



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

Policy # 00257

Original Effective Date: 04/13/2010

Current Effective Date: 10/09/2023

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### When Services May Be Eligible for Coverage

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider use of the Oncotype DX<sup>®‡</sup> Colon Cancer Assay of tumor tissue for an individual with stage II colon cancer being evaluated for adjuvant chemotherapy to be **eligible for coverage\*\***.

#### Patient Selection Criteria

Coverage eligibility may be considered for the use of the Oncotype DX<sup>®‡</sup> Colon Cancer Assay of tumor tissue for an individual with stage II colon cancer being evaluated for adjuvant chemotherapy when **ALL** the following criteria are met:

- For an adult individual with stage II colon cancer who have undergone surgical resection and the test will be used to guide decision about use of adjuvant chemotherapy; **AND**
- Requested test was not done before; **AND**
- The test is not used in conjunction or in addition to other prognostic genetic tests of tumor specimen or circulating tumor DNA (ct-DNA), i.e. Signatera<sup>™‡</sup> ctDNA test.

### When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers all other gene expression assays (e.g., GeneFx Colon, ColoPrint, ColDx) and other uses of Oncotype DX<sup>®‡</sup> Colon Cancer Assay for

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determining the prognosis of stage II or stage III colon cancer following surgery to be **investigational**.\*

Based on review of available data, the Company considers circulating tumor DNA assays (e.g., Colvera Assay) for determining the prognosis of stage II or III colon cancer following surgery to be **investigational**.\*

## **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**

<b>Previous</b>	<b>Updated</b>	<b>Definition</b>
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

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**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

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

## **Background/Overview**

### ***Colon Cancer***

According to estimates by the National Cancer Institute, in 2022 over 151,000 new cases of colorectal cancer will be diagnosed in the U.S., and nearly 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 amongst non-Hispanic Black patients (incidence rate of 45.7 per 100,000), which were 20% and 50% higher than rates amongst 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.

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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 the 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 versus 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, CAPEOX (capecitabine and oxaliplatin), or FOLFOX (5-FU and oxaliplatin) 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 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 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% to 20%) of the population with improved disease-free survival who may derive no benefit or may exhibit deleterious effects from adjuvant 5-FU 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.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

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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 ctDNA testing for predicting recurrent colon cancer is available under the auspices of CLIA. 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<sup>®†</sup> Colon (Helomics Therapeutics; also known as ColDx, Almac Diagnostics)
- Oncotype DX<sup>®†</sup> Colon Recurrence Score (Genomic Health)
- Colvera<sup>®†</sup> ctDNA test (Clinical Genomics)

### **Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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.

### **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

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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 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 the 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. 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 that the technology results in an improvement in the net health outcome.

### **Supplemental Information**

#### **Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### ***National Comprehensive Cancer Network***

Current clinical practice guidelines from the National Comprehensive Cancer Network (v. 2.2023) on colon cancer state that "there are insufficient data to recommend the use of multigene assays...or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy" in patients with stage II or III colon cancer.

"In summary, the information from these tests can further inform the risk of recurrence over other risk factors, but the panel questions the value added. Furthermore, evidence of predictive value in terms of the potential benefit of chemotherapy is lacking. Therefore, the panel believes

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that there are insufficient data to recommend the use of multigene assays, Immunoscore, or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy. ESMO has released similar recommendations regarding these assays, stating that their role in predicting chemotherapy benefit is uncertain. The NCCN Panel encourages enrollment in clinical trials to help with the generation of additional data on these assays.”

### 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.

### Ongoing and Unpublished Clinical Trials

Some ongoing trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT04264702 <sup>a</sup>	BESPOKE Study of ctDNA Guided Therapy in Colorectal Cancer	1,000	Jun 2024
NCT04068103	Circulating Tumor DNA Testing in Predicting Treatment for Patients With Stage IIA Colon Cancer After Surgery	1,408	Jul 2024
NCT04120701	Circulating Tumor DNA Based Decision for Adjuvant Treatment in Colon Cancer Stage II	1,980	Jan 2028

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

## References

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### **Policy History**

Original Effective Date: 04/13/2010

Current Effective Date: 10/09/2023

04/08/2010	Medical Policy Committee approval
04/21/2010	Medical Policy Implementation Committee approval. New policy.
04/07/2011	Medical Policy Committee approval
04/13/2011	Medical Policy Implementation Committee approval. No change to coverage.
04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013	Coding revised.
04/04/2013	Medical Policy Committee review
04/24/2013	Medical Policy Implementation Committee approval. Changed investigational statement to include all gene expression assays, instead of only Oncotype Dx.
03/06/2014	Medical Policy Committee review
03/19/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/05/2015	Medical Policy Committee review
03/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
03/03/2016	Medical Policy Committee review
03/16/2016	Medical Policy Implementation Committee approval. Added stage 3 to existing INV statement.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes

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03/02/2017	Medical Policy Committee review
03/15/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/01/2018	Medical Policy Committee review
03/21/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/07/2019	Medical Policy Committee review
03/20/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/05/2020	Medical Policy Committee review
03/11/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/05/2020	Medical Policy Committee review
11/11/2020	Medical Policy Implementation Committee approval. Title changed from “Multigene Expression Assays for Predicting Recurrence in Colon Cancer” to “Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer”. Added an investigational statement for circulating tumor DNA assays for determining the prognosis of stage II or III colon cancer following surgery.
11/04/2021	Medical Policy Committee review
11/10/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/01/2022	Medical Policy Committee review
09/07/2022	Medical Policy Implementation Committee approval. Added a “When Services May Be Eligible for Coverage” section with Patient Selection Criteria for use of the Oncotype DX <sup>®‡</sup> Colon Cancer Assay. Included “all other gene expression assays (e.g. GeneFx Colon) and other uses of Oncotype DX <sup>®‡</sup> Colon Cancer Assay” to the investigational statement for determining the prognosis of stage II or stage III colon cancer following surgery. Added “(e.g., Colvera Assay)” to the investigational statement for circulating tumor DNA assays for determining the prognosis of stage II or III colon cancer following surgery.
09/07/2023	Medical Policy Committee review

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09/13/2023 Medical Policy Implementation Committee approval. Added ColoPrint and ColDx as examples other gene expression assays in the investigational statement. Added a citation from NCCN in the Supplemental Information section. Updated the version of the NCCN reference.

Next Scheduled Review Date: 09/2024

### **Coding**

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)®, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0229U, 81525 Add codes effective 10/01/2023: 81479, 81599, 84999
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

**\*Investigational** – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  1. Consultation with technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

**\*\*Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;

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

Policy # 00257

Original Effective Date: 04/13/2010

Current Effective Date: 10/09/2023

- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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**NOTICE:** Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

**NOTICE:** If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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