



# Protocol for the Examination of Specimens From Patients With Non-Hodgkin Lymphoma/Lymphoid Neoplasms

Version: NonHodgkin 3.2.0.1

Protocol Posting Date: October 2013

This protocol is **NOT** required for accreditation purposes

\*This protocol applies to non-Hodgkin lymphoma involving any site.

## The following should NOT be reported using this protocol:

Plasma cell neoplasms (consider the plasma cell neoplasm protocol)
Bone marrow biopsies with lymphoma (consider the bone marrow protocol)
Mycosis fungoides
Sézary syndrome

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

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## Accreditation Requirements

This protocol can be utilized for clinical care purposes, but is not required for accreditation purposes.

**CAP Laboratory Accreditation Program Protocol Required Use Date: Not applicable**

## Surgical Pathology Cancer Case Summary

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Protocol posting date: October 2013

### NON-HODGKIN LYMPHOMA/LYMPHOID NEOPLASMS: Biopsy, Resection

**Note: This case summary is recommended for reporting Non-Hodgkin lymphoma specimens, but is not required for accreditation purposes.**

**Select a single response unless otherwise indicated.**

#### Specimen (select all that apply) (note A)

- Lymph node(s)  
 Other (specify): \_\_\_\_\_  
 Not specified

#### Procedure

- Biopsy  
 Resection  
 Other (specify): \_\_\_\_\_  
 Not specified

#### Tumor Site (select all that apply) (note B)

- Lymph node(s), site not specified  
 Lymph node(s)  
     Specify site(s): \_\_\_\_\_  
 Other tissue(s) or organ(s): \_\_\_\_\_  
 Not specified

#### Histologic Type (note C)

- Histologic type cannot be assessed

#### Precursor Lymphoid Neoplasms

- B lymphoblastic leukemia/lymphoma, not otherwise specified (NOS)<sup>#</sup>  
 B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL1*  
 B lymphoblastic leukemia/lymphoma with t(v;11q23); *MLL* rearranged  
 B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22); *TEL-AML1 (ETV6-RUNX1)*  
 B lymphoblastic leukemia/lymphoma with hyperdiploidy  
 B lymphoblastic leukemia/lymphoma with hypodiploidy (hypodiploid acute lymphoblastic leukemia/lymphoma [ALL])  
 B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32); *IL3-IGH*  
 B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *E2A-PBX1 (TCF3-PBX1)*  
 T lymphoblastic leukemia/lymphoma

#### Mature B-Cell Neoplasms

- B-cell lymphoma, subtype cannot be determined (Note: not a category within the WHO classification)  
 Chronic lymphocytic leukemia/small lymphocytic lymphoma  
 B-cell prolymphocytic leukemia  
 Splenic B-cell marginal zone lymphoma  
 Hairy cell leukemia  
 *Splenic B-cell lymphoma/leukemia, unclassifiable*  
 *Splenic diffuse red pulp small B-cell lymphoma*

+ Data elements preceded by this symbol may be clinically important but are not yet validated or regularly used in patient management.

- \_\_\_ *Hairy cell leukemia-variant*
- \_\_\_ Lymphoplasmacytic lymphoma
- \_\_\_ Gamma heavy chain disease
- \_\_\_ Mu heavy chain disease
- \_\_\_ Alpha heavy chain disease
- \_\_\_ Plasma cell myeloma
- \_\_\_ Solitary plasmacytoma of bone
- \_\_\_ Extraosseous plasmacytoma
- \_\_\_ Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- \_\_\_ Nodal marginal zone lymphoma
- \_\_\_ *Pediatric nodal marginal zone lymphoma*
- \_\_\_ Follicular lymphoma
- \_\_\_ *Pediatric follicular lymphoma*
- \_\_\_ *Primary intestinal follicular lymphoma*
- \_\_\_ Primary cutaneous follicle center lymphoma
- \_\_\_ Mantle cell lymphoma
- \_\_\_ Diffuse large B-cell lymphoma (DLBCL), NOS
- \_\_\_ T cell/histiocyte-rich large B-cell lymphoma
- \_\_\_ Primary DLBCL of the central nervous system (CNS)
- \_\_\_ Primary cutaneous DLBCL, leg type
- \_\_\_ *Epstein-Barr virus (EBV)-positive DLBCL of the elderly*
- \_\_\_ DLBCL associated with chronic inflammation
- \_\_\_ Lymphomatoid granulomatosis
- \_\_\_ Primary mediastinal (thymic) large B-cell lymphoma
- \_\_\_ Intravascular large B-cell lymphoma
- \_\_\_ Anaplastic lymphoma kinase (ALK)-positive large B-cell lymphoma
- \_\_\_ Plasmablastic lymphoma
- \_\_\_ Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- \_\_\_ Primary effusion lymphoma
- \_\_\_ Burkitt lymphoma
- \_\_\_ B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- \_\_\_ B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma
- \_\_\_ Other (specify): \_\_\_\_\_

#### Mature T- and NK-Cell Neoplasms

- \_\_\_ T-cell lymphoma, subtype cannot be determined (Note: not a category within the WHO classification)
- \_\_\_ T-cell prolymphocytic leukemia
- \_\_\_ T-cell large granular lymphocytic leukemia
- \_\_\_ *Chronic lymphoproliferative disorder of NK cells*
- \_\_\_ Aggressive NK-cell leukemia
- \_\_\_ Systemic EBV-positive T-cell lymphoproliferative disease of childhood
- \_\_\_ Hydroa vacciniforme-like lymphoma
- \_\_\_ Adult T-cell leukemia/lymphoma
- \_\_\_ Extranodal NK/T-cell lymphoma, nasal type
- \_\_\_ Enteropathy-associated T-cell lymphoma
- \_\_\_ Hepatosplenic T-cell lymphoma
- \_\_\_ Subcutaneous panniculitis-like T-cell lymphoma
- \_\_\_ Primary cutaneous anaplastic large cell lymphoma
- \_\_\_ Lymphomatoid papulosis
- \_\_\_ Primary cutaneous gamma-delta T-cell lymphoma
- \_\_\_ *Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma*
- \_\_\_ *Primary cutaneous CD4-positive small/medium T-cell lymphoma*
- \_\_\_ Peripheral T-cell lymphoma, NOS
- \_\_\_ Angioimmunoblastic T-cell lymphoma

- Anaplastic large cell lymphoma, ALK-positive
- Anaplastic large cell lymphoma, ALK-negative*
- Other (specify): \_\_\_\_\_

**Histiocytic and Dendritic Cell Neoplasms**

- Histiocytic sarcoma
- Langerhans cell histiocytosis
- Langerhans cell sarcoma
- Interdigitating dendritic cell sarcoma
- Follicular dendritic cell sarcoma
- Fibroblastic reticular cell tumor*
- Indeterminate dendritic cell tumor*
- Disseminated juvenile xanthogranuloma

**Posttransplant Lymphoproliferative Disorders (PTLD)<sup>##</sup>**

Early lesions:

- Plasmacytic hyperplasia
- Infectious mononucleosis-like PTLD
  
- Polymorphic PTLD
- Monomorphic PTLD (B- and T/NK-cell types)  
 Specify subtype: \_\_\_\_\_
- Classical Hodgkin lymphoma type PTLD<sup>###</sup>

*Note: Italicized histologic types denote provisional entities in the 2008 WHO classification.*

<sup>#</sup> An initial diagnosis of “B lymphoblastic leukemia/lymphoma, NOS” may need to be given before the cytogenetic results are available.

<sup>##</sup> These disorders are listed for completeness, but not all of them represent frank lymphomas.

<sup>###</sup> Classical Hodgkin lymphoma type PTLD can be reported using either this protocol or the separate College of American Pathologists protocol for Hodgkin lymphoma.<sup>1</sup>

**+ Pathologic Extent of Tumor (select all that apply) (note D)**

- +  Bone marrow involvement
- +  Other site involvement  
 + Specify site(s): \_\_\_\_\_

**+ Additional Pathologic Findings**

+ Specify: \_\_\_\_\_

**Immunophenotyping (flow cytometry and/or immunohistochemistry) (note E)**

- Performed, see separate report: \_\_\_\_\_
- Performed  
 Specify method(s) and results: \_\_\_\_\_
- Not performed

**+ Cytogenetic Studies (note E)**

- +  Performed, see separate report: \_\_\_\_\_
- +  Performed  
 + Specify method(s) and results: \_\_\_\_\_
- +  Not performed

+ Data elements preceded by this symbol may be clinically important but are not yet validated or regularly used in patient management.

**+ Molecular Genetic Studies (note E)**

- + \_\_\_ Performed, see separate report: \_\_\_\_\_
- + \_\_\_ Performed
  - + Specify method(s) and results: \_\_\_\_\_
- + \_\_\_ Not performed

**+ Clinical Prognostic Factors and Indices (select all that apply) (note F)**

- + \_\_\_ International Prognostic Index (IPI) (specify): \_\_\_\_\_
- + \_\_\_ Follicular Lymphoma International Prognostic Index (FLIPI) (specify): \_\_\_\_\_
- + \_\_\_ B symptoms present
- + \_\_\_ Other (specify): \_\_\_\_\_

**+ Comment(s)**

## Explanatory Notes

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### A. Specimen

Any number of specimen types may be submitted in the evaluation of lymphoid neoplasms. Lymph nodes, skin, gastrointestinal (GI) tract, bone marrow, spleen, thymus, and tonsils are among the most common. Specimens submitted with a suspected diagnosis of lymphoma require special handling in order to optimize the histologic diagnosis and to prepare the tissue for molecular and other ancillary special studies.<sup>2,3</sup> The guidelines detailed below are suggested for specimen handling in cases of suspected lymphoma.

- Tissue should be received fresh. Unsectioned lymph nodes should not be immersed in fixative, and care should be taken to make thin slices of the node to ensure optimal penetration of fixative.
- The fresh specimen size, color, and consistency should be recorded, as should the presence or absence of any visible nodularity, hemorrhage, or necrosis after serial sectioning at 2-mm intervals perpendicular to the long axis of the lymph node.
- Touch imprints may be made from the freshly cut surface, and the imprints fixed in alcohol or air dried.
- For cytogenetic studies or culture of microorganisms: submit a fresh portion of the node (or other specimen type) sterilely in appropriate medium.
- For immunophenotyping by flow cytometry: submit a fresh portion of the specimen in appropriate transport medium such as RPMI.
- Fixation (record fixative[s] used for individual slices of the specimen):
  - Estimated time from excision to fixation should be noted, if possible, as this may impact preservation or recovery of certain analytes such as RNA and phosphoproteins in fixed tissues.
  - Zinc formalin or B5 produces superior cytologic detail but is not suitable for DNA extraction and may impair some immunostains (eg, CD30). B5 also has the additional limitation of requiring proper hazardous-materials disposal.
  - Formalin fixation is preferable when the tissue sample is limited, as it is most suitable for many ancillary tests such as molecular/genetic studies, in-situ hybridization, and immunophenotyping.
  - Over-fixation (ie, more than 24 hours in formalin, more than 4 hours in zinc formalin or B5) should be avoided for optimal immunophenotypic reactivity.
- Snap-frozen tissue is optimal for DNA and RNA extraction.
  - Place in aluminum foil or cover in OCT.
  - Immerse in dry ice/isopentane slush or liquid nitrogen.
  - Store at -80°C until needed.

### B. Tumor Site

The anatomic sites that constitute the major structures of the lymphatic system include groups and chains of lymph nodes, the spleen, the thymus, Waldeyer's ring (a circular band of lymphoid tissue that surrounds the oropharynx, consisting of the palatine, lingual, and pharyngeal tonsils), the vermiform appendix, and the Peyer's patches of the ileum.<sup>2,3</sup> Minor sites of lymphoid tissue include the bone marrow, mediastinum, liver, skin, lung, pleura, and gonads. Involvement of extranodal sites is more common in non-Hodgkin lymphomas (NHL) than in Hodgkin lymphoma. In addition, some NHL, such as mycosis fungoides and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), occur predominantly or entirely in extranodal sites.

### C. Histologic Type

This protocol recommends assigning histologic type based on the World Health Organization (WHO) classification of lymphoid neoplasms.<sup>4</sup> It was originally published in 2001 and recently was revised and updated in 2008.<sup>5</sup> This classification encompasses both nodal and extranodal lymphomas and provides distinction of individual lymphoid neoplasms based upon morphologic, immunophenotypic, cytogenetic, and clinical features. While histologic examination typically is the gold standard, the majority of the lymphoid neoplasms will require the utilization of 1 or more other ancillary techniques, such as immunophenotyping, molecular studies, and/or cytogenetics, to arrive at the correct diagnosis.<sup>4-10</sup> If the specimen is inadequate or suboptimal for a definitive diagnosis and subtyping, this information should also be relayed to the clinician with an explanation of what makes the specimen inadequate or suboptimal.

**D. Pathologic Extent of Tumor (Stage)**

In general, the TNM classification has not been used for staging of lymphomas because the site of origin of the tumor is often unclear and there is no way to differentiate among T, N, and M. Thus, a special staging system (Ann Arbor system) is used for both Hodgkin lymphoma and NHL.<sup>11,12</sup> It was originally published over 30 years ago for staging Hodgkin lymphoma. The Ann Arbor classification for lymphomas has been applied to NHL by the American Joint Committee on Cancer (AJCC)<sup>13</sup> and the International Union Against Cancer (UICC) except for mycosis fungoides and Sezary syndrome.<sup>14</sup>

For multiple myeloma, the Durie-Salmon staging system is recommended by the AJCC.<sup>13-15</sup> The international staging system for multiple myeloma is useful for determining survival.<sup>13</sup> The Ann Arbor classification and Durie-Salmon staging systems are shown below. It should also be realized that the St. Jude staging system is commonly used for pediatric patients.<sup>16</sup>

Historically, pathologic staging depended on the biopsy of multiple lymph nodes on both sides of the diaphragm, splenectomy, wedge liver biopsy, and bone marrow biopsy to assess distribution of disease. Currently, staging of NHL is more commonly clinical than pathologic. Clinical staging generally involves a combination of clinical, radiologic, and surgical data. Physical examination, laboratory tests (eg, complete blood examination and blood chemistry studies including lactate dehydrogenase [LDH] and liver function tests), imaging studies (eg, computed tomography scans, magnetic resonance imaging studies, and positron emission tomography), biopsy (to determine diagnosis, histologic type, and extent of disease), and bone marrow examination are often required. In patients at high risk for occult CNS involvement, cerebrospinal fluid cytology should be performed.

There is almost universal agreement that the stage of the NHL is prognostically significant.<sup>17-20</sup> Correct diagnosis and staging are the key factors in National Comprehensive Cancer Network treatment schema that most clinicians utilize.<sup>21</sup>

**AJCC/UICC Staging for Non-Hodgkin Lymphomas**

Stage I	Involvement of a single lymph node region (I), or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE) <sup>#, ##</sup>
Stage II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II), or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE) <sup>##, ###</sup>
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which also may be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE+S) <sup>##, ###, ^</sup>
Stage IV	Diffuse or disseminated involvement of 1 or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver, bone marrow, or nodular involvement of the lung(s) or cerebral spinal fluid. <sup>##, ###, ^</sup>

<sup>#</sup> Multifocal involvement of a single extralymphatic organ is classified as stage IE and not stage IV.

<sup>##</sup> For all stages, tumor bulk greater than 10 to 15 cm is an unfavorable prognostic factor.

<sup>###</sup> The number of lymph node regions involved may be indicated by a subscript: eg, II<sub>3</sub>. For stages II to IV, involvement of more than 2 sites is an unfavorable prognostic factor.

<sup>^</sup> For stages III to IV, a large mediastinal mass is an unfavorable prognostic factor.

*Note:* Direct spread of a lymphoma into adjacent tissues or organs does not influence classification of stage.

**AJCC/UICC Staging for Plasma Cell Myeloma**

Stage I	Hemoglobin greater than 10.0 g/dL Serum calcium 12 mg/dL or less Normal bone x-rays or a solitary bone lesion IgG less than 5 g/dL IgA less than 3 g/dL Urine M-protein less than 4 g/24 hours
Stage III	One or more of the following are included: Hemoglobin less than 8.5 g/dL Serum calcium greater than 12 mg/dL Advanced lytic bone lesions IgG greater than 7 g/dL IgA greater than 5 g/dL Urine M-protein greater than 12 g/24 hours
Stage II	Disease fitting neither stage I nor stage III

*Note:* Patients are further classified as (A) serum creatinine less than 2.0 mg/dL or (B) serum creatinine 2.0 mg/dL or greater. The median survival for stage IA disease is about 5 years, and that for stage IIIB disease is 15 months.<sup>13,14</sup>

**E. Immunophenotyping and Molecular Genetic Studies**

Immunophenotyping can be performed by flow cytometry<sup>8</sup> or immunohistochemistry. Each has its advantages and disadvantages. Flow cytometry is rapid (hours), quantitative, and allows multiple antigens to be evaluated on the same cell simultaneously. Antigen positivity, however, cannot be correlated with architecture or cytologic features. Immunohistochemistry requires hours/days to perform, quantitation is subjective, but importantly it allows correlation of antigen expression with architecture and cytology. Not all antibodies are available for immunohistochemistry, particularly in fixed tissues, but one of its advantages is that it can be performed on archival tissue. Both techniques can provide diagnostic as well as clinically relevant information (eg, identification of therapeutic targets such as CD20). Molecular studies now play an increasingly important role in the diagnosis of hematopoietic neoplasms. They aid not only in helping establish clonality but also in determining lineage, establishing the diagnosis of specific disease entities, and monitoring minimal residual disease.<sup>10,22-24</sup>

**Immunophenotypes and Genetics**

The following is to be used as a guideline for the more common immunophenotyping and cytogenetic findings for each entity.<sup>3,4,8,22-27</sup> It is however, not entirely comprehensive and individual cases may vary somewhat in their immunophenotypic and cytogenetic profile.

**Precursor Lymphoid Neoplasms**

**B Lymphoblastic Leukemia/Lymphoma, NOS:** sIG-, cytoplasmic  $\mu$  chain (30%), CD19+, CD20-/+, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10+/-, CD34+/-, CD13-/+, CD33-/+, *IGH* gene rearrangement +/-, *IGL* gene rearrangement -/+, TCR gene rearrangement -/+, variable cytogenetic abnormalities

**B Lymphoblastic Leukemia/Lymphoma With t(9;22)(q34;q11.2); *BCR-ABL1*:** sIG-, cytoplasmic  $\mu$  chain (30%), CD19+, CD20-/+, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10+/-, CD34+/-, CD13-/+, CD33-/+, *IGH* gene rearrangement +/-, *IGL* gene rearrangement -/+, TCR gene rearrangement -/+, t(9;22)(q34;q11.2), may have either p190 kd or p210 kd *BCR-ABL1* fusion protein.

**B Lymphoblastic Leukemia/Lymphoma With t(v;11q23); *MLL* Rearranged:** sIG-, cytoplasmic  $\mu$  chain (30%), CD19+, CD20-/+, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10-, CD34+/-, CD13-/+, CD33-/+, CD15 +/-, *IGH* gene rearrangement +/-, *IGL* gene rearrangement -/+, TCR gene rearrangement -/+, t(v;11q23)

**B Lymphoblastic Leukemia/Lymphoma With t(12;21)(p13;q22); *TEL-AML1 (ETV6-RUNX1)*:** sIG-, cytoplasmic  $\mu$  chain (30%), CD19+, CD20-, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10+, CD34+/-, CD13+/-, CD33-/+, CD15 +/-, *IGH* gene rearrangement +/-, *IGL* gene rearrangement -/+, TCR gene rearrangement -/+, t(12;21)(p13;q22)



B Lymphoblastic Leukemia/Lymphoma With Hyperdiploidy: *sIG*-, cytoplasmic  $\mu$  chain (30%), CD19+, CD20-/-, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10+/-, CD34+/-, CD13-/-, CD33-/-, *IGH* gene rearrangement +/-, *IGL* gene rearrangement +/-, TCR gene rearrangement +/-, hyperdiploid (>50 chromosomes, often with extra copies of chromosomes 21, X, 4 and 14) without structural abnormalities

B Lymphoblastic Leukemia/Lymphoma With Hypodiploidy: *sIG*-, cytoplasmic  $\mu$  chain (30%), CD19+, CD20-/-, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10+/-, CD34+/-, CD13-/-, CD33-/-, *IGH* gene rearrangement +/-, *IGL* gene rearrangement +/-, TCR gene rearrangement +/-, hypodiploid with 45 chromosomes to near haploid

B Lymphoblastic Leukemia/Lymphoma With t(5;14)(q31;q32); *IL3-IGH*: *sIG*-, cytoplasmic  $\mu$  chain (30%), CD19+, CD20-, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10+, CD34+/-, CD13+/-, CD33-/-, CD15 +/-, *IGH* gene rearrangement +/-, *IGL* gene rearrangement +/-, TCR gene rearrangement +/-, t(5;14)(q31;q32)

B Lymphoblastic Leukemia/Lymphoma With t(1;19)(q23;p13.3); *E2A-PBX1 (TCF3-PBX1)*: *sIG*-, cytoplasmic  $\mu$  chain (30%), CD19+, CD20-, CD22+, PAX5+, CD79a+, TdT+, HLA-DR+, CD10+, CD34+/-, CD13+/-, CD33-/-, CD15 +/-, *IGH* gene rearrangement +/-, *IGL* gene rearrangement +/-, TCR gene rearrangement +/-, t(1;19)(q23;p13.3)

T Lymphoblastic Leukemia/Lymphoma: TdT+, CD7+, CD3+/- (usually surface CD3-), variable expression of other PanT antigens, CD1a+/-, often CD4 and CD8 double positive or double negative, *IG*-, PanB-; variable TCR gene rearrangements; *IGH* gene rearrangement +/-, chromosomal abnormalities are common and often involve 14q11-14, 7q35, or 7p14-15

### Mature B-Cell Neoplasms

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Faint *sIGM*+, *sIGD*+/-, *cIG*+/-, panB+ (CD19+, CD20+), CD5+, CD10-, CD23+, CD43+, CD11c-/-; *IGH* and *IGL* gene rearrangements; trisomy 12; del 13q, del(17p), or del(11q) can be seen

B-Cell Prolymphocytic Leukemia: *sIGM*, *sIGD*+/-, pan B+ (CD19, CD20, CD22, CD79a, CD79b and FMC-7), CD5 -/-, CD23-/-, del(17p), t(11;14)(q13;q32), breakpoints involving 13q14

Splenic B-Cell Marginal Zone Lymphoma: *sIGM*+, *sIGD*+/-, CD20+, CD79a+, CD5-, CD10-, CD23-, CD43-, nuclear cyclin D1-, CD103-, allelic loss at 7q31-32 (40%)

Hairy Cell Leukemia: *sIG*+ (*IGM*, *IGD*, *IGG*, or *IGA*), PanB+, CD79a+, CD79b-, DBA.44+, CD123+, CD5-, CD10-, CD23-, CD11c+, CD25+, FMC7+, CD103+ (mucosal lymphocyte antigen as detected by B-ly7), tartrate resistant acid phosphatase (TRAP)+; *IGH* and *IGL* gene rearrangements, no specific cytogenetic findings

Splenic Diffuse Red Pulp Small B-Cell Lymphoma: *sIGG*+, *sIGD*+/-, *sIGM*+/-, CD20+, DBA.44+, CD5-, CD103-/-, CD123-, CD25-, CD11c-/-, CD10-, CD23-, t(9;14)(p13;q32) occasionally seen, rarely abnormalities in TP53 or del 7q

Hairy Cell Leukemia-Variant: *sIGG*+, PanB+, DBA.44+, CD11c+, CD103+, FMC7+, CD25-, CD123-, Annexin A1-, TRAP-IHC-, no specific cytogenetic findings

Lymphoplasmacytic Lymphoma: *sIGM*+, *sIGD*+/-, *cIG*+, PanB+, CD19+, CD20+, CD138+ (in plasma cells), CD79a+, CD5-, CD10-, CD43+/-, CD25-/-; *IGH* and *IGL* gene rearrangements, no specific cytogenetic findings

Alpha Heavy Chain Disease (Immunoproliferative Small Intestinal Disease): cytoplasmic alpha heavy chain+, CD20+ (lymphocytes), CD138+ (plasma cells), light chain-

Gamma Heavy Chain Disease: *IgG* heavy chain+, CD79a+, CD20+ (on lymphocytes), CD138+ (in plasma cells), CD5-, CD10-, light chain-, abnormal karyotype in 50% without recurring abnormalities

Mu Heavy Chain Disease: monoclonal cytoplasmic mu heavy chain+, B-cell antigen+, CD5-, CD10-, surface light chain-

Plasma Cell Myeloma: *cIG+* (*IGG*, *IGA*, rare *IGD*, *IGM*, or *IGE* or light chain only), PanB-(CD19-, CD20-, CD22-), CD79a+/-, CD45-/+ , HLA-DR-/+ , CD38+, CD56+/-, CD138+, EMA-/+ , CD43+/-, cyclin D1+; *IGH* and *IGL* gene rearrangements; numerical and structural chromosomal abnormalities are common, including trisomies (often involving odd numbered chromosomes), deletions (most commonly involving 13q14), and translocations (often involving 14q32)

Solitary Plasmacytoma of Bone: *cIG+* (*IGG*, *IGA*, rare *IGD*, *IGM*, or *IGE* or light chain only), PanB-(CD19-, CD20-, CD22-), CD79a+/-, CD45-/+ , HLA-DR-/+ , CD38+, CD56+/-, CD138+, EMA-/+ , CD43+/-, cyclin D1+; *IGH* and *IGL* gene rearrangements; deletions, most commonly 13q, and occasional translocations, in particular t(11;14)(q13;q32)

Extrasosseous Plasmacytoma: *cIG+* (*IGG*, *IGA*, rare *IGD*, *IGM*, or *IGE* or light chain only), PanB-(CD19-, CD20-, CD22-), CD79a+/-, CD45-/+ , HLA-DR-/+ , CD38+, CD56+/-, CD138+, EMA-/+ , CD43+/-, cyclin D1+; *IGH* and *IGL* gene rearrangements; deletions, most commonly 13q, and occasional translocations, in particular t(11;14)(q13;q32)

Extranodal Marginal Zone Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT Lymphoma): *sIG+* (*IGM* or *IGA* or *IGG*), *sIGD-*, *cIG-/+*, PanB+, CD5-, CD10-, CD23-, CD43-/+; *IGH* and *IGL* gene rearrangements, *BCL1* and *BCL2* germline, trisomy 3 or t(11;18)(q21;q21) may be seen

Nodal Marginal Zone Lymphoma: *sIGM+*, *sIGD-*, *cIG-/+*, PanB+, CD5-, CD10-, CD23-, CD43-/+; *IGH* and *IGL* gene rearrangements, *BCL1* and *BCL2* germline

Follicular Lymphoma: *sIG+* (usually *IGM +/- IGD*, *IGG*, *IGA*), PanB+, CD10+/-, CD5-/+ , CD23-/+ , CD43-, CD11c-, CD25-; overexpression of *BCL2*+ (useful to distinguish from reactive follicles), *BCL6*+; *IGH* and *IGL* gene rearrangements, t(14;18)(q32;q21) with rearranged *BCL2* gene (70-95% in adults)

Pediatric Follicular Lymphoma: *sIG+* (usually *IGM +/- IGD*, *IGG*, *IGA*), PanB+, CD10+/-, CD5-, CD23-/+ , CD43-, CD11c-, CD25-; overexpression of *BCL2*-, *BCL6*+, t(14;18) with rearranged *BCL2* gene -

Primary Cutaneous Follicle Center Lymphoma: CD20+, CD79a+, CD10+/-, *BCL2*-/+ , *BCL6*+, CD5-, CD43-, *BCL2* gene rearrangement-/+

Mantle Cell Lymphoma: *sIGM+*, *sIGD+*, lambda>kappa, PanB+, CD5+, CD10-/+ , CD23-, CD43+, CD11c-, CD25-, cyclin D1+; *IGH* and *IGL* gene rearrangements, t(11;14)(q13;q32); *BCL1* gene rearrangements (CCND1/cyclinD1) common

Diffuse Large B-Cell Lymphoma (DLBCL), NOS: PanB+, surface or cytoplasmic *IGM>IGG>IGA*, CD45+/-, CD5-/+ , CD10+/-, *BCL6 +/-*, 3q27 region abnormalities involving *BCL6* seen in 30% of cases, t(14;18) involving *BCL2* seen in 20-30% of cases, *MYC* rearrangement seen in 10% of cases

T Cell/Histiocytic-Rich Large B-Cell Lymphoma: PanB+, *BCL6*+, *BCL2*-/+ , EMA -/+ , background comprised of CD3 and CD5 positive T-cells and CD68+ histiocytes

Primary DLBCL of the CNS: CD20+, CD22, CD79a, CD10-/+ , *BCL6*+/-, *IRF4/MUM1*+/-, *BCL2*+/-, *BCL6* translocations+/-, del 6q and gains of 12q, 22q, and 18q21 common

Primary Cutaneous DLBCL, Leg Type: *sIG+*, CD20+, CD79a+, CD10-, *BCL2*+, *BCL6*+, *IRF4/MUM1*+, *FOX-P1*+; translocations involving *MYC*, *BCL6*, and *IGH* genes are common

EBV-Positive Diffuse Large B-Cell Lymphoma of the Elderly: CD20+/-, CD79a+/-, CD10-, *IRF4/MUM1*+/-, *BCL6*-, *LMP*+, *EBER*+

DLBCL Associated With Chronic Inflammation: CD20+/-, CD79a+/-, CD138-/+ , *IRF4/MUM1*-/+ , CD30-/+ , T-cells markers-/+ , *LMP*+/-, *EBER*+/-

Lymphomatoid Granulomatosis: CD20+, CD30+/-, CD79a+/-, CD15-, LMP+/-, EBER+.

Primary Mediastinal (Thymic) Large B-Cell Lymphoma: sIG+/-, PanB+, (especially CD20, CD79a), CD45+/-, CD15-, CD30+/- (weak), IRF4/MUM1 +/-, BCL2+/-, BCL6+/-, CD23+, MAL+; *IGH* and *IGL* gene rearrangements

Intravascular Large B-Cell Lymphoma: Pan B+ (CD19, CD20, CD22, CD79a), CD5+/-, CD10+/-, IRF4/MUM1+

ALK-Positive Large B-Cell Lymphoma: ALK+, CD138+, EMA+, VS38+, CD45+/-, CD4+/-, CD57+/-, CD20-, CD79a-, CD3-, CD30+/-, IRF4/MUM1+/-, t(2;17)(p23;q23)+/-, t(2;5)(p23;35)-/+

Plasmablastic Lymphoma: CD38+, CD138+, Vs38c+, IRF4/MUM1+, CD79a+/-, EMA +/-, CD30+/-, CD45+/-, CD20+/-, PAX5+/-, EBER+/-, EMA+/-, CD30+/-

Large B-Cell Lymphoma Arising in HHV8-Associated Multicentric Castleman Disease: CD20+/-, CD79a-, CD38+/-, CD138-, EBER-, lambda light chain restricted

Primary Effusion Lymphoma: CD45+/-, CD30+/-, CD38+/-, CD138+/-, EMA+/-, CD19-, CD20-, CD79a-, CD3+/-, BCL6-, HHV8/KSHV+, EBV+/-, *IGH* and *IGL* gene rearrangements

Burkitt Lymphoma: sIGM+, PanB+, CD5-, CD10+, BCL6+, CD38+, CD77+, CD43+, CD23-; Ki-67 (95-100%), BCL2-; TdT-, *IGH* and *IGL* gene rearrangements, t(8;14)(q24;q32) and variants t(2;8)(p12;q24) and t(8;22)(q24;q11); rearranged *MYC* gene; EBV common (95%) in endemic cases and infrequent (15-20%) in sporadic cases, intermediate incidence (30-40%) in HIV-positive cases

B-Cell Lymphoma, Unclassifiable, With Features Intermediate Between Diffuse Large B-cell Lymphoma and Burkitt Lymphoma: PanB+, CD10+, BCL6+, BCL2+/-, IRF4/MUM1-, Ki-67 (50-100%), 8q24/*MYC* translocation (35-50%), *BCL2* translocation (15%), and occasionally both translocations (so called double hit lymphoma)

B-Cell Lymphoma, Unclassifiable, With Features Intermediate Between Diffuse Large B-cell Lymphoma and Classical Hodgkin Lymphoma: CD45+/-, CD20+/-, CD79a+/-, CD30+/-, CD15+/-, PAX5+/-, OCT-2+/-, BOB.1+/-, CD10-, ALK-

### Mature T-Cell and NK-Cell Neoplasms

T-Cell Prolymphocytic Leukemia: PanT+ (CD2, CD3, CD5, CD7), CD25-, CD4+/CD8->CD4+/CD8+>CD4-/CD8-, TCL1+, TdT-, CD1a-; TCR gene rearrangements, 75% show inv 14 with breakpoints at q11 and q32, 10% have a reciprocal tandem translocation t(14;14)(q11;q32)

T-Cell Large Granular Lymphocytic Leukemia: PanT+ (CD2, CD3+, CD5+/-), CD7-, TCR+, CD4-, CD8+, CD16+, CD56-, CD57+, CD25-, TIA1+, granzyme B+, TdT-; most cases show clonal TCR gene rearrangements

Chronic Lymphoproliferative Disorder of NK Cells: sCD3-, cCD3+, CD16+, CD56 (weak), TIA1+, granzyme B+, CD8+/-, CD2+/-, CD7+/-, CD57+/-, EBV-, karyotype is typically normal

Aggressive NK-Cell Leukemia: CD2+, sCD3-, cCD3+, CD56+, TIA+/-, CD16+/-, CD57-, Fas ligand+, EBV+, del(6)(q21q25) and del(11q) can be seen

Systemic EBV-Positive T-Cell Lymphoproliferative Disease of Childhood: CD2+, CD3+, TIA+, CD8+ (if associated with acute EBV infection), EBER+, CD56-, TCR gene rearrangements+

Hydroa Vacciniforme-like Lymphoma: Cytotoxic T-cell or less often CD56+ NK-cell phenotype, EBER+/-, TCR gene rearrangement+

Adult T-Cell Leukemia/Lymphoma (HTLV1+): PanT+ (CD2+, CD3+, CD5+), CD7-, CD4+, CD8-, CD10+, CD25+, TdT-; TCR gene rearrangements, clonally integrated HTLV1

Extranodal NK/T-Cell Lymphoma: CD2+, CD5-/+ , CD7-/+ , CD3-/+ , granzyme B+, TIA1+, CD4-, CD8-, CD56+/-, TdT-; usually no TCR or Ig gene rearrangements; usually EBV positive

Enteropathy-associated T-cell Lymphoma: CD3+, CD7+, CD4-, CD8-/+ , CD103+, TdT-

Hepatosplenic T-cell Lymphoma: CD2+, CD3+, TCR gamma-delta+, TCR alpha-beta rarely +, CD5-, CD7+, CD4-, CD8-/+ , CD56+/-, CD25-; TCRG gene rearrangements +/-, variable TCRB gene rearrangements -/+; isochromosome 7q and trisomy 8 common

Subcutaneous Panniculitis-like T-Cell Lymphoma: CD8+, granzyme B+, TIA1+, perforin+, TCR alpha/beta +, CD4-, CD56-

Lymphomatoid Papulosis: CD4+, CD2-/+ , CD3+, CD5-/+ , TIA1+, granzyme B+/-, CD30+/-; TCR gene rearrangements+/-

Primary Cutaneous Anaplastic Large-Cell Lymphoma: CD4+, TIA1+/-, granzyme B+/-, perforin+/-, CD30+, CD2-/+ , CD5-/+ , CD3-/+ , CLA+, ALK-, EMA-/+; TCR gene rearrangements+/-

Primary Cutaneous Gamma-Delta T-Cell Lymphoma: TCR gamma/delta+, CD2+, CD3+, CD5-, CD56+, CD7+/-, CD4-, CD8-/+ , Beta F1-

Primary Cutaneous CD8-positive Aggressive Epidermotropic Cytotoxic T-cell Lymphoma: CD3+, CD8+, granzyme B+, perforin+, TIA1+, CD45RA+/-, CD2-/+ , CD4-, CD5-, CD7-, EBV-, Beta F1+; TCR gene rearrangements (alpha/beta)+

Primary Cutaneous CD4-Positive Small/Medium T-Cell Lymphoma: CD3+, CD4+, CD8-, CD30-, TCR gene rearrangements+

Peripheral T-Cell Lymphoma, NOS: PanT variable (CD2+/-, CD3+/-, CD5-/+ , CD7-/+), most cases CD4+, some cases CD8+, a few cases are CD4-/CD8-, or CD4+/CD8+; TCR gene rearrangements+

Angioimmunoblastic T-Cell Lymphoma: PanT+ (often with variable loss of some PanT antigens), usually CD4+, PD1+, CXCL13+; TCR gene rearrangements in 75%; *IGH* gene rearrangements in up to 30%, EBV often positive in B-cells

Anaplastic Large Cell Lymphoma, ALK Positive: CD30+, ALK+, EMA+/-, CD3-/+ , CD2+/-, CD4+/-, CD5+/-, CD8-/+ , CD43+/-, CD25+, CD45+/-, CD45RO+/-, TIA1+/-, granzyme+/-, perforin+/-, EBV-, TCR gene rearrangements+/-, t(2;5)(p23;35) in 80% of cases, t(1;2)(q25;p23) in 10-15% of cases. Other various translocations can also be seen.

Anaplastic Large Cell Lymphoma, ALK Negative: CD30+ (strong/intense staining), CD2+/-, CD3+/-, CD5-/+ , CD4+/-, CD8-/+ , CD43+, TIA1+/-, granzyme B+/-, perforin +/-, ALK-, TCR gene rearrangements+

### Histiocytic and Dendritic Cell Neoplasms

Histiocytic Sarcoma: CD45+, CD163+, CD68+, lysozyme+, CD45RO+/-, HLA-DR+/-, CD4+/-, S100-/+ , CD1a-, CD21-, CD35-, CD13, CD33, myeloperoxidase-, lack *IGH* and TCR gene rearrangements

Langerhans Cell Histiocytosis: CD1a+, langerin+, S100+, vimentin+, CD68+, HLA-DR+, CD4-/+ , CD30+, most B- and T-cell markers are negative, there are no consistent cytogenetic abnormalities

Langerhans Cell Sarcoma: CD1a+, langerin+, S100+, vimentin+, CD68+, HLA-DR+, CD4-/, CD30+, most B- and T-cell markers are negative, there are no consistent cytogenetic abnormalities

Interdigitating Dendritic Cell Sarcoma: S100+, vimentin+, CD1a-, langerin-, CD45+/-, CD68+/-, lysozyme+/-, p53+/-, CD21-, CD23-, CD35-, CD34-, CD30-, myeloperoxidase-, most B and T-cell markers are negative, lack *IGH* and TCR gene rearrangements

Follicular Dendritic Cell Sarcoma: Clusterin+, CD21+, CD35+, CD23+, KiM4p+, desmoplakin+, vimentin+, fascin+, EDGR+, HLA-DR+, CD1a-, myeloperoxidase-, lysozyme-, CD34-, CD30-, CD3-, CD79a-, lack *IGH* and TCR gene rearrangements

Disseminated Juvenile Xanthogranuloma: vimentin+, CD14+, CD68+, CD163+, factor XIIIa+/-, fascin+/-, S100-/, CD1a-, langerin-, lack *IGH* and TCR gene rearrangements

## F. Clinical Prognostic Factors and Indices

The specific histologic type of the lymphoid neoplasm, stage of disease, as well as the International Prognostic Index (IPI score) are the main factors used to determine treatment in adults.<sup>13,21,28-33</sup> The 5 pretreatment characteristics that have been shown to be independently statistically significant are: age in years ( $\leq 60$  versus  $> 60$ ); tumor stage I or II (localized) versus III or IV (advanced); number of extranodal sites of involvement (0 or 1 versus  $> 1$ ); patient's performance status (0 or 1 versus 2 to 4); and serum LDH (normal versus abnormal). Based on the number of risk factors, patients can be assigned to 1 of 4 risks groups: low (0 or 1), low intermediate (2), high intermediate (3), or high (4 or 5). Patients stratified by the number of risk factors were found to have very different outcomes with regard to complete response (CR), relapse-free survival (RFS), and overall survival (OS).<sup>13</sup> Studies show that low-risk patients had an 87% CR rate and an OS rate of 73% at 5 years compared to high-risk patients who had a 44% CR rate and a 26% 5-year overall survival rate.<sup>13</sup> A revised IPI (R-IPI) has been proposed for patients with diffuse large B-cell lymphoma who are treated with rituximab plus CHOP chemotherapy.<sup>34</sup> In pediatric cases, there is no equivalent of the IPI, and prognosis is based on stage and type of lymphoma.<sup>16</sup>

A separate prognostic index has become accepted for follicular lymphoma. The Follicular Lymphoma International Prognostic Index (FLIPI) appears to provide greater discrimination and stratification among patients with follicular lymphoma.<sup>35</sup> It evaluates 5 adverse prognostic risk factors including age ( $> 60$  years versus  $\leq 60$  years), Ann Arbor stage (III to IV versus I to II), hemoglobin level ( $< 120$  g/L versus  $\geq 120$  g/L), number of nodal areas ( $> 4$  versus  $\leq 4$ ) and serum LDH level (above normal level versus normal or below). Patients are stratified into 3 risk groups: low risk (0-1 adverse factors), intermediate (2 adverse factors) and poor risk ( $\geq 3$  adverse factors).

Prognostic indices are also under development in other lymphoid neoplasms such as mantle cell lymphoma and T-cell lymphomas.

Although not always provided to the pathologist by the physician submitting the specimen, certain specific clinical findings are known to be of prognostic value in all stages of NHL. In particular, systemic symptoms of fever (greater than  $38^{\circ}\text{C}$ ), unexplained weight loss (more than 10% body weight) in the 6 months before diagnosis, and drenching night sweats are used to define 2 categories for each stage of NHL: A (symptoms absent) and B (symptoms present). The presence of B symptoms is known to correlate with extent of disease (stage and tumor bulk), but symptoms also have been shown to have prognostic significance for cause-specific survival that is independent of stage.<sup>6,28-33,36</sup>

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