Validation of ER/PR Immunohistochemistry

The newly published ASCO-CAP Guidelines (Badve ER et al, J Clin Oncol 34:344-32, 2010) mandate that all laboratories performing ER and PR immunohistochemistry (IHC) must employ a validated assay. A companion publication to the ASCO-CAP guidelines (Fitzgibbons P et al., Arch Pathol Lab Med 134:234-21, 2010) contains specific recommendations for how such assays can be validated.

Test validation generally requires comparison with a standard; however, as in the case with HER2 IHC testing, there is no “gold standard” for ER and PR IHC assessment. Ideally, for a predictive test such as ER and PR IHC, test validation would demonstrate prediction of clinical outcome (e.g., response to tamoxifen), but it is recognized that few laboratories have such resources available. Therefore, these validation guidelines recommend several alternative validation methods, all of which require showing 90% agreement for positive test results and 95% agreement for negative test results (recognizing that false negatives are a bigger potential problem with ER and PR IHC than are false positives). These methods can include comparing a laboratory’s ER/PR IHC assay results with results obtained in another laboratory using a testing method that has been validated against clinical outcome. As noted in the ASCO-CAP ER and PR testing guidelines, there are only a limited number of assays that can serve as a clinically validated standard, e.g., for ER analysis, and these assays employ the SP1, 1D5, 6F11, and the ER-2-23 clones.

The ER and PR IHC assays performed at PhenoPath Laboratories employ the rabbit monoclonal antibody SP1 for ER and the mouse monoclonal Pgr636 clone for PR. Both of these assays have undergone extensive technical as well as clinical validation, the latter employing a cohort of over 4,000 patients from the British Columbia Cancer Agency (Cheang MC et al., J Clin Oncol 24:5367-44, 2006).

Recommendations of Fitzgibbons et al for initial test validation for all laboratory-developed and laboratory-modified ER and PR IHC assays (i.e., those not incorporating an FDA-cleared assay) include comparing results of at least 40 positive and 40 negative cases, with at least ten of the positive cases showing low-level positivity (i.e., between 1 and 10% of cells positive). Please contact one of our friendly and helpful Client Services representatives at PhenoPath Laboratories to take advantage of the validation services for ER and PR (as well as HER2) IHC assays currently being offered to pathology laboratories across the United States.

PhenoPath Laboratories is pleased to announce the newest addition to our sales team, Kelly Lynn McHugh, Director of Business Development. Kelly is responsible for sales efforts throughout the eastern region of the US. Kelly is also actively involved in our business-to-business contract negotiations and the evaluation of various alliance models with our valued business partners.

Kelly attended the University of North Florida where she earned her B.S. degree in Health Science with an emphasis on chemistry. Kelly has lived in Florida since 1981 and now resides in Miami.

Kelly’s professional background includes a brief stint with Consolidated Laboratories, an entrepreneurial start up, five years in hospital sales with Quest Diagnostics, and seven years as Business Development Director with LabCorp.

In addition to her busy professional life, Kelly enjoys physical fitness, dancing and attending concert events for various musical artists. Her interests include cooking, entertaining friends and family, and traveling for fun.
In non-small cell lung cancer, approximately 5-7% of cases have translocations involving the anaplastic lymphoma kinase (ALK) gene and the human echinoderm microtubule-associated protein-like 4 (EML4) gene. Although standard tyrosine kinase inhibitors, such as those that target EGFR, inhibit ALK poorly, novel tyrosine kinase inhibitors have recently been developed that demonstrate dramatic clinical activity towards EML4-ALK positive lung cancers. PhenoPath Laboratories now offers an ALK FISH assay that has been validated to detect EML4-ALK translocations in lung cancer and this assay will aid in determining patient eligibility for this novel class of ALK-specific tyrosine kinase inhibitors.

References:

While relatively uncommon, the positive identification of germ cell tumors is of critical importance given the availability of effective and even curative therapy for many of them. And while the identification of many germ cell tumors, particularly in the testis and ovary, can be made based on evaluation of hematoxylin and eosin stains, more recently a series of immunohistochemical markers have proven useful in the subclassification of germ cell tumors into yolk sac tumor, seminoma, embryonal carcinoma, and choriocarcinoma, including placental alkaline phosphatase (PLAP), c-kit (CD117), CD30, glypican 3, and HCG. While each of these markers has utility, none can claim to be ‘germ cell specific.’ However, a novel marker, SALL4, has now been demonstrated to function as what can best be described as a ‘pan germ cell’ marker, distinguishing virtually all germ cell from nongerm cell tumors (1,2). SALL4 is a zinc finger nuclear transcription factor that is essential to early embryogenesis. In the study by Cao et al published last year in the Am J Surg Pathol, more than 90% of germ cell tumors, regardless of subtype, were demonstrated to be SALL4 positive. SALL4 also proved to be a superb marker for the identification of intratubular germ cell neoplasia (ITGCN), as well as spermatocytic seminomas, which are notorious for their failure to express germ cell markers. Of all 275 non-testicular tumors studied, very weak positive staining was seen in only 10, yielding a specificity of greater than 96%. In a subsequent publication, however, SALL4 expression was found to be equally effective in identifying metastatic germ cell tumors (3) as well as those arising in extragonadal sites (4). Caution should be employed, however, as a very recent study has demonstrated SALL4 as a marker of fetal gut differentiation, and expressed in hepatoid gastric carcinomas (5).

The major utility of SALL4 would therefore appear to be the identification of ITGCN and spermatocytic seminoma, e.g., in the testis, as well as the positive identification of metastatic germ cell tumors and those primary to extragonadal sites (e.g., the mediastinum and central nervous system).

References:
3. Cao D et al., Cancer 115:2640-51, 2009 metastatic
PhenoPath Laboratories is pleased to now offer a Real Time PCR assay to evaluate tumors for the most common activating KRAS mutations that involve codons 12 and 13. The PhenoPath KRAS Real Time PCR assay uses an allele-specific PCR method that has been validated to detect KRAS mutations when as little as 1% of the sample is involved by mutant DNA. This Real Time PCR methodology for KRAS mutation assessment has several advantages over traditional PCR, which include improved turnaround time, greater assay sensitivity and specificity with smaller DNA samples, and no need for capillary electrophoresis steps. The detection of KRAS mutations by the PhenoPath Real Time PCR assay will continue to provide critical and predictive information for you and your clinicians with regard to patient eligibility for anti-EGFR therapy.

VISIT US AT THE FOLLOWING MEETINGS
For up-to-date information, visit our website: www.phenopath.com

Clinical Cytometry Society Companion Meeting @ 2010 ASCP Annual Meeting
10/27/10, San Francisco Marriott Marquis, San Francisco, CA
Presentations
10/27/10, 2:15-5:15 PM: Steven J. Kussick, MD, PhD presents “Update in Clinical Cytometry” www.ascp.org

WSSP 2010 Fall Meeting
11/6/10, Fred Hutchinson Cancer Research Center, Seattle, WA
Presentations
11/6/10, 1:30-2:45 PM: Harry Hwang, MD presents “Molecular Testing in Lung and Colorectal Cancer: What a Pathologist Needs to Know” www.wsspath.org

California Society of Pathologists 63rd Annual Convention: Seminars in Pathology
12/1/10 - 12/4/10, Hyatt Regency San Francisco in Embarcadero Center, San Francisco, CA
Presentations
12/3/10, 11:00 AM to Noon: Allen M. Gown, MD presents Special Lecture “W/U of Unknown Primary”
12/4/10, 8:30 AM to Noon: Allen M. Gown, MD presents “Diagnostic Problems in Surgical Pathology”
PhenoPath Booth Exhibit www.calpath.org

Harvard Medical School & Massachusetts General Hospital present Surgical Pathology for the Practicing Pathologist
1/15-18, 2011, Camelback Inn, Scottsdale, AZ
Presentations
1/17/11, 9:00-10:00 AM: Allen M. Gown, MD presents “Immunohistochemical Analysis of Carcinomas of Unknown Primary: Strategies and Solutions”
1/18/11, 7:30-8:30 AM: Allen M. Gown, MD presents “Novel Immunohistochemical Markers with Applications to Problems in Diagnostic Pathology”
1/18/11, 12:00-1:00 PM: Allen M. Gown, MD presents “Role of Immunohistochemistry in Evaluating Large and Small Cell Undifferentiated Malignant Tumors” www.cme.hms.harvard.edu/courses/scottsdale

Florida Society of Pathologists 37th Annual Anatomic Pathology Conference
2/11/11 - 2/13/11, Disney’s Grand Floridian Resort & Spa, Lake Buena Vista, FL
PhenoPath Booth Exhibit www.flpath.org/

USCAP 2011
2/26/11 - 3/4/11, Henry B. Gonzalez Convention Center, San Antonio, TX
PhenoPath Booth Exhibit www.uscap.org
Dr. Nancy Kiviat, M.D., of Harborview Medical Center, Seattle, WA, presented “New Approaches to the Diagnosis, Detection, Management and Prevention of Cervical Neoplasia” at the Quarterly Pathology/Immunohistochemistry Conference on Monday, October 18, 2010.

Over the last decade, Dr. Kiviat has served as the Chair of the Department of Anatomic Pathology at Harborview Medical Center, as well as Professor of Pathology, and Adjunct Professor in the Dept. of Medicine at the University of Washington.

In June, she stepped down as Chair to focus on the development of Molecular Diagnostics at Harborview Medical Center. Dr. Kiviat is also a Full Member with a joint appointment in the Program in Cancer Biology at the Fred Hutchinson Cancer Research Center. Dr. Kiviat is board-certified by the American Board of Pathology in anatomic pathology and cytopathology.

Dr. Kiviat's research focuses on studies of HIV-1, HIV-2, and HPV-related cancers, as well as breast cancer, especially in Africa. She directs projects examining issues related to cervical cancer control, both in developing countries and in the U.S., and studies exploring management of women in this country with abnormal Pap smears. She directs several studies examining risk factors for HIV-1 and HIV-2 genital tract shedding in women and men. In addition, over the last 5 years Dr. Kiviat has been involved in several projects examining the development of biomarkers for detection of cervical, heart, and ovarian cancer. Currently there are ongoing NIH-funded projects in Seattle and Senegal, West Africa.

Dr. Kiviat has published over 200 peer-reviewed articles. Dr. Kiviat is also a renowned speaker who has lectured extensively nationally and internationally in the field of anatomic pathology.