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Medical Policy Manual

Topic: Multigene Expression Assays for Predicting Recurrence in Colon Cancer

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Section: Genetic Testing

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Several 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; Coloprint®, Agendia NV; Genefx Colon®, Precision Therapeutics; OncoDefender™-CRC (colon and rectal cancer), Everist Genomics; and Oncotype DX® colon cancer test, Genomic Health, Inc.

Background

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 pathological risk factors. The 12-gene expression test is intended to be used as an aid in indentifying those stage II patients most likely to experience recurrence after surgery and therefore those 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 very good, with survival rates of 75% to 80% at 5 years.[1] Meta-analysis of several trials of adjuvant therapy vs. 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.[1] 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).[2] However, the clinical and pathological 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.

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.[3] 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 be of critical important in how to study, interpret, and use a particular GEP test.

Regulatory Status

To date, no gene expression test for evaluation of prognosis in stage II 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.

MEDICAL POLICY CRITERIA

I. Gene expression assays are considered **investigational** for determining the prognosis of stage II colon cancer, including but not limited to the following genetic tests:

A. ColonPRS®
B. Coloprint® Agendia NV
C. Genefx Colon®
D. OncoDefender™-CRC
E. Oncotype DX® colon cancer test

SCIENTIFIC EVIDENCE

To date, no studies have compared the clinical decisions made as a result of GEP test results to decisions made based on existing methods of risk analysis. There is no published information on the clinical utility of the GEP tests; that is the impact from use of GEP results on improved patient outcomes or how the GEP tests guided decisions related to the patient's treatment or management. In the absence of information showing a direct effect on outcomes or establishing a strong chain of evidence, the clinical utility of testing remains unclear. Further, the clinician's ability to assess individualized risk and predict

response to adjuvant therapy for GEP tests for patients with stage II colon cancer has not been demonstrated in the literature.

Literature Appraisal

Technology Assessment

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.[4] Two of the commercially available assays described in this policy were reviewed; OncotypeDx Colon Cancer and Coloprint. No prospective studies were identified that assessed change in net health outcome with use of a GEP assay. Furthermore, no studies were identified that used a net reclassification analysis and subsequently evaluated the impact of the reclassification on net health outcome. Additionally, the 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.

Non-randomized studies

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.[5] Patients were stratified into high risk and low risk, and a second validation test was 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. The assay described in this study, ColonPRS®, is marketed as a research use only test and has specific warnings against clinical use.

ColoPrint®

- Salazar et al. in 2011 described the development of an 18-gene expression test (the ColoPrint® test).[6] A total of 188 samples were prospectively collected from patients with colorectal cancers. From this pool of genes, an optimal set of 18 non-redundant 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 nested small independent validation study, using a patient cohort of 206, 60% of patients were identified as low risk and 40% as high risk. However, the population studied was 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.[7] 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.

- In a recent study, ColoPrint was used to evaluate the risk of cancer recurrence and assist in treatment decisions in stage II patients. ColoPrint identified most stage II patients (73.3%) as low risk.[7] The 5-year distant-metastasis free survival was 94.9% for low-risk patients and 80.6% for high-risk patients. In multivariable analysis, ColoPrint was the only significant parameter to predict the development of distant metastasis. Authors concluded that ColoPrint was able to predict the development of distant metastasis of patients with stage II colon cancer and facilitate the identification of patients who may be safely managed without chemotherapy. These treatment decisions were not compared to decisions that would have been made in the absence of genetic testing.

Genefx Colon®

Kennedy et al. in 2011 reported on the development of a 634-probe set signature.[8] A training set of 215 patients (142 low risk and 73 high risk) were identified based on disease-free survival at 5 years. 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 in the high-risk group. The signature also predicted cancer-related death in the high-risk group. The authors noted a further retrospective validation of the test is planned in a large cohort of stage II colon cancer samples.

OncoDefender®

Lenehan et al. in 2012 reported on their development of a 5-gene test, the OncoDefender®.[9] 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.

As part of the same study, an external validation test 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 Il). The test appeared to distinguish patients at high- versus low-risk of recurrence with a hazard ratio 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 hazard ratios than observed using the molecular signature. The study alluded to but did not directly address clinical utility.

Oncotype DX®

- O'Connell et al. described the development of the 12-gene expression test.[10] 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-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 significant seven-gene prognostic signature and a separate six-gene predictive signature. Five reference genes were 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.[11] 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 Practice Guidelines

Current clinical practice guidelines from National Comprehensive Cancer Network (NCCN) state that data are insufficient "to recommend the use of multigene assays to determine adjuvant therapy" in patients with stage II colon cancer.[12]

Summary

The available evidence indicates that gene expression profile (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). Further, 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 genetic expression profiles testing is considered investigational for all indications, including use to predict the likelihood of disease recurrence for patients with colon cancer.

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13. BlueCross BlueShield Association Medical Policy Reference Manual "Multigene Expression Assay for Predicting Recurrence in Colon Cancer." Policy No. 2.04.61

CROSS REFERENCES

Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening, Genetic Testing, Policy No. 12

Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20

CODES	NUMBER	DESCRIPTION
There are no specific codes for the 12-gene expression test (Oncotype DX® colon cancer test). The correct CPT codes to use are the unlisted CPT codes listed below:		
CPT	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis
	84999	Unlisted chemistry procedure
	88299	Unlisted cytogenetic study
HCPCS	None	