blood® Special Report

Check for updates

Genomic profiling for clinical decision making in lymphoid neoplasms

Laurence de Leval,[1,*] Ash A. Alizadeh,[2-5] P. Leif Bergsagel,[6] Elias Campo,[7] Andrew Davies,[8] Ahmet Dogan,[9] Jude Fitzgibbon,[10] Steven M. Horwitz,[11] Ari M. Melnick,[12] William G. Morice,[13] Ryan D. Morin,[14-16] Bertrand Nadel,[17] Stefano A. Pileri,[18] Richard Rosenquist,[19,20] Davide Rossi,[21] Itziar Salaverria,[22] Christian Steidl,[23] Steven P. Treon,[24] Andrew D. Zelenetz,[11,12] Ranjana H. Advani,[25] Carl E. Allen,[26] Stephen M. Ansell,[27] Wing C. Chan,[28] James R. Cook,[29] Lucy B. Cook,[30] Francesco d'Amore,[31] Stefan Dirnhofer,[32] Martin Dreyling,[33] Kieron Dunleavy,[34] Andrew L. Feldman,[13] Falko Fend,[35] Philippe Gaulard,[36,37] Paolo Ghia,[38] John G. Gribben,[10] Olivier Hermine,[39] Daniel J. Hodson,[40,41] Eric D. Hsi,[42] Giorgio Inghirami,[43] Elaine S. Jaffe,[44] Kennosuke Karube,[45] Keisuke Kataoka,[46,47] Wolfram Klapper,[48] Won Seog Kim,[49] Rebecca L. King,[13] Young H. Ko,[50] Ann S. LaCasce,[24] Georg Lenz,[51] José I. Martin-Subero,[52] Miguel A. Piris,[53] Stefania Pittaluga,[44] Laura Pasqualucci,[54-56] Leticia Quintanilla-Martinez,[35] Scott J. Rodig,[57] Andreas Rosenwald,[58] Gilles A. Salles,[11] Jesus San-Miguel,[59] Kerry J. Savage,[23] Laurie H. Sehn,[23] Gianpietro Semenzato,[60] Louis M. Staudt,[61] Steven H. Swerdlow,[62] Constantine S. Tam,[63] Judith Trotman,[64] Julie M. Vose,[65] Oliver Weigert,[33] Wyndham H. Wilson,[61] Jane N. Winter,[66] Catherine J. Wu,[24] Pier L. Zinzani,[67] Emanuele Zucca,[21] Adam Bagg,[68] and David W. Scott[23,*]

[1]Institute of Pathology, Department of Laboratory Medicine and Pathology, Lausanne University Hospital and Lausanne University, Lausanne, Switzerland; [2]Division of Oncology, Department of Medicine, [3]Stanford Cancer Institute, [4]Institute for Stem Cell Biology and Regenerative Medicine, and [5]Division of Hematology, Department of Medicine, Stanford University, Stanford, CA; [6]Division of Hematology, Department of Internal Medicine, Mayo Clinic, Phoenix, AZ; [7]Haematopathology Section, Hospital Clínic, Institut d'Investigaciones Biomèdiques August Pi I Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain; [8]Centre for Cancer Immunology, University of Southampton, Southampton, United Kingdom; [9]Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [10]Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; [11]Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY; [12]Department of Medicine, Weill Cornell Medicine, New York, NY; [13]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN; [14]Department of Molecular Biology and Biochemistry, Simon Fraser University, Burnaby, BC, Canada; [15]Genome Sciences Centre, BC Cancer, Vancouver, BC, Canada; [16]BC Cancer Centre for Lymphoid Cancer, Vancouver, BC, Canada; [17]Aix Marseille University, CNRS, INSERM, CIML, Marseille, France; [18]Haematopathology Division, IRCCS, Istituto Europeo di Oncologia, IEO, Milan, Italy; [19]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; [20]Clinical Genetics, Karolinska University Laboratory, Karolinska University Hospital, Solna, Sweden; [21]Institute of Oncology Research and Oncology Institute of Southern Switzerland, Faculty of Biomedical Sciences, Università della Svizzera Italiana, Bellinzona, Switzerland; [22]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [23]Centre for Lymphoid Cancer, BC Cancer and University of British Columbia, Vancouver, Canada; [24]Dana Farber Cancer Institute, Boston, MA; [25]Division of Oncology, Department of Medicine, Stanford University, Stanford, CA; [26]Division of Pediatric Hematology-Oncology, Baylor College of Medicine, Houston, TX; [27]Mayo Clinic Cancer Center, Rochester, MN; [28]Department of Pathology, City of Hope National Medical Center, Duarte, CA; [29]Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, OH; [30]Centre for Haematology, Imperial College London, London, United Kingdom; [31]Department of Hematology, Aarhus University Hospital, Aarhus, Denmark; [32]Institute of Medical Genetics and Pathology, University Hospital Basel, University of Basel, Basel, Switzerland; [33]Department of Medicine III, LMU Hospital, Munich, Germany; [34]Division of Hematology and Oncology, Georgetown Lombardi Comprehensive Cancer Centre, Georgetown University Hospital, Washington, DC; [35]Institute of Pathology and Neuropathology, Eberhard Karls University of Tübingen and Comprehensive Cancer Center, University Hospital Tübingen, Tübingen, Germany; [36]Department of Pathology, University Hospital Henri Mondor, AP-HP, Créteil, France; [37]Faculty of Medicine, IMRB, INSERM U955, University of Paris-Est Créteil, Créteil, France; [38]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [39]Service D'hématologie, Hôpital Universitaire Necker, Université René Descartes, Assistance Publique Hôpitaux de Paris, Paris, France; [40]Wellcome MRC Cambridge Stem Cell Institute, Cambridge Biomedical Campus, Cambridge, United Kingdom; [41]Department of Haematology, University of Cambridge, Cambridge, United Kingdom; [42]Department of Pathology, Wake Forest School of Medicine, Winston-Salem, NC; [43]Department of Pathology and Laboratory Medicine, Weill Cornell Medicine, New York, NY; [44]Hematopathology Section, Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD; [45]Department of Pathology and Laboratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan; [46]Division of Molecular Oncology, National Cancer Center Research Institute, Toyko, Japan; [47]Division of Hematology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan; [48]Hematopathology Section and Lymph Node Registry, Department of Pathology, University Hospital Schleswig-Holstein, Kiel, Germany; [49]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, South Korea; [50]Department of Pathology, Cheju Halla General Hospital, Jeju, Korea; [51]Department of Medicine A, Hematology, Oncology and Pneumology, University Hospital Muenster, Muenster, Germany; [52]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain; [53]Department of Pathology, Jiménez Díaz Foundation University Hospital, CIBERONC, Madrid, Spain; [54]Institute for Cancer Genetics, [55]Department of Pathology & Cell Biology, and [56]The Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY; [57]Department of Pathology, Brigham and Women's Hospital, Boston, MA; [58]Department of Pathology, University of Würzburg, Würzburg, Germany; [59]Clínica Universidad de Navarra, Navarra, Cancer Center of University of Navarra, Cima Universidad de Navarral, Instituto de Investigacion Sanitaria de Navarra, Centro de Investigación Biomédica en Red de Céncer, Pamplona, Spain; [60]Department of Medicine, University of Padua and Veneto Institute of Molecular Medicine, Padova, Italy; [61]Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD; [62]Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA; [63]Alfred Hospital and Monash University, Melbourne, Australia; [64]Haematology Department, Concord Repatriation General Hospital, Sydney, Australia; [65]Department of Internal Medicine, Division of Hematology-Oncology, University of Nebraska Medical Center, Omaha, NE; [66]Feinberg School of Medicine, Northwestern University, Chicago, IL; [67]IRCCS Azienda Ospedaliero-Universitaria di Bologna Istitudo di Ematologia "Seràgnoli" and Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale Università di Bologna, Bologna, Italy; and [68]Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

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. Although 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 because 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 the 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 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 because 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 past 10 to 15 years, the genomic landscapes of many lymphoid neoplasms were characterized at an unprecedented scale.[6] Although a predominant gene mutation was identified in only a few lymphoma entities, such as the *MYD88*^{L265P} mutation in lymphoplasmacytic lymphoma (LPL) and *BRAF*^{V600E} mutation in hairy cell leukemia,[7,8] in most lymphoid neoplasms, a much more diverse pattern is observed with only a small number 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, and passenger mutations.[12-14] Despite the heterogeneous mutation landscapes between distinct diseases, there are also common themes of affected cellular processes and signaling pathways (supplemental Figure 1 and supplemental Table 1 [available on the *Blood* website]). Based on newly acquired knowledge, clinically relevant genomic aberrations have been identified with diagnostic, prognostic, and predictive impact in different entities.[15,16] Although the

		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	✓	✓	✓	✓		✓

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 (AS-PCR, fragment analysis, Sanger sequencing, and others). [2]Includes gene expression arrays, NanoString, and 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, whereas an inverted red triangle indicates a limited/insufficient detection capacity. AS-PCR, allele-specific oligonucleotide polymerase chain reaction; CNA, copy number aberration; IG, immunoglobulin; indel, insertion-deletion; RT-MLPA, reverse transcriptase multiplex ligation–dependent probe amplification; TR, T-cell receptor locus. Created with BioRender.com.

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

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 the assessment of coding regions of genes or whole-genome sequencing (WGS). These methods have different capacities to detect somatic aberrations because 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 (SNVs) and indels or specific gene fusions are detected (Figure 1).[19] Capture-based panels enable simultaneous interrogation of SNVs and indels, copy-number aberrations (CNAs) (ie, 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 the most relevant types of genomic aberrations associated with lymphoproliferations.[22-24]

Gene expression profiling (GEP) and DNA methylation analyses have been pivotal in identifying 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]

The application of clinical molecular diagnostics to lymphoid proliferations is currently constrained by several practical considerations. The optimal source consists of nucleic acids extracted from fresh surgical biopsy specimens or liquid samples (blood or bone marrow), but clinical assays must be adapted to formalin-fixed paraffin-embedded (FFPE) tissues, which is the main diagnostic material, and to limited samples (eg, 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 (eg, sequence coverage/depth, background artifacts), the need for unique molecular identifiers, and turnaround time. Key aspects related to variant interpretation and reporting include variant classification systems used,[37-39] variants of uncertain significance, and the presence of clonal hematopoiesis (CH). 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 remains 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 (ctDNA), or liquid biopsy specimens, 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 patients with CLL/SLL. The somatic hypermutation (SHM) 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 with IGHV-mutated (M) CLL (<98% identity compared with germ line 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 [BTKis], BH3 mimetic with anti-CD20 antibody) has become the standard of care for U-CLL.[43-47] Stereotyped B-cell receptors (BcRs) occur in 41% of cases, with some subsets having distinctive outcomes (supplemental Table 2).[48-53]

Among CNAs routinely detected by FISH (del(11q), trisomy 12, del(13q), and del(17p)),[54] del(17p) confers 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 (supplemental Figure 2) and affect cellular signaling pathways: BcR (IGLV3-21^{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*, *CHD2*).[52,60] Although *TP53* aberrations are typically biallelic (ie, del(17p) and *TP53* mutation), isolated *TP53* mutations can also occur in the absence of del(17p). Both clonal (variant allele frequency > 10%) and subclonal (<10%) *TP53* mutations[61,62] are associated with poor chemoimmunotherapy response. *TP53*

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

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

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 (eg, pediatric-type FL)		WGS for the detection of CNAs and SVs WTS to detect microenvironment signatures
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)	IGHV mutation status*: 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*; 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)*: FISH		Prognostic and del(17p) is predictive. FISH testing should be performed before each new course of therapy	
	TP53 mutations*: HTS		Prognostic and predictive. *TP53* sequencing should be performed before each new course of therapy unless already demonstrated	
	Detection of complex karyotype (≥5 abnormalities): cytogenetics* 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[463]		
Follicular lymphoma (FL)	*BCL2* rearrangement†: FISH (or cytogenetics)	Consider if BCL2 IHC is negative. Further workup of *BCL2*-R–negative FL shown in scenario 1B in Table 3		
	EZH2 mutation†: HTS		*EZH2* mutation is predictive of response to EZH2 inhibition.[81] Tazemetostat is approved by the FDA for use in patients with *EZH2*-mutated FL (detected by an FDA-approved test) 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)	

AS-PCR, allele-specific polymerase chain reaction; BcR, B-cell receptor; BL, Burkitt lymphoma; BTK, Bruton's tyrosine kinase; CHL, classic Hodgkin lymphoma; cMCL, conventional MCL; CLL, chronic lymphocytic leukemia; COO, cell-of-origin; ctDNA, circulating tumor DNA; DLBCL, diffuse large B-cell lymphoma; FDA, Food and Drug Administration; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; IGHV, immunoglobulin heavy variable; IHC, immunohistochemistry; LBCL-*IRF4*, large B-cell lymphoma with *IRF4* rearrangement; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MHG, molecular high grade; MM, multiple myeloma; MRD, measurable residual disease; MZL, marginal zone lymphoma; NMZL, nodal MZL; NMM, newly diagnosed multiple myeloma; nnMCL, non-nodal MCL; NOS, not otherwise specified; R-CHOP, rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone; SLL, small lymphocytic lymphoma; SMM, smoldering multiple myeloma; SMZL, splenic MZL; SNP, single nucleotide polymorphism; wt, wild-type.

*Required/strongly recommended in the National Comprehensive Cancer Network 2022 guidelines.

†Useful in certain circumstances in the National Comprehensive Cancer Network 2022 guidelines.

‡IHC for TP53 has reported 82% sensitivity for *TP53* missense mutations.[468]

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

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

Table 1 (continued)

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Marginal zone lymphomas (MZL)	*BCL2* and *CCND1* rearrangements: FISH† *MYD88* L265 mutation†: 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 MZL of mucosa associated lymphoid tissue (MALT lymphoma)	*MALT1*, *BCL10*, *FOXP1* rearrangements†: FISH +3, +18[88]: cytogenetics and FISH	Detection is useful in certain circumstances to support the diagnosis		
	t(11;18) *BIRC3*::*MALT1**: 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 MZL	del(7q)†, +3, +18[88]: cytogenetics and FISH *KLF2*, *NOTCH2* mutations[88]: HTS	Detection is useful in certain circumstances to support the diagnosis		
Nodal MZL	+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†: 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 nnMCL vs cMCL
	CCND2 and *CCND3* rearrangement†: FISH	Consider in *CCND1*-R–negative tumors		
	TP53 mutation*: 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;*,§ gain of odd numbered chromosomes: FISH on bone marrow plasma cells (CD138-positive selected sample strongly recommended)*	Diagnostic of the ICC subtypes of MM	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)*; *TP53* mutations[464] For SMM: t(4;14) *NSD2*::IGH; t(14;16) IGH::*MAF*; 1q gain/amplification; del(13)[145] and *MYC* rearrangement[139]: FISH and HTS	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	
Lymphoplasmacytic lymphoma	*MYD88* L265 mutation: AS-PCR testing on bone marrow* (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†: highly sensitive HTS-based method		Predictive of primary resistance to ibrutinib therapy[160]	

AS-PCR, allele-specific polymerase chain reaction; BcR, B-cell receptor; BL, Burkitt lymphoma; BTK, Bruton's tyrosine kinase; CHL, classic Hodgkin lymphoma; cMCL, conventional MCL; CLL, chronic lymphocytic leukemia; COO, cell-of-origin; ctDNA, circulating tumor DNA; DLBCL, diffuse large B-cell lymphoma; FDA, Food and Drug Administration; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; IGHV, immunoglobulin heavy variable; IHC, immunohistochemistry; LBCL-*IRF4*, large B-cell lymphoma with *IRF4* rearrangement; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MHG, molecular high grade; MM, multiple myeloma; MRD, measurable residual disease; MZL, marginal zone lymphoma; NMZL, nodal MZL; NMM, newly diagnosed multiple myeloma; nnMCL, non-nodal MCL; NOS, not otherwise specified; R-CHOP, rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone; SLL, small lymphocytic lymphoma; SMM, smoldering multiple myeloma; SMZL, splenic MZL; SNP, single nucleotide polymorphism; wt, wild-type.

*Required/strongly recommended in the National Comprehensive Cancer Network 2022 guidelines.

†Useful in certain circumstances in the National Comprehensive Cancer Network 2022 guidelines.

‡IHC for TP53 has reported 82% sensitivity for *TP53* missense mutations.[468]

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

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

Table 1 (continued)

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Diffuse large B-cell lymphoma, NOS 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*	Required to exclude HGBCL-DH-*BCL2* and HGBCL-DH-*BCL6*	See "High-grade B-cell lymphoma"	Genetic subtype assignment (eg, LymphGen[187]) by panel, exome or WGS and *BCL2* and *BCL6* rearrangement detection and WTS or targeted gene expression panels (DHITsig[29]/MHG signature[199]) HTS-based ctDNA testing[465] for response-adapted management
	COO determination: GEP or widely used IHC surrogates*	Required to assign DLBCL, NOS gene expression subtypes	Prognostic for outcomes following R-CHOP (GEP)[466]; 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*	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 benefits from treatment intensification[467]	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*	Required to exclude HGBCL-DH-*BCL2* and HGBCL-DH-*BCL6*		
Pediatric lymphomas				Detection of CNAs and SVs using HTS
Pediatric-type FL **Pediatric nodal MZL**	*BCL2* or *BCL6* rearrangements†: FISH *IRF8*, *MAP2K1 TNFRSF14* mutations†: HTS B-cell clonality testing	Useful in certain circumstances for diagnosis; see also scenario 3A in Table 3. Of note, pediatric-type FL and pediatric nodal MZL 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*		
Large B-cell lymphoma with *IRF4* rearrangement	*IRF4* rearrangement: FISH *CARD11*, *IRF4* mutations†: HTS	FISH required for diagnosis of LBCL-*IRF4* rearrangement Useful in certain circumstances for diagnosis; see also scenario 3A in Table 3.		

AS-PCR, allele-specific polymerase chain reaction; BcR, B-cell receptor; BL, Burkitt lymphoma; BTK, Bruton's tyrosine kinase; CHL, classic Hodgkin lymphoma; cMCL, conventional MCL; CLL, chronic lymphocytic leukemia; COO, cell-of-origin; ctDNA, circulating tumor DNA; DLBCL, diffuse large B-cell lymphoma; FDA, Food and Drug Administration; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; IGHV, immunoglobulin heavy variable; IHC, immunohistochemistry; LBCL-*IRF4*, large B-cell lymphoma with *IRF4* rearrangement; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MHG, molecular high grade; MM, multiple myeloma; MRD, measurable residual disease; MZL, marginal zone lymphoma; NMZL, nodal MZL; NMM, newly diagnosed multiple myeloma; nnMCL, non-nodal MCL; NOS, not otherwise specified; R-CHOP, rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone; SLL, small lymphocytic lymphoma; SMM, smoldering multiple myeloma; SMZL, splenic MZL; SNP, single nucleotide polymorphism; wt, wild-type.

*Required/strongly recommended in the National Comprehensive Cancer Network 2022 guidelines.

†Useful in certain circumstances in the National Comprehensive Cancer Network 2022 guidelines.

‡IHC for TP53 has reported 82% sensitivity for *TP53* missense mutations.[468]

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

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

Table 1 (continued)

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
Classic Hodgkin lymphoma				ctDNA for the 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]

AS-PCR, allele-specific polymerase chain reaction; BcR, B-cell receptor; BL, Burkitt lymphoma; BTK, Bruton's tyrosine kinase; CHL, classic Hodgkin lymphoma; cMCL, conventional MCL; CLL, chronic lymphocytic leukemia; COO, cell-of-origin; ctDNA, circulating tumor DNA; DLBCL, diffuse large B-cell lymphoma; FDA, Food and Drug Administration; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; IGHV, immunoglobulin heavy variable; IHC, immunohistochemistry; LBCL-*IRF4*, large B-cell lymphoma with *IRF4* rearrangement; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; MHG, molecular high grade; MM, multiple myeloma; MRD, measurable residual disease; MZL, marginal zone lymphoma; NMZL, nodal MZL; NMM, newly diagnosed multiple myeloma; nnMCL, non-nodal MCL; NOS, not otherwise specified; R-CHOP, rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone; SLL, small lymphocytic lymphoma; SMM, smoldering multiple myeloma; SMZL, splenic MZL; SNP, single nucleotide polymorphism; wt, wild-type.

*Required/strongly recommended in the National Comprehensive Cancer Network 2022 guidelines.

†Useful in certain circumstances in the National Comprehensive Cancer Network 2022 guidelines.

‡IHC for TP53 has reported 82% sensitivity for *TP53* missense mutations.[468]

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

aberrations can arise at relapse/progression and thus, if not previously identified, should be evaluated before 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 (supplemental Table 3).

Epigenetic alterations can also affect 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 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 (1) recurrent mutations in genes encoding, in particular, several epigenetic regulators (eg, *CREBBP*, *KMT2D*, *EZH2*), as well as transcription factors (eg, *MEF2B*, *FOXO1*, *STAT6*) and components of the mechanistic target of rapamycin (mTOR) signaling pathway (eg, *RRAGC*, *ATP6V1B2*); and (2) perturbations in interactions with their immune environment (eg, *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 or predictive value at diagnosis for patients treated with standard chemoimmunotherapy. FDA approval mandates *EZH2* mutation detection for the treatment with the EZH2 inhibitor tazemetostat[81] in patients having received at least 2 previous 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 vs 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 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) 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 a lack of antibiotic response in *H pylori*–positive cases.[91] The t(14;18)(q32;q21) IGH::*MALT1* translocation is usually 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]

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

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

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
T-cell neoplasms	TRG and/or TRB gene rearrangements*,†: PCR-based assays with fragment analysis or HTS	Demonstration of monoclonal TCR 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 and disease classification and detect driver fusions[282,469] 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	
ALCL, ALK-positive	*ALK* gene fusions†: IHC, FISH, or transcript detection	Mandatory to establish the diagnosis of ALK-positive ALCL	Use of ALK inhibitors	HTS to guide second-/third-generation ALK inhibitors in cases of resistance to ALK inhibitors[470]
ALCL, ALK-negative	*DUSP22-IRF4* (6p25.3) rearrangement†: FISH; *TP63* (3q28) rearrangement†: FISH	*DUSP22*-R defines a subtype of ALK- ALCL[2]; see scenario 4E in Table 3	Treatment may be adapted according to genomic configuration with (possibly) less aggressive therapy in patients with *DUSP22*-R ALCL‡	
TFHL angioimmunoblastic type; follicular type; NOS	*TET2*, *DNMT3A*, *IDH2*, *RHOA* mutations†: HTS (or PCR-based for *RHOA*^{G17V} and *IDH2*^{R172})	Useful in certain circumstances to support the diagnosis; see scenario 4B in Table 3	*DNMT3A* hotspot mutation may be predictive of nonresponse to standard chemotherapy and associated with adverse prognosis[471]	
PTCL, 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[469] (or IHC surrogate[472]) for risk stratification and patient selection
HSTCL	I(7q), trisomy 8†: FISH or cytogenetics *INO80*, *PIK3CD*, *SETD2*, *STAT5B*, *STAT3*, *TET3*, *SMARCA2* mutations†: HTS	Useful in certain circumstances to support the diagnosis; see scenario 4C in Table 3		

Figure 5 shows the potential therapeutic targeting of specific genetic alterations that may be common to several T/NK-cell neoplastic entities.

ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; ENKTCL, extranodal NK/T-cell lymphoma; HSTCL, hepatosplenic T-cell lymphoma; HTLV, human T-lymphotropic virus; LPD, lymphoproliferative disorder; NK-LGLL, chronic lymphoproliferative disorder of natural killer cells; TFHL, follicular helper T-cell lymphoma; T-LGLL, T-cell large granular lymphocytic leukemia.

*Required/strongly recommended in the National Comprehensive Cancer Network 2022 guidelines.

†Useful in certain circumstances in the National Comprehensive Cancer Network 2022 guidelines.

‡National Comprehensive Cancer Network 2022 treatment guidelines.

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

Table 2 (continued)

Entity	Genetic alteration: test	Diagnostic use	Clinical impact	Future assays
ENKTCL, nasal type	*CD274* SVs and amplifications: HTS		Useful in certain circumstances for prediction of response to PD1 inhibitors[329-332]	Integrated HTS and TME 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[340,473]	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)[340,346,474]	
T-LGLL and NK-LGLL	*STAT3* and *STAT5B* mutations†: HTS	Useful in certain circumstances to support the diagnosis; see scenario 4C in 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*	Strongly recommended for establishing the diagnosis; see scenario 4C in Table 3	Prognosis: complex karyotype (≥3 aberrations) indicative of less favorable prognosis[366]	

Figure 5 shows the potential therapeutic targeting of specific genetic alterations that may be common to several T/NK-cell neoplastic entities.

ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; ENKTCL, extranodal NK/T-cell lymphoma; HSTCL, hepatosplenic T-cell lymphoma; HTLV, human T-lymphotropic virus; LPD, lymphoproliferative disorder; NK-LGLL, chronic lymphoproliferative disorder of natural killer cells; TFHL, follicular helper T-cell lymphoma; T-LGLL, T-cell large granular lymphocytic leukemia.

*Required/strongly recommended in the National Comprehensive Cancer Network 2022 guidelines.

†Useful in certain circumstances in the National Comprehensive Cancer Network 2022 guidelines.

‡National Comprehensive Cancer Network 2022 treatment guidelines.

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 (eg, *NOTCH2*, *NOTCH1*, *SPEN*), genes involved in noncanonical NF-κB signaling (eg, *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 2 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; supplemental Figure 3).

Mantle cell lymphoma

MCL includes 2 subtypes: conventional MCL (cMCL) and the less common leukemic non-nodal MCL (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 (IHC) 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, it 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*, and *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, accumulates 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

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

Table 3. Utility of genomic testing in selected diagnostic settings

Diagnostic scenario	Genomic testing
Scenario 1: Small B-cell lymphomas	
1A: CD5-positive small B-cell lymphoma: SLL/CLL; MCL; CD5-positive MZLs	Demonstration of *CCND1*, *CCND2*, or *CCND3* rearrangement establishes the diagnosis of MCL; demonstration of *BCL2* rearrangement is rare in SLL/CLL and favors FL. Overlapping and heterogeneous mutational landscapes; mutations in the following genes have the most discriminant value: *ATM*, *BIRC3*, *MEF2B* (favor MCL); *BRAF*, *KLF2*, *NOTCH2*, and *PTPRD* (favor MZLs), *NOTCH1*, *SF3B1*, *XPO1* (favor SLL/CLL)
1B: CD5-negative, CD10-negative, *BCL2-R*–negative small B-cell lymphoma: MZLs (including pediatric type); *BCL2-R*–negative, CD23-positive follicle center lymphoma; FL (without *BCL2-R*); hairy cell leukemia (tumor presentation)	Demonstration of *BCL6* rearrangement or 1p36 deletion favors FL. Overlapping and heterogeneous mutational landscapes; mutations in the following genes have the most discriminant value: *KLF2*, *NOTCH2*, *PTPRD*, *CARD11*, *IRF8*, *MAP2K1* (favor MZLs and pediatric-type MZL); *CREBBP*, *EZH2*, *TNFRSF14* (in FLs), *STAT6* (favor *BCL2-R*–negative, CD23-positive follicle center lymphoma); *BRAF* (in virtually all hairy cell leukemias, also in some MZLs)
1C: Cutaneous involvement by follicular B-cell lymphoma: primary cutaneous follicle center lymphoma; systemic FL	Demonstration of *BCL2* rearrangement favors systemic FL 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 vs systemic cases
Scenario 2: B-cell neoplasms with plasmacytic differentiation and plasma cell neoplasms	
2A: Small B-cell lymphoma with plasmacytic differentiation: LPL; nodal MZLs; splenic MZL; extranodal MZL (MALT lymphoma); FL	Demonstration of *BCL2* rearrangement supports the diagnosis of FL. Demonstration of trisomies of chromosomes 3 and 18 or del(7q) supports the diagnosis of MZL. Translocations of *MALT1*, *FOXP1*, and *BCL10* are specific for MALT lymphomas. *MYD88*^{L265P} mutation is highly suggestive of LPL but not entirely specific because it is also found in a subset of other small B-cell lymphomas. Coexisting *CXCR4* mutation further increases the specificity for LPL. Overlapping and heterogeneous mutational landscapes; mutations in the following genes have the most discriminant value: *MYD88* and *CXCR4* (favor LPL); *BRAF*, *KLF2*, *NOTCH2*, *PTPRD*, *TNFAIP3* (favor MZLs); *CREBBP*, *EZH2*, *TNFRSF14* (favor FL)
2B: Bone marrow with IgM-secreting neoplasm: IgM MGUS, plasma cell type; IgM MGUS, NOS; LPL; 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 LPL 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 vs lymphoma or myeloma
2C: Small B-cell lymphoma, with spleen, bone marrow, or blood involvement: splenic MZL; hairy cell leukemia; splenic diffuse red pulp small B-cell lymphoma; hairy cell leukemia variant; MCL	Demonstration of *CCND1* rearrangement establishes the diagnosis of MCL. 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* and *NOTCH2* (favor splenic MZL); and those in *BCOR* and *CCND3* (favor splenic diffuse red pulp small B-cell lymphoma)
2D: EBV-negative plasmablastic neoplasm: plasmablastic lymphoma; plasmablastic MM; ALK-positive DLBCL	Demonstration of translocations of CCND or MAF families or *NSD2* indicates an MM; *ALK* translocations (generally substituted by IHC) define ALK-positive DLBCL. Demonstration of *MYC* rearrangement while supporting the diagnosis of plasmablastic lymphoma does not exclude plasmablastic MM. Overlapping and heterogeneous mutational landscapes; mutations in the following genes more frequent in plasmablastic lymphoma: *EP300*, *MYC*, *SOCS1*, *STAT3*, *TET2*, and *TP53*

Refer to supplemental Figure 1 and supplemental Table 1 for prevalence of genetic aberrations in the major entities.

BIA, breast implant–associated; CHL, classic Hodgkin lymphoma; EATL, enteropathy-associated T-cell lymphoma; EBV, Epstein-Barr virus; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; MGUS, monoclonal gammopathy of undetermined significance; PMBCL, primary mediastinal large B-cell lymphoma; PTCL, peripheral T-cell lymphoma; RCDII, type II refractory celiac disease.

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

Table 3 (continued)

Diagnostic scenario	Genomic testing
Scenario 3: LBCLs	
3A: Nodal-based follicular B-cell lymphoproliferations with a predominance of large cells in the pediatric population: pediatric-type FL; follicular hyperplasia; LBCL-*IRF4* rearrangement; in adults: FL grade 3A; FL grade 3B; LBCL-*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 FL and excludes pediatric entities. *BCL6* rearrangement occurs in both grade 3A and 3B cases, more commonly in 3B, but not in pediatric-type FL Demonstration of *IRF4* (or IGH, IGK or IGL) rearrangements is essential for supporting LBCL-*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 LBCL-*IRF4*. Overlapping and heterogeneous mutational landscapes; mutations in the following genes have the most discriminant value: *IRF8* and *MAP2K1* (pediatric-type FL; note that the same mutations are found in pediatric nodal MZL); *IRF4* and *MYC* (LBCL-*IRF4*); *CARD11* (LBCL-*IRF4* and FL, not in pediatric-type FL); *BCL2*, *CREBBP*, *EZH2*, and *KMT2D* (FL)
3B: Aggressive mature B-cell lymphomas: BL; LBCL with 11q aberration; HGBCL (NOS; with *MYC* and *BCL2* rearrangements; with *MYC* and *BCL6* rearrangements); DLBCL, 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 4. Mutations in *ID3* and *TCF3* favor BL whereas *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 BL
3C: LBCL involving mediastinum: PMBCL; DLBCL, NOS involving mediastinum; mediastinal gray-zone lymphoma	Demonstration of *BCL2 or BCL6* rearrangement favors DLBCL, NOS, as these uncommonly occur in PMBCL; conversely, *CIITA* rearrangement, *CD274* rearrangement or CNV are typical of primary mediastinal lymphomas. Mutations in *IL4R*, *ITPKB*, *NFKBIE*, *SOCS1*, *STAT6*, and *XPO1* are characteristic of PMBCL, while several genes often mutated in DLBCL, NOS, such as *CD79B*, *CREBBP*, *KMT2D*, *MYD88*, *PIM1*, and others, are not altered in PMBCL. Mediastinal gray-zone lymphoma has genomic features closer to PMBCL than to DLBCL, NOS, but distinctive genomic features between mediastinal gray-zone lymphoma and PMBCL are not described. Gene expression–based tests differentiate PMBCL from DLBCL, NOS
3D: Cyclin D1–positive blastoid or pleomorphic B-cell neoplasm: MCL; DLBCL, NOS positive for cyclin D1 expression; DLBCL, NOS with *CCND1* rearrangement	Demonstration of *CCND1* translocation indicates MCL or DLBCL with *CCND1* rearrangement. Demonstration of additional *BCL2*, *BCL6*, or *MYC* rearrangement is common in DLBCL with *CCND1* translocation. Blastoid MCL may harbor secondary *MYC* rearrangement or *TP53* mutations. Mutations in *ATM*, *BIRC3*, *NSD2*, and *UBR5* support mantle cell lymphoma
Scenario 4: T-cell lymphoproliferations	
4A: Hodgkin/Reed-Sternberg(–like) cells in a T-cell background: CHL; nodular lymphocyte-predominant B-cell lymphoma; T-cell/histiocyte-rich LBCL; TFHL; PTCL NOS.	Clonality testing for IG and TR rearrangements is useful in the differential diagnosis because a monoclonal TR rearrangement supports a diagnosis of T-cell lymphoma and argues against CHL or B-cell lymphomas; conversely, monoclonal IG rearrangements may be variably demonstrated in CHL, nodular lymphocyte-predominant B-cell lymphoma, and T-cell/histiocyte-rich LBCL as well as in PTCLs with an associated B-cell component (more often present in TFHLs). Demonstration of mutations in genes commonly mutated in T-cell lymphomas (*CARD11*, *CD28*, *DNMT3A*, *IDH2*, *PLCG1*, *RHOA*, *STAT3*, and *TET2*) supports that diagnosis; caution is required when interpreting mutations present only in *TET2* and/or *DNMT3A*, which can be related to CH
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 TFHL	Demonstration of a monoclonal TR gene rearrangement or somatic mutations in other genes is useful in the distinction between reactive vs neoplastic expansions of TFH cells. Demonstration of mutations in genes commonly mutated in TFHL (most specific: *IDH2* and *RHOA*; others: *CARD11*, *CD28*, *DNMT3A*, *PLCG1*, and *TET2*) supports TFHL; caution is required when interpreting mutations present only in *TET2* and/or *DNMT3A*, which can be related to CH 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 MZLs or FLs

Refer to supplemental Figure 1 and supplemental Table 1 for prevalence of genetic aberrations in the major entities.

BIA, breast implant–associated; CHL, classic Hodgkin lymphoma; EATL, enteropathy-associated T-cell lymphoma; EBV, Epstein-Barr virus; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; MGUS, monoclonal gammopathy of undetermined significance; PMBCL, primary mediastinal large B-cell lymphoma; PTCL, peripheral T-cell lymphoma; RCDII, type II refractory celiac disease.

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

Table 3 (continued)

Diagnostic scenario	Genomic testing
4C: EBV-negative cytotoxic T-lymphocytosis in blood, bone marrow, or spleen: T-LGLL; HSTCL; reactive T-cell expansions	Monoclonal TR gene rearrangements or somatic mutations (*PIK3CD*, *SETD2*, *STAT3*, *STAT5B*, and *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 $T\gamma\delta^{-}$LGLL: *SETD2* (exclusive to HSTCL), *STAT3* (less common in HSTCL than in T-LGLL), *STAT5B* (less common in T-LGLL than in HSTCL)
4D: Intestinal T-cell lymphoproliferations: RCDII; EATL; 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 RCDII, 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 are *JAK1* and *STAT3* (more commonly mutated in EATL) and *GNAI2*, *JAK3*, *SETD2*, and *STAT5B* (more commonly mutated in MEITL)
4E: Lymphoproliferations of large CD30-positive T cells: ALCL, ALK-positive; ALCL, ALK-negative; BIA-ALCL; PTCL, NOS; primary cutaneous CD30-positive lymphoproliferative disorders; transformed mycosis fungoides; subsets of EATL, or ENKTCL	Demonstration of *ALK* rearrangement (generally substituted by IHC) defines ALCL, ALK-positive. Demonstration of *DUSP22* rearrangement in ALK-negative CD30-positive large-cell lymphoproliferations establishes the diagnosis of ALCL, ALK-negative, over PTCL, NOS, but does not discriminate between primary cutaneous vs systemic ALCL, ALK-negative. *VAV1* and *TP63* rearrangements occur in small subsets of ALCL, ALK-negative but are not specific for that entity. Demonstration of *ALK*, *DUSP22*, or *TP63* translocations exclude BIA cases, whereas chromosome 20q loss is characteristic of that entity. Overlapping and heterogeneous mutational landscapes, including mutations in *STAT3* and *JAK1*, are common to several entities
Scenario 5: Successive neoplasms	
Clonal relationship between successive hematologic neoplasms	Analysis of IG or TR gene rearrangements helps to distinguish between clonally related and clonally unrelated neoplasms and to establish transdifferentiation 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 vs divergent evolution and secondary genomic alterations

Refer to supplemental Figure 1 and supplemental Table 1 for prevalence of genetic aberrations in the major entities.

BIA, breast implant–associated; CHL, classic Hodgkin lymphoma; EATL, enteropathy-associated T-cell lymphoma; EBV, Epstein-Barr virus; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; MGUS, monoclonal gammopathy of undetermined significance; PMBCL, primary mediastinal large B-cell lymphoma; PTCL, peripheral T-cell lymphoma; RCDII, type II refractory celiac disease.

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 reprogramming with overexpression of OxPhos, MYC, alternative NF-κB, and mTOR pathways.[120-123]

Multiple myeloma

Classification of 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 5 nonoverlapping 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 the 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),

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

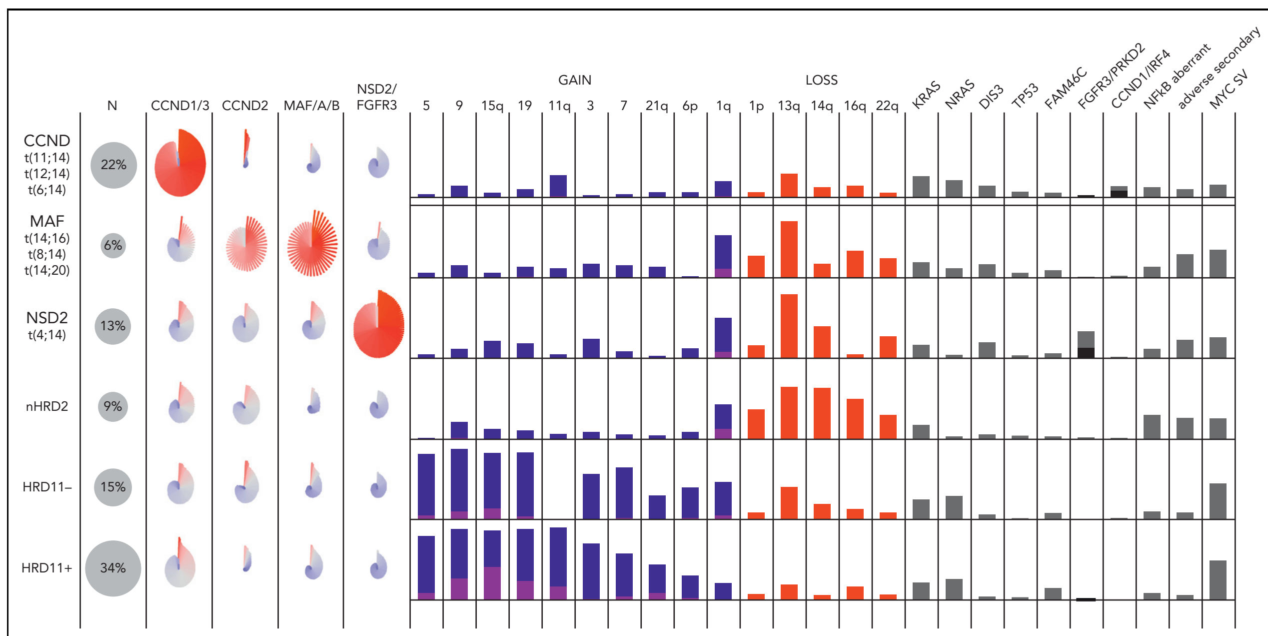

Figure 2. The molecular classification of MM. Data from the COMMpass study (clinical trial identifier: NCT0145297) are summarized, showing the 5 nonoverlapping subgroups and their associated gene expression, CNVs, SVs, and SNVs. The pinwheels show the expression of CCND, MAF, NSD2, and FGFR3 for individual 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-positive) and without (HRD11-negative) trisomy 11, and the patients without translocations or hyperdiploidy are labeled nHRD2 (MM, NOS). Mutations of *FGFR3* (black) and *PRKD2* (gray) are common in NSD2, whereas mutations of *CCND1* (black) and *IRF4* (gray) are common in CCND. A variety of different mutations can activate NF-κB (*TRAF3*, *BIRC2/3*, and others). Adverse secondary events include biallelic inactivation of *CDKN2C*, *TP53*, or *RB1*. *MYC* SVs are most common in hyperdiploid MM.

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% to 97% and 30% to 40% of patients with IgM-secreting LPL (Waldenström macroglobulinemia; WM/LPL), respectively,[148] and in 50% to 90% and 10% to 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, though rarely non-L265P variants have been identified.[148,150-152] *MYD88*^{Mut} triggers BTK-directed NF-κB prosurvival signaling, whereas *CXCR4* mutations trigger extracellular signal-regulated kinase (ERK) and protein kinase B (AKT) signaling relevant to drug resistance, particularly BTKi.[148] In LPL/WM, *MYD88* and *CXCR4* mutations affect 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 because management can differ.[155] *MYD88* mutation status should ideally be determined by allele-specific (AS) PCR-based diagnostics because HTS may miss up to one-third of *MYD88*^{Mut} WM/LPL, particularly those with low bone marrow disease burden.[159] *CXCR4* mutations are typically subclonal and affect the 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 two-thirds of *CXCR4*^{Mut} may be missed by HTS, particularly those with low disease burden and low variant allele frequencies.[166] CXCR4 antagonists are being investigated in WM/LPL. Heterozygous loss of 6q, present in up to half of the patients with WM, 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 are associated with poor outcomes, though patients carrying these mutations respond to ibrutinib.[170,171]

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

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 center B-cell–like (GCB) DLBCL COO subtypes[25] should be distinguished by GEP,[173] or approximated by 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 3 independent studies[184-186] that used multiplatform 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 testis, 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, the 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 vs light zone origin and MYC target gene expression.[187] LymphGen classifies ~63% of DLBCL tumors, with ~6% assigned to more than 1 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, whereas others may be classifiable into existing subtypes using WGS, GEP, epigenetic profiling, and analysis of the TME.

Given the above, efficient progress toward 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

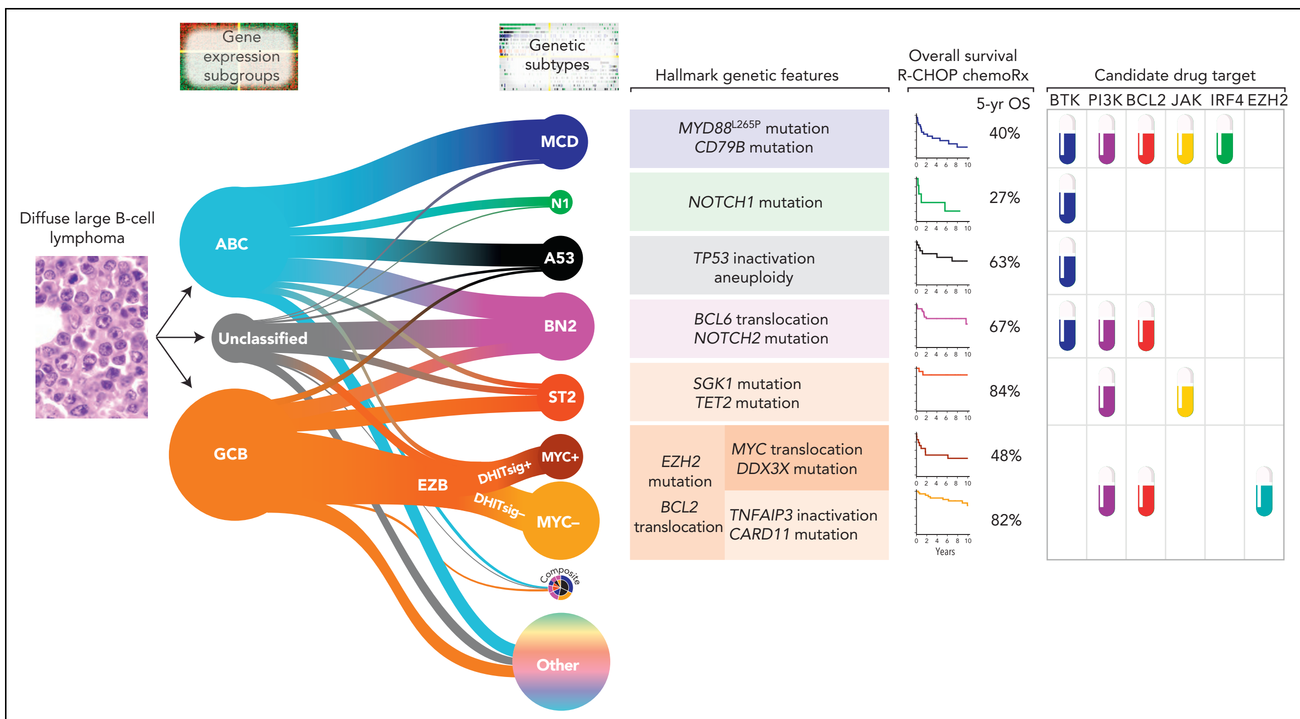

Figure 3. Genetic subgroups of DLBCL illustrated using the LymphGen algorithm. The relationships between COO and the probabilistic assignments to genetics-based subgroups are shown. The size of the subgroup circles approximates the proportions of patients in each group, with the prevalence based on Schmitz et al,[185] adjusted for a population-based distribution of COO subgroups. Tumors assigned with high confidence to ≥2 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. OS following R-CHOP chemoimmunotherapy along with inferred drug targets are shown. GCB, germinal center B-cell–like.

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

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 the 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* (ie, "pseudo-double hit"),[197] the upcoming World Health Organization classification has removed this category,[198] although 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"[199] or "double-hit signature" (DHIT-sig).[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 or reassigned to defined entities.

Burkitt lymphoma

BL is characterized by *MYC* translocations, which almost exclusively involve an IG 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 patients with immunodeficiency, including individuals with HIV infection.[202] Pathogenesis may vary according to the EBV status, as reflected by 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 that typically occur in pediatric and young adult populations have characteristic genomic aberrations. Pediatric-type FL (PTFL) 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] The presence of *IRF4*, *MYC*, or *BCL6* rearrangement exclude

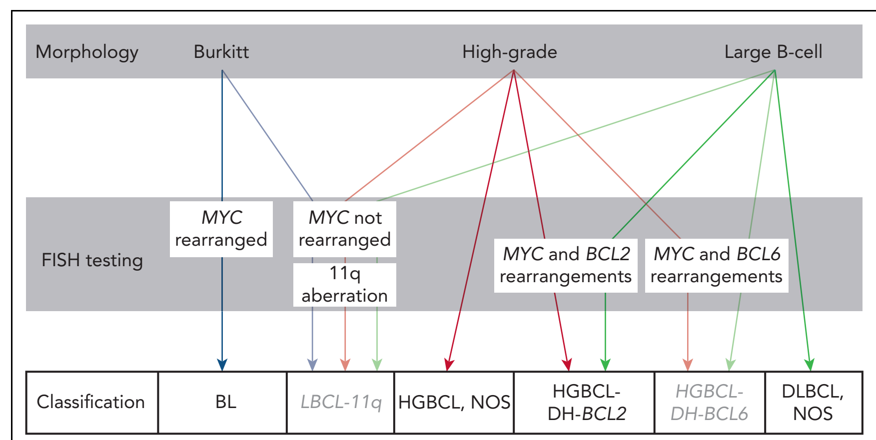

Figure 4. Approach to diagnosing HGBCL. Lymphomas that potentially fall into the HGBCL categories can have high-grade (blastoid or intermediate [between BL and large-cell]) morphology or resemble DLBCL. Tumors with morphology resembling BL and other HGBCL are assigned to the provisional entity *LBCL 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 HGBCL, NOS, acknowledging that rare *MYC* rearrangements cryptic to FISH have been observed.

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

pediatric-type FL. Of note, pediatric nodal MZL 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 the presence of *IRF4* somatic mutations, could support inclusion in this diagnostic category.[218,220] LBCL-*IRF4* also presents rarely in adults. Moreover, *IRF4* rearrangement may be observed in other LBCLs 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 lymphoma (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, but several assays can be considered to increase diagnostic precision and aid biomarker development. GEP assays suitable for FFPE biopsy specimens have been developed to differentiate DLBCL from PMBCL.[229-231] WES has revealed the contrasting mutational landscape of PMBCL to DLBCL and CHL (supplemental Figure 1).[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 (eg, *B2M*, *TNFAIP3*, *GNA13* mutations) from extramediastinal ("non-thymic") cases (supplemental Figure 1),[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 a lack of validation in treatment-intense[239] and response-adapted[240,241] trials. Outcome prediction models in relapsed CHL and pediatric patients await further validation.[242-244] Although the mutational landscape of CHL is established,[245-247] mutational testing for clinical purposes is hampered by the scarcity of the malignant Hodgkin Reed-Sternberg cells. Recent studies suggest the clinical utility of FISH-determined 9p24.1 amplification (harboring *CD274*, *PDCD1LG2*, and *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-cell and NK-cell neoplasms

Anaplastic large cell lymphomas

ALCL comprises 4 clinically, pathologically, and genetically distinct subtypes: 2 systemic forms (ALCL, ALK-positive and ALCL, ALK-negative) and 2 site-specific forms (primary cutaneous ALCL [pcALCL] 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; 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 IHC.[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% to 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 chemorefractory,[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

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

NK and T-cell neoplasms	Genetic lesions	Mechanism	Potential therapeutic intervention	
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)	TCR
TFHL, PTCL NOS	*FYN::TRAF3IP2*	NF-kappaB activation	IkB kinase inhibitors (c)	TCR
TFHL	*ITK::SYK*	SYK and JAK3/STAT5 activation	JAK3 inhibitor (tofacitinib), dual SYK and JAK inhibitor (cerdulatinib) (c)	TCR
ALK- ALCL, PTCL NOS, ATLL	*VAV1* fusions	VAV1 and RAC1 activation	RAC1 inhibitor (azathioprine) (c)	TCR
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
ALK- ALCL, BIA-ALCL, CD30+ PTCL NOS, ITLPD-GI	*JAK2* fusions	STAT5 phosphorylation		JAK/STAT
ALK+ ALCL	*ALK* fusions	STAT3 phosphorylation	ALK inhibitors (crizotinib, alectinib) (a)	JAK/STAT
ALK- ALCL	*FRK* fusions	STAT3 phosphorylation	Kinase inhibitor (dasatinib) (c)	JAK/STAT
PTCL NOS, TFHL-F	*ITK::FER*	STAT3 phosphorylation	JAK3 inhibitor (tofacitinib), kinase inhibitors (c)	JAK/STAT
ALK- ALCL	*ROS1* fusions	STAT3 phosphorylation	ROS1 inhibitor (JNJ-ROS1i-A) (c)	JAK/STAT
ALK- ALCL	*TYK2* fusions	STAT1 phosphorylation	JAK inhibitors, TYK2 inhibitor (deucravacitinib) (c)	JAK/STAT
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)	Epigenetics
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)	Others
ALK- ALCL	*ERBB4* fusions or truncated transcripts	ERBB4 overexpression	Inhibitors of ERBB-family kinases (lapatinib) (c)	Others

Figure 5. Recurrent genetic lesions in mature NK-cell 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 TcR signaling, JAK/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). AITL, Angioimmunoblastic T-cell lymphoma; ATLL, adult T-leukemia/lymphoma; CTCL, cutaneous T-cell lymphoma; ITLPD-GI, indolent clonal T-cell LPD of the gastrointestinal tract; TFHL-F, TFHL, follicular type; T-PLL, T-cell prolymphocytic leukemia. Sources referenced: 268, 270, 278, 284, 291, 293, 330, 338, 339, 341, 345, 475-487.

JAK/signal transducer and activator of transcription (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 follicular helper T-cell lymphoma (TFHL) and peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS), most common genetic abnormalities, including SNVs, CNAs, and rearrangements, affect genes of epigenetic regulators (eg, *TET2*, *DNMT3A*, *IDH2*), T-cell receptor (TcR) signaling and activation (eg, *RHOA*, *VAV1*, *CD28*, *ICOS*, *FYN*, *LCK*), phosphatidylinositol 3-kinase/protein kinase B pathway, and tumor suppressor genes (eg, *TP53*, *CDKN2A*, *ATM*, *PTEN*, *RB1*).[279-284] (supplemental Figure 1) 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; Figure 5).

The diagnosis of PTCL integrates clonality assessment, which is performed by TR rearrangement 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 TR rearrangement–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] whereas others are more characteristic of phenotypic subtypes. Specifically, TFHLs 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, 2 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 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 patients with TFHL, 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

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

TP53 and *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, the 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 PTCLs

Extranodal T-cell and NK-cell lymphoma entities derive mostly from innate cells, are relatively organ-specific, and often portend poor outcomes. Although their recognition relies primarily on morphological 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 5).[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 primarily target *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 supports the neoplastic nature of these processes. Because 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-cell large granular lymphocytic leukemia (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] Germ line 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 disease of T-cell 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 those in ENKTCL.[328] A large integrative multiomics analysis of ENKTCL biopsies defined 3 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]

CTCLs 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 are associated with more severe clinical presentation and a higher risk of hemophagocytic syndrome.[334-336]

Leukemic/disseminated NK and 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 TcR/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 programmed death-ligand 1 (PD-L1) overexpression.[341] Other commonly targeted pathways include transcriptional regulation (alterations in the 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 a *STAT3* mutation is strongly linked to $CD8^+$ T-LGLL characterized by neutropenia and the $CD16^+/CD56^-$ phenotype.[352,354,355] Other genes have been found recurrently (*TNFAIP3*) and occasionally (eg, *BCL11B*, *FLT3*, *PTPN23*) mutated in patients with T-LGLL.[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-cell prolymphocytic leukemia (T-PLL) is characterized by chromosomal inversions or translocations involving TCL1 family genes, best demonstrated by FISH,[362] resulting in constitutive overexpression 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]

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

Histiocytic and dendritic cell neoplasms (HDCNs)

In myeloid-derived HDCNs (Langerhans cell histiocytosis [LCH], Erdheim-Chester disease [ECD], juvenile xanthogranuloma, Rosai-Dorfman-Destombes disease [RDDD]), mutually exclusive recurrent mutations in MAPK (*BRAF*, *ARAF*, *NRAS*, *KRAS*, *MAPK1/2*) and, less frequently, in phosphatidylinositol-3-kinase (*PIK3CA*) pathways have been reported.[372-388] None of these mutations are specific for HDCNs because 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, the severity of disease is associated with the 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 CH.[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 *KIF5B*), 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 RDDD, although at a 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 1 gene in the MAPK pathway (most commonly *BRAF*) are also detected.[398] By contrast, follicular dendritic/reticular cell sarcomas and EBV^{+} inflammatory follicular dendritic cell/fibroblastic reticular cell tumors are of mesenchymal origin, unrelated to a hematopoietic precursor.[399] Follicular dendritic cell sarcoma (FDCS) shows mutations affecting *CDKN2A*, *NFKBIA*, *TP53*, and *BIRC3*.[397,398] GEP 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; for example, *BRAF*^{V600E} is associated with an increased risk of relapse and CNS disease in LCH. Determining mutations is also required to determine the suitability of specific inhibitors (eg, ALK, BRAF^{V600E}, second-generation RAF or MEK). Vemurafenib is approved by the FDA 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 patients with LCH 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 the 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 represents an unmet clinical need.

Technologies poised to enter clinical practice

WGS: ongoing opportunities for discovery

Although WES has clearly informed on the diverse protein-coding mutations relevant to individual cancers, WGS interrogates the understudied regions, allowing SVs, CNAs, and noncoding 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 (eg, *BCL2*) or those forming a functional fusion gene (eg, *NPM1*::*ALK*) can be diagnostic, prognostic, or predictive for targeted therapies. For oncogenes having promiscuous rearrangement partners (eg, *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 noncoding 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.[330]

ctDNA and lymphoma liquid biopsies

Circulating tumor DNA (ctDNA) represents the fraction of cell-free DNA released by tumor cells into body fluids (ie, blood plasma, cerebrospinal fluid).[417] Therefore, ctDNA is an easily accessible source of tumor DNA amenable to serial minimally invasive sampling for the genotyping or monitoring of diverse malignancies.[418] 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] The sensitivity of HTS assays incorporating molecular barcodes and/or bioinformatics that suppress error rates can even surpass amplicon-based PCR approaches, with monitoring detection limits approaching 10^{-7}.[419] However, most currently available commercial noninvasive tumor genotyping methods seldom

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

achieve detection of actionable genotypes below ~0.5% allelic levels.[420]

Given its high positive predictive value, ctDNA genotyping represents a potential tool for supporting lymphoma diagnosis in certain clinical situations, such as inaccessible tumor sites, and to overcome sampling biases.[420] 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.[417] In addition to this use of baseline liquid biopsies for genotyping and subtype classification,[24] ctDNA measurement at baseline allows for measurement of tumor burden,[421] and serial measurements allow for dynamic monitoring of tumor response and residual disease[422] (Figure 6).

These applications likely allow ctDNA to complement and enhance conventional imaging for staging and response assessments.[423] Nevertheless, clinical translation of ctDNA analysis in the management of lymphoma requires further understanding of the (1) pathophysiology of cell-free DNA across lymphomas; (2) impact of preanalytics on ctDNA assay results; (3) technical validity and real-time feasibility of state-of-the-art ctDNA assays; and (4) clinical utility of ctDNA assays to guide diagnosis, treatment tailoring, and residual disease identification.[424]

Single cell analyses

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, and epigenome to proteome analysis (supplemental Table 4).[425] 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),[35,426] deconvolution of cell heterogeneity,[427,428] tracking of tumor, and immune cell clonal dynamics at unprecedented resolution,[429,430] and has challenged the COO dogma toward a highly plastic view of cancer where dynamic transitions of cell states coexist within the tumor bulk.[431,432]

Although 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 affecting clinical decision making. Thus, across blood malignancies, routine application of SCA can be envisioned for the purposes

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

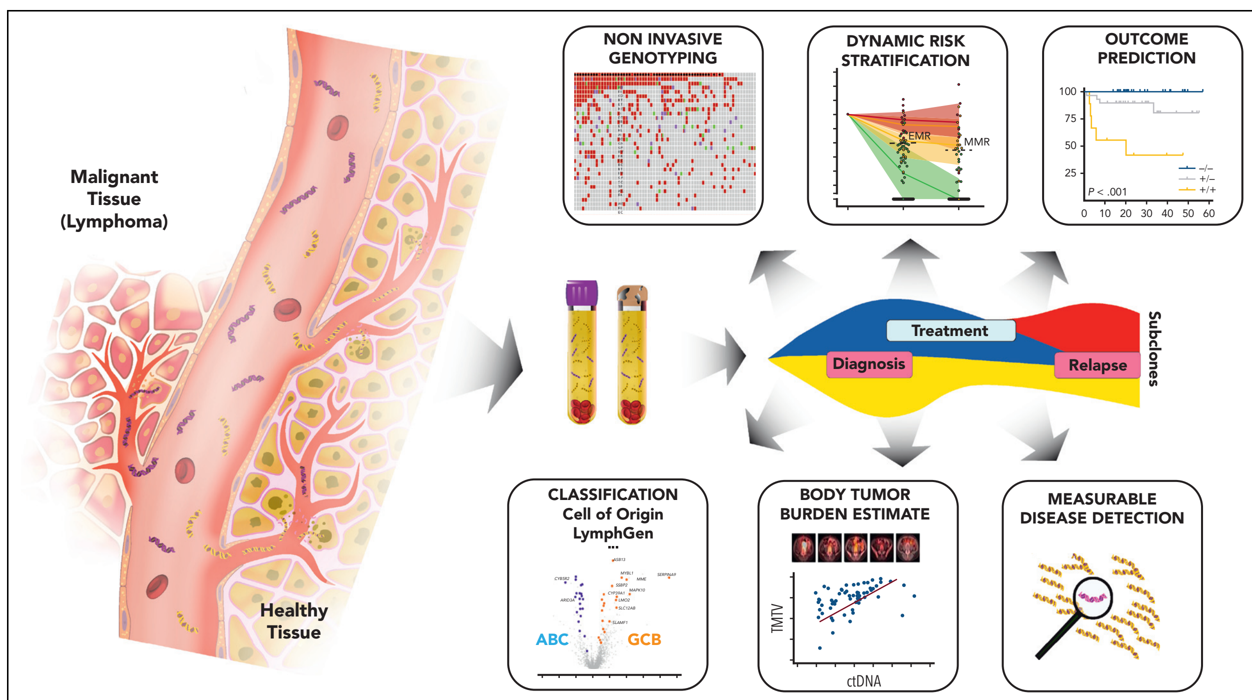

Figure 6. Applications of ctDNA in lymphoma. Schematic illustrates the potential applications of liquid biopsy assessment, as used for the identification of clinically actionable adverse-risk features in lymphomas at different disease milestones. A lymphoid tumor (left of vessel) is imagined as being accessible through blood plasma by analysis of 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).[488] 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,[424] 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),[24] allows for the identification of patients with high tumor burden,[246,421] histological subtypes,[489] and prediction of outcomes.[422] Assessment of ctDNA during and after lymphoma treatment facilitates the detection of both emerging resistance mutations and MRD before progression,[419] with potential for noninvasive prediction of relapse and transformation.[490] Tumor evolution in an anecdotal patient with DLBCL 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). EMR, early molecular response; MMR, major molecular response; TMTV, total metabolic tumor volume.

of diagnosis; for neoplastic and immune population monitoring while on treatment; for monitoring of MRD; and for guiding treatment decisions upon relapse.[433,434]

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 (supplemental Table 4), and robust and standardized practices for biospecimen collection and computational analyses.

DNA methylation and chromatin profiling

Epigenetic mechanisms play a critical role 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.[27,28,102,435-438] On the other hand, aberrant cytosine methylation patterning is a universal finding in lymphoid neoplasms.[439,440] Mechanisms driving this process include the hypermethylation effect of epigenetic modifier mutations such as in *TET2*,[441-446] the hypomethylating bystander effect of AID where methylcytosine is replaced with unmethylated nucleotides,[447] and lymphoma proliferative history associated with gradual accumulation of DNA methylation changes in repressed/heterochromatic regions.[430,435] These factors contribute to lymphomagenesis, generate intraclonal heterogeneity, and have significant clinical impact.[435,448-451] Lymphoid neoplasms harbor recurrent hypermethylation of specific genes, including the canonical tumor suppressor gene *CDKN2A*, related to disease progression,[452] and *SMAD1*, which is a biomarker for chemotherapy resistance[453] that can be reversed using DNA methyltransferase inhibitors[454] and is currently under validation in a phase 2/3 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.[455-458] Aberrant chromatin patterns are caused by mutations in epigenetic modifiers[439] 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[459-461]; *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 activation-induced cytidine deaminase–induced genomic instability.[462]

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 groundbreaking 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 depend on defining clinically useful distinctions supported by widely available supportive diagnostics.

Acknowledgment

Laura Hilton contributed to the production of figures.

Authorship

Contribution: L.d.L. and D.W.S. conceived the structure of the manuscript, coordinated the writing, and wrote and edited the manuscript; and all authors wrote or contributed to the contents of the manuscript and approved it.

Conflict-of-interest disclosure: L.d.L. reports consultancy for AbbVie, Bayer, Bio Ascend, Lunaphore, Novartis. A.A.A. reports consultancy for Celgene, Chugai, Genentech, Gilead, Janssen, Pharmacyclics, and Roche; research funding from Celgene and Pfizer; and ownership interests CiberMed, ForeSight, and FortySeven. E.C. reports consultancy for Genmab, Illumina, NanoString, and Takeda; educational honoraria from AstraZeneca, EUSA Pharma, Janssen, and Takeda; is a named inventor on a patent describing the use of gene expression to subtype aggressive B-cell lymphomas, one of which is licensed to NanoString Technologies, and an author in a protected bioinformatic pipeline (IgCaller) licensed to Diagnostica Longwood. A. Dogan reports consultancy for EUSA Pharma, Incyte, and Loxo; and research funding from Roche and Takeda. S.M.H. reports consultancy for Cimieo Therapeutics, Daiichi Sankyo, Kyowa Hakko Kirin, ONO Pharmaceuticals, SecuraBio, Shoreline Biosciences, Takeda, Tubulis, and Yingli Pharma; and research funding from ADC Therapeutics, Affimed, C4, Celgene, Crispr Therapeutics, Daiichi Sankyo, Kyowa Hakko Kirin, Millennium/Takeda, Seattle Genetics, and Verastem/SecuraBio. A.M.M. reports consulting for AstraZeneca, Epizyme, Exo Therapeutics, Janssen, and Treeline Biosciences; and research funding from AstraZeneca, Epizyme, and Janssen. R.R. reports consultancy for AbbVie, AstraZeneca, Illumina, Janssen, and Roche. D.R. reports consultancy for AbbVie, AstraZeneca, BeiGene, BMS, and Janssen; and research funding from AbbVie, AstraZeneca, BeiGene, BMS, and Janssen. C.S. reports consultancy for AbbVie, Bayer, and Seattle Genetics; and research funding from Trillium Therapeutics, BMS, and Epizyme. S.P.T. reports consultancy for BeiGene, Janssen, and Pharmacyclics; and research funding from BeiGene, BMS, Eli Lilly, Janssen, Pharmacyclics, and X4 Pharmaceuticals. A.D.Z. reports consultancy for Amgen, AstraZeneca, BeiGene, BMS/Celgene/JUNO, Genentech/Roche, Gilead/Kite, Janssen, MEI Pharma, Novartis, and Pharmacyclics/AbbVie; scientific advisory board for Adaptive Biotechnologies and Lymphoma Research Foundation; and research funding from AbbVie, BeiGene, Genentech/Roche, and MEI Pharma. C.E.A. reports consultancy for Electra and Sobi; and research support from Roche/Genetech. W.C.C. is a named inventor on a patent describing the use of gene expression to subtype aggressive B-cell lymphomas, one of which is licensed to NanoString Technologies. L.C. reports advisory boards for AbbVie and Roche. F.d'A. reports advisory board for Kyova Kirin; and research funding from Servier. S.D. reports consultancy for Incyte, Roche, and Takeda. M.D. reports speakers' honoraria from Amgen, AstraZeneca, Bayer, BMS/Celgene, Gilead/Kite, Incyte, Janssen, Novartis, and Roche; scientific advisory board for AstraZeneca, Bayer, BMS/Celgene, Genmab, Gilead/Kite, Incyte, Janssen, Lilly/Loxo, MorphoSys, Novartis, and Roche; and research funding (institutional) from AbbVie, Bayer, BMS/Celgene, Gilead/Kite, Janssen, and Roche. K.D. reports scientific advisory board for AbbVie, ADC Therapeutics, AstraZeneca, BeiGene, Daiichi Sankyo, Genentech, Genmab, Incyte, and MorphoSys. A.L.F. reports research funding from Seattle Genetics; and is a named inventor on technology for which Mayo Clinic holds unlicensed patents. F.F. reports advisory boards or

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

speaker honoraria from EUROPharma, Roche, and Stemline; and research funding from Stemline. P. Gaulard reports consultancy for Gilead and Takeda; and research funding from Alderan, Innate Pharma, Sanofi, and Takeda. P. Ghia reports consultancy for AbbVie, AstraZeneca, BeiGene, BMS, Janssen, Lilly/Loxo, MSD, and Roche; and research funding from AbbVie, AstraZeneca, and Janssen. J.G.G. reports honoraria from AbbVie, Amgen, AstraZeneca, BMS, Gilead/Kite, Janssen, and Novartis; and research funding from AstraZeneca, BMS, and Janssen. O.H. reports holding stock in AB science; is a cofounder of AB science and Inatherys; and reports research funding from AB science, AbbVie, Alexion, BMS, Inatherys, Innate Pharma, and Takeda. D.J.H. reports research funding from AstraZeneca. E.D.H. reports consultancy for Abcon, Astellas, Cytomx, and Novartis; and research funding from AbbVie, Eli Lilly, and Virtuoso. K. Karube reports speaker honoraria from AstraZeneca, Chugai Pharmaceutical, Eisai, Kyowa Kirin, Janssen, Otsuka Pharmaceutical, Takeda, Symbio, and Meiji Seika Pharma; and research funding from Takeda. K. Kataoka reports honoraria from Astellas Pharma, AstraZeneca, Chugai Pharmaceutical, Eisai, Kyowa Kirin, Janssen, Novartis, Ono Pharmaceutical, Otsuka Pharmaceutical, Sumitomo Dainippon Pharma, and Takeda; and research funding from Asahi Kasei Pharma, Chugai Pharmaceutical, Chordia Therapeutics, Eisai, Kyowa Kirin, Japan Blood Products Organization, JCR Pharmaceutical, Mochida Pharmaceutical, Nippon Shinyaku, Ono Pharmaceutical, Otsuka Pharmaceutical, Shionogi, Sumitomo Dainippon Pharmaceutical, Takeda, and Teijin Pharma; is a named inventor on a patent for genetic alterations as a biomarker in T-cell lymphomas and for PD-L1 abnormalities as a predictive biomarker for immune checkpoint blockade therapy; and reports stocks in Asahi Genomics. W.S.K. reports research funding from BeiGene, Boryong, Kyowa Kirin, Merck, Roche, and Sanofi. G.L. reports consultancy for AbbVie, ADC, AstraZeneca, Bayer, BMS, Celgene, Constellation, Gilead, Genmab, Incyte, Janssen, Karyopharm, MorphoSys, NanoString, Novartis, Roche, and Takeda; speakers' honoraria from AbbVie, Bayer, Celgene, Janssen, and Roche; and research funding from AstraZeneca, Bayer, Celgene, Gilead, Janssen, MorphoSys, Novartis, and Roche. L.P. reports research funding from AstraZeneca. M.A.P. reports speaker honoraria and advisory board fees from Celgene, Gilead, Janssen, Kyowa Kirin, Millennium/Takeda, and NanoString. S.J.R. reports research funding from BMS and Merck. G.A.S. reports consulting and advisory boards for AbbVie, Bayer, BeiGene, BMS/Celgene, Epizyme, Genentech/Roche, Genmab, Incyte, Janssen, Kite/Gilead, Loxo, Miltenyi, Molecular Partners, MorphoSys, Nordic Nanovector, Novartis, Rapt, Regeneron, and Takeda; and is a shareholder of Owkin. J.S.-M. reports consultancy and advisory boards for AbbVie, Amgen, BMS, Celgene, GSK, Haemalogix, Janssen-Cilag, Karyopharm, MSD, Novartis, Regeneron, Roche, Sanofi, SecuraBio, and Takeda. K.J.S. reports consultancy for BMS, Janssen, Kyowa, Merck, Novartis, and Seattle Genetics; and research funding from BMS. L.H.S. reports consulting and honoraria from AbbVie, Acerta, Amgen, Apbiologix, AstraZeneca, Celgene, Chugai, Gilead, Incyte, Janssen, Kite, Karyopharm, Lundbeck, Merck, MorphoSys, Roche/Genentech, Sandoz, Seattle Genetics, Servier, Takeda, Teva, TG Therapeutics, and Verastem; and research funding from Roche/Genentech and Teva. L.M.S. is one of the developers of the LymphGen software, and NCI has applied for copyright protection for this software; and is an inventor on NCI patents relevant to cell-of-origin classification of DLBCL. C.S.T. reports honoraria from AbbVie, BeiGene, and Janssen. J.T. reports research funds (institutional) from BeiGene, BMS, Cellectar, Janssen, Pharmacyclics, Roche, and Takeda. C.J.W. reports equity in BioNTech; research funds from Pharmacyclics. P.L.Z. reports consultancy for MSD TG Therapeutics, EUSAPharma, and Novartis; advisory board and speakers' bureau for BeiGene, BMS, Celltrion, EUSAPharma, Gilead, Incyte, Janssen-Cilag, Kyowa Kirin, MSD TG Therapeutics, Novartis, Roche, Servier, and Takeda; and advisory board for ADC Therapeutics, Sandoz, and Secura Bio. D.W.S. reports consultancy for AbbVie, AstraZeneca, Incyte, and Janssen; research funds from Janssen and Roche/Genentech; and is a named inventor on a patent describing the use of gene expression to subtype aggressive B-cell lymphomas, one of which is licensed to NanoString Technologies. The remaining authors declare no competing financial interests.

ORCID profiles: L.d.L., 0000-0003-3994-516X; A.A.A., 0000-0002-5153-5625; P.L.B., 0000-0003-1523-7388; E.C., 0000-0001-9850-9793; A. Davies, 0000-0002-7517-6938; A. Dogan, 0000-0001-6576-5256; J.F., 0000-0002-9069-1866; S.M.H., 0000-0002-6399-2006; A.M.M., 0000-0002-8074-2287; W.G.M., 0000-0002-5801-2501; R.D.M., 0000-0003-2932-7800; B.N., 0000-0002-4644-5617; S.A.P., 0000-0001-8032-5128; R.R., 0000-0002-0211-8788; I.S., 0000-0002-2427-9822; C.S., 0000-0001-9842-9750; S.P.T., 0000-0001-6393-6154; A.D.Z., 0000-0003-1403-6883; C.E.A., 0000-0002-6625-739X; S.M.A., 0000-0003-1244-6758; W.C.C., 0000-0002-6243-6008; J.R.C., 0000-0003-0456-8085; L.B.C., 0000-0002-8234-5090; F.d'A., 0000-0002-4032-6633; M.D., 0000-0002-0358-5249; K.D., 0000-0003-1985-8296; A.L.F., 0000-0001-5009-4808; F.F., 0000-0002-5496-293X; P. Gaulard, 0000-0002-4243-905X; P. Ghia, 0000-0003-3750-7342; J.G.G., 0000-0002-8505-7430; O.H., 0000-0003-2574-3874; D.J.H., 0000-0001-6225-2033; E.D.H., 0000-0001-8623-4067; G.I., 0000-0001-5566-0864; E.S.J., 0000-0003-4632-0301; K. Karube, 0000-0002-1205-858X; K. Kataoka, 0000-0002-8263-9902; W.K., 0000-0001-7208-4117; R.L.K., 0000-0002-7132-0226; Y.H.K., 0000-0002-4383-0579; A.S.L., 0000-0001-7349-0176; G.L., 0000-0002-4728-1693; M.A.P., 0000-0001-5839-3634; S.P., 0000-0001-7688-1439; L.P., 0000-0001-6819-7370; L.Q.-M., 0000-0001-7156-5365; S.J.R., 0000-0003-1761-9769; A.R., 0000-0001-7282-8374; G.A.S., 0000-0002-9541-8666; J.S.-M., 0000-0002-9183-4857; K.J.S., 0000-0002-5835-9863; L.H.S., 0000-0003-1860-9765; G.S., 0000-0002-6061-4595; L.M.S., 0000-0002-1735-2892; S.H.S., 0000-0002-3832-3329; C.S.T., 0000-0002-9759-5017; J.T., 0000-0001-8009-4593; J.M.V., 0000-0003-1015-7434; O.W., 0000-0002-0987-7373; W.H.W., 0000-0002-2862-9711; J.N.W., 0000-0001-7542-3305; C.J.W., 0000-0002-3348-5054; P.L.Z., 0000-0002-2112-2651; E.Z., 0000-0002-5522-6109; A.B., 0000-0002-1669-468X; D.W.S., 0000-0002-0435-5947.

Correspondence: Laurence de Leval, Institute of Pathology, Lausanne University Hospital, 25 rue du Bugnon, 1011-Lausanne, Switzerland; email: laurence.deleval@chuv.ch; and David W. Scott, BC Cancer Research Institute, 675 West 10th Ave, Vancouver, BC V5Z 1L3, Canada; email: dscott8@bccancer.bc.ca.

Footnotes

Submitted 3 May 2022; accepted 15 August 2022; prepublished online on *Blood* First Edition 24 August 2022. https://doi.org/10.1182/blood.2022015854.

*L.d.L. and D.W.S. contributed equally to this work.

Data are available on request from the corresponding authors, Laurence de Leval (laurence.deleval@chuv.ch) and David W. Scott (dscott8@bccancer.bc.ca).

The online version of this article contains a data supplement.

REFERENCES

1. Swerdlow SH, Campo E, Harris NL, et al., eds. *WHO Classification of Tumours of the Haematopoietic and Lymphoid Tissues*. Revised 4th ed. IARC; 2017.

2. Campo E, Jaffe ES, Cook JR, et al. The international consensus classification of mature lymphoid neoplasms: a report from the Clinical Advisory Committee. *Blood*. 2022;140(11):1229-1253.

3. Zech L, Haglund U, Nilsson K, Klein G. Characteristic chromosomal abnormalities in biopsies and lymphoid-cell lines from patients with Burkitt and non-Burkitt lymphomas. *Int J Cancer*. 1976;17:47-56.

4. Langerak AW, Groenen PJTA, Brüggemann M, et al. EuroClonality/BIOMED-2 guidelines for interpretation and reporting of Ig/TCR clonality testing in suspected lymphoproliferations. *Leukemia*. 2012;26(10):2159-2171.

5. van den Brand M, Rijntjes J, Mobs M, et al. Next-generation sequencing-based clonality assessment of Ig gene rearrangements: a multicenter validation study by EuroClonality-NGS. *J Mol Diagn*. 2021;23(9):1105-1115.

6. Rosenquist R, Bea S, Du MQ, Nadel B, Pan-Hammarstrom Q. Genetic landscape and deregulated pathways in B-cell lymphoid malignancies. *J Intern Med*. 2017;282(5):371-394.

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

7. Tiacci E, Trifonov V, Schiavoni G, et al. BRAF mutations in hairy-cell leukemia. *N Engl J Med*. 2011;364(24):2305-2315.

8. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. *N Engl J Med*. 2012; 367(9):826-833.

9. Pasqualucci L, Trifonov V, Fabbri G, et al. Analysis of the coding genome of diffuse large B-cell lymphoma. *Nat Genet*. 2011; 43(9):830-837.

10. Puente XS, Bea S, Valdes-Mas R, et al. Non-coding recurrent mutations in chronic lymphocytic leukaemia. *Nature*. 2015; 526(7574):519-524.

11. Parry M, Rose-Zerilli MJJ, Ljungström V, et al. Genetics and prognostication in splenic marginal zone lymphoma: revelations from deep sequencing. *Clin Cancer Res*. 2015;21(18):4174-4183.

12. Landau DA, Carter SL, Stojanov P, et al. Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. *Cell*. 2013;152(4):714-726.

13. Morin RD, Mungall K, Pleasance E, et al. Mutational and structural analysis of diffuse large B-cell lymphoma using whole-genome sequencing. *Blood*. 2013;122(7):1256-1265.

14. Keats JJ, Chesi M, Egan JB, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood*. 2012;120(5): 1067-1076.

15. Rosenquist R, Rosenwald A, Du MQ, et al. Clinical impact of recurrently mutated genes on lymphoma diagnostics: state-of-the-art and beyond. *Haematologica*. 2016;101(9): 1002-1009.

16. Buhler MM, Martin-Subero JI, Pan-Hammarstrom Q, Campo E, Rosenquist R. Towards precision medicine in lymphoid malignancies. *J Intern Med*. 2022;292(2): 221-242.

17. Mansouri L, Thorvaldsdottir B, Laidou S, Stamatopoulos K, Rosenquist R. Precision diagnostics in lymphomas – recent developments and future directions. *Semin Cancer Biol*. 2022;84:170-183.

18. Davis AR, Stone SL, Oran AR, et al. Targeted massively parallel sequencing of mature lymphoid neoplasms: assessment of empirical application and diagnostic utility in routine clinical practice. *Mod Pathol*. 2021; 34(5):904-921.

19. Sutton LA, Ljungström V, Mansouri L, et al. Targeted next-generation sequencing in chronic lymphocytic leukemia: a high-throughput yet tailored approach will facilitate implementation in a clinical setting. *Haematologica*. 2015;100(3):370-376.

20. Intlekofer AM, Joffe E, Batlevi CL, et al. Integrated DNA/RNA targeted genomic profiling of diffuse large B-cell lymphoma using a clinical assay. *Blood Cancer J*. 2018;8(6):60.

21. Scherer F, Kurtz DM, Diehn M, Alizadeh AA. High-throughput sequencing for noninvasive disease detection in hematologic malignancies. *Blood*. 2017; 130(4):440-452.

22. Stewart JP, Gazdova J, Darzentas N, et al. Validation of the EuroClonality-NGS DNA capture panel as an integrated genomic tool for lymphoproliferative disorders. *Blood Adv*. 2021;5(16):3188-3198.

23. Navrkalova V, Plevova K, Hynst J, et al. Lymphoid NeXt-generation sequencing (LYNX) panel: a comprehensive capture-based sequencing tool for the analysis of prognostic and predictive markers in lymphoid malignancies. *J Mol Diagn*. 2021; 23(8):959-974.

24. Scherer F, Kurtz DM, Newman AM, et al. Distinct biological subtypes and patterns of genome evolution in lymphoma revealed by circulating tumor DNA. *Sci Transl Med*. 2016;8:364ra155.

25. Alizadeh AA, Eisen MB, David RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*. 2000;403:503-511.

26. Rosenwald A, Wright G, Chan WC, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. *N Engl J Med*. 2002; 346(25):1937-1947.

27. Kulis M, Heath S, Bibikova M, et al. Epigenomic analysis detects widespread gene-body DNA hypomethylation in chronic lymphocytic leukemia. *Nat Genet*. 2012; 44(11):1236-1242.

28. Oakes CC, Seifert M, Assenov Y, et al. DNA methylation dynamics during B cell maturation underlie a continuum of disease phenotypes in chronic lymphocytic leukemia. *Nat Genet*. 2016;48(3):253-264.

29. Ennishi D, Jiang A, Boyle M, et al. Double-hit gene expression signature defines a distinct subgroup of germinal center B-cell-like diffuse large B-cell lymphoma. *J Clin Oncol*. 2019;37(3):190-201.

30. Scott DW, Mottok A, Ennishi D, et al. Prognostic significance of diffuse large B-cell lymphoma cell of origin determined by digital gene expression in formalin-fixed paraffin-embedded tissue biopsies. *J Clin Oncol*. 2015;33(26):2848-2856.

31. Crotty R, Hu K, Stevenson K, et al. Simultaneous identification of cell of origin, translocations, and hotspot mutations in diffuse large B-cell lymphoma using a single RNA-sequencing assay. *Am J Clin Pathol*. 2020;155(5):748-754.

32. Skaftason A, Qu Y, Abdulla M, et al. Transcriptome sequencing of archived lymphoma specimens is feasible and clinically relevant using exome capture technology. *Genes Chromosomes Cancer*. 2022;61(1):27-36.

33. Scott DW, Gascoyne RD. The tumour microenvironment in B cell lymphomas. *Nat Rev Cancer*. 2014;14(8):517-534.

34. Steen CB, Luca BA, Esfahani MS, et al. The landscape of tumor cell states and ecosystems in diffuse large B cell lymphoma. *Cancer Cell*. 2021;39(10):1422-1437.e1410.

35. Aoki T, Chong LC, Takata K, et al. Single-cell transcriptome analysis reveals disease-defining T-cell subsets in the tumor microenvironment of classic Hodgkin lymphoma. *Cancer Discov*. 2020;10(3): 406-421.

36. Meggendorfer M, Jobanputra V, Wrzeszczynski KO, et al. Analytical demands to use whole-genome sequencing in precision oncology. *Semin Cancer Biol*. 2022;84:16-22.

37. Li MM, Datto M, Duncavage EJ, et al. Standards and guidelines for the interpretation and reporting of sequence variants in cancer: a joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. *J Mol Diagn*. 2017;19(1):4-23.

38. Mateo J, Chakravarty D, Dienstmann R, et al. A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT). *Ann Oncol*. 2018;29(9):1895-1902.

39. Horak P, Griffith M, Danos AM, et al. Standards for the classification of pathogenicity of somatic variants in cancer (oncogenicity): joint recommendations of Clinical Genome Resource (ClinGen), Cancer Genomics Consortium (CGC), and Variant Interpretation for Cancer Consortium (VICC). *Genet Med*. 2022;24(5):986-998.

40. Damle RN, Wasil T, Fais F, et al. Ig V gene mutation status and CD38 expression as novel prognostic indicators in chronic lymphocytic leukemia. *Blood*. 1999;94(6): 1840-1847.

41. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig VH genes are associated with a more aggressive form of chronic lymphocytic leukemia. *Blood*. 1999; 94(6):1848-1854.

42. Agathangelidis A, Chatzidimitriou A, Chatzikonstantinou T, et al. Immunoglobulin gene sequence analysis in chronic lymphocytic leukemia: the 2022 update of the recommendations by ERIC, the European Research Initiative on CLL. *Leukemia*. 2022;36:1961-1968.

43. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens Versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018; 379(26):2517-2528.

44. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380(23):2225-2236.

45. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised,

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

open-label, phase 3 trial. *Lancet Oncol.* 2019;20(1):43-56.

46. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib–rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med.* 2019; 381(5):432-443.

47. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2020;21(9):1188-1200.

48. Maura F, Cutrona G, Fabris S, et al. Relevance of stereotyped B-cell receptors in the context of the molecular, cytogenetic and clinical features of chronic lymphocytic leukemia. *PLoS One.* 2011;6(8):e24313.

49. Stamatopoulos K, Belessi C, Moreno C, et al. Over 20% of patients with chronic lymphocytic leukemia carry stereotyped receptors: pathogenetic implications and clinical correlations. *Blood.* 2006;109(1): 259-270.

50. Agathangelidis A, Darzentas N, Hadzidimitriou A, et al. Stereotyped B-cell receptors in one-third of chronic lymphocytic leukemia: a molecular classification with implications for targeted therapies. *Blood.* 2012;119(19):4467-4475.

51. ten Hacken E, Gounari M, Ghia P, Burger JA. The importance of B cell receptor isotypes and stereotypes in chronic lymphocytic leukemia. *Leukemia.* 2019;33(2):287-298.

52. Nadeu F, Diaz-Navarro A, Delgado J, Puente XS, Campo E. Genomic and epigenomic alterations in chronic lymphocytic leukemia. *Annu Rev Pathol.* 2020;15(1):149-177.

53. Agathangelidis A, Chatzidimitriou A, Gemenetzi K, et al. Higher-order connections between stereotyped subsets: implications for improved patient classification in CLL. *Blood.* 2021;137(10): 1365-1376.

54. Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med.* 2000;343(26):1910-1916.

55. Rigolin GM, Del Giudice I, Bardi A, et al. Complex karyotype in unfit patients with CLL treated with ibrutinib and rituximab: the GIMEMA LLC1114 phase 2 study. *Blood.* 2021;138(25):2727-2730.

56. Schweighofer CD, Coombes KR, Majewski T, et al. Genomic variation by whole-genome SNP mapping arrays predicts time-to-event outcome in patients with chronic lymphocytic leukemia: a comparison of CLL and HapMap genotypes. *J Mol Diagn.* 2013;15(2):196-209.

57. Baliakas P, Jeromin S, Iskas M, et al. Cytogenetic complexity in chronic lymphocytic leukemia: definitions, associations, and clinical impact. *Blood.* 2019;133(11):1205-1216.

58. Nadeu F, Royo R, Clot G, et al. IGLV3-21R110 identifies an aggressive biological subtype of chronic lymphocytic leukemia with intermediate epigenetics. *Blood.* 2021;137(21):2935-2946.

59. Maity PC, Bilal M, Koning MT, et al. IGLV3-21*01 is an inherited risk factor for CLL through the acquisition of a single-point mutation enabling autonomous BCR signaling. *Proc Natl Acad Sci U S A.* 2020; 117(8):4320-4327.

60. Landau DA, Wu CJ. Chronic lymphocytic leukemia: molecular heterogeneity revealed by high-throughput genomics. *Genome Med.* 2013;5(5):47.

61. Bomben R, Rossi FM, Vit F, et al. TP53 mutations with low variant allele frequency predict short survival in chronic lymphocytic leukemia. *Clin Cancer Res.* 2021;27(20): 5566-5575.

62. Rossi D, Khiabanian H, Spina V, et al. Clinical impact of small TP53 mutated subclones in chronic lymphocytic leukemia. *Blood.* 2014;123(14):2139-2147.

63. Austen B, Powell JE, Alvi A, et al. Mutations in the ATM gene lead to impaired overall and treatment-free survival that is independent of IGVH mutation status in patients with B-CLL. *Blood.* 2005;106(9):3175-3182.

64. Smith CIE, Burger JA. Resistance mutations to BTK inhibitors originate from the NF-κB but not from the PI3K-RAS-MAPK arm of the B cell receptor signaling pathway. *Front Immunol.* 2021;12:689472.

65. Wang E, Mi X, Thompson MC, et al. Mechanisms of resistance to noncovalent Bruton's tyrosine kinase inhibitors. *N Engl J Med.* 2022;386(8):735-743.

66. Blombery P. Mechanisms of intrinsic and acquired resistance to venetoclax in B-cell lymphoproliferative disease. *Leuk Lymphoma.* 2020;61(2):257-262.

67. Mansouri L, Wierzbinska JA, Plass C, Rosenquist R. Epigenetic deregulation in chronic lymphocytic leukemia: clinical and biological impact. *Semin Cancer Biol.* 2018;51:1-11.

68. Del Giudice I, Raponi S, Della Starza I, et al. Minimal residual disease in chronic lymphocytic leukemia: a new goal? *Front Oncol.* 2019;9:689.

69. Fürstenau M, De Silva N, Eichhorst B, Hallek M. Minimal residual disease assessment in CLL: ready for use in clinical routine? *HemaSphere.* 2019;3(5): e287.

70. Wierda WG, Rawstron A, Cymbalista F, et al. Measurable residual disease in chronic lymphocytic leukemia: expert review and consensus recommendations. *Leukemia.* 2021;35(11):3059-3072.

71. Carbone A, Roulland S, Gloghini A, et al. Follicular lymphoma. *Nat Rev Dis Primers.* 2019;5(1):83.

72. Pasqualucci L, Dominguez-Sola D, Chiarenza A, et al. Inactivating mutations of acetyltransferase genes in B-cell lymphoma. *Nature.* 2011;471(7337):189-195.

73. Morin RD, Mendez-Lago M, Mungall AJ, et al. Frequent mutation of histone-modifying genes in non-Hodgkin lymphoma. *Nature.* 2011; 476(7360):298-303.

74. Morin RD, Johnson NA, Severson TM, et al. Somatic mutations altering EZH2 (Tyr641) in follicular and diffuse large B-cell lymphomas of germinal-center origin. *Nat Genet.* 2010; 42(2):181-185.

75. Okosun J, Wolfson RL, Wang J, et al. Recurrent mTORC1-activating RRAGC mutations in follicular lymphoma. *Nat Genet.* 2016;48(2):183-188.

76. Cheung KJ, Johnson NA, Affleck JG, et al. Acquired TNFRSF14 mutations in follicular lymphoma are associated with worse prognosis. *Cancer Res.* 2010;70(22): 9166-9174.

77. Boice M, Salloum D, Mourcin F, et al. Loss of the HVEM tumor suppressor in lymphoma and restoration by modified CAR-T cells. *Cell.* 2016;167(2):405-418.e413.

78. Zhu D, McCarthy H, Ottensmeier CH, Johnson P, Hamblin TJ, Stevenson FK. Acquisition of potential N-glycosylation sites in the immunoglobulin variable region by somatic mutation is a distinctive feature of follicular lymphoma. *Blood.* 2002;99(7):2562-2568.

79. Pastore A, Jurinovic V, Kridel R, et al. Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. *Lancet Oncol.* 2015;16(9):1111-1122.

80. Huet S, Tesson B, Jais J-P, et al. A gene-expression profiling score for prediction of outcome in patients with follicular lymphoma: a retrospective training and validation analysis in three international cohorts. *Lancet Oncol.* 2018;19(4):549-561.

81. Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *Lancet Oncol.* 2020;21(11):1433-1442.

82. Nann D, Ramis-Zaldivar JE, Müller I, et al. Follicular lymphoma t(14;18)-negative is genetically a heterogeneous disease. *Blood Adv.* 2020;4(22):5652-5665.

83. Barasch NJK, Liu YC, Ho J, et al. The molecular landscape and other distinctive features of primary cutaneous follicle center lymphoma. *Hum Pathol.* 2020;106: 93-105.

84. Zhou XA, Yang J, Ringbloom KG, et al. Genomic landscape of cutaneous follicular lymphomas reveals 2 subgroups with clinically predictive molecular features. *Blood Adv.* 2021;5(3):649-661.

85. Okosun J, Bodor C, Wang J, et al. Integrated genomic analysis identifies recurrent mutations and evolution patterns driving the initiation and progression of

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

follicular lymphoma. *Nat Genet*. 2014;46(2):176-181.

86. Pasqualucci L, Khiabanian H, Fangazio M, et al. Genetics of follicular lymphoma transformation. *Cell Rep*. 2014;6(1):130-140.

87. Green MR, Kihira S, Liu CL, et al. Mutations in early follicular lymphoma progenitors are associated with suppressed antigen presentation. *Proc Natl Acad Sci U S A*. 2015;112(10):E1116-E1125.

88. Rossi D, Bertoni F, Zucca E. Marginal-zone lymphomas. *N Engl J Med*. 2022;386(6):568-581.

89. Zucca E, Bertoni F. The spectrum of MALT lymphoma at different sites: biological and therapeutic relevance. *Blood*. 2016;127(17):2082-2092.

90. Vela V, Juskevicius D, Dirnhofer S, Menter T, Tzankov A. Mutational landscape of marginal zone B-cell lymphomas of various origin: organotypic alterations and diagnostic potential for assignment of organ origin. *Virchows Arch*. 2022;480(2):403-413.

91. Liu H, Ruskon-Fourmestraux A, Lavergne-Slove A, et al. Resistance of t(11;18) positive gastric mucosa-associated lymphoid tissue lymphoma to Helicobacter pylori eradication therapy. *Lancet*. 2001;357(9249):39-40.

92. Rinaldi A, Mian M, Chigrinova E, et al. Genome-wide DNA profiling of marginal zone lymphomas identifies subtype-specific lesions with an impact on the clinical outcome. *Blood*. 2011;117(5):1595-1604.

93. Gailllard B, Cornillet-Lefebvre P, Le QH, et al. Clinical and biological features of B-cell neoplasms with CDK6 translocations: an association with a subgroup of splenic marginal zone lymphomas displaying frequent CD5 expression, prolymphocytic cells, and TP53 abnormalities. *Br J Haematol*. 2021;193(1):72-82.

94. Clipson A, Wang M, de Leval L, et al. KLF2 mutation is the most frequent somatic change in splenic marginal zone lymphoma and identifies a subset with distinct genotype. *Leukemia*. 2015;29(5):1177-1185.

95. Pillonel V, Juskevicius D, Ng CKY, et al. High-throughput sequencing of nodal marginal zone lymphomas identifies recurrent BRAF mutations. *Leukemia*. 2018;32(11):2412-2426.

96. Spina V, Khiabanian H, Messina M, et al. The genetics of nodal marginal zone lymphoma. *Blood*. 2016;128(10):1362-1373.

97. Bonfiglio F, Bruscaggin A, Guidetti F, et al. Genetic and phenotypic attributes of splenic marginal zone lymphoma. *Blood*. 2022;139(5):732-747.

98. Puente XS, Jares P, Campo E. Chronic lymphocytic leukemia and mantle cell lymphoma: crossroads of genetic and microenvironment interactions. *Blood*. 2018;131(21):2283-2296.

99. Martín-Garcia D, Navarro A, Valdés-Mas R, et al. CCND2 and CCND3 hijack immunoglobulin light-chain enhancers in cyclin D1– mantle cell lymphoma. *Blood*. 2019;133(9):940-951.

100. Sander B, Quintanilla-Martinez L, Ott G, et al. Mantle cell lymphoma—a spectrum from indolent to aggressive disease. *Virchows Arch*. 2016;468(3):245-257.

101. Peterson JF, Baughn LB, Ketterling RP, et al. Characterization of a cryptic IGH/CCND1 rearrangement in a case of mantle cell lymphoma with negative CCND1 FISH studies. *Blood Adv*. 2019;3(8):1298-1302.

102. Queiros AC, Beekman R, Vilarrasa-Blasi R, et al. Decoding the DNA methylome of mantle cell lymphoma in the light of the entire B cell lineage. *Cancer Cell*. 2016;30(5):806-821.

103. Clot G, Jares P, Giné E, et al. A gene signature that distinguishes conventional and leukemic nonnodal mantle cell lymphoma helps predict outcome. *Blood*. 2018;132(4):413-422.

104. Nadeu F, Martin-Garcia D, Clot G, et al. Genomic and epigenomic insights into the origin, pathogenesis, and clinical behavior of mantle cell lymphoma subtypes. *Blood*. 2020;136(12):1419-1432.

105. Pararajalingam P, Coyle KM, Arthur SE, et al. Coding and noncoding drivers of mantle cell lymphoma identified through exome and genome sequencing. *Blood*. 2020;136(5):572-584.

106. Hill HA, Qi X, Jain P, et al. Genetic mutations and features of mantle cell lymphoma: a systematic review and meta-analysis. *Blood Adv*. 2020;4(13):2927-2938.

107. Yi S, Yan Y, Jin M, et al. Genomic and transcriptomic profiling reveals distinct molecular subsets associated with outcomes in mantle cell lymphoma. *J Clin Invest*. 2022;132(3):e153283.

108. Müller H, Walter W, Hutter S, et al. Aberrant somatic hypermutation of CCND1 generates non-coding drivers of mantle cell lymphomagenesis. *Cancer Gene Ther*. 2022;29:484-493.

109. Bea S, Valdes-Mas R, Navarro A, et al. Landscape of somatic mutations and clonal evolution in mantle cell lymphoma. *Proc Natl Acad Sci U S A*. 2013;110(45):18250-18255.

110. Jain P, Zhang S, Kanagal-Shamanna R, et al. Genomic profiles and clinical outcomes of de novo blastoid/pleomorphic MCL are distinct from those of transformed MCL. *Blood Adv*. 2020;4(6):1038-1050.

111. Eskelund CW, Dahl C, Hansen JW, et al. TP53 mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy. *Blood*. 2017;130(17):1903-1910.

112. Delfau-Larue MH, Klapper W, Berger F, et al. High-dose cytarabine does not overcome the adverse prognostic value of CDKN2A and TP53 deletions in mantle cell lymphoma. *Blood*. 2015;126(5):604-611.

113. Halldórsdóttir AM, Lundin A, Murray F, et al. Impact of TP53 mutation and 17p deletion in mantle cell lymphoma. *Leukemia*. 2011;25(12):1904-1908.

114. Ferrero S, Rossi D, Rinaldi A, et al. KMT2D mutations and TP53 disruptions are poor prognostic biomarkers in mantle cell lymphoma receiving high-dose therapy: a FIL study. *Haematologica*. 2020;105(6):1604-1612.

115. Eskelund CW, Albertsson-Lindblad A, Kolstad A, et al. Lenalidomide plus bendamustine-rituximab does not overcome the adverse impact of TP53 mutations in mantle cell lymphoma. *Haematologica*. 2018;103(11):e541-e543.

116. Aukema SM, Hoster E, Rosenwald A, et al. Expression of TP53 is associated with the outcome of MCL independent of MIPI and Ki-67 in trials of the European MCL Network. *Blood*. 2018;131(4):417-420.

117. Scott DW, Abrisqueta P, Wright GW, et al. New molecular assay for the proliferation signature in mantle cell lymphoma applicable to formalin-fixed paraffin-embedded biopsies. *J Clin Oncol*. 2017;35(15):1668-1677.

118. Holte H, Beiske K, Boyle M, et al. The MCL35 gene expression proliferation assay predicts high-risk MCL patients in a Norwegian cohort of younger patients given intensive first line therapy. *Br J Haematol*. 2018;183(2):225-234.

119. Croci GA, Hoster E, Beà S, et al. Reproducibility of histologic prognostic parameters for mantle cell lymphoma: cytology, Ki67, p53 and SOX11. *Virchows Arch*. 2020;477(2):259-267.

120. Zhang L, Yao Y, Zhang S, et al. Metabolic reprogramming toward oxidative phosphorylation identifies a therapeutic target for mantle cell lymphoma. *Sci Transl Med*. 2019;11(491):eaau1167.

121. Zhang S, Jiang VC, Han G, et al. Longitudinal single-cell profiling reveals molecular heterogeneity and tumor-immune evolution in refractory mantle cell lymphoma. *Nat Commun*. 2021;12(1):2877.

122. Thompson ER, Nguyen T, Kankanige Y, et al. Single-cell sequencing demonstrates complex resistance landscape in CLL and MCL treated with BTK and BCL2 inhibitors. *Blood Adv*. 2022;6(2):503-508.

123. Rahal R, Frick M, Romero R, et al. Pharmacological and genomic profiling identifies NF-κB-targeted treatment strategies for mantle cell lymphoma. *Nat Med*. 2014;20(1):87-92.

124. Bergsagel PL, Kuehl WM, Zhan F, Sawyer J, Barlogie B, Shaughnessy J Jr. Cyclin D dysregulation: an early and unifying pathogenic event in multiple myeloma. *Blood*. 2005;106(1):296-303.

125. Chesi M, Stein CK, Garbitt VM, et al. Monosomic loss of MIR15A/MIR16-1 is a driver of multiple myeloma proliferation and disease progression. *Blood Cancer Discov*. 2020;1(1):68-81.

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

126. Zhan F, Huang Y, Colla S, et al. The molecular classification of multiple myeloma. *Blood*. 2006;108(6):2020-2028.

127. Broyl A, Hose D, Lokhorst H, et al. Gene expression profiling for molecular classification of multiple myeloma in newly diagnosed patients. *Blood*. 2010;116(14): 2543-2553.

128. Walker BA, Mavrommatis K, Wardell CP, et al. Identification of novel mutational drivers reveals oncogene dependencies in multiple myeloma. *Blood*. 2018;132(6): 587-597.

129. Chng WJ, Dispenzieri A, Chim CS, et al. IMWG consensus on risk stratification in multiple myeloma. *Leukemia*. 2014;28(2): 269-277.

130. Corre J, Munshi NC, Avet-Loiseau H. Risk factors in multiple myeloma: is it time for a revision? *Blood*. 2021;137(1):16-19.

131. Sonneveld P, Goldschmidt H, Rosiñol L, et al. Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials. *J Clin Oncol*. 2013;31(26):3279-3287.

132. Giri S, Grimshaw A, Bal S, et al. Evaluation of daratumumab for the treatment of multiple myeloma in patients with high-risk cytogenetic factors: a systematic review and meta-analysis. *JAMA Oncol*. 2020;6(11): 1759-1765.

133. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. *Lancet Haematol*. 2020; 7(6):e456-e468.

134. Kumar SK, Harrison SJ, Cavo M, et al. Venetoclax or placebo in combination with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (BELLINI): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2020;21(12):1630-1642.

135. Shaughnessy JD Jr, Zhan F, Burington BE, et al. A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. *Blood*. 2006;109(6): 2276-2284.

136. Kuiper R, Broyl A, de Knegt Y, et al. A gene expression signature for high-risk multiple myeloma. *Leukemia*. 2012;26(11): 2406-2413.

137. Egan JB, Shi C-X, Tembe W, et al. Whole-genome sequencing of multiple myeloma from diagnosis to plasma cell leukemia reveals genomic initiating events, evolution, and clonal tides. *Blood*. 2012;120(5): 1060-1066.

138. Samur MK, Samur AA, Fulciniti M, et al. Genome-wide somatic alterations in multiple myeloma reveal a superior outcome group. *J Clin Oncol*. 2020;38(27):3107-3118.

139. Misund K, Keane N, Stein CK, et al. MYC dysregulation in the progression of multiple myeloma. *Leukemia*. 2020;34(1):322-326.

140. Oben B, Froyen G, Maclachlan KH, et al. Whole-genome sequencing reveals progressive versus stable myeloma precursor conditions as two distinct entities. *Nat Commun*. 2021;12(1):1861.

141. Maclachlan KH, Rustad EH, Derkach A, et al. Copy number signatures predict chromothripsis and clinical outcomes in newly diagnosed multiple myeloma. *Nat Commun*. 2021;12(1):5172.

142. Rustad EH, Yellapantula VD, Glodzik D, et al. Revealing the impact of structural variants in multiple myeloma. *Blood Cancer Discov*. 2020;1(3):258-273.

143. Bustoros M, Sklavenitis-Pistofidis R, Park J, et al. Genomic profiling of smoldering multiple myeloma identifies patients at a high risk of disease progression. *J Clin Oncol*. 2020;38(21):2380-2389.

144. Boyle EM, Deshpande S, Tytarenko R, et al. The molecular make up of smoldering myeloma highlights the evolutionary pathways leading to multiple myeloma. *Nat Commun*. 2021;12(1):293.

145. Mateos M-V, Kumar S, Dimopoulos MA, et al. International Myeloma Working Group risk stratification model for smoldering multiple myeloma (SMM). *Blood Cancer J*. 2020;10(10):102.

146. Merz M, Hielscher T, Schult D, et al. Cytogenetic subclone formation and evolution in progressive smoldering multiple myeloma. *Leukemia*. 2020;34(4): 1192-1196.

147. Bolli N, Maura F, Minvielle S, et al. Genomic patterns of progression in smoldering multiple myeloma. *Nat Commun*. 2018;9(1): 3363.

148. Treon SP, Xu L, Guerrera ML, et al. Genomic landscape of Waldenstrom macroglobulinemia and its impact on treatment strategies. *J Clin Oncol*. 2020; 38(11):1198-1208.

149. Xu L, Hunter ZR, Tsakmaklis N, et al. Clonal architecture of CXCR4 WHIM-like mutations in Waldenström macroglobulinaemia. *Br J Haematol*. 2016;172(5):735-744.

150. Varettoni M, Zibellini S, Defrancesco I, et al. Pattern of somatic mutations in patients with Waldenström macroglobulinemia or IgM monoclonal gammopathy of undetermined significance. *Haematologica*. 2017;102(12): 2077-2085.

151. Varettoni M, Arcaini L, Zibellini S, et al. Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in Waldenström's macroglobulinemia and related lymphoid neoplasms. *Blood*. 2013;121(13):2522-2528.

152. Castillo JJ, Itchaki G, Gustine JN, et al. A matched case-control study comparing features, treatment and outcomes between patients with non-IgM lymphoplasmacytic lymphoma and Waldenström macroglobulinemia. *Leuk Lymphoma*. 2020; 61(6):1388-1394.

153. Hunter ZR, Xu L, Tsakmaklis N, et al. Insights into the genomic landscape of MYD88 wild-type Waldenström macroglobulinemia. *Blood Adv*. 2018;2(21):2937-2946.

154. Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenström macroglobulinemia. *Blood*. 2014;123(18):2791-2796.

155. Treon SP, Gustine J, Xu L, et al. MYD88 wild-type Waldenstrom macroglobulinaemia: differential diagnosis, risk of histological transformation, and overall survival. *Br J Haematol*. 2018;180(3):374-380.

156. Abeykoon JP, Paludo J, King RL, et al. MYD88 mutation status does not impact overall survival in Waldenström macroglobulinemia. *Am J Hematol*. 2018; 93(2):187-194.

157. Laribi K, Poulain S, Willems L, et al. Bendamustine plus rituximab in newly-diagnosed Waldenström macroglobulinaemia patients. A study on behalf of the French Innovative Leukaemia Organization (FILO). *Br J Haematol*. 2019; 186(1):146-149.

158. Dimopoulos M, Sanz RG, Lee H-P, et al. Zanubrutinib for the treatment of MYD88 wild-type Waldenström macroglobulinemia: a substudy of the phase 3 ASPEN trial. *Blood Adv*. 2020;4(23):6009-6018.

159. Kofides A, Hunter ZR, Xu L, et al. Diagnostic next-generation sequencing frequently fails to detect MYD88L265P in Waldenström macroglobulinemia. *HemaSphere*. 2021; 5(8):e624.

160. Treon SP, Meid K, Gustine J, et al. Long-term follow-up of ibrutinib monotherapy in symptomatic, previously treated patients with Waldenström macroglobulinemia. *J Clin Oncol*. 2021;39(6):565-575.

161. Castillo JJ, Meid K, Gustine JN, et al. Long-term follow-up of ibrutinib monotherapy in treatment-naive patients with Waldenstrom macroglobulinemia. *Leukemia*. 2022;36(2): 532-539.

162. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study. *Blood*. 2020;136(18):2038-2050.

163. Poulain S, Roumier C, Venet-Caillault A, et al. Genomic landscape of CXCR4 mutations in Waldenström macroglobulinemia. *Clin Cancer Res*. 2016; 22(6):1480-1488.

164. Castillo JJ, Xu L, Gustine JN, et al. CXCR4 mutation subtypes impact response and survival outcomes in patients with

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

Waldenström macroglobulinaemia treated with ibrutinib. *Br J Haematol*. 2019;187(3):356-363.

165. Wang Y, Gali VL, Xu-Monette ZY, et al. Molecular and genetic biomarkers implemented from next-generation sequencing provide treatment insights in clinical practice for Waldenström macroglobulinemia. *Neoplasia*. 2021;23(4):361-374.

166. Gustine JN, Xu L, Yang G, et al. Bone marrow involvement and subclonal diversity impairs detection of mutated CXCR4 by diagnostic next-generation sequencing in Waldenström macroglobulinaemia. *Br J Haematol*. 2021;194(4):730-733.

167. Guerrera ML, Tsakmaklis N, Xu L, et al. MYD88 mutated and wild-type Waldenström's macroglobulinemia: characterization of chromosome 6q gene losses and their mutual exclusivity with mutations in CXCR4. *Haematologica*. 2018;103(9):e408-e411.

168. Jiménez C, Alonso-Álvarez S, Alcoceba M, et al. From Waldenström's macroglobulinemia to aggressive diffuse large B-cell lymphoma: a whole-exome analysis of abnormalities leading to transformation. *Blood Cancer J*. 2017;7(8):e591.

169. Xu L, Tsakmaklis N, Yang G, et al. Acquired mutations associated with ibrutinib resistance in Waldenström macroglobulinemia. *Blood*. 2017;129(18):2519-2525.

170. Poulain S, Roumier C, Bertrand E, et al. TP53 mutation and its prognostic significance in Waldenstrom's macroglobulinemia. *Clin Cancer Res*. 2017;23(20):6325-6335.

171. Gustine JN, Tsakmaklis N, Demos MG, et al. TP53 mutations are associated with mutated MYD88 and CXCR4, and confer an adverse outcome in Waldenström macroglobulinaemia. *Br J Haematol*. 2019;184(2):242-245.

172. Hilton LK, Tang J, Ben-Neriah S, et al. The double-hit signature identifies double-hit diffuse large B-cell lymphoma with genetic events cryptic to FISH. *Blood*. 2019;134(18):1528-1532.

173. Scott DW, Wright GW, Williams PM, et al. Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. *Blood*. 2014;123(8):1214-1217.

174. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood*. 2004;103(1):275-282.

175. Lenz G, Wright G, Dave SS, et al. Stromal gene signatures in large-B-cell lymphomas. *N Engl J Med*. 2008;359:2313-2323.

176. Davis RE, Ngo VN, Lenz G, et al. Chronic active B-cell-receptor signalling in diffuse large B-cell lymphoma. *Nature*. 2010;463(7277):88-92.

177. Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. *Nat Med*. 2015;21(8):922-926.

178. Lionakis MS, Dunleavy K, Roschewski M, et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. *Cancer Cell*. 2017;31(6):833-843.e835.

179. Grommes C, Younes A. Ibrutinib in PCNSL: the curious cases of clinical responses and aspergillosis. *Cancer Cell*. 2017;31(6):731-733.

180. Younes A, Sehn LH, Johnson P, et al. Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal center B-cell diffuse large B-cell lymphoma. *J Clin Oncol*. 2019;37(15):1285-1295.

181. Wilson WH, Wright GW, Huang DW, et al. Effect of ibrutinib with R-CHOP chemotherapy in genetic subtypes of DLBCL. *Cancer Cell*. 2021;39(12):1643-1653.e1643.

182. Davies A, Cummin TE, Barrans S, et al. Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2019;20(5):649-662.

183. Nowakowski GS, Chiappella A, Gascoyne RD, et al. ROBUST: a phase III study of lenalidomide plus R-CHOP versus placebo plus R-CHOP in previously untreated patients with ABC-type diffuse large B-cell lymphoma. *J Clin Oncol*. 2021;39(12):1317-1328.

184. Chapuy B, Stewart C, Dunford AJ, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. *Nat Med*. 2018;24(5):679-690.

185. Schmitz R, Wright GW, Huang DW, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. *N Engl J Med*. 2018;378(15):1396-1407.

186. Lacy SE, Barrans SL, Beer PA, et al. Targeted sequencing in DLBCL, molecular subtypes, and outcomes: a Haematological Malignancy Research Network report. *Blood*. 2020;135(20):1759-1771.

187. Wright GW, Huang DW, Phelan JD, et al. A probabilistic classification tool for genetic subtypes of diffuse large B cell lymphoma with therapeutic implications. *Cancer Cell*. 2020;37(4):551-568.e514.

188. Runge HFP, Lacy S, Barrans S, et al. Application of the LymphGen classification tool to 928 clinically and genetically-characterised cases of diffuse large B cell lymphoma (DLBCL). *Br J Haematol*. 2021;192(1):216-220.

189. Kotlov N, Bagaev A, Revuelta MV, et al. Clinical and biological subtypes of B-cell lymphoma revealed by microenvironmental signatures. *Cancer Discov*. 2021;11(6):1468-1489.

190. Copie-Bergman C, Cuilliere-Dartigues P, Baia M, et al. MYC-IG rearrangements are negative predictors of survival in DLBCL patients treated with immunochemotherapy: a GELA/LYSA study. *Blood*. 2015;126(22):2466-2474.

191. Rosenwald A, Bens S, Advani R, et al. Prognostic significance of MYC rearrangement and translocation partner in diffuse large B-cell lymphoma: a study by the Lunenburg Lymphoma Biomarker Consortium. *J Clin Oncol*. 2019;37(35):3359-3368.

192. Chong LC, Ben-Neriah S, Slack GW, et al. High-resolution architecture and partner genes of MYC rearrangements in lymphoma with DLBCL morphology. *Blood Adv*. 2018;2(20):2755-2765.

193. Allahyar A, Pieterse M, Swennenhuis J, et al. Robust detection of translocations in lymphoma FFPE samples using targeted locus capture-based sequencing. *Nat Commun*. 2021;12(1):3361.

194. Cucco F, Barrans S, Sha C, et al. Distinct genetic changes reveal evolutionary history and heterogeneous molecular grade of DLBCL with MYC/BCL2 double-hit. *Leukemia*. 2020;34(5):1329-1341.

195. Evrard SM, Pericart S, Grand D, et al. Targeted next generation sequencing reveals high mutation frequency of CREBBP, BCL2 and KMT2D in high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements. *Haematologica*. 2019;104(4):e154-e157.

196. Collinge BJ, Hilton LK, Wong J, et al. The mutational landscape of double/triple hit high-grade B-cell lymphoma with *BCL2* rearrangement (DH/TH-*BCL2*) - an LLMPP project. *Hematol Oncol*. 2021;39(S2).

197. Johnson SM, Umakanthan JM, Yuan J, et al. Lymphomas with pseudo-double-hit BCL6-MYC translocations due to t(3;8)(q27;q24) are associated with a germinal center immunophenotype, extranodal involvement, and frequent BCL2 translocations. *Hum Pathol*. 2018;80:192-200.

198. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia*. 2022;36(7):1720-1748.

199. Sha C, Barrans S, Cucco F, et al. Molecular high-grade B-cell lymphoma: defining a poor-risk group that requires different approaches to therapy. *J Clin Oncol*. 2019;37(3):202-212.

200. Collinge BJ, Hilton LK, Wong J, et al. Characterization of the genetic landscape of

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

high-grade B-cell lymphoma,–NOS - an LLMPP project. *Hematol Oncol*. 2021; 39(S2).

201. Richter J, John K, Staiger AM, et al. Epstein-Barr virus status of sporadic Burkitt lymphoma is associated with patient age and mutational features. *Br J Haematol*. 2022;196(3):681-689.

202. Crombie J, LaCasce A. The treatment of Burkitt lymphoma in adults. *Blood*. 2021; 137(6):743-750.

203. Abate F, Ambrosio MR, Mundo L, et al. Distinct viral and mutational spectrum of endemic Burkitt lymphoma. *PLoS Pathog*. 2015;11(10):e1005158.

204. Grande BM, Gerhard DS, Jiang A, et al. Genome-wide discovery of somatic coding and noncoding mutations in pediatric endemic and sporadic Burkitt lymphoma. *Blood*. 2019;133(12):1313-1324.

205. Schmitz R, Young RM, Ceribelli M, et al. Burkitt lymphoma pathogenesis and therapeutic targets from structural and functional genomics. *Nature*. 2012; 490(7418):116-120.

206. Hutcheson RL, Chakravorty A, Sugden B. Burkitt lymphomas evolve to escape dependencies on Epstein-Barr virus. *Front Cell Infect Microbiol*. 2021;10:606412.

207. Newman AM, Zaka M, Zhou P, et al. Genomic abnormalities of TP53 define distinct risk groups of paediatric B-cell non-Hodgkin lymphoma. *Leukemia*. 2022;36(3): 781-789.

208. Gong C, Krupka JA, Gao J, et al. Sequential inverse dysregulation of the RNA helicases DDX3X and DDX3Y facilitates MYC-driven lymphomagenesis. *Mol Cell*. 2021;81(19): 4059-4075.e4011.

209. Schmidt J, Gong S, Marafioti T, et al. Genome-wide analysis of pediatric-type follicular lymphoma reveals low genetic complexity and recurrent alterations of TNFRSF14 gene. *Blood*. 2016;128(8):1101-1111.

210. Martin-Guerrero I, Salaverria I, Burkhardt B, et al. Recurrent loss of heterozygosity in 1p36 associated with TNFRSF14 mutations in IRF4 translocation negative pediatric follicular lymphomas. *Haematologica*. 2013;98(8):1237-1241.

211. Louissaint A Jr, Schafernak KT, Geyer JT, et al. Pediatric-type nodal follicular lymphoma: a biologically distinct lymphoma with frequent MAPK pathway mutations. *Blood*. 2016;128(8):1093-1100.

212. Ozawa MG, Bhaduri A, Chisholm KM, et al. A study of the mutational landscape of pediatric-type follicular lymphoma and pediatric nodal marginal zone lymphoma. *Mod Pathol*. 2016;29(10):1212-1220.

213. Schmidt J, Ramis-Zaldivar JE, Nadeu F, et al. Mutations of MAP2K1 are frequent in pediatric-type follicular lymphoma and result in ERK pathway activation. *Blood*. 2017;130(3):323-327.

214. Salmeron-Villalobos J, Egan C, Borgmann V, et al. PNMZL and PTFL: morphological variants with a common molecular profile - a unifying hypothesis. *Blood Adv*. 2022;6(16):4661-4674.

215. Lim S, Lim KY, Koh J, et al. Pediatric-type indolent B-cell lymphomas with overlapping clinical, pathologic, and genetic features. *Am J Surg Pathol*. 2022.

216. Salaverria I, Philipp C, Oschlies I, et al. Translocations activating IRF4 identify a subtype of germinal center-derived B-cell lymphoma affecting predominantly children and young adults. *Blood*. 2011;118(1):139-147.

217. Klapper W, Kreuz M, Kohler CW, et al. Patient age at diagnosis is associated with the molecular characteristics of diffuse large B-cell lymphoma. *Blood*. 2012;119(8): 1882-1887.

218. Ramis-Zaldivar JE, Gonzalez-Farré B, Balagué O, et al. Distinct molecular profile of IRF4-rearranged large B-cell lymphoma. *Blood*. 2020;135(4):274-286.

219. Salaverria I, Martin-Guerrero I, Burkhardt B, et al. High resolution copy number analysis of IRF4 translocation-positive diffuse large B-cell and follicular lymphomas. *Genes Chromosom Cancer*. 2013;52(2):150-155.

220. Liu Q, Salaverria I, Pittaluga S, et al. Follicular lymphomas in children and young adults: a comparison of the pediatric variant with usual follicular lymphoma. *Am J Surg Pathol*. 2013;37(3):333-343.

221. Frauenfeld L, Castrejon-de-Anta N, Ramis-Zaldivar JE, et al. Diffuse large B-cell lymphomas in adults with aberrant coexpression of CD10, BCL6, and MUM1 are enriched in IRF4 rearrangements. *Blood Adv*. 2022;6(7):2361-2372.

222. Salaverria I, Martin-Guerrero I, Wagener R, et al. A recurrent 11q aberration pattern characterizes a subset of MYC-negative high-grade B-cell lymphomas resembling Burkitt lymphoma. *Blood*. 2014;123(8): 1187-1198.

223. Grygalewicz B, Woroniecka R, Rymkiewicz G, et al. The 11q-gain/loss aberration occurs recurrently in MYC-negative Burkitt-like lymphoma with 11q aberration, as well as MYC-positive Burkitt lymphoma and MYC-positive high-grade B-cell lymphoma, NOS. *Am J Clin Pathol*. 2017;149(1):17-28.

224. Wagener R, Seufert J, Raimondi F, et al. The mutational landscape of Burkitt-like lymphoma with 11q aberration is distinct from that of Burkitt lymphoma. *Blood*. 2019;133(9):962-966.

225. Gonzalez-Farre B, Ramis-Zaldivar JE, Salmeron-Villalobos J, et al. Burkitt-like lymphoma with 11q aberration: a germinal center-derived lymphoma genetically unrelated to Burkitt lymphoma. *Haematologica*. 2019;104(9):1822-1829.

226. Pienkowska-Grela B, Rymkiewicz G, Grygalewicz B, et al. Partial trisomy 11, dup(11)(q23q13), as a defect characterizing lymphomas with Burkitt pathomorphology without MYC gene rearrangement. *Med Oncol*. 2011;28(4):1589-1595.

227. Bonetti P, Testoni M, Scandurra M, et al. Deregulation of ETS1 and FLI1 contributes to the pathogenesis of diffuse large B-cell lymphoma. *Blood*. 2013;122(13):2233-2241.

228. Rinaldi A, Capello D, Scandurra M, et al. Single nucleotide polymorphism-arrays provide new insights in the pathogenesis of post-transplant diffuse large B-cell lymphoma. *Br J Haematol*. 2010;149(4):569-577.

229. Mottok A, Wright G, Rosenwald A, et al. Molecular classification of primary mediastinal large B-cell lymphoma using routinely available tissue specimens. *Blood*. 2018;132(22):2401-2405.

230. Duns G, Viganò E, Ennishi D, et al. Characterization of DLBCL with a PMBL gene expression signature. *Blood*. 2021; 138(2):136-148.

231. Bobee V, Ruminy P, Marchand V, et al. Determination of molecular subtypes of diffuse large B-cell lymphoma using a reverse transcriptase multiplex ligation-dependent probe amplification classifier: a CALYM study. *J Mol Diagn*. 2017;19(6):892-904.

232. Mottok A, Hung SS, Chavez EA, et al. Integrative genomic analysis identifies key pathogenic mechanisms in primary mediastinal large B-cell lymphoma. *Blood*. 2019;134(10):802-813.

233. Chapuy B, Stewart C, Dunford AJ, et al. Genomic analyses of PMBL reveal new drivers and mechanisms of sensitivity to PD-1 blockade. *Blood*. 2019;134(26):2369-2382.

234. Pittaluga S, Nicolae A, Wright GW, et al. Gene expression profiling of mediastinal gray zone lymphoma and its relationship to primary mediastinal B-cell lymphoma and classical Hodgkin lymphoma. *Blood Cancer Discov*. 2020;1(2):155-161.

235. Dunleavy K, Grant C, Eberle FC, Pittaluga S, Jaffe ES, Wilson WH. Gray zone lymphoma: better treated like Hodgkin lymphoma or mediastinal large B-cell lymphoma? *Curr Hematol Malig Rep*. 2012;7(3):241-247.

236. Sarkozy C, Hung SS, Chavez EA, et al. Mutational landscape of gray zone lymphoma. *Blood*. 2021;137(13):1765-1776.

237. Sánchez-Espiridión B, Sánchez-Aguilera A, Montalbán C, et al. A TaqMan low-density array to predict outcome in advanced Hodgkin's lymphoma using paraffin-embedded samples. *Clin Cancer Res*. 2009;15(4):1367-1375.

238. Scott DW, Chan FC, Hong F, et al. Gene expression-based model using formalin-fixed paraffin-embedded biopsies predicts overall survival in advanced-stage classical Hodgkin lymphoma. *J Clin Oncol*. 2013; 31(6):692-700.

239. Jachimowicz RD, Klapper W, Glehr G, et al. Gene expression-based outcome prediction

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

in advanced stage classical Hodgkin lymphoma treated with BEACOPP. *Leukemia*. 2021;35(12):3589-3593.

240. Burton CH, Scott D, Kirkwood AA, et al. Application of a gene expression-based model in combination with FDG-PET imaging to predict treatment response in advanced Hodgkin lymphoma in the RATHL study (CRUK/07/03). *Hematol Oncol*. 2017;35(S2).

241. Scott DW, Li H, Harvey Y, et al. The 23-gene gene expression-based assay does not predict interim PET scan results after ABVD in advanced stage classical Hodgkin lymphoma in the US Intergroup S0816 trial. *Hematol Oncol*. 2017;35(S2).

242. Chan FC, Mottok A, Gerrie AS, et al. Prognostic model to predict post-autologous stem-cell transplantation outcomes in classical Hodgkin lymphoma. *J Clin Oncol*. 2017;35(32):3722-3733.

243. Johnston RL, Mottok A, Chan FC, et al. A gene expression–based model predicts outcome in children with intermediate-risk classical Hodgkin lymphoma. *Blood*. 2022; 139(6):889-893.

244. Calvente L, Tremblay-LeMay R, Xu W, et al. Validation of the RHL30 digital gene expression assay as a prognostic biomarker for relapsed Hodgkin lymphoma. *Br J Haematol*. 2020;190(6):864-868.

245. Tiacci E, Ladewig E, Schiavoni G, et al. Pervasive mutations of JAK-STAT pathway genes in classical Hodgkin lymphoma. *Blood*. 2018;131(22):2454-2465.

246. Spina V, Bruscaggin A, Cuccaro A, et al. Circulating tumor DNA reveals genetics, clonal evolution, and residual disease in classical Hodgkin lymphoma. *Blood*. 2018; 131(22):2413-2425.

247. Wienand K, Chapuy B, Stewart C, et al. Genomic analyses of flow-sorted Hodgkin Reed-Sternberg cells reveal complementary mechanisms of immune evasion. *Blood Adv*. 2019;3(23):4065-4080.

248. Roemer MGM, Redd RA, Cader FZ, et al. Major histocompatibility complex class II and programmed death ligand 1 expression predict outcome after programmed death 1 blockade in classic Hodgkin lymphoma. *J Clin Oncol*. 2018;36(10):942-950.

249. Sobesky S, Mammadova L, Cirillo M, et al. In-depth cell-free DNA sequencing reveals genomic landscape of Hodgkin's lymphoma and facilitates ultrasensitive residual disease detection. *Med*. 2021;2(10):1171-1193.e1111.

250. Foss H, Anagnostopoulos I, Araujo I, et al. Anaplastic large-cell lymphomas of T-cell and null-cell phenotype express cytotoxic molecules. *Blood*. 1996;88(10):4005-4011.

251. Benharroch D, Meguerian-Bedoyan Z, Lamant L, et al. ALK-positive lymphoma: a single disease with a broad spectrum of morphology. *Blood*. 1998;91(6):2076-2084.

252. Melchers RC, Willemze R, Bekkenk MW, et al. Frequency and prognosis of associated malignancies in 504 patients with lymphomatoid papulosis. *J Eur Acad Dermatol Venereol*. 2020;34(2):260-266.

253. Melchers RC, Willemze R, van de Loo M, et al. Clinical, histologic, and molecular characteristics of anaplastic lymphoma kinase-positive primary cutaneous anaplastic large cell lymphoma. *Am J Surg Pathol*. 2020;44(6):776-781.

254. Prokoph N, Larose H, Lim MS, Burke GAA, Turner SD. Treatment options for paediatric anaplastic large cell lymphoma (ALCL): current standard and beyond. *Cancers (Basel)*. 2018;10(4):99.

255. Larose H, Prokoph N, Matthews JD, et al. Whole exome sequencing reveals NOTCH1 mutations in anaplastic large cell lymphoma and points to Notch both as a key pathway and a potential therapeutic target. *Haematologica*. 2021;106(6):1693-1704.

256. Parrilla Castellar ER, Jaffe ES, Said JW, et al. ALK-negative anaplastic large cell lymphoma is a genetically heterogeneous disease with widely disparate clinical outcomes. *Blood*. 2014;124(9):1473-1480.

257. Pedersen MB, Hamilton-Dutoit SJ, Bendix K, et al. DUSP22 and TP63 rearrangements predict outcome of ALK-negative anaplastic large cell lymphoma: a Danish cohort study. *Blood*. 2017;130(4):554-557.

258. Luchtel RA, Zimmermann MT, Hu G, et al. Recurrent MSCE116K mutations in ALK-negative anaplastic large cell lymphoma. *Blood*. 2019;133(26):2776-2789.

259. Hapgood G, Ben-Neriah S, Mottok A, et al. Identification of high-risk DUSP22-rearranged ALK-negative anaplastic large cell lymphoma. *Br J Haematol*. 2019;186(3): e28-e31.

260. Feldman AL, Dogan A, Smith DI, et al. Discovery of recurrent t(6;7)(p25.3;q32.3) translocations in ALK-negative anaplastic large cell lymphomas by massively parallel genomic sequencing. *Blood*. 2011;117(3): 915-919.

261. Luchtel RA, Dasari S, Oishi N, et al. Molecular profiling reveals immunogenic cues in anaplastic large cell lymphomas with DUSP22 rearrangements. *Blood*. 2018; 132(13):1386-1398.

262. Karai LJ, Kadin ME, Hsi ED, et al. Chromosomal rearrangements of 6p25.3 define a new subtype of lymphomatoid papulosis. *Am J Surg Pathol*. 2013;37(8): 1173-1181.

263. Wada DA, Law ME, Hsi ED, et al. Specificity of IRF4 translocations for primary cutaneous anaplastic large cell lymphoma: a multicenter study of 204 skin biopsies. *Mod Pathol*. 2011;24(4):596-605.

264. Fauconneau A, Pham-Ledard A, Cappellen D, et al. Assessment of diagnostic criteria between primary cutaneous anaplastic large-cell lymphoma and CD30-rich transformed mycosis fungoides; a study of 66 cases. *Br J Dermatol*. 2015;172(6): 1547-1554.

265. Vasmatzis G, Johnson SH, Knudson RA, et al. Genome-wide analysis reveals recurrent structural abnormalities of TP63 and other p53-related genes in peripheral T-cell lymphomas. *Blood*. 2012;120(11):2280-2289.

266. Boi M, Rinaldi A, Kwee I, et al. PRDM1/BLIMP1 is commonly inactivated in anaplastic large T-cell lymphoma. *Blood*. 2013;122(15):2683-2693.

267. Klairmont MM, Ward N. Co-occurring rearrangements of DUSP22 and TP63 define a rare genetic subset of ALK-negative anaplastic large cell lymphoma with inferior survival outcomes. *Leuk Lymphoma*. 2022;63(2):506-508.

268. Scarfò I, Pellegrino E, Mereu E, et al. Identification of a new subclass of ALK-negative ALCL expressing aberrant levels of ERBB4 transcripts. *Blood*. 2016;127(2):221-232.

269. Chiarle R, Simmons WJ, Cai H, et al. Stat3 is required for ALK-mediated lymphomagenesis and provides a possible therapeutic target. *Nat Med*. 2005;11(6): 623-629.

270. Crescenzo R, Abate F, Lasorsa E, et al. Convergent mutations and kinase fusions lead to oncogenic STAT3 activation in anaplastic large cell lymphoma. *Cancer Cell*. 2015;27(4):516-532.

271. Fitzpatrick MJ, Massoth LR, Marcus C, et al. JAK2 rearrangements are a recurrent alteration in CD30+ systemic T-cell lymphomas with anaplastic morphology. *Am J Surg Pathol*. 2021;45(7):895-904.

272. Hu G, Dasari S, Asmann YW, et al. Targetable fusions of the FRK tyrosine kinase in ALK-negative anaplastic large cell lymphoma. *Leukemia*. 2018;32(2):565-569.

273. Lobello C, Tichy B, Bystry V, et al. STAT3 and TP53 mutations associate with poor prognosis in anaplastic large cell lymphoma. *Leukemia*. 2021;35(5):1500-1505.

274. Velusamy T, Kiel MJ, Sahasrabuddhe AA, et al. A novel recurrent NPM1-TYK2 gene fusion in cutaneous CD30-positive lymphoproliferative disorders. *Blood*. 2014;124(25):3768-3771.

275. Quesada AE, Zhang Y, Ptashkin R, et al. Next generation sequencing of breast implant-associated anaplastic large cell lymphomas reveals a novel STAT3-JAK2 fusion among other activating genetic alterations within the JAK-STAT pathway. *Breast J*. 2021;27(4):314-321.

276. Laurent C, Nicolae A, Laurent C, et al. Gene alterations in epigenetic modifiers and JAK-STAT signaling are frequent in breast implant–associated ALCL. *Blood*. 2020; 135(5):360-370.

277. Los-de Vries GT, de Boer M, van Dijk E, et al. Chromosome 20 loss is characteristic of breast implant–associated anaplastic large cell lymphoma. *Blood*. 2020;136(25): 2927-2932.

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

278. Moskowitz AJ, Ghione P, Jacobsen E, et al. A phase 2 biomarker-driven study of ruxolitinib demonstrates effectiveness of JAK/STAT targeting in T-cell lymphomas. *Blood*. 2021;138(26):2828-2837.

279. Vallois D, Dobay MPD, Morin RD, et al. Activating mutations in genes related to TCR signaling in angioimmunoblastic and other follicular helper T-cell–derived lymphomas. *Blood*. 2016;128(11):1490-1502.

280. Heavican TB, Bouska A, Yu J, et al. Genetic drivers of oncogenic pathways in molecular subgroups of peripheral T-cell lymphoma. *Blood*. 2019;133(15):1664-1676.

281. Maura F, Dodero A, Carniti C, et al. CDKN2A deletion is a frequent event associated with poor outcome in patients with peripheral T-cell lymphoma not otherwise specified (PTCL-NOS). *Haematologica*. 2020;106(11):2918-2926.

282. Drieux F, Ruminy P, Sater V, et al. Detection of gene fusion transcripts in peripheral T-cell lymphoma using a multiplexed targeted sequencing assay. *J Mol Diagn*. 2021;23(8):929-940.

283. Debackere K, Marcelis L, Demeyer S, et al. Fusion transcripts FYN-TRAF3IP2 and KHDRBS1-LCK hijack T cell receptor signaling in peripheral T-cell lymphoma, not otherwise specified. *Nat Commun*. 2021;12(1):3705.

284. Watatani Y, Sato Y, Miyoshi H, et al. Molecular heterogeneity in peripheral T-cell lymphoma, not otherwise specified revealed by comprehensive genetic profiling. *Leukemia*. 2019;33(12):2867-2883.

285. Syrykh C, Gorez P, Péricart S, et al. Molecular diagnosis of T-cell lymphoma: a correlative study of PCR-based T-cell clonality assessment and targeted NGS. *Blood Adv*. 2021;5(22):4590-4593.

286. Dobson R, Du PY, Rásó-Barnett L, et al. Early detection of T-cell lymphoma with T follicular helper phenotype by RHOA mutation analysis. *Haematologica*. 2021;107(2):489-499.

287. Nicolae A, Bouilly J, Lara D, et al. Nodal cytotoxic peripheral T-cell lymphoma occurs frequently in the clinical setting of immunodysregulation and is associated with recurrent epigenetic alterations. *Mod Pathol*. 2022;35(8):1126-1136.

288. Genovese G, Kähler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N Engl J Med*. 2014;371(26):2477-2487.

289. Tiacci E, Venanzi A, Ascani S, et al. High-risk clonal hematopoiesis as the origin of AITL and NPM1-mutated AML. *N Engl J Med*. 2018;379(10):981-984.

290. Lewis NE, Petrova-Drus K, Huet S, et al. Clonal hematopoiesis in angioimmunoblastic T-cell lymphoma with divergent evolution to myeloid neoplasms. *Blood Adv*. 2020;4(10):2261-2271.

291. Lemonnier F, Dupuis J, Sujobert P, et al. Treatment with 5-azacytidine induces a sustained response in patients with angioimmunoblastic T-cell lymphoma. *Blood*. 2018;132(21):2305-2309.

292. Ghione P, Faruque P, Mehta-Shah N, et al. T follicular helper phenotype predicts response to histone deacetylase inhibitors in relapsed/refractory peripheral T-cell lymphoma. *Blood Adv*. 2020;4(19):4640-4647.

293. Falchi L, Ma H, Klein S, et al. Combined oral 5-azacytidine and romidepsin are highly effective in patients with PTCL: a multicenter phase 2 study. *Blood*. 2021;137(16):2161-2170.

294. Küçük C, Jiang B, Hu X, et al. Activating mutations of STAT5B and STAT3 in lymphomas derived from γδ-T or NK cells. *Nat Commun*. 2015;6(1):6025.

295. Hu G, Phillips JL, Dasari S, et al. Targetability of STAT3-JAK2 fusions: implications for T-cell lymphoproliferative disorders of the gastrointestinal tract. *Leukemia*. 2020;34(5):1467-1471.

296. Xiao W, Gupta GK, Yao J, et al. Recurrent somatic JAK3 mutations in NK-cell enteropathy. *Blood*. 2019;134(12):986-991.

297. Sharma A, Oishi N, Boddicker RL, et al. Recurrent STAT3-JAK2 fusions in indolent T-cell lymphoproliferative disorder of the gastrointestinal tract. *Blood*. 2018;131(20):2262-2266.

298. Craig RS, Nupam P, Vundavalli VM, et al. Genetic and phenotypic characterization of indolent T-cell lymphoproliferative disorders of the gastrointestinal tract. *Haematologica*. 2020;105(7):1895-1906.

299. Montes-Moreno S, King RL, Oschlies I, et al. Update on lymphoproliferative disorders of the gastrointestinal tract: disease spectrum from indolent lymphoproliferations to aggressive lymphomas. *Virchows Arch*. 2020;476(5):667-681.

300. Roberti A, Dobay MP, Bisig B, et al. Type II enteropathy-associated T-cell lymphoma features a unique genomic profile with highly recurrent SETD2 alterations. *Nat Commun*. 2016;7:12602.

301. Moffitt AB, Ondrejka SL, McKinney M, et al. Enteropathy-associated T cell lymphoma subtypes are characterized by loss of function of SETD2. *J Exp Med*. 2017;214(5):1371-1386.

302. Tomita S, Kikuti YY, Carreras J, et al. Monomorphic epitheliotropic intestinal T-cell lymphoma in Asia frequently shows SETD2 alterations. *Cancers (Basel)*. 2020;12(12):3539.

303. Veloza L, Cavalieri D, Missiaglia E, et al. Monomorphic epitheliotropic intestinal T-cell lymphoma comprises morphologic and genomic heterogeneity impacting outcome. *Haematologica*. 2022.

304. Cording S, Lhermitte L, Malamut G, et al. Oncogenetic landscape of lymphomagenesis in coeliac disease. *Gut*. 2022;71(3):497-508.

305. Verkarre V, Romana SP, Cellier C, et al. Recurrent partial trisomy 1q22-q44 in clonal intraepithelial lymphocytes in refractory celiac sprue. *Gastroenterology*. 2003;125(1):40-46.

306. Soderquist CR, Lewis SK, Gru AA, et al. Immunophenotypic spectrum and genomic landscape of refractory celiac disease type II. *Am J Surg Pathol*. 2021;45(7):905-916.

307. Tometten I, Felgentreff K, Hönig M, et al. Increased proportions of γδ T lymphocytes in atypical SCID associate with disease manifestations. *Clin Immunol*. 2019;201:30-34.

308. Roden AC, Morice WG, Hanson CA. Immunophenotypic attributes of benign peripheral blood gammadelta T cells and conditions associated with their increase. *Arch Pathol Lab Med*. 2008;132(11):1774-1780.

309. Zhang S, Bayerl MG. Florid splenic γ/δ T-cell proliferation in patients with splenomegaly and cytopenias: a "high stakes" diagnostic challenge. *Hum Pathol*. 2017;66:216-221.

310. Wlodarska I, Martin-Garcia N, Achten R, et al. Fluorescence in situ hybridization study of chromosome 7 aberrations in hepatosplenic T-cell lymphoma: isochromosome 7q as a common abnormality accumulating in forms with features of cytologic progression. *Genes Chromosom Cancer*. 2002;33(3):243-251.

311. Weidmann E. Hepatosplenic T cell lymphoma. A review on 45 cases since the first report describing the disease as a distinct lymphoma entity in 1990. *Leukemia*. 2000;14(6):991-997.

312. Pro B, Allen P, Behdad A. Hepatosplenic T-cell lymphoma: a rare but challenging entity. *Blood*. 2020;136(18):2018-2026.

313. Nicolae A, Xi L, Pittaluga S, et al. Frequent STAT5B mutations in γδ hepatosplenic T-cell lymphomas. *Leukemia*. 2014;28(11):2244-2248.

314. McKinney M, Moffitt AB, Gaulard P, et al. The genetic basis of hepatosplenic T-cell lymphoma. *Cancer Discov*. 2017;7(4):369-379.

315. Hong M, Lee T, Young Kang S, Kim S-J, Kim W, Ko Y-H. Nasal-type NK/T-cell lymphomas are more frequently T rather than NK lineage based on T-cell receptor gene, RNA, and protein studies: lineage does not predict clinical behavior. *Mod Pathol*. 2016;29(5):430-443.

316. Li Z, Xia Y, Feng LN, et al. Genetic risk of extranodal natural killer T-cell lymphoma: a genome-wide association study. *Lancet Oncol*. 2016;17(9):1240-1247.

317. Lin GW, Xu C, Chen K, et al. Genetic risk of extranodal natural killer T-cell lymphoma: a genome-wide association study in multiple populations. *Lancet Oncol*. 2020;21(2):306-316.

318. Tian X-P, Ma S-Y, Young KH, et al. A composite single-nucleotide polymorphism prediction signature for

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

extranodal natural killer/T-cell lymphoma. *Blood*. 2021;138(6):452-463.

319. Jiang L, Gu Z-H, Yan Z-X, et al. Exome sequencing identifies somatic mutations of DDX3X in natural killer/T-cell lymphoma. *Nat Genet*. 2015;47(9):1061-1066.

320. Koo GC, Tan SY, Tang T, et al. Janus kinase 3-activating mutations identified in natural killer/T-cell lymphoma. *Cancer Discov*. 2012;2(7):591-597.

321. Lee S, Park HY, Kang SY, et al. Genetic alterations of JAK/STAT cascade and histone modification in extranodal NK/T-cell lymphoma nasal type. *Oncotarget*. 2015;6(19):17764-17776.

322. Song TL, Nairismägi M-L, Laurensia Y, et al. Oncogenic activation of the STAT3 pathway drives PD-L1 expression in natural killer/T-cell lymphoma. *Blood*. 2018;132(11):1146-1158.

323. Montes-Mojarro IA, Chen BJ, Ramirez-Ibarguen AF, et al. Mutational profile and EBV strains of extranodal NK/T-cell lymphoma, nasal type in Latin America. *Mod Pathol*. 2020;33(5):781-791.

324. Dong G, Liu X, Wang L, et al. Genomic profiling identifies distinct genetic subtypes in extra-nodal natural killer/T-cell lymphoma. *Leukemia*. 2022;36(8):2064-2075.

325. Gao Y, Li Y, Ma G, Zhao G, Liu H. KMT2D and TP53 mutation status improve the prognostic value of the International Prognostic Index (IPI) stratification in ENKTL patients. *Neoplasma*. 2020;67(3):636-643.

326. Xiong J, Cui BW, Wang N, et al. Genomic and transcriptomic characterization of natural killer T cell lymphoma. *Cancer Cell*. 2020;37(3):403-419.e406.

327. Arai A. Chronic active Epstein-Barr virus infection: the elucidation of the pathophysiology and the development of therapeutic methods. *Microorganisms*. 2021;9(1):180.

328. El Hussein S, Medeiros LJ, Khoury JD. Aggressive NK cell leukemia: current state of the art. *Cancers (Basel)*. 2020;12(10): 2900.

329. Kataoka K, Miyoshi H, Sakata S, et al. Frequent structural variations involving programmed death ligands in Epstein-Barr virus-associated lymphomas. *Leukemia*. 2019;33(7):1687-1699.

330. Lim JQ, Huang D, Tang T, et al. Whole-genome sequencing identifies responders to pembrolizumab in relapse/refractory natural-killer/T cell lymphoma. *Leukemia*. 2020;34(12):3413-3419.

331. Kwong Y-L, Chan TSY, Tan D, et al. PD1 blockade with pembrolizumab is highly effective in relapsed or refractory NK/T-cell lymphoma failing l-asparaginase. *Blood*. 2017;129(17):2437-2442.

332. Li X, Cheng Y, Zhang M, et al. Activity of pembrolizumab in relapsed/refractory NK/T-cell lymphoma. *J Hematol Oncol*. 2018; 11(1):15.

333. Cho J, Kim SJ, Park WY, et al. Immune subtyping of extranodal NK/T-cell lymphoma: a new biomarker and an immune shift during disease progression. *Mod Pathol*. 2020;33(4):603-615.

334. Gayden T, Sepulveda FE, Khuong-Quang DA, et al. Germline HAVCR2 mutations altering TIM-3 characterize subcutaneous panniculitis-like T cell lymphomas with hemophagocytic lymphohistiocytic syndrome. *Nat Genet*. 2018;50(12):1650-1657.

335. Sonigo G, Battistella M, Beylot-Barry M, et al. HAVCR2 mutations are associated with severe hemophagocytic syndrome in subcutaneous panniculitis-like T-cell lymphoma. *Blood*. 2020;135(13):1058-1061.

336. Koh J, Jang I, Mun S, et al. Genetic profiles of subcutaneous panniculitis-like T-cell lymphoma and clinicopathological impact of HAVCR2 mutations. *Blood Adv*. 2021;5(20): 3919-3930.

337. Cook LB, Melamed A, Niederer H, et al. The role of HTLV-1 clonality, proviral structure, and genomic integration site in adult T-cell leukemia/lymphoma. *Blood*. 2014;123(25): 3925-3931.

338. Kataoka K, Nagata Y, Kitanaka A, et al. Integrated molecular analysis of adult T cell leukemia/lymphoma. *Nat Genet*. 2015; 47(11):1304-1315.

339. Kogure Y, Kameda T, Koya J, et al. Whole-genome landscape of adult T-cell leukemia/lymphoma. *Blood*. 2022;139(7):967-982.

340. Marçais A, Lhermitte L, Artesi M, et al. Targeted deep sequencing reveals clonal and subclonal mutational signatures in adult T-cell leukemia/lymphoma and defines an unfavorable indolent subtype. *Leukemia*. 2021;35(3):764-776.

341. Kataoka K, Shiraishi Y, Takeda Y, et al. Aberrant PD-L1 expression through 3′-UTR disruption in multiple cancers. *Nature*. 2016;534(7607):402-406.

342. Nakagawa M, Schmitz R, Xiao W, et al. Gain-of-function CCR4 mutations in adult T cell leukemia/lymphoma. *J Exp Med*. 2014; 211(13):2497-2505.

343. Kataoka K, Iwanaga M, Iasunaga J-i, et al. Prognostic relevance of integrated genetic profiling in adult T-cell leukemia/lymphoma. *Blood*. 2018;131(2):215-225.

344. Sakamoto Y, Ishida T, Masaki A, et al. CCR4 mutations associated with superior outcome of adult T-cell leukemia/lymphoma under mogamulizumab treatment. *Blood*. 2018; 132(7):758-761.

345. Tanaka N, Mori S, Kiyotani K, et al. Genomic determinants impacting the clinical outcome of mogamulizumab treatment for adult T-cell leukemia/lymphoma. *Haematologica*. 2022.

346. Sakamoto Y, Ishida T, Masaki A, et al. Clinical significance of TP53 mutations in adult T-cell leukemia/lymphoma. *Br J Haematol*. 2021;195(4):571-584.

347. Koskela HLM, Eldfors S, Ellonen P, et al. Somatic STAT3 mutations in large granular lymphocytic leukemia. *N Engl J Med*. 2012; 366(20):1905-1913.

348. Rajala HLM, Eldfors S, Kuusanmäki H, et al. Discovery of somatic STAT5b mutations in large granular lymphocytic leukemia. *Blood*. 2013;121(22):4541-4550.

349. Teramo A, Barilà G, Calabretto G, et al. STAT3 mutation impacts biological and clinical features of T-LGL leukemia. *Oncotarget*. 2017;8(37):61876-61889.

350. Bhattacharya D, Teramo A, Gasparini VR, et al. Identification of novel STAT5B mutations and characterization of TCRβ signatures in CD4+ T-cell large granular lymphocyte leukemia. *Blood Cancer J*. 2022;12(2):31.

351. Andersson EI, Tanahashi T, Sekiguchi N, et al. High incidence of activating STAT5B mutations in CD4-positive T-cell large granular lymphocyte leukemia. *Blood*. 2016; 128(20):2465-2468.

352. Barilà G, Teramo A, Calabretto G, et al. Stat3 mutations impact on overall survival in large granular lymphocyte leukemia: a single-center experience of 205 patients. *Leukemia*. 2020;34(4):1116-1124.

353. Teramo A, Barilà G, Calabretto G, et al. Insights into genetic landscape of large granular lymphocyte leukemia. *Front Oncol*. 2020;10:152-159.

354. Shi M, He R, Feldman AL, et al. STAT3 mutation and its clinical and histopathologic correlation in T-cell large granular lymphocytic leukemia. *Hum Pathol*. 2018; 73:74-81.

355. Muñoz-García N, Jara-Acevedo M, Caldas C, et al. STAT3 and STAT5B mutations in T/NK-cell chronic lymphoproliferative disorders of large granular lymphocytes (LGL): association with disease features. *Cancers (Basel)*. 2020; 12(12):3508-3530.

356. Jerez A, Clemente MJ, Makishima H, et al. STAT3 mutations unify the pathogenesis of chronic lymphoproliferative disorders of NK cells and T-cell large granular lymphocyte leukemia. *Blood*. 2012;120(15):3048-3057.

357. Baer C, Kimura S, Rana MS, et al. CCL22 mutations drive natural killer cell lymphoproliferative disease by deregulating microenvironmental crosstalk. *Nat Genet*. 2022;54(5):637-648.

358. Gasparini VR, Binatti A, Coppe A, et al. A high definition picture of somatic mutations in chronic lymphoproliferative disorder of natural killer cells. *Blood Cancer J*. 2020;10(4):42-52.

359. Pastoret C, Desmots F, Drillet G, et al. Linking the KIR phenotype with STAT3 and TET2 mutations to identify chronic lymphoproliferative disorders of NK cells. *Blood*. 2021;137(23):3237-3250.

360. Olson TL, Cheon H, Xing JC, et al. Frequent somatic TET2 mutations in chronic NK-LGL

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

leukemia with distinct patterns of cytopenias. *Blood*. 2021;138(8):662-673.

361. Kawakami T, Sekiguchi N, Kobayashi J, et al. STAT3 mutations in natural killer cells are associated with cytopenia in patients with chronic lymphoproliferative disorder of natural killer cells. *Int J Hematol*. 2019;109(5):563-571.

362. Sun Y, Tang G, Hu Z, et al. Comparison of karyotyping, TCL1 fluorescence in situ hybridisation and TCL1 immunohistochemistry in T cell prolymphocytic leukaemia. *J Clin Pathol*. 2018;71(4):309-315.

363. Virgilio L, Lazzeri C, Bichi R, et al. Deregulated expression of *TCL1* causes T cell leukemia in mice. *Proc Natl Acad Sci U S A*. 1998;95(7):3885-3889.

364. Gritti C, Dastot H, Soulier J, et al. Transgenic mice for MTCP1 develop T-cell prolymphocytic leukemia. *Blood*. 1998;92(2):368-373.

365. Herling M, Patel KA, Teitell MA, et al. High TCL1 expression and intact T-cell receptor signaling define a hyperproliferative subset of T-cell prolymphocytic leukemia. *Blood*. 2008;111(1):328-337.

366. Hu Z, Medeiros LJ, Fang L, et al. Prognostic significance of cytogenetic abnormalities in T-cell prolymphocytic leukemia. *Am J Hematol*. 2017;92(5):441-447.

367. Stilgenbauer S, Schaffner C, Litterst A, et al. Biallelic mutations in the ATM gene in T-prolymphocytic leukemia. *Nat Med*. 1997;3(10):1155-1159.

368. Stoppa-Lyonnet D, Soulier J, Laugé A, et al. Inactivation of the ATM gene in T-cell prolymphocytic leukemias. *Blood*. 1998;91(10):3920-3926.

369. Schrader A, Crispatzu G, Oberbeck S, et al. Actionable perturbations of damage responses by TCL1/ATM and epigenetic lesions form the basis of T-PLL. *Nat Commun*. 2018;9(1):697.

370. Andersson EI, Pützer S, Yadav B, et al. Discovery of novel drug sensitivities in T-PLL by high-throughput ex vivo drug testing and mutation profiling. *Leukemia*. 2018;32(3):774-787.

371. Wahnschaffe L, Braun T, Timonen S, et al. JAK/STAT-activating genomic alterations are a hallmark of T-PLL. *Cancers (Basel)*. 2019;11(12):1833.

372. Berres M-L, Lim KPH, Peters T, et al. BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. *J Exp Med*. 2014;211(4):669-683.

373. Milne P, Bigley V, Bacon CM, et al. Hematopoietic origin of Langerhans cell histiocytosis and Erdheim-Chester disease in adults. *Blood*. 2017;130(2):167-175.

374. Allen CE, Merad M, McClain KL. Langerhans-cell histiocytosis. *N Engl J Med*. 2018;379(9):856-868.

375. McClain KL, Bigenwald C, Collin M, et al. Histiocytic disorders. *Nat Rev Dis Primers*. 2021;7(1):73.

376. Badalian-Very G, Vergilio J-A, Degar BA, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood*. 2010;116(11):1919-1923.

377. Haroche J, Cohen-Aubart F, Emile J-F, et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. *Blood*. 2013;121(9):1495-1500.

378. Brown NA, Furtado LV, Betz BL, et al. High prevalence of somatic MAP2K1 mutations in BRAF V600E–negative Langerhans cell histiocytosis. *Blood*. 2014;124(10):1655-1658.

379. Chakraborty R, Burke TM, Hampton OA, et al. Alternative genetic mechanisms of BRAF activation in Langerhans cell histiocytosis. *Blood*. 2016;128(21):2533-2537.

380. Facchetti F, Pileri SA, Lorenzi L, et al. Histiocytic and dendritic cell neoplasms: what have we learnt by studying 67 cases. *Virchows Arch*. 2017;471(4):467-489.

381. Garces S, Medeiros LJ, Patel KP, et al. Mutually exclusive recurrent KRAS and MAP2K1 mutations in Rosai-Dorfman disease. *Mod Pathol*. 2017;30(10):1367-1377.

382. Durham BH, Lopez Rodrigo E, Picarsic J, et al. Activating mutations in CSF1R and additional receptor tyrosine kinases in histiocytic neoplasms. *Nat Med*. 2019;25(12):1839-1842.

383. Shanmugam V, Griffin GK, Jacobsen ED, Fletcher CDM, Sholl LM, Hornick JL. Identification of diverse activating mutations of the RAS-MAPK pathway in histiocytic sarcoma. *Mod Pathol*. 2019;32(6):830-843.

384. Egan C, Nicolae A, Lack J, et al. Genomic profiling of primary histiocytic sarcoma reveals two molecular subgroups. *Haematologica*. 2020;105(4):951-960.

385. Haroche J, Cohen-Aubart F, Amoura Z. Erdheim-Chester disease. *Blood*. 2020;135(16):1311-1318.

386. Sengal A, Velazquez J, Hahne M, et al. Overcoming T-cell exhaustion in LCH: PD-1 blockade and targeted MAPK inhibition are synergistic in a mouse model of LCH. *Blood*. 2021;137(13):1777-1791.

387. Gatalica Z, Bilalovic N, Palazzo JP, et al. Disseminated histiocytoses biomarkers beyond BRAFV600E: frequent expression of PD-L1. *Oncotarget*. 2015;6(23):19819-19825.

388. Kemps PG, Picarsic J, Durham BH, et al. ALK-positive histiocytosis: a new clinicopathologic spectrum highlighting neurologic involvement and responses to ALK inhibition. *Blood*. 2022;139(2):256-280.

389. Chakraborty R, Hampton OA, Shen X, et al. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. *Blood*. 2014;124(19):3007-3015.

390. Nelson DS, Quispel W, Badalian-Very G, et al. Somatic activating ARAF mutations in Langerhans cell histiocytosis. *Blood*. 2014;123(20):3152-3155.

391. Chakraborty R, Abdel-Wahab O, Durham BH. MAP-kinase-driven hematopoietic neoplasms: a decade of progress in the molecular age. *Cold Spring Harb Perspect Med*. 2021;11(5):a034892.

392. Milne P, Abhyankar HA, Scull BP, et al. Cellular distribution of mutations and association with disease risk in Langerhans cell histiocytosis without BRAFV600E. *Blood Adv*. 2022;6(16):4901-4904.

393. Feldman AL, Arber DA, Pittaluga S, et al. Clonally related follicular lymphomas and histiocytic/dendritic cell sarcomas: evidence for transdifferentiation of the follicular lymphoma clone. *Blood*. 2008;111(12):5433-5439.

394. Shao H, Xi L, Raffeld M, et al. Clonally related histiocytic/dendritic cell sarcoma and chronic lymphocytic leukemia/small lymphocytic lymphoma: a study of seven cases. *Mod Pathol*. 2011;24(11):1421-1432.

395. Cohen Aubart F, Roos-Weil D, Armand M, et al. High frequency of clonal hematopoiesis in Erdheim-Chester disease. *Blood*. 2021;137(4):485-492.

396. McClain KL, Picarsic J, Chakraborty R, et al. CNS Langerhans cell histiocytosis: common hematopoietic origin for LCH-associated neurodegeneration and mass lesions. *Cancer*. 2018;124(12):2607-2620.

397. Massoth LR, Hung YP, Ferry JA, et al. Histiocytic and dendritic cell sarcomas of hematopoietic origin share targetable genomic alterations distinct from follicular dendritic cell sarcoma. *Oncol*. 2021;26(7):e1263-e1272.

398. Griffin GK, Sholl LM, Lindeman NI, Fletcher CD, Hornick JL. Targeted genomic sequencing of follicular dendritic cell sarcoma reveals recurrent alterations in NF-κB regulatory genes. *Mod Pathol*. 2016;29(1):67-74.

399. Laginestra MA, Tripodo C, Agostinelli C, et al. Distinctive histogenesis and immunological microenvironment based on transcriptional profiles of follicular dendritic Cell sarcomas. *Mol Cancer Res*. 2017;15(5):541-552.

400. Diamond EL, Subbiah V, Lockhart AC, et al. Vemurafenib for BRAF V600-mutant Erdheim-Chester disease and Langerhans cell histiocytosis: analysis of data from the histology-independent, phase 2, open-label VE-BASKET study. *JAMA Oncol*. 2018;4(3):384-388.

401. Diamond EL, Durham BH, Ulaner GA, et al. Efficacy of MEK inhibition in patients with histiocytic neoplasms. *Nature*. 2019;567(7749):521-524.

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

402. Donadieu J, Larabi IA, Tardieu M, et al. Vemurafenib for refractory multisystem Langerhans cell histiocytosis in children: an international observational study. *J Clin Oncol*. 2019;37(31):2857-2865.

403. Eckstein OS, Visser J, Rodriguez-Galindo C, Allen CE; Group tN-LS. Clinical responses and persistent BRAF V600E+ blood cells in children with LCH treated with MAPK pathway inhibition. *Blood*. 2019;133(15):1691-1694.

404. Schwentner R, Kolenová A, Jug G, et al. Longitudinal assessment of peripheral blood BRAFV600E levels in patients with Langerhans cell histiocytosis. *Pediatr Res*. 2019;85(6):856-864.

405. Hyman DM, Diamond EL, Vibat CR, et al. Prospective blinded study of BRAFV600E mutation detection in cell-free DNA of patients with systemic histiocytic disorders. *Cancer Discov*. 2015;5(1):64-71.

406. Cohen Aubart F, Emile JF, Carrat F, et al. Targeted therapies in 54 patients with Erdheim-Chester disease, including follow-up after interruption (the LOVE study). *Blood*. 2017;130(11):1377-1380.

407. Arthur SE, Jiang A, Grande BM, et al. Genome-wide discovery of somatic regulatory variants in diffuse large B-cell lymphoma. *Nat Commun*. 2018;9(1):4001.

408. Hübschmann D, Kleinheinz K, Wagener R, et al. Mutational mechanisms shaping the coding and noncoding genome of germinal center derived B-cell lymphomas. *Leukemia*. 2021;35(7):2002-2016.

409. Morin RD, Arthur SE, Hodson DJ. Molecular profiling in diffuse large B-cell lymphoma: why so many types of subtypes? *Br J Haematol*. 2022;196(4):814-829.

410. Hilton LK, Dreval K, Soudi S, et al. Constrained FL: a genetically distinct subgroup of follicular lymphoma with low rates of somatic hypermutation and a reduced propensity for histologic transformation. *Blood*. 2021;138(S1). Abstract 807.

411. Thomas N, Dreval K, Gerhard DS, et al. Genetic subgroups inform on pathobiology in adult and pediatric Burkitt lymphoma. *medRxiv*. Preprint posted online 8 December 2021. https://doi.org/10.1101/2021.12.05.21267216

412. Fuster C, Martín-Garcia D, Balagué O, et al. Cryptic insertions of the immunoglobulin light chain enhancer region near CCND1 in t(11;14)-negative mantle cell lymphoma. *Haematologica*. 2020;105(8):e408-e411.

413. Polonis K, Schultz MJ, Olteanu H, et al. Detection of cryptic CCND1 rearrangements in mantle cell lymphoma by next generation sequencing. *Ann Diagn Pathol*. 2020;46:151533.

414. Barwick BG, Neri P, Bahlis NJ, et al. Multiple myeloma immunoglobulin lambda translocations portend poor prognosis. *Nat Commun*. 2019;10(1):1911.

415. Shuai S, Suzuki H, Diaz-Navarro A, et al. The U1 spliceosomal RNA is recurrently mutated in multiple cancers. *Nature*. 2019;574(7780):712-716.

416. Wiestner A, Tehrani M, Chiorazzi M, et al. Point mutations and genomic deletions in CCND1 create stable truncated cyclin D1 mRNAs that are associated with increased proliferation rate and shorter survival. *Blood*. 2007;109(11):4599-4606.

417. Diaz LA Jr, Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. *J Clin Oncol*. 2014;32(6):579-586.

418. Wan JCM, Massie C, Garcia-Corbacho J, et al. Liquid biopsies come of age: towards implementation of circulating tumour DNA. *Nat Rev Cancer*. 2017;17(4):223-238.

419. Kurtz DM, Soo J, Co Ting Keh L, et al. Enhanced detection of minimal residual disease by targeted sequencing of phased variants in circulating tumor DNA. *Nat Biotechnol*. 2021;39(12):1537-1547.

420. Deveson IW, Gong B, Lai K, et al. Evaluating the analytical validity of circulating tumor DNA sequencing assays for precision oncology. *Nat Biotechnol*. 2021;39(9):1115-1128.

421. Alig S, Macaulay CW, Kurtz DM, et al. Short diagnosis-to-treatment interval is associated with higher circulating tumor DNA levels in diffuse large B-cell lymphoma. *J Clin Oncol*. 2021;39(23):2605-2616.

422. Kurtz DM, Scherer F, Jin MC, et al. Circulating tumor DNA measurements as early outcome predictors in diffuse large B-cell lymphoma. *J Clin Oncol*. 2018;36(28):2845-2853.

423. Huet S, Salles G. Potential of circulating tumor DNA for the management of patients with lymphoma. *JCO Oncol Pract*. 2020;16(9):561-568.

424. Roschewski M, Rossi D, Kurtz DM, Alizadeh AA, Wilson WH. Circulating tumor DNA in lymphoma: principles and future directions. *Blood Cancer Discov*. 2022;3(1):5-15.

425. Gohil SH, Iorgulescu JB, Braun DA, Keskin DB, Livak KJ. Applying high-dimensional single-cell technologies to the analysis of cancer immunotherapy. *Nat Rev Clin Oncol*. 2021;18(4):244-256.

426. Zheng L, Qin S, Si W, et al. Pan-cancer single-cell landscape of tumor-infiltrating T cells. *Science*. 2021;374(6574):abe6474.

427. Haebe S, Shree T, Sathe A, et al. Single-cell analysis can define distinct evolution of tumor sites in follicular lymphoma. *Blood*. 2021;137(21):2869-2880.

428. Hanna BS, Llaó-Cid L, Iskar M, et al. Interleukin-10 receptor signaling promotes the maintenance of a PD-1(int) TCF-1(+) CD8(+) T cell population that sustains anti-tumor immunity. *Immunity*. 2021;54(12):2825-2841.e2810.

429. Gut'errez C, Al'Khafaji AM, Brenner E, et al. Multifunctional barcoding with ClonMapper enables high-resolution study of clonal dynamics during tumor evolution and treatment. *Nat Cancer*. 2021;2(7):758-772.

430. Gaiti F, Chaligne R, Gu H, et al. Epigenetic evolution and lineage histories of chronic lymphocytic leukaemia. *Nature*. 2019;569(7757):576-580.

431. Milpied P, Cervera-Marzal I, Mollichella ML, et al. Human germinal center transcriptional programs are de-synchronized in B cell lymphoma. *Nat Immunol*. 2018;19(9):1013-1024.

432. Holmes AB, Corinaldesi C, Shen Q, et al. Single-cell analysis of germinal-center B cells informs on lymphoma cell of origin and outcome. *J Exp Med*. 2020;217(10):e20200483.

433. Cohen YC, Zada M, Wang S-Y, et al. Identification of resistance pathways and therapeutic targets in relapsed multiple myeloma patients through single-cell sequencing. *Nat Med*. 2021;27(3):491-503.

434. Gohil SH, Wu CJ. Dissecting CLL through high-dimensional single-cell technologies. *Blood*. 2019;133(13):1446-1456.

435. Duran-Ferrer M, Clot G, Nadeu F, et al. The proliferative history shapes the DNA methylome of B-cell tumors and predicts clinical outcome. *Nat Cancer*. 2020;1(11):1066-1081.

436. Roos-Weil D, Giacopelli B, Armand M, et al. Identification of 2 DNA methylation subtypes of Waldenström macroglobulinemia with plasma and memory B-cell features. *Blood*. 2020;136(5):585-595.

437. Queiros AC, Villamor N, Clot G, et al. A B-cell epigenetic signature defines three biologic subgroups of chronic lymphocytic leukemia with clinical impact. *Leukemia*. 2015;29(3):598-605.

438. Giacopelli B, Zhao Q, Ruppert AS, et al. Developmental subtypes assessed by DNA methylation-iPLEX forecast the natural history of chronic lymphocytic leukemia. *Blood*. 2019;134(8):688-698.

439. Duy C, Béguelin W, Melnick A. Epigenetic mechanisms in leukemias and lymphomas. *Cold Spring Harb Perspect Med*. 2020;10(12):a034959.

440. Oakes CC, Martin-Subero JI. Insight into origins, mechanisms, and utility of DNA methylation in B-cell malignancies. *Blood*. 2018;132(10):999-1006.

441. Lemonnier F, Couronné L, Parrens M, et al. Recurrent TET2 mutations in peripheral T-cell lymphomas correlate with TFH-like features and adverse clinical parameters. *Blood*. 2012;120(7):1466-1469.

442. Zang S, Li J, Yang H, et al. Mutations in 5-methylcytosine oxidase TET2 and RhoA cooperatively disrupt T cell homeostasis. *J Clin Invest*. 2017;127(8):2998-3012.

443. Asmar F, Punj V, Christensen J, et al. Genome-wide profiling identifies a DNA methylation signature that associates with TET2 mutations in diffuse large B-cell

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

lymphoma. *Haematologica*. 2013;98(12):1912-1920.

444. Liu P, Jiang W, Zhao J, Zhang H. Integrated analysis of genome-wide gene expression and DNA methylation microarray of diffuse large B-cell lymphoma with TET mutations. *Mol Med Rep*. 2017;16(4):3777-3782.

445. Rosikiewicz W, Chen X, Dominguez PM, et al. TET2 deficiency reprograms the germinal center B cell epigenome and silences genes linked to lymphomagenesis. *Sci Adv*. 2020;6(25):eaay5872.

446. Dominguez PM, Ghamlouch H, Rosikiewicz W, et al. TET2 deficiency causes germinal center hyperplasia, impairs plasma cell differentiation, and promotes B-cell lymphomagenesis. *Cancer Discov*. 2018;8(12):1632-1653.

447. Dominguez PM, Teater M, Chambwe N, et al. DNA methylation dynamics of germinal center B cells are mediated by AID. *Cell Rep*. 2015;12(12):2086-2098.

448. De S, Shaknovich R, Riester M, et al. Aberration in DNA methylation in B-cell lymphomas has a complex origin and increases with disease severity. *PLoS Genet*. 2013;9(1):e1003137.

449. Chambwe N, Kormaksson M, Geng H, et al. Variability in DNA methylation defines novel epigenetic subgroups of DLBCL associated with different clinical outcomes. *Blood*. 2014;123(11):1699-1708.

450. Landau DA, Clement K, Ziller MJ, et al. Locally disordered methylation forms the basis of intratumor methylome variation in chronic lymphocytic leukemia. *Cancer Cell*. 2014;26(6):813-825.

451. Pan H, Jiang Y, Boi M, et al. Epigenomic evolution in diffuse large B-cell lymphomas. *Nat Commun*. 2015;6:6921.

452. Alhejaily A, Day AG, Feilotter HE, Baetz T, Lebrun DP. Inactivation of the CDKN2A tumor-suppressor gene by deletion or methylation is common at diagnosis in follicular lymphoma and associated with poor clinical outcome. *Clin Cancer Res*. 2014;20(6):1676-1686.

453. Clozel T, Yang S, Elstrom RL, et al. Mechanism-based epigenetic chemosensitization therapy of diffuse large B-cell lymphoma. *Cancer Discov*. 2013;3(9):1002-1019.

454. Stelling A, Wu CT, Bertram K, et al. Pharmacological DNA demethylation restores SMAD1 expression and tumor suppressive signaling in diffuse large B-cell lymphoma. *Blood Adv*. 2019;3(20):3020-3032.

455. Beekman R, Chapaprieta V, Russiñol N, et al. The reference epigenome and regulatory chromatin landscape of chronic lymphocytic leukemia. *Nat Med*. 2018;24(6):868-880.

456. Chapuy B, McKeown MR, Lin CY, et al. Discovery and characterization of super-enhancer-associated dependencies in diffuse large B cell lymphoma. *Cancer Cell*. 2013;24(6):777-790.

457. Ott CJ, Federation AJ, Schwartz LS, et al. Enhancer architecture and essential core regulatory circuitry of chronic lymphocytic leukemia. *Cancer Cell*. 2018;34(6):982-995.e987.

458. Ordoñez R, Kulis M, Russiñol N, et al. Chromatin activation as a unifying principle underlying pathogenic mechanisms in multiple myeloma. *Genome Res*. 2020;30(9):1217-1227.

459. Béguelin W, Popovic R, Teater M, et al. EZH2 is required for germinal center formation and somatic EZH2 mutations promote lymphoid transformation. *Cancer Cell*. 2013;23(5):677-692.

460. Béguelin W, Teater M, Meydan C, et al. Mutant EZH2 induces a pre-malignant lymphoma niche by reprogramming the immune response. *Cancer Cell*. 2020;37(5):655-673.e611.

461. Caganova M, Carrisi C, Varano G, et al. Germinal center dysregulation by histone methyltransferase EZH2 promotes lymphomagenesis. *J Clin Invest*. 2013;123(12):5009-5022.

462. Leung W, Teater M, Durmaz C, et al. SETD2 haploinsufficiency enhances germinal center-associated AICDA somatic hypermutation to drive B cell lymphomagenesis. *Cancer Discov*. 2022;12(7):1782-1803.

463. Liu H, Wang W, Tang G, et al. Lymphomatous variant of hairy cell leukaemia: a distinctive presentation mimicking low-grade B-cell lymphoma. *Histopathology*. 2015;67(5):740-745.

464. Davies FE, Pawlyn C, Usmani SZ, et al. Perspectives on the risk-stratified treatment of multiple myeloma. *Blood Cancer Discov*. 2022;3(4):273-284.

465. Kurtz DM, Esfahani MS, Scherer F, et al. Dynamic risk profiling using serial tumor biomarkers for personalized outcome prediction. *Cell*. 2019;178(3):699-713.e619.

466. Read JA, Koff JL, Nastoupil LJ, Williams JN, Cohen JB, Flowers CR. Evaluating cell-of-origin subtype methods for predicting diffuse large B-cell lymphoma survival: a meta-analysis of gene expression profiling and immunohistochemistry algorithms. *Clin Lymphoma Myeloma Leuk*. 2014;14(6):460-467.e462.

467. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. *Blood*. 2014;124(15):2354-2361.

468. Rodrigues JM, Hassan M, Freiburghaus C, et al. p53 is associated with high-risk and pinpoints TP53 missense mutations in mantle cell lymphoma. *Br J Haematol*. 2020;191(5):796-805.

469. Amador C, Bouska A, Wright G, et al. Gene expression signatures for the accurate diagnosis of peripheral T-cell lymphoma entities in the routine clinical practice. *J Clin Oncol*. 2022:Jco2102707.

470. Hare L, Burke GAA, Turner SD. Resistance to targeted agents used to treat paediatric ALK-positive ALCL. *Cancers (Basel)*. 2021;13(23):6003.

471. Lemonnier F, Safar V, Beldi-Ferchiou A, et al. Integrative analysis of a phase 2 trial combining lenalidomide with CHOP in angioimmunoblastic T-cell lymphoma. *Blood Adv*. 2021;5(2):539-548.

472. Amador C, Greiner TC, Heavican TB, et al. Reproducing the molecular subclassification of peripheral T-cell lymphoma-NOS by immunohistochemistry. *Blood*. 2019;134(24):2159-2170.

473. Artesi M, Marcais A, Durkin K, et al. Monitoring molecular response in adult T-cell leukemia by high-throughput sequencing analysis of HTLV-1 clonality. *Leukemia*. 2017;31(11):2532-2535.

474. Kataoka K, Koya J. Clinical application of genomic aberrations in adult T-cell leukemia/lymphoma. *J Clin Exp Hematop*. 2020;60(3):66-72.

475. Gambacorti Passerini C, Farina F, Stasia A, et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. *J Natl Cancer Inst*. 2014;106(2):djt378.

476. Fukano R, Mori T, Sekimizu M, et al. Alectinib for relapsed or refractory anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: an open-label phase II trial. *Cancer Sci*. 2020;111(12):4540-4547.

477. Yoshida N, Shigemori K, Donaldson N, et al. Genomic landscape of young ATLL patients identifies frequent targetable CD28 fusions. *Blood*. 2020;135(17):1467-1471.

478. Sekulic A, Liang WS, Tembe W, et al. Personalized treatment of Sézary syndrome by targeting a novel CTLA4:CD28 fusion. *Mol Genet Genomic Med*. 2015;3(2):130-136.

479. Dierks C, Adrian F, Fisch P, et al. The ITK-SYK fusion oncogene induces a T-cell lymphoproliferative disease in mice mimicking human disease. *Cancer Res*. 2010;70(15):6193-6204.

480. Pechloff K, Holch J, Ferch U, et al. The fusion kinase ITK-SYK mimics a T cell receptor signal and drives oncogenesis in conditional mouse models of peripheral T cell lymphoma. *J Exp Med*. 2010;207(5):1031-1044.

481. Fathi NN, Mohammad DK, Görgens A, et al. Translocation-generated ITK-FER and ITK-SYK fusions induce STAT3 phosphorylation and CD69 expression. *Biochem Biophys Res Commun*. 2018;504(4):749-752.

482. Zhang LL, Pan HX, Wang YX, Guo T, Liu L. Genome profiling revealed the activation of IL2RG/JAK3/STAT5 in peripheral T-cell lymphoma expressing the ITK-SYK fusion gene. *Int J Oncol*. 2019;55(5):1077-1089.

483. Debackere K, van der Krogt JA, Tousseyn T, et al. FER and FES tyrosine kinase fusions in

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023

follicular T-cell lymphoma. *Blood*. 2020;135(8):584-588.

484. Boddicker RL, Razidlo GL, Dasari S, et al. Integrated mate-pair and RNA sequencing identifies novel, targetable gene fusions in peripheral T-cell lymphoma. *Blood*. 2016;128(9):1234-1245.

485. Bachy E, Camus V, Thieblemont C, et al. Romidepsin plus CHOP versus CHOP in patients with previously untreated peripheral T-cell lymphoma: results of the Ro-CHOP phase III study (conducted by LYSA). *J Clin Oncol*. 2022;40(3):242-251.

486. Horwitz SM, Koch R, Porcu P, et al. Activity of the PI3K-δ,γ inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma. *Blood*. 2018;131(8):888-898.

487. Khodadoust MS, Feldman TA, Yoon DH, et al. Cpi-818, an oral interleukin-2-inducible T-cell kinase inhibitor, is well-tolerated and active in patients with T-cell lymphoma. *Blood*. 2020;136(Supplement 1):19-20.

488. Rossi D, Kurtz DM, Roschewski M, Cavalli F, Zucca E, Wilson WH. The development of liquid biopsy for research and clinical practice in lymphomas: report of the 15-ICML workshop on ctDNA. *Hematol Oncol*. 2020;38(1):34-37.

489. Esfahani MS, Hamilton EG, Mehrmohamadi M, et al. Inferring gene expression from cell-free DNA fragmentation profiles. *Nat Biotechnol*. 2022;40(4):585-597.

490. Meriranta L, Alkodsi A, Pasanen A, et al. Molecular features encoded in the ctDNA reveal heterogeneity and predict outcome in high-risk aggressive B-cell lymphoma. *Blood*. 2022;139(12):1863-1877.

Downloaded from http://ashpublications.org/blood/article-pdf/140/21/2193/2055222/blood_bld-2022-015854-c-main.pdf by guest on 28 September 2023