This Protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

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<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
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<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
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<td>With stage 2 or stage 3 colon cancer</td>
<td>• Gene expression profiling tests</td>
<td>• Risk prediction based on clinicopathologic factors</td>
<td>• Disease-specific survival</td>
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<td>• Test validity</td>
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<td>• Change in disease status</td>
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Description
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.

Summary of Evidence
The evidence for the use of gene expression profiling (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.

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

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.

Medicare Advantage

The Oncotype DX® colon cancer test may be considered medically necessary when used to determine prognosis and determine the treatment plan.

Background

Of patients with stage 2 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 be used as an aid for identifying stage 2 patients most likely to experience recurrence after surgery and most likely to benefit from additional treatment.

Colorectal cancer is classified as stage 2 (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 3 disease, also called Dukes C) and has not metastasized to distant sites (stage 4 disease). Primary treatment is surgical resection of the primary cancer and colonic anastomosis. After surgery prognosis is 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 2 patients found statistically significant, although 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 as an option for resected patients with high-risk stage 2 disease (i.e., 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 system relies on a variety of factors, including tumor substage 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, 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.

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 (e.g., stage 3A) whose predicted survival may actually exceed that of some stage 2 patients (e.g., stage 2C).

Of interest, a recent 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 small proportion (15%-20%) of the population with improved DFS who may derive no benefit or may exhibit
deleterious effects from adjuvant fluorouracil/leucovorin-based treatments. Patient MSI and MMR status 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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

**References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.


35. Noridian Healthcare Solutions, LLC, (Jurisdiction - California - Entire State, American Samoa, Guam, Hawaii, Northern Mariana Islands, Nevada) Local Coverage Determination (LCD): MolDX: Molecular Diagnostic Tests (MDT) (L35160), Revision Effective Date for services performed on or after 10/01/2015.