

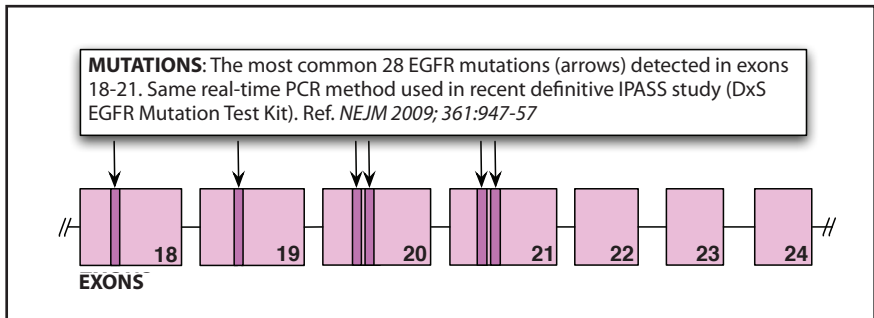


PhenoPath Now Available at EGFR Mutation Analysis BY REAL-TIME PCR



The epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor that has been found to play an important role in cancer, particularly in non-small cell lung carcinoma as well as in colorectal adenocarcinomas. Responsiveness to anti-EGFR therapies such as gefitinib in lung cancer has been linked to the presence of specific mutations in the tyrosine kinase domain of EGFR (1, 3). The EGFR mutation test now offered at PhenoPath Laboratories uses real-time PCR for rapid assessment of DNA extracted from paraffin-embedded tissues for the most commonly found EGFR mutations which involve exons 18 through 21 of the EGFR gene. This assay has been validated against sequenced clinical samples and is the same assay used to establish patient eligibility and efficacy in many recent clinical trials, including the Iressa™ Pan-Asia Study or IPASS (3). The PhenoPath EGFR assay, produced by DxS-Diagnostic Innovations/Qiagen, is identical to that selected by AstraZeneca and Boehringer Mannheim to serve as the companion diagnostic kit for their respective anti-EGFR therapies.

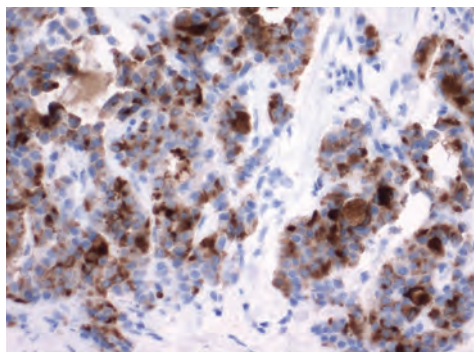
EGFR mutations occur in approximately 10-20% of lung non-small cell carcinoma (2). The EGFR mutation test offered at PhenoPath Laboratories is a rapid, sensitive, and accurate test that identifies patients who would be more likely to respond to selective anti-EGFR therapies such as gefitinib. In conjunction with EGFR FISH analysis, this real-time PCR-based EGFR mutation test allows for the most up-to-date and complete assessment of EGFR status, to help identify patients eligible for anti-EGFR therapy.



1. Lynch et al., Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to Gefitinib. NEJM 2004; 350:2129-39
2. John et al., Overview of molecular testing in non-small-cell lung cancer: mutational analysis, gene copy number, protein expression and other biomarkers of EGFR for the prediction of response to tyrosine kinase inhibitors. Oncogene 2009; 28:S14-S23
3. Mok et al., Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. NEJM 2009; 361:947-57

GCDFP-15 New Clone

The gross cystic disease fluid protein-15 (GCDFP-15) was first described by Haagensen and colleagues 30 years ago (1); it is a 15K MW protein that has been employed as a marker of breast carcinomas. While the antibody's primary use is a marker to distinguish breast from non-breast (e.g., lung) carcinomas at metastatic sites, the antibody does suffer from relatively low sensitivity, although studies from PhenoPath Laboratories presented at the 2009 USCAP Meeting demonstrated a combined sensitivity of 86% for breast carcinoma when GCDFP-15 was used in conjunction with another breast marker, mammaglobin (2). Much of the published literature employs the D6 anti-GCDFP-15 clone first described in the mid 1980s. A new clone, 23A3, has been available the past few years, and PhenoPath switched to this clone, based on our validation studies which demonstrated significantly increased sensitivity (78.3% in our most recent studies). Not only were a higher fraction of breast cancer cases positive, but within individual tumors we found a higher fraction of cancer cells positive, with a better signal to noise ratio than with the D6 monoclonal. Our studies show that employing antibodies to mammaglobin in conjunction with GCDFP-15 can increase overall sensitivity in a small but significant amount, as 7.2% of all breast cancers in our study of 447 breast cancers displayed a GCDFP-15-negative, mammaglobin-positive immunophenotype.



Metastatic breast cancer positive for expression of GCDFP-15 using new 23A3 clone

It should be noted, however, that GCDFP-15 cannot absolutely distinguish breast from lung carcinomas, as highlighted by Striebel and colleagues, who demonstrated that 5.2% of primary lung adenocarcinomas were GCDFP-15-positive using the same 23A3 clone (3). While the vast majority of the latter were TTF-1-positive, a small percentage were not.

References: 1. Haagensen DEJ, et al. *J Natl Cancer Inst* 62:239-247, 1979. 2. Shaw AJ et al. *Mod Pathol* 22:67A, 2009. 3. Striebel JM et al. *Am J Surg Pathol* 32:426-432, 2008.

COX2

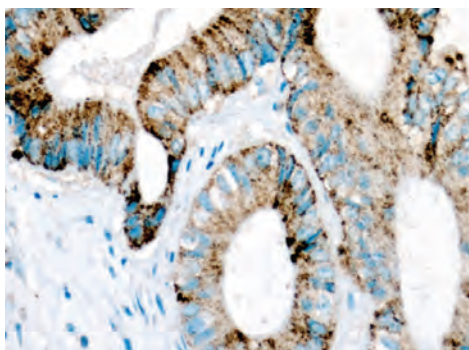
A Prognostic and Predictive Marker of Colorectal Adenocarcinoma

While many prospective studies have demonstrated that regular aspirin use is associated with a lower risk of colorectal adenocarcinoma, a recent study in the *Journal of the American Medical Association* demonstrated that the 5- and 10-year survival of 1,279 patients already diagnosed with colorectal adenocarcinoma was significantly increased by aspirin treatment. (In multivariate analysis, the hazard ratio associated with regular aspirin use after diagnosis was 0.71 for colorectal cancer-specific mortality.)

Given aspirin's mode of action, targeting cyclo-oxygenase (COX) 1 and 2, immunohistochemical assessment of COX-2 expression was performed in 459 of the patients. Regular aspirin use after diagnosis was associated with a lower risk of colorectal cancer-specific mortality among participants in whom primary tumors showed high levels of COX-2 expression (multivariate hazard ratio, 0.39), whereas aspirin use was not associated with lower risk among those with adenocarcinomas manifesting low levels or absent COX2 expression (multivariate hazard ratio, 1.22).

These studies suggest that patient selection for aspirin treatment can be determined by performing COX2 immunohistochemistry on the primary colorectal adenocarcinoma. PhenoPath Laboratories offers COX2 IHC analysis which has been validated and in use for more than 5 years.

Reference: Chan AT, Ogino S, Fuchs CS. *Aspirin use and survival after diagnosis of colorectal cancer. JAMA* 302:649-659, 2009.



Colorectal adenocarcinoma showing high levels of expression of COX2

PhenoPeople

Profile



Jonathan Culp

PhenoPath Laboratories is pleased to welcome Jonathan Culp as the Midwest Anatomical Pathology Specialist. Jonathan's responsibilities include introducing new products and services to current and future customers, increasing awareness of the company's quality stance, and demonstrating how PhenoPath can expand and grow a practice's business while offering the finest patient care.

Jonathan brings a strong sales background to the company, working for Loth, Inc., a workspace solutions provider, managing complex corporate and government contracts. Among his many awards, he was named Rookie of the Year and continually shattered sales goals and quotas due to his attention to detail and outstanding client service. In addition, while in college, Jonathan was a franchise owner of College Pro Painters, managing a team of college students selling house-painting services in multiple cities.

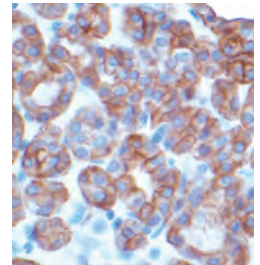
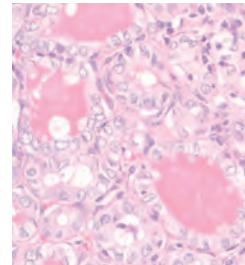
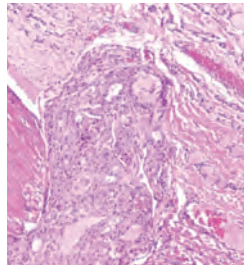
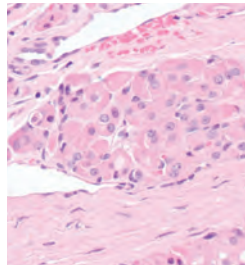
Jonathan graduated from Bowling Green State University, Ohio, where he was the starting center for the Falcons football team and was named Academic All-District and All-Conference as well as BGSU Male Student Athlete of the Year.

Jonathan has a number of interests, including travel, music, physical fitness, exploring exotic new foods and cheering on the Cincinnati Bengals.

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Featuring **Dr. Jennifer Hunt** At Our Winter Conference



Jennifer L. Hunt, M.D., M.Ed. will present “My Approach for Follicular Thyroid Tumors” at the PhenoPath Winter Conference on **Thursday, January 14, 2010**. The format of the conference is a social hour commencing at **6:30 p.m.**, followed by Dr. Hunt’s lecture at 7:30 p.m. A light catered dinner will be served during the social hour.

Dr. Hunt is an Associate Professor at Harvard Medical School, and Associate Chief of Pathology, Director of Quality and Safety in the Department of Pathology at Massachusetts General Hospital in Boston, MA. She obtained her medical training at the University of Pennsylvania School of Medicine in Philadelphia, PA, and continued there with a residency in anatomic pathology, and a fellowship in molecular pathology.

Dr. Hunt is also involved in research related to tumorigenesis in head and neck and endocrine-related neoplasia. Her focus is on molecular diagnostic approaches to understanding tumor pathogenesis, prognosis, and diagnosis. Her training and background in Molecular Genetic Pathology led to an interest in discovery and validation of new biomarkers for head and neck cancers and thyroid cancer. Dr. Hunt also leads research in quality assurance, performance improvement, and laboratory operations.

Dr. Hunt has experience in new assay development for clinical use, both clinical validation and ongoing laboratory accreditation. She has over 80 peer-reviewed research publications, is a Deputy Editor-in-Chief for the *Archives of Pathology and Laboratory Medicine*, and has been actively involved in national and international pathology societies.