Blue Cross Blue Shield of Michigan

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Blue Cross Blue Shield of Michigan Medical Policy

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Enterprise:	Blue Cross Blue Shield of Michigan
Department	Medical Affairs
Effective Date:	1/1/2016
Next Review Date	3rd Quarter, 2025

Genetic Testing – Leukemia and Lymphoma

Procedure codes: 81218, 81245, 81261-64, 81310, 81315-16, 81340-42, 81402

Background:

Leukemia is a cancer of the blood cells, normally affecting the white blood cells. There are four main types of leukemia: acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL), or chronic lymphocytic leukemia (CLL). Additionally, there are other types and subtypes of leukemia.

Lymphoma is a type of cancer that originates in the lymphatic system. There are two main types of lymphoma. Hodgkin's lymphoma, causes the cells in the lymphatic system to abnormally reproduce, eventually making the body less able to fight infection. All other types of lymphoma are called Non-Hodgkin's lymphomas.

Advances in molecular diagnostics have resulted in the identification of gene arrangements and cytogenetic translocations that aid in the diagnosis and treatment of these diseases.
The Southern blot method can be used to analyze total DNA (genome); and polymerase chain reaction (PCR) testing allows amplification of a specific gene or DNA sequence. Certain markers that have been identified may also help monitor disease progression and response to

therapy, therefore providing both the clinician and patient with treatment options.

Medical Policy Statement:

The safety and effectiveness of genetic testing or analysis in specified situations has been established. Molecular analysis, including polymerase chain reaction (PCR) testing and Southern blot analysis, may be clinically appropriate when used for the prognosis and management of leukemia and lymphoma.

Rationale:

The identification of specific mutations in gene arrangements has aided in the establishment of definitive diagnoses of leukemia or lymphoma, and/or one of its various forms. The development of laboratory techniques such as Southern blot transfer and polymerase chain reaction have simplified the process of detecting specific DNA molecules. "The utility of molecular techniques such as Southern blot hybridization analysis and polymerase chain reaction in the assessment of the clonality in lymphoproliferative disorders is well established". (Kojo et al. 2000)[1]

The information this analysis provides about the gene activity may allow for more accuracy when classifying tumors or cancerous cells, and predict a patient's response to treatment and outcome. As a result, treatments can be adapted and more precisely targeted (LLS).

FLT3 gene

Mutations in FLT3 are common in acute myelogenous leukemia (AML) and have been associated with poorer survival in children and in younger adults with normal cytogenetics receiving intensive chemotherapy (Chin et al, 2006)[2]. "Molecular studies have identified a number of genetic abnormalities that can be used to guide prognosis and management of AML. Cytogenetically normal AML (CN-AML) is the largest defined subgroup of AML, comprising approximately 45% of all AML cases. Despite the absence of cytogenetic abnormalities, these cases often have genetic mutations that affect outcomes, 6 of which have been identified. The FLT3 gene that encodes FMS-like receptor tyrosine kinase (TK) 3, a growth factor active in

hematopoiesis, is mutated in 33-49% of CN-AML cases; among those, 28-33% consist of internal tandem duplications (ITD), 5-14% are missense mutations in exon 20 of the TK activation loop, and the rest are point mutations in the juxtamembrane domain. All FLT3 mutations result in a constitutively activated protein and confer a poor prognosis." (BCBSA, 2013)[3]

This test is appropriate to order when the diagnosed AML has a normal karotype. Detection of an FLT3 mutation indicates a poor prognosis. If not detected, testing for the NPM1 gene would be indicated. (Mayo Medical Laboratories, 2014)[4]

NPM1 gene

The NPM1 gene encodes a phosphoprotein which moves between the nucleus and the cytoplasm. Acute myeloid leukemia with mutated NPM1, in the absence of a coexisting internal tandem duplication (ITD) in the FMS-like tyrosine kinase 3 gene (FLT3 ITD), is associated with a favorable prognosis in patients with normal cytogenetics and other intermediate risk karotypes (1-4). In adults NPM-1 mutated AML is strongly associated with acute myelomonocytic and acute monocytic leukemias. Approximately 80-90% of acute monocytic leukemias have NPM-1 length mutations (Arber et al. 2008)[5]. NPM1 testing is useful for risk stratification in patients with cytogenetically normal AML.

Appropriate use of this test is at the time of initial diagnosis of AML, and to monitor response to therapy (MRD testing). In AML patients with a normal karotype, the absence of an FLT3 mutation and the presence of the NPM1 mutation, a better outcome is indicated. (Mayo Medical Laboratories, 2014)[6]

CEBPA Variants

CEBPA (CCAAT/enhancer binding protein) is a transcription-factor gene that plays a role in cell cycle regulation and cell differentiation. Variants to *CEBPA* are found in approximately 15% of AML patients with a normal karyotype.11-13 *CEBPA* variants can be either biallelic (double variants) or monoallelic. Monoallelic variants are prognostically similar to *CEBPA* WT variant and do not confer a favorable prognosis in CN-AML; double variants of *CEBPA* have shown a

better prognosis with higher rates of CR and OS after standard induction chemotherapy. (BCBSA, 2017)

Summary of Evidence

For individuals who have cytogenetically normal acute myeloid leukemia (AML) who receive genetic testing for variants in *FLT3*, *NPM1*, *CEBPA* to risk-stratify AML, the evidence includes retrospective observational studies and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related mortality and morbidity. *FLT3* internal tandem duplication (*FLT3*-ITD) variants confer a poor prognosis, whereas *NPM1* (without *FLT3*-ITD variant) and biallelic *CEBPA* variants confer a favorable prognosis. The prognostic effect of *FLT3* tyrosine kinase domain variants is uncertain. Data have suggested an overall survival benefit with transplantation for patients with *FLT3*-ITD, but do not clearly demonstrate an overall survival benefit of transplantation for patients with *NPM1* and *CEBPA* variants. Major professional societies and practice guidelines have recommended testing for these variants to risk-stratify and to inform treatment management decisions, including possible hematopoietic cell transplant. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.(BCBSA, 2017)[23]

IGH/IGK genes

Clonality analysis of B-cell populations can aid in the diagnosis of lymphoproliferative disorders. The immunoglobulin heavy chain (IgH) gene and the immunoglobulin kappa (IgK) gene undergo rearrangement early in the development of B-cells. In a polyclonal population of B-cells (normal), each cell has a unique rearrangement that forms a heterogeneous pattern. A monoclonal population of B-cells, (which sometimes correlates to neoplastic), will form a homogeneous pattern that can be seen by PCR testing. Approximately 95% of B-cell lymphomas produce a clonal PCR product when both IgH and IgK testing is performed.

“In an appropriate clinical and pathologic context, identifying a clonal IgH gene rearrangement

Is supportive of the presence of lymphoid malignancy, particularly B-cell malignancy. However, even in cases where the diagnosis is unequivocal, finding a clone by IgH PCR is most useful in providing a "molecular fingerprint" of the tumor, which can then be used for subsequent minimal residual disease (MRD) testing following attempts at curative therapy." (uphs.upenn)[7]

IgVH gene

The immunoglobulin variable region heavy chain (IgVH) gene encodes antibodies that function in the immune response. IgVH mutation status identifies 2 CLL disease subtypes with differing clinical course: indolent and aggressive. Patients with hypermutated IgVH have a better prognosis (median survival 293 months). Patients without hypermutated IgVH have a poorer prognosis (median survival 117 months). 50-70% of patients have evidence of IgVH mutations. Getting a clear idea of prognosis is important so that therapy can be tailored for that particular prognosis.

It is appropriate to use this test as part of the diagnostic process, and to monitor response to therapy (MRD testing).
These tests are indicated for detection of:
Clonal B-cell populations in suspected lymphoproliferative disorders, (e.g. mantle cell lymphoma);
For lymph node or extra-nodal tissue: when it is not fully characterized or is questionable for malignant lymphoma;
Or, when bone marrow morphology is either involved by malignant lymphoma, or results of Bone marrow staging are equivocal. (Mayo Medical Laboratories, Malignant Lymphoma Guideline)

PML/RARA genes

The promyelocytic leukemia (PML) gene provides instructions for a protein that acts as a tumor suppressor. The protein is located in the nucleus of a cell, and interacts with other proteins involved in cell proliferation and apoptosis. A somatic mutation involving the PML gene can result in a cancer of bone marrow, acute promyelocytic leukemia. APL is characterized by

accumulated white blood cells (promyelocytes) in the bone marrow. A translocation between parts of the genes on chromosomes 15 and 17 (PML and RARA, respectively)) forms a fused gene, PML-RARalpha. The PML-RARa protein allows abnormal cells to proliferate, and blocks the ability to differentiate white blood cells at the promelocyte stage. Excess promyelocytes accumulate in bone marrow, and normal white blood cells cannot form.

Acute APL is characterized by severe coagulopathy that is often present at the time of diagnosis (Tallman, et al 1993). Optimal treatment requires rapid initiation of treatment with all-trans retinoic acid and supportive care measures (Sanz et al, 2009). Patients with an initial diagnosis of APL, as well as detection of minimal residual disease or reoccurrence can be confirmed by detection of the PML-RARA fusion.

It is appropriate to perform PCR testing for the PML/RARA fusion gene, when bone marrow morphology and/or flow cytometric immunophenotyping confirm acute leukemia and the possibility of APL. It can also be used to monitor disease during and after treatment. (Patients who remain positive or become positive again after treatment will relapse and benefit from early intervention). (Mayo Medical Laboratories, 2014).

TRB/TRD/TRG genes

The distinction between certain benign cutaneous lymphocytic infiltrates and cutaneous T-cell lymphoma can be a challenging problem in clinical practice (Cozzio, et al 2008). The marked diversity of somatic T-cell receptor (TCR) gene rearrangements serves as a valuable marker to distinguish abnormal T-cell proliferations from reactive processes. A monoclonal expansion of a T-cell population will result in the predominance of a single TCR-gene rearrangement pattern. In contrast, reactive T-cell expansions are polyclonal with no single clonotypic population predominating in the population of T-cells. These distributive differences in both TCR sequence and genomic rearrangement fragment sizes can be detected by molecular techniques (ie, PCR) and used to determine if a population of T cells shows monoclonal or polyclonal features (Mayo Medical Labs, 2014).

T-cell receptor gene rearrangement helps distinguish between benign lymphadenopathy and malignant lymphoma. The presence of monoclonal gene rearrangement generally indicates the

presence of a T-lymphocytic neoplasm, while polyclonal patterns are more indicative of benign reactive conditions (Aetna, 2014).

These tests are indicated for detection of clonal T-cell populations in suspected lymphoproliferative disorders. For lymph node or extra-nodal tissue: when it is not fully characterized or is questionable for malignant lymphoma; or, when bone marrow morphology is either involved by malignant lymphoma, or results of bone marrow staging are equivocal. (Mayo Medical Labs, Malignant Lymphoma Guideline)[8]

BCR-ABL1

(*reference policy determination (retired) for BCR-ABL1 (T 9;22) Chronic Myelogenous Leukemia Translocation Testing; related procedures 81206- 81208)*

Various types of laboratory tests involving BCR-ABL1 detection are associated with chronic myelogenous leukemia (BCBSA 2.04.85, 2014) [9] and acute lymphoblastic leukemia (ALL). These tests aid in diagnosis, monitoring of minimal residual disease during treatment or remission, and identification of drug resistance or response.

Qualitative BCR-ABL genetic testing and/or fluorescence in situ hybridization (FISH) are used to establish an initial diagnosis and/or rule out CML or Philadelphia chromosome (Ph)-positive ALL. The chromosomal analysis and FISH also help determine the percentage of blood or bone marrow cells that are affected. BCR-ABL1 fusion gene identification, along with the presence of the Ph chromosome and other distinguishing cellular abnormalities in the bone marrow, confirm the disease. In addition, because of its high sensitivity and strong association with outcomes, quantitative RT-PCR measurement of BCR-ABL1 RNA transcript levels is utilized when measuring response to treatment.

Conclusion

Evaluating lymph nodes, bone marrow, and other tissues for the presence of lymphoma generally requires a multiparameter approach. A substantial proportion of cases need additional studies in order to establish a definitive diagnosis. Molecular analysis including such modalities as PCR, Southern blot, or FISH are used to help identify benign lymphadenopathy

from a malignant lymphoma. In addition, molecular analysis can sometimes assist with the prognosis and management of a specific disease.

Scope:

This policy applies to all underwritten contracts; and, self-funded or ASC contracts, pending customer approval.

BCBSM Policy History

Policy Effective Date	BCBSM Signature Date	Comments
1/1/2014	6/5/2014	BCBSM medical policy established
1/1/2014	9/24/2015	Annual review, no revisions
1/1/2014	6/3/2016	Annual review, no revisions
1/1/2014	9/27/2017	Annual review, references updated
1/1/2014	11/20/2018	Annual review, no revisions
1/1/2014	9/24/2019	Annual review, no revisions
1/1/2014	7/9/2020	Annual review, no revisions
1/1/2014	7/15/2021	Annual review, no revisions
1/1/2014	7/7/2022	Annual review, no revisions
1/1/2014	7/13/2023	Annual review, no revisions
1/1/2014	7/11/2024	Retired, see Joint policies

Medicare Information:

An LCD or NCD was not found

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