The Clinical Applications of Next-Generation Sequencing and ctDNA/cfDNA in Lymphoma

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Abstract: Next-generation sequencing (NGS) technology plays a pivotal role in understanding the molecular landscape in oncology by providing a comprehensive analysis of genomic mutations. The detection and analysis of mutations have improved through tumor evaluation with various imaging techniques, tissue biopsies, and noninvasive liquid biopsy. NGS offers a multitude of diagnostic, prognostic, and management options that demonstrate a paradigm shift in how we care for patients with cancer. However, the roles of NGS and liquid biopsy in clinical practice still need to be standardized in protocols and guidelines so that they can be implemented broadly. Studies have shown promising evidence that liquid biopsy can be applied across the lymphoma landscape. These results demonstrate an expanding area of precision medicine research as oncology care continues to move toward minimally invasive and noninvasive genomic sequencing. The continued exploration of NGS in clinical practice may lead to more personalized therapeutic interventions in the hope of improving management, risk stratification, and outcomes in patients with lymphoma.

Keywords
Biomarker, liquid biopsy, lymphoma, next-generation sequencing, prognostication, risk profiling

Introduction

Next-generation sequencing (NGS) has revolutionized genomics by allowing the rapid sequencing of large amounts of DNA, thereby enabling the comprehensive analysis of genomic alterations. Lymphomas are highly heterogeneous at the molecular level, and this heterogeneity influences both clinical behavior and treatment responses. NGS technology can aid diagnosis, prognostication, and targeted

intervention by identifying high-risk features, complex karyotypes, and evolution throughout the disease course. Recent studies have highlighted a paradigm shift in genomic research, with NGS improving our understanding of the molecular underpinnings of lymphomas and enabling personalized therapeutic interventions.[1,2] Despite progress in implementing NGS, limitations in clinical practice remain. Addressing these challenges through advancements in bioinformatics and collaborative efforts is essential to broaden the application of NGS.

The incidence of malignant lymphoma has been steadily increasing, with recent data demonstrating that lymphoma is the most prevalent hematologic malignancy among adults in the United States.[3] Traditional prognostic methods rely on both clinical and histopathologic features, requiring the use of tissue biopsies, serologic tumor markers, imaging, immunohistochemical (IHC) analyses, and fluorescence in situ hybridization (FISH) studies.[4-9] Circulating tumor DNA (ctDNA), a component of DNA released by cancer cells, has gained interest as an analyte for liquid biopsies to provide insight into evolving tumor dynamics and treatment responses over time.[10-13] In addition, the detection of ctDNA alongside other markers can aid in finding measurable residual disease (MRD) to identify patients at risk for relapse.

MRD detection in lymphoma affords critical insight into treatment efficacy and risk of disease relapse. The achievement of MRD-negative status reflects an important endpoint, with the potential to inform prognosis as well as subsequent treatment decisions.[14-16] Developments in liquid biopsy are enhancing our ability to characterize lymphoproliferative malignancies and analyze complex genomic data, enabling the more precise monitoring of disease and treatment response.[10-13,17] This review illustrates how NGS can provide new opportunities for the diagnosis, prognostication, and management of lymphoma, thereby optimizing approaches to precision oncology and patient outcomes.

Current Understanding of NGS Technology

NGS technology is altering our understanding of hematologic malignancies, a highly heterogeneous group of disorders.[4-6,18] The diagnosis, prognostication, and management of lymphoproliferative disorders depend on an understanding of genomic aberrations and risk stratification.[4-7,19-21] Traditional methods for diagnosis and risk stratification use invasive tissue biopsies, flow cytometry data, IHC, and FISH studies.[4-9] Current methods of NGS used in lymphoma include whole-genome sequencing (WGS), whole-exome sequencing (WES), and targeted sequencing.[22-28]

WGS affords comprehensive analyses of the entire genomic DNA sequence, identifying coding and noncoding mutations, copy number alterations (CNAs), structural variants (SVs), and single nucleotide variants (SNVs), all of which contribute to genetic heterogeneity and affect clinical outcomes.[22,23] WES, by contrast, selectively analyzes coding regions, offering a smaller yet significant dataset of disease-related mutations.[26,27] Both techniques aid in molecular profiling to enhance the understanding of tumor heterogeneity and oncogenic mutations.[22,23,26,27] In comparison, targeted sequencing focuses on a specific gene panel and therefore has a narrower scope. One method for implementing these targeted sequencing techniques is through liquid biopsies, in which the use of peripheral blood or cerebrospinal fluid (CSF) enables noninvasive or minimally invasive characterization.[24,29] Liquid biopsies can detect clonality, SNVs, SVs, and copy number variants (CNVs), and results align with those of conventional methods like FISH and polymerase chain reaction (PCR).[29] These techniques enhance risk stratification, disease monitoring, and assessment of therapeutic response.[2,29]

Targeted panel sequencing, a form of NGS, is a more cost-effective tool than standard single-gene testing for biomarker testing in oncology practice.[30] However, techniques for testing and analysis remain widely variable, with no standardized methodology approved by guideline committees or organizations. Phased variant enrichment and detection sequencing (phasED-Seq) is a method within NGS used to identify not only multiple somatic mutations within individual DNA fragments but also phased proximal variants, thereby enhancing the sensitivity of MRD detection.[28]

Liquid biopsy is a novel approach that analyzes circulating biomarkers, cell-free DNA (cfDNA), and ctDNA to characterize malignancies.[10-13,17,31-33] Circulating cfDNA is physiologically released from cells undergoing apoptosis and necrosis.[12,13,17] Higher concentrations of cfDNA are frequently observed in patients with chronic inflammatory, infectious, or malignant conditions, regardless of stage.[17] Fragments released by tumor cells into the circulation have become an attractive target to improve the detection of malignancies.[10-13,17,31-33] Enhanced detection of ctDNA in body fluids enables the detection of genetic anomalies, allowing a comprehensive analysis of tumor heterogeneity throughout treatment.[10-13,17,33] Additionally, ctDNA has clinical applications with regard to quantification of the tumor burden, characterization of genomic aberrations, and monitoring for residual or relapsing disease throughout treatment.[12,13,17,31,33]

Current Therapeutic Implications of NGS in Lymphoma

Advances in liquid biopsies and analytic NGS techniques

have led to an exponential increase in their use. From both a research and a clinical standpoint, NGS allows genomic characterization, assessment of tumor heterogeneity, and monitoring of disease status through noninvasive blood sampling. Although tissue biopsy or peripheral blood flow cytometry is the gold standard in detecting mutational variants, the noninvasive evaluation of ctDNA via NGS can complement tumor assessment in lymphoma.[34] Although liquid biopsy has significant potential, many questions remain unanswered. Herein, we discuss the current implementation of NGS in distinct lymphoma subtypes.

Follicular Lymphoma

Follicular lymphoma (FL) is an indolent type of non-Hodgkin lymphoma (NHL) with a variable clinical course; patients often receive maintenance anti-CD20 therapy.[4] Although FL is characterized as a relatively indolent B-cell malignancy, a subset of patients with high-risk disease experience an aggressive course or progression of disease within 24 months (POD24) following induction therapy.[4] NGS can detect clinically relevant genomic variants and enhance the understanding of tumor heterogeneity, with studies showing spatial and temporal discordance in tumors.[4] This capability highlights the importance of using multimodal approaches alongside liquid biopsy to detect mutations such as BCL2 rearrangements and epigenetic modifiers with clinical implications.[34]

Maintenance anti-CD20 therapy after induction has been the standard of care for more than 10 years,[35] but the utility of MRD and positron emission tomography/computed tomography (PET/CT) monitoring to conduct response-adapted treatment plans has been investigated further. Approximately 20% of patients experience POD24, which demonstrates tumor aggressiveness.[36,37] A phase 3 trial looked at the targeted MRD testing of circulating B-cell lymphoma/leukemia 2/immunoglobulin heavy chain (BCL2/IgH) with PCR in peripheral blood and bone marrow samples in combination with PET/CT to assess the efficacy of a response-adapted treatment.[38] Luminari and colleagues reported significant results demonstrating better 3-year progression-free survival (PFS) with continuing rituximab maintenance than with the response-adapted approach based on PET/CT.[38] The response-adapted approach established that standard disease monitoring with PET/CT and limited targeted NGS is not a reliable way to diagnose relapse. Further specific MRD-driven therapeutic strategies should be examined in future studies.[38,39]

NGS is an important tool for disease classification and prognostication in FL. Tools for risk stratification include the Follicular Lymphoma International Prognostic Index (FLIPI) and the m7-FLIPI, which incorporates 7 mutations (*ARID1A, EZH2, EP300, FOXO1, MEF2B, CREBBP,* and *CARD11*), and the Eastern Cooperative Oncology Group (ECOG) status to improve risk predictions.[40] By identifying mutational status on the basis of NGS, patients at greater risk of treatment failure and death can be identified earlier.[40] In addition, molecular analyses provide opportunities to implement targeted therapeutics, including enhancer of zeste homolog 2 (EZH2) inhibitors. Tazemetostat (Tazverik, Epizyme) is a first-in-class EZH2 inhibitor that received accelerated approval for relapsed/refractory FL after demonstrating significant antitumor activity and durable responses.[41] These findings illustrate how NGS can enhance FL prognosis, treatment monitoring, and disease management.

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is an aggressive but curable mature B-cell malignancy; approximately two-thirds of patients achieve remission following first-line chemoimmunotherapy.[42] However, nearly one-third of patients experience relapse or the development of disease refractory to standard therapies, with subsequently poor outcomes. NGS and related molecular tools contribute not only to an improved understanding of DLBCL heterogeneity and classification but also to disease monitoring throughout treatment.[5]

A prospective study evaluated the prognostic value of ctDNA before and during therapy to predict outcomes and enable comparisons with established tools, including the International Prognostic Index (IPI) and interim PET/CT.[43] Levels of ctDNA before and after treatment were assessed to compare early molecular responses (EMRs) after 1 cycle of therapy with major molecular responses (MMRs) after 2 cycles.[43] Event-free survival at 24 months was improved in patients who received frontline therapy with subsequent EMR or MMR.[43] Molecular responses, as determined by ctDNA, were predictive of outcomes even after adjustment for IPI scores and PET/CT findings, signifying the independent prognostic value of this tool.[43] Subsequent retrospective studies monitoring ctDNA demonstrated a significant correlation between the IPI score and level of ctDNA, in addition to identifying immunoglobulin biomarkers with clinical value, emphasizing the ability of ctDNA to indicate a patient's prognosis alongside validated tools.[44]

Enhanced tumor knowledge can guide therapeutic decision making in newly diagnosed DLBCL. The Smart Start trial evaluated the role of a targeted regimen of rituximab, lenalidomide, and ibrutinib (Imbruvica, Pharmacyclics; RLI) as first-line treatment.[45] These drugs in isolation demonstrated improved overall response rates (ORRs) in patients with relapsed non–germinal center B-cell–like (non-GCB) DLBCL in comparison with

GCB DLBCL.[45] The study demonstrated a high ORR and durable responses, with a PFS rate of 91.3% and overall survival (OS) rate of 96.6%, signifying the efficacy of targeted treatment in specific disease subsets.[45] Similarly, the identification of high-risk *TP53* mutations can guide therapy through novel drugs that act by restoring p53 activity, inhibiting downstream pathways, or directly targeting abnormal p53 by inducing cell death.[46]

The effect of NGS in DLBCL extends beyond risk stratification and prognostication. Monitoring for MRD negativity, obtained from ctDNA detection at the end of therapy (EOT), is a potential novel endpoint for treatment in the front line and after chimeric antigen receptor (CAR) T-cell therapy.[16,47] Roschewski and colleagues examined the quantification of ctDNA after induction therapy with curative intent to assess outcomes.[16] Genotyping was successfully completed in 109 patients (97%), with blood specimens profiled following each additional cycle of therapy.[16] The rate of MRD negativity increased with each additional cycle, with 26% of patients achieving MRD negativity after cycle 1 vs 91% of patients at EOT.[16] Furthermore, clearance of ctDNA after any of the first 3 cycles correlated with improved rates of PFS.[16] Minson and colleagues reviewed high-risk untreated LBCL in patients before and after 1 cycle of rituximab, cyclophosphamide, vincristine, and doxorubicin (R-CHOP) and found that among those with partial morphologic remission after induction, none progressed and 78% converted to complete morphologic remission. Additionally, cfDNA analysis showed that the samples of 8 of 10 patients were MRD-negative following induction.[48] The use of ctDNA MRD at EOT is a potential endpoint, given the strong correlation with clinical outcomes.

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a rare, heterogeneous malignancy with distinct clinical features. The most recent revisions of the World Health Organization (WHO) classification, as well as the International Consensus Classification (ICC), subclassify MCL into 3 categories: in situ mantle cell neoplasia, classic MCL, and non-nodular MCL.[49,50] These subsets not only are influenced by differences pertaining to the genetic landscape—including *SOX11*, *CCND1*, and *IGHV* mutations—but also afford prognostic value; in situ MCL and non-nodal MCL indicate more indolent disease, whereas classic MCL is more aggressive.[49,50] Prognostic tools in MCL include the Mantle Cell Lymphoma International Prognostic Index (MIPI) and subsequent derivatives such as the simplified MIPI (s-MIPI), the biological MIPI (MIPI-b), the MIPI-B-miR, and the combined MIPI (MIPI-c).[51] However, given the vast heterogeneity of MCL, including high-risk morphology, complex karyotypes, and genetic aberrations (*TP53*, *NOTCH1*, *KMT2D*, *SOX11*, and *CARD11*), incorporating genomic technologies to identify these features allows more precise prognostic stratification.[52-55]

NGS techniques have been implemented to detect ctDNA in peripheral blood, signifying the role of ctDNA as a way to monitor MRD in patients with MCL. In a prospective study, Lakhotia and Roschewski monitored patients with MCL undergoing induction with bortezomib and dose-adjusted etoposide, doxorubicin, and cyclophosphamide with prednisone, vincristine, and rituximab (DA-EPOCH-R), followed by either observation or bortezomib maintenance. PFS and OS were longer in patients without detectable ctDNA following 2 cycles of induction than in patients with residual disease (median PFS, 2.7 vs 1.8 years; P=.005; median OS, 13.8 vs 7.4 years; P=.03).[13] Wang and colleagues demonstrated the effect of detectable MRD in patients following frontline treatment with autologous stem cell transplant (ASCT).[56] Sequencing of variable-diversity-joining (VDJ) recombination was used to detect MRD in grafts and showed that larger MRD loads correlated with reduced PFS and OS.[56]

MRD status can influence decisions related to continuation of therapy and time-limited treatment. The GELTAMO study, which followed patients receiving first-line therapy alongside ibrutinib and rituximab (IR), stopped treatment in two-thirds of patients on the basis of undetectable MRD.[57] In another recent study, by Ruan, treatment-naive patients received acalabrutinib (A; Calquence, AstraZeneca), lenalidomide (L), and rituximab (R), with disease monitoring driven by MRD status.[58] MRD-negative status at the conclusion of induction therapy guided decisions to discontinue AL after 24 cycles or 36 cycles, with results indicating high rates of durable remission when a time-limited approach was used.[58] The value of achieving MRD negativity translates into improved clinical outcomes and may present an opportunity to guide therapy de-escalation, although more studies are needed to determine the long-term implications.

T-Cell Lymphomas

T-cell lymphomas are a biologically heterogeneous group of NHLs that include primary cutaneous T-cell lymphomas (CTCLs) and peripheral T-cell lymphomas (PTCLs), with variable defining clinical and histologic features. Analyses of clinically relevant signaling pathways, including the tumor necrosis factor signaling pathway, indicated significant differences among chemotherapy-sensitive and chemotherapy-resistant groups, affording new insights into the underlying mechanisms of treatment resistance.[59] Additionally, variations related to *FAT1*, *TP53*, *PRDM1*, *CDKN2A/B*, *RB1*, *PTEN*, *MYC*, and *STAT3* enable disease subclassification and correlate with prognosis.[60,61]

The sequencing of ctDNA with a focus on T-cell

receptors (TCRs) among patients receiving frontline therapy for PTCL has contributed to the growing knowledge of tumor-specific clonotypes and intrapatient heterogeneity.[62] Approximately three-quarters of patients had tumor-specific clonotypes of the TCRβ (*TRB*) or TCRγ (*TRG*) gene, including in both tissue (86%) and serum (67%), at baseline.[62] Samples revealed significant intrapatient heterogeneity; 74% of patients had both clonotypes, 68% had more than one TCRγ clonotype, and 9% had multiple TCRβ or TCRγ clonotypes.[62] Results of monitoring of ctDNA throughout treatment were also assessed; ctDNA was cleared in 38% of patients after 2 cycles, whereas 46% of patients had detectable ctDNA at EOT.[62] The presence of ctDNA at EOT correlated with poor survival outcomes in PTCL.[62]

Primary CTCLs, which present with skin and hematologic symptoms, are classified according to key clinical and histologic features.[63] Advances in disease classification, coupled with genetic sequencing, allow a more complete genetic and epigenetic understanding of this disease. Epigenetic remodeling, cell cycle regulation, and activation of oncogenic pathways have been identified across CTCL subtypes.[64] The JAK/STAT signaling pathway in particular was implicated in several CTCL subgroups, which can be combined with additional biomarkers to inform management.[64] Ultimately, despite several molecular alterations with relevance to both the diagnostic and prognostic understanding of CTCL, future studies are needed to complement classification and identify genes or signaling pathways that provide opportunities for novel therapies.

Classic Hodgkin Lymphoma

Classic Hodgkin lymphoma (cHL) is a B-cell malignancy characterized by Hodgkin and Reed-Sternberg (HRS) tumor cells, stromal infiltrate, and immune complexes that contribute to its pathogenesis.[65] The limited quantity of HRS cells in biopsy specimens previously hindered extensive genomic analysis, but advances in fluorescence-activated cell sorting and WGS have revealed driver mutations, SVs, and chromosomal gains over time.[65] Temporal sequencing has shown that SVs with recombination-activating genes, driver mutations (eg, *B2M*, *BCL7A*, *GNA13*, and *PTPN1*), and activation-induced cytidine deaminase frequently precede chromosomal gains in cHL, contributing to our understanding of cHL biology.[65] Developments in NGS for ctDNA have demonstrated that this tool is comparable with genetic analyses of HRS cells, supporting its role not only in genotyping but also in monitoring changes over time.[66] These innovative techniques capitalize on the utility of liquid biopsy to offer insight into the genetic landscape and microenvironment of cHL, enabling improvements in risk prediction, disease detection, and targeted treatment.

Understanding the tumor microenvironment through ctDNA is important for NGS in cHL. The identification of CNVs and oncogenic driver mutations—including *TNFAIP3*, *ITPKB*, and *SOCS1*—allows the enhancement of risk stratification that correlates with PFS.[67] Another study exploring the role of ctDNA as a tool to measure tumor burden and residual disease during and after therapy showed that baseline levels of ctDNA reflected tumor burden, with lower levels reported in patients at early stages than in those with advanced disease.[68] Moreover, reduction in ctDNA levels during treatment correlated with early-stage favorable disease, and ctDNA clearance at EOT occurred in 24 of 26 patients (96%), including all patients with early-stage favorable disease and 89% of patients with early-stage unfavorable or advanced disease.[68] Clearance of ctDNA as determined by MRD assay was associated with improved PFS following 2 cycles of treatment (P=.025) as well as at EOT (P=.0012).[68] In a comparison with implementing PET/CT to monitor disease response, the study reported a high rate of false positives when imaging was used in patients with cHL undergoing frontline programmed cell death protein 1 (PD-1) blockade and chemotherapy.[68] A follow-up study by the same group reported similar findings when ctDNA MRD monitoring was used during and after treatment to predict treatment failure in early and advanced cHL.[69] Furthermore, the evaluation of cfDNA in cHL has demonstrated the ability to enhance tumor genotyping, predict responses, and aid in MRD detection to guide therapy.[70] More studies are needed to determine the optimal approach for disease monitoring over the course of treatment.

Central Nervous System Lymphoma

Although lymphomas confined to the central nervous system (CNS) are uncommon, they can be challenging to characterize and monitor, given the invasive nature of tissue sample acquisition.[71] Levels of ctDNA are significantly lower in blood plasma, further complicating disease detection.[71] However, the application of targeted NGS at the time of diagnosis has revealed value in using cfDNA to identify somatic mutations and genetic biomarkers among patients with primary CNS lymphoma (PCNSL).[72] Among patients with newly diagnosed PCNSL, NGS has been used to detect SNVs, CNVs, and genomic aberrations associated with inferior survival, thereby contributing to risk stratification.[73] Disease-specific mutations—including *MYD88* alterations, which are present in more than 70% of PCNSLs—have diagnostic and prognostic value.[74] Targeted sequencing is capable of identifying not only *MYD88* mutations through cfDNA but also the disappearance of this mutation following

chemotherapy.[74]

It is also important to detect secondary CNS lymphoma in patients with DLBCL. Cerebrospinal fluid (CSF) can be used to detect signs of lymphoma. Charifa and colleagues analyzed cfDNA and cell-free ribonucleic acid (cfRNA) in CSF from patients who had metastatic tumors in the CNS.[75] In this study, CSF testing revealed clinically relevant information in 82% of patients with metastatic tumors when cfDNA was assessed.[75] This can be important when patients who appear to be in remission still have disease in the CSF.

Indications for NGS in Lymphoma

Genomic profiling has improved our understanding of the biological and molecular mechanisms that influence various lymphoma subtypes, thereby improving classification and risk stratification. The effect of NGS in the diagnostic and prognostic settings has been established across subtypes, from indolent forms of FL and MCL to aggressive DLBCL.

An expanding area of research in liquid biopsy is its role in minimally invasive and noninvasive genomic sequencing conducted longitudinally. Although tissue biopsy remains the gold standard for diagnostic purposes, additional tissue biopsies are rarely collected throughout treatment owing to their invasive nature. Sampling from peripheral blood via liquid biopsy presents an opportunity to monitor a patient's lymphoma over time, demonstrating temporal heterogeneity that can guide further management. Spina and colleagues monitored ctDNA over time among patients with cHL, demonstrating evolutions in mutational patterns with the development of novel mutations at disease recurrence.[66] In addition, Araf and colleagues revealed the presence of temporal changes and clonal expansions at disease transformation in FL.[4] Liquid biopsy will move patient care toward more individualized precision medicine plans, identifying early relapse and predicting response on the basis of molecular mutations detected.

The implications of NGS include the ability to track disease and monitor disease progression. Throughout treatment, ctDNA clearance following induction, at midpoint cycles, and at EOT is associated with superior outcomes and sustained remission among patients with varying forms of both cHL and NHL.[62,68,76] Additionally, ctDNA is a novel marker to monitor disease status alongside traditional PET/CT, demonstrating improved predictive value with regard to subsequent disease progression.[43,68,77] These studies provide promising evidence of the value of the use of ctDNA for disease monitoring in terms of surveillance, treatment response, and evolving tumor dynamics.

Questions remain regarding the ability of MRD to inform decisions regarding treatment de-escalation vs continuation. Despite the intuitive notion that de-escalation is warranted in patients with MRD negativity, whereas intensification or continuation of maintenance regimens should benefit those with MRD positivity, studies have revealed the benefit of maintenance in both populations.[78] Hoster and colleagues measured MRD status and its relevance in rituximab maintenance to individualize consolidation strategies in MCL, demonstrating that maintenance therapy benefited MRD-negative individuals (PFS: hazard ratio [HR], 0.38; 95% CI, 0.21-0.63; OS: HR, 0.37; 95% CI, 0.20-0.68).[78] These results suggest the benefit of continued maintenance strategies in MCL on the basis of MRD negativity, despite a desire for treatment de-escalation. Intensification of treatment and consolidation strategies in large cell lymphomas and MCL are also currently being explored in clinical trials; in one innovative trial, patients with DLBCL and MRD-positive disease after frontline treatment are receiving consolidation off-the-shelf CAR T-cell therapy.

Conclusion

In recent years, high-throughput NGS and liquid biopsy have emerged as exciting tools in lymphoproliferative malignancies, with various clinical applications. Liquid biopsies and NGS represent a new paradigm for oncology; unlike traditional tissue biopsy, they enable minimally invasive or noninvasive methods for disease analysis. Lymphomas are highly heterogeneous malignancies, with somatic mutations, signaling pathway alterations, and epigenetic aberrations that have both diagnostic and prognostic implications. An improved understanding of the genomic landscape of these lymphomas and further validated research of NGS prognostic scores are needed to allow a better understanding of disease subtypes and predictions regarding disease activity.

Despite encouraging data surrounding genomic analysis by liquid biopsy, current assays are highly variable and not standardized. Several studies have demonstrated the role of liquid biopsy in contributing to genomic characterization and risk stratification. In particular, the value of ctDNA has been explored to aid in tumor quantification and prognostication not only at baseline but also over the course of treatment. Favorable ctDNA responses and MRD-negative status confer superior outcomes across lymphoma subtypes.

MRD status is a novel biomarker with significant potential for influencing de-escalation, escalation, or consolidation of therapy. Current trials are ongoing to evaluate serial MRD status to drive decisions concerning treatment de-escalation or consolidation, with the

potential to affect real-world decisions for patients in the clinic pending their results. However, a more standardized approach to MRD monitoring is necessary before these tests can be translated into routine clinical decision making. Furthermore, it is imperative to see consistent data regarding patient outcomes when MRD is used as a clinical decision tool to influence therapies. The applicability of MRD testing varies across lymphoma subtypes, indicating a need for future studies to explore assays in different lymphoproliferative diseases. Continued developments in liquid biopsy have greatly altered the landscape of malignant lymphomas, with immense clinical potential to guide management in the near future.

Disclosures

Dr Albitar works for (employed) a diagnostic company offering clinical liquid biopsy testing. Drs Albitar and Goy own stocks in a diagnostic company offering clinical liquid biopsy testing. Dr Feldman has equity/ownership in Genomic Testing Cooperative and Outcomes Matter Innovations (OMI). Dr Goy owns stock in Genomic Testing Cooperative and has served on the board of directors for Cancer Outcomes Tracking and Analysis (COTA) and Genomic Testing Cooperative.

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