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The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee

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Abstract:
Since the publication of the Revised European-American Classification of mature lymphoid neoplasms in 1994, subsequent updates of the classification of mature lymphoid neoplasms have been generated through iterative international efforts to achieve broad consensus among hematopathologists, geneticists, molecular scientists, and clinicians. Significant progress in the characterization of malignancies of the immune system in the last years, with many new insights provided by genomic studies, have led to the current proposal. We have followed the same process that was successfully used for the 3rd and 4th editions of the WHO classification of hematological neoplasms. The definition, recommended studies, and criteria for the diagnosis of many entities have been extensively refined. Some categories considered provisional are now upgraded to definite entities. Terminology of some diseases has been revised to adapt nomenclature to the current knowledge of their biology, but these modifications have been restricted to well-justified situations. Major findings from recent genomic studies have impacted the conceptual framework and diagnostic criteria for many disease entities. These changes will have an impact on optimal clinical management. The conclusions of this work are summarized in this report as the proposed International Consensus Classification (ICC) of mature lymphoid, histiocytic, and dendritic cell tumors.

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The International Consensus Classification of Mature Lymphoid Neoplasms: A Report from the Clinical Advisory Committee

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Abstract

Since the publication of the Revised European-American Classification of mature lymphoid neoplasms in 1994, subsequent updates of the classification of mature lymphoid neoplasms have been generated through iterative international efforts to achieve broad consensus among hematopathologists, geneticists, molecular scientists, and clinicians. Significant progress in the characterization of malignancies of the immune system in the last years, with many new insights provided by genomic studies, have led to the current proposal. We have followed the same process that was successfully used for the 3rd and 4th editions of the WHO classification of hematological neoplasms. The definition, recommended studies, and criteria for the diagnosis of many entities have been extensively refined. Some categories considered provisional are now upgraded to definite entities. Terminology of some diseases has been revised to adapt nomenclature to the current knowledge of their biology, but these modifications have been restricted to well-justified situations. Major findings from recent genomic studies have impacted the conceptual framework and diagnostic criteria for many disease entities. These changes will have an impact on optimal clinical management. The conclusions of this work are summarized in this report as the proposed International Consensus Classification (ICC) of mature lymphoid, histiocytic, and dendritic cell tumors.

Introduction

The publication of the Revised European and American Lymphoma (REAL) classification of lymphoid neoplasms in 1994,[1] and its subsequent validation across the world in 1997[2] represented a "change of paradigm" in the classification of these tumors. This classification provided a novel framework for recognition of individual disease entities based on a constellation of features, including morphology, immune phenotype, clinical presentation, and genomics. This effort led to the WHO classification,[3] published in 2001, which extended the same conceptual approach to all hematopoietic and lymphoid neoplasms. The process was a joint effort of the Society for Hematopathology (SH) and European Association for Haematopathology (EAHP) together with hematologists, oncologists and scientists through joint Clinical Advisory Committees (CAC) at which collegial discussions led to broad consensus.[4,5] The classification rapidly became the international standard, with publication of subsequent updates in 2008 and 2017.[4-7] Since 2017 we have seen significant progress in the characterization of malignancies of the immune system, with many new insights provided by genomic studies. Initial planning and discussion for the current International Consensus Classification took place in April, 2021 at the 20th meeting of the EAHP/SH. An international committee undertook the organization of the next CAC, which was held in September, 2021. The subsequent discussions included 14 working groups (Supplemental Table 1), with broad international participation. The conclusions of that meeting are summarized in this report with the proposal of the International Consensus Classification (ICC) (Table 1).

The definition of most entities remains unchanged but criteria for diagnosis and recommended ancillary studies have been extensively refined. Some categories considered provisional in 2017 are now upgraded to definite entities. Terminology of some diseases has been revised to adapt nomenclature to the current knowledge of their biology, but these modifications have been restricted to well justified situations. Some categories such as multiple myeloma and EBV-positive T-cell lymphoproliferative disorders (LPD) of children have undergone major revision. Major findings from recent genomic studies have had an impact on the conceptual framework of some diseases, which are largely addressed in a companion article of this series. This manuscript will review the major revisions in the criteria and definition of mature lymphoid, histiocytic and dendritic cell tumors (Tables 2-4).

Mature B-cell neoplasms

Chronic lymphocytic leukemia

The diagnostic criteria for **chronic lymphocytic leukemia** (CLL) and **monoclonal B-cell lymphocytosis** (MBL) are well established.[5,8] Immunophenotype is determined by flow cytometry with a panel of CD19, CD5, CD23, CD20, Kappa and Lambda that may be expanded in selected cases with CD43, CD79b, CD81, CD200, CD10, ROR1 to clarify the diagnosis.[8] The mutational status of the IGHV and *TP53*/17p alterations need to be evaluated at the time when patients require treatment.[8] Although the (epi)genomic profile of CLL has been intensively investigated in the last decade,[9-11] the clinical translation of the vast majority of the findings still requires further study. Factors likely to have significant clinical relevance include subclonal *TP53* mutations with low variant allelic frequency (VAF <10%), BCR stereotypes (e.g stereotype 2 and 8), specific mutated genes (e.g. *NOTCH1*, *SF3B1*, *BIRC3*), and IGLV3-21^{R110} mutation.[12-17] Complex karyotype defined as ≥3 aberrations is currently applied in alignment with thresholds derived from other disease settings.[8] However, in CLL a distinct threshold of ≥5 abnormalities may better stratify very high-risk patients.[18] Although the prognostic impact of all these and other parameters has been shown in retrospective studies, clinical implementation will require methodological evaluation, standardization and validation in prospective studies.

Pathologists also recognize a tissue-based MBL, usually as an incidental nodal finding of an infiltrate of CLL-type cells without proliferation centers in individuals without significant lymphadenopathy.[19,20] These cases are usually associated with MBL in peripheral blood. At the other end of the CLL spectrum, the CAC emphasized the need to distinguish accelerated CLL from diffuse large B-cell (Richter) transformation, the latter containing sheets of large cells and not just expanded proliferation centers.[21] The recent identification of reversible proliferations of sheets of large cells (Richter-like) in patients in which ibrutinib has been temporarily interrupted is a challenging situation to be considered in the interpretation of such cases.[22,23] These patients should be managed with caution and reevaluated after the reintroduction of ibrutinib.

The criteria for the diagnosis of **B-cell prolymphocytic leukemia** were also reviewed and the group considered that the entity needs to be recognized only after rigorous exclusion of other lymphoid neoplasms, particularly transformation from CLL, mantle cell lymphoma (MCL) or splenic marginal zone lymphoma (SMZL).

Splenic marginal zone lymphoma

Splenic marginal zone lymphoma (SMZL) cannot be diagnosed based on extent of bone marrow or peripheral blood involvement alone. The presence of a clonal B-cell population in these locations with a

phenotype consistent with MZL requires clinical or imaging evidence of splenic involvement for the diagnosis of an overt lymphoma. Distinction of SMZL from splenic diffuse red pulp small B-cell lymphoma requires evaluation of splenic histology. Next generation sequencing (NGS) studies have identified recurrent mutations including *KLF2, NOTCH2, TNFAIP3, KMT2D,* and *TP53* among others.[24-26] Sequencing studies may support the diagnosis of SMZL, but the overlap with other entities make NGS profiles inadequate to establish a diagnosis in isolation. Recent data have described genetically-defined subsets of SMZL with prognostic differences.[27] *MYD88* mutations remain valuable in the differential diagnosis of SMZL versus LPL.

Lymphoplasmacytic lymphoma and IgM MGUS

The diagnostic criteria for **lymphoplasmacytic lymphoma** (LPL) have been refined from the revised 4th edition of the WHO classification.[7] In keeping with the diagnostic criteria proposed by the International Workshop on Waldenström's Macroglobulinemia, a diagnosis of LPL may be rendered in cases with abnormal lymphoplasmacytic aggregates in the bone marrow and evidence of clonal B-cells and plasma cells, even when the aggregates represent <10% of cellularity of the trephine biopsy.[28] Molecular studies for *MYD88* and *CXCR4* mutations are strongly encouraged in the workup of suspected LPL. *MYD88* mutations in the TIR domain are found in >90% of LPL predominantly L265P, although rarely non-L265P variants may be present. Although not specific, *MYD88* mutations assist in the diagnosis of LPL in the appropriate clinicopathologic context,[29-31] but a small percentage of LPL are *MYD88* wild-type with alternative mutations downstream of MYD88 in the NFKB signaling pathway.[32,33] Absence of a *MYD88* mutation therefore does not completely exclude the diagnosis of LPL. *CXCR4* mutations are identified in up to 40% of LPL and, particularly the nonsense variants, have been associated with symptomatic hyperviscosity and resistance to ibrutinib therapy.[34-36] This effect however is complex and requires further research as treatment options expand.

The diagnosis of **IgM monoclonal gammopathy of undetermined significance** (IgM MGUS) is established in cases of IgM paraprotein with <10% bone marrow plasma cells and lacking lymphoplasmacytic B-cell aggregates sufficient for a diagnosis of LPL.[29,37] Two subtypes of IgM MGUS are now further distinguished,[32] the IgM MGUS of plasma cell type and the IgM MGUS, not otherwise specified (NOS). The rare IgM MGUS of plasma cell type is considered a precursor of multiple myeloma (MM) and is defined as showing clonal plasma cells without a detectable B-cell component and with wild type *MYD88*. This category also includes cases with t(11;14)(q13;q32) or other cytogenetic abnormalities

typical of MM. The remainder, IgM MGUS, NOS, includes all cases with a *MYD88* mutation, those with detectable monotypic/monoclonal B-cells but without abnormal lymphoplasmacytic aggregates diagnostic of LPL, and lacking evidence of other small B-cell neoplasms. Routine fluorescence in situ hybridization (FISH) studies and *MYD88* mutation analysis are recommended to identify the rare cases more likely to progress to MM rather than LPL or other B-cell neoplasms.

Primary cold agglutinin disease is recognized as a new diagnostic category, distinct from LPL or IgM MGUS. This disease lacks *MYD88* L265P mutation but displays recurrent trisomies of chromosomes 3, 12 and 18, and recurrent mutations in *KMT2D* and *CARD11*.[38-40]

Plasma cell neoplasms

Clinicians participating in the CAC strongly supported the term multiple myeloma over plasma cell myeloma. **Multiple myeloma (MM)** is a genetically heterogeneous disease with two main groups defined by cytogenetics. Namely 40-50% of cases show recurrent IGH translocations with a variety of partner genes, whereas up to 55% of MM lack IGH translocations and are characterized by hyperdiploidy, with a small subset not falling into either category.[41,42] These primary genetic abnormalities are present in precursor conditions and persist throughout the disease course. They are associated with prognosis, treatment response, as well as other clinical and phenotypic features and have a strong correlation with the gene expression profile.[41,43-45] Therefore, MM can be formally divided into mutually exclusive diagnostic groups, 1) MM NOS and 2) MM with recurrent genetic abnormalities, including MM with *CCND* family translocations, MM with *MAF* family translocation, MM with *NSD2* translocation and MM with hyperdiploidy. Detection of t(4;14), t(14;16) as well as secondary changes including del(17p), amp1q, del(1p) identifies patients with high-risk disease.[46-48] Currently, interphase FISH is the technique of choice for cytogenetic characterization, and consensus FISH panels for MM have been published.[47] The role of mutational analysis requires further study, particularly given the frequent sub-clonal evolution and spatial heterogeneity in MM.[45,49-51]

Monoclonal gammopathy of undetermined significance (MGUS) of non-IgM type is a virtually universal precursor to MM.[52] Although most MGUS are asymptomatic, several conditions associated with clonal Ig secretion in the absence of overt malignancy have been recognized, termed **monoclonal gammopathy of renal** or **clinical significance** (**MGRS** and **MGCS**).[53,54] However, these do not represent separate disease entities, but are descriptive terms, which can be added as clinical feature to the underlying diagnosis (e.g. MGUS).

Smoldering or asymptomatic multiple myeloma, defined as lacking features of active MM (SLiM CRAB criteria) or AL amyloidosis,[37] exhibits broad variability in progression to active MM. Risk stratification with models proposed for this situation should be employed to select patients suited for early therapeutic intervention.[55]

Solitary plasmacytomas of bone and **primary extramedullary plasmacytomas** are plasma cell neoplasms with low to moderate risk for progression to MM.[56,57] Since minimal marrow involvement detected by flow cytometry (i.e., clonal plasma cells present but < 10%) is of major prognostic importance, particularly with solitary plasmacytomas of bone, this feature should be incorporated into the diagnosis of these entities.[56,58]

For clarity, primary amyloidosis should be termed **Ig light chain (AL) amyloidosis** and needs to be separated from **localized AL amyloidosis** (also termed amyloid tumor), a rare disorder with excellent prognosis and rare progression to systemic AL amyloidosis.[59-61]

Marginal zone lymphomas

There is no indication to separately classify **extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma)** based on site of presentation except for cutaneous MZL, which is now designated separately as a lymphoproliferative disorder (see section below on cutaneous lymphomas). The clinical management approach, however, may differ between anatomic sites (e.g. gastric MALT). In **nodal MZL**, there is recognition of significant heterogeneity, but no consensus on further alterations to the diagnostic criteria. The diagnosis of large cell transformation of MZL should continue to rest on the finding of diffuse sheets of large cells.

Follicular lymphoma

For follicular lymphoma (FL), the consensus was to retain morphological grading (grade 1-2, 3A and 3B) according to previously described criteria.[7] Whether patients with grade 3A have a more adverse prognosis and deserve different management than grade 1-2 remains debatable,[62-64] and needs to be re-evaluated in the future, given evolving non-cytotoxic therapeutic approaches. Grade 3B more clearly differs in its clinical behavior and patients are usually managed as diffuse large B-cell lymphoma (DLBCL).[65,66] Hence, distinction between grade 3A and 3B is critical, with some higher-grade lesions difficult to classify.[67] The consensus was that presence of FISH detectable *BCL2*-rearrangement (*BCL2*-R)

and CD10 positivity both favor grade 3A FL (Figure 1). In addition, 3B cases expressing IRF4/MUM1 should be evaluated for *IRF4* alterations,[68,69] especially in younger patients. Routine screening for *MYC*-rearrangement (*MYC*-R) is not recommended to detect the rare FL cases carrying both *BCL2*-R and *MYC*-R, although those cases might have a more aggressive outcome.[70-73] Proliferation index using Ki67-staining can be specified, but has uncertain clinical significance in isolation,[74] and is not required for grading. Routine molecular testing is currently unnecessary but can be useful in selected cases for differential diagnosis (e.g. pediatric-type FL, plasmacytic differentiation, marginal zone lymphoma, *BCL2*-R negative cases). Detection of *EZH2* mutations provides additional information when treatment with an *EZH2* inhibitor is being considered.[75] Use of an NGS panel for clinical prognostication, such as the m7-FLIPI,[76] remains investigational.

Nodal FL negative for *BCL2*-R is heterogeneous, both genetically and clinically.[77-79] The specific subtype of ***BCL2-R-negative, CD23-positive follicle center lymphoma*** was proposed as a provisional new entity based on correlation of CD23 with *STAT6* mutation, low stage disease, and often a predominant diffuse growth pattern. This variant typically presents with localized inguinal involvement.

Pediatric-type FL remains a clearly defined entity with recurrent genomic alterations and excellent prognosis with conservative management.[80-83] Distinction from FL Grade 3B remains critical. Recent work has suggested that Pediatric-type FL may be related to the pediatric variant of MZL, which had been listed as Provisional in the classification.[84] **Testicular FL**, recognized as a new distinct entity of FL in young boys, shares pathological and clinical features with pediatric-type FL, as most cases can be managed conservatively, without systemic chemotherapy.[85,86]

Large B-cell lymphoma with *IRF4* rearrangement, upgraded now to a definite entity**,** is most common in children and young adults, and usually has at least a partially follicular growth pattern.[69] However, the same disease can be seen uncommonly in adults. FISH for *IRF4*-R must be performed for diagnosis. Cases lacking demonstrable rearrangements should have evidence of either IGH or IGK/IGL breaks. Detection of *IRF4* mutation may support the diagnosis.[69] *IRF4*-R can occur in other aggressive B-cell lymphomas associated with *BCL2*-R or *MYC*-R, mainly in adults, and in this context is not specific for the entity.[69]

Mantle cell lymphoma

The *CCND1* translocation with IG genes is the genetic hallmark of mantle cell lymphomas (MCL). Some cases with the same morphology, phenotype, and SOX11 expression as conventional MCL, lack *CCND1*

rearrangements but have *CCND2* or *CCND3* translocations, sometimes cryptic.[87-90] These cases must be also diagnosed as MCL. *CCND2/CCND3* translocation by FISH or mRNA overexpression should be demonstrated in these cases, since immunohistochemistry for these cyclins is not discriminant.[91] The t(11;14)(q13;q32) may also be a secondary event in the progression of some mature B-cell lymphomas. Those cases should not be diagnosed as MCL.[92-97] *CCND1* rearrangement has been also found in large B-cell lymphomas associated with *MYC*, and *BCL2* or *BCL6* translocations. The negativity of CD5 and SOX11 and the presence of mutations uncommon in MCL favors the diagnosis of DLBCL over MCL.[96] On the other hand, *MYC* may be rearranged in *bona fide* MCL, usually with blastoid/pleomorphic morphology, and aggressive behavior.[98-101] The term "double-hit" MCL in these cases is not recommended and they should not be included in the "high-grade B-cell" category. Some of these cases may be SOX11-negative or express TdT.[100] Genomic studies may help in the differential diagnosis with other lymphomas.

MCL with more aggressive or indolent behavior need to be identified. The unfavorable outcome of blastoid/pleomorphic variants, high Ki67 (≥30%) and *TP53* deletions/mutations has been extensively confirmed and should be evaluated, preferably at diagnosis, in all cases.[102-106] Determination of the Ki67 proliferative index is currently based on visual inspection according to previous described criteria.[105] Whether the evaluation of proliferation, or other quantitative parameters suggested in this ICC proposal, will benefit from quantitative flow cytometry, RNA technologies, or computer-assisted image analysis in clinical practice will require standardization and validation studies. Genomic complexity is also associated with worse outcome, but further studies are needed before incorporation into clinical practice.[99,107,108] At the other end of the spectrum, most leukemic non-nodal MCL (nnMCL) are clinically indolent, although the acquisition of *TP53* alterations and genomic complexity confer an adverse prognosis. These cases are considered a subtype of MCL since the t(11;14) is acquired in precursor B cells as in conventional MCL.[99,107,108] Recognition of nnMCL relies on a combination of clinical and pathological characteristics. Features that favor this diagnosis are non- or limited (stage 1, ≤3 cm) nodal presentation, SOX11 expression negative or low (<10%), CD23 and CD200 positivity, and hypermutated IGHV (<98%).[108-112] Absence of *ATM* mutations/deletions and *CCND1* mutations are also features of nnMCL.[99] MCL with isolated gastrointestinal involvement usually has an indolent behavior and should be clinically recognized although more data are needed to determine the significance.[113-115]

Diffuse large B-cell lymphomas

DLBCL, NOS encompasses all cases of nodal and extranodal large B-cell lymphoma that do not belong to a specific diagnostic category (Table 1). It is not a single disease but a collection of morphologically, genetically and clinically different diseases. Therefore, it can be subdivided into morphological variants, phenotypic variants, and molecular or genetic categories. The role of morphological variants such as centroblastic, immunoblastic, and anaplastic and phenotypic variants such as "DLBCL, CD5+"[116-119] and "DLBCL, double expressor (MYC/BCL2)"[120-122] should be deemphasized. These variants have (weak) adverse prognostic impact and do not reflect true biological subgroups but rather represent the end results of different biological pathways. The conference considered that at this time, the cell-of-origin designation in DLBCL, NOS[123,124] should be maintained. The cell-of-origin distinction is a basic biological division of DLBCL with prognostic impact that can be widely deployed using either IHC (germinal center B-cell-like (GCB) and non-GCB cases) or gene expression (GCB, activated B-cell-like (ABC) and unclassified cases) algorithms. However, the largely disappointing results of trials of upfront treatment of DLBCL, NOS incorporating targeted agents, using cell-of-origin for patient selection, underscores the lack of sufficient detail of this binary classification and highlights the importance of a more molecularly-based approach.[125-130] Recently, molecular/cytogenetic profiling studies have independently identified 5-7 new functional genetic subgroups of DLBCL, strongly emphasizing the validity of this concept, but failing to classify all cases (see accompanying paper) (Figure 2).[131-134] A combination of cell-of-origin and molecular subclassification may provide more precise patient stratification for developing future clinical trials.[135] Overall, cell-of-origin is retained for the present time with the expectation that transition to a molecular genetic classification will be feasible in the near future.

An intensely debated but ultimately unresolved issue is whether an umbrella term such as "Extranodal Lymphoma ABC (non-GCB) type" should be created for (some) extranodal DLBCL. This would primarily (but not exclusively) include DLBCL cases arising in immune-privileged sites such as **primary DLBCL of the central nervous system** (PCNSL) and **primary DLBCL of the testis** but possibly also **primary cutaneous DLBCL, leg type**, primary breast type, **intravascular large B-cell lymphoma**, and primary adrenal lymphomas. The rationale is that most of the lymphomas in these locations are non-GCB/ABC-type, share biology and seem to display common molecular features such as the high prevalence of *MYD88*^{L265P} and *CD79B* mutations that characterize the DLBCL MCD/C5 genetic subgroup (Figure 2).[135-140] In particular, PCNSL and primary DLBCL of the testis share both clinical and molecular features, and for this reason, primary DLBCL of the testis is now considered a distinct entity (See Tables 1, 2). Although

grouping the extranodal lymphomas arising in immune-privileged sites certainly is a reasonable proposal, there are also many caveats including the fact that particularly in some anatomic sites these lymphomas are heterogeneous, and in many settings the pathologist may have incomplete data regarding the presence of other sites of disease. In the end, although many participants were inclined to group several of the extranodal DLBCL entities/variants, the majority felt that such a subcategorization of DLBCL is premature, and recognition of specific entities will be better captured by upcoming molecular categorization, integrated with more traditional criteria.

Large B-cell lymphoma with 11q aberration. The 2016 WHO classification recognized the provisional entity, *Burkitt-like lymphoma with 11q aberration*, identified originally as a lesion clinically and pathologically resembling BL but lacking *MYC*-R. These cases are more frequently seen in children and young adults with good prognosis. Subsequent studies have demonstrated the morphology and phenotype of these tumors to be more variable than originally described, including cases with mainly large cells.[141-143] Importantly, genetic studies also suggest these cases are distinct from BL and closer to conventional DLBCL with germinal center B-cell derivation harboring more complex karyotypes and absence of typical BL mutations.[141-145] As such, this provisional entity is now renamed as ***large B-cell lymphoma with 11q aberration*** (Figure 4). Chromosome 11q gains and losses typical of these cases can be identified using FISH strategies. Although some studies suggest that only 11q loss may be acceptable, more information is needed before a strong recommendation can be made. Chromosomal microarray is required if FISH is equivocal for the typical pattern of gains and losses.[141]

"HHV-8- and EBV-negative primary effusion-based lymphoma" is a new provisional entity recognized based on unifying features that include presentation in elderly, HIV-negative patients with medical conditions that lead to fluid overload suggesting chronic serosal stimulation in pathogenesis. Most cases have been reported from Japan (60%), and often have a history of hepatitis C infection.[146-148] These patients usually have good prognosis with reported spontaneous regression or cure with drainage alone. Most cases show centroblastic morphology, express at least one B-cell marker and show a GCB gene expression profile. Other HHV-8-negative effusion-based lymphomas occur and are biologically and clinically heterogeneous. These should be classified as one of the well-defined lymphomas presenting as an effusion.

Large B-cell lymphoproliferative disorders (LPD) and viral agents

EBV-positive polymorphic B-cell lymphoproliferative disorder, NOS is a term used for EBV-positive B-cell proliferations with or without known immunodeficiency that cannot be more precisely categorized. The term should be reserved for cases with altered lymph node architecture and a polymorphic infiltrate that do not fulfill criteria for the diagnosis of lymphoma or there is uncertainty due to a small size or low-quality biopsy.[149,150] EBV-positive B-cell proliferations should be classified as lymphoma, if the criteria of a well-defined EBV-associated lymphoma are fulfilled (e.g. EBV-positive DLBCL, NOS, plasmablastic lymphoma). In tissues with low to modest numbers of EBV-positive B cells without distortion of the nodal architecture, the term EBV reactivation is preferred. EBNA2 immunostaining is recommended in this or other clinical settings because it supports an EBV latency pattern III which suggests an underlying immunodeficiency. It is negative in most EBV-positive tumors in otherwise healthy persons.

EBV-positive DLBCL, NOS , is an aggressive lymphoma that can present over a wide age range; however, patients younger than 45 years have better prognosis.[151-153] By definition >80% of the malignant cells should express EBER.[152,154,155] The morphology is variable. A T-cell/histiocyte-rich large B-cell lymphoma-like pattern is frequently seen in younger patients and associated with better prognosis. In adults the pattern may be monomorphic or polymorphic but these patterns do not have prognostic impact.[152,154-156] The differential diagnosis with EBV-positive classic Hodgkin Lymphoma (CHL) can be challenging; however, expression of B-cell markers in >50% of the tumor cells, extranodal presentation, and/or EBV latency III favors the diagnosis of EBV-positive DLBCL, NOS. Extended B-cell antibody panels are critical in this setting.[157] DLBCL associated with chronic inflammation and fibrin-associated DLBCL remain discrete entities, separate from EBV+ DLBCL, NOS.

EBV-positive mucocutaneous ulcer was introduced in the 2016 WHO classification as a provisional entity,[5] but is now considered a definite entity.[149,156,158-160] These are solitary lesions, usually in the oropharyngeal mucosa. Cutaneous and gastrointestinal presentations are usually associated with iatrogenic immunosuppression. In cases with $\geq$2 skin lesions the term EBV-positive B-cell polymorphic LPD, or when appropriate, EBV-positive DLBCL, NOS, or other specific type of EBV-positive lymphoma/LPD is preferred.[160,161]

Lymphomatoid granulomatosis (LyG) is a rare angiocentric and angiodestructive lymphoproliferative disease composed of a variable number of EBV-positive B-cells admixed with numerous reactive T-cells. Pulmonary involvement is required for the diagnosis.[162] Although the disease is well defined, there are significant overlapping features with other immunodeficiency-related EBV-positive B-cell LPDs.[162,163]

Isolated CNS or gastrointestinal tract involvement by an EBV-positive lesion resembling LyG is observed usually in the context of known causes of defective immune surveillance (EBV latency III).[164,165] In this scenario, the diagnosis of EBV-positive polymorphic B-cell LPD or EBV+ DLBCL, NOS should be rendered.

HHV-8-associated lymphoproliferations include multicentric Castleman disease, HHV-8 germinotropic LPD, HHV-8-positive DLBCL, NOS, primary effusion lymphoma (PEL) and extra-cavitary PEL.[166] There are significant overlapping features among these disorders.[166,167] PEL and extra-cavitary PEL in HIV-positive patients are usually HHV-8 and EBV-positive; however, in elderly, HIV-negative individuals, EBV is usually negative.[166,168-170] In extra-cavitary presentations, the diagnosis of HHV-8-positive DLBCL, NOS should be favored in EBV-negative cases with cytoplasmic IgM, lambda and/or associated with multicentric Castleman disease.[171]

High-grade B-cell lymphomas

The 2016 WHO classification included two categories of high-grade B-cell lymphoma (HGBCL): HGBCL, NOS, and HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements ("double-hit" or "triple-hit", HGBCL-DH/TH).[5] HGBCL-DH now comprises two groups: **HGBCL with *MYC* and *BCL2* rearrangements** (with or without *BCL6* rearrangement) (HGBCL-DH-*BCL2*) and a new provisional entity, ***HBGBL with MYC and BCL6 rearrangements*** *(HGBCL-DH-BCL6)*. HGBCL-DH-*BCL2* and *HGBCL-DH-BCL6* entities continue to exclude FL and the morphology (large cell or high-grade cytology) should be reported (Figure 3).

Studies performed since the 2016 WHO classification support HGBCL-DH-*BCL2* as an aggressive lymphoma of GCB origin with distinct biology from other GCB-DLBCL, NOS and *HGBCL-DH-BCL6.*[172-177] It can occur in patients with or without prior FL. Data to support distinct biology in the *HGBCL-DH-BCL6* cases are less compelling;[172,173] however, it has been retained as a provisional entity to allow for continued study based on poor outcomes seen in some studies.[175,178-181] While "pseudo"-double-hit lymphomas (*MYC*-R with *BCL6* partner) account for up to 30% of *HGBCL-DH-BCL6*,[182] strategies to identify this are not essential at this time. Neither copy-number increase, nor amplification, of these genes is sufficient to substitute for rearrangement in these categories.[183-186] Furthermore, the significance of the *MYC* partner gene remains controversial; *MYC*-R with both IG and non-IG partners are included at present.[180,187,188]

While acknowledged as a heterogeneous category, HGBCL, NOS remains in this classification as a diagnosis of exclusion for tumors which are not HGBCL-DH but which have intermediate sized cells,

often with blastoid or Burkitt-like cytology (Figure 3), but cannot be classified as DLBCL or Burkitt lymphoma (BL).[189,190] These cases are rare and the diagnosis can only be made on well-fixed and preserved specimens as large cell cytology must be excluded. DLBCL with starry-sky morphology, and/or high proliferation index do not merit recategorization as HGBCL, NOS.

Previously, TdT expression in HGBCL/DLBCL was sufficient to reclassify these cases as lymphoblastic leukemia/lymphoma[7]. However, the mutational landscape of TdT-positive HGBCL now supports their inclusion as mature lymphomas with "expression of TdT" noted in the diagnostic line.[191-193] Distinction between these cases and acute leukemia must involve thorough phenotypic and genetic evaluation.[192-195]

Diagnostic criteria for **Burkitt lymphoma** (BL) remain largely unchanged. However, data have emerged to segregate TdT-positive cases from the BL category. These rare cases have an immature B-cell phenotype and molecular features of precursor B cells including evidence of IG:*MYC* translocation arising from aberrant VDJ recombination, frequent lack of a productive IGH rearrangement, DNA methylation patterns similar to other pre-B-cell acute leukemias, and recurrent *NRAS*/*KRAS* mutations.[196] Based on these data, designating these cases as B-lymphoblastic leukemia/lymphoma with *MYC*-R is appropriate to recognize their biology and allow clinicians to consider appropriate treatment options (see Arber et al in this series).[197,198]

Hodgkin lymphomas

The CAC conference discussed key issues related to the classification of Hodgkin lymphomas, and cases with borderline diagnostic criteria. The conference concluded that new terminology is warranted for nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), based on major biological and clinical differences with CHL and with close relationship to T-cell/histiocyte-rich large B-cell lymphoma.[199] The term **nodular lymphocyte predominant B-cell lymphoma** (NLPBL) was accepted by consensus. The value of identifying variant histology in NLPBL was recognized, with the suggestion that typical cases, "Fan patterns" A, B and C or Grade 1, be distinguished from "Fan patterns" D, E and F or Grade 2.[200] Cases falling within Grade 2 generally show loss of a well-formed nodular pattern, and increased infiltration by T-cells with reduction of background small B-cells. Cases with Grade 2 histology may warrant treatment as DLBCL, but clinical features should play a role in treatment decisions.[201] Rare examples of NLPBL are EBV-positive, with uncertain clinical implications.[202]

The major subtypes of CHL remain unchanged. A standard immunohistochemical panel employing CD30, CD15, IRF4/MUM1, PAX5, CD20, CD3 and LMP1 or EBER in situ hybridization is advised. Additional immunohistochemical or clonality studies may be warranted in the setting of atypical histological or clinical features.

A major topic of discussion related to the criteria for **mediastinal gray zone lymphoma** (MGZL). This is the preferred term over what was previously designated B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and CHL. A diagnosis of MGZL requires both morphological (high tumor cell density) and immunophenotypic criteria (at least 2 B-cell markers with strong expression).[203,204] Cases of otherwise typical nodular sclerosis CHL, with variable expression of CD20 are still designated as CHL, although a close biological relationship to primary mediastinal large B-cell lymphoma remains.[205] Sequential primary mediastinal large B-cell lymphoma and nodular sclerosis CHL reinforce the concept of MGZL, as such cases have been demonstrated to be of common clonal origin. However, clinical and genomic data indicate that most non-mediastinal GZL are distinct from MGZL and as such these cases should be diagnosed as DLBCL, NOS. Finally, nearly all EBV-positive DLBCL, while they may contain admixed Hodgkin/Reed-Sternberg-like cells, differ at the genomic level from MGZL, and should be retained within the category of EBV-positive DLBCL.[152,206]

Mature T and NK-cell neoplasms

Discussion of the T-cell and NK-cell neoplasms at the CAC meeting focused on those areas in which new insights into the pathogenesis and clinical behavior have occurred. Thus, only a subset of this large and diverse group of tumors will be covered.

Viral related Mature T- and NK-cell neoplasms

EBV-positive T and NK-cell lymphoproliferative disorders in children are now separated among four major groups**: Hydroa vacciniforme LPD**, **severe mosquito bite allergy**, **chronic active EBV (CAEBV) disease**, and **systemic EBV-positive T-cell lymphoma of childhood** (Table 4). All occur with increased frequency in Asia and Latin America. Hydroa vacciniforme LPD presents with skin lesions on sun-exposed areas with EBV-infected T or NK cells and very high levels of EBV DNA in blood.[7,207,208] This disease was previously referred to as hydroa vacciniforme-like LPD; however, it is now known that all HV lesions have EBV. Some patients, especially whites, have stable disease involving only the skin (classic hydroa vacciniforme LPD)[209] while others, especially Asians[210] and Hispanics have concomitant systemic EBV-positive T- or NK-cells involving internal organs (systemic hydroa vacciniforme LPD).[207,211,212] This latter

group eventually requires similar treatment as CAEBV disease.[213] CAEBV disease is a progressive disorder of ≥ 3 months in duration in which patients have markedly increased levels of EBV DNA in the blood and infiltration of organs by EBV-infected lymphocytes in the absence of a known immunodeficiency.[214-216] This illness was previously referred to as CAEBV infection; however, since most adults are chronically infected with EBV, the term CAEBV disease is preferred. Previously, CAEBV disease included patients with EBV-infected T, NK, or B cells. Many patients with B-cell CAEBV have been diagnosed with underlying primary immunodeficiency; therefore, CAEBV should only include T or NK cell disease.[217] Some patients in South America present with facial edema, high levels of EBV DNA in T or NK cells in the blood, and EBV in internal organs; these patients should be classified as CAEBV disease and not as hydroa vacciniforme LPD.[218] New genetic studies have shown that CAEBV disease shares similar somatic mutations (e.g. *DDX3D* and *KMT2D*) as T and NK-cell lymphomas indicating that it is a pre-malignant condition. Furthermore, the EBV genome harbors intragenic deletions common in various EBV-associated neoplastic disorders but not detected in reactive conditions such as infectious mononucleosis, suggesting an important role of these mutations in EBV-associated neoplasia.[219]

Primary nodal EBV-positive T/NK cell lymphoma is a rare disease introduced in the 2016 WHO classification as a variant of PTCL, NOS.[7] New findings have led to designation of this lymphoma as a provisional entity.[220] It presents more commonly in elderly and/or immunodeficient patients, lacks nasal involvement and is more often of T rather than NK cell lineage.[221,222] This lymphoma is characterized by a dismal outcome, low genomic instability, upregulation of immune pathways (checkpoint protein PD-L1) that promote immune evasion, and downregulation of EBV miRNAs.[223,224]

Extranodal T-cell and NK-cell neoplasms involving the gastrointestinal tract

The two main types of primary intestinal T-cell lymphomas are **enteropathy-associated T-cell lymphoma** (EATL), which may be preceded by refractory celiac disease, and **monomorphic epitheliotropic intestinal T-cell lymphoma** (MEITL).[7] Novel immunophenotypic and genomic data reinforce their distinction.[225] Expression of SYK is absent in EATL.[226] Most cases of EATL are TCR-silent, whereas most cases of MEITL express the T-cell receptor (TCR), and derive more frequently from gamma-delta T cells than alpha-beta T cells.[226-230] MEITL has highly recurrent alterations in *SETD2*, resulting in defective trimethylation of H3K36, and frequent mutations in *STAT5B, JAK3, TP53* and *GNAI2*.[229-233] Type II refractory celiac disease is a precursor of EATL and has therefore been added to the classification. EATL and type II refractory celiac disease have frequent gain-of-function mutations in

STAT3 and *JAK1*.[230,234-236] Intestinal T-cell lymphoma, NOS remains an entity for overtly malignant primary intestinal EBV-negative T-cell lymphomas, after EATL, MEITL and other PTCL entities, notably adult T-cell lymphoma/leukemia, have been excluded.

Two groups of indolent LPD of the gastrointestinal tract are recognized, according to their T-cell or NK-cell derivation.[237-240] The clonal nature of the T-cell cases (**indolent clonal T-cell LPD of the gastrointestinal tract**), which variably express CD4 and/or CD8, is further supported by the finding of gene alterations in a subset of the cases.[241-243] The intestinal NK-cell proliferation formerly referred to as NK-cell enteropathy[238] or lymphomatoid gastropathy,[244] is now recognized as a neoplasm designated as **indolent NK cell LPD of the gastrointestinal tract**.[237] These two entities are EBV-negative and have a limited propensity to infiltrate the gastrointestinal tract, with a superficial distribution.

Peripheral T-cell lymphoma, NOS

PTCL, NOS is mainly a nodal lymphoma that remains a diagnosis of exclusion (Figure 5). Two molecular subgroups, namely PTCL-TBX21 and PTCL-GATA3, have been identified based on their GEP resembling Th1 and Th2 cells, respectively. The PTCL-GATA3 subgroup has been associated with a worse outcome in some studies and has greater genomic complexity.[245] The PTCL-TBX21 subgroup has better prognosis, fewer copy number alterations and more frequent mutations in genes regulating DNA methylation.[245] These subgroups may be recognized using an immunohistochemistry-based algorithm of four markers (TBX21, CXCR3, GATA3, CCR4).[246-248] In addition, the expression of cytotoxic molecules delineates a subgroup of aggressive PTCL, NOS which tend to occur in patients with impaired immunity and mostly cluster to PTCL-TBX21.[245,249] Designation of PTCL, NOS according to the molecular subgroups is not routinely incorporated into clinical diagnosis and requires further studies for clinical validation.

Follicular helper T-cell lymphoma

Since the discovery that T follicular helper (TFH) cells represent the normal cell counterpart of the neoplastic cells in angioimmunoblastic T-cell lymphoma (AITL),[250,251] a larger subset of nodal PTCL not diagnostic of AITL have been found to express markers of normal TFH cells and/or have a GEP enriched in that of normal TFH cells.[252] The 2016 WHO classification created an umbrella category of "nodal lymphomas of TFH origin", covering three entities, namely AITL, follicular T-cell lymphoma and PTCL with TFH phenotype showing a diffuse or T-zone pattern without follicular dendritic cell (FDC) expansion.[5] A TFH phenotype was defined by the expression of two, or preferably three, phenotypic

markers of normal TFH cells, among which those most widely used are CD10, BCL6, CXCL13, PD1 and ICOS.[252-254] In addition to a TFH immunophenotype, multiple studies have reinforced the notion that these three entities are unified by a common genetic landscape.[252,253,255] Loss-of-function mutations in genes regulating DNA and histone methylation, specifically *TET2* and/or *DNMT3A* are present in about 80% and 30-40% of the cases, respectively, and several lines of evidence indicate that AITL in many instances develops on a background of clonal hematopoiesis. Other alterations include highly recurrent *RHOA*^{G17V} hotspot mutation, mutations in *IDH2*^{R172} and in genes involved in the T-cell receptor (TCR) signaling.[252,256]*IDH2* mutations appear restricted to AITL with characteristic large clear cell cytomorphology.[254] Several pathogenic fusions involving *CD28, ICOS, VAV1* have been reported.[257] Overall, the combinatory pattern of mutations in genes related to epigenetics and TCR signaling is a feature common to all nodal lymphomas of TFH origin. These lymphomas show a better response to histone deacetylase inhibitors compared to other PTCLs, suggesting the clinical relevance of the TFH phenotype.[258-260] For these reasons, the ICC unifies systemic lymphomas of TFH origin as a single entity, **follicular helper T-cell lymphoma** (TFH lymphoma), with three subtypes: angioimmunoblastic-type (AITL), follicular-type, and not otherwise specified (NOS). By definition, this entity is restricted to primary nodal/systemic cases and excludes primary cutaneous small/medium CD4-positive T-cell LPD or other specified subtypes of cutaneous lymphomas with a TFH phenotype.[261] The criteria to distinguish the three TFH lymphoma subtypes remain essentially unchanged and rely mainly on morphology and immunoarchitecture, especially the tumor microenvironment and distribution of follicular dendritic cells. For establishing the TFH immunophenotype, which is critical for the diagnosis of TFH lymphomas of follicular type and NOS, we recommend the use of a five-marker panel (see above). Because *RHOA*^{G17V} or *IDH2*^{R172} are so characteristic of TFH lymphomas, especially of the AITL-type, NGS studies are valuable in supporting a diagnosis of TFH lymphoma (see companion paper).[262]

Anaplastic Large Cell Lymphoma

ALK-negative ALCL remains a distinct systemic entity. **Primary cutaneous ALCL** and **breast implant-associated ALCL** must be excluded of this category. Criteria for the diagnosis remain unchanged. Cases should resemble ALK-positive ALCL with common pattern, have strong, uniform CD30 expression, and lack ALK expression. *DUSP22-R* ALK-negative ALCL is now defined as a genetic subtype of systemic ALK-negative ALCL based on distinct morphological, phenotypic, genomic, and epigenetic features.[192,263-267] *DUSP22*-R is present in 19-30% of ALK-negative ALCLs and FISH testing is recommended in all ALK-

negative ALCLs. *DUSP22*-R ALCL tends to have a favorable prognosis, but some cases may behave aggressively, probably related to high IPI and other high risk clinical features.[263,266-268] *TP63* rearrangements are associated with poor prognosis. Rare cases with co-existing *TP63*-R and *DUSP22*-R require further study.[269] Cases with *JAK2*-R may resemble CHL, providing a potential diagnostic pitfall.[270]

Breast implant-associated-ALCL is upgraded to a definite entity based on its unique clinical, genomic, and molecular features distinct from other ALCLs.[271-276] Pathologic and clinical staging is important to determine prognosis and assess the need for chemotherapy. Formation of a mass lesion, capsular invasion, and lymph node involvement are adverse prognostic features.[198,277,278] Comprehensive capsulectomy sampling,[279] margin evaluation and use of TNM staging criteria (T1: *in situ*: tumor cells in seroma and/or on capsular luminal surface; T2: early capsule infiltration; T3: aggregates/sheets infiltrating capsule; T4: infiltration beyond capsule) are recommended.[278]

Cutaneous lymphomas

Several significant changes are being introduced in the ICC regarding primary cutaneous lymphomas. Primary cutaneous marginal zone lymphoproliferations will now be recognized as distinct from other MALT lymphomas. They will now be called **primary cutaneous marginal zone LPD**, rather than lymphoma, because of their extremely indolent behavior with disease-specific survivals approaching 100% without requiring aggressive therapies. Cutaneous recurrences, however, are common. Primary cutaneous marginal zone LPD show significant differences compared to MALT lymphomas at other sites.[7,280-286] Two subtypes of this disorder are recognized, largely but not exclusively identified based on whether they are heavy chain class-switched or IgM.[7,283,286-288] Approximately three-quarters of primary cutaneous marginal zone LPD are class-switched and predominantly IgG+ with up to ~40% expressing IgG4[286,289] These cases often have other unique features including abundant reactive T cells and peripherally located plasma cells. Caution must be taken with IgM+ cases to exclude non-cutaneous primary disease.[281,284,288] Uncommon class-switched cases are clonally related to IgM+ primary cutaneous marginal zone LPDs, and have features more like typical MALT lymphomas.[288] Molecular/genetic studies of both of primary cutaneous marginal zone and primary cutaneous follicle center lymphoma have further supported their recognition as distinct entities and have potential diagnostic utility.[290-292]

Primary cutaneous DLBCL, leg type remains a distinct entity. Many cases share the molecular/cytogenetic features seen in DLBCL of MCD/C5 type, a finding also shared with PCNSL, primary DLBCL of the testis and intravascular large B-cell lymphoma.[133,135,138,293,294] About 25% of the latter are restricted to the skin and reported to have a better prognosis than the systemic variant.[138,295,296] Primary cutaneous DLBCL, leg type, is considered to be of non-GCB/ABC type, but one study reported that these cases may be more heterogeneous in terms of their cell-of-origin, with frequent *MYD88* and *CD79B* mutations.[297] However, this study includes a high number of unclassified cases by GEP and triple positive cases by Hans algorithm (CD10, BCL6, IRF4/MUM1). Consistent with the recognition that some high-grade B-cell lymphomas can be TdT+, some of these case have been reported with TdT positivity, which should not prompt reclassification as a B lymphoblastic neoplasm.[298,299]

There are new molecular/cytogenetic data regarding a variety of cutaneous T-cell lymphomas of biologic and, to some extent, clinical and potential therapeutic interest. This includes specific findings such as the germline *HAVCR2* mutations in many patients with **subcutaneous panniculitis-like T-cell lymphomas**[300-302] and also the more extensive genetic and epigenetic findings in other cutaneous T-cell lymphomas, including mycosis fungoides and Sézary syndrome.[303] There is only one significant change, however, in the classification of the primary cutaneous T-cell lymphomas. Consistent with a general trend to greater conservatism, primary cutaneous acral CD8 positive T-cell lymphoma, in spite of its very monotonous and atypical morphological appearance, is now classified as a **primary cutaneous acral CD8 positive T-cell LPD,** largely because of its very indolent course and general need for only local type therapies or even observation.[304-306] Although ~20% of cases do recur either locally or more extensively, only one case with extracutaneous spread is described, and a 100% survival rate is reported independent of treatment modality.[282,306] Some do still advise clinical caution.[307] Aiding in their distinction from other CD8+ cutaneous T-cell lymphomas is their characteristic dot-like CD68 positivity in the neoplastic cells.[308] A rare CD4+/CD8+ case has been reported.[309]

Immunodeficiency-associated Lymphoproliferative Disorders

The iatrogenic immunodeficiency-associated LPD include post-transplant LPD (PTLD), and the separately designated LPD arising in patients receiving methotrexate or other immunosuppressive agents.[7] While there are some common histological features shared by EBV-positive B-cell LPD in diverse clinical settings,[150] there was a consensus to retain PTLD as a separate subgroup based in part on major differences in clinical management. Subclassification of PTLD, not all of which are EBV-positive, remains

unaltered from the 2017 WHO classification.[7] While studies of other iatrogenic-immunodeficiency-associated LPD are much more limited, it is recommended that they be classified in a fashion analogous to PTLD. This was a topic not discussed in great detail at the CAC and requires further study.

Histiocytic and Dendritic Cell Neoplasms

The classification of histiocytic and dendritic cell neoplasms has matured in recent years.[310] While delineation of B-cell and T-cell lymphomas developed from a concerted effort to relate the tumors to developmental and functional subsets of the normal immune system,[311] many of the histiocytoses were initially thought to be reactive or inflammatory conditions. The list includes Erdheim-Chester disease, Rosai-Dorfman-Destombes disease, and Langerhans cell histiocytosis.

Study of the molecular pathogenesis of these neoplasms indicates convergence along a common pathway, with frequent mutations in the mitogen-activated protein kinase (MAPK) pathway.[312,313] A smaller subset of cases show evidence of activation of the PI3K signaling pathway.[314] These insights have led to advances in therapy, with the introduction of targeted therapy through inhibition of *RAS, RAF, MEK* and *mTOR*.[310,314] Nevertheless, many of the observed mutations are not specific to any individual entity. For example, $BRAF^{V660E}$ mutations can be encountered in all members of the disease family, inclusive of isolated Langerhans cell histiocytosis, systemic Erdheim-Chester disease, and histiocytic/dendritic cell sarcomas. ALK-positive histiocytosis is a relatively new addition to the list of histiocytic neoplasms,[315,316] and involves rearrangements of *ALK,* leading to activation of signaling pathways. First described by Chan et al.[317], the cells have a mature histiocytic phenotype and often foamy cytoplasm. Cases presenting in infancy usually present with systemic disease, while cases in adults are more often localized.

EBV-positive inflammatory follicular dendritic cell/fibroblastic reticular cell (FDC/FRC) tumor is an indolent proliferation of stromal cells of mesenchymal origin not derived from hematopoietic stem cells. Neoplastic cells are EBV-positive and associated with a rich inflammatory background. Spleen and liver are the most common sites, but the tumor also arises in other extranodal locations.[318-320]

Conclusion

The clinicopathological, molecular and genomic information generated on lymphoid neoplasms in the last 5 years provides solid grounds to refine the diagnostic criteria of several entities, consolidate the status of categories previous defined as provisional and identified some new entities. The explosion of genomic data is impacting our understanding of these diseases and starting to be introduced into

routine clinical practice for diagnosis and management strategies. However, in many areas, incorporation of these data in general practice requires further validation and standardization.

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We dedicate this report to the memory of Paul Kleihues (21 May 1936–17 March 2022, former Director of the International Agency for Research on Cancer (IARC) (1994 to 2003), a visionary leader who created the modern WHO Blue Book series for the classification of tumors.

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Authors contributions

All authors contributed to the contents of this manuscript. EC, ESJ, JRC, MD, LQ-M, DWS, SHS, JNW, and ADZ coordinated the work of the Clinical Advisory Committee and edited the final manuscript.

Conflict of Interest

None of the authors has a relevant conflict of interest concerning this report

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Table 1. International Consensus Classification of Mature Lymphoid and Histiocytic/dendritic Cell Neoplasms

MATURE B-CELL NEOPLASMS

Chronic lymphocytic leukemia /small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis
CLL type
Non-CLL type
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
IgM monoclonal gammopathy of undetermined significance (MGUS)
IgM MGUS, plasma cell type*
IgM MGUS, NOS*
Primary cold agglutinin disease*

Heavy chain diseases
Mu heavy chain disease
Gamma heavy chain disease
Alpha heavy chain disease
Plasma cell neoplasms
Non-IgM monoclonal gammopathy of undetermined significance
Multiple myeloma (Plasma cell myeloma)*
- Multiple myeloma NOS
- Multiple myeloma with recurrent genetic abnormality
  - Multiple myeloma with *CCND* family translocation
  - Multiple myeloma with *MAF* family translocation
  - Multiple myeloma with *NSD2* translocation
  - Multiple myeloma with hyperdiploidy

Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases
Immunoglobulin light chain amyloidosis (AL)*
Localized AL amyloidosis*
Light chain and heavy chain deposition disease

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Primary cutaneous marginal zone lymphoproliferative disorder*
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia
Duodenal-type follicular lymphoma
BCL2-R *negative, CD23-positive follicle center lymphoma*
Primary cutaneous follicle center lymphoma
Pediatric-type follicular lymphoma
Testicular follicular lymphoma*

Large B-cell lymphoma with *IRF4* rearrangement*
Mantle cell lymphoma
In situ mantle cell neoplasia
Leukemic non-nodal mantle cell lymphoma

Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)
Germinal center B-cell subtype
Activated B-cell subtype
*Large B-cell lymphoma with 11q aberration**
Nodular lymphocyte predominant B-cell lymphoma*
T cell/histiocyte-rich large B-cell lymphoma

Primary DLBCL of the central nervous system
Primary DLBCL of the testis*
Primary cutaneous DLBCL, leg type
Intravascular large B-cell lymphoma
*HHV-8 and EBV-negative primary effusion-based lymphoma**

EBV-positive mucocutaneous ulcer*
EBV-positive DLBCL, NOS
DLBCL associated with chronic inflammation
Fibrin-associated DLBCL
Lymphomatoid granulomatosis
EBV-positive polymorphic B-cell lymphoproliferative disorder, NOS*

ALK-positive large B-cell lymphoma
Plasmablastic lymphoma
HHV8-associated lymphoproliferative disorders
Multicentric Castleman disease
HHV8-positive germinotropic lymphoproliferative disorder
HHV8-positive DLBCL, NOS
Primary effusion lymphoma

Burkitt lymphoma
High-grade B-cell lymphoma, with *MYC* and *BCL2* rearrangements*
*High-grade B-cell lymphoma with MYC and BCL6 rearrangements**
High-grade B-cell lymphoma, NOS

Primary mediastinal large B-cell lymphoma
Mediastinal gray-zone lymphoma*

CLASSIC HODGKIN LYMPHOMA
Nodular sclerosis classic Hodgkin lymphoma
Lymphocyte-rich classic Hodgkin lymphoma
Mixed cellularity classic Hodgkin lymphoma
Lymphocyte-depleted classic Hodgkin lymphoma

MATURE T-AND NK-NEOPLASMS
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Adult T-cell leukemia/lymphoma

EBV-positive T/NK LPD of childhood*
Hydroa vacciniforme LPD
- Classic
- Systemic

Severe mosquito bite allergy
Chronic active EBV disease (T and NK-cell phenotype)
Systemic EBV-positive T-cell lymphoma of childhood
Extranodal NK/T-cell lymphoma, nasal type
Aggressive NK cell leukemia
*Primary nodal EBV-positive T/NK-cell lymphoma**

Enteropathy-associated T-cell lymphoma
Type II refractory celiac disease*
Monomorphic epitheliotropic intestinal T-cell lymphoma
Intestinal T-cell lymphoma, NOS
Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract*
Indolent NK cell lymphoproliferative disorder of the gastrointestinal tract*
Hepatosplenic T-cell lymphoma

Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous small/medium CD4-positive T-cell lymphoproliferative disorder
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous acral CD8-positive T-cell lymphoproliferative disorder*
Primary cutaneous CD8-positive aggressive epidermotropic cytotoxic T-cell lymphoma

Peripheral T-cell lymphoma, NOS
Follicular helper T-cell lymphoma*
Follicular helper T-cell lymphoma, angioimmunoblastic type (Angioimmunoblastic T-cell lymphoma)
Follicular helper T-cell lymphoma, follicular type
Follicular helper T-cell lymphoma, NOS
Anaplastic large cell lymphoma, ALK-positive
Anaplastic large cell lymphoma, ALK-negative
Breast implant-associated anaplastic large cell lymphoma

IMMUNODEFICIENCY-ASSOCIATED LYMPHOPROLIFERATIVE DISORDERS

Post-transplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD
Polymorphic PTLD
Monomorphic PTLD (B- and T/NK-cell types)+
Classic Hodgkin lymphoma PTLD+

Other iatrogenic immunodeficiency associated lymphoproliferative disorders

HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Indeterminate dendritic cell histiocytosis*
Interdigitating dendritic cell sarcoma*
ALK-positive histiocytosis*
Disseminated juvenile xanthogranuloma
Erdheim/Chester disease
Rosai-Dorfman-Destombes disease*

Follicular dendritic cell sarcoma
Fibroblastic reticular cell sarcoma*
EBV-positive inflammatory follicular dendritic cell/fibroblastic reticular cell tumor*

*Changes from the 2016 WHO classification
+These lesions are classified according to the lymphoma to which they correspond
Italics: Provisional tumor entities.

Table 2. Highlights of changes in the International Consensus Classification of small-B cell lymphoid neoplasms

Entity/Category	Change
Chronic lymphocytic leukemia	Need to evaluate IGHV mutational status and *TP53*/17p alterations at time of treatment. Reversible Richter-like proliferations in patients in which BTK inhibitor has been interrupted must be distinguished from DLBCL transformation.
Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia)	A diagnosis of lymphoplasmacytic lymphoma may be made with lymphoplasmacytic aggregates in trephine biopsies <10% of cellularity with evidence of clonal B-cells and plasma cells. Molecular studies for *MYD88*^{L265P} and *CXCR4* mutations are strongly encouraged in the workup of suspected lymphoplasmacytic lymphoma.
MGUS	Two types of IgM MGUS are recognized – a "plasma cell type" and a not otherwise specified (NOS) type. Monoclonal gammopathy of renal or clinical significance is recognized but does not represent a separate disease entity.
Primary Cold Agglutinin Disease	Recognized as a new distinct entity. *MYD88*^{L265P} mutations absent.
Multiple myeloma	The term multiple myeloma is preferred over plasma cell myeloma. Multiple myeloma should be subclassified into one of 4 mutually exclusive cytogenetic groups ("Multiple myeloma with recurrent cytogenetic abnormalities") or designated as NOS.
Solitary plasmacytoma of bone and extraosseous plasmacytoma	Minimal bone marrow involvement by clonal plasma cells is of major prognostic importance, particularly with solitary plasmacytomas of bone.
Primary cutaneous marginal zone LPD	Now recognized as a distinct entity to be segregated from other MALT lymphomas and designated as a lymphoproliferative disorder. Two subtypes are distinguished largely based on expression of either class-switched immunoglobulin or IgM.
Follicular lymphoma	Cytological grades are maintained. In FL grade 3, *BCL2*-rearrangement and CD10 positivity both favor grade 3A over 3B. FL grade 3B cases expressing IRF4/MUM1 should be evaluated for *IRF4* alteration, especially in younger patients. Routine molecular testing is currently not required, but can be useful in selected cases for differential diagnosis and specific

	therapeutic options (e.g. EZH2 inhibitors).
BCL2-*R negative, CD23-positive follicle center lymphoma*	Recognized as a specific form of follicle center lymphoma, frequently, but not always, with a diffuse pattern, pelvic/inguinal location, and common *STAT6* mutations.
Primary cutaneous follicle center lymphoma	Molecular/cytogenetic studies further support its segregation from other follicular lymphomas and may help predict subsequent extracutaneous dissemination.
Testicular follicular lymphoma	Testicular follicular lymphoma is recognized as a distinct form of FL in young boys.
Large B-cell lymphoma with *IRF4* rearrangement	Upgraded to a definite entity. Occasionally identified also in adults with similar features as in children. Definition does not include aggressive B-cell lymphomas with *IRF4* rearrangements that may be associated with *BCL2*-R or *MYC*-R.
Mantle cell lymphoma	Definition is expanded to include genetic variants with *CCND2* and *CCND3* rearrangements with IG genes in otherwise typical mantle cell lymphoma. Aggressive B-cell lymphomas with secondary *CCND1* rearrangements should not be diagnosed as mantle cell lymphoma.

Table 3. Highlights of changes in the International Consensus Classification of aggressive B-cell lymphomas

Diffuse large B-cell lymphoma, NOS	The cell-of-origin designation in DLBCL, NOS should be maintained but it is considered insufficient to fully capture the biological complexity of these tumors. Molecular profiling studies have identified 5-7 new functional genetic subgroups of DLBCL that may provide more precise patient stratification in the future.
Large B-cell lymphoma with 11q aberration	This term replaces Burkitt-like lymphoma with 11q aberration and the entity is still considered provisional. Molecular studies indicate it is closer to DLBCL than Burkitt lymphoma.
Nodular lymphocyte predominant B-cell lymphoma	This term replaces nodular lymphocyte predominant Hodgkin lymphoma, recognizing major biological and clinical differences from classic Hodgkin lymphoma. Close relationship to T-cell/histiocyte-rich large B-cell lymphoma is emphasized.
Primary DLBCL of the testis	Now recognized as a specific entity closely related to primary DLBCL of the central nervous system. Most cases share molecular/cytogenetic features of the MCD/C5[125-130] type of DLBCL, similar to some other primary extranodal large B-cell lymphomas of ABC subtype.
HHV-8 and EBV-negative primary effusion-based lymphoma	Recognized as a provisional entity frequently associated with fluid overload. Cases conforming to other well-defined lymphomas should not be included.
EBV-positive mucocutaneous ulcer	Now recognized as a definite entity and diagnostic criteria have been refined.
EBV-positive DLBCL, NOS	Tumors are morphologically heterogeneous but the distinction of polymorphic vs monomorphic does not have prognostic significance in the elderly. The T-cell/histiocyte-rich large B-cell lymphoma–like pattern, more common in younger patients (<45 years), is distinct from what has been termed polymorphic.
Lymphomatoid granulomatosis	Lymphomatoid granulomatosis is generally diagnosed in the absence of known immunodeficiency and per definition requires pulmonary involvement. Isolated CNS or GI involvement by an EBV-positive lesion resembling lymphomatoid granulomatosis is usually associated with immunodeficiency and EBV latency III. These cases should

	be classified as EBV-positive B-cell LPD or EBV-positive DLBCL, NOS, and not as lymphomatoid granulomatosis.
EBV-positive polymorphic B-cell LPD, NOS	A term used for B-cell proliferations with or without known immunodeficiency when the morphological changes do not fulfill the criteria of a well-defined EBV-positive lymphoma. In patients with focal EBV-positive B cells and preserved lymph node architecture the term EBV reactivation is preferred.
Primary effusion lymphoma (PEL) and extra-cavitary PEL	In EBV-negative extra-cavitary cases, a diagnosis of HHV-8-positive DLBCL, NOS is preferred, particularly if IgM, lambda positive.
Burkitt Lymphoma	Neoplasms with a precursor B-cell phenotype and *MYC* rearrangement will be called B-lymphoblastic leukemia/lymphoma with *MYC* rearrangement rather than Burkitt leukemia or lymphoma.
High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangement	The category is redefined to exclude cases with only *MYC* and *BCL6* rearrangements. Some cases may express TdT without being considered a B-lymphoblastic neoplasm.
High-grade B-cell lymphoma with MYC and BCL6 rearrangements	With the change in the definition of HGBCL with *MYC* and *BCL2* rearrangements, this provisional category was added.
Mediastinal gray-zone lymphoma	Criteria for distinction from classic Hodgkin lymphoma have been refined. Clinical and genomic data indicate that most non-mediastinal gray zone lymphoma are distinct from mediastinal gray zone lymphoma and as such these cases should be diagnosed as DLBCL, NOS.

Table 4. Highlights of changes in the International Consensus Classification of peripheral T-cell lymphomas and histiocytic tumors

Hydroa vacciniforme lymphoproliferative disorder	This term replaces the previous Hydroa vacciniforme-like LPD and two forms are recognized, classic and systemic: *Classic*: Indolent, self-limited, more common in whites. *Systemic:* severe, fever, lymphadenopathy, often liver involvement, More common in Asians and Latin Americans Treatment similar to CAEBV disease
Chronic active EBV disease	The term chronic active EBV disease replaces chronic active EBV infection and is restricted to cases of T and NK-cell phenotype; B-cell cases are excluded. Mutations in *DDX3D* and *KMT2D* indicate the neoplastic nature of the disease.
Primary nodal EBV-positive T/NK cell lymphoma	Introduced in the 2016 WHO classification as a variant of PTCL, NOS; it is now considered a provisional entity.
Type II refractory celiac disease*	Type II refractory celiac disease is accepted as precursor of EATL. and has therefore been added to the classification.
Indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract	Considered a definite entity and name changed to acknowledge monoclonal nature. It may have neoplastic-type gene mutations and rearrangements and may progress to more aggressive disease.
Indolent NK cell lymphoproliferative disorder of the gastrointestinal tract	Mutational studies provide evidence for the neoplastic origin. The term replaces both NK cell enteropathy and lymphomatoid gastropathy.
Subcutaneous panniculitis-like T-cell lymphomas	Molecular studies have recognized germline *HAVCR2* mutations in a subset of cases.
Primary cutaneous acral CD8 positive T-cell lymphoproliferative disorder	Now considered a lymphoproliferative disorder rather than an overt lymphoma.
Follicular helper T-cell lymphoma (TFH lymphoma)	Considered a single entity encompassing three subtypes: angioimmunoblastic-type (angioimmunoblastic T-cell lymphoma), follicular-type, and not otherwise specified (NOS).
ALK-negative anaplastic large cell lymphoma	*DUSP22-R* ALK-ALCL is now defined as a genetic subtype of systemic ALK-negative ALCL. *JAK2* rearrangements or coexisting *TP63* and *DUSP22* rearrangements seen rarely; understanding their significance requires further study.

Breast implant-associated anaplastic large cell lymphoma	Upgraded from a provisional to a definite entity. Use of TNM staging criteria recommended to facilitate clinical management.
Histiocytic and Dendritic Cell Neoplasms	ALK-positive histiocytosis is accepted as an entity in the classification. A subset of Rosai-Dorfman-Destombes disease is identified as neoplastic based on clonal genetic alterations.
EBV-positive Inflammatory follicular dendritic cell/fibroblastic reticular cell tumor	The name of this entity has been changed. Tumor is preferred over sarcoma due to the indolent nature of these lesions. Heterogeneity in lineage is recognized.

Figure Legends:

Figure 1: Suggested diagnostic studies in follicular lymphoma grade 3. Upper left. A case of follicular lymphoma grade 3A is depicted with H&E and Giemsa stains. Note the admixture of centrocytes and centroblasts (>15 HPF) highlighted in the Giemsa stain. Upper right. A case of follicular lymphoma grade 3B is depicted with H&E and Giemsa stains. The follicles are composed of sheets of centroblasts with open chromatin, several nucleoli and abundant basophilic cytoplasm highlighted with the Giemsa stain. Upper middle. A case of follicular lymphoma is depicted with ambiguous morphology. The cells are medium-sized with open chromatin but inconspicuous nucleoli unlike centroblasts (arrows), but without the cytological features of centrocytes. In cases with ambiguous morphology (blue arrow), the presence of *BCL2* rearrangement and/or CD10 expression favors the diagnosis of follicular lymphoma grade 3A; the absence of these, favors follicular lymphoma grade 3B. In cases of follicular lymphoma grade 3B with IRF4/MUM1 expression, *IRF4*-FISH analysis is recommended to exclude the diagnosis of large B-cell lymphoma with *IRF4* rearrangement. (all figures original magnification x400; hematoxylin and eosin, and Giemsa stains)

Figure 2. Algorithm for the diagnostic work-up of aggressive B-cell lymphomas. The current algorithm for diagnosing aggressive large B-cell lymphomas starts with biopsy collection of a lymph node (excision or needle biopsy), or a biopsy of an extra-nodal site. The diagnosis of the different lymphoma entities is based on a combination of morphology, immunophenotype, EBER *in situ* hybridization, FISH analysis and B-cell clonality analysis. The advances in the understanding of diffuse large B-cell lymphoma herald in the near future a transition to a molecular genetic classification (red arrow). This genetic classification is based on mutational profile, somatic copy-number alterations and structural variants. The depicted molecular subtypes were identified in 3 different studies indicating that these subgroups reflect true biological differences.[131,132,134] Based on these molecular studies, a predictor model was developed that dissects the cell-of-origin and stratifies further the molecular classification into 7 genetic subtypes with apparently clinical relevance.[133] The different abbreviations indicate the names given in the different studies to the same identified biological group.

Figure 3: Morphological characterization of highly proliferative B-cell lymphomas. (A, B) This diffuse large B-cell lymphoma, NOS has many mitotic figures but many of the neoplastic cells are typical large transformed cells, not resembling either Burkitt lymphoma cells or B-lymphoblasts. Chromosomal analysis showed a complex karyotype but there was no evidence of *MYC* or *BCL2* rearrangement. (C,D) This high-grade B-cell lymphoma, NOS is composed of relatively small blastoid-appearing cells with many

mitotic figures, reminiscent of a B-lymphoblastic leukemia/lymphoma. TdT was negative. It had a complex karyotype that included t(14;18)(q32;q21) and i(17)(q10). (E, F) This high-grade B-cell lymphoma with *MYC* and *BCL6* rearrangements (without evidence of an IGH-*BCL2*) resembles Burkitt lymphoma with intermediate-sized transformed cells and a starry sky appearance with scattered tingible body macrophages. The cytospin (inset) demonstrated cytoplasmic vacuoles. Also, unlike classic Burkitt lymphoma, it was BCL2 protein positive and only had equivocal CD10 positivity. (Hematoxylin & eosin stains except for Wright-Giemsa stain for the inset, A, C, E original magnification 40x, B, D, F original magnification 100x)

Figure 4: Large B cell lymphoma with 11q alterations. The left image shows a low power view of a case with large cell morphology, abundant mitoses and the characteristic starry-sky pattern with abundant macrophages with coarse apoptotic bodies (original magnification x200; hematoxylin and eosin). Higher magnification reveals the large centroblastic morphology of the tumor cells (original magnification x400; hematoxylin and eosin). FISH analysis demonstrated the typical 11q alterations (blue: centromere; red: 11q24 loss, green: 11q23 gain). The cytology of the cells might be medium to large-sized cells. The morphology and mutational profile justify the change in the name of this entity (previously, Burkitt-like lymphoma with 11q alterations).

Figure 5: Algorithm for the classification work-up of nodal peripheral T cell lymphomas (PTCL). The current algorithm for diagnosing PTCL requires immunophenotypic study with a panel of markers that, together with viral analysis (HTLV1, EBV), will orient the pathologist to consider and diagnose specific entities. In ambiguous cases, sequencing studies may assist in the diagnosis of some entities, particularly T-follicular helper cell lymphoma. PTCL, NOS is established when other specific entities are excluded. Phenotypic or gene expression profile may subdivide these cases but this subclassification is not routinely incorporated into clinical diagnosis and requires further studies for clinical validation.

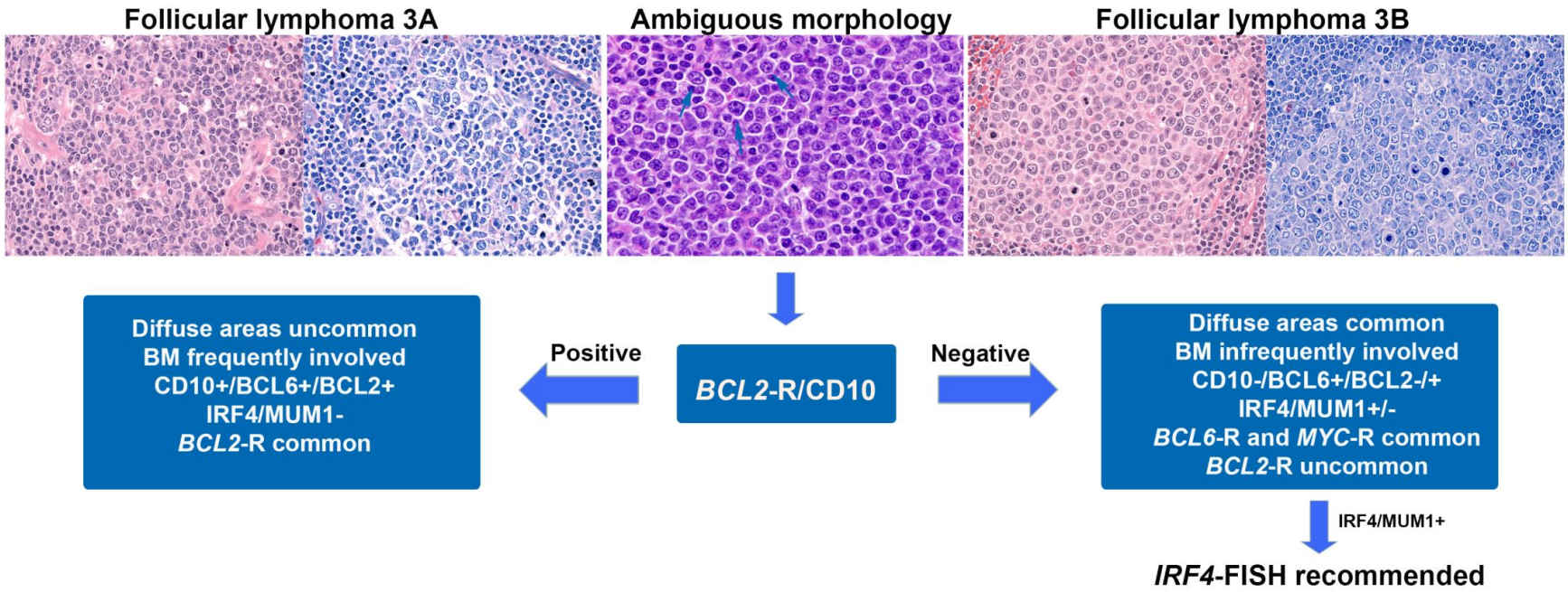
Follicular lymphoma 3A
Ambiguous morphology
Follicular lymphoma 3B
Diffuse areas uncommon
BM frequently involved
CD10+/BCL6+/BCL2+
IRF4/MUM1-
BCL2-R common
Positive
BCL2-R/CD10
Negative
Diffuse areas common
BM infrequently involved
CD10-/BCL6+/BCL2-/+
IRF4/MUM1+/-
BCL6-R and MYC-R common
BCL2-R uncommon
IRF4/MUM1+
IRF4-FISH recommended

Figure 1

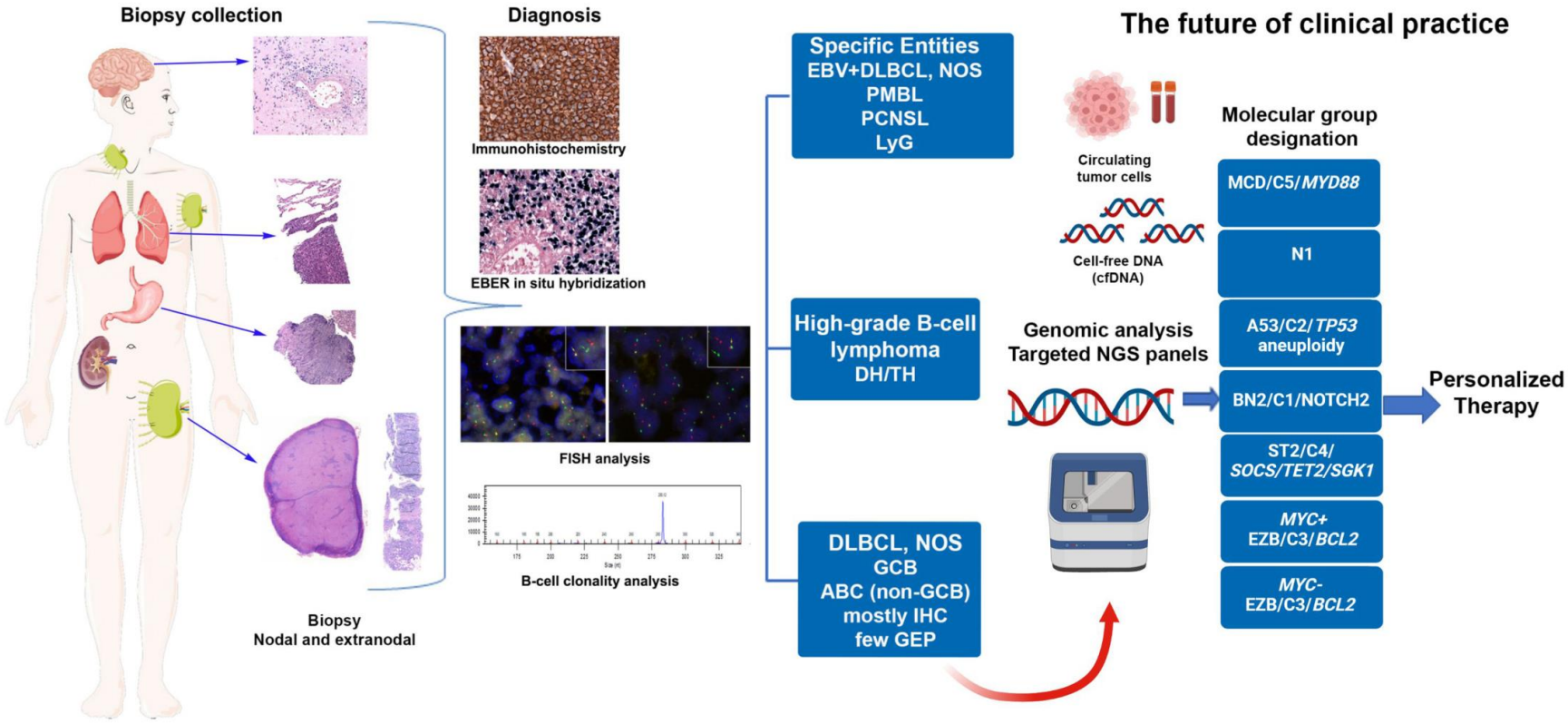
Biopsy collection
Diagnosis
Immunohistochemistry
EBER in situ hybridization
FISH analysis
B-cell clonality analysis
Biopsy
Nodal and extranodal
Specific Entities
EBV+DLBCL, NOS
PMBL
PCNSL
LyG
High-grade B-cell lymphoma
DH/TH
DLBCL, NOS
GCB
ABC (non-GCB)
mostly IHC
few GEP
The future of clinical practice
Circulating tumor cells
Cell-free DNA (cfDNA)
Genomic analysis
Targeted NGS panels
Molecular group designation
MCD/C5/MYD88
N1
A53/C2/TP53 aneuploidy
BN2/C1/NOTCH2
ST2/C4/ SOCS/TET2/SGK1
MYC+ EZB/C3/BCL2
MYC- EZB/C3/BCL2
Personalized Therapy

Figure 2

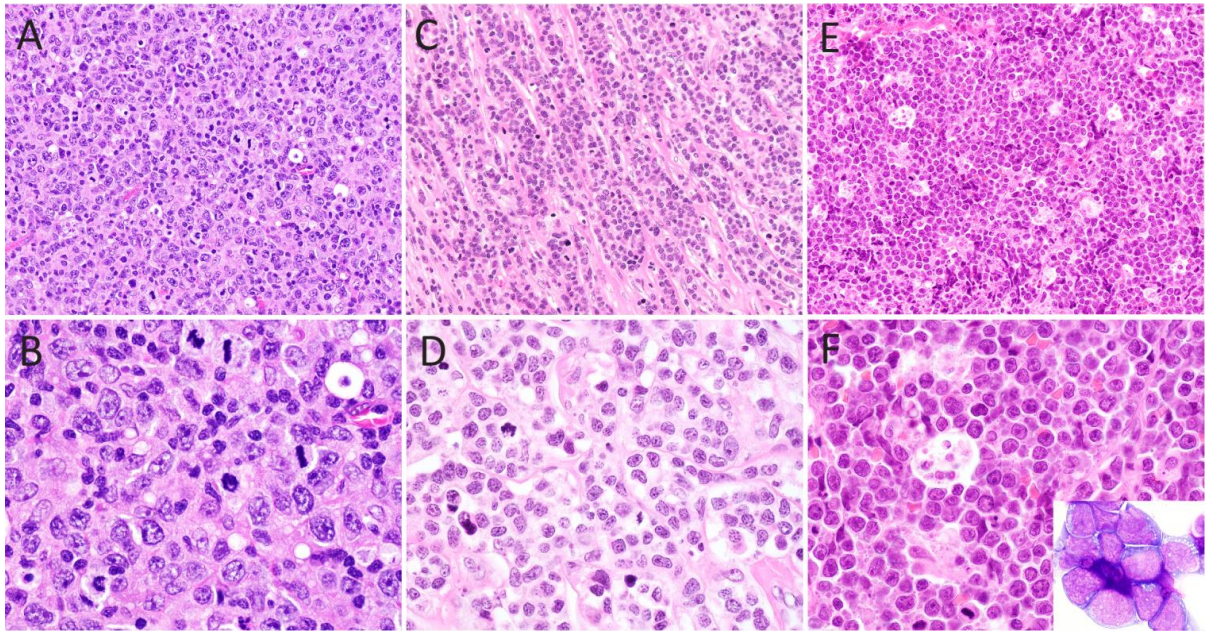

Figure 3

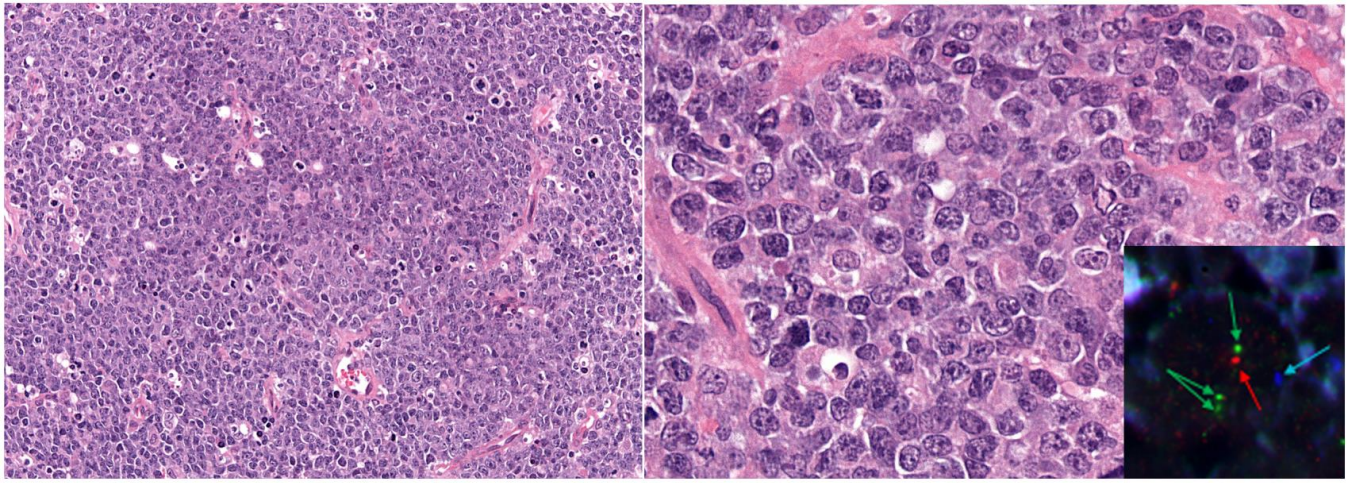

Figure 4

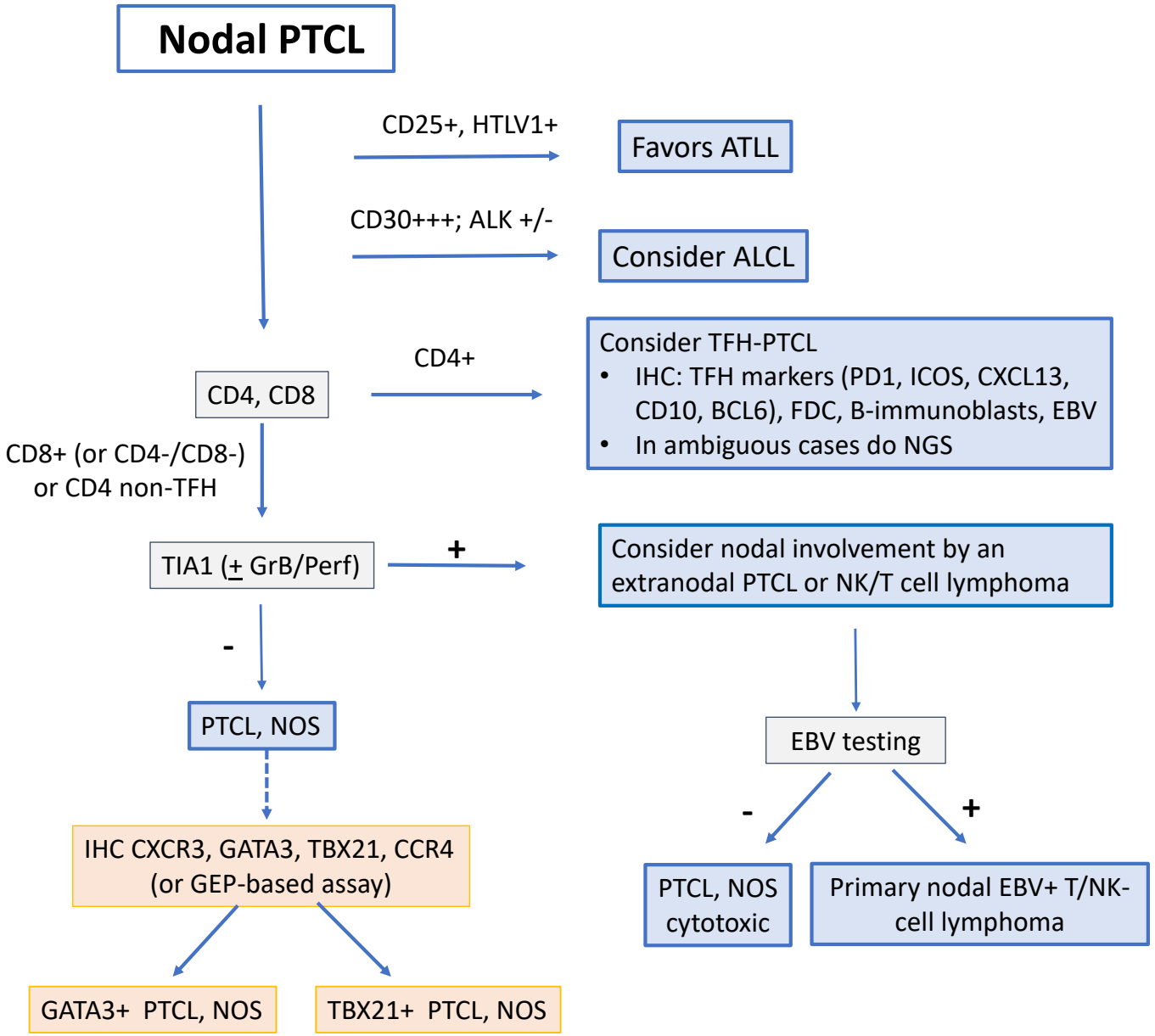
Nodal PTCL
CD25+, HTLV1+
Favors ATLL
CD30+++; ALK +/-
Consider ALCL
CD4, CD8
CD4+
Consider TFH-PTCL
• IHC: TFH markers (PD1, ICOS, CXCL13, CD10, BCL6), FDC, B-immunoblasts, EBV
• In ambiguous cases do NGS
CD8+ (or CD4-/CD8-) or CD4 non-TFH
TIA1 (± GrB/Perf)
+
Consider nodal involvement by an extranodal PTCL or NK/T cell lymphoma
-
PTCL, NOS
EBV testing
-
+
IHC CXCR3, GATA3, TBX21, CCR4 (or GEP-based assay)
PTCL, NOS cytotoxic
Primary nodal EBV+ T/NK-cell lymphoma
GATA3+ PTCL, NOS
TBX21+ PTCL, NOS

Figure 5