Cross-disease stratification by genetic classifier Lymphly reveals shared molecular programs across B-cell malignancies

BostonGene

Abstract #ABCL-443

Dmitrii Snitkin*, **Pavel Zemskiy***, **Andrey Suponin**, **Mark Meerson**, **Ekaterina Nesterenko**, **Alexander Bagaev**, **Alexander Nesmelov**, **Konstantin Chernyshov**, **Nikita Kotlov**

BostonGene Corporation, Waltham, MA

*These authors contributed equally to this work

Context

Biopharmaceutical developers face significant hurdles stratifying heterogeneous diffuse large B-cell lymphoma (DLBCL) cohorts, leading to diluted therapeutic efficacy and stalled clinical trials. While existing subtyping classifiers depend on clinically impractical multi-omics, the shared molecular relationships spanning DLBCL and other B-cell malignancies remain largely unmapped. To break this clinical bottleneck, we developed Lymphly—an evidence-based classifier that integrates pathway-relevant genomic alterations to refine DLBCL subtyping and uncover cross-disease targets.

Objective

Assess Lymphly's ability to identify shared molecular programs across DLBCL and related B-cell lymphomas and to perform clinically relevant cross-disease stratification.

Design

Integrative retrospective analysis of internal and publicly available molecular datasets.

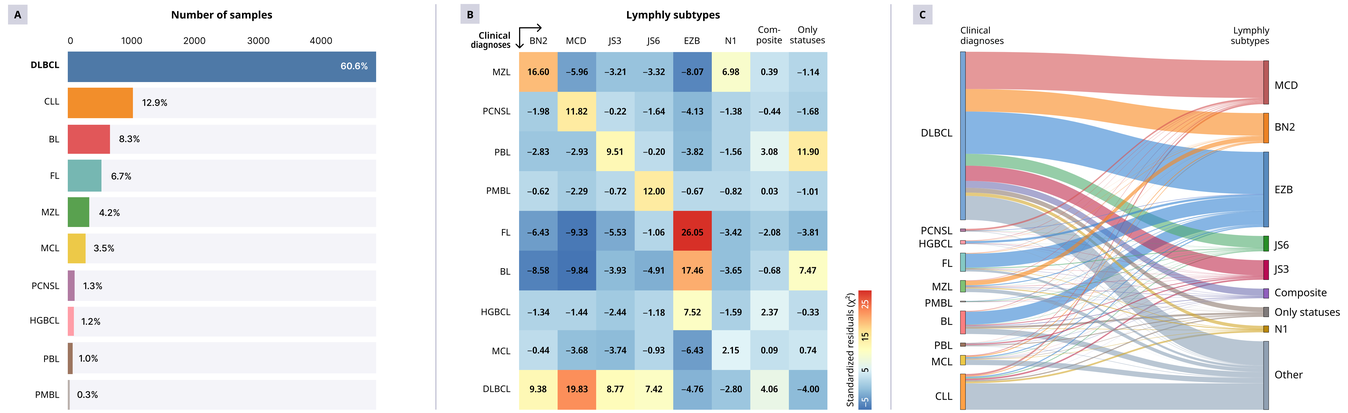
Methods

Lymphly was applied to 4,353 DLBCL and 3,243 non-DLBCL B-cell lymphoma samples with available molecular data from internal and publicly available datasets[2–19] (**Figure 1A**). Samples were assigned to canonical subtypes (EZB, MCD, BN2, N1), newly refined subtypes (JS3, JS6), and orthogonal genomic statuses. Cross-disease subtype mapping was assessed for DLBCL and non-DLBCL samples.

Results

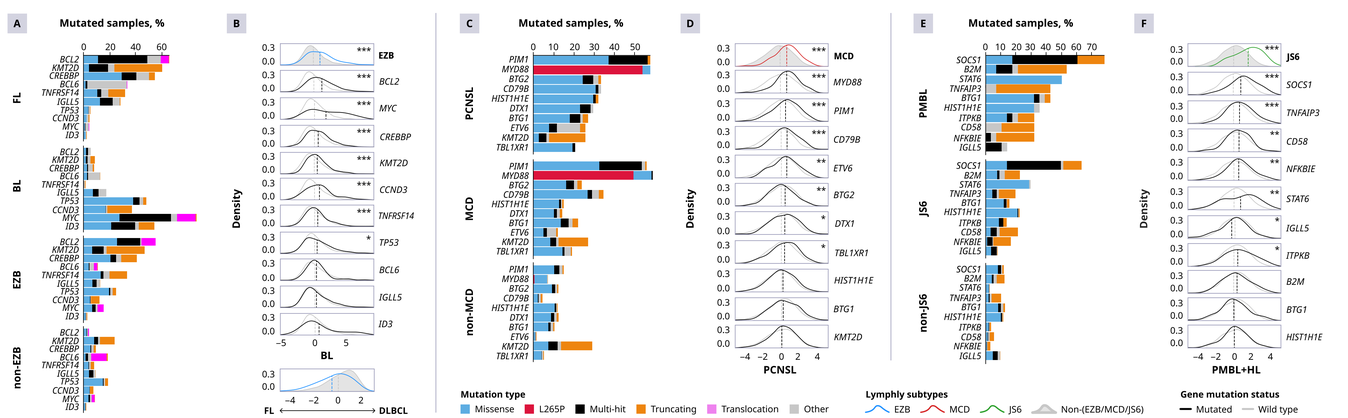
Certain Lymphly-detected DLBCL subtypes prevailed within specific B-cell malignancies (**Figure 1B**, **C**), demonstrating the convergence of their molecular phenotypes (**Figure 2**). EZB was enriched in FL and BL samples, reflecting the subtype's germinal-center B-cell (GCB)-like origin and shared genetic and transcriptional features with these diagnoses (**Figures 2A**, **B**). MCD DLBCL closely mirrored PCNSL in gene expression and genetic profile, featuring prevalent *MYD88* (primarily L265P), *PIM1*, and *CD79B* mutations (**Figures 2C**, **D**). BN2—featuring mutations affecting *NOTCH2* and NF-κB signaling—was enriched among MZL, particularly SMZL, samples. Newly classified subtypes JS6 and JS3 linked DLBCL to other B-cell lymphoma entities: GCB-like JS6 aligned with PMBL via recurrent *SOCS1* mutations and shared PMBL/HL signature among JS6 samples (**Figures 2E**, **F**), whereas JS3 aligned biologically with PBL.

Figure 1. Meta-cohort composition and concordance between clinical diagnoses and Lymphly molecular subtypes



Molecular subtyping of B-cell lymphomas by Lymphly. **A.** Bar graph showing the number of samples across diagnostic categories, including DLBCL and other B-cell lymphoma entities analyzed. **B.** Heatmap showing statistical relationships between clinical diagnoses and Lymphly-defined DLBCL subtypes (including "composite" and "only statuses"). "Only statuses" refers to samples without an assigned subtype but positive for at least one Lymphly status: A+, TP53+, or MYC+. "Composite" refers to samples assigned to two subtypes. Cell values are standardized residuals from a χ^2 test: positive and negative values indicate diagnosis–subtype combinations occurring more and less often, respectively, than expected if the clinical diagnosis and Lymphly subtype were unrelated. **C.** Sankey diagram showing the distribution of clinical diagnoses across Lymphly-defined DLBCL molecular subtypes, with flow width proportional to sample number.

Figure 2. Molecular characterization of Lymphly subtypes and their non-DLBCL counterparts



Genomic and gene expression features shared by DLBCL genetic subtypes and their non-DLBCL counterparts. **A, C, E.** Mutation frequencies of most mutated genes in PCNSL (n = 123) **(A)**, FL (n = 525), BL (n = 665) **(C)**, and PMBL (n = 28) **(E)** compared to their frequencies in analogous DLBCL genetic subtypes: MCD (n = 1,007), EZB (n = 1,134), and JS6 (n = 323). *BCL2* mutations and translocations as well as *KMT2D*, *CREBBP*, and *TNFRSF14* mutations rendered EZB similar to FL instead of BL. BL was characterized primarily by *MYC* mutations/translocations alongside *ID3* and *CCND3* mutations. Only available data on *MYC* translocation are presented, although its identification is necessary for BL diagnosis **(A)**. *PIM1* and *MYD88* mutations (specifically *MYD88*-L265P) were prominent in PCNSL and MCD **(C.)**. PMBL-associated mutations were more prevalent in JS6 than non-JS6 cases, with exceptional prevalence of *SOCS1* mutations **(E)**. **B, D, F.** Density plots showing distributions of ssGSEA scores for BL,[20] signature distinguishing FL (left-pointing arrow) from DLBCL (right-pointing arrow),[21] PCNSL,[22] and PMBL/HL[23] signatures across DLBCL genetic subtypes and their association with mutations in the most mutated genes shown in **A**, **C**, and **E**. Asterisks indicate significance determined by Mann–Whitney *U* test (FDR-adjused): * — p < 0.05; ** — p < 0.01; *** — p < 0.001. Dashed lines indicate mean values.

Conclusions

By bridging discrete disease boundaries, Lymphly offers a novel, cross-disease genomic platform that identifies shared molecular targets across B-cell lymphomas. Its interpretable framework circumvents complex multiomic requirements, delivering robust stratification even within heterogeneous sequencing datasets. By mapping molecularly aligned patient cohorts across indications, Lymphly equips clinical researchers and developers with a scalable tool to accelerate cross-indication clinical development, de-risk trial enrollment, and optimize patient selection at every clinical stage.

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Abbreviations

BL — Burkitt lymphoma, CLL — Chronic lymphocytic leukemia, DLBCL — Diffuse large B-cell lymphoma, FL — Follicular lymphoma, HGBCL — High-grade B-cell lymphoma, MCL — Mantle cell lymphoma, MZL — Marginal zone lymphoma, PBL — Plasmablastic lymphoma, PCNSL — Primary central nervous system lymphoma, PMBL — Primary mediastinal B-cell lymphoma, SMZL — Splenic MZL

Contact: Alexander Bagaev

aleksander.bagaev@bostongene.com