Description of Procedure or Service

Gene expression profiling (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 candidates for adjuvant chemotherapy.

According to estimates by the National Cancer Institute, in 2018 over 140,000 new cases of colorectal cancer will be diagnosed in the United States, and over 50,600 people will die of this cancer. Five-year survival estimates are around 65%.

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 pathological 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 2 (also called Dukes B) when it has spread outside the colon and/or rectum to nearby tissue, but is not detectable in the lymph nodes (stage 3 disease also called Dukes C) and has not metastasized to distant sites (stage 4 disease). 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. Meta-analysis of several trials of adjuvant therapy vs. 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 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. 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 (NCCN) 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 whose predicted survival may actually exceed that of some stage 2 patients.
Multigene Expression Assay for Predicting Recurrence in Colon Cancer

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.

Regulatory Status
To date, no gene expression test for evaluation of prognosis in stage 2 or stage 3 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.

Gene Expression Profiling tests (GEP) for colon cancer that are currently commercially available include the following:

- ColoPrint® (18-Gene Colon Cancer Recurrence Assay (Agendia)
- GeneFX-Colon™ (Helomics, also known as ColDx)
- OncoDefender-CRC™ (Everist Genomics)
- OncotypeDx® Colon Recurrence Score (Genomic Health)

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

The multigene expression assay is considered investigational for predicting recurrence in colon cancer. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Multigene Expression Assay for Predicting Recurrence in Colon Cancer is covered

Not applicable

When Multigene Expression Assay for Predicting Recurrence in Colon Cancer is not covered

Gene expression assays for determining the prognosis of stage 2 or stage 3 colon cancer following surgery are considered investigational.

Policy Guidelines

For individuals who have stage 2 or stage 3 colon cancer who receive GEP tests, the evidence includes development and validation studies and one decision impact study. Relevant outcomes are disease-specific survival, test accuracy and validity and change in disease status. The available evidence indicates that GEP testing for colon cancer can improve risk prediction, particularly the risk of recurrence in patients with stage 2 or stage 3 colon cancer. However, the degree of difference in risk
Multigene Expression Assay for Predicting Recurrence in Colon Cancer

Evidence to date is insufficient to permit conclusions on whether GEP classification is sufficient to modify treatment decisions in stage 2 or 3 patients. Studies showing management changes as a consequence of testing do not demonstrate whether such changes improve outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina website at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service code: 81525

It could also be coded using an unlisted code such as 84999 or 88299.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Medical Director – 9/2011


Medical Director – 6/2012


Senior Medical Director – 10/2012


Medical Director review 8/2015
Multigene Expression Assay for Predicting Recurrence in Colon Cancer


Specialty Matched Consultant Advisory Panel- 4/2018


Policy Implementation/Update Information

5/10/11 New policy developed. The multigene expression assay is considered investigational for predicting recurrence in colon cancer. Specialty Matched Consultant Advisory Panel review 4/27/11. (adn)

10/11/11 “Policy Guidelines” updated. Reviewed by Senior Medical Director. Reference added. (btw)

5/15/12 Specialty Matched Consultant Advisory Panel review 4/18/2012. No change to policy intent. (btw)

7/10/12 Added the following statement to the Description section to indicate; “ColoPrint, an 18-gene signature test was launched by Agendia June 1, 2012 for predicting the risk of distant recurrence for stage II colon cancer. This test has not been FDA approved and is only available as a laboratory-developed assay service by Agendia.” Medical Director review 6/25/12. Reference added. (btw)

10/30/12 Description section revised. The When Not Covered statement changed from “The 12-gene expression test (Oncotype DX® colon cancer test) is considered investigational, including use for predicting the likelihood of disease recurrence for patients with stage II colon cancer following surgery.” to “Gene expression assays for determining the prognosis of stage II colon cancer following surgery are considered investigational.” Policy Guidelines updated. References added. Senior Medical Director review 10/14/12. (btw)

4/30/13 Specialty Matched Consultant Advisory Panel review 4/17/2013. No change to policy. (btw)

10/1/13 Reference added. (btw)


11/11/14 Reference added. (lpr)

5/26/15 Specialty Matched Consultant Advisory Panel review 4/29/2015. No change to policy. (lpr)
Multigene Expression Assay for Predicting Recurrence in Colon Cancer

10/30/15  Updated Description and Policy Guidelines sections. Under “When Not Covered” section, added Stage 3 colon cancer as investigational indication. Medical director review 8/2015. Reference added. (lpr)

12/30/15  Added CPT code 81525 to Billing/Coding section for effective date 1/1/2016. (lpr)

5/31/16   Updated Policy Guidelines. Specialty Matched Consultant Advisory Panel review 4/27/2016. No change to policy. (lpr)

8/30/16   Updated Description, Policy Guidelines and Regulatory sections. Reference added. No change to policy statement. (lpr)

5/26/17   Specialty Matched Consultant Advisory Panel review 4/26/2017. No change to policy statement. (lpr)

9/29/17   Updated Policy Guidelines and Regulatory Status sections. Reference added. No change to policy statement. (lpr)

5/11/18   Specialty Matched Consultant Advisory Panel review 4/25/2018. No change to policy statement. (lpr)

9/7/18    Reference added. (lpr)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.