Ph-Like Acute Lymphoblastic Leukemia Panel by FISH

Indications for Ordering

- Recommended FISH panel for individuals suspected of having *BCR-ABL1*-like B-cell acute lymphoblastic leukemia (B-ALL) (Ph-like ALL)
- Order when other major prognostic markers (eg, *BCR-ABL1, ETV6/RUNX1*) are negative
- Aid in diagnosis of *BCR-ABL1*-like B-ALL with chromosomal rearrangement involving *CRLF2, JAK2, EPOR, CSF1R, ABL1, ABL2, PDGFRB*
- Provide risk stratification and therapeutic management of patients with *BCR-ABL1*-like B-ALL

Test Description - Methodology

- Performed on bone marrow (BM) or peripheral blood cells on unstimulated cultures from either direct harvest or 24-hour culture
- Multiple fluorescence in situ hybridization (FISH) probes target specific genes

Tests to Consider

Primary test(s)

Ph-Like Acute Lymphocytic Leukemia (ALL) Panel by FISH 3000455

- Diagnosis, prognosis, and monitoring of *BCR-ABL1*-like B-ALL
- Probes included in this panel
  - *CRLF2* rearrangement
  - *JAK2* rearrangement
  - *EPOR* rearrangement
  - *CSF1R* rearrangement
  - *ABL1* rearrangement
  - *ABL2* rearrangement
  - *PDGFRB* rearrangement
- To order probes individually, see Chromosome FISH, Interphase

Related test(s)

Leukemia/Lymphoma Phenotyping by Flow Cytometry 2008003

- Aid in evaluation of hematopoietic neoplasms
- Monitor therapy in patients with established diagnosis of hematopoietic neoplasms

Chromosome Analysis, Bone Marrow 2002292

- Diagnosis, prognosis, and monitoring of hematopoietic neoplasms

Chromosome Analysis, Bone Marrow with Reflex to Genomic Microarray 2007130

- Diagnosis, prognosis, and monitoring of hematopoietic neoplasms
- Microarray performed when karyotype results are reported as "normal" or "no growth"

Cytogenomic SNP Microarray – Oncology 2006325

- Preferred test for fresh specimens at time of diagnosis to detect prognostically important genomic abnormalities in leukemias/lymphomas and solid tumors involving
  - Loss/gain of DNA
  - Loss of heterozygosity (LOH)
- Monitor disease progression and response to therapy

Acute Lymphocytic Leukemia (ALL) panel by FISH, Pediatric 2002719

- Risk stratification and therapeutic management in children with newly diagnosed B-ALL

Acute Lymphocytic Leukemia (ALL) panel by FISH, Adult 2002647

- Risk stratification and therapeutic management in adults with newly diagnosed B-ALL

Chromosome FISH, Interphase 2002298

- Use to order individual or multiple FISH probes if standard FISH panels are not desired
- Specific FISH probes must be requested
  - *CRLF2*
  - *JAK2*
  - *EPOR*
  - *CSF1R*
  - *ABL1*
  - *ABL2*
  - *PDGFRB*

Disease Overview

Incidence

- B-ALL occurs in 1.6/100,000 individuals per year
- *BCR-ABL1*-like ALL (Ph-like ALL) occurs in
  - 10% of children with standard-risk B-ALL
  - 15% of children with NCI-defined, high-risk B-ALL
  - 21% of adolescents with B-ALL
  - 27% of young adults with B-ALL
  - 20% of adults with B-ALL

Treatment issues

- Clinical trials being developed to test hypothesis that treatment with ABL-class fusions (*ABL1*, *ABL2*, *PDGFRB*, *CSF1R* rearrangement) with tyrosine kinase inhibitors will greatly improve typically poor outcome
- Patients with *JAK* translocations (*CRLF2, JAK2, EPOR* rearrangement) may be candidates for treatment with JAK inhibitors

Prognostic issues

Overall, patients with *BCR-ABL1*-like ALL have a poor prognosis.

Genetics

Genes – *CRLF2, JAK2, EPOR, CSF1R, ABL1, ABL2, PDGFRB*

Structure/Function

- *CRLF2* rearrangement
  - Results from either an interstitial deletion within Xp22.3 or Yp11.3, which juxtaposes *CRLF2* to the promoter of the *P2RY8* gene or a translocation; involves *IGH*
  - Results in *CRLF2* overexpression
  - Accounts for about half of *BCR-ABL1*-like ALL
- *JAK2* rearrangement
  - At least 10 fusion partners have been reported
  - Results in constitutive activation of JAK/STAT pathways
  - Accounts for 15% of young adults with *BCR-ABL1*-like ALL and 5% of children and adolescents with *BCR-ABL1*-like ALL
- *EPOR* rearrangement
  - Results from the juxtaposition of the *EPOR* gene to the enhancer regions of immunoglobulin heavy or κ loci
  - Results in constitutive activation of JAK/STAT pathways
  - Accounts for 4% of *BCR-ABL1*-like ALL
- Rearrangements of *ABL*-class genes
  - *CSF1R* rearrangement
  - *ABL1* rearrangement
  - *ABL2* rearrangement
  - *PDGFRB* rearrangement
  - Accounts for 13% of *BCR-ABL1*-like ALL

Test Interpretation

Results

- Normal – no evidence of rearrangement involving *CRLF2, JAK2, EPOR, CSF1R, ABL1, ABL2,* or *PDGFRB*
- Abnormal – one of the described rearrangements detected

Limitations

- Panel detects only the specific aberrations targeted by the probes
- Chromosome alterations outside the regions complementary to these FISH probes will not be detected

References

- Swerdlow SH, Campo E, et al: WHO classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC: Lyon 2017
- Tran TH1, Loh ML. Ph-like acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2016 Dec 2; 2016(1):561-566