Medical Coverage Policy | Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer

EFFECTIVE DATE: 01|01|2024
POLICY LAST REVIEWED: 09|16|2026

OVERVIEW

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.

This policy addresses the following test(s):

- Oncotype DX® Colon (Genomic Health) CPT code 81525

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

The following gene expression profile (GEP) and circulating tumor DNA (ctDNA) test(s) for the prognostic markers of stage II or III colon cancer following surgery may be considered medically necessary for the following test(s):

- Oncotype DX® Colon (Genomic Health) CPT code 81525

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, **R.I.G.L. §27-19-81** described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable benefits/coverage

BACKGROUND

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 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.

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.

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:

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

CODING

Medicare Advantage Plans and Commercial Products
The following CPT code(s) are medically necessary for Medicare Advantage Plans and Commercial Products when filed with an ICD-10 Diagnosis Code(s)* listed below:

The following CPT code(s) can be used for Oncotype DX® Colon test:

81525 Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score

***ICD-10 Diagnosis Code(s)**
C18.0-C20
C21.1

RELATED POLICIES
Biomarker Testing Mandate

PUBLISHED
Provider Update, November 2026
Provider Update, December 2025
Provider Update, December 2024
Provider Update, November 2023

REFERENCES

1. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determination (LCD): MolDX: Molecular Diagnostic Tests (MDT) (L35160)
2. Centers for Medicare and Medicaid Services (CMS). Local Coverage Article: Billing and Coding: MolDX: Oncotype DX® Colon Cancer (A54484)
3. National Cancer Institute, Surveillance Epidemiology and End Results Program. Cancer Stat Facts: Colorectal Cancer. n.d.; https://seer.cancer.gov/statfacts/html/colorect.html. Accessed June 10, 2026.
4. Musselwhite LW, May FP, Salem ME, et al. Colorectal Cancer: In the Pursuit of Health Equity. Am Soc Clin Oncol Educ Book. Mar 2021; 41: 108-117. PMID 34010044
5. Figueredo A, Coombes ME, Mukherjee S. Adjuvant therapy for completely resected stage II colon cancer. Cochrane Database Syst Rev. Jul 16 2008; 2008(3): CD005390. PMID 18646127
6. Washington State Health Care Authority. Gene Expression Profile Testing of Cancer Tissue: Final Evidence Report. 2018. https://www.hca.wa.gov/assets/program/gene-expression-final-rpt-20180220_0.pdf. Accessed June 10, 2026.
7. Vilar E, Gruber SB. Microsatellite instability in colorectal cancer-the stable evidence. Nat Rev Clin Oncol. Mar 2010; 7(3): 153-62. PMID 20142816
8. Makhoul R, Alva S, Wilkins KB. Surveillance and Survivorship after Treatment for Colon Cancer. Clin Colon Rectal Surg. Dec 2015; 28(4): 262-70. PMID 26648797
9. Kennedy RD, Bylesjo M, Kerr P, et al. Development and independent validation of a prognostic assay for stage II colon cancer using formalin-fixed paraffin-embedded tissue. J Clin Oncol. Dec 10 2011; 29(35): 4620-6. PMID 22067406
10. Niedzwiecki D, Frankel WL, Venook AP, et al. Association Between Results of a Gene Expression Signature Assay and Recurrence-Free Interval in Patients With Stage II Colon Cancer in Cancer and Leukemia Group B 9581 (Alliance). J Clin Oncol. Sep 01 2016; 34(25): 3047-53. PMID 27432924
11. O'Connell MJ, Lavery I, Yothers G, et al. Relationship between tumor gene expression and recurrence in four independent studies of patients with stage II/III colon cancer treated with surgery alone or surgery plus adjuvant fluorouracil plus leucovorin. J Clin Oncol. Sep 01 2010; 28(25): 3937-44. PMID 20679606
12. Gray RG, Quirke P, Handley K, et al. Validation study of a quantitative multigene reverse transcriptase-polymerase chain reaction assay for assessment of recurrence risk in patients with stage II colon cancer. J Clin Oncol. Dec 10 2011; 29(35): 4611-9. PMID 22067390

13. Venook AP, Niedzwiecki D, Lopatin M, et al. Biologic determinants of tumor recurrence in stage II colon cancer: validation study of the 12-gene recurrence score in cancer and leukemia group B (CALGB) 9581. J Clin Oncol. May 10 2013; 31(14): 1775-81. PMID 23530100
14. Yothers G, O'Connell MJ, Lee M, et al. Validation of the 12-gene colon cancer recurrence score in NSABP C-07 as a predictor of recurrence in patients with stage II and III colon cancer treated with fluorouracil and leucovorin (FU/LV) and FU/LV plus oxaliplatin. J Clin Oncol. Dec 20 2013; 31(36): 4512-9. PMID 24220557
15. Reimers MS, Kuppen PJ, Lee M, et al. Validation of the 12-gene colon cancer recurrence score as a predictor of recurrence risk in stage II and III rectal cancer patients. J Natl Cancer Inst. Nov 2014; 106(11). PMID 25261968
16. Yamanaka T, Oki E, Yamazaki K, et al. 12-Gene Recurrence Score Assay Stratifies the Recurrence Risk in Stage II/III Colon Cancer With Surgery Alone: The SUNRISE Study. J Clin Oncol. Aug 20 2016; 34(24): 2906-13. PMID 27325854
17. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. Aug 30 2001; 345(9): 638-46. PMID 11547717
18. Black ER, Falzon L, Aronson N. Gene Expression Profiling for Predicting Outcomes in Stage II Colon Cancer (Technical Brief. No. 13). Rockville, MD: Agency for Healthcare Research and Quality; 2012.
19. Oki E, Watanabe J, Sato T, et al. Impact of the 12-gene recurrence score assay on deciding adjuvant chemotherapy for stage II and IIIA/B colon cancer: the SUNRISE-DI study. ESMO Open. Jun 2021; 6(3): 100146. PMID 33984677
20. Brenner B, Geva R, Rothney M, et al. Impact of the 12-Gene Colon Cancer Assay on Clinical Decision Making for Adjuvant Therapy in Stage II Colon Cancer Patients. Value Health. Jan 2016; 19(1): 82-7. PMID 26797240
21. Cartwright T, Chao C, Lee M, et al. Effect of the 12-gene colon cancer assay results on adjuvant treatment recommendations in patients with stage II colon cancer. Curr Med Res Opin. Feb 2014; 30(2): 321-8. PMID 24127781
22. Srivastava G, Renfro LA, Behrens RJ, et al. Prospective multicenter study of the impact of oncotype DX colon cancer assay results on treatment recommendations in stage II colon cancer patients. Oncologist. May 2014; 19(5): 492-7. PMID 24710310
23. National Comprehensive Cancer Network (NCCN). Colon Cancer (v.6.2026). https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1428/. Accessed June 10, 2026.
24. Aliyeva T, Siddiqui H, Natche J, et al. Prognostic Value of Circulating Tumor DNA for Recurrence Risk in Stage III Colorectal Cancer: A Systematic Review and Meta-Analysis. Clin Colorectal Cancer. Mar 2026; 25(1): 77-86. PMID 41266203
25. Young GP, Pedersen SK, Mansfield S, et al. A cross-sectional study comparing a blood test for methylated BCAT1 and IKZF1 tumor-derived DNA with CEA for detection of recurrent colorectal cancer. Cancer Med. Oct 2016; 5(10): 2763-2772. PMID 27726312
26. Murray DH, Symonds EL, Young GP, et al. Relationship between post-surgery detection of methylated circulating tumor DNA with risk of residual disease and recurrence-free survival. J Cancer Res Clin Oncol. Sep 2018; 144(9): 1741-1750. PMID 29992492
27. Symonds EL, Pedersen SK, Murray D, et al. Circulating epigenetic biomarkers for detection of recurrent colorectal cancer. Cancer. Apr 01 2020; 126(7): 1460-1469. PMID 31909823
28. Musher BL, Melson JE, Amato G, et al. Evaluation of Circulating Tumor DNA for Methylated BCAT1 and IKZF1 to Detect Recurrence of Stage II/Stage III Colorectal Cancer (CRC). Cancer Epidemiol Biomarkers Prev. Dec 2020; 29(12): 2702-2709. PMID 32958500
29. Tie J, Cohen JD, Lahouel K, et al. Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer. N Engl J Med. Jun 16 2022; 386(24): 2261-2272. PMID 35657320
30. Tie J, Wang Y, Loree JM, et al. Circulating tumor DNA-guided adjuvant therapy in locally advanced colon cancer: the randomized phase 2/3 DYNAMIC-III trial. Nat Med. Dec 2025; 31(12): 4291-4300. PMID 41115959
31. Baxter NN, Kennedy EB, Bergsland E, et al. Adjuvant Therapy for Stage II Colon Cancer: ASCO Guideline Update. J Clin Oncol. Mar 10 2022; 40(8): 892-910. PMID 34936379

32. Dasari A, Morris VK, Allegra CJ, et al. ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal-Anal Task Forces whitepaper. Nat Rev Clin Oncol. Dec 2020; 17(12): 757-770. PMID 32632268

CLICK THE ENVELOPE ICON BELOW TO SUBMIT COMMENTS

This medical policy is made available to you for informational purposes only. It is not a guarantee of payment or a substitute for your medical judgment in the treatment of your patients. Benefits and eligibility are determined by the member's subscriber agreement or member certificate and/or the employer agreement, and those documents will supersede the provisions of this medical policy. For information on member-specific benefits, call the provider call center. If you provide services to a member which are determined to not be medically necessary (or in some cases medically necessary services which are non-covered benefits), you may not charge the member for the services unless you have informed the member and they have agreed in writing in advance to continue with the treatment at their own expense. Please refer to your participation agreement(s) for the applicable provisions. This policy is current at the time of publication; however, medical practices, technology, and knowledge are constantly changing. BCBSRI reserves the right to review and revise this policy for any reason and at any time, with or without notice. Blue Cross & Blue Shield of Rhode Island is an independent licensee of the Blue Cross and Blue Shield Association.