MEDICAL POLICY – 12.04.61
Multigene Expression Assay for Predicting Recurrence in Colon Cancer

BCBSA Ref. Policy: 2.04.61
Effective Date: Oct. 1, 2017
Last Revised: Sept. 21, 2017
Replaces: N/A

RELATED MEDICAL POLICIES:
12.04.506 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

Surgery is a very successful treatment for most cases of colon cancer. Seventy-five to 80 percent of stage 2 colon cancers are cured by surgery alone. If there is a high risk the cancer could come back, chemotherapy may be used after colon cancer surgery. Certain genetic tests may be used to try to determine who is at high risk of the colon cancer coming back. There is not enough scientific evidence to show if these genetic tests are the same as or better than the usual ways of identifying the risk of colon cancer returning. These genetics tests are considered unproven.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene expression assay</td>
<td>Gene expression assays for determining the prognosis of stage</td>
</tr>
</tbody>
</table>
**Type of Test**

<table>
<thead>
<tr>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>testing</strong></td>
</tr>
<tr>
<td><strong>II or III colon cancer following surgery are considered investigational.</strong></td>
</tr>
</tbody>
</table>

**Note:** See Regulatory Status for commercial tests currently available.

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81525</td>
<td>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 (Oncotype DX® Colon Cancer Assay)</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
</tr>
<tr>
<td>88299</td>
<td>Unlisted cytogenetic study</td>
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</tbody>
</table>

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**Related Information**

**Genetic Counseling**

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing.
Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**Benefit Application**

Assays of genetic expression in tumor tissue are complex test procedures. Each specific test will likely be available at one or a limited number of reference laboratories.

**Evidence Review**

**Description**

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

**Background**

Of patients with stage II colon cancer, 75% to 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 clinic and pathologic risk factors. Genomic tests are intended to facilitate identifying the stage II patients most likely to experience recurrence after surgery and most likely to benefit from additional treatment.

Colorectal cancer is classified as stage II (also called Dukes B) when it has spread outside the colon and/or rectum to nearby tissue but is not detectable in lymph nodes (stage III disease, also called Dukes C) and has not metastasized to distant sites (stage IV disease). Primary treatment is surgical resection of the primary cancer and colonic anastomosis. After surgery, the prognosis is typically good, with survival rates of 75% to 80% at five years.\(^1\) A 2008 meta-analysis of 50 studies of adjuvant therapy versus surgery alone in stage II patients found statistically significant, though small, absolute benefit of chemotherapy for disease-free survival (DFS) but not for overall survival.\(^1\) Therefore, adjuvant chemotherapy with 5-fluorouracil or capecitabine is recommended only for resected patients with high-risk stage II disease (ie, those with poor prognostic features).\(^2\)
However, clinical and pathologic 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 diagnostic system relies on a variety of factors, including tumor substages 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, an inadequately low number of sampled lymph nodes at surgery (≤12), histologic features of aggressiveness, a high preoperative carcinoembryonic antigen level, and indeterminate or positive resection margins. Of interest, a 2010 review has noted that microsatellite instability (MSI) and mismatch repair (MMR) deficiency in colon cancer may represent confounding factors to be considered in treatment. These factors may identify a minority (15%-20%) of the population with improved disease-free survival who may derive no benefit or may exhibit deleterious effects from adjuvant 5-fluorouracil plus leucovorin-based treatments. Patient MSI and MMR status may be critically important in how to study, interpret, and use a particular GEP test.

**Summary of Evidence**

For individuals who have stage II or III colon cancer who receive gene expression profiling (GEP) testing, the evidence includes development and validation studies and decision-impact studies. Relevant outcomes are disease-specific survival, test accuracy and validity, and change in disease status. The available evidence has shown that GEP tests for colon cancer can improve risk prediction, particularly the risk of recurrence in patients with stage II or III colon cancer. However, the degree of difference in the risk conferred by the test is small. Evidence to date is insufficient to permit conclusions on whether GEP classification is sufficient to modify treatment decisions in stage II or III 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.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.
Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00903565a</td>
<td>A Prospective Study for the Assessment of Recurrence Risk in Stage II Colon Cancer Patients Using ColoPrint (PARSC)²⁰</td>
<td>1200</td>
<td>Dec 2017</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

² Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

Current clinical practice guidelines from the National Comprehensive Cancer Network (v.2.2017) on colon cancer state that “there is insufficient data to recommend the use of multigene assays to determine adjuvant therapy” in patients with stage II or III colon cancer.²

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.

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 Laboratory Improvement Amendments (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 this test.

Gene expression profiling tests for colon cancer currently commercially available include:

- ColoPrint® 18-Gene Colon Cancer Recurrence Assay (Agendia)
- GeneFx™ Colon (Helomics Therapeutics; also known as ColDx, Almac Diagnostics)
- OncoDefender-CRC™ (Everist Genomics)
Oncotype DX® Colon Recurrence Score (Genomic Health)

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/14/10</td>
<td>Add to Pathology/Laboratory Section - New Policy</td>
</tr>
<tr>
<td>06/13/11</td>
<td>Replace Policy - Policy updated with literature search. References 3, 4, and 7 added; reference 2 updated. No change to policy statements. ICD-10 codes added to policy.</td>
</tr>
<tr>
<td>11/10/11</td>
<td>Replace Policy – New literature identified; rationale revised; references 4 and 5 added; no change to policy statement.</td>
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<tr>
<td>05/24/12</td>
<td>Policy renumbered to 12.04.61 (previously 2.04.61) and reassigned to new Genetic Testing category.</td>
</tr>
<tr>
<td>10/26/12</td>
<td>Replace Policy. Description and rationale sections revised based on a literature review through June 2012. References 5-16 added. Other references renumbered or removed. ICD-10 codes are now effective 10/01/2014. Policy statement unchanged.</td>
</tr>
<tr>
<td>01/11/13</td>
<td>Effective 1/1/13, CPT codes 81200 – 81479 will be used for lab testing; these replace codes 83891 – 83912 which are deleted effective 12/31/12.</td>
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<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
</tr>
<tr>
<td>10/14/13</td>
<td>Replace policy. Policy updated with literature review through July 16, 2013; references 3, 17-19, and 22 added; reference 2 updated. No change to policy statement. CPT code range 81200 – 81479 removed; code 81479 retained on policy.</td>
</tr>
<tr>
<td>11/20/14</td>
<td>Annual Review. Policy updated with literature review through July 9, 2014; references 18-19, 24-26, and 28 added; references 2, 21, and 27 updated.</td>
</tr>
<tr>
<td>10/13/15</td>
<td>Annual Review. Policy updated with literature review through June 30, 2015; references 3, 23, and 28-31 added. Stage 3 colon cancer added to investigational policy statement.</td>
</tr>
<tr>
<td>01/19/16</td>
<td>Coding update. New CPT code 81525, effective 1/1/16, added to policy.</td>
</tr>
<tr>
<td>07/07/17</td>
<td>Policy moved into new format; no changes to policy statement.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and
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  - Qualified interpreters
  - Information written in other languages

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building

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Daytay a Pakdaa ket naglaon iti Napateg nga Impormasion. Daytay a pakdaa mabalini nga adda ket naglaon iti napateg nga impormasion maipanggep iti aplikasyon wenyen coverage babaen iti Premera Blue Cross. Daytay ket mabalini dagiti importante a peeta iti daytay a pakdaar. Mabalini nga adda rumbeng nga aramidenyo nga addang sakkay dagiti partikular a naituding nga aldaw tapno mapagtalinedyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytay nga impormasion ken tulong ti bukodyo a pagasao nga awan ti bayadayo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

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