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TEST UPDATES and ANNOUNCEMENTS

November 4, 2010

Dear Colleague:

Pathology, Inc. is pleased to announce the addition of **KRAS Mutation Analysis** to our molecular test menu. This assay utilizes polymerase chain reaction (PCR) followed by Pyrosequencing for mutation detection and identification.

KRAS MUTATION ANALYSIS

The presence of **KRAS mutations** in the primary or metastatic tumor is associated with **lack of response to the anti-EGFR inhibitor drugs**. Both ASCO and NCCN recommend KRAS mutation analysis be performed for colorectal cancer patients before considering administering anti-EGFR therapy.

Please submit either formalin-fixed, paraffin-embedded (FFPE) blocks containing at least 50% tumor or five (5) 10µm thick unstained paraffin sections (containing at least 50% tumor) on plain glass slides along with an H&E stained slide. We examine three codons, 12, 13 and 61, for the presence of mutations. Our method of PCR/Pyrosequencing is highly sensitive and specific, able to identify as little as 5% mutant KRAS in a background of wild-type genomic DNA.

We thank you for choosing Pathology, Inc. and look forward to your continued support. For additional information, please visit our website at www.pathologyinc.com or contact client services at 877-922-7284.

Sincerely,

A handwritten signature in black ink, appearing to read 'Alfred Lui', is positioned above the printed name.

Alfred Lui, M.D.
Chief Medical Officer

New Tests (Pathology, Inc.)

6050 KRAS Mutation Analysis

Component	Method	Result	Mutations Identified
KRAS	PCR/Pyrosequencing	Normal/Abnormal	Wild-type/Mutations in codons 12, 13, 61

Specimen/Stability	Formalin-fixed, paraffin-embedded tissue (FFPE). Submit paraffin block containing at least 50% malignant cells representing either primary or metastatic tumor OR Five(5) 10µm thick unstained paraffin sections on plain glass slides plus an H&E stained slide: Ambient temperature; DO NOT FREEZE
Report	4 days
Sensitivity	Limit of detection is 5% mutant in a background of wild-type genomic DNA
Clinical Utility	<p>Identification of KRAS mutation(s) is associated with lack of benefit to anti-EGFR therapy. American Society of Clinical Oncology (ASCO)¹ and National Comprehensive Cancer Network (NCCN) Guidelines² 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 CRC in which anti-EGFR therapies are being considered.</p> <p>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.”¹</p> <p>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]</p> <p>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.³</p> <p>KRAS mutations are found in the following percentages of cancers: 59% pancreas, 32% of biliary tract, 32% of large intestine, 20% of small intestine, 19% of gastrointestinal tract, 18% of lung, 15% of ovary, 15% thymus, 14% of endometrium, and 10% soft tissue.⁴</p> <p>References:</p> <ol style="list-style-type: none"> 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 Feb 2 www.nccn.org 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 101:715–721, 2009 Wang et al. KRAS mutation testing in human cancers: The pathologist’s role in the era of personalized medicine. Adv Anat Pathol 2010;17:23-32.