KRAS Testing for Anti-EGFR Response in Metastatic Colorectal Cancer

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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What is KRAS mutation analysis

Definition

KRAS mutation analysis on metastatic colorectal cancer (mCRC) tissue helps identify patients who are most likely to respond to EGFR-targeted therapy (Erbitux® and Vectibix®).¹⁻⁴

- EGFR-targeted therapies usually bind EGFR, block its signaling to KRAS, and inhibit cellular proliferation, angiogenesis, and metastasis.³
- Approximately 40% of mCRC tumors have an activating KRAS mutation.³
- Anti-EGFR therapy is ineffective for treating mCRC tumors with an activating KRAS mutation because EGFR no longer controls KRAS activation.
- Thus, testing identifies the subset of patients who are resistant to anti-EGFR treatment, avoiding unnecessary drug toxicity and cost.³,⁵,⁶ In addition, some patients with KRAS mutant tumors were found to have an inferior outcome when treated with EGFR-targeted therapy.³,⁷

Test information

- **KRAS Targeted Mutation Analysis** identifies specific KRAS gene mutations — usually including at least the seven most common mutations in codons 12 and 13 of exon 2 that account for most activating mutations.³,⁸ Expanded targeted-mutation
panels will detect additional activating mutations in exons 3 and 4 of the KRAS gene, including mutations in codons 59, 61, 117, and 146.

- **KRAS Gene Sequencing Analysis** identifies most clinically significant mutations in the KRAS gene, including the common activating mutations detected by the targeted mutation assays described above. It has the broadest coverage in KRAS testing, looking at most, if not all, coding areas within the gene. Sequencing may be performed on the KRAS gene alone, or on the KRAS gene as part of a multi-gene panel typically performed by next-generation sequencing.

**Guidelines and evidence**

- The National Comprehensive Cancer Network states (NCCN, 2019): ²
  
  o “All patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS (KRAS and NRAS) and BRAF mutations individually or as part of a next-generation sequencing (NGS) panel. Patients with any known KRAS mutation (exon 2, 3, 4) or NRAS mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab.”

- Evidence based guidelines from the American Society of Clinical Oncology (ASCO, 2017) state: “Patients with CRC being considered for anti-EGFR therapy must receive RAS mutational testing. Mutational analysis should include KRAS and NRAS codons 12 and 13 of exon 2, 59 and 61 of exon 3, and 117 and 146 of exon 4.” ¹

- These guidelines do not recommend a specific test methodology.

**Criteria**

KRAS mutation testing is indicated in individuals with metastatic colorectal cancer.

**References**


