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

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 have been developed 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 genetic tests are considered investigational (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
**Type of Test** | **Investigational**
---|---
Gene expression assay testing | Gene expression assays for determining the prognosis of stage II or III colon cancer following surgery are considered investigational.

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**

**Genetics Nomenclature Update**

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table 1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.
The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

### Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td></td>
<td>Change in the DNA sequence</td>
</tr>
<tr>
<td>Familial variant</td>
<td></td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
</tr>
</tbody>
</table>

### Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

### Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic
counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, 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**

*Colon Cancer*

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.\(^1\) Five-year survival estimates are around 65%.

**Treatment**

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 clinical and pathologic risk factors. Genomic tests are intended to facilitate identifying 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. A Cochrane review by Figueredo et al (2008), assessing 50 studies of adjuvant therapy versus surgery alone in stage II patients, found a small though statistically significant absolute benefit of chemotherapy for disease-free survival but not for overall survival. 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).

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 subtype stage 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 review by Vilar and Gruber (2010) has noted that microsatellite instability and mismatch repair 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 microsatellite instability and mismatch repair status may be critically important in how to study, interpret, and use a particular gene expression profile test.

**Summary of Evidence**

For individuals who have stage II or III colon cancer who receive 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 testing 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 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td><strong>Ongoing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00903565(^a)</td>
<td>A Prospective Study for the Assessment of Recurrence Risk in Stage II Colon Cancer Patients Using ColoPrint (PARSO)(^6)</td>
<td>1200</td>
<td>Dec 2019</td>
</tr>
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</table>

NCT: national clinical trial.
\(^a\) Denotes industry-sponsored or cosponsored trial.

Practice Guidelines and Position Statements

Current clinical practice guidelines from the National Comprehensive Cancer Network (v.2.2018) 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.\(^3\)

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, 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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Multigene expression assay testing for predicting
recurrent colon cancer is available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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


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**History**

<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>
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<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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<td>05/24/12</td>
<td>Policy renumbered to 12.04.61 (previously 2.04.61) and reassigned to new Genetic</td>
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<td>Date</td>
<td>Comments</td>
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<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>
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<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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<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
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<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>
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<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>
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<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>
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<tr>
<td>01/19/16</td>
<td>Coding update. New CPT code 81525, effective 1/1/16, added to policy.</td>
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<tr>
<td>07/07/17</td>
<td>Policy moved into new format; no changes to policy statement.</td>
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U.S. Department of Health and Human Services
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