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Advances in Molecular Diagnosis, Prognostication and Targeted Therapy in Lymphoma: A Comprehensive Updated Review

Gamal Abdul Hamid [1,*] and Ali Bawahal [2]

[1] *The National Oncology Center-Aden, Faculty of Medicine and Health Sciences, University of Aden.*
[2] *The National Oncology Center - Shabwah, Faculty of Medicine and Health Sciences, University of Shabwah.*

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Abstract

The integration of molecular genetics into lymphoma diagnostics and management has revolutionized hematologic oncology. This comprehensive review synthesizes the latest advances in molecular diagnostic techniques, risk stratification, and targeted therapeutic approaches for B-cell and T-cell lymphomas, with reference to contemporary guidelines and emerging clinical research. The paradigm shifts from morphology-based to genetics-integrated diagnostics has significantly enhanced diagnostic accuracy, prognostic precision, and personalized treatment strategies. We detail the clinical utility of fluorescence in situ hybridization (FISH), next-generation sequencing (NGS), gene expression profiling (GEP), and emerging technologies, along with their implications for targeted therapy selection, resistance monitoring, and clinical trial design. Special emphasis is placed on actionable genetic alterations that guide therapeutic decisions in routine practice and investigational settings.

Keywords: Lymphoma; Molecular Genetics; FISH; NGS; Targeted Therapy; Precision Medicine; WHO Classification; Prognostic Biomarkers; Treatment Resistance; Hematopathology

1. Introduction

Lymphomas represent a heterogeneous spectrum of malignancies arising from B-lymphocytes, T-lymphocytes, or natural killer cells, with diverse clinical behaviors, treatment responses, and outcomes. Historically, classification systems such as Rappaport (1956), Kiel (1974), and the Working Formulation (1982) relied predominantly on morphological features and architectural patterns [1]. The landmark Revised European-American Classification of Lymphoid Neoplasms (REAL, 1994) introduced the concept of defining distinct disease entities through a combination of morphology, immunophenotype, genetic features, and clinical characteristics [2]. This multidimensional approach was subsequently adopted and refined by the World Health Organization (WHO) Classification, now in its 5th edition (2022), which firmly establishes genetic data as a cornerstone of lymphoma diagnosis and subclassification [3].

The clinical imperative for molecular diagnostics stems from the profound heterogeneity observed within morphologically similar lymphomas. For instance, diffuse large B-cell lymphoma (DLBCL), while morphologically uniform, encompasses distinct molecular subtypes with divergent outcomes and therapeutic sensitivities [4]. Similarly, mantle cell lymphoma (MCL) demonstrates a spectrum from indolent to highly aggressive disease, often correlated with specific genetic aberrations like TP53 mutations [5]. This review provides a detailed, contemporary update on the role of molecular diagnostics in lymphoma, focusing on validated genetic hallmarks, clinically significant prognostic biomarkers, and emerging therapeutic targets that are shaping current standards of care and future research directions.

* Corresponding author: Gamal Abdul Hamid

2. Molecular Diagnostic Techniques in Lymphoma: Principles and Applications

2.1. Conventional Cytogenetics and Karyotyping

Conventional G-banded karyotyping analyzes metaphase chromosomes to identify numerical abnormalities (aneuploidy) and large structural rearrangements (translocations, deletions, inversions). While it provides a genome-wide view, its resolution is limited to approximately 5–10 megabases, and it requires viable, dividing cells from fresh specimens, often a challenge with low-proliferative or paucicellular samples [6]. It remains valuable for detecting complex karyotypes, which are adverse prognostic markers in entities like peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) and TP53-mutated chronic lymphocytic leukemia (CLL) [7].

2.2. Fluorescence In Situ Hybridization (FISH)

FISH employs fluorescently labeled DNA probes complementary to specific genomic loci, allowing visualization of alterations in both dividing and interphase nuclei. It does not require cell culture, offers higher resolution (~50–200 kb), and is the clinical gold standard for detecting recurrent translocations and copy number alterations [8].

- Break-Apart Probes: Useful for genes with multiple translocation partners (e.g., MYC, BCL2, BCL6, ALK). Separation of normally co-localized fluorochromes indicates a rearrangement.
- Dual-Fusion Probes: Confirm specific translocations by generating two fusion signals (e.g., IGH: CCND1 in MCL, IGH: BCL2 in FL).

Locus-Specific Identifier (LSI) and Enumeration Probes: Detect deletions (e.g., del(17p) in CLL) or amplifications.

FISH is critical for diagnosing Burkitt lymphoma (BL; MYC rearrangement), distinguishing double-hit/triple-hit lymphomas, confirming MCL, and identifying ALK rearrangements in ALCL [9].

2.3. Polymerase Chain Reaction (PCR) and Sanger Sequencing

PCR amplifies specific DNA sequences from small amounts of template. In lymphoma diagnostics, its primary applications include:

- Detection of Specific Translocations: Using consensus primers for common breakpoint regions (e.g., IGH::BCL2 in FL) [10].
- Clonality Assessment: Analysis of immunoglobulin heavy chain (IGH) or T-cell receptor (TCR) gene rearrangements to establish monoclonal populations, aiding in differentiating reactive lymphocytosis from lymphoma.
- Minimal Residual Disease (MRD) Monitoring: Quantitative PCR (qPCR) using allele-specific primers for patient-specific IGH rearrangements or fusion transcripts (e.g., BCR:ABL1-like fusions) provides sensitive MRD assessment in CLL, FL, and mantle cell lymphoma [11].
- Targeted Mutation Detection: Sanger sequencing, though low-throughput, reliably identifies hotspot mutations (e.g., MYD88 L265P in >90% of Waldenström macroglobulinemia cases) [12].

2.4. Microarray-Based Technologies

- Comparative Genomic Hybridization (CGH) Arrays: Detect copy number variations (CNVs) across the genome by comparing patient DNA to a reference. It identifies gains/losses at higher resolution than karyotyping [13].
- Single Nucleotide Polymorphism (SNP) Arrays: Combine CNV detection with identification of copy-neutral loss of heterozygosity (LOH), common in FL and DLBCL, often involving tumor suppressor genes [14].

While largely supplanted by NGS in research, arrays remain useful for genome-wide CNV assessment in clinical studies of genetic complexity.

2.5. Next-Generation Sequencing (NGS)

NGS represents a paradigm shift, enabling simultaneous analysis of millions of DNA fragments. Its applications in lymphoma are multifaceted [15]

- Targeted Gene Panels: Focus on 50–500 genes recurrently mutated in lymphomas (e.g., TP53, MYD88, EZH2, NOTCH1, CREBBP). They offer deep coverage, high sensitivity for low-variant allele frequencies, and are cost-effective for routine clinical use.
- Whole Exome Sequencing (WES): Sequences all protein-coding regions (~1–2% of the genome), useful for discovering novel mutations and comprehensive profiling in research.
- Whole Genome Sequencing (WGS): Provides the most complete view, including non-coding regions, structural variants, and complex rearrangements, but remains costly and primarily a research tool.
- RNA Sequencing (RNA-Seq): Transcriptome analysis can detect gene fusions, aberrant gene expression signatures, and splice variants. It is becoming the new standard for molecular subtyping (e.g., LymphGen classifier in DLBCL) and fusion discovery [16].

NGS is indispensable for identifying the mutational landscape guiding prognosis (e.g., TP53 in MCL/CLL) and therapy (e.g., EZH2 mutations predicting response to tazemetostat in FL) [17].

2.6. Gene Expression Profiling (GEP)

GEP using microarrays measures mRNA levels of thousands of genes simultaneously. Its seminal contribution was the identification of cell-of-origin (COO) subtypes in DLBCL: germinal center B-cell-like (GCB) and activated B-cell-like (ABC), with prognostic and therapeutic implications [18]. While largely replaced by RNA-seq in research, its legacy persists through immunohistochemical (IHC) surrogate algorithms (Hans, Choi, Tally) used in daily practice [19].

3. Molecular Subtypes, Prognostic Markers, and Therapeutic Implications

3.1. Aggressive B-Cell Lymphomas

Diffuse Large B-Cell Lymphoma (DLBCL, NOS)

- Cell-of-Origin (COO): GCB subtype has a better prognosis with standard R-CHOP. ABC subtype has inferior outcomes and enriched activation of NF-dB and B-cell receptor signaling [18].
- Molecular Subtypes (Schmitz/Lacy-Huang Classification): Defined by NGS, these subtypes have clinical relevance [4, 20]:
  - MCD/C5 (MYD88L265P and CD79B mut): Associated with ABC, extranodal (CNS) involvement; potential sensitivity to BTK inhibitors (ibrutinib).
  - BN2/C1 (BCL6 fusions and NOTCH2 mut): May have better prognosis.
  - N1 (NOTCH1 mut): Rare, aggressive.
  - EZB/C3 (EZH2 mut and BCL2 translocations): Resembles GCB; EZH2 mutations are targetable.
  - A53 (TP53 mut/inactivation): Poor prognosis, associated with complex genetics.

Double/Triple-Hit Lymphomas: Defined by rearrangements in MYC plus BCL2 and/or BCL6. These high-grade B-cell lymphomas have very poor prognosis with R-CHOP, prompting trials with intensive regimens (DA-EPOCH-R) or novel agents [21].

3.1.1. Burkitt Lymphoma (BL)

- Hallmark: MYC translocation with an immunoglobulin gene enhancer (IGH, IGK, IGL).
- Molecular Subgroups: Sequencing reveals subgroups with different mutations: DGG-BL (*TCF3/ID3* mutations), IC-BL (immune evasion), and Q53-BL (TP53 mutated, poorest outcome) [22].
- Diagnostic Challenge: Distinguishing BL from MYC-rearranged DLBCL is critical due to differing therapies. BL typically shows simple karyotype, MYC translocation with an IG partner, and a mutational signature involving ID3 and TCF3 [23]. BL that dichotomizes based upon EBV status and mutational profile also differ in their timing of the MYC translocation, occurring during somatic hypermutation (SHM) in EBV positive BL and more typically during class switch recombination (CSR) in EBV-negative BL. Testing for TP53 mutations is also of value in BL, providing important prognostic information for risk stratification.

3.2. Indolent B-Cell Lymphomas

3.2.1. Follicular Lymphoma (FL)

- Hallmark: t (14;18) (q32; q21) IGH: BCL2 in 85–90% of cases, leading to BCL2 overexpression [24].

- Prognostic Mutations: The m7-FLIPI model incorporates mutations in EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, and CARD11 [25]. EZH2 mutations (~25% of cases) confer a favorable prognosis and predict response to the EZH2 inhibitor tazemetostat [17].
- Histological Transformation: Progression to DLBCL is associated with acquired mutations in MYC, TP53, CDKN2A, and B2M [26].

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

- IGHV Mutation Status: Unmutated IGHV (U-CLL) is associated with more aggressive disease and inferior progression-free survival, independent of traditional staging [27].
- Mutated (M-CLL): Better prognosis.
- Cytogenetic Risk (Dohner Hierarchy):
  - Favorable: Isolated del(13q).
  - Intermediate: Trisomy 12, normal karyotype.
  - Unfavorable: del(11q) (ATM), complex karyotype.
  - Very Poor: del(17p) (TP53) and/or TP53 mutation; these patients are refractory to chemoimmunotherapy and require targeted agents (BTK or BCL2 inhibitors) [28].
- Recurrent Mutations: NOTCH1 (associated with transformation), SF3B1 (poor outcome), BIRC3 (alternative NF-κB pathway activation) [29].

3.2.2. Mantle Cell Lymphoma (MCL)

- Pathognomonic: t(11;14)(q13;q32) CCND1::IGH, leading to cyclin D1 overexpression (detectable by IHC or FISH) [30].
- Prognostic Impact of Mutations:
  - KMT2D mutations: Common, biological significance under investigation [31].
  - TP53 mutations/deletions: The strongest adverse prognostic factor, associated with blastoid morphology, chemo-resistance, and shorter survival. They mandate upfront use of BTK inhibitor-based regimens (e.g., ibrutinib + venetoclax trials) [5, 32].

SOX11 Expression: Distinguishes conventional (SOX11+) from indolent leukemic non-nodal (SOX11-) MCL [33].

3.2.3. Lymphoplasmacytic Lymphoma / Waldenström Macroglobulinemia (LPL/WM)

Diagnostic Marker: MYD88 L265P mutation in >90% of cases. Its absence should prompt consideration of other lymphomas with plasmacytic differentiation [12].

  - Therapeutic Implications: CXCR4 mutations (30–40%) confer partial resistance to ibrutinib, leading to slower IgM decline and lower response rates [34].

3.2.4. Marginal Zone Lymphomas (MZL)

  - Extranodal MZL (MALT lymphoma): Genetics are often linked to chronic antigen stimulation. Translocations include t (11;18) BIRC3:MALT1 (predictive of antibiotic resistance in gastric MALT), t(14;18) IGH::MALT1, and t (3;14) FOXP1: IGH [35].
- Splenic MZL (SMZL): Characterized by NOTCH pathway mutations (NOTCH2, NOTCH1), KLF2 mutations, and frequent del(7q) [36].
- Nodal MZL (NMZL): Shares mutations with SMZL but also harbors PTPRD and BRAF mutations in subsets [37].

3.3. T-Cell and NK-Cell Lymphomas

3.3.1. Anaplastic Large Cell Lymphoma (ALCL)

- ALK-Positive ALCL: Defined by rearrangements of ALK (most commonly t(2;5) NPM1::ALK). It has an excellent prognosis with chemotherapy, and ALK inhibitors (crizotinib, alectinib) are highly active in relapsed/refractory disease [38].
- ALK-Negative ALCL: Genetically heterogeneous. Rearrangements of DUSP22 (6p25.3) confer a prognosis similar to ALK+ ALCL, whereas TP63 rearrangements are associated with very poor outcomes. JAK/STAT pathway mutations are also common [39].
- Nodal T-follicular Helper (TFH) Cell Lymphomas

- This group includes angioimmunoblastic T-cell lymphoma (AITL), follicular T-cell lymphoma, and nodal PTCL with TFH phenotype.
- Recurrent Mutations: Epigenetic modifiers TET2 (most common), DNMT3A, and IDH2 R172 mutations. RHOA G17V is a highly specific, gain-of-function mutation promoting aberrant signaling [40].
- Clonal Hematopoiesis: *TET2/DNMT3A* mutations are often found in antecedent clonal hematopoiesis, suggesting a stepwise lymphomagenesis [41].
- Peripheral T-Cell Lymphoma, Not Otherwise Specified (PTCL-NOS)
- Molecular Subtypes (Iqbal/GEO Classification):
  - PTCL-GATA3: High expression of GATA3, associated with TP53 mutations, PI3K pathway activation, and worst prognosis [42].
  - PTCL-TBX21: High expression of TBX21, associated with TET2 mutations and better survival [42].
  - PTCL-OTHER: Intermediate group.
- IHC for GATA3 and TBX21 can serve as practical surrogates for this classification [43].

4. Clinical Integration: From Diagnosis to Therapy

4.1. Diagnostic Refinement

Molecular techniques resolve morphologically ambiguous cases. Examples include:

- Differentiating blastoid MCL from lymphoblastic lymphoma (Cyclin D1+ vs. TdT+).
- Confirming CLL versus mantle cell lymphoma in CD5+ small B-cell lymphomas (FISH for CCND1).
- Identifying MYD88 L265P to confirm LPL/WM versus other IgM-secreting disorders [44].

4.2. Prognostic Stratification

Molecular data are integral to modern prognostic indices:

- CLL-IPI: Integrates IGHV status and TP53 abnormality [45].
- m7-FLIPI in FL [25].
- Genetic subtypes in DLBCL and MCL (TP53 status) [4, 5].

4.3. Guiding Targeted Therapy

- BTK Inhibitors (Ibrutinib, Acalabrutinib, Zanubrutinib): Standard in CLL (especially with del(17p)/TP53 mut), MCL, and WM. Active in ABC-DLBCL with *MYD88/CD79B* mutations [46].
- BCL2 Inhibitor (Venetoclax): Highly effective in CLL and FL, with activity in MCL. Resistance can emerge via BCL2 mutations [47].
- EZH2 Inhibitor (Tazemetostat): Approved for relapsed/refractory FL with EZH2 mutation and EZH2 wild-type FL [17].
- PI3K Inhibitors (Idelalisib, Duvelisib, Copanlisib): Used in relapsed FL, CLL, and MZL [48].
- ALK Inhibitors: Standard in relapsed ALK+ ALCL [38].
- JAK/STAT Inhibitors: Investigational in ALK- ALCL and PTCL with relevant pathway activation [49].
- Immunomodulatory Drugs (Lenalidomide): Particularly active in ABC-DLBCL and MZL, potentially synergizing with antagonism of the IKZF1/IKZF3 pathway [50].

4.4. Monitoring Treatment Response and Resistance

- MRD Monitoring: qPCR or NGS-based assays for IGH rearrangements or patient-specific mutations provide deep remission assessment in CLL, FL, and MCL. MRD negativity correlates with superior PFS and OS [11].
- Detecting Resistance Mutations: NGS on relapsed samples identifies mutations conferring resistance, such as:
  - BTK C481S (ibrutinib resistance in CLL/MCL) [51].
  - PLCγ2 mutations (ibrutinib resistance) [52].
  - BCL2 Gly101Val mutations (venetoclax resistance) [53].
  - Liquid Biopsy: Analysis of circulating tumor DNA (ctDNA) offers a non-invasive method for dynamic monitoring of tumor burden, clonal evolution, and emerging resistance, with growing clinical validation [54].

5. Case Vignettes Illustrating Clinical Decision-Making

5.1. Case 1: DLBCL with Ambiguous Morphology

A 58-year-old man presents with a rapidly growing neck mass. Biopsy shows large B-cell lymphoma. IHC is non-informative (GCB vs. non-GCB markers equivocal). FISH is negative for MYC, BCL2, and BCL6 rearrangements. NGS using a 100-gene lymphoma panel reveals a MYD88 L265P mutation and a CD79B mutation. This genetic profile is highly characteristic of the MCD/C5 molecular subtype of DLBCL, which is typically non-GCB (ABC) and originates from extranodal sites [4]. This finding supports enrollment in a clinical trial evaluating R-CHOP plus a BTK inhibitor rather than standard R-CHOP alone.

5.2. Case 2: CLL with Early Progression

A 72-year-old woman presents with asymptomatic lymphocytosis. Flow cytometry confirms CLL. FISH shows del(13q). IGHV sequencing reveals a mutated status. Watchful waiting is initiated. Two years later, she develops progressive lymphadenopathy and cytopenias. Repeat FISH now shows del(17p). NGS confirms a TP53 mutation and reveals a new NOTCH1 mutation. Given the high-risk genetics (del(17p)/TP53 mut, unmutated IGHV not present but NOTCH1 adverse), chemoimmunotherapy (e.g., FCR) is contraindicated [28]. Treatment with a covalent BTK inhibitor (acalabrutinib) combined with venetoclax is initiated based on clinical trial evidence for this high-risk population [46].

5.3. Case 3: Mantle Cell Lymphoma at Diagnosis

A 65-year-old man presents with weight loss and generalized lymphadenopathy. Excisional biopsy shows a diffuse proliferation of small-to-medium sized lymphocytes with irregular nuclei. IHC: CD20+, CD5+, SOX11+, Cyclin D1+. FISH confirms t(11;14). NGS performed on the diagnostic tissue identifies a pathogenic TP53 mutation with a variant allele frequency of 45%. Given the presence of this high-risk feature, the patient is not considered for standard intensive chemotherapy (e.g., R-DHAP followed by ASCT) but is instead enrolled in a frontline clinical trial or treated with an ibrutinib-based regimen per NCCN guidelines, which recommend targeted therapy over chemoimmunotherapy for TP53-mutated MCL [5, 32].

6. Future Directions and Challenges

- Routine Clinical NGS: Expansion from targeted panels to whole exome or transcriptome sequencing as costs decrease, enabling more comprehensive profiling [15].
- Multi-Omic Integration: Combining genomics, transcriptomics, epigenomics, and proteomics for a holistic view of lymphomagenesis and tumor microenvironment interactions [55].
- Artificial Intelligence and Machine Learning: AI algorithms applied to digital pathology images, integrated with molecular data, may improve diagnostic accuracy and predict genetic subtypes from H&E slides alone [56].
- Functional Precision Medicine: Using ex vivo drug sensitivity testing on patient-derived cells to guide therapy selection [57].
- Liquid Biopsy for Early Detection and Monitoring: Development of highly sensitive ctDNA assays for detecting molecular relapse before clinical/radiographic progression [54].
- Overcoming Therapeutic Resistance: Understanding clonal evolution and developing next-generation inhibitors (e.g., non-covalent BTK inhibitors like pirtobrutinib for patients with BTK C481S mutations) [58].
- Global Implementation: Ensuring equitable access to advanced molecular diagnostics across different healthcare systems remains a significant challenge [59].

7. Conclusion

The field of lymphoma has been fundamentally transformed by molecular genetics. Diagnostic classification is now a synthesis of morphology, immunophenotype, and genetic data, as enshrined in the WHO system [3]. Beyond diagnosis, genetic profiling provides critical prognostic information and reveals actionable therapeutic targets, forming the basis of modern precision medicine in hematologic oncology. Techniques like FISH and NGS have moved from research tools to essential components of clinical workflow [8, 15]. The future promises even deeper integration of multi-omic data, liquid biopsies, and AI, driving toward more personalized, predictive, and ultimately more effective management of patients with lymphoma.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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