Review Series

blood

PRECISION HEMATOLOGY

Diagnosis and classification of hematologic malignancies on the basis of genetics

Justin Taylor,[1,*] Wenbin Xiao,[2,*] and Omar Abdel-Wahab[1,3]

[1]Human Oncology and Pathogenesis Program, Department of Medicine, [2]Department of Pathology, and [3]Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

Genomic analysis has greatly influenced the diagnosis and clinical management of patients affected by diverse forms of hematologic malignancies. Here, we review how genetic alterations define subclasses of patients with acute leukemias, myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPNs), non-Hodgkin lymphomas, and classical Hodgkin lymphoma. These include new subtypes of acute myeloid leukemia defined by mutations in *RUNX1* or *BCR-ABL1* translocations as well as a constellation of somatic structural DNA alterations in acute lymphoblastic leukemia. Among patients with MDS, detection of mutations in *SF3B1* define a subgroup of patients with the ring sideroblast form of MDS and a favorable prognosis. For patients with MPNs, detection of the *BCR-ABL1* fusion delineates chronic myeloid leukemia from classic *BCR-ABL1*$^{-}$ MPNs, which are largely defined by mutations in *JAK2*, *CALR*, or *MPL*. In the B-cell lymphomas, detection of characteristic rearrangements involving *MYC* in Burkitt lymphoma, *BCL2* in follicular lymphoma, and *MYC/BCL2/BCL6* in high-grade B-cell lymphomas are essential for diagnosis. In T-cell lymphomas, anaplastic large-cell lymphoma is defined by mutually exclusive rearrangements of *ALK*, *DUSP22/IRF4*, and *TP63*. Genetic alterations affecting *TP53* and the mutational status of the immunoglobulin heavy-chain variable region are important in clinical management of chronic lymphocytic leukemia. Additionally, detection of *BRAF*V600E mutations is helpful in the diagnosis of classical hairy cell leukemia and a number of histiocytic neoplasms. Numerous additional examples provided here demonstrate how clinical evaluation of genomic alterations have refined classification of myeloid neoplasms and major forms of lymphomas arising from B, T, or natural killer cells. (*Blood*. 2017; 130(4):410-423)

Introduction

Hematologic malignancies have historically been at the vanguard among cancers in the use of genetic analyses for diagnosis, classification, prognostication, and therapeutic decision-making. Genetic characterization is vital in the clinical evaluation of nearly every form of hematologic malignancy and has continuously evolved with increased genomic evaluation of cancer and improvements in molecular diagnostic technologies. Here, we review how genetic analysis contributes to the diagnosis and/or management of acute leukemias, chronic myeloid neoplasms, B- and T-/natural killer (NK)-cell lymphomas, as well as multiple myeloma. We specifically focus on the genetic alterations essential for establishing diagnoses and/or determining standard clinical care.

Acute leukemia

Acute myeloid leukemia

The detection of chromosomal abnormalities by cytogenetic analysis is critically important in diagnosis and therapeutic decision-making in acute myeloid leukemia (AML). Detection of t(8;21)(q22;q22.1), inv(16)(p13.1q22), t(16;16)(p13.1;q22), or translocations generating *PML-RARA* fusion transcripts allow the diagnosis of AML to be made even without the presence of ≥20% blasts.[1] In addition, these specific cytogenetic alterations are associated with good prognosis among AML patients. In contrast, other cytogenetic abnormalities or a complex karyotype (defined as the presence of ≥3 cytogenetic abnormalities in the absence of recurring translocations or inversions designated by the World Health Organization [WHO] Classification of Tumours of Haematopoietic and Lymphoid Tissues[2]) are associated with adverse prognosis.[3] However, a large proportion of patients do not bear these cytogenetic alterations and the identification that *CEBPA*, *NPM1*, and *FLT3* internal tandem duplication (ITD) mutations predict response to induction and consolidation chemotherapy for cytogenetically normal AML patients younger than 60 years of age was a major advance in the last decade.[4] On this basis, 2 AML entities are included among cytogenetically defined subtypes of AML (Table 1): AML with mutated *NPM1* and AML with biallelic *CEBPA* mutations. The favorable prognostic significance of mutated *CEBPA* appears limited to those patients with biallelic *CEBPA* mutations that lack *FLT3* or *NPM1* mutations.[5] Similarly, the effects of mutant *NPM1* are superseded by concurrent *FLT3-ITD* mutations, particularly when the *FLT3-ITD* allelic ratio is ≥50%.[4,6] Several additional examples of concurrent additional genetic alterations impacting the outcome of established genetic predictors have been recognized recently in AML. One that is commonly recognized in clinical practice is the adverse prognostic impact of *KIT* mutations among patients with t(8;21) or inv(16)/t(16;16) AML.[1,7]

Submitted 6 February 2017; accepted 2 May 2017. Prepublished online as *Blood* First Edition paper, 9 June 2017; DOI 10.1182/blood-2017-02-734541.

*J.T. and W.X. contributed equally to this work.

Table 1. Genetic alterations of diagnostic use and/or therapeutic or prognostic value in routine clinical practice in select myeloid neoplasms

Disease subtype*	Genes†	Frequency, %	Normal function	Technology used to detect	Prognostic marker‡	Genotype-directed therapies
AML	**t(8;21)(q22;q22.1); *RUNX1-RUNX1T1***	7	RUNX1 and CBFB are core-binding factor transcription factors	Karyotype, FISH	Favorable	
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	5		Karyotype, FISH	Favorable	
	PML-RARA	13	Retinoic acid receptor	FISH, PCR	Favorable	ATRA, Arsenic
	t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*	4	Histone methyltransferase			
	t(6;9)(p23;q34.1); *DEK-NUP214*	1	Nucleoporin (NUP214)		Adverse	
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*	1	Transcription factor		Adverse	
	t(1;22)(p13.3;q13.3); *RBM15-MKL1*	<1	RNA-binding protein (RBM15) and transcription factor (MKL1)			
	NPM1	29	Nucleolar phosphoprotein	Sequencing	Favorable	MRD monitoring
	FLT3-ITD, TKD	37	Receptor tyrosine kinase	Sequencing, PCR	Adverse	FLT3 inhibitors
	Biallelic *CEBPA*	9	Transcription factor	Sequencing	Favorable	
	RUNX1	10	Transcription factor	Sequencing	Adverse	
	AML with *BCR-ABL1*	1	Tyrosine kinase		Adverse	TKIs
	IDH1/2	15-20	α-KG hydroxylase in TCA cycle	Sequencing		Trials involving mutant IDH1/2 inhibitors
	MLL-PTD, rearranged	5	Histone methyltransferase	FISH, PCR, sequencing	Adverse (in selected cases)	
	Chromatin†	13	Epigenetic regulation	Sequencing	Adverse	
	Spliceosome†	5	Pre-mRNA splicing	Sequencing	Adverse	Trials involving splicing inhibitors
	TP53	2	Tumor suppressor	Sequencing	Adverse	
	KIT	5	Tyrosine kinase	Sequencing		TKIs
MDS	***SF3B1***	15-30	Pre-mRNA splicing	Sequencing	Favorable	Trials involving splicing inhibitors
	Del5q	6	Multiple genes	Karyotype	Favorable	Lenalidomide
	ASXL1	15-20	Epigenetic regulation	Sequencing	Adverse	
MPNs						
BCR-ABL1$^+$	***BCR-ABL1***	~100	Tyrosine kinase	FISH, PCR		TKIs
Non-*BCR-ABL1*	***SETBP1***		Multiple roles	Sequencing		
	JAK2	74	Tyrosine kinase	Sequencing, PCR		
	CALR	17	Endoplasmic reticulum	Sequencing, PCR	Favorable	
	MPL	3	Thrombopoietin receptor	Sequencing		
	ASXL1	7-25	Epigenetic regulation	Sequencing	Adverse	
	CSF3R	100	G-CSF receptor	Sequencing		Ruxolitinib
MDS/MPN						
CMML	TET2	61	DNA hydroxymethylation	Sequencing		
	SRSF2	47	Pre-mRNA splicing	Sequencing		Trials involving splicing inhibitors
	ASXL1	44	Epigenetic regulation	Sequencing	Adverse	
MDS/MPN-RS-T	*SF3B1*	67	Pre-mRNA splicing	Sequencing		Trials involving splicing inhibitors
	JAK2	44	Tyrosine kinase	Sequencing, PCR		
Mastocytosis	*KIT*	81	Tyrosine kinase	Sequencing		TKIs

AML, acute myeloid leukemia; ATRA, all-trans retinoic acid; CBFB, core-binding factor-β subunit; CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia; FISH, fluorescence in situ hybridization; G-CSF, granulocyte–colony-stimulating factor; IDH, isocitrate dehydrogenase; MDS, myelodysplastic syndrome; MDS/MPN, myelodysplastic syndrome/myeloproliferative neoplasm; MDS/MPN-RS-T, myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis; MRD, minimal residual disease; mRNA, messenger RNA; PCR, polymerase chain reaction; TCA cycle, tricarboxylic acid cycle; TKI, tyrosine kinase inhibitor.

*Gene/cytogenetic names in bold are of diagnostic value.

†Genes mutated in this category are defined by Döhner et al[1] and Papaemmanuil et al.[8]

‡Those genes left blank do not have clear prognostic relevance currently.

Since the widespread implementation of genetic analysis of *FLT3*, *NPM1*, and *CEBPA* in AML patients clinically, numerous additional recurrent genetic alterations with potential prognostic and therapeutic relevance have been described in AML patients.[6,8,9] To this end, the categories of AML with *RUNX1* mutation and AML with *BCR-ABL1* fusion were added as provisional entities.[2] The *RUNX1*-mutated subtype of AML was created because of data identifying that *RUNX1*-mutated AML was exclusive of recurrent genetic abnormalities recognized by the WHO and has adverse clinical outcomes. Nonetheless, numerous additional recurrent genetic alterations in AML remain

unaccounted for in entities recognized by the WHO and frequently coexist with *RUNX1* mutations in AML.[2,10] For example, mutations in *TP53* or *ASXL1* are nearly universally associated with adverse outcome in AML[6,8,11] and other myeloid neoplasms,[12-14] often independent of other established prognostic variables, and are highlighted by expert guidelines in clinical management of AML.[1] Moreover, recent analysis of 1540 AML patients ages 18 to 65 years by cytogenetics and targeted sequencing of 111 genes identified that 48% of AML patients did not have a recurrent genetic abnormality recognized by the 2008 WHO classification.[8] The consideration of multiple genetic alterations simultaneously across a large cohort of AML patients allowed the identification of distinct groups of AML based on patterns of coexisting and exclusive mutations. This analysis delineated 11 classes of AML, each with distinct diagnostic and clinical features. In addition to the categories defined by the WHO, 3 new AML subgroups emerged: AML with mutations in chromatin and/or spliceosome genes, AML with mutations in *TP53* and/or aneuploidy, and AML with *IDH2*R172 mutation (Table 1). Patients in the "chromatin-spliceosome" or "*TP53*-aneuploidy" groups (which account for nearly one-third of AML) had adverse outcomes,[8] arguing that analysis of at least the 13 genes contained within these 2 groups will be important to evaluate in future studies.

AML with myelodysplasia-related changes and therapy-induced AML

The concept of AML with myelodysplastic features was first added to the WHO classification in 2001 and is defined by ≥20% blasts and dysplasia in ≥50% of the cells in ≥2 myeloid cell lineages.[15] However, the diagnostic challenge of identifying dysplasia-related changes combined with the recognition that such patients often harbored cytogenetic abnormalities characteristic of myelodysplastic syndrome (MDS)-related changes led to the incorporation of 18 different cytogenetic abnormalities whose presence is sufficient to diagnose AML with myelodysplasia-related changes (AML MRCs), even if morphologic criteria for dysplasia are not met.[2] In addition, recent work has described molecular alterations encountered in AML patients that are highly suggestive of antecedent MDS or therapy-induced AML (t-AML) even in the absence of overt dysplasia.[16] In this study, the presence of mutations in a spliceosomal gene (*SF3B1*, *SRSF2*, *U2AF1*, or *ZRSR2*), *ASXL1*, *EZH2*, *BCOR*, or *STAG2* was >95% specific for AML with an antecedent hematologic malignancy. Detection of these mutations among AML patients thought to have de novo AML appears to define a clinically distinct group of patients whose disease behaves like those with clinically diagnosed AML MRCs and t-AML with equivalent poor outcomes.[16] Thus, evaluation of the above mutations in clinical practice may be critically important given the especially poor outcomes associated with AML MRCs and t-AML.

AML not otherwise specified and familial AML

Recent genomic analyses of AML have helped to identify novel genomic alterations in morphologically distinct forms of AML. For example, the genomic underpinnings of acute megakaryoblastic leukemia (AMKL), both those associated with Down syndrome (DS) and non-DS-AMKL, have been extensively characterized. It is now recognized that non-DS-AMKL harbors a number of driving rearrangements, many of which are unique to this form of AML, such as *RBM15-MKL1*, *CBFA2T3-GLIS2*, and *NUP98-KDM5A* fusions in addition to *KMT2A* rearrangements.[17] In contrast, DS-associated AMKL as well as the transient abnormal myelopoiesis associated with DS are marked by *GATA1* mutations and mutations of the JAK-STAT pathway (reviewed recently by Antonarakis[18]), the latter of which also occur in the acute lymphoblastic leukemia (ALL) encountered in DS.[19] The link between germ line alterations and predisposition to myeloid neoplasms in conditions beyond DS is now increasingly recognized and has led to establishment of a category of "myeloid neoplasms with germ line predisposition" in the 2016 WHO revision. This topic has been reviewed recently[20] and includes patients with germ line mutations in *CEBPA*, *DDX41*, *RUNX1*, *ANKRD26*, *ETV6*, and *GATA2* among a host of conditions marked by bone marrow (BM) failure syndromes, telomere dysfunction, and germ line mutations activating RAS signaling.

Other diseases recognized to be distinct enough from AML to garner their own category in the newest WHO classification include blastic plasmacytoid dendritic cell neoplasm (BPDCN).[2] Although BPDCN harbors a gene expression profile similar to AML and has mutations in genes commonly altered in myeloid neoplasms such as *TET2*, *ASXL1*, RNA-splicing factors, and *TP53*, the cell of origin is believed to be a plasmacytoid dendritic cell.[21,22] Interestingly, at least 1 genetic alteration, the balanced translocation t(3;5)(q21;q31), which appears specific to BPDCN has recently been identified.[23] This translocation results in haploinsufficiency of *NR3C1* (encoding the glucocorticoid receptor) and overexpression of a long noncoding RNA (*lincRNA-3q*), both of which functionally contribute to BPDCN pathogenesis.[23] Additionally, expression of the transcription factor TCF4 was recently shown to be a faithful diagnostic biomarker of BPDCN and master regulator of the BPDCN oncogenic program that can be targeted by bromodomain and extraterminal inhibitors.[24]

B-cell acute lymphoblastic leukemia

Comprehensive genomic analysis of B-cell acute lymphoblastic leukemia (B-ALL) has identified genomic alterations of diverse types as important in clinical decision-making, including structural abnormalities resulting in gross chromosomal alterations and gene fusions, smaller copy-number alterations (particularly microdeletions), and individual point mutations. A variety of genetic alterations within each of these categories are associated with favorable or adverse outcome and it is now clear that high-risk genetic alterations are 4 times more common in adults compared with children with B-ALL.[25] High hyperdiploidy (51-65 chromosomes) and t(12;21)(p13;q22) (encoding the *ETV6-RUNX1* fusion) are associated with favorable outcome (Table 2). In contrast, hypodiploidy (≤45 chromosomes), t(17;19) (encoding the *TCF3-HLF* fusion), and *KMT2A* fusions are each associated with adverse outcome. In addition, *BCR-ABL1* fusions are associated with adverse outcome and are essential in determining whether therapeutic regimens containing a tyrosine kinase inhibitor (TKI) should be used. Landmark work demonstrating that a subset of *BCR-ABL1*$^-$ B-ALL patients harbors gene expression programs similar to *BCR-ABL1*$^+$ ALL has led to recognition of a provisional subtype of *BCR-ABL1*–like ALL.[26] These patients contain any of an entire set of activating fusions involving *ABL1*, *ABL2*, *CRLF2*, *CSF1R*, *EPOR*, *JAK2*, *NTRK3*, *PDGFRβ*, and *TYK2*, each of which might confer responsiveness to a TKI.[27]

In addition to fusion genes, ALL with intrachromosomal amplification of chromosome 21 (defined by ≥5 copies of *RUNX1* on a single abnormal chromosome 21 in metaphase fluorescence in situ hybridization [FISH]) is now recognized as a provisional entity of ALL due to its poor outcomes and should be treated as high-risk disease.[28] In addition, small deletions targeting the genes *IKZF1*, *ERG*, *CDKN2A/B*, *PAX5*, *EBF1*, *RB1*, *ETV6* (among others) are often subclonal in B-ALL but may modify prognosis associated with the previously described genomic alterations in B-ALL. Finally, subclonal mutations in *RAS*-signaling intermediates are also common

Table 2. Genetic alterations of diagnostic use and/or therapeutic or prognostic value in routine clinical practice in ALL

Disease subtype*	Genes†	Frequency, %	Normal function	Technology used to detect	Prognostic marker‡	Genotype-directed therapies
B-ALL	*BCR-ABL1*	25	Tyrosine kinase	FISH, PCR	Adverse	TKIs
	BCR-ABL1-like	10-20	Various but nearly all are mitogenic-signaling molecules	GEP	Adverse	TKIs
	iAmp 21	2	*RUNX1* transcription factor	FISH	Adverse	
	Hypodiploidy (≤45 chromosomes)	3-6		Karyotype	Adverse	
	t(17;19)(q22;p13); *TCF3-HLF*	Rare	Transcription factor	Karyotype, FISH	Adverse	
	t(v;11q23.3); *KMT2A* fusions	2-10	Histone methyltransferase	Karyotype, FISH	Adverse	
	High hyperdiploidy (51-65 chromosomes)	20%-30% (children); 5%-10% (adults)		Karyotype	Favorable	
	t(12;21)(p13;q22); *ETV6-RUNX1*	20%-30% (children)	Transcription factor	Karyotype, FISH	Favorable	
	t(5;14)(q31.1;q32.3); *IL3-IGH*	Rare	Cytokine signaling	Karyotype, FISH		
	t(1;19)(q23;p13.3); *TCF3-PBX1 (E2A-PBX1)*	2-6	Transcription factor	Karyotype, FISH		
T-ALL	*NOTCH1*	50-60	Signaling molecule regulating T-cell development	Sequencing		Clinical trials of anti-NOTCH therapies
	CDKN2A/B	50-60	Cell cycle regulation	Karyotype, FISH		
	PHF6	20-40	Unknown	Sequencing		
	FBXW7	10-15	E3 Ubiquitin ligase for NOTCH1	Sequencing		
ETP-ALL	*RUNX1*	20	Transcription factor	Sequencing	Adverse	
	DNMT3a	15	DNA methyltransferase	Sequencing	Adverse	
	ETV6	10-15	Transcription factor	Sequencing		
	IDH1/2		α-KG hydroxylase in TCA cycle	Sequencing		Trials involving mutant IDH1/2 inhibitors
	FLT3	5-10	Tyrosine kinase	Sequencing		Trials involving FLT3 inhibitors
	TET2		DNA hydroxymethylation	Sequencing		

B-ALL, B-cell acute lymphoblastic leukemia; ETP-ALL, early T-cell precursor acute lymphoblastic leukemia; GEP, gene expression profiling; T-ALL, T-cell acute lymphoblastic leukemia. Other abbreviations are explained in Table 1.

*Additional recurrent mutations and structural variations are known to be present in B- and T-ALL but only those with known diagnostic, prognostic, and/or therapeutic utility are shown here.

†Mutations in gene names in bold are of diagnostic value.

‡Those genes left blank do not have clear prognostic relevance currently.

in B-ALL and are being heavily investigated as prognostic and therapeutic targets.[29]

T-cell acute lymphoblastic leukemia

Although several subgroups of T-cell ALL (T-ALL) are known to exist based on gene expression profiling (GEP) and immunophenotypic analyses, the clinical relevance of most subtypes of T-ALL are either unclear or controversial (reviewed recently by Girardi et al,[30] Iacobucci and Mullighan,[31] and Belver and Ferrando[32]). Currently, the early T-cell precursor (ETP) subgroup (ETP-ALL) is the only subtype of T-ALL recognized as a provisional entity in the 2016 WHO revision (Table 2). ETP-ALL frequently has mutations in *RUNX1* and/or *ETV6* in addition to genes that are more commonly associated with myeloid neoplasms and are otherwise rare in T-ALL (such as *FLT3*, *IDH1/2*, *TET2*, and *DNMT3A* mutations). Non-ETP subtypes of T-ALL, in contrast, are associated with activating *NOTCH1* mutations in over half of all patients and an additional 10% to 15% of cases have *FBXW7* mutations, which also result in increased NOTCH signaling. Mutations in *PHF6* are also seen in 20% to 40% of T-ALL and are largely restricted to non-ETP T-ALL cases.[33] Chromosomal alterations are also seen commonly in T-ALL and include loss of *CDKN2A/B* through chromosome 9 deletion in ~50% to 60% of non-ETP T-ALL patients. Finally, translocations and noncoding region mutations[34-36] resulting in ectopic expression of transcription factors such as *TAL1*, *TAL2*, *LYL1*, *LMO1*, *LMO2*, *TLX1*, *TLX3*, *ZEB2*, *MYB*, and *MYC* are common in non-ETP T-ALL (but the clinical relevance of these alterations is not well defined).

Myelodysplastic syndromes and myeloproliferative disorders

Myelodysplastic syndromes

Diagnosis of MDS is based on morphologic detection of dysplasia in the BM and classified based on the number of dysplastic lineages (ie, single lineage vs multilineage dysplasia) and percentage of blasts in the BM (MDS with excess blasts 1 or 2) in a patient with cytopenia. Given that detection of dysplasia in a patient with otherwise unexplained cytopenias can sometimes be challenging, there has been great hope that detection of genetic abnormalities might improve the ability to accurately diagnose MDS. However, because many of the most common mutations that occur in MDS have also recently been found in the blood of healthy individuals, termed clonal hematopoiesis of indeterminate potential, somatic mutations are specifically excluded as a diagnostic criterion for MDS. Currently, MDS with isolated deletion of 5q (del(5q) (defined as MDS with deletion of 5q and up to 1 additional cytogenetic abnormality, unless that abnormality is monosomy 7 or del(7q)) is the only form of MDS associated with a specific genetic abnormality recognized by the WHO.[2] Del(5q) MDS has a unique pathophysiology conferred by haploinsufficiency of genes on chromosome 5q[37] and is clinically important to identify because it is associated with a generally favorable prognosis and responsiveness to lenalidomide (Table 1). Detection of *TP53* mutations, however, may alter the clinical course and response to lenalidomide in del(5q) MDS in

Table 3. Genetic alterations of diagnostic use and/or therapeutic or prognostic value in routine clinical practice in select B-cell lymphoid neoplasms

Disease subtype	Genes*	Frequency, %	Normal function	Technology used to detect	Prognostic marker†	Genotype-directed therapies
CLL/SLL	*NOTCH1*	Up to 15	Notch pathway	Sequencing	Adverse	Trials of NOTCH inhibitors
	SF3B1	15-20	mRNA splicing	Sequencing	Adverse	
	TP53 mutation or deletion	7-15	Tumor suppressor	Sequencing and cytogenetic/	Adverse	
	ATM mutation or deletion	9-12	Tumor suppressor	FISH analysis	Adverse	
LPL	***MYD88***	~90	Couples TLR to NF-κB	Sequencing		BTK inhibitors
	CXCR4	~30	Chemokine receptor	Sequencing		Trials of CXCR4 inhibitors
HCL	***BRAF***	~100	MAPK pathway	Sequencing		BRAF inhibitors
	MAP2K1‡	~50% in HCL-v	MAPK pathway	Sequencing	Adverse	
FL/GCB DLBCL	***BCL2***	50-90	Antiapoptotic	FISH		Venetoclax
	KMT2D/MLL2	89/27	H3K4 methyltransferase	Sequencing		
	CREBBP	41/42	Histone acetyltransferase	Sequencing		Trials of HDAC inhibitors
	EP300	9/10	Histone acetyltransferase	Sequencing		
	EZH2	7/22	H3K27 methyltransferase	Sequencing		Trials of EZH2 inhibitors
	MEF2B	13/8-18	Transcription factor	Sequencing		
	MAP2K1‡	43% in pediatric-type FL	MAPK pathway	Sequencing		
ABC DLBCL	*MYD88*	29	Couples TLR to NF-κB	Sequencing		Trials of IRAK1/4 inhibitors
	CARD11	10	Couples BCR to NF-κB	Sequencing		Trials of MALT1 inhibitors
	CD79A/CD79B	3/18	Components of BCR	Sequencing		Trials of BTK, SYK inhibitors
	TNFAIP3	57	Inhibits NF-κB	Sequencing		Proteasome inhibitors
Burkitt	***MYC***	~100	Transcription factor	FISH		Trials of BET inhibitors
	ID3	~70	Inhibitors of TCF3	Sequencing		
	TCF3	~30	Regulates mTOR pathway	Sequencing		
MCL	**t(11;14)(q13;q32); *IG/CCND1* translocations**	80%-90%	Cell cycle regulator	FISH		
	IG/CCND2 translocations	~50% of *CCND1*$^-$ MCL		FISH		
	NOTCH1/2	10-15	Signaling molecule involved in cell differentiation	Sequencing	Adverse	
cHL/PMBL	*PD-L1/L2*	~95	Inhibit T-cell activation			PD-1/PD-L1 blockade
	B2M	70/64	MHC class I coexpression	Sequencing	Favorable	
	TNFAIP3	44-60/36	Inhibits NF-κB	Sequencing		
	PTPN1	20/22	Phosphatase	Sequencing		

ABC DLBCL, activated B-cell diffuse large B-cell lymphoma; BCR, B-cell receptor; BET, bromodomain and extraterminal; BTK, Bruton tyrosine kinase; cHL/PMBL, classical Hodgkin lymphoma/primary mediastinal B-cell lymphoma; Chr., chromosome; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FL/GCB DLBCL, follicular lymphoma/germinal center B-cell lymphoma; HCL, hairy cell leukemia; HCL-v, HCL-variant; HDAC, histone deacetylase; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MHC, major histocompatibility complex; mTOR, mammalian target of rapamycin; PCM/MM, plasma cell myeloma/multiple myeloma; SNP, single-nucleotide polymorphism; TLR, Toll-like receptor.

*Mutations in gene names in bold are of diagnostic value.

†Those genes left blank do not have clear prognostic relevance currently.

‡*MAP2K1* mutations are detected in HCL-v and HCL expressing *IGHV4-34*, and pediatric-type FL.

Table 3. (continued)

Disease subtype	Genes*	Frequency, %	Normal function	Technology used to detect	Prognostic marker†	Genotype-directed therapies
PCM/MM	Hyperdiploidy	50	Chr. 3, 5, 7, 9, 11, 15, 19 and/or 21	FISH or SNP array	Favorable	
	t(11;14)	15-20	Cyclin D1	FISH	Unfavorable if *CCND1* mutated, otherwise neutral	
	t(4;14)	15	FGFR3/MMSET	FISH	Unfavorable	
	t(14;16)/ t(14;20)	5/1	c-MAF/MAFB (upregulate cyclin D2)	FISH	Unfavorable	
	t(6;14)	1	Cyclin D3	FISH	Unfavorable	
	1q gain/del(1p)/del(17p)	40/30/10		FISH or SNP array	Unfavorable	
	MYC translocations	15-20	MYC upregulation	FISH	Unfavorable	
	KRAS/NRAS/BRAF	20/20/10	Components of MAPK pathway	Sequencing		

ABC DLBCL, activated B-cell diffuse large B-cell lymphoma; BCR, B-cell receptor; BET, bromodomain and extraterminal; BTK, Bruton tyrosine kinase; cHL/PMBL, classical Hodgkin lymphoma/primary mediastinal B-cell lymphoma; Chr., chromosome; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; FL/GCB DLBCL, follicular lymphoma/germinal center B-cell lymphoma; HCL, hairy cell leukemia; HCL-v, HCL-variant; HDAC, histone deacetylase; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma; MHC, major histocompatibility complex; mTOR, mammalian target of rapamycin; PCM/MM, plasma cell myeloma/multiple myeloma; SNP, single-nucleotide polymorphism; TLR, Toll-like receptor.

*Mutations in gene names in bold are of diagnostic value.

†Those genes left blank do not have clear prognostic relevance currently.

‡*MAP2K1* mutations are detected in HCL-v and HCL expressing *IGHV4-34*, and pediatric-type FL.

addition to adversely affecting prognosis in all subtypes of MDS, arguing for routine evaluation of *TP53* alterations in MDS.[38]

In addition to del(5q) MDS, the detection of ringed sideroblasts (RS) in a patient with MDS represents a unique category of MDS (MDS-RS). Interestingly, recent work has identified that mutations in the RNA-splicing factor *SF3B1* have a remarkably high positive predictive value for disease phenotype with RS of 97.7%, whereas the absence of these mutations has an equivalent negative predictive value.[39] On this basis, MDS-RS can now be diagnosed with ≥5% RS if an *SF3B1* mutation is present, whereas >15% RS are required in patients lacking an *SF3B1* mutation.[2] The link between *SF3B1* mutations and morphologic presence of RS also extends to MDS/myeloproliferative neoplasm (MPN) with RS and thrombocytosis (MDS/MPN-RS-T; previously known as RARS-T). MDS/MPN-RS-T is frequently associated with coexistence of *JAK2*V617F mutations (33%-77% of MDS/MPN-RS-T patients and commonly found in *BCR-ABL1*$^-$ MPNs) with *SF3B1* mutations (83%-90% MDS/MPN-RS-T),[40-42] thus explaining the biology of this disease, which has clinical and genetic features of both MDS and MPNs. The molecular genetics of other forms of MDS/MPNs have been described in several excellent reviews.[43-45]

In addition to the use of genetic alterations for diagnosis of specific subtypes of MDS, cytogenetic alterations are established in clinical prognostic schema in routine clinical practice in MDS. Moreover, several landmark studies have identified that specific molecular genetic alterations further refine prognosis within clinically and cytogenetically defined subgroups of MDS[12,46,47] and predict outcome after allogeneic transplantation.[48,49] The use of molecular genetic alterations to determine prognosis of MDS has recently been extensively reviewed.[37]

Myeloproliferative neoplasms

Given the frequently overlapping clinical and morphological features of MPNs and the discovery of unique genetic hallmarks of specific subtypes of MPNs (reviewed recently by Zoi and Cross[50]), the use of molecular genetic alterations is essential in diagnosis, prognosis, and therapeutic decision-making for MPN patients and physicians. First, detection of the *BCR-ABL1* fusion transcript is essential in diagnosis of chronic myeloid leukemia (CML) and excluding a potential diagnosis of CML in a patient with another chronic MPN, which may present in a clinically indistinguishable manner from CML. In addition, evaluation for rearrangements involving *PDGFRA*, *PDGFRB*, or *FGFR1*, or the *PCM1-JAK2* fusion should also be considered. Although patients bearing these rearrangements may present with eosinophilia and/or lymphoproliferation, they may lack any clinical or phenotypic characteristics to discriminate them from other forms of MPN.[51] These conditions are also distinct from chronic eosinophilic leukemia, not otherwise specified, which does not harbor any of these translocations.[52]

In patients lacking any of the aforementioned rearrangements, detection of mutually exclusive mutations in *JAK2*, *CALR*, or *MPL* defines >90% of patients with a classic, *BCR-ABL1*$^-$ MPN. In 2005, *JAK2*V617F mutations were identified in 90% of polycythemia vera and 50% of essential thrombocytosis (ET) and myelofibrosis (MF) patients.[53-56] More recently, a series of mutations was discovered in the remaining *JAK2*V617F–wild-type MPN patients including *JAK2* exon 12 mutations in polycythemia vera[57] as well as *MPL* and *CALR* mutations in ET and MF patients.[58-60] Further work is now ongoing to define the genetic alterations present in those ET and MF patients who lack the *JAK2*, *CALR*, or *MPL* mutation (so-called "triple-negative MPN" patients).

Molecularly distinct from the above chronic myeloid neoplasms are 2 disorders that are frequently diagnostically and therapeutically challenging: atypical CML (aCML) and chronic neutrophilic leukemia (CNL). Both aCML and CNL lack the *BCR-ABL1* fusion; however, activating mutations in *CSF3R* define CNL and are present in nearly 100% of cases[61] (Table 1). In contrast, *CSF3R* mutations are present in <10% of aCML cases and aCML is also morphologically defined by the presence of granulocytic dysplasia (which places aCML under the rubric of MDS/MPN overlap conditions).[62] Although >20% of aCML patients harbor driving mutations in *SETBP1*[63] and/or *ETNK1*,[64] these alterations are also occasionally found in other forms of MDS, MPN, and MDS/MPN at lower frequencies.

Lymphoma and chronic lymphocytic leukemia

Chronic lymphocytic leukemia/small lymphocytic lymphoma

Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma is often marked by cytogenetic aberrations (up to 80% of patients may have cytogenetic alterations by FISH), which are critical in risk-stratification.[65] Patients with 17p deletions or TP53 mutations have the worst prognosis and poor survival when treated with standard therapy; however, the novel Bruton tyrosine kinase (BTK) inhibitor ibrutinib has improved outcomes in this particular group of patients.[66,67] In addition to cytogenetic alterations, discrimination of CLL patients on the degree of mutation of the immunoglobulin heavy-chain variable-region (*IGHV*) gene also has prognostic and therapeutic importance. A mutated *IGHV* in CLL has long been associated with favorable outcome and was recently shown to be a key predictor of long-term remissions with chemoimmunotherapy.[68] For these reasons, analysis of *TP53* and *IGHV* mutational status has recently been incorporated into a new International Prognostic Index for treatment-naive CLL patients (the CLL–International Prognostic Index).[69] Finally, sequencing of >100 whole genomes[70,71] and >500 whole exomes[71-74] of CLL patients has now revealed recurrent somatic mutations, including those potentially associated with adverse outcome such as mutations in *NOTCH1*, *SF3B1*, and *ATM* (discussed in several excellent recent reviews: Rodríguez et al,[75] Kipps et al,[76] Guièze and Wu,[77] and Lazarian et al[78]; Table 3). With the exception of *TP53* alterations, however, detection of other mutations in CLL is not currently included in routine clinical practice in CLL as their prognostic relevance is not clear. At the same time, mutations affecting *SF3B1*, *NOTCH1*, *XPO1*, and several other genes recurrently mutated in CLL are being heavily evaluated as potential therapeutic targets.

Follicular lymphoma

The t(14;18) (q32;q21)/*IGH-BCL2* gene rearrangement, resulting in overexpression of the antiapoptotic protein BCL2, is the defining feature of grade 1-2 follicular lymphoma (FL). In contrast, *BCL2* rearrangements are less common in grade 3A FL and *BCL6* rearrangements are often detected in t(14;18)$^-$ grade 3B FL.[79] In addition to these diagnostic cytogenetic alterations, molecular genetic studies in FL over the last 10 years have now identified that mutations in epigenetic modifiers are extremely common in FL including mutations in *KMT2D/MLL2*, *CREBBP*, *EP300*, *MEF2B*, and *EZH2* (occurring as *EZH2* Y641 hotspot mutations) (Table 3). During transformation of FL to large-cell lymphoma, alterations deregulating cell-cycle progression and DNA damage responses (*CDKN2A/B*, *MYC*, and *TP53*) are more frequent.[80] By incorporating mutational status in 7 genes (*EZH2*, *ARID1A*, *MEF2B*, *EP300*, *FOXO1*, *CREBBP*, and *CARD11*), a new clinicogenetic risk model (termed "m7-FLIPI") was proposed,[81] whose prognostic value is to be validated in future prospective studies.

Genomic analyses of FL have also now identified several unique entities of FL. For example, pediatric-type FL is now recognized as a distinct entity in the 2016 WHO classification. At a molecular level, pediatric-type FL is characterized by lack of *BCL2*, *BCL6*, or *MYC* rearrangements, low genomic complexity, and a low frequency of mutations in epigenetic modifiers but a high prevalence of MAPK pathway mutations (frequently *MAP2K1*, and rarely *MAPK1* and *RRAS*, mutations).[82,83] In addition, a new provisional entity of large B-cell lymphoma with *IRF4* rearrangement is also now recognized. This entity also occurs in children and young adults, and lacks *BCL2* rearrangement, but needs to be distinguished from pediatric-type FL.[84] Most cases carry *IG/IRF4* rearrangements but the mutational profile beyond this remains to be clarified. Finally, 1 unique subtype of FL known as diffuse-appearing FL has now been recognized which typically presents as a large localized inguinal mass without *BCL2* rearrangements, but with 1p36 deletions and frequent *STAT6* and *TNFRSF14* mutations.[85] These latter 2 genetic alterations are also both occasionally seen in typical FL albeit at lower frequencies.[86]

Lymphoplasmacytic lymphoma

Lymphoplasmacytic lymphoma (LPL) is an indolent small B-cell neoplasm with overlapping clinical/pathologic features with marginal zone lymphoma. Waldenström macroglobulinemia is a manifestation of LPL associated with an immunoglobulin M (IgM) paraprotein in the blood. Identification of mutations in *MYD88*, a gene encoding an adaptor in the Toll-like receptor pathway, at L265P can facilitate the diagnosis of LPL as ~90% of LPL/Waldenström macroglobulinemia patients harbor this mutation in contrast to only 5% to 15% of marginal zone lymphoma[87-90] (Table 3). *MYD88* mutations are less frequent in nodal LPL although cases with wild-type *MYD88* tend to have atypical morphologic features, leading to the suggestion that some such cases should be excluded from a diagnosis of LPL.[91] *MYD88*L265P mutations are also found in IgM (but not IgG or IgA) monoclonal gammopathy of unknown significance and not in multiple myeloma (MM) even if IgM expressing.[92] Moreover, the combination of genotypes in *MYD88* and *CXCR4* appears to be an important determinant of response of LPL to ibrutinib, with those patients bearing *MYD88*L265P but lacking a *CXCR4* mutation experiencing the best response.[93]

Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma. GEP studies revealed 2 subtypes of DLBCL based on cell of origin: activated B-cell–like (ABC) and germinal center B-cell–like (GCB), as well as an unclassified intermediate group.[94,95] Separating ABC from GCB subtype has important clinical implications as ABC subtype has poor response to rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)–based regimens while being more sensitive to ibrutinib.[96] This may be partly attributable to the mutational profiles differentially represented in ABC and GCB subtypes. The ABC subtype exhibits dependence on constitutive activation of the B-cell receptor (BCR) and/or NF-κB signaling pathways, owing to frequent somatic mutations of genes within these pathways, including *CD79A/B*, *CARD11*, *MYD88*, and *TNFAIP3*, whereas mutations in *EZH2*, *GNA13*, and *SGK1* genes are enriched in the GCB subtype (Table 3).[97,98] Nevertheless, both GCB and ABC subtypes of DLBCL share recurrent mutations in genes involved in immune surveillance (such as *B2M* and *CD58*), chromatin modification (such as *MLL2/3*, *CREBBP*, and *EP300*), regulation of

Table 4. Genetic alterations of diagnostic use and/or therapeutic or prognostic value in routine clinical practice in select NK- and T-cell neoplasms

Disease subtype	Genes*	Frequency, %	Normal function	Technology used to detect	Prognostic marker†	Genotype-directed therapies
ALCL	***ALK* rearrangement**	100% of ALK$^+$ ALCL	Kinase	FISH	Favorable	ALK inhibitors
	***DUSP22/IRF4* rearrangement**	30% of ALK$^-$ ALCL	Phosphatase	FISH	Favorable	
	TP63 rearrangement	8% of ALK$^-$ ALCL	Tumor suppressor	FISH	Adverse	
	STAT3	38% of ALK$^-$ ALCL	JAK-STAT signaling intermediate	Sequencing		JAK/STAT inhibitors
AITL/PTCL	*RHOA*	67/18	GTPase	Sequencing		
	IDH2	~13/0	α-KG hydroxylase in TCA cycle	Sequencing		Trials of mutant IDH2 inhibitors
	TET2	~70/30	DNA hydroxymethylation	Sequencing		Trials of hypomethylating agents
	DNMT3A	~23/12	DNA methyltransferase	Sequencing		
Other T/NK lymphoma	*STAT3*	Up to 70% in LGL, 10% in γδ-TCL	JAK-STAT signaling intermediate	Sequencing		JAK/STAT inhibitors
	STAT5B	Up to 35% in γδ-TCL	JAK-STAT signaling intermediate	Sequencing	Adverse in LGL	JAK/STAT inhibitors
	SETD2	Up to 90% in MEITL and 25% in γδ-TCL	H3K36 trimethyltransferase	Sequencing		
	PLCγ	15% in PTCL NOS	Component of TCR pathway	Sequencing		PLCγ inhibitors

AITCL/PTCL, angioimmunoblastic T-cell lymphoma/peripheral T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; TCL: T-cell lymphoma; LGL, large granular lymphocytic leukemia; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; PLC, phospholipase C.

*Mutations in gene names in bold are of diagnostic value.

†Those genes left blank do not have clear prognostic relevance currently.

BCL6 protein activity (*MEF2B*), and cell cycle or apoptosis (such as *FOXO1* and *TP53*) (reviewed recently by Intlekofer and Younes[99]).

The role of *MYC* alterations in DLBCL has been extensively studied in recent years (see review by Ott et al[100]). *MYC* rearrangements are detected in 5% to 15% of DLBCL not otherwise specified (NOS) and are often associated with GCB phenotype (~70%). *IG* are the partner genes in nearly 50% of these cases (reviewed recently by Campo[101]). Half of *MYC*-rearranged DLBCL also have concurrent *BCL2* or, to a lesser extent, *BCL6* translocations (so-called "double hit" [DH] or "triple hit" lymphoma) which have been reclassified as high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements in the 2016 WHO revision. Most studies highlight the adverse impact of *MYC* rearrangements in DLBCL[102,103] and a few suggest the importance of *MYC* partner genes.[102,104] However, it is still controversial whether MYC rearrangements as a single hit or its frequent association with BCL2or BCL6 (DH) alterations is responsible for the aggressive behavior (reviewed recently by Swerdlow[105]). In this regard, a recent prospective randomized study clearly demonstrates that *MYC* rearrangements with *IG* genes, but not with other partner genes, have a negative prognostic impact in patients with DLBCL treated with chemoimmunotherapy, regardless of concurrent *BCL2* or *BCL6* translocations.[106] In contrast to many reports in the literature, concurrent *BCL2* or *BCL6* translocations (DH cases) did not have independent prognostic value in that study. This discrepancy may at least partly be due to the difference in case selection as B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BL), often has DH (30%-50%) and a more aggressive outcome[107]; they were almost entirely excluded in this study but might have been included in previously published retrospective studies.[108,109] Extra copies of *MYC* and/or *BCL-2* appear to confer worse prognosis but this finding needs to be validated by additional studies.[110,111] The coexpression of MYC and BCL2 proteins in DLBCL, so-called dual/double expressor DLBCL, often has ABC phenotype and is associated with inferior survival even in the absence of translocations.[112,113] Dual/double expressor DLBCL remains in the DLBCL, NOS category in the 2016 WHO revision.[114]

Burkitt lymphoma, primary mediastinal large B-cell lymphoma, and Hodgkin lymphoma

The defining feature of BL is an *IG/MYC* translocation (Table 3). Frequent recurrent somatic mutations in *TCF3*, or in its negative regulator *ID3*, are found in ~70% of sporadic and immunodeficiency-related BL and 40% of endemic cases.[115,116] A new provisional entity is designated as Burkitt-like lymphoma with 11q aberration to include a subset of lymphomas that resemble BL morphologically, to a large extent phenotypically and by GEP, but which lack *MYC* rearrangements. Instead, these have a chromosome 11q alteration characterized by proximal gains and telomeric losses.[114,117]

Primary mediastinal large B-cell lymphoma (PMBL) and classical Hodgkin lymphoma (cHL) share many genetic/molecular aberrations including alterations of chromosome 9p24.1/*PD-L1/PD-L2* and mutations in multiple genes (*B2M*, *TNFAIP3*, *PTPN1*).[118-120] *PD-L1/PD-L2* alterations become a defining feature of cHL and blockade of the PD-1/PD-L1 pathway has been successful in treating refractory cHL.[121] *B2M* mutations and *CIITA* alterations lead to diminished major histocompatibility complex class I and II expression in cHL and PMBL, respectively.[120,122] Additionally, mutations in the nuclear export protein *XPO1* were recently discovered in ~25% of both PMBL and cHL with much research going into the pathogenic mechanisms underlying this frequent alteration.[123]

Mantle cell lymphoma

Mantle cell lymphoma (MCL) is characterized by the presence of an *IG/CCND1* translocation (Table 3). SOX11 expression has diagnostic utility in cyclin D1$^-$ MCL.[124] Furthermore, *IG/CCND2* but not *CCND3* translocations are detected in half of cyclin D1$^-$ MCL.[125] Interestingly, *CCND3* upregulation and mutation has been recently described in splenic diffuse red-pulp small B-cell lymphoma and BL

but not MCL.[115,116,126] Genomic studies in MCL have revealed additional driver mutations in genes including *ATM*, *TP53*, *CCND1*, and *UBR5*.[127] *NOTCH1* and *NOTCH2* mutations, although less frequent in MCL, are associated with poor prognosis and are potential therapeutic targets.[127,128]

Hairy cell leukemia

The discovery of *BRAF*V600E mutations provided a molecular basis to distinguish classic hairy cell leukemia (cHCL) from hairy cell leukemia (HCL) variant and HCL expressing *IGHV4-34*,[129,130] forms of HCL which are histologically similar but known to have a more aggressive clinical course and are less likely to respond to purine analog therapy compared with cHCL. Mutations in *MAP2K1*, encoding the kinase just downstream of BRAF, were identified in HCL variant,[131] and *IGHV4-34*$^+$ HCL.[131] Interestingly, mutations in *BRAF*V600E and *MAP2K1* appear to sensitize HCL to RAF[132,133] and MEK[134,135] inhibitors, respectively. On the other hand, the clinical significance of somatic mutations in *CDKN1B*, identified in up to 16% of HCL cases with coexisting *BRAF*V600E mutations, remains uncertain.[136] Of note, besides molecular testing, BRAFV600E can be reliably detected at the protein level by immunohistochemical stain using a mutant protein-specific antibody.[137]

Plasma cell myeloma or multiple myeloma

Plasma cell myeloma (PCM) or MM has well-defined precursor states termed monoclonal gammopathy of undetermined significance and smoldering MM, which provide a unique model to understand the sequence of genomic aberrations that begins with germ line events that predispose to the disease, followed by primary events, before the secondary acquisition of genomic aberrations that ultimately lead to disease progression and resistance to treatment (reviewed recently by Robiou du Pont et al[138] and Manier et al[139]). Genome-wide association studies have revealed genetic loci associated with increased risk of developing MM and specific disease phenotypes.[140-142] Primary events are usually divided into hyperdiploid (HD) and non-HD subtypes. HD is characterized by gains of chromosomes 3, 5, 7, 9, 11, 15, 19, and/or 21 and is often associated with longer survival. Non-HD harbors translocations involving immunoglobulin heavy chains (*IGH*), mainly t(4;14), t(6;14), t(11;14), t(14;16), and t(14;20), and recurrent unbalanced changes including 1q gains and losses at 1p, 6q, 8p, 13q, 14q, 16q, and 17p. Abnormalities such as t(4;14), t(14;16), del(17p), del (1p32), and 1q gains are considered high risk. Secondary events include copy-number variations, translocations involving *MYC*, and somatic mutations often affecting MAPK (*KRAS*, *NRAS*, *BRAF*), NF-κB (*TRAF3*, *CYLD*, *LTB*), and DNA repair pathways (*TP53*, *ATM*, *ATR*). Mutations involving the MAPK pathway and NF-κB pathway are detected in ~40% and ~20% of MM patients, respectively.[143-146] The clinical significance of MAPK and NF-κB pathway mutations is uncertain but they do not appear to impact progression-free or overall survival. In contrast, mutations affecting DNA repair pathways are associated with an unfavorable outcome. Whole-exome sequencing studies have identified clonal heterogeneity as a consistent feature of MM, where patients often harbor ≥ 5 to 6 subclones at diagnosis. Patients may even harbor ≥2 mutations in genes involved in the same pathway (eg, *KRAS*, *NRAS*, or *BRAF* mutations), likely due to these mutations residing in different subclones.[139,144,145]

Mature T/NK neoplasms

The role of genetic alterations/mutations has long been appreciated in the diagnosis and classification of T-/NK-cell neoplasms. In fact, translocations activating anaplastic lymphoma kinase (ALK) were among the first chromosomal rearrangements identified in lymphoma and, depending on the presence of ALK translocations, the T-cell lymphoma known as anaplastic large-cell lymphoma (ALCL) is further subclassified into ALK$^+$ and ALK$^-$ subgroups[147] (Table 4). GEP studies have shown that ALK$^-$ ALCL has a signature similar to that of ALK$^+$ ALCL but well separated from other NK-/T-cell lymphomas.[148,149] ALK$^-$ ALCL often harbors convergent mutations and kinase fusions that lead to constitutive activation of the JAK/STAT3 pathway, which is also critical for the pathogenesis of ALK$^+$ ALCL.[150] Pharmacologic inhibition of JAK/STAT3 represents a promising strategy for the treatment of molecularly stratified ALCL. Recent studies also demonstrated that rearrangements involving *DUSP22/IRF4* on chromosome 6p25 identify a unique subset of ALK$^-$ ALCL that tends to be morphologically monomorphic, usually lacking cytotoxic granules, and marked by good prognosis, whereas a mutually exclusive subset of patients with *TP63* rearrangements has an exceptionally aggressive course.[151]

Recurrent genetic abnormalities have been recently reported in angioimmunoblastic T-cell lymphoma (AITL) and less frequently in peripheral T-cell lymphoma (PTCL) NOS including *TET2*, *IDH2*, *DNMT3A*, *RHOA*, and *CD28* mutations, as well as gene fusions such as *ITK-SYK* and *CTLA4-CD28* (reviewed recently by Wang et al[152] and Iqbal et al[153]). Interestingly, *TET2* and *IDH1/2* mutations are established as being mutually exclusive in myeloid malignancies due to the partially convergent biochemical effects of these alterations.[154] At the same time, *TET2* and *IDH1/2* mutations frequently coexist within AITL,[155,156] often even in the same cells. The presence of mutations in genes enriched in myeloid neoplasm in AITL also raises the question of the cell of origin of these T-cell lymphomas. Most recently, 2 subtypes of PTCL NOS, characterized by high expression of either *GATA3* or *TBX21*, were identified as having prognostic and biologic significance.[157]

Frequent *STAT3* and *STAT5B* mutations have been identified in various mature NK- and T-cell neoplasms. Somatic-activating *STAT3* mutations are identified in up to 70% of large granular lymphocyte leukemia (LGL).[158] The related *STAT5B* is mutated far less in LGL, but more commonly in T-cell prolymphocytic leukemia[159] and enteropathy-associated T-cell lymphoma, type II (renamed as monomorphic epitheliotropic intestinal T-cell lymphoma [MEITL] in the 2016 WHO revision).[160-162] Both *STAT3* and *STAT5B* are also mutated in γδ-hepatosplenic/cutaneous T-cell lymphoma and nasal-type NK-/T-cell lymphoma[160,163,164] (Table 4). *SETD2* mutations were recently identified in up to 90% of MEITL and 25% of γδ-hepatosplenic T-cell lymphoma.[162,165] In addition to mutations affecting the JAK-STAT pathway and epigenetic modifiers, recurrent mutations targeting the T-cell receptor signaling pathway are also frequently observed in many types of T-cell lymphomas including adult T-cell leukemia/lymphoma, PTCL, and cutaneous T-cell lymphomas (mycosis fungoides and Sézary syndrome).[166-169]

Histiocytic neoplasms

Advances in the genomic analyses of clinically and histologically diverse histiocytic neoplasms over the last 10 years has greatly informed our understanding and treatment of these disorders. Recurrent mutations activating MAPK signaling are present in the majority of patients with Langerhans cell histiocytosis (LCH) and Erdheim-Chester disease (ECD; newly added as a distinct entity in the 2016 WHO revision[114]) with ~50% of patients having a *BRAF*V600E mutation[170] while *BRAF*V600 wild-type patients harbor mutually exclusive *MAP2K1*, *ARAF*, *NRAS*, or *KRAS* mutations (reviewed recently by Durham et al[171]). Rare in-frame activating deletions in

BRAF[172] as well activating *BRAF*, *ALK*, and *NTRK1* fusions have also been identified in *BRAF*V600 wild-type cases.[134] Detection of these mutations has led to clinical use of BRAF as well as MEK inhibitors in patients affected by these conditions with remarkable success. In contrast to LCH and ECD, recent work has also identified fusions of *ETV3-NCOA2* in nearly all cases with indeterminate cell histiocytosis identifying a unique genetic hallmark for this histologic entity.[173]

Discussion

Genetic characterization of a wide array of hematologic malignancies has helped to define genetic biomarkers delineating specific entities of myeloid and lymphoid neoplasms. Many of these alterations are now incorporated into WHO-defined criteria for diagnostic evaluation as reviewed here. At the same time, there are numerous examples of genetic alterations that are not routinely evaluated in standard clinical practice but may define specific disease entities due to their association with disease prognosis and/or emerging importance in therapeutic use. Given the growing number of these alterations, small sequencing panels that focus on a limited number of genes may not be sufficient, especially in the lymphoid malignancies. Moreover, increased discovery of clinically important mutations and structural variations not detectable by cytogenetics, FISH, or small gene panels (such as copy-number changes, amplifications, deletions, and gene fusions) begets the need for means to comprehensively evaluate molecular alterations of a variety of types in clinical practice. To this end, a number of targeted DNA-sequencing[174-177] and combined DNA/RNA-sequencing[178,179] panels evaluating recurrently altered genes across hematopoietic malignancies have been described, some of which are commercially available (reviewed recently by Kuo and Dong,[180] Meldrum et al,[181] and Kanagal-Shamanna et al[182]) and allow use of formalin-fixed paraffin-embedded specimens. Further improvements in next-generation sequencing technologies (reviewed by Sheikine et al[183]) are expected to allow evaluation of mutations across the entire coding regions of hundreds to thousands of genes while also providing information on copy-number status and gene fusions in a clinically relevant timeframe.

Given the large number of patients required to evaluate the effects of most genetic alterations on clinical outcome,[184] it is very likely that the results of ongoing retrospective and prospective studies of cohorts of leukemia and lymphoma patients will be required to modify how genetic analyses are incorporated into clinical practice beyond diagnostic purposes in the future. In addition to improving clinical detection of known genetic alterations for diagnostic, prognostic, and therapeutic purposes, further efforts to systematically sequence known recurrently mutated genes and characterize exomes, genomes, and transcriptomes in an unbiased fashion are very likely to produce further examples of disease-defining alterations in hematologic malignancies. There are now emerging examples of recurrent mutations in the non-coding genome resulting in the ectopic expression and activation of oncogenes as well as inactivation of tumor suppressors. Although these currently have only been defined in T-ALL[34-36] and CLL,[71] it is possible that such recurrent alterations may exist in a wide variety of hematopoietic malignancies. As technologies and therapies improve, iterative ongoing research is needed in both common and uncommon disease entities to fully define the pathogenic and prognostic alterations important in hematologic malignancies.

Acknowledgments

The authors thank Ahmet Dogan for help in critical evaluation of this manuscript.

J.T. was supported by grants from the American Society of Hematology, the American Association of Cancer Research, the Conquer Cancer Foundation and American Society of Clinical Oncology (ASCO), and the Robert Wood Johnson Foundation. O.A.-W. was supported by grants from the Edward P. Evans Foundation, the Taub Foundation, the Hairy Cell Leukemia Foundation, the Histiocytosis Association, the Erdheim-Chester Disease Global Alliance, the Department of Defense Bone Marrow Failure Research Program (BM150092 and W81XWH-12-1-0041), National Institutes of Health, National Heart, Lung, and Blood Institute (R01 HL128239), an award from the Starr Foundation (I8-A8-075), the Leukemia & Lymphoma Society, and the Pershing Square Sohn Cancer Research Alliance.

Authorship

Contribution: J.T., W.X., and O.A.-W. wrote the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

ORCID profiles: J.T., 0000-0003-4407-6325; W.X., 0000-0001-8586-8500; O.A.-W., 0000-0002-3907-6171.

Correspondence: Omar Abdel-Wahab, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065; e-mail: abdelwao@mskcc.org.

References

1. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447.
2. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391-2405.
3. Grimwade D, Hills RK, Moorman AV, et al; National Cancer Research Institute Adult Leukaemia Working Group. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood*. 2010;116(3):354-365.
4. Schlenk RF, Döhner K, Krauter J, et al; German-Austrian Acute Myeloid Leukemia Study Group. Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. *N Engl J Med*. 2008;358(18):1909-1918.
5. Green CL, Koo KK, Hills RK, Burnett AK, Linch DC, Gale RE. Prognostic significance of CEBPA mutations in a large cohort of younger adult patients with acute myeloid leukemia: impact of double CEBPA mutations and the interaction with FLT3 and NPM1 mutations. *J Clin Oncol*. 2010;28(16):2739-2747.
6. Patel JP, Gönen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med*. 2012;366(12):1079-1089.
7. Duployez N, Marceau-Renaut A, Boissel N, et al. Comprehensive mutational profiling of core binding factor acute myeloid leukemia. *Blood*. 2016;127(20):2451-2459.
8. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med*. 2016;374(23):2209-2221.
9. Ley TJ, Miller C, Ding L, et al; Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N Engl J Med*. 2013;368(22):2059-2074.

10. Gaidzik VI, Teleanu V, Papaemmanuil E, et al. RUNX1 mutations in acute myeloid leukemia are associated with distinct clinico-pathologic and genetic features. *Leukemia*. 2016;30(11): 2160-2168.
11. Metzeler KH, Becker H, Maharry K, et al. ASXL1 mutations identify a high-risk subgroup of older patients with primary cytogenetically normal AML within the ELN Favorable genetic category. *Blood*. 2011;118(26):6920-6929.
12. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med*. 2011;364(26):2496-2506.
13. Itzykson R, Kosmider O, Renneville A, et al. Prognostic score including gene mutations in chronic myelomonocytic leukemia. *J Clin Oncol*. 2013;31(19):2428-2436.
14. Stein BL, Williams DM, O'Keefe C, et al. Disruption of the ASXL1 gene is frequent in primary, post-essential thrombocytosis and post-polycythemia vera myelofibrosis, but not essential thrombocytosis or polycythemia vera: analysis of molecular genetics and clinical phenotypes. *Haematologica*. 2011;96(10): 1462-1469.
15. Vardiman J, Reichard K. Acute myeloid leukemia with myelodysplasia-related changes. *Am J Clin Pathol*. 2015;144(1):29-43.
16. Lindsley RC, Mar BG, Mazzola E, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. *Blood*. 2015;125(9): 1367-1376.
17. de Rooij JD, Branstetter C, Ma J, et al. Pediatric non-Down syndrome acute megakaryoblastic leukemia is characterized by distinct genomic subsets with varying outcomes. *Nat Genet*. 2017;49(3):451-456.
18. Antonarakis SE. Down syndrome and the complexity of genome dosage imbalance. *Nat Rev Genet*. 2017;18(3):147-163.
19. Izraeli S, Vora A, Zwaan CM, Whitlock J. How I treat ALL in Down's syndrome: pathobiology and management. *Blood*. 2014;123(1):35-40.
20. Feurstein S, Drazer MW, Godley LA. Genetic predisposition to leukemia and other hematologic malignancies. *Semin Oncol*. 2016;43(5):598-608.
21. Menezes J, Acquadro F, Wiseman M, et al. Exome sequencing reveals novel and recurrent mutations with clinical impact in blastic plasmacytoid dendritic cell neoplasm. *Leukemia*. 2014;28(4):823-829.
22. Stenzinger A, Endris V, Pfarr N, et al. Targeted ultra-deep sequencing reveals recurrent and mutually exclusive mutations of cancer genes in blastic plasmacytoid dendritic cell neoplasm. *Oncotarget*. 2014;5(15):6404-6413.
23. Emadali A, Hoghoughi N, Duley S, et al. Haploinsufficiency for NR3C1, the gene encoding the glucocorticoid receptor, in blastic plasmacytoid dendritic cell neoplasms. *Blood*. 2016;127(24):3040-3053.
24. Ceribelli M, Hou ZE, Kelly PN, et al. A druggable TCF4- and BRD4-dependent transcriptional network sustains malignancy in blastic plasmacytoid dendritic cell neoplasm. *Cancer Cell*. 2016;30(5):764-778.
25. Moorman AV, Chilton L, Wilkinson J, Ensor HM, Bown N, Proctor SJ. A population-based cytogenetic study of adults with acute lymphoblastic leukemia. *Blood*. 2010;115(2): 206-214.
26. Mullighan CG, Miller CB, Radtke I, et al. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. *Nature*. 2008; 453(7191):110-114.
27. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. *N Engl J Med*. 2014;371(11):1005-1015.
28. Moorman AV, Richards SM, Robinson HM, et al; UK Medical Research Council (MRC)/National Cancer Research Institute (NCRI) Childhood Leukaemia Working Party (CLWP). Prognosis of children with acute lymphoblastic leukemia (ALL) and intrachromosomal amplification of chromosome 21 (iAMP21). *Blood*. 2007;109(6): 2327-2330.
29. Oshima K, Khiabanian H, da Silva-Almeida AC, et al. Mutational landscape, clonal evolution patterns, and role of RAS mutations in relapsed acute lymphoblastic leukemia. *Proc Natl Acad Sci USA*. 2016;113(40):11306-11311.
30. Girardi T, Vicente C, Cools J, De Keersmaecker K. The genetics and molecular biology of T-ALL. *Blood*. 2017;129(9):1113-1123.
31. Iacobucci I, Mullighan CG. Genetic basis of acute lymphoblastic leukemia. *J Clin Oncol*. 2017;35(9):975-983.
32. Belver L, Ferrando A. The genetics and mechanisms of T cell acute lymphoblastic leukaemia. *Nat Rev Cancer*. 2016;16(8): 494-507.
33. Van Vlierberghe P, Palomero T, Khiabanian H, et al. PHF6 mutations in T-cell acute lymphoblastic leukemia. *Nat Genet*. 2010; 42(4):338-342.
34. Rahman S, Magnussen M, León TE, et al. Activation of the LMO2 oncogene through a somatically acquired neomorphic promoter in T-cell acute lymphoblastic leukemia. *Blood*. 2017;129(24):3221-3226.
35. Abraham BJ, Hnisz D, Weintraub AS, et al. Small genomic insertions form enhancers that misregulate oncogenes. *Nat Commun*. 2017;8: 14385.
36. Mansour MR, Abraham BJ, Anders L, et al. Oncogene regulation. An oncogenic super-enhancer formed through somatic mutation of a noncoding intergenic element. *Science*. 2014; 346(6215):1373-1377.
37. Sperling AS, Gibson CJ, Ebert BL. The genetics of myelodysplastic syndrome: from clonal haematopoiesis to secondary leukaemia. *Nat Rev Cancer*. 2017;17(1):5-19.
38. Jädersten M, Saft L, Smith A, et al. TP53 mutations in low-risk myelodysplastic syndromes with del(5q) predict disease progression. *J Clin Oncol*. 2011;29(15):1971-1979.
39. Malcovati L, Papaemmanuil E, Bowen DT, et al; Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium and of the Associazione Italiana per la Ricerca sul Cancro Gruppo Italiano Malattie Mieloproliferative. Clinical significance of SF3B1 mutations in myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms. *Blood*. 2011;118(24):6239-6246.
40. Broséus J, Alpermann T, Wulfert M, et al; MPN and MPNr-EuroNet (COST Action BM0902). Age, JAK2(V617F) and SF3B1 mutations are the main predicting factors for survival in refractory anaemia with ring sideroblasts and marked thrombocytosis. *Leukemia*. 2013;27(9): 1826-1831.
41. Jeromin S, Haferlach T, Grossmann V, et al. High frequencies of SF3B1 and JAK2 mutations in refractory anemia with ring sideroblasts associated with marked thrombocytosis strengthen the assignment to the category of myelodysplastic/myeloproliferative neoplasms. *Haematologica*. 2013;98(2):e15-e17.
42. Patnaik MM, Lasho TL, Finke CM, et al. Predictors of survival in refractory anemia with ring sideroblasts and thrombocytosis (RARS-T) and the role of next-generation sequencing. *Am J Hematol*. 2016;91(5):492-498.
43. Talati C, Padron E. An exercise in extrapolation: clinical management of atypical CML, MDS/MPN-unclassifiable, and MDS/MPN-RS-T. *Curr Hematol Malig Rep*. 2016;11(6):425-433.
44. Odenike O, Onida F, Padron E. Myelodysplastic syndromes and myelodysplastic/myeloproliferative neoplasms: an update on risk stratification, molecular genetics, and therapeutic approaches including allogeneic hematopoietic stem cell transplantation. *Am Soc Clin Oncol Educ Book*. 2015;e398-e412.
45. Locatelli F, Niemeyer CM. How I treat juvenile myelomonocytic leukemia. *Blood*. 2015;125(7): 1083-1090.
46. Papaemmanuil E, Gerstung M, Malcovati L, et al; Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium. Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood*. 2013;122(22):3616-3627, quiz 3699.
47. Haferlach T, Nagata Y, Grossmann V, et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. *Leukemia*. 2014; 28(2):241-247.
48. Della Porta MG, Gallì A, Bacigalupo A, et al. Clinical effects of driver somatic mutations on the outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem-cell transplantation. *J Clin Oncol*. 2016; 34(30):3627-3637.
49. Lindsley RC, Saber W, Mar BG, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. *N Engl J Med*. 2017; 376(6):536-547.
50. Zoi K, Cross NC. Genomics of myeloproliferative neoplasms. *J Clin Oncol*. 2017;35(9):947-954.
51. Reiter A, Gotlib J. Myeloid neoplasms with eosinophilia. *Blood*. 2017;129(6):704-714.
52. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med*. 2003;348(13):1201-1214.
53. Baxter EJ, Scott LM, Campbell PJ, et al; Cancer Genome Project. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet*. 2005;365(9464):1054-1061.
54. James C, Ugo V, Le Couédic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. *Nature*. 2005;434(7037):1144-1148.
55. Kralovics R, Passamonti F, Buser AS, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. *N Engl J Med*. 2005;352(17):1779-1790.
56. Levine RL, Wadleigh M, Cools J, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. *Cancer Cell*. 2005;7(4):387-397.
57. Scott LM, Tong W, Levine RL, et al. JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. *N Engl J Med*. 2007;356(5): 459-468.
58. Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. *N Engl J Med*. 2013;369(25):2379-2390.
59. Nangalia J, Massie CE, Baxter EJ, et al. Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. *N Engl J Med*. 2013; 369(25):2391-2405.
60. Pikman Y, Lee BH, Mercher T, et al. MPLW515L is a novel somatic activating mutation in

myelofibrosis with myeloid metaplasia. *PLoS Med*. 2006;3(7):e270.

61. Maxson JE, Gotlib J, Pollyea DA, et al. Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML. *N Engl J Med*. 2013;368(19):1781-1790.
62. Gotlib J. How I treat atypical chronic myeloid leukemia. *Blood*. 2017;129(7):838-845.
63. Piazza R, Valletta S, Winkelmann N, et al. Recurrent SETBP1 mutations in atypical chronic myeloid leukemia. *Nat Genet*. 2013;45(1):18-24.
64. Gambacorti-Passerini CB, Donadoni C, Parmiani A, et al. Recurrent ETNK1 mutations in atypical chronic myeloid leukemia. *Blood*. 2015;125(3): 499-503.
65. 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.
66. Strati P, Keating MJ, O'Brien SM, et al. Outcomes of first-line treatment for chronic lymphocytic leukemia with 17p deletion. *Haematologica*. 2014;99(8):1350-1355.
67. Farooqui MZ, Valdez J, Martyr S, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial. *Lancet Oncol*. 2015;16(2):169-176.
68. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood*. 2016;127(3):303-309.
69. International CLL-IPI working group. An international prognostic index for patients with chronic lymphocytic leukaemia (CLL-IPI): a meta-analysis of individual patient data. *Lancet Oncol*. 2016;17(6):779-790.
70. Puente XS, Pinyol M, Quesada V, et al. Whole-genome sequencing identifies recurrent mutations in chronic lymphocytic leukaemia. *Nature*. 2011;475(7354):101-105.
71. Puente XS, Beà S, Valdés-Mas R, et al. Non-coding recurrent mutations in chronic lymphocytic leukaemia. *Nature*. 2015;526(7574): 519-524.
72. Quesada V, Conde L, Villamor N, et al. Exome sequencing identifies recurrent mutations of the splicing factor SF3B1 gene in chronic lymphocytic leukemia. *Nat Genet*. 2011;44(1): 47-52.
73. Landau DA, Tausch E, Taylor-Weiner AN, et al. Mutations driving CLL and their evolution in progression and relapse. *Nature*. 2015; 526(7574):525-530.
74. Landau DA, Carter SL, Stojanov P, et al. Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. *Cell*. 2013;152(4): 714-726.
75. Rodríguez D, Bretones G, Arango JR, et al. Molecular pathogenesis of CLL and its evolution. *Int J Hematol*. 2015;101(3):219-228.
76. Kipps TJ, Stevenson FK, Wu CJ, et al. Chronic lymphocytic leukaemia. *Nat Rev Dis Primers*. 2017;3:16096.
77. Guièze R, Wu CJ. Genomic and epigenomic heterogeneity in chronic lymphocytic leukemia. *Blood*. 2015;126(4):445-453.
78. Lazarian G, Guièze R, Wu CJ. Clinical implications of novel genomic discoveries in chronic lymphocytic leukemia. *J Clin Oncol*. 2017;35(9):984-993.
79. Bosga-Bouwer AG, van Imhoff GW, Boonstra R, et al. Follicular lymphoma grade 3B includes 3 cytogenetically defined subgroups with primary t(14;18), 3q27, or other translocations: t(14;18) and 3q27 are mutually exclusive. *Blood*. 2003; 101(3):1149-1154.
80. Pasqualucci L, Khiabanian H, Fangazio M, et al. Genetics of follicular lymphoma transformation. *Cell Reports*. 2014;6(1):130-140.
81. 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.
82. 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.
83. 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.
84. Salaverria I, Philipp C, Oschlies I, et al; Molecular Mechanisms in Malignant Lymphomas Network Project of the Deutsche Krebshilfe; German High-Grade Lymphoma Study Group; Berlin-Frankfurt-Münster-NHL trial group. 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.
85. Katzenberger T, Kalla J, Leich E, et al. A distinctive subtype of t(14;18)-negative nodal follicular non-Hodgkin lymphoma characterized by a predominantly diffuse growth pattern and deletions in the chromosomal region 1p36. *Blood*. 2009;113(5):1053-1061.
86. Siddiqi IN, Friedman J, Barry-Holson KQ, et al. Characterization of a variant of t(14;18) negative nodal diffuse follicular lymphoma with CD23 expression, 1p36/TNFRSF14 abnormalities, and STAT6 mutations. *Mod Pathol*. 2016;29(6): 570-581.
87. 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.
88. Martinez-Lopez A, Curiel-Olmo S, Mollejo M, et al. MYD88 (L265P) somatic mutation in marginal zone B-cell lymphoma. *Am J Surg Pathol*. 2015;39(5):644-651.
89. Varettoni M, Arcaini L, Zibellini S, et al. Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in Waldenstrom's macroglobulinemia and related lymphoid neoplasms. *Blood*. 2013;121(13): 2522-2528.
90. Hunter ZR, Yang G, Xu L, Liu X, Castillo JJ, Treon SP. Genomics, signaling, and treatment of Waldenström macroglobulinemia. *J Clin Oncol*. 2017;35(9):994-1001.
91. Hamadeh F, MacNamara SP, Aguilera NS, Swerdlow SH, Cook JR. MYD88 L265P mutation analysis helps define nodal lymphoplasmacytic lymphoma. *Mod Pathol*. 2015;28(4):564-574.
92. Jiménez C, Sebastián E, Chillón MC, et al. MYD88 L265P is a marker highly characteristic of, but not restricted to, Waldenström's macroglobulinemia. *Leukemia*. 2013;27(8): 1722-1728.
93. Treon SP, Xu L, Hunter Z. MYD88 mutations and response to ibrutinib in Waldenström's macroglobulinemia. *N Engl J Med*. 2015;373(6): 584-586.
94. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature*. 2000; 403(6769):503-511.
95. Rosenwald A, Wright G, Chan WC, et al; Lymphoma/Leukemia Molecular Profiling Project. 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.
96. 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.
97. 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.
98. Pasqualucci L, Dalla-Favera R. The genetic landscape of diffuse large B-cell lymphoma. *Semin Hematol*. 2015;52(2):67-76.
99. Intlekofer AM, Younes A. Precision therapy for lymphoma–current state and future directions. *Nat Rev Clin Oncol*. 2014;11(10):585-596.
100. Ott G, Rosenwald A, Campo E. Understanding MYC-driven aggressive B-cell lymphomas: pathogenesis and classification. *Blood*. 2013; 122(24):3884-3891.
101. Campo E. MYC in DLBCL: partners matter. *Blood*. 2015;126(22):2439-2440.
102. Savage KJ, Johnson NA, Ben-Neriah S, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. *Blood*. 2009;114(17):3533-3537.
103. Barrans S, Crouch S, Smith A, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. *J Clin Oncol*. 2010;28(20):3360-3365.
104. Pedersen MO, Gang AO, Poulsen TS, et al. MYC translocation partner gene determines survival of patients with large B-cell lymphoma with MYC- or double-hit MYC/BCL2 translocations. *Eur J Haematol*. 2014;92(1): 42-48.
105. Swerdlow SH. Diagnosis of 'double hit' diffuse large B-cell lymphoma and B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma: when and how, FISH versus IHC. *Hematology Am Soc Hematol Educ Program*. 2014;2014:90-99.
106. Copie-Bergman C, Cuillière-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.
107. Salaverria I, Siebert R. The gray zone between Burkitt's lymphoma and diffuse large B-cell lymphoma from a genetics perspective. *J Clin Oncol*. 2011;29(14):1835-1843.
108. Johnson NA, Savage KJ, Ludkovski O, et al. Lymphomas with concurrent BCL2 and MYC translocations: the critical factors associated with survival. *Blood*. 2009;114(11):2273-2279.
109. Snuderl M, Kolman OK, Chen YB, et al. B-cell lymphomas with concurrent IGH-BCL2 and MYC rearrangements are aggressive neoplasms with clinical and pathologic features distinct from Burkitt lymphoma and diffuse large B-cell lymphoma. *Am J Surg Pathol*. 2010;34(3): 327-340.
110. Li S, Seegmiller AC, Lin P, et al. B-cell lymphomas with concurrent MYC and BCL2 abnormalities other than translocations behave similarly to MYC/BCL2 double-hit lymphomas. *Mod Pathol*. 2015;28(2):208-217.
111. Lu TX, Fan L, Wang L, et al. MYC or BCL2 copy number aberration is a strong predictor of outcome in patients with diffuse large B-cell lymphoma. *Oncotarget*. 2015;6(21): 18374-18388.

112. Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. *J Clin Oncol*. 2012; 30(28):3452-3459.

113. Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/ BCL2 protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. *Blood*. 2013;121(20): 4021-4031, quiz 4250.

114. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016;127(20):2375-2390.

115. Love C, Sun Z, Jima D, et al. The genetic landscape of mutations in Burkitt lymphoma. *Nat Genet*. 2012;44(12):1321-1325.

116. Richter J, Schlesner M, Hoffmann S, et al; ICGC MMML-Seq Project. Recurrent mutation of the ID3 gene in Burkitt lymphoma identified by integrated genome, exome and transcriptome sequencing. *Nat Genet*. 2012;44(12):1316-1320.

117. Salaverria I, Martin-Guerrero I, Wagener R, et al; Molecular Mechanisms in Malignant Lymphoma Network Project; Berlin-Frankfurt-Münster Non-Hodgkin Lymphoma Group. 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.

118. Gunawardana J, Chan FC, Telenius A, et al. Recurrent somatic mutations of PTPN1 in primary mediastinal B cell lymphoma and Hodgkin lymphoma. *Nat Genet*. 2014;46(4): 329-335.

119. Roemer MG, Advani RH, Ligon AH, et al. PD-L1 and PD-L2 genetic alterations define classical hodgkin lymphoma and predict outcome. *J Clin Oncol*. 2016;34(23):2690-2697.

120. Reichel J, Chadburn A, Rubinstein PG, et al. Flow sorting and exome sequencing reveal the oncogenome of primary Hodgkin and Reed-Sternberg cells. *Blood*. 2015;125(7):1061-1072.

121. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. *N Engl J Med*. 2015;372(4):311-319.

122. Mottok A, Woolcock B, Chan FC, et al. Genomic alterations in CIITA are frequent in primary mediastinal large B cell lymphoma and are associated with diminished MHC class II expression. *Cell Reports*. 2015;13(7): 1418-1431.

123. Jardin F, Pujals A, Pelletier L, et al. Recurrent mutations of the exportin 1 gene (XPO1) and their impact on selective inhibitor of nuclear export compounds sensitivity in primary mediastinal B-cell lymphoma. *Am J Hematol*. 2016;91(9):923-930.

124. Mozos A, Royo C, Hartmann E, et al. SOX11 expression is highly specific for mantle cell lymphoma and identifies the cyclin D1-negative subtype. *Haematologica*. 2009;94(11): 1555-1562.

125. Salaverria I, Royo C, Carvajal-Cuenca A, et al. CCND2 rearrangements are the most frequent genetic events in cyclin D1(-) mantle cell lymphoma. *Blood*. 2013;121(8):1394-1402.

126. Curiel-Olmo S, Mondéjar R, Almaraz C, et al. Splenic diffuse red pulp small B-cell lymphoma displays increased expression of cyclin D3 and recurrent CCND3 mutations. *Blood*. 2017; 129(8):1042-1045.

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

128. Kridel R, Meissner B, Rogic S, et al. Whole transcriptome sequencing reveals recurrent NOTCH1 mutations in mantle cell lymphoma. *Blood*. 2012;119(9):1963-1971.

129. Xi L, Arons E, Navarro W, et al. Both variant and IGHV4-34-expressing hairy cell leukemia lack the BRAF V600E mutation. *Blood*. 2012;119(14): 3330-3332.

130. Tiacci E, Pettirossi V, Schiavoni G, Falini B. Genomics of hairy cell leukemia. *J Clin Oncol*. 2017;35(9):1002-1010.

131. Waterfall JJ, Arons E, Walker RL, et al. High prevalence of MAP2K1 mutations in variant and IGHV4-34-expressing hairy-cell leukemias. *Nat Genet*. 2014;46(1):8-10.

132. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med*. 2015; 373(8):726-736.

133. Tiacci E, Park JH, De Carolis L, et al. Targeting mutant BRAF in relapsed or refractory hairy-cell leukemia. *N Engl J Med*. 2015;373(18): 1733-1747.

134. Diamond EL, Durham BH, Haroche J, et al. Diverse and targetable kinase alterations drive histiocytic neoplasms. *Cancer Discov*. 2016; 6(2):154-165.

135. Andritsos LA, Anghelina M, Grieselhuber NR, et al. Trametinib for the treatment of IGHV4-34, MAP2K1 mutant variant hairy cell leukemia [abstract]. *Blood*. 2016;128(22). Abstract 5598.

136. Dietrich S, Hüllein J, Lee SC, et al. Recurrent CDKN1B (p27) mutations in hairy cell leukemia. *Blood*. 2015;126(8):1005-1008.

137. Ritterhouse LL, Barletta JA. BRAF V600E mutation-specific antibody: a review. *Semin Diagn Pathol*. 2015;32(5):400-408.

138. Manier S, Salem KZ, Park J, Landau DA, Getz G, Ghobrial IM. Genomic complexity of multiple myeloma and its clinical implications. *Nat Rev Clin Oncol*. 2017;14(2):100-113.

139. Robiou du Pont S, Cleynen A, Fontan C, et al. Genomics of multiple myeloma. *J Clin Oncol*. 2017;35(9):963-967.

140. Broderick P, Chubb D, Johnson DC, et al. Common variation at 3p22.1 and 7p15.3 influences multiple myeloma risk. *Nat Genet*. 2011;44(1):58-61.

141. Chubb D, Weinhold N, Broderick P, et al. Common variation at 3q26.2, 6p21.33, 17p11.2 and 22q13.1 influences multiple myeloma risk. *Nat Genet*. 2013;45(10):1221-1225.

142. Johnson DC, Weinhold N, Mitchell J, et al. Genetic factors influencing the risk of multiple myeloma bone disease. *Leukemia*. 2016;30(4): 883-888.

143. Chapman MA, Lawrence MS, Keats JJ, et al. Initial genome sequencing and analysis of multiple myeloma. *Nature*. 2011;471(7339): 467-472.

144. Bolli N, Avet-Loiseau H, Wedge DC, et al. Heterogeneity of genomic evolution and mutational profiles in multiple myeloma. *Nat Commun*. 2014;5:2997.

145. Lohr JG, Stojanov P, Carter SL, et al; Multiple Myeloma Research Consortium. Widespread genetic heterogeneity in multiple myeloma: implications for targeted therapy. *Cancer Cell*. 2014;25(1):91-101.

146. Walker BA, Boyle EM, Wardell CP, et al. Mutational spectrum, copy number changes, and outcome: results of a sequencing study of patients with newly diagnosed myeloma. *J Clin Oncol*. 2015;33(33):3911-3920.

147. Jaffe ES. Anaplastic large cell lymphoma: the shifting sands of diagnostic hematopathology. *Mod Pathol*. 2001;14(3):219-228.

148. Agnelli L, Mereu E, Pellegrino E, et al; European T-Cell Lymphoma Study Group. Identification of a 3-gene model as a powerful diagnostic tool for the recognition of ALK-negative anaplastic large-cell lymphoma. *Blood*. 2012;120(6):1274-1281.

149. Piccaluga PP, Fuligni F, De Leo A, et al. Molecular profiling improves classification and prognostication of nodal peripheral T-cell lymphomas: results of a phase III diagnostic accuracy study. *J Clin Oncol*. 2013;31(24): 3019-3025.

150. 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.

151. 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.

152. Wang M, Zhang S, Chuang SS, et al. Angioimmunoblastic T cell lymphoma: novel molecular insights by mutation profiling. *Oncotarget*. 2017;8(11):17763-17770.

153. Iqbal J, Wilcox R, Naushad H, et al. Genomic signatures in T-cell lymphoma: How can these improve precision in diagnosis and inform prognosis? *Blood Rev*. 2016;30(2):89-100.

154. Figueroa ME, Abdel-Wahab O, Lu C, et al. Leukemic IDH1 and IDH2 mutations result in a hypermethylation phenotype, disrupt TET2 function, and impair hematopoietic differentiation. *Cancer Cell*. 2010;18(6):553-567.

155. Sakata-Yanagimoto M, Enami T, Yoshida K, et al. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. *Nat Genet*. 2014;46(2):171-175.

156. Cairns RA, Iqbal J, Lemonnier F, et al. IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. *Blood*. 2012;119(8): 1901-1903.

157. Iqbal J, Wright G, Wang C, et al; Lymphoma Leukemia Molecular Profiling Project and the International Peripheral T-cell Lymphoma Project. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. *Blood*. 2014; 123(19):2915-2923.

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

159. Kiel MJ, Velusamy T, Rolland D, et al. Integrated genomic sequencing reveals mutational landscape of T-cell prolymphocytic leukemia. *Blood*. 2014;124(9):1460-1472.

160. 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;6:6025.

161. Nicolae A, Xi L, Pham TH, et al. Mutations in the JAK/STAT and RAS signaling pathways are common in intestinal T-cell lymphomas. *Leukemia*. 2016;30(11):2245-2247.

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

163. 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.

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

165. 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.

166. Elenitoba-Johnson KS, Wilcox R. A new molecular paradigm in mycosis fungoides and Sézary syndrome. *Semin Diagn Pathol*. 2017; 34(1):15-21.

167. Kiel MJ, Sahasrabuddhe AA, Rolland DC, et al. Genomic analyses reveal recurrent mutations in epigenetic modifiers and the JAK-STAT pathway in Sézary syndrome. *Nat Commun*. 2015;6: 8470.

168. Vallois D, Dobay MP, 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.

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

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

171. Durham BH, Diamond EL, Abdel-Wahab O. Histiocytic neoplasms in the era of personalized genomic medicine. *Curr Opin Hematol*. 2016; 23(4):416-425.

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

173. Brown RA, Kwong BY, McCalmont TH, et al. ETV3-NCOA2 in indeterminate cell histiocytosis: clonal translocation supports sui generis. *Blood*. 2015;126(20):2344-2345.

174. Cheng DT, Mitchell TN, Zehir A, et al. Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): a hybridization capture-based next-generation sequencing clinical assay for solid tumor molecular oncology. *J Mol Diagn*. 2015;17(3): 251-264.

175. Bolli N, Manes N, McKerrell T, et al. Characterization of gene mutations and copy number changes in acute myeloid leukemia using a rapid target enrichment protocol. *Haematologica*. 2015;100(2):214-222.

176. Conte N, Varela I, Grove C, et al. Detailed molecular characterisation of acute myeloid leukaemia with a normal karyotype using targeted DNA capture. *Leukemia*. 2013;27(9): 1820-1825.

177. Kwok B, Hall JM, Witte JS, et al. MDS-associated somatic mutations and clonal hematopoiesis are common in idiopathic cytopenias of undetermined significance. *Blood*. 2015;126(21):2355-2361.

178. He J, Abdel-Wahab O, Nahas MK, et al. Integrated genomic DNA/RNA profiling of hematologic malignancies in the clinical setting. *Blood*. 2016;127(24):3004-3014.

179. Zheng Z, Liebers M, Zhelyazkova B, et al. Anchored multiplex PCR for targeted next-generation sequencing. *Nat Med*. 2014;20(12): 1479-1484.

180. Kuo FC, Dong F. Next-generation sequencing-based panel testing for myeloid neoplasms. *Curr Hematol Malig Rep*. 2015;10(2):104-111.

181. Meldrum C, Doyle MA, Tothill RW. Next-generation sequencing for cancer diagnostics: a practical perspective. *Clin Biochem Rev*. 2011;32(4):177-195.

182. Kanagal-Shamanna R, Singh RR, Routbort MJ, Patel KP, Medeiros LJ, Luthra R. Principles of analytical validation of next-generation sequencing based mutational analysis for hematologic neoplasms in a CLIA-certified laboratory. *Expert Rev Mol Diagn*. 2016;16(4): 461-472.

183. Sheikine Y, Kuo FC, Lindeman NI. Clinical and technical aspects of genomic diagnostics for precision oncology. *J Clin Oncol*. 2017;35(9): 929-933.

184. Moffitt AB, Dave SS. Clinical applications of the genomic landscape of aggressive non-Hodgkin lymphoma. *J Clin Oncol*. 2017;35(9):955-962.