MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Flow Cytometry**
Policy Number	**2.02.57**
Category	**Technology Assessment**
Original Effective Date	**07/21/22**
Committee Approval Date	**07/21/22, 07/20/23, 07/18/24**
Current Effective Date	**07/18/24**
Archived Date	**NA**
Archive Review Date	**NA**
Product Disclaimer	• *Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.* • *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.* • *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.* • *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.*

POLICY STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, flow cytometry has been medically proven to be effective and, therefore, is considered **medically necessary** when clinical documentation demonstrates a need for testing to diagnose or monitor **ANY** of the following indications:
   A. Hematopoietic/hematologic cancers (e.g., bi- or tri-lineage cytopenias, lymphomas, leukemia, myeloproliferative and lymphoproliferative disorders, myelodysplastic syndrome);
   B. Mast cell neoplasms;
   C. Plasma cell disorders;
   D. Primary Immunodeficiency disorders (PIDS);
   E. Primary Platelet Disorders, Non-neoplastic;
   F. Human immunodeficiency virus (HIV) and acquired immunodeficiency virus syndrome (AIDS);
   G. Paroxysmal nocturnal hemoglobinuria;
   H. Gestational trophoblastic disease;
   I. Post-operative monitoring after organ transplantation.

II. Based upon our criteria and assessment of the peer-reviewed literature, flow cytometry has been medically proven to be effective and, therefore, is considered **medically necessary** to detect measurable residual disease (MRD) in patients with leukemia, lymphoma, or multiple myeloma (MM).

III. Based upon our criteria and assessment of the peer-reviewed literature, flow cytometry does not improve patient outcomes and, therefore, is considered **not medically necessary** for any other indication.

Refer to Corporate Medical Policy #2.02.54 Measurable Residual Disease Assessment Testing

POLICY GUIDELINES

I. Testing for MRD may be performed by either flow cytometry or next-generation sequencing (NGS). Testing for MRD by both laboratory methods concurrently is not medically appropriate as it is duplicative testing.

II. Laboratories performing clinical tests must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).

DESCRIPTION

Flow cytometry is a technology that rapidly analyzes single cells or particles as they flow past single or multiple lasers while suspended in a prepared solution. Each particle is analyzed for visible light scatter and one or more fluorescence parameters. Samples from blood, bone marrow, and solid tissue can be separated into single cells and analyzed for number, size, shape, viability, and granularity of the cells in the sample. With the advances in newly developed reagents and more sophisticated data analysis algorithms, flow cytometry has emerged as a powerful tool with applications for immunology, molecular biology, cancer biology, and infectious disease monitoring.

Hematopoietic Neoplasm Evaluation and Monitoring

Hematopoietic neoplasm evaluation and monitoring is the most common use of flow cytometry. Immunophenotyping for assignment of lineage, identification of prognostic subgroups, and post-therapeutic monitoring for diagnosing and monitoring hematopoietic neoplasms is obtained via flow cytometry.

HIV Infection Monitoring

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

Immunodeficiency

Flow cytometry is used for the diagnosis of ~~i~~immunodeficiencies associated with defects in the expression of cell surface proteins. There are more than two hundred forms of primary immune deficiency diseases and include syndromes such as Common Variable Immune Deficiency (CVD), Wiscott-Aldrich syndrome, Severe Combined Immunodeficiency disease (SCID), Di George syndrome, and chronic granulomatous disease.

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired hematopoietic stem cell disorder in which red blood cells break apart prematurely. The destruction of defective red blood cells by a person's own immune systems leads to episodes of hemoglobin in the urine evidence by dark-colored or blood colored urine, which is most prominent in the morning. Flow cytometry is used to diagnose PNH by detecting deficiencies in the antigens on red blood cells, monocytes, and/or granulocytes.

Gestational Trophoblastic Disease

Gestational trophoblastic disease (GTD) is a group or rare diseases in which abnormal trophoblast cells grow inside the uterus after conception. The most common type of GTD is the hydatidiform mole. Flow cytometry analysis of nuclear DNA determine ploidy and cell cycle analysis from the gestational trophoblastic tissue.

Post-Operative Monitoring After Organ Transplantation

Applications of flow cytometry after organ transplantation include diagnosis of antibody mediated rejection (AMR), graft prognosis and therapeutic monitoring.

RATIONALE

Hematopoietic Neoplasm Evaluation And Monitoring

Immunophenotyping by flow cytometry has become standard practice in the evaluation and monitoring of patients with hematopoietic neoplasia. The 2006 Bethesda International Consensus Recommendations on the Flow Cytometric Immunophenotypic Analysis of Hematolymphoid Neoplasia (Davis et al., 2007) indicated that flow cytometry is useful for the evaluation of cytopenia, 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 such as staging disease to document the extent of involvement, detecting potential therapeutic targets, assessment of response to therapy, documentation of progression or relapse, diagnosis of addition intercurrent treatment-

related or coincidental hematolymphoid neoplasm, evaluate of disease acceleration or transformation, and prognostication. Flow cytometry is general not indicated for mature neutrophilia, polyclonal hypergammaglobulinemia, polycythemia, thrombocytosis, or basophilia because they are not usually associated with hematolymphoid malignancy or associated with hematolymphoid neoplasms that are not detectable by flow cytometry. The flow cytometric testing performed should be comprehensive enough to identify all major categories of hematopoietic neoplasia relevant to the clinical circumstances, including, but not limited to, the submitted medical indication(s) and account for all major cell populations present in the specimen, but does not need to identify all hematopoietic cell types.

The American Society for Clinical Pathology (2018) Choosing Wisely statement, "Do not perform peripheral blood flow cytometry to screen for hematological malignancy in the settings of mature neutrophilia, basophilia, erythrocytosis, thrombocytosis, isolated anemia, or isolated thrombocytopenia." The role of peripheral blood flow cytometry for hematologic neoplasia is limited to settings in which either there are morphologically abnormal cells identified on a peripheral blood smear review (blasts, lymphoma cells) or there are clinical and/or laboratory findings that suggest a high pre-test probability for the presence of a disorder amenable to the immunophenotypic detection of neoplastic cells in the blood. The latter includes patients with neutropenia, absolute lymphocytosis, lymphadenopathy, or splenomegaly. The likelihood of flow cytometry of blood producing diagnostic results in the settings enumerated in the recommendation above is extremely low; bone marrow sampling with morphologic analysis (and appropriate ancillary diagnostic testing) may be indicated in those scenarios.

The National Comprehensive Cancer Network (NCCN) guidelines note that flow cytometry may be used to assess the following hematologic lymphoid cancers: acute lymphoblastic leukemia, chronic myeloid leukemia, lymphomas, hairy cell leukemia, myeloproliferative neoplasms, myelodysplastic disorders, multiple myeloma, systemic mastocytosis, and waldenstrom's macroglobinemia. Flow cytometry is not mentioned as a laboratory method used for the diagnosis or management of solid tumors, including any of the following: bladder, brain, breast, colon, endometrium, gastric, kidney, lung, neuroblastoma, ovary, prostate, or rectum.

HIV Infection Monitoring

A review article by Clift (2015), provided a history of the development of flow cytometry where its clinical usefulness was realized during the HIV/AIDS pandemic. Developments in antibodies against antigens on the surface of T-cells and markers of all immune components led to the broad use of these entities led to definition the cluster of differentiation (CD) nomenclature in the examination of human peripheral blood mononuclear cells (PBMCs) and other immune components. Flow cytometry has become the gold standard in estimating CD4 counts as well as detecting CD3, CD8, and CD45 which are elevated in patients with AIDS. Flow cytometry was able to detect AIDS and its progression but aided in the understanding of the underlying mechanism for HIV entry into the cells. Flow cytometry continues to be used to evaluate the success of HAART therapy in treating patients with AIDS or those infected with HIV. The author also explains other uses for flow cytometry in studying immunology of patients after vaccine therapies, during cancer treatment, and in myeloproliferative disorders.

Immunodeficiency

A review article by Fleisher et al. (2016) summarized the application of flow cytometry in the diagnosis and/or evaluation of primary immunodeficiency disorders (PIDDs). Flow cytometry can measure defects in the expression of cell surface proteins associated with particular immunodeficiencies. Flow cytometry can differentiate the expression of interferon gamma receptor 1 monocytes in the setting of suspected Mendelian susceptibility to mycobacterial disease (MSMD), screen for PIDDs associated with defective intracellular protein expression, and screen for functional abnormalities. Flow cytometry for any immune evaluation must include percentage and absolute number as well as comparison of patient results with appropriate age matched reference data.

Paroxysmal Nocturnal Hemoglobinuria

An International Consensus statement for the diagnosis and treatment of paroxysmal nocturnal hemoglobinuria (Cancado et al. 2021) stated flow cytometry is the most useful and accepted method to confirm the diagnosis of PNH. Some clinicians also use annual flow cytometry to screen patients with an underlying bone marrow disorder (e.g., AA, myelodysplastic syndrome [MDS]) for the development of subclinical PNH. It is performed by fluorescently labeling monoclonal antibodies that bind to glycosylphosphatidylinositol (GPI)-anchored proteins. If greater than two blood cells

lineages are reduced or absent, then PNH is suspected. PNH is classified into three categories: classic, in the setting of another specified bone marrow disorder, and subclinical PNH. Treatment includes supportive care, allogeneic hematopoietic stem cell transplantation and eculizumab, an anti-C5 monoclonal antibody.

Post-Operative Monitoring After Organ Transplantation

A summary article by Bray et al. (2011) described progress in HLA antibody detection in transplant patients using flow cytometry. The primary goal of HLA antibody testing for transplant patients is to assess a given patient's potential risk for graft loss by determining immunological status before/after transplantation. Knowledge of antibodies to human leukocyte antigens (HLA) allows for tailoring donor selection, immunosuppression regimens, and posttransplant patient care based on HLA antibodies that are present. A method to analyze antibodies is important since an antibody to any mismatched donor antigens or alleles may indicate an acute rejection episode or slow progression of chronic rejection/allograft nephropathy. Flow cytometry is a sensitive technique with a final crossmatch assay that uses donor lymphocytes and via microparticles to enable understanding of HLA-specific alloantibodies. Single antigen-coated multiplexed flow cytometric bead arrays and Luminex bead assays now allow concurrent detection of antibody to a number of HLA Class I and Class II antigens and alleles. The combination of highly sensitive antibody assessments combined with flow cytometric crossmatching has resulted in more transplants to sensitized individuals with a greater degree of safety.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

CPT Codes

Code	Description
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
81479	Unlisted molecular pathology procedure
86356	Mononuclear cell antigen, quantitative (e.g., flow cytometry), not otherwise specified, each antigen

HCPCS Codes

Code	Description
No codes	

ICD10 Codes

Code	Description
B20	Human immunodeficiency virus [HIV] disease
C81.00-C81.99	Hodgkin lymphoma (code range)
C82.00-C82.99	Follicular lymphoma (code range)
C83.00-C83.99	Non-follicular lymphoma (code range)
C84.00-C84.99	Mature T/NK-cell lymphomas (code range)
C85.10-C85.99	Other specified and unspecified types of non-Hodgkin lymphoma (code range)
C86.0-C86.6	Other specified types of T/NK-cell lymphoma (code range)
C88.0-C88.9	Malignant immunoproliferative diseases and certain other B-cell lymphomas (code range)
C90.00-C90.32	Multiple myeloma and malignant plasma cell neoplasms (code range)
C91.00-C91.92	Lymphoid leukemia (code range)
C92.00-C92.92	Myeloid leukemia (code range)
C93.00-C93.92	Monocytic leukemia (code range)
C94.00-C94.82	Other leukemias of specified cell type (code range)
C95.00-C95.92	Leukemia of unspecified cell type (code range)
C96.0-C96.9	Other and unspecified malignant neoplasms of lymphoid, hematopoietic, and related tissue (code range)
D45	Polycythemia vera
D46.0-D46.Z	Myelodysplastic syndromes (code range)
D47.01-D47.Z9	Other neoplasms of uncertain behavior of lymphoid, hematopoietic, and related tissue (code range)
D56.0-D56.9	Thalassemia (code range)
D57.00-D57.819	Sickle-cell disorders (code range)
D58.9	Hereditary hemolytic anemia, unspecified
D59.0-D59.9	Acquired hemolytic anemia (code range)
D60.0-D60.9	Acquired pure red cell aplasia (erythroblastopenia) (code range)
D61.01-D61.9	Other aplastic anemias and other bone marrow failure syndromes (code range)
D63.0-D63.8	Anemia in chronic diseases classified elsewhere (code range)
D64.0-D64.9	Other anemias (code range)
D65	Disseminated intravascular coagulation [defibrination syndrome]
D70.0-D70.9	Neutropenia (code range)
D71	Functional disorders of polymorphonuclear neutrophils
D72.0-D72.9	Other disorders of white blood cells (code range)

Code	Description
D75.0-D75.9	Other and unspecified diseases of blood and blood-forming organs (code range)
D76.1-D76.3	Other specified diseases with participation of lymphoreticular and reticulohistiocytic tissue (code range)
D80.0-D80.9	Immunodeficiency with predominantly antibody defects (code range)
D81.0-D81.9	Combined immunodeficiencies (code range)
D82.0-D82.9	Immunodeficiency associated with other major defects (code range)
D83.0-D83.9	Common variable immunodeficiency (code range)
D84.0-D84.9	Other immunodeficiencies (code range)
D89.0-D89.9	Other disorders involving the immune mechanism, not elsewhere classified (code range)
E34.0	Carcinoid syndrome
E85.0-E85.9	Amyloidosis (code range)
E88.09	Other disorders of plasma-protein metabolism, not elsewhere classified
I88.0-I88.9	Nonspecific lymphadenitis (code range)
I89.1	Lymphangitis
I89.8	Other specified noninfective disorders of lymphatic vessels and lymph nodes
I89.9	Noninfective disorder of lymphatic vessels and lymph nodes, unspecified
J15.3	Pneumonia due to streptococcus, group B
J15.4	Pneumonia due to other streptococci
J90	Pleural effusion, not elsewhere classified
J91.0-J91.0	Pleural effusion in conditions classified elsewhere (code range)
O01.0-O01.9	Hydatidiform mole (code range)
O02.0	Blighted ovum and nonhydatidiform mole
O98.711-O98.719	Human immunodeficiency virus [HIV] disease complicating pregnancy (code range)
R59.0-R59.9	Enlarged lymph nodes (code range)
R64	Cachexia
R75	Inconclusive laboratory evidence of human immunodeficiency virus [HIV]
R76.9	Abnormal immunological finding in serum, unspecified
T86.00-T86.898	Complications of transplanted organs and tissue (code range)
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
Z48.21-Z48.298	Encounter for aftercare following organ transplant (code range)
Z52.001-Z52.89	Donors of organs and tissues (code range)
Z76.82	Awaiting organ transplant status

Code	Description
Z85.6	Personal history of leukemia
Z85.71-Z85.79	Personal history of other malignant neoplasms of lymphoid, hematopoietic, and related tissues (code range)
Z94.0	Transplanted organ and tissue status

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*Key Article

KEY WORDS

Flow cytometry

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

Based upon our review, Flow Cytometry is not addressed in National or Regional Medicare coverage determinations or policies.

However, please refer to the Medicare Managed Care Manual/Chapter 4: Benefits and Beneficiary Protections (Rev.121, Issued: 04-22-16)/Section 90 National and Local Coverage Determinations/Subsection 90.4.1 MAC with Exclusive Jurisdiction over a Medicare Item or Service:

In some instances, one Medicare A/B MAC processes all of the claims for a particular Medicare-covered item or service for all Medicare beneficiaries around the country. This generally occurs when there is only one provider of a particular item or service (for example, certain pathology and lab tests furnished by independent laboratories). In this situation, MA plans must follow the coverage policy reflected in an LCD issued by the A/B MAC that enrolled the provider and processes all the Medicare claims for that item or service.
[https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS019326] accessed 06/21/24.