MAYO CLINIC LABORATORIES

Test Definition: COGBF

B-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Children's Oncology Group Enrollment Testing, FISH, Varies

Overview

Useful For

Detecting, at diagnosis, recurrent common chromosome abnormalities associated with B-cell acute lymphoblastic leukemia/lymphoma (B-ALL) and BCR::ABL1-like acute lymphoblastic leukemia/lymphoma in patients being considered for enrollment in Children's Oncology Group (COG) clinical trials and research protocols

As an adjunct to conventional chromosome studies in pediatric patients with B-ALL and Ph-like ALL being considered for enrollment in COG protocols

Evaluating specimens in which chromosome studies are unsuccessful

This test **should not be used** to screen for residual B-ALL/LBL

Reflex Tests

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

Testing Algorithm

This test is only performed on specimens from pediatric patients being considered for enrollment in a Children's Oncology Group (COG) protocol. Additional charges will be incurred for all reflex or additional probe sets performed. Analysis charges will be incurred based on the number of cells analyzed per probe set. If no cells are available for analysis, no analysis charges will be incurred.

This test is performed as panel testing only using the following analysis algorithm.

The **diagnostic** pediatric/young adult B-cell acute lymphoblastic leukemia/lymphoma (B-ALL) fluorescence in situ hybridization (FISH) panel includes testing for the following abnormalities using the FISH probes listed:
CRLF2 (Xp22.33) or (Yp11.32) rearrangement, CRLF2 break-apart probe set
t(1;19)(q23;p13) or *TCF3::PBX1* fusion, PBX1/TCF3 probe set
Hyperdiploidy or +4,+10,+17, D4Z1/D10Z1/D17Z1 probe set
t(8;14)(q24.21;q32) or *IGH::MYC* fusion, MYC/IGH probe set
t(8q24.21;var) or *MYC* rearrangement, MYC break-apart probe set
t(9;22)(q34;q11.2) or *BCR::ABL1* fusion, ABL1/BCR probe set
t(11q23;var) or *KMT2A* rearrangement, KMT2A break-apart probe set
t(12;21)(p13;q22) or *ETV6::RUNX1* fusion or iAMP21, ETV6/RUNX1 probe set
t(14q32;var) or *IGH* rearrangement, IGH break-apart probe set

If results for the initial panel are negative or demonstrate nonclassical abnormalities, the B-ALL with *BCR*::*ABL1*-like features panel will be performed as a secondary panel. This panel includes testing for the following kinase activating chromosome abnormalities, using the FISH probes listed below, as well as *IKZF1* deletion, which often accompanies *BCR*::*ABL1*-like ALL.
t(1q25;var) or *ABL2* rearrangement, ABL2 break-apart probe set
t(5q32;var) or *PDGFRB* rearrangement, PDGFRB break-apart probe set
t(9p24.1;var) or *JAK2* rearrangement, JAK2 break-apart probe set
t(9q34;var) or *ABL1* rearrangement, ABL1 break-apart probe set
7p- or *IKZF1* deletion, IKZF1/CEP7 probe set

Appropriate ancillary probes may be performed at consultant discretion to render comprehensive assessment. Any additional probes used will have the results included within the final report and will be performed at an additional charge. In the following situations, additional (reflex) testing may be performed at the laboratory's discretion and may be influenced by available karyotype results or other FISH testing.

When a *KMT2A* rearrangement is identified, testing with 1 or more dual-fusion (D-FISH) probe sets in an attempt to identify the translocation partner for the following abnormalities:
t(4;11)(q21;q23) or *KMT2A::AFF1* fusion, AFF1/KMT2A probe set
t(6;11)(q27;q23) or *KMT2A::AFDN* ;fusion, AFDN/KMT2A probe set
t(9;11)(p22;q23) or *KMT2A::MLLT3* fusion, MLLT3/KMT2A probe set
t(10;11)(p12;q23) or *KMT2A::MLLT10* fusion, MLLT10/KMT2A probe set
t(11;19)(q23;p13.1) or *KMT2A::MLLT1* fusion, KMT2A/ELL probe set
t(11;19)(q23;p13.3) or *KMT2A::ELL* fusion, KMT2A/MLLT1 probe set

When an unbalanced *CRLF2* rearrangement is identified concurrently with an IGH rearrangement, testing will be performed using the CRLF2/IGH probe set to identify a potential t(X;14)(p22.33;q32) or t(Y;14)(p11.32;q32) cryptic translocation may be performed.

In the absence of *BCR::ABL1* fusion, when an extra or atypical ABL1 signal is identified, testing using the ABL1 break-apart probe set to identify a potential variant translocation involving *ABL1,* t(9;var)(q34;?) may be performed.

In the absence of *ETV6::RUNX1* fusion, when an extra ETV6 signal is identified, testing using the ETV6 break-apart probe set to evaluate for the presence or absence of a potential rearrangement involving *ETV6* t(12;var)(p13;?) may be performed.

When a *MYC* rearrangement is identified, both the BCL2 and BCL6 break-apart probe sets will be performed.

If an unbalanced rearrangement of BCL2 is identified, testing using the IGH/BCL2 probe to identify a potential t(14;18)(q32;q21) or *IGH::BCL2* fusion may be performed.

For more information see B-Lymphoblastic Leukemia/Lymphoma Genetic Testing Guidelines.

Special Instructions

- B-Lymphoblastic Leukemia/Lymphoma Genetic Testing Guidelines

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 pediatric patients being considered for enrollment in a Children's Oncology Group (COG) protocol. If this test is ordered and the laboratory is informed that the patient is not on a COG protocol, this test will be canceled and automatically reordered by the laboratory as BALFP / Pediatric B-Lymphoblastic Leukemia/Lymphoma panel, FISH, Varies.

At follow-up, conventional cytogenetic studies (CHRBM / Chromosome Analysis, Hematologic Disorders, Bone Marrow) and targeted B-cell ALL fluorescence in situ hybridization probes can be evaluated based on the abnormalities identified in the diagnostic study. Order BALMF / B-Cell Acute Lymphoblastic Leukemia/Lymphoma (ALL), Specified FISH, Varies and request specific probes or abnormalities.

Additional Testing Requirements

At diagnosis, conventional cytogenetic studies (COGBM / Chromosome Analysis, Hematologic Disorders, Children's Oncology Group Enrollment Testing, Bone Marrow) and this panel should be performed. If there is limited specimen available, only this test will be performed.

Shipping Instructions

Advise Express Mail or equivalent if not on courier service.

Necessary Information

1. Children's Oncology Group (COG) registration number and protocol **number** should be submitted with each specimen. The laboratory will not reject testing if this information is not provided; however, appropriate testing may be compromised or delayed.

2. A reason for testing must be provided. If this information is not provided, an appropriate indication for testing may be entered by Mayo Clinic Laboratories.

3. 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, but appropriate testing and interpretation may be compromised or delayed.
4. If the patient has received an opposite sex bone marrow transplant, note this information on the request.
5. If the patient has Down syndrome, note this information on the request.

Specimen Required

Submit only 1 of the following specimens:

Preferred
Specimen Type: Bone marrow
Container/Tube:
Preferred: Yellow top (ACD)
Acceptable: Green top (sodium heparin) or lavender top (EDTA)
Specimen Volume: 2 to 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 (sodium 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 aChildren's Oncology Group Test Request (T829) with the specimen.

Specimen Minimum Volume

Bone marrow: 1 mL; Whole blood: 2 mL

Reject Due To

Fresh tissue	Reject

Specimen Stability Information

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

Clinical & Interpretive

Clinical Information

In the United States, the incidence of acute lymphoblastic leukemia (ALL) is roughly 6000 new cases per year (as of 2019). ALL accounts for approximately 70% of all childhood leukemia cases (aged 0-19 years), making it the most common type of childhood cancer. Approximately 85% of pediatric cases of ALL are B-cell lineage (B-ALL) and 15% are T-cell lineage (T-ALL). It has a peak incidence at age 2 to 5 years. The incidence decreases with increasing age, before increasing again at around age 50 years. ALL is slightly more common in male patients than female patients. There is an increased incidence of ALL in individuals with Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, X-linked agammaglobulinemia, and severe combined immunodeficiency. The overall cure rate for ALL in children is about 90% and about 45% to 60% of adults have long-term disease-free survival. *CRLF2/IGH* rearrangements are more commonly observed in patients with Down syndrome or of Hispanic descent.

Specific genetic abnormalities are identified in most cases of B-ALL, either by conventional chromosome studies or fluorescence in situ hybridization (FISH) studies. For more than 25 years, the Mayo Clinic Genomics Laboratory has served as a Children's Oncology Group (COG) accredited laboratory for the performance of cytogenetic testing in pediatric patients being considered for enrollment in COG clinical trials and research. The laboratory is highly equipped to perform the time sensitive and critical cytogenetic testing necessary to assign risk stratification and facilitate enrollment in COG protocols.

Each of the B-ALL genetic subgroups is important to detect and can be critical prognostic markers. The decision for early transplantation may be made if t(9;22)(q34;q11.2), *MLL* (*KMT2A*) translocations, *RUNX1* duplication/amplification (iAMP21) or a hypodiploid clone is identified. In contrast, if the *ETV6/RUNX1* fusion is detected by FISH or hyperdiploidy is identified by chromosome studies, the patient has a favorable prognosis and transplantation is rarely considered.

A newly recognized World Health Organization entity *BCR-ABL1*-like ALL, also known as Philadelphia chromosome-like acute lymphoblastic leukemia (Ph-like ALL), is increasing in importance due to the poor prognosis seen in pediatric, adolescent, and young adult ALL. Common features of this entity involve rearrangements with tyrosine kinase genes involving the following genes: *ABL2, PDGFRB, JAK2, ABL1, CRLF2,* and *P2RY8.* Deletion of *IKZF1* often accompanies this entity. Some patients who have failed conventional therapies have demonstrated favorable responses to targeted therapies in clinical trials when rearrangements involving these specific gene regions have been identified.

Evaluation of the *MYC* gene region is included in all diagnostic B-ALL panels to evaluate for Burkitt lymphoma. If a positive result is obtained, additional testing for the *BCL2* and *BCL6* gene regions will be performed.

Metaphase FISH confirmation of classic translocations that are cryptic and not visually detectable by chromosome

analysis [ie, t(12;21) associated with *ETV6/RUNX1* fusion] is performed, as required by COG, and is included as part of the electronic case submission by the Mayo Clinic Genomics Laboratory to COG for central review.

Additional cytogenetic techniques such as chromosomal microarray (CMAH / Chromosomal Microarray, Hematologic Disorders, Varies) may be helpful to resolve questions related to ploidy (hyperdiploid clone vs doubled hypodiploid clone) or to resolve certain clonal structural rearrangements such as the presence or absence of intra-chromosomal amplification of chromosome 21 (iAMP21). A summary of the characteristic chromosome abnormalities identified in B-ALL is listed in the following table.

Table. **Common Chromosome Abnormalities in B-cell Acute Lymphoblastic Leukemia/Lymphoma**

Leukemia type	**Cytogenetic change**	**Typical demographic**	**Risk category**
B-acute lymphoblastic leukemia/lymphoma	t(12;21)(p13;q22), *ETV6::RUNX1*	Pediatric	Favorable
	Hyperdiploidy	Pediatric	Favorable
	t(1;19)(q23;p13.3), *TCF3::PBX1*	Pediatric	Intermediate to favorable
	t(9;22)(q34;q11.2), *BCR::ABL1*	All ages	Unfavorable
	iAMP21, *RUNX1*	Pediatric	Unfavorable
	t(11q23;var), *KMT2A* rearrangement	All ages	Unfavorable
	t(4;11)(q21;q23), *KMT2A::AFF1*	All ages	Unfavorable
	t(6;11)(q27;q23), *KMT2A::AFDN*	All ages	Unfavorable
	t(9;11)(p21.3;q23), *KMT2A::MLLT3*	All ages	Unfavorable
	t(10;11)(p12;q23), *KMT2A::MLLT10*	All ages	Unfavorable
	t(11;19)(q23;p13.3), *KMT2A::MLLT1*	All ages	Unfavorable
	t(11;19)(q23;p13.1), *KMT2A::ELL*	All ages	Unfavorable
	t(14q32;var), *IGH* rearrangement	All ages	Variable
	t(X;14)(p22;q32)/t(Y;14)(p11;q32), *IGH::CRLF2*	Adolescent/ young adult	Unfavorable
	t(Xp22.33;var) or t(Yp11.32;var), *CRLF2* rearrangement	All ages	Unfavorable
	t(8q24.21;var), *MYC* rearrangement *representing Burkitt or other mature B-cell lymphoma	Pediatric/ adolescent/ young adult	
	Complex karyotype (> or =4 abnormalities)	Adult	Unfavorable
	Low hypodiploidy/near-triploidy	Adult	Unfavorable
	Near-haploid/hypodiploid	All ages	Unfavorable
	del(7p) *IKZF1* deletion	All ages	Unfavorable in absence of *ERG* deletion

BCR::ABL1-like acute lymphoblastic leukemia/lymphoma	t(1q25;var), *ABL2* rearrangement	Pediatric/ adolescent/ young adult	Unfavorable
	t(5q32;var), *PDGFRB* rearrangement		
	t(9p24.1;var), *JAK2* rearrangement		
	t(9q34;var), *ABL1* rearrangement		
	t(Xp22.33;var) or t(Yp11.32;var), *CRLF2* rearrangement		
	t(Xp22.33;var) or t(Yp11.32;var), *P2RY8* rearrangement		

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 set.

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 in a targeted B-cell acute lymphoblastic leukemia/lymphoma FISH panel test.

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

If no FISH signals are observed post-hybridization, the case will be released indicating a lack of FISH results.

Clinical Reference

1. Moorman AV, Harrison CJ, Buck GAN, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood. 2007;109(8):3189-3197
2. Moorman AV. The clinical relevance of chromosomal and genetic abnormalities in B-cell precursor acute lymphoblastic leukemia. Blood Rev. 2012;26(3):123-135
3. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med. 2014;371(11):1005-1015
4. Mullighan CG. The genomic landscape of acute lymphoblastic leukemia in children and young adults. Hematology Am Soc Hematol Educ Program. 2014;2014(1):174-180. doi:10.1182/asheducation-2014.1.174

5. 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

Performance

Method Description

This test is performed using commercially available and laboratory-developed probes. Deletion of *IKZF1* on chromosome 7 and gain or losses of chromosomes 4, 10, and 17 are detected using enumeration strategy probes. Rearrangements involving *CRLF2, ABL2, BCL3, PDGFRB, MYC, JAK2*, *ABL1, MLL, ETV6, IGH,* and *BCL2* are detected using dual-color break-apart (BAP) strategy probes. Dual-color, dual-fusion fluorescence in situ hybridization (D-FISH) strategy probe sets are used to detect t(X/Y;14), t(1;19), t(8;14), t(9;22), t(12;21), t(14;18), and in reflex testing when a rearrangement of the *KMT2A* gene is detected. Amplification of the *RUNX1* gene region is detected using a D-FISH probe to enumerate copies of the RUNX1 probe. For enumeration and BAP strategy probe sets, 100 interphase nuclei are scored; 200 interphase nuclei are scored when D-FISH probes are used. 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

Mayo Clinic Laboratories - Rochester Main Campus

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 account representative. 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. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

88271 x 2, 88275, 88291-FISH Probe, Analysis, Interpretation; 1 probe set
88271 x 2, 88275-FISH Probe, Analysis; each additional probe set (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
COGBF	COG, ALL (B-cell), FISH	102100-5

Result ID	Test Result Name	Result LOINC® Value
602296	Result Summary	50397-9
602297	Interpretation	69965-2
602298	Result Table	93356-4
602299	Result	62356-1
GC019	Reason for Referral	42349-1
GC020	Specimen	31208-2
602301	Source	31208-2
602302	Method	85069-3
602303	Additional Information	48767-8
602304	Disclaimer	62364-5
602305	Released By	18771-6