

Flow Cytometry

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

CMS Policy

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, 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, leucopenia 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 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, CD11b, 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).

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CMS Policy (continued)

- **Acute Leukemia**

The diagnosis and management of acute leukemia depend 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, CD 10); T cell (CD2, CD3, CD4, CD5, CD7 and CD8); B cell (CD19, CD20); myeloid cell (CD13, CD14, CD15, CD 33, CD 64 and CD17); 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.

- **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 CD 23) 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.

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CMS Policy (continued)

- **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 B- cells antigens. Neoplastic mast cells have a similar antigen profile, but also can coexpress CD2 and CD25, which helps in distinguishing malignant mast cells from mastocytosis.

- **Paroxysmal 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.

- **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.

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CMS Policy (continued)

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/GPIIIb 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.

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, Noridian 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.

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Please refer to the [Limitations or Utilization Guidelines](#) section on previous page(s) for frequency information.

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.**

Code	Description
B20	Human immunodeficiency virus [HIV] disease
C61	Malignant neoplasm of prostate
C78.4	Secondary malignant neoplasm of small intestine
C83.38	Diffuse large B-cell lymphoma, lymph nodes of multiple sites
C90.00	Multiple myeloma not having achieved remission
D47.2	Monoclonal gammopathy
D64.9	Anemia, unspecified
D69.6	Thrombocytopenia, unspecified
D72.810	Lymphocytopenia
D72.818	Other decreased white blood cell count
D72.819	Decreased white blood cell count, unspecified
D72.820	Lymphocytosis (symptomatic)
D80.1	Nonfamilial hypogammaglobulinemia
D80.2	Selective deficiency of immunoglobulin A [IgA]
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.6	Antibody defic w near-norm immunoglob or w hyperimmunoglob
D82.4	Hyperimmunoglobulin E [IgE] syndrome
D83.0	Com variab immunodef w predom abnlt of B-cell nums & functn
D83.1	Com variab immunodef w predom immunoreg T-cell disorders
D83.8	Other common variable immunodeficiencies
D84.821	Immunodeficiency due to drugs
D84.89	Other immunodeficiencies
D89.89	Oth disrd involving the immune mechanism, NEC
R89.7	Abnormal histolog findings in specimens from oth org/tiss
Z21	Asymptomatic human immunodeficiency virus infection status

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Disclaimer:

This diagnosis code reference guide is provided for informational purposes only as an aid to physicians and office staff in determining when an ABN (Advance Beneficiary Notice) is necessary, as of the date last updated. 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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