# Acute Myeloid Leukemia (AML) Genetic Testing

**Procedures addressed**

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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What is Acute Myeloid Leukemia

Definition

Acute myeloid leukemia (AML) is a neoplasm resulting from the clonal expansion of myeloid blasts in the peripheral blood (PB), bone marrow (BM), or other tissues. It is a heterogeneous disease clinically, morphologically and genetically.

- The required blast percentage for a diagnosis of AML is ≥ 20% myeloblasts and/or monoblasts/promonocytes and /or megakaryoblasts in the PB or BM. The diagnosis of AML can also be made when the blasts percentage is <20% if the increase blast count is associated with: t(8;21)(q22;q22.1), inv(16)(p13.1;q22) or t(16;16) (p13.1;q22), or t(15;17)(q24.1;q21.2).

- A large number of recurrent cytogenetic abnormalities and mutated genes are recognized in AML. Some of these genetic abnormalities are associated with unique phenotype and prognostic features and are classified under acute myeloid leukemia with recurrent genetic abnormalities. The AMLs with no recurrent genetic abnormalities are classified under acute myeloid leukemia, not otherwise specified.

- In AML, the pretreatment cytogenetic abnormalities represent the single most important prognostic factor for predicting remission rates, relapse risk, and overall survival rate. Even in de novo AMLs with no chromosomal abnormalities the clinical outcome is heterogeneous.
• Studies have shown that molecular abnormalities including NPM1, FLT3-ITD, CEBPA, IDH1/2, DNMT3A, KIT and other mutations are important for prognostication not only in AMLs with a normal karyotype but also in other AML subsets. Some of these molecular abnormalities also affect the choice of treatment for patients with AML.

• After treatment is selected and initiated, treatment response can be monitored by assessing the blast cell percentage in bone marrow using morphology and immunophenotyping. Individuals who have chromosomal abnormalities at initial diagnosis are monitored for disappearance (indicates remission) and re-emergence (indicates relapse) of these abnormalities.

Test information

• The various diagnostic modalities that are utilized for front-end diagnostics are specified by the National Comprehensive Cancer Network (NCCN, 2018). These components include standard morphologic examinations on the blood and bone marrow, immunohistochemical staining, cytogenetics, flow cytometry, etc. However, this policy only pertains to those molecular techniques, which have either prognostic and/or predictive (that is, influencing chemotherapy selection with improved outcomes) implications.

• The specific methodology used to identify molecular markers is dependent upon the type of marker being investigated.

  o DNA mutations are generally detected through targeted mutation analysis of hotspots, sequencing parts of a single gene or the whole gene, or sequencing panels of multiple genes via next-generation sequencing (NGS).

  o Chromosome abnormalities, such as translocations or deletions, may be detected through direct visualization of the chromosomes (karyotyping), in situ hybridization of probes (e.g., FISH) to detect deletions or duplications that are too small to see directly, or DNA-based methods that identify deletions or translocation breakpoints.

  o Gene expression profiling simultaneously measures the amount of RNA or protein being made by many genes. Expression patterns may be used to predict the type of cancer present, tumor aggressiveness, and therapy needs.

Guidelines and evidence

• The National Comprehensive Cancer Network (NCCN, 2018) states the following in regards to genetic testing in individuals with AML:

  o “A variety of gene mutations are associated with specific prognoses (category 2A) and may guide medical decision making (category 2B) (See AML-A).
Currently, c-KIT, FLT3-ITD, FLT3-TKD, NPM1, CEBPA, IDH1/IDH2, and TP53 are included in this group; however, this field is evolving rapidly. While the above mutations should be tested in all patients, multiplex gene panels and next-generation sequencing analysis may be used to obtain a more comprehensive prognostic assessment (Papaemmanuil E, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med 2016;374:2209-2221). The information obtained may have prognostic impact in AML, may influence medical decision making regarding consolidation with chemotherapy versus an allogeneic hematopoietic stem cell transplant, or determination for eligibility for clinical trial participation."

- Some FDA labels require results from molecular marker tests to effectively or safely use the therapy for a specific cancer type. A list of all Pharmacogenomic Biomarkers included in FDA labeling and associated implications can be found here.

- Whereas the above mentioned biomarkers constitute established evaluation pathways for AML, there are many emerging mutations that might have clinical relevance to various types of AML that are not yet considered standard of care.

Criteria

Introduction

Medical necessity criteria differ based on the type of testing being performed (i.e., individual tumor markers separately chosen based on the cancer type versus pre-defined panels of tumor markers).

Single gene testing for AML

- The member has AML and will benefit from information provided by the requested molecular marker test based on at least one of the following:
  - An oncology therapy FDA label requires results from the marker test to effectively or safely use the therapy for the member’s AML, or
  - NCCN guidelines include the tumor marker test in the management algorithm for AML and all other requirements are met (specific pathology findings, staging, etc.); however, the tumor marker must be explicitly included in the guidelines and not simply included in a footnote as an intervention that may be considered, or
  - The NCCN Biomarker Compendium has a level of evidence of at least 2A for the tumor marker’s application to AML
Panel testing for AML

Gene panels that are specific to hematological cancers and include the following genes will be eligible for reimbursement according to the criteria outlined in this policy: NPM1, FLT3, CEBPA, IDH1, IDH2, DNMT3A, KIT and TP53. This sequencing panel will only be considered for reimbursement when billed with the appropriate panel CPT code: 81450.

- Genetic Counseling
  - Pre and post-test counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous panel testing for AML, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Member has a diagnosis of AML, and
  - The results of the test will directly impact the diagnostic and treatment options that are recommended for the patient, AND
- Rendering laboratory is a qualified provider for service per Health Plan policy

Billing and reimbursement considerations

- When multiple CPT codes are billed for components of a panel and there is a more appropriate CPT code representing the panel, the laboratory will be redirected to the appropriate panel code(s).
- Panels of over 50 genes billed with CPT code 81455 are considered excessive in individuals with AML and will not be reimbursed.

References


7. US Food and Drug Administration. Table of Pharmacogenomic Biomarkers in Drug Labeling. Available at: [http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm](http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)