Molecular profiling in diffuse large B cell lymphomas

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Diffuse large B cell lymphoma

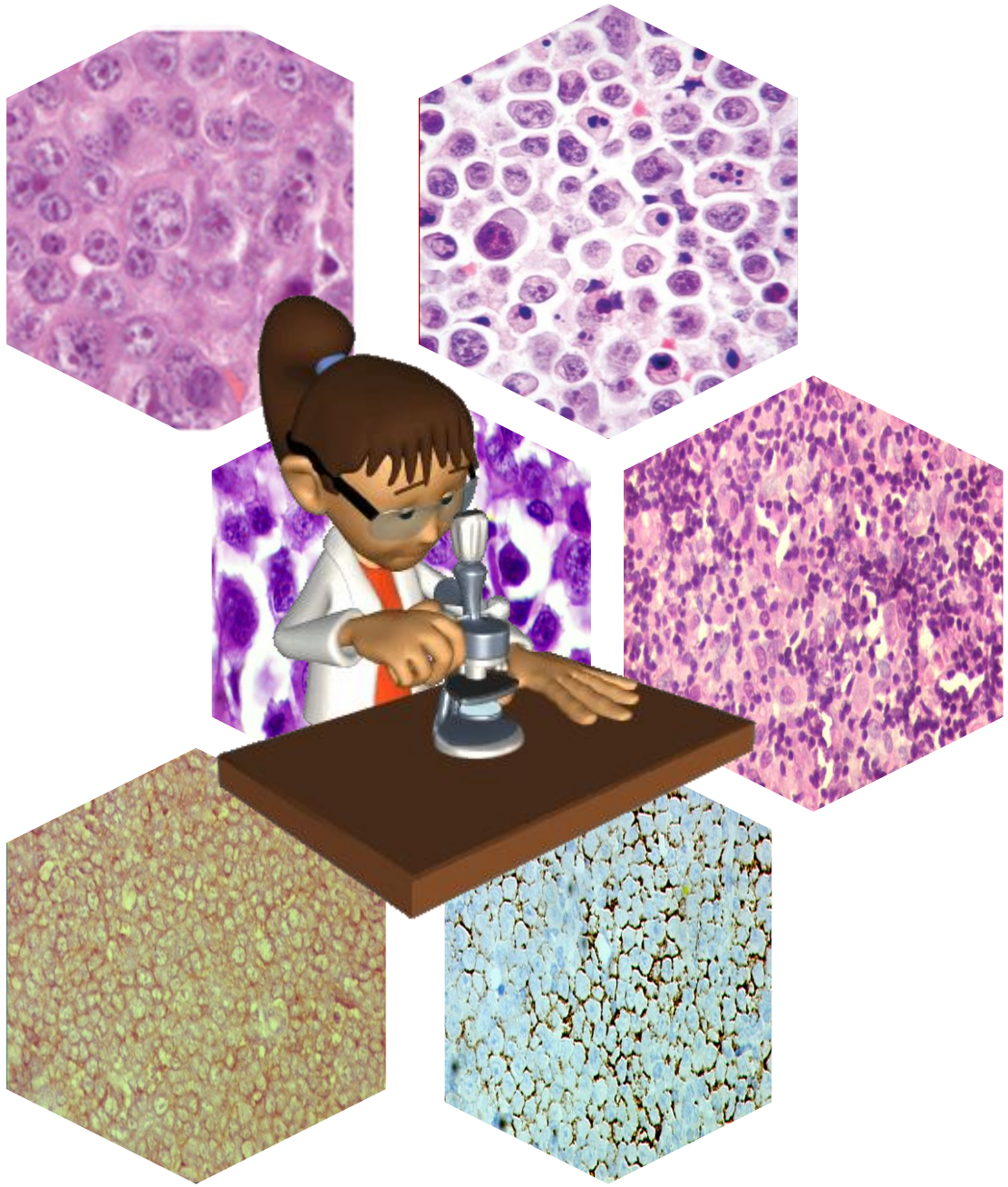
CD20 + Large cell lymphoma

T cell rich B cell variants

CD20 negative large cell lymphomas

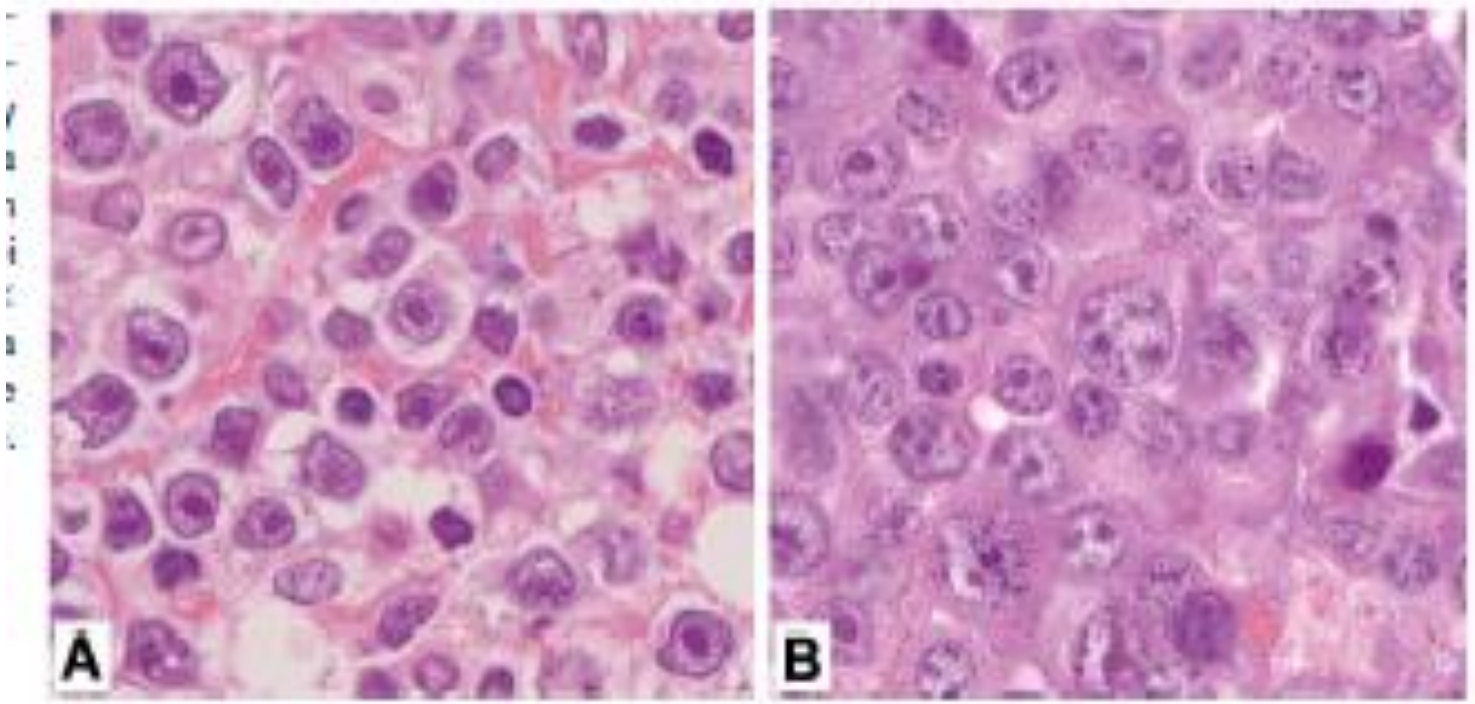
High grade B cell

Unique variants of Large cell lymphomas



Morphology

Immunoblastic morphology but not the immunohistochemical GCB/nonGCB classifier predicts outcome in diffuse large B-cell lymphoma in the RICOVER-60 trial of the DSHNHL



949 patients - Immunoblastic morphology was associated with poor prognosis when Hans algorithm failed. But criteria for this morphology has low concordance ***Blood*.** **2010;116(23):4916-4925**

Anaplastic morphology is associated with CD30 expression has aggressive course, because of associated poor prognostic factors, such as high IPI and MYC/BCL2 co-expression Am J Surg Pathol 2017;41(10):1322–32.

REVIEW ARTICLE OPEN

LYMPHOMA

Leukemia (2022) 36:1720 – 1748

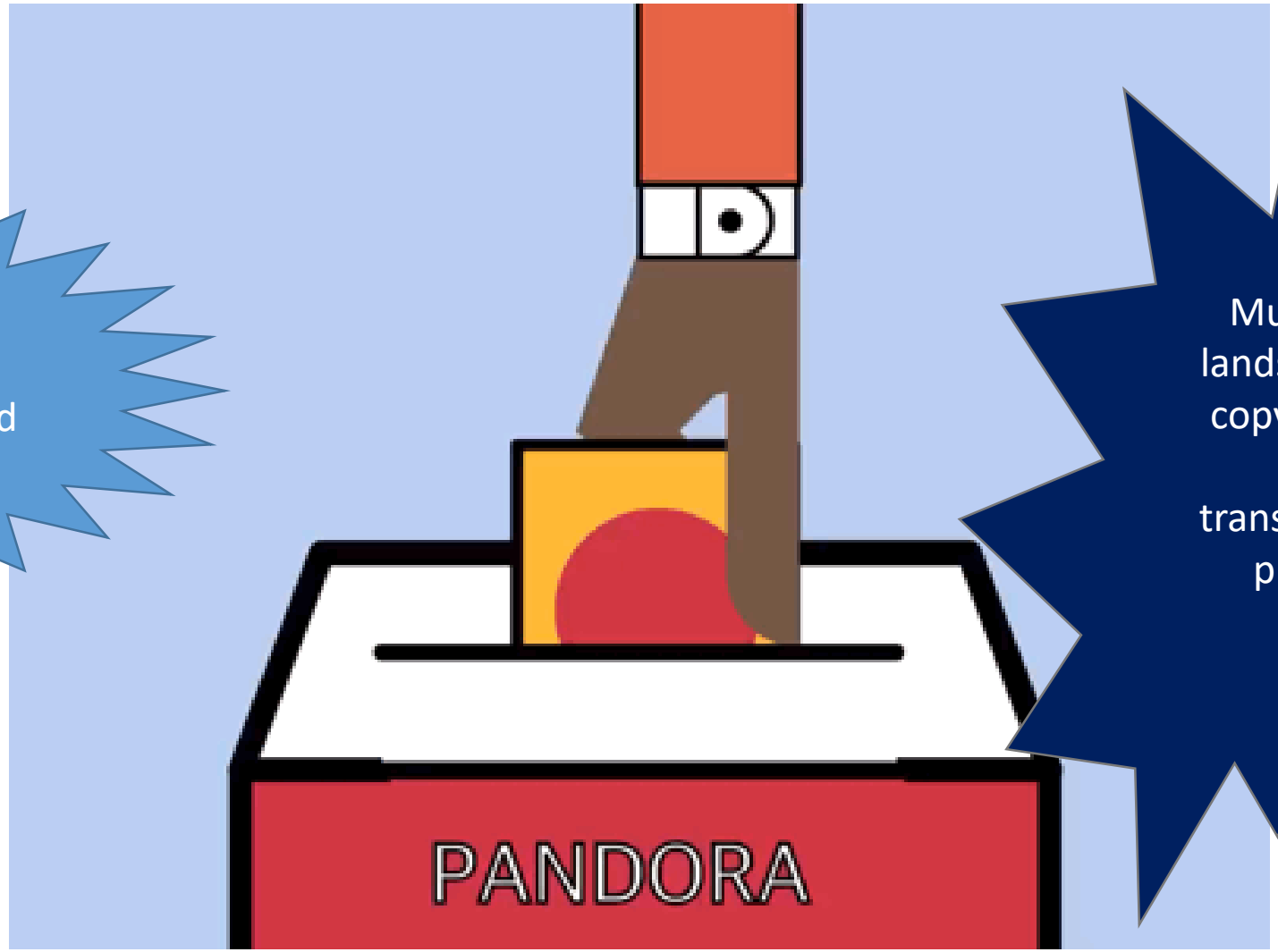
The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms

The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee

WHO 2022	ICC 2022
DLBL NOS	DLBL NOS – GCB/ ABC
T cell / histiocytic rich B cell lymphoma	
High grade B cell lymphoma with 11 q aberration	Large B cell lymphoma with 11 q aberration
Large cell lymphoma with IRF4 rearrangements	
ALK + Large B cell lymphoma	
Lymphomatoid granulomatosis	
Intravascular Large B cell lymphoma	
	Nodular lymphocyte predominant B cell lymphoma
Primary DLBL of immune privileged sites	Primary DLBL of CNS Primary DLBL of tested
Primary cutaneous DLBL of leg type	
EBV positive Mucocutaneous ulcer	
EBV + DLBL NOS	
EBV + polymorphic B cell lymphoproliferative disorder	
DLBL associated with chronic inflammation	
Fibrin associated DLBL	
Fluid overload associated DLBL	

WHO 2022	ICC 2022
-	HHV8/EBV negative Primary effusion based lymphoma
HHV8+ associated disease	
HHV8 positive germinotrophic DLBL	
HHV8 + DLBL	
PEL	
Burkitt lymphoma	
High grade B cell lymphoma with MYC/bcl2 rearrangement	High grade B cell lymphoma with MYC/bcl2 rearrangement
	High grade B cell lymphoma with MYC/bcl6 rearrangement
	High Grade B cell NOS
Primary mediastinal large B cell lymphoma	
Mediastinal Gray zone lymphoma	

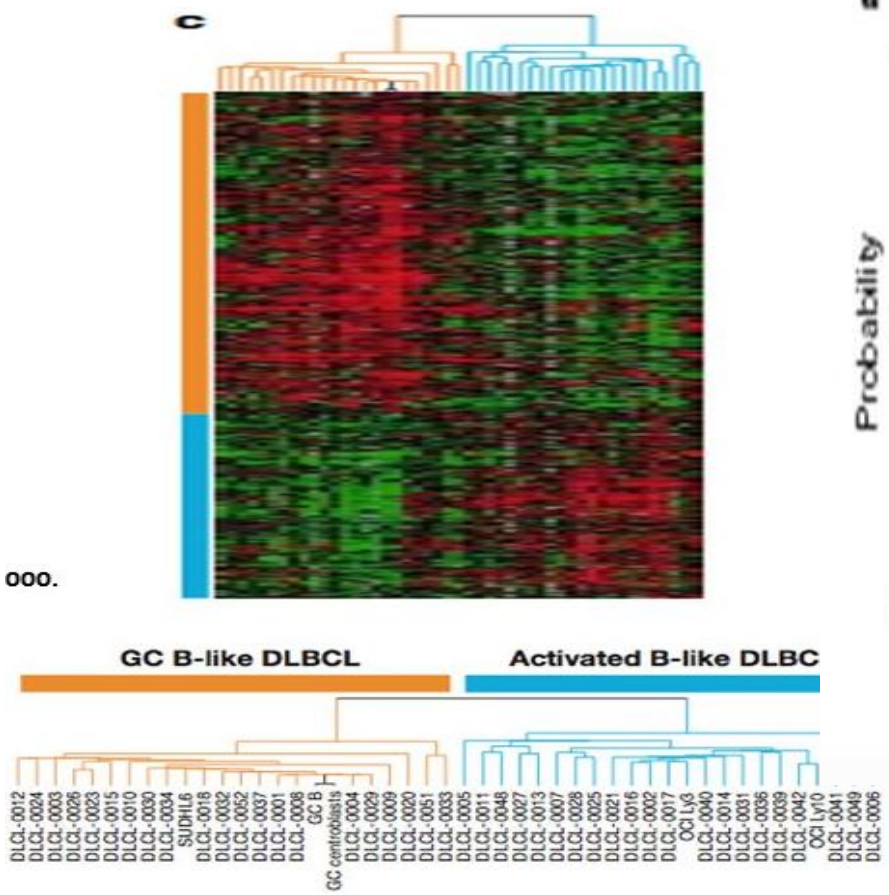
Gene expression profiling using microarrays , CGH and Nanostring platform



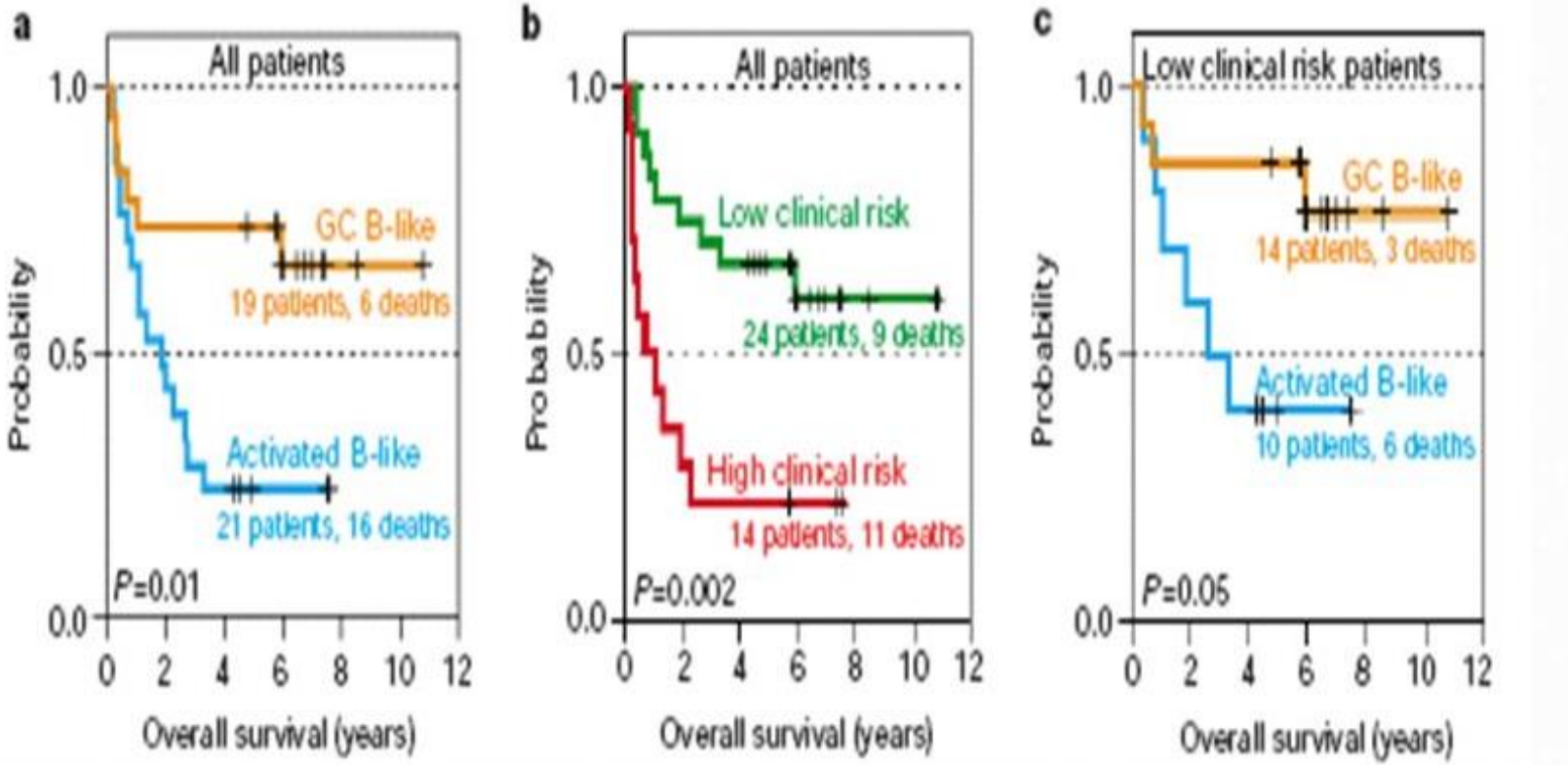
Mutational landscape and copy number with transcriptional profiling

Existing Molecular profiling techniques

Cell of origin



Alizadeh et al Nature. 2000;403(6769):503-511

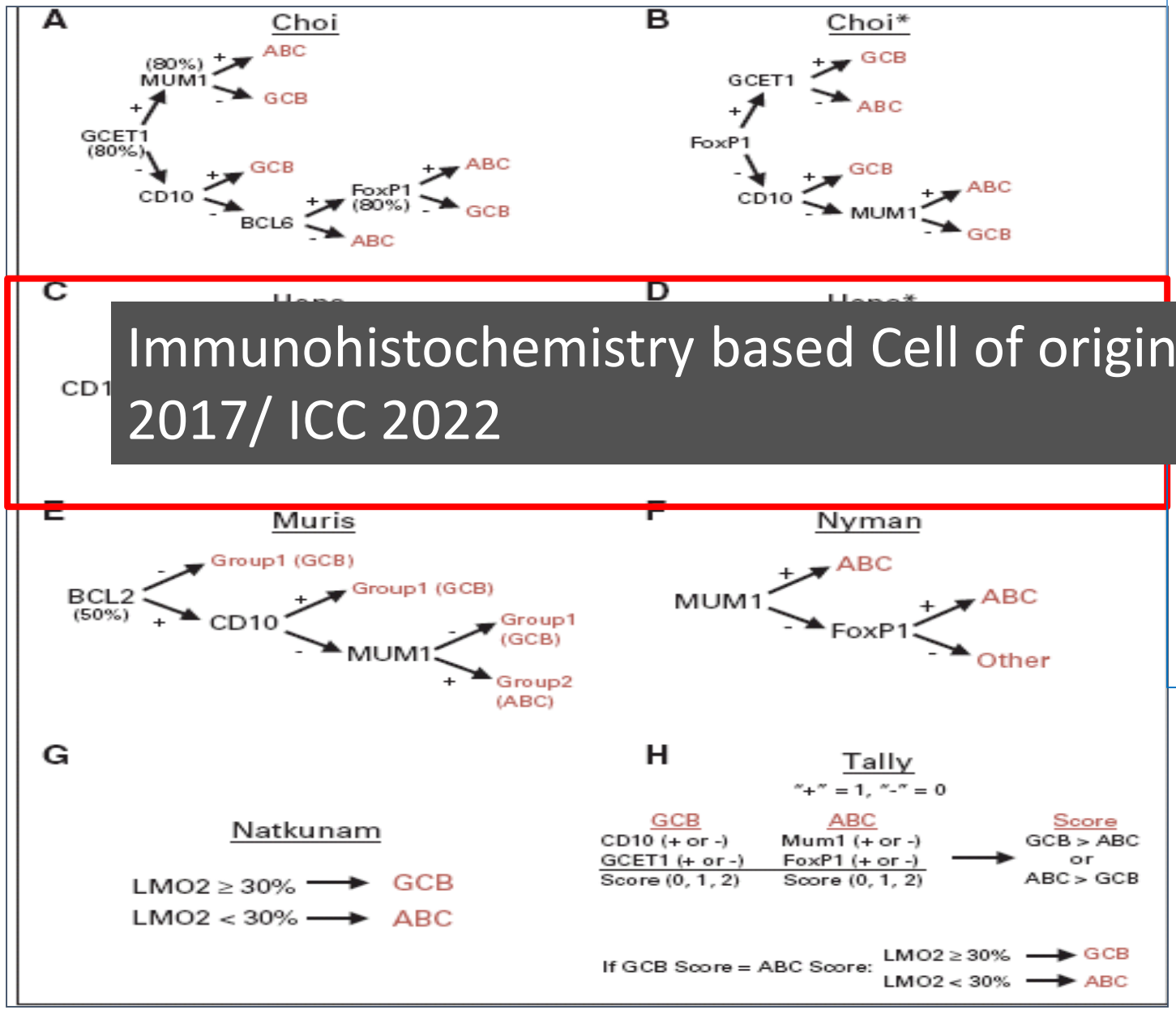


Rosenwald A et introduced a third UC group and hence term GCB Vs Non-GCB

GCB-DLBCLs - alterations in chromatin-modifying enzymes, PI3K signaling, Gα - migration pathway components and *BCL2*

ABC DLBL - increased NF-kB activity, and a subset genetic alterations in NF-kB modifiers and proximal components
of the B cell receptor (BCR) pathway and perturbed terminal B cell differentiation

Immunohistochemistry classifiers



Immunohistochemistry based Cell of origin are mandatory as per WHO 2017/ ICC 2022

- proportion of misclassified cases as high as 60% for some algorithms when compared with GEP
- Choi , Nyman and Hans algorithm high concordance with microarray data
- All of the algorithms divided patients into groups with significantly DFS/OAS but with different hazard ratios -independent of the International

Adults/Lymphoma

Study Phase III Trial LNH 03-2B – used CD10, BCL6, MUM1, MYC, and BCL2 and coexpression of MYC/BCL2 . Non-GCB tumors had worse PFS and OS with R-CHOP Vs R-ACVBP. JCO 2014; 36

In a meta-anaylsis -no significant difference in OS between patients designated as GCB or non-GCB subtype by the Hans method but GCB subtype by the Muris method were compared with ABC patients significant differences in OS and PFS were observed. Clin Lymph Myeloma 2014

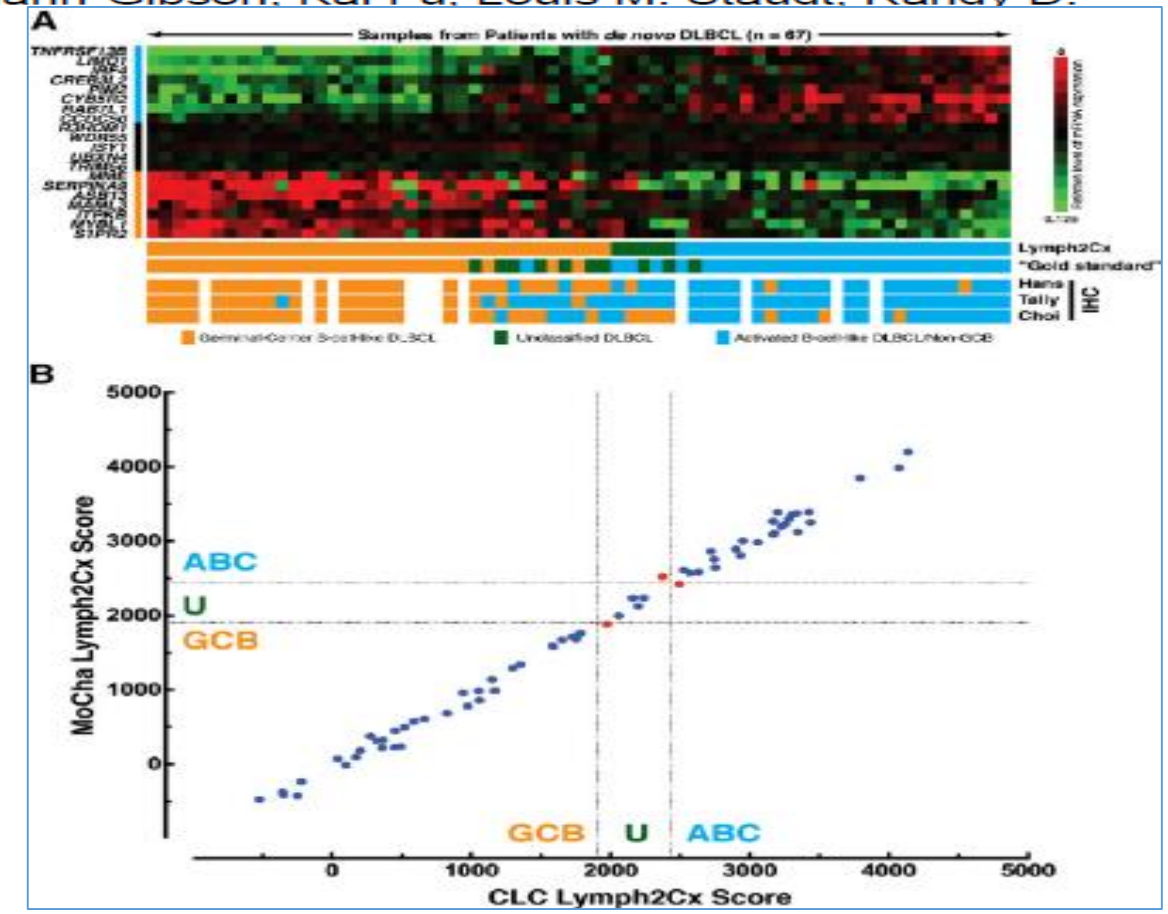
blood®
2014 123: 1214-1217
doi:10.1182/blood-2013-11-536433 originally published online January 7, 2014

Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue

David W. Scott, George W. Wright, P. Mickey Williams, Chih-Jian Lih, William Walsh, Elaine S. Jaffe, Andreas Rosenwald, Elias Campo, Wing C. Chan, Joseph M. Connors, Erlend B. Smeland, Anja Mottok, Rita M. Braziel, German Ott, Jan Delabie, Raymond R. Tubbs, James R. Cook, Dennis D. Weisenburger, Timothy C. Greiner, Betty J. Glinsmann-Gibson, Kai Fu, Louis M. Staudt, Randy D. Gascoyne and Lisa M. Rimsza

FFPET biopsies of de novo DLBCL that had been classified using the original GEP methods and published algorithm. Out of 95 gene - Fifteen genes, along with 5 housekeeping genes, were selected for COO assignment - The Lymph2Cx assay

The Lymph2Cx assay provided concordant COO calls in 96% of 49 repeatedly sampled tumor and in 100% of 83 FFPET biopsies tested across reagent lots. Critically, no frank misclassification (activated B-cell–like DLBCL to germinal center B-cell–like DLBCL or vice versa) was observed. *J Clin Oncol 2015;33:2848-2856. ©*



Two prospective German clinical trials (RICOVER-60 and R-MegaCHOEP) using Nanostring analysis of FFPE samples failed to show any significant difference in PFS or OS between GCB and ABC subtypes J CO 2017

What is the state of COO based classification in 2022

- It is reproducible and has some prognostic benefit:- 4 signatures(LymphC2X COO, MYC activity, B-cell receptor signaling, oxidative phosphorylation, and immune response) in 175 samples of the HOVON-84 trial on a panel of 117 genes using the NanoString platform -COO ABC-type was confirmed as poor prognosis. Cancers 2022, 14, 1346
- However COO distinction does not fully account for the heterogeneous responses and outcomes following either R-CHOP therapy or newer targeted therapy

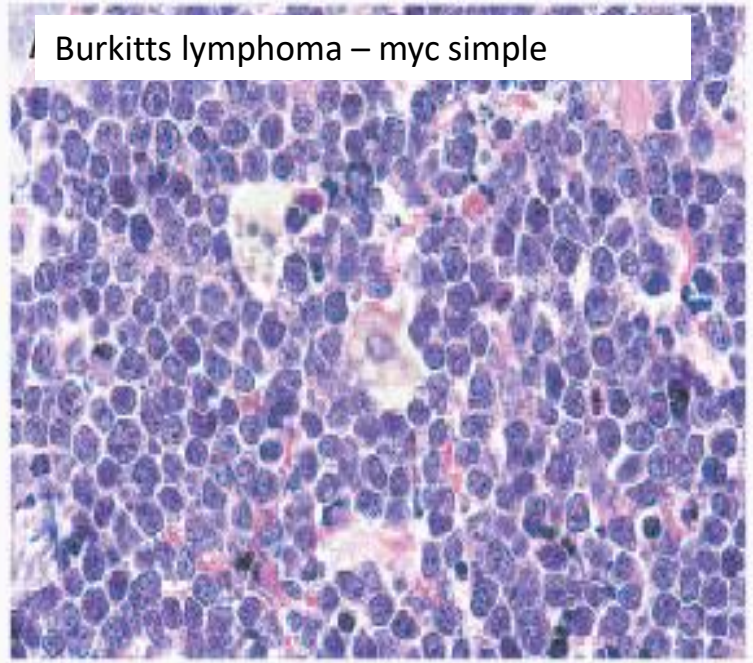
Subsequent gene expression studies

- B-cell–associated gene signatures (BAGS) - Gene expression signatures unique to naive, centroblast, centrocyte, memory, and plasmablast B cells from human tonsils were identified and used to classify DLBL from three trials. BAGS2Clinic Updated on Nanostring platform -Survival analysis of the memory B-cell and plasmablastic subgroups, defined as ABC lymphomas, showed inferior PFS and OS. J Clin Oncol. 2015;33(12):1379-1388. Blood Adv. 2018 Jul 10; 2(13): 1542–1546.
- Stromal gene signatures in DLBL: “germinal-center B-cell,” “stromal-1,” reflected extracellular-matrix deposition and histiocytic infiltration behaved better than “stromal-2” reflected tumor blood-vessel density in CHOP /R-CHOP treated group . NEJM 2008;27:359:2313-23

New Eng Journal Of Medicine 2006; 354:2419-30

Molecular classification aggressive B cell Lymphomas

- **"Myc-simple" - lymphomas with *IG-myc* fusions and a low chromosomal complexity score (<6) No *IGH-BCL2* and *BCL6* translocations.**
- **"Myc-complex" - lymphomas with non–*IG-myc* fusions or with *IG-myc* fusions that have a high chromosomal complexity score, an *IGH-BCL2* fusion, or *BCL6* breakpoint, or any combination of these – Double hit or triple Hit lymphomas**
- **"Myc-negative" tumors comprising *myc*-negative lymphomas.**


Burkitts lymphoma – myc simple

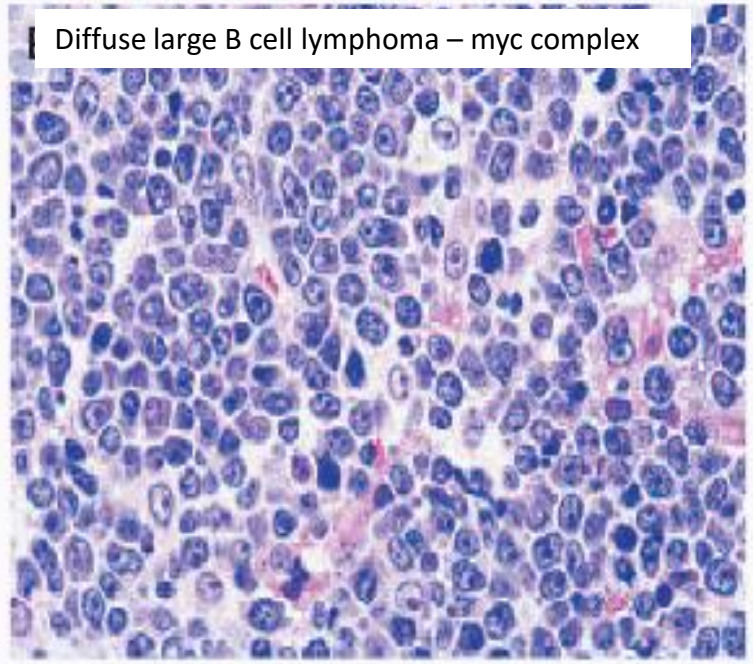

Diffuse large B cell lymphoma – myc complex

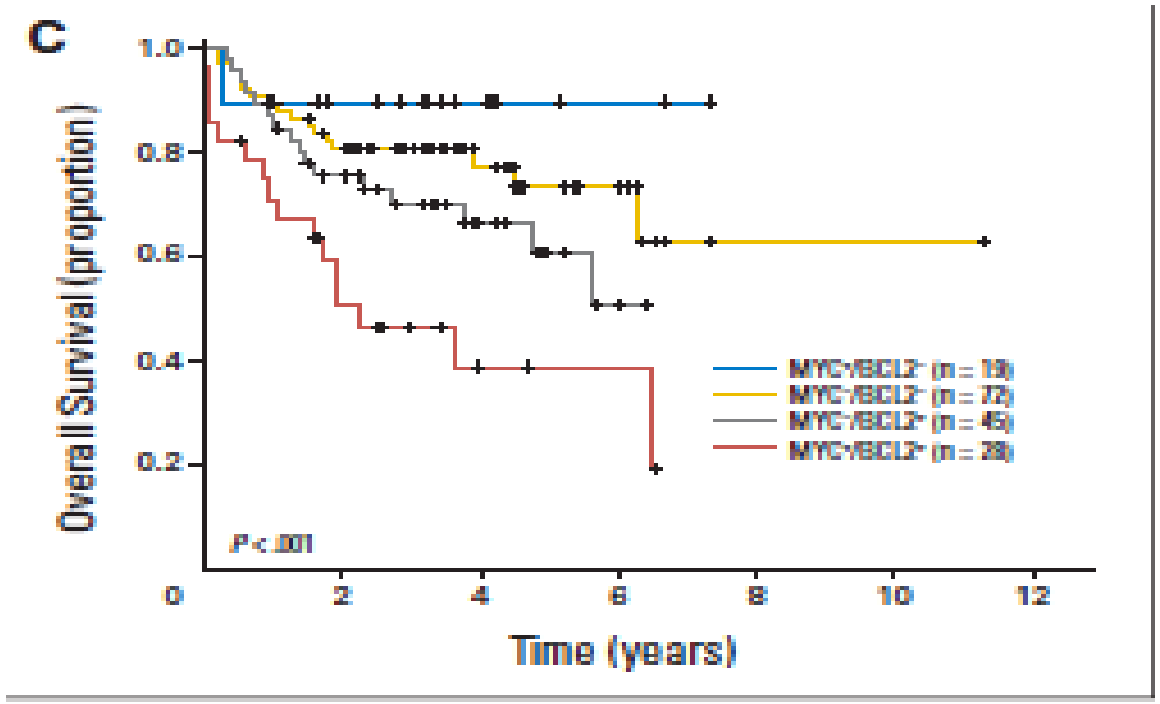
Table 1. Select recent studies in aggressive B-cell lymphoma looking at (differential) outcomes of patients with HGBL and DHL/THL

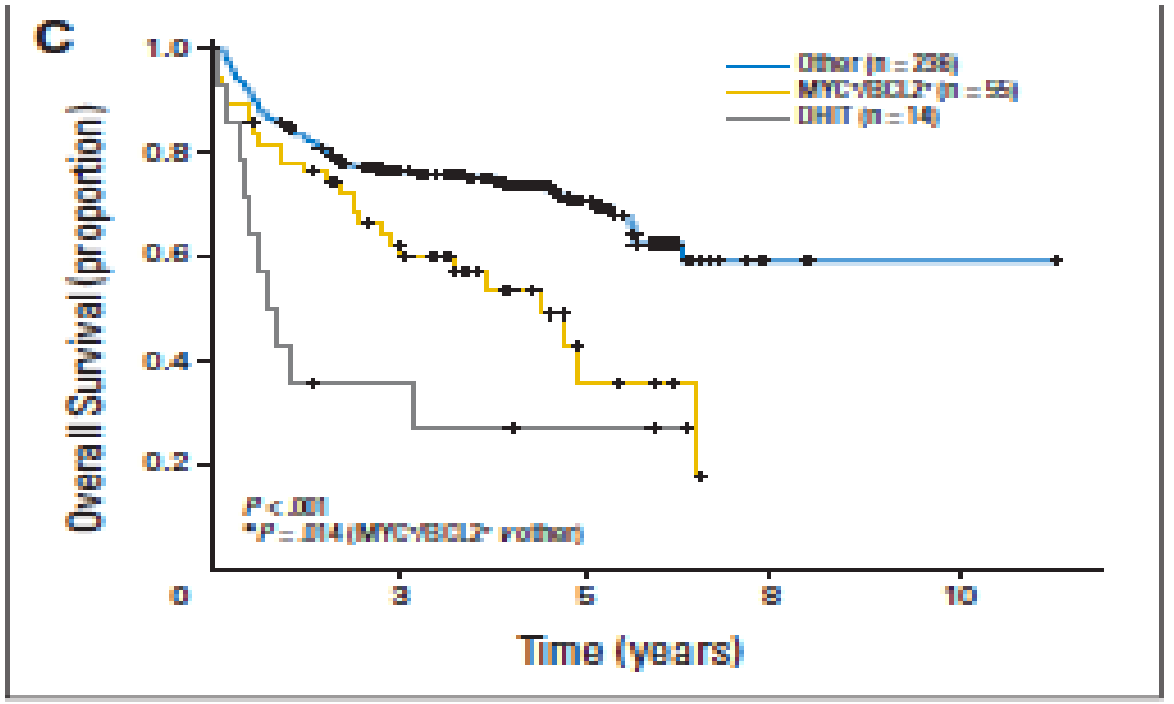
Study	N	Patient population/study	DHL/THL %	Treatment	Outcome
Rosenwald et al[14]	2383: (*MYC*-R in 11%)	DLBCL and HGBL/ retrospective analysis of prospective and patient registry studies	5.8%	R-CHOP	*MYC*-R was associated with shorted PFS and OS; neg. prognostic impact of *MYC*-R only with *BCL2* and/or *BCL6* and an *IG* partner.
Dunleavy et al[15]	5				4-year EFS and OS were 71% and 77%. No difference for SH vs DHL/THL.
Chamuleau et al[29]	82	*MYC*-R DLBCL/prospective, single-arm multicenter trial	Approx 27%* had *MYC*-R (SH); 73% had DHL/THL	R-CHOP + lenalidomide	2-year EFS and OS were 63% and 73%.
Leppä et al[17]	139	DLBCL and high-IPI score/high-risk cohort/ prospective, single-arm, multicenter trial	12% had DHL	Dose-dense chemo (MTX/R-CHOEP-14, ARA C	5-year FFS and OS were 74% and 83%. No significant worse outcome for DHL group.
McMillan et al[16]	111	DLBCL and IPI 3–5; 12% had HGBL/prospective study.	12% had DHL; FISH performed in approx. 50%	R-CODOX-M/R-IVAC	2-year PFS and OS were 68% and 76%. No worse out-come for DHL.
Laude et al[18]	160	All patients had HGBL/retro-spective study	81% had DHL; 19% had THL	R-CHOP vs intensive chemotherapy	At 32 months, 2 and 4-year PFS were 40% and 28% for R-CHOP; 57% and 52% for intensive therapy.

With RCHOP poor behaviour with intensive regimens(DA REPOCH) better behaviour

Hematology Am Soc Hematol Educ Program 2021; 2021 (1): 157–163.

Concurrent Expression of MYC and BCL2 in Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone





J Clin Oncol 2012;30:3452-3459.

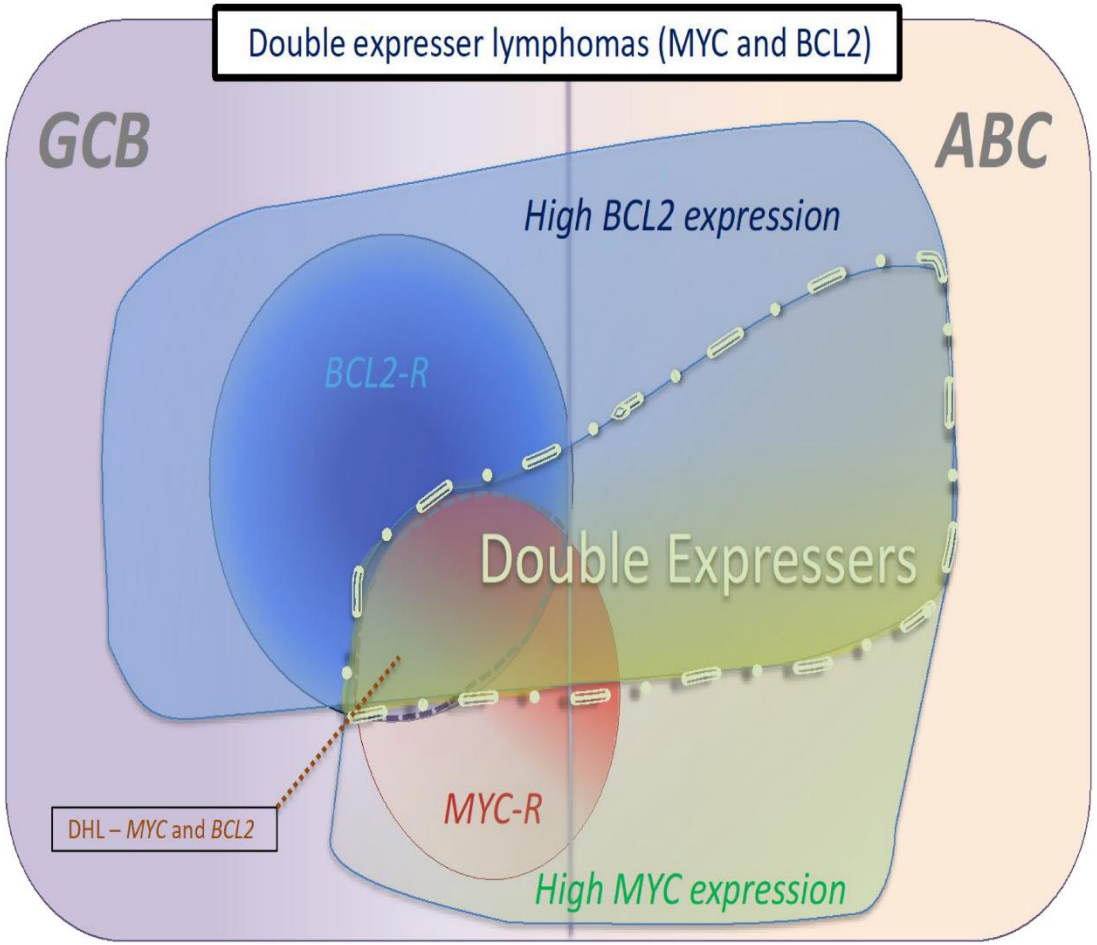
➢**Immunohistochemical analysis for MYC and BCL2(double expressor) used as a surrogate for MYC and BCL2 cytogenetic status (True double hit)**

➢**The immunohistochemical threshold of ≥40% for MYC and >50% for BCL2 is used to define DEL.**

Several problems with IHC scoring, including inter-user variability, different manufacturers or clones of antibody and variable laboratory operating procedures

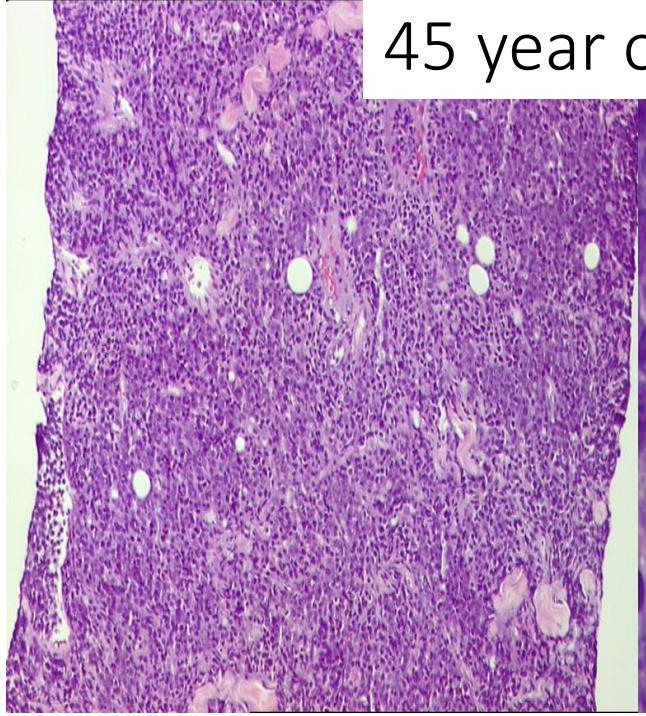
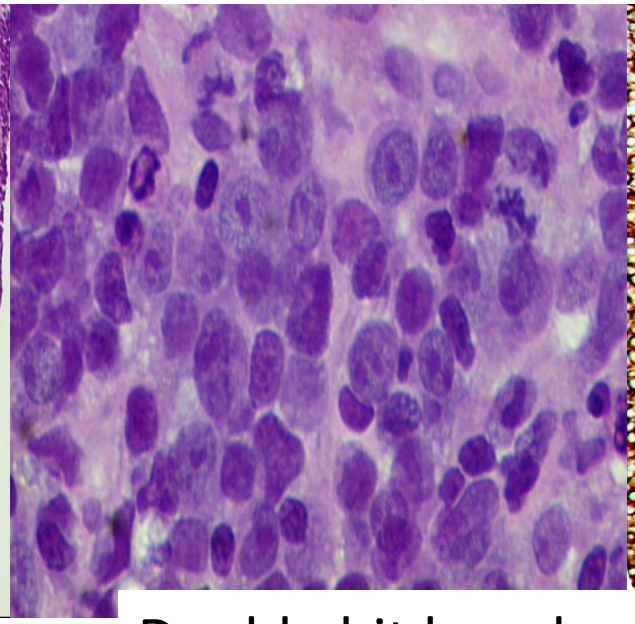
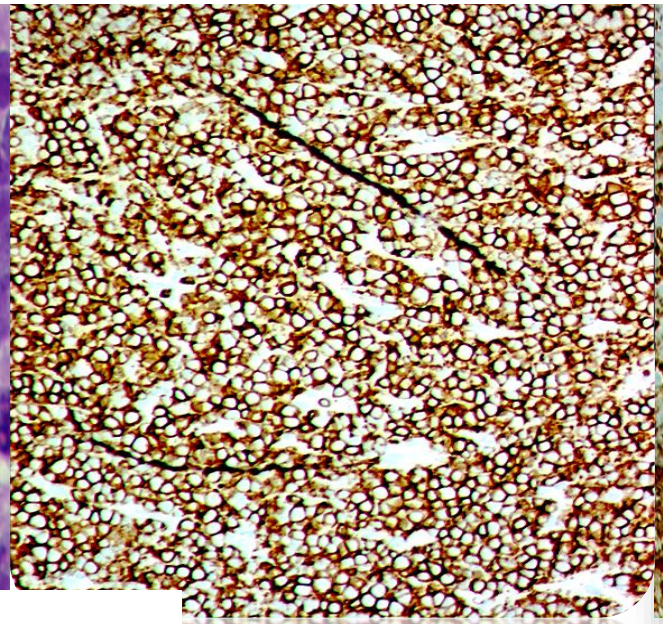
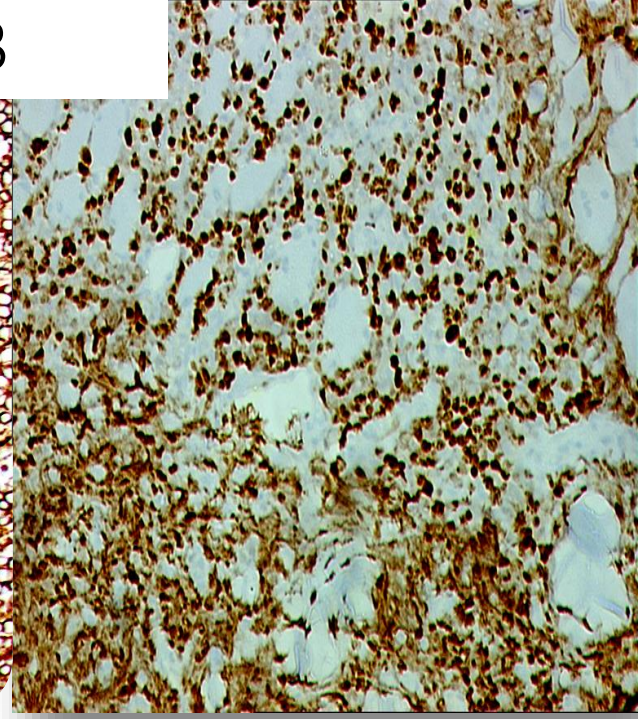
Double expresser is not Double hit

- 20 to 30 % of DE lymphomas are DHL
- DH survival 13 % vs 35% for DE
- 80% to 90% of DHL are GCB Vs DEL 63% are Non GCB.
- To use the double protein IHC expression (DPE) of MYC (≥40%) and BCL2 (≥50%) would result in screening of 34% of DLBCL cases but would result in missing 25% of cases
- To perform FISH on GCB type with double protein expression would limit testing to 11–14% of cases.

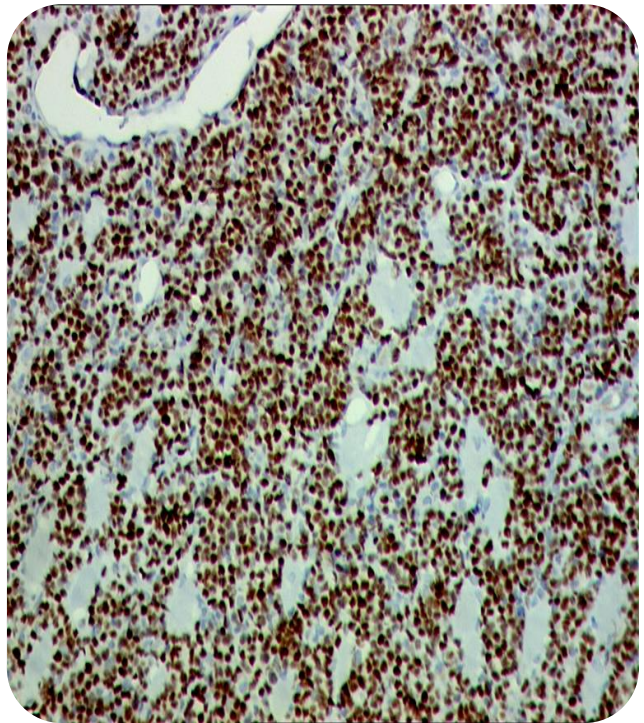
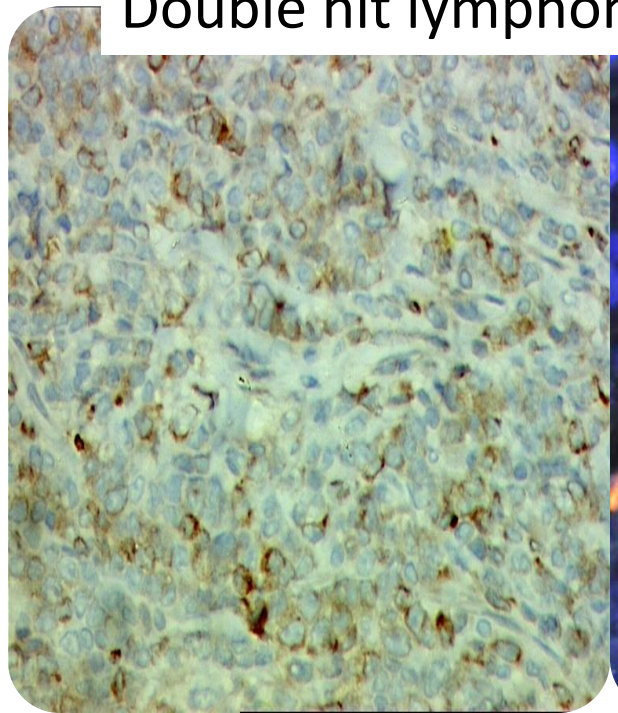
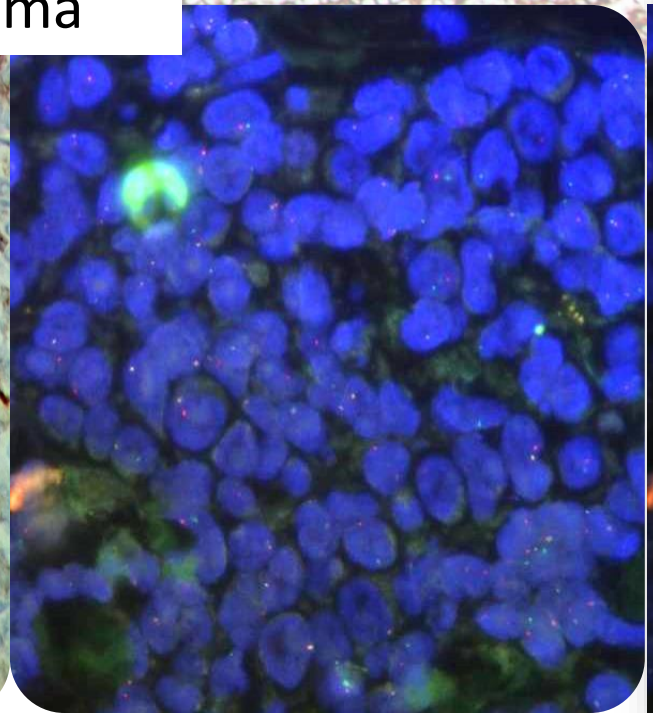
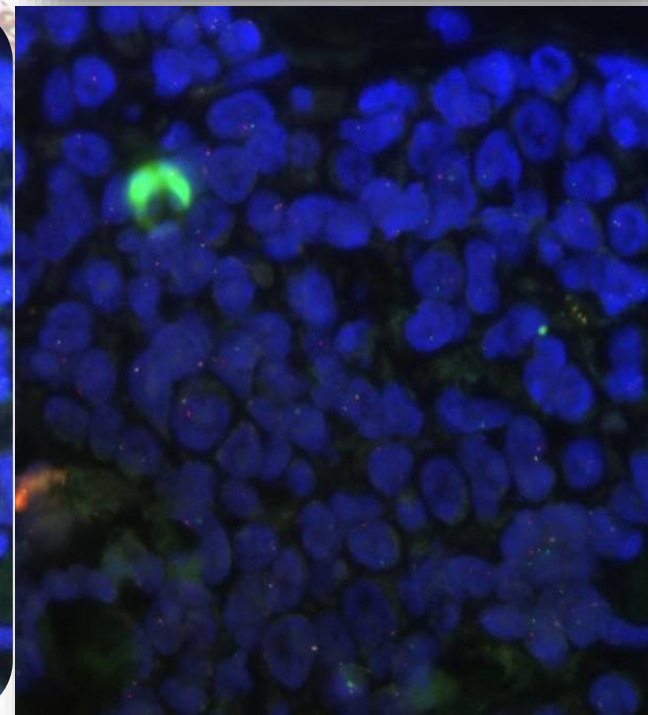


Hematology Am Soc Hematol Educ Program 2021; 2021 (1): 157–163.

45 year old man with Stage IVE disease, ECOG PS 3

Double hit lymphoma

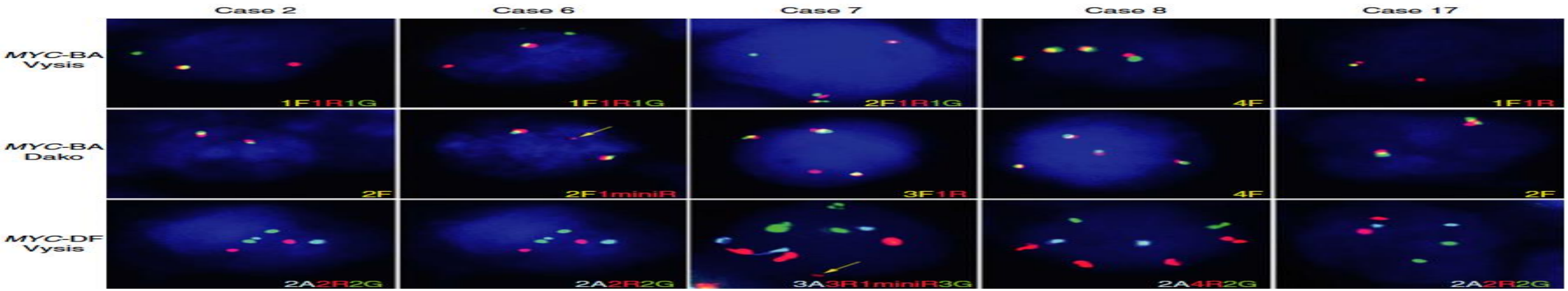





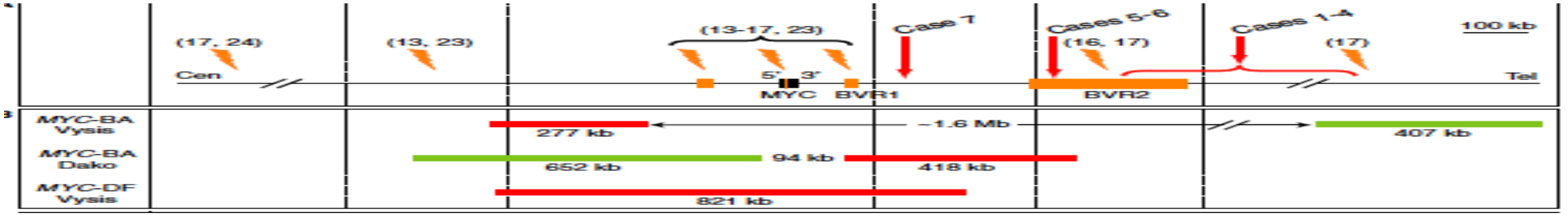
Histopathology

Histopathology 2013, 63, 418–424. DOI: 10.1111/his.12178

MYC status determination in aggressive B-cell lymphoma: the impact of FISH probe selection

Ana M Muñoz-Mármol,[1] Carolina Sanz,[1,2] Gustavo Tapia,[1,3] Ruth Marginet,[1] Aurelio Ariza[1,3] & José L Mate[1,3]

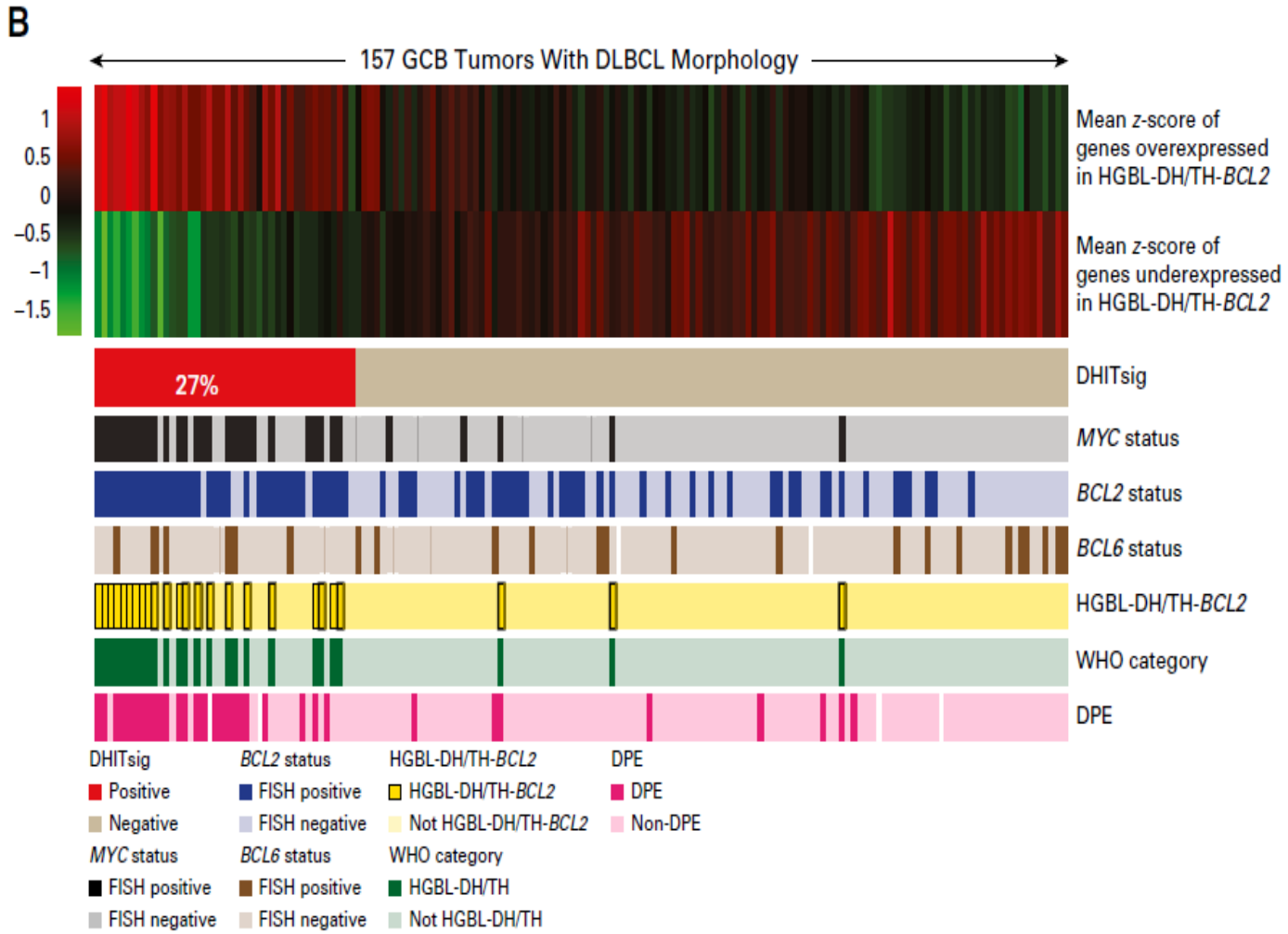




91 aggressive DLBL, MYC was rearranged with a non- IGH partner, a significant proportion of cases showed conflictive results. , Cases 1–4 showed a positive break-apart hybridization pattern with the Vysis BA probe other neg because a far 3' translocation event, telomeric to the region covered by both the Vysis DF and Dako probe

Double-Hit Gene Expression Signature Defines a Distinct Subgroup of Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma

M. Grande, BSc[2]; Susana Ben-Neriah,



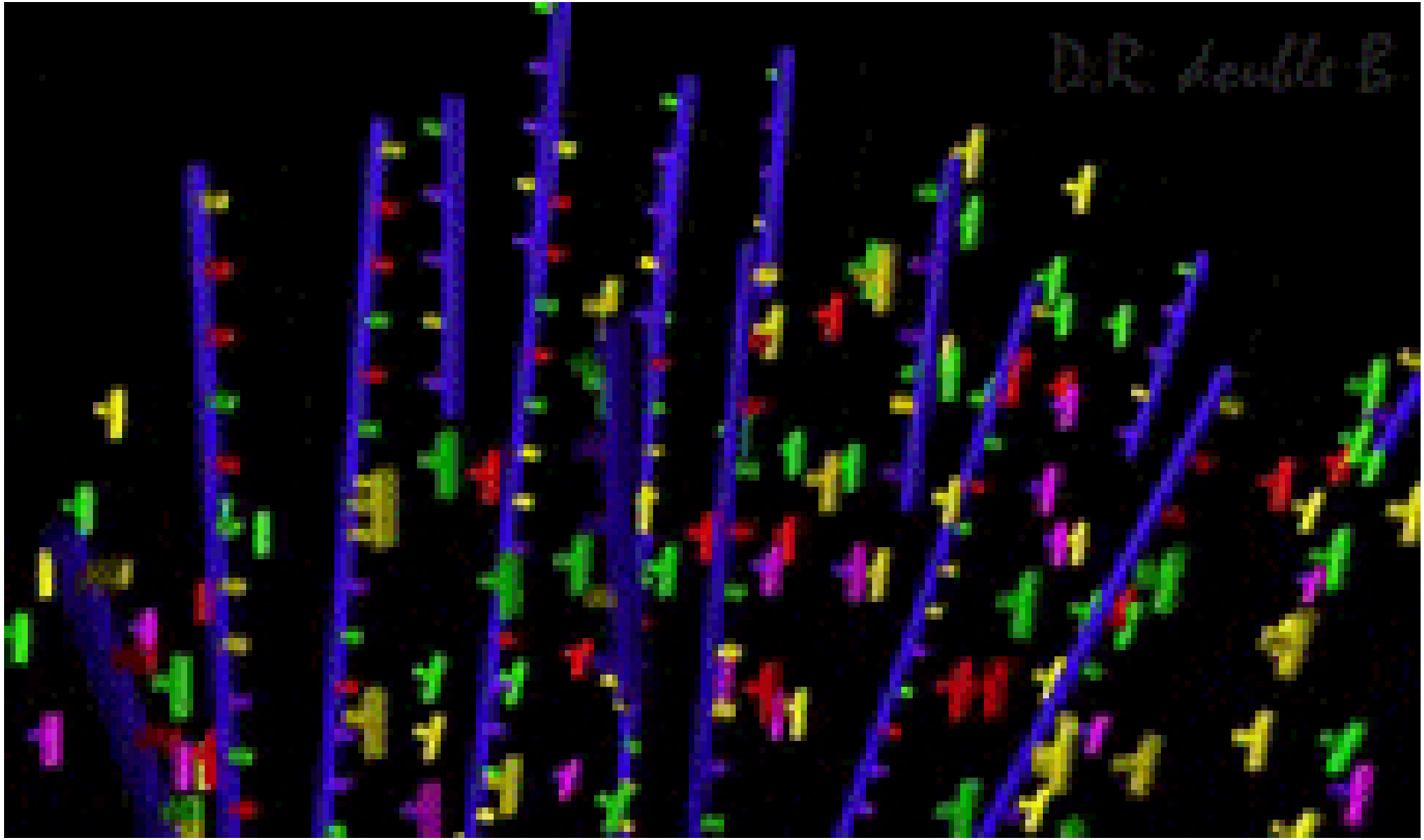
J Clin Oncol 37:190-201. © 2018

A 104-gene double-hit signature (DHITsig) that assigned 27% of GCB-DLBCLs to the DHITsig-positive group, with only one half harboring MYC and BCL2 rearrangements (HGBL-DH/TH- BCL2).

DHITsig-positive patients had inferior outcomes after RCHOP compared with DHITsig-negative patients (5-year time to progression rate, 57% and 81%, respectively;

NanoString gene expression assay (DLBCL90) was developed, which identifies DLBCL cases with an outcome similar to those with double- or triple-hit DLBCL with
both *MYC* and *BCL2* rearrangements.

Discovery of mutational profiling by Next generation sequencing



nature medicine

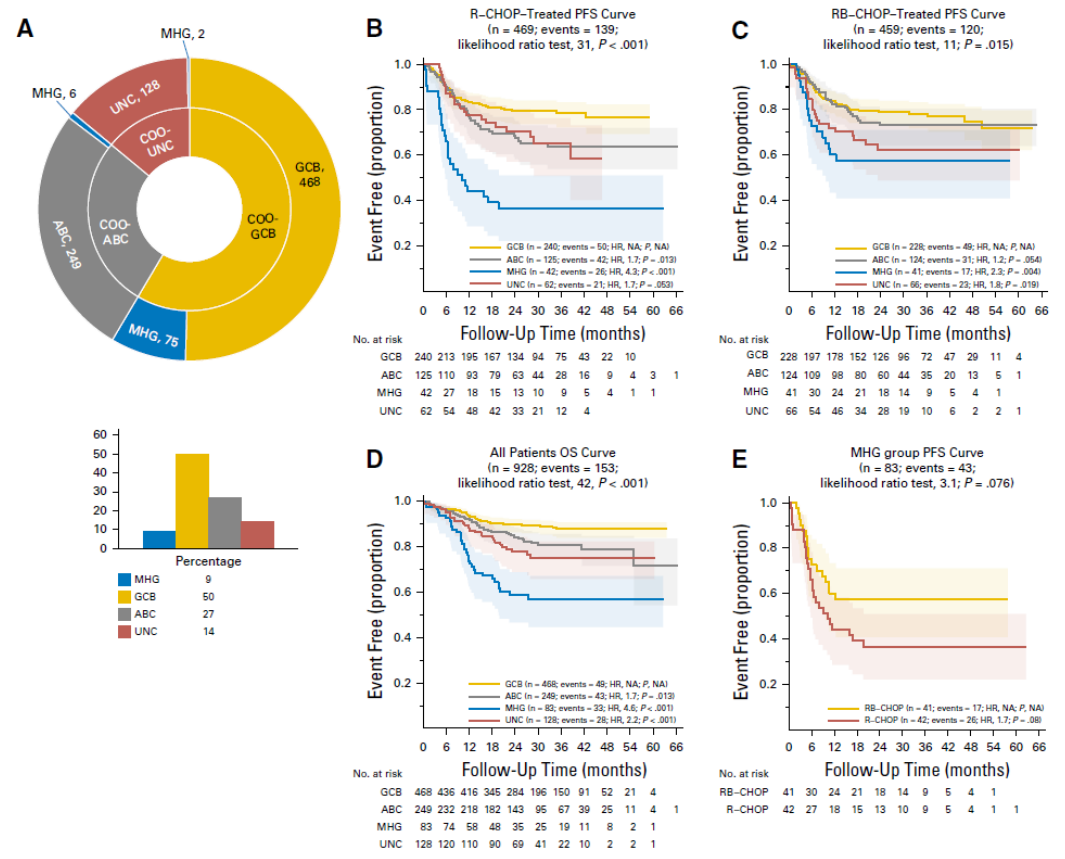
RESOURCE

https://doi.org/10.1038/s41591-018-0016-8

Bjoern Chapuy , Margaret Shipp et al Harvard

Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes

Nat Med. 2018;24:679-690



A data-driven clustering strategy to mutational and copy number data derived from whole-exome and targeted sequencing of 304 DLBCL

1. C0 - No mutation detected
2. C1 - enriched for BCL6 fusion and NOTCH2 mutation
3. C2 - mutation of TP53 and widespread copy number alteration
4. C3 - BCL2 and mutation of CREBBP and EZH2
5. C4 was enriched for somatic hypermutation of SGK1 and genes encoding histone linker proteins
6. C5 cluster, enriched for MYD88 and CD79B mutations

PFS for favorable DLBCL clusters C0, C1, C4, intermediate in C2-DLBCLs and unfavorable for C3 and C5 DLBCLs

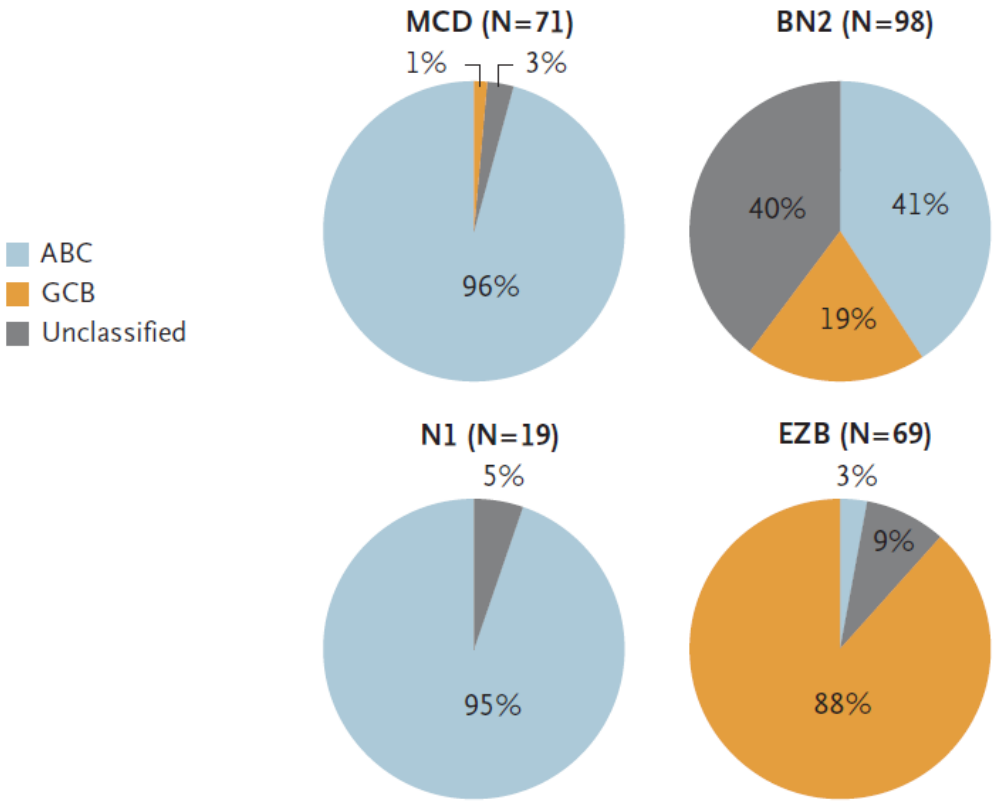
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

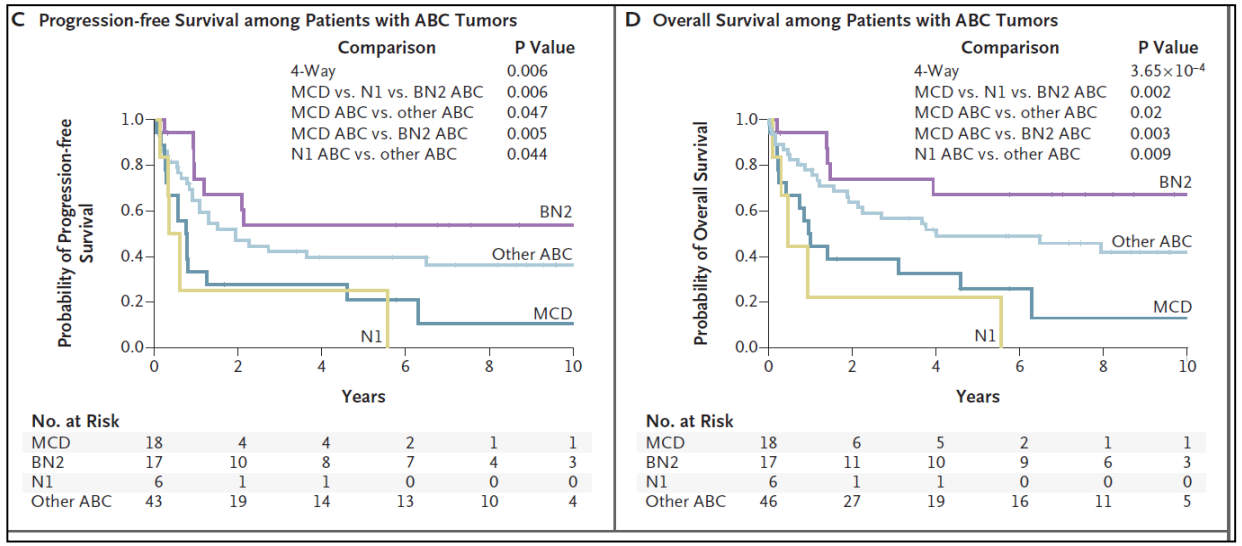
Schmitz and Staudt - NCI

Genetics and Pathogenesis of Diffuse Large B-Cell Lymphoma

transcriptional profiling, whole-exome sequencing, targeted mutation sequencing and array-based copy number analysis on 574 cases of DLBCL



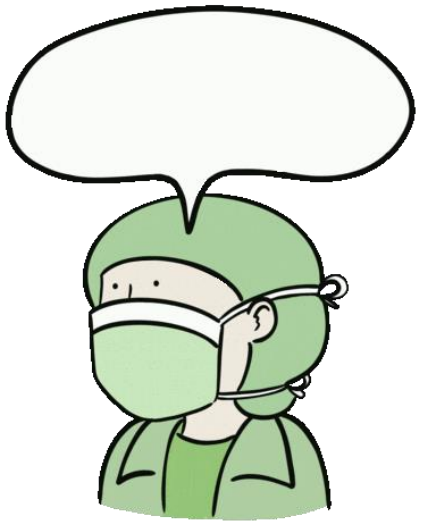
1. MCD :- MYD88 and CD79B mutations (MCD) ABC DLBL (PCNS/PTL)
2. EZB :- enriched for EZH2 mutation and BCL2 translocation (EZB) and was prototypical of GCB DLBCL. **MYC+ / MYC-**
3. BN2:- BCL6 structural alterations and NOTCH2 mutations
4. N1:- . ABC patients with mutations in NOTCH1 that were mutually exclusive with other ABC or NOTCH2 mutations , CLL like



N Engl J Med 2018;378:1396-407.

COO class	Sub genomic classification		Recurrent genetic alterations	10 yr PFS
ABC	Chapuy/Shipp	**C1**	**Bcl6 NOTCH2**	**70**
		C 5	MYD88, CD79B, BCL2, MALT1	40
	Schmitz/Staudt	MCD	MYD88, CD79B	10
		N1	NOTCH	0
GCB	Chapuy/Shipp	**C 3**	**EZH2, BCL2, CREBBP**	**40**
		C4	Core histone genes, immune evasion molecules, JAK/STAT members, BCR/PI3K intermediates, NFKB signaling	70
	Schmitz/Staudt	EZB	EZH2, BCL2	60
ABC + GCB	Chapuy/Shipp	C 2	TP53, del17p	40
	Schmitz/Staudt	BN2	Bcl6, NOTCH2	60

Issue with these studies

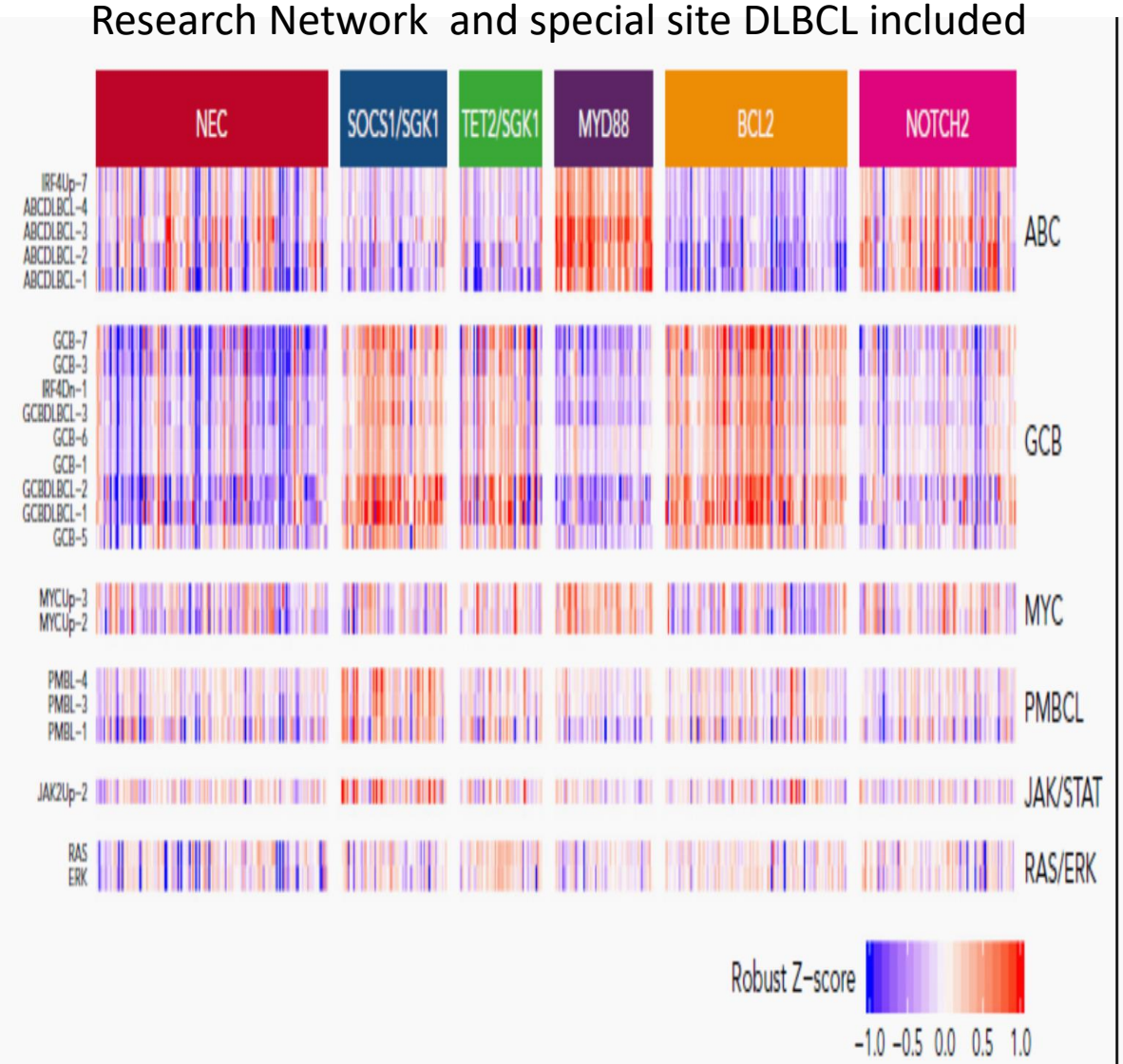


- Many clustering methods produce different results when different tumors are included during the clustering process. They are not appropriate in clinical settings where molecular diagnoses are required in real time for individual tumors. Cancer Cell. 2020 April 13; 37(4): 551–568
- Another issue was that patient population was from clinical trial (Ricover 60 Harvard) or specialized centers (NCI) and lacked real world picture.

Targeted sequencing in DLBCL, molecular subtypes, and outcomes: a Haematological Malignancy Research Network report

Lacy SE et al. Blood. 2020;135(20):1759-1771

Population based study - 928 patients diagnosed with DLBCL and sequenced under the Haematological Malignancy Research Network and special site DLBCL included

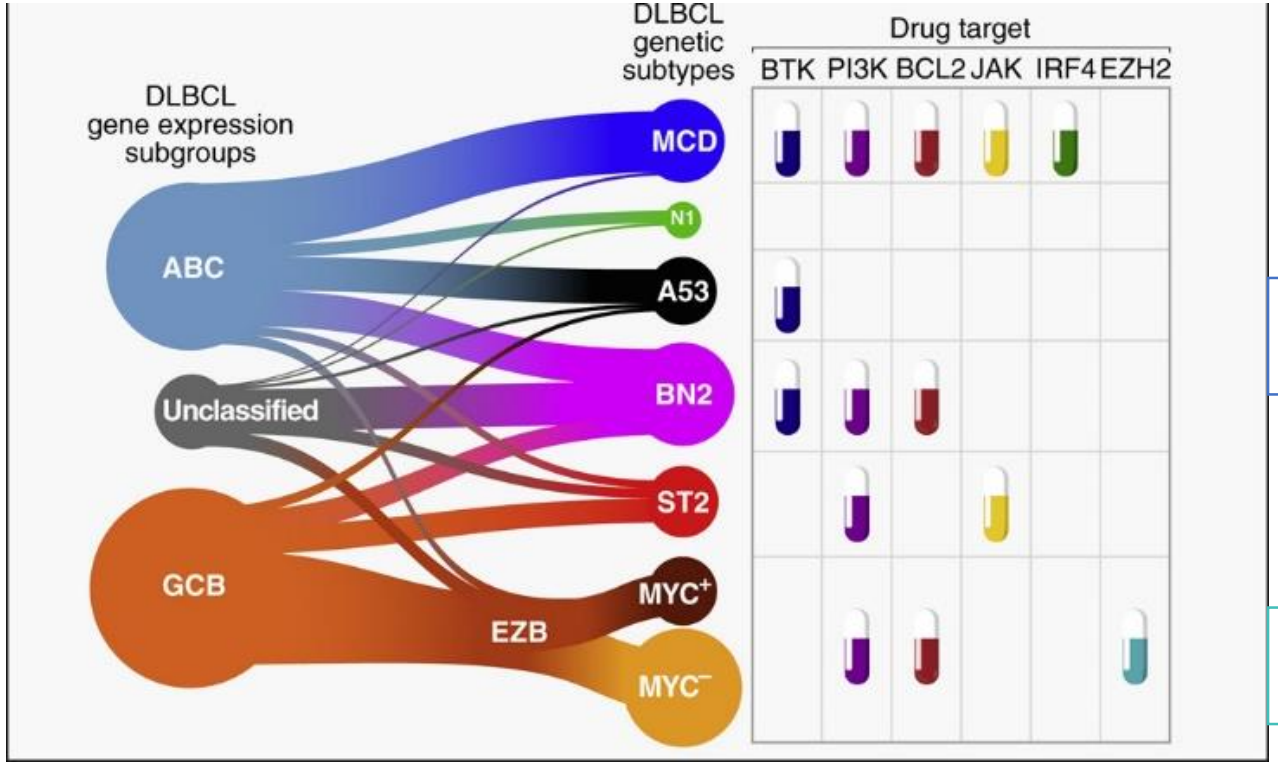


- MYD88 – MCD/C5
- NOTCH2 – BN2/ C1
- Bcl2 – included myc rearranged cases
- **The SOCS1/SGK1 group** mutations, SOCS1, CD83, SGK1, NFKBIA, HIST1H1E, and STAT3 and = C4 cluster. PMBCL).
- **TET2/SGK1 cluster** mutations including TET2, SGK1, KLHL6, ZFP36L1, BRAF, MAP2K1, and KRAS. GCB in origin C4 cluster.
- NEC though NOTCH1 not uniform NOTCH1 mutant cases were in NEC group and was associated with poor prognosis

Table 3. Comparison of main clusters

Current study	Chapuy et al[17]	Schmitz et al[16]	Notes
MYD88 MYD88, PIM1, CD79B, ETV6, CDKN2A	**C5** CD79B, MYD88, ETV6, PIM1, TBL1XR1	**MCD** MYD88, CD79B	Strongly associated with ABC-type DLBCL. The most robust group, occurring in all reports. Contains the majority of cases with PCNSL and primary testicular lymphoma. Associated with a poor prognosis
BCL2 EZH2, BCL2, CREBBP, TNFRSF14, KMT2D	**C3** BCL2, CREBBP2, EZH2, KMT2D, TNFRSF14	**EZB** BCL2 translocation, EZH2	Strongly associated with GCB-type DLBCL. Mutational profile is shared with follicular lymphoma. Contains the majority of cases of transformed follicular lymphoma and cases with a concurrent diagnosis of follicular lymphoma. Generally favorable prognosis, although enriched for cases of double-hit lymphoma and MHG
SOCS1/SGK1 SOCS1, CD83, SGK1, NFKBIA, HIST1H1E	**C4** SGK1, HIST1H1E, NFKBIE, BRAF, CD83		Predominantly GCB-type DLBCL. Shares genetic and gene expression features of PMBCL. Associated with the most favorable prognosis
TET2/SGK1 TET2, BRAF, SGK1, KLHL6, ID3			A less strongly identifiable subtype emerging from SGK1 when applying the Akaike information criterion (supplemental Methods). Has very strong similarity to SOCS1/SGK1 but differentiated by the addition of TET2 and BRAF and the lack of SOCS1 and CD83. Associated with a favorable prognosis
NOTCH2 NOTCH2, BCL10, TNFAIP3, CCND3, SPEN	**C1** BCL6 translocation, BCL10, TNFAIP3, UBE2A, CD70	**BN2** BCL6 translocation, NOTCH2	Not associated with any cell of origin. Shares mutational similarity to MZL but not enriched for cases of transformed MZL. Less strongly defined than other subgroups (supplemental Methods)

NEC NOTCH1, REL amplification, TP53		**Other**	A default category, containing cases that could not be classified elsewhere. Contains cases with no detected mutation. Likely to also contain cases belonging to both NOTCH1 and TP53/CNA subgroups. Even though 3 abnormalities are significantly enriched in this group, their q-values are far less extreme than those of characteristic mutations from the other subtypes
	C2 TP53, frequent deletions		Characterized by TP53 mutation and widespread copy number changes. Due to limited CNA in our study, these cases were predominantly allocated to the NEC group
	C0 No detected abnormalities		Cases with no detectable mutation were allocated to the NEC group
		N1 **NOTCH1**	Characterized by NOTCH1 mutation, this was significantly elevated in our NEC group but only mutated in 2.5% of samples. Associated with poor outcome



LymphGen algorithm

LymphGen uses the presence or absence of each subtype predictor feature to provide a probability that a tumor belongs to the subtype.

Core type >90% (core) or 50%–90% as extended. Tumors that were core members of more than one subtype were termed “genetically composite”

Six types of DLBL emerged each with unique drug able target

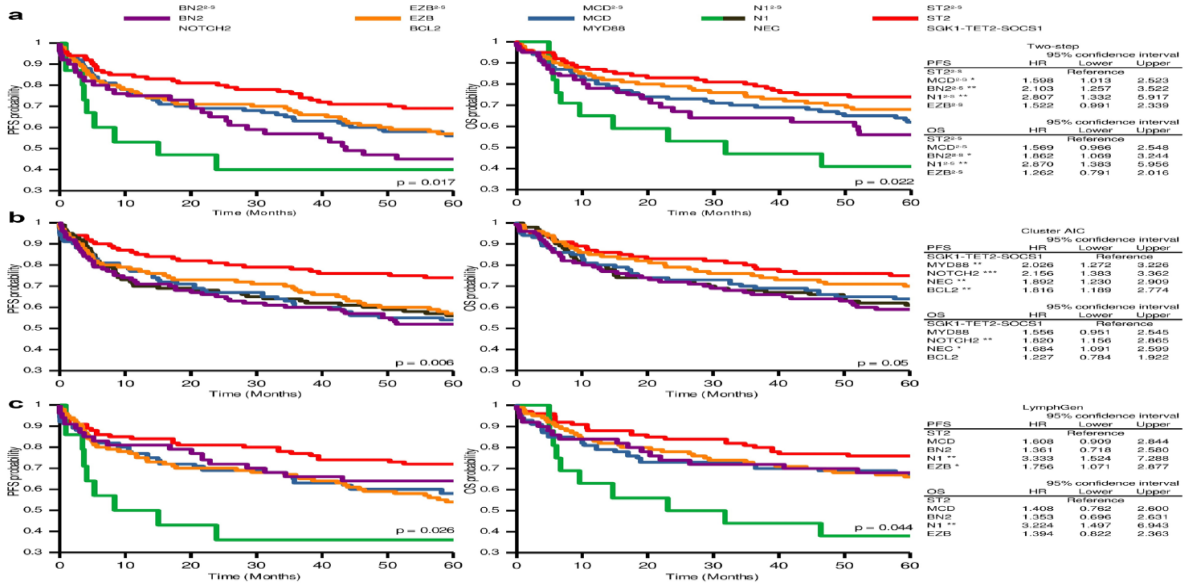
In the NCI cohort, the LymphGen algorithm identified 47.6% core cases, 9.8% extended cases, and 5.7% genetically composite cases

- ✓MCD (including MYD88 L265P and CD79B mutations)
- ✓BN2 (including BCL6 translocations and NOTCH2 mutations),
- ✓N1 (including NOTCH1 mutations)
- ✓EZB (including EZH2 mutations and BCL2 translocations).
- **✓“A53 -TP53 mutations**
- **✓ST2 - SGK1 and TET2 mutated**

Wright et al

Cancer Cell. 2020 April 13; 37(4): 551–568

Proposal and validation of a method to classify genetic subtypes of diffuse large B cell lymphoma



Targeted sequencing of 293 genes to DNA extracted from FFPE biopsies from 928 cases of DLBCL.

Two step classifier based on optimized panel with a minimal set of markers (26 genes and the BCL2 and BCL6 translocations)

Compared Lymphgen, Lacy(AIC cluster) and two gene classifier :-

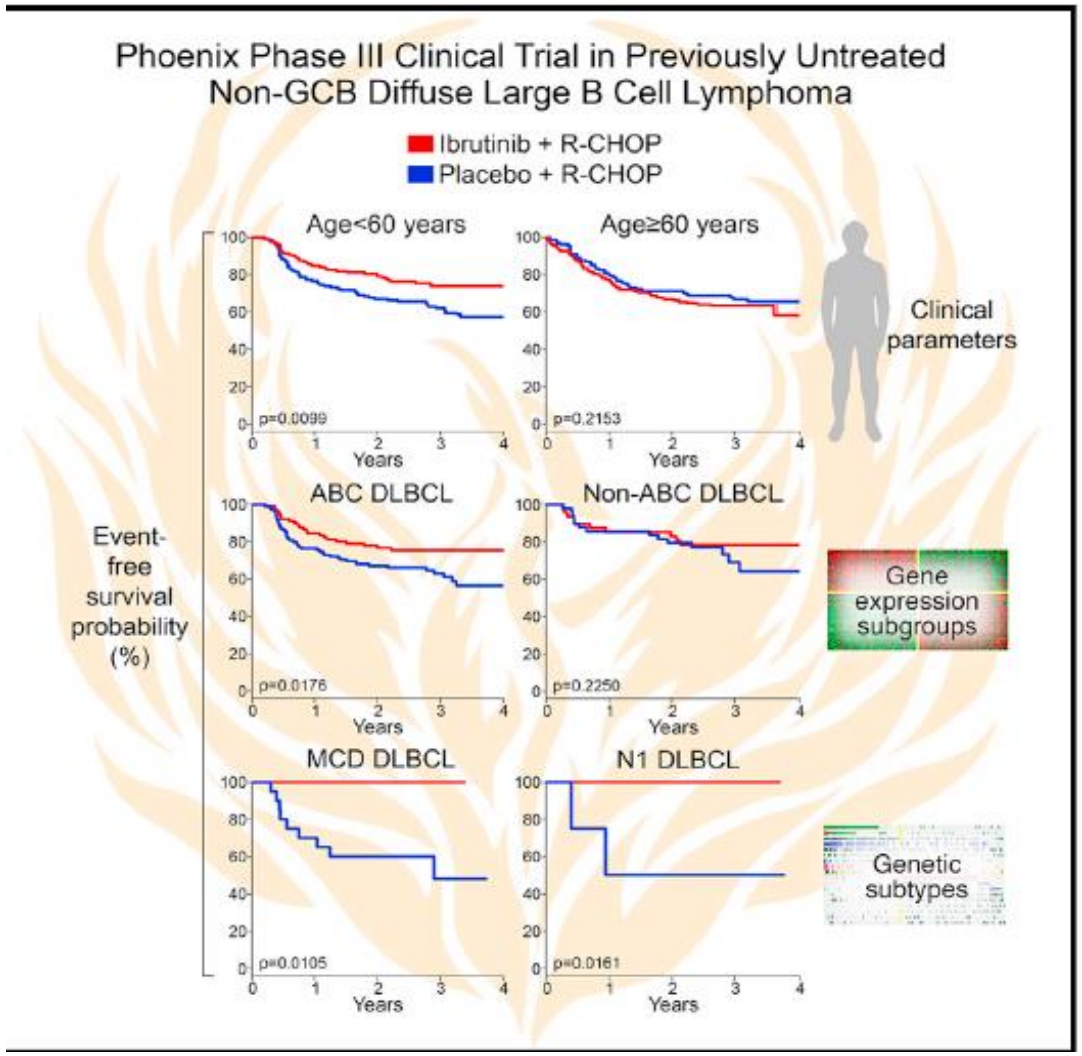
80% similar groups-

BN22-S/BN2/NOTCH2 group differed the most depending on the classifier used, showing shorter OS and PFS with the two-step classification and the AIC cluster compared with LymphGen

The three classifiers showed similar PFS and OS - ST22-S/ST2/SGK1-TET2-SOCS1 is the group with the best clinical outcome. N12-S and N1 showed the shortest OS

UK Haematological Malignancy Research Network (HMRN)

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



Highlights

- BTK inhibitor ibrutinib plus R-CHOP is effective in younger patients with ABC DLBCL
- Genetic subtypes of DLBCL differ in genotype, phenotype, and oncogenic mechanisms
- MCD and N1 subtypes acquire mutations that promote chronic active BCR signaling
- Patients with the MCD and N1 subtypes have 100% survival with ibrutinib plus R-CHOP

Wilson et al. show that patients with two genetic subtypes of DLBCL—MCD and N1—have 100% survival when treated with the BTK inhibitor ibrutinib plus R-CHOP chemotherapy but ≤50% survival when treated with R-CHOP alone. Both subtypes acquire mutations fostering B cell receptor signaling and BTK dependence, accounting for the therapeutic response.

Wilson et al., 2021, Cancer Cell 39, 1643–1653

Questions that these to studies raised

- DLBL can be unified into few subtypes with some good prognostic groups uniformly emerged (ST2 group 75 to 80% OS) N1 and EZB-MYC subtype was worse behaving ; five-year OS was 27% in the NCI study and 40% using a modified HMRN classification.
- Questions still need to be answered

?Variant populations - The Harvard study reported clinical outcomes on 259 DLBL treated with R-CHOP-like therapy and the RICOVER-60 trial of elderly DLBCL . The NCI study included 240 patients, enriched for ABC DLBCL. HMRN was most applicable as it was real world based.

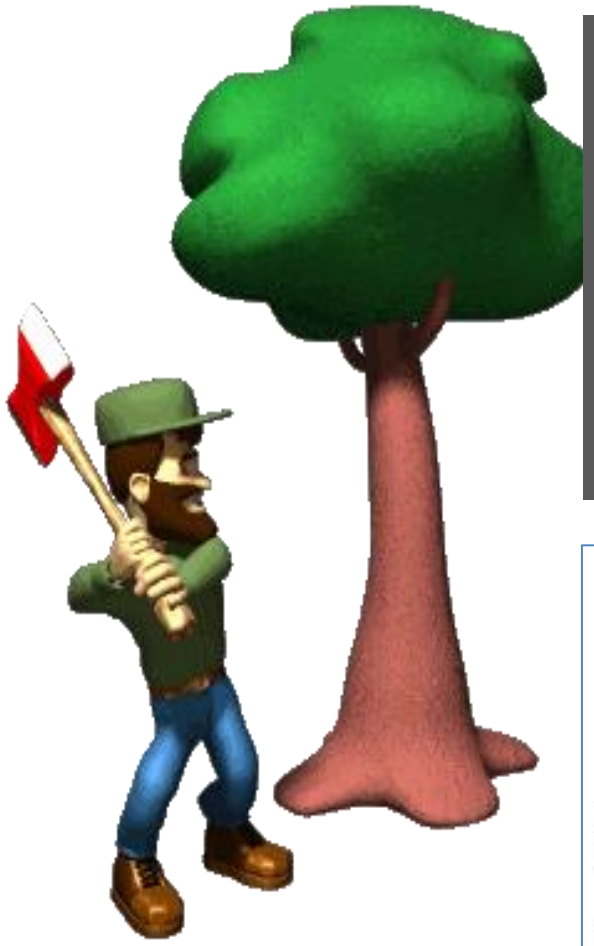
? Different groups because of differences in methodology e.g,

= major issue with TP53 mutations - HMRN did not identify a distinct TP53/CNA cluster though TP53 mutation was associated with a worse prognosis in the NEC, BCL2 and MYD88 cluster. But in NOTCH2 or SOCS1/SGK1 clusters no iimpact and was absent in the TET2/SGK1 cluster. SGK groups were not seen in other groups – population cohort study

Outcome variations is same groups

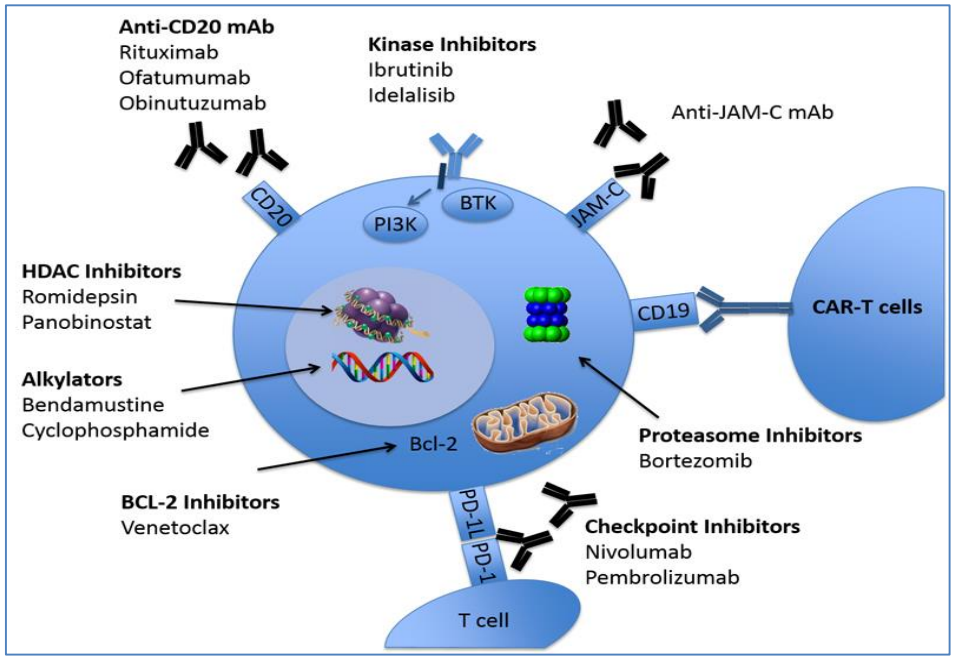
- EZB patients had an intermediate outcome (5 yr OS 70%) in the NCI study, a good outcome in the HMRN study (five-year OS 82%) but one of the poorest survivals (five-year OS 60%) in the study by Harvard group.
- The MCD subtype had an extremely poor survival in the NCI study (five-year OS 40%) but better in Harvard study (five-year OS 60%).
- The BN2 subgroup shows an intermediate outcome in the NCI study (five-year OS 67%), an excellent outcome in the Harvard study (five-year OS 80%), but a poor outcome in the HMRN study (five-year OS 55%).

Br J Haematol, 2021; 196: 814-829.



More aggressive – PMDBCL/ double hit etc

DA- REPOCH



Going beyond

R CHOP

JCO 2020; 35: 3565.

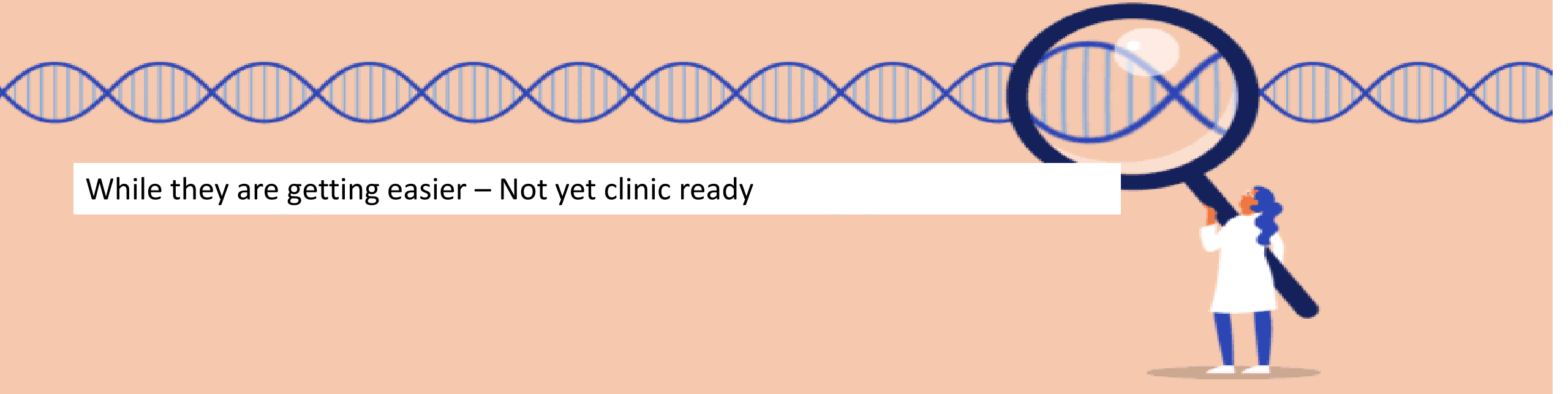
Challenges to implementing impactful genomic assays in routine clinical care

- Platform harmonization and applicability to clinical practice with faster TAT
- Ethnic differences e.g Chinese patients with DLBL had different frequency of mutations, Likewise Indian reports highlight paucity of MYD88 in DLBL.
- Need to add these in prospective trials where newer agents can be tested
- Clinical factors like age, stage of disease will alter course of same molecular subtype through choice of agent

Br J Haematol, 2021; 196: 814-829.

The conclusion

The newer molecular profiling classifications have highlighted that within the heterogeneous group of DLBL beyond cell of origin which has explained some causes for failure of COO classification in some clinical trials



While they are getting easier – Not yet clinic ready