The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 12, 2025

GENOMIC PROFILING IN HEMATOLOGIC MALIGNANCIES: FROM DIAGNOSIS TO PERSONALIZED THERAPY

Razia Iqbal[*1], Shahid Mahmood[*2], Syed Hasnain Abbas[3], Hurmat E Zainab[4], Nimra Saleem[5], Hafiza Pakeeza Abid[6], Sania Abdul Samad[7]

[*1, * 2, 4, 5, 6, 7] *Department of Zoology, University of Gujrat, Gujrat 50700, Pakistan*
[3] *Aziz Bhatti Shaheed Teaching Hospital, Gujrat 50700, Pakistan*

[*1]razia.iqbal@uog.edu.pk, [*2]shahid.mahmood@uog.edu.pk

DOI: https://doi.org/10.5281/zenodo.20457361

Keywords
Malignancies, Germline predisposition, Transplantation, Genomic profiling, Mutation, Cytogenetics, Cardiotoxic, Stem cell

Article History
Received: 25 October 2025
Accepted: 09 December 2025
Published: 23 December 2025

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Corresponding Author: *
Razia Iqbal
Shahid Mahmood

Abstract
The clinical management of hematologic malignancies is entering a new era, largely driven by combining next-generation sequencing (NGS) and thorough genomic profiling (CGP). This article discusses the profound impact of these innovations on the practice of medicine in hematologic malignancies, highlighting their transition from research instruments to tools of precision medicine. Presently, integrated DNA and RNA profiling tests show great practicability of patient samples such as peripheral blood, bone marrow, and formalin-fixed paraffin-embedded tissue yielding sufficient material for genomic interrogations. Instead of the old method of focusing on a single gene, integrated CGP covers all types of somatic mutations, like base substitutions, insertions/deletions, copy number alterations, as well as complex gene fusions. From genomes analysis, it comes out that the great majority of patients carry at least one reportable driver mutation, and most of them have potentially targetable mutations which can be addressed by FDA-approved or investigational drugs. Most important recurrent mutations such as TP53 TET2 DNMT3A, FLT3, only guide therapy choices but also serve as a foundation for diagnostic and prognostic evaluation in various histologies that include AML MDS CLL, and lymphoid malignancies

Introduction

Precision medicine in the field of hematology refers to the personalization of the strategy of a patient's oncological treatment based on the genetic profile of the patient, his molecular composition and even his lifestyle and his exposure to environmental factors. Historically, the treatment of hematologic malignancies was very nonspecific and was based upon the diagnostic categories in general use at that time. As a result, therapeutic outcomes in patients were quite different from patient to patient. Fortunately, modern progress in genomic databases and molecular diagnostic modalities now allows for the accurate definition of the major changes in the cancer cells that regulate their behavior and therapeutic responsiveness. There are three distinct eras in cellular drug therapy for blood cancers that could be defined as Phase I (pre-2010), which was defined by the one-size-fits-all paradigm of cytotoxic drugs (Collins & Varmus, 2015). Germline predisposition (GPD) to myeloid neoplasms is a fundamental but yet relatively unrecognized feature of myeloid neoplasms; studies indicated that GPD occurs in approximately 5-10% of cases.1

GDP can be divided into three categories. First, within the context of hematopoietic stem cell transplantation (HSCT), the identification of GPD is imperative, as it may be necessary to choose a sibling donor with an identical

germline mutation in order to prevent graft failure or to prevent the development of a malignancy, namely leukemia, of donor origin. On the other hand, peripheral blood specimens are prone to contamination by tumor-derived DNA; skin fibroblasts, by contrast, are the best substrate for determining germline status. Driven Mutations are the result of investigation of 1540 subjects, stratified with acute myeloid leukemia into genomic subgroups. The largest subgroup (27%) is mainly defined by initiating mutations in epigenetic regulatory genes such as DNMT3A. The phenotypic effect of the individual mutation is modulated by the genetic environment; e.g., the adverse prognostic consequence of FLT3-ITD is most significant when co-morbid with gene mutations in NPM1 and DNMT3A (Churpek & Godley, 2019; Papaemmanuil et al, 2016).

It is a non-invasive way of monitoring the disease progression, especially do analysis of circulating tumor DNA and cell-free DNA. Plasma is isolated from a blood sample collected in stabilization tubes such as Streck BCT and ultra-deep sequencing is carried out using techniques such as CAPP-seq, PhasED-seq or other advanced sequencing techniques. These approaches have been demonstrated to produce a decrease of 2-logs of ctDNA levels (Wan et al., 2017; Heitzer et al., 2019; Short et al., 2020).

Targeted and immunotherapies: Second-generation agents like Acalabrutinib and Zanubrutinib are not only safer but least cardiotoxic as compared with Ibrutinib. Venetoclax has radically changed the treatment situation of elderly patients with acute myeloid leukemia, because its combination with azacitidine has proved to significantly extend survival. These "living drugs" and T-cell redirectors (e.g. Teclistamab) have had documented response rates from 60% to 74% in heavily pretreated patients with multiple myeloma (Byrd et al., 2013; Woyach et al., 2022)

Technological advancements in molecular diagnostics

NGS forms the basis of current profiling techniques for molecular diagnostics. The fact that millions of pieces of DNA and RNA are processed at the same time is what makes its main advantage, allowing to detect mutations, copy number variations (CNVs), and chromosomal translocations. Several research papers have suggested that diagnostic panels with features of such scope may identify major alterations in up to 82% of cases. Notably, clinicians have gained the ability to analyze individual cells, which has enabled them to track clonal dynamics and evolutionary processes and further gain insight into how some leukemic clones bypass therapy and trigger relapse. Optical genome mapping (OGM) provides an extremely detailed barcode of the genome, which has a resolution that is much higher than conventional cytogenetics; therefore, it could be the superior substitute for classical cytogenetics in the ability to inspect parts of the chromosome at a higher resolution (Goodwin et al., 2016; Metzker, 2010).

Diagnostic and risk assessment

Presently, the molecular characterization of tumors plays a pivotal role in the process of diagnostic and therapeutic decision making of clinicians, in accordance with the guidelines of the World Health Organization (WHO) and the International Consensus Classification (ICC). Genomic profiling clarifies the mutations in FLT3, IDH1/2 and NPM1; in addition to disease subtypes, these alterations also determine treatment choice in relation to risk stratification. Contemporary next-generation sequencing platforms offer the possibility of yielding results in 23 days, thus making timely information possible, because malignant cells, especially in acute myeloid leukemia (AML), are rapidly dividing. Moreover, this technique distinguishes between such subtypes as Philadelphia chromosome-positive (Ph+) and Philadelphia chromosome-negative without the BCR-ABL1 fusion, which has a comparable gene expression signature and may be susceptible to the tyrosine kinase inhibitors (TKIs) in acute lymphoblastic leukemia (ALL). Integrating twenty genomic features with clinical data, this model not only improves the process of pattern recognition, but also provides the basic framework to predict the overall survival risk of individuals with much greater precision than current systems based on staging. (Goodwin et al., 2016; Metzker, 2010).

Genomic profiling is being widely accepted as a useful approach to identify therapeutically targetable mutations and predict therapeutic resistance. A study of non-myeloid malignancies showed that the discovery of resistance variants resulted in termination of ineffective agents or selection of alternative therapies in 69% of patients. Current points of therapeutic emphasis include FLT3 inhibitors, for example gilteritinib for acute myeloid leukemia; BTK inhibitors, which are an example of ibrutinib for chronic lymphocytic leukemia, and BCMA targeting therapies for multiple myeloma. Monitoring of minimal residual disease (MRD) using highly-sensitive next generation sequencing is helping to detect the presence of residual malignant cells at very low levels and therefore helping to make decisions on how to escalate or de-escalate therapy. Goodwin et al. (2016), Metzker (2010), Byrd et al. (2013), Woyach et al. (2022), and Short et al. (2020).

Identifying mutations that are amenable to therapeutic intervention is instrumental in guiding oncologists from a generic concept of targeted therapy as a homogenous solution. For example, targeted agents such as FLT3-inhibitors such as midostaurin and gilteritinib or IDH1/2-inhibitors ivosidenib and enasidenib had a proven positive effect on the prognosis of patients with acute myeloid leukemia. Similarly, in acute lymphoblastic leukemia, finding of Philadelphia-like subtypes is an advancement in the potential applicability of tyrosine kinase inhibitors in the absence of the classical Philadelphia chromosome. Furthermore, comprehensive genomic profiling is extremely helpful in the identification of variants involved in therapeutic resistance. An example is detection of BTK C481S or PLCG2 mutations in chronic lymphocytic leukemia, this suggests withdrawal of ineffective covalent BTK inhibitors in favour of the next generation of agents such as pirtobrutinib (Byrd et al., 2013; Woyach et al., 2022).

The combination of artificial intelligence (AI) and machine learning methodologies is helping to boost the power of bioinformatics pipelines. For example, these methodologies make it easy to distinguish pathogenic mutations from artifacts introduced during sequencing. Conversely, liquid biopsy assays based on the interrogations of circulating tumor DNA are providing a non -invasive means of real-time therapeutics monitoring and enabling early molecular relapse detections (Wan et al., 2017; Heitzer et al., 2019).

Diagnostic Accuracy

Both DNA and RNA panels, at one timepoint, are capable of detecting immunoglobulin heavy chain (IGH) translocations, rare fusion genes, and copy number changes (CNAs) - all of which are very important for the most recent subclassification of the disease according to WHO and International Consensus Classification (ICC) standards. Research findings suggest that these multi-faceted types of tests can detect clinically relevant diagnostic alterations in as many as 82% of patients and at the same time, they help in identifying the subtype-defining fusions in Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL). Actually one of the main things that will help predict patient's survival and relapses in acute myeloid leukemia (AML), multiple myeloma (MM), and several other diseases is knowing whether mutations have been done or not. Almost all the biomarkers are still hidden; only a few such as TP53, FLT3, and NPM1 are identified. NPM1 mutations are usually a sign of a good prognosis, on the other hand, FLT3 ITD and TP53 mutations are considered bad prognosis markers and in AML, these are characteristics of high-level chemotherapy resistance. IRMMa (Individualized Risk in Multiple Myeloma) a personalized prognosis scoring system is a major advancement in this field. It contains 20 genomics markers such as 1q21 gains/amp, TP53 loss, and 1p deletions (Moia, R., Talotta, D., Almasri, M., Cosentino, C., & Gaidano, G. 2023).

Genomic profiling is an extremely sensitive technique to identify Measurable Residual Disease (MRD). The net effect is that physicians can detect even a handful of cancer cells which remain invisible under a standard microscope. Moreover, single cell genotyping is a very novel technique to say characterize and explain how cancer cells in a person's body change and evolve over time. For examples, the research of evolution of drug resistant leukemic clones and

their changes over time makes it possible for the physician to switch drugs even before the patient manifests signs of relapse. Besides that, liquid biopsies not only facilitate the detection of circulating tumor DNA (ctDNA), but at the same time allow non, continuous, and non, invasive monitoring by evaluating the patient's treatment response and the early molecular relapse detection (Wan et al. 2017; Heitzer et al. 2019) (Short et al. 2020).

Conclusion

A significant cause of challenge that the industry continues to face despite all the advancements is that the cost of the test acts as a major barrier. Besides these, the factors, such as the disparities between physical locations in accessing one's and the lack of a method for standardizing in the interpretation of data by labs, are also contributing. With the help of innovative technologies like spatial transcriptomics, one aim is to integrate multi, omic data into a single detailed genetic report that will provide each patient with a continuous clinical timeline in a very efficient manner.

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