Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer

Description

Gene expression profile (GEP) and circulating tumor DNA (ctDNA) tests have been developed for use as prognostic markers of 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.

OBJECTIVE

The objective of this evidence review is to determine whether gene expression profile testing improves the net health outcome in individuals with stage II or III colon cancer who are being considered for adjuvant chemotherapy.

POLICY STATEMENT

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

Circulating tumor DNA assays for determining the prognosis of stage II or III colon cancer following surgery are considered investigational.

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**Policy Guidelines**

**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 PG1). 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 PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<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>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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</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.

**Benefit Application**

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

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FDA 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 and circulating tumor DNA (ctDNA) 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 profile and ctDNA 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 (Evenst Genomics)
- Oncotype DX Colon Recurrence Score (Genomic Health)
- Signatera ctDNA test (Natera)

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

RATIONALE

Summary of Evidence

For individuals who have stage II or III colon cancer who receive gene expression profile (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 risk conferred by the test is small. Evidence to date does not 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 have not demonstrated whether such changes improve outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have stage II or III colon cancer who receive circulating tumor DNA (ctDNA) testing, the evidence includes cohort studies. Relevant outcomes are disease-specific survival, test accuracy and validity, and change in disease status. Two cohort studies reported an association between positive ctDNA results and risk of recurrence of colon cancer. In one study, the recurrence rate among patients with positive ctDNA levels was 77% (10 of 13 patients); no patients with negative ctDNA experienced a relapse over a median follow-up of 49 months (range 11-70 months). In the other, the recurrence rate at 3 years was 70% in patients with a positive ctDNA test compared to 11.9% of those with a negative ctDNA test. While these studies showed an association between ctDNA results and risk of recurrence, they are limited by their observational design and relatively small numbers of patients with positive results. Management decisions were not based on ctDNA test results. There are no controlled studies of management changes made in response to ctDNA test results compared to other risk factors, and no studies showing whether testing improved outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

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SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Current clinical practice guidelines from the National Comprehensive Cancer Network (v.4.2020) 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.¹

The guidelines do not comment on circulating tumor DNA testing to guide decision about adjuvant chemotherapy, but state, "Research into additional possible predictive markers may allow for more informed decision-making in the future."

U.S. Preventive Services Task Force Recommendations

Not applicable

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.

REFERENCES


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<thead>
<tr>
<th>Date</th>
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<th>Description</th>
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<tr>
<td>December 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review; reference 31 added. Policy statement unchanged.</td>
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<tr>
<td>December 2017</td>
<td>Replace policy</td>
<td>Policy updated with literature review through June 22, 2017; references 20, 23, and 31 added; reference 2 updated. Policy statement unchanged.</td>
</tr>
<tr>
<td>December 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through June 7, 2018; reference 1 added; reference 3 updated. Policy statements unchanged.</td>
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<td>December 2019</td>
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<td>Policy updated with literature review through June 13, 2019; references added. Policy statement unchanged.</td>
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<tr>
<td>December 2020</td>
<td>Replace policy</td>
<td>Policy updated with literature review through July 8, 2020; references added. Added new intervention and policy statement: Circulating tumor DNA testing is considered investigational. Policy title changed to &quot;Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer.&quot;</td>
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