



Duals in Lymphoma: The Role of NGS and Mutational Profiling in B Cell Lymphomas

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Disclosures

- Consulting: Abbvie, Regeneron (IDMC)
- Advisory Board: Genentech, Ipsen, Tempus
- Research Funding: Genentech (institutional)

What's in a name?

“Disease does not exist until we have agreed that it does —
by perceiving, naming, and responding to it.”

- *Charles Rosenberg, medical historian*

Are clinical groupings useful for clinical practice? No

The committee concluded that grouping the B- and T/NK-cell neoplasms into prognostic categories would serve no clear purpose and could hamper understanding of the specific features of some of the diseases. There are no groups of diseases that require identical treatment, and if treatment must be individualized to a specific disease, grouping serves no purpose and may be misleading. The entities listed in the classification are clearly defined and clinically relevant, and it is necessary for oncologists and pathologists dealing with these diseases to understand each of them. In practice, treatment of a specific patient is determined not by which broad prognostic group the lymphoma falls into, but by the specific *histologic* type of lymphoma, with the addition of grade *within* the tumor type, if applicable, and *clinical prognostic factors* such stage, age, performance status, and/or the international prognostic index (IPI) [18].

Annals of Oncology 11 (Suppl. 1): S3–S10, 2000.
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Symposium article

Lymphoma classification – from controversy to consensus: The R.E.A.L. and WHO Classification of lymphoid neoplasms

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We already subset large B-cell lymphomas...

- Based on **morphologic**, **immunophenotypic**, **genomic**, and **clinical** insights, LBCL has become an umbrella term for many unique entities
 - Some **with** and some **without** distinct management differences

1974



2001



2022

Table 3 The Kiel classification⁷

Low-grade malignancy

- Malignant lymphoma (ML)—lymphocytic (CLL and others)
- ML—lymphoplasmacytoid (immunocytic)
- ML—centrocytic
- ML—centroblastic-centrocytic
 - Follicular (with or without sclerosis)
 - Follicular (with or without sclerosis) and diffuse
 - Diffuse (with or without sclerosis)

High-grade malignancy

- ML—centroblastic
- ML—lymphoblastic
 - Burkitt type
 - Convuluted-cell type
 - Others
- ML—immunoblastic

Diffuse large B-cell lymphoma

Variants: centroblastic; immunoblastic; T-cell or histiocyte rich; anaplastic large cell

Mediastinal (thymic) large B-cell lymphoma

Intravascular large B-cell lymphoma

Primary effusion lymphoma

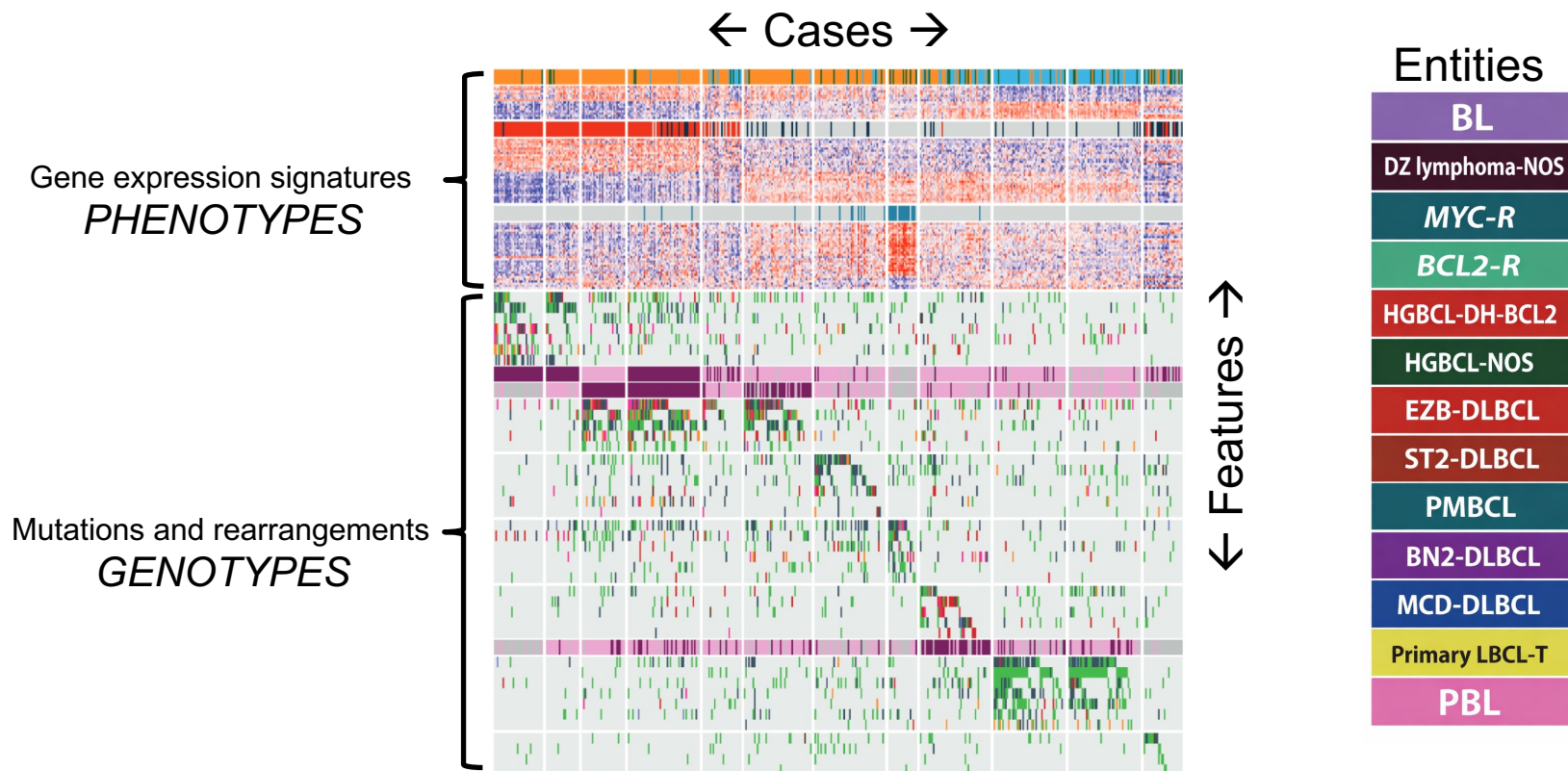
Burkitt lymphoma (BL)

Variants: BL with plasmacytoid differentiation; atypical Burkitt / Burkitt-like

Lymphomatoid granulomatosis

Large B-cell lymphomas
Diffuse large B-cell lymphoma, NOS
T-cell/histiocyte-rich large B-cell lymphoma
Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with <i>MYC</i> and <i>BCL2</i> rearrangements
ALK-positive large B-cell lymphoma
Large B-cell lymphoma with <i>IRF4</i> rearrangement
High-grade B-cell lymphoma with 11q aberrations
Lymphomatoid granulomatosis
EBV-positive diffuse large B-cell lymphoma
Diffuse large B-cell lymphoma associated with chronic inflammation
Fibrin-associated large B-cell lymphoma
Fluid overload-associated large B-cell lymphoma
Plasmablastic lymphoma
Primary large B-cell lymphoma of immune-privileged sites
Primary cutaneous diffuse large B-cell lymphoma, leg type
Intravascular large B-cell lymphoma
Primary mediastinal large B-cell lymphoma
Mediastinal grey zone lymphoma
High-grade B-cell lymphoma, NOS

What do we already know?



Gene Expression Signatures

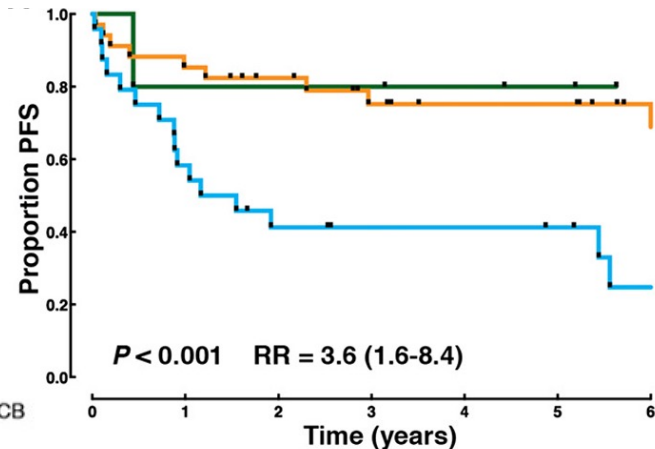
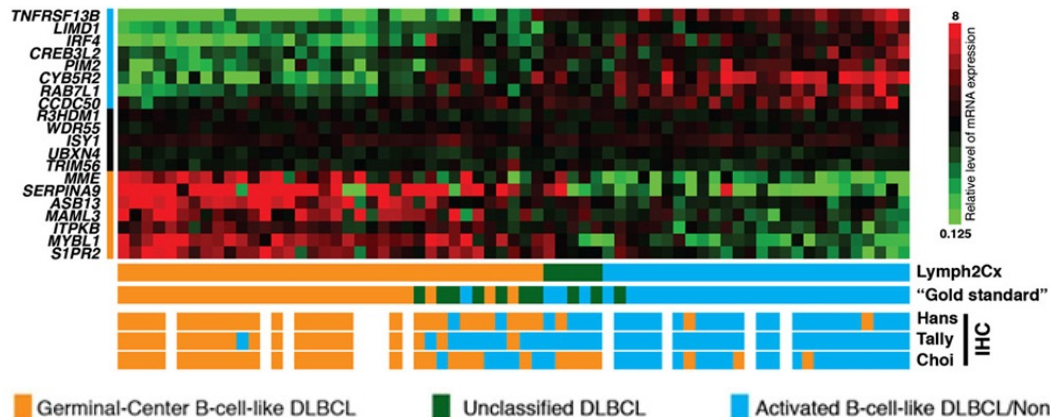
PMBCLsig

DZsig

COO

- Cell of Origin → Lymph2Cx (Nanostring)

- Comparison of gene expression of tumors with B cells at different stages of differentiation



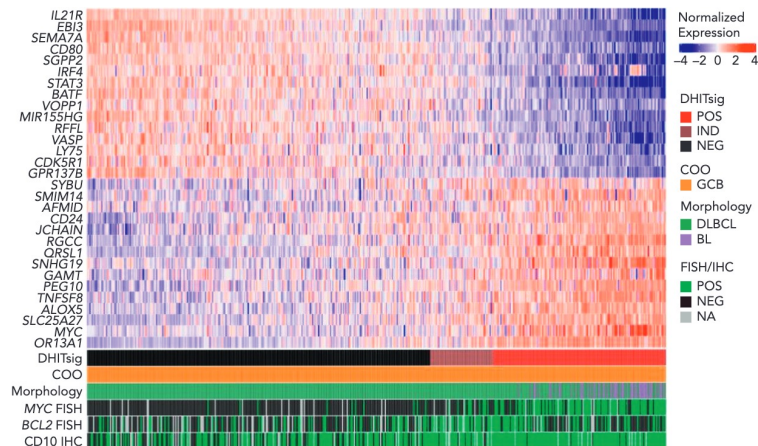
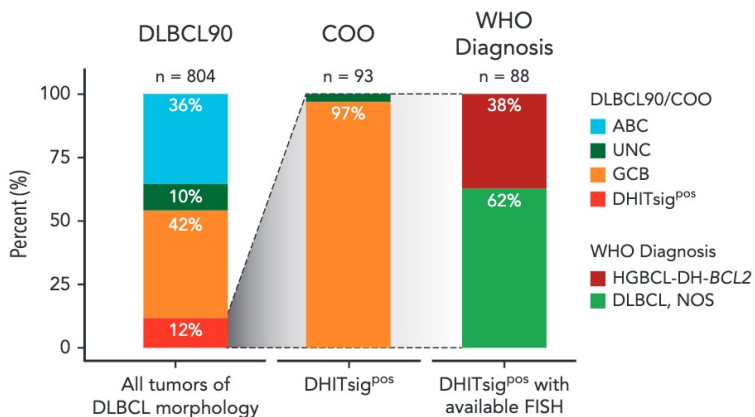
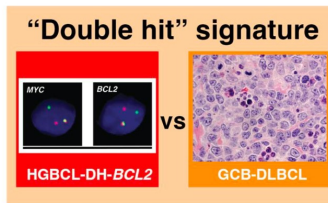
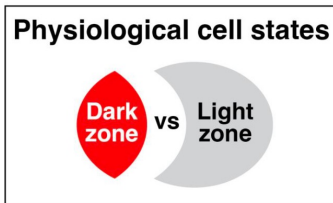
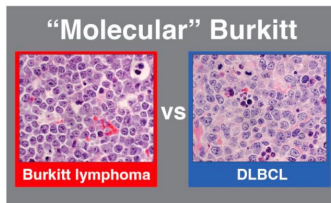
Gene Expression Signatures

PMBCLsig

DZsig

COO

- Cell of Origin
- DZsig → DLBCL90 (Nanostring)



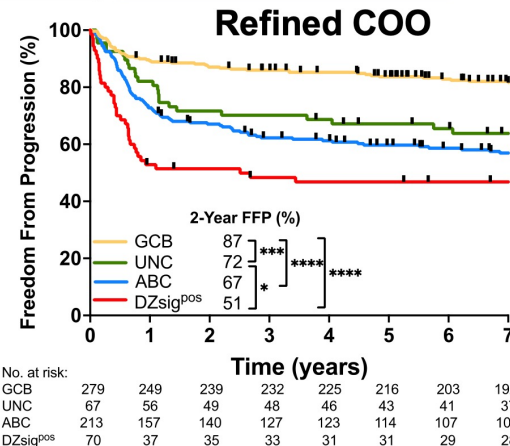
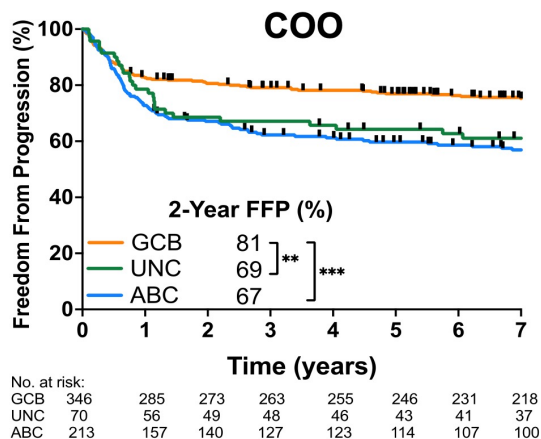
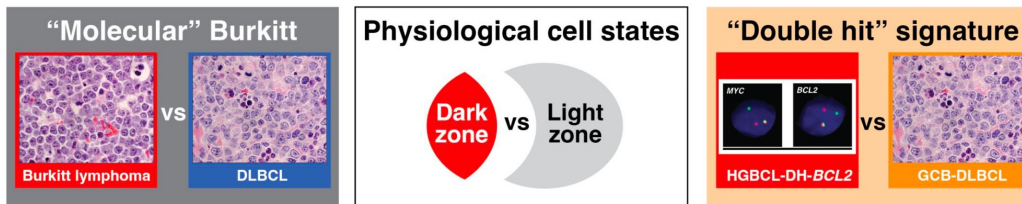
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Gene Expression Signatures

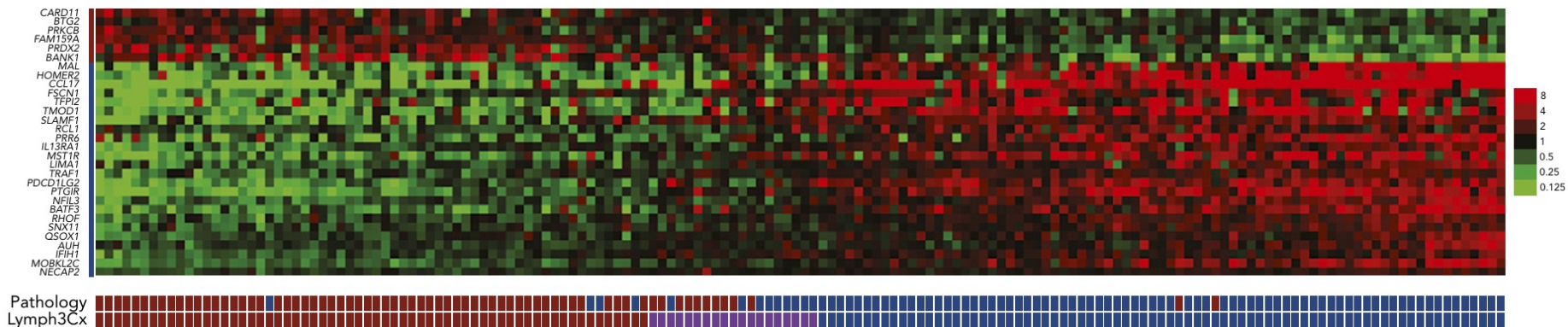
PMBCLsig

DZsig

COO

- Cell of Origin
- DZsig
- **PMBCLsig → Lymph3Cx (Nanostring)**

DLBCL
PMBCL
uncertain DLBCL/
PMBCL



Gene Expression Signatures

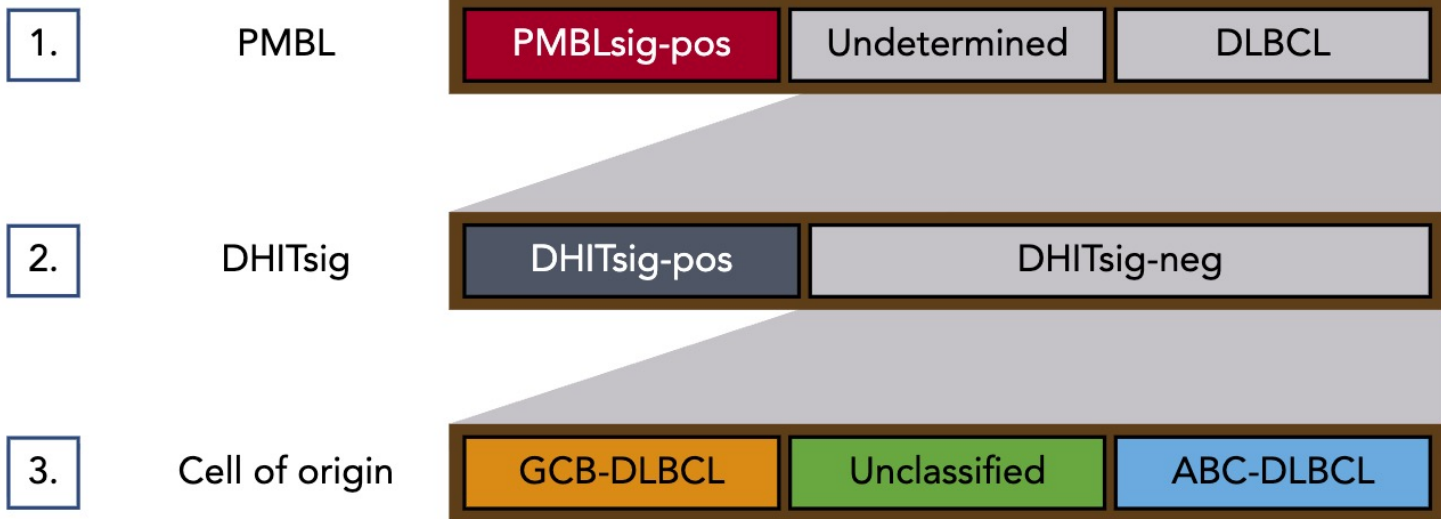
PMBCLsig

DZsig

COO

- FFPE RNA → Nanostring
 - *Will there be / do we need IHC surrogates?*

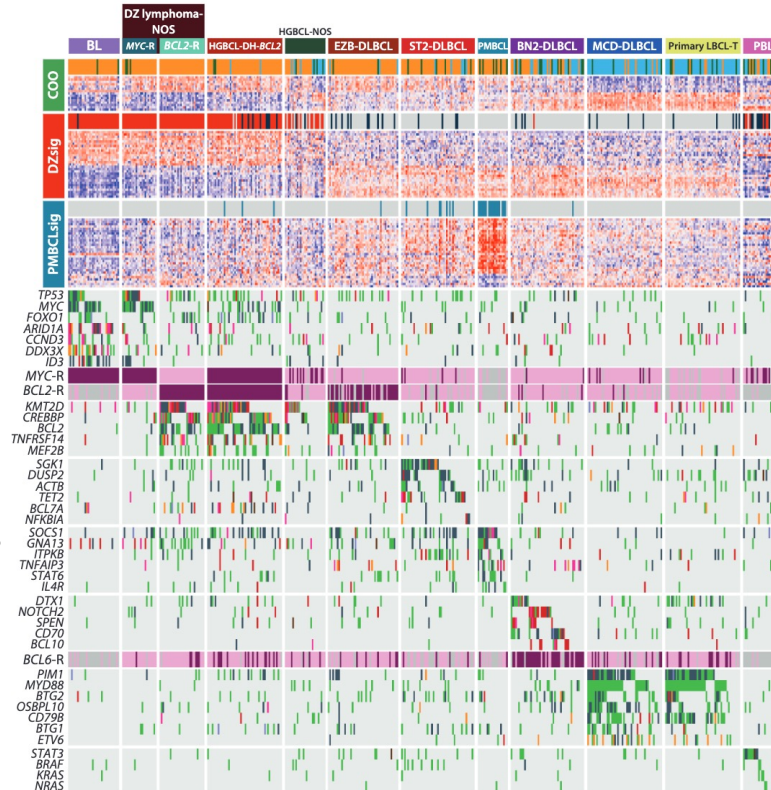
TIER GE signature



What do we already know?

Gene expression signatures
PHENOTYPES

Mutations and rearrangements
GENOTYPES

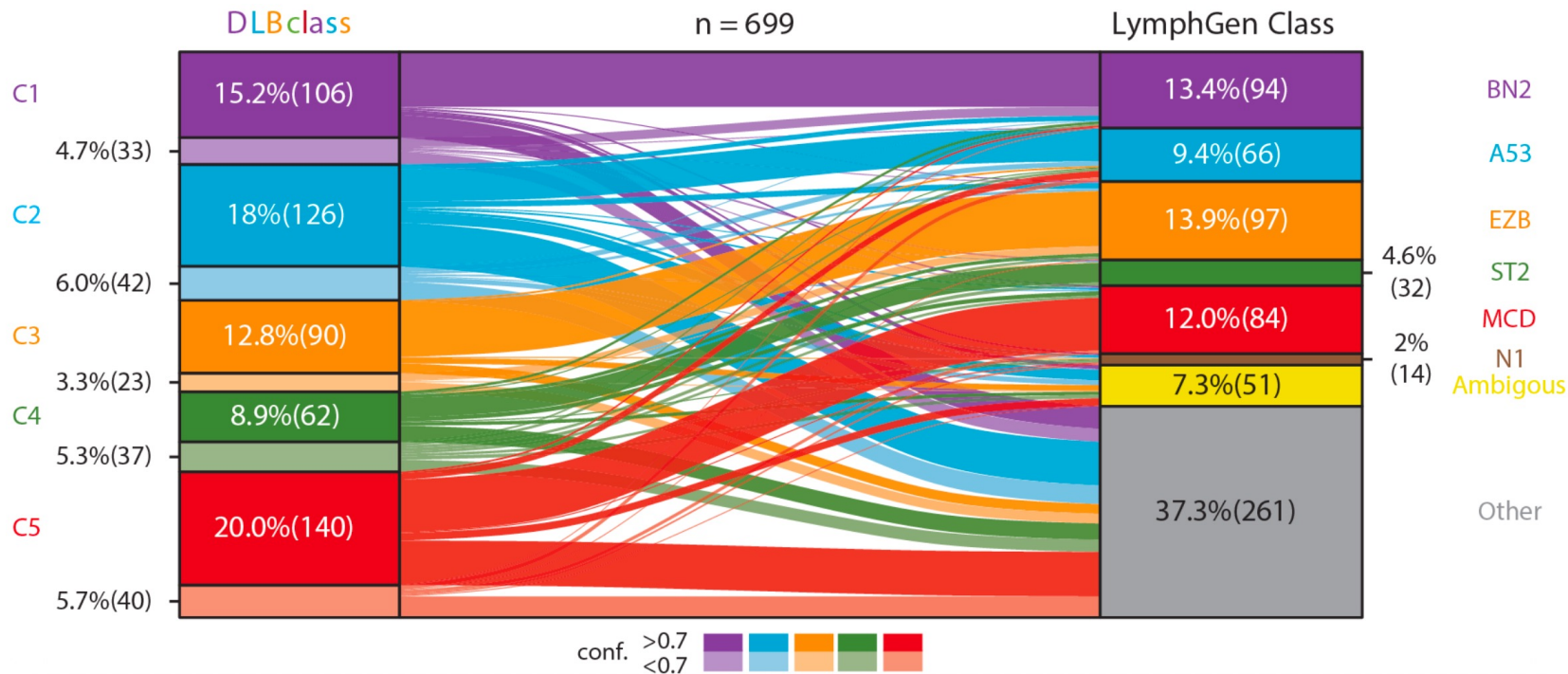


Entities



Genomic Alterations → DLBclass

- Whole exome sequencing + *MYC*, *BCL2*, and *BCL6* FISH



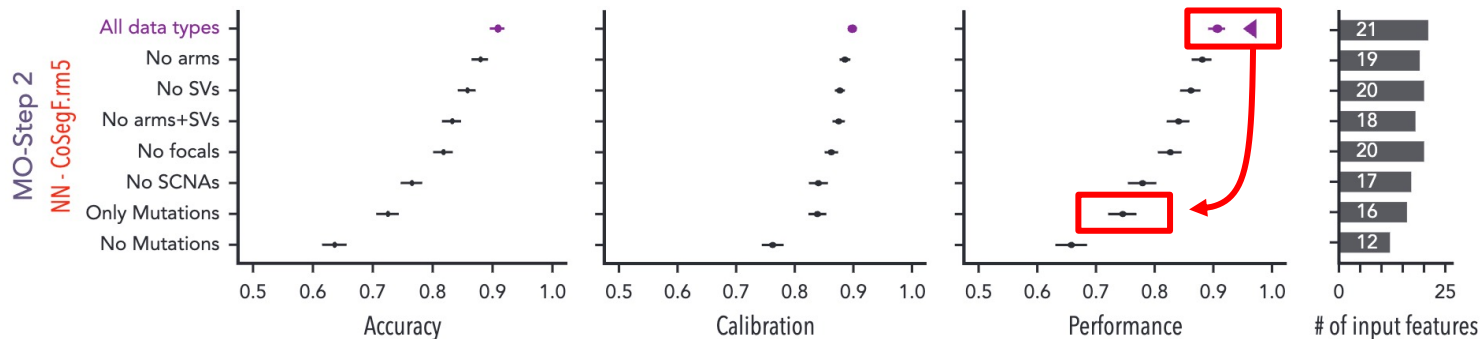
Genomic Alterations → DLBclass

- 163 individual features grouped into 21 metafeatures

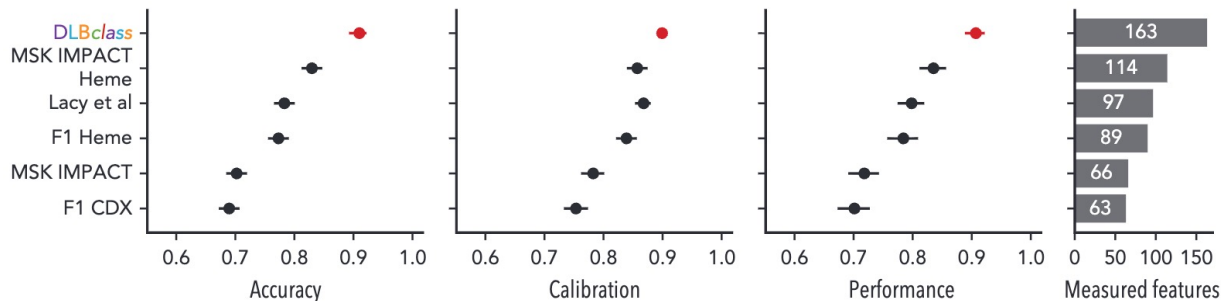
	Metafeatures	Features	
C1	M1 – BCL6	BCL6, <i>BCL6</i>	Mutations Gains Losses SVs
	M2 – NOTCH2 pathway	DTX1, NOTCH2, SPEN	
	M3 – NFKB pathway	BCL10, MYD88 ^{OTHER} , NFKBIE, TNFAIP3, TNIP1	
	M4 – Other	BCL7A, BTG2, CCDC27, CXCR4, EBF1, GNAI2, IKZF3, LYN, POU2F2, RHOA, SMG7, TMEM30A, TUBGCP5, UBE2A, ZEB2, 3q28, 5p, 5q	
	M5 – Immune escape	CD70, FAS, CD58, B2M, FADD, HLA-B	
	M6 – TP53	TP53, 17p	
	M7 – 21q	21q	
C2	M8 – Sum CN arms	6q, 17p, 1q*, 3p, 3q, 5p, 5q*, 6p, 7p, 7q, 9q, 11p, 11q, 12p, 12q, 13q, 18p, 19q, 21q	
	M9 – Sum CN focals	EP300, CD274, ZNF423, 1p13.1, 1p31.1, 1p36.11, 1p36.32, 1q42.12, 2q22.2, 3p21.31, 4q21.22, 4q35.1*, 8q12.1, 9p21.3, 9q21.13*, 10q23.31, 12p13.2, 13q14.2, 13q34, 13q14.2, 14q32.31, 15q15.3, 16q12.1, 17q25.1, 18q23, 19p13.2, 19p13.3, 19q13.32, 1q23.3*, 2p16.1, 3q28, 6p21.1, 7q22.1, 8q24.22, 9p24.1, 11q23.3, 17q24.3, 18q21.32, 18q22.2	
	M10 – BCL2	BCL2, <i>BCL2</i>	
	M11 – Chromatin Modifiers	CREBBP, EP300, EZH2, KMT2D	
C3	M12 – Other	EEF1A1, GNA13, GNAI2, HVCN1, IRF8, MAP2K1, MEF2B, MEF2C, POU2AF1, RAC2, SOCS1, TNFRSF14, 6q14.1, 12q	
	M13 – PTEN plus	PTEN, 10q23.31, 13q14.2	
	M14 – MYC	<i>MYC</i>	
	M15 – Histones	HIST1H1B, HIST1H1C, HIST1H1D, HIST1H1E, HIST1H2AC, HIST1H2BC, HIST1H2AM	
C4	M16 – SGK1 plus	BRAF, CD83, CD274, CXCR4, KLHL6, KRAS, MEF2C, METAP1D, NFKBIA, PTEN, PTPN6, RAC2, SESN3, SF3B1, SOCS1, SGK1, STAT3, TET2	
	M17 – DUSP2	ACTB, CRIP1, DUSP2, LTB, PABPC1, ZFP36L1, YY1	
	M18 – Other	ATP2A2, BCL11A, BTG1, BTG2, CARD11, CCDC27, ETV6, ETS1, GRHRP, HLA-A, HLA-B, HLA-C, IGLL5, IKZF3, IRF2BP2, IRF4, LYN, METAP1D, MYD88, OSBPL10, PIM1, PIM2, POU2F2, PRDM1, SF3B1, TBL1XR1, TMSB4X, TOX, ZC3H12A, ZFP36L1	
C5	M19 – MYD88 CD79B	CD79B ^{mut} /MYD88 ^{L265P}	
	M20 – Sum CN	1q42.12, 6q14.1, 6q21, 6p21.33, 8q12.1, 9p21.3, 19p13.2, 1q32.1, 3p, 3q, 18p, 18q, 18q21.32, 18q22.2, 19q, 19q13.42	
MISC	M21 – 2p16.1	2p16.1	

How do we optimally classify DLBCL?

- All genomic data types are required for optimal DLBCL classification



- Despite their breadth, many commercial assays may be inadequate



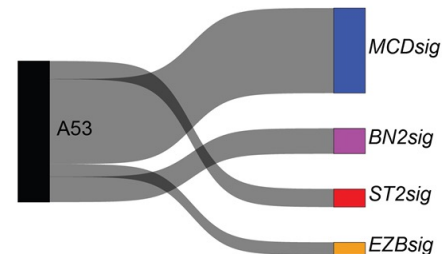
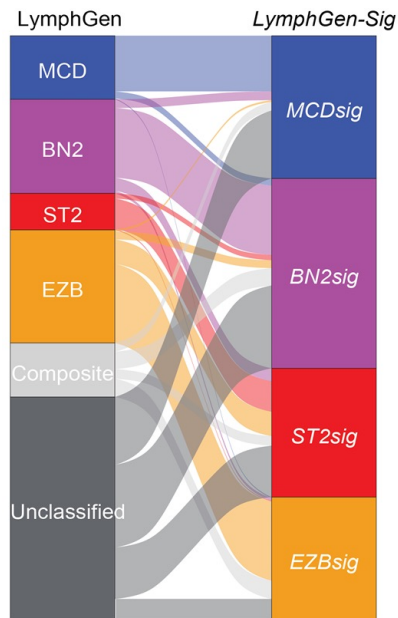
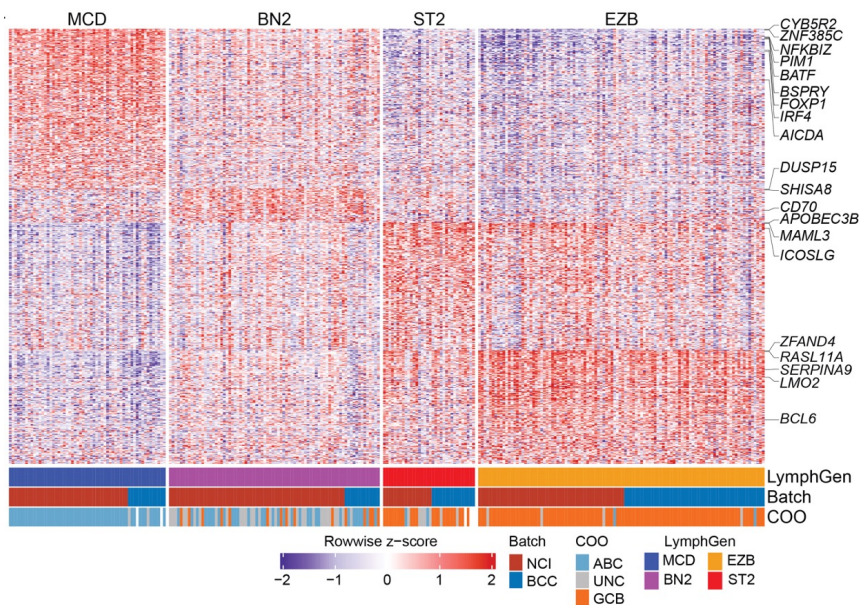
Can we integrate genotype and phenotype?

LymphGen-Sig: Integrating genetic and transcriptional states to predict therapeutic response in DLBCL

Sravya Tumuluru, Alan Cooper, Yanwen Jiang, Connie Lee Batlevi, Will Harris, Gilles Salles, Marek Trnny, Georg Lenz, Franck Morschhauser, Fabrice Jardin, Sandhya Balasubramanian, Matthew Sugidono, Alex F. Herrera, Justin Kline, James K. Godfrey

doi: <https://doi.org/10.64898/2026.02.20.26346725>

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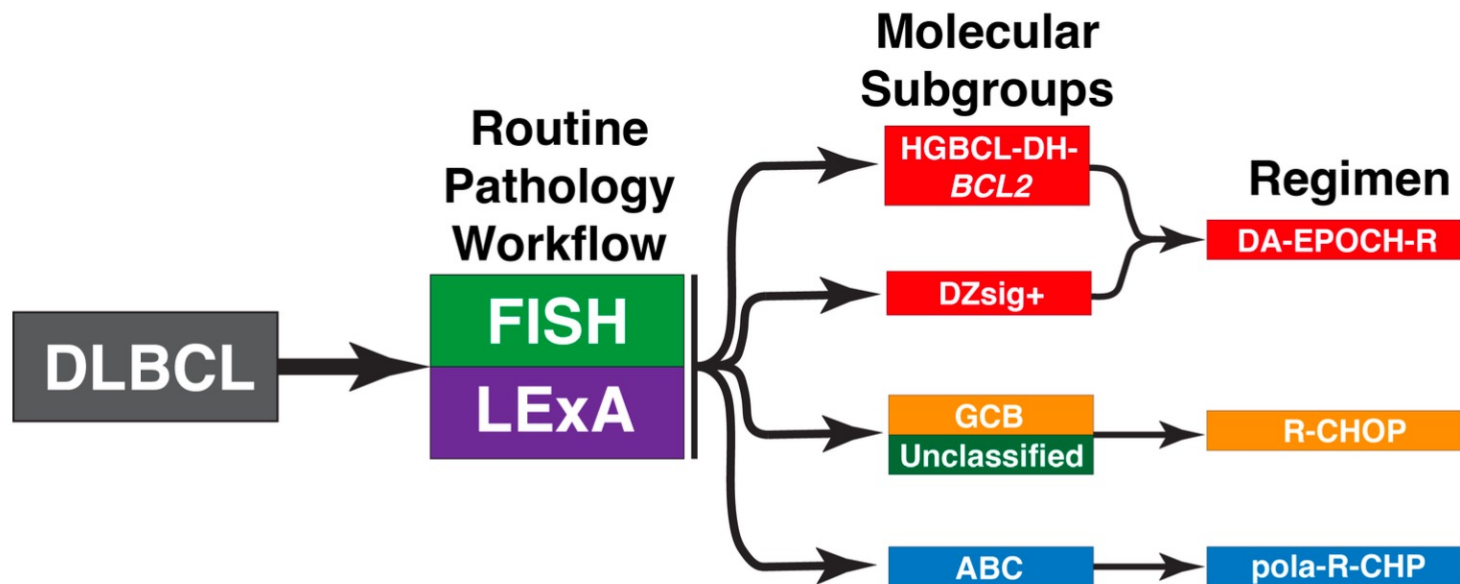


NCI/BCCA- A53 DLBCLs

LymphGen-Sig class

		MCDsig	BN2sig	ST2sig	EZBsig
LymphGen class	A53	47 (60%)	14 (18%)	10 (13%)	7 (9%)
	MCD	64 (88%)	8 (11%)	0 (0%)	1 (1%)
	BN2	10 (9%)	80 (74%)	15 (14%)	3 (3%)
	ST2	0 (0%)	6 (14%)	35 (83%)	1 (2%)
EZB	2 (2%)	9 (7%)	28 (22%)	91 (70%)	

BC Cancer Treatment Selection



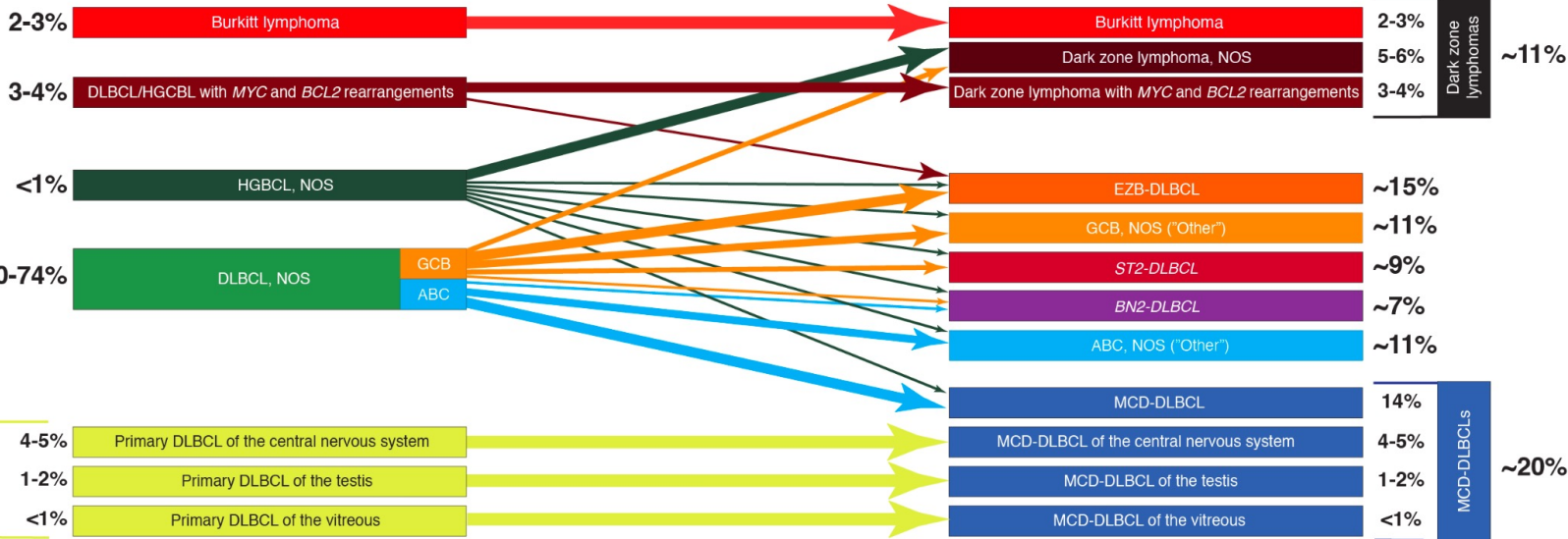
LExA: Lymphoma Expression Assay
Routine since October 2023

What will the future look like?

- In my opinion, we can't let **perfect** be the enemy of **good**

- Example: *Hans IHC COO* is utilized and informative despite limitations

Need DA-EPOCH-R
(+/- BsAb, consolidation?)



**WHO HAEM-5
Category**

**Proposed genomics-
informed category**


Need Pola-R-CHP
(+/- BTKi, CNS ppx?)



What will the future look like?

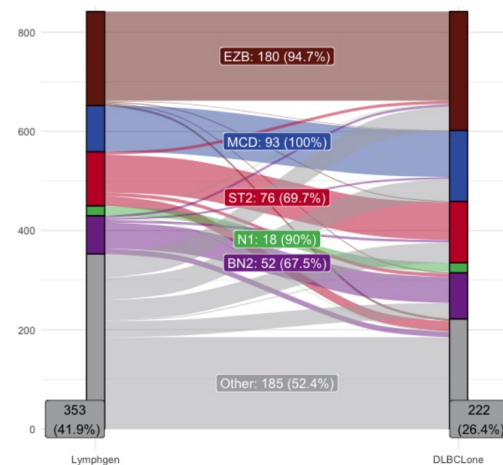
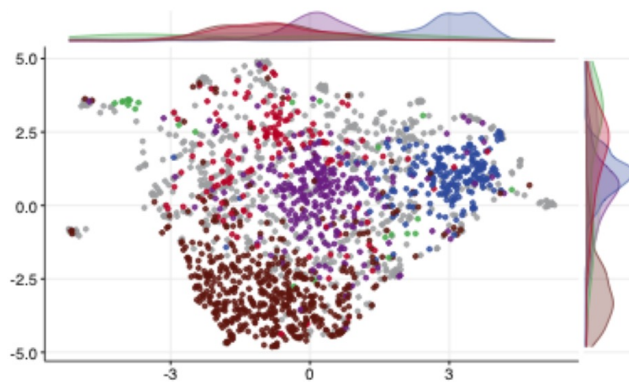
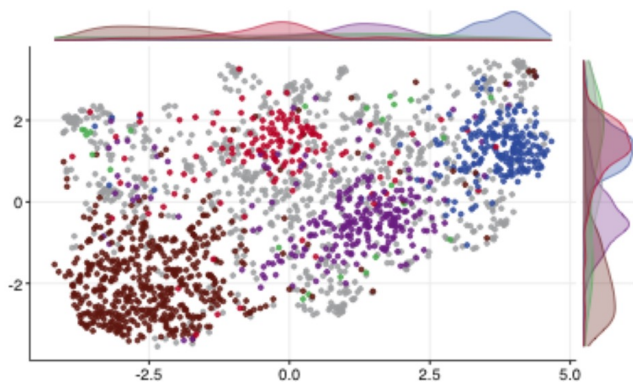
- In my opinion, we can't let **perfect** be the enemy of **good**
 - *Example: Hans IHC COO is utilized and informative despite limitations*
- Adaptable systems are key
 - *Example #1: Nanostring assays >> bulk RNA-seq*
 - *Example #2: DLBCLone*

DLBCLone: A unified framework for neighbourhood-based genetic subtyping of lymphomas

Luke Klossok, Kostiantyn Dreval, Manuela Cruz, Jasper C.H. Wong, Sierra Gillis, Brett Collinge, Christian Steidl, David W. Scott, Laura K. Hilton,  Ryan D. Morin

doi: <https://doi.org/10.1101/2025.09.18.25335809>

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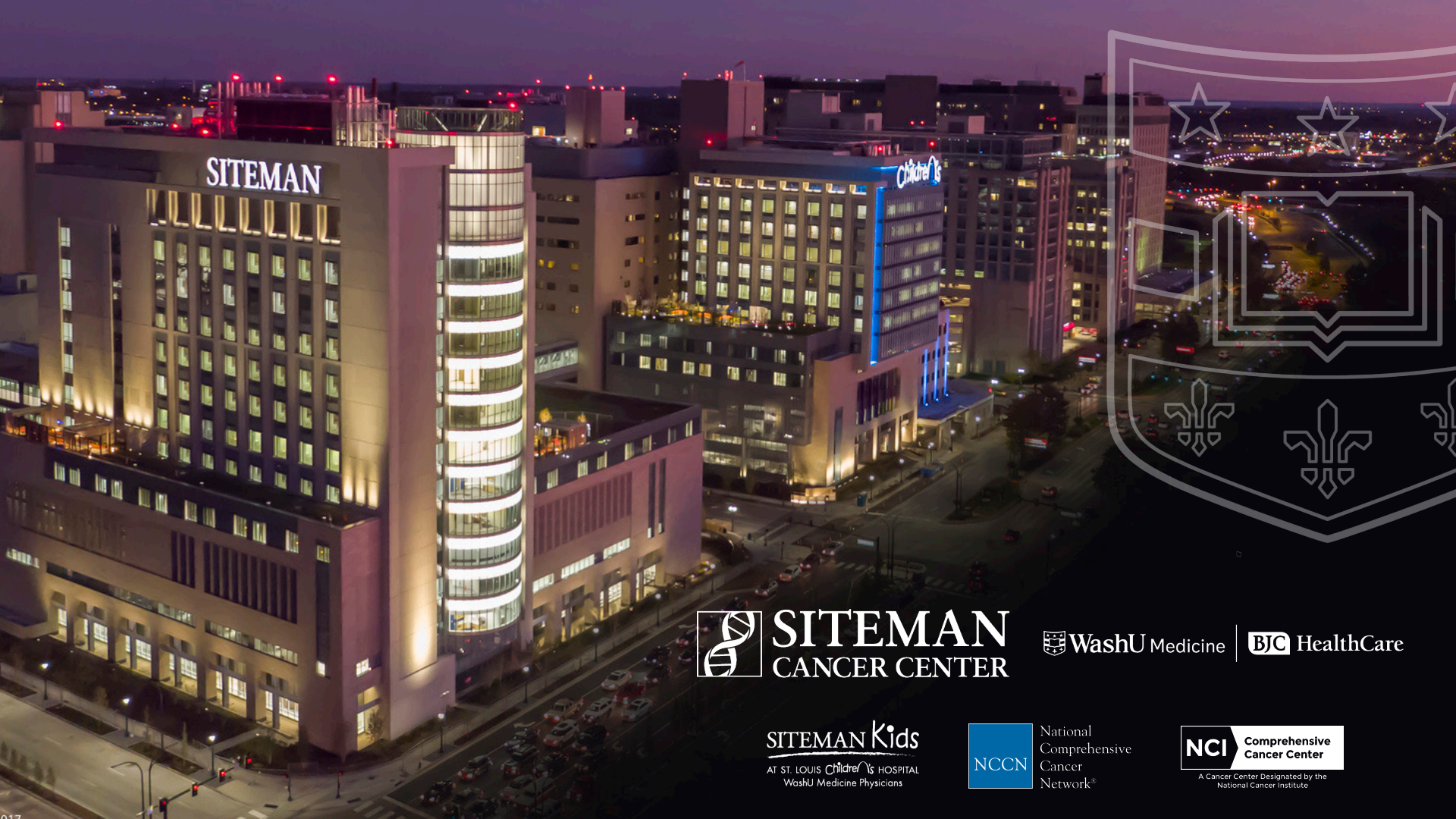


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 - *Example #2: DLBCLone*
- While unified **diagnostic** classification is vital (i.e., WHO + ICC), we don't need to wait for one international **prognostic/risk** stratification approach or **treatment algorithm** to let biology inform management
- We are stuck in a catch-22 → insurance won't reimburse B-NHL NGS/GEP due to lack of integration into guidelines/trials/product labels, but we don't apply NGS/GEP (on or off trial) due to lack of reimbursement
 - *If we reimburse BCR clonality assays, there's no reason to deny reasonable implementation of NGS to aid in diagnostic assessments*



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