Multigene Expression Assay for Predicting Colon Cancer Recurrence

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I. Policy Description

Colorectal cancer (CRC) involves the accumulation of genetic and epigenetic modifications within pathways that regulate proliferation, apoptosis, and angiogenesis resulting in carcinoma of the colon and rectum. Tumors originate in adenomas or flat dysplasia and evolve into different morphologic patterns with invasion and expansion.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

1) Gene expression assays for determining the prognosis of stage II colon cancer following surgery **DOES NOT MEET COVERAGE CRITERIA**

III. Table of Terminology

Term	Definition
CEA	Carcinoembryonic antigen
CLIA'88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid
CRC	Colorectal cancer
ctDNA	Circulating tumor deoxyribonucleic acid
DFS	Disease free survival
ESCP	European Society of Coloproctology
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
mCRC	Metastatic colorectal cancer
MMR	Mismatch repair
MMR-P	Mismatch repair proficient
NCCN	National Comprehensive Cancer Network

NSABP	National Surgical Adjuvant Breast and Bowel Project
OS	Overall survival
RS	Recurrence score

IV. Scientific Background

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the United States following lung cancer. 22% of patients with colorectal cancer will present with metastatic colorectal cancer (mCRC) at diagnosis and a significantly poorer prognosis. The five-year survival is 14% in patients with distant metastases from CRC, as compared to 71% for all CRC patients.

Approximately one-quarter of the patients with colon cancer present with stage II disease. The current National Comprehensive Cancer Network (NCCN) guidelines include adjuvant chemotherapy as a treatment option in this setting, particularly for high-risk stage II patients, as determined by clinical and pathological parameters. Although some of the routinely used parameters for estimating recurrence risk, such as T-stage and mismatch repair (MMR) status, are well established, they may not be reliable predictors of recurrence risk in this population.

Proprietary Testing

Gene expression assays have been commercially produced to predict prognosis of colon cancer. The 12-gene Oncotype DX Colon Cancer Assay (Genomic Health, Inc., Redwood City, CA) is a reverse transcriptase polymerase chain reaction–based assay that provides a Recurrence Score (RS) result. This test assesses the activity level of 12 genes (7 cancer-related genes, 5 reference genes), and this gene expression is scored from 1-100. This test is intended for resected stage II, MMR-P or stage III A/B colon cancer. Low risk is a score under 30, moderate risk is 31-40, and higher risk is ≥41.

The ColDx assay (Almac Diagnostics, Craigavon, Northern Ireland) uses microarray technology for assessing the gene expression of 634 genes to stratify patients into low and high recurrence risk groups. ColDx identified 73 high risk patients with a hazard ratio of 2.62 during cross validation. In an independent validation, the assay identified high-risk patients with a hazard ratio of 2.53.

ColoPrint (Agendia, Amsterdam, The Netherlands) is a gene expression classifier that uses whole-genome expression data of 18 key genes to distinguish patients with low versus high risk of disease relapse. In a study using 206 fresh frozen tumor tissue samples from 188 patients with stage I through IV CRC, ColoPrint classified “60% of patients as low risk and 40% as high risk,” and was “superior to American Society of Clinical Oncology criteria in assessing the risk of cancer recurrence without prescreening for microsatellite instability.” In a study of 416 stage II colon cancer patients, “ColoPrint identified 63% of patients as low risk with a 5-year ROR of 10%, whereas high-risk patients (37%) had a 5-year ROR of 21%.” Alternatively, the 2013 NCCN clinical risk factors could not distinguish low and high-risk patients.

Clinical Utility and Validity

Several studies have evaluated the impact of the gene expression profiling on clinical decision making in certain colon cancer subgroups. Brenner et al (Brenner et al., 2016) assessed the clinical impact of the 12-gene Colon Cancer Recurrence Score Assay in treatment of T3 mismatch repair proficient (MMR-P) stage II colon cancer. Out of 269 patients, 102 patients had their treatment changed because of the

assay's results. The authors concluded that testing significantly impacted adjuvant treatment decisions in clinical practice.

Cartwright et al. (2014) performed a web-based survey evaluating the impact of the 12-gene Colon Cancer Recurrence Score Assay in stage II colon cancer patients. 346 oncologists were surveyed about their use of the Oncotype DX assay including questions about courses of treatment before and after using the assay and the stage of cancer their patient had. The authors found that 29% of treatment recommendations were changed for patients receiving Recurrence Score testing. Srivastava et al. (2014) conducted a prospective study assessing the impact of recurrence score results on physician recommendations regarding adjuvant chemotherapy in T3 MMR-P stage II colon cancer patients. 141 patients were eligible for analysis, and the study concluded that treatment recommendation changes were made for 63 (45%) of patients.

Chang et al. (2020) reviewed the "entire database" of the OncoType Colon Recurrence Score test to identify any age-related differences in Recurrence Score (RS) and single-gene results. 20478 Stage II and IIIA/B colon cancer patients were included. RS results were categorized into low, medium, and high risk, and single-gene results were organized by median and interquartile ranges. 72.5% of all patients and 72.6% of patients under 40 years old were found to have a low-risk RS. However, there were no significant differences in either RS or single-gene results among the four age groups (<40, 40-54, 55-64, >65). Young-onset cancer was also not found to differ by gene expression in individual RS genes. Overall, most patients in stages II or III colon cancer were found to have low-risk disease per the OncoType assay.

Allar et al. (2022) evaluated how the OncoType Colon Recurrence Score influences clinical practice. The study included 105 patients with stage IIa colon cancer and investigated the association between the RS and the decision to offer adjuvant chemotherapy after resection. 52 patients underwent RS testing, seven (13%) of whom received adjuvant chemotherapy. The authors found no significant effect or clear association of RS on the odds of undergoing chemotherapy. The authors conclude that "RS was not associated with the decision to start adjuvant chemotherapy" and suggest that "the RS should not be obtained in patients with stage IIa colon cancer."

V. Guidelines and Recommendations

National Comprehensive Cancer Network (NCCN)

Regarding the OncoType DX colon cancer assay, the NCCN remarks that clinical validation in patients with stages II or III cancer from the QUASAR and NSABP clinical trials shows that "the recurrence scores are prognostic for recurrence, DFS [disease free survival], and OS [overall survival] in stage II and stage III colon cancer but are not predictive of benefit to adjuvant therapy". ColoPrint, an 18-gene classifier for recurrence risk, was also found to independently predict recurrence risk and is currently being validated to predict 3-year relapse rates in patients with stage II colon cancer in a prospective trial. Similarly, ColDx, a microarray based multigene assay, was found to independently predict recurrence risk. However, despite these tests' ability to further inform risk of recurrence, the panel questions the value added. The panel also noted that "evidence of predictive value in terms of the potential benefit of chemotherapy is lacking" and that "there are insufficient data to recommend the use of multi-gene assays, Immunoscore, or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy."

American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and American Society of Clinical Oncology Joint Guidelines

The joint guidelines state that further research is required to study the clinical validity and utility of gene expression profiling assays in colon cancer patients.

European Society for Medical Oncology (EMSO)

ESMO notes that "…pathological staging and gene expression signatures have failed to accurately predict disease recurrence and prognosis [of CRC]."

Research Committee and the Guidelines Committee of the European Society of Coloproctology (ESCP)

This systematic review was performed by the committee to assess the consensus levels "in guidelines from member countries of the European Society of Coloproctology, with supporting evidence". This review focuses on follow-up strategies for patients "after treatment with curative intent of nonmetastatic colorectal cancer."

In this review, the committee concluded that "laboratory tests other than CEA [carcinoembryonic antigen] should not be part of follow-up", although it noted that only 8 of 21 guidelines reviewed addressed this topic.

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), or for QUEST Integration members under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VIII. Evidence-based Scientific References

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IX. Policy History

Policy approved by Medical Directors	9/20/2022
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