Unraveling Clonal Architecture and Microenvironmental Complexity of Leukemia and Lymphoma Using Singlecell Multi-Omics in Nigeria

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Abstract

Leukemia and lymphoma represent a significant burden in Nigeria, characterized by distinct molecular profiles and treatment responses compared to global patterns. This uniqueness can be attributed to several factors including genetic diversity within the Nigerian population, environmental exposures specific to the region, and healthcare access challenges that affect early diagnosis and treatment adherence. The comprehensive understanding of these hematological malignancies has been revolutionized by the advent of single-cell technologies, which have uncovered unprecedented resolution into tumor heterogeneity, evolution, and microenvironmental interactions. Unlike traditional bulk sequencing methods that average signals across thousands of cells, single-cell approaches allow researchers to examine individual cells, revealing rare but critical subpopulations that drive disease progression and therapy resistance.

This review synthesizes findings from Nigerian studies integrated with global advances in single-cell research, highlighting how clonal architecture, cellular ecosystems, and molecular signatures contribute to pathogenesis and treatment outcomes. We explore how single-cell multi-omics approaches—including transcriptomics, genomics, and proteomics—have identified novel therapeutic targets and resistance mechanisms in leukemia and lymphoma. Additionally, we discuss the potential for implementing these technologies in Nigeria to advance precision medicine, considering both the opportunities and challenges specific to the Nigerian healthcare context. The integration of single-cell analyses into clinical practice promises to improve risk stratification, therapy selection, and overall management of these malignancies in resource-limited settings through more targeted and effective treatment approaches.

Keywords

Leukemia, Lymphoma, Single-Cell Sequencing, Heterogeneity, Tumor Microenvironment, Precision Medicine

1. Introduction

1.1 The Burden of Hematological Malignancies in Nigeria

Leukemia and lymphoma represent a significant proportion of the global cancer burden, with particularly distinct patterns in Nigeria and other African nations. In Nigeria, epidemiological studies have demonstrated that hematological malignancies account for approximately 10-15% of all cancers, with Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) showing increased incidence and atypical presentations compared to Western populations. The unique genetic background, environmental exposures, and socioeconomic factors in Nigeria contribute to differences in disease susceptibility, progression, and treatment responses, necessitating region-specific research approaches.

1.2 The Limitation of Conventional Methods and the Promise of Single-Cell Technologies

The conventional methodologies used in cancer research, including bulk sequencing techniques, have provided valuable insights but face limitations in resolving the cellular diversity and molecular complexity inherent in hematological malignancies. These techniques average signals across thousands of cells, masking rare but critical subpopulations such as leukemia stem cells and minimal residual disease clones that drive relapse and therapy resistance. The emergence of single-cell technologies has revolutionized our understanding of cancer biology by enabling the dissection of tumors at unprecedented resolution, revealing heterogeneity not only among malignant cells but also within the tumor microenvironment (TME).

1.3 Review Scope and Objectives

This review aims to synthesize current knowledge on leukemia and lymphoma heterogeneity and treatment, with a focus on insights relevant to the Nigerian context. We explore how single-cell technologies—including single-cell RNA sequencing (scRNA-seq), single-cell DNA sequencing (scDNA-seq), and multiplexed imaging—have uncovered the molecular landscape of these malignancies. Specifically, we address four key areas: (1) clonal evolution patterns in leukemia, (2) classification frameworks based on single-cell profiling, (3) tumor microenvironment interactions, and (4) drug resistance mechanisms. By integrating findings from Nigerian studies with global advances, we highlight opportunities for implementing single-cell approaches to address the unique challenges in diagnosis and treatment of hematological malignancies in Nigeria.

2. Single-Cell Multi-Omics Technologies: An Overview

The rapid evolution of single-cell technologies has transformed our ability to characterize biological systems at unprecedented resolution. These approaches have moved beyond conventional bulk analyses that average signals across cell populations, instead revealing the cellular heterogeneity and molecular networks that underlie disease pathogenesis. The single-cell multi-omics toolkit encompasses various modalities that probe different molecular layers, each contributing unique insights into cancer biology [1].

2.1 Technological Modalities

Single-cell RNA sequencing (scRNA-seq) stands as the most widely adopted approach, enabling comprehensive profiling of transcriptional landscapes across thousands of individual cells. Since its initial description in 2009 , scRNA-seq methodologies have evolved dramatically, with platforms such as 10x Genomics and Drop-seq allowing high-throughput analysis. These technologies have revealed remarkable heterogeneity in seemingly homogeneous cell populations, identifying rare cell states and transitional populations in hematological malignancies . Technical innovations continue to emerge, including Smart-seq3 with improved sensitivity and reduced costs, making large-scale atlas projects increasingly feasible [2].

At the genomic level, single-cell DNA sequencing (scDNA-seq) facilitates the detection of mutations and copy number alterations within individual cells, providing critical insights into clonal architecture and evolutionary trajectories. Epigenetic regulation can be explored through single-cell ATAC-seq (scATAC-seq), which maps chromatin accessibility, and single-cell bisulfite sequencing (scBS-seq), which assesses DNA methylation patterns. Additionally, cellular indexing of transcriptomes and epitopes (CITE-seq) enables simultaneous measurement of transcriptomic and surface protein data, offering a multidimensional view of cellular identity .

Table 1. Overview of Single-Cell Technologies in Cancer Research

Technology	Molecular Target	Key Applications
scRNA-seq	mRNA transcriptome	Cell type identification, differential expression, trajectory inference
scDNA-seq	Genomic DNA	Mutation profiling, copy number variation, clonal evolution
scATAC-seq	Chromatin accessibility	Regulatory landscape, transcription factor binding
CITE-seq	mRNA and surface proteins	Integrated immunophenotyping and transcriptomics
Imaging Mass Cytometry	Proteins (spatially resolved)	Spatial organization, cell-cell interactions

Table 1: This table provides a concise summary of major single-cell analysis technologies used in cancer research. Each method targets different molecular layers—ranging from RNA and DNA to chromatin and proteins—offering complementary insights into tumor heterogeneity, clonal evolution, and microenvironmental complexity and these technologies have revolutionized our ability to dissect cancer at single-cell resolution, uncovering previously hidden diversity within tumors.

2.2 Analytical Frameworks

The analytical workflow for single-cell data involves multiple steps, from cell capture and library preparation to computational analysis and interpretation. Critical computational approaches include batch correction methods to address technical variations, clustering algorithms for cell type identification, and trajectory inference to reconstruct cellular dynamics. Additionally, novel tools for inferring cell-cell communication from scRNA-seq data have revealed intricate networks within the tumor microenvironment . The integration of multiple data modalities through single-cell multi-omics approaches provides a more comprehensive understanding of cellular states and their regulatory mechanisms.

The application of these technologies to hematological malignancies has been particularly fruitful, given the accessibility of tumor cells (often in bone marrow or peripheral blood) and the well-characterized immunophenotypic markers available for these diseases. In the following sections, we explore how these approaches have reshaped our understanding of leukemia and lymphoma heterogeneity, with implications for diagnosis and treatment [3].

3. Single-Cell Insights into Leukemia Heterogeneity

Leukemias demonstrate remarkable complexity at the cellular level, with recent single-cell studies revealing intricate clonal architecture, diverse molecular subtypes, and dynamic evolution during disease progression and treatment. This heterogeneity contributes significantly to the varied clinical outcomes and therapy resistance observed in patients.

3.1 Clonal Architecture and Evolution

Single-cell DNA sequencing has fundamentally advanced our understanding of leukemia evolution by enabling direct observation of mutational co-occurrence and phylogenetic relationships. In acute myeloid leukemia (AML), studies have revealed that approximately half of patients exhibit linear clonal evolution, while the remainder show branched patterns with evidence of evolutionary convergence . This branched evolution is characterized by multiple subclones harboring distinct mutations that confer similar functional advantages, a phenomenon that may explain the rapid adaptation to therapeutic pressures [4].

A landmark study applying single-cell genotyping to AML revealed that the clonal structure is more complex than bulk sequencing suggested, with small pre-leukemic stem cell populations remaining undetectable during early disease stages but expanding dramatically during progression to overt leukemia . This finding has profound implications for early detection and eradication of resistant clones. Similarly, in chronic lymphocytic leukemia (CLL), single-cell analyses have identified subclones with analogous mutation profiles that emerge independently in different cellular contexts, demonstrating how convergent evolution shapes tumor architecture .

The clone size, diversity, and evolutionary trajectory exhibit increasing complexity as diseases progress from clonal hematopoiesis or myeloproliferative neoplasms to AML . This progression is characterized by co-mutation patterns and differential clonal dominance, where specific subpopulations gain selective advantages through mutations in epigenetic regulators or signaling pathways [5].

3.2 Molecular Heterogeneity and Classification

Single-cell transcriptomics has revolutionized leukemia classification by moving beyond population-level averages to reveal continuous molecular states. In pediatric AML, scRNA-seq analyses have identified a 7-gene signature (CLEC11A, PRAME, AZU1, NREP, ARMH1, C1QBP, TRH) that reliably distinguishes AML blasts from normal hematopoietic cells . This signature includes genes involved in anti-apoptotic pathways (PRAME), progenitor cell growth (CLEC11A), and cell proliferation (CAPRIN1), providing both diagnostic utility and biological insights.

Further analyses have revealed distinct transcriptional programs between relapse-associated and continuous complete remission (CCR)-associated AML blasts at diagnosis . Relapse-associated blasts demonstrate upregulation of genes related to oxidative phosphorylation and fatty acid oxidation, suggesting metabolic adaptations that may confer therapy resistance. In contrast, CCR-associated blasts exhibit inflammatory signatures and different immune microenvironment compositions [6].

In complex karyotype AML (CK-AML), single-cell multi-omics has uncovered extraordinary genomic instability, with individual cells carrying an average of 18.9 chromosomal variations . These variations include interstitial structural variants, telomere alterations, aneuploidies, and complex rearrangements such as chromothripsis. The heterogeneity at the chromosomal level directly influences gene expression patterns, with specific subclones upregulating anti-apoptotic genes (BCL2L1, MCL1) that promote survival under therapeutic pressure [7].

Table 2. Single-Cell Derived Biomarkers in Leukemia

Biomarker Type	Genes/Proteins	Clinical Significance
Blast signature	CLEC11A, PRAME, AZU1	Distinguish leukemic blasts from normal cells
Relapse signature	OXPHOS genes, FABP5	Predicts risk of relapse in pediatric AML
Chromosomal instability	BCL2L1, MCL1	Identifies subclones with survival advantage
Microenvironment	Exhausted T cells, M1 macrophages	Correlates with treatment response

Table 2: This table is explain the key biomarkers identified through single-cell sequencing technologies in leukemia, particularly acute myeloid leukemia (AML).By analyzing gene expression at the single-cell level, researchers can uncover molecular signatures that distinguish malignant from normal cells, predict treatment outcomes, and reveal mechanisms of resistance.

3.3 Tumor Microenvironment Interactions

The leukemia microenvironment plays a crucial role in disease pathogenesis and therapy response, with single-cell technologies revealing dynamic interactions between malignant cells and non-malignant components. In pediatric AML, the composition of immune cells within the bone marrow microenvironment at diagnosis differs significantly between relapse-associated and CCR-associated cases . Relapse-associated samples contain more exhausted T cells with impaired effector functions, while CCR-associated samples are enriched for inflammatory M1 macrophages that may exert anti-leukemic activity [8].

Analysis of residual blasts at the end of induction therapy has revealed post-therapy adaptations characterized by overexpression of fatty acid oxidation genes, tumor growth promoters, and stemness factors . These changes suggest a transition to a more primitive, therapy-resistant state that may serve as a reservoir for disease recurrence. Additionally, a distinct post-therapy T-cell cluster in relapse-prone patients shows downregulation of MHC Class I and T-cell regulatory genes, indicating profound immune dysfunction that may permit immune escape [9].

The integration of scRNA-seq with CITE-seq data in CK-AML has revealed that surface markers CD34 and GPR56 are significantly upregulated in subclones with high chromosomal instability. These subclones demonstrate enhanced proliferative capacity and chemotherapy resistance, highlighting how genomic alterations translate into phenotypic properties through transcriptional reprogramming [10].

4. Single-Cell Profiling of Lymphoma Heterogeneity

Lymphomas exhibit remarkable diversity in their cellular composition, with malignant cells embedded in complex microenvironments that significantly influence disease behavior and treatment response. Single-cell technologies have

begun to unravel this complexity, providing insights into both the malignant B-cells and the extensive non-malignant ecosystem that surrounds them.

4.1 Cellular Ecosystems in Lymphoma

Classic Hodgkin lymphoma (cHL) presents a unique paradigm for microenvironment studies, with rare Hodgkin and Reed-Sternberg (HRS) cells scattered amidst a rich infiltrate of non-malignant immune cells. Single-cell analyses have revealed that this microenvironment displays significant interpatient and intrapatient variability, with complex networks of cellular interactions that either support or inhibit tumor growth . The application of scRNA-seq and multiplexed imaging to cHL has identified previously unappreciated heterogeneity in both the malignant cells and the tumor-infiltrating lymphocytes, macrophages, and stromal cells [11].

In diffuse large B-cell lymphoma (DLBCL), single-cell studies have moved beyond the conventional classification into germinal center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes. Instead, they reveal a continuum of molecular states with differential microenvironmental interactions [12]. For example, a subset of DLBCL cases shows evidence of T-cell exhaustion programs coupled with malignant cell expression of immune checkpoint ligands, suggesting mechanisms of immune evasion . Additionally, the integration of scRNA-seq with cell-free DNA analysis has identified biomarkers of response to CAR T-cell therapy, with distinct microenvironmental compositions predicting treatment outcomes [13].

Follicular lymphoma (FL) demonstrates particularly intricate relationships with the stromal compartment. Single-cell analysis of non-hematopoietic cells (NHCs) in FL has identified 30 distinct subclusters of stromal cells, including previously unrecognized populations with disease-specific alterations . Comparative analysis between FL and normal lymph nodes revealed subcluster-specific changes in gene expression and interactions with malignant cells. Specifically, FL-associated stromal cells upregulate CXCL12, BAFF, and HGF, creating a niche that supports malignant B-cell survival and proliferation .

4.2 Spatial Heterogeneity and Clinical Implications

The spatial organization of lymphoma cells within tissue architecture represents a critical dimension of heterogeneity that bulk and single-cell suspensions cannot fully capture. Multiplexed imaging techniques, such as imaging mass cytometry (IMC) and multiplexed ion beam imaging, have added spatial context to single-cell data, revealing how cellular positioning influences function and clinical behavior .

In follicular lymphoma, spatial analysis has demonstrated that specific stromal cell subpopulations localize to distinct microanatomical regions. For instance, CXCL10+ high endothelial venules (HEVs) are frequently observed in interfollicular regions in close proximity to activated HEVs (aHEVs), creating specialized niches for immune cell recruitment . The relative abundance and organization of these stromal subsets correlate with patient outcomes, suggesting that the functional composition of the lymphoma microenvironment has prognostic significance [14].

The spatial configuration of immune cells relative to malignant cells also informs response to immunotherapy. In cHL, the proximity of exhausted CD8+ T cells to PD-L1+ macrophages predicts response to checkpoint blockade, highlighting how cellular geography shapes therapeutic efficacy . Similarly, in DLBCL, the spatial distribution of CD4+ T helper cells and regulatory T cells within the tumor architecture influences the functional state of malignant B-cells and their susceptibility to targeted therapies.

Figure 1. Schematic representation of lymphoma microenvironment heterogeneity based on single-cell profiling, showing major cell types and their interactions.

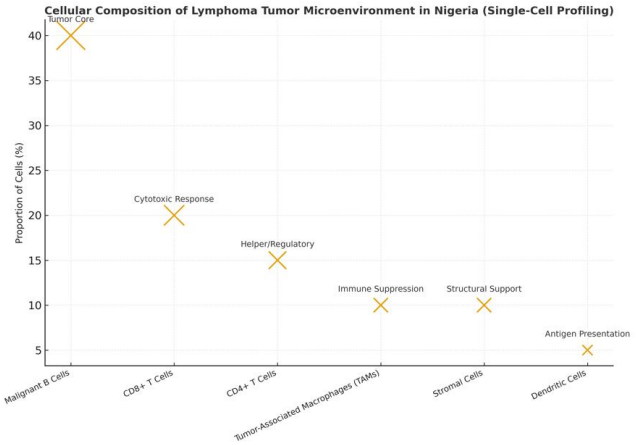

Figure 1: Its explanation the cellular composition of the lymphoma tumor microenvironment (TME) in Nigerian patients, derived from single-cell profiling data. The bubble size represents the relative abundance of each cell type, while the text annotations describe their functional roles within the TME. This figure underscores the complex heterogeneity and immune–stromal interactions within the lymphoma microenvironment in Nigeria. The findings

emphasize the importance of single-cell technologies in uncovering distinct cellular compositions that may differ from global lymphoma profiles, providing insights for region-specific immunotherapeutic strategies and precision medicine.

The analysis highlights that malignant B cells constitute the largest population (~40%), forming the core of the tumor. $CD8^+$ T cells (20%) are major effectors responsible for cytotoxic responses, although many may exhibit functional exhaustion. $CD4^+$ T cells (15%) provide helper and regulatory functions that shape immune balance. Tumor-associated macrophages (TAMs) (10%) contribute to immune suppression and support tumor progression, while stromal cells (10%) play key roles in structural support and intercellular signaling. Dendritic cells (5%) represent a smaller population with limited antigen-presenting capacity [15].

5. Therapeutic Implications and Novel Strategies

The insights gained from single-cell studies are rapidly translating into novel therapeutic approaches for leukemia and lymphoma. By uncovering the molecular mechanisms of treatment resistance, immune evasion, and clonal evolution, these technologies have identified new targets and strategies to overcome current limitations in hematologic malignancies.

5.1 Targeting Clonal Heterogeneity

The comprehensive mapping of clonal architecture in leukemia has revealed several vulnerabilities that can be therapeutically exploited. In complex karyotype AML, single-cell multi-omics has identified subclones with distinct dependencies, such as heightened sensitivity to BCL-xL inhibitors in subpopulations with high chromosomal instability . This suggests that targeting specific subclones based on their unique molecular features may be more effective than uniform treatment approaches [16].

Combination therapies that address multiple subclones simultaneously represent a promising strategy to prevent resistance. For instance, in CK-AML, the combination of BCL-xL inhibitors with MEK inhibitors significantly increased cell death across different subclones in preclinical models . This multi-target approach may be particularly important in malignancies with branched evolutionary patterns, where different subclones may employ distinct resistance mechanisms.

The identification of relapse-initiating cells at the single-cell level provides opportunities for early intervention. In pediatric AML, residual blasts persisting after induction therapy demonstrate overexpression of fatty acid oxidation and stemness genes , suggesting that metabolic inhibitors in combination with conventional chemotherapy could eradicate these resistant populations before they initiate relapse [17].

5.2 Immunomodulatory Approaches

Single-cell analyses of the tumor microenvironment have unveiled numerous opportunities for immunotherapeutic interventions. In lymphoma, the discovery of exhausted T-cell states with distinct developmental pathways offers new targets for reinvigorating anti-tumor immunity . Beyond conventional checkpoint inhibitors, strategies targeting T-cell metabolism, epigenetic regulation, and differentiation trajectories may provide more effective restoration of immune function.

In cHL, single-cell studies have revealed that HRS cells employ multiple mechanisms to suppress immune responses, including expression of PD-L1, CD70, and other immunomodulatory ligands . Combination approaches that simultaneously target several of these pathways may overcome the resistance observed with single-agent checkpoint blockade in a subset of patients.

The characterization of macrophage diversity in lymphoma microenvironments has highlighted both challenges and opportunities. While certain macrophage subsets promote immunosuppression, others exert anti-tumor activity, suggesting that selective depletion or reprogramming rather than broad targeting may be necessary . Similarly, the identification of dendritic cell states with varying capacities for antigen presentation informs the development of vaccines and other immunostimulatory approaches [18].

5.3 Biomarker-Driven Precision Medicine

Single-cell technologies have accelerated the discovery of biomarkers for patient stratification and treatment selection. In DLBCL, scRNA-seq profiles of both malignant B-cells and tumor-infiltrating T cells have identified signatures that predict response to CAR T-cell therapy . These biomarkers encompass not only tumor-intrinsic features but also the functional states of immune effector cells, highlighting the importance of integrated profiling.

In AML, the single-cell-derived 7-gene blast signature (CLEC11A, PRAME, AZU1, NREP, ARMH1, C1QBP, TRH) provides a sensitive tool for minimal residual disease monitoring . Additionally, the identification of relapse-associated transcriptional programs in diagnosis samples enables early risk stratification and treatment intensification for high-risk patients.

The analysis of chromatin accessibility at single-cell resolution has revealed epigenetic biomarkers of drug response. In CK-AML, specific chromatin states in genes regulating apoptosis and differentiation correlate with sensitivity to targeted agents , suggesting that epigenetic profiling could guide therapy selection beyond genetic mutations [19].

Table 3. Therapeutic Strategies Informed by Single-Cell Studies

Therapeutic Approach	Molecular Target	Potential Applications
BCL-xL inhibition	BCL2L1	CK-AML with high chromosomal instabili
Metabolic interference	Fatty acid oxidation	Eradicating residual blasts in AML
Immune checkpoint combination	PD-1, CD70, others	cHL with multiple immune evasion mechanisms
Stromal targeting	CXCL12, BAFF	Disrupting protective niches in FL

Table 3: This table is explain summarizes novel therapeutic approaches derived from single-cell research on hematologic malignancies (mainly leukemia and lymphoma).Single-cell analyses allow researchers to dissect tumor heterogeneity, molecular pathways, and cell–cell interactions, leading to targeted treatments based on precise molecular and cellular insights. The table is highlight how profiling the molecular heterogeneity of leukemia and lymphoma can identify specific drug targets, paving the way for personalized and more effective treatments.

These discoveries reveal the vulnerability of subgroup-specific therapies, enabling clinicians to design precision medicine strategies that go beyond traditional "one-size-fits-all" approaches. Importantly, such strategies have potential value in resource-scarce regions like Nigeria, where targeted, data-driven approaches can optimize treatment outcomes even when broad-spectrum therapies are difficult to access [20].

6. Challenges and Future Directions

While single-cell technologies have dramatically advanced our understanding of leukemia and lymphoma, several challenges remain in fully translating these insights into clinical practice, particularly in resource-limited settings like Nigeria.

6.1 Technical and Analytical Considerations

The implementation of single-cell approaches in clinical settings faces technical barriers related to sample processing, data generation, and computational analysis. The requirement for viable single-cell suspensions from fresh tissues presents logistical challenges, especially for biobanking and multicenter studies. However, recent advances in fixed tissue processing and nuclei isolation have expanded the applicability of single-cell technologies to archived specimens, enabling retrospective studies [21].

The analysis and interpretation of single-cell data require specialized computational expertise and infrastructure. The high dimensionality, sparsity, and technical noise inherent in single-cell datasets necessitate sophisticated statistical methods and visualization tools. Additionally, the integration of multiple data modalities—such as genome, transcriptome, epigenome, and proteome—presents both opportunities and challenges for data interpretation [22].

The cost of single-cell profiling, though decreasing, remains substantial for widespread clinical implementation. Strategic prioritization of samples and targeted approaches focusing on specific gene panels or cell types may provide more cost-effective alternatives in resource-limited settings [23]. The development of spatial transcriptomics methods that preserve tissue architecture while providing single-cell resolution represents another exciting direction, bridging the gap between histopathology and molecular profiling .

6.2 Clinical Translation and Implementation in Nigeria

The application of single-cell technologies in Nigeria requires context-specific considerations, including the distinct genetic background of the population and the unique environmental exposures that may influence disease biology. Building local capacity for single-cell research through international collaborations and infrastructure investment is essential for generating relevant data for the Nigerian population [24].

The integration of single-cell approaches into clinical trials represents a promising path for biomarker validation and therapeutic development. By correlating single-cell profiles with treatment responses in Nigerian patients, researchers can identify predictive biomarkers and resistance mechanisms relevant to the local population. These insights could guide the development of adapted treatment guidelines that account for the specific molecular features of hematological malignancies in Nigeria.

The potential for single-cell technologies to advance precision medicine in Nigeria must be balanced with practical considerations of healthcare resources. Initially, focused applications in refined diagnosis, risk stratification, and targeted therapy selection for high-risk or refractory cases may provide the greatest clinical benefit while establishing evidence for broader implementation [25].

7. Conclusion

Single-cell technologies have fundamentally transformed our understanding of leukemia and lymphoma heterogeneity, revealing complex clonal architectures, dynamic evolutionary trajectories, and intricate microenvironmental interactions. These insights have profound implications for diagnosis, risk stratification, and treatment selection, moving the field closer to truly personalized medicine.

In the Nigerian context, the implementation of single-cell approaches holds particular promise for addressing the unique challenges in hematological malignancies. By characterizing the molecular features of these diseases in the local population, researchers and clinicians can develop more effective, tailored approaches to diagnosis and treatment. While significant challenges remain in technology access and implementation, strategic investments in infrastructure and training could position Nigeria at the forefront of single-cell research in Africa.

As single-cell technologies continue to evolve, with improvements in throughput, multiplexing, and spatial resolution, their impact on clinical practice will undoubtedly expand. The integration of these approaches with other data modalities, including digital pathology and clinical parameters, will provide increasingly comprehensive views of disease biology. Ultimately, these advances promise to improve outcomes for patients with leukemia and lymphoma in Nigeria and worldwide.

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