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:	RETIRED 7/1/2026

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.

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	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the 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
Variant Classification	Definition

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

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.

Cross-References:

MP 2.267 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
MP 2.316 Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment of Metastatic Colorectal Cancer (KRAS, NRAS, BRAF and HER2)
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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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

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.

III. DESCRIPTION/BACKGROUND

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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.

Colon Cancer

According to estimates by the National Cancer Institute, in 2024 over 152,000 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%. Disparities in colorectal cancer outcomes have been identified in different subgroup classifications based on race and ethnicity, age, socioeconomic status, insurance access, geography, and environmental exposures. For example, in the U.S. between 2012-2016, mortality rates were highest among non-Hispanic Black patients (incidence rate of 45.7 per 100,000), which were 20% and 50% higher than rates among non-Hispanic White and Asian patients, respectively. Additionally, non-Hispanic Black patients may have limited opportunities for therapeutic interventions due to experiencing higher inequities in comorbidities.

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 (5-FU), capecitabine, iCAPEOX (capecitabine and oxaliplatin), or FOLFOX (5-FU and oxaliplatin) is recommended only for resected patients with high-risk stage II disease (i.e., 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 the surface of the visceral peritoneum) 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, and indeterminate or positive resection margins. Gene expression profiling (GEP) and circulating tumor DNA (ctDNA) tests are intended to facilitate identifying stage II patients most likely to experience recurrence after surgery and most likely to benefit from additional treatment.

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 GEP 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 (CLIA). 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 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 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 that the technology results in an improvement in the net health outcome.

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. Several cohort studies have reported an association between positive ctDNA results and risk of recurrence of colon cancer. However, 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. Management decisions were not based on ctDNA test results. One randomized trial studied management changes made in response to ctDNA test results compared to other risk factors, but progression-free survival was similar between groups. The evidence is insufficient to determine that the technology results in an improvement in the net 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.

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

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical

advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. 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	0229U							

VIII. REFERENCES

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IX. POLICY HISTORY

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MP 2.315	**03/31/2020 Consensus Review.** No change to policy statement. References reviewed and updated. Codes reviewed with no changes.
	03/03/2021 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.
	09/02/2021 Administrative Update. Addition of new code 0261U to INV coding table. Effective date 10/01/2021.
	12/14/2022 Consensus Review. No change to policy statement. References, Cross-References, Background reviewed and updated. Code 0229U added.
	08/14/2023 Consensus Review. No change to policy statement. References reviewed and updated. Coding reviewed.
	12/13/2023 Administrative Update. Addition of new code 0421U
	01/19/2024 Administrative Update. Clinical benefit added.
	10/07/2024 Consensus Review. No change to policy statement. Policy Guidelines, Cross-referenced policies, Background, Rationale and Definitions updated. References added. Removed CPT code 0421U.
	12/16/2024 Administrative Update. Removed NCCN Statement.
	08/05/2025 Consensus Review. No change to policy statement. Removed CPT codes 0261U, 84999 & 88299. Removed Benefit Variations Section and updated Disclaimer.
	03/09/2026 Retirement Review. EviCore Delegation.

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