Review Article

The role of pathologic testing in the diagnosis and management of patients with diffuse large B cell lymphoma: a narrative review

Michael Schneider^, Daniel Landsburg^

Division of Hematology/Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Contributions: (I) Conception and design: Both authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: Both authors; (V) Data analysis and interpretation: Both authors; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Daniel Landsburg, MD. Division of Hematology/Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, PCAM 12-182, 3400 Civic Center Blvd, Philadelphia, PA 19104, USA. Email: daniel.landsburg@pennmedicine.upenn.edu.

Background and Objective: Diffuse large B cell lymphoma (DLBCL) is the most common lymphoid malignancy in adults. More than half of patients with new DLBCL diagnoses are cured with front line immunochemotherapy, yet subsets of patients identified by pathologic testing are at higher risk of relapse. However, these pathologic classification systems remain imperfect and their implications for treatment are uncertain. We aim to discuss recent work in this area and explore its potential applications for improving patient treatment in the clinic.

Methods: A literature review using the PubMed and Google Scholar databases was conducted to identify studies focused on molecular testing in DLBCL using keywords: DLBCL, molecular testing, and next generation sequencing (NGS). The authors selected and reviewed papers of relevance and importance to this topic.

Key Content and Findings: Molecular testing using immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), gene expression profiling, and NGS all have important roles in characterizing DLBCL. Established systems of pathologic classification based on cell of origin (COO) or translocations in *MYC*, *BCL2*, and *BCL6* by FISH as well as increased expression of MYC and BCL2 protein by IHC can be useful in risk stratifying patients, but how they should be best utilized to guide therapeutic choices remains uncertain. Comprehensive genomic analysis allows for more precise clustering of patients that may be useful in guiding individualized treatment choices for patients, and NGS may be a practical surrogate for experimental assays.

Conclusions: Increased utilization of pathologic testing has allowed for more specific classification and risk stratification of DLBCL. However, more work is needed in order to best utilize those tests which are available in clinical laboratories in a cost-effective, timely manner that will allow for identifying novel therapeutic approaches for specific patients most likely to benefit from them.

Keywords: Diffuse large B cell lymphoma (DLBCL); molecular testing; lymphoid malignancy

Received: 15 September 2023; Accepted: 19 December 2023; Published online: 20 March 2024.
doi: 10.21037/aol-23-19
View this article at: https://dx.doi.org/10.21037/aol-23-19

^ ORCID: Michael Schneider, 0000-0001-7270-5235; Daniel Landsburg, 0000-0002-5077-4181.

Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma with about 150,000 new cases annually worldwide (1). The majority of patients newly diagnosed with this disease are cured with standard immunochemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (2). However, about 40% of patients fail to respond to or relapse after treatment with R-CHOP (3).

Patients who are not cured with frontline therapies are more likely to have a poor outcome, although some can be cured with subsequent lines of therapy (4). Historically, fit patients with relapsed or refractory disease are treated with high dose chemotherapy followed by autologous stem cell transplant with cure rates of about 30% (5,6). However, patients with primary refractory disease or early relapse after front line therapy have particularly poor outcomes with this approach. Recently, CAR T cell therapies have been approved in this setting with superior outcomes to autologous stem cell transplant (7,8). However, still more than half of these patients ultimately relapse (7,8).

There is importantly also a growing armamentarium that has become available for subsequent, palliative lines of therapy for DLBCL patients. Drugs including targeted small molecule inhibitors (9,10), antibody-drug conjugates (11,12), bispecific antibodies (13,14), cellular therapies (15-17), and others can extend the lives and palliate the symptoms of patients who have relapsed after or are not candidates for curative intent therapies. However, which patients are most likely to benefit from which therapies remains incompletely understood.

Despite substantial improvements to later lines of therapy for DLBCL patients, the best chance of cure remains with front line treatments. Standard clinical assays are able to risk stratify patients, but to this point have had only very limited implications in therapeutic decision making. Variability in patient responses reflect biologic heterogeneity across cases of DLBCL (18-20). There remains an important need for better approaches to risk stratify patients with DLBCL and to better target intensified treatment regimens to those most likely to benefit from them. There is also an important need to tailor later lines of therapy to individual patients. More recently, molecular techniques, such as comprehensive genomic analyses or clinical laboratory mutation analysis, may have utility in achieving these goals. In this narrative review, we will discuss recent work in this area and how it might be applied in the future to better treat patients in the clinic. We present this article in accordance with the Narrative Review reporting checklist (available at https://aol.amegroups.com/article/view/10.21037/aol-23-19/rc).

Methods

This narrative review was intended to discuss the role of pathologic, molecular and genetic testing in DLBCL. The analysis was performed in the PubMed and Google Scholar databases, which were searched for studies discussing molecular testing in patients with DLBCL (*Table 1*). There was no specified time frame. All international peer-reviewed papers in English language including retrospective, observational, prospective, randomized, and real world studies were included. No exclusion criteria were used. All the authors were involved in the selection and reviewing of the relevant publications.

Molecular testing in DLBCL

Cell of origin (COO) classifications

One of the established classification systems for DLBCLs is based on their COO with prognostic and therapeutic

Table 1 The search strategy summary

Items	Specification
Date of search	June 1st, 2023, and September 1st, 2023
Databases and other sources searched	PubMed, Google Scholar
Search terms used	Diffuse large B-cell lymphoma, molecular testing, next generation sequencing
Timeframe	Inception to September 1st, 2023
Inclusion criteria	Included relevant international peer-reviewed papers in the English language
Selection process	Both authors were involved in the selection and review of relevant publications

Table 2 Summary of front line trials evaluating modified chemotherapy regimens

Trial	Treatments	Patient population	Results
ROBUST (29)	Lenalidomide + R-CHOP *vs.* R-CHOP	ABC COO	2-year PFS: 67% *vs.* 64% (P=0.29)
REMoDL-B (32)	Bortezomib + R-CHOP *vs.* R-CHOP	GCB and non-GCB COO	5-year OS: 79% *vs.* 76% (P=0.32)
PHOENIX (28,30)	Ibrutinib + R-CHOP *vs.* R-CHOP	Non-GCB COO	EFS HR: 0.934 (P=0.59)
POLARIX (33)	Pola-R-CHP *vs.* R-CHOP	GCB and non-GCB COO	2-year OS: 88.6% *vs.* 88.7% (P=0.75)

R-CHOP, immunochemotherapy consisting of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; pola-R-CHP, combination of rituximab, cyclophosphamide, doxorubicin, and prednisone; COO, cell of origin; GCB, germinal center B cell type; ABC, activated B cell type; PFS, progression-free survival; OS, overall survival; EFS, event-free survival; HR, hazard ratio.

implications. Well accepted immunohistochemistry (IHC) based protocols, including the Hans (21) and Tally (22) algorithms, can be used to determine a germinal center B cell (GCB) or activated B cell (ABC)/non-GCB COO classification for these lymphomas. Gene expression profiling strategies can also be used to determine COO classification (23-25) with enhanced prognostic value (26), but are not commonly used in clinical practice. GCB DLBCLs appear to develop from normal GCBs, while ABC DLBCLs arise from post-GCBs in a phase between activation and plasmacytic differentiation (27).

Lymphomas classified as GCB type have superior outcomes when compared with ABC or non-GCB type DLBCL in patients treated with R-CHOP (25). Efforts to improve outcomes for patients with non-GCB DLBCL by adding non-cytotoxic agents to R-CHOP therapy has been largely unsuccessful (28-31), although recent studies suggest potential benefit of some modified treatment regimens (*Table 2*). A subgroup analysis of the REMoDL-B trial, suggests improved survival outcomes with the addition of bortezomib to R-CHOP in patients with ABC COO (32). The POLARIX trial also showed an early progression-free survival (PFS) advantage can be achieved by replacing vincristine with polatuzumab (pola-R-CHP) in this subgroup (33,34).

Despite no clear benefit in the front line (29,31), some therapies did appear to be more effective in certain COO subgroups in patients with relapsed disease. For example, lenalidomide was shown to be more effective than standard of care therapies in multiply relapsed non-GCB lymphomas, but not in GCB lymphomas (35). Similarly, patients with relapsed ABC lymphomas were significantly more likely to respond to ibrutinib than patients with GCB lymphomas (36). Additionally, using gene expression profiling to classify DLBCL specimens by COO, bortezomib sensitized patients with ABC type lymphoma to chemotherapy, but did not benefit patients with GCB type DLBCL (37).

Gene expression profiling has been used to identify distinct genetic pathways that are associated with each COO subtype including established oncogenes and tumor suppressors (38). In preclinical models, targeting the transcription factor encoding gene *SBIP* was able to slow the growth of cells derived from ABC type DLBCL, but not GCB type DLBCL (38). Another study identified upregulation of nuclear factor (NF)-κB pathway signaling in ABC, but not GCB DLBCL. Repression of the NF-κB pathway was toxic to ABC derived DLBCL cell lines, but not GCB derived cell lines in preclinical models (39). Activating NF-κB pathway mutations were associated with inferior outcomes among DLBCL patients treated with R-CHOP (40). Patients with relapsed or refractory ABC type DLBCL who were treated with bortezomib, which inhibits the NF-κB pathway *in vitro*, in combination with chemotherapy appeared to derive a benefit that was not seen in patients with GCB type DLBCL (37), as above. Treatment with ibrutinib, which blocks B cell receptor signaling upstream of the NF-κB pathway generated significantly higher response rates in patients with ABC type lymphomas than in patients with GCB lymphomas (36). Further studies like these will help to identify potential actionable targets that may improve outcomes for future patients.

Other IHC based testing in DLBCL

While cell of origin testing is currently the most clinically useful IHC based test, other markers have historically been found to have prognostic utility. About 5-10% of patients diagnosed with DLBCL have IHC positive for CD5 at the time of diagnosis and the significance of this marker has been reviewed in detail previously (41). While some of these

patients may have transformed disease from occult chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) or mantle cell lymphoma (MCL), which almost always express CD5 (42), there appears to be a histologically distinct subset with *de novo* CD5 expression (43). These are typically associated with an ABC phenotype (44,45) and high international prognostic index (IPI) scores (46). As a result, patients with CD5 positive disease have relatively poor prognosis (46-48). Some studies have suggested that the negative prognostic impact of CD5 expression may be independent of other factors including COO and IPI (45,49,50), however there remains very limited data from prospective clinical trials to support the use of escalated therapies in these patients (41). Due to an absence of strong data to drive treatment strategies and the fact that CD5 positivity is often confounded by other poor prognostic signals, it is not frequently used in clinical decision making.

Another commonly utilized immunohistochemical stain in DLBCL is MIB-1 or Ki-67, which is expressed in actively cycling cells and is used as a marker of tumor proliferation. Higher Ki-67 levels are associated with poor prognosis in DLBCL, but did not add additional prognostic value to IPI scores (51,52). Interestingly, a high Ki-67 proliferation index was more predictive of poor outcomes in patients with GCB type lymphoma than in those with ABC type (53). Broadly, high Ki-67 correlates with more aggressive tumors, but remains limited in its clinical utility for DLBCL patients as it has not been shown to predict response to specific therapies.

MYC, *BCL2*, *and BCL6 abnormalities*

Cytogenetic abnormalities in *MYC*, *BCL2*, and *BCL6* detected by fluorescence *in situ* hybridization (FISH) also have prognostic utility in patients with newly diagnosed DLBCL. Translocations in the *MYC* gene, seen in about 10% of DLBCL patients, are associated with poor outcomes (54,55), particularly when found together with either *BCL2* or *BCL6* rearrangements (56,57) colloquially referred to as "double hit" or "triple hit" lymphomas. In one large cohort study, this negative prognostic impact of the *MYC* translocation was only present when the translocation partner was the immunoglobulin gene and *BCL2* and/or *BCL6* translocation was also present (58). More recent work has suggested that patients with *MYC* and *BCL6* rearrangements have more heterogenous disease (59), which has led some to no longer classify tumors with these alterations as "double hit" lymphomas (60). Strategies using intensified chemotherapy regimens in this subset of patients have shown improved PFS, but not overall survival (OS) (61,62) and remain controversial.

One group used RNA sequencing to establish a high grade B cell lymphoma double hit signature that included 104 unique genes. Using an independent validation cohort, they were able to demonstrate that their gene signature was in fact prognostic for patients with DLBCL receiving R-CHOP independent of FISH translocation status (63). Further, this gene signature was able to identify a cohort of patients with high risk of disease relapse after R-CHOP who tested negative for *MYC* translocations (64). This work suggests that FISH testing may not capture the complete subset of patients at increased risk of relapse.

Others have evaluated patient samples for overexpression of MYC and BCL2 proteins in the presence or absence of translocations using IHC. This captures a larger group of patients as nearly all patients with translocations express high levels of protein. It also captures patients with ABC COO disease, which very rarely presents with translocations in *MYC*, but can present with elevated expression of these proteins. This "double expressor" status has also been associated with poor outcomes with front line R-CHOP (65,66), but intensified therapy is not typically recommended in this cohort of patients (in the absence of gene translocations) due to high levels of biological heterogeneity among them (67).

High levels of MYC and BCL2 protein expression have been linked to increased signaling through the B cell receptor pathway (68), which has led to interest in using Bruton's tyrosine kinase inhibitors in these patients. Interestingly, patients with relapsed or refractory double expressor DLBCL had high response rates to ibrutinib monotherapy (69). Further, in a subgroup analysis of the PHOENIX trial evaluating the addition of ibrutinib to front line R-CHOP in patients with non-GCB DLBCL (28), patients in the ibrutinib arm who were double expressors (as measured by RNA sequencing) had improved event-free, but not OS in the ibrutinib arm (30). When *MYC* and *BCL2* expression status were elevated in an RNA-sequencing analysis both event-free and OS were significantly improved. Additionally, increased *MYC/BCL2* co-expression was correlated with increased rates of $MYD88^{L265P}$ and *CD79B* mutations (30).

These data demonstrate that alterations in *MYC* and *BCL2* expression are imperfect prognostic markers and may function only as a surrogate for changes in the expression patters of other genes. Perhaps more precise tools, including

Table 3 Summary of reported clustering algorithms, associated individual genes, and prognostic implications

Reference	Clusters	Associated COO	Associated genes	Prognosis
Chapuy *et al.* 2018 *Nature Medicine* (72)	Cluster 0, n=12	n/a	n/a	5-year PFS =78%
	Cluster 1, n=56	ABC	*NOTCH2*, *BCL10*, *FAS*, *CD70*, *BCL6*, *PD-L1*, *PD-L2*	5-year PFS =72%
	Cluster 2, n=64	n/a	*TP53*, *CDKN2A*, *RB1*	5-year PFS =57%
	Cluster 3, n=55	GCB	*BCL2*, *CREBBP*, *EZH2*, *PTEN*, *KMT2D*, *TNFRSF14*	5-year PFS =49%
	Cluster 4, n=51	GCB	*CD83*, *CD58*, *NFKBIE*, *NFKBIA*, *CARD11*, *SKG1*, *RHOA*	5-year PFS =74%
	Cluster 5, n=64	ABC	*BCL2*, *CD79B*, *MYD88*, *PIM1*, *ETV6*	5-year PFS =53%
Schmitz *et al.* 2018 *NEJM* (73)	MCD, n=71	ABC	*MYD88*, *CD79B*, *SPIB*, *CDKN2A*	5-year OS =26%
	BN2, n=98	n/a	*NOTCH2*, *BCL6*, *SPEN*, *DTX1*, *PRKCB*, *BCL10*	5-year OS =36%
	N1, n=19	ABC	*NOTCH1*, *IRF4*, *TNFAIP3*	5-year OS =65%
	EZB, n=69	GCB	*BCL2*, *EZH2*, *REL*, *CREBBP*, *KMT2D*	5-year OS =68%
Lacy *et al.* 2020 *Blood* (74)	MYD88, n=152	ABC	*MYD88*, *PIM1*, *CD79B*, *ETV6*, *CDKN2A*	5-year OS =42.1%
	BCL2, n=176	GCB	*EZH2*, *BCL2*, *CREBBP*, *TNFRSF14*, *KMT2D*	5-year OS =62.5%
	SOCS1/SGK1, n=111	GCB	*SOCS1*, *CD83*, *SGK1*, *NFKBIA*, *HIST1HE*	5-year OS =64.9%
	TET2/SGK1, n=98	GCB	*TET2*, *BRAF*, *SGK1*, *KLHL6*, *ID3*	5-year OS =60.1%
	NOTCH2, n=143	n/a	*NOTCH2*, *BCL10*, *TNFAIP3*, *CCND3*, *SPEN*	5-year OS =48.1%
	NEC, n=248	n/a	*NOTCH1*, *REL*, *TP53*	5-year OS =53.6%
Sha *et al.* 2019 *JCO* (75)	Molecular high grade	GCB, N=83	*MYC*, *KMT2D*, *BCL2*, *TP53*, *TNFRSF14*, *EZH2*, *DDX3X*	3-year PFS =37%
	Non-molecular high grade	n/a, N=845	n/a	3-year PFS =72%

COO, cell of origin; n/a, not available; PFS, progression-free survival; ABC, activated B cell type; GCB, germinal center B cell type; OS, overall survival.

NGS and gene expression panels (63,64), can more directly detect the alterations affecting prognosis and responsiveness to different/escalated therapies. These types of tools will likely be useful in directing frontline and subsequent lines of therapy in DLBCL patients.

NGS and DLBCL clusters

More recently, several groups have done work seeking to use more comprehensive genomic analyses to more effectively identify clinically relevant DLBCL subgroups. Early work in this area used large gene expression panels to develop a 13 gene microarray that effectively segregated patients with a high risk of relapse (12% 5-year OS) and low risk of relapse (70% 5-year OS) in response to CHOP based therapy (70). More recent work utilized an unbiased CRISPR screen to identify genetic drivers of DLBCL and generated a prognostic model that outperformed COO, IPI, and MYC/BCL2 expression levels (71).

Chapuy *et al.* used whole exome sequencing to classify tumors into five different clusters (72). Clusters 1 (associated with *NOTCH2* activating mutations and NF-κB pathway mutations) and 5 (associated with *BCL2* gain, $MYD88^{L265P}$, and *CD79B* mutations) were composed of predominantly ABC-type DLBCL. Patients with cluster 1 tumors had significantly better prognosis compared with patients in cluster 5 when treated with front line R-CHOP. Cluster 3 (associated with *BCL2* translocation and mutations in epigenetic modifiers including *EZH2*) and 4 (associated with mutations in NF-κB, B cell receptor pathway, and immune evasion molecules) tumors were associated with GCB type. Patients with cluster 4 tumors had superior PFS compared with those in cluster 3. Cluster 2 tumors harbored frequent *TP53* inactivating mutations and were also associated with poor prognosis (*Table 3*). Over 95% of DLBCL specimens in this cohort could be classified into one of these five

clusters suggesting potential real world feasibility as a tool to risk stratify patients within a known COO subtype (72).

A similar study from Schmitz *et al.* developed a clustering algorithm that divided tumor samples into four distinct clusters characterized by *MYD88*^{L265P} and *CD79B* mutations (MCD); *BCL6* fusions and *NOTCH2* mutations (BN2); *EZH2* mutations and *BCL2* translocations (EZB); and *NOTCH1* mutations (N1) (73). The MCD and BN2 clusters were both associated with ABC COO with those in the MCD cluster having significantly worse PFS after treatment with R-CHOP. The EZB cluster was associated with GCB COO and these patients had the best prognosis after treatment with R-CHOP. Those in the N1 cluster had poor prognosis (73) (*Table 3*). Intriguingly, when these clusters were applied to patient samples from the PHOENIX trial, patients in the poor prognosis MCD and N1 clusters had dramatically improved OS with the addition of ibrutinib to front line therapy suggesting valuable therapeutic implications (76). Unfortunately, only 47% of tumor samples fit within these cluster definitions limiting its clinical potential (73).

One group used targeted mutational analysis only to define clusters similar to those described in the studies above. Unfortunately, these clusters had only limited prognostic value (74). Another study using targeted mutational analysis was able to define a subset of patients with features of a Burkitt lymphoma-like gene expression pattern enriched for mutations in *KMT2D*, *BCL2*, *MYC*, and *DDX3X*. Specimens in this cluster made up 9% of all cases evaluated, were all of GCB COO, and were associated with poor prognosis (75) (*Table 3*). Additionally, work has shown that somatic hypermutation (77) and clonal evolution/mutation (78) patterns can also be used to divide DLBCL specimens into distinct subtypes with prognostic significance (77). Others have used microenvironmental signatures (79) and groupings based on host immune response (80) to group DLBCL subtypes. These approaches theoretically could have a role in determining which patients are likely to respond to newly approved immunotherapies like CAR T cells and bispecific antibodies.

In an effort to enhance clinical applicability of these techniques, Wright *et al.* developed the LymphGen assay, which assigns probabilistic values to tumor samples based on mutations identified (81). This publicly available tool allows for sequencing analysis on any patient specimen to be used to categorize it into one or more groups. As more work is completed, this tool will likely have increasing utility in therapeutic decision making.

The utility of circulating tumor DNA (ctDNA) in DLBCL

Another emerging tool for use in DLBCL management is ctDNA testing or "liquid biopsies". These tests allow for the detection of DNA shed from tumors through peripheral blood draws bypassing the need for more invasive tumor biopsies (82) and are already widely clinically utilized in some solid malignancies (83). Early work in DLBCL has shown that ctDNA is a sensitive and specific tool useful for identifying and surveilling disease. Pretreatment ctDNA levels and their trends in response to therapy can be utilized as independent prognostic markers for patients (84,85). Early work has also shown that liquid biopsies can be used to stratify GCB and ABC COO (85,86). Further, ctDNA testing can detect specific somatic mutations that may help direct targeted therapies or could be used to help classify patients into distinct clusters (as above) (87-89). In some cases, ctDNA testing was found to be more sensitive than testing on standard biopsies (88).

Liquid biopsies may also have utility in disease monitoring and surveillance after treatment. Several studies have demonstrated that ctDNA is sensitive and specific for detecting occult malignancy (90,91). These tests may detect disease earlier and less ambiguously than standard surveillance methodologies like imaging scans (90,91). While not yet approved or widely utilized clinically, these technologies continue to evolve and may play an important role in disease monitoring and treatment decision making for DLBCL in the future (92,93).

Discussion

A variety of standard-of-care and investigational pathologic techniques are available to characterize DLBCL specimens. Established methodologies including IHC for COO classification and FISH for identification of *MYC*, *BCL2* and *BCL6* translocations have important prognostic significance for patients with these malignancies (*Figure 1*). While these strategies are readily performed in a timely manner in most clinical labs, they have significant limitations and may not accurately risk stratify all patients with DLBCL. How the results of these tests should be utilized in clinical decision making remains uncertain and controversial.

The aforementioned studies using comprehensive genomic analysis to define clusters or subgroups of DLBCL/HGBL tumors certainly provide encouragement

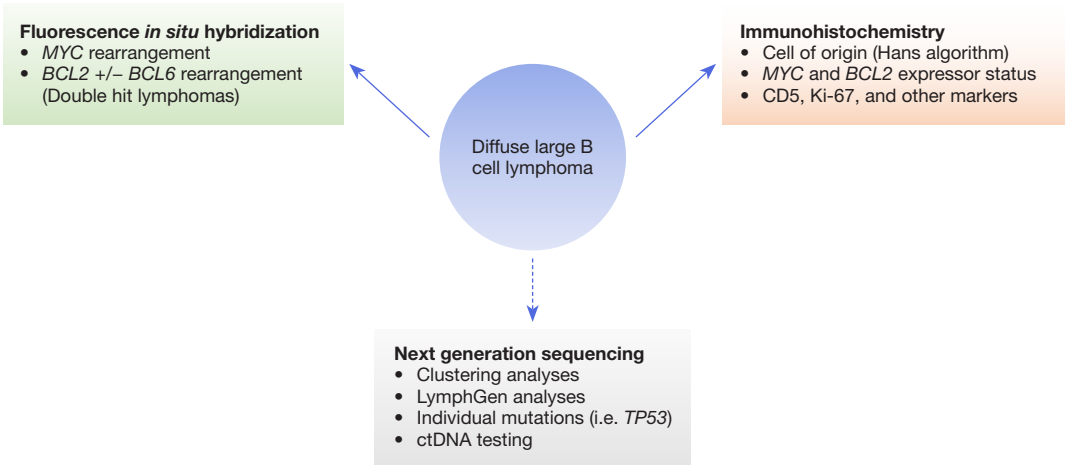

Figure 1 Summary of molecular testing in DLBCL. Fluorescence *in situ* hybridization testing and immunohistochemical tests for cell of origin, MYC/BCL2 expression, and other markers are standard of care in the workup of DLBCL. Genetic sequencing methodologies are emerging as potentially important and useful tools to more effectively characterize and treat patients with DLBCL. DLBCL, diffuse large B cell lymphoma; ctDNA, circulating tumor DNA.

that it is possible to improve upon our ability to risk-stratify and potentially individualize therapy for newly diagnosed patients with these diseases. The challenge remains to determine how best to deploy these tests clinically and how to incorporate them into recommendations made to patients in need of treatment.

Tumor sample mutational analysis is available in most clinical labs. At our institution, we regularly perform these tests on patient DLBCL specimens with high success rate (>92%) and short median turnaround time (18 days) (94). Results of these tests can be used to group patients into clusters using LymphGen (81) or similar platforms that can be used to direct therapeutic decisions in challenging cases (*Figure 1*). While not yet available, it stands to reason that commercial laboratories could soon develop versions of a lymphoma mutation panel with a short turnaround time as is done for other types of tumors.

Another issue to explore is whether the goal of clinical laboratory mutation analysis should be to replicate cluster assignment as experimentally defined in the work described above (72-74) or to identify relevant individual mutations associated with the clusters without as strong a focus on definitive subgroup assignment. Individual "high-risk" mutations including *TP53* (95,96), *MYD88* (97), *MYC* (98), and *EZH2* (99) reported in these studies are reported to be predictive of patient outcomes after treatment with R-CHOP. These types of results would be more easily incorporated into patient care than cluster assignment. For example, based upon the results of the aforementioned Wilson study (76), one could use mutations in any of $MYD88^{L265P}$, *CD79B* or *NOTCH1* as a surrogate for the MCD or N1 subgroups and offer R-CHOP with ibrutinib in the front line setting to fit patients in these categories. Finally, there may be significant variability of both mutations detected and signaling pathways affected within a genetic subgroup, which may have implications for efforts to offer a single targeted therapy to all patients whose tumors are classified within a specific subgroup. For example, *EZH2* mutations are almost exclusively detected in EZB tumors, but <50% of EZB tumors actually harbor an *EZH2* mutation (81), so it is not clear that all patients with EZB tumors would benefit from treatment with *EZH2* inhibitor therapy.

A very recent study took advantage of this idea to design a basket trial (100). In this very exciting trial, patients were screened using a 20 gene panel to classify them into one of six genetic subgroups based on the clustering systems and individual mutations described above. All patients received one cycle of R-CHOP while awaiting their sequencing results and then were randomized into a control group that would receive an additional 5 cycles of R-CHOP or an experimental group to receive R-CHOP plus an additional agent tailored to their genetic classification (100). The addition of targeted agents based on genetic subtype classification impressively improved OS outcomes (100) further suggesting an important role for the incorporation

of genomic data into front line treatment decisions. Future work will help us to better understand specific genetic subgroups and more effectively cluster patients into groups that might benefit from personalized escalated therapies.

Conclusions

We now have an embarrassment of riches of pathologic data available to help guide the risk-stratification and management of patients with newly diagnosed DLBCL. Moving forward, it would be a worthwhile effort to create a standardized targeted lymphoma mutation panel, guided by the findings from the investigations discussed above (63,72-75,100) and others, which can be routinely performed by clinical laboratories with a short turnaround time sufficient to direct patient care (101). Such a panel could be utilized by clinical trials in this patient population so results obtained in the experimental setting could be easily translated. While results of pathologic testing have not translated into major advances in clinical management of newly diagnosed DLBCL patients over the past several years, they have the potential to do so in the years to come.

Acknowledgments

Funding: This work was supported in part by Abramson Cancer Center's Ruth L. Kirschstein National Research Service Award T32 Cancer Center Research Training Program Training Grant (T32-CA009615).

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://aol.amegroups.com/article/view/10.21037/aol-23-19/rc

Peer Review File: Available at https://aol.amegroups.com/article/view/10.21037/aol-23-19/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://aol.amegroups.com/article/view/10.21037/aol-23-19/coif). M.S. is supported by Abramson Cancer Center's Ruth L. Kirschstein National Research Service Award T32 Cancer Center Research Training Program Training Grant (T32-CA009615). D.L. serves as an unpaid editorial board member of *Annals of Lymphoma* from June 2023 to May 2025. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Morton LM, Wang SS, Devesa SS, et al. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 2006;107:265-76.
2. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab com-pared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346:235-42.
3. Sehn LH. A decade of R-CHOP. Blood 2010;116:2000-1.
4. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800-8.
5. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refrac-tory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol 2014;32:3490-6.
6. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28:4184-90.
7. Westin JR, Oluwole OO, Kersten MJ, et al. Survival with Axicabtagene Ci-loleucel in Large B-Cell Lymphoma. N Engl J Med 2023;389:148-57.
8. Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis

of an open-label, randomised, phase 3 trial. Lancet 2022;399:2294-308.
9. Kalakonda N, Maerevoet M, Cavallo F, et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, phase 2 trial. Lancet Haematol 2020;7:e511-22.
10. Salles G, Duell J, González Barca E, et al. Tafasitamab plus lenalidomide in relapsed or refractory diffuse large B-cell lymphoma (L-MIND): a multicentre, prospective, single-arm, phase 2 study. Lancet Oncol 2020;21:978-88.
11. Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol 2021;22:790-800.
12. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol 2020;38:155-65.
13. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 2022;387:2220-31.
14. Thieblemont C, Phillips T, Ghesquieres H, et al. Epcoritamab, a Novel, Subcu-taneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. J Clin Oncol 2023;41:2238-47.
15. Jacobson C, Locke FL, Ghobadi A, et al. Long-Term (≥4 Year and ≥5 Year) Overall Survival (OS) By 12- and 24-Month Event-Free Survival (EFS): An Updated Analysis of ZUMA-1, the Pivotal Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients (Pts) with Refractory Large B-Cell Lymphoma (LBCL). Blood 2021;138:1764.
16. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet 2020;396:839-52.
17. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 2019;380:45-56.
18. Pasqualucci L, Trifonov V, Fabbri G, et al. Analysis of the coding genome of diffuse large B-cell lymphoma. Nat Genet 2011;43:830-7.
19. Morin RD, Mungall K, Pleasance E, et al. Mutational and structural analysis of diffuse large B-cell lymphoma using whole-genome sequencing. Blood 2013;122:1256-65.
20. Bastos-Oreiro M, Suárez-González J, Andrés-Zayas C, et al. Incorporation of next-generation sequencing in clinical practice using solid and liquid biopsy for pa-tients with non-Hodgkin's lymphoma. Sci Rep 2021;11:22815.
21. Hans CP, Weisenburger DD, Greiner TC, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood 2004;103:275-82.
22. Meyer PN, Fu K, Greiner TC, et al. Immunohistochemical methods for pre-dicting cell of origin and survival in patients with diffuse large B-cell lymphoma treated with rituximab. J Clin Oncol 2011;29:200-7.
23. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503-11.
24. Gutiérrez-García G, Cardesa-Salzmann T, Climent F, et al. Gene-expression profiling and not immunophenotypic algorithms predicts prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Blood 2011;117:4836-43.
25. Scott DW, Wright GW, Williams PM, et al. Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraf-fin-embedded tissue. Blood 2014;123:1214-7.
26. Yoon N, Ahn S, Yong Yoo H, et al. Cell-of-origin of diffuse large B-cell lym-phomas determined by the Lymph2Cx assay: better prognostic indicator than Hans algorithm. Oncotarget 2017;8:22014-22.
27. Sandoval-Sus JD, Chavez J, Dalia S. A New Therapeutic Era in GCB and ABC Diffuse Large B-cell Lymphoma Molecular Subtypes: A Cell of Origin-Driven Re-view. Curr Cancer Drug Targets 2016;16:305-22.
28. Younes A, Sehn LH, Johnson P, et al. Randomized Phase III Trial of Ibrutinib and Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Non-Germinal Center B-Cell Diffuse Large B-Cell Lymphoma. J Clin Oncol 2019;37:1285-95.
29. Nowakowski GS, Chiappella A, Gascoyne RD, et al. ROBUST: A Phase III Study of Lenalidomide Plus R-CHOP Versus Placebo Plus R-CHOP in Previously Un-treated Patients With ABC-Type Diffuse Large B-Cell Lymphoma. J Clin Oncol 2021;39:1317-28.
30. Johnson PWM, Balasubramanian S, Hodkinson B, et al. Clinical impact of ib-rutinib plus R-CHOP in untreated DLBCL coexpressing BCL2 and MYC in the phase 3 PHOENIX trial. Blood Adv 2023;7:2008-17.
31. Leonard JP, Kolibaba KS, Reeves JA, et al. Randomized Phase II Study of R-CHOP With or Without Bortezomib in Previously Untreated Patients With Non-Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma. J

Clin Oncol 2017;35:3538-46.
32. Davies AJ, Stanton L, Caddy J, et al. Five-year survival results from the re-modl-b trial (ISRCTN 51837425) show improved outcomes in diffuse Large b-cell lymphoma molecular subgroups from the addition of bortezomib to r-CHOP chemoimmunotherapy. Blood 2022;140:1770-2.
33. Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. N Engl J Med 2022;386:351-63.
34. Sheng Z, Li D, Chen B, et al. Superiority of polatuzumab vedotin over other novel agents in previously untreated ABC-type diffuse large B-cell lymphoma: a network meta-analysis of 20 RCTs. Ann Hematol 2023;102:1011-7.
35. Czuczman MS, Trn ný M, Davies A, et al. A Phase 2/3 Multicenter, Random-ized, Open-Label Study to Compare the Efficacy and Safety of Lenalidomide Versus Investigator's Choice in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Clin Cancer Res 2017;23:4127-37.
36. Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med 2015;21:922-6.
37. Dunleavy K, Pittaluga S, Czuczman MS, et al. Differential efficacy of borte-zomib plus chemotherapy within molecular subtypes of diffuse large B-cell lym-phoma. Blood 2009;113:6069-76.
38. Lenz G, Wright GW, Emre NC, et al. Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. Proc Natl Acad Sci U S A 2008;105:13520-5.
39. Davis RE, Brown KD, Siebenlist U, et al. Constitutive nuclear factor kappaB activity is required for survival of activated B cell-like diffuse large B cell lym-phoma cells. J Exp Med 2001;194:1861-74.
40. Bohers E, Mareschal S, Bouzelfen A, et al. Targetable activating mutations are very frequent in GCB and ABC diffuse large B-cell lymphoma. Genes Chromosomes Cancer 2014;53:144-53.
41. Durani U, Ansell SM. CD5+ diffuse large B-cell lymphoma: a narrative review. Leuk Lymphoma 2021;62:3078-86.
42. Kaufmann O, Flath B, Späth-Schwalbe E, et al. Immunohistochemical detection of CD5 with monoclonal antibody 4C7 on paraffin sections. Am J Clin Pathol 1997;108:669-73.
43. Matolcsy A, Chadburn A, Knowles DM. De novo CD5-positive and Richter's syndrome-associated diffuse large B cell lymphomas are genotypically distinct. Am J Pathol 1995;147:207-16.
44. Tagawa H, Suguro M, Tsuzuki S, et al. Comparison of genome profiles for identification of distinct subgroups of diffuse large B-cell lymphoma. Blood 2005;106:1770-7.
45. Tang H, Zhou H, Wei J, et al. Clinicopathologic significance and therapeutic implication of de novo CD5+ diffuse large B-cell lymphoma. Hematology 2019;24:446-54.
46. Zhao P, Li L, Zhou S, et al. CD5 expression correlates with inferior survival and enhances the negative effect of p53 overexpression in diffuse large B-cell lymphoma. Hematol Oncol 2019;37:360-7.
47. Ma XB, Zhong YP, Zheng Y, et al. Coexpression of CD5 and CD43 predicts worse prognosis in diffuse large B-cell lymphoma. Cancer Med 2018;7:4284-95.
48. Ennishi D, Takeuchi K, Yokoyama M, et al. CD5 expression is potentially pre-dictive of poor outcome among biomarkers in patients with diffuse large B-cell lymphoma receiving rituximab plus CHOP therapy. Ann Oncol 2008;19:1921-6.
49. Thakral B, Medeiros LJ, Desai P, et al. Prognostic impact of CD5 expression in diffuse large B-cell lymphoma in patients treated with rituximab-EPOCH. Eur J Haematol 2017;98:415-21.
50. Xu-Monette ZY, Tu M, Jabbar KJ, et al. Clinical and biological significance of de novo CD5+ diffuse large B-cell lymphoma in Western countries. Oncotarget 2015;6:5615-33.
51. Broyde A, Boycov O, Strenov Y, et al. Role and prognostic significance of the Ki-67 index in non-Hodgkin's lymphoma. Am J Hematol 2009;84:338-43.
52. He X, Chen Z, Fu T, et al. Ki-67 is a valuable prognostic predictor of lymphoma but its utility varies in lymphoma subtypes: evidence from a systematic me-ta-analysis. BMC Cancer 2014;14:153.
53. Tang YL, Zhou Y, Cheng LL, et al. BCL2/Ki-67 index predict survival in ger-minal center B-cell-like diffuse large B-cell lymphoma. Oncol Lett 2017;14:3767-73.
54. Savage KJ, Johnson NA, Ben-Neriah S, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. Blood 2009;114:3533-7.
55. Barrans S, Crouch S, Smith A, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol 2010;28:3360-5.
56. Horn H, Ziepert M, Becher C, et al. MYC status in concert with BCL2 and BCL6 expression predicts outcome in diffuse large B-cell lymphoma. Blood 2013;121:2253-63.
57. Hu S, Xu-Monette ZY, Tzankov A, et al. MYC/BCL2

protein coexpression contributes to the inferior survival of activated B-cell subtype of diffuse large B-cell lymphoma and demonstrates high-risk gene expression signatures: a report from The International DLBCL Rituximab-CHOP Consortium Program. Blood 2013;121:4021-31; quiz 4250.
58. Rosenwald A, Bens S, Advani R, et al. Prognostic Significance of MYC Rear-rangement and Translocation Partner in Diffuse Large B-Cell Lymphoma: A Study by the Lunenburg Lymphoma Biomarker Consortium. J Clin Oncol 2019;37:3359-68.
59. Cucco F, Barrans S, Sha C, et al. Distinct genetic changes reveal evolutionary history and heterogeneous molecular grade of DLBCL with MYC/BCL2 double-hit. Leukemia 2020;34:1329-41.
60. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neo-plasms. Leukemia 2022;36:1720-48.
61. Howlett C, Snedecor SJ, Landsburg DJ, et al. Front-line, dose-escalated im-munochemotherapy is associated with a significant progression-free survival ad-vantage in patients with double-hit lymphomas: a systematic review and me-ta-analysis. Br J Haematol 2015;170:504-14.
62. Landsburg DJ, Falkiewicz MK, Maly J, et al. Outcomes of Patients With Dou-ble-Hit Lymphoma Who Achieve First Complete Remission. J Clin Oncol 2017;35:2260-7.
63. Ennishi D, Jiang A, Boyle M, et al. Double-Hit Gene Expression Signature De-fines a Distinct Subgroup of Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma. J Clin Oncol 2019;37:190-201.
64. Hilton LK, Tang J, Ben-Neriah S, et al. The double-hit signature identifies double-hit diffuse large B-cell lymphoma with genetic events cryptic to FISH. Blood 2019;134:1528-32.
65. Johnson NA, Slack GW, Savage KJ, et al. Concurrent expression of MYC and BCL2 in diffuse large B-cell lymphoma treated with rituximab plus cyclophospha-mide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30:3452-9.
66. Green TM, Young KH, Visco C, et al. Immunohistochemical double-hit score is a strong predictor of outcome in patients with diffuse large B-cell lymphoma treated with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol 2012;30:3460-7.
67. Ngu H, Takiar R, Phillips T, et al. Revising the treatment pathways in lymphoma: new standards of care—how do we choose? Am Soc Clin Oncol Educ Book 2022;42:1-14.
68. Wang WG, Jiang XN, Liu ZB, et al. MYC Protein-positive Diffuse Large B-Cell Lymphoma Features an Activated B-Cell Receptor Signal Pathway. Am J Surg Pathol 2017;41:541-9.
69. Landsburg DJ, Hughes ME, Koike A, et al. Outcomes of patients with re-lapsed/refractory double-expressor B-cell lymphoma treated with ibrutinib mono-therapy. Blood Adv 2019;3:132-5.
70. Shipp MA, Ross KN, Tamayo P, et al. Diffuse large B-cell lymphoma outcome prediction by gene-expression profiling and supervised machine learning. Nat Med 2002;8:68-74.
71. Reddy A, Zhang J, Davis NS, et al. Genetic and Functional Drivers of Diffuse Large B Cell Lymphoma. Cell 2017;171:481-494.e15.
72. Chapuy B, Stewart C, Dunford AJ, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. Nat Med 2018;24:679-90.
73. Schmitz R, Wright GW, Huang DW, et al. Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma. N Engl J Med 2018;378:1396-407.
74. Lacy SE, Barrans SL, Beer PA, et al. Targeted sequencing in DLBCL, molecular subtypes, and outcomes: a Haematological Malignancy Research Network report. Blood 2020;135:1759-71.
75. Sha C, Barrans S, Cucco F, et al. Molecular High-Grade B-Cell Lymphoma: Defining a Poor-Risk Group That Requires Different Approaches to Therapy. J Clin Oncol 2019;37:202-12.
76. Wilson WH, Wright GW, Huang DW, et al. Effect of ibrutinib with R-CHOP chemotherapy in genetic subtypes of DLBCL. Cancer Cell 2021;39:1643-1653.e3.
77. Alkodsi A, Cervera A, Zhang K, et al. Distinct subtypes of diffuse large B-cell lymphoma defined by hypermutated genes. Leukemia 2019;33:2662-72.
78. Jiang Y, Redmond D, Nie K, et al. Deep sequencing reveals clonal evolution patterns and mutation events associated with relapse in B-cell lymphomas. Genome Biol 2014;15:432.
79. Kotlov N, Bagaev A, Revuelta MV, et al. Clinical and Biological Subtypes of B-cell Lymphoma Revealed by Microenvironmental Signatures. Cancer Discov 2021;11:1468-89.
80. Monti S, Savage KJ, Kutok JL, et al. Molecular profiling of diffuse large B-cell lymphoma identifies robust subtypes including one characterized by host inflam-matory

response. Blood 2005;105:1851-61.
81. Wright GW, Huang DW, Phelan JD, et al. A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications. Cancer Cell 2020;37:551-568.e14.
82. Haber DA, Velculescu VE. Blood-based analyses of cancer: circulating tumor cells and circulating tumor DNA. Cancer Discov 2014;4:650-61.
83. Cescon DW, Bratman SV, Chan SM, et al. Circulating tumor DNA and liquid biopsy in oncology. Nat Cancer 2020;1:276-90.
84. Kurtz DM, Scherer F, Jin MC, et al. Circulating Tumor DNA Measurements As Early Outcome Predictors in Diffuse Large B-Cell Lymphoma. J Clin Oncol 2018;36:2845-53.
85. Scherer F, Kurtz DM, Newman AM, et al. Distinct biological subtypes and patterns of genome evolution in lymphoma revealed by circulating tumor DNA. Sci Transl Med 2016;8:364ra155.
86. Bohers E, Viailly PJ, Dubois S, et al. Somatic mutations of cell-free circulating DNA detected by next-generation sequencing reflect the genetic changes in both germinal center B-cell-like and activated B-cell-like diffuse large B-cell lymphomas at the time of diagnosis. Haematologica 2015;100:e280-4.
87. Rossi D, Diop F, Spaccarotella E, et al. Diffuse large B-cell lymphoma geno-typing on the liquid biopsy. Blood 2017;129:1947-57.
88. Camus V, Sarafan-Vasseur N, Bohers E, et al. Digital PCR for quantification of recurrent and potentially actionable somatic mutations in circulating free DNA from patients with diffuse large B-cell lymphoma. Leuk Lymphoma 2016;57:2171-9.
89. Sun P, Chen C, Xia Y, et al. Mutation Profiling of Malignant Lymphoma by Next-Generation Sequencing of Circulating Cell-Free DNA. J Cancer 2019;10:323-31.
90. Roschewski M, Dunleavy K, Pittaluga S, et al. Circulating tumour DNA and CT monitoring in patients with untreated diffuse large B-cell lymphoma: a correlative biomarker study. Lancet Oncol 2015;16:541-9.
91. Kurtz DM, Green MR, Bratman SV, et al. Noninvasive monitoring of diffuse large B-cell lymphoma by immunoglobulin high-throughput sequencing. Blood 2015;125:3679-87.
92. Roschewski M, Rossi D, Kurtz DM, et al. Circulating Tumor DNA in Lym-phoma: Principles and Future Directions. Blood Cancer Discov 2022;3:5-15.
93. Lauer EM, Mutter J, Scherer F. Circulating tumor DNA in B-cell lymphoma: technical advances, clinical applications, and perspectives for translational research. Leukemia 2022;36:2151-64.
94. Landsburg DJ, Caponetti GC, Bagg A, et al. Clinical laboratory mutation anal-ysis performed on aggressive B cell non-Hodgkin lymphoma patient biopsies. J Clin Oncol 2022. doi: 10.1200/JCO.2022.40.16_suppl.e19561.
95. Xu-Monette ZY, Wu L, Visco C, et al. Mutational profile and prognostic sig-nificance of TP53 in diffuse large B-cell lymphoma patients treated with R-CHOP: report from an International DLBCL Rituximab-CHOP Consortium Program Study. Blood 2012;120:3986-96.
96. Landsburg DJ, Morrissette JJ, Nasta SD, et al. TP53 mutations predict for poor outcomes in patients with newly diagnosed aggressive B-cell lymphomas in the current era. Blood Adv 2023;7:7243-53.
97. Rovira J, Karube K, Valera A, et al. MYD88 L265P Mutations, But No Other Variants, Identify a Subpopulation of DLBCL Patients of Activated B-cell Origin, Extranodal Involvement, and Poor Outcome. Clin Cancer Res 2016;22:2755-64.
98. Xu-Monette ZY, Deng Q, Manyam GC, et al. Clinical and Biologic Significance of MYC Genetic Mutations in De Novo Diffuse Large B-cell Lymphoma. Clin Cancer Res 2016;22:3593-605.
99. Oñate-Ocaña LF, Ponce-Martínez M, Taja-Chayeb L, et al. A Cohort Study of the Prognostic Impact of Exon-16 EZH2 Mutations in a Mexican-Mestizo Population of Patients with Diffuse Large B-Cell Lymphoma. Rev Invest Clin 2021;73:362-70.
100. Zhang MC, Tian S, Fu D, et al. Genetic subtype-guided immunochemotherapy in diffuse large B cell lymphoma: The randomized GUIDANCE-01 trial. Cancer Cell 2023;41:1705-1716.e5.
101. Sujobert P, Le Bris Y, de Leval L, et al. The Need for a Consensus Next-generation Sequencing Panel for Mature Lymphoid Malignancies. Hemasphere 2019;3:e169.

doi: 10.21037/aol-23-19
Cite this article as: Schneider M, Landsburg D. The role of pathologic testing in the diagnosis and management of patients with diffuse large B cell lymphoma: a narrative review. Ann Lymphoma 2024.