

Lab: Flow Cytometry

CPT: 88182, 88184, 88185, 88187, 88188, 88189, 86355, 86356, 86357, 86359, 86360, 86361, 86367

CMS Policy for Alabama, Georgia, North Carolina, South Carolina, Tennessee, Virginia, and West Virginia

Local policies are determined by the performing test location. This is determined by the state in which your performing laboratory resides and where your testing is commonly performed.

Medically Supportive ICD Codes are listed on subsequent page(s) of this document.

Coverage Indications, Limitations, and/or Medical Necessity

Flow cytometry (FCM) is a complex process to examine blood, body fluids, cerebrospinal fluid (CSF), bone marrow, lymph node, tonsil, spleen and other solid tissues. The use of peripheral blood and fine needle aspirate material avoids more invasive procedures for diagnosis.

A flow cytometer evaluates the physical and/or chemical characteristics of single cells as the cells pass individually in a fluid stream through a measuring device. Surface receptors, intracellular molecules, and DNA bind with fluorescent dyes that allow detection and evaluation.

When light of one wave length excites electrons of certain chemicals to energy levels above their ground state and upon return to ground state emits light of a longer wavelength, fluorescence is produced. A flow cytometer detects cell characteristics by measuring the fluorescence produced by fluorochromes conjugated either directly with cell components or conjugated to antibodies directed against cell components.

Indications

Cytopenias and Hypercellular Hematolymphoid Disorders

Hematolymphoid neoplasia can present with cytopenias (anemia, leukopenia and/or thrombocytopenia) or elevated leukocyte counts. If medical review and preliminary laboratory testing fails to reveal a cause, bone marrow aspiration and biopsy are indicated to rule out an infiltrative process or a stem cell disorder. FCM is essential to evaluate hematolymphoid lineages. Although anemia commonly occurs in nonneoplastic diseases, anemia alone should not automatically trigger FCM.

FCM may be useful in hypercellular hematolymphoid disorders to differentiate reactive conditions from neoplastic conditions. In the absence of blasts, neutrophilic leukocytosis is not generally an indication for FCM. Isolated polycythemia and basophilia are not sufficient to warrant FCM.

Lymphomas

In the current World Health Organization (WHO) classification, all non-Hodgkin lymphomas (NHLs) are distinct clinicopathologic entities defined by their clinical features, morphology, immunophenotype and, where appropriate, their genetic abnormalities. Immunophenotyping by FCM allows multiparameter evaluation of single cells and the ability to work on very small samples.

Most new cases of suspected NHL undergo initial immunophenotypic analysis as part of the routine handling of a specimen. A standard lymphoma panel is designed to identify abnormal populations of B cells, T cells and/or NK cells. A standard lymphoma panel might include a combination of markers from the following categories: T cells (CD2, CD3, CD4, CD5, CD7, CD8); B cells (CD19, CD20, CD23); Kappa and lambda surface immunoglobulins light chains; plasma cells (CD38 and CD138); CALLA (CD10); CD45; CD56: FMC-7, CD103, CD11c, CD13, CD14, CD15, CD16 and CD34.

The immunophenotypes of lymphomas are widely known and FCM allows appropriate classification of most cases. However, atypical patterns occur and pose significant diagnostic difficulties where aberrant antigen expression patterns must be reconciled with morphology. Additional markers may be required to characterize the abnormal population of cells including markers of immature cells (HLA-DR), B cells (CD22) and myeloid cells (CD14, CD15, CD33, CD64, CD117).

Acute Leukemia

The diagnosis and management of acute leukemia depends on the detection, identification and characterization of leukemic cells. The identification of leukemic cells is straightforward in most occasions. However, each acute leukemia subgroup has heterogeneous biologic characteristics, many of which are associated with a different response to therapy.

As part of a routine diagnostic workup, most suspected acute leukemia cases undergo initial multiparameter immunophenotypic analysis, combined with morphology, cytochemistry, cytogenetics, and molecular biology. A standard acute leukemia FCM panel is designed to determine whether leukemic blasts are of myeloid or lymphoid origin, and then to further classify the neoplastic cells (myeloid blasts, B lymphoblasts, abnormal promyelocytes, monoblasts, etc). An acute leukemia panel might include a combination of cell markers from the following categories: stem cell lineage (CD34), immature cell lineage (HLA-DR, CD10); T cell (CD2, CD3, CD4, CD5, CD7 and CD8); B cell (CD19, CD20); myeloid cell (CD13, CD14, CD15, CD33, CD64 and CD117); CD38, CD45, and CD56.

When the routine panel is insufficient to characterize the leukemic cells, additional antibodies including erythroid markers (CD71 and glycophorin A), megakaryocytic markers (CD41, CD61) or cytoplasmic markers may be indicated.

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Chronic Lymphocytic Leukemia (CLL) & Other Chronic Lymphoproliferative Diseases (CLPD)

The history, physical exam (lymphadenopathy, splenomegaly and/or hepatomegaly), laboratory findings (lymphocytosis, granulocytopenia, anemia, thrombocytopenia), and lymphocyte morphology are suggestive of CLL. The diagnosis is established by paradoxical co-expression of CD5 on peripheral lymphocytes that express B cell markers (CD19, CD20, CD21 and CD23) with Kappa or lambda immunoglobulin light chain restriction. Additional markers such as CD38 and ZAP70 may provide important prognostic information.

FCM can distinguish CLL, the peripheral counterpart of small lymphocytic lymphoma, often diagnosed in lymph node biopsies, from other indolent lymphocytic malignancies including prolymphocytic leukemia, Waldenstrom's macroglobulinemia, leukemic phase of lymphomas, hairy cell leukemia, T-cell CLL, adult T-cell leukemia, large granulocytic leukemia and cutaneous T-cell lymphoma and natural killer (NK) disorders including KIR expression.

Plasma Cell Disorders

Plasma cell disorders are often identified through a combination of clinical, laboratory studies (urine or serum gamma globulins), morphologic, and radiologic findings. FCM immunophenotyping is useful to identify abnormal plasma cells, and the distinction between lymphoid and plasma cell neoplasms, and between reactive plasma cells and neoplastic plasma cells.

The initial FCM workup for a plasma cell disorder may include the basic lymphoma panel markers with additional markers such as CD28 and CD117.

Myelodysplastic Syndromes (MDS)

The gold standard for an MDS diagnosis is assessment of bone marrow smears for dysplastic changes. FCM may assist in MDS determination through the identification of abnormal maturing myeloid cells. An abnormal phenotype by FCM is a minimal diagnostic MDS criteria to establish a definitive diagnosis.

MDS has a definite risk and rate of progression to acute leukemia. Standard FCM leukemia panels are indicated to evaluate progression and onset of leukemia.

Chronic Myeloproliferative Disorders (CMPD)

Although genetic (Philadelphia chromosome and BCR/abl) and molecular studies (Jak 2) are the accepted cornerstone for the identification and classification of CMPDs, FCM may assist in the distinction from reactive hematopoietic proliferations and is important in the enumeration of blasts in the distinction from acute leukemia and an accelerated phase of CMPD.

CMPD also has a definite risk and rate of progression to acute leukemia. Standard FCM leukemia panels are indicated to evaluate progression and onset of leukemia.

Mast Cell Neoplasms

Mast cell neoplasms are uncommon disorders. Mast cells coexpress multiple markers including CD9, CD33, CD45, CD68, CD117, but also lack several myelomonocytic antigens including CD14, CD15, CD16 and most T- and Bcell antigens. Neoplastic mast cells have a similar antigen profile, but also can coexpress CD2 and CD25, which help in distinguishing malignant mast cells from mastocytosis.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is a rare clonal hematopoietic disorder of stem cells. This condition is caused by genetic mutation that results in the absence of over a dozen surface antigens on red and white blood cells. FCM can diagnose PNH by assessing both the red and white blood cells for the absence of these antigens.

Minimal Residual Disease (MRD)

FCM analysis for MRD must identify phenotypic features characteristic of the disease of interest. The MRD flow analysis should not rely on an exact match between the phenotype of the residual disease and the original diagnostic specimen because phenotypes can change over time and with treatment. The antibody combinations should be chosen to maximize detection of disease, limit the impact of phenotypic variation, and permit detection of disease following antibody directed therapy.

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HIV Infection

HIV-1 infection causes significant changes in the number of CD4 and CD8 positive lymphocytes. CD4 count falls roughly 30% while CD8 count increases within 6 months after seroconversion, causing a decrease in the CD4/CD8 ratio

Following HIV-1 diagnosis, FCM should include enumeration of mature T cells (CD3), helper T cells (CD4) and suppressor T cells (CD8) to ensure all major T cell subsets are accounted for (the sum of helper CD4 and suppressor CD8 T cells is roughly close to the total number of CD3 positive T cells). This ensures that the absolute CD4 is not artificially decreased due to sample degradation or other artifact.

A WBC count with differential also needs to be performed to calculate the absolute CD4 count (absolute lymphocyte count times CD4%).

Organ Transplants

In order to differentiate early rejection, immunosuppressive therapy toxicity or infection, FCM may be indicated to monitor postoperative organ transplants. CD3 is useful to monitor the effectiveness of certain immunosuppressive therapies. When the transplant patient demonstrates symptoms for the above conditions, repeated analysis may be required.

DNA Analysis

Carcinoma, Non-hematolymphoid Tumors

DNA analysis of tumor for ploidy and percent S-phase cells may be necessary for a few selective patients with carcinomas. When the obtained prognostic information will affect treatment decisions in patients with low stage (localized) disease, FCM results are useful.

Molar Pregnancy

FCM is useful to evaluate molar and partial molar pregnancies. Using a method to quantify DNA, similar to that used for evaluation of carcinomas, partial moles (triploid), can be distinguished from normal placenta and complete molar (diploid) pregnancies.

Primary Immunodeficiencies (PIDS)

PIDs are rare disorders that reflect inherited abnormalities in the development and maturation of cells responsible for immune function. More than 120 inherited immunodeficiency disorders are currently recognized. Affected individuals are prone to repeated infections, allergies, autoimmune disorders, and malignancies. Diagnosis typically occurs at an early age.

FCM may be indicated for diagnostic purposes and is usually limited to T (CD3, CD4, CD8), B (CD20) and NK cell (CD56) markers. Additional disease specific markers may be indicated.

Primary Platelet Disorders, Non-neoplastic

FCM is used for platelet analysis in quantitative and qualitative disorders such as Glanzmann Thrombasthenia (GT) and Bernard-Soulier Disease (B-S). GT is a rare inherited or acquired platelet disorder. Hereditary GT is defined by platelets with decreased expression or absence of the GPIIa/GPIIb receptor. This receptor is responsible for the initial platelet plug at the site of endothelial injury. Absence of the receptor may result in increased bleeding.

Acquired GT is likely an autoimmune phenomenon with the presence of GPIIb/GPIIIa blocking antibodies. FCM may be used to determine the functional effect and identify the molecular targets of these antibodies.

B-S is another rare inherited disorder that prevents the initial binding of platelets at the site of endothelial injury by absence of or presence of abnormal surface GPIa/V/IX receptor. Abnormalities of this receptor prevent attachment of platelets to subendothelial or free von Willebrand's factor with subsequent tendency to bleed.

FCM may be used to measure antibodies directed at specific loci of the GPIa/V/IX receptor, which include GPIb (CD42b), GPIX (CD42a), and GPV (CD42d). FCM is also used to assess the size of platelets in the initial evaluation of B-S disease. In B-S disease, platelets are generally larger than normal. FCM can distinguish B-S platelets from fragmented RBCs and debris by antibodies directed to the GPIb/IX/V receptor.

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Red Cell and White Cell Disorders, Non-neoplastic

FCM is a valuable tool to establish abnormal or defective red blood cell, leukocyte and lymphocyte surface receptors, transmembrane molecules, and intracellular DNA. It may be used in acquired and congenital red cell conditions such as in quantifying fetomaternal hemorrhage and hereditary spherocytosis, hereditary elliptocytosis, and hereditary persistence of fetal hemoglobin in the context of compound hemoglobinopathy syndromes.

FCM is a sensitive and specific method to identify leukocyte receptor abnormalities for the diagnosis of chronic granulomatous disease and CD11b deficiency. It is an efficient method to identify lymphocytes HLA B27 associated with uveitis, ankylosing spondylitis, Reiter's syndrome and sacroiliitis.

Limitations

Since FCM immunophenotypes for most common lymphomas and leukemias are well characterized, Palmetto GBA does **NOT** consider it "reasonable and necessary" to perform more than 24 markers in a panel. When atypical or unusual FCM results are obtained, the selective addition of more markers may be indicated.

The flow report must document the specific indication for each marker over the 24 marker limit.

The FCM report must document the specific indication for **each** marker over the 24-marker limit. FCM reports without clear justification for each marker over 24 will be denied.

Documentation Requirements:

Laboratories and physicians that request FCM studies **MUST** provide legible documentation of clinical and morphologic findings, cell counts (quantitative values), radiology and cytogenetic findings when available.

The referring physician or pathologist **MUST** provide the most specific suspected diagnosis or differential diagnosis to allow the performing laboratory to determine an appropriate panel of cell markers.

The performing laboratory **MUST** select an appropriate panel of cell markers for the suspected diagnosis.

Since Palmetto GBA expects the need for markers in excess of 24 to be rare, providers must include the following documentation to justify additional marker selection with their redetermination request:

- clinical information summary
- specific marker results
- diagnosis and interpretation
- rationale to support each additional marker in excess of 24

Redeterminations filed without this specific final report information shall be denied as not reasonable or necessary.

A flow cytometry report listing the antibodies performed and the percentage and expressed markers does **NOT** meet this documentation requirement for initial redetermination consideration or for the appeal process.

Hospital and reference labs must ensure the documentation in the medical record justifies the selection of the billed cell markers.

Flow cytometry is a dynamic field. Palmetto GBA will evaluate requests for coverage extension that are supported by peer reviewed literature.

Compliance with the provisions listed in this policy will be subject to postpayment data analysis and subsequent medical review. Failure to document and maintain supporting medical information in the patient's record or in the FCM report may result in overpayments and/or RAC referral.

Utilization Guidelines

Medicare does not expect to see labs routinely perform more than 24 markers per specimen.

Comprehensive marker panels used to indiscriminately "screen" specimens, regardless of the submitted suspected diagnosis, are not considered reasonable and necessary.

An FCM performed more than every 3 months to monitor stable HIV infection is not considered reasonable or necessary. More frequent studies may be indicated if a patient develops drug resistance and needs to be treated with another antiviral(s).

DNA analysis for selected patients with carcinomas may be appropriate **ONLY** once after diagnosis and before treatment is initiated.

Palmetto GBA expects the initial flow evaluation to contain a greater number of antibody determinations than a subsequent follow-up study. MDS and CMPD are general exceptions because these disorders are at risk for developing leukemia. Progression to leukemia may necessitate cytoplasmic markers.

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CPT/HCPCS Codes

Group 1 Codes:

88182	Cell marker study
88184	Flowcytometry/ tc 1 marker
88185	Flowcytometry/tc add-on
88187	Flowcytometry/read 2-8
88188	Flowcytometry/read 9-15
88189	Flowcytometry/read 16 & >

Group 2 Paragraph:

Quantitative Codes in immunology section:

Group 2 Codes:

86355	B cells total count
86356	Mononuclear cell antigen
86357	Nk cells total count
86359	T cells total count
86360	T cell absolute count/ratio
86361	T cell absolute count
86367	Stem cells total count

Group 1 Paragraph: The CPT/HCPCS codes included in this LCD will be subjected to “procedure to diagnosis” editing. The following lists include only those diagnoses for which the identified CPT/HCPCS procedures are covered. If a covered diagnosis is not on the claim, the edit will automatically deny the service as not medically necessary.

Medicare is establishing the following limited coverage for CPT/HCPCS codes 88182, 88184, 88185, 88187, 88188, 88189, 86355, 86356, 86357, 86359, 86360, 86361 and 86367:

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There is a frequency associated with this test. Please refer to the Limitations or Utilization Guidelines section on previous page(s).

The ICD10 codes listed below are the top diagnosis codes currently utilized by ordering physicians for the limited coverage test highlighted above that are also listed as medically supportive under Medicare's limited coverage policy. **If you are ordering this test for diagnostic reasons that are not covered under Medicare policy, an Advance Beneficiary Notice form is required.**

***Note—Bolded diagnoses below have the highest utilization**

Code	Description
B20	Human immunodeficiency virus [HIV] disease
C61	Malignant neoplasm of prostate
D47.3	Essential (hemorrhagic) thrombocythemia
D64.9	Anemia, unspecified
D69.6	Thrombocytopenia, unspecified
D72.810	Lymphocytopenia
D72.819	Decreased white blood cell count, unspecified
D72.9	Disorder of white blood cells, unspecified
D80.1	Nonfamilial hypogammaglobulinemia
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.4	Selective deficiency of immunoglobulin M [IgM]
D80.6	Antibody deficiency with near-normal immunoglobulins or with hyperimmunoglobulinemia
D89.9	Disorder involving the immune mechanism, unspecified
R59.9	Enlarged lymph nodes, unspecified
R80.9	Proteinuria, unspecified
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
Z85.72	Personal history of non-Hodgkin lymphomas

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Last updated: 10/1/20

Disclaimer:

This diagnosis code reference guide is provided as an aid to physicians and office staff in determining when an ABN (Advance Beneficiary Notice) is necessary. Diagnosis codes must be applicable to the patient's symptoms or conditions and must be consistent with documentation in the patient's medical record. Quest Diagnostics does not recommend any diagnosis codes and will only submit diagnosis information provided to us by the ordering physician or his/her designated staff. The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

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