IMMUNOHISTOCHEMISTRY (IHC) TESTING

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This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee's specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

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BACKGROUND

The pathologist relies upon knowledge of morphologic patterns of tumors to recognize and correctly make diagnoses at the microscope. These tissue diagnoses are often the basis for important clinical decisions. In some cases microscopic morphology alone may not be diagnostic. In the case of major surgical resections, examination of the gross specimen in the laboratory and appropriate selection of tissue sections is often sufficient protocol to allow the pathologist to render a diagnosis. In some cases, ancillary studies are necessary. The pathologist has an armamentarium of diagnostic tools, including scanning electron microscopy and special stains, to complement interpretation of hematoxylin and eosin stained tissue (H & E). Immunohistochemical stains are one of the tools that aid in the generation of precise diagnoses that allow for the judicious use of state of the art treatments like stem cell transplantation and proton therapy.
Immunohistochemistry (IHC) is the use of antibodies to detect proteins in tissue samples. The basis of the test is the antibody-antigen interaction that occurs when monoclonal or polyclonal antibodies are applied to tissue sections cut from patient specimens. This reaction can be identified at the microscope by color on slides; a stain that is usually brown signals the presence of the protein in question. These ancillary stains do not replace standard interpretation of H & E slides but complement the routinely stained material obtained from patient specimens. The stains are named in descriptive terms of the antigen in some cases (for example, gross cystic disease fluid protein, a breast marker) and by cluster designation numbers in others (for example, CD3, a T-cell antigen). Some of the antigens that IHC can detect include immunoglobulins, cell surface markers, receptors, enzymes, proto-oncogenes, and pathogens. Thus, IHC can be applied to detect pathogens, to identify the tissue of origin of cancer, and to diagnose disease processes where identification of a cellular protein provides diagnostic clues. IHC is an important tool used by pathologists to establish definitive diagnoses and to provide important prognostic information to aid in clinical decision making.

On rare occasions, one immunohistochemical stain may be enough to support a definitive diagnosis, but most of the time, a panel of immunohistochemical stains must be interpreted and matched to staining patterns reported for a particular disease to make a definitive diagnosis. Interpretations of the immunohistochemical stains are recorded in pathology reports that become part of a patient’s permanent record where they influence clinical decisions.

In cancer, IHC provides both diagnostic and prognostic information. In terms of making a diagnosis, IHC can aid the pathologist in cases where microscopic morphology alone is not determinative or in cases where a tumor phenotype is necessary for selecting the appropriate therapy. An example of IHC’s utility for prognosis is its use to assess the estrogen and progesterone status of adenocarcinoma of the breast, an important step in predicting prognosis and planning therapy.

The pathologist’s recognition of the microscopic morphologic patterns of tumors is one of the cornerstones of diagnostic surgical pathology. When there is a need to differentiate one gland-forming tumor from another, immunohistochemical stains can provide a staining signature pattern that allows classification of the tumor’s histologic type, as is the case when a pathologist determines the tissue of origin for a metastasis that has been found clinically. The same can be said for other problematic morphologic patterns, such as that of the small round cell tumors, which have several different potential tissues of origin, each with varying treatments that depend on the definitive diagnosis.

In the ovary, for example, there is the issue not only of distinguishing one type of ovarian cancer from the other but of distinguishing an ovarian primary from a metastasis, and in some cases, that metastasis will have an unknown primary cancer.

In a case with a gland-forming pattern, CK7 and CK20 staining can help to distinguish an endometrioid adenocarcinoma, which in spite of the name is a primary tumor of the ovary, from a metastatic colorectal adenocarcinoma. An ovarian endometrioid adenocarcinoma generally stains positively with CK7 and a metastatic colorectal adenocarcinoma generally stains positively with CK20.

To aid the pathologist with diagnostic dilemmas, there are panels for differential diagnoses that have been established by pathologists considered experts in their field of diagnostic surgical pathology. These panels, while
for the most part not subjected to performance studies, reflect the best standard of practice in pathology. The application of IHC panels to the practice of diagnostic surgical pathology is the topic of many an exhaustive review by experts in the field.

In contrast to diagnostic cases involving the ovary, where IHC is helpful in a small number of cases when H & E staining does not allow for a definitive diagnosis, the field of hematopathology is largely dependent on ancillary studies like IHC, flow cytometry, and sometimes cytogenetics and molecular studies.

When a lymph node is biopsied, the pathologist makes some general observations from H & E stained material. Based on initial morphologic observations at the microscope, the pathologist makes a differential diagnosis and uses a panel of IHC stains to provide a precise diagnosis. The interpretation of these immunohistochemical stains includes observations about which cells in the lymph node architecture are expressing the antigen, how strongly the cells are staining, and which compartment or membrane of the cell stains.

In the diagnosis of lymphoma, IHC identifies the tumor phenotype, provides information about abnormal populations seen on flow cytometry, and distinguishes between reactive and neoplastic populations.

Lymphomas are a heterogeneous group of malignancies with varying prognoses and treatments. While each lymphoid neoplasm has a characteristic immunohistochemical staining pattern known as its phenotype, there are cases where a lymphoma fails to stain with typical biomarkers or expresses markers of other tumors. For this reason, reactivity of one IHC antibody must be considered in totality with the rest of the IHC immunophenotype, the clinical information and ancillary studies. The lymphomas illustrate how a panel of immunohistochemical stains is necessary to arrive at a definitive diagnosis because no single antigen is lineage specific.

In the case of metastatic disease where the primary cancer has yet to be identified, a panel of IHC stains is again useful to provide clinicians a roadmap for clinical workup that saves thousands of healthcare dollars, in comparison to a “shoot from the hip” approach of scanning numerous organs and performing multiple endoscopies in search of the primary site of cancer.

The lung is the most common site of metastatic disease, and the pathologist is sometimes faced with trying to decide if the malignancy present on routinely prepared H & E slides represents a primary lung cancer or a metastasis. IHC is often used to provide probabilistic evidence. For example, an adenocarcinoma metastatic to the lung that is positive for estrogen receptor, gross cystic disease fluid protein and negative for TTF-1 would lead the pathologist to suggest in his diagnostic report that the metastasis could be a breast primary. This diagnosis would be based on probabilistic reasoning because, although rare, some lung primaries can stain positively for estrogen receptor. This information would then lead clinicians to proceed with clinical breast examination and diagnostic imaging studies of the breast to lead to a definitive diagnosis.

The ability of IHC to highlight architectural features is sometimes necessary to make a definitive diagnosis. In the distinction of benign ductal and terminal ductal lobular proliferations from invasive carcinoma of the breast, the use of two or more myoepithelial markers is recommended to determine the presence or absence of the myoepithelial layer, which is not preserved in invasive ductal carcinoma.

In a similar fashion, cytokeratin stains can help define bile duct architecture to allow the pathologist to address the issue of bile duct destruction after liver transplantation.
The value of IHC to detect micrometastases in head and neck cancer cases has yet to be determined but holds promise. It has been estimated that 10% of head and neck cancers recur in spite of node negativity in the original pathology report used at staging.\(^7\)

In head and neck squamous cell carcinoma, the number of lymph nodes involved by cancer is an independent predictor of survival. IHC stains for cytokeratin could be used to screen lymph nodes for small foci of cancer that might be missed on routine H & E staining. It has yet to be proven by clinical studies if the upstaging of patients by the IHC identification of micrometastases would benefit patient outcomes.\(^7\)

Breast cancer is an area of practice where IHC results are critical to the selection of therapy. Since the 1980s, estrogen and progesterone receptor status have provided important information for decisions about the applicability of hormone therapy for breast cancer. Some breast tumors respond to treatment with hormone therapy. Hormone therapy of breast cancer can entail oopherectomy (in the case of women) or pharmacotherapy. In current practice, tumors that are estrogen and progesterone receptor (ER/PR) positive are treated with hormone therapy and tumors that are ER/PR negative are not.

The application of IHC to this clinical setting has spanned several decades of practice, and clinical guidelines for the preparation and interpretation of ER/PR diagnostic materials have been published.\(^8\) These guidelines cover everything from preanalytical preparation (such as how long the biopsy material must remain in fixative) to microscopic interpretation (the proper reporting of the pathologist’s microscopic observations). A recent study from a comprehensive cancer center reported that the new guidelines are providing cost savings.\(^9\)

IHC staining can also assist with the diagnosis of benign neoplasms, such as schwannomas, in addition to neoplastic lesions with a spectrum of neoplastic potential, such as gastrointestinal stromal tumors. IHC can distinguish gastrointestinal stromal tumors from the mesenchymal tumors in their differential diagnosis.\(^10\)

IHC is also useful in the diagnostic workup of non-neoplastic disease. Identification of hepatitis B antigens is possible with immunohistochemical staining of liver biopsies. Immunohistochemical staining of colon biopsies for cytomegalovirus is the gold standard for the diagnosis of cytomegalovirus reactivation in ulcerative colitis patients; some reports have indicated that early treatment of CMV reactivation reduces the rate of colectomy.\(^11\) IHC can detect Treponema pallidum in cases of proctitis caused by the spirochete.

IHC can also identify immunoglobulins. In pancreatic biopsies, the identification of IgG4 by IHC is a criterion for the diagnosis of autoimmune pancreatitis.\(^12\)

IHC plays a major role in the diagnosis of muscular dystrophies, a clinically heterogeneous group of disorders. In these cases, IHC detects characteristic protein defects in muscle biopsies.\(^13\) IHC can also aid in the diagnosis of some lipid storage myopathies, such as very-long-chain acyl-coenzyme A dehydrogenase deficiency.\(^14\)
For the following CPT code(s) in Table 1, the patient should have a diagnosis (ICD-10-CM) code(s) listed in the attached files below.

**Table 1. HPCPS Codes (Alphanumeric, CPT® AMA)**

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tr>
<td>88341</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; each additional single antibody stain procedure (list separately in addition to code for primary procedure)</td>
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<tr>
<td>88342</td>
<td>Immunohistochemistry (including tissue immunoperoxidase), each</td>
</tr>
<tr>
<td>88344</td>
<td>Immunohistochemistry or immunocytochemistry, per specimen; each multiplex antibody stain procedure</td>
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**ICD-10 Diagnosis Codes (Proven)**

CMP-031 IHC ICD10
REFERENCES


### POLICY HISTORY/REVISION HISTORY

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<tr>
<td>01/21/2017</td>
<td>Updated ICD10 codes as per CMS recommendations. Removed ICD9 code file.</td>
</tr>
<tr>
<td>10/01/2015</td>
<td>Removed ICD9 code table. Replaced with embedded ICD9/ICD10 pdf files.</td>
</tr>
<tr>
<td>01/01/2015</td>
<td>Added CPT codes 88341 and 88344 as per 2015 AMA updates.</td>
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