

Test Specific Guidelines

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 is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required..

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

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.¹ 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.²⁻⁶ 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.⁷ 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:^{8,9}

"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."⁸

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."¹⁰

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.^{11,12} For pediatric leukemia, though, the prognostic value of detecting residual disease by flow cytometry appears to be limited in multi-variate analysis.¹³

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.^{14,15} In certain cases, molecular genotyping may be employed.¹⁶

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.¹⁷ 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.²² A study by Wolfson, et al. (2008) yielded similar results in patients with cervical cancer.²³

HIV infection monitoring

Flow cytometry is used for HIV infection monitoring to accurately and reliably evaluate the number of CD4 positive T lymphocytes.²⁰

Immunodeficiency

Flow cytometry is used in the diagnosis, classification, and monitoring of immunodeficiencies.²¹ The disorders may be associated with absent or impaired cell proteins (primary disease), leukocyte dysfunction, or markers of immune status in lymphocytes (secondary disease).¹ 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.^{21,22} A multi-center

consortium has proposed a standard strategy in evaluating primary immunodeficiency disorders by flow cytometry.²³

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.¹ A limited, focused flow cytometry panel for the surface antigens of interest is commonly employed on peripheral blood.^{24,25,26}

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).

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.⁸ 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.^{9,27}

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.²⁸ 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.^{11,29}

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.³⁻⁶ In those cases in which a new leukemia diagnosis needs confirmation and further characterization, additional flow cytometry markers are usually employed.³⁰ Monitoring of a known hematopoietic neoplasm requires fewer flow cytometry markers.³¹ 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.

Billing and reimbursement considerations:

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*. When possible, the ICD code submitted with the claim should reflect the clinical and flow cytometric findings.

Claims resulting from flow cytometric analysis of two or more tissue or fluid samples from an individual patient may be subject to post-service medical necessity review.

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).²⁰

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.

Billing and reimbursement considerations:

The most commonly required flow cytometry studies for HIV are represented by marker-specific CPT codes (e.g., 86361). The non-specific flow cytometry codes (88184, 88185, 88187-88189) should not be used when a more specific code exists. Post-service medical necessity review may be employed when non-specific flow cytometry codes are used for HIV monitoring.

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 and is not reimbursable.

CPT 88182 is reimbursable when billed for the evaluation of gestational trophoblastic disease.

Billing and reimbursement considerations:

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

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.

Billing and reimbursement considerations:

Claims for CPT 88184 or 88185 not including an approvable 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. All other claims will be subject to post-service medical necessity review.

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.

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

ICD Codes

ICD codes in this section may be used to support or refute medical necessity as described in the above criteria.

Table: ICD Code Indications for Flow Cytometry Tier 1 Testing**ICD Codes and Descriptions.**

<u>ICD Code or Range</u>	<u>Description</u>
<u>C91.00</u>	<u>Acute lymphoblastic leukemia not having achieved remission</u>
<u>C91.02</u>	<u>Acute lymphoblastic leukemia, in relapse</u>
<u>C92.00</u>	<u>Acute myeloblastic leukemia, not having achieved remission</u>
<u>C92.02</u>	<u>Acute myeloblastic leukemia, in relapse</u>
<u>C92.40</u>	<u>Acute promyelocytic leukemia, not having achieved remission</u>
<u>C92.42</u>	<u>Acute promyelocytic leukemia, in relapse</u>
<u>C92.50</u>	<u>Acute myelomonocytic leukemia, not having achieved remission</u>
<u>C92.52</u>	<u>Acute myelomonocytic leukemia, in relapse</u>
<u>C92.60</u>	<u>Acute myeloid leukemia with 11q23-abnormality not achieve remission</u>
<u>C92.62</u>	<u>Acute myeloid leukemia with 11q23-abnormality in relapse</u>
<u>C92.A0</u>	<u>Acute myeloid leuk with multilin dysplasia, not achieve remission</u>
<u>C92.A2</u>	<u>Acute myeloid leuk with multilin dysplasia, in relapse</u>
<u>C93.00</u>	<u>Acute monoblastic/monocytic leukemia, not achieve remission</u>
<u>C93.02</u>	<u>Acute monoblastic/monocytic leukemia, in relapse</u>
<u>C93.1X</u>	<u>Chronic myelomonocytic leukemia</u>
<u>C93.3X</u>	<u>Juvenile myelomonocytic leukemia</u>
<u>C94.00</u>	<u>Acute erythroid leukemia, not having achieved remission</u>
<u>C94.02</u>	<u>Acute erythroid leukemia, in relapse</u>
<u>C94.20</u>	<u>Acute megakaryoblastic leukemia not achieve remission</u>
<u>C94.22</u>	<u>Acute megakaryoblastic leukemia, in relapse</u>
<u>C94.30</u>	<u>Mast cell leukemia not having achieved remission</u>
<u>C94.32</u>	<u>Mast cell leukemia, in relapse</u>
<u>C94.40</u>	<u>Acute panmyelosis with myelofibrosis not achieve remission</u>
<u>C94.42</u>	<u>Acute panmyelosis with myelofibrosis, in relapse</u>
<u>C94.6</u>	<u>Myelodysplastic disease, not classified</u>
<u>C95.00</u>	<u>Acute leukemia of unspecified cell type not achieve remission</u>
<u>C95.02</u>	<u>Acute leukemia of unspecified cell type, in relapse</u>
<u>D46.X</u>	<u>Myelodysplastic syndromes</u>
<u>D61.X</u>	<u>Other aplastic anemias and other bone marrow failure syndromes</u>

Table: ICD Code Indications for Flow Cytometry Tier 2 Testing**ICD Codes and Descriptions.**

<u>ICD Code or Range</u>	<u>Description</u>
<u>C37</u>	<u>Malignant neoplasm of thymus</u>
<u>D47.X</u>	<u>Other neoplasms of uncertain behavior of lymphoid, hematopoietic, and related tissue</u>
<u>C82.X</u>	<u>Follicular lymphoma</u>
<u>C83.X</u>	<u>Non-follicular lymphoma</u>
<u>C84.X</u>	<u>Mature T/NK-cell lymphomas</u>
<u>C85.X</u>	<u>Other specified and unspecified types of non-Hodgkin lymphoma</u>
<u>C86.X</u>	<u>Other specified types of T/NK-cell lymphoma</u>
<u>C88.X</u>	<u>Malignant immunoproliferative diseases and certain other B-cell lymphomas</u>
<u>C90.X</u>	<u>Multiple myeloma and malignant plasma cell neoplasms</u>
<u>C91.01</u>	<u>Acute lymphoblastic leukemia, in remission</u>
<u>C91.10- C91.Z2</u>	<u>Lymphoid leukemia</u>
<u>C92.01</u>	<u>Acute myeloblastic leukemia, in remission</u>
<u>C92.41</u>	<u>Acute promyelocytic leukemia, in remission</u>
<u>C92.51</u>	<u>Acute myelomonocytic leukemia, in remission</u>
<u>C92.61</u>	<u>Acute myeloid leukemia with 11q23-abnormality, in remission</u>
<u>C92.A1</u>	<u>Acute myeloid leukemia with multilineage dysplasia, in remission</u>
<u>C94.01</u>	<u>Acute erythroid leukemia, in remission</u>
<u>C94.21</u>	<u>Acute megakaryoblastic leukemia, in remission</u>
<u>C94.31</u>	<u>Mast cell leukemia, in remission</u>
<u>C94.41</u>	<u>Acute panmyelosis with myelofibrosis, in remission</u>
<u>C95.01</u>	<u>Acute leukemia of unspecified cell type, in remission</u>
<u>C95.90</u>	<u>Leukemia, unspecified not having achieved remission</u>
<u>C95.91</u>	<u>Leukemia, unspecified, in remission</u>
<u>C96.X</u>	<u>Other and unspecified malignant neoplasms of lymphoid, hematopoietic and related tissue</u>
<u>D47.0X</u>	<u>Mast cell neoplasms of uncertain behavior</u>
<u>D47.2</u>	<u>Monoclonal gammopathy</u>

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

Table: ICD Codes Not Approvable For Flow Cytometry**ICD Codes and Descriptions.**

<u>ICD Code or Range</u>	<u>Description</u>
<u>A00.X-B99.X</u>	<u>Certain infectious and parasitic diseases</u>
<u>C43.X</u>	<u>Malignant melanoma of skin</u>
<u>C81.X</u>	<u>Hodgkin lymphoma</u>

<u>ICD Code or Range</u>	<u>Description</u>
<u>C92.1X</u>	<u>Chronic myeloid leukemia, BCR/AB- positive</u>
<u>C92.2X</u>	<u>Atypical chronic myeloid leukemia, BCR/AL-negative</u>
<u>D00.X-D09.X</u>	<u>In situ neoplasms</u>
<u>D10.X-D36.X</u>	<u>Benign neoplasms, except benign neuroendocrine tumors</u>
<u>D45</u>	<u>Polycythemia vera</u>
<u>D47.1</u>	<u>Chronic myeloproliferative disease</u>
<u>D47.3</u>	<u>Essential (hemorrhagic) thrombocythemia</u>
<u>D50.X-D53.X</u>	<u>Nutritional anemia</u>
<u>D55.X</u>	<u>Anemia due to enzyme disorders</u>
<u>D56.X</u>	<u>Thalassemia</u>
<u>D57.X</u>	<u>Sickle-cell disorders</u>
<u>D58.X</u>	<u>Other hereditary hemolytic anemia</u>
<u>D62</u>	<u>Acute posthemorrhagic anemia</u>
<u>D63.X</u>	<u>Anemia in chronic diseases classified elsewhere</u>
<u>D68.X</u>	<u>Other coagulation defects</u>
<u>D72.0X</u>	<u>Genetic anomalies of leukocytes</u>
<u>D72.1X</u>	<u>Eosinophilia</u>
<u>D72.823</u>	<u>Leukemoid reaction</u>
<u>D72.824</u>	<u>Basophilia</u>
<u>D72.825</u>	<u>Bandemia</u>
<u>D72.828</u>	<u>Other elevated white blood cell count</u>
<u>D72.829</u>	<u>Elevated white blood cell count, unspecified</u>
<u>D72.89</u>	<u>Other specified disorders of white blood cells</u>
<u>D72.9</u>	<u>Disorder of white blood cells, unspecified</u>
<u>D75.1</u>	<u>Secondary polycythemia</u>
<u>D86.X</u>	<u>Sarcoidosis</u>
<u>E00.X-E89.X</u>	<u>Endocrine, nutritional and metabolic diseases</u>

<u>ICD Code or Range</u>	<u>Description</u>
<u>F01.X-F99.X</u>	<u>Mental, Behavioral and Neurodevelopmental disorders</u>
<u>G00.X-G99.X</u>	<u>Diseases of the nervous system</u>
<u>H00.X-H59.X</u>	<u>Diseases of the eye and adnexa</u>
<u>I00.X-I79.X</u>	<u>Diseases of the circulatory system</u>
<u>J00.X-J89.X</u>	<u>Diseases of the respiratory system</u>
<u>K00.X-K99.X</u>	<u>Diseases of the digestive system</u>
<u>L00.X-L97.X</u>	<u>Diseases of the skin and subcutaneous tissue</u>
<u>M00.X-M99.X</u>	<u>Diseases of the musculoskeletal system and connective tissue</u>
<u>N00.X-N62.X</u>	<u>Diseases of the genitourinary system</u>
<u>S00.X-T88.X</u>	<u>Injury, poisoning and certain other consequences of external causes</u>
<u>Z00.X-Z05.X</u>	<u>Persons encountering health services for examinations</u>
<u>Z13.X</u>	<u>Encounter for screening for other diseases and disorders</u>
<u>Z21</u>	<u>Asymptomatic human immunodeficiency virus [HIV] infection status</u>
<u>Z23</u>	<u>Encounter for immunization</u>
<u>Z31.X</u>	<u>Encounter for procreative management</u>

Table: ICD Code Indications for CPT 88182

ICD Codes and Descriptions.

<u>ICD Code or Range</u>	<u>Description</u>
<u>O01.X</u>	<u>Hydatidiform mole</u>
<u>O02.9</u>	<u>Abnormal product of conception, unspecified</u>

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Introduction

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