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# Clinically relevant core genes for hematologic malignancies in clinical NGS panel testing

**TO THE EDITOR:** Recent advancements in next-generation sequencing (NGS) technologies have enabled comprehensive genomic characterization of hematological malignancies. This has led to the discovery of numerous biomarkers, transforming the diagnosis, risk stratification, and personalized therapeutic intervention for these diseases. With the clinical significance of molecular testing, an increasing number of laboratories offer NGS analysis for hematological malignancies. Although various in-house and commercial panels are available, the target of genomic regions and genes of each panel are different. Therefore, I want to suggest several clinically relevant core genes for hematologic malignancies panels focusing on DNA testing, and, it will be helpful when employing clinically applicable NGS panel testing for hematologic malignancies.

## MYELOID MALIGNANCIES PANEL

According to the recently released 5th edition of the World Health Organization Classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms [1], the myeloid malignancies panel should target genes of newly defined entities: *NPM1* and *CEBPA*, and molecular alterations defining "AML, myelodysplasia-related", such as *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1*, and *ZRSR2* for acute myeloid leukemia. Newly defined entities for myelodysplastic neoplasms (MDS), *SF3B1* and *TP53*, and the diagnostic criteria for BCR-ABL1-negative myeloproliferative neoplasms (MPN), *JAK2, CALR, MPL, CSF3R*, and *KIT*, should also be targeted.

With respect to prognosis, the recently released Molecular International Prognostic Scoring System for myelodysplastic syndromes (IPSS-M) [2] offers a curated list of 31 genes that merit prioritization. Also, certain genes are known to correlate with poor prognosis in *BCR::ABL1*-negative MPN. Moreover, the myeloid malignancy panel requires testing for therapeutic markers, such as *FLT3* mutations (including *FLT3*-ITD) and *IDH1/2* mutations to select targeted drugs for acute myeloid leukemia (AML), and *ABL1* mutations to assess the response to tyrosine kinase inhibitor drugs for chronic myeloid leukemia (CML) [3].

In addition to, the 5th edition of the WHO classification of hematolymphoid tumors recognizes subtypes of myeloid neoplasms associated with germline predisposition to myeloid and histiocytic/dendritic neoplasms [1], and genes for these subtypes should be included in the panel. A comprehensive summary of the genes related to myeloid malignancies and their clinical significance is presented in Table 1.

## ACUTE LYMPHOBLASTIC LEUKEMIA PANEL

In the recently released 5th edition of the World Health Organization classification of hematolymphoid tumors: lymphoid neoplasms [4], the category denoted as *BCR::ABL1*-like features have gained acknowledgment for their diverse array of genetic abnormalities, including JAK-STAT alterations, *ABL1* class fusions, and various other mutations. Mutations in *SH2B3, IL7R*, and *JAK1/2/3* have been linked to JAK-STAT alteration [5]. Moreover, the ICC 2022 classification introduced two distinctive entities characterized by hotspot point mutations: *IKZF1* N159Y and *PAX5* P80R [6]. In T-cell lymphoblastic leukemia (T-ALL), *NOTCH1* activating mutations and CDKN2A/B deletions represented pivotal pathogenic genes, collectively detected in 50–60% of cases, and approximately 30% of T-ALL cases exhibiting *NOTCH1* mutations were concomitant with *FBXW7* mis-

**Table 1.** Genetic alterations of diagnostic, prognostic, and therapeutic impacts in myeloid malignancies.

| Gene | AML | | | MDS | | | MPN | | | Germline predisposition |
|---|---|---|---|---|---|---|---|---|---|---|
| | Diagnostic | Prognostic | Therapeutic | Diagnostic | Prognostic | Therapeutic | Diagnostic | Prognostic | Therapeutic | |
| *ANKRD26* | | | | | | | | | | O |
| *ASXL1* | O[b] | Adverse | | | Adverse | | | Adverse | | |
| *BCOR* | O[b] | | | | Adverse | | | | | |
| *BCORL1* | | | | | Adverse | | | | | |
| *BLM* | | | | | | | | | | O |
| *CALR* | | | | | | | O | | | |
| *CBL* | | | | | Adverse | | | | | |
| *CEBPA* | O[a] | Favorable | | | | | | | | O |
| *CSF3R* | | | | | | | O | | | |
| *DDX41* | | | | | | | | | | O |
| *DNMT3A* | | Adverse | | | Adverse | | | Adverse | | |
| *ETV6* | | | | | Adverse | | | | | O |
| *EZH2* | O[b] | | | | Adverse | | | Adverse | | |
| *FLT3* | | Adverse (*FLT3*-ITD) | O (midostaurin, gilteritinib, quizartinib) | | Adverse (*FLT3*-ITD +TKD) | | | | | |
| *GATA2* | | | | | | | | | | O |
| *IDH1* | | | O (ivosidenib, olutasidenib) | | | | | Adverse | | |
| *IDH2* | | | O (enasidenib) | | Adverse | | | Adverse | | |
| *JAK2* | | | | | | | O | | | O |
| *KIT* | | | | | | | O | | | |
| *KRAS* | | | | | Adverse | | | Adverse | | |
| *MLL* (*KMT2A*) | | | | | Adverse | | | | | |
| *MPL* | | | | | | | O | | | |
| *NPM1* | O[a] | Favorable | | | Adverse | | | | | |
| *NRAS* | | | | | Adverse | | | Adverse | | |
| *RUNX1* | O[b] | Adverse | | | Adverse | | | | | |
| *SAMD9* | | | | | | | | | | O |
| *SAMD9L* | | | | | | | | | | O |
| *SETBP1* | | | | | Adverse | | | | | |
| *SF3B1* | O[b] | | | O[a] | Favorable or adverse[c] | | | | | |
| *SRSF2* | O[b] | | | | Adverse | | | | | |
| *STAG2* | O[b] | | | | Adverse | | | | | |
| *TET2* | O | Adverse | | | | | | Adverse | | |
| *TP53* | | Adverse | | O[a] | Adverse | | | Adverse | | O |
| *U2AF1* | O[b] | | | | Adverse | | | Adverse | | |
| *WT1* | | Adverse | | | Adverse | | | | | |
| *ZRSR2* | O[b] | | | | | | | | | |

[a]Target genes of newly defined entities. [b]MDS-related molecular genetic abnormalities. [c]Adverse prognosis is *SF3B1* mutation in the presence of isolated del(5q), that is, del(5q) alone or with one additional aberration excluding -7/del(7q). The *SF3B1* mutation without mutations in *BCOR, BCORL1, RUNX1, NRAS, STAG2, SRSF2,* or del(5q) was found to be favorable.
Abbreviations: AML, acute myeloid leukemia; MDS, myelodysplastic neoplasm; MPN, myeloproliferative neoplasm.

sense mutations [7]. In contrast to T-ALL, early T-cell precursor acute lymphoblastic leukemia (ETP-ALL) were manifested with distinctive genetic anomalies that distinguished it from conventional T-ALL. ETP-ALL lacked the common alterations observed in T-ALL, including *NOTCH1* mutations and *CDKN2A/B* deletions. ETP-ALL was presented with a high incidence of mutations typically associated with acute myeloid leukemia (AML) [8].

In terms of prognosis, certain genes, including *TP53* and those associated with chromatin modification such as *CREBBP* and *SETD2,* had demonstrated a correlation with an unfavorable prognosis in B-ALL. Moreover, copy number deletions of *IKZF1* have been linked to poorer outcomes; in particular, the *IKZF1* plus condition, characterized by the deletion of *IKZF1* along with co-occurring deletions in *CDKN2A*, *CDKN2B*, *PAX5*, or *PAR1* in the absence of

*ERG* deletion, was associated with worse prognostic outcomes, especially in pediatric patients with B-ALL [9]. Moreover, both B-ALL cases exhibiting *BCR::ABL1*-like features and those characterized as early T-cell precursor (ETP)-ALL represented a subtype of high-risk acute lymphoblastic leukemia (ALL). The presence of genetic mutations associated with these diagnostic entities is also indicative of poor prognosis, further underscoring the clinical implications of the molecular aberrations [10]. Among the genetic alterations associated with relapse, activating mutations in the 5'-Nucleotidase Cytosolic II (*NT5C2*) gene are notably prevalent and are detected in approximately 10% of relapsed B-precursor acute lymphoblastic leukemia (ALL) cases and in about 20% of T-cell ALL cases [11].

Similar to CML, it is essential to test for *ABL1* mutations and the *PDGFRB* C843G mutation, as they confer resistance to the tyrosine kinase inhibitors (TKIs) frequently used in the treatment of individuals with Philadelphia chromosome-positive ALL (ph+-ALL) [12]. Moreover, *CREBBP* mutations have been identified as contributors to glucocorticoid resistance in B-cell precursor acute lymphoblastic leukemia [9]. It is also crucial to consider the impact of germline variants in drug-metabolizing enzyme genes, specifically *TPMT* and *NUDT15*, and on the risk of thiopurine toxicity, which is integral to the successful treatment of ALL [13]. These insights underscore the significance of genetic testing

**Table 2.** Genetic alterations of diagnostic, prognostic, and therapeutic impacts in acute lymphoblastic leukemia.

| Gene | B-ALL | | | T-ALL | | | Germline predisposition |
|---|---|---|---|---|---|---|---|
| | Diagnostic | Prognostic | Therapeutic | Diagnostic | Prognostic | Therapeutic | |
| *ABL1* | | | O (TKI resistance) | | | | |
| *BRAF* | O (*BCR::ABL1*-like) | Adverse | | | | | |
| *CDKN2A* | | Adverse | | | | | |
| *CREBBP* | | Adverse | O (glucocorticoid therapy resistance) | | | | |
| *DNMT3A* | | | | O (ETP-ALL) | Adverse | | |
| *EED* | | | | O (ETP-ALL) | Adverse | | |
| *EP300* | | | | O (ETP-ALL) | Adverse | | |
| *ETV6* | | | | | | | O |
| *EZH2* | | | | O (ETP-ALL) | Adverse | | |
| *FBXW7* | | | | O (cT-ALL) | | | |
| *FLT3* | O (*BCR::ABL1*-like) | Adverse | | O (ETP-ALL) | Adverse | | |
| *GATA3* | | | | O (ETP-ALL) | Adverse | | |
| *IKZF1* | O (N159Y) | Adverse | | | | | O |
| *IL7R* | O (*BCR::ABL1*-like) | Adverse | | O (ETP-ALL) | Adverse | | |
| *JAK1* | O (*BCR::ABL1*-like) | Adverse | | O (ETP-ALL) | Adverse | | |
| *JAK2* | O (*BCR::ABL1*-like) | Adverse | | | | | |
| *JAK3* | O (*BCR::ABL1*-like) | Adverse | | O (ETP-ALL) | Adverse | | |
| *KRAS* | O (*BCR::ABL1*-like) | Adverse | | O (ETP-ALL) | Adverse | | |
| *NF1* | O (*BCR::ABL1*-like) | Adverse | | O (ETP-ALL) | Adverse | | |
| *NOTCH1* | | | | O (cT-ALL) | | | |
| *NRAS* | O (*BCR::ABL1*-like) | Adverse | | O (ETP-ALL) | Adverse | | |
| *NT5C2* | | Adverse | O (chemotherapy resistance) | | | | |
| *NUDT15* | | | O (thiopurine toxicity) | | | | |
| *PAX5* | O (P80R) | | | | | | O |
| *PDGFRB* | | | O (C843G; TKI resistance) | | | | |
| *PHF6* | | | | O (ETP-ALL) | Adverse | | |
| *PTPN11* | O (*BCR::ABL1*-like) | Adverse | | O (ETP-ALL) | Adverse | | |
| *RUNX1* | | | | O (ETP-ALL) | Adverse | | O |
| *SETD2* | | Adverse | O (chemotherapy resistance) | O (ETP-ALL) | Adverse | | |
| *SH2B3* | | | | O (ETP-ALL) | Adverse | | |
| *SUZ12* | | | | O (ETP-ALL) | Adverse | | |
| *TP53* | | Adverse | | | Adverse | | O |
| *TPMT* | | | O (thiopurine toxicity) | | | | |
| *WT1* | | | | O (ETP-ALL) | Adverse | | |

Abbreviations: cT-ALL, conventional T-cell acute lymphoblastic leukemia; ETP-ALL, early T-cell acute lymphoblastic leukemia.

in developing therapeutic strategies and predicting treatment responses in patients with ALL. A comprehensive summary of the genes related to ALL and their clinical significance is provided in Table 2.

## LYMPHOID NEOPLASM PANEL

The genetic landscape of lymphoma and chronic lymphocytic leukemia (CLL) presents substantial complexity and diversity in most cases. Recent years have witnessed a rapid accumulation of knowledge, revealing a growing catalogue of recurrently mutated genes and their consequential clinical implications, which have been facilitated by advancements in next-generation sequencing technologies. Certain gene mutations within this spectrum have a significant influence on the diagnostic, prognostic, and therapeutic aspects of lymphoid neoplasms. Furthermore, recent multiplatform genomic studies have shed light on genetic subtypes and distinctive genetic features of Diffuse Large B-cell Lymphoma (DLBCL) [14]. These findings improve our understanding of the genetic underpinnings of DLBCL, which is a critical advancement in this field. The genes associated with lymphoma and chronic lymphocytic leukemia, along with their clinical significance encompassing diagnostic, prognostic, and therapeutic impacts, are compiled and presented in

**Table 3.** Genetic alterations of diagnostic, prognostic, and therapeutic impacts in lymphoma and chronic lymphocytic leukemia.

| | Disease | Gene | Diagnostic | Prognostic | Therapeutic | Reference |
|---|---|---|---|---|---|---|
| B-cell lymphoid neoplasm | CLL/SLL | *ATM* | O | Adverse | | [7] |
| | | *BIRC3* | O | Adverse | O (fludarabine refratory) | [15] |
| | | *BTK* | O | | O (C481S; ibrutinib resistance) | [16] |
| | | *NOTCH1* | O | Adverse (Richter syndrome) | | [7] |
| | | *SF3B1* | O | Adverse | | [7] |
| | | *TP53* | O | Adverse | O (fludarabine refratory; Idelalisib, Idelalisib+rituximab indication) | [7] |
| | WM/LPL | *CXCR4* | O | Adverse | | [17] |
| | | *MYD88* L265P | O | Favorable | | [17] |
| | HCL | *BRAF* V600E | O | | | [7] |
| | ABC DLBCL | *BTG1* | O (MCD subtype) | Adverse | | [14, 18] |
| | | *CD79B* | O (MCD subtype) | Adverse | | [14, 18] |
| | | *CDKN2A* | O (MCD subtype) | Adverse | | [14, 18] |
| | | *MYD88* L265P | O (MCD subtype) | Adverse | | [14, 18] |
| | | *NOTCH1* | O (N1 subtype) | Adverse | | [14, 18] |
| | | *PIM1* | O (MCD subtype) | Adverse | | [14, 18] |
| | | *TP53* | O (A53 subtype) | Adverse | | [14, 18] |
| | GCB DLBCL/FL | *EZH2* | O (EZB subtype) | Favorable | O (tazemetostat in FL) | [3, 14, 18] |
| | | *FAS* | O (EZB subtype) | Favorable | | [14, 18] |
| | | *SGK1* | O (ST2 subtype) | Favorable | | [14, 18] |
| | | *SOCS1* | O (ST2 subtype) | Favorable | | [14, 18] |
| | | *TET2* | O (ST2 subtype) | Favorable | | [14, 18] |
| | | *TNFRSF14* | O (EZB subtype) | Favorable | | [14, 18] |
| | SMZL | *NOTCH2* | O | Adverse | | [7] |
| | | *TP53* | | Adverse | | [16] |
| | cHL/PMBL | *B2M* | O | Favorable | | [7] |
| | | *TNFAIP3* | O | | | [7] |
| T-cell lymphoid neoplasm | BL | *CCND3* | O | | | [19] |
| | | *ID3* | O | | | [7] |
| | | *TCF3* | O | | | [7] |
| | LGLL | *STAT3* | O | | | [16] |
| | | *STAT5B* | O | | | [16] |
| | AITL/PTCL | *DNMT3A* | O | | | [16] |
| | | *IDH2* | O | | | [16] |
| | | *RHOA* | O | | | [16] |
| | | *TET2* | O | | | [16] |
| | NKTCL | *DDX3X* | | Adverse | | [16, 20] |

Abbreviations: AITL/PTCL, angioimmunoblastic T-cell lymphoma/peripheral T-cell lymphoma; BL, burkitt lymphoma; cHL/PMBL, classical Hodgkin lymphoma/primary mediastinal large B-cell lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; GCB DLBCL/FL, germinal center B-cell diffuse large B-cell lymphoma/follicular lymphoma; HCL, hairy cell leukemia; ABC DLBCL, activated B-cell diffuse large B-cell lymphoma; LGLL, large granular lymphocytic leukemia; NKTCL, NK-T cell lymphoma; SMZL, splenic marginal zone lymphoma; WM/LPL, Waldenstrom macroglobulinemia/lymphoplasmacytic lymphoma.

Table 3 [3, 7, 14-20] with corresponding references.

## CONCLUSIONS

The evolution of diagnostic methodologies, risk stratification guidelines, and targeted therapies for hematologic malignancies underscores the escalating significance of thoroughly assessing an extensive array of genetic biomarkers when making informed decisions about front-line patient care. Next-generation sequencing (NGS) has emerged as a valuable tool for the prompt delivery of results across a wide spectrum of genetic targets. Moreover, the expeditious establishment of an NGS test system and its streamlined integration into clinical processes should be considered for efficient patient care.

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# *TP53* mutation is a high-risk factor for Richter's syndrome based on circulating tumor DNA

**TO THE EDITOR:** Richter's syndrome (RS) is the progression of CLL to aggressive lymphoma. It occurs in 2–10% of CLL cases and is known to involve several immune and genetic factors; however, the mechanism remains unclear [1, 2]. According to previous retrospective paired-sample studies, genetic aberrations of the *TP53* and *C-MYC* genes, chromosomal abnormalities such as non-del (13q) or del (17p), and unmuted immunoglobulin heavy chains are high-risk factors [1, 2].