access genetics

KRAS Mutation Analysis in Colorectal Cancer

Introduction:

- Colorectal cancer is the second leading cause of cancer-related death in the Western world. Mutations in the KRAS oncogene have been associated with resistance to anti-EGFR antibody therapy. The American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the FDA have all issued recommendations regarding KRAS mutation testing for patients with metastatic colorectal carcinoma.

KRAS Mutations in Colorectal Cancers[1]:

1. KRAS is mutated in approximately 40% of metastatic Colorectal Cancer[1].
2. Mutations in codons 12, 13, and 61 account for > 99% of somatic mutations in this gene[1].
3. Clinical and research studies suggest patients with KRAS mutations in codons 12, 13, and 61 are resistant to anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody therapies[2,3].

MAPK/Erk Pathway

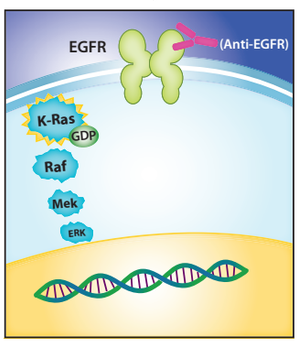

Figure: Inhibition of EGFR by the EGFR-Inhibitor leads to K-Ras inactivation and inhibition of downstream signaling and cellular proliferation.

MAPK/Erk Pathway

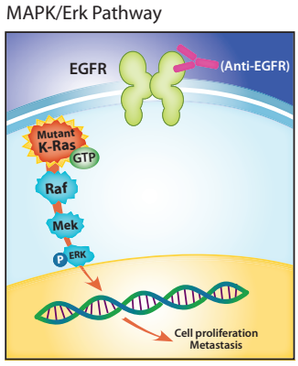

Figure: Mutated K-Ras constitutively activates the MAPK/Erk pathway in the presence of EGFR-Inhibitor resulting in cellular proliferation and metastasis.

Recommendations for Testing:

1. **The American Society of Clinical Oncology (ASCO) recommends all patients with metastatic colorectal cancer, who are candidates for anti-EGFR monoclonal antibody therapy, have their tumor tested for KRAS mutations[4].**
2. **Based on the National Comprehensive Cancer Network (NCCN) guidelines, patients with KRAS codon 12 or 13 mutations may not be candidates for anti-EGFR monoclonal antibody therapy[5].**
3. **Current FDA labeling for Cetuximab (Erbitux) and Panitumumab (Vectibix) indicates that use for the treatment of colorectal cancer is not recommended when a KRAS codon 12 or 13 mutation is present.**

KRAS Molecular Biology[6]:

K-Ras is one of the Ras GDP/GTP binding proteins and a member of the MAPK/Erk transmembrane signal transduction system of proteins. This pathway modulates cellular proliferation, differentiation and senescence. Wild-type Ras proteins cycle between active GTP-bound and inactive GDP-bound conformations. Mutations in KRAS result in the constitutive activation of this pathway which increases the risk of cellular transformation.

Additional Indications for Testing:

Research studies suggest KRAS mutation analysis may be used as a diagnostic, prognostic, and therapeutic indicator for the following: Non-Small Cell Lung Cancer, Pancreatic, Breast, Ovarian, Esophageal, Bile Duct, Thyroid, Endometrial & Gastric Cancers.

Testing Methodology:

- Tumor tissue is microdissected and DNA is extracted from formalin-fixed, paraffin embedded tissue blocks.
- Extracted DNA is amplified by PCR using primers specific for exons 2 and 3 of the KRAS gene. Following PCR the products are subjected to digestion by SURVEYOR® Nuclease. Result interpretation is performed by analysis of peak height and size data generated through fluorescence detection by automated electrophoresis.
- This laboratory-developed test (LDT) has not been cleared or approved by the U.S. Food and Drug Administration (FDA).

Testing Limitations:

- The status of KRAS mutations may differ between primary and metastatic samples of tumor[7].
- This assay detects mutations at selected loci within the KRAS gene, but is not specific to the level of the DNA sequence. If clinically indicated, characterization of the precise KRAS mutation by methods of DNA sequencing may be requested.

Sensitivity:

- When compared to sequencing, this assay provides increased sensitivity, with a high level of detection of mutant KRAS within a wild-type background.

Resources:

1. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
2. American Society of Clinical Oncology Provisional Clinical Opinion: Testing of KRAS Gene Mutations in Patients with Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monocolonal Antibody Therapy. Journal of Clinical Oncology. 27(12): 2091 – 2096.
3. American Cancer Society Colorectal Cancer Facts and Figures 2008-2010: http://www.cancer.org/Research/CancerFactsFigures/colorectal cancer-facts--figures-2008-2010.

References:

1. Wellcome Trust Sanger Institute. Catalogue of somatic mutations in cancer. Retrieved from http://www.sanger.ac.uk/perl/genetics/CGP/cosmic?action=bycancer&ln=KRAS&sn=large_intestine&ss=colon.
2. Karapetis CS, et al. (2008). K-ras mutations and benefit from cetuximab in advance colorectal cancer. N Engl J Med, 359:1757-65.
3. Loupakis, F., et al. (2009). KRAS codon 61, 146 and BRAF mutations predict resistance to Cetuximab plus irinotecan in KRAS Codon 12 and 13 wild-type metastatic colorectal cancer. British Journal of Cancer. 101: 715-721.
4. Allegra, C.J., et al. (2009). American Society of Clinical Oncology Provisional Clinical Opinion: Testing of KRAS Gene Mutations in Patients with Metastatic Colorectal Carcinoma to Predict Response to Anti-Epidermal Growth Factor Receptor Monocolonal Antibody Threrapy. Journal of Clinical Oncology. 27(12): 2091 – 2096.
5. Engstrom, P.F., Arnoletti, J.P., et al. (2010). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. 2.2011. Retrieved from http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
6. V-KI-RAS2 Kirsten Rat Sarcoma Viral Oncogene Homolog; KRAS (190070). (n.d.). In OMIM. Retrieved from http://www.ncbi.nlm.nih.gov/omim/190070.
7. Artale S, Sartore-Bianchi A, Veronese SM, et al. (2008). Mutations of KRAS and BRAF in primary and matched metastatic sites of colorectal cancer. Journal of Clinical Oncology. 26(25):4217-4219.

Test Information:

For Specimen requirements, shipping instructions, and test information **click here.**