Local Coverage Determination (LCD): Genomic Sequence Analysis Panels in the Treatment of Acute Myelogenous Leukemia (AML) (L36926)

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Contractor Information

Contractor Name	Contract Type	Contract Number	Jurisdiction	State(s)
National Government Services, Inc.	MAC - Part A	06101 - MAC A	N/A	Illinois
National Government Services, Inc.	MAC - Part B	06102 - MAC B	N/A	Illinois
National Government Services, Inc.	MAC - Part A	06201 - MAC A	N/A	Minnesota
National Government Services, Inc.	MAC - Part B	06202 - MAC B	N/A	Minnesota
National Government Services, Inc.	MAC - Part A	06301 - MAC A	N/A	Wisconsin
National Government Services, Inc.	MAC - Part B	06302 - MAC B	N/A	Wisconsin
National Government Services, Inc.	A and B and HHH MAC	13101 - MAC A	J - K	Connecticut
National Government Services, Inc.	A and B and HHH MAC	13102 - MAC B	J - K	Connecticut
National Government Services, Inc.	A and B and HHH MAC	13201 - MAC A	J - K	New York - Entire State
National Government Services, Inc.	A and B and HHH MAC	13202 - MAC B	J - K	New York - Downstate
National Government Services, Inc.	A and B and HHH MAC	13282 - MAC B	J - K	New York - Upstate
National Government Services, Inc.	A and B and HHH MAC	13292 - MAC B	J - K	New York - Queens
National Government Services, Inc.	A and B and HHH MAC	14111 - MAC A	J - K	Maine
National Government Services, Inc.	A and B and HHH MAC	14112 - MAC B	J - K	Maine
National Government Services, Inc.	A and B and HHH MAC	14211 - MAC A	J - K	Massachusetts
National Government Services, Inc.	A and B and HHH MAC	14212 - MAC B	J - K	Massachusetts
National Government Services, Inc.	A and B and HHH MAC	14311 - MAC A	J - K	New Hampshire
National Government Services, Inc.	A and B and HHH MAC	14312 - MAC B	J - K	New Hampshire
National Government Services, Inc.	A and B and HHH MAC	14411 - MAC A	J - K	Rhode Island
National Government Services, Inc.	A and B and HHH MAC	14412 - MAC B	J - K	Rhode Island
National Government Services, Inc.	A and B and HHH MAC	14511 - MAC A	J - K	Vermont
National Government Services, Inc.	A and B and HHH MAC	14512 - MAC B	J - K	Vermont

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LCD Information

Document Information

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Genomic Sequence Analysis Panels in the Treatment of Acute Myelogenous Leukemia (AML)

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CMS National Coverage Policy Language quoted from Centers for Medicare and Medicaid Services (CMS), National Coverage Determinations (NCDs) and coverage provisions in interpretive manuals is italicized throughout the policy. NCDs and coverage provisions in interpretive manuals are not subject to the Local Coverage Determination (LCD) Review Process (42 CFR 405.860[b] and 42 CFR 426 [Subpart D]). In addition, an administrative law judge may not review an NCD. See Section 1869(f)(1)(A)(i) of the Social Security Act.

Unless otherwise specified, *italicized* text represents quotation from one or more of the following CMS sources:

Title XVIII of the Social Security Act (SSA):
Section 1862(a)(1)(A) excludes expenses incurred for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

Section 1833(e) prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

Section 1862(a)(7) excludes routine physical examinations, unless otherwise covered by statute.

CMS Publications:
CMS Publication 100-02, *Medicare Benefit Policy Manual*, Chapter 15, Section 80.1 – Laboratory services must meet applicable requirements of CLIA

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

Abstract
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.

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

Targeted genomic sequence analysis panel, hematolymphoid neoplasm, DNA analysis, 5-50 genes (CPT 81450) is a useful representation of the aggregate of these gene tests, and may be used as long as the panel contains, at a minimum, 5 or more gene tests for molecular biomarkers determined to meet Medicare coverage criteria (for example, NCCN Biomarkers Compendium Evidence Category I or 2A and associated clinical utility). Evaluation of other genes or genomic sequences not addressed by NCCN or other professional guidelines are not precluded, but their inclusion in panels recognized by this code should not be interpreted as endorsement of such testing by genomic sequencing procedures and laboratories and users of such testing are advised to adhere to traditional regulatory and institutional oversight mechanisms to assure their clinical validity and utility.

Indications and Limitations of Coverage

Genomic Sequential Analysis Panel represented by CPT 81450 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.

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Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

012x Hospital Inpatient (Medicare Part B only)
013x Hospital Outpatient
014x Hospital - Laboratory Services Provided to Non-patients
022x Skilled Nursing - Inpatient (Medicare Part B only)
023x Skilled Nursing - Outpatient

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the policy, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

0300 Laboratory - General Classification
0310 Laboratory Pathology - General Classification

CPT/HCPCS Codes
Group 1 Paragraph: CPT code 81450 Targeted Genomic Sequence Analysis Panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes, may be used as long as the panel contains, at a minimum, 5 or more gene tests for molecular biomarkers determined to meet Medicare coverage criteria as listed above.

Group 1 Codes:

81450	TARGETED GENOMIC SEQUENCE ANALYSIS PANEL, HEMATOLYMPHOID NEOPLASM OR DISORDER, DNA ANALYSIS, AND RNA ANALYSIS WHEN PERFORMED, 5-50 GENES (EG, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), INTERROGATION FOR SEQUENCE VARIANTS, AND COPY NUMBER VARIANTS OR REARRANGEMENTS, OR ISOFORM EXPRESSION OR MRNA EXPRESSION LEVELS, IF PERFORMED

ICD-10 Codes that Support Medical Necessity
Group 1 Paragraph: N/A

Group 1 Codes:

ICD-10 Codes	Description
C92.00	Acute myeloblastic leukemia, not having achieved remission
C92.02	Acute myeloblastic leukemia, in relapse
C92.30	Myeloid sarcoma, not having achieved remission
C92.32	Myeloid sarcoma, in relapse
C92.40	Acute promyelocytic leukemia, not having achieved remission
C92.42	Acute promyelocytic leukemia, in relapse
C92.50	Acute myelomonocytic leukemia, not having achieved remission
C92.52	Acute myelomonocytic leukemia, in relapse
C92.60	Acute myeloid leukemia with 11q23-abnormality not having achieved remission
C92.62	Acute myeloid leukemia with 11q23-abnormality in relapse
C92.A0	Acute myeloid leukemia with multilineage dysplasia, not having achieved remission
C92.A2	Acute myeloid leukemia with multilineage dysplasia, in relapse
C92.Z0	Other myeloid leukemia not having achieved remission
C92.Z2	Other myeloid leukemia, in relapse
C94.00	Acute erythroid leukemia, not having achieved remission
C94.02	Acute erythroid leukemia, in relapse

ICD-10 Codes that DO NOT Support Medical Necessity N/A

ICD-10 Additional Information

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General Information

Associated Information
N/A

Sources of Information and Basis for Decision
1. Schlenk RF, Dohner K, Krauter J, et al. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *N Engl J Med.* 2008;358:1909-18.

2. Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood.* 2010;116:354-65.

3. Marcucci G, Haferlach T, Dohner H. Molecular genetics of adult acute myeloid leukemia: prognostic and therapeutic implications. *J Clin Oncol* 2011;29:475-86. [Erratum, *J Clin Oncol.* 2011;29:1798.]

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6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia Version 2.2016. Available at http://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed: September 9, 2016.

7. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. *N Engl J Med.* 2016;374:2209-21.

8. Yohe S. Molecular Genetic Markers in Acute Myeloid Leukemia. *J Clin Med.* 2015 Mar;4(3):460–478.
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Revision History Information

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Associated Documents

Attachments N/A

Related Local Coverage Documents Article(s) A55378 - Response to Comments: Genomic Sequence Analysis Panels in the Treatment of Acute Myelogenous Leukemia (AML)

Related National Coverage Documents N/A

Public Version(s) Updated on 12/08/2016 with effective dates 02/01/2017 - N/A Back to Top

Keywords

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