05-86000-28

Original Effective Date: 02/15/09

Reviewed: 08/24/23

Revised: 01/01/24

Subject: Somatic Biomarker Testing (KRAS, NRAS, BRAF, HER2), Including Liquid Biopsy and MicroRNA Expression Testing, in Metastatic Colorectal Cancer

DESCRIPTION:

The epidermal growth factor receptor (EGFR) is overexpressed in colorectal cancer (CRC). EGFR-targeted therapy combined with monoclonal antibodies cetuximab and panitumumab have shown a clear survival benefit in patients with metastatic CRC. However, this benefit depends on a lack of variants in certain genes in the signaling pathway downstream from the EGFR. It has been hypothesized that knowledge of tumor cell KRAS, NRAS, and BRAF variant status might be used to predict nonresponse to anti-EGFR monoclonal antibody therapy. More recently, human epidermal growth factor receptor 2 (HER2) testing to select patients for targeted therapy has been proposed. Typically, the evaluation of biomarker status requires tissue biopsy. Circulating tumor DNA or circulating tumor cell testing (also known as a liquid biopsy) is proposed as a non-invasive alternative.

The association between colorectal cancer and the expression of the miR-31-3p microRNA has been studied in patients treated with anti-EGFR therapy. miR-31-3p expression has also been proposed as a possible predictor of drug response.

POSITION STATEMENT:

Note: Coverage may be governed by state or federal mandates.

KRAS, NRAS, BRAF, or HER2 testing of tumor tissue for members with metastatic colorectal cancer **meets the definition of medical necessity** to select treatment with FDA-approved therapies.

All other uses of KRAS, NRAS, BRAF, or HER2 testing of tumor tissue to guide colorectal cancer targeted therapy are considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

Circulating tumor DNA testing (liquid biopsy) to guide treatment in members with metastatic colorectal cancer is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

MicroRNA expression testing to predict anti-EGFR therapy response (e.g. miR-31now™) is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

BILLING/CODING INFORMATION:

CPT Coding:

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 (e.g., codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)
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)
88360	Morphometric analysis, tumor immunohistochemistry (eg, Her-2/neu, estrogen receptor/progesterone receptor), quantitative or semiquantitative, per specimen, each single antibody stain procedure; manual
88363	Examination and selection of retrieved archival (ie, previously diagnosed) tissue(s) for molecular analysis (eg, KRAS mutational analysis)
0069U	Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score (**Investigational**)
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number variations (FoundationOne® Liquid CDx) (**Investigational**)
0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements (Guardant360® CDx) (**Investigational**)
0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden (Guardant360®) (**Investigational**)

ICD-10 Diagnosis Codes That Support Medical Necessity:

C18.0 – C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C78.5	Secondary malignant neoplasm of large intestine and rectum

REIMBURSEMENT INFORMATION:

KRAS variant analysis, NRAS variant analysis, HER2 variant analysis, and BRAF variant analysis are to be used for a one-time decision point.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: The following National Coverage Determination (NCD) was reviewed on the last guideline reviewed date: Next Generation Sequencing (NGS) (90.2) located at cms.gov.

The following is located at fcso.com: Local Coverage Article Billing and Coding: Molecular Pathology and Genetic Testing A58918.

DEFINITIONS:

None applicable.

RELATED GUIDELINES:

Genetic Testing, 05-82000-28
Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes, 05-82000-31
Tumor/Genetic Markers, 05-82000-22

OTHER:

None applicable.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 08/24/23.

GUIDELINE UPDATE INFORMATION:

02/15/09	New Medical Coverage Guideline.
10/01/09	HCPCS Quarterly Update: added new code S3713.
12/15/09	Annual review: position statements maintained description section and references updated.
07/15/10	Annual review: position statements maintained and references updated.
06/15/11	Annual review: position statements maintained and references updated.
01/01/12	Annual HCPCS update. Added CPT code 81275.
04/01/12	Quarterly HCPCS update. Deleted code S3713. Annual review; position statements maintained and references updated.
04/15/13	Annual review; position statements maintained, references updated; formatting changes.
04/15/14	Annual review; Medicare program exception, and references updated.
01/01/16	Annual HCPCS/CPT update; code 81276 added, code 81275 revised.
07/15/16	Revision; guideline title, description, position statement, coding, and references updated; formatting changes.
10/01/16	Revision; formatting changes.
08/15/17	Review; BRAF position statement and references updated.
06/15/18	Review; description, position statements, and references updated.
09/15/19	Review; Circulating tumor DNA/liquid biopsy investigational statement added; policy title, description section and references updated.
09/15/20	Review; Position statement, coding, and references updated.
09/21/20	Revision; List of test examples updated.
10/15/21	Review: Position statements maintained; coding, test names, and references updated.
07/01/22	Quarterly CPT/HCPCS Update.
06/15/23	Revision: Note added to the position statement section.
09/15/23	Review: Position statements, policy title, and references updated.
01/01/24	Program exception and references updated.