23rd INTERNATIONAL ULTMANN CHICAGO LYMPHOMA SYMPOSIUM

APRIL 10-11, 2026

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LymphoMATCH: Are We Ready for Precision Medicine in DLBCL?

Brian Hill, MD, PhD

Director, Lymphoid Malignancies Program

Associate Professor of Medicine

Cleveland Clinic

Cancer Institute

Disclosures

- Research funding and consulting fees from:

  Genentech, Pharmacyclics, AbbVie, AstraZeneca, BeOne, ADC Therapeutics, Kite/Gilead, Incyte, BMS

- Graduated/trained at the University of Chicago (see next slide)

"The time to rise has been engaged
You're better best to rearrange
I'm talkin' here to me alone
I listen to the finest worksong..."
- Michael Stipe, lead singer, REM, 1987

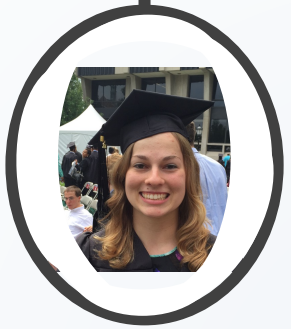
Sophie Hill
Ph.B. 1929

Beatrice Hill, PhD
BA, 1960
M.A., 1961

John Hill, PhD
B.A, 1963

Matthew Hill, MD, PhD
UChicago Anesthesiology, 2002

Brian Hill, MD, PhD
MD, 2005
UChicago Internal Medicine, 2008



Jennifer Hill, MD
B.A.2015

LymphoMATCH: Are We Ready for Precision Medicine in DLBCL?

- Who?
- What?
- When?
- Where?
- Why?

LymphoMATCH: Are We Ready for Precision Medicine in DLBCL?

- Who?
- What?
- When? 2027+
- Where?
- Why?

LymphoMATCH: Are We Ready for Precision Medicine in DLBCL?

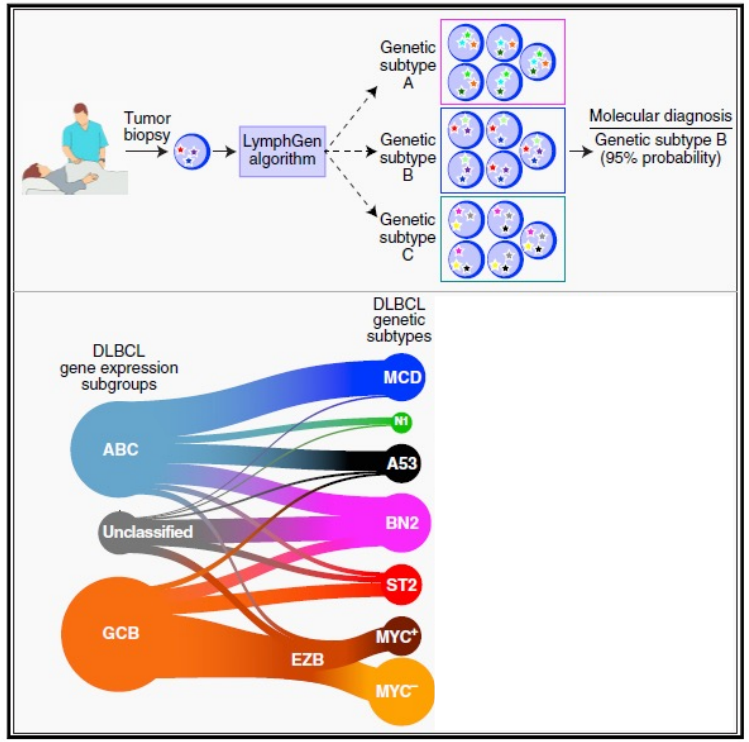
- **Why?**
  - Although patients with DLBCL have favorable outcomes with standard 1L chemotherapy (R-CHOP, Pola-RCHP, etc.), many relapse.
  - Treatment is toxic and difficult to tolerate even in fit patients, with potential for late effects including cardiotoxicity, peripheral neuropathy and secondary malignancies.
  - For older/frail patients, reduced intensity treatment is often unsafe and/or morbid.
  - Rationale incorporation of novel targeted agents will likely lead to safer/more tolerable and potentially more effective treatment.

LymphoMatch: Are We Ready for Precision Medicine in DLBCL?

Cancer Cell

A Probabilistic Classification Tool for Genetic Subtypes of Diffuse Large B Cell Lymphoma with Therapeutic Implications

Graphical Abstract



Authors

George W. Wright, Da Wei Huang, James D. Phelan, ..., Wyndham H. Wilson, David W. Scott, Louis M. Staudt

Highlights

- Diffuse large B cell lymphoma (DLBCL) consists of seven genetic subtypes
- The LymphGen algorithm classifies a DLBCL biopsy into one or more genetic subtypes
- The genetic subtypes have distinct clinical outcomes and pathway dependencies
- The genetic subtypes will aid the development of rationally targeted therapy of DLBCL

Wright et al., 2020, *Cancer Cell* 37, 551–568

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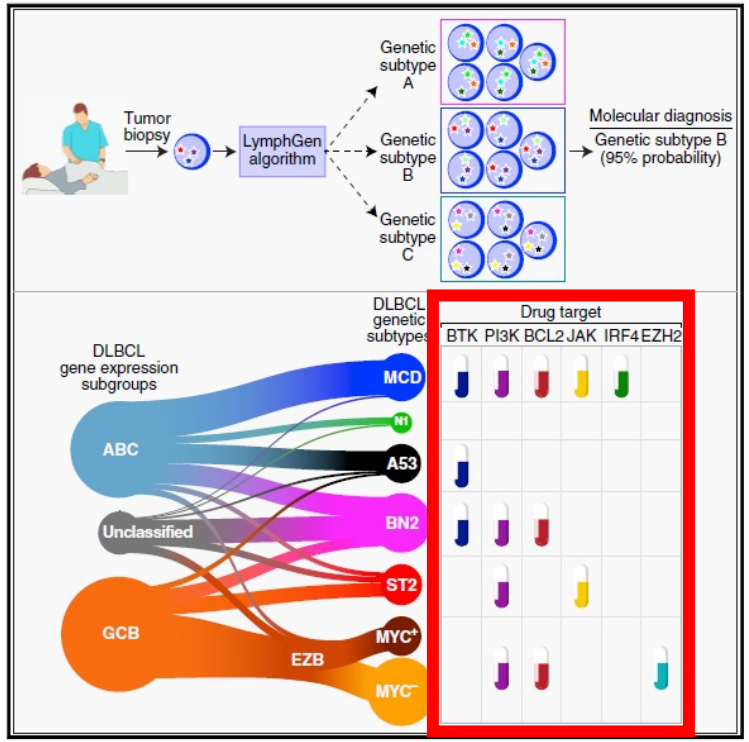

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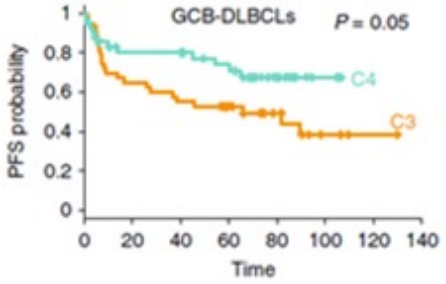
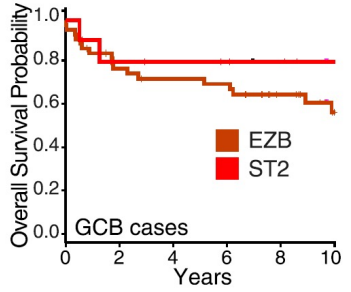
Integrated Genomic Approaches to Categorize DLBCL

COO	Risk	DLBclass[1]		LymphGEN[2]	
Germinal Center	Lower Risk	**Cluster 4** Histone mutations JAK/Stat and PI3K signaling NF-κB mutations		**ST2** SGK1 and TET2 JAK-Stat and PI3K signaling	
	Higher Risk	**Cluster 3** Bcl-2 translocations EZH2 mutations PI3K signaling		**EZB** Bcl-2 translocations EZH2 mutations	

1. Chapuy, et al. Blood 2025;145(18):2041-2055
2. Wright et al., 2020, *Cancer Cell* 37, 551–568

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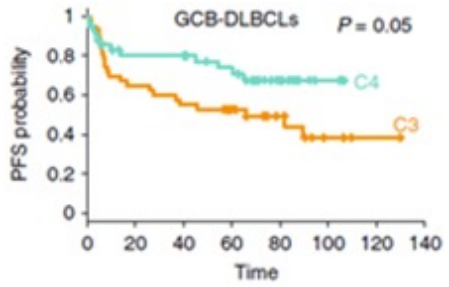
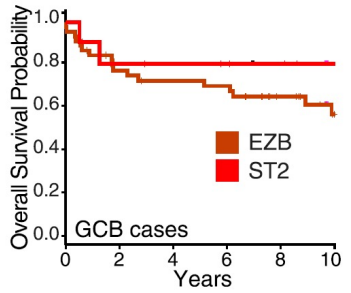
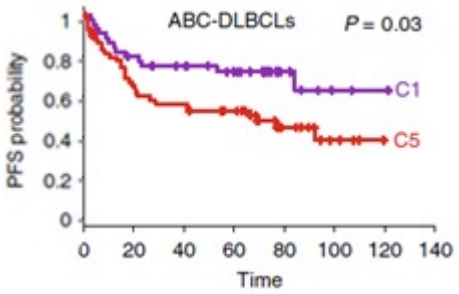
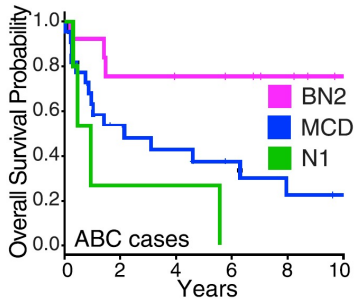
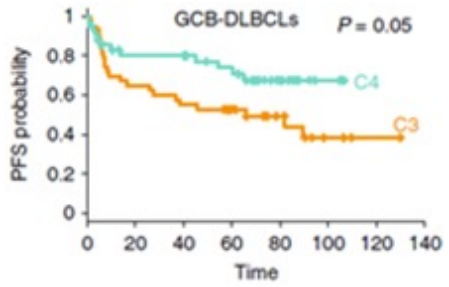
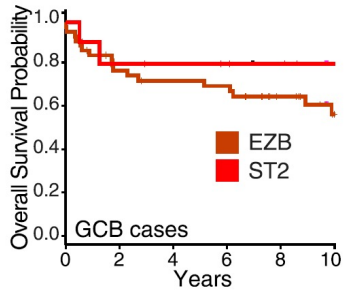
Germinal Center	Lower Risk	**Cluster 4** Histone mutations JAK/Stat and PI3K signaling NF-κB mutations		**ST2** SGK1 and TET2 JAK-Stat and PI3K signaling	
	Higher Risk	**Cluster 3** Bcl-2 translocations EZH2 mutations PI3K signaling		**EZB** Bcl-2 translocations EZH2 mutations	
ABC	Lower Risk	**Cluster 1** Immune evasion NOTCH2/NF-κB Bcl-6 translocations MYD88$^{non-L265P}$		**BN2** Immune evasion NOTCH2/NF-κB Bcl-6 translocations	
	Higher Risk	**Cluster 5** CD79B, MYD88^{L265P} 18q gains Bcl-2 expression		**MCD** CD79B MYD88^{L265P} Bcl-2 expression	

1. Chapuy, et al. Blood 2025;145(18):2041-2055
2. Wright et al., 2020, *Cancer Cell* 37, 551–568

Integrated Genomic Approaches to Categorize DLBCL Targeting C5/MCD Subtype

COO	Risk	DLBclass[1]		LymphGEN[2]	
Germinal Center	Lower Risk	**Cluster 4** Histone mutations JAK/Stat and PI3K signaling NF-κB mutations		**ST2** SGK1 and TET2 JAK-Stat and PI3K signaling	
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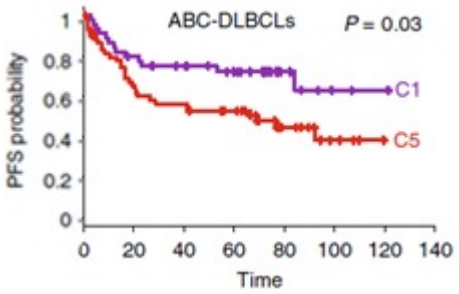
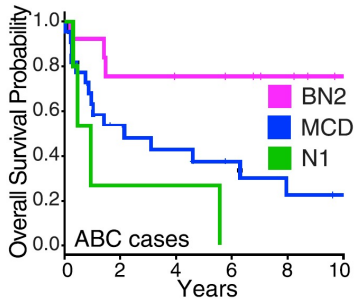
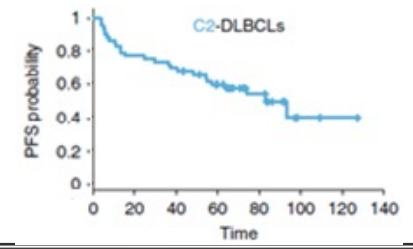
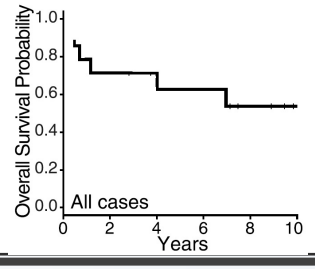
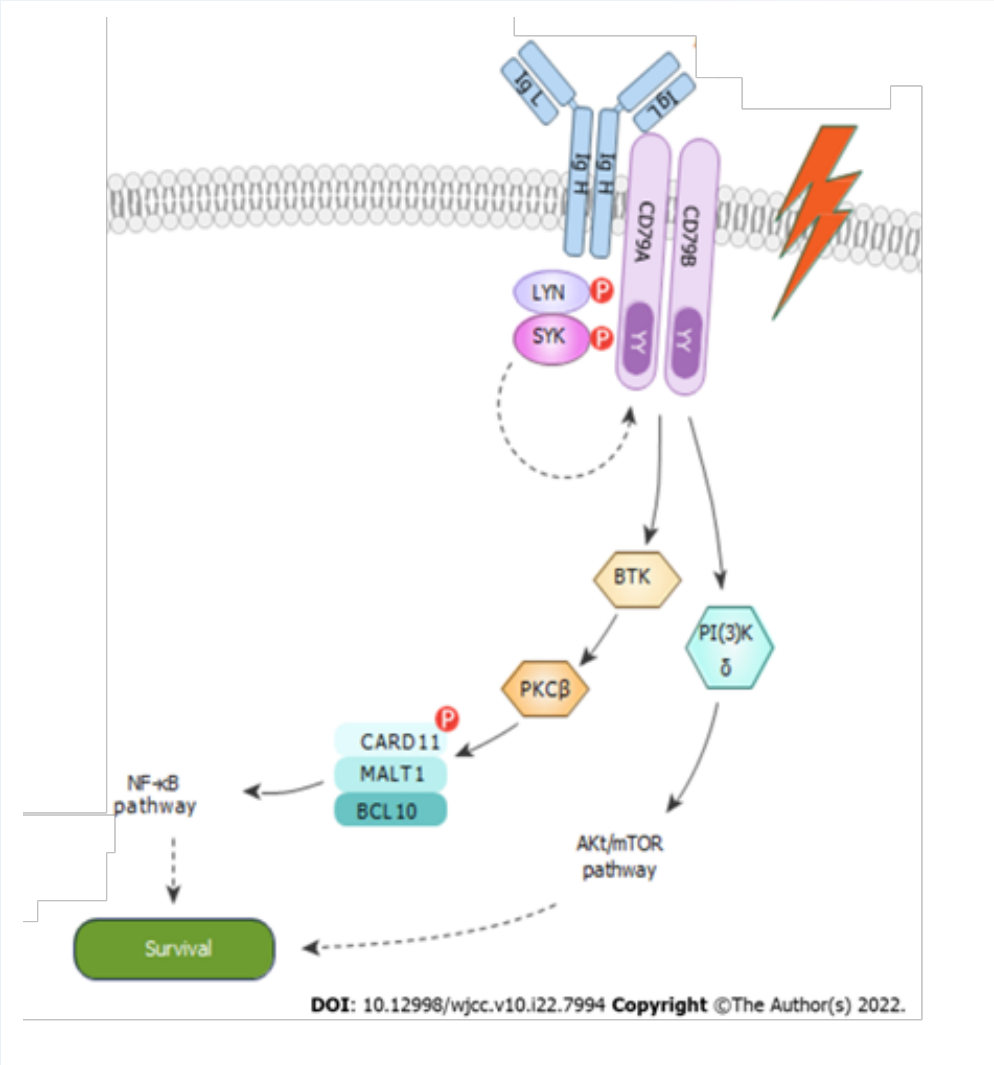
ABC	Lower Risk	**Cluster 1** Immune evasion NOTCH2/NF-κB Bcl-6 translocations MYD88non-L265P		**BN2** Immune evasion NOTCH2/NF-κB Bcl-6 tranlocations	
	Higher Risk	**Cluster 5** CD79B, MYD88L265P 18q gains Bcl-2 expression		**MCD** CD79B MYD88L265P Bcl-2 expression	
Other	Higher Risk	**Cluster 2** Inactivation of p53, CDKN2A		**A53** Aneuploidy and p53 inactivation	

Integrated Genomic Approaches to Categorize DLBCL Targeting C5/MCD Subtype



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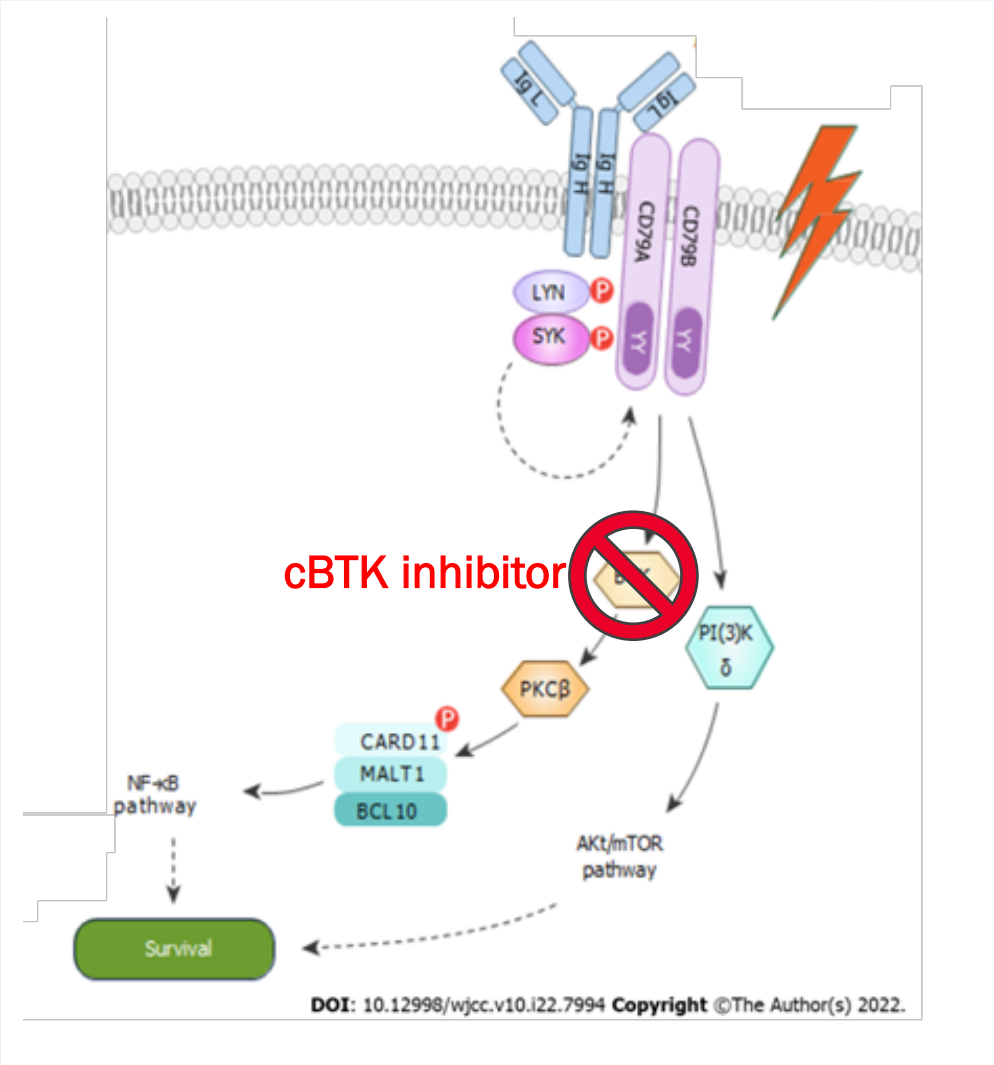


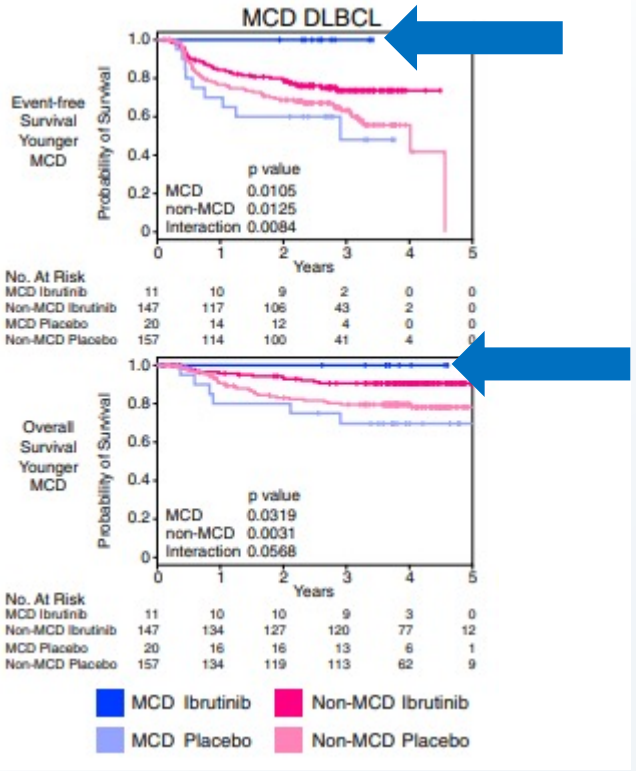
Cancer Cell

CellPress

Article

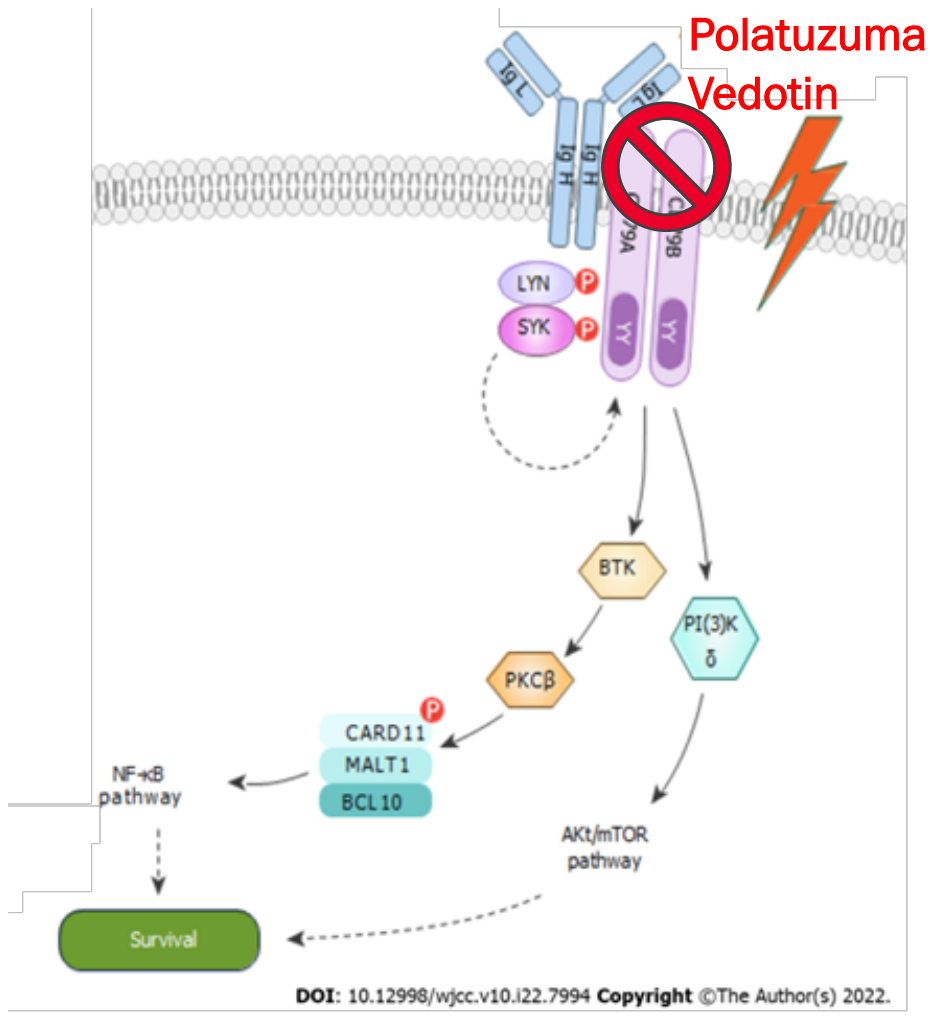
Effect of ibrutinib with R-CHOP chemotherapy in genetic subtypes of DLBCL

Wyndham H. Wilson,[1,5] George W. Wright,[2,5] Da Wei Huang,[1] Brendan Hodkinson,[3] Sriram Balasubramanian,[3] Yue Fan,[3] Jessica Vermeulen,[3] Martin Shreeve,[3] and Louis M. Staudt[1,4,6,*]

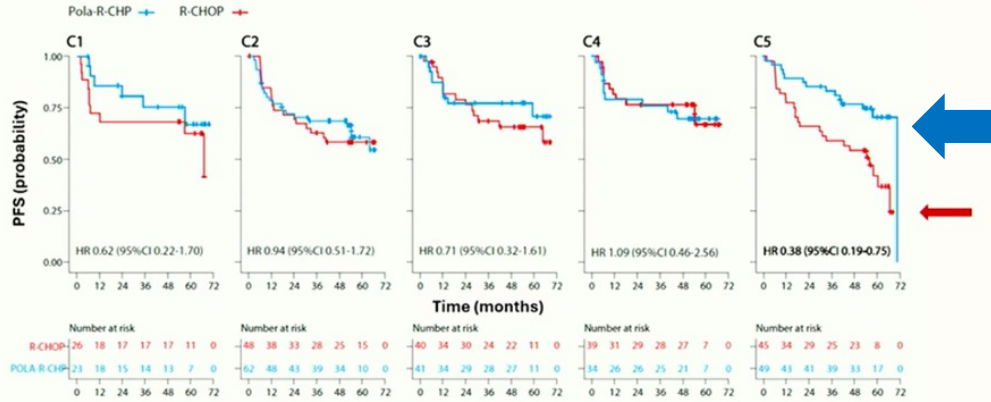


Wilson, et al., 2020, *Cancer Cell* 39, 1643-1653

Integrated Genomic Approaches to Categorize DLBCL Targeting C5/MCD Subtype



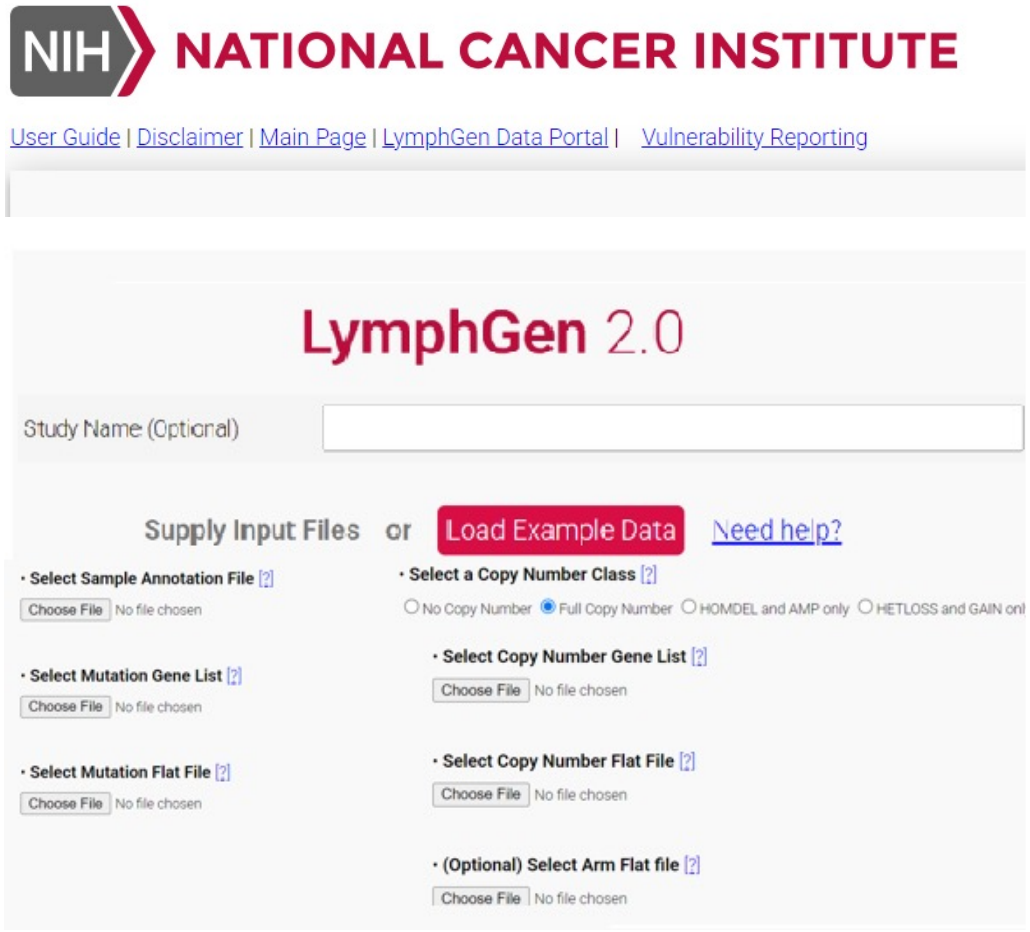
Benefit of Pola-R-CHP in Patients with Cluster 5 DLBCLs

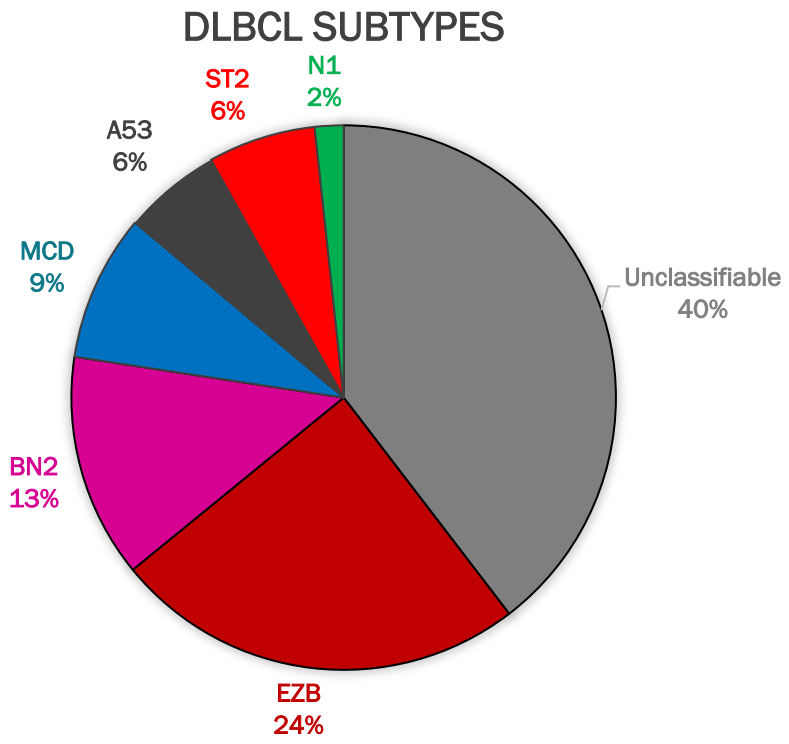


- Patients with C5 DLBCLs – 5-yr PFS higher in Pola-R-CHP versus R-CHOP treatment arm
  - Pola-R-CHP **70.4%** (95%CI 57.6-86.1)
  - R-CHOP **42.0%** (95% CI 28.0-63.0)
- Hazard ratio (HR) for Pola-R-CHP vs R-CHOP **0.38** (95% CI 0.19-0.75, **p=0.005**) in patients with C5 DLBCLs
- Pola-containing regimen abrogated the predicted poor outcome in C5 tumors.
- In contrast, 5-yr PFSs and HRs comparable for patients with C1-C4 DLBCLs in the two treatment arms

Calabretta E, et al. Hematol Oncol. 2025;43: eLBA1_70110.

The LymphGen Algorithm is Publicly Available but Can Only Classify ~60% of DLBCL into Subtypes





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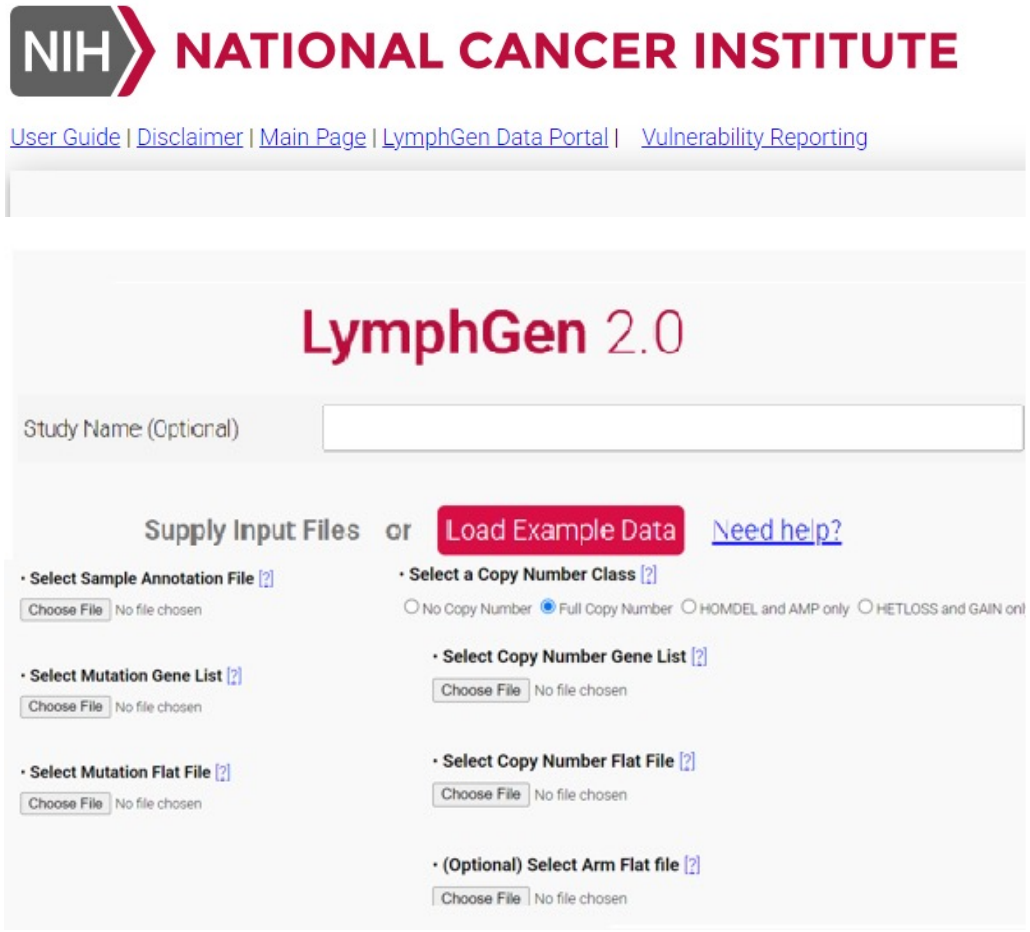
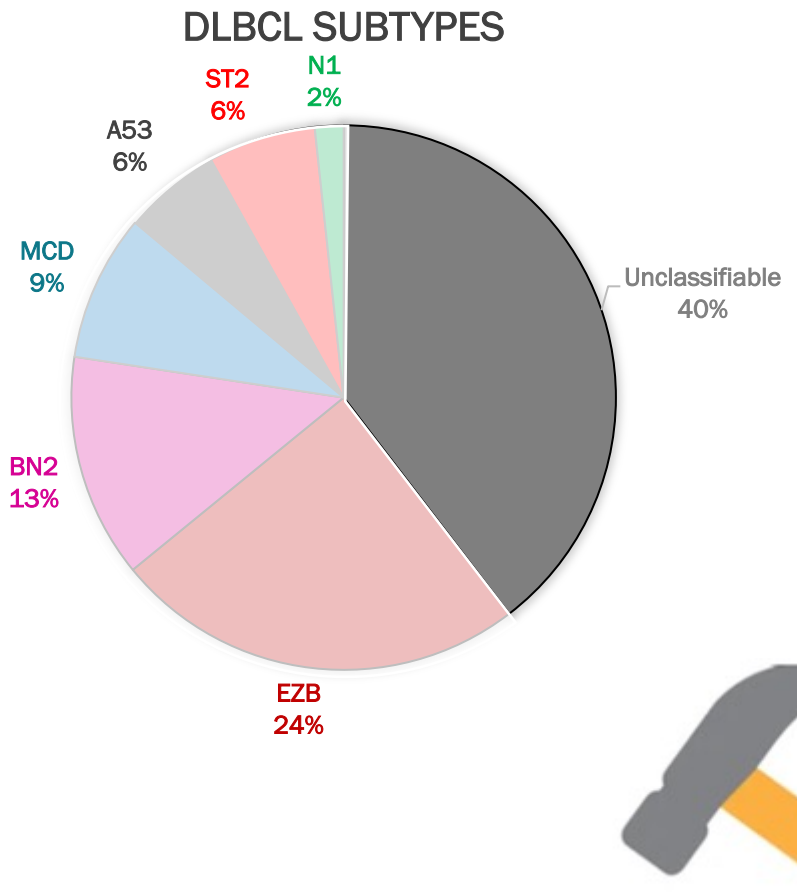
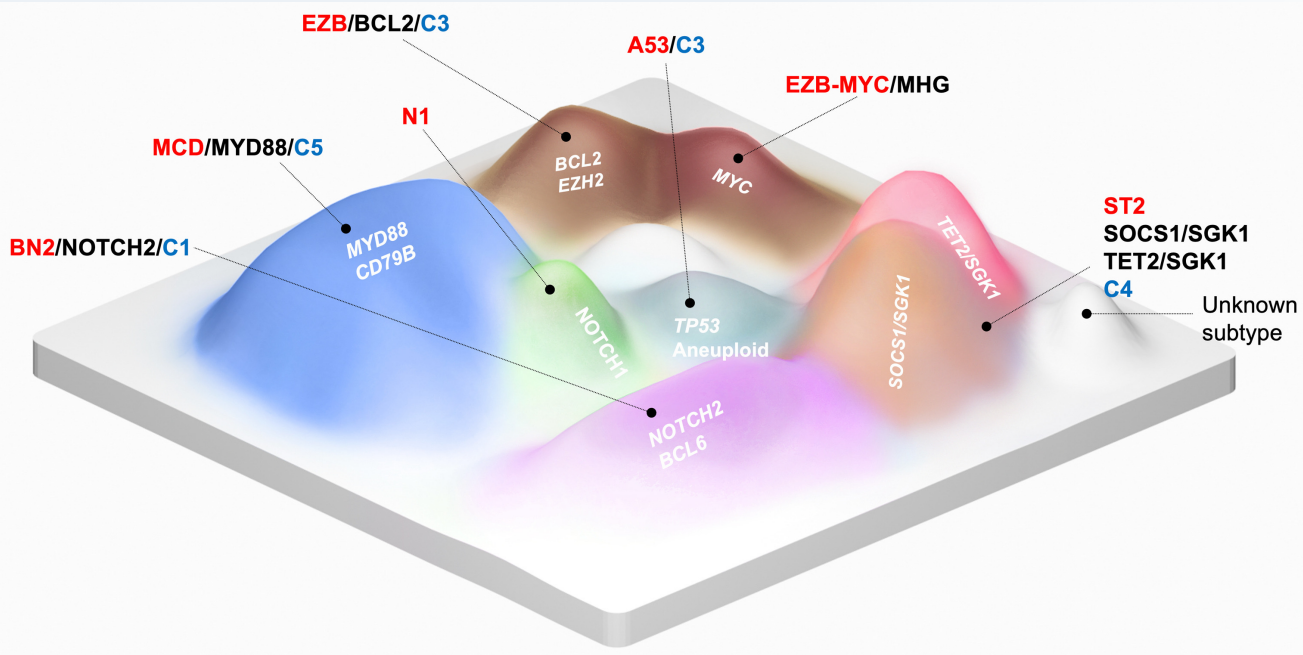
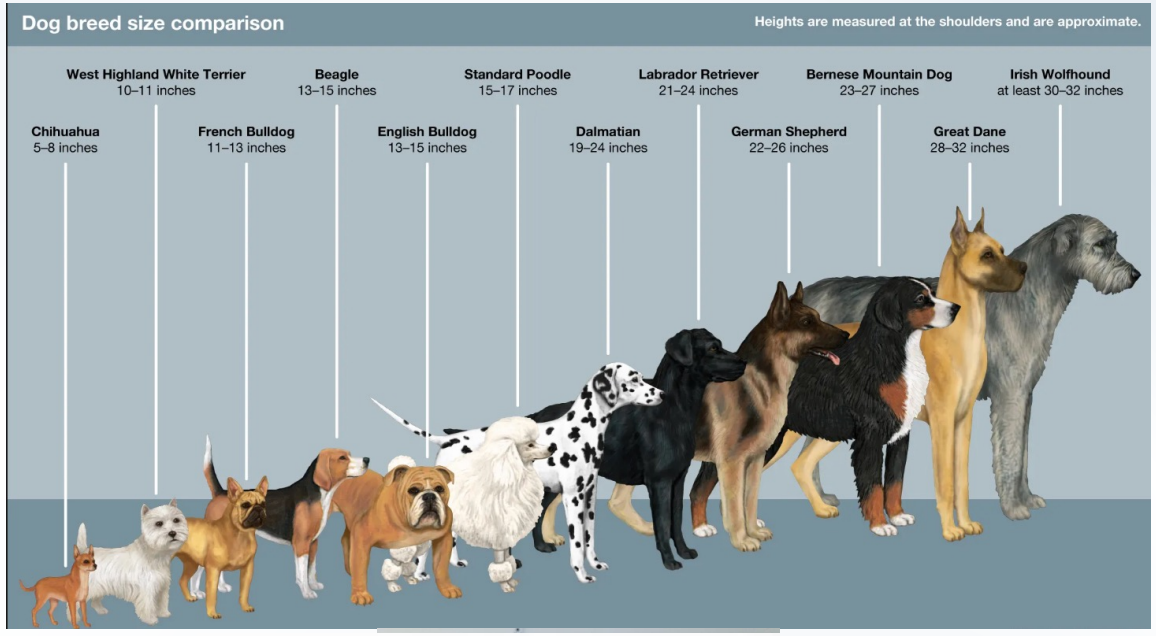
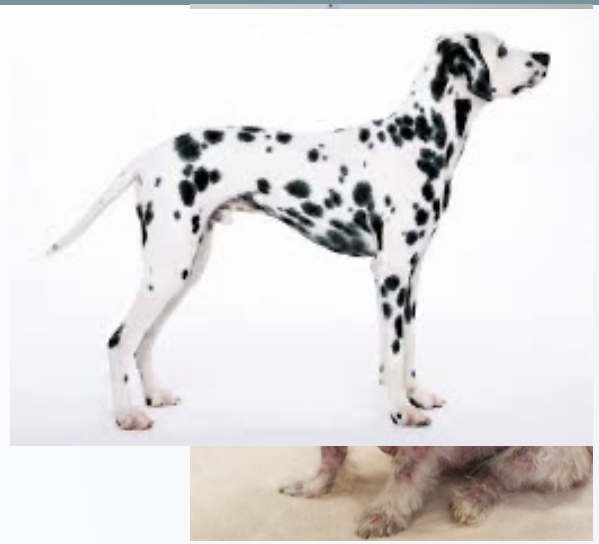




Homogeneity vs. Overclassification

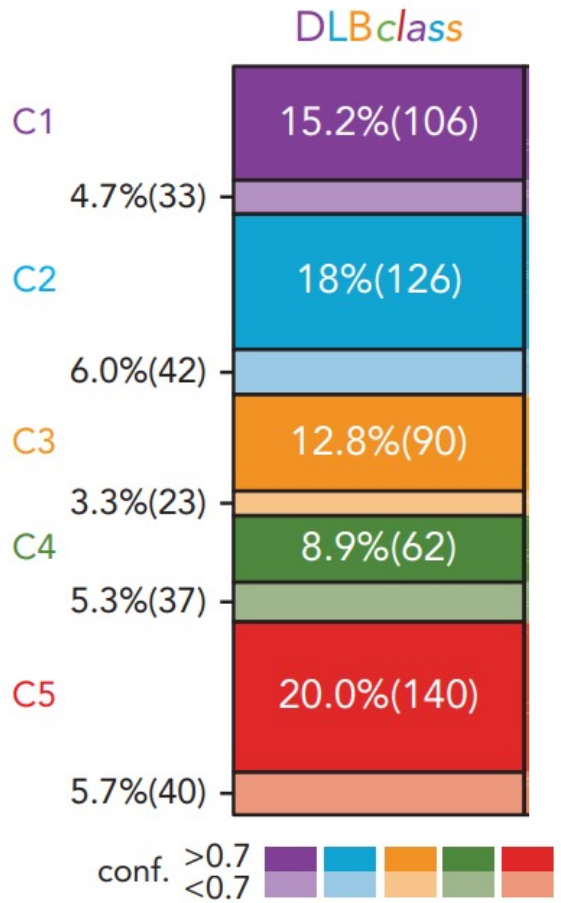






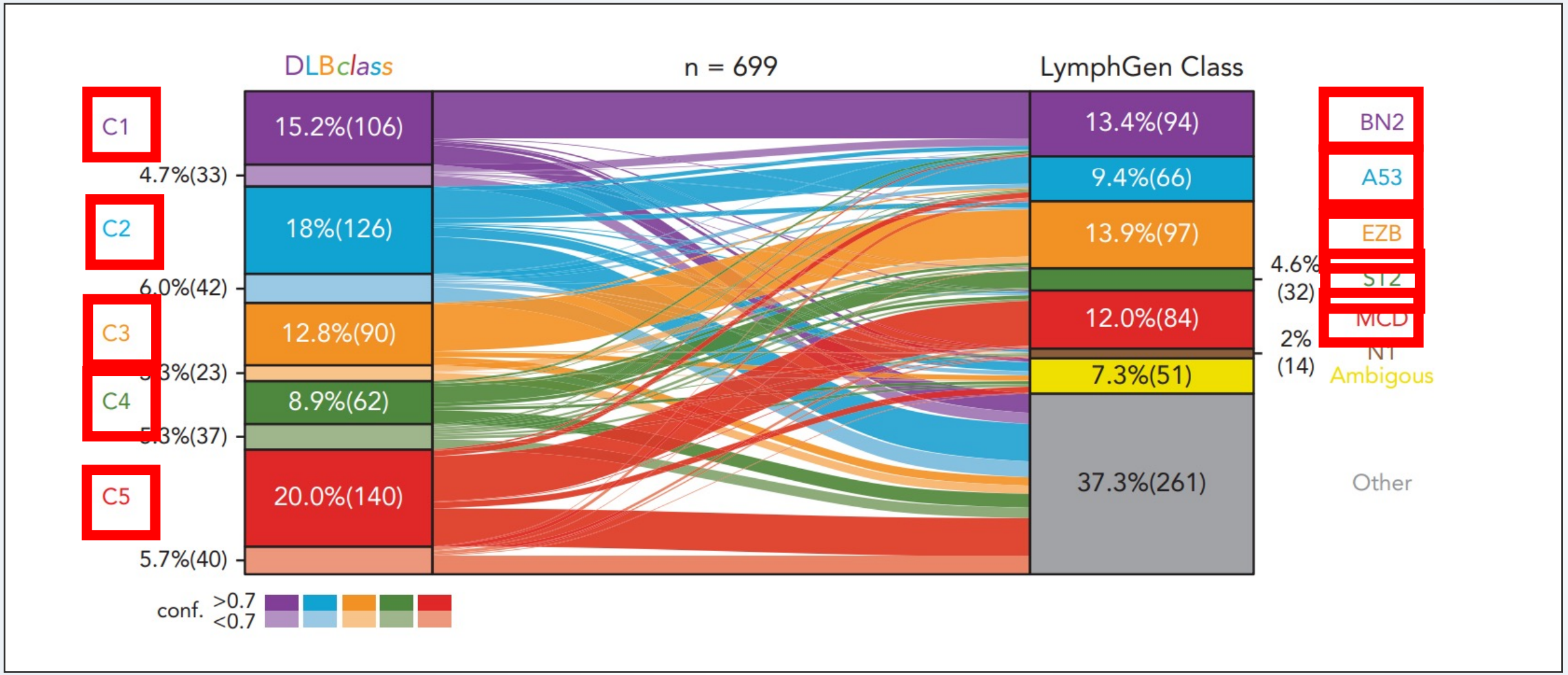
Cutmore NH, Krupka JA, Hodson DJ. Genetic Profiling in Diffuse Large B-Cell Lymphoma: The Promise and the Challenge. *Mod Pathol*. 2023;36(1):100007.

DLBclass



Chapuy, et al. Blood 2025;145(18):2041-2055

DLBclass



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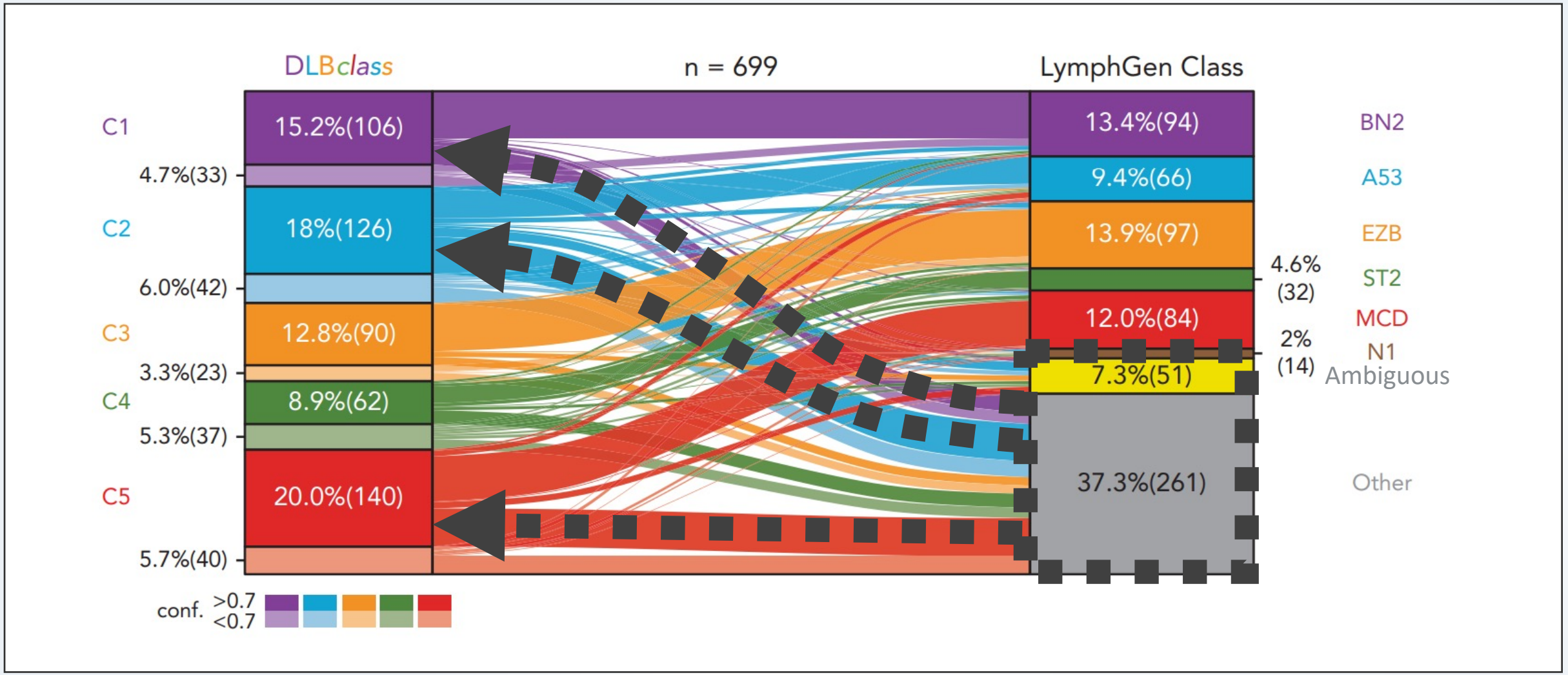

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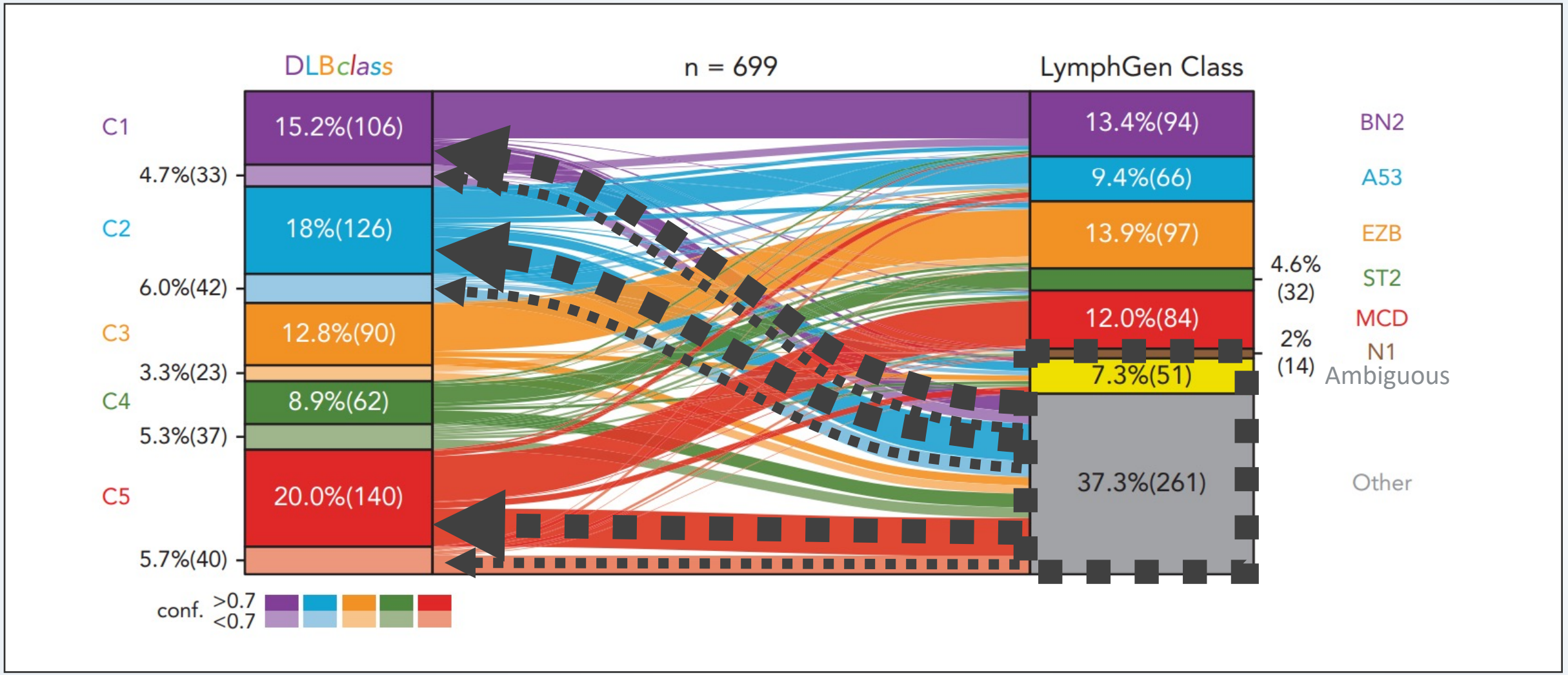

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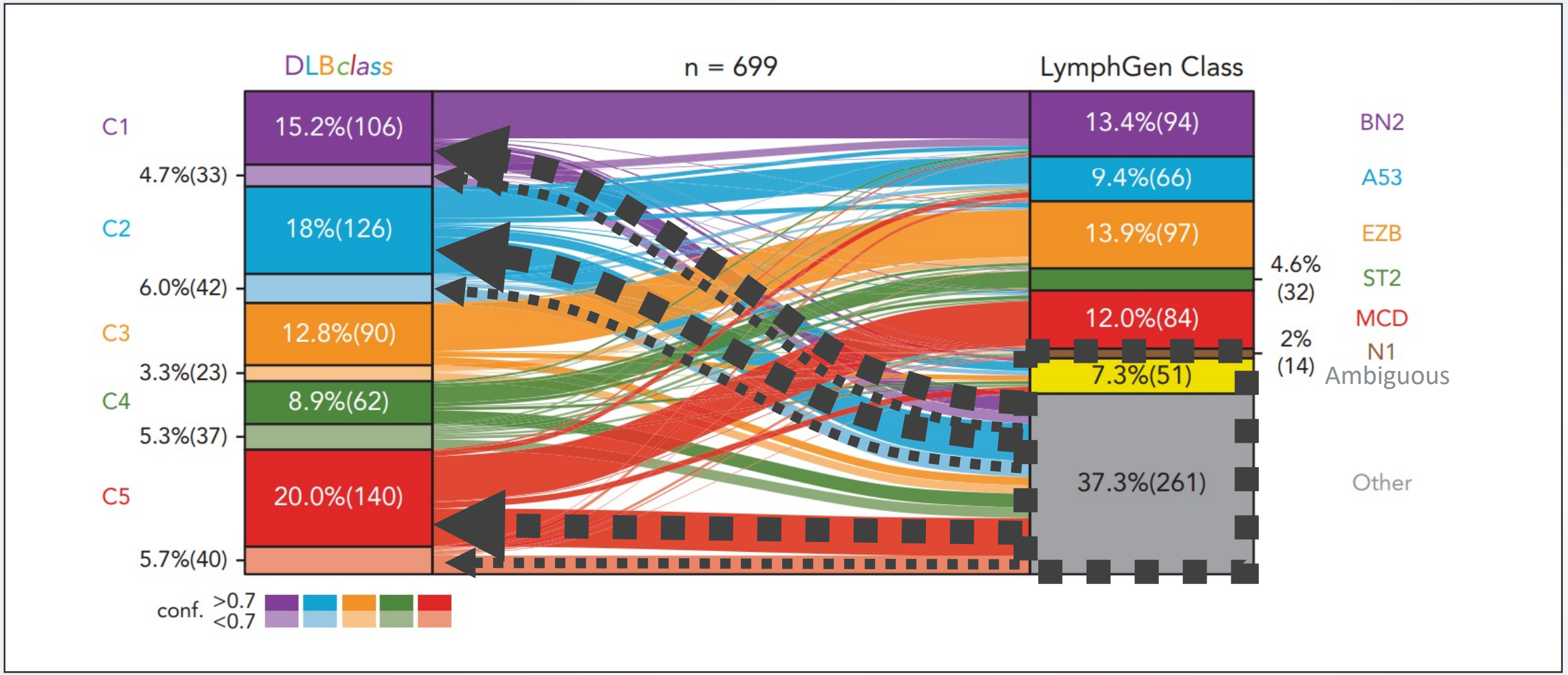
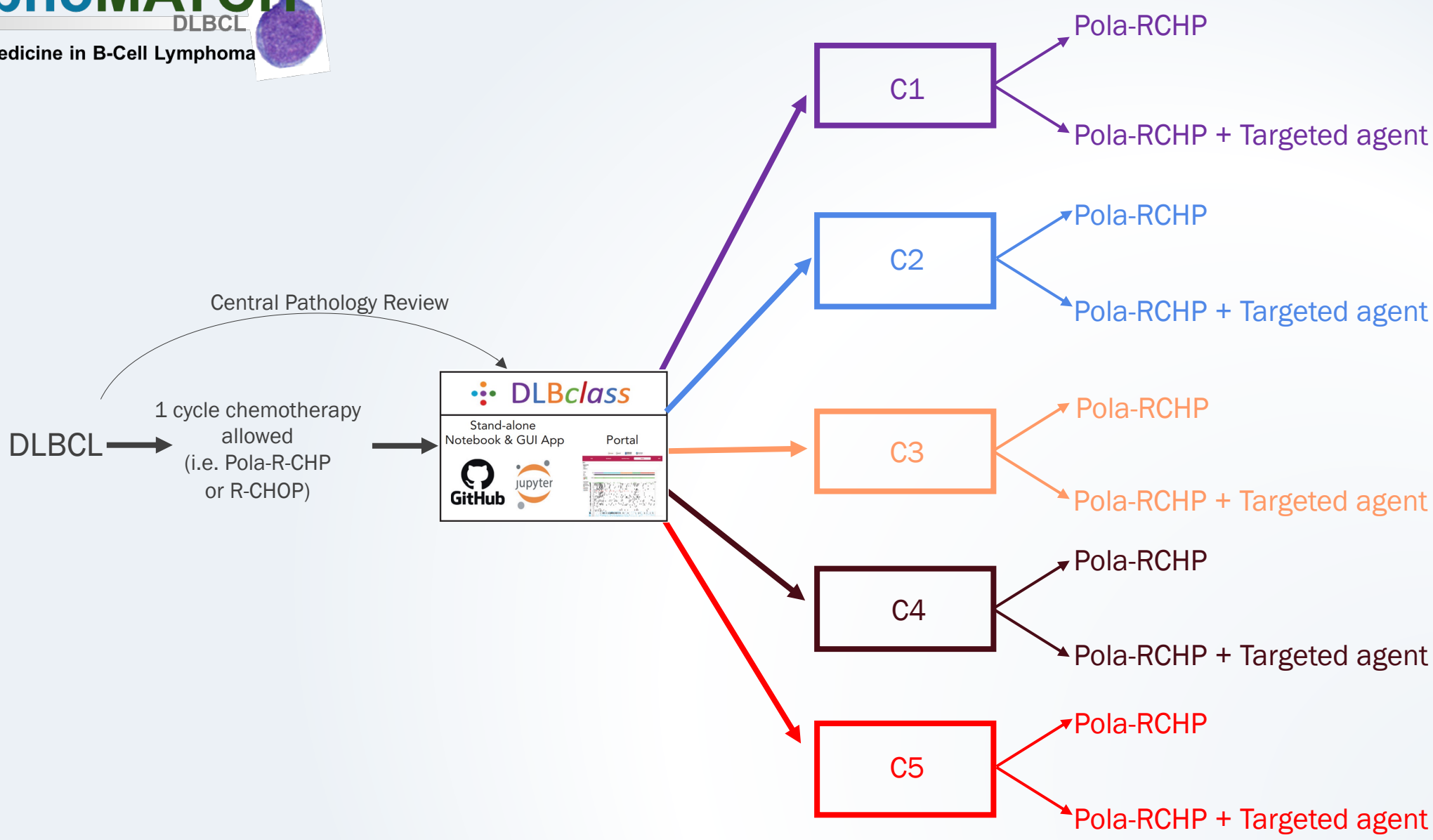


Chapuy, et al. Blood 2025;145(18):2041-2055

lymphoMATCH
DLBCL
Precision Medicine in B-Cell Lymphoma



LymphoMATCH: Are We Ready for Precision Medicine in DLBCL?

- Choice of classification scheme requires consideration of homogeneity of groups vs. under-classification.
- Standard of care is debatable and likely to evolve.
- Real-time testing for subtyping of DBLBCL requires a complex molecular assay that is not performed in routine clinical practice. Multiple efforts ongoing to vet various testing companies.
- Addition of targeted agents to standard backbone may lead to increased toxicity. Chemotherapy-free approaches are being rapidly developed.
- Logistically complex with activation of multiple arms across the NCTN poses feasibility challenges due to timelines of industry sponsors.

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