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 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

**Investigational**

**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>
</tr>
</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 clinical 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. 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. 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 substage 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.²

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.³ These factors may identify a minority (15%-20%) of the population with improved DFS 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.

a 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>
</tr>
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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 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 S09F, HHH Building
  Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
  Complaint forms are available at

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Arabic (Arabic):
يَبْْيُحُي هَذَا الْإِجْتِزَارَ مَعْوَلَاتٍ هَامَّةٍ. فَي بِحْيَ هَذَا الْإِجْتِزَارَ مَعْوَلَاتٍ مَهِمَّةٍ بِصَوْصٍ طَلِيقٍ أَو
المعطاة التي تزيد الحصول عليها من خلال Premera Blue Cross مثلاً ذلك في هذه المعاملة. يُحَلُّ تَأْخِذ إِجْتِزَارٍ إِفْتَرَةٍ هَاُلَعَالِيَةٍ عَلَى تَعْوَيْضَةِ الْمَعْوَلَةِ الْمَحْدُودَةِ وَالتَّلْفِيطِ، وَيَتَّخِذُ هَذَا الْإِجْتِزَارُ مَعْوَلَةً مَهِيمَةً بِصَوْصٍ طَلِيقٍ. يُحَلُّ تَأْخِذ إِجْتِزَارٍ إِفْتَرَةٍ هَاُلَعَالِيَةٍ عَلَى تَعْوَيْضَةِ الْمَعْوَلَةِ الْمَحْدُودَةِ وَالتَّلْفِيطِ، وَيَتَّخِذُ هَذَا الْإِجْتِزَارُ مَعْوَلَةً مَهِيمَةً بِصَوْصٍ طَلِيقٍ.

中文 (Chinese): 本通知有重要的信息。本通知可能有关于您通过 Premera Blue Cross 提交的申请或保险的重要信息。本通知内可能有重要日期。您可能需要在截止日期之前采取行动，以保留您的健康保险或者费用补贴。您有权利免费以您的母语得到本通知和帮助。请拨电话 800-722-1471 (TTY: 800-842-5357).


Français (French):

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Empòtan ladan. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lwa osna konsènan kouvéti asirans lan atravé Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kék aksyon avan sèten dat limit pou ka kònti kouvéti asirans sante w lwa osna pou yo ka ede w avèk demans yo. Se dwa w pou resewa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmong (Hmong):

Ilokano (Ilocano):
Daytoy a Pakdaa ket naglao iti Napetage nga Impormasion. Daytoy a pakdaa mabalin nga adda ket naglao iti napetage nga impormasion maipanggep iti aplikasyoneno weny coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a pelsa iti daytoy a pakdaa. Mabalin nga adda rumbeng nga aramidedo nga addang sakbay dagiti partikular a naluding nga adda aldaw tapno mapagtalinayeyo tig coverage tig salun-atyo weny tulong kadagit gastos. Adda karbengayo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagasaa nga awan ti bayadangyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

037338 (07-2016)
Premera Blue Cross.

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