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REVIEW ARTICLE

Precision Oncology in Hematological Malignancies: Pharmacogenomics for Enhanced Therapeutic Efficacy and Diminished Toxicity

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ABSTRACT

Hematological malignancies, including acute and chronic leukemias, lymphomas, and multiple myeloma, continue to present clinicians with diverse responses to traditional chemotherapies and kinase inhibitors due to myelosuppression, off-target effects, and acquired resistance. Pharmacogenomics lets you choose the right dose and regimen by showing how changes in important genes in the germ line affect pharmacokinetics, transporter activity, and target engagement. Critical pharmacogenes encompass ABC transporters (ABCB1, ABCC1) linked to multidrug efflux and relapse risk; cytochrome P450 isoforms (e.g., CYP2C19, CYP3A5) that affect tyrosine kinase inhibitor clearance; and TPMT and NUDT15, which are involved in thiopurine metabolism in acute lymphoblastic leukemia (ALL), where deficient variants lead to severe neutropenia. Pre-emptive genotyping has proven effective in diminishing toxicity rates, as evidenced by juvenile acute lymphoblastic leukemia datasets, achieving a 40–60% reduction in thiopurine-related events and enhancing event-free survival through tailored dosing. High initial costs, low-quality assays, limited access in low-resource areas, and equity disparities among diverse ancestries where NUDT15 variations are common continue to be challenges. Emerging multigene panels, AI-enhanced interpretation, and real-world data from initiatives such as the 100,000 Genomes Project promise improved remission rates and quality of life, indicating potential for further integration.

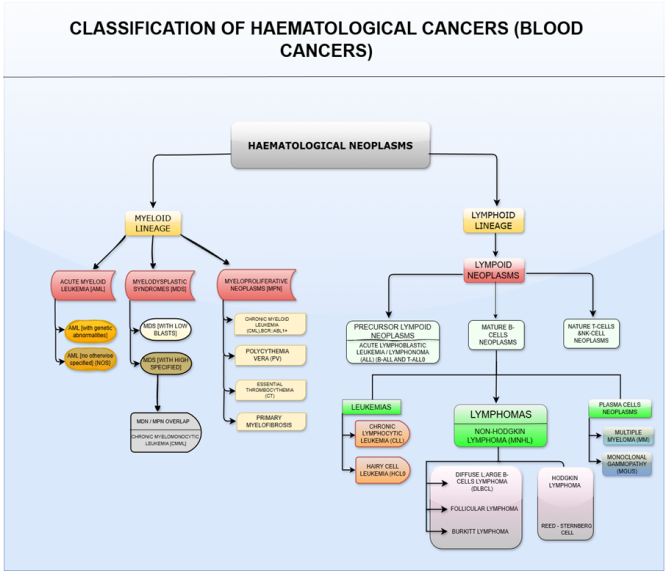
Keywords: Reducing drug toxicity, Variations in TPMT/NUDT15, Precision oncology, Pharmacogenomics, Blood cancers

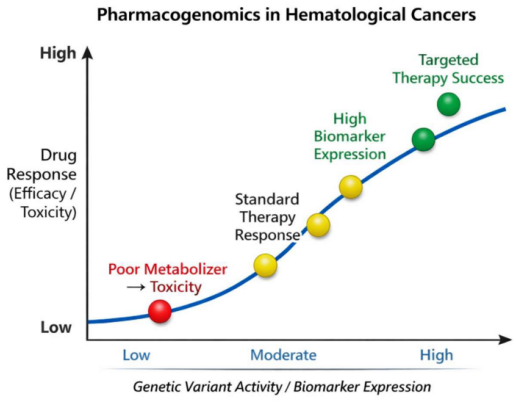
INTRODUCTION

Hematological malignancies—leukemias, lymphomas, and multiple myeloma—are becoming more common around the world. In 2019, there were more than 1.34 million new cases, and by 2030, that number is expected to rise to 4.6 million due to an aging population and better diagnosis[1-3]. These conditions lead to cytopenias, immunological dysregulation, and organ infiltration, resulting in significant morbidity by disrupting hematopoiesis through abnormal proliferation in bone marrow or lymphoid tissues. Although the 5-year survival rate for pediatric acute lymphoblastic leukemia (ALL) and favourable-risk subsets has risen from under 10% in the 1960s to 60–90% due to multi-agent chemotherapy (e.g., vincristine, anthracyclines) and targeted inhibitors (imatinib for BCR-ABL–positive chronic myeloid leukemia [CML], FLT3 antagonists for acute myeloid leukemia [AML]), variability in efficacy, durability, and tolerability among patients persists[4-7]. Pharmacogenomics addresses these issues by mapping germline polymorphisms —single-nucleotide variants in TPMT and NUDT15 that significantly reduce thiopurine catabolism in acute lymphoblastic leukemia, CYP450 variants altering tyrosine kinase inhibitor exposure, and ABCB1 haplotypes limiting intracellular drug accumulation—to predict phenotypes and direct dose optimization[8-11]. Clinical trials demonstrate that a shift from empirical dosage to genotype-guided precision

oncology significantly reduces severe adverse events while preserving relapse-free survival[12, 13].

This review examines the pharmacogenomic determinants of various hematological malignancies, emphasizing clinically actionable variants, supporting trial evidence, implementation barriers such as cost and equity, and emerging trajectories like next-generation sequencing panels integrated with artificial intelligence analytics—strategies that could diminish toxicity, enhance remission durability, and redefine therapeutic stewardship in hematologic oncology[14, 15].





THE CLINICAL ENVIRONMENT FOR HAEMA- TOLOGICAL CANCERS

Hematological malignancies disrupt critical hematopoietic and lymphoid processes, leading to unregulated clonal proliferation that undermines immune surveillance and blood cell formation. Leukemias (30–40% of cases), lymphomas (50–55%), and multiple myeloma (10–15%) are the most common types of these diseases. They make up 7–10% of all cancer diagnoses around the world. The rise in their frequency is associated with improved detection and longevity. Chronic variants evolve gradually, whereas acute variants progress rapidly through blast accumulation; all necessitate subtype-specific treatments informed by cytogenetics and genomics.

PATHOBIOLOGY AND CLASSIFYING DISEASES

Standard taxonomy, which follows WHO 5th edition criteria Table. 1, focuses on cell lineage, maturation arrest, and driver lesions. Myeloma starts in post-germinal plasma cells, lymphomas in lymphoid regions that aren't nodes, and leukemias in marrow progenitors. Ionizing radiation, benzene exposure, immunosuppression, and inherited predispositions like Li-Fraumeni syndrome constitute risk clusters.

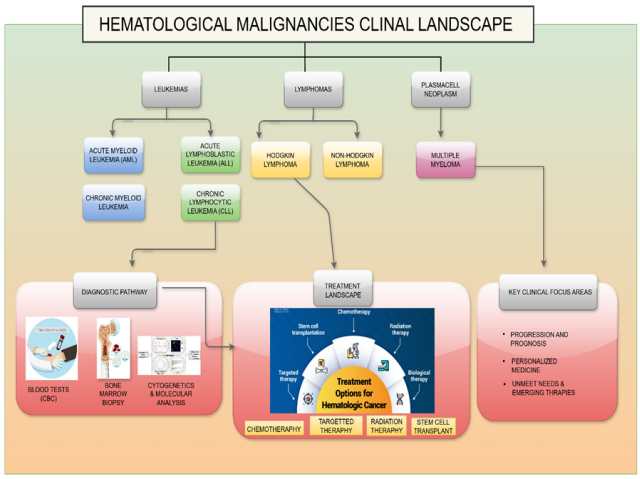


Table 1: Main Hematological Cancers—Types, Sources, and Causes

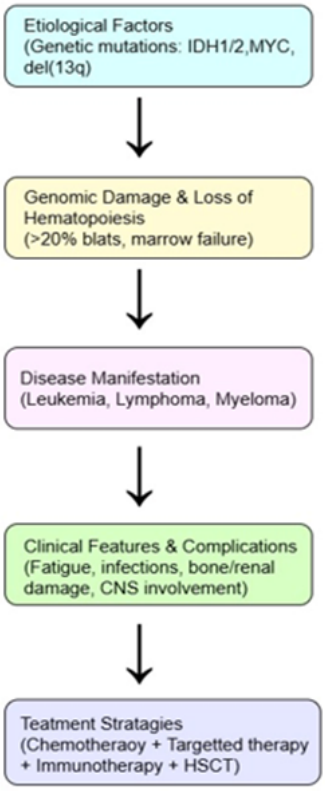
Category	Major Subtypes	Cell of Origin	Key Drivers/Risks
Leukemia	ALL, AML, CLL, CML	B/T precursors, myeloid stem	t (9;22) BCR-ABL; FLT3-ITD; EBV
Lymphoma	Hodgkin; NHL (DLBCL, FL, MCL)	Germinal center B-cells; T-cells	EBV, HTLV-1; t (14;18) BCL2
Myeloma	Hyper diploid; standard risk	Plasma cells (Ig-secreting)	t (11;14) CCND1; del(17p) TP53

This method helps with prognosis; for instance, low-IPI DLBCL responds well to R-CHOP, but Philadelphia+ ALL does not respond well without TKIs.

Spectrum Leukemia

Fatigue, bruising, and sepsis are signs of blasts (>20% marrow infiltration), which stop the production of red blood cells and platelets. In the elderly (median age 68 years) with

IDH1/2 or NPM1 hotspots, AML is the most common type of cancer. ALL peaks bimanually (in children aged 2 to 5 years and adults aged 40 and older), and CLL builds up slowly through del(13q)/ATM loss. Pharmacodynamic obstacles include sanctuary-site persistence (CNS in ALL) and quiescence-induced chemoresistance.



Lymphoma's Heterogeneity

In 40% of Hodgkin lymphomas, Reed-Sternberg cells are found in inflammatory stroma (1%). In DLBCL (30–40%) and follicular (20%) NHL subtypes, translocations like MYC/IgH are found. Extranodal spread (GI, CNS) complicates 20 to 30 percent of patients, and T/NK variants exhibit aggressiveness in the absence of rituximab synergy.

The Cause of Myeloma

Clonal plasma cells (>10% marrow/CD38++CD138+) release paraprotein that erodes bone by upregulating RANKL and producing amyloidogenic light chains that are nephrotoxic in 20% of cases. Even with bortezomib/daratumumab, high-risk cytogenetics (gain(1q), t(4;14)) indicate a median survival of under two years.

Therapeutic arsenal

Multimodality regimens (GCSF, transfusions) keep cytoreduction and cytoprotection in balance. Risk-adapted regimens have resulted in survival rates rising from under 10% in the 1960s to 60–85% in pediatric ALL/CR today.

Chemotherapy foundation

Myelosuppression necessitates hospitalization in 30–50% of induction phases, whereas alkylators (cyclophosphamide), antimetabolites (6-MP), and anthracyclines (daunorubicin) partially eradicate dividing clones. Intrathecal cytarabine reduces meningeal relapse (15% ALL).

Targeted and immunologic agents

TKIs (imatinib 400-800mg CML; midostaurin FLT3+ AML) reach MR4.5 in 60-80% of cases; mAbs (rituximab CD20, daratumumab CD38) work through ADCC/complement; CART (axi-cel brexu refractory DLBCL) gives 40-50% CR but causes cytokine storms in 20% of cases. Bispecifics (teclistamab BCMA-CD3 myeloma) arise for relapse.

Transplant consolidation

Allo-HSCT cures 50-70% of high-risk cases through GVL, utilizing marrow/PBSC/UCB; haploidentical KIR-mismatched grafts are optimized for the 2025 era post-cycle.

Pharmacogenomic foundations

Germline SNPs determine ADME variability: Phase I/II enzymes (CYP3A4/UGT1A1 irinotecan Gilbert's), Phase II (TPMT*3A), and transporters (ABCB1 3435C>T). The interplay between somatic tumors and germline (e.g., ABL T315I resistance) requires panels.

Clinical translation: pros and evidence

Genotyping decreases adverse drug reactions (ADRs): NUDT15 c.415C>T reduces occurrences by half in East Asian cohorts (14% carrier rate); TPMT-poor individuals (0.3%) face fatal neutropenia without intervention. In Ph+ ALL, upfront TKI raises EFS by 10–15%; UGT1A1*28 stops diarrhea from irinotecan.

Dose Optimization: Algorithmic trials are reduced by fifty percent (for example, 6-MP 30-90th percentile).
Efficacy Gains: DPYD*2A/UGT1A1 panels stop 5-FU/irinotecan from failing The St. Jude PGx ALL trial showed that 44% of people had side effects and none had a recurrence.

Problems with putting things into action

The cost-benefit ratio is bad if less than 5% of the test is actionable (USD 500–2000). EHR silos are bad. Ancestry bias affects India/Asia equity because 90% of the data is Caucasian and NUDT15 was not studied enough before 2015. Consent problems come up with incidentalomas (1–2% WGS).

Recent advances in precision blood oncology

AI (Alpha Missense) can read VUS with 80% accuracy. By 2027, NGS trios (tumor-normalgermline) will cost $1,000. Federated learning integrates multi-omic data, while liquid

biopsy MRD (ctDNA BCR-ABL/FLT3) forecasts relapse six months prior. Studies like 100K Genomes support 20% regimen changes in order to achieve 75% toxicity-free CR.

Table 2: Pharmacogenes in Blood Cancers That Can Be Used

Gene	Variant	Drug(s)	Cancer	Phenotype / Clinical Impact
TPMT	*TPMT* *2, *3A, *3C	6-MP / Azathioprine	ALL	Homozygous LOF → ~10% standard dose; severe leukopenia
NUDT15	R139C and other LOF variants	Mercaptopurine	ALL	High Asian prevalence; 30–70% dose reduction
CYP3A5	*CYP3A5* *3 allele	Tacrolimus (HSCT	CML/AML	Poor metabolizer → ↑ drug exposure
BCR-ABL1	T315I mutation	Imatinib	CML	T315I mutation → switch to ponatinib
FLT3	FLT3-ITD mutation	Gilteritinib	AML	FLT3-ITD / MRD+ → requires FLT3 inhibitor
ABCB1	3435C>T	Anthracyclines	AML/NHL	↑ Efflux activity → drug resistance

CPIC levels A/B support the pre-ALL dosage of TPMT/NUDT15, and a 40% decrease in toxicity has been shown.

CONCLUSION

Pharmacogenomics has transformed the management of hematological malignancies by converting germline variants —such as TPMT/NUDT15 deficiencies that reduce thiopurine tolerance, ABCB1 polymorphisms that enhance efflux resistance, and somatic hotspots (BCR-ABL T315I, FLT3-ITD)—into actionable dosing algorithms that decrease severe toxicities by 40-60% and promote event-free survival. The 100,000 Genomes Project's 20% regimen improvements and St. Jude's pediatric ALL trials show that it has moved from trial-and-error to preventive precision. This is especially true during high-stakes induction phases, when 5–10% of patients die from myelosuppression. Persistent challenges such as testing costs (USD 500–2,000/case), ancestry-biased evidence (NUDT15 overlooked in early Caucasian cohorts), EHR silos, and incidental findings limit scalability. But the fact that NGS prices are going down (less than $1,000 per trio by 2027) and AI is able to resolve VUS with 80% accuracy suggests that this technology is becoming more popular. Bispecific, MRD ctDNA monitoring, and federated multi-omics have the potential to achieve 75% toxicity-free remissions, hence mitigating disparities in regions like South Asia.

Pharmacogenomics marks the beginning of a new era in blood cancer research. Genotype-first management that maximizes cures, minimizes morbidity, and optimizes resource allocation necessitates interdisciplinary workflows, comprehensive ancestry databases, and policy harmonization to fully realize the potential of precision medicine.

References

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*. 2016; 127 (20) :2375-2390 . Available from: https://doi.org/10.1182/blood-2016-01-643569
2. Tanaka Y. Pharmacogenomics in hematological malignancy. *Rinsho Ketsueki*. 2022; 63 (10) :1353-1362 . Available from: https://doi.org/10.11406/rinketsu.63.1353
3. Maillard N, Guillemain J, Picard N, Loriot MA, Picard V, Del Bello A, *et al*. Pharmacogenomics in Solid Tumors and Blood Cancers: Making precision medicine fit your needs. *Research in pharmacology*. 176:106047, 2022.
4. Leong IUS, Cabrera CP, Cipriani V, Ross PJ, Turner RM, Stuckey A. Large-Scale Pharmacogenomics Analysis of Patients With Cancer Within the 100,000 Genomes Project Combining Whole-Genome Sequencing and Medical Records to Inform Clinical Practice. *Journal of Clinical Oncology*. 2025; 43 (6) :682-693 . Available from: https://doi.org/10.1200/jco.23.02761
5. Lubis IS, Anggadiredja K, Artarini AA, Sari NM, Suryawan N, Zazuli Z. NUDT15 Pharmacogenetics in Acute Lymphoblastic Leukemia: Synthesizing Progress for Personalized Thiopurine Therapy. *Medical Sciences*. 2025; 13 (3) :112 . Available from: https://doi.org/10.3390/medsci13030112
6. Sánchez-Bayona R, Catalán C, Cobos MA, Bergamino M. Pharmacogenomics in Solid Tumors: A Comprehensive Review of Genetic Variability and Its Clinical Implications. *Cancers*. 2025; 17 (6) :913 . Available from: https://doi.org/10.3390/cancers17060913
7. Cheok MH, Pottier N, Kager L, Evans WE. Pharmacogenetics in acute lymphoblastic leukemia. *Seminars in Hematology*. 2009; 46 (1) :39-51 . Available from: https://doi.org/10.1053/j.seminhematol.2008.09.002
8. Mai N, Fernandez N, Drilon A, Chakravarty D. Precision Oncology: 2025 in Review. *Cancer Discovery*. 2025; 15 (12) :2414-2421 . Available from: https://doi.org/10.1158/2159-8290.cd-25-1784
9. Zhang N, Wu J, Wang Q, Liang Y, Li X, Chen G, *et al*. Global burden of hematologic malignancies and evolution patterns over the

past 30 years. *Blood Cancer Journal*. 2023; 13 (1) . Available from: https://doi.org/10.1038/s41408-023-00853-3

10. Kumbhakar DV, Thakkar L, Akhand C, Sharaf S, Vemuganti GK. Nanomaterials targeting cancer stem cells to overcome drug resistance and tumor recurrence. *Frontiers in Oncology*. 2025; 15 . Available from: https://doi.org/10.3389/fonc.2025.1499283
11. Fokhrul Hossain, Samarpan Majumder, Justin David, Lucio Miele. Precision Medicine and Triple-Negative Breast Cancer: Current Landscape and Future Directions. *Cancers*. 2021; 13 (15) :3739 . Available from: https://doi.org/10.3390/cancers13153739
12. Pan T, Zhang J, Wang X, Song Y. Global burden and trends of hematologic malignancies based on Global Cancer Observatory 2022 and Global Burden of Disease 2021. *Experimental Hematology & Oncology*. 2025; 14 :98 . Available from: https://doi.org/10.1186/s40164-025-00684-x
13. Escalante-Bautista D, Haydeé RV, Cerecedo D. Novel Aspects of Leukemia Pharmacogenomics. *Leukemia*. 2022; :147-164 . Available from: https://doi.org/10.36255/exon-publications-leukemia-pharmacogenomics
14. A Decade of Progress: Transformative Advances in Blood Cancer. *AACR Cancer Progress Report*. 2025; :144-159, 162-176 . Available from: https://cancerprogressreport.aacr.org/wp-content/uploads/sites/2/2025/09/AACR_CPR_2025.pdf
15. Sun K, Wu H, Zhu Q, Gu K, Wei H, Wang S, *et al*. Global landscape and trends in lifetime risks of haematologic malignancies in 185 countries: population-based estimates from GLOBOCAN 2022. *eClinicalMedicine*. 2025; 83 :103193 . Available from: https://doi.org/10.1016/j.eclinm.2025.103193