Protocol for the Examination of Precursor and Mature Lymphoid Malignancies

Version: 1.0.0.0
Protocol Posting Date: September 2023
The use of this protocol is recommended for clinical care purposes but is not required for accreditation purposes.
This protocol applies to precursor and mature lymphoid malignancies involving blood, bone marrow, lymph node, cutaneous, extranodal/mucosal, or any other anatomic site.

The following tumor types should be reported using this protocol:

Tumor Type
B-lymphoblastic leukemia / lymphomas
+Pre-neoplastic lymphoid proliferations (optionally reported) including monoclonal B lymphocytosis
Mature B-cell neoplasms including: Follicular neoplasms, Mantle cell neoplasms, Lymphoplasmacytic lymphoma, Marginal zone lymphomas, Splenic B-cell lymphomas / leukemias, Large B-cell lymphomas, KSHV / HHV8-associated B-cell lymphoid proliferations and lymphomas, other mature B-cell neoplasms
Hodgkin lymphomas
Precursor T-cell neoplasms
Mature T-cell and NK-cell leukemias including: Primary cutaneous T-cell lymphoid proliferations and lymphomas, Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas, Hepatosplenic T-cell lymphoma, Anaplastic large cell lymphomas, Nodal T-follicular helper (TFH) cell lymphomas, Peripheral T-cell lymphoma, NOS
EBV-positive NK / T-cell lymphomas
EBV-positive T-cell and NK-cell lymphoid proliferations and lymphomas of childhood
Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation

The following tumor types should NOT be reported using this protocol:

Tumor Type
Myeloid/lymphoid neoplasms with eosinophilia and defining gene rearrangement, Acute leukemias of mixed or ambiguous lineage, plasmacytoid dendritic cell neoplasms (use Myeloid and Mixed/Ambiguous Lineage Neoplasms)
Plasma cell neoplasms, Immunoglobulin-related (AL) amyloidosis, Monoclonal immunoglobulin deposition disease, Heavy chain disease (use Plasma Cell Malignancies and Immunoglobulin Deposition Related Disorders)

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Accreditation Requirements
The use of this case summary is recommended for clinical care purposes but is not required for accreditation purposes. The core and conditional data elements are routinely reported. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

Summary of Changes

v 1.0.0.0

- New protocol replacing retired Hodgkin and Non-Hodgkin Lymphoma protocols

Reporting Template

Protocol Posting Date: September 2023
Select a single response unless otherwise indicated.

CASE SUMMARY: (PRECURSOR AND MATURE LYMPHOID MALIGNANCIES)

This protocol is for the reporting of precursor and mature B- and T-cell neoplasms. Hodgkin lymphoma is now included in this cancer case summary to reflect its ontogeny as a mature B-cell neoplasm. This cancer case summary can be used for blood, bone marrow, nodal and extranodal sites of involvement. Clinical staging and prognostic classifications have been removed from the Cancer Case Summaries as these are best performed by the managing physician. Plasma cell neoplasms are reported separately to reflect specific diagnostic features of those neoplasms and to simplify reporting requirements.

TUMOR

Site(s) of Tumor Involvement in Sample (Note A) (select all that apply)

___ Bone marrow (specify percent involvement of neoplastic cells): _____ %
___ Blood (specify percent involvement of neoplastic cells): _____ %
___ Anterior mediastinum
___ Lymph node
___ Cutaneous
___ Extranodal / mucosal site
___ Other (specify): _____

Final Integrated Diagnosis (Note B)

___ Precursor B-cell neoplasms
B-lymphoblastic leukemia / lymphomas
___ B-lymphoblastic leukemia / lymphoma, NOS
___ B-lymphoblastic leukemia / lymphoma with high hyperdiploidy
___ B-lymphoblastic leukemia / lymphoma with hypodiploidy
___ B-lymphoblastic leukemia / lymphoma with iAMP21
___ B-lymphoblastic leukemia / lymphoma with BCR::ABL1 fusion
___ B-lymphoblastic leukemia / lymphoma with BCR::ABL1-like features
___ B-lymphoblastic leukemia / lymphoma with KMT2A rearrangement
___ B-lymphoblastic leukemia / lymphoma with ETV6::RUNX1 fusion
___ B-lymphoblastic leukemia / lymphoma with ETV6::RUNX1-like features
___ B-lymphoblastic leukemia / lymphoma with TCF3::PBX1 fusion
___ B-lymphoblastic leukemia / lymphoma with IGH::IL3 fusion
___ B-lymphoblastic leukemia / lymphoma with TCF3::HLF fusion
___ B-lymphoblastic leukemia / lymphoma with other defined genetic alterations
Other precursor B-cell neoplasm
___ B-lymphoblastic leukemia / lymphoma, pending additional studies (specify): _____
___ Mature B-cell neoplasms
Pre-neoplastic lymphoid proliferations (optionally reported)
+___ Monoclonal B-cell lymphocytosis, CLL-type, low-count (specify absolute count of clonal cells, if possible) (x 10*9/L): _____ x 10*9/L
+___ Monoclonal B-cell lymphocytosis, CLL-type (specify absolute count of clonal cells, if possible) (x 10*9/L): _____ x 10*9/L
+___ Monoclonal B-cell lymphocytosis, non-CLL type (specify absolute count of clonal cells, if possible) (x 10*9/L) : _____ x 10*9/L
CLL / SLL
___ Chronic lymphocytic leukemia / small lymphocytic lymphoma

Follicular neoplasms
___ In situ follicular B-cell neoplasm
___ Follicular lymphoma, classic type (cFL)
___ Follicular lymphoma with unusual cytologic features (uFL)
___ Follicular lymphoma with predominantly diffuse growth pattern (dFL)
___ Follicular large B-cell lymphoma
___ Pediatric-type follicular lymphoma
___ Duodenal-type follicular lymphoma
___ Primary cutaneous follicle center lymphoma
Mantle cell neoplasms
___ In situ mantle cell neoplasm
___ Mantle cell lymphoma
___ Leukemic non-nodal mantle cell lymphoma
Lymphoplasmacytic lymphoma
___ Lymphoplasmacytic lymphoma
Marginal zone lymphomas
___ Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
___ Primary cutaneous marginal zone lymphoma
___ Nodal marginal zone lymphoma
___ Pediatric nodal marginal zone lymphoma
Splenic B-cell lymphomas / leukemias
___ Hairy cell leukemia
___ Splenic marginal zone lymphoma
___ Splenic diffuse red pulp small B-cell lymphoma
___ Splenic B-cell lymphoma / leukemia with prominent nucleoli
Large B-cell lymphomas
___ Diffuse large B-cell lymphoma, NOS
___ T-cell / histiocyte-rich large B-cell lymphoma
___ Diffuse large B-cell lymphoma / high grade B-cell lymphoma with MYC and BCL2 rearrangements
___ ALK-positive large B-cell lymphoma
___ Large B-cell lymphoma with IRF4 rearrangement
___ High grade B-cell lymphoma with 11q aberrations
___ Lymphomatoid granulomatosis
___ EBV-positive diffuse large B-cell lymphoma
___ Diffuse large B-cell lymphoma associated with chronic inflammation
___ Fibrin-associated large B-cell lymphoma
___ Fluid overload-associated large B-cell lymphoma
___ Plasmablastic lymphoma
___ Primary large B-cell lymphoma of immune-privileged sites
___ Primary cutaneous diffuse large B-cell lymphoma, leg type
___ Intravascular large B-cell lymphoma
___ Primary mediastinal large B-cell lymphoma
___ Mediastinal grey zone lymphoma
___ High-grade B-cell lymphoma, NOS
___ Burkitt lymphoma
KSHV / HHV8-associated B-cell lymphoid proliferations and lymphomas
___ Primary effusion lymphoma
___ KSHV / HHV8-positive diffuse large B-cell lymphoma
___ KSHV / HHV8-positive germinotropic lymphoproliferative disorder
Hodgkin lymphomas
___ Classic Hodgkin lymphoma

___ Nodular lymphocyte predominant Hodgkin lymphoma
Other mature B-cell neoplasm
___ Mature B-cell neoplasm (specify): _____
___ Precursor T-cell neoplasms
___ T-lymphoblastic leukemia / lymphoma, NOS
___ Early T-precursor lymphoblastic leukemia / lymphoma
___ Precursor T-cell neoplasm, pending additional studies (specify): _____
___ Mature T-cell and NK-cell neoplasms
Mature T-cell and NK-cell leukemias
___ T-prolymphocytic leukemia
___ T-large granular lymphocytic leukemia
___ NK-large granular lymphocytic leukemia
___ Adult T-cell leukemia / lymphoma
___ Sezary syndrome
___ Aggressive NK-cell leukemia
Primary cutaneous T-cell lymphoid proliferations and lymphomas
___ Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder
___ Primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder
___ Mycosis fungoides
___ Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Lymphomatoid papulosis
___ Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Primary cutaneous anaplastic large cell lymphoma
___ Subcutaneous panniculitis-like T-cell lymphoma
___ Primary cutaneous gamma / delta T-cell lymphoma
___ Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma
___ Primary cutaneous peripheral T-cell lymphoma, NOS
Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas
___ Indolent T-cell lymphoma of the gastrointestinal tract
___ Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract
___ Enteropathy-associated T-cell lymphoma
___ Monomorphic epitheliotropic intestinal T-cell lymphoma
___ Intestinal T-cell lymphoma, NOS
Hepatosplenic T-cell lymphoma
___ Hepatosplenic T-cell lymphoma
Anaplastic large cell lymphomas
___ ALK-positive anaplastic large cell lymphoma
___ ALK-negative anaplastic large cell lymphoma
___ Breast implant-associated anaplastic large cell lymphoma
Nodal T-follicular helper (TFH) cell lymphomas
___ Nodal TFH cell lymphoma, angioimmunoblastic-type
___ Nodal TFH cell lymphoma, follicular-type
___ Nodal TFH cell lymphoma, NOS
Other peripheral T-cell lymphoma
___ Peripheral T-cell lymphoma, NOS
EBV-positive NK / T-cell lymphomas
___ EBV-positive NK-cell and T-cell lymphoma
___ EBV-positive nodal T- and NK-cell lymphoma
___ Extranodal NK / T-cell lymphoma
EBV-positive T-cell and NK-cell lymphoid proliferations and lymphomas of childhood
___ Severe mosquito bite allergy
___ Hydroa vacciniforme lymphoproliferative disorder

___ Systemic chronic active EBV disease
___ Systemic EBV-positive T-cell lymphoma of childhood
Other mature T- or NK-cell neoplasm
___ Mature T- or NK-cell neoplasm (specify): _____
___ Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation
___ Hyperplasias arising in immune deficiency / dysregulation
___ Polymorphic lymphoproliferative disorders arising in immune deficiency / dysregulation
___ EBV-positive mucocutaneous ulcer
___ Lymphomas arising in immune deficiency / dysregulation
___ Inborn error of immunity-associated lymphoid proliferations and lymphomas
+Specify Name of Lesion: _____
+Specify Virus Status: _____
+Specify Type of Immunodeficiency: _____

+Possible Transformation from Indolent Lymphoma (Note C)
___ Not applicable
___ No overt evidence of transformation from more indolent lymphoma / other lymphoma type
___ Lymphoma favored to represent transformation event from indolent lymphoma (explain):
_____

SPECIAL STUDIES (Note D)

Immunohistochemistry
___ Not performed
___ Performed (specify results): _____
___ Pending

Flow Cytometry
___ Not performed
___ No aberrancy detected at level of sensitivity of assay
___ Positive for abnormal lymphoid population (specify immunophenotype, if possible):
_____
___ Pending

Conventional Cytogenetics
___ Not performed
___ Normal diploid karyotype
___ Abnormal karyotype (specify, if possible): _____
___ Pending

Fluorescence in situ Hybridization (select all that apply)
___ Not performed
___ Normal probes (specify loci tested): _____
___ Abnormal probes (specify loci tested): _____
___ Pending

Molecular Alterations Detected# (select all that apply)
 # Select all those with significant mutations
___ ALK translocation (specify): _____

___ MALT1 translocation (specify): _____
___ ATM mutation (specify): _____
___ B2M mutation (specify): _____
___ BCL10 translocation (specify): _____
___ BIRC3 mutation (specify): _____
___ BTK mutation (specify): _____
___ CARD11 mutation (specify): _____
___ CD79A / B mutation (specify): _____
___ BCR::ABL1 p190 fusion transcript
___ BCR::ABL1 p210 fusion transcript
___ BCR::ABL1, unspecified transcript
___ BCL2 mutation (specify): _____
___ BCL2 translocation (specify): _____
___ BCL6 mutation (specify): _____
___ BCL6 translocation (specify): _____
___ BRAF mutation (specify): _____
___ CDKN2A / 2B mutation (specify): _____
___ CCND1 (Cyclin D1) translocation (specify): _____
___ CCND2 (Cyclin D2) translocation (specify): _____
___ CCND3 (Cyclin D3) translocation (specify): _____
___ CXCR4 mutation (specify): _____
___ DUSP22 translocation (specify): _____
___ DNMT3A mutation (specify): _____
___ ETV6 mutation (specify): _____
___ ETV6::RUNX1 fusion (specify): _____
___ EZH2 mutation (specify): _____
___ FBXW7 mutation (specify): _____
___ GATA3 mutation (specify): _____
___ iAMP21 (specify): _____
___ IDH1 / 2 mutation (specify): _____
___ IGH::IL3 rearrangement (specify): _____
___ IGHV mutated (specify): _____
___ IGHV unmutated (specify): _____
___ IRF4 mutation (specify): _____
___ JAK1 mutation (specify): _____
___ JAK2 mutation (specify): _____
___ JAK3 mutation (specify): _____
___ KLKF2 mutation (specify): _____
___ KRAS mutation (specify): _____
___ KMT2A rearrangement (specify): _____
___ MYC rearrangement (specify): _____
___ MYD88 mutation (specify): _____
___ NOTCH1 mutation (specify): _____
___ NOTCH2 mutation (specify): _____
___ NRAS mutation (specify): _____
___ PDGFRA translocation (specify): _____
___ PLCG1 / 2 mutation (specify): _____
___ PTEN mutation (specify): _____
___ RB1 mutation (specify): _____

___ RHOA mutation (specify): _____
___ RPS15 mutation (specify): _____
___ SF3B1 mutation (specify): _____
___ STAT3 mutation (specify): _____
___ STAT5B mutation (specify): _____
___ STAT6 mutation (specify): _____
___ TET2 mutation (specify): _____
___ TCF3::PBX1 rearrangement (specify): _____
___ TCF3::HLF fusion rearrangement (specify): _____
___ TNFAIP3 mutation (specify): _____
___ TNFRSF14 mutation (specify): _____
___ TP53 mutation (specify): _____
___ TP63 translocation (specify): _____
___ TRAF3 mutation (specify): _____
___ XPO1 mutation (specify): _____
___ Other alterations detected (specify): _____
___ Pending: _____

+Specify Molecular Alterations Assayed: _____

COMMENTS

Comment(s): _____

Explanatory Notes

A. Site of Involvement in Sample

This cancer case summary may be used in any anatomical site that is involved including bone marrow, blood, mediastinum, lymph nodes, and skin/extranodal sites. If multiple sites are involved (for example, bone marrow and blood or cutaneous and lymph node) you may select multiple sites. For leukemias/lymphomas involving bone marrow or blood, specify the relative tumor percentage of nucleated cells.

B. Final Integrated Diagnosis

The final integrated diagnoses for the precursor and mature lymphoid neoplasms are based on the WHO 5th edition of Haematolymphoid Tumors.[1] The 5th edition significantly updates the last revision of the WHO 4th edition in 2017. There are important changes in terminology, diagnostic criteria, and increasing reliance on ancillary studies such as conventional karyotyping, fluorescence in-situ hybridization (FISH), and comprehensive molecular genetic profiling by next-generation sequencing with abilities to detect point mutations, insertions, deletions, copy number alterations, and gene rearrangements.

The final integrated diagnosis should be based on the major subsections of the WHO 5th edition, including precursor B lymphoid neoplasms, mature B-cell neoplasms, precursor T-cell lymphoid neoplasms, and mature T- and NK-cell neoplasms. It is worth noting that the WHO 5th edition includes the classification of Tumor like lesions with B-cell predominance and tumor like lesions with T-cell predominance. These were not included in the cancer case summary as these are not considered lymphoid neoplasms. Pre-neoplastic lymphoid proliferations, by virtue of being lymphoid neoplasms, albeit clinically not malignant, are included as an optional category in this cancer case summary (see below).

The diagnostic criteria for the entities in the WHO 5th edition are summarized in the WHO monograph and beyond the scope of the explanatory notes. Specific categories that may benefit from additional explanation regarding use of the cancer case summary are highlighted in the following sections.

Pending/other diagnostic category

This cancer case summary is designed to be used when a complete, integrated diagnosis can be rendered, including ancillary comprehensive immunophenotyping, cytogenetic, and molecular. There may be some who wish to use this cancer summary to render a preliminary diagnosis prior to receipt of all pending ancillary studies; ideally, this approach would be used when a cancer case summary can be updated/ addended/ amended or a new complete cancer protocol can be issued. To accommodate that use, an optional subcategory of pending diagnostic studies has been added to precursor B- and T-cell neoplasms as an optional choice. In addition, for mature B-and T-or NK-cell lymphoid neoplasms, the category of other has been added to allow reporting of cases pending further studies or alternate terminology. If using the PENDING option, when all diagnostic ancillary studies are complete, it is strongly recommended to ensure that an updated complete diagnostic cancer case summary is submitted by updating the report.

Precursor B-cell neoplasms

B-lymphoblastic leukemia (B-ALL) is used when the blood or bone marrow is the primary site of involvement, whereas B-lymphoblastic lymphoma (B-LBL) refers to neoplasms whose primary site of involvement are lymph nodes or extra-nodal sites. Historically, B-lymphoblastic leukemia is used to denote cases with 25% or more bone marrow blasts. The distinction between B-lymphoblastic leukemia and lymphoma is somewhat arbitrary, especially when both sites are involved, and for that reason, the cancer case summary lists B-lymphoblastic leukemia/lymphoma as a single category.

B-lymphoblastic leukemia/lymphoma, NOS is reserved for those neoplasms that lack diagnostic criteria for other subtypes after comprehensive testing. Do not use this category for B-lymphoblastic leukemia/lymphoma cases that are pending additional studies.

B-lymphoblastic leukemia/lymphoma with high hyperdiploidy should be rendered when the karyotype identifies 51-65 chromosomes with the absence of other specific genetic subtypes defined by karyotype and/or FISH. In the setting of a failed karyotype, FISH studies for chromosomes X, 4, 6, 10, 14, 17, 18, and 21 can help identify high hyperdiploidy B-ALL.

B-lymphoblastic leukemia/lymphoma with hypodiploidy is defined by the presence of fewer than 43 chromosomes with the absence of other specific genetic subtypes. Care must be taken to avoid misinterpretation of "pseudo-hyperdiploidy" due to doubling of previously hypodiploid cells.[2] The diagnostic criteria for B-cell lymphoblastic leukemia/lymphoma with *BCR::ABL1* -like features are described in detail in the WHO 5th edition. While initially defined by gene expression profiling, the lack of availability of this method commercially often necessitates the use of fluorescence in-situ hybridization (FISH)/ molecular studies for genetic alterations, including those involving *PDGFRb* (5q32), *BCR/ABL1-ASS1* t(9;22), *JAK2* (9p24.1), *EPOR* (19p13.2) and *CRLF2* (Xp22.33/Yp11.32).[1]

B-lymphoblastic leukemia/lymphoma with other defined genetic alterations encompasses those with the following genetic alterations. It is worth noting that many of these rearrangements are cryptic on conventional karyotype and require sequencing-based methodologies (RNA and/or DNA based NGS, RT-PCR) or break-apart FISH studies.[1]

List of B-lymphoblastic leukemia with other defined genetic alterations:
B lymphoblastic leukemia with *DUX4* rearrangement
B lymphoblastic leukemia with *MEF2D* rearrangement
B lymphoblastic leukemia with *ZNF384* rearrangement
B lymphoblastic leukemia with *PAX5alt*
B lymphoblastic leukemia with *PAX5* p.P80R
B lymphoblastic leukemia with *NUTM1* rearrangement
B lymphoblastic leukemia with *MYC* rearrangement

Table 1: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF B-LYMPHOBLASTIC LEUKEMIAS/LYMPHOMAS[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
B-lymphoblastic leukemia/lymphoma, NOS	• B-ALL: more than 20% of B lymphoblasts by flow cytometry with B-cell lineage markers • B-LBL: At histology effaced lymph node architecture or diffuse infiltration of an organ by a monomorphic population of blasts with B immunophenotype (CD19, CD22, c CD79a, and/or PAX5) and markers of immaturity (TdT, CD34, and/or CD99), surface immunoglobulin negative. CD34 and TdT expression may be absent in rare cases and pose a diagnostic challenge	Exclusion of a more specific category listed below using ancillary methods including karyotype, FISH and molecular genetics studies
B-lymphoblastic leukemia/lymphoma	• Meets criteria for diagnosis of B-ALL/LBL	Single nucleotide polymorphism (SNP) arrays to

with high hyperdiploidy	• Karyotype comprising 51-65 chromosomes in the absence of other subtype-defining translocations by karyotyping and/or FISH • Flow cytometry DNA Index can be an indicator of high hyperdiploidy but cannot confirm the precise chromosomal gains	better exclude double near-haploid/low hypodiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy	• Meets criteria for diagnosis of B-ALL/LBL • Karyotyping and/or FISH showing less than 44 chromosomes • Flow cytometry DNA Index can be an indicator of hypodiploidy but cannot confirm the precise chromosomal losses	Single nucleotide polymorphism (SNP) arrays to better identify 'masked' hypodiploidy
B-lymphoblastic leukemia/lymphoma with iAMP21	• Meets criteria for diagnosis of B-ALL/LBL • Demonstration of ≥5 copies of *RUNX1* per cell, with ≥3 or more copies on a single abnormal chromosome 21	
B-lymphoblastic leukemia/lymphoma with *BCR::ABL1* fusion	• Meets criteria for B-ALL/LBL • Detection of the *BCR::ABL1* fusion • Exclusion of cases of B-ALL that acquire *BCR::ABL1* secondarily during therapy	Exclusion of lymphoid blast crisis of chronic myeloid leukemia
B-lymphoblastic leukemia/lymphoma with *BCR::ABL1*-like features	• Meets criteria for B-ALL/LBL • *BCR::ABL1*-like gene signature and/or genomic alteration described for this type	
B-lymphoblastic leukemia/ lymphoma with *KMT2A* rearrangement	• Meets criteria for B-ALL/LBL • Demonstration of *KMT2A* rearrangement	Identification of *KMT2A* rearrangement partner
B-lymphoblastic leukemia/lymphoma with *ETV6::RUNX1* fusion	• Meets criteria for B-ALL/LBL • Demonstration of *ETV6::RUNX1* rearrangement	
B-lymphoblastic leukemia/lymphoma with *TCF3::PBX1* fusion	• Meets criteria for B-ALL/LBL • Demonstration of *TCF3::PBX1* rearrangement	
B-lymphoblastic leukemia/lymphoma with *IGH::IL3* fusion	• Meets criteria for B-ALL/LBL • Demonstration of *IGH::IL3* rearrangement	
B-lymphoblastic leukemia/lymphoma with *TCF3::HLF* fusion	• Meets criteria for B-ALL/LBL • Demonstration of *TCF3::HLF* rearrangement	
B-lymphoblastic leukemia/lymphoma with other defined genetic alterations	• Meets general criteria for B-ALL/LBL • Demonstration of a specific genetic abnormality as defined in this section. • Absence of genetic mutations of other definitive and provisional B-ALL types. • Specific genetic abnormalities – B-lymphoblastic leukemia with *DUX4* rearrangement – .B-lymphoblastic leukemia with *MEF2D* rearrangement	Depends on particular subtype

	– B-lymphoblastic leukemia with *ZNF384* rearrangement – B-lymphoblastic leukemia with *PAX5*alt – B-lymphoblastic leukemia with PAX5 p.P80R – B-lymphoblastic leukemia with *NUTM1* rearrangement – B-lymphoblastic leukemia with *MYC* rearrangement	

Pre-neoplastic and neoplastic small lymphocytic proliferations

The reporting of the pre-neoplastic lymphoid category of monoclonal B-cell lymphocytosis is optional for the cancer case summary. With the development of high-sensitivity flow cytometry immunophenotypic assays, monoclonal B-cell lymphocytosis may be detected with increasing frequency depending on patient age-ranging from 5% (40-50 years) to upwards of 50-75% (over 90 years).[3] If monoclonal B-cell lymphocytosis is to be reported, it is recommended to record the absolute count of the clonal B-cell population- not the absolute lymphocyte count or absolute B lymphocyte count. This will allow for distinction between low-count monoclonal B-cell lymphocytosis, CLL-type (absolute clonal lymphocyte population is below 0.5 x 10^9/L), and monoclonal B-cell lymphocytosis, CLL-type (≥0.5 x 10^9/L) in the blood. It is important to note that this diagnosis should not be rendered if there are other clinical features of lymphoma (lymphadenopathy, organomegaly) or established diagnosis of B-cell lymphoid neoplasm.
Different categories of the optional category of pre-neoplastic lymphoid proliferations:

Table 2: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF PRE-NEOPLASTIC LYMPHOID PROLIFERATIONS[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
Monoclonal B-cell lymphocytosis	• Demonstration of a monotypic B-cell population (light-chain restriction or rarely lack of surface light chain expression by flow cytometry or monoclonal immunoglobulin gene rearrangement with a peripheral B-cell count of <5 x 10^9/L • Absence of lymphadenopathy, organomegaly, or any features diagnostic of another B-lymphoproliferative disorder • Low count MBL/clonal-cell expansion: Clonal B-cell count <0.5 x 10^9/L and typical CLL/SLL phenotype • CLL/SLL-type MBL: clonal B-cell count ≥0.5 x 10^9/L and typical CLL/SLL phenotype • Non-CLL/SLLMBL: Any clonal B-cell expansion without typical CLL/SLL phenotype	CLL/SLL type: CD5+, CD23+, LEF1+

Chronic Lymphocytic Leukemia

Table 3: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)[1]

Diagnosis	Essential Diagnostic Features
Chronic lymphocytic leukemia/small lymphocytic lymphoma	• Classic morphology of CLL cells and absolute B-cell count >5 × 10^9/L in blood • Flow cytometry (on blood and/or bone marrow aspirate samples) shows expression of CD5, CD19, CD20 (dim), CD23 (variable) and monotypic surface light chain(dim) • Histopathology/immunohistochemistry demonstrate CD20+/weak+, CD5+/weak+, CD23 (variable), LEF1+ and SOX11-. No expression of cyclin D1 (except for a few weakly positive proliferation center cells.)

Splenic B-cell lymphomas and leukemias

Table 4: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF SPLENIC B-CELL LYMPHOMAS AND LEUKEMIAS[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
Hairy cell leukemia	• Characteristic morphology (in a blood or bone marrow smear) characterized by small to intermediate size cells with oval to indented nuclei with bland ground-glass chromatin, absent or inconspicuous nucleoli, and variably abundant pale-staining cytoplasm with circumferential fine villous cytoplasmic projections and/or in a bone marrow biopsy specimen a characteristic “fried-egg” appearance with cells having oval or indented nuclei, abundant cytoplasm, and prominent cell-to-cell borders • Strong positivity for CD20 and Annexin-1 by immunohistochemistry or co-expression of CD20/CD11c/CD103/CD25 by flow cytometry and/or immunohistochemistry	• Clonal *BRAF* p.V600E (NP_004324.2) mutation • Useful adjuncts are the expression of CD123, bright CD22, bright CD200, bright surface immunoglobulins, cyclin-D1, and TBX21/T-Bet • CD5 and CD10 are usually negative but there are rare exceptions
Splenic marginal zone lymphoma	• Small B-cell lymphoma involving bone marrow and/or blood composed of small lymphoid cells with villous processes • Neoplastic cells express pan-B-cell markers, IgM and IgD and are negative for BCL6, annexin A1, CD103, cyclin D1, SOX11 and LEF1 • Other splenic and nodal B-cell lymphomas should be excluded • Clinical or imaging studies that show splenomegaly	• Neoplastic cells negative for CD5 and CD10
Splenic diffuse red pulp small B-cell lymphoma (SDRPL)	• Diffuse infiltration of the spleen by monomorphic small B-cells, accompanied by atrophic white pulp	• Absence of *BRAF* p.V600E (NP_004324.2) mutation

	• Blood with circulating small cells with abundant cytoplasm, broad-based and unevenly distributed cytoplasmic villous projections are well-visible and inconspicuous nucleolus • Immunophenotype compatible with SDRPL	• Absence of lymphadenopathy other than splenic hilar lymph node involvement
Splenic B-cell lymphoma/leukemia with prominent nucleoli	• Circulating medium-sized lymphoid cells with prominent nucleoli or convoluted nuclei. Although rare cells in the peripheral blood may show poorly defined cytoplasmic projections, circumferential fine villous (hairy) projections are absent • Presence of B-cell antigens CD19, CD20, CD79a, or PAX5 • Absence of characteristic phenotype of HCL, including expression of CD25, annexin A1, cyclin D1, and TRAP	• Diffuse involvement of the splenic red pulp with atrophic white pulp, but most cases are diagnosed without a spleen specimen • Absence of *BRAF* p.V600E (NP_004324.2) mutation

Lymphoplasmacytic Lymphoma/Marginal Zone lymphoma

Table 5: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF LYMPHOPLASMACYTIC LYMPHOMA AND MARGINAL ZONE LYMPHOMAS[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
Lymphoplasmacytic lymphoma	• BM infiltration by >10% small lymphocytes with plasmacytoid and/or plasma cell differentiation • Immunophenotype of LPL cells: IgM+, CD19+, CD20+, CD22+, CD25+, CD10-, CD23-, CD103-, CD138+/-	• Detection of *MYD88* (NP_002459.2:p.L265P) [NGS based assays may show false negative in 1/3 of cases] • Detection of CXCR4 somatic mutation • Serum electrophoresis and immunofixation shows presence of monoclonal IgM
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue	• Lymphoma arising in an extranodal site • Atypical small/medium-sized lymphoid cell proliferation mimicking reactive MALT and showing architectural distortion • Expression of B-lineage markers • Exclusion of other small B-cell neoplasms, e.g., follicular lymphoma, mantle cell lymphoma, small lymphocytic lymphoma, lymphoplasmacytic lymphoma and plasmacytoma	• Demonstration of light chain restriction on B-cells +/- monotypic plasma cells or clonal immunoglobulin (Ig) gene rearrangement • Remnants of underlying inflammatory background e.g., reactive lymphoid follicles, Hashimoto thyroiditis in thyroid or lymphoepithelial sialadenitis in salivary gland
Primary cutaneous marginal zone lymphoma	• Morphology consistent with MZL • Presence of CD5-negative, CD10-negative small B cells	• Lesions often on trunk or arms

	• Demonstration of monotypic plasma cells, monotypic B-cells, and/or clonal immunoglobulin (Ig) gene rearrangement • No evidence of extracutaneous disease at the time of diagnosis • Exclusion of other cutaneous lymphomas	• Reactive lymphoid follicles in lesion
Nodal marginal zone lymphoma	• Proliferation predominantly of small, mature B-cells with scant to moderate amount of pale cytoplasm, with or without plasmacytic differentiation • Architectural distortion in a nodular/follicular, parafollicular, interfollicular, or diffuse growth pattern • Absence of markers supporting follicular lymphoma, mantle cell lymphoma or other specific small B-cell lymphomas; presence of markers such as Myeloid cell nuclear differentiation antigen (MNDA) or immunoglobulin superfamily receptor translocation-associated 1 (IRTA1)	• Residual follicles with follicular colonization • Detection of monotypic Ig light chain expression in B-cells and/or plasma cells • Detection of clonal immunoglobulin gene (Ig) rearrangements in challenging cases
Pediatric nodal marginal zone lymphoma	• Partial effacement of LN architecture by interfollicular proliferation of marginal zone cells with monocytoid and centrocyte-like morphology • Monoclonal *IGH* and/or *IGK* genes rearrangements • Immunophenotype compatible with marginal zone B-cells (BCL6-, CD43+/-)	• Residual follicles with PTGC-like features • Follicular colonization • Monotypic light chain restriction • Increased PD1+ cells in reactive germinal centers

Follicular Lymphoma

The category of In-situ follicular neoplasia (ISFN) was recognized to highlight cases in which the neoplastic cells are confined only to follicles with no extension past the mantle zones or interfollicular areas. Morphologic features by themselves are not diagnostic for this entity- although subtle changes in composition of the follicles and particularly the germinal center may suggest this diagnosis. ISFN is distinguished from normal, reactive lymphoid follicles by the presence of cells within the follicle that express abnormally bright/intense CD10 and BCL2. As there is typically partial involvement of the follicles, there exists an internal control for expression intensity of CD10 and BCL2 that can be compared to the adjacent follicular mantle zones that show less intense expression than ISFN. ISFN invariably carries BCL2 gene rearrangements; no precursor lesion is described for BCL2 gene rearrangement negative follicular lymphoma.

The grading and reporting of follicular lymphoma has changed in the WHO 5th edition of Hematolymphoid Tumors. Classic follicular lymphoma (cFL) encompasses grades 1-3A, maintains a follicular pattern, and is composed of a mixture of centrocytes and centroblasts (CB) (larger, transformed cells) as was defined in WHO 4th edition revision. Previously follicular lymphoma was graded on the basis of the number of centroblasts/transformed cells per 10 high-powered fields (HPF, 0.159 mm diameter), with grade 3A being defined as greater than 15 CB and grade 3B, those cases devoid of centrocytes. Given difficulties in reproducibility and lack of significant outcomes differences with existing treatment regimens, cFL will

encompass those previously defined as grade 1-3A, with grade 3B (those with absence of centrocytes) being defined as follicular large B-cell lymphoma. One may still consider reporting a grade if this is an agreed-upon practice at the local facility, but for cancer case summary reporting purposes, such distinction is not required. Follicular lymphoma with unusual cytologic features is to be used for rare cases without typical centrocyte morphology, be it immature chromatin or large centrocyte cells with fine chromatin and inconspicuous nucleoli.[4,5] Follicular lymphoma with a predominantly diffuse pattern (dFL) is another recognized variant most reliably diagnosed on excisional biopsy specimens, often involving the inguinal region and showing some microfollicles as well as diffuse areas, CD10 and CD23 positivity, absence of *IGH::BCL2* rearrangement and often abnormalities of chromosome 1p36 and/or mutations of *TNFRSF14*.[6]

Table 6: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF FOLLICULAR LYMPHOMA[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
In situ follicular B-cell neoplasm	• Variable numbers of B-cells within germinal centers staining intensely for BCL2 • Maintained lymph node or extranodal lymphoid tissue architecture, and lacking features of classic FL	• Strong CD10 expression in the BCL2-positive B-cells within the follicles
Follicular lymphoma	• B-cell lymphoma composed of varying proportions of centrocytes (CC) and/or centroblasts (CB)/large, transformed cells, with the dominance of CC in the majority of cases • Immunophenotype compatible with germinal center B-cell origin with positivity to markers such as CD10, BCL6, MEF2B, GCET1, GCET2 or LMO2	• At least partly follicular growth pattern • *BCL2* or rarely *BCL6* rearrangements and/or lack of *IRF4* rearrangement
Pediatric-type follicular lymphoma	• Pediatric and young adult age group (usually age <40 years, most 2-25 years) • Localized nodal disease • Purely follicular growth with marked architectural distortion and germinal center marker expression • Predominance of intermediate to large-size 'blastoid'cells and high proliferation fraction • Absence of diffuse proliferation of large cells meeting criteria for DLBCL • Evidence of B-cell monoclonality by immunophenotyping or genetic • Absence of *BCL2, BCL6,* and *MYC* rearrangements • Absence of strong, uniform MUM1 expression and/or absence of *IRF4* rearrangement	• Markedly expansile follicles • Mutations in *MAP2K1* and *TNFRSF14*
Duodenal-type follicular lymphoma	• Germinal center B-cell lymphoma with tumor cells confined predominantly to the mucosa of the intestine, and characterized by follicles composed	• Exclusion of secondary involvement from nodal/systemic FL, especially when atypical

	predominantly of centrocytes, and with positivity for germinal center markers and BCL2	pathological features are observed
Primary cutaneous follicle center lymphoma	• Follicular and/or diffuse proliferation of centrocytes and admixed centroblasts (diffuse lymphomas comprising exclusively centroblasts/immunoblasts are excluded) • B cells with co-expression of germinal center markers (BCL6 and/or CD10 or other germinal center markers) • No extracutaneous involvement by lymphoma	• Localization to head or trunk • Evidence of B-cell monoclonality • Absent or weak BCL2 expression (often) • Lack of MUM1 expression • Lack of *BCL2* rearrangement (often)

Mantle cell lymphoma

In situ mantle cell neoplasm (ICMCN) is defined as the presence of mantle zone cells harboring *CCND1::IGH* fusions with resultant cyclin D1 overexpression confined to the follicular mantle. The immunophenotype may differ from overt nodal mantle cell lymphoma, with some cases showing absence of CD5 or SOX117.[7] Leukemic non-nodal mantle cell lymphoma (nnMCL) represents a subset of clinically indolent mantle cell lymphoma cases that involve the bone marrow, blood and spleen without significant lymphadenopathy. Similar to mantle cell lymphoma, expression of CD5, bright CD20, and cyclin D1 overexpression attributable to a *CCND1::IGH* fusion are present. However, these cases are characteristically negative/weak for SOX11, show lower proliferative indexes by Ki-67, and may have some immunophenotypic overlap with chronic lymphocytic leukemia (CLL), including expression of CD200 and CD23.[8]

Table 7: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF MANTLE CELL LYMPHOMA[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
In situ mantle cell neoplasm	• Preservation of lymphoid architecture without expansion of the mantle zone • Cyclin D1-positive B-cells predominantly restricted to the inner layers of mantle zones of lymphoid follicles • Staging negative for overt MCL	Detection of a CCND1 rearrangement in the mantle cells could be performed in unclear cases
Mantle cell lymphoma	• Lymphoma cells of B-lineage (CD20-positive and usually CD5-positive) • Morphology of classic variant (monomorphic and centrocyte-like) or less often variant morphology • Cyclin D1-positive and/or detection of CCND1 rearrangement and/or SOX11-positive	Very rare cases lack cyclin D1 expression and *CCDN1::IGH*. In these cases, SOX11 is positive.
Leukemic non-nodal mantle cell lymphoma	• Typical clinical presentation (lymphocytosis, mostly asymptomatic; no or insignificant nodal involvement) • Usually monomorphic small to medium-sized cells of B-lineage (CD20+) • Cyclin D1 positive and/or detection of CCND1 rearrangement	SOX11 (commonly negative)

Large B-cell lymphomas

There have been important changes to the category of Large B-cell lymphomas in the WHO 5th edition Classification of Hematolymphoid Tumors that warrant clarification to appropriately use the cancer case summary.

The category of Diffuse Large B-cell lymphoma, NOS (DLBCL, NOS), defines lymphomas composed of medium to large cells with a diffuse or only vaguely nodular growth pattern. Cytologically, three subsets may be seen: centroblastic (large, irregular cells with ample cytoplasm, non-prominent nucleoli); immunoblastic (moderate, more basophilic cytoplasm with prominent central nucleolus); or anaplastic (marked cytomegaly with bizarre nuclear features).

Gene expression profiling (GEP) studies recognized cell of origin and divided large B-cell lymphomas into germinal center B-cell like (GCB), activated B-cell like (ABC), and unclassified (~15%) groups, and the ABC group was reported to have a worse prognosis.[9] However, not all studies have confirmed the association with worse prognosis, and more recent studies using GEP and other high-throughput methods have developed a far more granular system likely to be employed in the near future.[10,11] Immunohistochemistry is typically employed as a surrogate for GEP in this classification: GCB and non-GCB groups can be derived using these methods, with imperfect correlation but more clinical availability. The commonly used Hans algorithm uses greater than 30% expression of CD10, BCL6, and MUM1 to separate into GCB and ABC/Non-GCB.[12]

Molecular/genetic analysis to evaluate for the presence of *BCL2* and *MYC* gene rearrangements is strongly recommended in cases that are morphologically diffuse large B-cell lymphoma or high-grade B-cell lymphoma (see discussion below). Fluorescence in-situ hybridization (FISH) panels targeting *BCL2* and *MYC* (and often *BCL6*) rearrangements via break-apart and/or fusion probes are the most common method. Cases that demonstrate a *BCL2* and *MYC* rearrangement should be assigned to the category DLBCL with *MYC* and *BCL2* gene rearrangements. Those cases that show a *MYC* rearrangement or *MYC* and *BCL6* should be reported as diffuse large B-cell lymphoma, NOS in the cancer case summary. The findings of *BCL6* and *MYC* rearrangement should be reported in the case and annotated in the molecular genetic findings portion of the Cancer Case Summary.

High-grade B-cell lymphoma, NOS (HGBCL, NOS) is reserved for tumors that are composed of intermediate size cells with Burkitt-like or blastoid morphology and frequently evidence of high tumor proliferation (apoptotic bodies or high Ki-67 proliferative fraction). It is to be distinguished from Burkitt lymphoma in which the tumor cells are more uniform compared to the more variable nuclear and cytoplasmic variability in high-grade B-cell lymphoma, NOS. It is also important to exclude lymphoma types with similar morphology that possess defining molecular genetic findings including diffuse large B-cell lymphoma with *MYC* and *BCL2* rearrangements, large B-cell lymphoma with *IRF4* rearrangement, high-grade B-cell lymphoma with 11q alterations and blastoid mantle cell lymphoma.

EBV-positive diffuse large B-cell lymphoma

Diagnosis of this entity is challenging and requires knowledge of clinical features and Epstein Barr virus (EBV) status of the lymphoma. Morphologically, these are similar to diffuse large B-cell lymphoma; however, the number of neoplastic lymphocytes may be variable and display morphologic features of Hodgkin/Reed Sternberg (HRS) like cells and express bright, uniform intensity of CD30. A distinguishing feature of EBV-positive large B-cell lymphoma is expression of EBV-associated markers (typically EBV-encoded small RNA - EBER). There is considerable overlap with the immune deficiency and dysregulation associated lymphoproliferative disorders, EBV+ mucocutaneous ulcer, and lymphomatoid granulomatosis. If there is a known immunosuppressive state- such as transplantation, immunodeficiency syndrome or

iatrogenic immunosuppression-the category of immune deficiency and dysregulation associated lymphoproliferative disorders should be used. This distinction can be difficult in the setting of immune senescence and there is likely some overlap; this category is best applied in the setting of a high proportion of tumor cells positive for EBV. EBV+ mucocutaneous ulcer is typically unifocal, localized, superficial, and involves mucocutaneous sites compared with the more frequent nodal and disseminated EBV+ large B-cell lymphoma. Lymphomatoid granulomatosis (LYG), another EBV-associated lymphoproliferative disorder, typically shows an angiocentric pattern in the lungs, and less often other extranodal sites, with variable numbers of small and large EBV+ cells increasing in number in higher grade lesions (Grade 3 LYG).

Table 8: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF LARGE B-CELL LYMPHOMA[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
Diffuse Large B-cell lymphoma, NOS	• Large B-cell lymphoma with a diffuse pattern (vague nodularity is acceptable if not follicular) • Mature B-cell phenotype • Exclusion of other specific entities of large B-cell lymphoma	• Cell of origin subtyping • Reporting of isolated *MYC* or simultaneous *MYC* and *BCL6* rearrangements • Genetic testing, if relevant for clinical decision making
T-cell/histiocyte-rich large B-cell lymphoma	• Diffuse effacement of lymph node architecture • Singly scattered large B-cells, without formation of aggregates or sheets • Reactive background rich in histiocytes and small T cells, with no (or few) scattered small B-cells • Absence of FDC meshworks by CD21 or CD23 stain • Absence of nodular lymphocyte predominant Hodgkin lymphoma	• Lymph node excision is preferred • Exclude EBV association
Diffuse large B-cell lymphoma/high grade B-cell lymphoma with MYC and BCL2 rearrangements	• Morphology and phenotype consistent with aggressive B-cell lymphoma (large B-cell, Burkitt-like, or blastoid) • Evidence of concurrent *MYC* and *BCL2* rearrangements (with or without *BCL6* rearrangement)	• Germinal center B-cell phenotype • Determination of TdT protein expression status. • Determination of *MYC* fusion partner
ALK-positive large B-cell lymphoma	• Large cell morphology • Plasmablastic immunophenotype (plasma cell-associated markers such as CD138, MUM1, VS38c, BLIMP1, XBP1 positive and CD20 negative/variable and weak) • *ALK* expression	• *ALK* genetic alterations (usually translocations) • No EBV association

Large B-cell lymphoma with IRF4 rearrangement	• Intermediate or large cell morphology and follicular and/or diffuse growth pattern • Mature B-cell immunophenotype with co-expression of BCL6 and MUM1 • *IRF4* translocation. If *IRF4* rearrangement analysis cannot be performed, the proper clinical setting in combination with a typical immunophenotype allows the diagnosis but as “not molecularly confirmed”	• Evidence of the *IGH::IRF4* translocation • Absence of *BCL2* and *MYC* gene rearrangement
High-grade B-cell lymphoma with 11q aberrations	• Lymphoma with an intermediate/blastoid or Burkitt-like morphology • Typical immunophenotype (B-cell markers+, CD10+, BCL6+, BCL2-) • Chromosome 11q-gain/loss, telomeric loss, or telomeric LOH pattern • Exclusion of a *MYC* translocation	• Expression of CD56, CD16 or CD8 in the absence of CD38high by flow cytometry
Lymphomatoid granulomatosis	• Extranodal disease (usually lungs) • Polymorphous lymphoid infiltrate with striking angiocentricity • Transmural involvement of small to medium-sized vessels by variable numbers of EBV+ large B-cells admixed, with abundant small T lymphocytes • Exclusion of immune deficiency other than immune senescence	

EBV-positive diffuse large B-cell lymphoma	• Partial or total architectural effacement of affected tissue • Atypical lymphoid infiltrate composed of either sheets of large malignant cells or many scattered large, transformed cells of variable morphology including, HRS-like cells in a richly cellular reactive background, often accompanied by necrosis • Large cells confirmed to be of B-cell lineage (e.g., CD20, PAX5, CD79a) • EBV present in most (>50%) of large B-cells • Absence of in-born or acquired immunodeficiency or a history of lymphoma • Exclusion of other EBV-related lymphomas and lymphoproliferative disorders	• EBV DNA detectable in serum or whole blood (in selected cases)
Diffuse large B-cell lymphoma associated with chronic inflammation	• Large B-cell lymphoma • Setting of local chronic inflammation • EBV association • Exclusion of other EBV-associated neoplasms	• Occurrence in a natural or acquired confined body or tissue space • Pyothorax-associated lymphoma is the prototype
Fibrin-associated large B-cell lymphoma	• Microscopic aggregates of atypical large B-lymphocytes in fibrinous debris • At sites of chronic fibrin deposition in confined natural or acquired anatomic spaces and sites • No mass of lymphoma cells; no infiltration into pre-existing normal parenchymal tissue	• Non-GCB B-cell immunophenotype • EBV positivity
Fluid overload-associated large B-cell lymphoma	• Large cell lymphoma restricted to body-cavity effusions • Secondary involvement by systemic lymphoma excluded • B-cell immunophenotype • KSHV/HHV8 negative	• Clonal Ig gene rearrangement

Plasmablastic lymphoma	• Lymphoma with plasmablastic/immunoblastic morphology • Expression of plasma cell-associated antigens (e.g., MUM1, CD138, BLIMP1) • Negativity for CD20, PAX5, ALK and KSHV/HHV8	• EBV (EBER) in ~60% of cases • Detection of *MYC* rearrangements • Detection of clonal Ig gene rearrangements
Primary large B-cell lymphoma of immune-privileged sites	• Large B-cell lymphoma primarily confined to the CNS, vitreoretina (VR), or testis at presentation • Exclusion of secondary involvement by other entities of large B-cell lymphoma • Exclusion of immune deficiency/dysregulation-related settings	• Post germinal center B-cell phenotype (MUM1+; BCL6+; CD10-) • Absence of EBV (in >97% of cases) • Demonstration of clonal B cell population or a *MYD88* and/or *CD79B* hotspot mutations in cases in which histology is not definitive (e.g., corticosteroid-mitigated PCNS-LBCL or PVRL-LBCL)
Primary cutaneous diffuse large B-cell lymphoma, leg type	• Dermal and/or subcutaneous infiltration by sheets of large cells (centroblasts, immunoblasts, blastoid cells) • Mature B-cell immunophenotype • Diffuse growth with absence of follicular dendritic cell meshworks • Skin-confined disease at presentation	• Strong *BCL2* expression • IgM+ and MUM1+, non-GCB phenotype
Intravascular large B-cell lymphoma	• Large lymphoid cells with centroblastic, immunoblastic, or rarely anaplastic morphology • Restricted to intravascular spaces, especially capillaries; a minimal extravascular component is acceptable • Pan B-cell markers positive	• KSHV/HHV8 negative (LANA immunohistochemistry) • EBV-negative by EBER in situ hybridization
Primary mediastinal large B-cell lymphoma	• Large B cell lymphoma in the anterior mediastinum • Mature B-cell immunophenotype, accompanied by at least partial expression of CD23 and/or CD30	• Distinctive stromal sclerosis • Expression of at least one of the following markers: MAL, CD200, PD-L1 and PD-L2 • Copy gain or rearrangement of CD274/PDCD1LG2 locus and/or rearrangement involving *CIITA (C2TA)*

High-grade B-cell lymphoma, NOS	• Intermediate-size or blastoid cytomorphology not consistent with either diffuse large B-cell lymphoma or Burkitt lymphoma • Lack of TdT and CD34 expression to exclude lymphoblastic lymphoma. Lack of cyclin D1 expression to exclude MCL • Absence of a double hit translocation involving *MYC* and *BCL2* • Absence of the 11q23.2-q23.3 gain and 11q24.1-qter deletion pattern of HGBL-11q	• 'Double hit' B-cell lymphoma gene expression signature • *KMT2D* and *TP53* mutations

Burkitt Lymphoma

Burkitt lymphoma (BL) is characterized by monomorphic medium/intermediate-size cells with dense basophilic cytoplasm, high proliferative fraction with frequent apoptotic bodies, and *MYC* gene rearrangements detectable by FISH in most cases. As in some cases, *MYC* rearrangements can be cryptic and missed by conventional FISH studies, absence of *MYC* rearrangement in the presence of other typical morphological and immunophenotypic features should not deter from a diagnosis of BL. BL is in the differential diagnosis of HGBCL, NOS, and morphologically with HGBCL/DLBCL with *MYC* and *BCL2* rearrangements. Rearrangements of *MYC* and *BCL2* or *BCL6* exclude the diagnosis of BL. In cases with BL morphology and immunophenotype that lack a *MYC* gene rearrangement, it is important to exclude high-grade B-cell lymphoma with 11q aberration (duplication, inversion, or deletion). Alterations of 11q are not specific to HGBCL with 11q aberration and may occur in cases otherwise diagnostic of BL or HGBCL, NOS with *MYC* rearrangements.[13]

Table 9: SUMMARY OF MAJOR DIAGNOSTIC FEATURES OF DLCBL, NOS, HIGH-GRADE B-CELL LYMPHOMA AND BURKITT LYMPHOMA[1]

Diagnosis	Morphology	Molecular Genetic Findings
Diffuse Large B-cell lymphoma	• Large cells- centroblastic, immunoblastic or anaplastic	Absence of defining molecular genetic findings; may have *MYC* or *MYC* and *BCL6* rearrangements
Diffuse large B-cell lymphoma/high-grade B-cell lymphoma with MYC and BCL2 rearrangements	• Variable ranging from DLBCL- like to blastoid	*MYC* and *BCL2* rearrangements, additional alterations may be present
High-grade B-cell lymphoma, NOS	• Medium-sized cells, some nuclear and cytoplasmic variability	Absence of defining molecular genetic findings
HGBCL with 11q aberration	• Medium size, uniform, blastoid	Absence of *MYC* gene rearrangement, aberrations of 11q
Burkitt lymphoma	• Medium-sized, monomorphic lymphoma cells with basophilic cytoplasm and multiple small nucleoli CD20 and CD10 positivity	*MYC* gene rearrangement

	• Absence or (rarely) weak expression of BCL2	

KSHV/HHV-8 associated B-cell lymphoid proliferations and lymphomas

Kaposi sarcoma herpesvirus/human herpesvirus 8 (KSHV/HHV8) associated lymphoid proliferations and lymphomas encompass the diagnostic categories of primary effusion lymphoma (PEL)/extracavitary primary effusion lymphoma (EC-PEL), KSHV/HHV8 positive diffuse large B-cell lymphoma and KSHV-8/HHV8-positive germinotropic lymphoproliferative disorder. There is an update in the nomenclature in the WHO 5th edition Hematolymphoid Tumors to incorporate the full name of the associated virus (Kaposi sarcoma herpesvirus/human herpesvirus 8-KSHV/HHV8). There are a few areas of clarification that are important for the use of this diagnostic category in the Lymphoid cancer case summary.

The vast majority of KSHV/HHV8-associated lymphomas are associated with immune deficiency/dysregulation (IDD). However, there do exist cases that do not appear to have associated overt IDD. For those that arise in the clinical setting of IDD, the use of the Lymphoma arising in the setting of immune deficiency/dysregulation (IDD) is preferred. (See discussion below on IDD-associated lymphomas).

Primary effusion lymphoma is most common in patients with HIV/AIDS and treated with immunosuppression. Typically, PEL presents with pleural, pericardial, or abdominal cavity effusion containing variably immunoblastic/plasmablastic cells with a terminal B-cell immunophenotype (CD19-, CD20-, PAX5-, OCT2-, CD79a-, CD138+, CD38+, MUM1+, EMA+), and expression of the activation marker CD30.[14] HHV8 is, by definition, positive by immunohistochemistry for KSHV/HHV8 latent protein LANA1. Co-infection with EBV, demonstrable by in-situ hybridization for Epstein Barr virus encoded early RNA (EBER), occurs frequently in HIV/AIDS, less often in endemic (Mediterranean) or immune senescence-associated cases. PEL may present as a solid extracavitary mass (EC-PEL).
There is considerable diagnostic overlap between KSHV/HHV8-positive diffuse large B-cell lymphoma and EC-PEL. KSHV/HHV8-positive diffuse large B-cell lymphoma is distinguished by expression of IgM and absence of immunoglobulin somatic hypermutation (SHM) as the tumor cell of origin tumor is a naïve IgM+ without immunoglobulin somatic hypermutation (SHM).[15]

Table 10: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF KSHV/ HHV8 ASSOCIATED B-CELL LYMPHOID PROLIFERATIONS AND LYMPHOMAS[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
Primary effusion lymphoma	• Large B-cell lymphoma presenting as a serous effusion in the pleural, pericardial, or abdominal cavity • A tumor mass, directly associated with the effusion is accepted. Absence of lymph node or other extranodal involvement • Large pleomorphic malignant cells with immunophenotype of terminally differentiated B-cells • KSHV/HHV8 positive (usually by LANA immunohistochemistry)	• The presence of EBV, although neither necessary nor sufficient, is supportive of the diagnosis
KSHV/HHV8-positive diffuse large B-cell lymphoma	• Presentation with primary nodal and/or splenic involvement • Effacement of architecture by large blasts/transformed B-cells with generally	• Demonstration of immunoglobulin somatic hypermutations (SHM)

	plasmablastic, immunoblastic, or anaplastic morphology • Positive immunostaining for LANA (KSHV/HHV8) and IgM	• EBER in situ hybridization (usually negative, but it can be positive in some cases)
KSHV/HHV8-positive germinotropic lymphoproliferative disorder	• Retained lymph node architecture with some germinal centers partially or completely replaced by clusters or sheets of plasmablastic, immunoblastic and/or anaplastic cells • Positive immunostaining for LANA (KSHV/HHV8)	• Positive in situ hybridization for EBV (EBER) and no evidence of clonal Ig gene rearrangement

Hodgkin lymphoma

In this revision, the separate cancer case summary for Hodgkin Lymphoma that included classic Hodgkin lymphoma (CHL) and nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) was removed to reflect that these neoplasms are of B-cell origin.

While there are four subtypes of CHL recognized- nodular sclerosis, lymphocyte-rich, mixed-cellularity, and lymphocyte depleted- reporting of these in the cancer case summary is not required as there is limited prognostic relevance with modern treatments.

The diagnostic features of CHL and NLPHL are well covered in the WHO 5th edition monograph. For purposes of using the cancer case summary, it is important to remember that CHL may arise in the setting of immune deficiency and dysregulation (IDD), and when appropriate that category should be utilized.

Table 11: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF HODGKIN LYMPHOMA[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
Classic Hodgkin lymphoma	• Primary nodal or mediastinal presentation • HRS cells and variants in a reactive microenvironment composed of varying proportions of small • Lymphocytes, eosinophils, histiocytes, plasma cells, and neutrophils • Immunophenotype of HRS cells: CD30+, PAX5+ (weak to moderate), CD15+/-, CD20-/ weak/ heterogeneous, CD45-	• Immunophenotype of HRS cells: decreased expression of OCT2 and BOB1 • EBV positive (~20% of nodular sclerosis and ~70% of mixed cellularity) • Histological subtyping (if possible) • Exclusion of mimics of CHL by appropriate work-up
Nodular lymphocyte predominant Hodgkin lymphoma	• Nodular architecture, at least focally • LP tumor cells: Single, scattered large cells with multilobated nuclei, vesicular chromatin, and one or more, generally small, nucleoli • Immunophenotype: Uniform positivity for several B-cell antigens (usually CD20-positive)	• Characteristic immunophenotype of LP cells (CD20, OCT2, BCL6) and of background TFH cells (PD1-positive) rosetting around tumor cells • Defining growth patterns (A-F). Since this may be highly challenging on core

	• Immune microenvironment: Many small lymphocytes, histiocytes, and follicular dendritic cells; no significant eosinophils	needle core biopsies, a lymph node excision is preferred

Precursor T-cell neoplasms

The diagnostic categories from the revised WHO 4th edition Hematolymphoid classification are retained in the WHO 5th edition. T-lymphoblastic leukemia/lymphoma, NOS represents a neoplasm of T-cells with an immature immunophenotype demonstrated by expression of CD34, CD1a, CD117, CD99, or TdT. Remaining markers, when expressed, reflect various stages of T-cell maturation, including expression of cytoplasmic CD3, typically bright CD7, diminished CD5, variable CD4, and CD8 with frequent co-expression. Early T-precursor lymphoblastic leukemia/lymphoma is distinct in having a more immature immunophenotype with committed T-cell lineage (expression of cytoplasmic CD3, absent CD1a, absent CD8) and expression of stem cell and myeloid markers (one or more CD34, HLA-DR, CD11b, CD13, CD33, CD65, CD117).[16]

The cancer case summary combines T-lymphoblastic leukemia and lymphoma. By convention, when bone marrow and blood are involved, leukemia is used; involvement of lymph nodes, thymus, or other extranodal sites are termed T-lymphoblastic lymphomas. Treatment protocols define T-lymphoblastic leukemia as having 25% or more blasts in the marrow when both sites are involved. This distinction can be made in the narrative diagnostic report; the cancer case summary allows reporting of the percentage of neoplastic cells in the bone marrow and/or blood.

Table 12: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF PRECURSOR T-CELL NEOPLASMS[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
T-lymphoblastic leukemia/lymphoma, NOS	• The presence of hematopoietic progenitors of T lineage, defined largely by the expression of surface and/or cytoplasmic CD3, having an aberrant immunophenotype	• The number of abnormal T progenitors or blasts exceeds 20% in the peripheral blood or bone marrow, or involves an extramedullary site • However, unlike myeloid neoplasms, a defined number of blasts in blood or marrow is not required for the diagnosis of T-ALL/LBL. In practice, the diagnosis should be made with care when blasts are <20%, as there is no convincing evidence to suggest outcome is adversely affected by deferring therapy until blasts reach 20%
Early T-precursor lymphoblastic leukemia/lymphoma	• Lymphoblastic leukemia/lymphoma features by morphology • Blasts must express an early T-precursor immunophenotype characterized by the following: – Positive for cytoplasmic CD3	

	– Absent (<5% positive blasts) CD1a and CD8 expression – Absent or dim (<75% positive blasts) CD5 expression – Positive (≥25% positive blasts) for 1 or more myeloid (CD11b, CD13, CD33, CD65, CD117) and/or stem cell (CD34, HLA-DR) markers – Negative (<3%) myeloperoxidase	

Mature T-cell and NK-cell neoplasms

There has been a significant increase in the understanding of mature T- and NK-cell lymphomas, particularly regarding underlying molecular genetic alterations. Despite this, the diagnostic categories from the revised 4th edition of WHO remain largely the same, with some notable changes.

Mature T-cell and NK-cell leukemias

Chronic lymphoproliferative disorder of NK-cells was changed to NK-large granular lymphocytic leukemia (NK-LGLL) to reflect clonal nature and maintain consistency with the nomenclature of T- large granular lymphocytic leukemia.

Table 13: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF MATURE T-CELL AND NK-CELL LEUKEMIAS[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
T-prolymphocytic leukemia	• Lymphocytosis >5x10^9/L with T-PLL immunophenotype in peripheral blood or bone marrow • T-cell monoclonality • *TCL1A* or *MTCP1* rearrangement, alternatively TCL1A protein expression	• Detection of a juxtaposition of the *TCL1A* or *MTCP1* gene next to a T-cell receptor (*TCR*) locus mostly the *TRA/TRD* locus
T-large granular lymphocytic leukemia	• An increase in circulating cytotoxic T-cells, often greater than 2x10^9/L but may be less • Presence of a T-cell population (usually CD8 positive) with down-regulation of CD5 and/or CD7 and/or abnormal expression of CD16 and NK-cell associated receptors • Evidence of T-cell monoclonality (or oligoclonality) • Presence of two of these three essential criteria in association with one desirable criterion is sufficient for a diagnosis of T-LGLL	• Bone marrow immunohistochemistry revealing shows intra-sinusoidal cytotoxic T-cell infiltrates • *STAT3* mutation
NK-large granular lymphocytic leukemia	• An increase in circulating NK-cells, typically greater than 2x10^9/L, persisting greater than 6 months • Flow cytometric evidence of blood or bone marrow involvement by a uniform	•

	population of surface CD3 negative, CD16 positive NK-cell population • Killer cell Ig-like receptors (KIRs) restricted pattern of expression, demonstrated by flow cytometry analysis (either a dominant expression of a relevant KIR or lack of them), is accepted as a surrogate marker of clonal expansion • Bone marrow involved by intra-sinusoidal cytotoxic CD8 positive NK-cells and/or the presence of *STAT3* and/or *TET2* mutations with NK-cell lineage confirmed by flow cytometry • If both 2 and 3 are present, a diagnosis of NK-LGLL can be established in the absence of documented persistence of an absolute blood NK-cell count of greater than $2x10^9$/L •	
Adult T-cell leukemia/lymphoma	• Neoplastic lymphoid cell proliferation with mature T-cell phenotype • Occurrence in HTLV-1 carrier	• Lymphoid cells with prominent convolutions and lobulation • Identification of monoclonal integration of HTLV-1 (may not be commercially available)
Sezary syndrome	• Erythroderma involving greater than 80% body surface area • Evidence of blood involvement defined by demonstration of clonal *TCR* gene rearrangements and either an absolute Sézary cell count ≥1000/μL or CD4/CD8 ratio >10, CD4+CD7- cells ≥40% or CD4+CD26- cells ≥30%	•
Aggressive NK-cell leukemia	• Acute presentation, with fever and systemic symptoms • Systemic (multi-organ) proliferation of neoplastic lymphoid cells • NK-cell immunophenotype • Lack of TCR protein expression and/or lack of clonal rearrangement of *TCR* genes	• EBER positivity (positive in ~90% of cases) • Hemophagocytic lymphohistiocytosis

Primary Cutaneous T-cell lymphoid proliferations and lymphomas

The category cutaneous peripheral T-cell lymphomas, rare subtypes in the WHO 4th edition, was expanded to separately list the diagnostic entities of subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous gamma/delta T-cell lymphoma, primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma and finally primary cutaneous peripheral T-cell lymphoma, NOS.

Table 14: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF PRIMARY CUTANEOUS T-CELL LYMPHOID PROLIFERATIONS AND LYMPHOMAS[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
Primary cutaneous CD4-positive small or medium T-cell lymphoproliferative disorder	• Asymptomatic solitary skin lesion located head and neck > trunk > extremities • One of the 2 architectural patterns (nodular and/or diffuse versus band-like) • Predominance of CD4+ small/medium-sized pleomorphic T cells admixed with B-cell component • TFH cell phenotype: strong PD1 expression by atypical cells +/- ICOS, BCL6, CXCL13 but CD10 negative	• Adnexotropism • Absence of lymphoid follicles • Scattered reactive cells: CD8+ T-cells, CD30+ cells, plasma cells, eosinophils, and histiocytes
Primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder	• Dense predominantly dermal non-epidermotropic infiltrate of atypical small to medium-sized CD8-positive cytotoxic T-cells • Typical clinical presentation of a usually solitary nodule at acral sites • No extracutaneous involvement at diagnosis	• Characteristic Golgi dot-like expression of CD68 by tumor cells • Monoclonal rearrangement of *TCR* genes • Absence of immunodeficiency, EBV always negative
Mycosis fungoides	In early stage MF: • Presence of persistent and/or progressive patches and plaques especially in sun-protected areas • Presence of small to medium-sized atypical T-cells with hyperchromatic hyperconvoluted (cerebriform) nuclei, preferentially in the epidermis In tumor stage MF: • Evidence of concurrent or preceding patches and plaques with histologic features characteristic of MF	• Loss of pan T-cell antigens • Demonstration of clonal *TCR* gene rearrangements in skin biopsy in selected cases
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Lymphomatoid papulosis	• Infiltrates of mostly medium-sized, scattered (type A) or numerous (type C) atypical lymphoid cells with expression of CD30 and various background infiltrates expressing T-cell markers • Clinical presentation with waxing and waning papulo-nodular skin lesions • Spontaneous regression within weeks to a few months • Exclusion of other lymphomas by clinico-pathological correlation	• Detection of clonal rearrangement of *TCR* genes may be helpful in selected cases (especially in LyP subtype A)
Primary cutaneous CD30-positive T-cell lymphoproliferative disorder: Primary cutaneous anaplastic large cell lymphoma	• Distribution limited to skin and/or mucosa • Cells with anaplastic, pleomorphic, or immunoblastic morphology • CD30 expression in >75% of tumor cells • No clinical history or evidence of mycosis fungoides, in order to exclude diagnosis	

	of mycosis fungoides with CD30+ large cell transformation • No history of lesions waxing and waning (exclude lymphomatoid papulosis)	
Subcutaneous panniculitis-like T-cell lymphoma	• Lobular subcutaneous infiltrate composed predominantly of atypical CD3+, CD8+, ßF1+, T-cells	• Detection of clonal rearrangements of *TCR* genes may be helpful in selected cases • Absence of gamma-delta T-cell receptor and EBV expression within the atypical cells
Primary cutaneous gamma/delta T-cell lymphoma	• Monoclonal proliferation of CD3+, TCR gamma/delta+ T-cells in skin or subcutis • Exclusion of other lymphomas such as lymphomatoid papulosis and/or classic mycosis fungoides • EBV negative	• CD4-/CD8- or CD4-/CD8+ phenotype • At least one cytotoxic marker expressed (TIA1, granzyme B, perforin) • No extracutaneous disease at diagnosis (may evolve later)
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma	• Epidermotropic and adnexotropic cutaneous infiltrate composed of pleomorphic cytotoxic αβT-lymphocytes • Lesions do not self-heal (as seen in lymphomatoid papulosis)	• Demonstration of activating mutations or gene fusions of the JAK2 pathway
Primary cutaneous peripheral T-cell lymphoma, NOS	• Diffuse or nodular dermal infiltrates of atypical T-lymphocytes • No extracutaneous involvement of the lymphoma at time of diagnosis • Diagnosis of exclusion; does not meet the diagnostic criteria of defined CTCL entities	• Molecular studies to exclude other specific entities in selected cases

Intestinal T-cell and NK-cell lymphoid proliferations and lymphomas

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract was updated in the WHO 5th edition to indolent T-cell lymphoma to reflect an often protracted clinical course, but still with significant clinical symptoms and ability to disseminate.

Indolent NK-cell lymphoproliferative disorder of the gastrointestinal tract was added in the WHO 5th edition to capture cases that were previously diagnosed as NK-cell enteropathy- a clinically indolent, often regressing, non-disseminating atypical proliferation of NK-cells (CD2+, CD56+, CD7+, TIA-1+, granzyme B+, surface CD3-) in mucosal sites in the gastrointestinal tract. The recent discovery of frequent mutations supports the interpretation that this disease represents a neoplastic proliferation.[17] An important consideration in the differential diagnosis is the clinically aggressive extranodal NK/T-cell lymphoma. Distinction is made based on deep mucosal involvement, near-universal association with EBV(EBER in-situ hybridization+), and clinical aggressive course.

Table 15: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF INTESTINAL T-CELL AND NK-CELL LYMPHOID PROLIFERATIONS AND LYMPHOMAS AND HEPATOSPLENIC T-CELL LYMPHOMA[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
Indolent T-cell lymphoma of the gastrointestinal (GI) tract	• Non-destructive, predominantly non-epitheliotropic infiltrate of small mature lymphocytes confined to the GI mucosa +/- submucosa • T-lineage (CD4+, CD8+, CD4+/CD8+ or CD4-/CD8-), with TCRαβ expression • Low proliferation index (Ki-67 <10%)	• Detection of clonal *TCR* rearrangement (or somatic mutations) can assist in distinction from an inflammatory disorder
Indolent NK-cell lymphoproliferative disorder of the GI tract	• Superficial mucosal (and exceptionally lymph node) infiltrate of atypical cells with NK-cell immunophenotype • EBV negative	• Lack of clonal *TCR* gene rearrangements
Enteropathy-associated T-cell lymphoma	• An infiltrate of pleomorphic medium-sized to large lymphoid cells • Variable inflammatory background often including many eosinophils and histiocytes • Uninvolved intestinal mucosa shows features of CD (villous atrophy, crypt hyperplasia, intraepithelial lymphocytosis) • T-cell lineage, often with a CD4- CD8- phenotype, with expression of cytotoxic markers	• CD30 positivity (usually in cases of large cell or anaplastic morphology) • In problematic cases, presence of *JAK*1 JH1-kinase and/or *STAT3* SH2 domain hotspot mutations can assist in distinguishing EATL from MEITL
Monomorphic epitheliotropic intestinal T-cell lymphoma	• Dense infiltration by relatively monotonous medium-sized or occasionally large lymphoma cells • Typically lacking necrosis • Epitheliotropism is common • No histological evidence of celiac disease in uninvolved mucosa • T-lineage, commonly CD3+, CD5−, CD4−, CD8+, CD56+, TIA1+ • EBV negative	• *SETD2* inactivation due to mutation or deletion is very common. Often *JAK3* and *STAT5* mutations
Intestinal T-cell lymphoma, NOS	• Lymphoma with the bulk of disease localized to the GI tract • Medium to large-sized lymphoma cells • Expression of T-lineage markers • Exclusion of defined types of GI T- and NK-cell lymphoma	• Clonal *TCR* rearrangement
Hepatosplenic T-cell lymphoma	• Characteristic pattern of extranodal disease (sinusoidal involvement) • Sinusoidal involvement of bone marrow, liver, or spleen • Small to intermediate-size lymphoma cells without intracytoplasmic granules	• Characteristic immunophenotype: CD4-, CD5-/+, CD8-/+, CD56+/- • Isochromosome (7q); trisomy 8

	• Cytotoxic T-cell lineage	

Anaplastic large cell lymphoma

A minor change in nomenclature was adopted in the WHO 5th edition Hematolymphoid classification by listing ALK-positive or ALK-negative before anaplastic large cell lymphoma to reflect the importance of this distinction. ALK-negative anaplastic large cell lymphomas remain a heterogenous group. *DUSP22* rearrangements are not uncommon (20-30%) within this group and may be recognizable by "doughnut cell" morphology, LEF1 expression, and absence of marked pleomorphism.[18] The prognostic significance of *DUSP22* rearrangement is uncertain with earlier reports showing prognosis comparable to ALK-positive anaplastic large cell lymphoma; more recent studies show a prognosis intermediate between ALK-negative and ALK-positive.[19] Less frequent *TP63* rearrangements can also be identified that are associated with a poor prognosis.[19] It is important to distinguish systemic ALK-negative anaplastic large cell lymphoma from clinically localized variants primary cutaneous anaplastic large cell lymphoma and breast implant-associated anaplastic large cell lymphoma.

Table 16: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF ANAPLASTIC LARGE CELL LYMPHOMA[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
ALK-positive anaplastic large cell lymphoma	• ALK expression in lymphoma cells • Characteristic strong uniform expression of CD30 in lymphoma cells	•
ALK-negative anaplastic large cell lymphoma	• Complete or partial infiltration of lymph node or extranodal tissue by large pleomorphic cells with lobated nuclei, distinct nucleoli, including "hallmark cells" • Uniform strong expression of CD30 • Absence of ALK protein expression or *ALK* rearrangement • Negative for EBV	• Expression of T-cell markers and cytotoxic markers, albeit with frequent losses • Clonal rearrangement of *TCR* gene • Rearrangements of *DUSP22* (20-30% of ALK- cases) and *TP63* (about 5% of ALK- cases) or mutations of *JAK2* or *STAT3* (about 30% of cases) can be detected by appropriate molecular methods
Breast implant-associated anaplastic large cell lymphoma	• Presence of breast implant; CD30+ lymphoma cells with anaplastic features • Proven T-cell lineage supported by expression of one or more T-lineage markers and/or clonal *TCR* gene rearrangement	• Identification of lymphoma cells on luminal side of capsule in properly oriented tissue sections

Nodal T-follicular helper (TFH) cell lymphoma

Nodal T-follicular helper (TFH) cell lymphomas represent a category of mature T-cell neoplasms that share immunophenotypic features of T-follicular helper cells. In the WHO 5th edition Hematolymphoid Classification of Tumors the different subgroups of this lymphoma were grouped with the common prefix-nodal TFH cell lymphoma- followed by the particular subtype, including angioimmunoblastic-type, follicular type, and not otherwise specific (NOS). The lymphomas in this category share an immunophenotype that involves the expression of at least 2 T-follicular helper markers, the most commonly used being PD1, ICOS,

BCL6, CXCL13, and CD10 along with variable CD2, CD3, CD5, and often diminished intensity of CD7.[20] The entities in this category are distinguished by architectural pattern with angioimmunoblastic showing a polymorphous infiltrate with background expanded follicular dendritic cell networks and prominent proliferations of high endothelial venules (HEV). Nodal TFH cell lymphoma, follicular type has a distinct follicular pattern without associated follicular dendritic or HEV proliferations. Finally, nodal TFH cell lymphoma, NOS is reserved for cases with more abundant tumor cells and lack of background polymorphous infiltrate or HEV proliferation. There may be significant overlap between tumor cell-rich nodal TFH cell lymphoma, angioimmunoblastic type, and the not otherwise specified (NOS) subtype. *RHOA* mutations are particularly common in this group (up to 70% of nTFHL-AI). It is important to note that these lymphomas often contain marked B-cell proliferations composed of immunoblasts that may progress to overt large B-cell lymphomas, commonly EBV-positive.

Table 17: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF NODAL T-FOLLICULAR HELPER (TFH) CELL LYMPHOMA[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
Nodal TFH cell lymphoma, angioimmunoblastic-type	• Nodal disease • CD4-positive (occasionally CD4-negative), CD8-negative atypical lymphoid cells • Extrafollicular follicular dendritic cell (FDC) expansion and high endothelial venule (HEV) hyperplasia (mild in tumor cell-rich cases)	• Expression of ≥2 TFH markers, including strong PD1 • Clonal *TCR* gene rearrangement and/or mutation involving *RHOA* p.G17V(NP_001655.1) and/or *IDH2* p.R172 • *TET2* and *DNMT3A* mutations very common • EBV-positive B-cells
Nodal TFH cell lymphoma, follicular-type	• Follicular growth pattern (FL-like or PTGC-like) • No extrafollicular FDC expansion • CD4-positive (occasionally CD4-negative), CD8-negative atypical T-cells that express ≥2 TFH markers including strong PD1	• • Lack of polymorphous infiltrate and HEV hyperplasia • Clonal *TCR* gene rearrangement and/or mutation involving *RHOA* p.G17V (NP_001655.1), *IDH2* mutations rare • *t(5;9)(q33;q22)*/ITK::SYK may be detected • *TET2* and *DNMT3A* mutations very common
Nodal TFH cell lymphoma, NOS	• Nodal disease with effaced architecture/T-zone pattern by a morphologically atypical and/or immunophenotypically aberrant atypical T-cell infiltrate that is CD4-positive, CD8-negative, and expresses at least 2 TFH markers, including strong PD1. • Lack of extrafollicular FDC hyperplasia, perifollicular distribution of neoplastic T-	• Clonal *TCR* gene rearrangement and/or mutation involving *RHOA* p.G17V (NP_001655.1), *IDH2* mutations rare • *TET2* and *DNMT3A* mutations very common

	cells, and follicular growth pattern	

Other peripheral T-cell lymphomas

Peripheral T-cell lymphoma (PTCL), NOS should be reserved for those cases that do not fit into another defined diagnostic category. These neoplasms do not express 2 or more of T-follicular helper markers; ALK+ and ALK- anaplastic large cell lymphomas and extranodal NK/T-cell lymphoma are excluded. Most PTCL, NOS cases lack substantial numbers of EBV+ (EBER) cells.

Table 18: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF PERIPHERAL T-CELL LYMPHOMA, NOS[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
Peripheral T-cell lymphoma, NOS	• Presence of an abnormal T-cell infiltrate, which is morphologically or immunophenotypically aberrant and/or monoclonal by ancillary studies • The tumor cells are negative or express only one TFH marker (to distinguish from nodal TFH cell lymphomas) and only show EBER in scattered B-cells (to distinguish from EBV-positive nodal T and NK-cell lymphoma) • Exclusion of other nodal or extranodal mature T and NK cell lymphomas (i.e., ALK+ anaplastic large cell lymphoma, ALK- anaplastic large cell lymphoma, adult T-cell leukemia/lymphoma, extranodal NK/T-cell lymphoma)	• Clonal *TCR* gene rearrangements • Distinguish PTCL-TBX21 and PTCL-GATA3 using antibodies specific for TBX21, CXCR3, GATA3 and CCR4 (not readily available in most commercial labs)

EBV-positive NK-cell and T-cell lymphomas

EBV-positive nodal NK-cell and T-cell lymphoma is a predominantly lymph node-based neoplastic proliferation of cytotoxic T-cells or NK-cells in which the vast majority of the tumor cells are positive for Epstein Barr virus by EBV-encoded small RNA (EBER) in situ hybridization. Most of these rare lymphomas have a cytotoxic T-cell immunophenotype, with the minority having an NK-cell phenotype. These are distinguished from extranodal NK/T-cell lymphomas by having a predominantly nodal presentation, frequent expression of T-cell markers including CD8, and lack of CD56 expression as genetics features.[1]

Extranodal NK/T-cell lymphoma, nasal type from the WHO 4th edition revised classification had the qualifier "nasal type" removed in the WHO 5th edition to reflect that it may occur in other locations. Extranodal NK/T-cell lymphoma predominantly occurs (80% of cases) in the nasal cavity, paranasal sinuses, nasopharynx, and oropharynx. The remaining cases (20%) involve skin, gastrointestinal tract, and testis, among others. Tumor cells may range from small to large in a given case but an angiocentric growth pattern with associated necrosis with EBV-positive tumor cells are present in all cases.

Table 19: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF EBV-POSITIVE NK-CELL AND T-CELL LYMPHOMAS[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
EBV-positive nodal T- and NK-cell lymphoma	• Cytotoxic T-cell or NK-cell lymphoma • EBER present in the majority of neoplastic cells	

	• Tumor primarily localized within lymph nodes but may involve a limited number of extranodal sites, no nasal involvement • Exclusion of immune deficiency associated T- and NK-cell lymphoproliferative diseases, ENKTL and systemic EBV-positive lymphoproliferative diseases of childhood, and aggressive NK-cell leukemia with progression or secondary involvement of lymph nodes	
Extranodal NK/T-cell lymphoma	• Infiltration of extranodal tissues by lymphoma cells with variable morphology • NK or cytotoxic T-cell phenotype • Virtually all of tumor cells are positive for EBER	• An angiocentric growth pattern occurs in ~70% of cases • Necrosis is very common

EBV-positive T-cell and NK-cell lymphoid proliferations and lymphomas of childhood

There has been some update to the nomenclature for this group of rare Epstein Barr virus-associated lymphoproliferative disorders that have a predilection for Asians and Native Americans from Mexico, Central and South America, and most commonly occur in childhood. Severe mosquito bite allergy is a cutaneous form of chronic active EBV disease with high fever and marked skin involvement occurring after mosquito bites. Hydroa vacciniforme lymphoproliferative disease is a related process with similar morphology but absence of clear association with mosquito bites and, in the classic non-systemic form, localized to sun-exposed skin. Systemic chronic active EBV disease is a systemic EBV+ lymphoproliferative process lasting longer than 3 months, more commonly T-cell compared to NK-cell, that involves multiple organs, bone marrow, and spleen. There may be associated hemophagocytic syndrome (HLH) and the prognosis is poor. Finally, EBV-positive T-cell lymphoma of childhood represents a cytologically obvious lymphoma often with prior chronic active EBV disease.

It is important to note that this group is reserved for the immunocompetent. If there is a prior inborn error of immunity or other immune deficiency or dysregulation (IDD) the resultant process should be classified in that category.

Table 20: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF EBV-POSITIVE T-CELL AND NK-CELL LYMPHOID PROLIFERATIONS OF CHILDHOOD[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
Severe mosquito bite allergy	• High fever and severe skin manifestations after mosquito bites • Bite site biopsy shows lymphoid infiltrate with NK-cell, or less commonly T-cell, immunophenotype • EBER positive	• High circulating EBV-DNA load • Lack of T-cell receptor protein expression and/or clonal *TCR* gene rearrangement in cases of NK-cell origin
Hydroa vacciniforme lymphoproliferative disorder	• Classic HV-LPD: no persistent systemic symptoms, lymphadenopathy, hepatosplenomegaly, hepatitis, hemophagocytic syndrome, or NK-cell lymphocytosis	

	• Systemic HV-LPD: ≥1 of the persistent symptoms listed above, or signs of extracutaneous disease • Papulovesicular skin eruption with or without photo-exacerbation that heals with varioliform scarring • Peri-vascular and peri-adnexal atypical lymphoid infiltrate of cytotoxic T- or NK-cells • EBER positive	
Systemic chronic active EBV disease	• Infectious mononucleosis-like symptoms persisting >3 months • Increased EBV-DNA in peripheral blood or EBER-positive cells in affected organs with evidence of EBV infection in T- or NK-cells • Exclusion of known immunodeficiency, malignancy, or autoimmune disorders	
Systemic EBV-positive T-cell lymphoma of childhood	• Multi-organ infiltration by EBV+ atypical T-cells • Absence of immunodeficiency • Fever and systemic symptoms	• Clonal *TCR* gene rearrangements • Hemophagocytic lymphohistiocytosis (HLH) • Hepatosplenomegaly • Abnormal karyotype

Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation

The WHO 5th edition Classification of Hematolymphoid Tumors incorporates the changes proposed by the 2015 Workshop of the Society for Hematopathology/European Association for Hematopathology to develop a more standardized framework for reporting of lymphoid proliferations/lymphomas associated with immune deficiency and dysregulation that incorporated three major elements: 1) histologic lesion; 2) presence of oncogenic virus(es); and 3) nature/etiology of the immunodeficiency.

The WHO 5th edition Classification of Hematolymphoid Tumors recognizes mass lesions that are not overt lymphomas- notably entities considered under hyperplasias arising in immune deficiency/dysregulation (IDD), Polymorphic lymphoproliferative disorders arising in IDD and EBV-positive mucocutaneous ulcer. As these do not represent overt lymphomas- the reporting in considered optional in this cancer case summary. Briefly, the category of hyperplasias arising in IDD encompasses more uniform lymphoid/plasma cell proliferations without effacement of lymphoid architecture. Polymorphic lymphoproliferative disorders arising in IDD shows more cytologic atypia and architectural effacement. EBV-positive mucocutaneous ulcer represents a typically localized, superficial ulcer of mucosal sites or skin composed of an EBV-positive polymorphous lymphoid infiltrate with immunoblasts and HRS-like cells. A more detailed discussion is provided in the WHO 5th edition Classification of Hematolymphoid Tumors.[1]

Lymphomas arising in immune deficiency/dysregulation (IDD) and inborn error of immunity-associated lymphoid proliferations and lymphomas may represent any lymphoma that may occur in immunocompetent patients, including small B-cell lymphomas, diffuse large B-cell lymphomas, Burkitt lymphoma, classical Hodgkin lymphoma, and T-cell lymphomas, among others. The 2015 Society for Hematopathology/European Association for Hematopathology proposed that reporting should incorporate the nature of the lesion, presence of oncogenic virus(es), and type of immunodeficiency.

These elements are included in the cancer case summary as optional elements. Examples of such reporting include:

Example #1
Report narrative diagnosis: Diffuse large B-cell lymphoma, EBV+, autoimmune setting

_X_ Lymphoma arising in immune deficiency/dysregulation
-Name of lesion (specify): Diffuse large B-cell lymphoma
-Virus status (specify): EBV
-Type of immunodeficiency (specify): Autoimmunity

Example #2
Report narrative diagnosis: Primary effusion lymphoma, KSHV/HHV8+, EBV+, acquired immunodeficiency (HIV/AIDS)

_X_ Lymphoma arising in immune deficiency/dysregulation
-Name of lesion (specify): Primary effusion lymphoma
-Virus status (specify): KSHV/HHV8, EBV
-Type of immunodeficiency (specify): Acquired immunodeficiency (HIV/AIDS)

Example #3
Report narrative diagnosis: Extranodal marginal zone B-cell lymphoma, no viruses detected, common variable immunodeficiency

_X_ Inborn error of immunity-associated lymphoid proliferations and lymphomas
-Name of lesion (specify): Extranodal marginal zone B-cell lymphoma
-Virus status (specify): None
-Type of immunodeficiency (specify): Common variable immunodeficiency

Table 21: SUMMARY OF ESSENTIAL AND DESIRABLE DIAGNOSTIC FEATURES FOR CATEGORY OF LYMPHOID PROLIFERATIONS AND LYMPHOMAS ASSOCIATED WITH IMMUNE DEFICIENCY AND DYSREGULATION (IDD)[1]

Diagnosis	Essential Diagnostic Features	Desirable Diagnostic Features
Hyperplasias arising in immune deficiency/dysregulation (IDD)	• Setting confirmed or highly suspicious for immune deficiency/dysregulation • Lack of architectural effacement • Heterogeneous lymphoid and/or plasmacytic proliferations without atypia • One of the following features: – Detection of EBV/EBER in tissue in the majority of hyperplasias – Detection of KSHV/HHV8 in multicentric Castleman disease – Other specific features related to IDD (e.g., CD4/CD8 double-negative-cell proliferations in ALPS)	

Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation (IDD)	• Setting confirmed or highly suspicious for immune deficiency/dysregulation • Architectural effacement • Polymorphous infiltrate with a spectrum of stages of B-cell differentiation • Atypical large cells positive for CD20 (variable), CD30 (variable), and PAX5 • EBV+ demonstrated in tissue (EBV viral load measurements in the blood are not sufficient for diagnosis)	• *IG* gene rearrangement studies to support exclusion of lymphoma
EBV-positive mucocutaneous ulcer	• Setting confirmed or highly suspicious for immune deficiency/dysregulation • Well-circumscribed shallow ulcer in mucosal or cutaneous sites with a polymorphous lymphoid infiltrate • Atypical large cells positive for CD20 (variable), CD30 (variable), and PAX5 • EBV+ in tissue (EBV viral load measurements in blood are not sufficient for diagnosis)	• Band of CD3+ T-cells at the periphery
Lymphomas arising in immune deficiency/dysregulation (IDD)	• Setting confirmed or highly suspicious for immunodeficiency or immune dysregulation setting • Meets diagnostic criteria for corresponding lymphomas in immunocompetent patients	• Detection of EBV (EBER) and/or KSHV/HHV8 (LANA) in tissue (EBV viral load measurements in the blood are not sufficient for diagnosis) • Demonstration of clonal B- or T-cell populations by molecular techniques in challenging cases
Inborn error of immunity(IEI)-associated lymphoid proliferations and lymphomas	• Criteria for EBV+ B-LPD are the same as those specified in specific sections • Lymphoma diagnostic criteria are the same as those of sporadic lymphomas • EBV status must be assessed and the immunodeficiency background (IEI) should be mentioned • A diagnosis of granulomatous and/or CD8+ T-cell-rich lesion requires exclusion of an infectious • Etiology or occult malignancy, such as T-cell/histocyte rich B-cell lymphoma or overt T-cell lymphoma	• Molecular classification including germline genetic testing for the underlying inborn error of immunity

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C. Transformation from Indolent Lymphoma

Transformation from indolent lymphoma (optional)

Histologic transformation occurs when a morphologically higher-grade lymphoma that is clonally related arises in a patient with a previously diagnosed or concurrent more indolent low-grade lymphoma. Common examples include the transformation of follicular lymphoma to a diffuse large B-cell lymphoma. The prognosis of transformation is worse compared to de novo high-grade lymphoma.[1] It can be difficult to

determine if the higher-grade lymphoma is clonally related to the prior indolent lymphoma - for example, up to 20% of DLBCL arising in the setting of prior chronic lymphocytic leukemia (CLL) are clonally unrelated.[2] Demonstration of clonal relationship between the transformed lymphoma and prior lymphoma are recommended; most frequently this involves demonstration of shared clonal Ig gene rearrangements or specific shared driver mutations.

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D. Special Studies

Immunohistochemistry

If immunohistochemistry is utilized to immunophenotype the leukemia/lymphoma cells specify the results in the cancer case summary. There is no proscriptive way to accomplish this and can reflect what is used at the institutional level. Suggested reporting methods could utilize (+) for positive result and (-) for negative and include descriptors if there is variability in staining (focal, patchy) or intensity (dim, bright staining). Immunohistochemistry is delineated separately from immunophenotyping by flow cytometry as there might be differences due to the different sensitivities of the assays (flow cytometry is typically more sensitive), differences in antibody used, differences in localization of the antigens (immunohistochemistry may be positive for cytoplasmic antigens that are negative on surface analysis by flow cytometry). To avoid potential confusion, these results are separated out even though some may be redundant.

Flow cytometry

Flow cytometry is a quantitative method for rapid, multiparametric evaluation of the expression of cell surface and cytoplasmic antigens of a large number of cells. If flow cytometry was performed, report if there was no aberrancy detected in the sample at the level of sensitivity of the assay or specify what specific alterations were detected. As there is significant variability in the reporting of results the cancer case summary does not require a specific method. It is recommended to report the results of the tumor cell population in a semi-quantitative manner that would allow those reviewing the report to determine if there is heterogenous expression (not all tumor cells are positive) and the level of expression on the population. Examples of this reporting include: CD20 dim+ (low level expression of CD20), CD20+ (moderate level of expression of CD20), CD20++ (bright expression of CD20), CD20-/+ het (variable heterogeneous expression of CD20).

Cytogenetics

Report if conventional/karyotype cytogenetic analysis was performed on the sample, and if performed, the result. For those samples with abnormal karyotypes, specify the result.

Molecular alterations detected

With the advent of increasingly sophisticated molecular genetic techniques such as next-generation sequencing (NGS), chromosomal microarrays and large fluorescence in-situ hybridization panels reporting

all these results in a synoptic format is a challenge. As many of these alterations are diagnostically, prognostically, or therapeutically important- reporting in a succinct manner is necessary. To make reporting easier for the pathologist and highlight what is most important for the treating clinician, this cancer case summary requires the reporting of any positive/abnormal alterations that were detected, followed by an optional listing of all the alterations that were tested. The cancer case summary lists some of the most common alterations that occur in lymphoid neoplasms, but it is in no way comprehensive. The option exists to provide those not specifically listed under “Other alterations listed (specify)”, where the user would enter what molecular alteration was detected.

After each alteration, there is a specific field where users can delineate, if desired, the specific alterations, method (NGS, FISH), or additional information (variant allele frequency-VAF) that would be useful for that institution. While preferable to include specific information, this can also reference a separate report with this information (separate molecular pathology report). An example of how to use this section is as follows:

Molecular alterations detected
__X__RHOA mutation, (specify): NGS, VAF 47%
__X__TP53 mutation, mutation, (specify): NGS, VAF 35%

Molecular alterations assayed:
(List): *ABL1, ABL2, ALK, ARHGEF1, ARID1A, ARID2, ASXL1, ATM, B2M, BCL2, BCL6, BCOR, BIRC3, BRAF, BTK, CARD11, CCND1, CCND2, CCND3, CD274, CD79A, CD79B, CDKN1B, CDKN2A, CDKN2B, CIITA, CREBBP, CRLF2, CSF1R, CTCF, CTNNB1, CXCR4, DDX3X, DIS3, DNMT3A, EBF1, EGR1, EP300, EPOR, ETV6, EZH2, FAM46C, FAS, FAT1, FBXW7, FGFR3, FOXO1, GATA3, GNA13, GNAI2, HIST1H1E, HRAS, ID3, IDH1, IDH2, IKBKB, IKZF1, IKZF3, IRAK4, ITPKB, JAK1, JAK2, JAK3, KLF2, KMT2D, KRAS, MALT1, MAP2K1, MAP3K14, MAPK1, MED12, MEF2B, MYC, MYCN, MYD88, NF1, NFKBIE, NOTCH1, NOTCH2, NOTCH3, NRAS, NT5C2, P2RY8, PDGFRB, PHF6, PIK3CA, PIK3CD, PIK3R1, PIM1, PLCG1, PLCG2, POT1, PPM1D, PRDM1, PRPS1, PTEN, PTPN11, RB1, REL, RHOA, RIPK1, RPS15, RUNX1, S1PR2, SAMHD1, SETD2, SF3B1, SGK1, SH2B3, SOCS1, SPEN, STAT3, STAT5B, STAT6, TBL1XR1, TCF3, TET2, TLR2, TNFAIP3, TNFRSF14, TP53, TRAF2, TRAF3, UBR5, WT1, XPO1, ZFHX4, ZMYM3.*

This method can simplify the reporting of large numbers of genes to highlight only those with alterations identified. It also provides a means of listing what was assayed- such lists can be typically obtained from laboratory performing the molecular studies. This is less labor intensive than listing all the negative results.