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Genomic Profiling for Clinical Decision Making in Lymphoid Neoplasms

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Abstract:
With the introduction of large-scale molecular profiling methods and high-throughput sequencing technologies, the genomic features of most lymphoid neoplasms have been characterized at an unprecedented scale. While the principles for the classification and diagnosis of these disorders, founded on a multidimensional definition of disease entities, have been consolidated over the past 25 years, novel genomic data have markedly enhanced our understanding of lymphomagenesis and enriched the description of disease entities at the molecular level. Yet the current diagnosis of lymphoid tumors is largely based on morphological assessment and immunophenotyping, with only few entities being defined by genomic criteria. This paper, which accompanies the International Consensus Classification of mature lymphoid neoplasms, will address how established assays and newly developed technologies for molecular testing already complement clinical diagnoses and provide a novel lens on disease classification. More specifically, their contributions to diagnosis refinement, risk stratification and therapy prediction will be considered for the main categories of lymphoid neoplasms. The potential of whole-genome sequencing, circulating tumor DNA analyses, single-cell analyses and epigenetic profiling will be discussed, as these will likely become important future tools for implementing precision medicine approaches in clinical decision-making for patients with lymphoid malignancies.

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Abstract:

With the introduction of large-scale molecular profiling methods and high-throughput sequencing technologies, the genomic features of most lymphoid neoplasms have been characterized at an unprecedented scale. While the principles for the classification and diagnosis of these disorders, founded on a multidimensional definition of disease entities, have been consolidated over the past 25 years, novel genomic data have markedly enhanced our understanding of lymphomagenesis and enriched the description of disease entities at the molecular level. Yet the current diagnosis of lymphoid tumors is largely based on morphological assessment and immunophenotyping, with only few entities being defined by genomic criteria. This paper, which accompanies the International Consensus Classification of mature lymphoid neoplasms, will address how established assays and newly developed technologies for molecular testing already complement clinical diagnoses and provide a novel lens on disease classification. More specifically, their contributions to diagnosis refinement, risk stratification and therapy prediction will be considered for the main categories of lymphoid neoplasms. The potential of whole-genome sequencing, circulating tumor DNA analyses, single-cell analyses and epigenetic profiling will be discussed, as these will likely become important future tools for implementing precision medicine approaches in clinical decision-making for patients with lymphoid malignancies.

Introduction:

Genetics is an integral part of contemporary classification of lymphoid neoplasms.[1,2] Recurrent chromosomal alterations, discovered by cytogenetics[3], were instrumental in defining certain lymphoma entities and, in select tumors, represent a cornerstone for diagnosis in complement to morphological and immunophenotypic analyses. Some rearrangements lead to either dysregulation of oncogenic proteins or expression of gene fusions. Fluorescence in situ hybridization (FISH) is most often used to detect chromosomal aberrations (**Figure 1**), with rearrangements detected using either fusion or break-apart probes. Clonality assessment of immunoglobulin (IG) and T-cell receptor (TR) loci rearrangements using PCR-based analyses[4] or, more recently, high-throughput sequencing (HTS)[5], is often useful in the assessment of lymphoid proliferations. However, the finding of clonal rearrangements is not always synonymous with lymphoid neoplasms, since dominant clones can be seen in reactive conditions as well, highlighting the importance of appropriate integration with all other pathologic features.[4]

With the introduction of HTS-based technologies over the last 10-15 years, the genomic landscapes of many lymphoid neoplasms were characterized at an unprecedented scale.[6] Whilst a predominant gene mutation was identified in only a few lymphoma entities, such as the *MYD88*^{L265P} mutation in lymphoplasmacytic lymphoma and *BRAF*^{V600E} mutation in hairy cell leukemia,[7,8] in most lymphoid neoplasms, a much more diverse pattern is observed with only a handful of variably frequent aberrations followed by a long tail of uncommonly mutated genes.[9-11] These studies have also disentangled the diverse (sub)clonal architecture of lymphoid neoplasms including early drivers, later alterations linked to clinical aggressiveness as well as passenger mutations.[12-14] Despite the heterogenous mutation landscapes between distinct diseases, there are also common themes of affected cellular processes and signaling pathways (**Figure S1 and Table S1**). Based on newly acquired knowledge, clinically relevant genomic aberrations have been identified with diagnostic, prognostic and predictive impact in different entities.[15,16] While the number of alterations that facilitate diagnosis and risk-

stratification is increasing, relatively few are currently linked to prediction of therapeutic response.[17,18]

HTS-based technologies range from targeted sequencing of a limited number of genes (gene panels) to whole-exome sequencing (WES) for assessment of coding regions of genes, or whole-genome sequencing (WGS). These methods have different capacities to detect somatic aberrations, as targeted approaches typically have a higher sequence depth than genome-wide technologies and, therefore, detect subclonal alterations with greater sensitivity and are more robust to lower tumor purity. In amplicon-based sequencing panels, a limited number of genes or hotspot regions are generally included (~20-50) and only single-nucleotide variants (SNV) and insertions-deletions (indels) or specific gene fusions are detected (**Figure 1**).[19] Capture-based panels enable simultaneous interrogation of SNVs and indels, copy-number aberrations (CNAs; i.e. deletions and amplifications) and structural variants (SVs, including rearrangements).[20,21] These comprehensive panels can include sequencing of DNA and/or RNA and assessment of other more complex markers, such as IG and TR rearrangements and DNA methylation. Recently developed 'all-in-one' capture-based panels can detect most relevant types of genomic aberrations associated with lymphoproliferations.[22-24]

Gene expression profiling (GEP) and DNA methylation analyses have been pivotal to identify lymphoma subgroups and "cell-of-origin" signatures.[25-29] Subsequently, selective targeted approaches have been developed to detect differential expression of key genes that inform on these subgroups.[29-31] Whole-transcriptome sequencing (WTS – commonly referred to as RNA-seq), an alternative unbiased method, may have future routine applications in clinical diagnostic laboratories.[32] Apart from tumor genetics, the tumor microenvironment (TME) plays a key role in shaping lymphoma development and response to treatment.[33] Advances in single-cell analysis (SCA) methodologies, along with tools for *in silico* deconvolution of bulk tissue WTS[34], are leading to a better understanding of tumor heterogeneity within its TME landscape[35].

Application of clinical molecular diagnostics to lymphoid proliferations is currently constrained by several practical considerations. While the optimal source consists of nucleic acids extracted from fresh surgical biopsies or liquid samples (blood or bone marrow), clinical assays must be adapted to formalin-fixed paraffin-embedded (FFPE) tissues, which is the main diagnostic material, and to limited samples (e.g. needle biopsies). Currently, targeted gene panels, WES and WTS are feasible for FFPE material, but WGS remains more challenging.[36] For HTS-based assays, important parameters include tumor cell content, technical performance (e.g. sequence coverage/depth, background artefacts), need for unique molecular identifiers, and turn-around-time. Key aspects related to variant interpretation and reporting include variant classification systems used[37-39], variants of uncertain significance (VUS), and presence of clonal hematopoiesis. For patients experiencing relapse, the most recent sample is usually preferentially analyzed, but comparison of sequential biopsies may be necessary depending on the clinical question posed.

Current classification of lymphoid tumors is still largely based on morphological assessment and immunophenotyping, but it is likely that future schemes will further integrate genomic-based features to characterize and define (sub)entities and direct therapies.[2] This paper, which accompanies the International Consensus Classification of mature lymphoid neoplasms[2], will address how genomic testing already complements existing criteria and provides a novel lens on disease classification. More specifically, its contributions to diagnostic refinement, risk stratification and therapy prediction will be considered for the main categories of lymphoid neoplasms (**Tables 1 and 2)** along with its value in helping resolve potentially challenging differential diagnoses (**Table 3**). Histiocytic and dendritic cell neoplasms, being of myeloid or mesenchymal derivation, have traditionally been discussed with lymphomas, given overlapping clinical presentation, and will be addressed in a similar fashion. Finally, how WGS, analysis of circulating tumor DNA, or liquid biopsies, epigenetic profiling and single-cell analyses may become important tools for implementing precision medicine approaches in clinical decision-making of patients with lymphoid malignancies in the near future, will be envisioned.

Mature B-cell neoplasms

Chronic lymphocytic leukemia/Small lymphocytic lymphoma

Molecular genetic characterization guides management of newly diagnosed CLL/SLL patients. The somatic hypermutation status of the clonally rearranged immunoglobulin heavy variable (IGHV) gene should be determined once as it remains constant through the disease course. [40,41] Compared to IGHV-mutated (M)-CLL (<98% identity compared to germline sequence), IGHV-unmutated (U)-CLL has shorter time-to-therapy initiation, remission duration with therapy, and overall survival (OS).[42] In patients without *TP53* aberration, chemoimmunotherapy remains a reasonable first-line treatment option for patients with M-CLL whereas initial targeted therapy (BTK inhibitors (BTKi), BH3 mimetic with anti-CD20 antibody) has become the standard-of-care for U-CLL.[43-47] Stereotyped B-cell receptors (BcR) occur in 41% of cases with some subsets having distinctive outcome (**Table S2**).[48-53]

Among CNAs routinely detected by FISH (del(11q), trisomy 12, del(13q) and del(17p))[54], del(17p) confer a poorer prognosis and predicts suboptimal responses to chemoimmunotherapy. Complex karyotype (≥5 abnormalities) confers poor outcome, even with targeted therapies[55], and can be detected by cytogenetics or SNP arrays.[56,57]

Driver mutations differ in U-CLL and M-CLL (**Figure S2**) and impact cellular signaling pathways: BcR (IGHV3-21^{R110})[58,59], TLR (*MYD88*), NF-κB (*BIRC3*), NOTCH (*NOTCH1, FBXW7*), DNA damage response (*ATM, TP53*), RNA processing (*SF3B1, XPO1*) and chromatin modification (*H1-4, ZMYM3, CHD*2).[52,60] While *TP53* aberrations typically are biallelic (i.e. del(17p) and *TP53* mutation), isolated *TP53* mutations can also occur in the absence of del(17p). Both clonal (variant allele frequency (VAF) >10%) as well as subclonal (<10%) *TP53* mutations[61,62] are associated with poor chemoimmunotherapy response. *TP53* aberrations can arise at relapse/progression and thus, if not previously identified, should be evaluated prior to each course of therapy. *ATM* mutations are associated with poor, nondurable responses to DNA-damaging chemotherapy.[63]

Mutations of *BTK, PLCG2* and *CARD11*[64,65] and of *BCL2*[66] have been associated with resistance to BTKi and venetoclax, respectively (**Table S3**).

Epigenetic alterations can also impact CLL outcomes.[67] However, none are routinely tested clinically. HTS and flow cytometry have been applied to the quantification of measurable residual disease (MRD) and might guide therapy in the future.[68,69] Consensus recommendations were recently published.[70]

Follicular lymphoma

The classic form of follicular lymphoma (FL), *in situ* follicular neoplasia and duodenal-type FL are all characterized by the t(14;18)(q32;q21) IGH::*BCL2* translocation deregulating BCL2 expression.[71] FL pathogenesis involves a complex network of genetic, epigenetic and microenvironmental factors, driven by (i) recurrent mutations in genes encoding, in particular, several epigenetic regulators (e.g. *CREBBP, KMT2D, EZH2*), as well as transcription factors (e.g. *MEF2B, FOXO1, STAT6*) and components of the mTOR signaling pathway (e.g. *RRAGC, ATP6V1B2*); and (ii) perturbations in interactions with their immune environment (e.g. *TNFRSF14* inactivation, N-glycosylation sites in the IGV genes).[71-78] However, identifying these lesions and combinations thereof[79], along with GEP signatures[80], has not yet entered routine testing, given the lack of reproducible prognostic/predictive value at diagnosis for patients treated with standard chemoimmunotherapy. FDA approval mandates *EZH2* mutation detection for treatment with the EZH2 inhibitor tazemetostat[81] in patients having received at least two prior systemic therapies, but this is not required for those lacking alternative options in later treatment lines.

Molecular analyses may assist in the differential diagnosis of *BCL2*-translocation negative FLs[82], which share genetic alterations with nodal FL although at different frequencies (*BCL2R*-negative CD23+ follicle center lymphoma, primary cutaneous follicle center lymphoma, pediatric-type FL, testicular FL, and large B-cell lymphoma with *IRF4* rearrangement (LBCL-*IRF4*)) and in distinguishing primary versus secondary cutaneous disease[83,84] (**Table 3**).

Phylogenetic analyses of spatial and temporally acquired mutations in t(14;18)-positive cells revealed a marked heterogeneity inferring the existence of a long-lived common mutated precursor B-cell (CPC) population, that is capable of evading treatment and seeding new episodes of disease.[85-87] Current challenges include characterizing this precursor B cell, identifying molecular predictors of early relapse/histologic transformation and recognizing better stratification factors, in the context of a rapidly evolving therapeutic landscape.

Marginal zone lymphomas

Extranodal (MALT), nodal (N), and splenic (S) marginal zone lymphomas (MZLs) have distinct genetic changes. Nevertheless, they commonly affect signaling pathways central to the homeostasis of normal MZ B cells, including BcR, NF□κB, and NOTCH.[88]

MALT lymphomas have distinct genomic alterations according to their primary anatomic site.[89,90] The t(11;18)(q21;q21) *BIRC3::MALT1* fusion occurs most often in gastric and pulmonary MALT lymphomas.[89] This rearrangement is more common in *Helicobacter pylori*-negative gastric MALT lymphomas and is associated with lack of antibiotic response in *H.pylori*-positive cases.[91] The t(14;18)(q32;q21) IGH*::MALT1* translocation usually is found in lung and ocular adnexa MALT lymphomas.[89] The t(3;14)(p14.1;q32) *FOXP1::*IGH translocation associates with thyroid and ocular adnexa MZL, and primary cutaneous marginal zone lymphoproliferative disorder (LPD).[89] The t(1;14)(p22;q32) *BCL10::*IGH translocation is found in gastric and lung MALT lymphomas and skin MZL-LPD.[89] Mutations of *TNFAIP3* are reported in all types of MZL, but enriched in ocular adnexa MALT lymphoma. Mutations of *FAS* are enriched in primary cutaneous MZ-LPDs.[90]

MALT lymphoma translocations are lacking in SMZL and NMZL. SMZL shows hemizygous deletion of 7q31-32[92], and, rarely, translocations juxtaposing *CDK6* to IG loci[93]. SMZL and NMZL have a common genetic background characterized by mutations of NOTCH genes (e.g. *NOTCH2*, *NOTCH1*, *SPEN*), genes involved in non-

canonical NF-κB signaling (e.g. *BIRC3*, *TRAF3*), and *KLF2*, a master regulator of both NOTCH and NF-κB signaling[94]. Among MZLs, *BRAF* and *PTPRD* mutations are nearly exclusive to NMZL.[95,96] SMZL comprises two main genetic clusters, characterized by mutations affecting NF-κB, NOTCH, and *KLF2* (NNK), or by mutations of *TP53*, MAPK, and TLR (DMT).[97] Cytogenetic and molecular features can assist in the differential diagnosis of MZL and other small B-cell lymphomas (**Table 3** and **Figure S3**).

Mantle cell lymphoma

MCL includes two subtypes, conventional (cMCL) and the less common leukemic non-nodal (nnMCL). Both share rearrangements involving *CCND1,* and less frequently *CCND2* or *CCND3,* mainly with IGH or IG light chain loci.[98,99] FISH break-apart probes are recommended for the detection of these rearrangements, although CCND1 immunohistochemistry typically obviates the need for *CCND1* FISH. Identification of uncommon cryptic translocations requires specific probes or HTS analysis.[99-101] cMCL derives from naïve-like B cells, carries unmutated IGHV genes, and has a different expression profile with typically high SOX11 levels. nnMCL originates in memory-like B cells, carries mutated IGHV genes, and is typically SOX11-negative.[102,103] In both subtypes, *CCND1* rearrangement is acquired in B-cell precursors mediated by RAG activity, although in a minority of cases occurs in mature B cells by IG class-switch and AID-driven mechanisms.[104] cMCL carries frequent (>15%) mutations in *ATM*, *KMT2D*, *TP53*, *BIRC3*, and the 3' untranslated region (3'UTR) of *CCND1* leading to higher oncogene expression. Less common mutations (5-15%) occur in *NSD2*, *NOTCH1/2*, *HNRNPH1, CARD11, SP140*, *SMARCA1* among others. The most common mutations in nnMCL are *CCND1* in the 5'-region (mediated by AID), and *TP53*.[104-108] MCL, particularly blastoid/pleomorphic of both subtypes, accumulate numerous and complex genomic structural alterations that worsen the prognosis, with *TP53*, *CDKN2A* deletions and *MYC* rearrangements being of particular impact.[104,109,110] *TP53* aberrations are associated with poor prognosis in patients undergoing chemoimmunotherapy and autologous stem cell transplant; future studies should focus on this very high-risk group.[103,111-116] The proliferation signature defines patients with different clinical trajectories.[117-119] Resistance to BTK or BCL2 inhibitors due to acquired *BTK* or *BCL2*

mutations is uncommon in MCL but may involve alterations in other genes and transcriptome reprograming with overexpression of OxPhos, MYC, alternative NF-κB and mTOR pathways.[120-123]

Multiple myeloma

Classification of multiple myeloma (MM) is based on primary abnormalities invariant through disease progression from monoclonal gammopathy of uncertain significance (MGUS) to smoldering (s)MM to MM.[2] Moreover, genomic profiling is important for risk stratification in which adverse genetic events may be acquired during disease progression. There are five non-overlapping disease subgroups: 1) CCND family translocation; 2) MAF family translocation, 3) *NSD2* translocation, 4) hyperdiploid (gains of chromosome 3,5,7,9,11,15,19, and 21), and 5) MM-NOS, lacking all preceding features.[124-127] In the future, the hyperdiploid group will likely be further subdivided, for instance based on the presence of trisomy 11 and CCND1 expression (**Figure 2**).[124,125] Disease classification currently relies on FISH assays (**Table 1**), but can be achieved more comprehensively using GEP and/or WGS.[124,126-128]

Adverse risk is associated with specific primary genetic events (t(4;14)(p16;q32) *NSD2*::IGH, t(14;16)(q32;q23) IGH*::MAF)* and, beyond these subgroups, secondary genetic events (1q gain/amplification, del(1p), del(17p) and *TP53* mutation).[129,130] Not all therapies have been shown to benefit patients with high-risk genetics; however, a prolongation of progression free survival (PFS) is seen with the addition of a proteosome inhibitor for patients with t(4;14) or del(17p), or of daratumumab or tandem stem cell transplant for these patients.[131-133] These data strongly support the use of a quadruplet regimen (an anti-CD38 antibody, a proteosome inhibitor, a thalidomide analog and a glucocorticoid) for the treatment of newly diagnosed high-risk MM. Genetics can also help guide therapy for standard-risk patients. For example, relapsed patients with t(11;14) benefit from treatment with venetoclax – an effect not observed in the cohort overall.[134] Much more prognostic information can be obtained from high-risk scores based on GEP (GEP70, EMC92) reflecting important biological aspects of the disease, such as proliferation.[135,136] WGS adds information about clonal heterogeneity,

focal CNAs, chromothripsis and important SVs, such as those involving *MYC*, present in almost half of newly diagnosed MM.[137-142] This may perhaps be most relevant for patients with sMM, where the presence of genetic events associated with adverse prognosis in newly diagnosed MM (t(4;14), t(14;16), add(1q), del(17p)), as well as others that are not (del(13q), *NRAS* and *KRAS* mutations, *MYC* rearrangements) are associated with more rapid progression to symptomatic MM, and may become the basis for a genetic definition of MM requiring treatment.[139,143-147]

Lymphoplasmacytic lymphoma

Somatic mutations in *MYD88* (*MYD88*^{Mut}) and *CXCR4* (*CXCR4*^{Mut}) occur in 95-97% and 30-40% of patients with IgM-secreting lymphoplasmacytic lymphoma (LPL) (Waldenström Macroglobulinemia; WM/LPL), respectively[148] and in 50-90% and 10-20% of patients with IGM MGUS, respectively.[148-151] In IgM MGUS, NOS, nearly all individuals with *MYD88*^{Mut} will progress to WM/LPL.[150] Up to 80% of non-IgM secreting LPL also harbor *MYD88*^{Mut}.[152] Nearly all *MYD88*^{Mut} IgM and non-IgM LPL and IgM MGUS, NOS cases express the L265P variant, through rarely non-L265P variants have been identified.[148,150-152] *MYD88*^{Mut} triggers BTK-directed NF-κB pro-survival signaling, while *CXCR4* mutations trigger ERK and AKT signaling relevant to drug resistance, particularly BTKi.[148] In LPL/WM, *MYD88* and *CXCR4* mutations impact disease presentation, prognosis, time-to-treatment initiation and/or treatment outcome.[148,153] Patients with wild-type *MYD88* (*MYD88*^{WT}) have NF-κB pathway activating mutations overlapping those found in DLBCL, are at higher risk of disease transformation and/or death, and show decreased response activity and/or shorter PFS following treatment with BTKi and bendamustine/rituximab.[148,153-157] Zanubrutinib shows major response activity in *MYD88*^{WT} and can be considered.[158] Other B-cell malignancies, including IgM-secreting MM, can be confused with *MYD88*^{WT} WM and should be ruled out since management can differ.[155] *MYD88* mutation status should ideally be determined by allele-specific (AS)-PCR-based diagnostics, since HTS may miss up to 1/3 of *MYD88*^{Mut} WM/LPL, particularly those with low bone marrow disease burden.[159] *CXCR4* mutations are typically subclonal, impact depth of response, time to attainment of major responses, and/or PFS following ibrutinib or zanubrutinib.[148,149,160-162] Over 40 nonsense

and frameshift variants of *CXCR4*^{Mut} are described.[149,153,163] Nonsense variants (most commonly *CXCR4*^{S338X}), are particularly associated with high serum IgM levels, symptomatic hyperviscosity, shorter time-to-treatment initiation, lower response activity and shorter PFS on ibrutinib, and shorter OS.[153,164,165] Up to 2/3 of *CXCR4*^{Mut} may be missed by HTS, particularly those with low disease burden, and low VAFs.[166] CXCR4 antagonists are being investigated in WM/LPL. Heterozygous loss of 6q, present in up to half of WM patients, is mutually exclusive of *CXCR4*^{Mut}, and includes regulatory genes of BTK (*IBTK*), BCL2 (*BCLAF1*), NF-κB (*HIVEP2*, *TNFAIP3*), and apoptosis (*FOXO3*).[148,167] Following ibrutinib treatment, tumor evolution leading to biallelic del(6q) has been observed.[168] The *BTK*^{C481} mutation has been observed in patients with WM/LPL with acquired resistance to ibrutinib, particularly those with *CXCR4*^{Mut}.[169] *TP53* mutations are rare in WM/LPL and associate with poor outcome, though patients carrying these mutations respond to ibrutinib.[170,171]

Diffuse large B-cell lymphoma

The molecular subclassification of DLBCL is key to understanding therapeutic efficacy. Currently, LBCL should be evaluated for rearrangements, typically by FISH (though imperfect[172]), to identify high-grade B-cell lymphoma (HGBCL) with *MYC* and *BCL2* rearrangements, which responds poorly to R-CHOP chemotherapy, and the provisional entity HGBCL with *MYC* and *BCL6* rearrangements.[2] The activated B-cell-like (ABC)- and germinal centre B-cell-like (GCB)-DLBCL "cell-of-origin" (COO) subtypes[25] should be distinguished by GEP[173], or approximated by immunohistochemistry (IHC)[174], providing useful prognostic information.[26,175] ABC-DLBCLs typically rely upon BcR-dependent NF-κB signaling for survival, engendering sensitivity to BTK inhibition.[176-179] Younger, newly diagnosed patients with ABC-DLBCL may benefit from the addition of a BTKi to R-CHOP[180,181], although this requires validation. However, recent clinical studies suggest that the binary COO classification is insufficiently granular to predict the efficacy of all precision medicine strategies.[182,183]

An important refinement and extension of the DLBCL COO classification emerged from three independent studies[184-186] that used multi-platform genomic profiling to detect

patterns of co-occurring genetic alterations, converging on ~7 subtypes with recurrent biological features (**Figure 3**). Several DLBCL genetic subtypes share core genomic alterations with indolent B-cell lymphomas, suggesting that some apparently de novo DLBCL may arise from clinically occult indolent lymphomas and that the evolutionary paths of DLBCL and indolent lymphomas share key driver events at their inception. The MCD DLBCL subtype encompasses genetically related primary extranodal entities, including primary DLBCL of the central nervous system and of the testes, among others, reflecting shared biology typified by BcR signaling and escape from immune recognition.[187] The genetic subtypes, with distinct outcomes following R-CHOP, reveal oncogenic pathways that suggest therapeutic vulnerabilities, providing a framework for future drug development. For example, addition of a BTKi to R-CHOP may be particularly beneficial in the MCD and N1 genetic subtypes.[181]

One publicly available approach to assign individual DLBCL tumors to genetic subtypes is the LymphGen algorithm, which performed comparably in 4 independent DLBCL cohorts.[187,188] One subtype, EZB, is further subdivided into MYC+ and MYC– subtypes based on a GEP signature[29] that reflects germinal center dark *versus* light zone origin and MYC target gene expression.[187] LymphGen classifies ~63% of DLBCL tumors with ~6% assigned to more than one subtype, indicating a compound pathogenesis. A key task ahead is to understand how to categorize the remaining 37% of DLBCLs that are unassigned using LymphGen. Some may represent rare, undescribed subtypes, while others may be classifiable into existing subtypes using WGS, GEP, epigenetic profiling, and analysis of the TME.

Given the above, efficient progress towards precision medicine for DLBCL will require the incorporation of genetic profiling in future clinical trials. At a minimum, this would entail WES (or WGS), analysis of *MYC*, *BCL2 and BCL6* rearrangements, and WTS to gauge the phenotype of the malignant cells and TME, both of which provide prognostic information.[26,34,175,189] Initially, this molecular profiling will likely be performed retrospectively, but our deepening understanding of the therapeutic vulnerabilities of

each genetic subtype will foster clinical trials that use genomic profiling to stratify patients into treatment arms.

High-grade B-cell lymphomas

HGBCL with *MYC* and *BCL2* (with or without *BCL6*) rearrangement (HGBCL-DH-*BCL2*) is diagnosed by detecting these rearrangements in tumors with high-grade or large B-cell morphology (**Figure 4**).[2] This is typically achieved using break-apart FISH probes, although up to 20% of diagnoses may be missed using this approach[172]. The partner gene for *MYC* is an IG locus in approximately half of HGBCL-DH-*BCL2*.[190,191] The existence of "cryptic" rearrangements and potential prognostic implication of partner loci[190,191] may lead to capture-based rearrangement detection supplanting FISH[192,193].

The mutational landscape of HGBCL-DH-*BCL2* is relatively homogeneous, with frequent mutations in *BCL2*, *KMT2D*, *CREBBP*, *TNFRSF14* and *EZH2*.[194-196] These mutations are frequent in FL, suggesting that these tumors either arise from (occult) FL or an FL-like precursor. In contrast, albeit based on modest numbers, the mutational landscape of HGBCL-DH-*BCL6* is heterogeneous.[194,196] Coupled with ~30% harboring t(3;8)(q27;q24) *BCL6*::*MYC* (i.e. "pseudo-double hit")[197], the upcoming WHO classification has removed this category[198], while it is retained as a provisional category in the International Consensus Classification[2], encouraging further investigation.

HGBCL-DH-*BCL2* and BL share a common GEP signature – "molecular high grade" (MHG)[199] or "double-hit signature" (DHITsig)[29]. These signatures, observed in a larger group of aggressive tumors (including EZB-MYC+[187]), encompass germinal center dark-zone programs. The biology of these poor prognosis "dark-zone" lymphomas requires exploration to determine whether shared targetable biology warrants defining a future lymphoma entity broader than that identified by gene rearrangements alone.

HGBCL, NOS, remains a rare category defined by morphology and lack of defining genomic rearrangements.[2] The molecular landscape is very diverse[200] and, where

available, molecular assessment is recommended to determine whether individual tumors can be aligned/reassigned to defined entities.

Burkitt lymphoma

Burkitt lymphoma (BL) is characterized by *MYC* translocations, which almost exclusively involve an immunoglobulin partner. *MYC* mutations due to aberrant activity of AID (somatic hypermutation (SHM)) are typically found, but most of them are likely inconsequential. BL in malaria-endemic regions is generally EBV-positive whereas this is less common in sporadic cases found elsewhere (adult 20%, pediatric 6%).[201] BL risk is higher in immunodeficient patients, including individuals with HIV infection.[202] Pathogenesis may vary according to EBV status, reflected in the higher prevalence of some driver mutations in EBV-negative tumors.[203-206] However, currently EBV status and genomic characteristics do not influence treatment decisions. Potential prognostic associations have been reported for *TP53* mutations and this could eventually improve risk stratification.[207] Patients with disease refractory to standard therapies represent an unmet clinical need[202], and genomic analysis has identified potential therapeutic vulnerabilities[205]. Many genes recurrently mutated in BL are also drivers in other lymphomas originating from germinal center B cells, with driver mutations more prevalent in BL highlighting distinguishing oncogenic mechanisms. These include mutations that inactivate the protein translation factor DDX3X, thereby buffering the proteotoxic stress caused by dysregulated MYC expression[208], and mutations in either *TCF3* or its negative regulator *ID3*[205]. TCF3 promotes constitutive BcR signaling that activates PI3 kinase and is essential to BL survival.[205] In contrast, *EZH2*, *CREBBP* and *KMT2D* mutations are rarely observed in BLs, though common in GCB-DLBCL.[203,204] Establishing the presence of such mutations could ultimately be combined with current criteria to improve the robustness of BL diagnosis and identify potential therapeutic targets.[205]

Pediatric B-cell lymphomas

Several types of B-cell lymphoma which typically occur in pediatric and young adult populations have characteristic genomic aberrations. Pediatric-type FL presents as

localized disease, has pure follicular morphology, high proliferation and lacks BCL2 expression and/or rearrangement. Molecular confirmation of monoclonality is crucial.[4,209] Lack of cytogenetic complexity and detection of *TNFRSF14* alterations and/or *MAP2K1* or *IRF8* mutations, in the absence of mutations in histone modifier genes, favor this diagnosis.[209-213] Presence of *IRF4, MYC* or *BCL6* rearrangement exclude pediatric-type FL. Of note, pediatric nodal marginal zone and PTFL share clinical and morphological features, low genetic complexity, and similar mutational and methylation profiles indicating that they are probably part of a single disease with differences in the histological spectrum.[214,215]

LBCL-*IRF4* frequently involves the head and neck or gastrointestinal tract. Tumors are composed of large cells, with or without follicular component expressing germinal center phenotype, and moderate/high levels of MUM1/IRF4. *IRF4* rearrangements are detectable by FISH break-apart probes.[216,217] Rearrangements of *BCL6* but not *BCL2,* may be observed. Frequently mutated genes include *IRF4*, most likely by juxtaposition to IG loci, *BCL6,* and NF-κB pathway genes (*CARD11*, *CD79B*, *MYD88*).[216,218] Losses of 17p and 11q12-qter gains, are characteristic.[216,218,219] In tumors with consistent pathological and clinical features but FISH-negative for *IRF4* rearrangement, the demonstration of IG rearrangement in the absence of *BCL2*, *BCL6* and *MYC* rearrangements, and/or presence of *IRF4* somatic mutations, could support inclusion in this diagnostic category.[218,220] LBCL-*IRF4* presents rarely also in adults. Moreover, *IRF4* rearrangement may be also observed in other large B-cell lymphomas in association with *BCL2* and/or *MYC* rearrangements and these tumors should not be classified as LBCL-*IRF4*.[221]

LBCL with 11q aberration (LBCL-11q) should be considered in tumors with high-grade/large cell morphology, germinal center phenotype and very high proliferation (>90%), without *MYC* rearrangement (**Figure 4**) . Most LBCL-11q carry the prototypical 11q23.2-q23.3 gain/11q24-qter loss but some have a single terminal loss or proximal gains together with terminal copy neutral loss of heterozygosity (CN-LOH).[222-225] In cytogenetic studies, the gained region is usually inverted.[223,226] Irrespective of

aberration patterns, *ETS1* and *FLI1* genes are included in the minimally deleted region or CN-LOH, differently to other 11q aberrations observed in DLBCL[227,228] The commercially available 11q FISH assay has limitations in detecting gain/CN-LOH and 11q-inverted-gain alteration patterns. Further genomic SV analyses to confirm the LBCL-11q diagnosis may be helpful in those cases. LBCL-11q cases have recurrent mutations in *ETS1, GNA13, BTG2* and *NFRKB* genes and lack typical BL alterations.[224,225]

Hodgkin and mediastinal lymphomas

Classic Hodgkin lymphoma (CHL), primary mediastinal large B-cell lymphoma (PMBCL) and mediastinal gray-zone lymphomas (MGZL) are related diseases that share common genetic alterations, phenotypes and clinical features, including anterior mediastinal involvement.[2] The current classification does not incorporate molecular diagnostics, while several assays can be considered to increase diagnostic precision, and aid biomarker development. GEP assays suitable for FFPE biopsies have been developed to differentiate DLBCL from PMBCL.[229-231] WES has revealed the contrasting mutational landscape of PMBCL to DLBCL and CHL (**Figure S1**).[232,233] GEP and WES studies in MGZL confirmed the presence of genetic and phenotypic features shared with, and intermediate between, CHL and PMBCL. The predominance of T-cell and macrophage-rich TME suggests a closer relationship to HL[234] and further studies are needed to refine borderline cases.[235] WES analysis helped distinguish mutational profiles of MGZL (e.g. *B2M*, *TNFAIP3*, *GNA13* mutations) vs extra-mediastinal ('non-thymic') cases (**Figure S1**),[236] the latter of which are no longer included in "gray-zone" lymphomas[1,2].

GEP studies have been reported in CHL with the goal to predict outcomes after standard-of-care treatments.[237,238] Overall, testing at diagnosis in adult CHL is disappointing with lack of validation in treatment-intense[239] and response-adapted trials[240,241]. Outcome prediction models in relapsed CHL and pediatric patients await further validation.[242-244] While the mutational landscape of CHL is established[245-247], mutational testing for clinical purposes is hampered by scarcity of the malignant Hodgkin Reed-Sternberg cells. Recent studies suggest the clinical utility of FISH-

determined 9p24.1 amplification (harboring *CD274*, *PDCD1LG2*, *JAK2*) as a favorable predictive biomarker in patients with relapsed/refractory CHL treated with PD1 inhibitors.[248] ctDNA-based assessments of remission status and MRD show promise for dynamic disease monitoring with potential implications for response-adapted therapy.[246,249]

Mature T- and NK-cell neoplasms

Anaplastic large cell lymphomas

Anaplastic large cell lymphoma (ALCL) comprises four clinically, pathologically, and genetically distinct subtypes: two systemic forms (ALCL, ALK-positive and ALCL, ALK-negative) and two site-specific forms (primary cutaneous (pc)ALCL, and breast implant-associated (BIA)-ALCL).[2] Accurate diagnosis of ALCL requires integration of histologic, immunophenotypic, genetic, and clinical data. Genetic and molecular characterization additionally aids in prognosis and potential therapeutic targets (**Table 2** and **Figure 5**).

Most ALCLs have clonally rearranged TR genes.[250] ALCL, ALK-positive is defined by the presence of *ALK* fusions encoding oncogenic proteins, typically identified by immunohistochemistry.[251] *ALK* rearrangement is occasionally seen in cases otherwise resembling pcALCL.[252,253] The partner is *NPM1* in >80% of cases. ALK tyrosine kinase inhibitors have efficacy in some clinical settings.[254] NOTCH pathway activation, resulting from recurrent *NOTCH1* mutations or *ALK* fusions, represents another candidate therapeutic target.[255]

ALCL, ALK-negative is genetically heterogeneous.[256] *DUSP22* rearrangement, seen in 19-30% of cases, defines a distinct genetic subtype associated with mutations of *MSC*[2]; prognosis is generally favorable but high-risk cases occur.[256-259] *DUSP22*-R also occurs in pcALCL and lymphomatoid papulosis.[260-264] ALCL, ALK-negative with *TP63* rearrangement appears largely chemo-refractory[256,257,265], and the losses of *TP53* and/or *PRDM1* are associated with inferior outcome[266]. pcALCL with *TP63* rearrangement may also follow an aggressive course.[265] Rare cases with dual

DUSP22/*TP63* rearrangements exist.[257,267] A subset of ALCL, ALK-negative expresses potentially targetable truncated ERBB4.[268]

ALCL, ALK-positive and about two-thirds of ALCL, ALK-negative share STAT3-mediated oncogenesis; genetic alterations driving STAT3 activation in ALCL, ALK-negative include *JAK1* and *STAT3* mutations, and rearrangement involving *ROS1*, *TYK2*, *FRK* and *JAK2*.[261,269-273] These findings also may be seen in pcALCL.[270,274] BIA-ALCL shows activating JAK/STAT alterations as well as epigenetic modifier mutations and loss of chromosome 20q13.13.[275-277] Therapies targeting the JAK/STAT pathway are being explored.[278] *TP53* mutations are detected in a small subset of systemic and BIA-ALCLs.[273,276]

TFH lymphoma and peripheral T-cell lymphoma, NOS

In TFH lymphoma and peripheral T-cell lymphoma (PTCL), NOS, most common genetic abnormalities including SNVs, CNAs and rearrangements, affect genes of epigenetic regulators (e.g. *TET2*, *DNMT3A*, *IDH2*), T-cell receptor signaling and activation (e.g. *RHOA*, *VAV1*, *CD28*, *ICOS*, *FYN*, *LCK*), PI3K/AKT pathway and tumor suppressor genes (e.g. *TP53*, *CDKN2A*, *ATM*, *PTEN*, *RB1*).[279-284] (**Figure S1**) Genetic testing of newly diagnosed nodal PTCL for commonly reported alterations, ideally using HTS-based panels targeting tumor DNA with high depth and, if necessary, RNA, may be clinically useful as the genomic profile may have implications for accurate diagnosis, risk stratification and therapy selection (**Table 2** and **Figure 5**).

The diagnosis of PTCL integrates clonality assessment which is performed by TR rearrangement (TRGR) analysis. Although these methods are sensitive, false positive results may occur in reactive conditions.[4] HTS-based gene panels may provide higher specificity for clonality in PTCL while preserving sensitivity comparable to TRGR-based analyses. Therefore, these panels may have broader diagnostic utility by providing both evidence of clonality and characteristic mutational profile.[285,286]

Some genetic aberrations, including tyrosine kinase gene fusions, are broadly seen across different types of nodal PTCL[282,283], while others are more characteristic of phenotypic subtypes. Specifically, follicular helper T-cell lymphomas (TFHL) frequently carry mutations of *TET2*, *DNMT3A*, *RHOA* and *IDH2,* rarely seen in combination in other PTCL[280,287], thus providing diagnostic utility. In PTCL, NOS, two molecular subgroups, namely PTCL-TBX21 and PTCL-GATA3, show distinct genetic profiles. PTCL-GATA3 demonstrates high genomic complexity characterized by biallelic deletion/mutation of *TP53*, *CDKN2A/B*, or *RB1*. Meanwhile PTCL-TBX21 shows low genomic complexity and few recurrent specific genetic changes, such as chromosome 5 gain and focal 14q32 gain including the *BCL11B* locus.[280]

TET2 and *DNMT3A* mutations, often seen in TFHL but also less commonly in other PTCL, NOS, are also the most frequent mutations seen in clonal hematopoiesis (CH).[288] Emerging evidence suggests that in TFHL, bone marrow myeloid precursors may also carry identical mutations, indicating a clonal link/filiation.[289,290] The background CH appears to be the source of myeloid neoplasms seen in TFHL patients, particularly after cytotoxic therapy.[290] Therefore, genomic analysis of marrow for CH clones at diagnosis and during disease monitoring may be required to assess the risk of development of a secondary myeloid neoplasm and ensure early diagnosis.[290] When interpreting mutational profiles, special attention should be given to avoid misinterpretation of background CH as tumor-specific mutations.

The mutational profile may also provide prognostic information. Mutations leading to loss of tumor suppressor genes, such as *TP53*, *CDKN2A*, have been associated with adverse outcomes in PTCL, NOS.[280,281] TFHL, which frequently carries mutations in genes regulating the epigenetic machinery, have a higher response rate to hypomethylating agents such as 5-azacytidine and histone deacetylase inhibitors such as romidepsin.[291-293] However, predictive value of individual gene mutations has not been clearly established, and whether there are implications in PTCLs not fitting the diagnostic criteria of TFHL is unknown.

Extranodal peripheral T-cell lymphomas

Extranodal T- and NK-cell lymphoma entities derive mostly from innate cells, are relatively organ-specific, and often portend poor outcome. While their recognition relies primarily on morphologic and immunophenotypic criteria and considering clinical features, genomic traits may be diagnostically useful. Frequent oncogenic activation of the JAK/STAT signaling pathway may be an attractive therapeutic target (**Figure 6**).[278,294,295]

Distinctive genomic features help differentiate between enteropathy-associated T-cell lymphoma (EATL), monomorphic epitheliotropic T-cell lymphoma (MEITL), and indolent T/NK LPDs of the gastrointestinal tract (**Table 3**). Alterations in the JAK/STAT pathway genes target primarily *STAT3* and *JAK1* in EATL, and *STAT5B* and *JAK3* in MEITL; a recurrent deletion in *JAK3* characterizes some indolent gastrointestinal NK-LPDs [296] and a proportion of indolent clonal T-cell LPDs of the gastrointestinal tract harbor hotspot *STAT3* mutations or *JAK2*::*STAT3* fusion.[297-299] Deleterious lesions of *SETD2* gene, translating into reduced H3K36 trimethylation, are almost constant in MEITL, rare in EATL and not found in indolent gastrointestinal T/NK LPDs.[298,300-303] Conversely, *KMT2D* and *TET2* are frequently mutated in EATL and gastrointestinal T-cell LPDs.[298,304,305] Detection of somatic mutations in indolent T/NK LPDs support the neoplastic nature of these processes. Since EATL-associated mutations or add(1q) are frequently present in type II refractory celiac disease (RCDII), HTS or FISH help assess intestinal intraepithelial lymphocyte proliferations and risk of transformation from RCDII to EATL.[304,306,307]

Hepatosplenic T-cell lymphoma (HSTCL) must be distinguished from T-large granular lymphocyte leukemias (T-LGLL), from reactive expansions of γδ T cells or florid γδ T-cell lymphoproliferations causing splenomegaly, with or without association to primary immune deficiency.[308,309] Diagnostic confirmation is supported by HSTCL-associated genomic imbalances (isochromosome 7q[310,311], trisomy 8[312]) or mutations (*INO80, PIK3CD, SETD2, TET3, SMARCA2;* and *STAT5B* or *STAT3*, also found in T-LGLL).[294,313,314]

Extranodal NK/T-cell lymphoma, nasal type (ENKTCL) has a heterogeneous derivation from NK or T cells.[315] Germline single-nucleotide polymorphisms (SNPs) associated with increased risk of ENKTCL[316,317] or with patient survival[318] have been described. Among the genomic landscape of ENKTCL[319-324], mutations in *DDX3X*, *TP53* and *KMT2D* reportedly confer a worse prognosis[325,326]. Chronic active EBV infection of T- or NK-cell type may harbor mutations in genes altered in ENKTCL[327], and the constellation of mutations found in aggressive NK-cell leukemia is similar to ENKTCL[328]. A large integrative multi-omics analysis of ENKTCL biopsies defined three molecular subtypes with different biology and vulnerabilities: tumor suppressor/immune modulator (TSIM); MYC-related, having the worst outcome; and histone epigenetic altered, having the best outcome.[326] Tumors harboring SVs or amplification of *CD274* may show greater sensitivity to immune checkpoint inhibitors.[329-332] Four TME subgroups defined by expression profiling alone, may represent immunotherapy biomarkers.[333]

Cutaneous T-cell lymphomas comprise a collection of diseases, with heterogeneous genomic portraits overlapping those of other T-cell lymphomas with particularly frequent CNAs. Germline or somatic mutations in *HAVCR2*, are specifically associated with subcutaneous panniculitis-like T-cell lymphoma, and associated with more severe clinical presentation and higher risk of hemophagocytic syndrome.[334-336]

Leukemic/disseminated NK-T-cell neoplasms

Adult T-cell lymphoma/leukemia is a virally driven neoplasm in which a single HTLV-1-positive clone expands, outcompeting thousands of other infected cells and undergoing malignant transformation.[337] The neoplastic cells harbor frequent gain-of-function alterations in T-cell receptor/NF-κB signaling, including activating mutations in *PLCG1* and *PRKCB*, *CTLA4/ICOS-CD28* fusions, and *REL* truncations.[338-340] Recurrent alterations targeting immune-related molecules are also observed, including SVs involving the 3′-UTR of *CD274*, resulting in PD-L1 overexpression.[341] Other commonly targeted pathways include transcriptional regulation (alterations in CIC-ATXN1 complex and *IKZF2* intragenic deletions), T-cell trafficking (*CCR4* and *CCR7* truncating

mutations), tumor suppression (*TP53*), and epigenetic modification (*ARID2*, *EP300*).[338,339,342] Aggressive subtypes show more genetic alterations, whereas *STAT3* mutations are more frequent in indolent subtypes.[343] Retrospective data have suggested that gain-of-function *CCR4* mutations are associated with significantly improved survival when treated with mogamulizumab[344,345] and that SNVs and CNAs of *TP53* are associated with inferior OS, regardless of treatment strategies.[346]

In T-LGLL, mutations in *STAT3* and *STAT5B* are the most common gain-of-function mutations.[347-349] In particular, *STAT3* mutations are a feature of CD8+ T-LGLL (~45%) and some T-γ/δ LGLL, whereas *STAT5B* mutations are mostly associated with the indolent CD4+ T-LGLL form (~60%)[350] or with the rare aggressive variant of CD8+ T-LGLL.[351-353] The presence of *STAT3* mutation is strongly linked to CD8+ T-LGLL patients characterized by neutropenia and the CD16+/CD56- phenotype.[352,354,355] Other genes have been found recurrently (*TNFAIP3*) and occasionally (*e.g. BCL11B, FLT3*, *PTPN23*) mutated in T-LGLL patients.[353]

Mutations of *STAT3* (~30%)[356],*TET2* (~25%) and *CCL22* (27%)[357] have been detected in NK-LGLL while this disorder appears to be devoid of *STAT5B* genetic lesions[358-360]. *TNFAIP3* mutation has been found in ~6% of NK-LGLL.[360,361]

T-prolymphocytic leukemia is characterized by chromosomal inversions or translocations involving TCL1 family genes, best demonstrated by FISH[362], resulting in constitutive over-expression of *TCL1A* or *MCTP1*, and found in virtually all cases.[363-365] Complex karyotypic abnormalities, present in >70% of cases, portend a poor prognosis.[366] Monoallelic deletions and/or mutations of *ATM* are common.[367-369] Up to 75% of patients harbor mutations in *STAT5B*, *JAK1* or *JAK3*.[370,371]

Histiocytic and dendritic cell neoplasms

In myeloid-derived HDCNs (Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (EDD), Juvenile Xanthogranuloma (JXG), Rosai-Dorfman-Destombes disease (RDDD)), mutually exclusive recurrent mutations in MAPK (*BRAF*, *ARAF*, *NRAS*,

KRAS, *MAPK1/2*) and, less frequently, PI3K (*PIK3CA*) pathways have been reported.[372-388] None of these mutations are specific for HDCNs, since they can occur in many tumors of different histogenesis. However, in HDCNs, these somatic alterations arise in the setting of relatively few other mutations.[382,389-391] *BRAF*^{V600E} is identified in the majority of LCH and ECD cases and the bone marrow may represent the primary tumor cell reservoir, given detection of *BRAF*^{V600E} in hematopoietic stem cells.[372-375] In LCH, severity of disease is associated with ability to detect *BRAF*^{V600E} (or other MAPK activating mutations) in myeloid precursors in bone marrow and peripheral blood.[372,392] In keeping with their hematopoietic origin, they can occur in association with myeloid, as well as B-cell and T-cell, neoplasms, with evidence of a shared clonal origin.[393,394] In adults, ECD lesions can bear evidence of mutations arising from clonal hematopoiesis.[395] In LCH-associated neurodegeneration (LCH-ND), *BRAF*^{V600E} has been detected in peripheral blood and brain biopsies/autopsy of patients with *BRAF*^{V600E}+ lesions, suggesting potential for shared clonal hematopoietic origins of systemic disease and LCH-ND.[396] ALK-positive histiocytosis is characterized by the fusion of *ALK* with different partners (typically *KIF3B*), leading to activation of signaling pathways and sensitivity to ALK-inhibitors.[388] RDDD likely represents a more diverse spectrum of biological conditions with a common phenotype with recurrent MAPK pathway mutations identified in RDD although at lower frequency than in other histiocytic diagnoses. Histiocytic sarcoma shows a history of lymphoid neoplasm in more than 20% of cases and frequently carries mutations of *CDKN2A* and *TP53*.[397] In most instances, mutations involving at least one gene in the MAPK pathway (most commonly *BRAF*) are also detected.[398] By contrast, follicular dendritic/reticular cell sarcomas (FDSC/FRCS) and EBV+ inflammatory follicular dendritic cell/fibroblastic reticular cell tumor are of mesenchymal origin, unrelated to a hematopoietic precursor.[399] FDCS shows mutations affecting *CDKN2A, NFKBIA, TP53* and *BIRC3*.[397,398] Gene expression profiling studies and immunohistochemical analyses have revealed constitutive overexpression of PD-L1 in LCH and FDCS, which might represent a target for immune checkpoint inhibitors.[386,387,399]

Identification of somatic alterations is clinically important in histiocytic disorders not only to confirm diagnosis, but also to inform risk stratification and therapy. *BRAF*^{V600E} is associated with increased risk of relapse and CNS disease in LCH, for example. Determining mutations is also required to determine suitability of specific inhibitors (e.g. ALK, BRAF^{V600E}, 2nd generation RAF or MEK). Vemurafenib is FDA approved for front-line therapy for ECD[400], and cobimetinib has breakthrough designation for study in adult histiocytic disorders[401]. Near universal responses are reported in pediatric LCH patients treated with MAPK inhibition in retrospective studies and prospective pediatric trials are in progress.[402,403] Finally, genomic characterization of histiocytic lesions is helpful to support identification of mutated cells in blood or bone marrow aspirate, which informs extent of disease and persistence of precursors.[389,392,404,405] In patients treated with MAPK inhibitors, *BRAF*^{V600E} typically remains detectable in peripheral blood and bone marrow, and high relapse/progression rates are associated with cessation of inhibitor therapy.[402,403,406] Systematic molecular investigations of these orphan neoplasms are warranted, to discover novel effective therapeutic targets, their treatment still representing an unmet clinical need.

Technologies poised to enter clinical practice

Whole-genome sequencing: ongoing opportunities for discovery

Although WES has clearly informed on the diverse protein coding mutations relevant to individual cancers, WGS interrogates the under-studied regions, allowing SVs, CNAs and non-coding mutations to be detected.[10,104,105,204,339,407,408] Therefore it represents an opportunity for identifying gaps in our understanding of the etiology of cancers and the shortcomings of current clinical assays (**Figure 1**). Some of the emerging genetic subgrouping systems for lymphomas rely on the presence of specific driver mutations (including SVs and CNAs) and patterns of SHM.[187,409-411]

SVs involving an oncogene and an active regulatory element causing ectopic oncogene expression (e.g. *BCL2*) or those forming a functional fusion gene (e.g. *NPM1*::*ALK*) can be diagnostic, prognostic or predictive for targeted therapies. For oncogenes having promiscuous rearrangement partners (e.g. *MYC*, *BCL6*), the identity of partners may

have a differential influence on prognosis.[191] Atypical examples of common SVs can arise from cassette-like insertions of oncogenes or enhancers or from complex rearrangements and these can be cryptic to FISH.[172,412,413] Functional *MYC* rearrangements can also reside distal to the gene[192], making their detection through targeted sequencing panels challenging[414].

Mutations affecting U1 spliceosomal RNA have been found in CLL and other cancers, causing broad perturbation of splicing.[415] There is also a growing list of non-coding mutations that alter splicing in cis by creating novel protein isoforms[10,339] or influencing the abundance of wild-type protein[105]. 3′ UTR SVs or mutations are known to increase the expression of multiple oncogenes such as *CCND1*[416], *CD274*[341] and *NFKBIZ*[407]. Such events are not readily detected by standard assays but could have therapeutic implications.[417]

Circulating tumor DNA and lymphoma liquid biopsies

Circulating tumor DNA (ctDNA) represents the fraction of cell-free DNA (cfDNA) released by tumor cells into body fluids (i.e., blood plasma, cerebrospinal fluid).[418] Therefore, ctDNA is an easily accessible source of tumor DNA amenable to serial minimally invasive sampling for the genotyping or monitoring of diverse malignancies.[419] HTS-based assays applied to ctDNA can detect IG and TR rearrangements, multiple classes of gene mutations, fusions, and CNAs.[21] Amplicon-based assays can also track single mutations at known loci.[21] Sensitivity of HTS assays incorporating molecular barcodes and/or bioinformatics that suppress error rate can even surpass amplicon-based PCR approaches, with monitoring detection limits approaching 10^{-7}.[420] However, most currently available commercial non-invasive tumor genotyping methods seldom achieve detection of actionable genotypes below ~0.5% allelic levels.[421]

Given its high positive predictive value, ctDNA genotyping represents a potential tool for supporting lymphoma diagnosis in certain clinical situations, like inaccessible tumor sites, and to overcome sampling biases.[421] Genotyping of ctDNA can provide information that may complement or potentially replace genomic interrogation of tissue

biopsies, and inform on newly acquired genetic changes following treatment. This may be relevant if actionable mutations are predictive biomarkers for treatment tailoring.[418] Beside this use of baseline liquid biopsies for genotyping and subtype classification[422], ctDNA measurement at baseline allows for measurement of tumor burden[423], and serial measurements allow for dynamic monitoring of tumor response and residual disease[424] (**Figure 6**).

These applications likely allow ctDNA to complement and enhance conventional imaging for staging and response assessments.[425] Nevertheless, clinical translation of ctDNA analysis in the management of lymphoma requires further understanding of: i) the pathophysiology of cfDNA across lymphomas; ii) the impact of pre-analytics on ctDNA assays results; iii) the technical validity, and real-time feasibility of state-of-the-art ctDNA assays; and iv) the clinical utility of ctDNA assays to guide diagnosis, treatment tailoring, and residual disease identification.[426]

Single cell analyses

Single cell analysis (SCA) is a breakthrough technology that directly addresses the challenge of complex heterogeneous cell populations in cancer, including immune cells of the TME. Currently, diverse SCA approaches exist, differing on the basis of throughput and data type, from genome, transcriptome, epigenome to proteome analysis (**Table S4**).[427] Ongoing efforts aim at integrating multiple data platforms at the individual cell level. This emerging technology has already enabled the functional characterization of cellular identity (including new immune cell types)[35,428], deconvolution of cell heterogeneity[429,430], tracking of tumor and immune cell clonal dynamics at unprecedented resolution[431,432], and has challenged the COO dogma towards a highly plastic view of cancer where dynamic transitions of cell states coexist within the tumor bulk.[433,434]

While SCA is presently insufficiently mature to supply specific recommendations for clinical practice, the field is rapidly developing with new tools for data generation/analysis alongside an avalanche of new biologic insights, together with

processing and cost streamlining. In particular, new workflows for spatial visualization compatible with FFPE tissues are anticipated to coalesce the expertise of pathologists, molecular biologists and cytometrists, with high potential for impacting clinical decision-making. Thus, across blood malignancies, routine application of SCA can be envisioned for the purposes of diagnosis; for neoplastic and immune population monitoring while on treatment; for monitoring of MRD; and for guiding treatment decisions upon relapse.[435,436]

Incorporation of SCA within the clinical arena will require the maturation of integrative multiomics analyses, access to appropriate (fresh/live-frozen) longitudinal specimens, including those from clinical trials (**Table S4**), and robust and standardized practices for biospecimen collection and computational analyses.

DNA methylation and chromatin profiling

Epigenetic mechanisms play critical roles in lymphomagenesis and have significant clinical diagnostic and outcome implications. Lymphoid tumors maintain a DNA methylation imprint of their cellular origin, which is useful for diagnostic and patient stratification purposes.[27,28,102,437-440] On the other hand, aberrant cytosine methylation patterning is a universal finding in lymphoid neoplasms.[441,442] Mechanisms driving this process include the hypermethylation effect of epigenetic modifier mutations such as in *TET2*[443-448], the hypomethylating bystander effect of AICDA where methylcytosine is replaced with unmethylated nucleotides[449], and lymphoma proliferative history associated with gradual accumulation of DNA methylation changes in repressed/heterochromatic regions[437,450]. These factors contribute to lymphomagenesis, generate intraclonal heterogeneity, and have significant clinical impact.[437,451-454] Lymphoid neoplasms harbor recurrent hypermethylation of specific genes, including the canonical tumor suppressor gene *CDKN2A*, related to disease progression[455], and *SMAD1,* which is a biomarker for chemotherapy resistance[456] that can be reversed using DNA methyltransferase inhibitors[457] and is currently under validation in a phase II/III clinical trial. It is warranted to bring at least some of these findings, including

epigenetic biomarkers for COO, proliferative history, and key genes into clinical practice.

Aberrant histone modifications are also critically relevant to lymphomagenesis. Recent genome-wide chromatin profiling studies have uncovered extensive changes in the activity of regulatory elements, which are targets of drugs such as BET inhibitors.[458-461] Aberrant chromatin patterns are caused by mutations in epigenetic modifiers[441] and aberrant transcription factor function. For example, gain-of-function mutations in *EZH2* cause profound spreading of the H3K27me3 promoter repressive mark, which is reversed by EZH2 inhibitors[462-464]; *KMT2D* loss-of-function mutations cause loss of enhancer-activating H3K4me1 marks and may be reverted through inhibition of histone demethylases, and the loss of gene body H3K36me3 due to *SETD2* mutations that causes AICDA-induced genomic instability.[465]

Conclusion:

The ultimate goal of disease classification is to provide a biologically and clinically relevant framework, reflecting pathogenetic paths, and encompassing therapeutically targetable alterations and vulnerabilities. The quality/depth and the amount of data massively generated by newer technologies encompass ground-breaking opportunities to refine classification and define useful structure within “not otherwise specified” disease entities. The diagnostic value of genomic characteristics and measurable impact on clinical management in many lymphoma entities still needs to be addressed, likely best achieved by retrospective and prospective genomic testing in clinical trials. Importantly, given identical DNA alterations, similar pathway alterations or expression signature being observed across pathologically and clinically distinct entities, morphology remains critical in the diagnostic process. Finally, tension is generated by the ideal that any classification should be applicable in a global fashion, including sites where access to resources and technologies are limited. The degree to which genomics will be further integrated into classification in the coming years will rest on defining clinically useful distinctions supported by widely available supportive diagnostics.

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Entity	Genetic alteration - test	Diagnostic use	Clinical impact	Future assays
B-cell neoplasms	IG gene rearrangement - PCR-based assays with fragment analysis or HTS	Useful in certain circumstances to demonstrate monoclonality of B-cell lymphoproliferations to establish a diagnosis; mandatory in certain entities (e.g. pediatric-type follicular lymphoma)		WGS for detection of CNAs and SVs. WTS to detect microenvironment signatures.
Chronic lymphocytic leukemia/small lymphocytic lymphoma	IGHV mutation status[a] – IGHV sequencing		Prognostic and predictive. IGHV gene mutational status remains stable through the disease course and only needs to be performed once.	Determining BcR stereotypy and IGLV3-21[R110] mutation status for risk stratification; tracking of resistance mutations (*BTK*, *PLCG2* and *BCL2* – see supplemental table 3); WGS for mutations, CNAs, SVs and complex karyotype determination; MRD testing using HTS to guide therapy decisions.
	del(11q), +12, del(13q), del(17p)[a] - FISH		Prognostic and del(17p) is predictive. FISH testing should be performed prior to each new course of therapy.	
	TP53 mutations[a] - HTS		Prognostic and predictive. *TP53* sequencing should be performed prior to each new course of therapy unless already demonstrated.	
	Detection of complex karyotype (≥5 abnormalities) – cytogenetics[a] or SNP arrays		Prognostic	
Hairy cell leukemia	*BRAF* V600E mutation – sequencing or IHC	Useful to support the diagnosis on biopsy samples and in cases with uncommon presentations[466]		
Follicular lymphoma	*BCL2* rearrangement[b] – FISH (or cytogenetics)	Consider if BCL2 IHC is negative. Further work-up of *BCL2*-R negative FL shown in scenario 1B of Table 3		
	EZH2 mutation[b] - HTS		*EZH2* mutation is predictive of response to EZH2 inhibition.[81] Tazemetostat is FDA approved in patients with *EZH2* mutated FL (detected by an FDA-approved tests) who have received at least 2 prior lines of systemic therapy (and all adult patients, including with wt *EZH2* with	

			relapsed/refractory disease and no other satisfactory alternative treatment options).	
Marginal zone lymphomas:	*BCL2* and *CCND1* rearrangements – FISH[b] *MYD88* L265 mutation[b] – AS-PCR or HTS	Detection prompts considering a diagnosis of other entities – see scenarios 1 and 2 in Table 3 and supplemental figure 3		
Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma)	*MALT1, BCL10, FOXP1* rearrangements[b] – FISH +3, +18[88] – cytogenetics and FISH	Detection is useful in certain circumstances to support the diagnosis		
	t(11;18) *BIRC3*::*MALT1*[a] - FISH in *H. pylori*-positive gastric MALT lymphoma		*MALT1* rearrangements are associated with lack of antibiotic response in *H. pylori*-positive gastric MALT lymphoma[91]	
Splenic marginal zone lymphoma	del(7q)[b], +3, +18[88] – cytogenetics and FISH *KLF2, NOTCH2* mutations[88] - HTS	Detection is useful in certain circumstances to support the diagnosis		
Nodal marginal zone lymphoma	+3, +18[88] – cytogenetics and FISH *KLF2, NOTCH2, PTPRP*[88] mutations - HTS	Detection is useful in certain circumstances to support the diagnosis		
Mantle cell lymphoma	*CCND1* rearrangement[b] - FISH	Consider if CCND1 IHC is negative		MRD testing using HTS to guide treatment decisions. WTS or targeted gene expression panel for proliferation and signatures of non-nodal versus conventional MCL.
	CCND2 and *CCND3* rearrangement[b] – FISH	Consider in *CCND1*-R negative tumors		
	TP53 mutation[a] – HTS*		Prognostic and guide management.[111]	
Multiple Myeloma (MM): MM NOS MM with recurrent genetic abnormality: - MM with CCND family translocation - MM with MAF family translocation - MM with *NSD2* translocation - MM with hyperdiploidy	t(4;14) *NSD2*::IGH; t(14;16) IGH::*MAF*; t(11;14) *CCND1*::IGH;[a] ** gain of odd numbered chromosomes - FISH on bone marrow plasma cells (CD138 positive selected sample strongly recommended))[a]	Diagnostic of the ICC subtypes of multiple myeloma	t(11;14) predictive of response to venetoclax.[134]	WGS for subtype assignment, risk stratification and decision making; MRD using HTS for decision making
	t(4;14) *NSD2*::IGH; t(14;16) IGH::*MAF*; amp(1q); del(1p), del(17p);[a] *TP53* mutations[467]; For SMM: t(4;14) *NSD2*::IGH; t(14;16) IGH::*MAF*; 1q gain/amplification; del(13)[145] and *MYC*	Risk stratification at diagnosis and relapse.	The adverse prognosis of high-risk genetics is partially overcome by the addition of a proteasome inhibitor[131] and/or anti-CD38 MoAb[132] to first line therapy.	

	rearrangement[139] - FISH and HTS			
Lymphoplasmacytic lymphoma	*MYD88* L265 mutation –AS-PCR testing on bone marrow[a] (or other highly sensitive HTS-based method – consider AS-PCR as a reflex test if negative)	Diagnostic. Aids in the differential with small B-cell lymphomas - see scenario 2A in Table 3		HTS methods for sensitive mutation detection
	CXCR4 mutations[b] – highly sensitive HTS-based method		Predictive of primary resistance to ibrutinib therapy.[160]	
Diffuse large B-cell lymphoma: Germinal center B-cell subtype Activated B-cell subtype	*MYC*, *BCL2* and/or *BCL6* rearrangement (latter two can be performed concurrently or only if *MYC* rearrangement is detected) – FISH[a]	Required to exclude HGBCL-DH-*BCL2* and HGBCL-DH-*BCL6*	See high-grade B-cell lymphoma	Genetic subtype assignment (e.g. LymphGen[187]) by panel, exome or WGS and *BCL2* and *BCL6* rearrangement detection and WTS or targeted gene expression panels (DHITsig[468]/MHG signature[199]); HTS-based ctDNA testing[469] for response-adapted management
	Cell-of-origin (COO) determination - gene expression profiling or widely used IHC surrogates[a]	Required to assign DLBCL, NOS gene expression subtypes	Prognostic for outcomes following R-CHOP (GEP)[470]; predictive of response to treatment at relapse[177].	
High-grade B-cell lymphomas (HGBCL): HGBCL with *MYC* and *BCL2* rearrangement (HGBCL-DH-*BCL2*) HGBCL with *MYC* and *BCL6* rearrangement (HGBCL-DH-*BCL6*) HGBCL, NOS	*MYC*, *BCL2* and/or *BCL6* rearrangement (latter two can be performed concurrently or only if *MYC* rearrangement is detected) – FISH[a]	Required for the diagnosis of HGBCL-DH-*BCL2* and HGBCL-DH-*BCL6*	Prognostic and predictive: HGBCL-DH-*BCL2* has poor prognosis with R-CHOP and likely benefit from treatment intensification.[471]	Rearrangement detection and *MYC* partner determination by HTS. HTS analysis of HGBCL, NOS tumors to assign these tumors to definitive disease categories
Burkitt lymphoma	*MYC*, *BCL2* and/or *BCL6* rearrangement (latter two can be performed concurrently or only if *MYC* rearrangement is detected) – FISH[a]	Required to exclude HGBCL-DH-*BCL2* and HGBCL-DH-*BCL6*		
Pediatric lymphomas:				
Pediatric-type follicular lymphoma Pediatric nodal marginal zone lymphoma	*BCL2* or *BCL6* rearrangements[b] – FISH *IRF8*, *MAP2K1* *TNFRSF14* mutations[b] – HTS B cell clonality testing	Useful in certain circumstances for diagnosis, see also scenario 3A in table 3. Of note, pediatric-type follicular lymphoma and pediatric nodal marginal zone lymphoma are not readily distinguishable by genomic features.		
Large B-cell lymphoma with 11q aberration	11q aberration – SNP array or FISH	Required for diagnosis of *LBCL-11q*		Detection of CNAs and SVs using HTS
Large B-cell lymphoma with *IRF4* rearrangement	*IRF4* rearrangement – FISH *CARD11, IRF4* mutations [b] - HTS	FISH required for diagnosis of LBCL-*IRF4* rearrangement Useful in certain circumstances for diagnosis, see also scenario 3A in table		

		3.		
Classic Hodgkin lymphoma				ctDNA for detection of genetic aberrations in the Hodgkin/Reed-Sternberg cells and for response-adapted therapy. Detection of amplification of 9p24.1 by FISH as a favorable biomarker for PD1 inhibitors in relapsed/refractory CHL.[248]

Table 1: Clinical impact of genomic testing in B-cell lymphoid neoplasms

[a] Required/strongly recommended in the NCCN 2022 guidelines

[b] Useful in certain circumstances in the NCCN 2022 guidelines

* Immunohistochemistry for TP53 has reported 82% sensitivity for *TP53* missense mutations[472]

** IGH break-apart FISH can be used to screen before the other FISH assays are performed

Abbreviations: AS-PCR: allele-specific polymerase chain reaction; BcR: B cell receptor; CNA: copy number alteration; ctDNA: circulating tumor DNA; FISH: fluorescence in situ hybridization; IHC: immunohistochemistry; HTS: high-throughput sequencing; IG: immunoglobulin; MRD: measurable residual disease; NMM: newly diagnosed multiple myeloma; SMM: smoldering multiple myeloma; SNP: single nucleotide polymorphism; SV: structural variant; WGS: whole genome sequencing; WTS: whole transcriptome sequencing.

Entity	Genetic alteration - test	Diagnostic use	Clinical impact	Future assays
T-cell neoplasms	TRG and/or TRB gene rearrangements [a, b] - PCR-based assays with fragment analysis or HTS	Demonstration of monoclonal TR gene rearrangement is (1) recommended to support a diagnosis of T-cell lymphoma especially when morphology and immunophenotyping are not fully conclusive for T-cell lymphoma/ leukemia, and to diagnose clonal T-LPD; (2) useful in the assessment of atypical T cell populations and establishing lineage in phenotypically ambiguous malignancies and (3) helping in the distinction between T and NK origin	Accurate diagnosis of a neoplastic T-cell proliferation	WTS or targeted gene expression assays to determine T-cell repertoire, disease classification and detect driver fusions.[282,473] WGS to detect CNAs and SVs. ctDNA assays for disease monitoring.
	Mutations and small indels in genes recurrently altered – HTS Various gene fusions – HTS or FISH	Useful in certain circumstances to establish clonality or to support the diagnosis of a specific entity	Mechanism of actionable alterations and how they could be targeted clinically is displayed in Figure 5	
Anaplastic large cell lymphoma, ALK-positive	*ALK* gene fusions [b] - IHC, FISH or transcript detection	Mandatory to establish the diagnosis of ALK+ ALCL	Use of ALK inhibitors	HTS to guide 2nd/3rd gen ALK inhibitors in cases of resistance to ALK inhibitors[474]
Anaplastic large cell lymphoma, ALK-negative	*DUSP22-IRF4* (6p25.3) rearrangement [b] - FISH; *TP63* (3q28) rearrangement [b] - FISH	*DUSP22*-R defines a subtype of ALK- ALCL[2] - see scenario 4E Table 3	Treatment may be adapted according to genomic configuration with (possibly) less aggressive therapy in patients with *DUSP22*-R ALCL[c]	
Follicular helper T-cell lymphoma (TFHL) angioimmunoblastic type; follicular type; NOS	*TET2, DNMT3A, IDH2, RHOA* mutations [b] - HTS (or PCR-based for $RHOA^{G17V}$ and $IDH2^{R172}$)	Useful in certain circumstances to support the diagnosis - see scenario 4B of Table 3	*DNMT3A* hotspot mutation may be predictive of non-response to standard chemotherapy and associated with adverse prognosis[475]	
Peripheral T-cell lymphoma, NOS	Mutations and small indels in genes recurrently altered – HTS.	Demonstration of genomic alterations useful in certain circumstances to establish clonality and support the diagnosis	Adverse prognostic impact of higher mutation load, complex genomic imbalances, *TP53* mutations and Th2 molecular subgroup.[280,281,284]	WGS, cytogenetics or array-based determination of SVs. Gene expression-based subtyping[473] (or IHC surrogate[476]) for risk stratification and patient selection
Hepatosplenic T-cell lymphoma	I(7q), trisomy 8[b] - FISH or cytogenetics *INO80, PIK3CD, SETD2, STAT5B, STAT3, TET3, SMARCA2* mutations[b] - HTS	Useful in certain circumstances to support the diagnosis - see scenario 4C Table 3		

Extranodal NK/T-cell lymphoma, nasal type	*CD274* SVs and amplifications – HTS		Useful in certain circumstances for prediction of response to PD1 inhibitors[329,331,332,417]	Integrated HTS and tumor microenvironment analysis for disease stratification and guiding treatment decisions[326,333]
Adult T-cell leukemia/lymphoma	Clonal HTLV-1 integration – HTS	Useful in certain circumstances to support the diagnosis in HTLV-1 carriers	Disease follow-up and clonal evolution[340,477]	HTS to assess risk of transformation in HTLV-1 carriers and guide treatment decisions[340]
	Mutations in genes related to immune function, signaling, cell cycle – HTS		Useful in certain circumstances for prognostic or predictive value. *CCR4* mutations predictive of response to mogamulizumab.[344,345] Some alterations indicative of unfavorable prognosis (*TP53* or *PRKBC* mutations; TCR/NF-κB pathway alterations in the indolent subtype)[340,346,478]	
T-cell large granular lymphocytic leukemia (T-LGLL) and chronic lymphoproliferative disorder of NK cells (NK-LGLL)	*STAT3* and *STAT5B* mutations[b] - HTS	Useful in certain circumstances to support the diagnosis - see scenario 4C Table 3	*STAT3* mutations relate with neutropenia	
T-cell prolymphocytic leukemia	inv(14)(q11q32), t(14;14)(q11;q32), t(X;14)(q28;q11), trisomy 8 - FISH (*TCL1A* or *MCTP1*) or cytogenetics[a]	Strongly recommended for establishing the diagnosis - see scenario 4C Table 3	Prognosis: complex karyotype (≥ 3 aberrations) indicative of less favorable prognosis[366]	

Table 2: Clinical impact of genomic testing in T-cell neoplasms

[a] Required/strongly recommended in the NCCN 2022 guidelines
[b] Useful in certain circumstances in the NCCN 2022 guidelines
[c] NCCN 2022 treatment guidelines
See also Figure 5 showing the potential therapeutic targeting of specific genetic alterations which may be common to several T/NK-cell neoplastic entities
Abbreviations: CNAs: copy number alterations; FISH: fluorescence in situ hybridization; HTS: high-throughput sequencing; IHC: immunohistochemistry; SVs: structural variants; WGS: whole genome sequencing

Diagnostic scenario	Genomic testing
1. Small B-cell lymphomas	
1A - CD5+ small B-cell lymphoma: small lymphocytic lymphoma/chronic lymphocytic leukemia; mantle cell lymphoma; CD5+ marginal zone lymphomas	Demonstration of *CCND1*, *CCND2* or *CCND3* rearrangement establishes the diagnosis of mantle cell lymphoma; demonstration of *BCL2* rearrangement is rare in small lymphocytic lymphoma/chronic lymphocytic leukemia and favors follicular lymphoma. Overlapping and heterogeneous mutational landscapes; mutations in the following genes have the most discriminant value: *ATM, BIRC3, MEF2B* (favor mantle cell lymphoma); *BRAF*. *KLF2, NOTCH2* and *PTPRD* (favor marginal zone lymphomas), *NOTCH1, SF3B1, XPO1* (favor small lymphocytic lymphoma/chronic lymphocytic leukemia).
1B – CD5-negative, CD10-negative, *BCL2-R* negative small B-cell lymphoma: marginal zone lymphomas (including pediatric type); *BCL2-R* negative, CD23-positive follicle center lymphoma; follicular lymphoma (without *BCL2-R*); hairy cell leukemia (tumor presentation)	Demonstration of *BCL6* rearrangement or 1p36 deletion favors follicular lymphoma. Overlapping and heterogeneous mutational landscapes; mutations in the following genes have the most discriminant value: *KLF2, NOTCH2, PTPRD* and *CARD11, IRF8, MAP2K1* (favor marginal zone lymphomas and pediatric type marginal zone lymphoma); *CREBBP, EZH2, TNFRSF14* (in follicular lymphomas), *STAT6* (favor *BCL2-R* negative, CD23-positive follicle center lymphoma); *BRAF* (in virtually all hairy cell leukemias, also in some marginal zone lymphomas)
1C - Cutaneous involvement by follicular B-cell lymphoma: primary cutaneous follicle center lymphoma; systemic follicular lymphoma	Demonstration of *BCL2* rearrangement favors systemic follicular lymphoma but does not exclude primary cutaneous follicle center lymphoma. Mutational landscapes overlap with less frequent incidence of mutations in *BCL2, CREBBP, EP300, EZH2, KMT2D* more frequent mutations in *TNFAIP3,* and similar occurrences of *TNFRSF14* mutations or 1p36 deletions in primary cutaneous versus systemic cases.
2. B-cell neoplasms with plasmacytic differentiation and plasma cell neoplasms	
2A - Small B-cell lymphoma with plasmacytic differentiation: lymphoplasmacytic lymphoma; nodal marginal zone lymphomas; splenic marginal zone lymphoma; extranodal marginal zone lymphoma (MALT lymphoma); follicular lymphoma	Demonstration of *BCL2* rearrangement supports the diagnosis of follicular lymphoma. Demonstration of trisomies of chromosomes 3 and 18, or del(7q) supports the diagnosis of marginal zone lymphoma. Translocations of *MALT1*, *FOXP1* and *BCL10* are specific for MALT lymphomas.

	MYD88^{L265P} mutation is highly suggestive of lymphoplasmacytic lymphoma but not entirely specific as it is also found in a subsets of other small B-cell lymphomas. Co-existing *CXCR4* mutation further increases the specificity for lymphoplasmacytic lymphoma. Overlapping and heterogeneous mutational landscapes; mutations in the following genes have the most discriminant value: besides *MYD88* and *CXCR4* (favor lymphoplasmacytic lymphoma); *BRAF, KLF2, NOTCH2, PTPRD, TNFAIP3* (favor marginal zone lymphomas); *CREBBP*, *EZH2*, *TNFRSF14* (favor follicular lymphoma)
2B - Bone marrow with IgM-secreting neoplasm: IgM monoclonal gammopathy of undetermined significance (MGUS), plasma cell type; IgM MGUS, NOS; lymphoplasmacytic lymphoma; IgM plasmacytoma; IgM plasma cell myeloma	Demonstration of translocations of CCND or MAF family genes or *NSD2* indicates a plasma cell neoplasm. Mutational landscapes are distinct with *MYD88*^{L265P} mutation present in most lymphoplasmacytic lymphoma and MGUS, NOS; other discriminant mutations involve *ARID1A, CD79B, CXCR4, KMT2D* (in lymphoplasmacytic neoplasms) and *BRAF, DIS3, KRAS, NRAS, TENT5C* and *TRAF3* (in plasma cell neoplasms). Genomic testing does not resolve the differential diagnosis of MGUS versus lymphoma or myeloma.
2C - Small B-cell lymphoma, with spleen, bone marrow or blood involvement: splenic marginal zone lymphoma; hairy cell leukemia; splenic diffuse red pulp small B-cell lymphoma; hairy cell leukemia-variant; mantle cell lymphoma	Demonstration of *CCND1* rearrangement establishes the diagnosis of mantle cell lymphoma. Detection of del(7q) is not discriminant in this context. Mutational landscapes are distinct with *BRAF*^{V600E} mutation being a highly diagnostically sensitive marker for hairy cell leukemia, although not entirely specific; other mutations supportive of diagnosis in this context include *MAP2K1* mutations (favor hairy cell leukemia-variant; those in *KLF2, NOTCH2* (favor splenic marginal zone lymphoma); and those in *BCOR* and *CCND3* (favor splenic diffuse red pulp small B-cell lymphoma).
2D - EBV-negative plasmablastic neoplasm: plasmablastic lymphoma; plasmablastic multiple myeloma; ALK-positive diffuse large B-cell lymphoma	Demonstration of translocations of CCND or MAF families or *NSD2* indicates a multiple myeloma; *ALK* translocations (generally substituted by immunohistochemistry) define ALK-positive DLBCL. Demonstration of *MYC* rearrangement while supporting the diagnosis of plasmablastic lymphoma, does not exclude plasmablastic multiple myeloma. Overlapping and heterogeneous mutational landscapes; mutations in the following genes more frequent in plasmablastic lymphoma: *EP300, MYC, SOCS1, STAT3, TET2, TP53.*

3. Large B-cell lymphomas	
3A - Nodal-based follicular B-cell lymphoproliferations with a predominance of large cells *in the pediatric population:* pediatric-type follicular lymphoma; follicular hyperplasia; large B-cell lymphoma with *IRF4* rearrangement; ***in adults:*** follicular lymphoma grade 3A; follicular lymphoma grade 3B; large B-cell lymphoma with *IRF4* rearrangement	Demonstration of monoclonal IG gene rearrangement is useful to establish the diagnosis of lymphoma over reactive hyperplasia, in particular in pediatric conditions. Demonstration of *BCL2* rearrangement favors grade 3A over grade 3B follicular lymphoma and excludes pediatric entities. *BCL6* rearrangement occurs in both grade 3A and 3B cases, more commonly in 3B, but not in pediatric-type follicular lymphoma. Demonstration of *IRF4* (or IGH, IGK or IGL) rearrangements is essential for supporting large B-cell lymphoma with *IRF4* rearrangement; demonstration of one or several *IRF4* mutations in exon 1-2 is a strong indicator of *IRF4* rearrangement including cryptic translocation. *IRF4* rearrangement can be present in association with other rearrangement(s) (*BCL2* or *MYC*) in DLBCLs and these do not qualify for large B-cell lymphoma with *IRF4* rearrangement. Overlapping and heterogeneous mutational landscapes; mutations in the following genes have the most discriminant value: *IRF8*, *MAP2K1* (pediatric-type follicular lymphoma (note that the same mutations are found in pediatric nodal marginal zone lymphoma)); *IRF4, MYC* (LBCL-*IRF4*)*; CARD11* (LBCL-*IRF4* and follicular lymphoma, not in pediatric-type follicular lymphoma); *BCL2*, *CREBBP*, *EZH2*, *KMT2D* (follicular lymphoma).
3B – Aggressive mature B-cell lymphomas: Burkitt lymphoma; large B-cell lymphoma with 11q aberration; high-grade B-cell lymphomas (NOS; with *MYC* and *BCL2* rearrangements; with *MYC* and *BCL6* rearrangements); diffuse large B-cell lymphoma, NOS	Demonstration or exclusion of *MYC*, *BCL2* and/or *BCL6* rearrangements or 11q aberrations, are essential in this differential diagnosis and should be applied according to the algorithm presented in Figure 5. Mutations in *ID3*, *TCF3* favor Burkitt lymphoma while *B2M, CREBBP*, *EZH2, MYD88*^{L265P}, *SOCS1* and *TNFRSF14* mutations favor other aggressive B-cell entities. Similarly, *BCL2* mutations imply the presence of IGH::*BCL2* thereby favoring entities other than Burkitt lymphoma.
3C - Large B-cell lymphoma involving mediastinum: primary mediastinal large B-cell lymphoma; diffuse large B-cell, NOS involving mediastinum; mediastinal gray-zone lymphoma	Demonstration of *BCL2 or BCL6* rearrangement favors DLBCL, NOS as these uncommonly occur in primary mediastinal large B-cell lymphoma; conversely *CIITA* rearrangement*, CD274* rearrangement or CNV are typical of primary mediastinal lymphomas. Mutations in *IL4R, ITPKB, NFKBIE, SOCS1, STAT6, XPO1* are characteristic of primary mediastinal large B-cell lymphoma, while several genes often mutated in diffuse large B-cell, NOS like *CD79B, CREBBP*, *KMT2D, MYD88, PIM1* and others are not altered in primary mediastinal large B-cell lymphoma. Mediastinal gray-zone lymphoma has genomic features

	closer to primary mediastinal large B-cell lymphoma than to diffuse large B-cell, NOS but distinctive genomic features between mediastinal gray-zone lymphoma and primary mediastinal large B-cell lymphoma are not described. Gene expression-based tests differentiate primary mediastinal large B-cell lymphoma from diffuse large B-cell, NOS.
3D - Cyclin D1-positive blastoid or pleomorphic B-cell neoplasm: mantle cell lymphoma; diffuse large B-cell lymphoma NOS positive for cyclinD1 expression; diffuse large B cell lymphoma NOS with *CCND1* rearrangement	Demonstration of *CCND1* translocation indicates mantle cell lymphoma or diffuse large B-cell lymphoma with *CCND1* rearrangement. Demonstration of additional *BCL2, BCL6* or *MYC* rearrangement is common in diffuse large B-cell lymphoma with *CCND1* translocation. Blastoid mantle cell lymphoma may harbor secondary *MYC* rearrangement or *TP53* mutations. Mutations in *ATM, BIRC3, NSD2, UBR5* support mantle cell lymphoma.
4. T-cell lymphoproliferations	
4A - Hodgkin/Reed-Sternberg(-like) cells in a T-cell background: classic Hodgkin lymphoma; nodular lymphocyte-predominant B-cell lymphoma; T-cell/histiocyte-rich large B-cell lymphoma; follicular helper T-cell (TFH) lymphoma; peripheral T-cell lymphoma NOS.	Clonality testing for IG and TR rearrangements is useful in the differential diagnosis as a monoclonal TR rearrangement supports a diagnosis of T-cell lymphoma and argues against classic Hodgkin lymphoma or B-cell lymphomas; conversely monoclonal IG rearrangements may be variably demonstrated in classic Hodgkin lymphoma, nodular lymphocyte-predominant B-cell lymphoma and T-cell/histiocyte-rich large B-cell lymphoma as well as in PTCLs with an associated B-cell component (more often present in TFH lymphomas). Demonstration of mutations in genes commonly mutated in T-cell lymphomas (*CARD11, CD28, DNMT3A, IDH2, PLCG1, RHOA, STAT3, TET2*) supports that diagnosis; caution is required when interpreting mutations present only in *TET2* and/or *DNMT3A* which can be related to clonal hematopoiesis.
4B - Expansions of T cells with follicular helper phenotype: reactive TFH cells in benign lymphadenopathies; reactive TFH cells in small B-cell lymphomas; early involvement by TFH lymphoma	Demonstration of a monoclonal TR gene rearrangement or somatic mutations in other genes is useful in the distinction between reactive versus neoplastic expansions of TFH cells. Demonstration of mutations in genes commonly mutated in TFH lymphomas (most specific: *IDH2, RHOA*; others: *CARD11, CD28, DNMT3A, PLCG1, TET2*) supports TFH lymphoma; caution is required when interpreting mutations present only in *TET2* and/or *DNMT3A* which can be related to clonal hematopoiesis and are not per se indicative of a T-cell neoplasm; in cases of reactive TFH expansions, the presence of mutations in genes related to B-cell lymphomas favor marginal zone or

	follicular lymphomas.
4C - EBV-negative cytotoxic T-lymphocytosis in blood, bone marrow or spleen: T-large granular lymphocytic leukemia (T-LGLL); hepatosplenic T-cell lymphoma (HSTCL); reactive T-cell expansions	Monoclonal TR gene rearrangements or somatic mutations (*PIK3CD, SETD2, STAT3, STAT5B, TNFAIP3*) favor neoplasia over reactive expansions. Isochromosome 7q is characteristic of HSTCL. Mutations in the following genes may help differentiating between HSTCL (CD8-/+ Tαβ or Tγδ) and CD8+Tαβ or Tγδ-LGLL: *SETD2* (exclusive to HSTCL), *STAT3* (less common in HSTCL than in T-LGLL), *STAT5B* (less common in T-LGLL than in HSTL).
4D - Intestinal T-cell lymphoproliferations: type II refractory celiac disease; enteropathy-associated T-cell lymphoma (EATL); monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL); intestinal T-cell lymphoma NOS; indolent gastrointestinal lymphoproliferative disorders	Demonstration of a monoclonal TR rearrangement is useful in the distinction of (type I refractory) celiac disease and type II refractory celiac disease, as well as for distinguishing indolent clonal T-lymphoproliferative disorders from prominent inflammatory infiltrates. T-cell or NK-cell lymphoproliferations are further supported by somatic mutations or fusions *(STAT3, JAK3*, *JAK2*::*STAT3,* others). Most discriminant mutated genes between EATL and MEITL: *JAK1, STAT3* (more commonly mutated in EATL) and *GNAI2, JAK3, SETD2, STAT5B* (more commonly mutated in MEITL)
4E - Lymphoproliferations of large CD30+ T cells: anaplastic large cell lymphoma, ALK-positive; anaplastic large cell lymphoma, ALK-negative; breast implant-associated anaplastic large cell lymphoma; peripheral T-cell lymphoma, NOS; primary cutaneous CD30+ lymphoproliferative disorders; transformed mycosis fungoides; subsets of enteropathy-associated T-cell lymphoma, or extranodal NK/T-cell lymphoma	Demonstration of *ALK* rearrangement (generally substituted by immunohistochemistry) defines anaplastic large cell lymphoma, ALK+. Demonstration of *DUSP22* rearrangement in ALK-negative CD30+ large cell lymphoproliferations establishes the diagnosis of ALCL, ALK- over PTCL, NOS, but does not discriminate between primary cutaneous versus systemic ALCL, ALK-. *VAV1* and *TP63* rearrangements occur in small subsets of ALCL, ALK- but are not specific for that entity. Demonstration of *ALK*, *DUSP22* or *TP63* translocations exclude breast implant-associated cases while chromosome 20q loss is characteristic of that entity. Overlapping and heterogeneous mutational landscapes, including mutations in *STAT3* and *JAK1* common to several entities.
5. Successive neoplasms	

Clonal relationship between successive hematological neoplasms	Analysis of IG or TR gene rearrangements helps to distinguish between clonally related and clonally unrelated neoplasms, and to establish trans-differentiation in cases of secondary histiocytic/dendritic cell neoplasms; interpretation may be ambiguous in cases of clonal evolution; sequencing-based clonality assays provide more precise results in that setting. Analysis of somatic mutations provides information on linear versus divergent evolution, and secondary genomic alterations.

Table 3: Utility of genomic testing in selected diagnostic settings
Refer to Supplemental Figure 1 and Supplemental Table 1 for prevalence of genetic aberrations in the major entities.

Figure Legends:

Figure 1: Detection capacity of genomic aberrations with different technologies.
[1.]Includes various technologies that may interrogate single nucleotide changes through to the sequence of the entire gene (allele-specific oligonucleotide polymerase chain reaction (AS-PCR), fragment analysis, Sanger sequencing and others)
[2.]Includes gene expression arrays, NanoString and reverse transcriptase multiplex ligation-dependent probe amplification (RT-MLPA) assays
[3.]Most technologies, except FISH, cannot detect subclonal CNAs (<20%) with high confidence
[4.]Including gene fusions
Ticks indicate good capacity to determine a certain aberration/feature, while an inverted red triangle indicates a limited/insufficient detection capacity.
Created with BioRender.com

Figure 2: The molecular classification of multiple myeloma.
Data from the COMMpass study (clinical trial identifier: NCT0145297) are summarized, showing the five non-overlapping subgroups and their associated gene expression, copy number, structural and single nucleotide variants. The pinwheels show the expression of CCND, MAF, NSD2 and FGFR3 for individual patients in each group. Gains of chromosomes (or arms) are shown in blue (1 copy) or purple (>1 copy). For illustration, the hyperdiploid subgroup is further subdivided into those with (HRD11+) and without (HRD11-) trisomy 11, and the patients without translocations or hyperdiploidy are labelled nHRD2 (MM, NOS). Mutations of *FGFR3* (black) and *PRKD2* (grey) are common in NSD2, while mutations of *CCND1* (black) and *IRF4* (grey) are common in CCND. A variety of different mutations can activate NF-κB (*TRAF3*, *BIRC2/3*, others). Adverse secondary events include biallelic inactivation of *CDKN2C*, *TP53* or *RB1*. *MYC* structural variants (MYC SV) are most common in hyperdiploid MM.

Figure 3: Genetic subgroups of DLBCL illustrated using the LymphGen algorithm.
The relationships between cell-of-origin and the probabilistic assignments to genetics-

based subgroups are shown. The size of the subgroup circles approximates the proportions of patients in each group, with these prevalences based on Schmitz *et al.* (ref 150), adjusted for a population-based distribution of COO subgroups. Tumors assigned with high confidence to two or more subgroups are assigned to the composite group, while ~37% of tumors are not assigned to any subgroup with sufficient confidence (Other). The hallmark genetic features are those frequent within that subgroup but are not required for that assignment. Overall survival following R-CHOP chemoimmunotherapy along with inferred drug targets are shown.

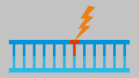
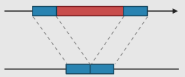
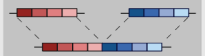
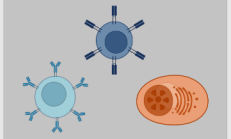
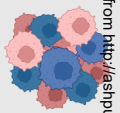
Figure 4: Approach to diagnosing high-grade B-cell lymphomas.
Lymphomas that potentially fall into the high-grade B-cell lymphoma categories can have high-grade (blastoid or intermediate (between Burkitt lymphoma (BL) and large cell)) morphology or resemble diffuse large B-cell lymphoma. Tumors with morphology resembling BL and other high-grade B-cell lymphomas (HGBCL) are assigned to the provisional entity *large B-cell lymphoma with 11q aberration* (*LBCL-11q*) if they lack *MYC* rearrangement and have 11q aberration. The full morphological spectrum of cases with this aberration requires further study. Other cases in this category present with large cell morphology. Tumors should not be assigned to *LBCL-11q* if they harbor concurrent *MYC* and *BCL2* or *MYC* and *BCL6* rearrangements. Tumors with morphology resembling BL and an immunophenotype consistent with BL, lacking both *MYC* rearrangement and 11q aberration, are likely diagnosed as high-grade B-cell lymphoma, NOS, acknowledging that rare *MYC* rearrangements cryptic to FISH have been observed.

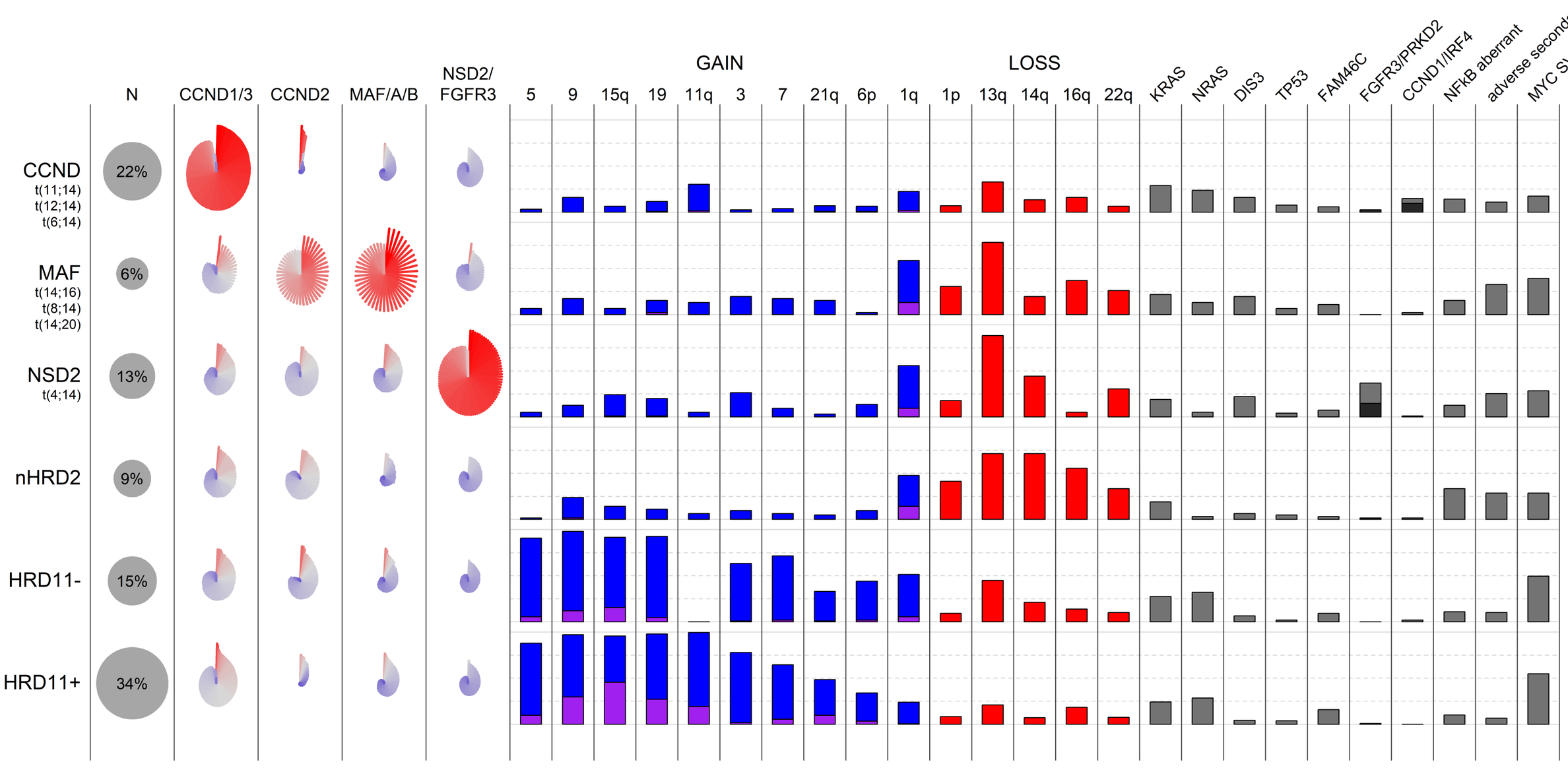
Figure 5: Recurrent genetic lesions in mature NK and T-cell neoplasms with potential therapeutic intervention.
Representative histology of entities with frequent genetic lesions potentially amenable to therapeutic intervention are shown on the left. The genetic lesions are presented according to functional groups related to T-cell receptor (TCR) signaling, Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, epigenetics or

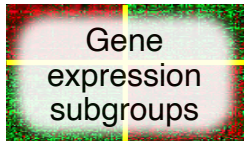
others. Therapeutic efficacy is supported by clinical trial (a), case reports, small case series or retrospective analyses (b), or experimental or *in silico* data (c).
Sources referenced: Ref [268,270,278,284,291,293,338,339,341,345,417,479-491]
Abbreviations: ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; ATLL: adult T-leukemia/lymphoma; CTCL: cutaneous T-cell lymphoma; BIA: breast implant-associated; CNA: copy number aberration; EATL: enteropathy-associated T-cell lymphoma; ENKTCL: extranodal NK/T-cell lymphoma; HSTL: hepatosplenic T-cell lymphoma; ITLPD-GI: indolent clonal T-cell lymphoproliferative disorder of the gastrointestinal tract; NK-LGLL: chronic lymphoproliferative disorder of NK-cells; TFHL: follicular helper T-cell lymphoma; TFHL-F: TFHL, follicular type; PTCL, NOS: peripheral T-cell lymphoma, not otherwise specified; T-LGLL: T-cell large granular lymphocytic leukemia; MEITL: monomorphic epitheliotropic intestinal T-cell lymphoma; SV: structural variant; T-PLL: T-prolymphocytic leukemia

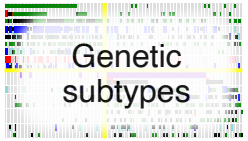
Figure 6: Applications of circulating tumor DNA (ctDNA) in lymphoma.
Schematic illustrates the potential applications of liquid biopsy assessment, as used for the identification of clinically actionable adverse risk features in lymphomas at different disease milestones. A lymphoid tumor (left of vessel) is imagined as being accessible through blood plasma by analysis of circulating tumor DNA (ctDNA) fragments. ctDNA is represented by purple double-stranded DNA molecules, and yellow double-strands represent non-tumor derived cell-free DNA molecules. The patient is evaluated by ctDNA profiling during various disease milestones over time (diagnosis, treatment, and relapse).[492] During this temporal sequence, ctDNA can inform risk at diagnosis, during therapy, immediately after induction therapy, in surveillance of disease, and at progression or disease transformation[426], as illustrated in the panels associated with each milestone. At diagnosis, profiling of tumor DNA obtained from either tissue biopsies or noninvasively through genotyping of plasma (depicted as blood collection tubes)[422], allows for the identification of patients with high tumor burden[246,423], histological subtypes[493], and prediction of outcomes[424]. Assessment of ctDNA during and after lymphoma treatment facilitates the detection of both emerging resistance mutations and measurable residual disease (MRD) before progression[420], with potential

for non-invasive prediction of relapse and transformation[494]. Tumor evolution in an anecdotal DLBCL patient is illustrated, showing tumor response and clonal evolution over the course of the disease (detectable subclones at diagnosis are shown in blue/yellow; an emergent subclone after therapy is shown in red).

		Single Nucleotide Variants/ InDels	Copy Number Alterations[3]	Structural Variants[4]	IG/TR Clonality	Cell of Origin	Tumor Purity
							
Targeted	Fluorescence *in situ* Hybridization		✓	✓			
	Single gene analyses[1]	✓			✓		
	Amplicon-based gene panel sequencing	✓			✓		
	Capture-based gene panel sequencing	✓	▽	✓	✓		▽
Digital/ Arrays	Genomic arrays		✓				✓
	Methylation arrays		✓			✓	✓
	Gene expression[2]					✓	
Genome Wide	Whole transcriptome sequencing	▽		▽	✓	✓	
	Whole exome sequencing	✓	▽	▽	✓		✓
	Whole genome sequencing	✓	✓	✓	✓		✓





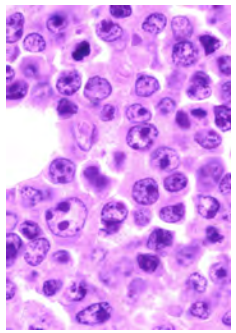


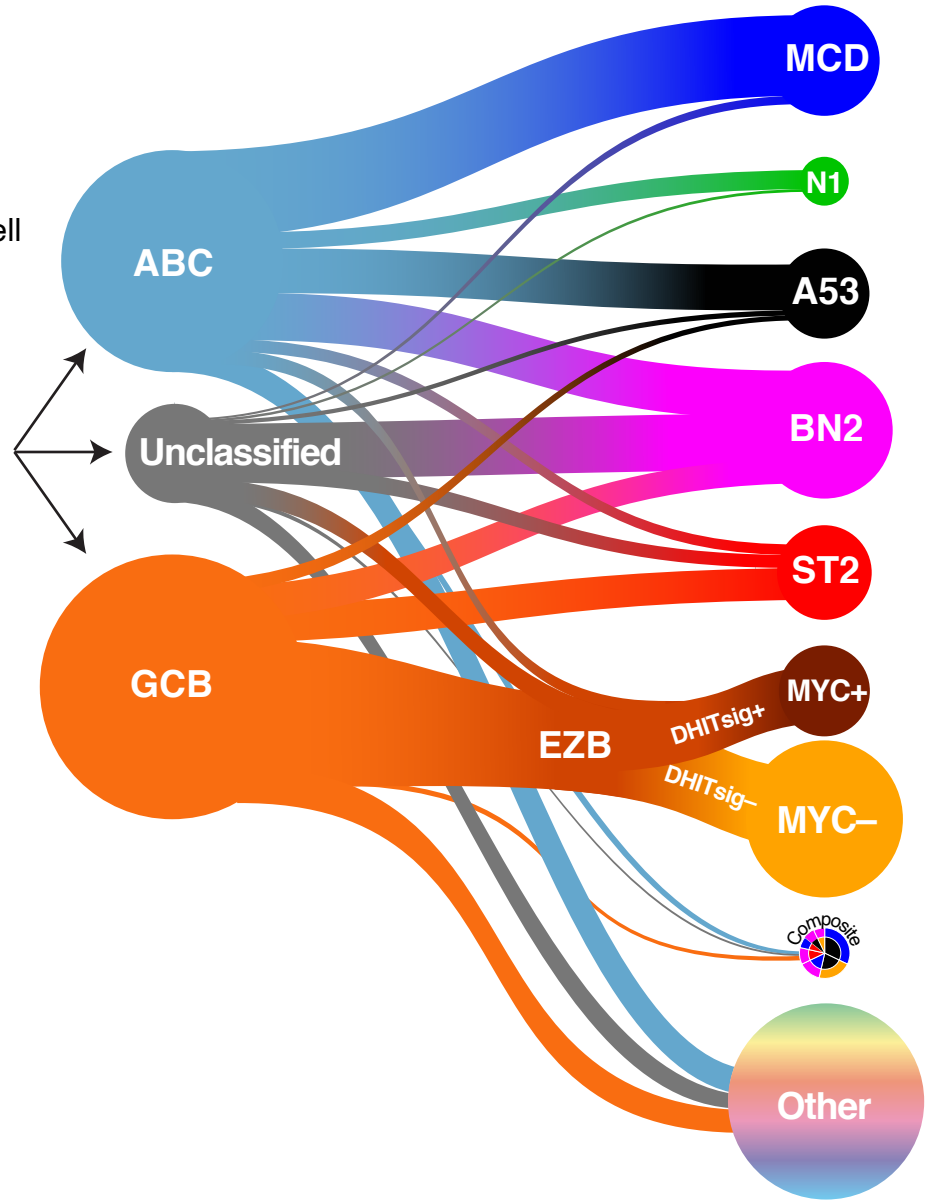
Hallmark genetic features

Overall survival
R-CHOP chemoRx

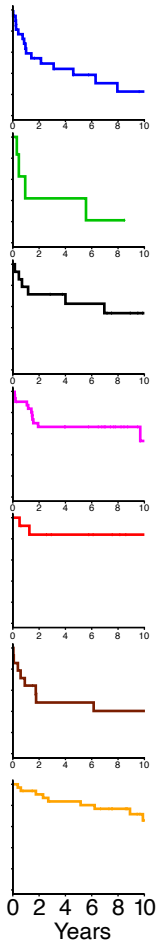
Candidate drug target

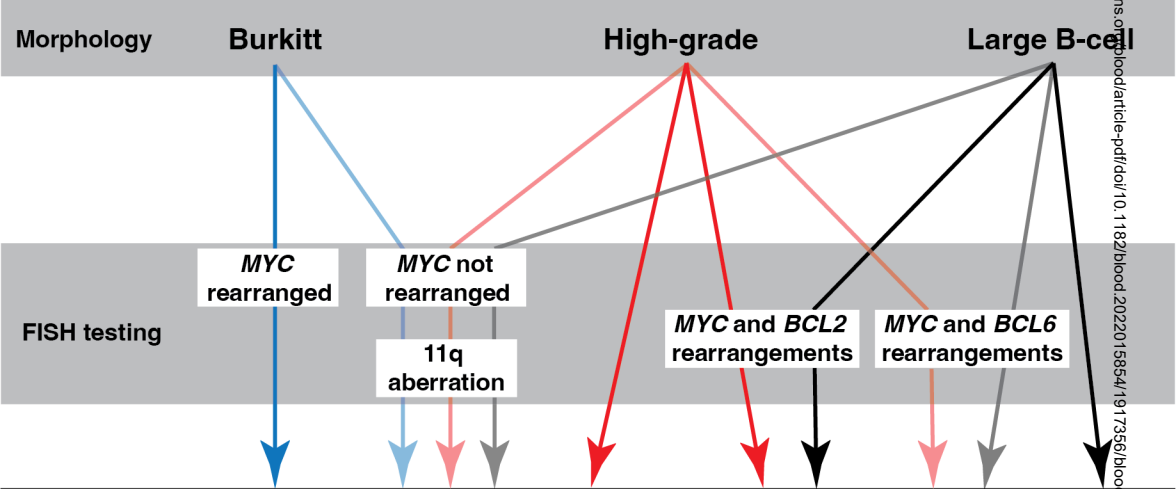
Diffuse large B-cell lymphoma

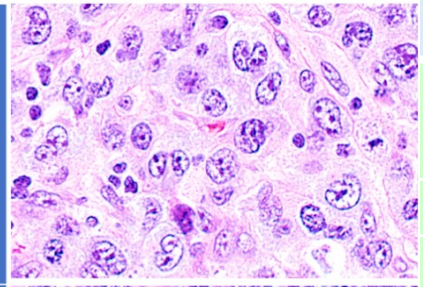
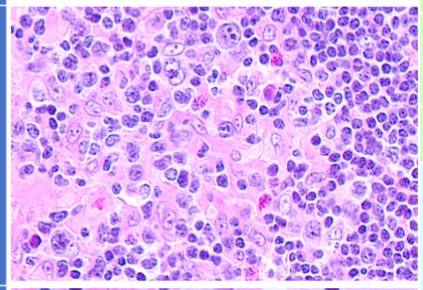
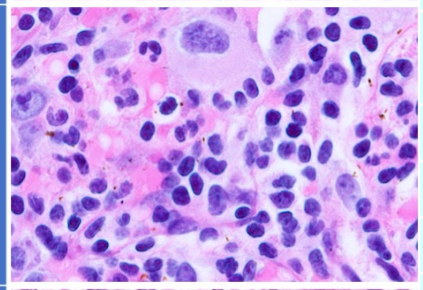
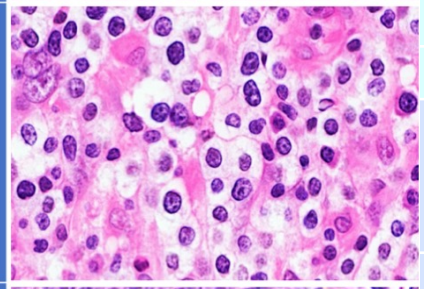
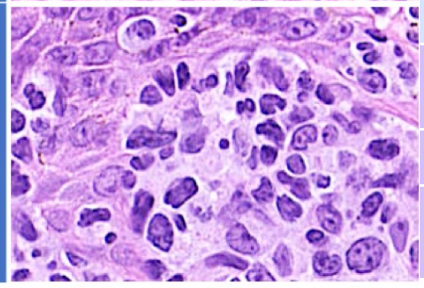




Hallmark genetic features		5-yr OS	BTK	PI3K	BCL2	JAK	IRF4	EZH2
MYD88^{L265P} mutation *CD79B* mutation		40%	■	■	■	■	■	
NOTCH1 mutation		27%	■					
TP53 inactivation aneuploidy		63%	■					
BCL6 translocation *NOTCH2* mutation		67%	■	■	■			
SGK1 mutation *TET2* mutation		84%		■		■		
EZH2 mutation	*MYC* translocation *DDX3X* mutation	48%		■	■			■
BCL2 translocation	*TNFAIP3* inactivation *CARD11* mutation	82%						





		NK AND T-CELL NEOPLASMS	GENETIC LESIONS	MECHANISM	POTENTIAL THERAPEUTIC INTERVENTION	
ALCL		**TFHL, PTCL NOS, CTCL, ATLL**	***CD28 FYN CARD11 PLCG1 RHOA* mutations**	TCR signaling activation	PI3K inhibitors (duvelisib, copanlisib), mTOR inhibitors (everolimus, temsirolimus), TKI (dasatinib), ITK inhibitor (CPI-818) (a, c)	TCR
		TFHL, CTCL, ATLL	***CD28* fusions**	Increased CD28 signaling	CTLA4 blockade (ipilimumab) (*CTLA4::CD28*) (b, c)	
		TFHL, PTCL NOS	***FYN::TRAF3IP2***	NF-kappaB activation	IkB kinase inhibitors (c)	
PTCL-NOS		**TFHL**	***ITK::SYK***	SYK and JAK3/STAT5 activation	JAK3 inhibitor (tofacitinib), dual SYK and JAK inhibitor (cerdulatinib) (c)	
		ALK- ALCL, PTCL NOS, ATLL	***VAV1* fusions**	VAV1 and RAC1 activation	RAC1 inhibitor (azathioprine) (c)	
		T-LGLL, NK-LGLL, T-PLL, MEITL, EATL, HSTL, ENKTCL, ALK- ALCL, BIA-ALCL, PTCL NOS	***JAK1 JAK2 JAK3 STAT3 STAT5B SOCS1* mutations**	STAT3 phosphorylation	JAK inhibitors (ruxolitinib, tofacitinib, gandotinib, momelotinib), dual SYK and JAK inhibitor (cerdulatinib) (a, c)	JAK/STAT
T-LGLL		**ALK- ALCL, BIA-ALCL, CD30+ PTCL NOS, ITLPD-GI**	***JAK2* fusions**	STAT5 phosphorylation		
		ALK+ ALCL	***ALK* fusions**	STAT3 phosphorylation	ALK inhibitors (crizotinib, alectinib) (a)	
		ALK- ALCL	***FRK* fusions**	STAT3 phosphorylation	Kinase inhibitor (dasatinib) (c)	
		PTCL NOS, TFHL-F	***ITK::FER***	STAT3 phosphorylation	JAK3 inhibitor (tofacitinib), kinase inhibitors (c)	
AITL		**ALK- ALCL**	***ROS1* fusions**	STAT3 phosphorylation	ROS1 inhibitor (JNJ-ROS1i-A) (c)	
		ALK- ALCL	***TYK2* fusions**	STAT1 phosphorylation	JAK inhibitors, TYK2 inhibitor (deucravacitinib) (c)	
		TFHL, PTCL NOS, CTCL, ATLL	***TET2 DNMT3A IDH2* mutations**	DNA hypermethylation Oncometabolite production ($IDH2^{R172}$)	Hypomethylating agents (5-azacytidine, decitabine), histone deacetylase inhibitors (romidepsin, belinostat, chidamide, vorinostat); IDH2 inhibitors (enasidenib) (a, b)	Epigenetics
		MEITL, HSTL	***SETD2* mutations deletions**	Loss of H3K36me3	Wee1 inhibitor (adavosertib) (c)	
ATLL		**ENKTCL, ATLL**	***CD274* CNA or SV**	PD-L1 overexpression	Anti-PD1 antibodies (pembrolizumab, nivolumab) (b, c)	Others
		ATLL	***CCR4* mutations**	Increased CCR4 expression	Anti-CCR4 antibody (mogamulizumab) (b)	
		ALK- ALCL	***ERBB4* fusions or truncated transcripts**	ERBB4 overexpresson	Inhibitors of ERBB-family kinases (lapatinib) (c)