guideline summary

Initial Diagnostic Workup of Acute Leukemia: ASCO Clinical Practice Guideline Endorsement Summary of the CAP and ASH Guideline

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Laboratory evaluation of patients who are suspected of having acute leukemia (AL) is critical, though complex, and has evolved significantly with the incorporation of advanced laboratory techniques. Aside from the traditional techniques (cytomorphology, cytochemistry, immunophenotyping by multiparameter flow cytometry or immunohistochemical staining, and molecular/cytogenetics study[1-3]) emerging advanced molecular diagnostics, such as next-generation sequencing technology, have become more important in the diagnosis and risk stratification of AL.[4-7]

In general, the aforementioned four traditional techniques form the backbone of the initial diagnostic workup of patients with AL, which leads to risk group stratification and fine tuning by molecular signatures. Recent advances in sequencing to define the molecular landscape have provided novel insights into the pathogenesis of AL, helped to identify new genetic subtypes of AL and additional risk factors, and have led to the development of novel treatment strategies and personalized medicine. However, appropriate ways of introducing molecular tests into the initial workup and of observing patients with AL, as well as to integrate them with conventional approaches, are still under debate[4] and require guidance.

In 2017, an evidence-based guideline for the initial workup of AL was published by the College of American Pathologists (CAP) and the American Society of Hematology (ASH).[8] Since that time, advances in molecular techniques and the identification and validation of new molecular markers via large cohorts have contributed to better risk stratification of patients with AL. Second, a revision of the WHO classification of tumors of hematopoietic and lymphoid tissues was described in 2016[9] and fully published in 2017,[10] which also led to new risk categories and refined subclassification. Therefore, the current ASH/CAP guidelines[8] were reviewed by ASCO Endorsement Expert Panelists, and discussion points—included in the main manuscript—are used to summarize issues that were identified from the updated literature.[11] Additional information is available at www.asco.org/hematologic-malignancies-guidelines. Patient information is available at www.cancer.net.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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THE BOTTOM LINE

Initial Diagnostic Workup of Acute Leukemia: ASCO Clinical Practice Guideline Endorsement Summary of the CAP and ASH Guideline

ASCO endorses the Initial Diagnostic Workup of Acute Leukemia Clinical Practice Guideline by CAP and ASH.

Guideline Questions

1. What clinical and laboratory information should be available during the initial diagnostic evaluation of a patient with AL?
2. What specimens and sample types should be evaluated during the initial workup of a patient with AL?
3. At the time of diagnosis, what tests are required for all patients for the initial evaluation of AL?
4. Which tests should be performed on only a subset of patients, including in response to results from initial tests and morphology?
5. Where should laboratory testing be performed?
6. How should test results and the diagnosis be correlated and reported?

Target Population Children and adults with acute leukemia.

Target Audience Primary care providers, nurses, medical oncologists, pediatric oncologists, hematologists, pathologists, radiation oncologist, and other providers.

Methods An ASCO Expert Panel was convened to consider endorsing the CAP and ASH initial diagnostic workup of AL clinical practice guideline recommendations that were based on a systematic review of the medical literature. The ASCO Expert Panel considered the methodology used in the 2017 guideline by assessing the results of the AGREE II review instrument. The ASCO Expert Panel carefully reviewed the 2017 guideline content to determine its appropriateness for ASCO endorsement.

Recommendations

Recommendation 1. The treating clinician should provide relevant clinical data or ensure that this is readily accessible by the pathologist *(Strong recommendation).*

NOTE. These data include, but are not limited to, the patient's age, sex, and ethnicity; history of any hematologic disorder or known predisposing conditions or syndromes; any prior malignancy; exposure to cytotoxic therapy, immunotherapy, radiotherapy, or other possibly toxic substances; and any additional clinical findings of diagnostic or prognostic importance. The treating clinician should also include any history of possibly confounding factors, such as recent growth factor therapy, transfusions, or other medications that might obscure or mimic the features of acute leukemia. The treating clinician should also obtain and provide information regarding family history of any hematologic disorders or other malignancies.

Recommendation 2. The treating clinician should provide relevant physical examination and imaging findings or ensure that these results are readily accessible by the pathologist *(Recommendation).*

NOTE. These findings include, but are not limited to, neurologic exam findings and the presence of tumor masses (eg, mediastinal), other tissue lesions (eg, cutaneous), and/or organomegaly.

Recommendation 3. The pathologist should review recent or concurrent CBCs and leukocyte differentials and evaluate a peripheral blood smear *(Strong recommendation).*

Recommendation 4. The treating clinician or pathologist should obtain fresh bone marrow aspirate for all patients who are suspected of AL, a portion of which should be used to make bone marrow aspirate smears for morphologic evaluation. If performed, the pathologist should evaluate an adequate bone marrow trephine core biopsy, bone marrow trephine touch preparations, and/or marrow clots in conjunction with bone marrow aspirates *(Strong recommendation).*

NOTE. If bone marrow aspirate material is inadequate or if there is a compelling clinical reason to avoid bone marrow examination, peripheral blood may be used for diagnosis and ancillary studies if sufficient numbers of blasts are present. If a bone marrow aspirate is unobtainable, touch imprint preparations of a core biopsy should be prepared and evaluated, and an additional core biopsy may be submitted, unfixed in tissue culture medium, for disaggregation for flow and genetic studies. Optimally, the same physician should interpret the bone marrow aspirate smears and the core biopsy specimens, or the interpretations of those specimens should be correlated if performed by different physicians.

Recommendation 5. In addition to morphologic assessment—blood and bone marrow—the pathologist or treating clinician should obtain sufficient samples and perform conventional cytogenetic analysis (ie, karyotype), appropriate molecular genetic and/or fluorescent in situ hybridization testing, and flow cytometric immunophenotyping. The flow cytometry panel should be sufficient to distinguish acute myeloid leukemia (AML), including acute

(continued on following page)

THE BOTTOM LINE (CONTINUED)

promyelocytic leukemia; T-cell acute lymphoblastic leukemia (ALL), including early T-cell precursor leukemias; B-cell precursor ALL (B-ALL); and AL of ambiguous lineage on all patients diagnosed with AL. Molecular genetic and/or fluorescent in situ hybridization testing does not, however, replace conventional cytogenetic analysis *(Strong recommendation).*

NOTE. If sufficient bone marrow aspirate or peripheral blood material is not available for flow cytometric immunophenotyping, immunohistochemical studies may be used as an alternative method for performing limited immunophenotyping. In addition, a second bone marrow core biopsy can be obtained and submitted, unfixed in tissue culture media, for disaggregation for genetic studies and flow cytometry.

Recommendation 6. For patients with suspected or confirmed AL, the pathologist may request and evaluate cytochemical studies to assist in the diagnosis and classification of AML *(Expert consensus opinion).*

Recommendation 7. The treating clinician or pathologist may use cryopreserved cells or nucleic acid, formalin-fixed, nondecalcified paraffin-embedded tissue, or unstained marrow aspirate or peripheral blood smears obtained and prepared from peripheral blood, bone marrow aspirate, or other involved tissues for molecular or genetic studies in which the use of such material has been validated. Such specimens must be properly identified and stored under appropriate conditions in a laboratory that complies with regulatory and/or accreditation requirements *(Recommendation).*

Recommendation 8. For patients with ALL receiving intrathecal therapy, the treating clinician should obtain a CSF sample. The treating clinician or pathologist should ensure that a cell count is performed and that examination/enumeration of blasts on a cytocentrifuge preparation is performed and reviewed by the pathologist *(Strong recommendation).*

Recommendation 9. For patients with AL other than those with ALL who are receiving intrathecal therapy, the treating clinician may, under certain circumstances, obtain a CSF sample when there is no clinical contraindication. The treating clinician or pathologist should ensure that a cell count is performed and that examination/enumeration of blasts on a cytocentrifuge preparation is performed and reviewed by the pathologist *(Expert consensus opinion).*

Recommendation 10. For patients with suspected or confirmed AL, the pathologist may use flow cytometry in the evaluation of CSF (*Recommendation).*

Recommendation 11. For patients who present with extramedullary disease without bone marrow or blood involvement, the pathologist should evaluate a tissue biopsy and process it for morphologic, immunophenotypic, cytogenetic, and molecular genetic studies, as recommended for bone marrow *(Strong recommendation).*

NOTE. Additional biopsies may be indicated to obtain fresh material for ancillary testing.

Recommendation 12. For patients with suspected or confirmed AL, the pathologist or treating clinician should ensure that flow cytometry analysis or molecular characterization is comprehensive enough to allow for the subsequent detection of minimal residual disease *(Strong recommendation).*

Recommendation 13. For pediatric patients with suspected or confirmed B-ALL, the pathologist or treating clinician should ensure that testing for t(12;21)(p13.2;q22.1); *ETV6-RUNX1,* t(9;22)(q34.1;q11.2); *BCR-ABL1*,*KMT2A* (*MLL*) translocation, *iAMP21*, and trisomy 4 and 10 is performed *(Strong recommendation).*

Recommendation 14. For adult patients with suspected or confirmed B-ALL, the pathologist or treating clinician should ensure that testing for t(9;22)(q34.1;q11.2); *BCR-ABL1* is performed. In addition, testing for *KMT2A* (*MLL*) translocations may be performed (*Strong recommendation* for testing for t(9;22)(q34.1;q11.2) and *BCR-ABL1*; *Recommendation* for testing for *KMT2A* [*MLL*] translocations).

Recommendation 15. For patients with suspected or confirmed ALL, the pathologist or treating clinician may order appropriate mutational analysis for selected genes that influence diagnosis, prognosis, and/or therapeutic management, which includes but is not limited to *PAX5, JAK1, JAK2,* and/or *IKZF1* for B-ALL and *NOTCH1* and/or *FBXW7* for T-ALL. Testing for the overexpression of CRLF2 may also be performed for B-ALL *(Recommendation).*

Recommendation 16. For pediatric and adult patients with suspected or confirmed AML of any type, the pathologist or treating clinician should ensure that testing for *FLT3*-ITD is performed. The pathologist or treating clinician may order mutational analysis that includes but is not limited to *IDH1*, *IDH2*, *TET2*, *WT1*, *DNMT3A*, and/or *TP53* for prognostic and/or therapeutic purposes (S*trong recommendation* for testing for *FLT3*-ITD; *Recommendation* for testing for other mutational analysis).

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THE BOTTOM LINE (CONTINUED)

Recommendation 17. For adult patients with confirmed core-binding factor (CBF) AML [AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* or inv(16)(p13.1q22)/t(16;16)(p13.1;q22); *CBFB-MYH11*], the pathologist or treating clinician should ensure that appropriate mutational analysis for *KIT* is performed. For pediatric patients with confirmed CBF-AML; *RUNX1-RUNX1T1* or inv(16)(p13.1q22) / t(16;16)(p13.1;q22); *CBFB-MYH11*, the pathologist or treating clinician may ensure that appropriate mutational analysis for *KIT* is performed (*Strong recommendation* for testing for *KIT* mutation in adult patients with CBF-AML; *Expert consensus opinion* for testing for *KIT* mutation in pediatric patients with CBF-AML).

Recommendation 18. For patients with suspected acute promyelocytic leukemia, the pathologist or treating physician should also ensure that rapid detection of *PML-RARA* is performed. The treating physician should also order appropriate coagulation studies to evaluate for disseminated intravascular coagulation *(Strong recommendation).*

Recommendation 19. For patients other than those with confirmed CBF-AML, acute promyelocytic leukemia, or AML with myelodysplasia-related cytogenetic abnormalities, the pathologist or treating clinician should ensure that mutational analysis for *NPM1*, *CEBPA*, and *RUNX1* is also performed *(Strong recommendation).*

Recommendation 20. For patients with confirmed AL, no recommendation is made for or against the use of global/gene-specific methylation, microRNA expression, or gene expression analysis for diagnosis or prognosis *(No recommendation).*

Recommendation 21. For patients with confirmed mixed-phenotype AL, the pathologist or treating clinician should ensure that testing for t(9;22)(q34.1;q11.2); *BCR-ABL1*, and *KMT2A* (*MLL*) translocations is performed *(Strong recommendation).*

Recommendation 22. All laboratory testing performed for the initial workup and diagnosis of a patient with AL must be performed in a laboratory that complies with regulatory and/or accreditation requirements *(Strong recommendation).*

Recommendation 23. If, after examination of a peripheral blood smear, it is determined that the patient will require immediate referral to another institution with expertise in the management of AL for treatment, the initial institution should, whenever possible, defer invasive procedures, including bone marrow aspiration and biopsies, to the treatment center to avoid duplicate procedures, associated patient discomfort, and additional costs *(Strong recommendation).*

Recommendation 24. If a patient is referred to another institution for treatment, the primary institution should provide the treatment center with all laboratory results, pathology slides, flow cytometry data, cytogenetic information, and a list of tests that are pending at the time of referral. Pending test results should be forwarded when they become available *(Strong recommendation).*

Recommendation 25. In the initial report, the pathologist should include laboratory, morphologic, immunophenotypic, and, if performed, cytochemical data, on which the diagnosis is based, along with a list of any pending tests. The pathologist should issue addenda/amended reports when the results of additional tests become available *(Strong recommendation).*

Recommendation 26. The pathologist and treating clinician should coordinate and ensure that all tests performed for classification, management, predicting prognosis, and disease monitoring are entered into the patient's medical records *(Strong recommendation).*

NOTE. This information should include the sample source, adequacy, and collection information, as applicable.

Recommendation 27. Treating physicians and pathologists should use the current WHO terminology for the final diagnosis and classification of AL *(Strong recommendation).*

Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at www.asco.org/hematologic-malignancies-guidelines. Patient information is available at www.cancer.net.

A link to the Initial Diagnostic Workup of Acute Leukemia Clinical Practice Guideline by CAP and ASH can be found at http://www.archivesofpathology.org.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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