed in low- or intermediate-risk patients. However, confidence intervals for these estimates were wide due to small numbers of patients and events in each risk group. For all stage 3 patients in any risk class, adjusted 5-year recurrence risk estimates exceeded 15%.

Clinical Utility
No studies of GEP for determining prognosis of patients with stage 2 colon cancer has been published demonstrating the effect of testing on overall reclassification of patients when compared with existing methods of risk analysis. Srivastava et al (2014) published a study showing the effect of Oncotype DX® results on treatment recommendations made according to traditional risk classifiers.[26] However, this study did not assess survival or recurrence outcomes. Currently, there is no published information on the impact of 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 has a positive net effect on outcomes, 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 gene expression profiling for predicting outcomes, including benefit from adjuvant chemotherapy, in patients with stage 2 colon cancer.[27] The 4 assays reviewed above that are commercially available for clinical use 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 2 patients, and whether or not results of GEP assays can stratify patients into groups defined by clinically meaningful differences in recurrence risk.

Ongoing and Unpublished 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 2 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 1200 patients. The last verification date for this study was February 2014.

Two ColoPrint® studies by Salazar et al are available in abstract form only.

Summary
The available evidence indicates that gene expression profile tests for colon cancer can improve risk prediction, particularly regarding the risk of recurrence in patients with stage 2 colon cancer. However, evidence to date is insufficient to permit conclusions on how gene expression profile (GEP) classification compares with other approaches for identifying recurrence risk in stage 2 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.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)
Current clinical practice guidelines from NCCN, V3.2014 Colon Cancer, state that data are insufficient "to recommend the use of multi-gene assays to determine adjuvant therapy" in patients with stage 2 colon cancer.2

U.S. Preventive Services Task Force Recommendations

Multigene expression assay testing is not a preventive service.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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Billing Coding/Physician Documentation Information

84999 Unlisted chemistry procedure
88299 Unlisted cytogenetic study

Additional Policy Key Words

N/A

Policy Implementation/Update Information

8/1/10	New policy; considered investigational.
8/1/11	No policy statement changes.
8/1/12	No policy statement changes.
10/1/12	No policy statement changes.
10/1/13	Policy statement clarified to remove specific brand name for the test; considered investigational for all versions of the test.
10/1/14	No policy statement changes.