BlueCross BlueShield Federal Employee Program.

# FEP Medical Policy Manual

## FEP 2.04.61 Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer

### Annual Effective Policy Date: January 1, 2024

### Original Policy Date: December 2011

### Related Policies:

2.04.53 - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, and HER2)

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

### Description

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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.

## OBJECTIVE

The objective of this evidence review is to determine whether gene expression profile testing or circulating tumor DNA testing improves the net health outcome in individuals with stage II or III colon cancer who are being considered for adjuvant chemotherapy.

## POLICY STATEMENT

Gene expression assays for determining the prognosis of stage II or III colon cancer following surgery are considered **investigational**.

Circulating tumor DNA assays for determining the prognosis of stage II or III colon cancer following surgery are considered **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

| 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. American College of Medical Genetics and Genomics-Association for Molecular Pathology 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 |

## 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.

# BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

# FDA REGULATORY STATUS

Some Plans may have contract or benefit exclusions for genetic testing.

Assays of genetic expression in tumor tissue and circulating tumor DNA are complex test procedures; a specific test will likely be available at 1 or a limited number of reference laboratories.

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 are 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 that are currently commercially available include:

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

# RATIONALE

## Summary of Evidence

For individuals who have stage II or III colon cancer who receive gene expression profile (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 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 [circulating tumor DNA] to estimate risk of recurrence or determine adjuvant therapy" in patients with stage II or III colon cancer.[4,]

### American Society of Clinical Oncology

In 2022, the American Society of Clinical Oncology published updated guidance on adjuvant chemotherapy for stage II colon cancer.[27,] The guideline stated that there was insufficient evidence on the predictive value of ctDNA to warrant a recommendation, but that a recommendation may be possible in the future if prospective data becomes available.

### National Cancer Institute

In 2020, an expert panel of the National Cancer Institute (the Colon and Rectal-Anal Task Forces) published a white paper on the use of ctDNA in colorectal cancer.[28,] For nonmetastatic colorectal cancer, the paper stated that ctDNA after surgery or completion of adjuvant therapy is highly associated with disease recurrence and can be used as a marker of minimal residual disease.

## 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.

# REFERENCES


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## POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

| Date | Action | Description |
|---|---|---|
| December 2011 | New policy | |
| December 2012 | Replace policy | Policy and references updated, rationale rewritten, no change to policy statement. |
| December 2013 | Replace policy | Policy updated with literature review; references 3, 17-19, and 22 added, reference 2 corrected. No change to policy statement. |
| December 2014 | Replace policy | Policy updated with literature review; references 18-19, 24-26, and 28added; references 2, 21, and 27 updated. No changes to policy statement. |
| December 2015 | Replace policy | Policy updated with literature review through June 30, 2015; references3, 23, and 28-31 added. Stage 3 colon cancer added to investigational policy statement. |
| December 2016 | Replace policy | Policy updated with literature review; reference 31 added. Policy statement unchanged. |
| December 2017 | Replace policy | Policy updated with literature review through June 22, 2017; references20, 23, and 31 added; reference 2 updated. Policy statement unchanged. |
| December 2018 | Replace policy | Policy updated with literature review through June 7, 2018; reference 1added; reference 3 updated. Policy statements unchanged. |
| December 2019 | Replace policy | Policy updated with literature review through June 13, 2019; references added. Policy statement unchanged. |
| December 2020 | Replace policy | Policy updated with literature review through July 8, 2020; references added. Added new intervention and policy statement: Circulating tumor DNA testing is considered investigational. Policy title changed to "Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer." |
| December 2021 | Replace policy | Policy updated with literature review through June 14, 2021; references added and updated. Policy statement unchanged. |
| December 2022 | Replace policy | Policy updated with literature review through June 22, 2022; references added and updated. Language regarding Signatera deleted as this has been added to policy 2.04.153. Policy statements unchanged. |
| December 2023 | Replace policy | Policy updated with literature review through June 28, 2023; references added. Policy statement unchanged. |