05-86000-28

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Reviewed: 09/25/25

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Subject: Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, NTRK, RET and HER2)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Position Statement | Billing/Coding | Reimbursement | Program Exceptions | Definitions | Related Guidelines

Other | References | Update

DESCRIPTION:

The epidermal growth factor receptor (EGFR) is overexpressed in colorectal cancer (CRC). EGFR-targeted therapy combined with monoclonal antibodies cetuximab and panitumumab has 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, BRAF variant status might be used to predict nonresponse to anti-EGFR monoclonal antibody therapy. NTRK gene fusions, which are rare kinase fusion events, are a potential therapeutic target for CRC patients who may benefit from tropomysosin receptor kinase (TRK) inhibitor therapy. RET gene fusions, which are also rare, are a potential therapeutic target for CRC patients who may benefit from tyrosine kinase inhibitor 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 (ctDNA) 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.

Summary and Analysis of Evidence: Patients with metastatic CRC who are being considered for targeted therapy with an FDA-approved drug and undergo somatic testing for KRAS, NRAS, BRAF, NTRK, HER2 or RET variants using tissue biopsy specimens to guide treatment, the evidence includes FDA-approved

therapeutics with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and National Comprehensive Cancer Network (NCCN) recommendations. Patients with metastatic CRC who are being considered for targeted therapy with FDA-approved drug and undergo somatic testing for KRAS, NRAS , NTRK, and BRAF variants using ctDNA (liquid biopsy), the evidence includes FDA-approved therapeutics with NCCN recommendations of 2A or higher and was not extensively evaluated. The evidence includes the pivotal studies leading to the FDA and NCCN recommendations. For patients with metastatic CRC who are being considered for targeted therapy with FDA-approved drug and undergo somatic testing for RET rearrangements using ctDNA (liquid biopsy), no evidence was identified. At the time of this review, no plasma tests have received FDA approval as companion diagnostics to select individuals with CRC for treatment with RAS inhibitors. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. and no studies were identified. Patients with metastatic CRC who are being considered for targeted therapy with FDA-approved drug and undergo somatic testing for HER2 overexpression using ctDNA (liquid biopsy), no evidence was identified. At the time of this review, no plasma tests have received FDA approval as companion diagnostics to select individuals with CRC for treatment with kinase inhibitors or anti-HER2 monoclonal antibodies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. and no studies were identified. The evidence to assess the association between metastatic colorectal cancer and the expression of miR-31-3p microRNA in individuals treated with anti-EGFR therapies includes small case studies. Anandappa, et al (2019) stated, “In conclusion, our results confirm the potential predictive role of miR-31-3p for the selection of patients undergoing anti-EGFR treatment. Further studies are needed to test if miR-31-3p might be combined with RAS testing in cfDNA to further identify best responders in specific clinical niches”. No clinical guidelines were found that recommend the testing. The evidence is insufficient to determine the effects of the technology on health outcomes.

POSITION STATEMENT:

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

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

Analysis of plasma (liquid biopsy) for somatic variants using an FDA-approved companion diagnostic plasma test to detect ctDNA **meets the definition of medical necessity** for members with metastatic CRC as an alternative to tissue biopsy to predict treatment response to an FDA-approved therapy.

All other uses of KRAS, NRAS, BRAF, RET, 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.

All other uses of 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:

81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis
81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis
81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis
81194	NTRK (neurotrophic receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis
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**)

REIMBURSEMENT INFORMATION:

KRAS, NRAS, BRAF, NTRK, RET or HER2 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.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

FDA List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools): https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

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 09/25/25.

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.
10/15/24	Review: Position statements, title, description, coding, and references updated.
10/15/25	Annual review: Position statements, description, title, coding and references updated.