



## Quest Diagnostics Introduces First Comprehensive Laboratory Test To Analyze KRAS, NRAS, and BRAF Gene Mutations in Reflex Testing Service

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EGFR Pathway Test analyzes in sequential reflex fashion more mutations potentially inhibiting anti-EGFR therapy response in metastatic colorectal cancer patients

MADISON, N.J., June 1 /PRNewswire-FirstCall/ -- Quest Diagnostics Incorporated (NYSE: DGX), the world's leading cancer diagnostics company, today launched the EGFR Pathway test (KRAS with reflex to NRAS, BRAF), the first laboratory-developed test from a national commercial reference laboratory for comprehensively identifying, in a single reflex test offering, genetic mutations in the KRAS, NRAS and BRAF genes. The test is designed to aid the identification of the roughly half of all metastatic colorectal cancer (mCRC) patients who, because of certain mutations of the epidermal growth factor receptor (EGFR) pathway, are believed to be unresponsive to anti-EGFR cancer therapies for mCRC. While some commercial laboratory tests for predicting anti-EGFR response analyze certain mutations of the KRAS and BRAF genes, such as codons 12 and 13 of KRAS, the Quest Diagnostics test detects mutations in codons 12, 13 and 61 of both the KRAS and NRAS genes and mutations in exons 11, 12, and 15 of the BRAF gene, in a sequential reflex manner.

(Note to journalists: For more information on the interplay of genes and pathways, please refer below to "About Cellular Pathways.")

"Our EGFR Pathway test will provide physicians with the most comprehensive data available from a single test offering for identifying RAS and BRAF gene mutations in patients with mCRC who may be considered for anti-EGFR therapy. Given that research suggests these gene mutations may inhibit therapeutic response in many patients, our goal is to give physicians a personalized diagnostic tool that can help them determine more reliably whether or not to provide therapy with EGFR antagonists to the individual patient," said Dr. Maher Albitar, M.D., medical director and chief of Research and Development, Hematology and Oncology, Quest Diagnostics.

Anti-EGFR therapies are designed to impede cellular proliferation caused by activation of EGFR, but can trigger several side effects, including fatigue, skin rash, and nausea and vomiting. Up to 40 percent of patients with mCRC in the U.S. have mutations in the KRAS gene that render anti-EGFR therapy ineffective. In January 2009, the American Society of Clinical Oncology (ASCO) produced a provisional clinical opinion (PCO) recommending that all patients with mCRC who are candidates for anti-EGFR therapy be tested for KRAS gene mutations (specifically in codons 12 and 13), and that anti-EGFR antibody therapy should not be administered if mutations are found.

However, fewer than 50 percent of patients with wild-type (normal) KRAS genes respond to anti-EGFR therapy, suggesting that additional mechanisms may affect response. Studies demonstrate that in patients with mCRC, about five percent may have mutations in the NRAS gene and eight percent may have mutations in the BRAF gene, and that mutations in these genes are associated with poor anti-EGFR treatment response. In February 2009, The New England Journal of Medicine published correspondence by Dr. Albitar and his colleagues at Quest Diagnostics regarding results of a study of 572 colon cancer samples that found that 11 percent of RAS mutations would have been missed if only codons 12 and 13 of the KRAS gene had been analyzed (as recommended by ASCO's PCO), and recommended RAS mutation testing include KRAS and NRAS encompassing codon 61 in addition to codons 12 and 13.

The Quest Diagnostics EGFR Pathway Test sequentially detects mutations along the EGFR Pathway, beginning with KRAS followed by NRAS and BRAF. If a mutation is identified before the entire series is analyzed, the reflex testing process stops, and the test result is provided to the physician. Since any individual patient is only likely to experience one mutation in either KRAS, NRAS and BRAF, combined testing for mutations from these three genes in the EGFR pathway would theoretically accurately classify more patients as non-responders than KRAS and/or BRAF testing alone.

"While KRAS mutation analysis of codons 12 and 13 is well established as an aid in predicting anti-EGFR therapy response, a growing body of research has revealed that other mutations in the EGFR signaling pathway, including those at codon 61 of KRAS and NRAS, also impede treatment response in patients with mCRC," said Jay G. Wohlgemuth, M.D., vice president, Science and Innovation, Quest Diagnostics. "Our new test will enable physicians to gain a deeper understanding of a patient's EGFR pathway status, based on the latest scientific research, than is available using competing tests. We believe this test is an important diagnostic advance that will help physicians potentially identify more non-responder EGFR patients who might be missed using standard KRAS assessments, potentially sparing a substantial number of patients lost time, not to mention side effects and high costs of anti-EGFR therapies."

In addition to the EGFR Pathway Test, the company launched individual laboratory tests for identifying mutations in the NRAS and BRAF genes for physicians who prefer to order individual tests. The company launched its first laboratory test for detecting mutations in the KRAS gene in August 2008.

Quest Diagnostics is the leader in cancer diagnostics, including tests for colorectal cancer. In addition to its EGFR Pathway and related laboratory tests, the company's Enterix business manufactures the InSure(R) fecal immunochemical test (FIT), an FDA-cleared FOBT test for use in screening for sources of lower gastrointestinal bleeding, based on laboratory testing of a stool-based specimen. Quest Diagnostics is also developing a molecular blood test based on Epigenomics AG's Septin 9 DNA methylation biomarker that can help physicians detect colorectal cancer based on a patient's blood specimen.

### About Cellular Pathways

Within each human cell, genes, lying adjacent to one another, form the basis for a pathway on which proteins cascade and signal the genes to perform tasks influencing cellular growth, death and proliferation. In some cancers, including mCRC, receptors of the epidermal growth factor protein that reside on each cell are abnormally activated, prompting a cascade effect across a cellular pathway and the potential for cancerous cellular proliferation. Anti-EGFR therapies interfere with the cell's epidermal growth factor receptor to impede cellular proliferation and prompt tumor cell death.

RAS is a family of genes encoding proteins that are involved in transmitting signals that influence cell growth and survival. Mutations in the RAS family of cancer-promoting oncogenes, which include KRAS and NRAS, are implicated in several cancers, including colorectal cancer. BRAF is an oncogene

of RAF, which is a family of proteins typically activated by RAS and which influence cellular activity.

#### About Quest Diagnostics

Quest Diagnostics is the world's leading provider of diagnostic testing, information and services that patients and doctors need to make better healthcare decisions. The company offers the broadest access to diagnostic testing services through its network of laboratories and patient service centers, and provides interpretive consultation through its extensive medical and scientific staff. Quest Diagnostics is a pioneer in developing innovative diagnostic tests and advanced healthcare information technology solutions that help improve patient care. Additional company information is available at [www.questdiagnostics.com](http://www.questdiagnostics.com).

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