

# Lymphoma (Aggressive) Panel by FISH

## Indications for Ordering

- Aid in diagnosis of aggressive large B-cell lymphoma with intermediate features between Burkitt lymphoma and diffuse large B-cell lymphoma (DLBCL)
- Confirmation of suspected double hit lymphoma

## Test Description

Fluorescence in situ hybridization (FISH)

- FISH probes include
  - *MYC*
  - *IGH*
  - *BCL2*
  - *BCL6*

## Tests to Consider

### Typical testing strategy

- Lymph node biopsy with morphologic and immunohistochemical evaluation
- Leukemia/lymphoma phenotyping by flow cytometry
- In aggressive B-cell lymphomas with a high proliferation index and/or with unusual morphologic, phenotypic, or clinical features
  - Tests for *MYC*, *BCL2*, and *BCL6*

### Panel tests

#### [Aggressive B-Cell Lymphoma FISH Reflex, Tissue 2012710](#)

- Formalin-fixed, paraffin-embedded (FFPE) tissue specimens
- If *MYC* (8q24) Gene Rearrangement by FISH is positive, then *IGH-BCL2* Fusion, t(14;18) by FISH will be added
- If *IGH-BCL2* Fusion, t(14;18) by FISH is negative, then *BCL6* (3q27) Gene Rearrangement by FISH will be added

#### [Lymphoma \(Aggressive\) Panel by FISH 2002650](#)

- Bone marrow (BM) or whole blood specimens; other specimens may be acceptable
- FFPE and frozen specimens unacceptable

### Individual tests

- FFPE tissue specimens

#### [MYC \(8q24\) Gene Rearrangement by FISH 2002345](#)

- Detects all *MYC* rearrangements, including t(8;14), t(2;8), and t(8;22)

#### [IGH-MYC t\(8;14\) by FISH 2001538](#)

#### [IGH-BCL2 Fusion, t\(14;18\) by FISH 2001536](#)

#### [BCL6 \(3q27\) Gene Rearrangement by FISH 2010107](#)

## Related tests

### [Leukemia/Lymphoma Phenotyping by Flow Cytometry 2008003](#)

- Aids in diagnosis of hematopoietic neoplasms

### [Chromosome FISH, Interphase 2002298](#)

- Specific probes must be requested
  - *MYC* break apart, *BCL2*, *BCL6*
- Fresh tissue specimens only

### [Chromosome Analysis, Bone Marrow 2002292](#)

- Diagnosis, prognosis, and monitoring of lymphoma in BM

### [Chromosome Analysis, Solid Tumor 2002296](#)

- May identify additional, useful cytogenetic abnormalities in tissues that are not targeted by FISH assays

## Disease Overview

### Prognostic issues

- B-cell lymphomas with 2 recurrent chromosomal breakpoint aberrations are referred to as double hit lymphomas and are classified as high-grade B-cell lymphomas with *MYC* and *BCL2* and/or *BCL6* (WHO 2016)
  - Usually involve *MYC* oncogene in association with *BCL2*, less often with *BCL6*
- Lymphomas with three translocations (usually *MYC/BCL2/BCL6*) are referred to as triple hit lymphomas
  - Rare
- Important to identify these lymphomas in diagnostic evaluation of morphologically aggressive lymphomas
  - They are highly resistant to standard chemotherapy
    - Poor outcome independent of regimen intensity or inclusion of rituximab
  - Individuals have shortened survival compared with those having Burkitt lymphoma or international prognostic index (IPI)-matched DLBCL

## Genetics

Breakpoints Used to Identify Double Hit or Triple Hit Lymphomas			
Oncogene	Break apart <i>MYC</i>	<i>BCL2</i>	<i>BCL6</i>
Locus	8q24	18q21	3q27
Biology	Accelerator of cell proliferation	Apoptosis inhibitor	Transcription modifier
Cytogenetics	Any <i>MYC</i> translocation	<i>BCL2/IGH</i> – t(14;18)(q32;q21)	<ul style="list-style-type: none"> <li><i>BCL6</i> most commonly has a non-IG translocation partner – <i>BCL6</i> (3q27)</li> <li>Uncommon partner – <i>BCL6/IGH</i> [t(3;14)(q27;q32)]</li> </ul>
Specific lymphomas associated with translocation	<ul style="list-style-type: none"> <li>Burkitt lymphoma</li> <li>DLBCL</li> <li>Aggressive B-cell lymphoma not otherwise specified (NOS)</li> </ul>	<ul style="list-style-type: none"> <li>Follicular lymphoma</li> <li>DLBCL</li> </ul>	<ul style="list-style-type: none"> <li>Follicular lymphoma</li> <li>DLBCL</li> <li>High grade lymphomas (rare)</li> </ul>

## Test Interpretation

### Results

- Abnormal – t(14;18)(q32;q21) (*IGH/BCL2* translocation) or other rearrangements involving *BCL6* and/or *MYC* detected
  - Presence of  $\geq 2$  translocations associated with poor prognosis in mature B-cell lymphomas
  - Single rearrangements can provide diagnostic and/or prognostic information in the appropriate context
- Normal – t(14;18)(q32;q21) (*IGH/BCL2* translocation) or other rearrangements involving *BCL6* or *MYC* not detected

### Limitations

- Interpretation of results requires correlation with morphology and immunophenotype
- MYC* and/or *BCL2* overexpression can be due to other mechanisms not detected by this test
- Chromosome alterations outside probe region are not detected