

Corporate Medical Policy

Immunohistochemistry AHS – P2018

File Name: immunohistochemistry
Origination: 01/01/2019
Last Review: 1/2024

Description of Procedure or Service

Definition

Immunohistochemistry (IHC) is a very sensitive and specific staining technique that uses anatomical, biochemical, and immunological methods to identify cells, tissues, and organisms by the interaction of target antigens with highly specific monoclonal antibodies and visualization through the use of a biochemical tag or label (Fitzgibbons et al., 2014).

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for immunohistochemistry when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore, member benefit language should be reviewed before applying the terms of this medical policy.

Indications and/or limitations of coverage

Code 88342 should be used for the first single antibody procedure and is reimbursed at one unit per specimen, up to four specimens, thus up to a maximum of four units, per date of service.

Code 88341 should be used for the first single antibody procedure and is reimbursed up to a maximum of 13 units per date of service.

Code 88344 should be used for each multiplex antibody per specimen, up to six specimens, per date of service.

Policy Guidelines

Immunohistochemistry (IHC) is used to identify certain components of tissues or cells (aka immunocytochemistry) via use of specific antibodies that can be visualized through a staining technique. The premise behind IHC is that distinct tissues and cells contain a unique set of antigens that allows them to be identified and differentiated. The selection of antibodies used for the evaluation of a specimen varies by the source of the specimen, the question to be answered, and the pathologist performing the test.

Importantly, an entirely sensitive and specific IHC marker rarely exists, and therefore, determinations are typically based on a pattern of positive and negative stains for a panel of several antibodies. The four most

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common IHC staining patterns include nuclear staining, cytoplasmic staining, membrane staining, and extracellular staining (Tuffaha et al., 2018). 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 (Lin & Chen, 2014).

Multiplex immunohistochemistry (mIHC) is a particular IHC technique that allows multiple targets in a single tissue to be detected simultaneously; this approach is able to characterize “the tumor microenvironment including vascular architecture and hypoxia, cellular proliferation, cell death as well as drug distribution” (Kalra & Baker, 2017). Hence, mIHC can assist in the development of parameter tumor maps. Other researchers have utilized mIHC for its novel ability to provide quantitative data on different types of tumor-infiltrating immune cells within a single tissue; this may improve cancer patient immunotherapy stratification (Hofman et al., 2019).

Clinical Utility and Validity

Immunohistochemistry can be used for a variety of purposes including: differentiation of benign from malignant tissue, differentiation among several types of cancer, selection of therapy, identification of the origin of a metastatic cancer, and identification of infectious organisms (Shah et al., 2012). IHC has many uses in the realm of tumor identification, and it has even been clinically used to pinpoint various breast cancer-specific markers, such as progesterone and estrogen receptors, gross cystic duct fluid protein, and mammaglobin (Hainsworth & Greco, 2022). Further, overexpression of the *HER2* oncogene, a predictive breast cancer biomarker, is often identified via IHC (Yamauchi & Bleiweiss, 2023). In regards to tumor identification, a specific type of IHC, known as pan-Trk IHC, has been shown to positively identify inflammatory myofibroblastic tumors with a nuclear and cytoplasmic staining pattern that may assist in targeted therapy (Yamamoto et al., 2019).

Antibodies for use in IHC are available as single antibody reagents or in mixtures of a combination of antibodies. More than 200 diagnostic antibodies are generally available in a large clinical IHC laboratory, and hundreds of antibodies are usually available in research laboratories. The list of new antibodies is growing rapidly with the discovery of new biomarkers by molecular methodologies (Lizotte et al., 2016). Several studies have shown that a relatively low number of antibodies are capable of accurately diagnosing specific cancers and identifying the primary source of a metastasis (Le Stang et al., 2019; Lizotte et al., 2016; Prok & Prayson, 2006).

Common markers to identify tumor origin (Lin & Chen, 2014):

Primary Site	Markers
Lung adenocarcinoma	TTF1, napsin A
Breast carcinoma	GATA3, ER, GCDFP15
Urothelial carcinoma	GATA3, UPII, S100P, CK903, p63
Squamous cell carcinoma	p40, CK5/6
RCC, clear cell type	PAX8, RCCma, pVHL, KIM-1
Papillary RCC	P504S, RCCma, pVHL, PAX8, KIM-1
Translocational RCC	TFE3
Hepatocellular carcinoma	Arginase-1, glypican-3, HepPar-1
Adrenal cortical neoplasm	Mart-1, inhibin-a, calretinin, SF-1
Melanoma	S100, Mart-1, HMB-45, MiTF, SOX10
Merkel cell carcinoma	CK20 (perinuclear dot staining), MCPyV
Mesothelial origin	Calretinin, WT1, D2-40, CK5/6, mesothelin
Neuroendocrine origin	Chromogranin, synaptophysin, CD56

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Upper GI tract	CDH17, CDX2, CK20
Lower GI tract	CDH17, SATB2, CDX2, CK20
Intrahepatic cholangiocarcinoma	pVHL, CAIX
Pancreas, acinar cell carcinoma	Glypican-3, antitrypsin
Pancreas, ductal adenocarcinoma	MUC5AC, CK17, Maspin, S100P, IMP3
Pancreas, neuroendocrine tumor	PR, PAX8, PDX1, CDH17, islet-1
Pancreas, solid pseudopapillary tumor	Nuclear b-catenin, loss of Ecadherin, PR, CD10, vimentin
Prostate, adenocarcinoma	PSA, NKX3.1, PSAP, ERG
Ovarian serous carcinoma	PAX8, ER, WT1
Ovarian clear cell carcinoma	pVHL, HNF-1b, KIM-1, PAX8
Endometrial stromal sarcoma	CD10, ER
Endometrial adenocarcinoma	PAX8/PAX2, ER, vimentin
Endocervical adenocarcinoma	PAX8, p16, CEA, HPV in situ hybridization, loss of PAX2
Thyroid follicular cell origin	TTF1, PAX8, thyroglobulin
Thyroid medullary carcinoma	Calcitonin, TTF1, CEA
Hyalinizing trabecular adenoma of the thyroid	MIB-1 (unique membranous staining pattern)
Salivary duct carcinoma	GATA3, AR, GCDFP-15, HER2/neu
Thymic origin	PAX8, p63, CD5
Seminoma	SALL4, OCT4, CD117, D2-40
Yolk sac tumor	SALL4, glypican-3, AFP
Embryonal carcinoma	SALL4, OCT4, NANOG, CD30
Choriocarcinoma	b-HCG, CD10, SALL4
Sex cord–stromal tumors	SF-1, inhibin-a, calretinin, FOXL2
Vascular tumor	ERG, CD31, CD34, Fli-1
Synovial sarcoma	TLE1, cytokeratin
Chordoma	Cytokeratin, S100
Desmoplastic small round cell tumor	Cytokeratin, CD99, desmin, WT1 (N-terminus)
Alveolar soft part sarcoma	TFE3
Rhabdomyosarcoma	Myogenin, desmin, MyoD1
Smooth muscle tumor	SMA, MSA, desmin, calponin
Ewing sarcoma/PNET	NKX2.2, CD99, Fli-1
Myxoid and round cell liposarcoma	NY-ESO-1
Low-grade fibromyxoid sarcoma	MUC4
Epithelioid sarcoma	Loss of INI1, CD34, CK
Atypical lipomatous tumor	MDM2 (MDM2 by FISH is a more sensitive and specific test), CDK4
Histiocytosis X	CD1a, S100
Angiomyolipoma	HMB-45, SMA
Gastrointestinal stromal tumor	CD117, DOG1
Solitary fibrous tumor	CD34, Bcl2, CD99
Myoepithelial carcinoma	Cytokeratin and myoepithelial markers; may lose INI1

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Myeloid sarcoma	CD43, CD34, MPO
Follicular dendritic cell tumor	CD21, CD35
Mast cell tumor	CD117, tryptase

Guidelines and Recommendations

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. The below section is not a comprehensive list of guidance for immunohistochemistry.

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 (Lin & Chen, 2014; Lin & Liu, 2014).

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” (Wolff et al., 2013). 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” (Wolff et al., 2018). The 2018 recommendations were affirmed in 2023 (Wolff et al., 2023).

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” (Wolff et al., 2018)

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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 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).

The European Society of Medical Oncology (ESMO)

The ESMO recommends that for cancers of an unknown primary site, “histology and IHC on good quality tissue specimens are required [III, A]” (Krämer et al., 2023). Particularly in the context for gastrointestinal carcinomas, ESMO states “Immunohistochemical loss of BRCA1-associated protein 1 (BAP1) or AT-rich interactive domain-containing protein 1A (ARID1A) can support the diagnosis but the final decision can only be made in conjunction with clinical and radiological findings.” Other mentions of IHC in their updated 2023 guidelines did not result in any other updated recommendations (Krämer et al., 2023).

State and Federal Regulations, as applicable

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.

Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 88341, 88342, 88344

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

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Specialty Matched Consultant Advisory Panel review 02/2020

Medical Director review 1/2022

Medical Director review 12/2022

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Medical Director review 1/2024

Policy Implementation/Update Information

- 1/1/19 New policy developed. BCBSNC will provide coverage for immunohistochemistry when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (an)
- 10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)
- 02/11/20 Reviewed by Avalon 4th Quarter CAB. Coding section updated. (eel)
- 03/10/20 Specialty Matched Consultant Advisory Panel 02/19/2020. No change to policy statement. (eel)
- 2/9/21 Reviewed by Avalon 4th Quarter CAB. Medical Director Review 1/2021. Description, Policy Guidelines, and References updates. Coverage Criteria updated for clarity. No change to policy statement. (bb)
- 7/27/21 Specialty Matched Consultant Advisory Panel 02/17/2021. Medical Director review 7/21/2017. Wording in policy, Indication and/or limitations of coverage, updated for clarifications of coverage for code 88341 and 88342. (jm)
- 2/8/22 Reviewed by Avalon 4th Quarter 2021 CAB. Medical Director Review 1/2022. Description, Policy Guidelines, and References updates. No change to policy statement. (tt)
- 2/7/23 Reviewed by Avalon 4th Quarter 2022 CAB. Medical Director Review 12/2022. Description, Policy Guidelines, and References updates. No change to policy statement. (tt)
- 2/21/24 Reviewed by Avalon 4th Quarter 2023 CAB. Medical Director Review 1/2024. Description, Policy Guidelines, and References updates. No change to policy statement. (tt)

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