

TEST UPDATE

Quick Facts

- ▶ **KRAS mutation analysis should be performed before initiating anti-EGFR therapy in patients with metastatic colorectal cancer.**
- ▶ **30%-40% of all colorectal cancers contain a mutated KRAS oncogene.**
- ▶ **Tumors with activating KRAS mutations will not respond to anti-EGFR therapies.**
- ▶ **Sequence analysis of the KRAS oncogene can identify all mutations in codons 12 and 13, provided that the tissue sections submitted to the laboratory have sufficient tumor burden.**
- ▶ **Order code is KRASSQ**

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CLINICAL APPLICATION

- KRAS mutation analysis is useful for the identification of patients who will likely not respond to anti-EGFR therapy.
- Tumors with activating mutations in codon 12 or 13 of the KRAS oncogene will not benefit from anti-EGFR therapies. 30% to 40% of colorectal cancers contain a mutated KRAS oncogene.
- The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommends the determination of KRAS mutation status in all patients with metastatic colorectal cancer who are candidates for anti-EGFR therapy.

CLINICAL BACKGROUND

- Epidermal growth factor receptor (EGFR), along with the signaling pathways downstream of EGFR, plays a cardinal role in regulation of cell growth and cell cycle progression. Over activation of EGFR, due to enhanced ligand response or complete ligand independence, is associated with unregulated growth and proliferation of tumor cells.
- Given the role of EGFR in colorectal cancer pathogenesis, monoclonal antibodies (Cetuximab and Panitumumab) that target EGFR have been FDA-approved in US for the treatment of refractory metastatic colorectal carcinoma (CRC).
- 20% of patients with CRC present with metastatic disease and an additional 30% to 40% develop metastasis during their disease course.
- KRAS mutations lead to stimulation of the RAS/MAPK signaling pathway independent of EGFR; therefore, tumors in patients with KRAS mutations will not respond to EGFR-directed monoclonal antibody therapy.
- The most common mutations occur in codon 12 (80%) and codon 13 (20%) in the KRAS oncogene.

TECHNICAL NOTES

- Tumors with lymph node or distant metastases can be used for KRAS mutation detection.
- To enhance the tumor purity and quantity, tumor sections will be reviewed and manually macrodissected by a pathologist.
- PCR amplification followed by sequence analysis will be performed using DNA extracted from enriched tumor samples.
- All 12 mutations previously reported to occur in codons 12 and 13 can be identified using sequencing analysis, provided that the tissue sections submitted to the laboratory have sufficient tumor burden.
- The limit of detection is approximately 5% KRAS mutation-positive tumor cells against the background of KRAS mutation-negative cells.

Test Information

DESCRIPTION	KRAS Mutation Detection by Sequence Analysis, Codons 12 and 13
METHOD	PCR and sequence analysis
ORDER CODE	KRASSQ
CPT CODE	88387, 83891, 83898, 83904x2, 83907, 83909x2, 83912
SPECIMEN REQUIREMENTS	Formalin-fixed paraffin-embedded tissue block, or 6 unstained 7-micron slides and one additional H&E stained slide.
COMMENTS	Unacceptable conditions: No tumor in tissue sections. Specimens fixed/processed in alternative fixatives (alcohol, Prefer®)
RANGES	Positive, negative and indeterminate for KRAS mutation.

Selected References

1. *Cunningham D, Humblet Y, Siena S et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med. 2004;351:337-345*
2. *Allegra CJ, Jessup JM, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. J Clin Oncol. 2009;27:2091-2096*
3. *Banck MS and Grothey A. Biomarkers of resistance to epidermal growth factor receptor monoclonal antibodies in patients with metastatic colorectal cancer. Clin Cancer Res. 2009;15(24):7492-7501*
4. *Whitehall V, Tran K, Umopathy A, et al. A multicenter blinded study to evaluate KRAS mutation testing methodologies in the clinical setting. J Mol Diag. 2009;11(6):543-552*

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