Local Coverage Determination (LCD): Genomic Sequence Analysis Panels in the Treatment of Hematolymphoid Diseases (L37606)

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CMS Publications:
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CMS Publication 100-04, *Medicare Claims Processing Manual*, Chapter 16, Section 40.7 Billing for Noncovered Clinical Laboratory Tests Section and 120.1 Clarification of the Use of the Term "Screening" or "Screen"

CMS Publication 100-04, *Medicare Claims Processing Manual*, Chapter 30, Section 50 Advance Beneficiary Notice of Noncoverage (ABN)

CMS Publication 100-08, *Medicare Program Integrity Manual*, Chapter 13, Local Coverage Determinations

CMS *National Correct Coding Initiative (NCCI) Policy Manual* for Medicare Services, Chapter 10, Pathology/Laboratory Services, (A) Introduction

CMS Publication 100-02, *Medicare Benefit Policy Manual*, Chapter 15, Section 80.6. 5 which describes the Surgical/Cytopathology Exception.

CMS *National Correct Coding Initiative (NCCI) Policy Manual* for Medicare Services, Chapter 10 Pathology/Laboratory Services which addresses reflex testing.

CMS Publication 100-03, *Medicare National Coverage Determinations (NCD) Manual*, Chapter 1, Part 3, Section 190.3 Cytogenetic Studies.

Code of Federal Regulations:
42 CFR, Section 410.32, indicates that diagnostic tests may only be ordered by the treating physician (or other treating practitioner acting within the scope of his or her license and Medicare requirements) who furnishes a consultation or treats a beneficiary for a specific medical problem and who uses the results in the management of the beneficiary's specific medical problem. Tests not ordered by the physician (or other qualified non-physician provider) who is treating the beneficiary are not reasonable and necessary (see Sec. 411.15(k)(1) of this chapter).

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

Acute Myelogenous Leukemia (AML)

Indications

Genomic Sequential Analysis Panel will be considered reasonable and necessary in the evaluation of blood or bone marrow samples in the following clinical circumstances:

- Newly diagnosed patients with AML who are undergoing induction therapy, and who are suitable candidates for post-induction transplantation or consolidation therapy at the time of testing, and meet one of the following cytogenetic criteria:
    - normal karyotype
    - core binding factor
- Previously diagnosed patients with AML, who have not responded to induction chemotherapy, or who have progressed following induction. The patient must be a candidate for transplantation at the time of the testing.
- Patients with AML, who have responded to treatment, either chemotherapy or transplantation, with evidence of relapse.

Myelodysplastic Syndromes (MDS)

Indications

Genomic Sequential Analysis Panel will be considered reasonable and necessary in the evaluation of blood or bone marrow samples in the following clinical circumstances:

- Patients with clinical signs or symptoms of myelodysplastic syndromes (MDS) or myelodysplastic/myeloproliferative overlap syndromes (MDS/MPN), in whom clinical, laboratory, and pathologic assessment are nondiagnostic.
- Newly diagnosed MDS or MDS/MPN patients either
    - stratified by the IPSS or IPSS-R as intermediate risk, or
    - in MDS with ringed sideroblasts/RARS.

Limitations

- Repeat Genomic Sequential Analysis Panel testing is not reasonable and necessary in MDS after initial diagnosis and risk stratification.

Myeloproliferative Neoplasms (MPN)

Indications and Limitations of Coverage

Genomic Sequential Analysis Panel will be considered reasonable and necessary in the evaluation of blood or bone marrow samples in the following circumstances:

- **Diagnosis:** Clinical signs or symptoms of myeloproliferative neoplasm (MPN) or myelodysplastic/myeloproliferative overlap syndromes (MDS/MPN) when
    - clinical, laboratory, and pathologic assessment are nondiagnostic; and
    - CML excluded (BCR-ABL1 negative)

1,2

- **Risk Stratification:** Newly diagnosed PMF not already classified as high-risk by Dynamic International Prognostic Scoring System (DIPSS) Plus[1,3,4]
- **Monitoring:** Higher-risk MF (INT-1, INT-2, High-Risk) with progression on therapy[1]

Summary of Evidence

Acute Myelogenous Leukemia (AML)

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy characterized by the clonal expansion of myeloid blasts, primarily in the peripheral blood and bone marrow. The American Cancer Society estimates that approximately 60,000 new cases of leukemia will be diagnosed in 2016, with one-third classified as acute myelogenous leukemia (AML). It accounts for the most annual deaths from leukemia in the United States. The median age of diagnosis is 67, with 54% diagnosed at 65 years or older (and approximately one third diagnosed at 75 years of age or older). Moreover, AML lies at one end of a spectrum of neoplastic myeloid diseases that includes myelodysplastic syndromes (MDS), which often progress to AML, and which are even more common in patients of advanced age, with an incidence of approximately 1/5000 patients over the age of 70.

AML is an aggressive disease that requires immediate diagnosis and treatment, with an average 5 yr survival rate of 28%, depending on a number of clinical and biologic variables, including acquired genetic alterations within the leukemic cells. Early treatment of AML generally consists of high-dose cytotoxic chemotherapy to induce remission, followed by consolidation (i.e., post-remission) chemotherapy and/or bone marrow transplantation.

Steadily accumulating genomic evidence shows that certain acquired genetic alterations within the leukemic cells are strong predictors of prognosis in AML and, accordingly, are essential factors in the decision whether a patient should undergo bone marrow transplantation (1-4). These alterations have been set aside as determinants of independent diagnostic categories in WHO AML guidelines, and as essential for AML management in NCCN guidelines (5,6).

Importantly, the indication for molecular biomarkers in AML is somewhat different from other cancers, such as non-small cell lung cancer, in that the markers themselves are often not the direct targets of treatment. In AML, these molecular genetic biomarkers are incorporated into a risk-based treatment stratification that determines whether or not to recommend transplantation.

Moreover, AML patients often have multiple combinations of these essential mutations, again in contrast to the mutually exclusive driver oncogene alterations seen in solid cancers such as non-small cell lung cancer. In AML, the clinical effect of driver mutations can be modified by the wider genomic milieu, either additively or interactively (7). Therefore, complete assessment of AML patients requires testing multiple biomarkers concurrently, rather than a sequential single-biomarker approach. In this regard, panel testing is becoming the preferred approach.

Myelodysplastic Syndromes (MDS)

The myelodysplastic syndromes (MDS) represent a spectrum of clonal bone marrow diseases, with heterogeneous presentations that typically include one or more cytopenias, defective differentiation of blood cell progenitors into mature functional cells, and an increased rate of progression to acute myeloid leukemia (AML). These secondary AML

cases carry a worse prognosis than de novo AML cases. Furthermore, there are myeloid neoplasms that share overlapping characteristics with both MDS and myeloproliferative neoplasms (MPNs), such as chronic myelomonocytic leukemia (CMML). The World Health Organization (WHO), has designated these diseases separately as MDS/MPNs, distinct from either MDS or MPNs (1).

According to the 2016 National Comprehensive Cancer Network (NCCN) Guidelines, the overall incidence of MDS is approximately 5/100,000 per year, primarily in adults. MDS is rare in patients under the age of 40, but much more common in older patients, with incidence of 30/100,000 among ages 70-79, and 60/100,000 in patients 80 years and older (2).

MDS treatment can range from surveillance/observation to high dose chemotherapy and bone marrow transplantation, with the principal determining factors being the patient's overall health and co-morbidities, and prognostic categorization.

MDS has historically been classified by a combination of traditional laboratory techniques, such as demonstration of stable cytopenias by complete blood count, microscopic examination of a bone marrow biopsy, and bone marrow cytogenetic studies. Other than the clinical feature of the number of cytopenias and specific cytogenetic changes found recurrently in MDS, all other diagnostic criteria in MDS rely upon light microscopy findings. These include the number of cell lineages (i.e., platelets, red blood cells, white blood cells) affected by dysplasia, the percentage of immature "blast" cells, and the presence or absence of a characteristic pattern of iron deposition in immature red blood cells called ring sideroblasts. Low risk MDS is associated with dysplasia affecting only one cell lineage, with or without ring sideroblasts, and isolated large deletions involving chromosome 5 (5q-). High risk disease is associated with dysplasia across multiple lineages, increased blast percentages, and complex karyotype. With the exception of SF3B1 mutations (see below), no specific mutations are incorporated into the current diagnostic criteria of MDS.

However, evidence has steadily accumulated over the first two decades of the 21st century showing that certain specific acquired genetic alterations within the myeloid cells are strong predictors of prognosis in MDS and, in the case of SF3B1, are necessary diagnostic markers as well (3-9). In addition, other somatic alterations may support the diagnosis of MDS in certain contexts. MDS can be challenging to diagnose, due to the subjective morphologic assessment of dysplasia, and a multitude of benign reactive conditions that can manifest as peripheral cytopenias and cytologic atypia that are especially prevalent in the elderly population. In this regard, the demonstration of these clonal molecular alterations in clinically and/or morphologically ambiguous cases can help establish a diagnosis of MDS and expedite therapy earlier in the disease course, before progression to a more overt, and life-threatening, condition. Accordingly, a number of specific genetic alterations are included in the NCCN guideline recommendations as necessary for the diagnosis and management of patients with MDS.

Forty-seven different gene mutations have been identified as recurring findings in MDS, including TET2, SF3B1, ASXL1, DNMT3A, SRSF2, RUNX1, TP53, U2AF1, EZH2, ZRSR2, STAG2, CBL, NRAS, JAK2, SETBP1, IDH1, IDH2, and ETV6. While some are more common than others, no single gene has been reported in more than approximately one-third of cases. Most of these are useful as adjunctive diagnostic markers for clinically/microscopically ambiguous cases, to help establish a more firm diagnosis and, potentially, as markers of clonal disease that can be used to monitor for disease progression and response to interventions.

Myeloproliferative Neoplasms (MPN)

The myeloproliferative neoplasms (MPNs) represent a group of rare clonal bone marrow diseases, have a median age at onset of 65-70 years, and heterogeneous presentations that typically include overgrowth of one or more of the myeloid cell lineages in the marrow, with increased circulation of mature forms in the peripheral blood, and an increased rate of progression to acute myeloid leukemia (AML). Symptomatology varies between the different diseases, typically related to the specific proliferating cell lineages.

MPNs can be subdivided in two main categories based upon the presence or absence of BCR-ABL1: chronic myeloid leukemia (CML) and non-CML MPNs.[2] The main non-CML MPNs, also termed classical MPNs, including essential thrombocythemia (ET), primary myelofibrosis (PMF), and polycythemia vera (PV), had traditionally been defined by laboratory criteria such as thrombocytosis, marrow fibrosis, and erythrocytosis, respectively. Non-CML MPN treatment can range from observation to targeted therapies to hematopoietic stem cell transplantation (HCT), with the principal determining factors being the patient's overall health and co-morbidities, presence of fibrosis or increased blasts, molecular and prognostic categorization. Other less common diagnostic entities within the non-CML MPNs include chronic neutrophilic leukemia (CNL) and chronic eosinophilic leukemia (CEL).

While the definitions of the entities within MPN are fairly distinct, in practice, phenotypic overlap is common, and definitive classification can be challenging based solely on clinical grounds and traditional laboratory tests, such as complete blood count (CBC) and bone marrow biopsy. At diagnosis, the discrimination from reactive conditions is often critical, and the demonstration of several specific clonal molecular alterations in clinically or morphologically ambiguous cases can expedite an MPN diagnosis before progression to a more overt, life-threatening, condition. Accordingly, one or more MPN-restricted, driver mutations are included in practice guideline recommendations as necessary for the diagnosis or management of patients with MPN or MPN-like conditions, including Janus kinase 2 (JAK2), calreticulin (CALR), and myeloproliferative leukemia virus (MPL).[5-7] Driver mutations are usually mutually exclusive.

JAK2 V617F mutations in exon 14 are the *sine qua non* of PV, reported in >90% of cases. Another 2-3% have missense mutations or small insertion/deletions in a secondary hotspot of JAK2, in exon 12.[8,9] The JAK2 V617F mutation is not specific within the MPNs, however, and has also been reported in approximately 40-60% of cases of ET and PMF. The JAK2 mutation is not present, however, in CML or in benign conditions that lead to secondary erythrocytosis and its presence is invaluable in this differential diagnosis.

Mutations in CALR exon 9, by contrast, are encountered in approximately 20-35% of patients with ET and PMF and are not characteristic of PV. Two alterations predominate: a 52 bp deletion (Type 1) that is more common in PMF or post-ET myelofibrosis, and a 5 bp insertion (Type 2) that is more common in ET, associated with more indolent disease and lower risk of thrombosis, despite an association with extremely high platelet counts. Beyond enabling a specific diagnosis, the presence of a CALR mutation portends a favorable prognosis in PMF (overall survival (OS) 17.7 years vs. 3.2 years with no mutations ("triple-negative" patients), and these patients have a lower rate of progression to AML over 10 years (9.4% vs. 34.4%).[10] CALR mutation also is associated with improved overall survival (82% vs. 56% at 4 years) and non-relapse mortality (7% vs. 31%) following transplantation for PMF.[1] The significance of CALR mutations in ET is dependent upon the type of mutation, as mentioned above, and less clear.

MPL mutations are another sequence alteration seen infrequently in ET and PMF, and predicts an increased risk of transfusion dependence in PMF.[10] MPL mutations, like JAK2 and CALR, portends a favorable prognosis across MPN, when compared to triple negative MPN (approximately 10%) that lack mutations in any of these three genes.[1]

In contrast to the favorable prognosis conferred by MPL, CALR, and JAK2, a number of other not MPN-restricted, non-driver, mutations are considered "high risk" for progressive disease and are associated with both a shorter OS and leukemic-free survival in PMF, including ASXL1, TET2, EZH2, SRSF2, SF3B1, SH2B3, U2AF1, TP53, IDH1, and IDH2.[1,5,6] These co-mutated, myeloid genes additively contribute to phenotypic variability and shifts, as well as progression to more aggressive disease.[6] Mutations in at least one of these genes confers a shortened median survival (81 vs. 148 months),[11] and the presence of 2 or more of these mutations reduces median survival from 12.2 years to 2.6 years.[12] However, a study of 570 patients with PMF demonstrated a counterbalancing effect of combining a low-risk mutation (CALR) with a high-risk mutation (ASXL1); the median OS was longest in CALR(+)/ASXL1(-) patients (10.4 years), shortest in CALR(-)/ASXL1(+) patients (2.3 years), and intermediate (5.8 years) when both are present or absent.[3] In triple-negative patients, these non-driver mutations serve as a major diagnostic criteria for both PMF and ET. WHO and NCCN guidelines recommend analysis of mutations in these genes

to assist in establishing an MPN diagnosis in the absence of mutations in MPL, CALR, and JAK2.[1,2]

Moreover, patients with progressive MPNs are candidates for several different therapies, including hypomethylating agents, induction chemotherapy, HCT, and clinical trials. Selecting between these options is a complex determination that includes several factors, and NCCN recommends the analysis of mutations in ASXL1, EZH2, IDH1/2, SRSF2, and TP53 (category 2A) to assist in risk stratification and treatment planning in select PMF patients.[1] Monitoring response to treatment is recommended every 3-6 months with additional molecular testing reserved for MF patients with INT-1-risk or INT-2-risk/high-risk disease to aid in decision-making regarding allogeneic HCT.[1]

Analysis of Evidence
(Rationale for Determination)

Acute Myelogenous Leukemia (AML)

The spectrum of genetic abnormalities that are relevant in AML is broad, and includes specific sequence variants within genes, copy number changes, and structural variants such as chromosomal translocations. Smaller scale mutations require a molecular diagnostics method (e.g., sequencing) for analysis, while larger scale chromosomal abnormalities may be analyzed using either molecular diagnostics or cytogenetics (e.g., FISH, karyotype) methods. Molecular diagnostics and cytogenetic testing play a complementary role in helping refine prognosis, particularly in cytogenetically intermediate risk normal karyotype AML (NK-AML), or those with core binding factor where KIT mutations help refine the prognosis (6,8). The following molecular genetic biomarkers are considered necessary for diagnosis and management of AML.

Table 1 Biomarkers that require a molecular diagnostics method (either via panel or individually):

Gene	Alteration	Clinical Utility	NCCN Biomarkers Category
CEBPA	Mutation	Favorable risk	2A
FLT3	Internal tandem duplication	Poor risk	2A
KIT	Mutation	Intermediate risk	2A
NPM1	Insertion mutation	Favorable risk	2A
TP53	Mutations, deletions	Poor risk	2A
RUNX1	Mutation	Distinct Diagnostic Category; Poor prognosis	*

* WHO 2016 AML Classification

These variants represent essential determinants of prognosis and therapy. As additional genetic variants are shown to similarly lead to safe and effective therapy selection and, therefore, meet Medicare coverage guidelines, additional genes may be added to Table 1.

Table 2 Biomarkers that can be assessed by either a molecular diagnostics method (panel only) or by a cytogenetics method:

Gene	Alteration	Clinical Utility
PML-RARA	Rearrangement	All-trans retinoic acid
BCR-ABL1	Rearrangement	Poor risk
CBFB-MYH11	Rearrangement	Favorable risk
DEK-NUP214	Rearrangement	Poor risk
MLLT3-KMT2A	Rearrangement	Intermediate risk

Other KMT2A	Rearrangements	Poor risk
GATA2, MECOM	Rearrangement	Poor risk
RUNX1-RUNX1T1	Rearrangement	Favorable risk
Deletion 5, 5q	Copy number loss	Poor risk
Deletion 7, 7q	Copy number loss	Poor risk
Trisomy 8	Copy number gain	Intermediate risk

Myelodysplastic Syndromes (MDS)

Five of these genes (TP53, EZH2, ETV6, RUNX1, ASXL1) have established independent value as prognostic determinants, and a mutation in any one of these five genes indicates more aggressive disease, worsened overall survival, and confers a prognosis equivalent to one step worse in the Revised International Prognostic Scoring System (IPSS-R) (3-4). Several other genes, including DNMT3A, U2AF1, SRSF2, CBL, PRPF8, SETBP1, and KRAS, have been associated with decreased survival, although are not formally incorporated into treatment determinations per 2016 NCCN guidelines. Mutations in TET2 have been associated with improved response rate to hypomethylating agents, but not with response duration or overall survival and, therefore, alterations in this gene are not currently recommended as sole determinants of treatment with this class of agents. Other mutations associated with response to specific therapies (but not yet FDA approved) include SF3B1 mutations, which are associated with a favorable response to DNA methyl transferase inhibitors (DNMTI), SRSF2 mutations, which are associated with a poor response to DNMTIs, and TP53, which is associated with a poor response to lenalidomide.

Mutations in SF3B1 are associated with MDS with ringed sideroblasts (previously designated as refractory anemia with ringed sideroblasts (RARS)), which confers a favorable prognosis. In the revised WHO classification, this diagnosis is established by the finding of at least 15% ringed sideroblasts by light microscopy or by the presence of an SF3B1 mutation and at least 5% ringed sideroblasts.

The spectrum of genetic abnormalities that are relevant in MDS is broad, and includes specific sequence variants within a large number of genes as well as a wide range of aberrations in other genes. While it is possible to assess the former of these with single gene assays, it is functionally impractical given the number of hotspot variants and number of genes. The latter require more complete coverage of the entire gene. In this regard, MDS is an appropriate indication for multiplexed sequencing, which is typically performed by next generation sequencing. The following molecular genetic biomarkers are considered necessary for diagnosis and management of select MDS.

Gene	Clinical Utility	NCCN Biomarkers Category
TP53	Poor risk	2A
EZH2	Poor risk	2A
ETV6	Poor risk	2A
ASXL1	Poor risk	2A
RUNX1	Poor risk	2A
SF3B1	Low risk; diagnosis of MDS with ringed sideroblasts/RARS	2A

In total, the required nucleotide or small insertion/deletion variants occur at numerous specific loci in six genes. These variants represent essential determinants of prognosis and therapy. As additional genetic variants are shown to similarly lead to safe and effective therapy selection and, therefore, meet Medicare coverage guidelines, additional

genes may be added to the above table.

Myeloproliferative Neoplasms (MPN)

The following molecular genetic biomarkers are considered necessary for diagnosis and management of select MPNs.

Gene	Clinical Utility	NCCN Category
JAK2	Diagnosis, intermediate prognosis, higher risk of thrombosis	2A
CALR	Diagnosis, improved survival, lower risk of thrombosis	2A
MPL	Diagnosis, intermediate prognosis, lower risk of thrombosis	2A
Triple negative	Inferior survival	2A
ASXL1	Diagnosis, Inferior survival, increased progression to leukemia	2A
EZH2	Diagnosis, Inferior survival	2A
IDH1/2	Diagnosis, Inferior leukemia-free survival	2A
SRSF2	Diagnosis, Inferior survival, increase progression to leukemia	2A
TP53	Diagnosis, Leukemic transformation	2A

In total, the required nucleotide or small insertion/deletion variants occur at numerous specific loci in eight genes. These variants represent essential determinants of prognosis and associated therapy. As additional genetic variants are shown to similarly lead to safe and effective therapy selection and, therefore, meet Medicare coverage guidelines, additional genes may be added to the above table.

General Information

Associated Information

N/A

Sources of Information

N/A

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Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
10/03/2019	R3	This LCD was converted to the new "no-codes" format. There has been no change in coverage with this LCD revision.	• Revisions Due To Code Removal
08/15/2019	R2	Consistent with Change Request 10901, all coding information, National coverage provisions, and Associated Information (Documentation Requirements, Utilization Guidelines) have been removed from the LCD and placed in the related Billing and Coding Article, A56793. There has been no change in coverage with this LCD revision.	• Provider Education/Guidance
08/01/2018	R1	Removed the following wording, “effective for services rendered on or after 12/01/2017” from the “ICD-10 Codes that Support Medical Necessity” sections- Group 1 and Group 2 paragraphs.	• Provider Education/Guidance

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)

A56793 - Billing and Coding: Genomic Sequence Analysis Panels in the Treatment of Hematolymphoid Diseases

A55974 - Response to Comments: Genomic Sequence Analysis Panels in the Treatment of Hematolymphoid Diseases

Related National Coverage Documents

N/A

Public Version(s)

Updated on 09/24/2019 with effective dates 10/03/2019 - N/A

Some older versions have been archived. Please visit the MCD Archive Site to retrieve them.

Keywords

N/A