Template for Reporting Results of Biomarker Testing of Specimens From Patients With Diffuse Large B-Cell Lymphoma, Not Otherwise Specified (NOS)

Template web posting date: July 2015

Authors
Eric Duncavage, MD, FCAP
Department of Pathology and Immunology, Washington University School of Medicine, Saint Louis, Missouri
Ranjana H. Advani, MD
Oncology Division, Stanford University Medical Center, Stanford, California
Steven Agosti, MD, FCAP
Pathology & Laboratory Medicine Service, James A. Haley Veterans Affairs Medical Center, Tampa, Florida
Randa Alsabeh, MD, FCAP
Department of Pathology, Kaiser Permanente Medical Center, Los Angeles, California
Philip Foulis, MD, FCAP
Pathology & Laboratory Medicine Service, James A. Haley Veterans Affairs Medical Center, Tampa, Florida
Christine Gibson, CTR
Moffitt Cancer Center, Tampa, Florida
Loveleen Kang, MD, FCAP
Pathology & Laboratory Medicine Service, James A. Haley Veterans Affairs Medical Center, Tampa, Florida
Joseph D. Khoury, MD, FCAP
Department Hematopathology, Division of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas
L. Jeffrey Medeiros, MD, FCAP
Department of Hematopathology, Division of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas
Robert S. Ohgami, MD, PhD, FCAP
Department of Pathology, Stanford Hospital and Clinics, Stanford, California
Dennis P. O'Malley, MD, FCAP
Department of Pathology, Clarient Pathology Services, Aliso Viejo, California
Keyur P. Patel, MD, PhD, FCAP
Department Hematopathology, Division of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas
Carla Wilson, MD, PhD, FCAP
Department of Pathology, University of New Mexico Health Sciences Center, Albuquerque, New Mexico

For the Members of the Cancer Biomarker Reporting Committee, College of American Pathologists
© 2015 College of American Pathologists (CAP). All rights reserved.

The College does not permit reproduction of any substantial portion of these templates without its written authorization. The College hereby authorizes use of these templates by physicians and other health care providers in reporting results of biomarker testing on patient specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these templates for commercial purposes without the written consent of the College.

The CAP also authorizes physicians and other health care practitioners to make modified versions of the templates solely for their individual use in reporting results of biomarker testing for individual patients, teaching, and carrying out medical research for non-profit purposes.

The CAP further authorizes the following uses by physicians and other health care practitioners, in reporting on surgical specimens for individual patients, in teaching, and in carrying out medical research for non-profit purposes: (1) Dictation from the original or modified templates for the purposes of creating a text-based patient record on paper, or in a word processing document; (2) Copying from the original or modified templates into a text-based patient record on paper, or in a word processing document; (3) The use of a computerized system for items (1) and (2), provided that the template data is stored intact as a single text-based document, and is not stored as multiple discrete data fields.

Other than uses (1), (2), and (3) above, the CAP does not authorize any use of the templates in electronic medical records systems, pathology informatics systems, cancer registry computer systems, computerized databases, mappings between coding works, or any computerized system without a written license from the CAP.

Any public dissemination of the original or modified templates is prohibited without a written license from the CAP.

The College of American Pathologists offers these templates to assist pathologists in providing clinically useful and relevant information when reporting results of biomarker testing. The College regards the reporting elements in the templates as important elements of the biomarker test report, but the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these templates as educational tools to assist pathologists in the useful reporting of relevant information. It did not issue them for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the templates might be used by hospitals, attorneys, payers, and others. The College cautions that use of the templates other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

The inclusion of a product name or service in a CAP publication should not be construed as an endorsement of such product or service, nor is failure to include the name of a product or service to be construed as disapproval.
**CAP Diffuse Large B-Cell Lymphoma Biomarker Template Revision History**

**Version Code**
The definition of the version code can be found at www.cap.org/cancerprotocols.

**Version:** DLBCL_Biomarkers 1.0.0.1

**Summary of Changes**

**RESULTS**

The following note was added:

*Note: If a marker is tested by more than one method (e.g., polymerase chain reaction and immunohistochemistry), please document the additional result(s) and method(s) in the Comments section of the report.*

The following data elements were changed to “select all that apply”:

- **Protein Expression** (by immunohistochemistry [IHC] or flow cytometry)
- **Chromosomal Abnormalities** (by fluorescence in situ hybridization [FISH])

**METHODS**

The following data element was changed to “select all that apply”:

- **Protein Expression**

Added the following data element and notes:

**COMMENT(S)**


All reported gene sequence variations should be identified following the recommendations of the Human Genome Variation Society (www.hgvs.org/mutnomen; accessed February 10, 2015).
Diffuse Large B-Cell Lymphoma Biomarker Reporting Template

Template web posting date: July 2015

Completion of the template is the responsibility of the laboratory performing the biomarker testing and/or providing the interpretation. When both testing and interpretation are performed elsewhere (eg, a reference laboratory), synoptic reporting of the results by the laboratory submitting the tissue for testing is also encouraged to ensure that all information is included in the patient’s medical record and thus readily available to the treating clinical team.

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL), NOT OTHERWISE SPECIFIED (NOS)

Select a single response unless otherwise indicated.

Note: Use of this template is optional.

+ SPECIMEN TYPE
  + ___ Peripheral blood
  + ___ Bone marrow
  + ___ Lymph Node (specify site): ________________
  + ___ Other (specify): ____________________

+ RESULTS

Note: If a marker is tested by more than one method (eg, polymerase chain reaction and immunohistochemistry), please document the additional result(s) and method(s) in the Comments section of the report.

+ Protein Expression (by immunohistochemistry [IHC] or flow cytometry) (select all that apply) (Notes A and B)
  + ___ BCL2
    + ___ Not detected
    + ___ Detected
  + ___ CD5
    + ___ Not detected
    + ___ Detected
  + ___ CD20
    + ___ Not detected
    + ___ Detected
  + ___ CD30
    + ___ Not detected
    + ___ Detected
  + ___ Ki-67
    + ___ Not detected
    + ___ Detected
  + ___ MYC
    + ___ Not detected
    + ___ Detected
  + ___ Other marker(s) tested (specify): ____________________
    + ___ Not detected
    + ___ Detected

+ Data elements preceded by this symbol are not required.
+ **Subtype Classification (Note C)**
  + ___ Germinal center-like
  + ___ Non-germinal center-like

+ **Chromosomal Abnormalities (by fluorescence in situ hybridization [FISH]) (select all that apply) (Note B)**
  + ___ MYC rearrangement
    + ___ Not detected
    + ___ Detected
    + ___ Other (specify): ____________________
  + ___ BCL2 rearrangement
    + ___ Not detected
    + ___ Detected
    + ___ Other (specify): ____________________
  + ___ BCL6 rearrangement
    + ___ Not detected
    + ___ Detected
    + ___ Other (specify): ____________________

+ **Other probes tested**
  + Specify probe: ____________________
  + Specify results: ____________________

+ **Cytogenetic testing complete karyotype (specify): ____________________

+ **Somatic Gene Mutations (by sequencing) (Note D)**
  + ___ Not detected
  + ___ Detected (specify variant): ____________________
  + ___ Other (specify): ____________________

+ **Other Markers Tested**
  + Specify marker: ____________________
  + Specify results: ____________________

+ **METHODS**

+ **Protein Expression (select all that apply) (Notes A and B)**
  + ___ IHC
    + ___ BCL2 (specify clone): ____________________
    + ___ CD5 (specify clone): ____________________
    + ___ CD20 (specify clone): ____________________
    + ___ CD30 (specify clone): ____________________
    + ___ Ki-67 (specify clone): ____________________
    + ___ MYC (specify clone): ____________________
    + ___ Other(s) (specify clone): ____________________
  + ___ Flow cytometry
    + ___ BCL2 (specify clone): ____________________
    + ___ CD5 (specify clone): ____________________
    + ___ CD20 (specify clone): ____________________
    + ___ CD30 (specify clone): ____________________
    + ___ Other(s) (specify clone): ____________________
  + ___ FISH
    + BCL2 probe:
      + ___ Break apart
      + ___ Fusion
Diffuse Large B-Cell Lymphoma • Biomarkers

+ **BCL6** probe:
  + ___ Break apart
  + ___ Fusion
+ **MYC** probe:
  + ___ Break apart
  + ___ Fusion

+ **Subtype Classification (Note C)**
  + ___ Hans (CD10, BCL-6, MUM1)
  + ___ Choi (GCET1, CD10, MUM1, BCL6, FOXP1)
  + ___ Tally (CD10, GCET1, MUM1, FOXP1, LMO2)
  + ___ Gene expression profiling (specify platform/method): ____________________________
  + ___ Other (specify): ____________________________

+ **Gene Sequencing (Note D)**
  + Gene sequencing platform (specify): ____________________________
  + Maximum sensitivity (variant allele frequency): ____________________________
  + Genes/exons sequenced (specify): ____________________________

+ **COMMENT(S)**
  ______________________________________________________________
  ______________________________________________________________

*Gene names should follow recommendations of The Human Genome Organisation (HUGO) Nomenclature Committee (www.genenames.org; accessed February 10, 2015).*

*All reported gene sequence variations should be identified following the recommendations of the Human Genome Variation Society (www.hgvs.org/mutnomen/; accessed February 10, 2015).*

+ Data elements preceded by this symbol are not required.
Explanatory Notes

A. Protein Expression
The antibodies listed are included in the template because they have therapeutic or prognostic significance.

CD20 assessment is mandatory for therapeutic planning because the standard therapy for diffuse large B-cell lymphoma (DLBCL) patients is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Knowledge of CD20 expression is therefore recommended as a justification for using rituximab.

CD30 assessment is recommended because of the potential utility of the anti-CD30 antibody drug conjugate, brentuximab vedotin. Approximately 10% to 15% of DLBCL cases express CD30, and these patients may be eligible for this agent if they fail standard therapy.

CD5 assessment is thought to be of prognostic value because a small subset (5%-10%) of DLBCL cases. Patients with CD5+ DLBCL have a more aggressive clinical course. These patients tend to be older and have elevated serum LDH levels, poorer performance status, and a higher frequency of central nervous system involvement.

MYC assessment by immunohistochemistry (IHC) is of prognostic value and needs to be evaluated in conjunction with conventional cytogenetic analysis or FISH to assess chromosome locus 8q24/MYC rearrangements. Approximately 10% of DLBCL cases carry MYC translocations, and up to 30% to 40% of cases overexpress MYC by IHC, with positivity defined in various studies as >40% or >50% positive cells. Therefore, MYC can be overexpressed via mechanisms other than translocation.

The combination of MYC and BCL2 and/or BCL6 gene rearrangements as shown by conventional cytogenetic or FISH analysis is known as double (or triple) hit lymphoma. Patients with this combination of abnormalities have a poor prognosis.

MYC positivity by IHC may be useful as a screen for MYC translocations as it is rare for a translocation positive case to be negative for MYC by IHC. MYC expression combined with BCL2 overexpression is also associated with a poorer prognosis (so-called IHC double hit lymphoma).

BCL2 assessment also has prognostic value and needs to be evaluated in conjunction with conventional cytogenetic analysis or FISH to assess chromosome locus 8q24/MYC rearrangements. In patients treated with CHOP, BCL2 overexpression correlates with poorer prognosis in the germinal center type of DLBCL. BCL2 overexpression combined with MYC overexpression correlates with a poorer prognosis (IHC double hit lymphoma).

B. Fluorescence In Situ Hybridization (FISH)
Recent studies have demonstrated that DLBCL with rearrangements of MYC and BCL2 or BCL6 comprise a distinct subgroup of cases, often termed double hit lymphomas, characterized by overlapping morphologic features with Burkitt lymphoma and a more aggressive clinical course.

C. Subtyping
Studies have shown there are prognostic differences in DLBCL that are germinal center derived (GC) versus non-germinal center derived (NGC). Several methodologies have been proposed for predicting GC versus NGC derivation. In general, DLBCL of GC type is associated with a better prognosis. The most commonly applied immunohistochemical methodologies, which serve as a substitute for gene expression arrays (a gold standard for GC versus NGC), are Hans classifier, Choi classifier, and Tally classifier.

D. Sequencing
Somatic variants in TP53, MYD88, PAX5, TNFRSF14, and other genes have been shown to correlate with cell of origin, patient outcome, and diagnosis in some studies. When such variants are identified they should be reported according to the Human Genome Variant Society (HCVS) guidelines nomenclature.
Background Documentation

Diffuse Large B-Cell Lymphoma • Biomarkers

References