Multigene Expression Assay for Predicting Recurrence in Colon Cancer

I. Description

Gene expression profile (GEP) tests have been developed and reported for use as prognostic markers in stage 2 or stage 3 colon cancer to help identify patients who are at high risk for recurrent disease and could be good candidates for adjuvant chemotherapy.

The evidence for the use of GEP tests in patients who have stage 2 or stage 3 colon cancer includes development and validation studies. Relevant outcomes are disease-specific survival, test accuracy, test validity, and change in disease status. The available evidence indicates that GEP tests for colon cancer can improve risk prediction, particularly the risk of recurrence in patients with stage 2 or stage 3 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 or stage 3 patients, or on how GEP classification impacts patient outcomes (clinical utility). There is even less evidence to permit conclusions about how GEP classification compares with other approaches for management of other stages of colon cancer. The evidence is insufficient to determine the effects of the technology on health outcomes.

II. Criteria/Guidelines

Gene expression assays for determining the prognosis of stage 2 and stage 3 colon cancer following surgery are not covered as they are not known to be effective in improving health outcomes.

III. Administrative Guidelines

There is no specific code for this laboratory test. These are the codes which would most likely be reported:

81599 Unlisted multianalyte assay with algorithmic analysis
84999 Unlisted chemistry procedure.
88299 Unlisted cytogenetic study.

Effective 01/01/16, there will be a CPT code specific to Oncotype DX Colon Cancer Assay –
81525 Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score

IV. Background

Of patients with stage 2 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 2 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 2 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 2 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 2 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 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 the presence of indeterminate or positive resection margins.

For patients with stage 3 colon cancer, current guidelines from the National Comprehensive Cancer Network recommend “6 months of adjuvant chemotherapy after primary surgical treatment.” However, some have questioned the benefit of adjuvant chemotherapy in subsets of patients with stage 3 disease (eg, stage 3A) whose predicted survival may actually exceed that of some stage 2 patients (eg, stage 2C).

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 be critically important in how to study, interpret, and use a particular GEP test.
Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Improvement Act (CLIA). Multigene expression assay testing for predicting recurrent colon cancer is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

V. 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, 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.

An updated literature search was performed using the MEDLINE database for the period of June 1, 2012 through June 30, 2015

Analytical Validity

Thirteen gene expression profile (GEP) assays have been developed and reported for use as a prognostic marker in stage 2 colon cancer since 2004. Four 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 2 and 27 stage 3 patients. Gene expression classification was reported to show a statistically significant decrease in 5-year disease-free survival in low-risk stage 2 patients and a trend toward a statistically significant decrease in low-risk stage 3 patients. This assay ColonPRS is being marketed as a research use only test and has specific warnings against clinical use. Although the test was marketed by Signal Genetics, L.L.C, it no longer appears on the company’s website. A telephone call to the company confirmed that ColonPRS was for internal research use only.

**ColoPrint**: Salazar et al. in 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 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 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. 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 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 2 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 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 observed for each gene.
External validation was performed on 251 patients with stage I and 2 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 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 2 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. 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.

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. CALGB 9581 randomized 1713 patients with stage 2 colon cancer to treatment with edrecolomab, an experimental monoclonal antibody, or observation; DFS 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 previously described. 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 independent of tumor stage, tumor grade, 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.27 NSABP C-07 randomized 2409 patients with stage 2 (28%) or stage 3 (72%) colon cancer to adjuvant chemotherapy with 5-FU plus leucovorin (FULV) or oxaliplatin plus FULV (FLOX). Yothers et al randomly selected 50% of patients who had tissue available (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%.

Reimers et al (2014) conducted a retrospective study using prospectively collected tumor specimens from the Dutch total mesenteric excision (TME) trial29 in patients with resectable colon cancer. The Dutch TME trial compared TME with and without radiotherapy in 1861 patients. Reimers et al used available tumor tissue from 569 stage 2 and stage 3 patients randomized to surgery alone; only 297 specimens (52%) were included in their analysis. Among patients with stage 2 rectal cancer (n=130), Oncotype® DX classified 63 patients (49%) as low risk, 37 patients (28%) as intermediate risk, and 30 patients (23%) as high risk. At median follow-up of 12 years (range, 1-14 years),30 5-year Kaplan-Meier recurrence risk estimates in the low-, intermediate-, and high-risk groups were 12% (95% CI, 6 to 24), 29% (95% CI, 17 to 47), and 53% (95% CI, 35 to 73), respectively. Five-year recurrence risk as high as 24% in patients classified as low risk by Oncotype® DX is likely too high to meaningfully inform clinical treatment decision making in patients with stage 2 rectal cancer. Oncotype® DX risk classification and estimated recurrence risks for patients with stage 3 rectal cancer were not reported.

Clinical Utility

No studies of a GEP for determining prognosis of patients with stage 2 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 2 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 2 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 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 1,200 patients. However, the ClinicalTrials.gov record has not been updated since March 2015.

**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 or stage 3 colon cancer. However, the 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**

Current clinical practice guidelines from NCCN (v.3.2015) on colon cancer state that data are insufficient “to recommend the use of multigene assays to determine adjuvant therapy” in patients with stage 2 or 3 colon cancer.

**Medicare National Coverage**

No national coverage determination.

**VI. Important Reminder**

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.
This Medical Policy has been developed through consideration of the medical necessity criteria under Hawa2’s Patients’ Bill of Rights and Responsibilities Act (Hawa2 Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawa2 law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References


