Flow Cytometry

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Introduction

Flow cytometry testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
Flow cytometry, cell cycle or DNA analysis	88182
Flow cytometry, cell surface, cytoplasmic, or nuclear marker, technical component only; first marker	88184
Flow cytometry, cell surface, cytoplasmic, or nuclear marker, technical component only; each additional marker (List separately in addition to code for first marker)	88185
Flow cytometry, interpretation; 2 to 8 markers	88187
Flow cytometry, interpretation; 9 to 15 markers	88188
Flow cytometry, interpretation; 16 or more markers	88189

Criteria

Introduction

Requests for flow cytometry testing are reviewed using these criteria. This guideline addresses common clinical applications of flow cytometry-based tests that are billed using CPT codes 88182, 88184, 88185, 88187-88189. It is not intended to encompass flow cytometry-based tests billed using more specific CPT codes (e.g., 86361).

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Hematopoietic Neoplasm Evaluation and Monitoring

Medical necessity requirements:

Because the flow cytometry markers used to evaluate a sample are necessarily different based on clinical indication, information from other evaluations (e.g., morphology), and sample type, this guideline addresses general principles of marker panel selection.[1] Multi-color flow cytometry panels improve the sensitivity for unique cell populations, and are useful for detecting minimal residual disease. Single tube analysis utilizing multiple markers may facilitate the evaluation of specimens with low cellularity.[,2,3]

In the initial evaluation of suspected hematopoietic neoplasm:

- Common non-neoplastic causes of the clinical presentation (e.g., infection or asplenia with leukocytosis, etc.) should be reasonably ruled out before flow cytometry is employed.
- A limited number of markers should be used in the initial evaluation that allows identification of major categories of neoplasia under consideration based on the clinical indication and morphologic findings.[4] In certain circumstances, such as in the evaluation of Sezary syndrome or multiple myeloma, as few as 6 markers is sufficient to establish a diagnosis.[5,6]
- Testing with additional markers is indicated to further characterize disease when the initial evaluation indicates the presence of a hematopoietic neoplasm.

For staging or evaluating residual disease in patients with a known diagnosis of hematopoietic neoplasm, a limited panel of markers characteristic of that neoplasm should be used. Morphologic assessment may obviate the need to perform flow cytometry in some cases. For example, in staging for Hodgkin lymphoma, flow cytometry is generally unnecessary unless a second neoplastic cell population is evident.

Most presentations, even non-specific indications that require evaluation of several lineages (e.g., anemia, thrombocytopenia, etc.), should generally not require more than 15 flow cytometry markers.[7-10] In those cases in which a new leukemia diagnosis needs confirmation and further characterization, additional flow cytometry markers are usually employed.[11] Monitoring of a known hematopoietic neoplasm requires fewer flow cytometry markers.[12] Given that no common indications support coverage of more than 14 units of CPT 88185, exceptions for less common indications other than acute leukemia that require more than 14 units of CPT 88185 will be considered on a case-by-case basis.

In addition to the one marker represented by CPT 88184, medical necessity will routinely be limited to 14 units of CPT 88185 for non-new leukemic cases, 26 units of CPT 88185 for new leukemia diagnoses, and 14 units of CPT 88185 for disease monitoring.

HIV Monitoring

Medical necessity requirements:

Flow cytometry is an important method for determining the percentage of lymphocytes that express antigens used to identify CD4+ T cells, and to directly measure absolute T cell counts in the case of single-platform technology (SPT).[13]

Four antibodies are routinely required (CD45, CD3, CD4, CD8), which may be applied in limited panel strategies.

For pediatric patients, additional antibodies may be required to determine CD19+ B-cell values, which is an indicator of immune status in this population.

Cell Cycle and DNA Analysis

Medical necessity requirements:

Flow cytometry to assess for cell cycle or DNA ploidy (CPT 88182) in the evaluation of solid tumors is considered not medically necessary.

CPT 88182 is medically necessary for 1 unit per DOS when evaluating gestational trophoblastic disease.

Other Clinical Indications

Medical Necessity Requirements:

Flow cytometry has a variety of applications that cannot all be adequately addressed by this guideline. All flow cytometry studies must be performed for well-validated and medically necessary indications.

More than one unit of either 88187, 88188, or 88189 on a date of service are generally not medically necessary.

Immunohistochemistry and flow cytometry generally should not be performed for the same or similar specimens obtained as a result of the same clinical episode, and only one of these methods should be necessary to establish a diagnosis.

When flow cytometry is billed with ICD codes that do not suggest one of the other clinical indications addressed in this guideline (See ICD code tables below), post-service medical necessity review may be employed. See the Lab Claim Reimbursement Policy for more information.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on

allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

Hematopoietic Neoplasm Evaluation and Monitoring

When otherwise reimbursable, the following limitations apply:

- In addition to the one marker represented by CPT 88184, reimbursement will routinely be limited to 14 units of CPT 88185 for non-new leukemic cases, 26 units of CPT 88185 for new leukemia diagnoses, and 14 units of CPT 88185 for disease monitoring.
- Claims for flow cytometry will be limited to 1 unit of CPT 88184 and 26 units of CPT 88185 per date of service when billed with an ICD code from Table: *ICD Code Indications for Flow Cytometry Tier 1 Testing*.
- Claims for flow cytometry will be limited to 1 unit of CPT 88184 and 14 units of CPT 88185 per date of service when billed with an ICD code from Table: *ICD Code Indications for Flow Cytometry Tier 2 Testing.*

HIV Monitoring

The non-specific flow cytometry codes (88184, 88185, 88187-88189) are not reimbursable when a more specific code exists.

Cell Cycle and DNA Analysis

CPT 88182 is reimbursable for 1 unit per DOS when billed with an ICD code from Table: *ICD Code Indications for CPT 88182*.

Other Clinical Indications

Claims for CPT 88184 or 88185 not including an ICD code from either Table: *ICD Code Indications for Flow Cytometry Tier 1 Testing* or Table: *ICD Code Indications for Flow Cytometry Tier 2 Testing* and including an ICD code from Table: *ICD Codes Not Approvable For Flow Cytometry* are not reimbursable.

Claims for CPT 88189 are only reimbursable when billed with an ICD code from Table: *ICD Code Indications for Flow Cytometry Tier 1 Testing*.

Claims for CPT 88188 or 88187 are reimbursable when billed with an ICD code from Table: *ICD Code Indications for Flow Cytometry Tier 1 Testing* or Table: *ICD Code Indications for Flow Cytometry Tier 2 Testing*.

Claims for more than one unit of either 88187, 88188, or 88189 on a date of service are generally not reimbursable and will be subject to post-service medical necessity review.

Claims for flow cytometry (CPT codes: 88184-88189) and immunohistochemistry (CPT codes: 88341-88344) on the same or similar specimens or on the same date of service will be subject to post-service medical necessity review.

ICD Codes

ICD codes used for automated claims processing for this guideline.

Table: ICD Code Indications for Flow Cytometry Tier 1 Testing

Codes and Descriptions.

Code or Range	Description
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.02	Acute lymphoblastic leukemia, in relapse
C92.00	Acute myeloblastic leukemia, not having achieved remission
C92.02	Acute myeloblastic leukemia, in relapse
C92.40	Acute promyelocytic leukemia, not having achieved remission
C92.42	Acute promyelocytic leukemia, in relapse
C92.50	Acute myelomonocytic leukemia, not having achieved remission
C92.52	Acute myelomonocytic leukemia, in relapse
C92.60	Acute myeloid leukemia with 11q23-abnormality not achieve remission
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.A0	Acute myeloid leuk with multilin dysplasia, not achieve remission
C92.A2	Acute myeloid leuk with multilin dysplasia, in relapse
C93.00	Acute monoblastic/monocytic leukemia, not achieve remission
C93.02	Acute monoblastic/monocytic leukemia, in relapse
C93.1X	Chronic myelomonocytic leukemia
C93.3X	Juvenile myelomonocytic leukemia

Code or Range	Description
C94.00	Acute erythroid leukemia, not having achieved remission
C94.02	Acute erythroid leukemia, in relapse
C94.20	Acute megakaryoblastic leukemia not achieve remission
C94.22	Acute megakaryoblastic leukemia, in relapse
C94.30	Mast cell leukemia not having achieved remission
C94.32	Mast cell leukemia, in relapse
C94.40	Acute panmyelosis with myelofibrosis not achieve remission
C94.42	Acute panmyelosis with myelofibrosis, in relapse
C94.6	Myelodysplastic disease, not classified
C95.00	Acute leukemia of unspecified cell type not achieve remission
C95.02	Acute leukemia of unspecified cell type, in relapse
D46.X	Myelodysplastic syndromes
D61.X	Other aplastic anemias and other bone marrow failure syndromes

Table: ICD Code Indications for Flow Cytometry Tier 2 Testing

Codes and Descriptions.

Code or Range	Description
C37	Malignant neoplasm of thymus
D47.X	Other neoplasms of uncertain behavior of lymphoid, hematopoietic, and related tissue
C82.X	Follicular lymphoma
C83.X	Non-follicular lymphoma
C84.X	Mature T/NK-cell lymphomas
C85.X	Other specified and unspecified types of non-Hodgkin lymphoma

Code or Range	Description
C86.X	Other specified types of T/NK-cell lymphoma
C88.X	Malignant immunoproliferative diseases and certain other B-cell lymphomas
C90.X	Multiple myeloma and malignant plasma cell neoplasms
C91.01	Acute lymphoblastic leukemia, in remission
C91.10-C91.Z2	Lymphoid leukemia
C92.01	Acute myeloblastic leukemia, in remission
C92.41	Acute promyelocytic leukemia, in remission
C92.51	Acute myelomonocytic leukemia, in remission
C92.61	Acute myeloid leukemia with 11q23-abnormality, in remission
C92.A1	Acute myeloid leukemia with multilineage dysplasia, in remission
C94.01	Acute erythroid leukemia, in remission
C94.21	Acute megakaryoblastic leukemia, in remission
C94.31	Mast cell leukemia, in remission
C94.41	Acute panmyelosis with myelofibrosis, in remission
C95.01	Acute leukemia of unspecified cell type, in remission
C95.90	Leukemia, unspecified not having achieved remission
C95.91	Leukemia, unspecified, in remission
C96.X	Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue
D47.0X	Mast cell neoplasms of uncertain behavior
D47.2	Monoclonal gammopathy

Code or Range	Description
D47.9	Neoplasm of uncertain behavior of lymphoid, hematopoietic and related tissue, unspecified
D47.ZX	Other specified neoplasms of uncertain behavior of lymphoid, hematopoietic and related tissue
D59.1	Other autoimmune hemolytic anemias
D59.5	Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]
D64.9	Anemia, unspecified
D69.41	Evans syndrome
D69.6	Thrombocytopenia, unspecified
D70.8	Other neutropenia
D70.9	Neutropenia,unspecified
D72.81X	Decreased white blood cell count
D72.820	Lymphocytosis (symptomatic)
D72.821	Monocytosis (symptomatic)
D75.81	Myelofibrosis
D76.X	Other specified diseases with participation of lymphoreticular and reticulohistiocytic tissue
E85.X	Amyloidosis
R16.1	Splenomegaly, not elsewhere classified
R18.0	Malignant ascites
R19.0X	Intra-abdominal and pelvic swelling, mass and lump
R22.X	Localized swelling, mass and lump of skin and subcutaneous tissue
R59.X	Enlarged lymph nodes
R93.X	Abnormal findings on diagnostic imaging of other body structures
Z94.81	Bone marrow transplant status
Z94.84	Stem cells transplant status

Table: ICD Codes Not Approvable For Flow Cytometry

Codes and Descriptions.

Code or Range	Description
A00.X-B99.X	Certain infectious and parasitic diseases
C43.X	Malignant melanoma of skin
C81.X	Hodgkin lymphoma
C92.1X	Chronic myeloid leukemia, BCR/AB-positive
C92.2X	Atypical chronic myeloid leukemia, BCR/AL-negative
D00.X-D09.X	In situ neoplasms
D10.X-D36.X	Benign neoplasms, except benign neuroendocrine tumors
D45	Polycythemia vera
D47.1	Chronic myeloproliferative disease
D47.3	Essential (hemorrhagic) thrombocythemia
D50.X-D53.X	Nutritional anemia
D55.X	Anemia due to enzyme disorders
D56.X	Thalassemia
D57.X	Sickle-cell disorders
D58.X	Other hereditary hemolytic anemia
D62	Acute posthemorrhagic anemia
D63.X	Anemia in chronic diseases classified elsewhere
D68.X	Other coagulation defects
D72.0X	Genetic anomalies of leukocytes
D72.1X	Eosinophilia
D72.823	Leukemoid reaction
D72.824	Basophilia
D72.825	Bandemia
D72.828	Other elevated white blood cell count
D72.829	Elevated white blood cell count, unspecified

Code or Range	Description
D72.89	Other specified disorders of white blood cells
D72.9	Disorder of white blood cells, unspecified
D75.1	Secondary polycythemia
D86.X	Sarcoidosis
E00.X-E89.X	Endocrine, nutritional and metabolic diseases
F01.X-F99.X	Mental, Behavioral and Neurodevelopmental disorders
G00.X-G99.X	Diseases of the nervous system
H00.X-H59.X	Diseases of the eye and adnexa
I00.X-I79.X	Diseases of the circulatory system
J00.X-J89.X	Diseases of the respiratory system
K00.X-K99.X	Diseases of the digestive system
L00.X-L97.X	Diseases of the skin and subcutaneous tissue
M00.X-M99.X	Diseases of the musculoskeletal system and connective tissue
N00.X-N62.X	Diseases of the genitourinary system
S00.X-T88.X	Injury, poisoning and certain other consequences of external causes
Z00.X-Z05.X	Persons encountering health services for examinations
Z13.X	Encounter for screening for other diseases and disorders
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
Z23	Encounter for immunization
Z31.X	Encounter for procreative management

Table: ICD Code Indications for CPT 88182

Codes and Descriptions.

Code or Range	Description
O01.X	Hydatidiform mole

Code or Range	Description
O02.89	Other abnormal products of conception
O02.9	Abnormal product of conception, unspecified

What is flow cytometry?

Definition

Flow cytometry is a method that uses lasers to detect cell characteristics, including their cell surface or cytoplasmic antigens, size, and granularity, by employing fluorescent conjugate-labeled antibodies and cell light scatter properties, or in the case of DNA analysis, a DNA binding fluorescent stain. Specimens are most commonly fluids such as blood or bone marrow aspirates, but it is also possible to test ground-up solid samples and other tissue samples such as ascites and pleural fluid, as well as fine needle aspirations of clinical abnormalities.

Flow cytometry procedure coding

The following combination(s) of CPT codes may be used unless more specific CPT codes exist (e.g., 86361). Any deviation from these CPT coding standards is subject to review and denial if not properly coded.

- 88182 is used to describe the technical component of cell cycle or DNA analysis.
- 88184 is used to describe the technical component of the first marker applied (maximum one unit)
- 88185 is used for each additional marker applied and billed with the applicable number of units. Therefore, 88185 should not be billed without 88184.
- Because CPT 88184 and 88185 describe only the technical component, there are three professional component interpretation codes that may be applied based on the number of markers assessed (each billed with a maximum of one unit):
    - CPT 88187 for evaluating 2 to 8 markers
    - CPT 88188 for evaluating 9 to 15 markers
    - CPT 88189 for evaluating 16 or more markers

Common uses

A variety of disorders are associated with distinct immunophenotypic profiles, which can be used to diagnose, subtype, or monitor these disorders.[14] The following are common uses of flow cytometry in medicine:

Hematopoietic neoplasm evaluation and monitoring

Hematopoietic neoplasm evaluation and monitoring is a common use of flow cytometry, which includes leukemia and lymphoma immunophenotyping and minimal residual disease (MRD) detection. MRD, in cases of acute leukemia, is when individuals with acute leukemia appear to be in morphologic remission on bone marrow samples, but neoplastic cells with an aberrant phenotype remain detectable by flow cytometry or other methods.

Initial flow cytometry panels for immunophenotypic evaluation are generally composed of a narrow selection of markers and made to account for major cell populations, aided by light scatter properties, and pre-analytic examination, such as of peripheral blood smears, bone marrow smears, or hematoxylin and eosin stained tissue sections, to limit the use of unnecessary flow cytometry markers.[7-10,15] An algorithmic approach using clinical information and the likelihood of identifying an abnormal cell population may be used to reduce the use of unnecessary markers.[16] More extensive flow cytometry evaluation should be reserved for those cases with a high likelihood of a new diagnosis of leukemia/lymphoma or other hematopoietic neoplasm based on morphologic review and initial panel evaluation:[1,2]

- "In particular, morphology is one of the primary screening tools that results in the ordering of flow cytometric testing and plays an important role in quality assurance for flow cytometry."[1]

Flow cytometry on peripheral blood should be limited to those settings in which there is a high pre-test probability of detecting an abnormal cell population:

- "The role of peripheral blood flow cytometry for hematologic neoplasia is limited to settings in which either there are morphologically abnormal cells identified on a peripheral blood smear review (blasts, lymphoma cells) or there are clinical and/or laboratory findings that suggest a high pre-test probability for the presence of a disorder amenable to the immunophenotypic detection of neoplastic cells in the blood. The latter includes patients with neutropenia, absolute lymphocytosis, lymphadenopathy, or splenomegaly."[17]

In minimal residual disease (MRD) evaluation, a limited panel based upon the patient's original disease immunophenotype may be employed, thereby obviating the need for an extended panel of flow cytometry markers. For example, limited marker strategies for monitoring plasma cell dyscrasia have been reported.[5,18] For pediatric leukemia, though, the prognostic value of detecting residual disease by flow cytometry appears to be limited in multi-variate analysis.[19]

Cell cycle or DNA analysis

DNA ploidy analysis is commonly used for the evaluation of gestational trophoblastic disease, as the distinction between partial hydatidiform mole, complete hydatidiform mole, and hydropic degeneration of chorionic villi is important for clinical management.[20,21] In certain cases, molecular genotyping may be employed.[22]

Although having demonstrated early promise as a prognostic marker, DNA ploidy analysis of solid tumors has not been widely adopted in clinical practice, and has largely been replaced by molecular prognostic markers.[23] Results of several studies of the technology are conflicting as well. Dayal, et al. (2013) in a breast cancer study, found that an independent association between tumor DNA content and overall survival could not be demonstrated on multi-variate analysis.[24] A study by Wolfson, et al. (2008) yielded similar results in patients with cervical cancer.[25]

HIV infection monitoring

Flow cytometry is used for HIV infection monitoring to accurately and reliably evaluate the number of CD4 positive T lymphocytes.[13]

Immunodeficiency

Flow cytometry is used in the diagnosis, classification, and monitoring of immunodeficiencies.[26] The disorders may be associated with absent or impaired cell proteins (primary disease), leukocyte dysfunction, or markers of immune status in lymphocytes (secondary disease).[14] Flow cytometry panel selection in the evaluation of immunodeficiency should be guided by the clinical findings. Testing requires a highly sophisticated laboratory, and in some cases, should be performed prior to genetic testing.[26,27] A multi-center consortium has proposed a standard strategy in evaluating primary immunodeficiency disorders by flow cytometry.[28]

Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH), a rare stem cell disorder, is diagnosed through the detection of deficient glycosylphosphatidylinositol (GPI) anchored antigens on red blood cells, monocytes, and/or granulocytes by flow cytometry.[14] A limited, focused flow cytometry panel for the surface antigens of interest is commonly employed on peripheral blood.[29-31]

References

Introduction

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