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.3,8

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 that account for more than 95% of activating mutations.3,8 It requires very little tumor
material for testing, and combines high sensitivity with efficiency. It is also relatively inexpensive and is designed to detect the most common mutations within the KRAS gene. Because it does not evaluate the whole KRAS gene, it will miss the less common mutations. KRAS mutation analysis uses fresh, frozen, or paraffin-embedded tissue from either a primary tumor or metastasis.  

- **KRAS Gene Sequencing Analysis** identifies most clinically significant mutations in the KRAS gene, including both common and rare changes. It has the broadest coverage in KRAS testing, looking at most, if not all, coding areas within the gene. However, sequence analysis requires more and higher quality tumor material for testing than PCR. This typically translates into being less efficient and more expensive than targeted mutation analysis. Direct sequence analysis has lower analytical sensitivity than some targeted, PCR based assays. However, the clinical relevance of a small percentage of cells with mutant KRAS has not been established.

**Guidelines and evidence**

- Consensus from the National Comprehensive Cancer Network (NCCN, 2018) “strongly recommends KRAS/NRAS genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer.” “Patients with known KRAS or NRAS mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified.”

- 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.”

- These guidelines do not recommend a specific test methodology.

**Criteria**

KRAS mutation testing is indicated in individuals with metastatic colorectal cancer prior to the initiation of treatment with cetuximab (Erbitux®) or panitumumab (Vectibix®) therapy.

**References**


