MEDICAL POLICY

POLICY TITLE	GENE EXPRESSION PROFILE TESTING AND CIRCULATING TUMOR DNA TESTING FOR PREDICTING RECURRENCE IN COLON CANCER
POLICY NUMBER	MP 2.315

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**3/1/2024**

I. POLICY

Gene expression assays for determining the prognosis of stage II or stage III colon cancer following surgery are considered **investigational.** There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Circulating tumor DNA assays for determining the prognosis of stage II or III colon cancer following surgery are considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

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

Previous	Updated	Definition
Mutation	Diseased-Associated Variant	Disease-associated change in the DNA sequence.
	Variant	Change in DNA sequence
	Familial Variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives.

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely Pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

Cross-reference:

MP 2.267 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
MP 2.316 KRAS, NRAS, and BRAF Variant Analysis (Including Liquid Biopsy) in Metastatic Colorectal Cancer
MP 2.326 General Approach to Genetic Testing
MP 5.013 Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

II. PRODUCT VARIATIONS

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FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

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III. DESCRIPTION/BACKGROUND

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Colon Cancer

According to estimates by the National Cancer Institute, in 2020 over 147,000 new cases of colorectal cancer will be diagnosed in the U. S., and over 53,000 people will die of this cancer. Five-year survival estimates are around 65%.

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 primary cancer and colonic anastomosis. After surgery, the prognosis is good, with survival rates of 75% to 80% at 5 years. A Cochrane review by Figueredo et al (2008), assessing 50 studies of adjuvant therapy vs 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, the 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.

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.

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:

- GeneFx Colon (Helomics Therapeutics; also known as ColDx, Almac Diagnostics)
- Oncotype DX Colon Recurrence Score (Genomic Health)
- Colvera ctDNA test (Clinical Genomics)

IV. RATIONALE

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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 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 followup 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.

V. DEFINITIONS

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ADENOMA is a benign tumor made of epithelial cells, usually arranged like a gland.

ADENOCARCINOMA is a malignant tumor arising from a glandular organ.

FAMILIAL ADENOMATOUS POLYPOSIS is an inherited disorder characterized by the development of myriad polyps in the colon beginning in late adolescence or early adulthood. Untreated, the condition leads to colon cancer.

LYNCH SYNDROME is a hereditary predisposition to nonpolyposis colorectal cancer and other solid tumors.

METACHRONOUS means not synchronous; multiple separate occurrences, such as multiple primary cancers developing at intervals.

MUTATION refers to an unusual change in genetic material occurring spontaneously or by induction.

NONINVASIVE refers to a device or procedure that does not penetrate the skin or enter any orifice in the body.

OSTEOMA refers to a benign bony tumor.

PHENOTYPE is the expression of genes present in an individual. This may be directly observable (e.g., eye color) or apparent only with specific tests (e.g. blood type).

POLYPOSIS refers to the presence of numerous polyps.

SYNCHRONOUS refers to occurring at the same time.

SCREENING refers to evaluating a patient for diseases such as cancer, heart disease, or substance abuse before they become clinically obvious**.**

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or

Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

Procedure Codes								
81525	84999	88299	0229U	0261U	0421U			

IX. REFERENCES

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X. POLICY HISTORY

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MP 5.013	**3/31/2020:** Consensus Review. No change to policy statement. References reviewed and updated. Codes reviewed with no changes.
	3/3/2021: Minor review. To align with BCBSA's policy, the title of the policy was changed to "Gene Expression Profile Testing and Circulating Tumor DNA testing for Predicting Recurrence in Colon Cancer". Added a new INV statement: Circulating tumor DNA assays for determining the prognosis of stage II or III colon cancer following surgery are considered investigational. Updated Policy Guidelines, Cross-references, Description/Background, Rationale, and References. No changes to coding. Added NCCN statement.
	9/2/2021: Administrative review. Addition of new code 0261U to INV coding table. Effective date 10/1/2021.
	12/14/2022: Consensus review. No change to policy statement. References, Cross-References, Background reviewed and updated. Code 0229U added.
	8/14/2023 Consensus review. No change to policy statement. References reviewed and updated. Coding reviewed.
	12/13/2023 Administrative review. Addition of new code 0421U
	1/19/2024 Administrative update. Clinical benefit added.