

Immunohistochemistry

Policy Number: AHS –P2018 – Immunohistochemistry	Initial Presentation Date: 11/15/2015 Original Presbyterian Effective Date: 07/01/2024 Revision Date: 12/03/2025 Revision Effective Date: 06/01/2026
--	---

[POLICY DESCRIPTION](#) | [RELATED POLICIES](#) | [INDICATIONS AND/OR LIMITATIONS OF COVERAGE](#) | [TABLE OF TERMINOLOGY](#) | [SCIENTIFIC BACKGROUND](#) | [GUIDELINES AND RECOMMENDATIONS](#) | [APPLICABLE STATE AND FEDERAL REGULATIONS](#) | [APPLICABLE CPT/HCPCS PROCEDURE CODES](#) | [EVIDENCE-BASED SCIENTIFIC REFERENCES](#) | [REVISION HISTORY](#)

I. Policy Description

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.¹

II. Related Policies

Policy Number	Policy Title
N/A	Not Applicable

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

- Code 88342 should be used for the first single antibody procedure and is reimbursed at one unit per specimen, up to four specimens, per date of service.
- Code 88341 should be used for each additional single antibody per specimen 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.

IV. Table of Terminology

Term	Definition
AFP	Alpha-fetoprotein
ARID1A	AT-rich interactive domain-containing protein 1A
ASCO	The American Society of Clinical Oncology
<i>Bcl2</i>	<i>BCL2 apoptosis regulator</i>

b-HCG	Beta human chorionic gonadotropin
<i>BRCA1</i>	Breast cancer type 1 susceptibility protein gene
BAP1	<i>BRCA1</i> associated protein 1
CAIX	Carbonic anhydrase IX
CAP	College of American Pathologists
CD1a	Cluster of differentiation 1a
CD5	Cluster of differentiation 5
CD10	Cluster of differentiation 10
CD21	Cluster of differentiation 21
CD30	Cluster of differentiation 30
CD31	Cluster of differentiation 31
CD34	Cluster of differentiation 34
CD35	Cluster of differentiation 35
CD43	Cluster of differentiation 43
CD56	Cluster of differentiation 56
CD99	Cluster of differentiation 99
CD117	Cluster of differentiation 117
<i>CDH17</i>	<i>Cadherin-17</i>
<i>CDK4</i>	<i>Cyclin-dependent kinase 4</i>
CDX2	Caudal-type homeobox 2
CEA	Carcinoembryonic antigen
CK	Creatine kinase
CK17	Cytokeratin 17
CK20	Cytokeratin 20
CK5/6	Cytokeratin 5/6
CK903	Cytokeratin 903
CLIA'88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CRC	Colorectal cancer
D2-40	Anti-Podoplanin
DNA	Deoxyribonucleic acid
DOG1	Delay of germination 1
ERG	ETS-related gene
ESMO	The European Society of Medical Oncology
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
Fli-1	Friend leukemia integration 1
FOXL2	Forkhead box protein L2
GATA3	GATA binding protein 3
GCDFP15	Gross cystic disease fluid protein 15
GI	Gastrointestinal tract
HepPar-1	General hepatocyte paraffin 1

<i>HER2</i>	<i>Human epidermal growth factor receptor 2</i>
HMB-45	Human melanoma black-45
HNF-1b	Hepatocyte nuclear factor 1 beta
HPV	Human papillomavirus
IHC	Immunohistochemistry
IMP3	U3 small nucleolar ribonucleoprotein protein IMP3
INI1	Integrase interactor 1
ISH	In situ hybridization
KIM-1	Kidney injury molecule-1
LDTs	Laboratory-developed tests
Maspin	Mammary serine protease inhibitor
MCPyV	Merkel cell polyomavirus
MDM2	Mouse double minute 2 homolog
MIB-1	MIB E3 ubiquitin protein ligase 1
mIHC	Multiplex immunohistochemistry
MiTF	Microphthalmia-associated transcription factor
MLH1	MutL homolog 1
MMR	Mismatch repair protein
MPO	Myeloperoxidase
MSA	Mammary serum antigen
MSH2	Mismatch repair protein Msh2
MSI	Microsatellite instability
MUC4	Mucin 4
MUC5AC	Mucin 5AC
MyoD1	Myoblast determination protein 1
<i>NANOG</i>	<i>Nanog Homeobox</i>
napsin A	Novel aspartic proteinase of the pepsin family A
NCCN	The National Cancer Coalition Network
NKX2.2	Homeobox protein
NKX3.1	Homeobox protein
NY-ESO-1	New York esophageal squamous cell carcinoma 1
OCT4	Octamer-binding transcription factor 4
p16	Cyclin-dependent kinase inhibitor 2A
p40	Protein subunit
P504S	Cytoplasmic protein
p63	Tumor protein p63
pan-Trk	Pan-tropomyosin-related-kinase
PAX2	Paired box 2
PAX8	Paired box 8
PDX1	Insulin promoter factor 1
PNET	Primitive neuro-ectodermal tumor
PSA	Prostate-specific antigen

PSAP	Phosphoserine aminotransferase
PTEN	Phosphatase and tensin homolog
pVHL	Von hippel–lindau tumor suppressor
RB	Retinoblastoma protein
RCC	Renal cell carcinoma
RCCma	Renal cell carcinoma marker
S100P	S100 calcium-binding protein p
SALL4	Sal-like protein 4
SATB2	Special AT-rich sequence-binding protein 2
SF-1	Steroidogenic factor 1
SOX10	SRY-box transcription factor 10
TFE3	Transcription factor E3
TLE1	Transducin-like enhancer protein 1
TTF1	Transcription termination factor, RNA polymerase I
UPII	Uroplakin II
WT1	Wilms tumor protein

V. Scientific Background

Immunohistochemistry (IHC) is used to identify certain components of tissues or cells (also known as 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 common IHC staining patterns include nuclear staining, cytoplasmic staining, membrane staining, and extracellular staining.² 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.³

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.”⁴ 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.⁵

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.⁶ 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.⁷ Further, overexpression of the *HER2* oncogene, a predicative breast cancer biomarker, is often identified via IHC.⁸ 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.⁹

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.¹⁰ 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.¹⁰⁻¹²

Common markers to identify tumor origin:³

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

VI. 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.^{3,13}

In 2024, CAP published an update to their guidelines on the principles of analytic validation of immunohistochemical assays. The guidelines include the following recommendations:¹⁴

1. “Laboratories must analytically validate all laboratory developed IHC assays and verify all FDA-cleared IHC assays before reporting results on patient tissues.
2. For initial analytic validation or verification of every assay used clinically, laboratories should achieve at least 90% overall concordance between the new assay and the comparator assay or expected results.
3. For initial analytic validation of nonpredictive laboratory-developed assays, laboratories should test a minimum of ten positive and ten negative tissues. When the laboratory medical director determines that fewer than 20 validation cases are sufficient for a specific marker (eg, rare antigen), the rationale for that decision needs to be documented.
4. For initial analytic validation of all laboratory-developed predictive marker assays, laboratories should test a minimum of 20 positive and 20 negative tissues. When the laboratory medical director determines that fewer than 40 validation tissues are sufficient for a specific marker, the rationale for that decision needs to be documented.

5. For initial analytic verification of all unmodified FDA-approved predictive marker assays, laboratories should follow the specific instructions provided by the manufacturer. If the package insert does not delineate specific instructions for assay verification, the laboratory should test a minimum of 20 positive and 20 negative tissues. When the laboratory medical director determines that fewer than 40 verification tissues are sufficient for a specific marker, the rationale for that decision needs to be documented.
6. For initial analytic validation of laboratory-developed assays and verification of FDA-approved or cleared predictive immunohistochemical assays with distinct scoring schemes (eg, HER2, PD-L1), laboratories should separately validate or verify each assay-scoring system combination with a minimum of 20 positive and 20 negative tissues. The set should include challenges based on the intended clinical use of the assay.
7. For laboratory-developed assays with both predictive and nonpredictive applications using the same scoring criteria, laboratories should treat these assays as predictive markers and test a minimum of 20 positive and 20 negative cases.
8. Laboratories should use validation tissues that have been processed using the same fixative and processing methods as cases that will be tested clinically, when possible.
9. For analytic validation of IHC performed on cytologic specimens that are not fixed in the same manner as the tissues used for initial assay validation, laboratories should perform separate validations for every new analyte and corresponding fixation method before placing them into clinical service.
10. A minimum of 10 positive and 10 negative cases is recommended for each validation performed on cytologic specimens, if possible. The laboratory medical director should consider increasing the number of cases if predictive markers are being validated. If the minimum of 10 positive and 10 negative cases is not feasible, the rationale for using fewer cases should be documented.
11. If IHC is regularly done on decalcified tissues, laboratories should test a sufficient number of such tissues to ensure that assays consistently achieve expected results. The laboratory medical director is responsible for determining the number of positive and negative tissues and the number of predictive and nonpredictive markers to test.
12. Laboratories should confirm assay performance with at least 1 known positive and 1 known negative tissue when a new antibody lot is placed into clinical service for an existing validated assay (a control tissue with known positive and negative cells is sufficient for this purpose).
13. Laboratories should confirm assay performance with at least 2 known positive and 2 known negative tissues when an existing validated assay has changed in any one of the following ways:
 1. Antibody dilution
 2. Antibody vendor (same clone)
 3. Incubation or retrieval times (same method).
14. Laboratories should confirm assay performance by testing a sufficient number of tissues to ensure that assays consistently achieve expected results when any of the following have changed:
 1. Fixative type
 2. Antigen retrieval method (eg, change in pH, different buffer, different heat platform)
 3. Detection system
 4. Tissue processing equipment
 5. Automated testing platform
 6. Environmental conditions of testing (eg, laboratory relocation, laboratory water supply)The laboratory medical director is responsible for determining how many predictive and nonpredictive markers and how many positive and negative tissues to test.
15. Laboratories should run a full revalidation (equivalent to initial analytic validation) when the antibody clone is changed for an existing validated assay.”

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.”¹⁵ 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.”¹⁶

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 two to four, 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.”¹⁶ The 2018 recommendations were affirmed in 2023.¹⁷

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.¹⁸ 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.”¹⁸

Further, the NCCN recommendations concerning genetic testing for colorectal cancer state, “the NCCN Panel recommends that, for patients or families where colorectal or endometrial tumor is available, one

of two options should be considered for testing among people meeting testing criteria: 1) tumor testing with IHC or MSI, or a comprehensive tumor NGS panel (that includes, at a minimum, the four MMR genes and *EPCAM*, *BRAF* [for CRC only], MSI, and other known familial cancer genes); or 2) germline MGPT that includes at least the four MMR genes and *EPCAM*. The NCCN Panel recommends tumor testing with IHC and/or MSI be used as the primary approach for pathology-lab-based universal screening.”¹⁹ 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 IHC testing for absence of 1 of the 4 DNA MMR proteins.”¹⁹

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].”²⁰ 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.²⁰

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, please visit the New Mexico Medicaid website: <https://www.hsd.state.nm.us/providers/rules-nm-administrative-code/>.

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.²¹ This shows that IHC assays are currently being utilized with molecular tests to assist in therapeutic decisions.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
88341	Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure
88342	Immunohistochemistry or immunocytochemistry, per spec; initial single antibody stain

88344	Immunohistochemistry or immunocytochemistry, per specimen; each multiplex antibody stain procedure
-------	--

Current Procedural Terminology® American Medical Association. All Rights reserved.

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

1. Fitzgibbons PL, Bradley LA, Fatheree LA, et al. Principles of analytic validation of immunohistochemical assays: Guideline from the College of American Pathologists Pathology and Laboratory Quality Center. *Archives of pathology & laboratory medicine*. Nov 2014;138(11):1432-43. doi:10.5858/arpa.2013-0610-CP
2. Tuffaha MSA, Guski H, Kristiansen G. Immunohistochemistry in Tumor Diagnostics. *Immunohistochemistry in Tumor Diagnostics*. 2018// 2018:1-9. doi:10.1007/978-3-319-53577-7_1
3. Lin F, Chen Z. Standardization of diagnostic immunohistochemistry: literature review and geisinger experience. *Archives of pathology & laboratory medicine*. Dec 2014;138(12):1564-77. doi:10.5858/arpa.2014-0074-RA
4. Kalra J, Baker J. Multiplex Immunohistochemistry for Mapping the Tumor Microenvironment. *Methods Mol Biol*. 2017;1554:237-251. doi:10.1007/978-1-4939-6759-9_17
5. Hofman P, Badoual C, Henderson F, et al. Multiplexed Immunohistochemistry for Molecular and Immune Profiling in Lung Cancer-Just About Ready for Prime-Time? *Cancers (Basel)*. Feb 27 2019;11(3)doi:10.3390/cancers11030283
6. Shah AA, Frierson HF, Cathro HP. Analysis of Immunohistochemical Stain Usage in Different Pathology Practice Settings. 2012-12-01 2012;doi:10.1309/AJCPAGVTCKDXKKOX
7. Hainsworth J, Greco F. Overview of the classification and management of cancers of unknown primary site. Updated March 24, 2025. <https://www.uptodate.com/contents/overview-of-the-classification-and-management-of-cancers-of-unknown-primary-site>
8. Yamauchi H, Bleiweiss I. HER2 and predicting response to therapy in breast cancer. Updated July 31, 2025. <https://www.uptodate.com/contents/her2-and-predicting-response-to-therapy-in-breast-cancer>
9. Yamamoto H, Nozaki Y, Kohashi K, Kinoshita I, Oda Y. Diagnostic utility of pan-Trk immunohistochemistry for inflammatory myofibroblastic tumors. *Histopathology*. Oct 3 2019;doi:10.1111/his.14010
10. Lizotte PH, Ivanova EV, Awad MM, et al. Multiparametric profiling of non-small-cell lung cancers reveals distinct immunophenotypes. *JCI insight*. Sep 8 2016;1(14):e89014. doi:10.1172/jci.insight.89014
11. Prok AL, Prayson RA. Thyroid transcription factor–1 staining is useful in identifying brain metastases of pulmonary origin. *Annals of Diagnostic Pathology*. 2006/04/01/ 2006;10(2):67-71. doi:10.1016/j.anndiagpath.2005.07.013
12. Le Stang N, Burke L, Blaizot G, et al. Differential Diagnosis of Epithelioid Malignant Mesothelioma With Lung and Breast Pleural Metastasis: A Systematic Review Compared With a Standardized Panel of Antibodies-A New Proposal That May Influence Pathologic Practice. *Archives of pathology & laboratory medicine*. Aug 7 2019;doi:10.5858/arpa.2018-0457-OA
13. Lin F, Liu H. Immunohistochemistry in undifferentiated neoplasm/tumor of uncertain origin. *Archives of pathology & laboratory medicine*. Dec 2014;138(12):1583-610. doi:10.5858/arpa.2014-0061-RA

14. Goldsmith JD, Troxell ML, Roy-Chowdhuri S, et al. Principles of Analytic Validation of Immunohistochemical Assays: Guideline Update. *Archives of pathology & laboratory medicine*. 2024;148(6):e111-e153. doi:10.5858/arpa.2023-0483-CP
15. Wolff AC, Hammond ME, Hicks DG, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Nov 1 2013;31(31):3997-4013. doi:10.1200/jco.2013.50.9984
16. Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jul 10 2018;36(20):2105-2122. doi:10.1200/jco.2018.77.8738
17. Wolff AC, Somerfield MR, Dowsett M, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO–College of American Pathologists Guideline Update. *Journal of Clinical Oncology*. 2023/08/01 2023;41(22):3867-3872. doi:10.1200/JCO.22.02864
18. NCCN. NCCN Guidelines Version 4.2025 Breast Cancer. Updated October 16, 2025. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
19. NCCN. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal Version 1.2025. Updated June 13, 2025. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf
20. Krämer A, Bochtler T, Pauli C, et al. Cancer of unknown primary: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. Mar 2023;34(3):228-246. doi:10.1016/j.annonc.2022.11.013
21. Khoury JD, Wang WL, Prieto VG, et al. Validation of Immunohistochemical Assays for Integral Biomarkers in the NCI-MATCH EAY131 Clinical Trial. *Clin Cancer Res*. Feb 1 2018;24(3):521-531. doi:10.1158/1078-0432.Ccr-17-1597

X. Revision History

Revision Date	Summary of Changes
12/03/2025 Revision Effective Date: 06/01/2026	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria
12/04/2024 Revision Effective Date: 04/07/2025	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria
Original Presbyterian Effective Date: 07/01/2024	Policy was adopted by Presbyterian Health Plan for all lines of business. Client request: Added New Mexico Medicaid link to Applicable State and Federal Regulations section: https://www.hsd.state.nm.us/providers/rules-nm-administrative-code/ .

