

Corporate Medical Policy

Flow Cytometry AHS–F2019

File Name:	flow_cytometry
Origination:	1/1/2019
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Description of Procedure or Service

Flow cytometry is a technique for live cell analysis that measures optical light scattering features to determine physical characteristics (Adan, Alizada, Kiraz, Baran, & Nalbant, 2017). This instrument is beneficial for calculating the number of cells in a biologic sample, as well as for measuring cellular properties, such as size, shape, viability, and granularity (Verbsky & Routes, 2018). Flow cytometry may also be used for diagnostic and prognostic purposes when monitoring certain diseases, and for identifying the presence of specific biomarkers.

Related Policies:

Minimal Residual Disease AHS-M2175

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for flow cytometry when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Flow Cytometry is covered

Reimbursement for flow cytometry immunophenotyping of cell surface markers is allowed for any of the following conditions:

- Cytopenias, lymphomas, leukemia and lymphoproliferative disorders or myelodysplastic syndrome;
- B-cell monitoring for immunosuppressive disorders;
- T-cell monitoring for HIV infection and AIDS
- Mast cell neoplasms
- Paroxysmal nocturnal hemoglobinuria
- Post-operative monitoring of members who have undergone organ transplantation
- Plasma cell disorders
- Primary Immunodeficiencies (PIDs), and PIDs involving T, NK
- Hypercellular Hematolymphoid Disorders

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- Chronic Lymphocytic Leukemia (CLL)
- Chronic Myeloproliferative Disorders (CMPD)
- Minimal Residual Disease (MRD)
- Molar pregnancy
- Primary Platelet Disorders, Non-neoplastic
- Red Cell and White Cell Disorders, Non-neoplastic

When Flow Cytometry is not covered

Reimbursement is not allowed for flow cytometry for any clinical conditions not listed above.

Policy Guidelines

Flow cytometry is a laboratory technique with the capability to measure optical and fluorescence characteristics from single cells or other particles between 0.2 and 150 micrometers in size, such as microorganisms, nuclei or chromosome preparations suspended in fluid (Brown & Wittwer, 2000; Verbsky & Routes, 2018). More than 100 companies constitute the flow cytometry market, leading to an industry worth of more than \$3 billion (Robinson & Roederer, 2015).

A typical flow cytometer contains five main components: a flow cell, a laser, optical parts, detectors which amplify signals, and an electronic or computer system (Verbsky & Routes, 2018). This device measures thousands of cells instantaneously by passing them through the laser beam, and it can even sort the cells into 96- or 384-well plates, tubes, and slides based on identified cellular properties (McKinnon, 2018). Size is determined by the forward angle light scatter, and internal properties such as cellular granularity are measured by the right-angle light scatter (Brown & Wittwer, 2000; Verbsky & Routes, 2018). These fluorescent light signals are converted into electronic signals and then analyzed by a computer to generate final results (McKinnon, 2018).

Fluorescent reagents may be used to enhance a sample before administration into the flow cytometer. These reagents may include DNA binding dyes, fluorescently conjugated antibodies, viability dyes, fluorescent expression proteins, and ion indicator dyes (McKinnon, 2018). Each fluorescent dye binds to cellular components differently, leading to distinguished outcomes when passed by the light source. A fluorochrome, or chemical that can re-emit light when excited, can assist in the detection of specific cellular properties. The use of multiple fluorochromes at once allows several characteristics to be identified instantaneously as different colors emit different wavelengths of light; common dyes include propidium iodide, phycoerythrin, and fluorescein (Brown & Wittwer, 2000).

Immunophenotyping is the most common use of flow cytometry and entails the identification of cellular markers from the immune system, such as T cell subsets and cytokines, as well as antigen-specific responses. Unfortunately, immunophenotyping faces issues in the clinical world due to a lack of standardized procedures (Finak et al., 2016). Current instruments allow for up to 28 colors to be used in immunophenotyping experiments, yet many researchers use less than this (McKinnon, 2018).

Clinical Validity and Utility

Technically, any biologic sample can be analyzed by flow cytometry. However, blood is the most common sample type, including both whole blood and peripheral blood mononuclear cells (Verbsky & Routes, 2018). Flow cytometry can be employed for prognostic and diagnostic purposes. This technique has been used to identify both primary immunodeficiencies and secondary or acquired immunodeficiencies such as HIV (Verbsky & Routes, 2018). Primary immunodeficiencies represent more than 300 known genetic disorders, and flow cytometry is a major component of the diagnosis of these disorders (Abraham & Aubert, 2016). Flow cytometry may also be used for prenatal diagnoses, hematology, transplantation, crop improvement, sperm sorting for sex preselection, post-bone marrow transplantation analyses, and during immunosuppression and chemotherapy treatments (Halder, Nath, & Jha, 2017; Verbsky & Routes, 2018).

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Today, many assays have been developed for flow cytometry purposes. These assays can identify biomarkers for cancer and stem cells, DNA and RNA, reactive oxygen species, and the functional status of yeast or bacteria (Robinson & Roederer, 2015). Newer techniques have also been developed such as mass cytometry: the combination of flow cytometry and mass spectrometry (Cosma, Nolan, & Gaudilliere, 2017). Flow fluorescent in situ hybridization (FISH) is another combinatory technique which is the combination of fluorescent in situ hybridization in suspension (FISHIS) and flow cytometry using DNA or gene-specific probes.

Flow cytometry techniques have been used to identify several types of cancer. Fromm, Thomas, and Wood (2009) used flow cytometry to identify classical Hodgkin lymphoma, neoplastic Hodgkin, and Reed Sternberg cells in lymph nodes with 88.7% sensitivity and 100% specificity. Paiva, Merino, and San Miguel (2016) state that next generation multiparameter flow cytometry “should be considered mandatory in the routine evaluation of multiple myeloma patients both at diagnosis and after therapy, and represents an attractive technique to integrate with high-throughput DNA and RNA-seq methods to help in understanding the mechanisms behind dissemination and chemoresistance of multiple myeloma.” Finally, Novikov et al. (2019) used flow cytometry immunophenotyping to identify malignant T-cell clones in mature peripheral T-cell lymphomas with 97% sensitivity and 91% specificity.

Wang et al. (2019) published a study on the applicability of multiparameter (multicolor) flow cytometry (MFC) for detecting MRD to predict relapse in patients with AML after allogeneic transplantation. The researchers also compared MFC to MRD status determined using real-time quantitative polymerase chain reaction (RT-qPCR) from 158 bone marrow samples from 44 different individuals. “Strong concordance was found between MFC-based and RT-qPCR-based MRD status ($\kappa = 0.868$).” Moreover, for individuals in complete remission (CR), “the positive MRD status detected using MFC was correlated with a worse prognosis [HRs (*P* values) for relapse, event-free survival, and overall survival: 4.83 (<0.001), 2.23 (0.003), and 1.79 (0.049), respectively]; the prognosis was similar to patients with an active disease before HSCT [hematopoietic stem cell transplantation] (Wang et al., 2019).”

The European Research Initiative on CLL (ERIC) & European Society for Clinical Cell Analysis (ESCCA) Harmonisation Project (Rawstron et al., 2018)

This group has published guidelines on chronic lymphocytic leukemia (CLL) in hopes to determine “35 potential flow cytometry markers as being “required,” “recommended,” “suggested,” “uninformative,” or “not sure” for the diagnosis of CLL (Rawstron et al., 2018).” A marker is required if >75% of ERIC/ESCCA members determine that it should be required, and a marker is pushed forward for review if >50% of all members determine that it should be recommended or required. Results are shown in the following figure:

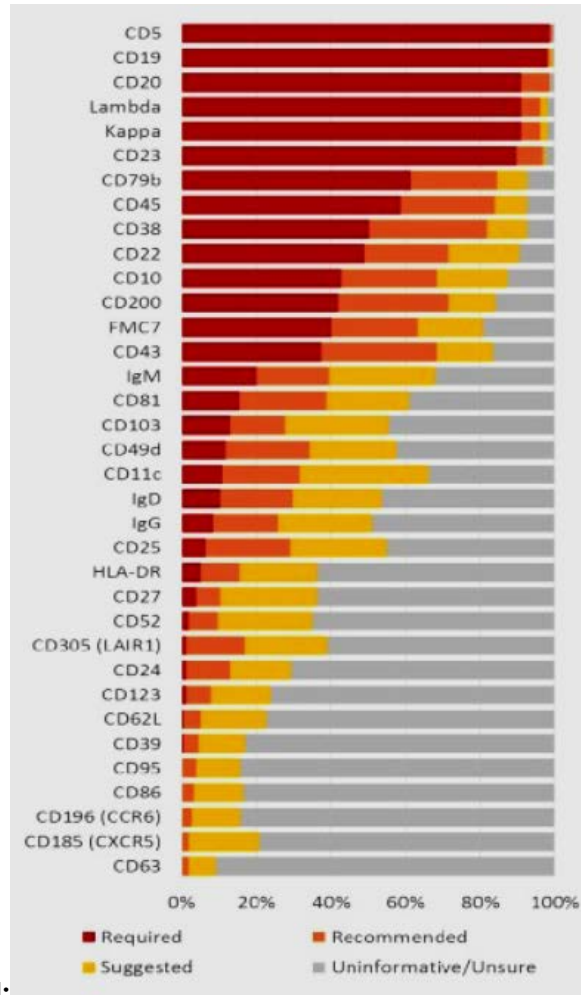


Figure 1 [taken from (Rawstron et al., 2018)]:

International/European Leukemia Net Working Group for Flow Cytometry in Myelodysplastic Syndromes (Porwit et al., 2014)

An international working party was organized to develop flow cytometry techniques in the classification of myelodysplastic syndromes (MDS). The group has stated the following guidelines:

- “In laboratories where comprehensive immunophenotyping can be performed, an MDS immunophenotyping panel... is recommended.
- In patients with cytological findings suggesting MDS of RCUD (refractory anemia subtype) or refractory anemia with ringed sideroblasts categories, aberrant flow cytometry (FCM) findings in the granulopoietic or myelomonocytic lineages may indicate multilineage dysplasia, which is of prognostic significance. Morphological findings in these cases should be thoroughly re-evaluated to avoid misclassification.
- It is important to note even small populations of myeloid progenitors with multiple immunophenotypic aberrant features (such as aberrant expression of CD7, CD56 or CD11b, see Table 1), since they indicate a higher risk of progression to AML. FCM findings in these cases should be included in the individual risk assessment (Porwit et al., 2014).”

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The Clinical Cytometry Society 2006 Bethesda International Consensus (Davis et al., 2007)

In 2006 a panel of subject matter experts was convened to define the clinical indications that warrant use of flow cytometry as well as the identity of the reagents that should be used in the initial and secondary evaluations for those conditions (Davis, 2007). The output of that gathering was the 2006 Bethesda International Consensus Recommendations on the Immunophenotypic Analysis of Hematolymphoid Neoplasia by Flow Cytometry. The panel indicated that flow cytometry is useful for the evaluation of cytopenias, elevated leukocyte count, observation of atypical cells or blasts and evaluation of body fluids, plasmacytosis or monoclonal gammopathy, organomegaly and tissue masses, and certain patient monitoring indications.

The Bethesda recommendations indicate that flow cytometry is not indicated for mature neutrophilia, polyclonal hypergammaglobulinemia, polycythemia, thrombocytosis, and basophilia because “they are usually not associated with hematolymphoid malignancy or associated with hematolymphoid neoplasms that are not detectable by” flow cytometry.

The Bethesda recommendations also indicate that selection of reagents for the initial evaluation panel should be based on specimen type (peripheral blood, bone marrow, tissue, etc.), clinical information and cell morphology studies. They identify initial panels for specific indications that range from a total of 4 reagents to a maximum of 12 reagents.

For secondary evaluation, where the initial evaluation is not conclusive or informative, the Bethesda recommendations again identify groups of reagents that should be used, based on indication. The secondary panels ranged from 5 to 23 reagents.

Specific recommendations for the initial evaluation were:

- B cells: CD5, CD10, CD19, CD20, CD45, Kappa, Lambda
- T cells and NK cells: CD2, CD3, CD4, CD5, CD7, CD8, CD45, CD56
- Myelomonocytic cells: CD7, CD11b, CD13, CD14, CD15, CD16, CD33, CD34, CD45, CD56, CD117, HLA-DR
- Myelomonocytic cells (limited): CD13, CD33, CD34, CD45
- Plasma cells CD19, CD38, CD45, CD56

For secondary evaluation, the Bethesda recommendations were:

- B cells: CD9, CD11c, CD15, CD22, cCD22, CD23, CD25, CD13, CD33, CD34, CD38, CD43, CD58, cCD79a, CD79b, CD103, FMC7, Bcl-2, cKappa, cLambda, TdT, Zap-70, cIgM
- T cells and NK cells: CD1a, cCD3, CD10, CD16, CD25, CD26, CD30, CD34, CD45RA, CD45RO, CD57, ab-TCR, gd-TCR, cTIA-1, T-beta chain isoforms, TdT
- Myelomonocytic cells: CD2, CD4, CD25, CD36, CD38, CD41, CD61, cCD61, CD64, CD71, cMPO, CD123, CD163, CD235a
- Plasma cells: CD10, CD117, CD138, cKappa, cLambda

The American Society of Clinical Oncology Tumor Markers Expert Panel (ASCO) (Harris et al., 2007; Locker et al., 2006)

In 2006, the American Society of Clinical Oncology (ASCO) updated the recommendations for the use of tumor marker tests in the prevention, screening, treatment, and surveillance of gastrointestinal cancers. They recommended that “Neither flow-cytometrically derived DNA ploidy (DNA index) nor DNA flow cytometric proliferation analysis (% S phase) should be used to determine prognosis of early-stage colorectal cancer.”

In 2007, ASCO updated the recommendations for the use of tumor marker tests in the prevention, screening, treatment, and surveillance of breast cancer (Harris et al, 2007). They noted that

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“DNA/ploidy by flow cytometry demonstrated insufficient evidence to support routine use in clinical practice”.

The Centers for Medicare and Medicaid (CMS) offer the following guidelines regarding Local Coverage Determination (LCD) for Flow Cytometry:

[https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34215&ContrId=362&ver=22&ContrVer=1&CntrctrSelected=362*1&Cntrctr=362&name=Noridian+Healthcare+Solutions%2c+LLC+\(Noridian+Healthcare+Solutions%2c+LLC+\(01311%2c+A+and+B+MAC%2c+J+-+E\)\)&DocType=All&LCntrctr=362*1&bc=AAIAAAQAAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34215&ContrId=362&ver=22&ContrVer=1&CntrctrSelected=362*1&Cntrctr=362&name=Noridian+Healthcare+Solutions%2c+LLC+(Noridian+Healthcare+Solutions%2c+LLC+(01311%2c+A+and+B+MAC%2c+J+-+E))&DocType=All&LCntrctr=362*1&bc=AAIAAAQAAAAAAA%3d%3d&)

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 86355, 86356, 86357, 86359, 86360, 86361, 86367, 88182, 88184, 88185, 88187, 88188, 88189, 88199

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

The following reimbursement limitations will apply for flow cytometry:

- *For flow cytometric immunophenotyping for the assessment of potential hematolymphoid neoplasia, use codes 88184-88189.*
- *Code 88184 should be used for the first marker, per specimen, and is reimbursable up to a maximum of two units per date of service.*
- *Code 88185 should be used for each additional marker, and is reimbursable up to a maximum of 35 units, per date of service.*
- *In patients with a neoplasm with an established immunophenotype, subsequent tests for that neoplasm should be limited to diagnostically relevant markers.*
- *Codes 88187, 88188, and 88189 should not be used together in any combination. They are mutually exclusive and reimbursable as a single unit only.*
- *Codes 88187-88189 should not be used in conjunction with codes 86355, 86356, 86357, 86359, 86360, 86361, 86367.*
- *Use codes 86355, 86357, 86359, 86360, 86361, or 86367 for cell enumeration. These codes are reimbursable as single units only.*

Bill Type Codes

012x	Hospital Inpatient (Medicare Part B only)
013x	Hospital Outpatient
014x	Hospital - Laboratory Services Provided to Non-patients
018x	Hospital - Swing Beds
021x	Skilled Nursing - Inpatient (Including Medicare Part A)
022x	Skilled Nursing - Inpatient (Medicare Part B only)
023x	Skilled Nursing - Outpatient
071x	Clinic - Rural Health
077x	Clinic - Federally Qualified Health Center (FQHC)
085x	Critical Access Hospital

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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: 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

Scientific Background and Reference Sources

Centers for Medicare and Medicaid. (2017). Local coverage determination: Flow cytometry. Retrieved May 8, 2017, from [https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34215&ContrId=362&ver=22&ContrVer=1&CntrctrSelected=362*1&Cntrctr=362&name=Noridian+Healthcare+Solutions%2c+LLC+\(Noridian+Healthcare+Solutions%2c+LLC+\(01311%2c+A+and+B+MAC%2c+J+-+E\)\)&DocType=All&LCntrctr=362*1&bc=AAIAAAQAAAAAAAA%3d%3d&](https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=34215&ContrId=362&ver=22&ContrVer=1&CntrctrSelected=362*1&Cntrctr=362&name=Noridian+Healthcare+Solutions%2c+LLC+(Noridian+Healthcare+Solutions%2c+LLC+(01311%2c+A+and+B+MAC%2c+J+-+E))&DocType=All&LCntrctr=362*1&bc=AAIAAAQAAAAAAAA%3d%3d&)

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Specialty Matched Consultant Advisory Panel 4/2020

Medical Director review 4/2020

Specialty Matched Consultant Advisory Panel 3/2021

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Policy Implementation/Update Information

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- 1/1/2019 New policy developed. Flow cytometry immunophenotyping of cell surface markers is considered medically necessary when criteria are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (lpr)
- 5/14/19 Reviewed by Avalon 1st Quarter 2019 CAB. No change to policy intent. (lpr)
- 10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (gm)
- 5/12/20 Specialty Matched Consultant Panel review 4/15/2020. Medical Director review 4/2020. Reviewed by Avalon 1st Quarter 2020 CAB. Updated Description, Policy Guidelines and References. (lpr)
- 4/6/21 Specialty Matched Consultant Advisory Panel review 3/17/2021. No change to policy statement. (lpr)
- 5/4/21 Reviewed by Avalon 1st Quarter 2021 CAB. Updated policy guidelines and references. Added related policy: Minimal Residual Disease under Description section. Under Billing/Coding section, updated coding guidelines for expanded use: CPT 88184 should be used for the first marker, per specimen, and is reimbursable up to a maximum of two units per date of service; CPT 88185 should be used for each additional marker and is reimbursable up to a maximum of 35 units per date of service. Medical Director review 4/2021. (lpr)

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