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 BRAFV600E 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)(p13.1q22), 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 Tissues2) 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%.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
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. To this end, the categories of AML with RUNX1 mutation and AML with BCR-ABL1 fusion were added as provisional entities. 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

<table>
<thead>
<tr>
<th>Disease subtype*</th>
<th>Genes†</th>
<th>Frequency, %</th>
<th>Normal function</th>
<th>Technology used to detect</th>
<th>Prognostic marker‡</th>
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<tr>
<td>AML</td>
<td>t(8;21)(q22;q22.1); RUNX1-RUNX1T1</td>
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<td>RUNX1 and CBFB are core-binding factor transcription factors</td>
<td>Karyotype, FISH</td>
<td>Favorable</td>
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<td></td>
<td>inv(16)(p13.1q22) or t(16;16) (p13.1;q22); CBFB-MYH11</td>
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<td>Karyotype, FISH</td>
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<td>PML-RARA</td>
<td>13</td>
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<td>inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM</td>
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<td>t(1;22)(p13.3q13.3); RBM15-MKL1</td>
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<td>Biallelic CEBPA</td>
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<td>RUNX1</td>
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<td>AML with BCR-ABL1</td>
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<td>Tyrosine kinase</td>
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<td>IDH1/2</td>
<td>15-20</td>
<td>α-KG hydroxylase in TCA cycle</td>
<td>Sequencing</td>
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<td>Trials involving mutant IDH1/2 inhibitors</td>
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<td>MLL-PTD, rearranged</td>
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<td>Adverse (in selected cases)</td>
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<td>Chromatin†</td>
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<td>Epigenetic regulation</td>
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<td></td>
<td>Spliceosome†</td>
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<td>Pre-mRNA splicing</td>
<td>Sequencing</td>
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<tr>
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<td>TP53</td>
<td>2</td>
<td>Tumor suppressor</td>
<td>Sequencing</td>
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<td>KIT</td>
<td>5</td>
<td>Tyrosine kinase</td>
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<td>TKIs</td>
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<td>MDS</td>
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<td>Favorable</td>
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<td>Del5q</td>
<td>6</td>
<td>Multiple genes</td>
<td>Karyotype</td>
<td>Favorable</td>
<td>Lenalidomide</td>
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<td></td>
<td>ASXL1</td>
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<td>MPNs</td>
<td>BCR-ABL1*</td>
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<td>FISH, PCR</td>
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<td>TKIs</td>
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<td>Non-BCR-ABL1</td>
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<td>Multiple roles</td>
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<td>JAK2</td>
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<td>Endoplasmic reticulum</td>
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<td>CALR</td>
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<tr>
<td></td>
<td>MPL</td>
<td>7-25</td>
<td>Epigenetic regulation</td>
<td>Sequencing</td>
<td>Adverse</td>
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<tr>
<td></td>
<td>ASXL1</td>
<td>100</td>
<td>G-CSF receptor</td>
<td>Sequencing</td>
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<td>Ruxolitinib</td>
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<td>SRSF2</td>
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<td>Pre-mRNA splicing</td>
<td>Sequencing</td>
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<td>SF3B1</td>
<td>44</td>
<td>Epigenetic regulation</td>
<td>Sequencing</td>
<td>Adverse</td>
<td>Trials involving splicing inhibitors</td>
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<tr>
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<td>ASXL1</td>
<td></td>
<td></td>
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<td></td>
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<td>MDS/MPN-RS-T</td>
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<td>Pre-mRNA splicing</td>
<td>Sequencing</td>
<td>Adverse</td>
<td>Trials involving splicing inhibitors</td>
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<tr>
<td>Mastocytosis</td>
<td>JAK2</td>
<td>44</td>
<td>Tyrosine kinase</td>
<td>Sequencing, PCR</td>
<td></td>
<td></td>
</tr>
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<td></td>
<td>KIT</td>
<td>81</td>
<td>Tyrosine kinase</td>
<td>Sequencing</td>
<td></td>
<td>TKIs</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukemia; ATRA, all-trans retinoic acid; CBFB, core-binding factor-β subunit; CML, chronic myelogenous leukemia; CMMML, 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 and Papaemmanuil et al.
‡Those genes left blank do not have clear prognostic relevance currently.

Table 1. Genetic alterations of diagnostic use and/or therapeutic or prognostic value in routine clinical practice in select myeloid neoplasms.
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.13 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.10 In this study, the presence of mutations in a spliceosomal gene (SF3B1, SRSF2, U2AF1, or ZRS2), 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, CBFα2T3-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 Antonarakis18), 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 recently20 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 blastoid 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-polymerase factors, and TP53, the cell of origin is believed to be a plasmacytoid dendritic cell.11,12 Interestingly, at least 1 genetic alteration, the balanced translocation t(3;5)(q13;q31), which appears specific to BPDCN has recently been identified.21 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.22 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 extratrabermal 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-ILF 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, PDGFRB, 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 normal 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, RBL1, 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
transcription factors such as RUNX1 and noncoding region mutations resulting in ectopic expression of these factors. In addition to genes that are more commonly associated with myeloid neoplasms and are otherwise rare in T-ALL (such as IDH1/2, TLX3, ZEB2, MYB, and MYC), certain transcription factors are also associated with activating mutations in T-ALL recognized as a provisional entity in the 2016 WHO revision. ETP-ALL frequently has mutations in NOTCH1 in 50% to 60% of non-ETP T-ALL patients. Finally, translocations (t(12;21)(p13;q22); ETV6-RUNX1) and (t(1;19)(q23;p13); TCF3-PBX1 (E2A-PBX1)) are common in non-ETP T-ALL (but the clinical relevance of these alterations is not well defined). Therapeutic targets.29

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

<table>
<thead>
<tr>
<th>Disease subtype*</th>
<th>Genes†</th>
<th>Frequency, %</th>
<th>Normal function</th>
<th>Technology used to detect</th>
<th>Prognostic marker‡</th>
<th>Genotype-directed therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-ALL</td>
<td>BCR-ABL1</td>
<td>25</td>
<td>Tyrosine kinase</td>
<td>FISH, PCR</td>
<td>Adverse</td>
<td>TKIs</td>
</tr>
<tr>
<td></td>
<td>BCR-ABL1-like</td>
<td>10-20</td>
<td>Various but nearly all are mitogenic-signaling molecules</td>
<td>GEP</td>
<td>Adverse</td>
<td>TKIs</td>
</tr>
<tr>
<td>iAmp 21</td>
<td>Hypodiploidy (≤45 chromosomes)</td>
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<td>RUNX1 transcription factor</td>
<td>FISH</td>
<td>Adverse</td>
<td></td>
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<tr>
<td></td>
<td>t(17;19)(q22;p13); TCF3-HLF</td>
<td>Rare</td>
<td>Transcription factor</td>
<td>Karyotype, FISH</td>
<td>Adverse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>t(1;19)(q31.3); KMT2A fusions</td>
<td>2-10</td>
<td>Histone methyltransferase</td>
<td>Karyotype, FISH</td>
<td>Adverse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High hyperdiploidy (51-65 chromosomes)</td>
<td>20%-30% (children); 5%-10% (adults)</td>
<td>Transcription factor</td>
<td>Karyotype, FISH</td>
<td>Adverse</td>
<td></td>
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<tr>
<td></td>
<td>t(12;21)(p13;q22); ETV6-RUNX1</td>
<td>20%-30% (children)</td>
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<td>t(5;14)(q31.1;q32.3); IL3-IGH</td>
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<td>t(1;19)(q23;p13.3); TCF3-PBX1</td>
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<td>FBXW7</td>
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<td>FLT3</td>
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</table>

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.

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)) as defined by 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 5q1 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

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 Ferrando32). Currently, the early 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 Ferrando32).
Table 3. Genetic alterations of diagnostic use and/or therapeutic or prognostic value in routine clinical practice in select B-cell lymphoid neoplasms

<table>
<thead>
<tr>
<th>Disease subtype</th>
<th>Genes*</th>
<th>Frequency, %</th>
<th>Normal function</th>
<th>Technology used to detect</th>
<th>Prognostic marker†</th>
<th>Genotype-directed therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLL/SLL</strong></td>
<td>NOTCH1</td>
<td>Up to 15</td>
<td>Notch pathway</td>
<td>Sequencing</td>
<td>Adverse</td>
<td>Trials of NOTCH inhibitors</td>
</tr>
<tr>
<td></td>
<td>SF3B1</td>
<td>15-20</td>
<td>mRNA splicing</td>
<td>Sequencing</td>
<td>Adverse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TP53 mutation or deletion</td>
<td>7-15</td>
<td>Tumor suppressor</td>
<td>Sequencing and cytogenetic/</td>
<td>Adverse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATM mutation or deletion</td>
<td>9-12</td>
<td>Tumor suppressor</td>
<td>FISH analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LPL</strong></td>
<td>MYD88</td>
<td>~90</td>
<td>Couples TLR to NF-κB</td>
<td>Sequencing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CXCR4</td>
<td>~30</td>
<td>Chemokine receptor</td>
<td>Sequencing</td>
<td></td>
<td>Trials of CXCR4 inhibitors</td>
</tr>
<tr>
<td><strong>HCL</strong></td>
<td>BRAFT</td>
<td>~100</td>
<td>MAPK pathway</td>
<td>Sequencing</td>
<td></td>
<td>BRAFT inhibitors</td>
</tr>
<tr>
<td></td>
<td>MAP2K1†</td>
<td>~50% in HCL-v</td>
<td>MAPK pathway</td>
<td>Sequencing</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FL/GCB DLBCL</strong></td>
<td>BCL2</td>
<td>50-90</td>
<td>Antiapoptotic</td>
<td>FISH</td>
<td></td>
<td>Venetoclax</td>
</tr>
<tr>
<td></td>
<td>KMT20/MLL2</td>
<td>89/27</td>
<td>H3K4 methyltransferase</td>
<td>Sequencing</td>
<td></td>
<td>Trials of HDAC inhibitors</td>
</tr>
<tr>
<td></td>
<td>CREBBP</td>
<td>41/42</td>
<td>Histone acetyltransferase</td>
<td>Sequencing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EP300</td>
<td>9/10</td>
<td>Histone acetyltransferase</td>
<td>Sequencing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EZH2</td>
<td>7/22</td>
<td>H3K27 methyltransferase</td>
<td>Sequencing</td>
<td></td>
<td>Trials of EZH2 inhibitors</td>
</tr>
<tr>
<td></td>
<td>MEF2B</td>
<td>13/8-18</td>
<td>Transcription factor</td>
<td>Sequencing</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>MAP2K1†</td>
<td>43% in pediatric-type FL</td>
<td>MAPK pathway</td>
<td>Sequencing</td>
<td></td>
<td></td>
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<tr>
<td><strong>ABC DLBCL</strong></td>
<td>MYD88</td>
<td>29</td>
<td>Couples TLR to NF-κB</td>
<td>Sequencing</td>
<td></td>
<td>Trials of IRAK1/4 inhibitors</td>
</tr>
<tr>
<td></td>
<td>CARD11</td>
<td>10</td>
<td>Couples BCR to NF-κB</td>
<td>Sequencing</td>
<td></td>
<td>Trials of MALT1 inhibitors</td>
</tr>
<tr>
<td></td>
<td>CD79A/CD79B</td>
<td>3/18</td>
<td>Components of BCR</td>
<td>Sequencing</td>
<td></td>
<td>Trials of BTK, SYK inhibitors</td>
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<tr>
<td></td>
<td>TNFAIP3</td>
<td>57</td>
<td>Inhibits NF-κB</td>
<td>Sequencing</td>
<td></td>
<td>Pentaxime inhibitors</td>
</tr>
<tr>
<td><strong>Burkitt</strong></td>
<td>MYC</td>
<td>~100</td>
<td>Transcription factor</td>
<td>FISH</td>
<td></td>
<td>Trials of BET inhibitors</td>
</tr>
<tr>
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<td>ID3</td>
<td>~70</td>
<td>Inhibitors of TCF3</td>
<td>Sequencing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TCF3</td>
<td>~30</td>
<td>Regulates mTOR pathway</td>
<td>Sequencing</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MCL</strong></td>
<td>t(11;14)</td>
<td>80%-90%</td>
<td>Cell cycle regulator</td>
<td>FISH</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>t(14;18)</td>
<td>10-15</td>
<td>Signal transduction molecule</td>
<td>FISH</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>cHL/PMBL</strong></td>
<td>PD-L1/L2</td>
<td>~95</td>
<td>Inhibit T-cell activation</td>
<td>Sequencing</td>
<td></td>
<td>PD-1/PD-L1 blockade</td>
</tr>
<tr>
<td></td>
<td>B2M</td>
<td>70/64</td>
<td>MHC class I coexpression</td>
<td>Sequencing</td>
<td></td>
<td>Favorable</td>
</tr>
<tr>
<td></td>
<td>TNFAIP3</td>
<td>44/60/36</td>
<td>Inhibits NF-κB</td>
<td>Sequencing</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>PTPN1</td>
<td>20/22</td>
<td>Phosphatase</td>
<td>Sequencing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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.\(^3^8\)

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.\(^3^9\) 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.\(^7\) 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),\(^4^0\) 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.\(^4^3\)\(^-^4^5\)

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\(^1^2,^4^6,^4^7\) and predict outcome after allogeneic transplantation.\(^4^8,^4^9\) The use of molecular genetic alterations to determine prognosis of MDS has recently been extensively reviewed.\(^3^7\)

### 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\(^5^0\)), 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 **PDGFRα**, **PDGFRβ**, or **FGFR1**, or the **PCGF1-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.\(^5^1\) These conditions are also distinct from chronic eosinophilic leukemia, not otherwise specified, which does not harbor any of these translocations.\(^5^2\)

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.\(^5^3\)\(^-^5^6\) 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\(^5^7\) as well as **MPL** and **CALR** mutations in ET and MF patients.\(^5^8\)\(^-^6^0\) 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 diagnosed 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. 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 and >500 whole exomes 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 Guyéze and Wu,77 and Lazarian et al78; 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, 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 HL has now been recognized which typically presents as a large localized inguinal mass without BCL2 rearrangements, but with 1p36 deletions and frequent STAT6 and TANKSF14 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 patients.87-89 (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.90 MYD88/L265P mutations are also found in IgM (but not IgG or IgA) monoclonal gammapathy of unknown significance and not in multiple myeloma (MM) even if IgM expressing.91 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-kB 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 ML2L3, CREBBP, and EP300), regulation of
BCL6 protein activity (MEF2B), and cell cycle or apoptosis (such as FOXO1 and TP53) (reviewed recently by Intlekofer and Younes\textsuperscript{96}).

The role of MYC alterations in DLBCL has been extensively studied in recent years (see review by Ott et al\textsuperscript{100}). MYC rearrangements are detected in 5% to 15% of DLBCL not otherwise specified (NOS) and are often associated with GCB phenotype (\textsim}\%). IG are the partner genes in nearly 50% of these cases (reviewed recently by Campo\textsuperscript{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\textsuperscript{102,103} and a few suggest the importance of MYC partner genes.\textsuperscript{102,104} However, it remains controversial whether MYC rearrangements as a single hit or its frequent association with BCL2 or BCL6 (DH) rearrangements is responsible for the aggressive behavior (reviewed recently by Swerdlow\textsuperscript{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.\textsuperscript{106} In contrast to many reports in the literature, concurrent BCL2 or BCL6 translocations (DH cases) did not have independent prognostic value in this 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\textsuperscript{107}; they were almost entirely excluded in this study but might have been included in previously published retrospective studies.\textsuperscript{108,109}

Extra copies of MYC and/or BCL2 appear to confer worse prognosis but this finding needs to be validated by additional studies.\textsuperscript{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.\textsuperscript{112,113} Dual/double expressor DLBCL remains in the DLBCL, NOS category in the 2016 WHO revision.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{121} B2M mutations and CIITA alterations lead to diminished major histocompatibility complex class I and II expression in cHL and PMBL, respectively.\textsuperscript{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.\textsuperscript{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\textsuperscript{−} MCL.\textsuperscript{124} Furthermore, Ig/CCND2 but not CCND3 translocations are detected in half of cyclin D1\textsuperscript{−} MCL.\textsuperscript{125} Interestingly, CCND3 upregulation and mutation has been recently described in splenic diffuse red-pulp small B-cell lymphoma and BL.

\begin{table}[h]
\centering
\caption{Genetic alterations of diagnostic use and/or therapeutic or prognostic value in routine clinical practice in select NK- and T-cell neoplasms.} 
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
\textbf{Disease subtype} & \textbf{Genes*} & \textbf{Frequency, %} & \textbf{Normal function} & \textbf{Technology used to detect} & \textbf{Prognostic marker†} & \textbf{Genotype-directed therapies} \\
\hline
\textit{ALCL} & \textit{ALK rearrangement} & 100% of ALK\textsuperscript{+} ALCL & Kinase & FISH & Favorable & ALK inhibitors \\
 & \textit{DUSP22/IRF4} & 30% of ALK\textsuperscript{−} ALCL & Phosphatase & FISH & Favorable & ALK inhibitors \\
 & \textit{TP53} & 8% of ALK\textsuperscript{−} ALCL & Tumor suppressor & Sequencing & Adverse & JAK/STAT inhibitors \\
 & \textit{STAT3} & 38% of ALK\textsuperscript{−} ALCL & JAK-STAT signaling intermediate & FISH & JAK/STAT signaling inhibitors \\
\hline
\textit{AITL/PTCL} & \textit{RH0A} & 67/18 & GTPase & Sequencing & & \\
 & \textit{IDH2} & \textsim}13/0 & α-KG hydroxylase in TCA cycle & Sequencing & & \\
 & \textit{TET2} & \textsim}70/30 & DNA hydroxymethylation & Sequencing & & \\
 & \textit{DNMT3A} & \textsim}23/12 & DNA methyltransferase & Sequencing & & \\
\hline
Other T/NK lymphoma & \textit{STAT3} & Up to 70% in LGL, 10% in γδ-TCL & JAK-STAT signaling intermediate & Sequencing & & \\
 & \textit{STAT5b} & Up to 35% in γδ-TCL & JAK-STAT signaling intermediate & Sequencing & JAK/STAT inhibitors & \\
 & \textit{SETD2} & Up to 90% in MEITL and 25% in γδ-TCL & H3K36 trimethyltransferase & Sequencing & & \\
 & \textit{PLCy} & 15% in PTCL NOS & Component of TCR pathway & Sequencing & JAK/STAT inhibitors & \\
\hline
\end{tabular}
\end{table}

\begin{itemize}
\item AITL/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.
\item *Mutations in gene names in bold are of diagnostic value.
\item †Those genes left blank do not have clear prognostic relevance currently.
\end{itemize}
but not MCL.\textsuperscript{115,116,126} Genomic studies in MCL have revealed additional driver mutations in genes including ATM, TP53, CCND1, and UBR5.\textsuperscript{127} NOTCH1 and NOTCH2 mutations, although less frequent in MCL, are associated with poor prognosis and are potential therapeutic targets.\textsuperscript{127,128}

**Hairy cell leukemia**

The discovery of BRAFV600E mutations provided a molecular basis to distinguish classic hairy cell leukemia (cHCL) from hairy cell leukemia (HCL) variant and HCL expressing IGHV4-34.\textsuperscript{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,\textsuperscript{131} and IGHV4-34+ HCL.\textsuperscript{131} Interestingly, mutations in BRAFV600E and MAP2K1 appear to sensitize HCL to RAF\textsuperscript{132,133} and MEK\textsuperscript{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 BRAFV600E mutations, remains uncertain.\textsuperscript{136} Of note, besides molecular testing, BRAFV600E can be reliably detected at the protein level by immunohistochemical stain using a mutant protein-specific antibody.\textsuperscript{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\textsuperscript{138} and Manier et al\textsuperscript{139}). Genome-wide association studies have revealed genetic loci associated with increased risk of developing MM and specific disease phenotypes.\textsuperscript{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(1;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.\textsuperscript{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.\textsuperscript{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\textsuperscript{+} and ALK\textsuperscript{−} subgroups.\textsuperscript{147} (Table 4). GEP studies have shown that ALK\textsuperscript{−} ALCL has a signature similar to that of ALK\textsuperscript{+} ALCL but well separated from other NK/T-cell lymphomas.\textsuperscript{148,149} ALK\textsuperscript{−} 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\textsuperscript{+} ALCL.\textsuperscript{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/RB4 on chromosome 6p25 identify a unique subset of ALK\textsuperscript{−} 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.\textsuperscript{151}

Recent 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, DNM3A, RHOA, and CD28 mutations, as well as gene fusions such as ITK-SYK and CTLA4-CD28 (reviewed recently by Wang et al\textsuperscript{152} and Iqbal et al\textsuperscript{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.\textsuperscript{154} At the same time, TET2 and IDH1/2 mutations frequently coexist within AITL,\textsuperscript{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.\textsuperscript{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).\textsuperscript{158} The related STAT5B is mutated far less in LGL, but more commonly in T-cell prolymphocytic leukemia\textsuperscript{159} and enteropathy-associated T-cell lymphoma, type II (renamed as morphomorphic epitheliotropic intestinal T-cell lymphoma [MElTIL] in the 2016 WHO revision).\textsuperscript{160-162} Both STAT3 and STAT5B are also mutated in γ6-hepatosplenic/cutaneous T-cell lymphoma and nasal-type NK-/T-cell lymphoma.\textsuperscript{160,163,164} (Table 4). SETD2 mutations were recently identified in up to 90% of MElTIL and 25% of γ6-hepatosplenic T-cell lymphomas.\textsuperscript{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).\textsuperscript{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\textsuperscript{114}) with ~50% of patients having a BRAFV600E mutation\textsuperscript{170} while BRAFV600 wild-type patients harbor mutually exclusive MAP2K1, ARAF, NRAS, or KRAS mutations (reviewed recently by Durham et al\textsuperscript{171}). Rare in-frame activating deletions in
BRAF\textsuperscript{172} as well activating BRAF, ALK, and NTRK1 fusions have also been identified in BRAFV600 wild-type cases.\textsuperscript{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.\textsuperscript{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\textsuperscript{174-177} and combined DNA/RNA-sequencing\textsuperscript{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,\textsuperscript{180} Meldrum et al.,\textsuperscript{181} and Kanagal-Shamanna et al.\textsuperscript{182}) and allow use of formalin-fixed paraffin-embedded specimens. Further improvements in next-generation sequencing technologies (reviewed by Shekine et al.\textsuperscript{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 genes in a clinically relevant timeframe.

Given the large number of patients required to evaluate the effects of most genetic alterations on clinical outcome,\textsuperscript{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\textsuperscript{34-36} and CLL,\textsuperscript{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 (18-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.

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