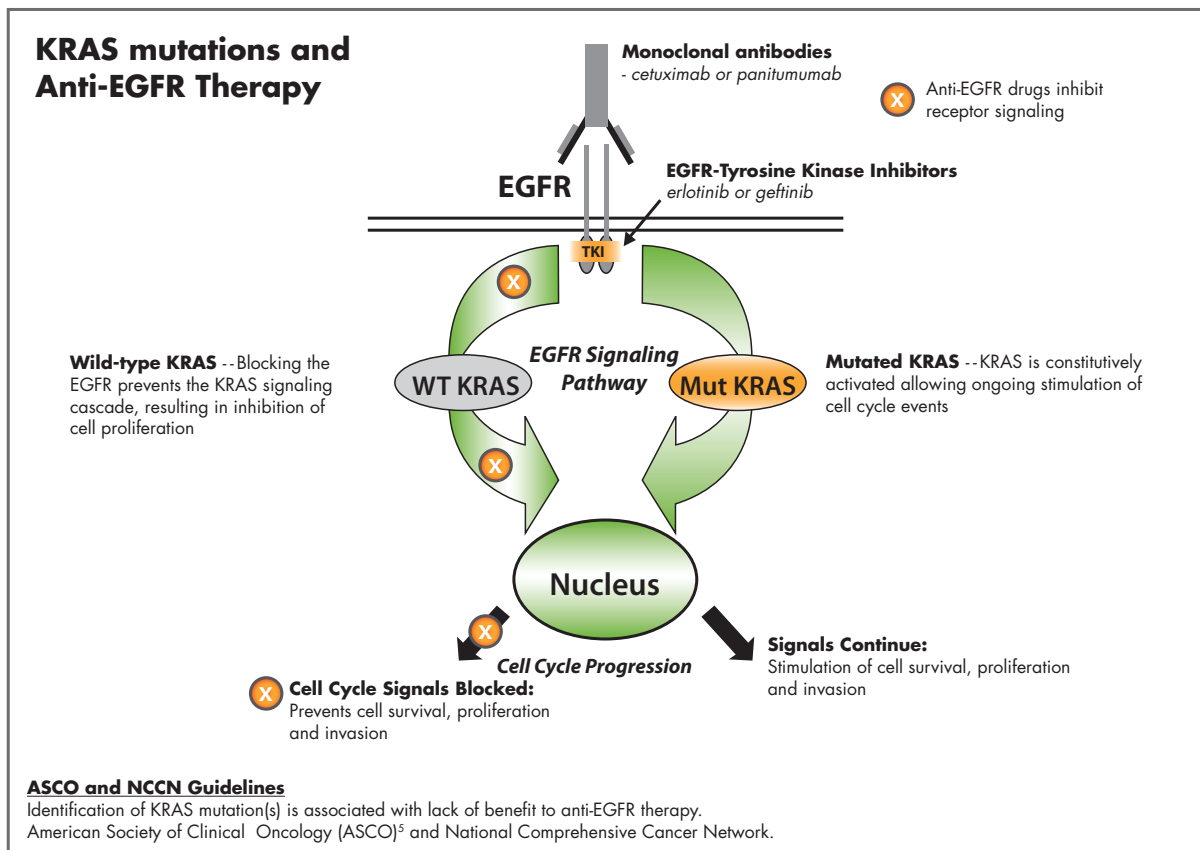


OVERVIEW - KRAS Mutations

The *KRAS* and *BRAF* genes are part of the *Ras* oncogene family whose gene products (small guanine nucleotide-binding proteins) are involved in the modulation of the cell cycle including cell differentiation, division, and apoptosis. This cell cycle pathway can be activated by the binding of epidermal growth factor to the epidermal growth factor receptor (EGFR).¹

Mutations in the *KRAS* gene result in the constitutive activation of the KRAS protein and subsequently, stimulation of the cell cycle independent of activation of the EGFR. For this reason, anti-EGFR therapy (i.e., monoclonal antibodies which block the binding of epidermal growth factor to the EGFR) is not effective in colorectal cancers displaying KRAS mutations. Mutations in the *KRAS* gene also affect response to anti-EGFR therapy in non-small cell lung cancer (NSCLC) patients.²⁻⁴

KRAS mutations are found in about 35-40% of colorectal cancer tumors and are associated with a poorer prognosis.⁴ KRAS mutations are found in the following percentages of cancers: 59% pancreas, 32% biliary tract, 32% large intestine, 20% small intestine, 19% gastrointestinal tract, 18% lung, 15% ovary, 15% thymus, 14% endometrium and 10% soft tissue.¹



ASCO AND NCCN GUIDELINES

Identification of KRAS mutation(s) is associated with lack of benefit to anti-EGFR therapy. American Society of Clinical Oncology (ASCO)⁵ and National Comprehensive Cancer Network (NCCN) Guidelines⁶ recommend that a determination of the KRAS gene status of either the primary tumor or site of a metastasis should be part of the pre-treatment work-up for all patients diagnosed with metastatic colorectal cancer in which anti-EGFR therapies are being considered.

PROVISIONAL ASCO CLINICAL OPINION

"Based on systematic reviews of the relevant literature, all patients with metastatic colorectal carcinoma who are candidates for anti-EGFR antibody therapy should have their tumor tested for KRAS mutations in a CLIA-accredited laboratory. If KRAS mutation in codon 12 or 13 is detected, then patients with metastatic colorectal carcinoma should not receive anti-EGFR monoclonal antibody therapy as part of their treatment."⁵

NCCN Guidelines recommend that a determination of the KRAS gene status of either the primary tumor or a site of metastasis should be part of the pre-treatment work-up for all patients diagnosed with metastatic colorectal cancer. Furthermore, NCCN has made the update that the epidermal growth factor receptor (EGFR) inhibitors, cetuximab (Erbix[®], Bristol-Myers Squibb Company/ImClone Systems Incorporated) and panitumumab (Vectibix[®], Amgen), either as single agents, or, in the case of cetuximab, in combination with other agents, are now recommended only for patients with tumors characterized by the wild-type KRAS gene. [www.nccn.org]

Additionally, mutations in codon 61 have been shown to predict resistance to cetuximab plus irinotecan in KRAS codon 12 and 13 wild-type metastatic colorectal cancer.⁷

FOR MORE INFORMATION,
877.922.7284
 call us at our toll-free number

REFERENCES:

1. Wang HL, Lopategui J, Amin MB and Patterson SD. KRAS mutation testing in human cancers: The pathologist's role in the era of personalized medicine. *Adv Anat Pathol* 2010;17:23-32.
2. Massarelli et al. KRAS mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. *Clin Cancer Res* 2007;13:2890-96.
3. Pao W, Wang TY, Riely GJ, et al. KRAS mutations and primary resistance of lung adenocarcinomas to gefitinib or erlotinib. *PLoS Med* 2005;2:57-61.
4. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with NSCLC treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol* 2005;23:5900-9.
5. 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;27:2091-6.
6. www.nccn.org
7. Loupakis F, Ruzzo A, Cremolini C, et al. KRAS codon 61, 146 and BRAF mutations predict resistance to cetuximab plus irinotecan in KRAS codon 12 and 13 wild-type metastatic colorectal cancer. *Br J Cancer* 2009;101:715-21.

CLINICAL UTILITY

- Mutations in the KRAS gene are associated with lack of benefit to anti-EGFR therapy
- ASCO and NCCN recommend all metastatic colorectal cancer patients being considered candidates for anti-EGFR therapy be tested for KRAS mutation status prior to initiation of treatment
- Predictive assay to help guide therapy in colorectal and non-small cell lung cancers

METHODOLOGY

Polymerase Chain Reaction/Pyrosequencing. Tumor cell DNA is extracted and PCR-amplified generating a DNA segment spanning codons 12, 13 and 61 of the KRAS gene. Pyrosequencing analysis is performed to identify mutations in these codons. The assay can detect the presence or absence of wild-type and mutant alleles in codons 12, 13 and 61; mutations in these codons are associated with lack of benefit to anti-EGFR therapy. The limit of detection is 5% mutant in a background of wild-type genomic DNA.

ORDERING INFORMATION

TEST CODE	TEST NAME
6050	KRAS Mutation Analysis
Specimen Requirements	Formalin Fixed Paraffin Embedded (FFPE) block containing at least 50% malignant cells representing either primary or metastatic tumor OR Five 10µm thick unstained paraffin sections on plain glass slides plus an H&E stained slide.
Collection	Send at room temperature or refrigerated. DO NOT FREEZE.
Report	4 days