Special Histochemical Stains and Immunohistochemical Stains

Policy # 00901
Original Effective Date: 01/01/2025
Current Effective Date: 01/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider special stains ordered by a pathologist or based on the documented recommendation of a pathologist after first reviewing a standard hematoxylin & eosin (H&E) or other standard first line stain to be **eligible for coverage.****

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers all of the following to be **not medically necessary**:**

- Reflex templates or pre-orders for special stains and/or immunohistochemical (IHC) stains prior to review of the routine hematoxylin and eosin (H&E) stain by the pathologist; or
- Use of special stains and/or IHC stains without clinical evidence that the stain is actionable or provides the treating physician with information that changes patient management; or
- Use of added stains when the diagnosis is already known based on morphologic evaluation of the primary stain.

Policy Guidelines

The surgical pathology report is expected to designate the specific block(s) upon which IHC testing is performed, the reason and results for IHC testing, the specific markers, and whether single antibody or a cocktail of antibodies is utilized. A statement alone in the pathology report that states, "IHC confirms the diagnosis" will not be considered reasonable and necessary.

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Special stains and IHC stains may be considered medically necessary even though they have not been specifically requested by the treating provider, when after review of routine H&E stains, the pathologist deems them necessary and ALL the following criteria are met:

- Services are medically necessary so that a complete and accurate diagnosis can be reported to the treating physician/practitioner;
- Results of the tests are communicated to and are used by the treating physician/practitioner in the treatment of the beneficiary; and
- Pathologist documents in their report why additional testing was done.

This indicates that reflex templates or pre-orders for special stains and/or IHC stains prior to review of the routine H&E stain by the pathologist are not reasonable and necessary. A pathologist must first review the H&E stain prior to ordering special stains or IHC.

Exceptions do exist and are recognized standards of care in the practice of pathology. These exceptions include but are not limited to renal, liver, and neuromuscular biopsies, and for the suspicion of an infectious disease, particularly in an immune compromised patient. In certain clearly defined circumstances, it may be reasonable to perform some IHC on sentinel lymph nodes when the frozen sections show they are free of tumor. The medical necessity for the special stain or IHC studies, and the results of the stain or IHC, must be documented in the surgical pathology report.

Background/Overview

Routine H&E staining is the corner stone of tissue-based microscopic diagnosis. Thin sections of tissue are stained with H&E to visualize the tissue morphology. Hematoxylin dye stains the cell nuclei blue and the eosin dye stains other structures pink/red. “Acid hematoxylin” is not a special stain given that all hemotoxylin stains are acidic. This stain has never been recognized by the Biological Stain Commission. It is not reasonable and necessary to claim this stain as a special stain. H&E staining is included as part of pathology services.

Special stains are called “special” because they are dyes used to stain particular tissues, structures, or pathogens such as bacteria that may not be visible by routine H&E staining. Special stains can identify whether a substance is present or absent, where the substance is located in the tissue specimen, and frequently, how many, or how much of a substance is present. There are special stains to identify bacteria, yeast, and fungi; for connective tissue, muscle, collagen, lipid and fibrin; for

nuclei acids; and multi-purpose stains to identify basement membranes, mucins, and various other cellular constituents. Two major categories for special stains are recognized: One is specifically for microorganisms; the second is for all other purposes (not microorganisms) and specifically excludes detection of enzyme constituents.

Immunohistochemistry (IHC) is a powerful tool for identifying substances and cells in tissue sections using the specificity of antigen-antibody reactions, where the antibody is linked to a colored indicator (stain) that can be seen with a microscope. More than 400 distinct antibody targets are currently available with varying sensitivity and specificity for a given target. A major use of IHC is to identify poorly differentiated malignant neoplasms (tumors) such as a carcinoma, lymphoma, melanoma, and sarcoma. Some IHC stains are useful in determining the primary site of a metastatic neoplasm, and others are used to guide specific therapies (e.g., Her2 IHC to determine potential response to trastuzumab).

IHC for Breast Pathology
The clinical care of patients with breast cancer depends upon the accurate diagnosis and the assessment of biomarkers. Hormone receptor assays and human epidermal growth factor receptor 2 (Her2) testing are recommended on all primary **invasive** breast cancers and on recurrent or metastatic cancers. At the current time, there is no recommendation for Her2 testing on in situ breast lesions outside of a clinical trial. While there are a number of promising additional biomarkers, such as Ki-67, PI3K and gene expression assays, the College of American Pathologists (CAP), the American Society of Clinical Oncologists®‡ (ASCO®‡) and the National Comprehensive Cancer Network®‡ (NCCN®‡) have not recognized these markers in patient treatment pathways.

Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) are well-established prognostic markers in invasive breast cancer management. The triple negative breast carcinoma subtype (ER-/PR-/Her2-) has been associated with worse overall prognosis in comparison with other subtypes in study populations consisting of ethnic minorities and young women.

Ki-67 expression is a biomarker for proliferation and has been associated with response to therapy, but methods of measurement are controversial. In December 2013 the CAP reported that there is “a lack of consensus on scoring, definition of low versus high expression, an appropriate cut point for positivity, or which part of the tumor should be scored (e.g., leading edge, hot spots, overall average)

((CAP)). There is also paucity of data on the effects of pre-analytical variables (e.g., ischemic time, length of fixation, antigen retrieval) on Ki-67 staining. For these reasons, routine testing of breast cancers for Ki-67 expression is not currently recommended by either ASCO®‡ or the NCCN®‡."

More recent evidence identifies the use of the PharmDx Ki-67 (MIB-1) by Agilent Technologies as a companion diagnostic test shown to define a high-risk population along with high risk clinicopathologic features (i.e., nodal status, tumor size, and grade). This is used to identify patients with an even greater risk of recurrence and thus has prognostic value in the population of patients with ER+, HER2- lymph node positive high risk breast cancer for use of the Cyclin-dependent 4 and 6 (CDK 4/6) inhibitor abermaciclib (Eli Lilly and Company) as adjuvant therapy in addition to endocrine therapy. With 19 months of median follow up time abemaciclib + endocrine therapy (ET) resulted in a 29% reduction in the risk of developing an invasive disease-free survival (IDFS) event [hazard ratio (HR) = 0.71, 95% confidence interval (CI) 0.58-0.87; nominal P = 0.0009]. At the additional follow-up analysis, with 27 months median follow-up and 90% of patients off treatment, IDFS (HR = 0.70, 95% CI 0.59-0.82; nominal P < 0.0001) and DRFS (HR = 0.69, 95% CI 0.57-0.83; nominal P < 0.0001) benefit was maintained. The absolute improvements in 3-year IDFS and distant relapse free survival (DRFS) rates were 5.4% and 4.2%, respectively. Whereas a high centrally determined Ki-67 index defined as greater than or equal to 20% was prognostic for recurrence in this treatment setting, it was not predictive of the treatment effect as abemaciclib benefit was observed regardless of Ki-67 index. Safety data were consistent with the known abemaciclib risk profile. This is supported by updates to the National Comprehensive Cancer Network (NCCN®‡) Guidelines and International Ki67 workgroup.

The clinical utility of testing for hormone receptors in in-situ breast cancer differs from those of invasive disease. 2020 ASCO®‡/CAP Guidelines for Ductal Carcinoma in-situ (DCIS) testing state: “ER testing in cases of newly diagnosed DCIS (without associated invasion) is recommended to determine potential benefit of endocrine therapies to reduce risk of future breast cancer. PR testing is considered optional” [recommendation 4, and subsequent discussion]. This is supported by the peer reviewed literature which supports the use of ER testing for in-situ breast neoplasia. The addition of PR testing should be determined in those settings where it has been deemed reasonable and necessary and its relevance has been documented in the pathology report and individual patient. Clinical guidelines have not been established for the use of Her2 or other biomarkers in patients with non-invasive breast neoplasia.

Basal phenotype markers (eg, IHC for CK5) are not routinely necessary. IHC stains such as E-cadherin, p27, or high molecular weight cytokeratin to distinguish ductal from lobular differentiation are not reasonable and necessary on every breast case, nor are myoepithelial cell markers such as p63 or smooth muscle myosin heavy chain routinely necessary on every case. The pathologist should determine the use of these markers when there are ambiguous histologic/morphologic findings on H&E and the distinction between lobular and ductal differentiation or usual ductal hyperplasia (UDH) versus atypical ductal hyperplasia (ADH) and DCIS are critical to the clinical management of the patient and its rationale is documented in the pathology report.

Special Stains and/or IHC for Gastrointestinal (GI) Pathology
Pathologists are often called upon to microscopically diagnose abnormalities seen on endoscopic exam of the esophagus, stomach, duodenum, and colon. Biopsy specimens constitute an important diagnostic patient service. Most normal and abnormal conditions of these organs can be detected by the use of the routine H&E stain alone.

For most esophageal, gastric, and duodenal specimens, it is not reasonable or necessary to perform special stains such as alcian blue – periodic acid Schiff (AB-PAS), or other mucin stains, such as diastase – PAS (D-PAS), or IHC stains such CDX-2 to determine if clinically meaningful intestinal metaplasia is present. In addition, it is not usually reasonable and necessary to perform special stains or IHC to determine the presence of H. pylori organisms.

Scientific data demonstrates that the combined number of gastric biopsies requiring special stains or IHC is roughly 20% of biopsies received and examined in a pathology practice. GI specialty practices with a large GI referral base or GI consultant pathologists may sometimes exceed this relative number of special stains/IHC, but one would not expect to see routine high utilization of special stains or IHC. To check utilization, we encourage providers to perform a self-audit on the number of separate gastric biopsies as compared to ancillary stains. The ancillary stain group should be less than 20% of the total gastric biopsies submitted. Providers that exceed the 20% criteria may be subject to additional action.

Over-utilization of special stains has also been observed with duodenal biopsies where CD3 and AB/D-PAS are used to help exclude intraepithelial lymphocytosis and gastric metaplasia. Both of these conditions, if present, are easily recognizable on H&E morphology. Mucin stains such as AB-

PAS or DPAS would be reasonable and necessary in limited circumstances, and rarely is CD3 warranted on duodenal biopsies which show villous architectural abnormalities.

Architectural and histologic features define colonic polyps including hyperplastic, inflammatory, and adenomatous lesions. Special stains and/or IHC stains are not reasonable and necessary for colon polyps despite textbooks noting, for example, thickened subepithelial collagen demonstrated by trichrome or collagen staining in hyperplastic polyps, or carcinoembryonic antigen (CEA) overexpression in hyperplastic polyps. While the information is of academic interest, special stains are not reasonable and necessary to make the diagnosis of various colonic polyps.

Lynch Syndrome (LS) is a genetic predisposition to colorectal cancer (CRC) and certain other malignancies, as a result of an autosomal dominant germline MMR gene mutation. There is benefit in identifying an asymptomatic individual with LS as it allows for early and intensive surveillance to detect colon polyps, which can prevent malignancies and reduce the risk of premature death.

- LS tumor screening for microsatellite instability (MSI)/deoxyribonucleic acid (DNA) mismatch repair (MLH1, MSH2, MSH6 and PMS2) by qualitative IHC is considered medically necessary and covered by Medicare for individuals with newly diagnosed colorectal cancer or endometrial cancer.

No definitive or clearly superior algorithm for LS screening has been recommended. MSI testing or IHC testing (with or without *BRAF V600E* mutation testing) for MLH1, MSH2, MSH6 and PMS2 of the tumor tissue are examples of preliminary testing strategies that could be used to select patients for subsequent diagnostic testing. Diagnostic testing involves MMR gene mutation (and deletion/duplication) testing of the proband, usually using a blood sample. LS is most commonly caused by mutations in the 2 MMR genes, MLH1 and MSH2 and less commonly by mutations in MSH6 and PMS. The presence of a BRAF mutation essentially excludes LS as virtually 100% of individuals with LS do not carry the BRAF mutation. The use of BRAF mutation testing by IHC is usually restricted to CRC cases with absent staining for MLH1.

If IHC is normal and there is clinical evidence to consider additional testing, MMR gene mutation testing may be warranted. IHC testing for LS is qualitative and does not require the use of tumor morphometry for evaluation.

MMR/MSI testing is reasonable and necessary when beneficiaries with colorectal cancer, gastroesophageal junction cancer, small bowel cancer, endometrial cancer and other solid tumors are being considered for immune checkpoint inhibitor therapy as recommended in the ASCO endorsement of the College of American Pathologists Guidelines for Mismatch Repair and Microsatellite Instability Testing.

Special Stains and/or IHC for Prostate Pathology
The accuracy of the pathologic diagnosis of prostate cancer is critical for optimal patient care. The diagnosis can usually be made on morphologic features such as growth pattern, nuclear atypia, and the absence of basal cells. However, it may be difficult to reach a firm diagnosis by routine H&E stain for small foci of cancer in needle biopsies because many benign conditions can mimic prostate cancer.

The IHC diagnosis of prostate cancer depends on panels of markers because not absolutely specific and sensitive marker for prostate cancer has yet been identified. These panels usually include at least 1 basal cell marker, such as high-molecular-weight cytokeratin (HMWCK) or p63, and the prostate cancer-specific marker, alpha-methyl-CoA-Racemase (AMACR). Although AMACR is considered a useful IHC marker in the diagnosis of prostate cancer, due to non-standardized immunostaining protocols, interpretation criteria and heterogeneous staining pattern, there is wide variation in the sensitivity and specificity of AMACR immunoreactivity in the diagnosis of prostate cancer. Furthermore, because AMACR expression has been demonstrated in high-grade prostatic intraepithelial neoplasia (PIN), atypical adenomatous hyperplasia/adenosis and nephrogenic adenoma, it is recommended that AMACR is best used together with basal cell markers in the work up of highly suspicious morphologic foci. AMACAR alone is insufficient to establish a diagnosis of cancer.

PTEN and MYC may provide some prognostic information but neither is part of any standard treatment protocol and neither should be routinely performed. ERG is another IHC that is more likely to be positive in cancer than in benign tissue, but it does not add information to conventional PIN4 testing. Similarly, neuroendocrine markers, such as IHC for synaptophysin, may be indicated in cases of recurrent/metastatic prostate carcinoma that have undergone small cell transformation after hormone therapy. The latter marker is only necessary for high grade, undifferentiated tumors and should not be used routinely.

PIN4 is an IHC cocktail of CK5/14, p63 and P504S that is used primarily to differentiate normal and neoplastic epithelial tissues. In prostate tissue, CK5 and CK14 are detected in basal cells of normal glands and PIN which is a precursor lesion to prostatic adenocarcinoma. However, expression of CK5 and CK14 is not identified in invasive prostatic adenocarcinoma. P63 is detected in nuclei of basal epithelium in normal prostate glands, but is not expressed in malignant prostate tumors. The use of PIN4 is best restricted to evaluation of morphologically highly suspicious foci because P504S (aka AMACR) is not specific for prostatic adenocarcinoma.

The International Society of Urological Pathology (ISUP) recommendations state that at the current time, there are no prognostic IHC or molecular studies that are recommended to be routinely performed on biopsy or resection specimens.

Special Stains and/or IHC for Lung Cancer
Experts in pulmonary pathology recommend starting the evaluation of non-small cell carcinomas with a combination of TTF-1 and p40 or p63 IHCs. Often these two stains are all that are needed to come to a reasonable diagnosis and retain enough tumor sample to complete molecular studies. In rare patients, a few additional IHCs or mucin stains may be needed.

Ki-67/MIB-1
Ki-67 and MIB-1 monoclonal antibodies are directed against different epitopes of the same proliferation-related antigen. These stains are used to determine the proliferative rate of a tumor. Ki-67 antigen or protein (hereafter Ki-67) is present during all active phases of the cell cycle (G1, S, G2, and mitosis), but is absent from resting cells (G0). By measuring the amount of tumor cells expressing Ki-67, an estimate of DNA synthesis can be determined which has been found comparable to a mitotic count performed on a standard H&E slide. Furthermore, Ki-67/MIB-1 antibodies have suffered from a lack of international standardization which has limited their clinical usefulness. This is noted above in the discussion of breast cancers.

Ki67 has been shown to be useful in the management and grading of neuroendocrine tumors of the gastrointestinal tract and pancreas. The North American Neuroendocrine Tumor Society (NANETS) in its consensus 2020 guidelines for the management and treatment of neuroendocrine tumors states these tumors should be graded according to the World Health Organization (WHO) Classification of Digestive system Tumors. Grading recommends “Ki67 and/or mitotic rate should be obtained. When both mitotic rate and Ki67 are obtained and grade is discrepant the higher grade determined

by mitotic rate or Ki67 is assigned with Grade 1 (G1) tumors showing <2 mitoses/10 HPF or <3% Ki67, Grade 2 (G2) tumors showing 2-20 mitoses/10 HPF or 3-20% Ki67 and Grade 3 (G3) tumors showing >20 mitoses/10 HPF or Ki67 > 20%".

When referring to Thoracic (lung) neuroendocrine tumors the NANETS society in the same consensus 2020 guidelines quoted above states "mitotic rate should be obtained. Use of the WHO and International Association for the Study of Lung Cancer grading system is recommended. Mitotic rate in mitoses /10 HPF is recommended. Ki-67 may be considered. Ki-67 (when necessary) is recommended along with mitotic rate to classify Grade 3 (G3) neuroendocrine lung tumors where mitotic rate >10 mitoses/10 HPF and Ki67 >20% classifies these as poorly differentiated neuroendocrine tumors".

Ki67 can be used as an aid in the distinction of low grade versus high grade neuroendocrine tumors where the biopsy or cytology specimen is limited or suffers from significant artefact.

Ki-67 by IHC has clinical utility in the workup of lymphomas. Ki-67 has several established applications including:

- Final confirmation for the diagnosis of any low-grade lymphoma. A number of publications show a worse prognosis for follicular lymphomas which appear to be grade 1 or 2 but demonstrate high Ki-67 labeling. Similarly, small lymphocytic lymphomas/CLL with a high proliferative rate ("prolymphocytic progression") may be best detected with Ki-67.
- Distinguishing higher versus lower grade mantle cell lymphoma. A small percentage of cases behave as low grade rather than intermediate grade, and Ki-67 is the most accurate means to detect this subgroup. In addition, distinguishing the highly aggressive blastoid variant is aided by Ki-67 IHC testing.
- Recognizing Burkitt and Burkitt-like grouping as distinct from diffuse large B-cell type. One of the most important qualifying criteria is Ki-67 labeling at greater than 90%.
- Plasma cell myeloma proliferative rate has long been established as 1 of the most accurate prognostic markers.

IHC for Predictive Marker Tumor Profiling

ER, PR, and Her2 hormonal receptor status have demonstrated clinical utility in invasive breast cancer, as well as ER, and PR when appropriate, for in-situ breast cancer. ER and PR are performed

by IHC specifically for tamoxifen therapy. Her2 testing has proven clinical utility in esophago-gastric and gastric cancers to determine response to trastuzumab.

Similarly, the efficacy of imatinib, a CD117 inhibitor, is determined by the mutation status of CD117 expression (c-KIT mutation). CD117 by IHC has a proven clinical benefit in GIST, some advanced dermatofibrosarcoma protuberans (DFSP), some lymphoblastic and myeloid leukemias, and mast cell tumors, and is a covered Medicare service when medically necessary. All predictive tumor profiles must have peer reviewed analytical and clinical validity.

However, IHC testing as above is distinctly different from chemotherapy sensitivity and/or resistance testing profiles offered by some labs to assist physicians in their selection of specific chemotherapeutic agents based on IHC antigen or protein expression in individual tumors. The goal stated by these profiles is to select a drug or combination of drugs from a panel of drugs to which a tumor has greater expression, and to avoid drugs to which the tumor has less expression.

Neither the ASCO nor the NCCN has endorsed chemosensitivity tumor profile testing by IHC. ASCO has stated, "the use of CSRA's (chemosensitivity and resistance assays) to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting." While the NCCN's Guidelines for Ovarian Cancer (V3.2014) states "chemosensitivity/resistance and/or other biomarker assays are being used in some NCCN member institutions for decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available. The current level of evidence is not sufficient (Category 3) to supplant standard of care chemotherapy." The NCCN panel also stated that in vitro chemosensitivity testing to choose a chemotherapy regimen for recurrent disease should not be recommended due to lack of demonstrated efficacy.

Chemosensitivity profile tumor panels, regardless of whether it is performed by IHC or chromogenic in-situ hybridization (CISH), is not reasonable and necessary for the reasons cited above.

Note, some of these markers are legitimate biomarkers for specified drugs when performed by mutation analysis or FISH testing.

IHC for Cervical/Gyn/Bladder/Kidney Tumors
Claims data indicate combinations of gram stain, PAS, Ki-67, p16 and ProExC stains on all cervical biopsies from select pathology practices, and combinations of p53, Ki-67, CD20 and CD44 on bladder biopsies from select pathology practices.

The use of IHC stains in endometrial cancer, ovarian cancer or a kidney neoplasm requires adequate documentation in the pathology report, such as "Because the differential histologic diagnosis is between an endometrioid carcinoma and a serous carcinoma, I performed an xxx stain. The controls worked appropriately and the results were positive indicating the tumor is a yyy."

IHC for Skin & Cutaneous/Central Nervous System (CNS) & Peripheral Nervous System (PNS) Lesions
It is well recognized that most skin lesions are diagnosed with routine H&E slides.

Routine IHC morphometric evaluation of skin biopsies are not reasonable and necessary.

There is a specific validated procedure for morphometric evaluation of distal leg skin for small fiber sensory neuropathy.

A systematic review published by the American Academy of Neurology (AAN), the American Association of Neuromuscular and Electrodiagnostic Medicine and the American Academy of Physical Medicine and Rehabilitation (AAPM&R) concluded specifically that "intraepidermal nerve fiber density determination, using anti protein gene product 9.5 immunohistochemistry is a validated and reproducible marker of small fiber sensory neuropathy". This is the only validated AND reproducible marker to be used for this determination.

This is reinforced in a recently published 2022 update on the diagnosis and treatment of Peripheral Autonomic Neuropathies. A recent review of peripheral autonomic neuropathies stated that these studies focused on small fiber neuropathy (SFN) of skin biopsies. The task force concluded that "Revision of the guidelines on the use of skin biopsy in the diagnosis of peripheral neuropathy, published in 2005, has become appropriate due to publication of more relevant papers. Most of the new studies focused on small fiber neuropathy (SFN), a subtype of neuropathy for which the diagnosis was first developed through skin biopsy examination. This revision focuses on the use of this technique to diagnose SFN. Task force members searched the Medline database from 2005, the

year of the publication of the first EFNS guideline, to June 30th, 2009. All pertinent papers were rated according to the EFNS and PNS guidance. After a consensus meeting, the task force members created a manuscript that was subsequently revised by two experts (JML and JVS) in the field of peripheral neuropathy and clinical neurophysiology, who were not previously involved in the use of skin biopsy. Distal leg skin biopsy with quantification of the linear density of intraepidermal nerve fibers (IENF), using generally agreed upon counting rules, is a reliable and efficient technique to assess the diagnosis of SFN (level A recommendation). Normative reference values are available for bright-field immunohistochemistry (level A recommendation) but not yet for confocal immunofluorescence or the blister technique. The morphometric analysis of IENF density, either performed with bright-field or immunofluorescence microscopy, should always refer to normative values matched for age (level A recommendation). Newly established laboratories should undergo adequate training in a well-established skin biopsy laboratory and provide their own stratified race, age, and gender-matched normative intraepidermal nerve fiber control values, intra- and interobserver reliability, and interlaboratory agreement. Quality control of the procedure at all levels is mandatory (Good Practice Point). Providing reference values is a useful parameter to determine the spatial distribution of involvement in peripheral nerve disease" This use of reference control criteria for comparison is considered an important parameter to cite and explain the in the pathology report to appropriately determine the significance of the immunohistochemical findings.

IHC for central nervous system (CNS) and peripheral nervous system (PNS) tumors and lesions at times may be used to differentiate primary from metastatic lesions. However, there is evidence that molecular biomarkers as well as immunohistochemistry may also be reasonable and necessary and appropriate for classification to determine appropriate therapy and prognosis in tumors or lesions of the central and peripheral nervous system. Although discussion of every specific marker is beyond the scope of this document the most recent consensus 2021 guidelines published by the World Health Organization offer a comprehensive discussion of the reasonable and necessary evaluation.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA

'88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

Recently, four clinical IHC biomarker assays (PTEN, RB, MLH1, and MSH2) have been validated for use as biomarkers in a nationwide clinical trial; these assays were then approved by the FDA as laboratory-developed tests to assist in the treatment selection of patients in clinical trials (Khoury et al., 2018). This shows that IHC assays are currently being utilized with molecular tests to assist in therapeutic decisions.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Supplemental Information

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Guidelines are lacking regarding the selection and number of antibodies that should be used for most immunohistochemistry evaluations. However, IHC is broadly used for conditions such as cancers, which are mentioned across many different societies.

College of American Pathologists (CAP)

The College of American Pathologists has published several reviews in Archives of Pathology & Laboratory Medicine that detail the quality control measures for IHC; further, CAP has also published more than 100 small IHC panels to address the frequently asked questions in diagnosis and differential diagnosis of specific entities. These diagnostic panels are based on literature, IHC

data, and personal experience. A single IHC marker approach (other than for pathogens such as cytomegalovirus or BK virus) is strongly discouraged since aberrant expression of a highly specific IHC marker can rarely occur. However, aberrant expression of the entire panel of highly specific IHC markers is nearly statistically impossible.

The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP)

The American Society of Clinical Oncology and the College of American Pathologists currently recommend that "all newly diagnosed patients with breast cancer must have a HER2 test performed". Also, for those who develop metastatic disease, a HER2 test must be done on tissue from the metastatic site, if available. In less common HER2 breast cancer patterns, as observed in approximately 5% of cases by dual-probe in situ hybridization (ISH) assays, new recommendations have been made to make a final determination of positive or negative HER2 tissue. This new "diagnostic approach includes more rigorous interpretation criteria for ISH and requires concomitant IHC review for dual-probe ISH groups… to arrive at the most accurate HER2 status designation (positive or negative) based on combined interpretation of the ISH and IHC assays;" further, "The Expert Panel recommends that laboratories using single-probe ISH assays include concomitant IHC review as part of the interpretation of all single-probe ISH assay results"

The 2018 update included the following changes from the prior 2013 update, particularly focusing on infrequent HER2 test results that were of "uncertain biologic or clinical significance":

- "Revision of the definition of IHC 2+ (equivocal) to the original FDA-approved criteria.
- Repeat HER2 testing on a surgical specimen if the initially tested core biopsy is negative is no longer stated as mandatory. A new HER2 test may (no longer should) be ordered on the excision specimen on the basis of some criteria (such as tumor grade 3).
- A more rigorous interpretation criteria of the less common patterns that can be seen in about 5% of all cases when HER2 status in breast cancer is evaluated using a dual-probe ISH testing. These cases, described as ISH groups 2 to 4, should now be assessed using a diagnostic approach that includes a concomitant review of the IHC test, which will help the pathologist make a final determination of the tumor specimen as HER2 positive or negative.

The Expert Panel also preferentially recommends the use of dual-probe instead of single-probe ISH assays, but it recognizes that several single-probe ISH assays have regulatory approval in many parts of the world". The 2018 recommendations were affirmed in 2023.

The National Cancer Coalition Network
The NCCN has made numerous recommendations for use of IHC to diagnose and manage various types of cancer. Cancers with clinically useful IHC applications include breast, cervical, various leukemias, and colorectal cancer.

The NCCN states that the determination of estrogen receptor, progesterone receptor, and HER2 status for breast cancer is recommended and may be determined by IHC (NCCN, 2023a). Specifically, the guidelines state that "the NCCN Panel endorses the College of American Pathologists (CAP) protocol for pathology reporting and endorses the ASCO CAP recommendations for quality control performance of HER2 testing and interpretation of IHC and ISH results." They also specifically endorse the ASCO/CAP HER2 testing guideline "Principles of HER2 testing," and state "HR testing (ER and PR) by IHC should be performed on any new primary or newly metastatic breast cancer using methodology outlined in the latest ASCO/CAP HR testing guideline." Additionally, "PR testing by IHC on invasive cancers can aid in the prognostic classification of cancers and serve as a control for possible false negative ER results. Patients with ER-negative, PR-positive cancers may be considered for endocrine therapies, but the data on this group are noted to be limited" (NCCN, 2023a).

Further, the NCCN recommendations concerning genetic testing for colorectal cancer state, "The panel recommends that for patients or families where colorectal or endometrial tumor is available, one of three options should be considered for workup: 1) tumor testing with IHC or MSI; 2) comprehensive NGS panel (that includes, at minimum, the four MMR genes and EPCAM, BRAF, MSI, and other known familial cancer genes); or 3) germline multi-gene testing that includes the four MMR genes and EPCAM. The panel recommends tumor testing with IHC and/or MSI be used as the primary approach for pathology-lab-based universal screening" (NCCN, 2023b). More recently, the NCCN has made additional recommendations to individuals diagnosed with any type of hereditary colorectal cancer (CRC) syndrome; these recommendations state that "all individuals newly diagnosed with CRC have either MSI or immunohistochemistry (IHC) testing for absence of 1 of the 4 DNA MMR proteins" (NCCN, 2023b).

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Policy History

Original Effective Date: 01/01/2025
Current Effective Date: 01/01/2025
10/03/2024 Medical Policy Committee review
10/08/2024 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 10/2025

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.