

Flow Cytometry

Policy Number: AHS – F2019 – Flow Cytometry	Prior Policy Name and Number, as applicable:
Policy Revision Date: 01/01/2025 Initial Policy Effective Date: 11/04/2021	

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I. Policy Description

Flow cytometry is a technique for live cell analysis that measures optical light scattering features to determine physical characteristics (Adan et al., 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, 2023). Flow cytometry may also be used for diagnostic and prognostic purposes when monitoring certain diseases, and for identifying the presence of specific biomarkers.

Flow cytometry-derived DNA content can be used for cell cycle analysis to estimate the percentages of a cell population in the various phases of the cell cycle; it can also be used with other reagents to analyze only the S phase. An S-phase fraction (SPF) is an assessment of how many cells are actively synthesizing DNA (UIHC, 2016). It is used as a measure of cell proliferation, particularly for cancer (Pinto et al., 1999). A high SPF value is indicative of rapid cancer growth (ACS, 2021).

For guidance on flow cytometry in minimal residual disease (MRD), please see AHS-M2175-Minimal Residual Disease (MRD).

II. Related Policies

Policy Number	Policy Title
AHS-M2175	Minimal Residual Disease
AHS-M2182	Genomic Testing for Hematopoietic Neoplasms

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the “Applicable State and Federal Regulations” section of this policy document.

- 1) Flow cytometry immunophenotyping of cell surface markers **MEETS COVERAGE CRITERIA** for any of the following conditions:
 - a) For individuals with cytopenias, lymphomas, leukemia, myeloproliferative and lymphoproliferative disorders, or myelodysplastic syndrome.
 - b) For B-cell monitoring for immunosuppressive disorders.
 - c) For T-cell monitoring for HIV infection and AIDS.
 - d) For individuals with mast cell neoplasms.
 - e) For individuals with paroxysmal nocturnal hemoglobinuria.
 - f) For preoperative or post-operative monitoring of individuals who will undergo or who have undergone organ transplantation.
 - g) For individuals with plasma cell disorders.
 - h) For individuals with primary immunodeficiencies (PIDs), and PIDs involving T, NK.
 - i) For individuals with primary platelet disorders (non-neoplastic).
 - j) For individuals with red cell and white cell disorders (non-neoplastic).
- 2) The following reimbursement limitations will apply for flow cytometry:
 - a) For flow cytometric immunophenotyping for the assessment of potential hematolymphoid neoplasia, use codes 88184-88189.
 - b) 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.
 - c) Code 88185 should be used for each additional marker and is reimbursable up to a maximum of 35 units, per date of service.
 - d) In patients with a neoplasm with an established immunophenotype, subsequent tests for that neoplasm should be limited to diagnostically relevant markers.
 - e) Codes 88187, 88188, and 88189 should not be used together for a single specimen in any combination.
 - f) Codes 88187, 88188, and 88189 are reimbursed at one unit per specimen, up to two specimens, per date of service.
 - g) Codes 88187-88189 should not be used in conjunction with codes 86355, 86356, 86357, 86359, 86360, 86361, 86367.
 - h) Use codes 86355, 86357, 86359, 86360, 86361, or 86367 for cell enumeration. These codes are reimbursable as single units only.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

- 3) Measurement of flow cytometry-derived DNA content (DNA Index) or cell proliferative activity (S-phase fraction or % S-phase) for prognostic or therapeutic purposes in the routine clinical management of cancers **DOES NOT MEET COVERAGE CRITERIA.**

IV. Table of Terminology

Term	Definition
AIDS	Acquired immune deficiency syndrome
AML	Acute myeloid leukemia
AMR	Antibody mediated rejection
ANKL	Aggressive NK-Cell leukemia
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
B-ALL	B-cell precursor acute lymphoblastic leukemia
CAEBV	Chronic active Epstein-Barr virus
CAP	College of American Pathologists
CLIA	Clinical Laboratory Improvement Amendments of '88
CLL	Chronic lymphocytic leukemia
CMPD	Chronic myeloproliferative disorders
CMS	Centers for Medicare and Medicaid
CR	Complete remission
CSF	Cerebrospinal fluid
DNA	Deoxyribose nucleic acid
ENKTL	Extranodal NK/T lymphoma
EBV	Epstein-Barr virus
ERIC	European Research Initiative on CLL
ESCCA	European Society for Clinical Cell Analysis
FCI	Flow cytometric immunophenotyping
FCM	Flow cytometry
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
FISHIS	Fluorescent in situ hybridization in suspension
FNAC	Fine needle aspiration cytology
GIST	Gastrointestinal stromal tumors
HIV	Human immunodeficiency virus infection
HSCT	Hematopoietic stem cell transplantation
IHC	Immunohistochemistry
ISGyP	International Society of Gynecological Pathologists
ISTH	International Society on Thrombosis and Haemostasis
LCDs	Local coverage determinations

LDTs	Laboratory developed tests
MDS	Myelodysplastic syndromes
MFC	Multiparameter (multicolor) flow cytometry
MRD	Minimal residual disease
NCDs	National coverage determinations
NCCN	National Comprehensive Cancer Network
NK	Natural killer
PIDs	Primary immunodeficiencies
RCUD	Refractory anemia subtype
RNA	Ribonucleic acid
RT-qPCR	Real-time quantitative polymerase chain reaction
SPF	S-phase fraction
T-ALL	T-cell acute lymphoblastic leukemia

V. Scientific Background

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, 2023). 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, 2023). 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, 2023). 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).

In the field of organ transplantation, the role of flow cytometry in pre-transplant crossmatching, as well for monitoring immune reconstitution following hematopoietic stem cell transplantation, is well-established.

More recently, the utility of flow cytometry in the post-transplant setting has been recognized. Post-transplant applications of flow cytometry include antibody mediated rejection (AMR) diagnosis, graft prognosis, and therapeutic monitoring (Maguire et al., 2014). The cellular immune response is important to monitor for a successful transplant and flow cytometry allows for measurement of this cellular response. Specifically, polyfunctional antigen-specific T cells can be protective in the patient's immune response and therefore become a barometer of transplant health. Additionally, flow cytometry may have use for analysis of CMV- and EBV-specific cells (along with cytokine formation within these cells), in order to provide a person's risk of susceptibility to major infections (CMV and EBV) that can impact whether the transplantation and graft will remain successful (Maguire et al., 2014).

Flow cytometry as a laboratory technique can measure and assess DNA ploidy through cell cycle analysis. DNA synthesis and replication errors are associated with cancer. Cancer is the uncontrolled growth and spread of abnormal cells and is increasingly shown to be initiated, propagated, and maintained by somatic genetic events (Johnson et al., 2014). Measuring ploidy is also of use when it comes to gestational trophoblastic disease, during which a group of tumors form in an abnormal pregnancy. Most gestational trophoblastic disease tumors are benign, but some have the potential to turn cancerous; usually, they are classified into two categories: hydatidiform moles and gestational trophoblastic neoplasia. Ploidy analysis through flow cytometry can help differentiate diploid from triploid conceptions, but cannot distinguish between a complete mole and a diploid nonmolar miscarriage or molar and nonmolar triploid (Horowitz et al., 2021; Seckl et al., 2013)

During the cell cycle, DNA synthesis is tightly regulated and only performed just as the cell is about to divide. This step of DNA replication is called the "S-phase" (Christensen, 2024). Dysfunction of DNA replication is significantly associated with cancer, and cancers frequently involve damage or removal of molecular regulators of replication (Van der Aa et al., 2013). Assessment of the fraction of cells in S-phase has been proposed as an indicator of neoplasm aggression. S-phase fraction (SPF) is thought to reflect proliferative activity of cancer and may provide prognostic or therapeutic information (Ermiah et al., 2012). Elevated proliferative activity may predict a worsened disease-free or overall survival in several cancers, such as breast, non-small cell lung, colorectal, ovarian, kidney, bladder, prostate, and endometrial cancers (Bagwell et al., 2001; Gawrychowski et al., 2003; Kenney et al., 2008; Mangili et al., 2008; Pinto et al., 2011; Ross, 1996). However, data supporting the use of SPF as a prognostic tool appears to be inconsistent at best (Locker et al., 2006).

Clinical Utility and Validity

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, 2023). 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, 2023). 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 et al., 2017; Verbsky & Routes, 2023).

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 et al., 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 et al. (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 et al. (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).

Jin et al. (2024) summarizes the recent progress in systemic chronic active Epstein-Barr virus (CAEBV) infection diagnosis and the utility of flow cytometry as a tool in this diagnosis. Systemic Epstein-Barr virus can have a challenging prognosis, ranging from asymptomatic to death within a few weeks. Many treatment strategies are currently ineffective and only allogeneic hematopoietic stem cell transplantation is curative. The early diagnosis of systemic CAEBV

could be potentially improved by examining NK/T cells using flow cytometry, effectively checking their immunological status. Flow cytometry is used to obtain as many targeted cells as possible and analyze cell size, cytoplasmic granularity, and differentiation antigens; in some cases, “the aberrant T/NK-cell population” found in CAEBV comprises less than 5% of cells in the bone marrow, and “these subtle changes may be detected via flow cytometry analyses only.” However, the authors caveat, “although [flow cytometry is] good at exploring the status of NK/T cells holistically, its application to CAEBV has been limited because of the presence of overlapping antibodies and a lack of comprehensive analysis studies.” As of now, flow cytometry is “mostly used to exclude lymphoma or leukemia in CAEBV patients.” However, CAEBV is a progressive disease that can become extranodal NK/T lymphoma or aggressive NK-Cell leukemia and a combination of clinical features and patient outcomes may help in earlier diagnosis of ANKL or ENKTL. Flow cytometry could, in the future, help indicate different NK Cell subtypes and differentiate the source of neoplasms (Jin et al., 2024).

Clinical Utility and Validity of DNA Ploidy Cell Cycle Analysis

Carlioni et al. (2017) evaluated the associations between SPF and peritoneal carcinomatosis from ovarian cancer. Fifty-three patients were examined, and although SPF differed among the different ploidy categories, no significant correlation was found between SPF and clinical pathological characteristics of patients. However, the authors did find that sensitivity to taxol was correlated with SPF, therefore concluding that “ploidy and SPF could facilitate the choice of therapy for patients with peritoneal carcinomatosis” (Carlioni et al., 2017).

Svanvik et al. (2019) examined 1113 patients diagnosed with stage I-III grade 1-3 endometrioid endometrial carcinoma in 2006-2011. They evaluated both DNA ploidy and SPF and set the SPF cutoff at eight percent. The authors found that five year relative survival was significantly associated with SPF and DNA ploidy through a univariate statistical analysis. However, when other variables such as age, grade, and stage were added, SPF and DNA ploidy became statistically insignificant. Therefore, the authors concluded that “S-phase fraction, DNA ploidy, and p53 overexpression did not improve identification of high-risk patients by stage, grade, and age in stage I-III endometrioid endometrial carcinoma” (Svanvik et al., 2019).

Thomas et al. (2020) completed a study to analyze the prognostic implications of DNA repair, DNA ploidy and telomerase in the malignant transformation risk assessment of leukoplakia. Samples from 200 patients with oral leukoplakia, 100 patients with oral cancer and 100 healthy controls were analyzed. The DNA ploidy content was measured with high resolution flow cytometry; the authors identified that “There was significant difference in the distribution of ploidy status, telomerase activity and DNA repair capacity among control, leukoplakia and oral cancer group ($p < 0.001$). When the molecular markers were compared with histological grading of leukoplakia, both DNA ploidy analysis and telomerase activity showed statistical significance ($p < 0.001$)” (Thomas et al., 2020).

Taniguchi et al. (2021) investigated the correlation between flow cytometry parameters such as DNA ploidy, DNA index and S-phase fraction and clinical prognostic factors such as mitotic count and Ki-67 labelling index (LI). The cancer of interest was gastrointestinal stromal tumors (GIST) and eighteen specimens from laparoscopic local gastrectomy were analyzed. The authors found these flow cytometry parameters to correlate well with mitotic count \leq five and Ki-67 LI

≤ six. DNA index was found to be 83.3% accurate in predicting mitotic count ≤ five and 77.8% accurate in predicting Ki-67 LI ≤ six, while S-phase fraction was found to be 94.4% accurate and 88.9% accurate, respectively. The authors concluded that “Rapid flow cytometry parameters can classify risk without the need for histological analysis” (Taniguchi et al., 2021).

Panwar et al. (2021) studied the evaluation of DNA ploidy and S-phase fraction in fine needle aspirates from breast carcinoma. Fifty breast cancer patients who underwent fine needle aspiration cytology (FNAC) were included in the study. The samples from FNAC underwent DNA ploidy and SPF analysis and Ki-67 was estimated. SPF and Ki-67 were compared with each other. "On DNA flow cytometry, 27 (54%) cases were aneuploid and 23 (46%) cases were diploid. The median SPF was 12.43% and 4.03% in aneuploid and diploid tumors respectively. Median Ki-67 among aneuploid tumors was 28.6% compared to 8.7% among diploid tumors. Aneuploid tumors were significantly associated with higher values of SPF and Ki-67, with Kappa 0.437 and agreement of 72%. Diploid tumors showed lower values of SPF and Ki-67, with Kappa 0.455 and agreement of 72.7%. Correlation among SPF and Ki-67 was highly significant with Kappa value 0.446, P value of .002 and agreement of 72.3%" (Panwar et al., 2021). The authors conclude that DNA ploidy and proliferative activity by flow cytometric SPF estimation can provide valuable prognostic information in breast cancer diagnosis.

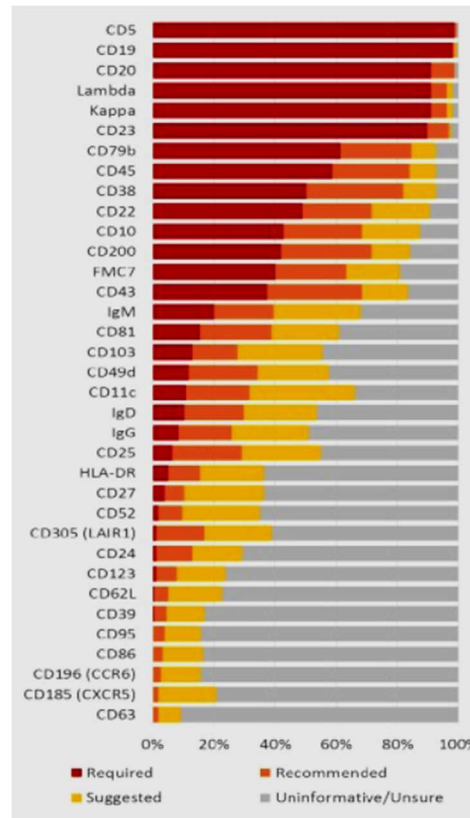
VI. Guidelines and Recommendations

Flow cytometry is broadly used for many conditions such as cancers, which are mentioned across many different societies. The below section is not a comprehensive list of guidance for flow cytometry.

The European Research Initiative on CLL (ERIC) & European Society for Clinical Cell Analysis (ESCCA) Harmonisation Project

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

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).

The Clinical Cytometry Society 2006 Bethesda International Consensus

In 2006, a panel of subject matter experts convened to define the clinical indications that warrant the use of flow cytometry, as well as to identify the reagents that should be used in the initial and secondary evaluations for those conditions (Davis et al., 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 four 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 five 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 natural killer (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)

In 2006, the ASCO updated the recommendations for the use of tumor marker tests in the prevention, screening, treatment, and surveillance of gastrointestinal cancers. These recommendations state 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” (Locker et al., 2006). This guideline also stated that for now, flow cytometric determination of DNA ploidy or proliferation should, at best, be considered an experimental tool.

In 2007, the 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); the authors noted that “DNA/ploidy by flow cytometry demonstrated insufficient evidence to support routine use in clinical practice.”

College of American Pathologists and the American Society of Hematology

In 2016, the College of American Pathologists (CAP) and the American Society of Hematology (ASH) published a joint guideline to outline their recommendations for the initial diagnostic workup of acute leukemia. Among their 27 recommendations, three statements (each rated “Strong Recommendation”) explicitly address the leveraging of flow cytometry in said process:

“5. In addition to morphologic assessment (blood and bone marrow), the pathologist or treating clinician should obtain sufficient samples and perform conventional cytogenetic analysis (i.e., karyotype), appropriate molecular genetic and/or fluorescent in situ hybridization (FISH) testing, and flow cytometric immunophenotyping (FCI). The flow cytometry panel should be sufficient to distinguish acute myeloid leukemia (including acute promyelocytic leukemia), T-cell acute lymphoblastic leukemia (T-ALL) (including early T-cell precursor leukemias), B-cell precursor ALL (B-ALL), and acute leukemia of ambiguous lineage on all patients diagnosed with acute leukemia. FISH and/or molecular genetic testing does not, however, replace conventional cytogenetic analysis.

Note — If sufficient bone marrow aspirate or peripheral blood material is not available for FCI, immunohistochemical studies may be used as an alternative method for performing limited immunophenotyping. In addition, a second bone marrow core biopsy can be obtained and submitted, unfixed in tissue culture media, for disaggregation for genetic studies and flow cytometry.”

“10. For patients with suspected or confirmed acute leukemia, the pathologist may use flow cytometry for the evaluation of CSF.”

“12. For patients with suspected or confirmed acute leukemia, the pathologist or treating clinician should ensure that flow cytometry analysis or molecular characterization is comprehensive enough to allow subsequent detection of minimal residual disease.”

A final recommendation (also a “Strong Recommendation”) mentioning flow cytometry referred to the use of its data, such that

“24. If a patient is referred to another institution for treatment, the primary institution should provide the treatment center with all laboratory results, pathology slides, flow cytometry data, cytogenetic information, and a list of pending tests at the time of the referral. Pending test results should be forwarded when they become available” (D. Arber, 2017).

International Society on Thrombosis and Haemostasis (ISTH)

The International Society on Thrombosis and Haemostasis SSC Subcommittee outlined several recommendations for which flow cytometric analysis of inherited and acquired platelet disorders should occur. Those clinical settings in which it believed would be helpful, guided by expert consensus, are reported below:

- “Diagnosis of inherited or acquired deficiencies of platelet surface glycoproteins (BSS, GT, inherited or immune-mediated GPVI defects)
- Diagnosis of platelet alpha granule secretion defects (such as gray platelet syndrome)
- Diagnosis of defects in specific platelet activation (signaling) pathways (such as RASGRP2, P2Y12, or TXA2R disorders)
- Diagnosis of GFI1B macrothrombocytopenia associated to platelet expression of CD34
- Diagnosis of disorders of platelet procoagulant activity (such as Scott syndrome and Stormorken syndrome)
- Assessment of increased platelet activation in prothrombotic syndromes (diabetes, anti-phospholipid syndrome or secondary to drug induced, non-immune platelet activation)
- Monitoring, if applicable, pharmacodynamic effect of P2Y12 antagonists (ticlopidine, clopidogrel, prasugrel, ticagrelor, cangrelor) with specifically designed test such as VASP P2Y12
- Determination of the fraction of immature platelets” (Frelinger et al., 2021).

National Comprehensive Cancer Network (NCCN)

NCCN clinical practice guidelines on diagnosis and/or management of Breast Cancer (Version 4.2024), Cervical Cancer (Version 3.2024), Colon Cancer (Version 4.2024), Small Cell Lung Cancer (Version 3.2024), and Non-Small Cell Lung Cancer (Version 7.2024) do not mention cell proliferation activity (S-phase fraction or % S-phase) as a management tool (NCCN, 2024).

International Society of Gynecological Pathologists (ISGyP) Endometrial Cancer Project: Guidelines from the Special Techniques and Ancillary Studies Group

These guidelines focus on biomarkers and their potential use for endometrial carcinoma.

The guideline remarks that “Other than markers which are useful in diagnosis, there are few specific studies that provide definitive evidence for the routine use of IHC [immunohistochemistry] or ploidy analysis in determining the prognosis of EC” and that “There is some literature on the association of ploidy with prognosis, with promising results, but there is a lack of definitive studies to determine its true prognostic impact.”

Overall, the guideline states that “Clearly, large prospective, well defined, uniform studies are needed to determine the possible role of IHC for specific biomarkers and ploidy analysis in the clinical setting” (Cho et al., 2019).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
86355	B cells, total count
86356	Mononuclear cell antigen, quantitative (eg, flow cytometry), not otherwise specified, each antigen
86357	Natural killer (NK) cells, total count
86359	T cells; total count
86360	T cells; absolute CD4 and CD8 count, including ratio
86361	T cells; absolute CD4 count
86367	Stem cells (ie, CD34), total count
88182	Flow cytometry, cell cycle or DNA analysis
88184	Flow cytometry, cell surface, cytoplasmic, or nuclear marker, technical component only; first marker
88185	Flow cytometry, cell surface, cytoplasmic, or nuclear marker, technical component only; each additional marker (List separately in addition to code for first marker)
88187	Flow cytometry, interpretation; 2 to 8 markers
88188	Flow cytometry, interpretation; 9 to 15 markers
88189	Flow cytometry, interpretation; 16 or more markers

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Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

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X. Review/Revision History

Effective Date	Summary
01/01/2025	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: Addition of “preoperative” to CC1f. Now reads: “f) For preoperative or post-operative monitoring of individuals who will undergo or who have undergone organ transplantation.” Removed CC3 pertaining to code information, as this does not fit the traditional format of Avalon coverage criteria and does not affect enforcement within this policy.
07/01/2023	Annual Review: Literature review did not necessitate changes to coverage criteria. Policy edited for clarity and consistency.

05/01/2023	<p>Updated background, guidelines, and evidence-based scientific references. M2136- DNA Ploidy Cell Cycle Analysis and F2019-Flow Cytometry merged into a single policy. With this merge came the addition of the following information to this policy: “The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient’s illness. 4) Measurement of flow cytometry-derived DNA content (DNA Index) or cell proliferative activity (S-phase fraction or % S-phase) for prognostic or therapeutic purposes in the routine clinical management of cancers DOES NOT MEET COVERAGE CRITERIA.” Removed CC1j “molar pregnancy”, as molar pregnancy screening is no longer done by flow cytometry. Additional changes made to CC2 for clarity in reimbursement limitations. CC2e previously read “Codes 88187, 88188, and 88189 should not be used together in any combination. They are mutually exclusive and reimbursable as a single unit only.” CC2e now reads “Codes 88187, 88188, and 88189 should not be used together for a single specimen in any combination.” And new CC added: CC2f added to address the allowance of up to 2 specimens per day (CC2b). “Codes 88187, 88188, and 88189 are reimbursed at one unit per specimen, up to two specimens, per date of service.”</p>
07/01/2022	<p>Annual Review: CC1a expanded to include myeloproliferative and now reads “a) Cytopenias, lymphomas, leukemia, myeloproliferative and lymphoproliferative disorders, or myelodysplastic syndrome” Removed CC1i, j, and k due to repetition “i. Hypercellular Hematolymphoid Disorders j. Chronic Lymphocytic Leukemia (CLL) k. Chronic Myeloproliferative Disorders (CMPD)” CPT changes: Removed code 88199</p>
11/04/2021	Initial Policy Implementation