MAYO CLINIC LABORATORIES

Test Definition: CILDF

Congenital Infantile Leukemia, Diagnostic FISH, Varies

Overview

Useful For

Detecting a neoplastic clone associated with the common chromosome abnormalities and classic rearrangements seen in congenital and infant patients with acute leukemia using laboratory-designed probe sets

An adjunct to conventional chromosome studies in congenital and infant patients with acute leukemia

Reflex Tests

Test Id	Reporting Name	Available Separately	Always Performed
CILDB	Probe, Each Additional (CILDF)	No, (Bill Only)	No

Testing Algorithm

This test includes a charge for the probe application, analysis, and professional interpretation of results for 4 probe sets (8 individual fluorescence in situ hybridization [FISH] probes). Additional charges will be incurred for all reflex or additional probe sets performed.

This FISH test allows different combinations of probes to be utilized based on the patient's age.

All probes marked with an asterisk* will be performed as automatic reflex testing if the initial evaluation of the primary gene target is disrupted or potentially disrupted. Patients found to have a *MYC* rearrangement will be automatically reflexed to the break-apart BCL6 and BCL2 probe sets. Patients found to have three copies of the KAT6A probe will be reflexed with D8Z2/MYC.

The FISH panel for patients **younger than 3 months of age (congenital acute leukemia)** includes testing for the following abnormalities using the FISH probes listed:
11q23 rearrangement, MLL (KMT2A)
*t(4;11)(q21;q23) AFF1/MLL
*t(9;11)(p22;q23) MLLT3/MLL
*t(10;11)(p12;q23) MLLT10/MLL
*t(11;19)(q23;p13.1) MLL/ELL
*t(11;19)(q23;p13.3) MLL/MLLT1
t(8;16), KAT6A/CREBBP
*D8Z2/MYC for trisomy 8
t(1;22), RBM15/MKL1
+13/+21, 13q14 and 21q22

If no classic abnormalities are observed and conventional chromosome results are available and abnormal, additional FISH probes may be offered.

The FISH panel for patients **3 to 18 months of age** (infant acute leukemia) is dependent on the reason for testing and the patient's diagnosis (acute myeloid leukemia [AML], B-cell acute lymphoblastic leukemia/lymphoma [B-ALL/LBL], or T-cell acute lymphoblastic leukemia/lymphoma [T-ALL/LBL].

AML: The initial FISH panel for patients with AML includes testing for the following abnormalities:
11q23 rearrangement, MLL (KMT2A)
*t(4;11)(q21;q23) AFF1/MLL
*t(9;11)(p22;q23) MLLT3/MLL
*t(10;11)(p12;q23) MLLT10/MLL
*t(11;19)(q23;p13.1) MLL/ELL

If an MLL(KMT2A) disruption is not identified, the following secondary AML FISH probes will be evaluated:
inv(16), MYH11/CBFB
*16q22 rearrangement, CBFB break-apart
t(8;21), RUNX1T1/RUNX1
t(15;17), PML/RARA
*17q21 rearrangement, RARA break-apart
-5/5q-, D5S630/EGR1
-7/7q-, D7Z1/ D7S486
inv(3) or t(3;3), RPN1/MECOM
*3q26.2 rearrangement, MECOM break-apart
t(6;9), DEK/NUP214
12p13 rearrangement, ETV6 break-apart
*t(7;12)(q36;p13), MNX1/ETV6
t(8;16), KAT6A/CREBBP
*D8Z2/MYC for trisomy 8
inv(16), GLIS2/CBFA2T3
11p15.4 rearrangement, NUP98 break-apart
*t(7;11)(p15;p15.4), HOXA9/NUP98
t(1;22), RBM15/MKL1

B-ALL/LBL: The initial FISH panel for patients with B-ALL/LBL includes testing for the following abnormalities:
11q23 rearrangement, MLL (KMT2A)
*t(4;11)(q21;q23) AFF1/MLL
*t(9;11)(p22;q23) MLLT3/MLL
*t(10;11)(p12;q23) MLLT10/MLL
*t(11;19)(q23;p13.3) MLL/MLLT1

If an MLL(KMT2A) disruption is not identified, the following secondary panel of B-ALL/LBL FISH probes will be evaluated:
+9/9p-, CDKN2A/D9Z1
t(9;22) BCR/ABL1
*9q34 rearrangement, ABL1 break-apart
-17/17p-, TP53/D17Z1
t(1;19)(q23;p13), PBX1/TCF3

Hyperdiploidy, +4,+10,+17: D4Z1/D10Z1/D17Z1
t(12;21)(p13;q22), ETV6/RUNX1 fusion and iAMP21
*12p13 rearrangement, ETV6 break-apart
*21q22 rearrangement, RUNX1 break-apart
14q32 rearrangement, IGH break-apart
t(Xp22.33;var) or t(Yp11.32;var), CRLF2 rearrangement
*t(X;14)(p22.33;q32) or t(Y;14)(p11.32;q32), CRLF2/IGH
t(Xp22.33;var) or t(Yp11.32;var), P2RY8 rearrangement
8q24.1 rearrangement, MYC break-apart
*3q27 rearrangement, BCL6 break-apart
*18q21 rearrangement, BCL2 break-apart

If a classic B-ALL/LBL abnormality is not identified in the first 11 probes analyzed, the following tertiary panel of B-cell ALL FISH probes will be evaluated:
1q25 rearrangement, ABL2 break-apart
5q32 rearrangement, PDGFRB break-apart
9p24.1 rearrangement, JAK2 break-apart
9q34 rearrangement, ABL1 break-apart
7p-, IKZF1/CEP7

T-ALL/LBL: The initial FISH panel for patients with T-ALL/LBL includes testing for the following abnormalities:
11q23 rearrangement, MLL (KMT2A) break-apart
*t(6;11)(q27;q23) MLLT4(AFDN)/MLL
*t(9;11)(p22;q23) MLLT3/MLL
*t(10;11)(p12;q23) MLLT10/MLL
*t(11;19)(q23;p13.3) MLL/MLLT1
*t(11;19)(q23;p13.1) MLL/ELL

If an MLL(KMT2A) disruption is not identified, the following secondary panel of T-ALL/LBL FISH probes will be evaluated:
+9/9p-, CDKN2A/D9Z1
t(9;22) BCR/ABL1 fusion, *ABL1* amplification
*9q34 rearrangement, ABL1 break-apart
-17/17p-, TP53/D17Z1
t(5;14), TLX3/BCL11B
7q34 rearrangement, TRB break-apart
*t(6;7) - MYB/TRB
*t(7;10) - TRB/TLX1
*t(7;11) - TRB/LMO1
*t(7;11) - TRB/LMO2
14q11.2 rearrangement, TRAD break-apart
*t(8;14) - MYC/TRAD
*t(10;14) - TLX1/TRAD
*t(11;14) - LMO1/TRAD
*t(11;14) - LMO2/TRAD

t(10;11), MLLT10/PICALM
1p33 rearrangement, TAL1/STIL

Method Name
Fluorescence In Situ Hybridization (FISH)

NY State Available
Yes

Specimen

Specimen Type
Varies

Ordering Guidance
This test is only performed on specimens from patients with acute leukemia who are 18 months of age or younger.

This test is intended to be ordered when the entire congenital infantile leukemia fluorescence in situ hybridization (FISH) panel is needed.

-If this test is ordered on a patient 19 months or older, this test will be canceled and automatically reordered by the laboratory as BALPF / B-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Pediatric, FISH, Varies; TALPF / T-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), FISH, Pediatric, Varies; or AMLPF / Acute Myeloid Leukemia (AML), FISH, Pediatric, Varies, based on patient's reason for testing.

-If this test is ordered and the laboratory is informed that the patient is on a Children's Oncology Group (COG) protocol, this test will be canceled and automatically reordered by the laboratory as COGBF / B-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Children's Oncology Group Enrollment Testing, FISH, Varies; COGTF / T-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Children's Oncology Group Enrollment Testing, FISH, Varies; or COGMF / Acute Myeloid Leukemia (AML), Children's Oncology Group Enrollment Testing, FISH, Varies, based on the patient's protocol.

If limited congenital infantile leukemia FISH probes are preferred, order CILMF / Congenital Infantile Leukemia, Specified FISH, Varies.

At follow-up, targeted FISH probes can be evaluated based on the abnormalities identified in the diagnostic study. Order CILMF / Congenital Infantile Leukemia, Specified FISH, Varies and request specific probes or abnormalities.

For testing paraffin-embedded tissue samples from patients with congenital infantile leukemia, order CILPF / Congenital Infantile Leukemia, FISH, Tissue.

Additional Testing Requirements

At diagnosis, conventional cytogenetic studies (CHRBM / Chromosome Analysis, Hematologic Disorders, Bone Marrow) and this panel should be performed.

Shipping Instructions

Advise Express Mail or equivalent if not on courier service.

Necessary Information

A reason for testing and a flow cytometry and/or a bone marrow pathology report should be submitted with each specimen. The laboratory will not reject testing if this information is not provided; however, appropriate testing and interpretation may be compromised or delayed. If not provided, an appropriate indication for testing may be entered by Mayo Clinic Laboratories.

Specimen Required

Submit only 1 of the following specimens:

Preferred
Specimen Type: Bone marrow
Container/Tube:
Preferred: Yellow top (ACD)
Acceptable: Green top (heparin) or lavender top (EDTA)
Specimen Volume: 2-3 mL
Collection Instructions:
1. It is preferable to send the first aspirate from the bone marrow collection.
2. Invert several times to mix bone marrow.
3. Send bone marrow specimen in original tube. **Do not aliquot.**
Acceptable
Specimen Type: Whole blood
Container/Tube:
Preferred: Yellow top (ACD)
Acceptable: Green top (heparin) or lavender top (EDTA)
Specimen Volume: 6 mL
Collection Instructions:
1. Invert several times to mix blood.
2. Send whole blood specimen in original tube. **Do not aliquot.**

Forms

If not ordering electronically, complete, print, and send a Hematopathology/Cytogenetics Test Request (T726) with the specimen.

Specimen Minimum Volume

Blood: 2 mL
Bone Marrow: 1 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Refrigerated		

Clinical & Interpretive

Clinical Information

While pediatric leukemia is the most common malignancy affecting children, acute leukemia occurring prior to the age of 18 months (infant leukemia) or occurring within the first 3 months of life (congenital leukemia) is relatively rare in occurrence. The incidence of congenital and infant acute leukemia cases (through 12 months of age) is estimated at only 30 to 40 cases/million/year, with the majority comprising infant cases. Nearly all cases of congenital and infant acute leukemia represent either acute myeloid leukemia (AML) or B-cell acute lymphoblastic leukemia/lymphoma (B-ALL/LBL) with only very rare cases of T-cell acute lymphoblastic leukemia/lymphoma identified in this age group.

Characteristic genetic abnormalities have been identified in both the congenital acute leukemia and infant acute leukemia setting, each with uniquely associated clinical-pathologic correlations. Rare but important patients with KAT6A/CREBBP translocations and congenital acute leukemia have been described with spontaneously remitting AML despite the lack of therapeutic intervention. In addition, transient abnormal myelopoiesis associated with Down syndrome is another common manifestation encountered in the neonatal setting that can be associated with the development of infant acute leukemia. In contrast, nearly 80% of infant acute leukemia cases are associated with MLL(KMT2A) translocation events with varying percentages of translocation partners based on an AML versus B-ALL/LBL presentation.

Due to the underlying genetic heterogeneity associated with both congenital and infant leukemia and the important prognostic, diagnostic and occasional therapeutic targets identified, appropriate genetic characterization of this uncommon acute leukemia presentation is critical. These thorough fluorescence in situ hybridization (FISH) panels have been developed by Mayo Clinic Laboratories to interrogate the more common AML and B-ALL abnormalities associated with both congenital and infant acute leukemias. These FISH probes have been validated both in bone marrow/blood (this test) and in paraffin (CILPF / Congenital Infantile Leukemia, FISH, Tissue), since a significant minority of these patients present clinically with isolated extramedullary (tissue) manifestations (ie, myeloid sarcoma).

Reference Values

An interpretive report will be provided.

Interpretation

A neoplastic clone is detected when the percent of cells with an abnormality exceeds the normal reference range for any given probe.

The absence of an abnormal clone does not rule out the presence of a neoplastic disorder.

Cautions

This test is not approved by the US Food and Drug Administration, and it is best used as an adjunct to clinical and pathologic information.

Fluorescence in situ hybridization (FISH) is not a substitute for conventional chromosome studies because the latter detects chromosome abnormalities associated with other hematological disorders that would be missed by this FISH panel test.

Bone marrow is the preferred sample type for this FISH test. If bone marrow is not available, a blood specimen may be used if there are neoplastic cells in the blood specimen (as verified by a hematopathologist).

Supportive Data

Each probe was independently tested and verified on unstimulated peripheral blood and bone marrow specimens. Normal cutoffs were calculated based on the results of 25 normal specimens. Each probe set was evaluated to confirm the probe set detected the abnormality it was designed to detect.

Clinical Reference

1. Swerdlow SH, Campo E, Harris NL, et al, eds: WHO Classification of Tumours. Vol 2. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. IARC Press; 2017
2. Tomizawa D: Recent progress in the treatment of infant acute lymphoblastic leukemia. Pediatr Int. 2015 Oct;57(5):811-819. doi: 10.1111/ped.12758
3. Inaba H, Zhou Y, Abla O, et al: Heterogeneous cytogenetic subgroups and outcomes in childhood acute megakaryoblastic leukemia: a retrospective international study. Blood. 2015 Sep 24;126(13):1575-1584. doi: 10.1182/blood-2015-02-629204
4. Coenen EA, Zwaan CM, Reinhardt D, et al: Pediatric acute myeloid leukemia with t(8;16)(p11;p13), a distinct clinical and biological entity: a collaborative study by the International-Berlin-Frankfurt-Munster AML-study group. Blood. 2013 Oct 10;122(15):2704-2713. doi: 10.1182/blood-2013-02-485524

Performance

Method Description

This test is performed using commercially available and laboratory-developed probes. Gain or loss of chromosomes 4, 5, 7, 8, 13, 17, and 21 are detected using enumeration strategy probes. Deletion of the *CDKN2A* locus on chromosome 9, *TP53* on chromosome 17, and deletion of *IKZF1* on chromosome 7 are detected using an enumeration strategy.

Rearrangements involving the following genes: *MLL* (*KMT2A*), *NUP98, ETV6, CBFB, RARA, ABL2, PDGFRB, MYC, JAK2*, *ABL1, IGH, CRLF2, P2RY8, TAL1/STIL, TRB,* and *TRAD* are detected using a dual-color break-apart (BAP) strategy probe. If a *MYC* gene region separation is identified, break-apart BCL2 and BCL6 will be evaluated using a dual-color break-apart (BAP) strategy probe. Dual-color, dual-fusion fluorescence in situ hybridization (D-FISH) strategy probe sets are used to detect inv(3), inv(16), t(8;21), t(15;17), t(6;9), t(8;16), t(3;21), t(1;3), t(1;22), t(7;11), t(7;12), t(9;22), t(12;21), t(1;19), t(5;14), t(9;22), t(10;11), and in reflex testing when a rearrangement of the *MLL, TRB*, *TRAD* gene region is observed. Amplification of *ABL1* (9q34) or *RUNX1* (iAMP21; 21q22) is detected using a D-FISH probe strategy. For enumeration and BAP strategy probe sets, 100 interphase nuclei are scored; 200 interphase nuclei are scored when D-FISH probes are

used. All results are expressed as the percent abnormal nuclei.(Unpublished Mayo method)

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
7 to 10 days

Specimen Retention Time
4 weeks

Performing Laboratory Location
Rochester

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification
This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
88271 x 8, 88275 x 4, 88291-FISH Probe, Analysis, Interpretation; 4 probe sets
88271 x 2, 88275-FISH Probe, Analysis; each additional probe set (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
CILDF	Cong Infantile Leukemia, Diag FISH	In Process

Result ID	Test Result Name	Result LOINC® Value
609598	Result Summary	50397-9
609599	Interpretation	69965-2
609600	Result Table	93356-4
609601	Result	62356-1
GC083	Reason for Referral	42349-1

GC084	Specimen	31208-2
609602	Source	31208-2
609603	Method	85069-3
609604	Additional Information	48767-8
609605	Disclaimer	62364-5
609606	Released By	18771-6