PhenoPath is pleased to announce the launch of extended RAS gene testing. PhenoPath now offers in-house KRAS and NRAS testing that aligns with the joint guidelines recently issued by ASCP, CAP, AMP and ASCO (see reference below). These consensus testing recommendations state that all patients with colorectal carcinoma being considered for anti-EGFR therapy must undergo “extended” RAS mutation testing that includes the following mutations: KRAS codons 12 and 13 (exon 2), KRAS codons 59 and 61 (exon 3), KRAS codons 117 and 146 (exon 4), NRAS codons 12 and 13 (exon 2), NRAS codons 59 and 61 (exon 3), and NRAS codons 117 and 146 (exon 4).

PhenoPath’s updated RAS testing menu includes the FDA-approved cobas® KRAS Mutation Test, which detects KRAS codon 12 and 13 mutations, and our extended RAS assay which utilizes a pyrosequencing-based method to detect mutations in the remaining KRAS and NRAS codons listed above. The FDA-approved Roche cobas® KRAS assay replaces PhenoPath’s prior test and similarly detects the seven most common KRAS exon 2 mutations.

PhenoPath recommends ordering RAS mutation testing in a reflexive manner, starting with the FDA-approved cobas® KRAS Mutation Test to test for KRAS exon 2 mutations, followed by extended RAS mutation testing if a KRAS exon 2 mutation is not detected.

CPT Code(s): 81276, 81311; 88381 may apply (reference only; CPTs may vary)

Turnaround Time: Within 5-8 business days of receipt

Specimen Requirements: Formalin-fixed, paraffin-embedded (FFPE) tissue block (preferred) or unstained slides (10 slides are usually sufficient)


PhenoPath has recently launched the t(8;14)MYC/IgH dual color dual fusion (DCDF) FISH assay for both fresh and FFPE tissues. This DCDF FISH assay will specifically detect the t(8;14) translocation involving the MYC and immunoglobulin heavy chain (IgH) genes and is of particular clinical utility in the evaluation of “double-hit” B cell lymphomas. A recent study has shown that patients with B cell lymphomas harboring a MYC rearrangement with an immunoglobulin gene translocation partner (i.e., IgH, Igκ, or Igλ genes) had shorter overall survival compared with MYC-non-Ig and MYC-negative patients. This same study showed that the MYC-non Ig translocation positive patients and MYC-negative patients had no survival difference (Copie-Bergmann et al., Blood 2015;126:2466-2474).

PhenoPath therefore recommends that the t(8;14) FISH assay be performed for further patient risk stratification as a reflex add-on test to the aggressive B-cell lymphoma panel, when the MYC break-apart (BRK) FISH assay is positive. Note that the t(8;14) FISH assay should not be considered a replacement for the MYC BRK FISH assay, which detects any rearrangement involving the C-MYC gene, including those with IgH, Igκ, and Igλ, and non-immunoglobulin genes.

Please contact Client Services at lab@phenopath.com or 888-927-4366, or visit www.phenopath.com, for more information.
New Marker of Small Cell Carcinoma of the Ovary – BRG1 (SMARCA4)

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare, poorly-differentiated ovarian malignancy, typically presenting in young women. Given the histology of this tumor, composed of small cells with hyperchromatic nuclei, the differential diagnosis typically includes other small blue round cell tumors; until recently, however, there have been no positive markers that can help define this tumor, and the diagnosis has often been one of exclusion. However, the discovery of mutations in the BRG1 (SMARCA4) gene in SCCOHT, which result in loss of protein expression, have opened the possibility of using IHC for loss of expression of the latter as a novel positive marker of SCCOHT. The presence of a mutation of BRG1/SMARCA4, a putative tumor suppressor, can be inferred from the IHC results showing loss of expression in SCCOHT (Ramos P et al., 2014). Several recent studies have confirmed the utility of this marker in the study of tumors presenting in the ovary. For example, in the definitive study of Conlon et al. (2016), loss of BRG1/SMARCA4 showed a sensitivity of 94% and a specificity of over 99% (279 other tumors tested). Antibodies to BRG1/SMARCA4 are now available at PhenoPath as highly sensitive and specific markers of SCCOHT. In addition to the use of antibodies to BRG1/SMARCA4 loss as a marker of SCCOHT, more recently loss of BRG1/SMARCA4 has been found in a subset of aggressive thoracic sarcomas, many of which display rhabdoid histologic features. In addition, SMARCA4 deficient lung adenocarcinomas have been identified as part of the subset manifesting an absence of TTF1 expression and HepPar1 positivity.

References:

Note complete loss of expression of BRG1/SMARCA4 from tumor nuclei compared with normal endothelial cells

Leong’s Manual of Diagnostic Antibodies for Immunohistology

A new book has been recently published that features major contributions by PhenoPath pathologists. Entitled, Leong’s Manual of Diagnostic Antibodies for Immunohistology (Cambridge University Press, Cambridge UK, 2016), it is the 3rd edition of a book first published by the late Dr. Anthony S.-Y. Leong, one of the seminal contributors to the field of diagnostic immunohistochemistry, along with Drs. Kumarasen Cooper and F. Joel W.-M. Leong. The book provides a comprehensive catalog of the major antibodies employed in diagnostic immunohistochemistry, giving thumbnail sketches of the background of each marker, the principal diagnostic applications, and sources of the antibody, along with references. Dr. Allen Gown is one of the editors of the new 3rd edition (along with Drs. Runjan Chetty and Kumarasen Cooper), with major contributions by PhenoPath pathologists Drs. Sandra Bohling, Harry Hwang, Steven Kussick, and David Ng.

At the end of July, the FDA also granted accelerated approval to nivolumab (OPDIVO®), another therapy. dMMR and MSI-H tumors have a higher frequency of DNA mutations than tumors with proficient MMR (pMMR) status, and, as a result, higher levels of abnormal antigens. It has been hypothesized that the patient’s immune cells may be more likely to recognize and attack dMMR and MSI-H tumor cells owing to the presence of larger numbers of mutated proteins in the latter.

Pembrolizumab (KEYTRUDA®) has shown substantial efficacy in the treatment of non small cell lung cancer, particularly in those patients manifesting PD-L1 expression levels within the tumor cell population of ≥1% (2nd line therapy) or ≥ 50% (first line therapy). However, more recent studies have demonstrated efficacy of pembrolizumab in the context of adult and pediatric patients with unresectable or metastatic solid tumors which manifest either microsatellite instability-high (MSI-H), identified by PCR, or mismatch repair deficiency (dMMR) as evidenced by immunohistochemistry. Colorectal, endometrial and gastrointestinal cancers have the highest rates of these mutations, but MSI-H and dMMR also appear, albeit less commonly, in cancers arising in the breast, prostate, bladder, thyroid gland and other sites. This ‘blanket’ FDA approval thus adds a second ‘biomarker’, beyond documenting PD-L1 expression in the tumor, that can help select patients for this novel therapy.

If you have any questions about testing for eligibility for PD-1 targeted therapies, please call Phenopath and ask to speak with one of our pathologists. At Phenopath, we offer all the testing for the different drugs targeting the PD-1/PD-L1 pathway, and all the expertise to help you and your oncologists obtain the most appropriate test. Download our updated Biomarker Testing for Checkpoint Inhibitors guide at www.phenopath.com, or contact Client Services to obtain a copy at 888-927-4366 or lab@phenopath.com

The International Society for Immunohistochemistry and Molecular Morphology (ISIMM) is a newly formed scholarly society devoted to the promotion of improved practice of diagnostic immunohistochemistry worldwide through creation of a forum for the discussion and exchange of new knowledge in immunohistochemistry and molecular morphology. isimm.org

ASCP 2017, Annual Meeting, September 6-8, 2017, Chicago, IL
Friday, September 8, 2017, 8:00AM-11:10AM, Morning Session
“Real World Immunohistochemistry: What You Need To Know to Successfully Employ It - ISIMM”

Speakers: Allen M. Gown, MD, Blake Gilks, MD, Clive R Taylor, MD, Emina Tolarovic, MD, PhD

Dr. Gown will speak on “Rational and Cost Effective Use of Antibody Panels in Diagnostic Immunohistochemistry.”

Over the past 20 years, immunohistochemistry (IHC) has evolved to take a central role in the practice of surgical pathology. Lymphomas, breast carcinomas, lung carcinomas and other tumor types are now routinely subclassified based on their molecular features, and this information guides patient care. The role of IHC in predicting response to treatment changes the expectations we place on the assay; it is no longer an adjunct to H&E but a stand alone test with a need for high levels of sensitivity and specificity, similar to an assay in the clinical pathology laboratory. In this session, a panel of four international experts will offer insights and feedback on the current and future role of IHC, and guidance on how to appropriately control and validate IHC tests. It will include presentation of the consensus recommendations of an expert panel on IHC quality assurance.

For more information, go to www.ascp.org/content/2017.
Thomas Brenn, MD, PhD will present “Pitfalls in the Diagnosis of Melanoma” at the PhenoPath Conference at 7:00pm on Thursday, September 14, 2017. Dr. Brenn will also give a lecture at noon the same day entitled, “Mesenchymal Tumors of the Skin” to which you are invited as well.

Dr. Thomas Brenn graduated from the Ruprecht-Karls University of Heidelberg (Heidelberg, Germany) where he received his MD and PhD degrees. After postdoctoral fellowships in the Departments of Genetics and Pathology at Stanford University (Stanford, CA, USA) and residency training in Anatomic Pathology at the Brigham and Women’s Hospital (Boston, MA, USA), he pursued subspecialty fellowships with Drs. Phillip McKee and Christopher Fletcher in Dermatopathology, Soft Tissue Tumor Pathology and Surgical Pathology. In 2003, Dr. Brenn joined the faculty of the Brigham and Women’s Hospital and Harvard Medical School and was a consultant in pathology at Dana Farber Cancer Institute. In 2007, he was made Consultant Dermatopathologist and Head of Dermatopathology at NHS Lothian University Hospitals Trust and Honorary Senior Lecturer at the University of Edinburgh (Edinburgh, Scotland). He is the current Chair of the Skin Working Group of the European Society of Pathology (ESP), Chief Examiner for the RCPath Diploma in Dermatopathology and Associate Editor for Histopathology. He has contributed to major textbooks in Dermatology and Dermatopathology and is a co-editor of the 4th edition of McKee’s Pathology of the Skin. His clinical and research interests are in the areas of cutaneous soft tissue tumors, skin adnexal tumors as well as melanocytic tumor pathology.