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Role of mutational signatures and clonality assessments in tailoring targeted therapies for lymphoma

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Abstract

Lymphomas are highly heterogeneous malignancies characterized by diverse genetic, epigenetic, and phenotypic profiles, which complicate diagnosis, prognosis, and treatment. Traditional bulk sequencing methods mask the complexity of intratumoral variation, often overlooking rare subclones that may drive disease progression and therapeutic resistance. Single-cell genomics has emerged as a transformative approach to decipher tumor heterogeneity at unprecedented resolution. This technology enables the dissection of individual cellular populations within lymphomas, offering insights into clonal evolution, transcriptional diversity, and microenvironmental interactions. By applying single-cell RNA sequencing (scRNA-seq), chromatin accessibility assays (scATAC-seq), and single-cell DNA sequencing (scDNA-seq), researchers can unravel lineage relationships, identify resistant subpopulations, and track dynamic changes in response to therapy. In lymphomas such as diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL), single-cell approaches have revealed distinct malignant and non-malignant cell states that correlate with treatment outcomes. Moreover, integrating single-cell data with spatial transcriptomics and immune profiling enhances the understanding of the tumor microenvironment, including immune evasion mechanisms. These insights can inform personalized treatment strategies, identify novel therapeutic targets, and enable early detection of relapse. Despite technical challenges such as data complexity, sample viability, and cost, the application of single-cell genomics in lymphoma research is rapidly advancing. Future directions include multi-omics integration, real-time patient monitoring, and clinical translation of predictive biomarkers. This review underscores the pivotal role of single-cell genomics in resolving tumor heterogeneity and predicting therapeutic resistance, positioning it as a cornerstone for next-generation precision oncology in lymphomas,

Keywords: Single-cell genomics; Tumor heterogeneity; Therapeutic resistance; Lymphoma; Precision oncology; Clonal evolution

1. Introduction

1.1. Background on Lymphoma Subtypes (Hodgkin vs. Non-Hodgkin)

Lymphomas represent a diverse group of hematologic malignancies originating from lymphoid cells, primarily affecting the lymph nodes and related immune tissues. These cancers are broadly categorized into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), each demonstrating distinct histopathological and molecular characteristics. Hodgkin lymphoma, marked by the presence of Reed-Sternberg cells, accounts for approximately 10% of all lymphoma cases and is more prevalent in younger adults [1]. In contrast, non-Hodgkin lymphoma includes a wide array of subtypes such as

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diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and Burkitt lymphoma (BL), with DLBCL being the most common [2].

NHLs vary greatly in terms of clinical aggressiveness, treatment response, and prognosis. Indolent forms, such as FL, tend to follow a slow course but are often incurable, whereas aggressive subtypes like BL may progress rapidly yet are more amenable to curative therapy [3]. The clinical heterogeneity of NHL underscores the necessity for nuanced classification systems that go beyond morphology and immunophenotyping.

1.2. Limitations of Conventional Therapy

Despite advances in immunochemotherapy regimens such as R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone), the long-term outcomes for many patients with aggressive or relapsed lymphomas remain suboptimal [4]. Resistance to first-line therapy and disease relapse are frequent challenges, particularly in cases involving high-grade transformation or refractory disease biology. Furthermore, conventional therapies are associated with considerable toxicity, and their effectiveness is often compromised by the molecular diversity within and between tumors [5].

Another limitation lies in the lack of personalized treatment approaches. Most clinical protocols rely on a standardized approach, failing to consider the genetic and clonal landscape of individual tumors. This one-size-fits-all strategy overlooks biologically distinct disease subgroups that may respond differently to therapy, ultimately limiting the efficacy of systemic treatments [6].

1.3. Rise of Precision Oncology in Hematologic Malignancies

The advent of precision oncology has revolutionized the treatment landscape for solid tumors and is increasingly gaining momentum in hematologic malignancies. Precision oncology is characterized by the integration of genomic, transcriptomic, and proteomic data to guide individualized therapeutic strategies. In lymphomas, genomic profiling has enabled the identification of recurrent mutations, chromosomal aberrations, and pathway dysregulations, paving the way for more targeted and rational treatment designs [7].

Recent developments in high-throughput sequencing technologies have further facilitated the characterization of lymphoid malignancies at unprecedented resolution. For instance, large-scale efforts such as the Lymphoma/Leukemia Molecular Profiling Project (LLMPP) have uncovered novel biomarkers and stratification tools that have already influenced clinical practice [8]. These initiatives highlight the feasibility of using molecular signatures to classify disease subtypes more accurately and predict therapy response.

Moreover, precision oncology offers the potential to identify actionable mutations and assess disease dynamics over time. Unlike static diagnostic tools, real-time genomic surveillance can guide adaptive therapeutic interventions, particularly in diseases characterized by clonal evolution and resistance mechanisms [9].

1.4. Define Mutational Signatures and Clonality: Relevance to Lymphoma

Mutational signatures refer to characteristic patterns of somatic mutations that reflect specific DNA damage and repair processes. These patterns, identifiable through statistical modeling of genomic data, can reveal insights into the biological history of a tumor. Signature analysis has been extensively applied in solid tumors and is now increasingly employed in lymphomas to unravel the mutational processes that drive pathogenesis [10].

For example, activation-induced cytidine deaminase (AID) and APOBEC enzyme activity are known contributors to the mutational burden in B-cell lymphomas. These signatures not only help differentiate subtypes but may also carry prognostic and therapeutic implications [11]. Some signatures have been associated with increased tumor aggressiveness or resistance to standard treatments, making them valuable tools for risk stratification and therapy selection.

Clonality, on the other hand, pertains to the genetic relatedness of tumor cell populations. Clonal assessments aim to determine whether a tumor is derived from a single progenitor cell or comprises multiple evolving subclones. In lymphomas, clonality is especially relevant given the hierarchical structure of B-cell development and the frequent occurrence of somatic hypermutation and class-switch recombination [12].

Assessing clonality helps identify dominant clones, track subclonal dynamics over time, and evaluate the effects of therapy on tumor composition. Importantly, understanding clonal evolution can elucidate mechanisms of drug

resistance and inform the timing of treatment escalation or de-escalation [13]. For instance, the expansion of minor subclones harboring resistance mutations during therapy often precedes clinical relapse and could be targeted preemptively in a personalized treatment plan.

1.5. Purpose and Scope of the Article

Given the limitations of conventional approaches and the promise of precision medicine, this article aims to explore the role of mutational signatures and clonality assessments in tailoring targeted therapies for lymphoma. It seeks to synthesize current knowledge on the genomic underpinnings of lymphoid malignancies and demonstrate how these molecular features can guide more effective and personalized interventions.

The subsequent sections will discuss the detection and interpretation of mutational signatures, highlight their prevalence in various lymphoma subtypes, and examine the tools used to assess clonal architecture. Additionally, the article will explore how integrating these data points supports clinical decision-making and enhances outcomes through more precise therapeutic targeting [14].

We will also address practical challenges, including data integration, assay standardization, and clinical implementation barriers. Real-world case studies and emerging technologies will be used to illustrate the translational impact of these approaches in modern lymphoma care. Ultimately, this article advocates for a paradigm shift—moving from generic protocols to genomically guided, clonality-informed therapy strategies that reflect the true complexity of lymphoid cancers [15].

2. Understanding mutational signatures in lymphoma

2.1. Definition and Biological Basis

Mutational signatures are characteristic patterns of somatic mutations within the cancer genome, reflecting the activity of underlying mutational processes. These processes may be endogenous, such as spontaneous deamination, replication errors, or the activity of enzymes like APOBEC or AID, or exogenous, such as exposure to ultraviolet radiation, tobacco smoke, or chemotherapeutic agents [5]. Each mutational process leaves a distinctive “fingerprint” in the DNA, which can be mathematically decomposed and classified into specific signatures.

The most commonly used framework for categorizing these patterns is provided by the Catalogue Of Somatic Mutations In Cancer (COSMIC), which groups them into single base substitutions (SBS), double base substitutions (DBS), and insertions and deletions (indels) [6]. SBS signatures, the most extensively studied, describe point mutations occurring at single nucleotide sites, typically within specific trinucleotide contexts. For instance, SBS1 arises from spontaneous deamination of methylated cytosine, while SBS2 and SBS13 are attributed to APOBEC activity [7].

Double base substitutions are relatively rare but provide distinct insights into DNA damage caused by mutagens or reactive oxygen species. Indel signatures, meanwhile, reflect DNA repair pathway defects, including mismatch repair (MMR) or homologous recombination deficiencies. Notably, the interpretation of these signatures requires statistical modeling using computational techniques such as non-negative matrix factorization (NMF), which deconvolves mutation catalogs into distinct, biologically relevant components [8].

In lymphomas, these signatures serve as both etiological markers and predictive tools, enabling a deeper understanding of tumor development, progression, and therapeutic vulnerability [9]. As mutational signature databases grow, their application in lymphoid malignancies is expected to become increasingly robust and clinically actionable.

2.2. Methods of Detection and Analysis

Identifying mutational signatures in lymphoma requires high-resolution genomic sequencing data. Whole-genome sequencing (WGS) remains the gold standard for comprehensive signature analysis, as it captures both coding and non-coding regions, allowing for the detection of mutation patterns across the entire genome [10]. However, the high cost and computational demand of WGS limit its widespread clinical use. Whole-exome sequencing (WES), which focuses on protein-coding regions, is a more accessible alternative but provides a narrower view of mutational activity, potentially overlooking critical non-coding signatures [11].

Following sequencing, mutation calls are annotated using bioinformatics pipelines such as Mutect2, VarScan, or Strelka. These calls are then aggregated into trinucleotide or other contextual matrices to quantify the contribution of various

mutational processes. Non-negative matrix factorization (NMF) and hierarchical Bayesian models are typically applied to deconvolute these data into discrete signatures that can be matched against the COSMIC reference database [12].

To standardize this process, computational tools such as SigProfiler, deconstructSigs, and MutationalPatterns have been developed, allowing researchers and clinicians to input variant data and receive signature profiles in return. These tools facilitate reproducibility and improve the comparability of studies across different platforms and laboratories [13].

Nevertheless, there are several limitations to current signature detection workflows. First, sample purity and sequencing depth can significantly affect the accuracy of mutation calls and the detection of low-frequency signatures. Second, technical artifacts introduced during library preparation or sequencing can confound genuine biological signals. Lastly, inter-sample variability and tumor heterogeneity necessitate larger cohorts and careful statistical modeling to avoid misclassification [14].

Standardization efforts are underway to address these challenges. The Pan-Cancer Analysis of Whole Genomes (PCAWG) consortium, for example, has proposed benchmarks and quality control metrics for signature attribution, enhancing the robustness of signature-based diagnostics [15]. Moreover, multi-institutional efforts are beginning to incorporate these tools into translational and clinical workflows, especially in trials investigating genomically guided therapy selection.

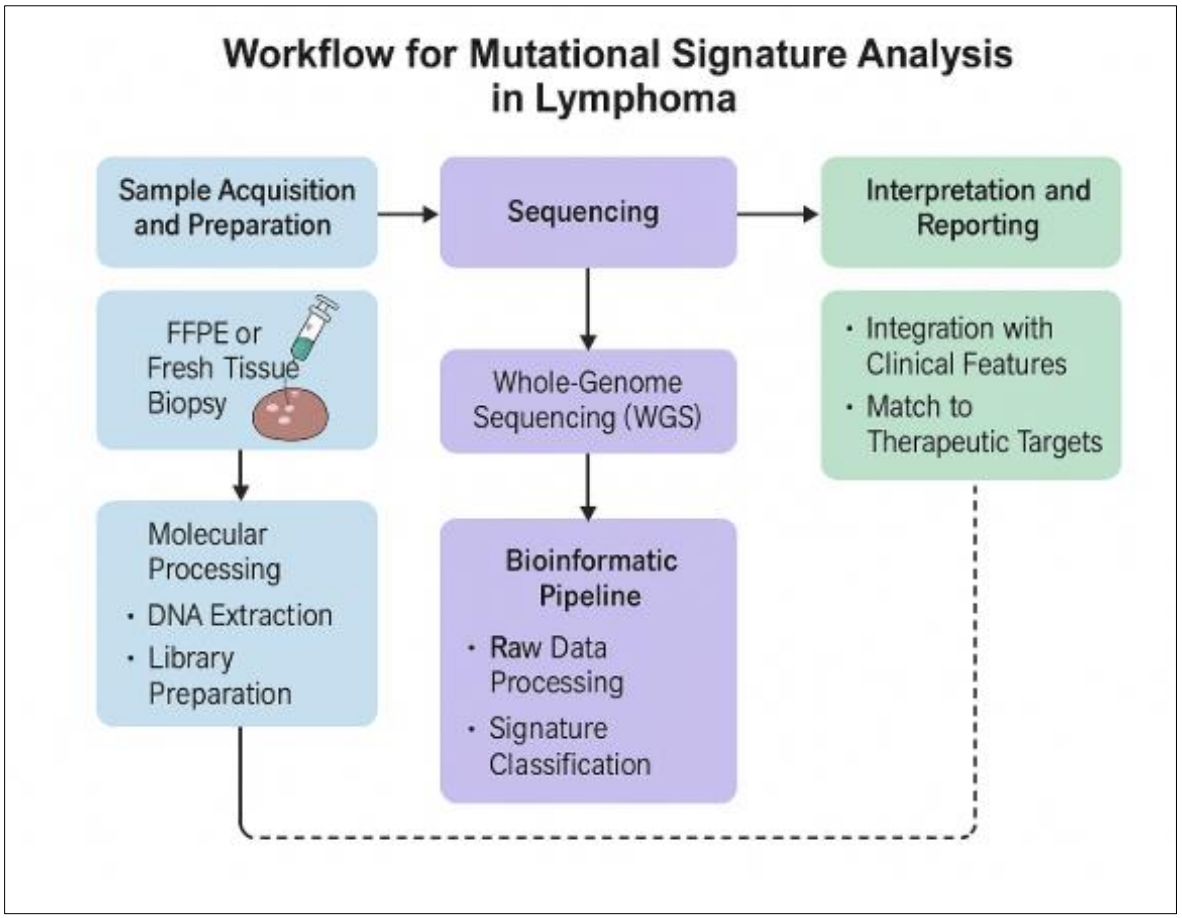

Figure 1 Workflow diagram illustrating the process of mutational signature analysis in lymphoma, from sample preparation and sequencing to computational deconvolution and clinical interpretation

As the field advances, integrating mutational signature analysis with real-time sequencing and decision-support systems may become routine in managing aggressive lymphomas or tracking therapy response, particularly where resistance is mediated by specific mutagenic processes.

2.3. Characterized Mutational Signatures in Specific Lymphoma Subtypes

While most research on mutational signatures has focused on solid tumors, a growing body of work is now characterizing specific signatures across different lymphoma subtypes. These include DLBCL, FL, MCL, and BL, each of which exhibits unique mutational profiles that can inform diagnosis, prognosis, and treatment strategy [16].

In diffuse large B-cell lymphoma (DLBCL), one of the most prevalent and aggressive subtypes, signatures associated with activation-induced cytidine deaminase (AID) and APOBEC enzyme activity are frequently observed. AID, critical for somatic hypermutation and class-switch recombination in germinal center B cells, is implicated in off-target mutations leading to SBS9 and SBS84 signatures [30]. These mutations typically affect oncogenes such as MYC, BCL6, or PIM1 and may drive early lymphomagenesis.

APOBEC-related signatures (e.g., SBS2 and SBS13) are also detected in a subset of DLBCL and are associated with a hypermutated phenotype that may influence response to immunotherapy or PI3K inhibitors [18]. In follicular lymphoma (FL), AID-related mutagenesis predominates, reflecting its germinal center origin. FLs also exhibit high clonal diversity and frequent mutations in epigenetic regulators such as EZH2, CREBBP, and KMT2D, many of which are shaped by recurring mutational processes [19].

Mantle cell lymphoma (MCL) often demonstrates less heterogeneity in terms of mutational signatures but may harbor indel patterns reflective of DNA repair deficiency, especially in blastoid variants. These indel signatures can portend poor prognosis and resistance to conventional regimens [20].

In Burkitt lymphoma (BL), characterized by MYC translocations and a highly proliferative phenotype, unique mutational signatures have been linked to mismatch repair deficiency (MMRd) and ultraviolet light exposure in certain endemic cases. SBS6, SBS15, and SBS44, often associated with MMRd, contribute to the elevated mutation burden observed in a subset of BL tumors, especially those occurring in immunocompromised individuals [21].

From a clinical standpoint, the presence of specific mutational signatures can aid in differential diagnosis, especially in ambiguous histologies. Moreover, signature profiling may assist in predicting therapy response or identifying therapeutic vulnerabilities. For instance, tumors with mismatch repair–deficient signatures may benefit from immune checkpoint blockade, while APOBEC-rich lymphomas may require novel agents that mitigate DNA hypermutation [22].

The clinical integration of mutational signatures remains an evolving field, but early evidence suggests that these patterns can stratify patients beyond conventional genomic biomarkers. As such, signature-guided classification could become an indispensable component of lymphoma precision medicine, particularly when combined with clonal profiling and real-time monitoring.

3. Clonality and clonal evolution in lymphoma

3.1. Concepts of Clonality and Intratumoral Heterogeneity

The concept of clonality in cancer describes the genetic lineage of tumor cells that originate from a common ancestral cell, known as the founder clone. In lymphomas, the founder clone typically arises from a single B- or T-cell precursor that has undergone malignant transformation [11]. However, due to ongoing genetic instability and selective pressures within the tumor microenvironment, this founder population often gives rise to subclones—genetically distinct offshoots that may vary in their proliferative capacities, resistance profiles, and metastatic potential.

These subclonal populations form the basis of intratumoral heterogeneity, a hallmark of cancer evolution that complicates both diagnosis and treatment. Subclones may either remain minor or expand through clonal sweeps, where selective advantages—such as resistance to therapy or enhanced proliferation—allow certain clones to dominate the tumor population [12].

An important related concept is clonal selection, whereby external forces like chemotherapy or immune surveillance preferentially eliminate sensitive clones while sparing or enriching resistant ones. This Darwinian process drives disease progression and relapse in lymphoma patients, especially in aggressive subtypes like diffuse large B-cell lymphoma (DLBCL) or mantle cell lymphoma (MCL) [13].

The degree of heterogeneity and clonal architecture has been directly associated with disease aggressiveness and prognosis. Tumors with high clonal diversity tend to be more adaptable and less responsive to monotherapy. For

instance, a high clonal burden at diagnosis correlates with shorter progression-free survival in follicular lymphoma (FL) and poorer outcomes in relapsed/refractory DLBCL [14].

Understanding these evolutionary dynamics is critical for precision oncology. Accurate assessment of clonal structures enables oncologists to track disease progression, predict treatment response, and tailor therapeutic strategies that address both dominant and emerging resistant subclones [15].

3.2. Technological Advances in Clonality Assessments

The last decade has seen significant advances in technologies used to assess clonality in hematologic malignancies. Traditionally, clonality was inferred from bulk sequencing approaches, which analyze DNA or RNA from a pool of cells and provide an averaged view of mutational landscapes. While informative, bulk methods cannot distinguish between individual clones, especially when subclones are present at low frequencies [16].

To overcome this limitation, single-cell sequencing has emerged as a transformative tool in lymphoma research. It enables the direct analysis of individual tumor cells, revealing not only their mutational profiles but also transcriptomic states, lineage trajectories, and epigenetic modifications. This technology has uncovered extensive clonal diversity even within morphologically homogeneous tumors [17]. However, its clinical adoption remains constrained by cost, technical complexity, and data interpretation challenges.

Another powerful tool is digital PCR (dPCR), which provides highly sensitive quantification of rare clonal variants. dPCR is particularly useful for detecting minimal residual disease (MRD), where traditional methods may lack the sensitivity to identify residual malignant clones post-treatment. MRD monitoring via dPCR has become a validated prognostic tool in multiple lymphoma subtypes, guiding therapy duration and intensification decisions [18].

In B-cell lymphomas, clonality is also assessed by examining B-cell receptor (BCR) gene rearrangements. During normal lymphocyte development, unique recombinations of V(D)J gene segments occur in the immunoglobulin heavy chain (IGH), generating a diverse BCR repertoire. The detection of a dominant, monoclonal IGH rearrangement indicates a clonal expansion, while the presence of multiple rearrangements may suggest biclonal disease or subclonal diversification [19].

Similarly, T-cell receptor (TCR) rearrangements are used to evaluate clonality in T-cell lymphomas. High-throughput sequencing platforms such as Adaptive Biotechnologies' ImmunoSEQ or ArcherDx's VariantPlex enable deep interrogation of immune receptor repertoires, supporting both diagnostic and MRD applications [20].

Despite their utility, clonality assessment techniques vary in sensitivity, resolution, and clinical applicability. The following table summarizes key comparative features:

Table 1 Comparison of Techniques for Clonality Detection in Lymphoma

Method	Resolution	Sensitivity	Clinical Utility
Bulk DNA Sequencing	Low	Moderate	Standard for mutation calling
Single-Cell Sequencing	High	High	Research-grade; not yet routine clinically
Digital PCR (dPCR)	Moderate	Very High	MRD detection and therapy monitoring
BCR/TCR Rearrangement PCR	High (clone-specific)	High	Diagnosis, MRD, and clonality confirmation

Standardizing these tools for clinical practice remains a priority, especially as next-generation sequencing (NGS) becomes integrated into lymphoma diagnostic algorithms [21].

3.3. Clonal Dynamics in Therapy Response and Relapse

Therapy exerts powerful selective pressure on tumor populations, often altering their clonal architecture. This phenomenon, known as clonal evolution, plays a central role in the development of resistance and relapse in lymphoma. At diagnosis, a tumor may appear to be dominated by a single clone, but therapy can lead to the expansion of previously minor subclones that harbor survival advantages [22].

A classic example is the emergence of chemo-resistant subclones following R-CHOP therapy in DLBCL. While initial response rates are high, a significant proportion of patients relapse with tumors that possess new mutations in genes associated with drug resistance, such as TP53 or BCL2. These genetic alterations are often absent or subclonal at baseline, highlighting the dynamic nature of clonal selection [23].

Longitudinal monitoring of clonal composition can provide early warnings of therapeutic failure. In follicular lymphoma, studies have shown that the appearance of a dominant EZH2-mutant clone during therapy correlates with poor prognosis and suggests early clonal divergence [24]. In mantle cell lymphoma, high clonal complexity post-induction therapy has been associated with rapid progression and limited benefit from maintenance regimens.

Importantly, not all resistant clones arise de novo. Some are therapy-induced as a result of treatment-associated mutagenesis. For example, cytotoxic drugs can introduce new mutations that confer fitness advantages to previously quiescent clones, leading to therapy-driven evolution rather than simple selection from pre-existing populations [25].

The integration of serial sequencing, both at the bulk and single-cell level, enables researchers and clinicians to map the trajectory of clonal changes over time. This includes identifying when a resistant subclone first emerges, how rapidly it expands, and how it responds to second-line therapy.

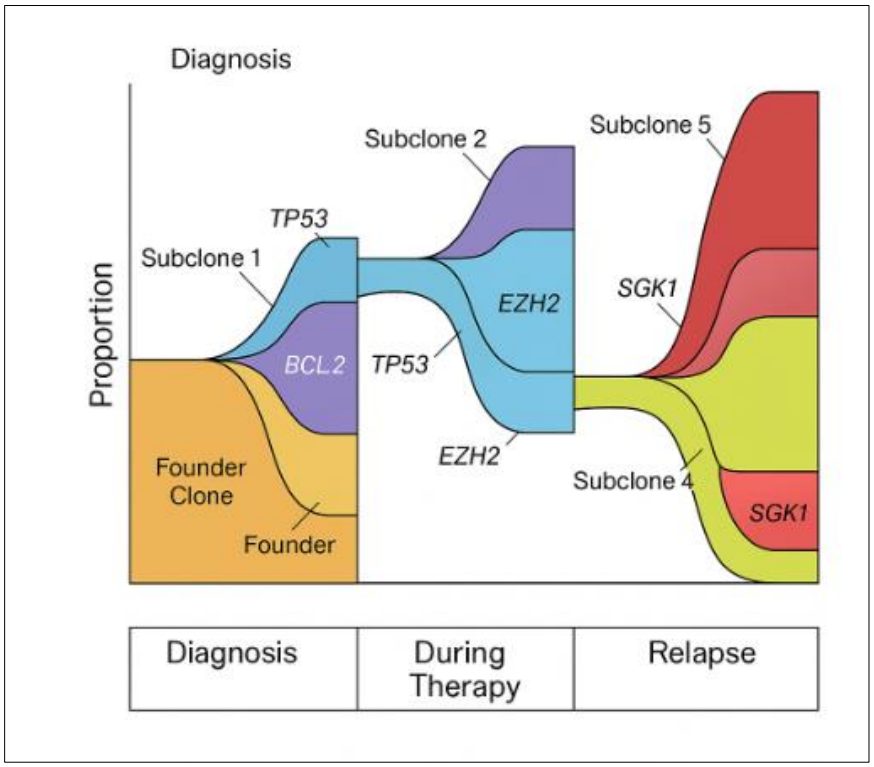

Figure 2 Longitudinal clonal evolution in lymphoma showing clonal dynamics at diagnosis, during therapy, and post-relapse, with mutation tracking across time points

These insights inform adaptive therapeutic strategies. Instead of waiting for relapse, oncologists may intervene proactively based on clonal trends—escalating therapy, switching agents, or adding novel treatments that target resistant clones [26].

Moreover, understanding the clonal basis of resistance opens the door to rational drug combinations designed to target both dominant and emergent clones simultaneously. This could reduce the risk of relapse and improve long-term disease control. For example, combining BCL2 inhibitors with immune checkpoint blockade has shown promise in targeting multiple clonal compartments in relapsed FL and DLBCL [27].

Ultimately, incorporating clonal assessments into standard care can personalize treatment across all stages of lymphoma—from initial diagnosis to salvage therapy—marking a key advancement in precision hematology.

4. Integration of mutational signatures and clonality in precision oncology

4.1. Linking Genomic Profiles to Targetable Mutations

Genomic profiling in lymphoma has enabled the identification of actionable driver mutations that contribute to oncogenesis and tumor maintenance. These include alterations in genes involved in B-cell receptor signaling (e.g., *CARD11*, *CD79B*), apoptosis regulation (*BCL2*, *TP53*), and chromatin remodeling (*EZH2*, *CREBBP*, *KMT2D*) [15]. Such driver mutations often emerge from selective evolutionary pressures and represent attractive therapeutic targets for pathway-directed agents.

Integrating mutational signatures enhances the interpretive power of genomic profiling by connecting mutation patterns to specific biological mechanisms. For example, tumors exhibiting AID-related mutational signatures often harbor rearrangements or mutations in *MYC*, *BCL6*, and other genes that drive germinal center-derived lymphomas [16]. Similarly, the presence of APOBEC signatures may point to genomic instability, rendering cells more susceptible to synthetic lethal strategies targeting DNA repair pathways.

The principle of synthetic lethality—where co-occurring gene disruptions lead to cell death—offers a compelling strategy for targeting tumors with defined mutational contexts. For instance, lymphomas with mutations in DNA damage response genes (e.g., *ATM*, *CHEK2*) may be vulnerable to PARP inhibitors [17]. The combination of signature analysis and mutation profiling can thus pinpoint critical vulnerabilities not evident through traditional sequencing alone.

Furthermore, these signatures often illuminate pathway dependencies, allowing for rational drug development and repurposing. Tumors with MMR-deficient signatures (e.g., SBS6, SBS15) exhibit heightened sensitivity to immune checkpoint blockade due to increased neoantigen burden [18]. Integrating this information with clonality data allows clinicians to design therapies that selectively disrupt the evolutionary core of the disease, preventing recurrence and clonal escape.

Ultimately, linking genomic profiles to actionable mutations via mutational signature interpretation transforms static sequencing data into dynamic, clinically actionable insights, enabling targeted interventions tailored to individual tumor biology [19].

4.2. Predictive Value of Signatures for Treatment Sensitivity

Mutational signatures serve not only as etiological clues but also as predictive biomarkers of treatment sensitivity. Certain signatures correlate strongly with therapeutic response, providing a framework for refining patient stratification and guiding the selection of precision therapies.

A prominent example is mismatch repair (MMR) deficiency, often reflected by mutational signatures such as SBS6, SBS15, and SBS26. These tumors exhibit high tumor mutation burden (TMB), a condition that enhances the generation of neoantigens and subsequently renders the malignancy more responsive to immune checkpoint inhibitors (ICIs) like anti-PD-1 or anti-CTLA-4 therapies [20]. Although primarily studied in solid tumors, MMR-deficiency has also been observed in subsets of aggressive lymphomas, including primary mediastinal B-cell lymphoma and Richter's transformation [21].

Another signature of therapeutic relevance is APOBEC-associated hypermutation, typically represented by SBS2 and SBS13. These mutations generate localized clusters of cytosine-to-thymine substitutions, contributing to increased mutational burden and genomic instability. In lymphoma, APOBEC activity is frequently associated with resistance to conventional chemotherapy but paradoxically may confer sensitivity to PI3K inhibitors due to pathway rewiring [22].

Emerging data suggest that APOBEC-enriched tumors are more likely to harbor *PIK3CA*, *PTEN*, and *AKT1* mutations—alterations that make the PI3K/AKT/mTOR axis an actionable therapeutic target. Thus, mutational signatures provide a layer of context that enhances the predictability of drug response beyond simple mutation presence or absence [23].

Importantly, signatures also inform resistance prediction. In DLBCL, for instance, SBS17—a pattern linked to oxidative stress—has been associated with early relapse after R-CHOP therapy, suggesting an aggressive phenotype and potential resistance to anthracyclines [24]. Identifying such patterns allows for early therapeutic escalation or inclusion in clinical trials exploring novel agents.

The utility of mutational signatures in predicting therapeutic efficacy is rapidly gaining traction and is now being incorporated into biomarker panels alongside traditional genomic markers, immune cell infiltration metrics, and MRD status [25]. These integrative approaches offer a holistic view of tumor behavior, enhancing personalized treatment strategies and improving outcomes in patients with refractory or high-risk lymphoma.

4.3. Clonality-Guided Risk Stratification and Therapy Design

The evolving understanding of tumor clonality has shifted the paradigm of therapy design from targeting a uniform disease entity to addressing a heterogeneous population of evolving clones. Stratifying patients based on clonal architecture allows oncologists to anticipate disease trajectory and optimize treatment selection.

One of the most significant advantages of clonality analysis is its ability to differentiate dominant from emerging subclones. Dominant clones, often responsible for bulk disease at presentation, may be effectively targeted by first-line therapies. However, minor subclones—frequently overlooked in bulk analyses—can harbor mutations conferring resistance, such as TP53 loss or MYD88 mutations, and expand under treatment pressure [26].

Therapies designed to eliminate dominant clones while suppressing the outgrowth of minor subclones are more likely to yield durable remissions. For example, the use of venetoclax, a BCL2 inhibitor, has shown activity in BCL2-dominant follicular lymphomas, while combination with agents targeting EZH2-mutated subclones can further delay resistance [27].

Clonal data also guide combination therapy decisions. By characterizing the subclonal architecture of a tumor, clinicians can choose drug pairs or triplets that simultaneously disrupt multiple evolutionary pathways. In relapsed/refractory DLBCL, dual inhibition of CD79B (via antibody-drug conjugates) and BCL6 (a transcriptional repressor) has demonstrated efficacy in tumors with bifurcated clonal drivers [28].

Importantly, understanding clonality enhances risk stratification. Patients with high clonal diversity, rapid clonal turnover, or therapy-induced clonal reshaping are more likely to experience relapse and may benefit from early hematopoietic stem cell transplantation or enrollment in adaptive clinical trials [29].

Table 2 Targeted Therapies Associated with Specific Mutational Signatures and Clonal Architectures

Mutational Signature / Clonal Feature	Associated Targetable Pathway	Therapeutic Agent(s)
SBS6 / MMR-deficiency	PD-1/PD-L1 pathway	Nivolumab, Pembrolizumab
APOBEC (SBS2, SBS13)	PI3K/AKT/mTOR pathway	Copanlisib, Duvelisib
EZH2-mutant Subclones	Epigenetic modification	Tazemetostat
TP53-disrupted Minor Clones	Apoptotic escape	Venetoclax + anti-CD20 combinations
CD79B and MYD88 L265P Co-dominance	BCR signaling and NF-κB	Ibrutinib, Zanubrutinib

Such integrations of signature and clonality data into therapeutic planning mark a critical step toward truly personalized lymphoma treatment. They allow oncologists to anticipate the evolutionary trajectories of tumors, minimize clonal escape, and maximize response durability.

As genomic technologies mature and become embedded in clinical practice, the fusion of mutational signatures with clonal analytics will increasingly inform frontline and salvage therapy decisions, setting a new standard for precision in hematologic oncology [30].

5. Clinical applications and case studies

5.1. Personalized Treatment Algorithms Using Genomic and Clonal Data

The convergence of genomics and clonal analytics is shaping the next generation of personalized treatment algorithms for lymphoma. By integrating whole-exome sequencing (WES) with minimal residual disease (MRD) assessments and computational classifiers, clinicians can stratify patients into therapeutic pathways with enhanced precision [19].

One emerging approach involves decision-tree models that incorporate genomic alterations, signature profiles, and clonal dominance to guide therapy. For example, in a high-risk follicular lymphoma case with dominant *EZH2* mutation and high AID-related signature burden, a frontline regimen incorporating epigenetic inhibitors may be considered. If MRD remains detectable post-induction, the algorithm may escalate treatment with PI3K inhibitors or refer the patient for stem cell transplantation [20].

In diffuse large B-cell lymphoma (DLBCL), the LymphGen classifier has gained traction as a genomic-based taxonomy system. This tool classifies DLBCL cases into genetically defined subgroups such as MCD (co-occurring *MYD88* and *CD79B* mutations), BN2, EZB, N1, and ST2, each with distinct clonal and molecular profiles [21]. LymphGen subtypes not only predict survival outcomes but also inform targeted therapy selection—such as BTK inhibitors in MCD-type and EZH2 inhibitors in EZB-type cases.

When combined with clonality data, these models become even more robust. For instance, identification of a high-risk subclone carrying *TP53* mutations despite favorable LymphGen classification may influence clinicians to pursue more aggressive therapy. Similarly, the clearance of MRD post-treatment in a genomically complex case may justify therapy de-escalation, minimizing toxicity without compromising outcomes [22].

Such integrated algorithms are particularly promising for adaptive trial designs, where therapy is modified based on real-time genomic and clonal data. These approaches support a shift away from static guidelines toward dynamic, biologically informed treatment planning that aligns with the evolving tumor landscape.

As implementation becomes more widespread, these decision-making tools are expected to transition from research settings into standard oncology practice, ultimately redefining how lymphoma therapy is designed, monitored, and adapted [23].

5.2. Case Reports and Trials Incorporating Signature/Clonality Data

The clinical validity of mutational signature and clonality assessments is increasingly supported by real-world data and prospective studies. Case reports and clinical trials offer valuable insights into how these tools can improve therapy precision, predict prognosis, and guide intervention timing.

The NCI-MATCH (Molecular Analysis for Therapy Choice) trial was among the first to explore treatment allocation based on genomic alterations, rather than histological subtype. Although not lymphoma-specific, the study included patients with relapsed lymphoid malignancies and utilized next-generation sequencing to match targeted therapies to actionable mutations—many of which were later linked to signature activity in retrospective analyses [24].

Another landmark initiative, Lymphoma TRACERx, is actively characterizing clonal evolution and mutational patterns in large patient cohorts. Preliminary results demonstrate that patients with higher baseline clonal diversity, as measured by single-cell or high-depth bulk sequencing, have shorter progression-free survival (PFS) and overall survival (OS), irrespective of traditional clinical prognostic markers [25].

In one FL case study, a patient with dominant *CREBBP* and *KMT2D* mutations responded poorly to standard immunochemotherapy. Retrospective analysis revealed co-existing APOBEC signatures and minor *TP53*-mutated subclones. Upon disease progression, targeted therapy including venetoclax and tazemetostat achieved partial remission—an outcome that would have been improbable without molecular reclassification [26].

Additionally, retrospective cohorts of DLBCL patients stratified by clonal burden and mutation signature show consistent differences in treatment response. SBS17 and SBS3, associated with oxidative damage and defective homologous recombination respectively, correlate with early relapse and inferior survival [27]. Patients with these signatures may benefit from early intensification or inclusion in clinical trials exploring PARP inhibitors and oxidative stress modulators.

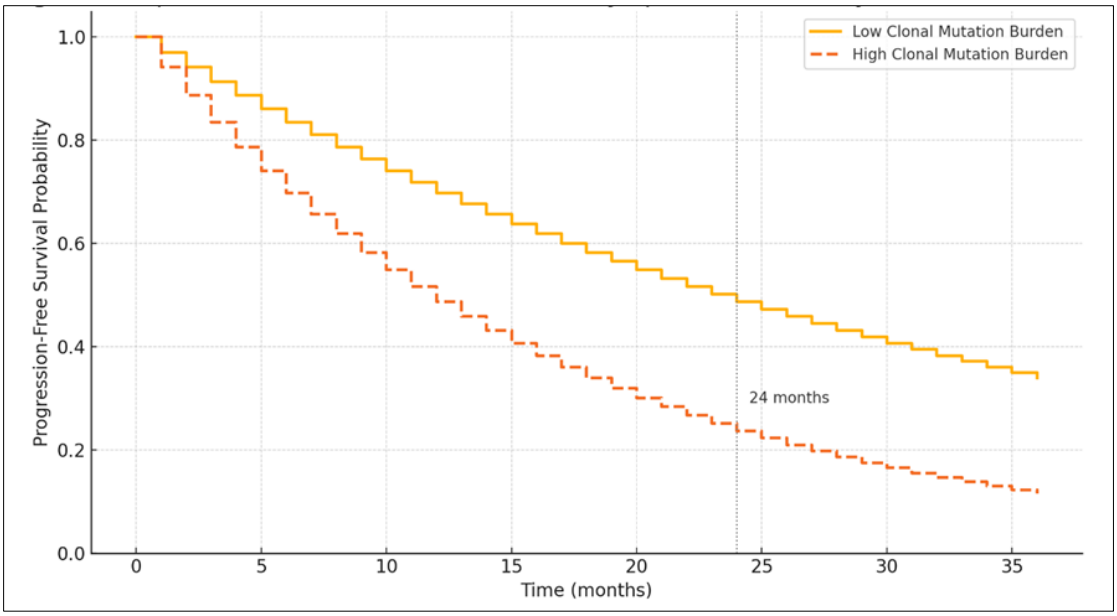

Figure 3 Kaplan-Meier survival curve comparing PFS in lymphoma patients stratified by clonal mutation burden (low vs. high), showing significant divergence at 24 months

Such studies underscore the real-world impact of genomic and clonal profiling on outcome prediction. Importantly, they validate that therapy guided by these tools can enhance not only precision but also durability of response, improving long-term outcomes across diverse lymphoma subtypes.

Looking ahead, incorporation of longitudinal sequencing data in future trials will allow for adaptive protocol designs, whereby treatment is modified based on emerging resistance clones or signature shifts. This could be transformative in managing relapsed/refractory disease, where timing and precision are critical determinants of survival [28].

5.3. Regulatory and Clinical Implementation Challenges

Despite the promise of signature and clonality-guided therapy, several regulatory and implementation challenges must be addressed to ensure broad clinical adoption. Among the most immediate are cost, turnaround time, and lack of standardized interpretation pipelines.

Comprehensive genomic sequencing—particularly WGS or high-depth single-cell approaches—remains expensive and labor-intensive. In many settings, insurance coverage is limited, and payers demand clear evidence of clinical utility before reimbursement is approved [29]. Moreover, the median turnaround time for sequencing results may range from two to six weeks, which can delay treatment decisions in aggressive lymphomas requiring urgent intervention.

There is also a lack of uniform bioinformatic standards for interpreting mutational signatures and clonality data. Different tools may yield variable results depending on mutation calling pipelines, sequencing depth, and statistical models. This variability can lead to inconsistent classification of patients and potential disparities in treatment access and quality [30].

Table 3 Barriers and Proposed Solutions for Implementing Signature-Based Therapy in Lymphoma

Barrier	Description	Proposed Solution
High Cost of Sequencing	WGS and scRNA-seq are expensive and resource-intensive	Expand insurance coverage; invest in public genomics
Turnaround Time for Analysis	Delays limit use in frontline aggressive cases	Develop rapid sequencing pipelines with AI support
Interpretation Variability	Non-standardized bioinformatics lead to inconsistent results	Establish universal diagnostic standards and QC rules
Limited Clinician Familiarity	Many oncologists lack training in genomics or clonal analytics	Introduce educational modules in oncology curricula
Ethical Concerns in Genomic Disclosure	Incidental findings may cause anxiety or affect family planning decisions	Implement ethical counseling and data consent models

Another critical concern involves ethical issues surrounding genomic risk disclosure. High-resolution genomic data may uncover incidental findings, such as hereditary mutations or germline predispositions, that have implications beyond the scope of lymphoma care. Patients must be informed and consent appropriately, and systems must be in place to manage the psychosocial and familial implications of such discoveries [32].

Training clinicians in genomic literacy is also essential. Without adequate understanding, there is risk of misinterpretation or underutilization of the data. Continuing education programs, multidisciplinary molecular tumor boards, and automated decision-support systems may help bridge this knowledge gap, promoting safer and more effective implementation [33].

Lastly, the regulatory framework for diagnostic approval and companion diagnostics remains underdeveloped in hematologic malignancies. While the FDA has approved signature-based therapies in solid tumors (e.g., pembrolizumab for MSI-high cancers), lymphoma-specific frameworks are still evolving. Stakeholders must engage collaboratively to validate assays, define reimbursement pathways, and ensure equitable access to precision diagnostics and therapies [34].

6. Emerging technologies and future directions

6.1. AI and Machine Learning in Genomic Signature Interpretation

Artificial intelligence (AI) and machine learning (ML) are revolutionizing how mutational signatures are interpreted, particularly in the context of large-scale cancer genomics datasets. One of the most promising applications is deep learning-based deconvolution, where neural networks are trained to detect subtle and complex mutation patterns within massive sequencing matrices [35]. These models outperform traditional non-negative matrix factorization (NMF) in capturing low-prevalence signatures and mixed mutational processes.

Recurrent neural networks and attention-based models, including transformer architectures, are now being used to predict the functional impact of mutational signatures, such as therapy resistance or immune evasion [31]. These tools can also infer likely combinations of mutagenic exposures that may not be apparent through statistical methods alone, thereby uncovering hidden drivers of lymphoma evolution [36].

In clinical practice, the integration of AI tools with electronic health records (EHRs) is transforming decision support. AI models can ingest structured and unstructured data—genomic, clinical, imaging, and laboratory—and correlate signature profiles with patient outcomes [37]. This allows oncologists to receive real-time, evidence-backed therapy recommendations tailored to individual tumor biology and prior treatment history [38].

Moreover, predictive algorithms trained on datasets from trials such as TCGA and LymphGen are enabling automated risk stratification, flagging patients with high-risk mutational profiles or emerging subclonal threats. These capabilities enhance precision oncology by not only interpreting molecular data but operationalizing it within clinical workflows [39].

As AI becomes increasingly embedded in clinical systems, regulatory standards and data quality will play a crucial role. To ensure safe implementation, AI outputs must be transparent, reproducible, and validated against clinically relevant endpoints—principles that remain central as genomic medicine evolves [40].

6.2. Spatial Genomics and Multi-Omics Clonal Profiling

While traditional sequencing provides high-dimensional molecular data, it often lacks the context of spatial organization, a crucial element in understanding lymphoid tissue architecture. Spatial genomics addresses this gap by preserving spatial coordinates while mapping genomic features within tissue sections [41]. Technologies such as MERFISH, GeoMx DSP, and Visium spatial transcriptomics are enabling researchers to visualize clonal architecture in situ, offering new perspectives on how malignant clones interact with their microenvironment [42].

In lymphomas, spatial genomics has revealed that dominant clones are often spatially segregated from immune-infiltrated regions, suggesting potential immune escape mechanisms. Conversely, subclonal populations frequently reside in peripheral zones of lymphoid structures, where they may evolve under microenvironmental pressure or immune selection [43]. Understanding this geographic distribution supports the rational placement of biopsy targets and informs intratumoral heterogeneity models.

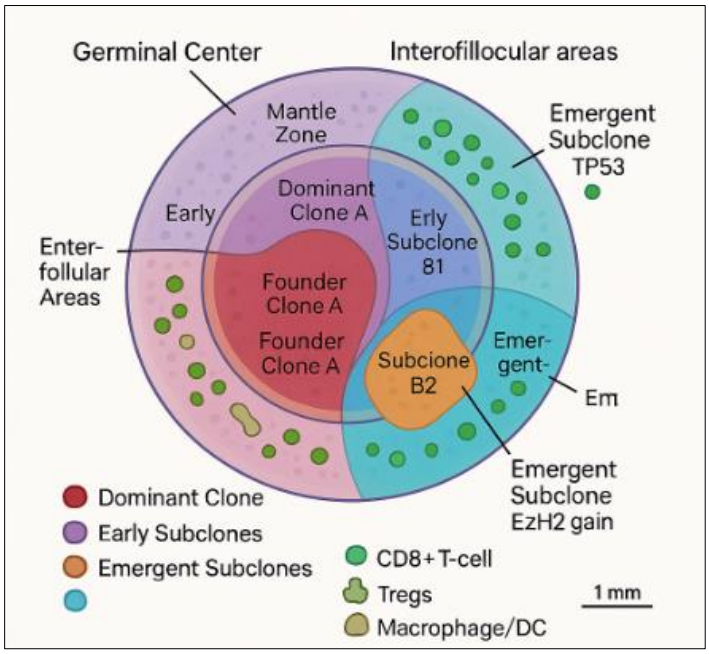

Figure 4 Spatial map of clonal architecture in a lymph node biopsy, highlighting dominant and subclonal mutation zones with immune infiltration overlays

The value of spatial genomics is magnified when integrated with multi-omics platforms, including metabolomics and epigenomics. Metabolomic profiling can identify nutrient gradients and hypoxia zones that promote the selection of specific clones, while epigenetic mapping uncovers chromatin accessibility patterns influencing gene expression and clonal fitness [44].

Together, these technologies allow for the construction of three-dimensional tumor atlases, combining genomic, transcriptomic, epigenomic, and spatial data into a unified framework. Such atlases offer unprecedented insight into tumor ecology, providing not only diagnostic and prognostic information but also actionable therapeutic targets based on clonal and spatial dependencies [45].

As cost and accessibility improve, spatial and multi-omic profiling will likely become integral to lymphoma diagnostics and real-time therapeutic guidance, especially in relapsed or anatomically complex disease settings [46].

6.3. Expanding Therapeutic Windows through Signature-Driven Combinations

The combination of mutational signature data with clonal dynamics is enabling a new generation of signature-driven polytherapies aimed at extending therapeutic windows and forestalling resistance. Unlike monotherapies, which often

drive clonal selection, combination regimens can simultaneously suppress multiple evolutionary trajectories, thereby improving the durability of response [43].

One strategy gaining traction involves targeting dominant clones while applying broader-acting agents to prevent subclonal emergence [47]. For instance, a patient with an EZB-type DLBCL dominated by an *EZH2* mutant clone might receive tazemetostat in combination with immunomodulatory drugs targeting APOBEC-enriched subclones. This approach preempts resistance by addressing the tumor's evolutionary reserve [48].

Signature-guided regimens are also informing the design of basket and umbrella clinical trials. Basket trials enroll patients based on shared mutational signatures or pathway dysregulation across histologically different cancers. For example, patients with mismatch repair-deficient signatures (SBS6, SBS26) may be eligible for a common ICI-based protocol, regardless of lymphoma subtype [49].

Umbrella trials, conversely, stratify patients within a single disease entity—such as DLBCL—into arms based on genomic and clonal features [50]. These trials allow for simultaneous evaluation of multiple targeted therapies, matched to patients' molecular profiles. The HARMONY project and LymphGen-Plus trials exemplify this approach, offering adaptive treatment algorithms based on real-time clonal and signature monitoring [51].

As more synergistic drug combinations are identified through preclinical models and AI-driven screening, clinical trial frameworks must evolve to accommodate adaptive dosing, real-time monitoring, and early switching based on clonal resistance signals [52]. This paradigm of personalized, adaptive polytherapy has the potential to radically improve outcomes, particularly for high-risk and treatment-refractory lymphoma patients [53].

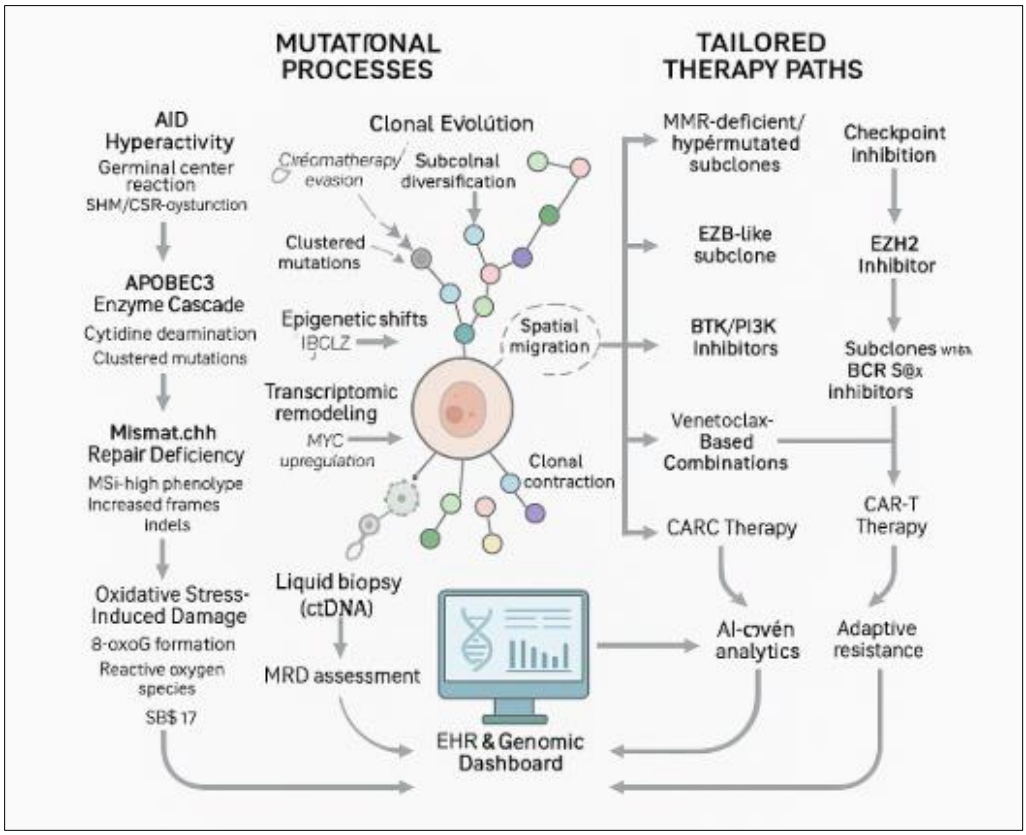

Figure 5 Schematic overview linking mutational processes, clonal evolution, and tailored therapy paths. The diagram illustrates how distinct mutational signatures contribute to clonal selection, therapeutic resistance, and the design of personalized treatment combinations

7. Conclusion and clinical implications

7.1. Summary of Major Findings

This article has provided an in-depth exploration of how mutational signatures and clonality assessments are reshaping precision therapy strategies in lymphoma. From foundational definitions to clinical applications, we have outlined how genomic alterations and their interpretive patterns serve as predictive, diagnostic, and therapeutic tools across various lymphoma subtypes.

Mutational signatures, such as those linked to AID, APOBEC, MMR deficiency, or oxidative stress, offer a window into the biological processes driving oncogenesis and resistance. These signatures, when paired with mutation profiling, expose vulnerabilities in tumor DNA repair pathways, apoptotic machinery, and immune signaling networks. In parallel, clonality assessments enable real-time tracking of disease evolution, from founder clone emergence to therapy-induced subclonal resistance.

Together, these two domains provide a dual lens through which oncologists can personalize treatment—targeting both static genetic drivers and dynamic evolutionary threats. By integrating signature profiling and clonal architecture, clinicians can predict therapeutic response, design multi-agent strategies, and adjust treatment in real time based on MRD status and subclonal shifts.

From technical advances such as single-cell sequencing and spatial genomics to emerging AI-powered interpretation tools, the landscape of lymphoma treatment is increasingly shaped by molecular resolution and evolutionary insight. The future of lymphoma care lies in leveraging this convergence to move from population-based protocols to individualized, adaptive therapy models.

7.2. Urgency of Integrating Mutational and Clonal Data in Hematologic Oncology

The integration of mutational and clonal data is no longer a conceptual luxury—it is a clinical necessity. As lymphoma treatment continues to evolve, the limitations of conventional staging systems and empiric chemotherapy regimens are becoming more apparent. Relapse rates remain unacceptably high in certain subtypes, and prolonged exposure to cytotoxic agents carries substantial morbidity.

Incorporating mutational signatures into diagnostic workflows allows for earlier identification of high-risk patients and guides the rational selection of targeted agents. Clonal data provide the dynamic context needed to interpret response patterns, anticipate resistance, and adjust therapy before disease progression becomes clinically evident.

The urgency is especially pronounced in aggressive and refractory lymphomas, where time-sensitive decisions can dramatically alter prognosis. Without genomic and clonal insight, clinicians are left to treat increasingly complex diseases with blunt instruments. Precision oncology, informed by mutation and clonal analytics, offers a more intelligent, responsive, and humane alternative.

Moreover, this integration is central to delivering value-based care. By tailoring treatment intensity to tumor biology, unnecessary toxicity and healthcare costs can be reduced, while improving long-term outcomes and quality of life for patients.

7.3. Call to Action for Translational Research and Clinical Integration

To fully realize the potential of mutational and clonal data in lymphoma therapy, a coordinated effort is required across research, clinical practice, and regulatory domains. First, translational research must prioritize functional validation of emerging mutational signatures and their mechanistic links to drug response. Large, multi-institutional cohorts should be used to establish signature-specific treatment outcomes and to refine classifiers that incorporate both genomic and clonal features.

Second, clinical infrastructure must adapt to support comprehensive molecular profiling at the point of care. Rapid sequencing platforms, AI-assisted data interpretation, and secure integration with electronic health records are essential. Education and training in genomic literacy should be embedded within hematology curricula to empower clinicians to interpret and act on molecular data confidently.

Third, stakeholders in policy and reimbursement must recognize the clinical utility of these tools and provide clear pathways for diagnostic approval and patient access. Precision diagnostics should not remain confined to academic centers or affluent systems—they must be democratized and integrated across all healthcare environments.

Finally, patients must be partners in this transformation. Transparent communication around the purpose, scope, and implications of genomic and clonal testing will foster trust and engagement. Consent processes should be robust yet accessible, and support services must be available to navigate any psychological or ethical complexities arising from deep molecular profiling.

In conclusion, the union of mutational signatures and clonality assessment represents not only a technical advance but a philosophical one. It moves lymphoma care away from reactive treatment and toward proactive, biologically informed management. Through continued investment in translational research and deliberate clinical integration, we can reshape the treatment paradigm to serve patients not just effectively—but precisely.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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