Along with the new year, a new crop of antibodies and assays are now available at PhenoPath Laboratories. Please call our Client Services staff or pathologists should you have specific questions about any of these assays.

KAPPA LIGHT CHAIN GENE REARRANGEMENT PCR

PhenoPath Laboratories is proud to announce kappa gene rearrangement PCR as a new molecular test offering. This test is based on the Euroclonality/BIOMED-2 consortium consensus primers for detection of kappa gene rearrangements in B cell lymphoid proliferations, and is of great utility in identifying clonal rearrangements when the IgH chain gene rearrangement PCR fails to do so. In normal B cell development, somatic recombination of the kappa light chain gene locus follows IgH gene rearrangement. If the kappa gene rearrangement produces a non-functional Vk-Jk product, segmental deletion of the non-functional rearrangement may occur with the kappa-deleting element (KDE). As the KDE rearrangement is typically not susceptible to somatic hypermutation, it therefore provides an attractive target for the detection of a clonal rearrangement when such somatic hypermutation causes the IgH chain gene PCR to fail. Use of kappa gene rearrangement PCR in conjunction with typical IgH chain gene PCR can allow for the detection of up to ~90% of B cell clonal rearrangements. PhenoPath Laboratories recommends use of kappa PCR as a reflexive test in most B cell gene rearrangement cases when the IgH gene PCR test is negative and the case is suspicious for a clonal rearrangement. In addition, use of this test in parallel with IgH chain gene rearrangement may be warranted in high priority aggressive B cell lymphoma cases. The PhenoPath Molecular Laboratory has optimized this test to detect clonal rearrangements in both fresh and paraffin-embedded tissues to a level of ~5% sensitivity. Please contact PhenoPath Labs Client Services for further information.

References:

BRACHYURY

Chordomas are rare malignant tumors that typically present along the spine, with almost half occurring in the sacrococcygeal region and almost 40% at the skull base. These tumors can display a characteristic histology, which includes nesting in a lobular fashion, and the presence of cells showing prominent vacuolization (“physalipherous” cells). In reality, however, there can be significant morphologic variability in the histologic appearance of these tumors, and while virtually all such tumors express cytokeration, co-expression of S100 protein has been described in 30-90% of tumors. Very recently, an antibody to a nuclear transcription factor called brachyury has been identified as a specific marker of both chordomas and of notochord, the embryological tissue to which chordomas are related. Most of the published studies have demonstrated that brachyury IHC is particularly helpful in distinguishing chondroid chordomas (positive) from chondrosarcomas (negative), as well as distinguishing chordomas (positive) from other ‘morphological mimics’, e.g., metastatic clear cell renal cell carcinomas and germ cell tumors (negative). One caveat in the application of this antibody is that brachyury is generally negative in areas of dedifferentiation of chordomas. Despite the latter, brachyury represents a powerful new marker to assist in the identification of chordomas, as well as distinction from histological mimics.

References:

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ARGINASE-1 Over the years, there have been described a number of putative liver-restricted immunohistochemical markers employed in the identification of hepatocellular carcinoma and its distinction from carcinomas metastatic to the liver. Some of these markers include alpha-fetoprotein, glypican-3, the presence of CEA- or CD10-defined bile canalicular structures in the tumor cells, the presence of CD34+ sinusoidal lining cells, and more recently the expression of the urea cycle enzyme, CPS-1 (carbamoyl phosphate synthetase), as identified by the HepPar1 antibody. The latter, in particular, was initially demonstrated to be a marker of high sensitivity and specificity for hepatocellular carcinoma, but more recent studies have demonstrated its shortcomings: the HepPar1 antibody displays a relative lack of sensitivity in the context of poorly differentiated hepatocellular carcinomas, and shows considerable “false positive” immunostaining in a subset of gastric, pulmonary, and other carcinomas, particularly (but not restricted to) those with ‘hepatoid’ features. However, another urea cycle enzyme, arginase-1, has been recently demonstrated to outperform HepPar1 as a marker of hepatocellular carcinoma. Unlike the HepPar1-defined CPS-1, arginase-1 was not found to be expressed in any gastric, pulmonary, or other non-hepatocellular carcinomas, and was found to be expressed in 96% of all hepatocellular carcinomas (v. 71% positive for the HepPar1-defined CPS-1), including 86% of poorly differentiated tumors. These data suggest that arginase-1 appears to represent the ‘king’ of hepatocellular carcinoma markers. As noted in the accompanying image, arginase-1 expression is found in both the nucleus and cytoplasm.


NUT midline carcinoma is a recently recognized, highly aggressive and lethal carcinoma without predilection for either sex. A highly aggressive tumor with an average survival time of less than one year, it was initially thought to be exclusively a childhood cancer; however, it has recently been shown that NUT midline carcinomas can affect people of all ages. Although NUT midline carcinomas are thought to be rare, they can be morphologically indistinguishable from other poorly differentiated carcinomas, and thus their true incidence is unknown. Indeed, one recent report found that approximately 20% of undifferentiated carcinomas of the upper aerodigestive tract not associated with EBV were found to represent NUT midline carcinomas. On H&E histology, NUT midline carcinomas generally present as monomorphic, poorly differentiated carcinomas with varying degrees of squamous differentiation; however, they can also mimic the appearance of germ cell tumors, PNET/ES, and lymphomas. NUT midline carcinomas are defined by the presence of chromosomal rearrangements involving the NUT (NUclear protein in T estis) gene, which is located on chromosome 15q14. In approximately 80% of cases the chromosomal translocation occurs between NUT and BRD4 on chromosome 19, resulting in the formation of a BRD4-NUT fusion gene and overexpression of the NUT protein. While FISH studies can theoretically be employed to confirm the diagnosis of NUT carcinoma, immunohistochemistry has proven to be the most efficacious method. Using a newly available monoclonal antibody to the NUT protein, a sensitivity of 87% and a specificity of 100% for NUT midline carcinomas was recently described, i.e., there was no positivity amongst 889 non-NUT midline carcinomas examined.

Reference:

Napsin A The thyroid transcription factor-1 (TTF-1) has proved over the years to be a remarkable marker of carcinomas of the lung, both non-neuroendocrine and neuroendocrine, although the sensitivity of this marker varies considerably amongst the various histologic subtypes (i.e., it is quite high in small cell carcinoma, in excess of 95%, but exceedingly low in mucinous bronchioloalveolar carcinomas and squamous cell carcinomas). TTF-1 expression has also been demonstrated, albeit usually at lower levels, in some carcinomas of the ovary, colon, bladder, prostate and other sites. However, evidence has been accumulating that another lung-restricted marker, napsin A, can complement TTF-1 by demonstrating comparable sensitivity and increased specificity. Napsin A is a member of the aspartic proteinase family of proteins, and in a number of studies has demonstrated a sensitivity in the range of 80-90% for lung non-neuroendocrine carcinoma. Apart from renal tubules and renal cell carcinomas, it does not appear to be expressed in epithelial cells or tumors outside of the lung. Immunohistochemistry demonstrates that napsin A expression in positive tumors manifests a coarse granular pattern as shown in the accompanying image. Napsin A has replaced surfactant apoA at PhenoPath as a ‘second’ lung-restricted marker.

References:

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Carbonic Anhydrase IX (CA IX) is a member of a family of zinc metalloenzymes that play a role in the regulation of extracellular and intracellular pH by assisting in the conversion of carbon dioxide and water into carbonic acid, protons, and bicarbonate ions. Due to its role in the regulation of pH, CA IX is inducible by hypoxia and influences cell proliferation, oncogenesis, and tumor progression. CA IX is a transmembrane protein with diverse tissue distribution, but is more commonly expressed in the normal human gastrointestinal tract and not in most other normal tissue. However, CA IX is expressed in a number of different tumors including carcinomas of the lung, breast, cervix, uterus, colon, bladder, and esophagus, and is most commonly expressed in renal cell carcinomas (RCC). Studies by Genega et al have shown that the expression of CA IX may be higher in clear cell RCC than other histologic types, and is associated with the grade of the tumor and clinical prognosis. Investigators have also shown that patients with tumors that have high CA IX expression may be more likely to respond to interleukin-2 (IL-2) therapy. Validation studies at PhenoPath have shown that expression of CA IX by immunohistochemistry (IHC) is present in normal gastric mucosa, biliary tract, and small intestine, but is negative in other normal tissues tested, including thyroid, lung, breast, kidney, bladder, prostate, colon, and rectum. Studies of renal tumors showed strong positive staining of 70% RCC, including 89% clear cell, with focal weak staining of 56% chromophobe types, respectively. The detection of CA IX by IHC may be useful when combined with other markers for distinguishing clear cell from chromophobe RCC and oncocytomas. However, CA IX is expressed in high-grade RCC and urothelial carcinomas, as well as other epithelial malignancies so it may not be useful in identifying carcinomas of unknown primary sites. Future important use of the detection of CA IX will be to correlate response to targeted therapies for RCC.

References:

CLIENT SATISFACTION SURVEY

We value our clients. To ensure we are meeting your needs and to realize opportunities for improvements to our service, we would appreciate your taking a few minutes to complete our on-line survey at www.phenopath.com.

Completed surveys will be entered into a random drawing for an Apple iPad (one survey per person). Participants may also submit a survey anonymously.

DEADLINE: FEBRUARY 15, 2011

2011 PhenoPath Calendars Available

PhenoPath has published its first annual PhenoPath wall calendar, spotlighting the high quality work provided year-round by our talented and dedicated team. To get your copy, contact lab@phenopath.com. Limited supply available.
Dr. Anais Malpica

Featured at Winter Quarterly Conference

Anais Malpica, M.D., of the University of Texas, M.D. Anderson Cancer Center, Houston, TX, will present “Mucinous Tumors in the Ovary, an Update” at the Quarterly Pathology/Immunohistochemistry Conference on Thursday, February 3, 2011. The format of the conference is a social hour commencing at 6:30 p.m., followed by Dr. Malpica’s lecture at 7:30 p.m. A light catered dinner will be served during the social hour.

Dr. Malpica is the Director of the Gynecologic Pathology Fellowship Program, Chief of the Section of Gynecologic Pathology, and Professor in the Department of Pathology at the University of Texas, M.D. Anderson Cancer Center.

Dr. Malpica’s research efforts are concentrated on understanding the clinicopathologic and immunohistochemical features of certain neoplasms and non-neoplastic processes of the gynecologic tract and female peritoneum. Her studies encompass the following areas:

1) Grading ovarian serous carcinoma;
2) The expression of hormone receptors in low- and high-grade serous carcinoma;
3) Ovarian serous tumors of low malignant potential with lymph node involvement;
4) Mucinous tumors of low malignant potential of the ovary;
5) Metastatic mucinous tumors to the ovary;
6) Clear cell carcinoma of the endometrium;
7) Undifferentiated carcinoma of the endometrium;
8) Immunohistochemical features of smooth muscle tumors of the uterus;
9) Dermatofibrosarcoma protuberans of the vulva; and
10) Peritoneal lesions such as multicystic peritoneal inclusion cysts, well-differentiated papillary mesothelioma and malignant mesothelioma of the female peritoneum.

Currently, Dr. Malpica is a member of the Graduate Medical Education Committee. She also serves on the Executive Committee of the Department of Pathology and Gynecologic Oncology Research Working Group.

Dr. Malpica is an editorial board member for the International Journal of Gynecological Pathology and Archives of Pathology and Laboratory Medicine. She also previously served on the editorial board for the journal Gynecologic Oncology. Furthermore, she is a reviewer for three other journals. Finally, over her postgraduate and professional career, Dr. Malpica has authored 165 articles published in peer-reviewed journals, 17 invited articles, 12 book chapters, one book, and numerous abstracts.