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COMPREHENSIVE REVIEW ON THERAPEUTIC APPLICATIONS OF AI IN LEUKAEMIA: A MULTI-OMICS APPROACH

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ABSTRACT: It is leukaemia, where immature white blood cells keep growing at a very fast pace and disrupt normal blood production. While there are many advances in treatment, genetics diversity, drug resistant and technological limits remain. Likewise, such AI combined with multi dimension approaches (genetics, transcriptomics, proteomics, metabolism, and epigenetics) has altered leukaemia research. Divining the diagnosis, risk assessment and precise plan for effective treatment from vast amounts of data allowed by AI is possible. In addition, it shortens the time of diagnosis, predicts responses to therapy, and explains how it fails. By integrating AI into mitigation of CML, tyrosine kinase inhibitor is first identified and targeted therapy is guided by other key biomarkers. Same is the case for AML which is mitigated by CK inhibitors and FLT3 inhibitors. Interruption and identification of various pathways by metabolomics and proteomics provide new therapeutic targets. More and more clinical studies show that AI assisted multi-omics strategies add value in making personalized care, reducing relapse, and increasing survival. Since challenges such as data integration, algorithm transparency, computational needs and ethics require collaboration among researchers, clinicians and policymakers, instant familiarity with the technology is not negligible. With the increase in AI, it will take precision medicine to the next step and change the treatment of leukaemia.

INTRODUCTION: Leukaemia is a class of haematological neoplasm that involves the abnormal formation of immature white blood cells and the interference with normal production of blood components by the bone marrow [1, 2]. It can be classified into Acute Lymphoblastic Leukaemia (ALL) and Acute Myeloid Leukaemia [AML]) and Chronic Lymphocytic Leukaemia [CLL] and Chronic Myeloid Leukaemia [CML]), with acute types progressing rapidly and chronic types often remaining asymptomatic for extended periods [3, 4].

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Challenges to the treatment of leukaemia including disease genetic heterogeneity, drug resistance, limitation of bone marrow transplantation, side effects of chemotherapy, lack of predictive power for response to chemotherapy [5, 6]. It continues to be a global health menace with an estimated 450,000 new cases a year or about 3 per cent of all cancers around the world. In particular, it is a major cause of cancer related morbidity and mortality and is particularly common in children and in the elderly.

Leukaemia is a critical hematologic malignancy with relative slow progress of their treatment in the context of cancer [7]. The following therapy could be revolutionized by the integration of artificial intelligence (AI) with multi-omics technologies including genomics, transcriptomics, proteomics and metabolomics. Omics data is immense and AI analyses can process it to discover novel biomarkers, predict response to treatment and identify resistance mechanisms, towards developing precise, personalized treatment strategies [8]. A multi-omics approach, combining genetic mutations, protein expression patterns and metabolic signatures allows integration and a holistic picture of the patient's disease. AI driven models' base therapies on patient specific patterns, optimizing outcomes while limiting adverse effects [9]. The major goal of the study was to analyse how AI and multi-omics integration have changed leukaemia therapy in the direction of precise and data driven, personalized treatment, in order to improve patient prognosis [10]. AI has an important role in leukaemia treatment by integrating complex datasets to optimize therapeutic decision making. With AI's evolution, the use in personalized treatment options for treatment of leukaemia patients is going to play an extremely important role in the present situation when it comes to limiting use of current treatment options [11]. Over the years, the advancements in treatment technologies have enabled better mortality rate and leukaemia prognosis, which is evident from the line graph represented based on consolidated data from the years 2000- 2023 **Fig. 1** [12,13].

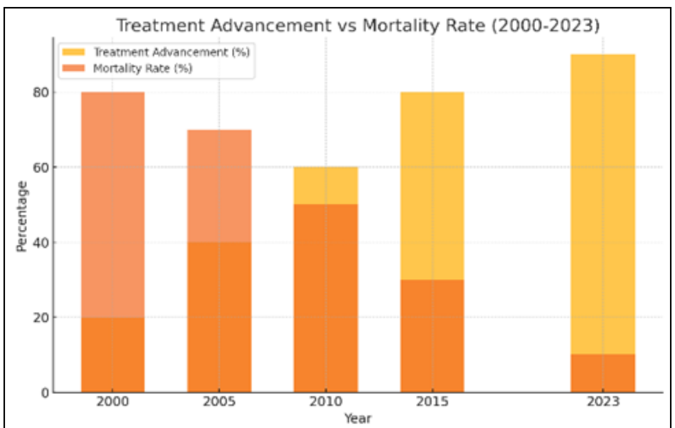

FIG. 1: (ADVANCEMENT IN TREATMENT OF LEUKAEMIA OVER YEARS VS THE MORTALITIY RATE OF LEUKAEMIA TREATMENT OUT COMES)

Multi Omics & Their Role in Leukemia: Multi omics combines different types of biomaterials to gain complete picture of leukaemia. Genomics, transcriptomics, proteomics, metabolomics, and epigenomics are included **Table 1.** Key deal breaking genetic changes are located in AML patients due to the existence of FLT3 and NPM1 mutations or the presence of BCR-ABL1 translocation in CML patients. Diagnosis and grouping of leukaemia subtypes are as the findings can guide the doctors on the disease progression and also to select the most effective treatments [14]. RNA expression pattern is studied by transcriptomics, which allows markers to detect the disease, to visualise treatment outcomes, and to predict the likelihood of relapse. Transcriptomics different leukaemia subtypes apart and also can track change in gene expression in response to treatment [15]. In turn, the genomic and transcriptomic insights allow doctors to spot leukaemia earlier before symptoms begin. That leads to prompt action and tailored treatments. Uncovering protein networks and metabolic pathways that do not work right in leukaemia cells has an influence of proteomics and metabolomics. Hence both proteomics and metabolomics enable the identification of leukaemia specific markers and identify key properties of the metabolism required by leukaemia cells. That is important to distinguish leukaemia from other blood cancers. For instance, leukaemia cells often use glucose differently, using many metabolic pathways more than normal. New ways of treating the disease are thus opened up [16, 17].

By studying single cells of leukaemia, single cell multi omics tech gives us even closer look and also shows differences in the disease along with finding leukaemia stem cells that can cause the disease to come back. The following findings are valuable in predicting the risk of relapse and to allow a more targeted treatment by attacking the factors that are responsible for the disease at the cellular level [18, 19]. Multi- omics suggests ways in which leukaemia clones evolve, allowing doctors to predict how the disease will progress. Tracking changes in genes, epigenetics and gene expression over time help doctors predict how the disease will evolve, whether it's going to recur, and how the patient will do. It leads them to find high risk patients that may need stronger treatments or closer watch [20, 21].

Transcriptomics and proteomics look for high risk signs: too much or too little of cancer-causing proteins or genes that make drugs less effective. It gives doctors a way to sort patients into risk groups more and to create treatment plans specific to a patient's own very molecular makeup [22]. With regard to the diagnostic application, multiomics can help identify the specific genetic and epigenetic changes characterizing subtypes of leukaemia, for example, BCR-ABL1 in CML, or other mutations, for example, FLT3, NPM1 and IDH1/2 in AML. These mutations are not only for the classification of subtypes but also as the early prognostic marker and the relapse risk predictor for early disease stages [23, 24]. This generation of transcriptomics data permits predicting overexpressed genes and monitoring subtle changes in expression which could be the reflecting molecules for the treatment of the leukaemia, contributing to early diagnosis of the disease or recovery from recurrence before any symptom appearance [25, 26]. In contrast to proteomics and metabolomics, these signatures from product of failed protein networks and metabolic pathways carry disease specific signatures of leukaemia but not of other diseases or disorder in the patient's blood [27]. This is multi omics in treatments, it identifies specific molecular targets that are unique to patients' leukaemia subtypes for development of targeted therapies. For example, like BCR-ABL1 positive CML, tyrosine kinase inhibitors may be used, and FLT3 inhibitors could be appropriate for patients with FLT3 mutations in AML [28].

Additionally, metabolomics and proteomics identify metabolic pathways that have been remodelled and become the niche where leukaemia cells depend, *etc*. These pathways may in fact be targeted for therapeutic use. Thus, according to Epigenomic data, it gives information of the mechanisms of drug resistance and Clinicians could develop new methods against it thus by designing drugs that target the specific mechanisms of drug resistance [29, 30]. This will be used to combine artificial intelligence with multiple-omics data to help analyse this type of large dataset and improve treatment decision and discover new leukaemia subtypes or more identifying drug targets [31, 32]. Overall, merging of multicompositional data turns over the diagnosis, prognosis and treatment of leukaemia, giving a complete and detailed point of view of the diseases at the molecular level. This gives healthcare professionals better tools for diagnosis, more accurate personalised treatment approaches, and the possible to predict relapse. And so patient outcomes improved as the side effects and relapse risks are lowered.

TABLE 1: TYPES OF MULTI OMICS

Types of multi omics	Definition
Genomics	The complete study of an organism's chromosome, which means genes and their variations [33]
Transcriptomics	The study of the RNA transcripts of the genome with particular emphasis on gene expression patterns [34, 35, 36]
Proteomics	Studying proteins at a large scale (i.e. their structure, their function and their interactions) [37]
Metabolomics	The analysis of metabolites and small molecules within cells, tissue, or organism [38]
Epigenomics	The study of changes to the genome, such as DNA methylation or histone. Modifications that change the expression of genes without changing DNA sequence [39]
Single cell multi – omics	Study of cellular heterogeneity by application of multi-omics techniques to individual cells [40]

Applications of Cancer Diagnosis and Prognosis with AI: The applications of artificial intelligence (AI) to oncology are now leading transformative progress toward diagnosing, predicting, and treating cancers. In the last four years clinical practice has changed in profound ways through the integration of machine learning (ML), deep learning (DL), and other AI driven tools [41, 42]. Convolutional neural networks (CNNs) are as good as 95% accurate at detecting early cancers from mammograms and blood based liquid biopsy AI systems have detected cancer markers with great accuracy of greater than 90% [43]. AI-powered systems are also used in imaging and pathology, improving accuracy with a 30% reduction in false positives in lung CT scans and help pathologists predict molecular profiles of tumour tissue, guiding personalized treatment strategy. Predictors of risk beyond the traditional metrics are being assessed using machine learning models incorporating multiple datasets (clinical and genomic), such as in prostate and breast cancer [44, 45]. Researches are conducted for better treatment planning in leukaemia care in which Al also uses multi-omics and imaging data to guide radiation therapy treatment planning and to accelerate drug discovery pipelines, getting new therapies to patients faster. As Al brings these advancements, it's creating the next frontier of precision medicine, closing the gaps in cancer care that are critical to effective and personalized treatment strategies. Now more than ever, the potential of Al to improve clinical outcomes while reducing burdens in healthcare become more and more apparent [46, 47].

Highlighting the Applications of Leukaemia Diagnosis and Prognosis with AI: With significant advancements in artificial intelligence (AI) for leukaemia diagnosis and prognosis, we can now diagnose the disease with greater precision and treat patients more efficiently [48, 49]. Recent developments include:

Improved Diagnostic Accuracy: Blood smear analysis and bone marrow samples are identified as the world's most challenging clinical diagnostic problems by AI deep learning models that demonstrate over 97% accuracy over traditional methods [50, 51].

Flow cytometry, of which AI is helping to improve leukaemia cell detection, is also furthered by AI assisted flow cytometry which has increased the detection of leukaemia cells while reducing human errors [52].

Risk Stratification and Prognosis: Genetic, proteomic, and transcriptomic data are integrated to predict patient outcomes [53]. Moreover, AI tools stratify patients as high and low risk before determining which personalized treatments are most effective [54, 55].

Addressing Drug Resistance: Identification of mechanisms of resistance to therapy, including chemotherapy and targeted therapies, relies on sets of AImodels [56, 57]. In addition, the AI enabled biomarker discovery allowed for the identification of new immunotherapy targets [58].

Personalized Treatment Plans: With the ability to integrate multi-omics data, AI can now offer tailored therapies to subtypes of leukaemia such as AML and CML which will be more effective with fewer side effects [59, 60].

Real-Time Monitoring: In this case, AI integrated wearable devices and health records give continuous tracking of disease progression and treatment response [61]. Moreover, predictive analytics platforms predict relapse risk for timely interventions [62].

Advancements in AI-Driven Multi-Omics Integration for Precision Medicine in Leukaemia: By integrating DNA methylation, gene expression, and drug sensitivity data with artificial intelligence (AI), have introduced state-of-the art prognostic models for acute myeloid leukaemia (AML) several times more accurate. The study identified molecular subtypes with differing survival outcomes which enabled more accurate risk stratification and tailored therapeutic strategies [63, 64, 65].

Using longitudinal clinical datasets, has applied machine learning algorithms with stunning success predicting the onset of chronic myeloid leukaemia (CML) years before it could be diagnosed using conventional diagnostics that allowed early detection and subsequent intervention to result in better long term patient outcomes [66, 67]. Using AI analysis, in their study on ALL, found biomarkers suggesting resistance to asparaginase therapy. This breakthrough laid the groundwork for alternative treatment protocols which when used in combination with other stakeholders retrieved relapse rates from paediatric patients to a great extent [68, 69]. A recent study has applied AI-driven multi-omics analysis to study drug resistance in AML, identifying new potential therapies *via* drug repurposing and providing hope for a few patients with refractory disease [70, 71, 72].

Having provided a comprehensive review of multi-omics integration for cancer diagnosis and prognosis, and concluded that multi-omics integration will transform leukaemia care by providing more precise predictive modelling, and better treatment personalization for this disease [73, 74, 75]. Furthermore, AI can stratify AML patients into well-defined prognostic groups from integrated multi omics data which in turn has provided a better way of improving prognostic accuracy. This has also helped to guide the development of personalized treatment strategies based on each patient's molecular profile – a new standard of care for leukaemia [76, 77, 78].

Case Reports: Smith *et al.* In their reportage of a case of chronic myeloid leukaemia (CML) in blast crisis, reported an application of multi-omics analysis to an approach to CAR-T therapy which investigated genomic sequencing, transcriptomics and proteomics for identification of actionable mutations and pathways, followed by targeted CAR-T therapy that has achieved remission by reducing blast cells drastically [79]. Lu *et al.* Using machine learning to integrate genomics, transcriptomics, and proteomics in chronic lymphocytic leukaemia (CLL) found a proliferative axis involving mTOR, MYC, and OXPHOS with prognostic value and prioritized therapeutic strategies and They showed the integration of multi-omics data and machine learning for predicting cancer therapeutic responses, illustrating molecular profiles assisting in selecting the ideal treatment for each patient [80].

Taylor *et al.* studied Multi-omics analysis of AML cohorts integrated genomic, transcriptomic and epigenomic data integrated to reveal actionable mutations (e.g. FLT3, NPM1), and epigenetic changes that guided recommendations for personalized treatment strategies, including FLT3 inhibitors and epigenetic therapies [66]. In a study conducted by Martinez *et al.* described how AI driven multi-omics integration was used to identify FLT3 and NPM1 mutations, dysregulated pathways, including PI3K-AKT, and overexpression of PD-L1 in a 45-year-old AML patient, to create a personalized treatment plan that included FLT3 inhibitors, immune checkpoint inhibitors, low dose chemotherapy and stem cell transplantation leading to complete molecular remission [81]. Collectively all the studies suggest that AI integration with multi-omics data is poised to yield precision medicine and personalized treatments for leukaemia.

Challenges and Limitations in AI-Driven Multi-Omics Integration for Leukaemia Care: Artificial intelligence (AI) integration with multi omics data for leukaemia research have greatly revolutionized leukaemia research with dramatic advancements in diagnosis, prognosis, and treatment personalization. Nevertheless, there are several challenges with this set of approaches that prevents it being fully implemented. The complexity of data integration is one of the biggest hurdles since multi omics datasets, including genomics, transcriptomics, proteomics and epigenomics, are intrinsically heterogeneous and need sophisticated computational frameworks to integrate their varied structures and scales [82, 83]. Furthermore, the issues of selection, validation, and acceptance of AI algorithms are also significant with many models being "black box" that is, they are uninterpretable and therefore not acceptable for clinical sites [84]. The quality of multi-omics data is also another important challenge that suffers from noise caused by biological variability and technical artifacts especially in the single cell sequencing data. Even with new methods to develop robust de-noising techniques [85, 86], this compromises the reliability of AI analyses. Also, the computational requirements of multi-omics analysis at the scale are substantial, and require significant infrastructure and resources, preventing the use of cutting-edge AI tools in resource constrained locations [87].

The translation of these innovations into clinical practice, however, is hindered by regulatory hurdles, data privacy concerns and standardized protocol and validation study requirements to ensure reproducibility and clinician trust [88]. While this growth presents challenges, advances in computational methods, improvements to data quality, and clinical standardization present the promise of breaking through these barriers and enabling AI informed multi-omics integration for leukaemia care and precision medicine [89]. The Indian Council of Medical Research (ICMR) guidelines emphasize the ethical importance of fairness, transparency, and non-discrimination while addressing concerns around data privacy and algorithmic bias, which are critical in AI integration [90]. Additionally, the potential impact on the patient-clinician relationship due to reduced personal interactions highlights the need for balancing technology with human touch[91]. Collaborative efforts among technologists, policymakers, and healthcare providers are essential for responsibly integrating AI into leukaemia care [92].

CONCLUSION: The integration of artificial intelligence with multi-omics data sets a transformative leap in leukaemia research and care. By making use of genomics, transcriptomics, proteomics, and metabolomics, AI has enabled a complete understanding of leukaemia at the molecular level. This has facilitated early detection, risk stratification, and the identification of therapeutic targets.

These advancements highlight the promise of improved patient outcomes, reduced treatment-related side effects, and enhanced strategies to overcome drug resistance. However, future efforts need to be made to develop state of art AI frameworks, which can better amalgamate diverse datasets in a more transparent and efficient manner. Leukaemia care would be equitable and reliable if AI use was built on robust computational infrastructure with ethical considerations. Further exploration of AI driven insights into metabolic pathways and epigenetic changes may reveal new therapeutic targets. However, to make these innovations routine clinical practice for better outcomes for the leukaemia patients, cross multidisciplinary collaboration between clinicians, technologists, and policy makers will be essential.

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