

<b>Policy Name:</b>	<b>Genetic Testing for Colorectal Cancer (CRC)</b>
<b>Effective Date:</b>	<b>10/19/2020</b>

## Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica plans. Please refer to the member’s plan document for specific coverage information. If there is a difference between this general information and the member’s plan document, the member’s plan document will be used to determine coverage. With respect to Medicare and Minnesota Health Care Programs, this policy will apply unless those programs require different coverage. Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions about this Medica coverage policy may call the Medica Provider Service Center toll-free at 1-800-458-5512.

Medica coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care and treatment.

## Coverage Policy

### **Diagnosis and Prediction of Heritable Colorectal Cancer (CRC)**

Genetic testing for susceptibility to colorectal cancer *requires prior authorization*.

**NOTE:** See Medica Utilization Management policy, *Genetic Testing for Susceptibility to Colorectal Cancer (CRC) Syndromes (III-DIA.06)*, for specific medical necessity criteria.

Single gene and panel testing for diagnosis and prediction of heritable (i.e., germline) CRC **IS COVERED** when the following syndromes are suspected and the medical necessity criteria for the defined population are met as specified in Medica’s Utilization Management policy (see above):

1. Lynch Syndrome (*EPCAM*, *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes)
2. Familial Adenomatous Polyposis (*APC* gene)
3. MUTYH-Associated Polyposis (*MUTYH* Gene)
4. Peutz-Jeghers Syndrome (*STK11* gene)
5. Cowden Syndrome (*PTEN* gene).

### **Gene Expression Tumor Profiling Assays**

Gene expression profiling assays for predicting colon cancer recurrence risk, including but not limited to Oncotype DX Colon Recurrence Score, are considered investigative and unproven and therefore **NOT COVERED**. There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

### **Other Tumor Testing for Colorectal Cancer**

Limited-gene tumor testing, including those to guide targeted drug treatment in CRC, is **COVERED** for:

1. *BRAF* p.V600 mutational analysis in newly diagnosed and untreated CRC when screening for Lynch syndrome (also known as hereditary nonpolyposis colon cancer/HNPCC)
2. *KRAS* and *NRAS* testing for metastatic CRC when anti-epidermal growth factor receptor (EGFR) therapy (e.g., Cetuximab [Erbix]; Panitumumab [Vectibix]) is being considered.

Microsatellite instability (MSI) tumor testing and/or mismatch repair (MRR) tumor protein immunohistochemistry (IHC) are **COVERED** for:

1. Newly diagnosed CRC to detect patients at increased risk of having Lynch Syndrome (HNPCC).
2. Sporadic colorectal cancer when targeted therapy is being considered.

All other **single or limited-gene** tumor testing is considered investigative and unproven and therefore **NOT COVERED** including those to guide targeted drug treatment in CRC. Examples include, but are not limited to, testing for *PIK3CA*, *PTEN*, *TP53*, *UGT1A1*, *MTHFR*, and *CDX2*. There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

**Large multigene panels**, including those to guide targeted pharmacogenetic treatment for CRC, considered investigative and unproven and therefore **NOT COVERED** unless required by the FDA. There is insufficient reliable evidence in the form of high quality peer-reviewed medical literature to establish the efficacy or effects on health care outcomes.

**Note:** Pharmacogenetic testing is **COVERED** when testing for a specific gene biomarker is required by the U.S. Food and Drug Administration (FDA) prior to initiating drug therapy. A list of FDA required tests (by test name and manufacturer) can be found on the FDA's site, List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools), located at: <https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools>.

**Note:** See also related Medica coverage policies; *Liquid Biopsy: Testing of Circulating Tumor Cells or Cell-Free Tumor DNA*, *KRAS Mutation Analysis for Predicting Response to Drug Therapy* and *Genetic and Pharmacogenetic Testing*.

**Note:** See related Medica Utilization Management policy, *Genetic Testing for Susceptibility to Colorectal Cancer (CRC) Syndromes (III-DIA.06)*, for specific medical necessity criteria.

## **Description**

Colorectal cancer is one of the most common malignant neoplasms and a leading cause of cancer death in the United States and worldwide. Molecular markers may be used to:

1. Determine a diagnosis
2. Determine risk of inheritance
3. Document clinical response to treatment.
4. Indicate disease (cancer) progression or remission

## **Diagnosis and Prediction of Heritable Colorectal Cancer**

Heritable CRCs are caused by gene mutations which are inherited and passed down from parent to child (germline mutations). These typically are life-long mutations that can affect multiple family members. Many single gene tests and multi-gene panels have been developed to predict likelihood developing or to diagnosis the various types of CRC. Colorectal cancer syndrome is a term that is applied to a number of familial cancers related to specific heritable mutations (e.g., Lynch syndrome, familial adenomatous polyposis, *MYH*-associated polyposis, Peutz-Jeghers syndrome, juvenile polyposis syndrome).

## **Gene Expression Profiling Assays**

Gene expression profiling assays for assessment of risk of colon cancer recurrence analyze gene expression mutations from tumor tissue samples (somatic mutations). These assays test tumor tissue for a number of genes that have been determined to be associated with an increased risk of recurrence. The resulting data are then analyzed using a proprietary algorithm and a Recurrence Score (RS) is calculated that quantifies the patient's risk of CRC recurrence. The proposed purpose of these tests is to provide prognostic and predictive information to assist in decisions regarding appropriate adjuvant therapy in individuals with stage II or III colon cancer. Multiple gene expression profile assays are available, including but not limited to:

1. Oncotype DX colon recurrence score (Genomic Health, Inc.). Oncotype DX quantifies expression of seven recurrence-risk genes and five reference genes. Prognosis is classified as either low, intermediate or high likelihood of recurrence.

2. ColoPrint (Agendia). This test quantifies expression of 18 genes and classified prognosis as either low versus high recurrence risk. This assay is also purported to predict three-year relapse rates in individuals with stage II colon cancer. According to the manufacturer, ColoPrint® is no longer being provided for this indication.
3. GeneFx® Colon. GeneFx® Colon is Helomics' U.S. licensed product of ColDx (Almac). This microarray-based multigene assay uses 482 genes to identify individuals with stage II colon cancer at high risk of recurrence.
4. ColonPRS® (Signal Genetics). ColonPRS® is a 163 gene expression assay for predicting risk of recurrence in individuals with colon cancer.
5. OncoDefender-CRC® (Everist Genomics). OncoDefender-CRC® is a five-gene assay used to assess the risk of recurrence of cancer in individuals previously treated with surgical resection of stage I or II colon cancer or stage I rectal cancer.
6. ColonSentry® (GeneNews). The ColonSentry test is a molecular diagnostic risk assessment test rather than a cancer detection test.
7. ResponseDX: Colon® (Response Genetics). This panel utilizes testing of multiple genes. The test predicts disease prognosis and selects patients who might benefit from alternative therapies and aids in selection of metastatic colorectal cancer patients that might benefit from EGFR-targeted monoclonal antibody therapies.

### **Other Tumor Testing for Colorectal Cancer**

Pharmacogenetic testing assesses molecular markers that are intended to predict response to a specific therapy or treatment regimen are known as predictive biomarkers. Molecular testing is intended to select targeted and conventional therapies for patients with CRC. Somatic mutations are commonly used to predict pharmacodynamics and drug response, but germline mutations can also be used and studied for prediction on an individual bases. A number of molecular biomarkers have been identified for use in selecting individuals with CRC who might likely benefit from enhanced treatment with targeted therapies (BRAF p.V600, KRAS, NRAS). For example, one of the main targeted therapies in CRC, for which knowledge of mutational status has shown to be useful, are the monoclonal antibody therapies that target the epidermal growth factor receptor (EGFR) signaling pathways. In addition, DNA mismatch repair status is recommended for all patients with CRC to evaluate for possible Lynch syndrome, and the presence of microsatellite instability has both prognostic and therapeutic implications in the choice of chemotherapy. MSI and MRR IHC tumor testing results are commonly interpreted together to evaluate risk of Lynch syndrome. High levels of MSI within a tumor are suggestive of defective MMR genes (e.g., EPCAM, MLH1, MSH2, MSH6, and PMS2), which are associated with Lynch Syndrome. IHC is a complementary testing strategy used to evaluate the expression of the MMR gene proteins. Absence of protein expression for one or more of the MMR genes tested by MMR IHC does not distinguish between somatic and germline mutations. MSI/MMR analysis are not classic genetic tests, but rather stratify the risk of having an inherited cancer predisposition syndrome, and identifies patients who might benefit from subsequent genetic testing. Other molecular biomarkers are currently under study.

### **FDA Approval**

Genetic tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA) Act of 1988. Premarket approval from the FDA is not required as long as the assay is performed in a laboratory facility that observes CLIA regulations and the test is not marketed for general distribution.

### **Prior Authorization**

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met. (

## Coding Considerations

Use the current applicable CPT/HCPCS code(s). The following codes are included below for informational purposes only, and are subject to change without notice. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement.

### CPT Codes:

- **0069U** - Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score
- **0111U** - Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue
- **81210** - BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
- **81275** - KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
- **81276** - KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
- **81301** - Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency)For Newly diagnosed CRC
- **81311** - NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
- **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

Original Effective Date: 10/19/2020

Re-Review Date(s):

### Coverage policy: *Gene Expression Profiling for Predicting Colon Cancer Recurrence Risk*

Original Effective Date: 2/1/2011

Re-Review Date(s): 9/1/2012

6/17/2015

1/4/2016 – administrative update; code update

5/16/2018

2/10/2020 – administrative update; format

10/19/2020 – incorporated into *Genetic Testing for Colorectal Cancer* policy

### Coverage policy: *Molecular Profiling in Colorectal Cancer to Guide Treatment*

Original Effective Date: 2/1/2011

Re-Review Date(s): 9/1/2012

6/17/2015

1/4/2016 – Administrative update; code update

5/17/2017

7/16/2018 – Administrative update; addition of “note”

2/20/2020 – Administrative update; format

10/19/2020 – incorporated into *Genetic Testing for Colorectal Cancer* policy

© 2020 Medica. Medica® is a registered service mark of Medica Health Plans. “Medica” refers to the family of health services companies that includes Medica Health Plans, Medica Community Health Plan, Medica Insurance Company, Medica Self-Insured, MMSI, Inc. d/b/a Medica Health Plan Solutions, Medica Health Management, LLC and the Medica Foundation.