L'ottimizzazione diagnostica del DLBCL

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ALMA MATER STUDIORUM A.D. 1088

MONDO
LINFOMI:
UN'INCREDIBILE DINAMICITÀ

13 SETTEMBRE 2023
Starhotels E.c.Ho.

Milano

Predominantly nodal

Diffuse large B-cell lymphoma, NOS
    Germinal center B-cell subtype
    Activated B-cell subtype

Large B-cell lymphoma with 11q aberration*

T cell/histiocyte-rich large B-cell lymphoma

Extranodal

Primary diffuse large B-cell lymphoma of the central nervous system

Primary diffuse large B-cell lymphoma of the testis*

Primary cutaneous diffuse large B-cell lymphoma, leg type

Intravascular large B-cell lymphoma

*HHV-8 and Epstein-Barr virus–negative primary effusion-based lymphoma**

Primary mediastinal large B-cell lymphoma

Mediastinal gray-zone lymphoma*

Epstein-Barr virus related

Epstein-Barr virus–positive diffuse large B-cell lymphoma, NOS

Diffuse large B-cell lymphoma associated with chronic inflammation
    Fibrin-associated diffuse large B-cell lymphoma

Large cell lymphoma with terminal B-cell differentiation

ALK-positive large B-cell lymphoma

Plasmablastic lymphoma

HHV-8–positive diffuse large B-cell lymphoma, NOS

Primary effusion lymphoma

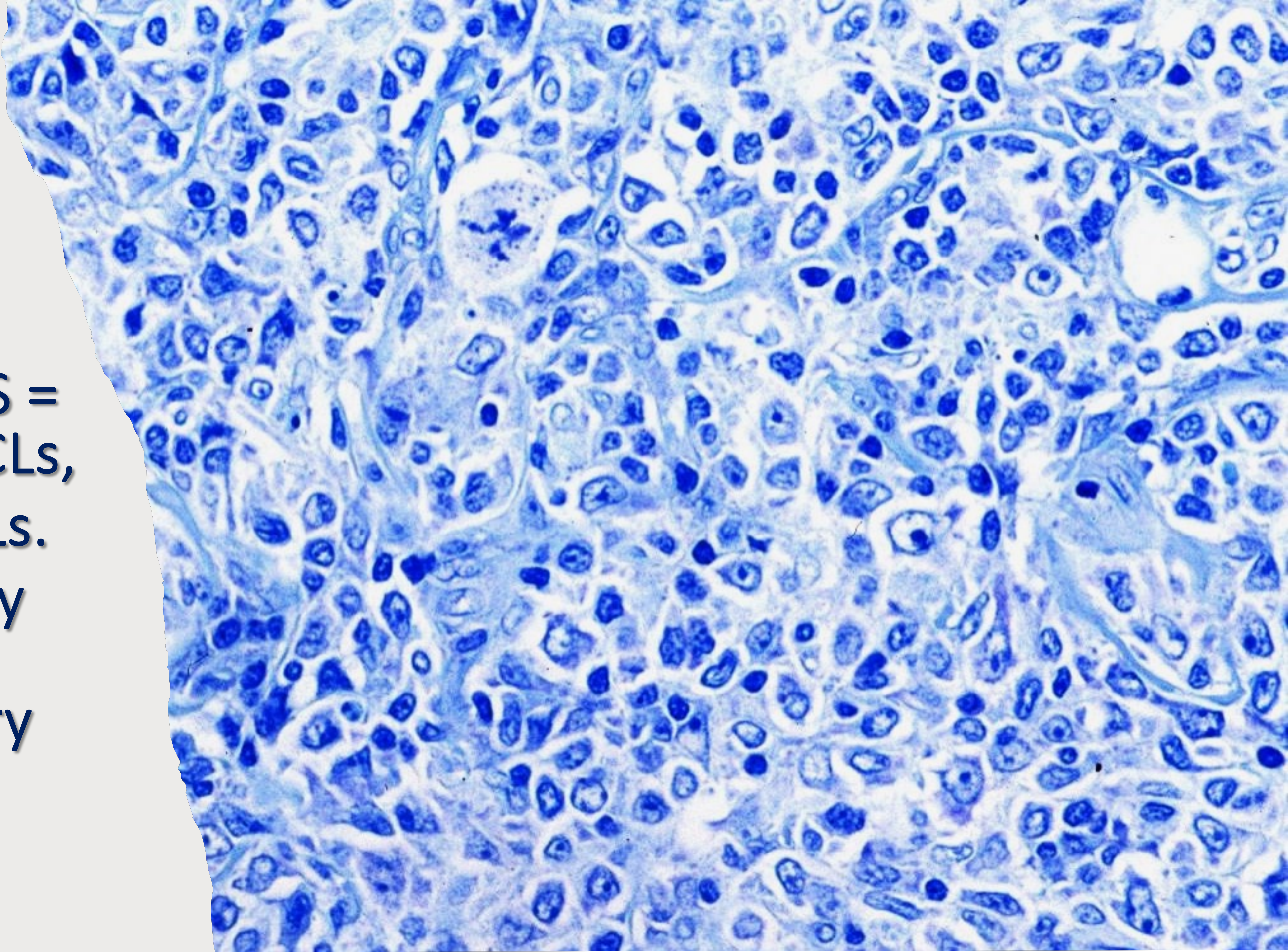
High grade B-cell lymphomas¶

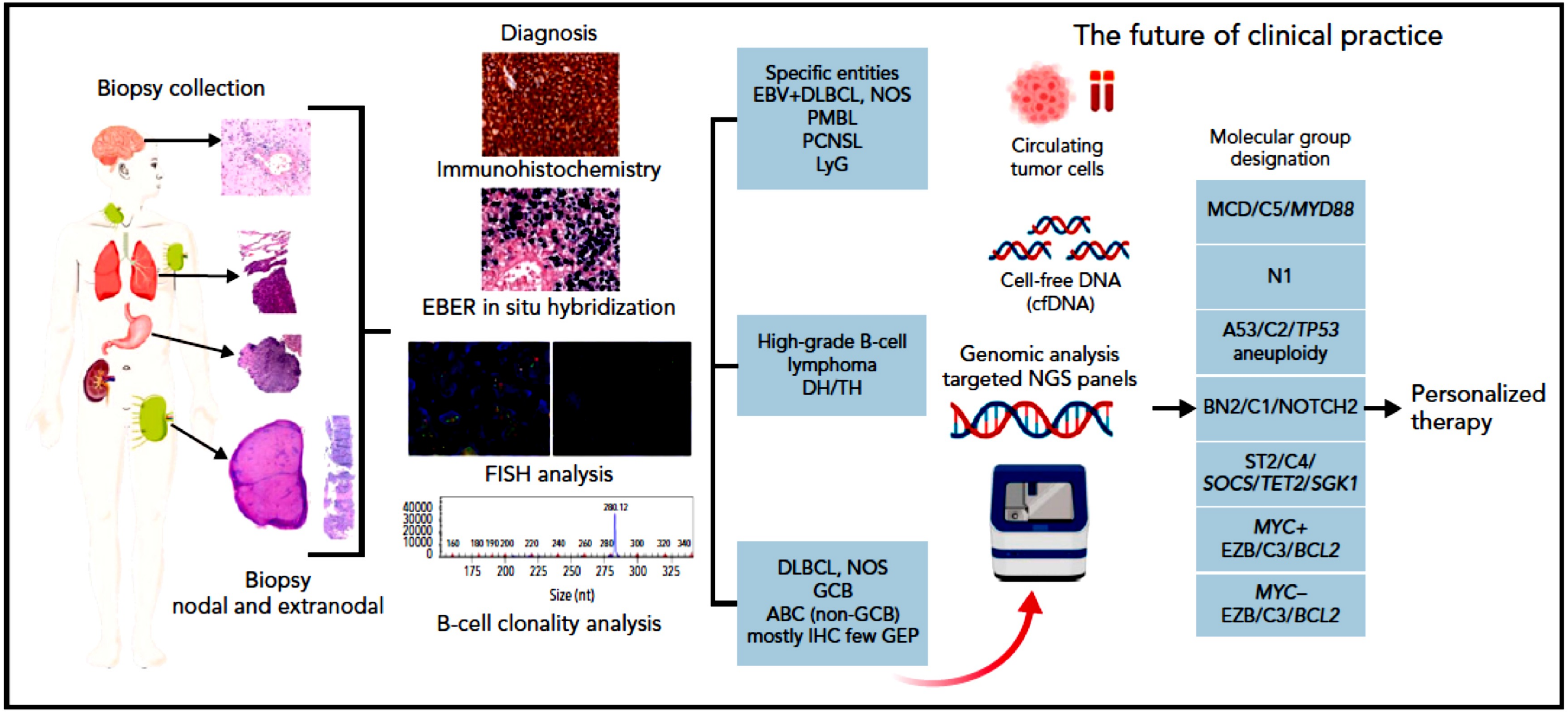
High-grade B-cell lymphoma, with MYC and BCL2 rearrangements*

*High-grade B-cell lymphoma with MYC and BCL6 rearrangements**

DLBCL, NOS = 80% of DBCLs, 40% of NHLs.

Morphology not contributory





Biopsy collection

Biopsy
nodal and extranodal

Diagnosis

Immunohistochemistry

EBER in situ hybridization

FISH analysis

B-cell clonality analysis

Specific entities
EBV+DLBCL, NOS
PMBL
PCNSL
LyG

High-grade B-cell
lymphoma
DH/TH

DLBCL, NOS
GCB
ABC (non-GCB)
mostly IHC few GEP

The future of clinical practice

Circulating
tumor cells

Cell-free DNA
(cfDNA)

Genomic analysis
targeted NGS panels

Molecular group
designation

MCD/C5/*MYD88*

N1

A53/C2/*TP53*
aneuploidy

BN2/C1/NOTCH2

ST2/C4/
SOCS/TET2/SGK1

MYC+
EZB/C3/*BCL2*

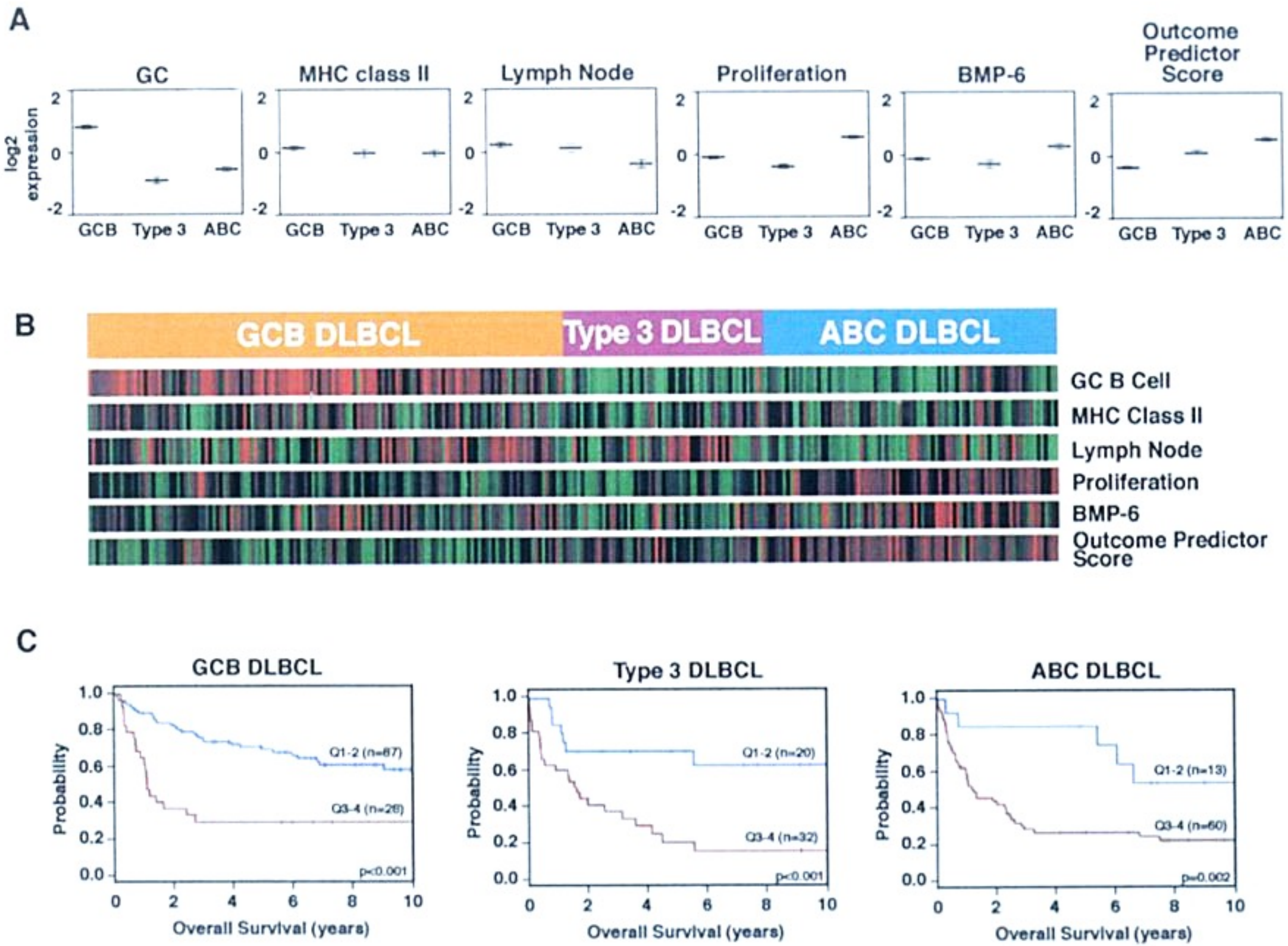
MYC–
EZB/C3/*BCL2*

Personalized
therapy

International Consensus Classification, Blood, 2022

Cell of Origin (COO)

Rosenwald A et al. NEJM, 346:1937-47, 2002. Wright G et al. PNAS, 100:9991-6, 2003.



Targeted Digital Gene expression profiling

Smaller samples

FFPE tissue, Blood, Cell Lines, Etc.

Input
Lyse and Go
Protocols

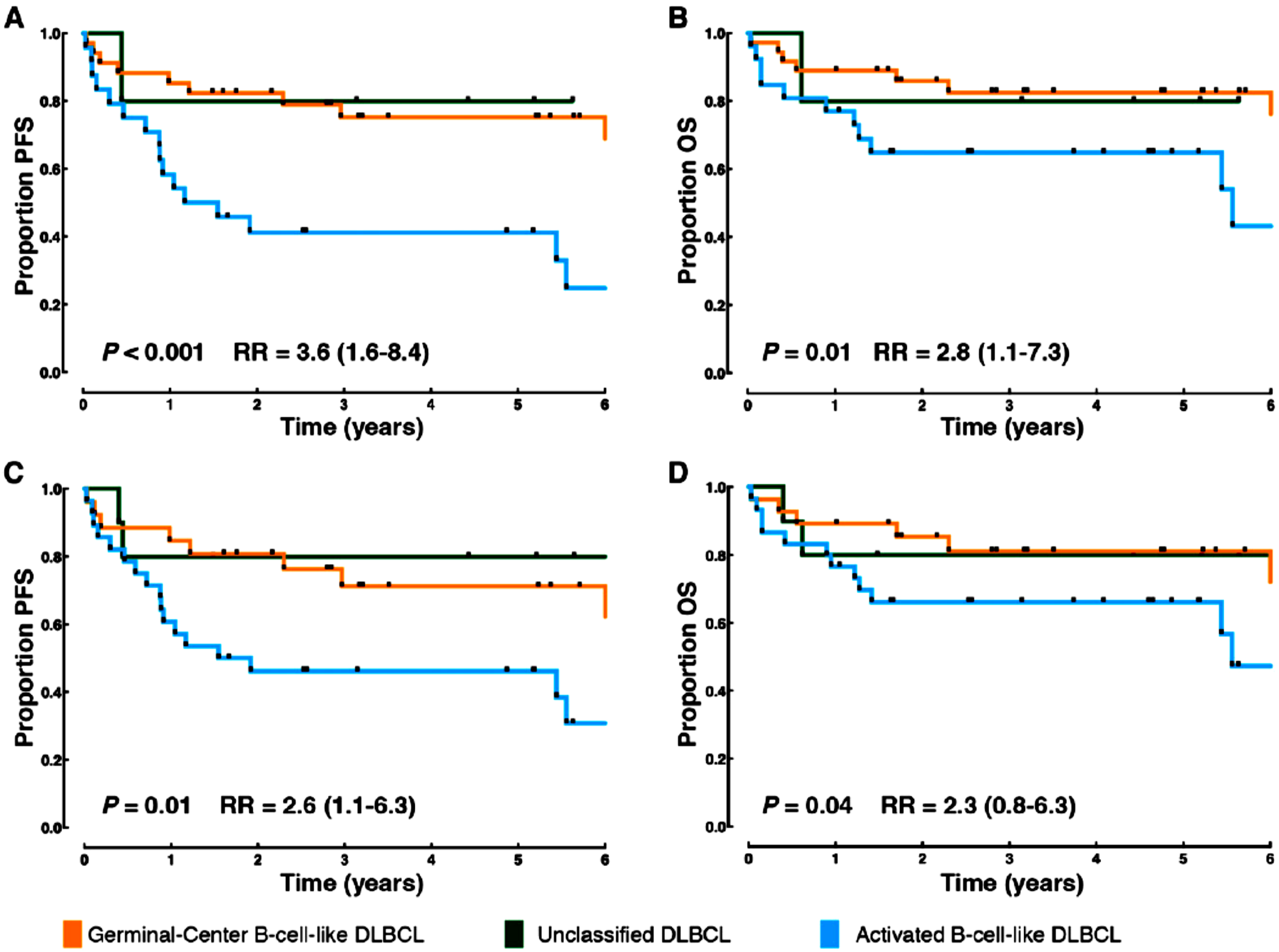
More biology

Proteins

- **Aβ**
- **APOE**
- **Iba1**
- **HLA-DR**

Genes

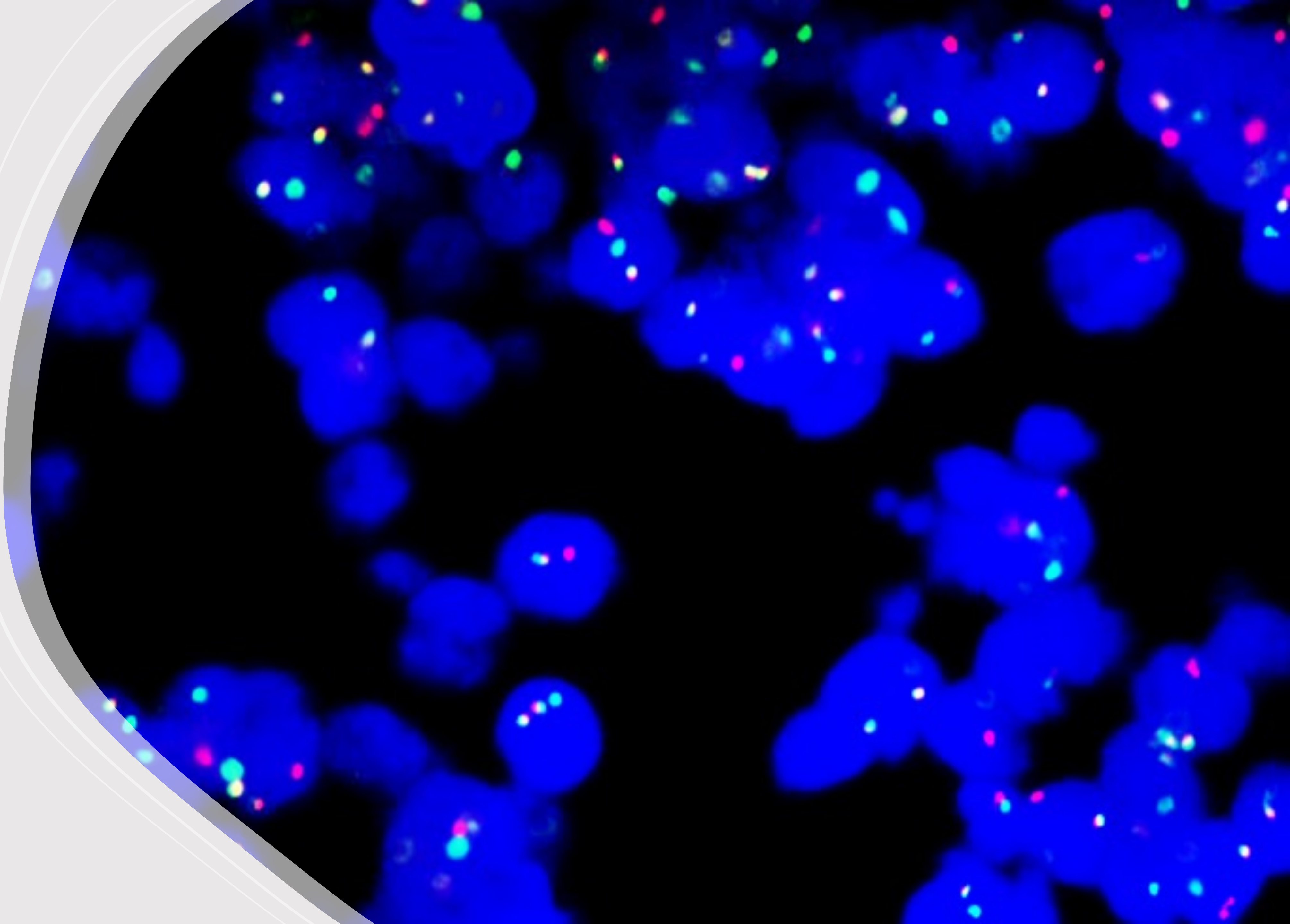
- Apoe
- Atm
- Akt1
- Bcl2
- Crip1
- Abcc3
- Akt2
- Cx3cr1
- Ago4
- Snca
- Pik3r1
- Mapk10
- Casp3
- Gria2
- Atp6v0e
- Bid
- Il1r1
- Anxa1
- Atg9a
- Bin1
- Ptgs2
- Grin2a
- Pik3ca
- Anapc15
- Pik3cb
- C3
- Bax
- Ngfr
- Bcas1
- Casp7
- Agt
- Creb1
- Csf1r
- Bmi1
- Pten
- Fas
- Cd33
- Pla2g4a
- Casp8
- Atp6v1a
- Birc2
- Cd69
- Mdm2
- Bad
- Cldn5
- Jun

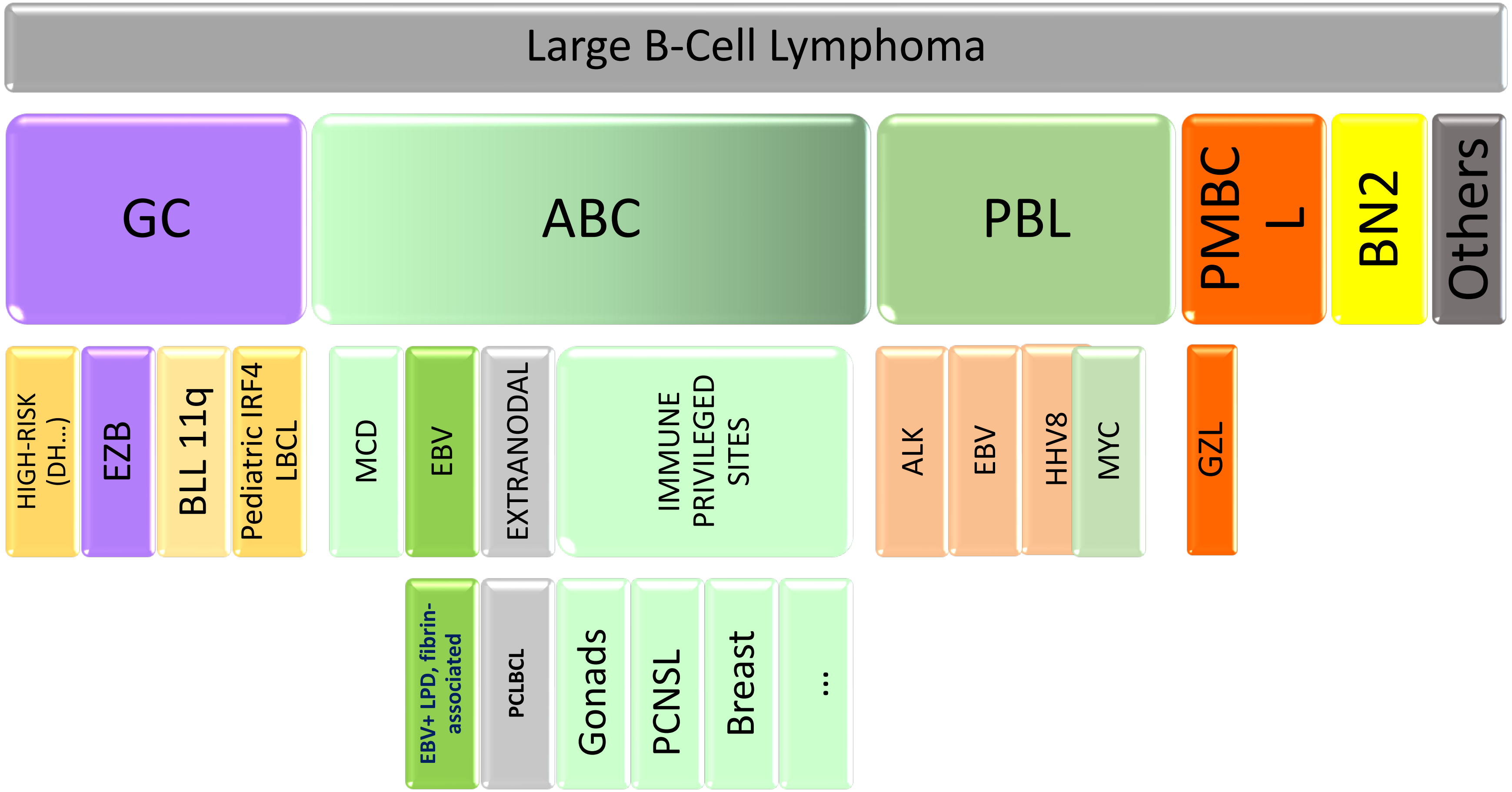

A
Proportion PFS
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
Time (years)
$P < 0.001$ RR = 3.6 (1.6-8.4)
B
Proportion OS
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
Time (years)
$P = 0.01$ RR = 2.8 (1.1-7.3)
C
Proportion PFS
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
Time (years)
$P = 0.01$ RR = 2.6 (1.1-6.3)
D
Proportion OS
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
Time (years)
$P = 0.04$ RR = 2.3 (0.8-6.3)
🟧 Germinal-Center B-cell-like DLBCL
⬛ Unclassified DLBCL
🟦 Activated B-cell-like DLBCL

FISH

MYC
BCL2
BCL6
IRF4
11q

EBER
ISH





Large B-Cell Lymphoma

GC
ABC
PBL
PMBCL
BN2
Others

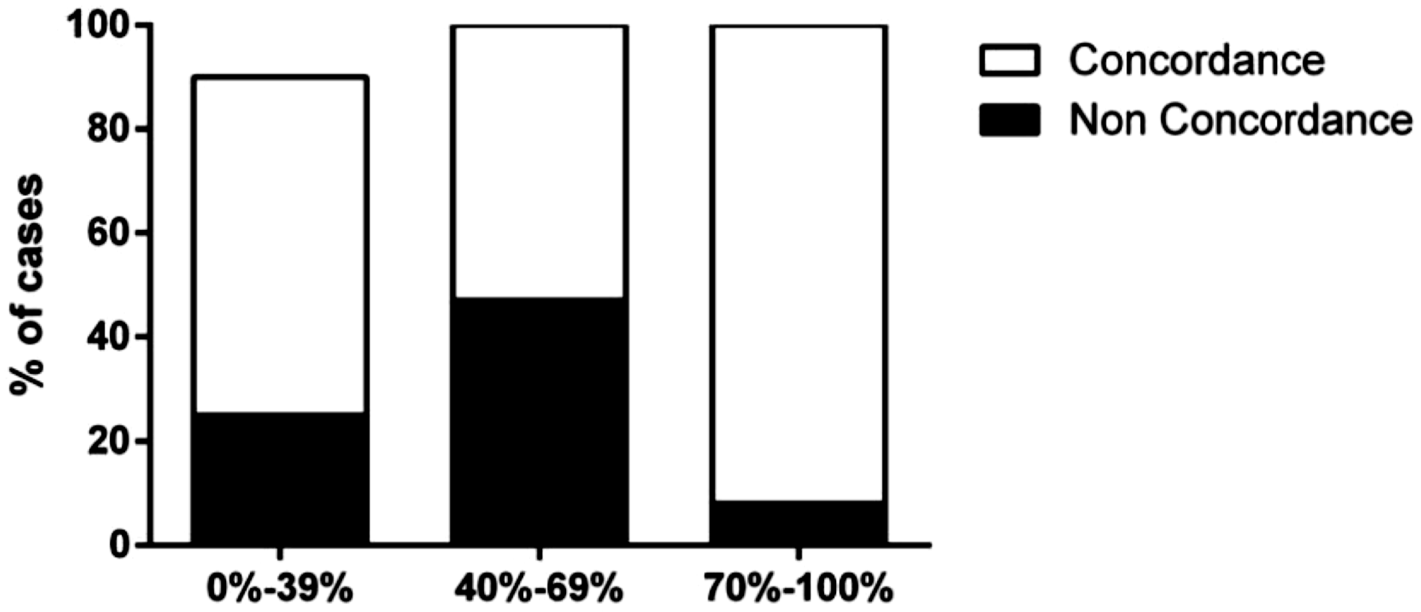
HIGH-RISK (DH…)
EZB
BLL 11q
Pediatric IRF4 LBCL
MCD
EBV
EXTRANODAL
IMMUNE PRIVILEGED SITES
ALK
EBV
HHV8
MYC
GZL

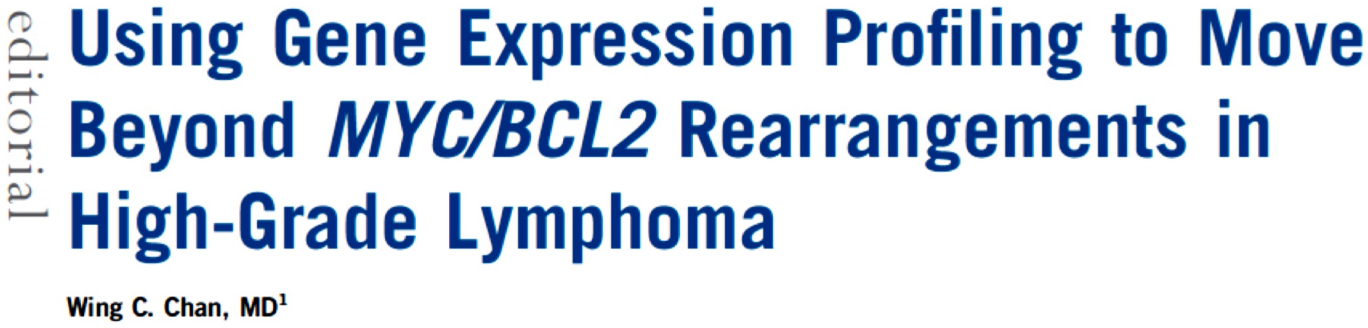
EBV+ LPD, fibrin-associated
PCLBCL
Gonads
PCNSL
Breast
…

MYC protein expression scoring and its impact on the prognosis of aggressive B-cell lymphoma patients

by Maria R. Ambrosio, Stefano Lazzi, Giuseppe Lo Bello, Raffaella Santi, Leonardo Del Porro, Maria M. de Santi, Raffaella Guazzo, Lucia Mundo, Luigi Rigacci, Sofia Kovalchuck, Noel Onyango, Alberto Fabbri, Emanuele Cencini, Pier Luigi Zinzani, Francesco Zaja, Francesco Angrilli, Caterina Stelitano, Maria G. Cabras, Giuseppe Spataro, Roshanak Bob, Thomas Menter, Massimo Granai, Gabriele Cevenini, Kikkeri N. Naresh, Harald Stein, Elena Sabattini, and Lorenzo Leoncini

Haematologica 2018 [Epub ahead of print]

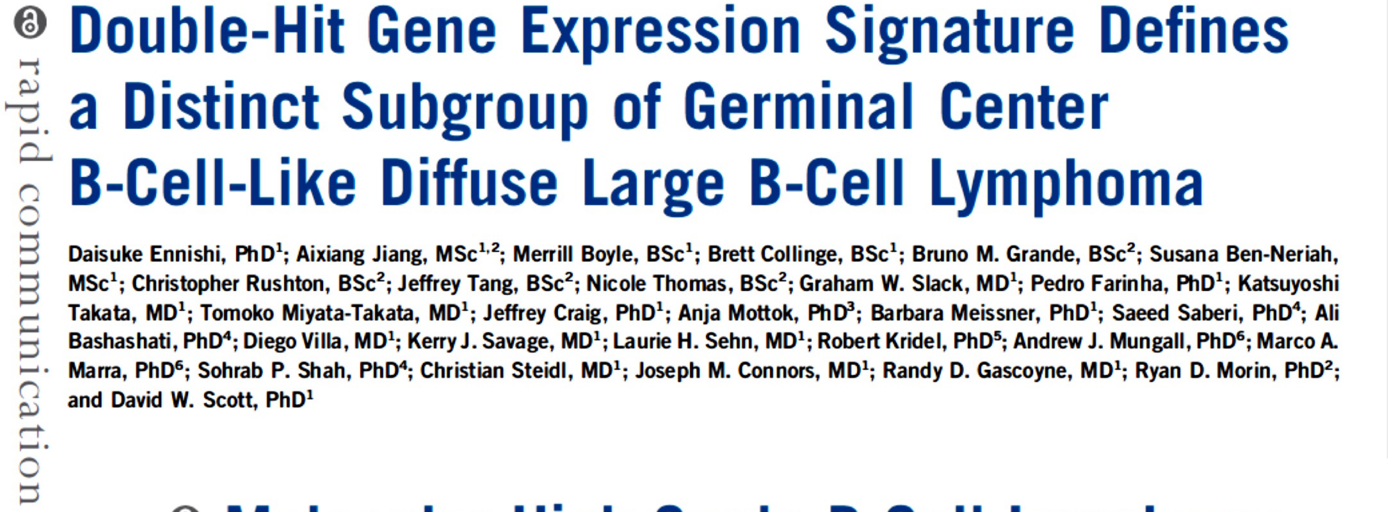




editorial

Using Gene Expression Profiling to Move Beyond *MYC/BCL2* Rearrangements in High-Grade Lymphoma

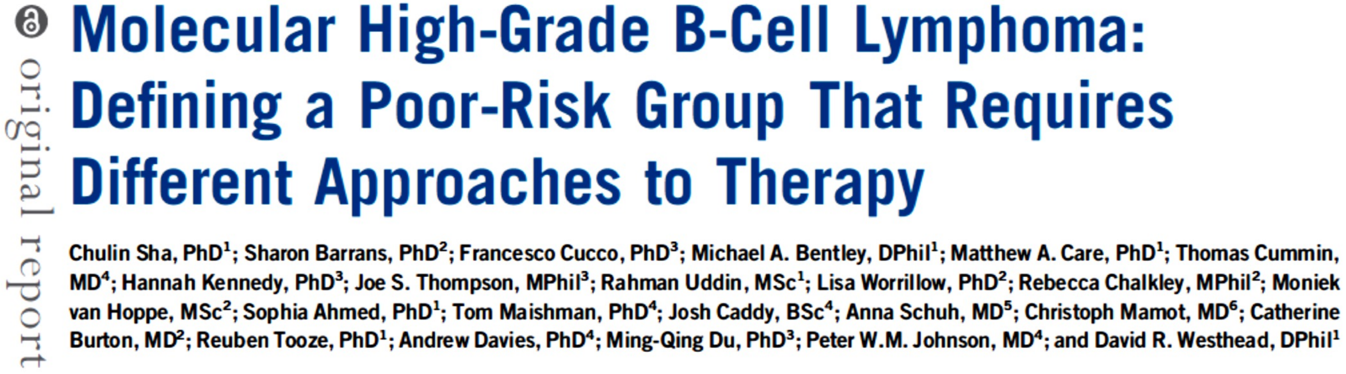
Wing C. Chan, MD[1]



rapid communication

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

Daisuke Ennishi, PhD[1]; Aixiang Jiang, MSc[1,2]; Merrill Boyle, BSc[1]; Brett Collinge, BSc[1]; Bruno M. Grande, BSc[2]; Susana Ben-Neriah, MSc[1]; Christopher Rushton, BSc[2]; Jeffrey Tang, BSc[2]; Nicole Thomas, BSc[2]; Graham W. Slack, MD[1]; Pedro Farinha, PhD[1]; Katsuyoshi Takata, MD[1]; Tomoko Miyata-Takata, MD[1]; Jeffrey Craig, PhD[1]; Anja Mottok, PhD[3]; Barbara Meissner, PhD[1]; Saeed Saberi, PhD[4]; Ali Bashashati, PhD[4]; Diego Villa, MD[1]; Kerry J. Savage, MD[1]; Laurie H. Sehn, MD[1]; Robert Kridel, PhD[5]; Andrew J. Mungall, PhD[6]; Marco A. Marra, PhD[6]; Sohrab P. Shah, PhD[4]; Christian Steidl, MD[1]; Joseph M. Connors, MD[1]; Randy D. Gascoyne, MD[1]; Ryan D. Morin, PhD[2]; and David W. Scott, PhD[1]



original report

Molecular High-Grade B-Cell Lymphoma: Defining a Poor-Risk Group That Requires Different Approaches to Therapy

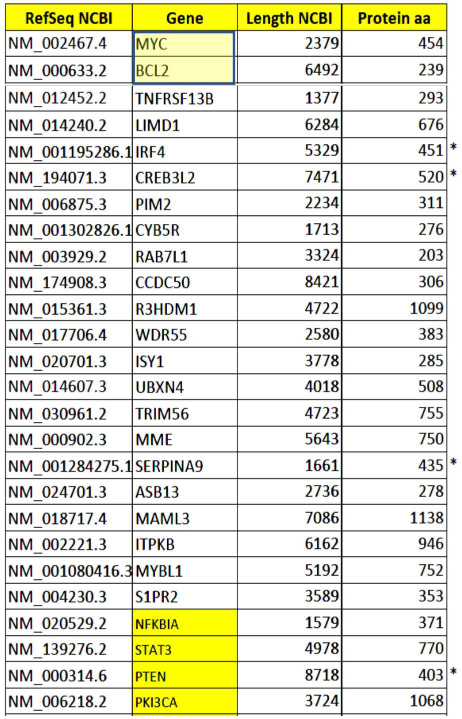
Chulin Sha, PhD[1]; Sharon Barrans, PhD[2]; Francesco Cucco, PhD[3]; Michael A. Bentley, DPhil[1]; Matthew A. Care, PhD[1]; Thomas Cummin, MD[4]; Hannah Kennedy, PhD[3]; Joe S. Thompson, MPhil[3]; Rahman Uddin, MSc[1]; Lisa Worrillow, PhD[2]; Rebecca Chalkley, MPhil[2]; Moniek van Hoppe, MSc[2]; Sophia Ahmed, PhD[1]; Tom Maishman, PhD[4]; Josh Caddy, BSc[4]; Anna Schuh, MD[5]; Christoph Mamot, MD[6]; Catherine Burton, MD[2]; Reuben Tooze, PhD[1]; Andrew Davies, PhD[4]; Ming-Qing Du, PhD[3]; Peter W.M. Johnson, MD[4]; and David R. Westhead, DPhil[1]

A 3-gene signature based on MYC, BCL-2 and NFKBIA improves risk stratification in diffuse large B-cell lymphoma

by Enrico Derenzini, Saveria Mazzara, Federica Melle, Giovanna Motta, Marco Fabbri, Riccardo Bruna, Claudio Agostinelli, Alessandra Cesano, Chiara Antonia Corsini, Ning Chen, Simona Righi, Elena Sabattini, Annalisa Chiappella, Angelica Calleri, Stefano Fiori, Valentina Tabanelli, Antonello Cabras, Giancarlo Pruneri, Umberto Vitolo, Alessandro Massimo Gianni, Alessandro Rambaldi, Paolo Corradini, Pier Luigi Zinzani, Corrado Tarella, and Stefano Pileri

Haematologica 2020 [Epub ahead of print]

Targeted Digital Gene Expression Profiling



RefSeq NCBI	Gene	Length NCBI	Protein aa	
NM_002467.4	MYC	2379	454	
NM_000633.2	BCL2	6492	239	
NM_012452.2	TNFRSF13B	1377	293	
NM_014240.2	LIMD1	6284	676	
NM_001195286.1	IRF4	5329	451	*
NM_194071.3	CREB3L2	7471	520	*
NM_006875.3	PIM2	2234	311	
NM_001302826.1	CYB5R	1713	276	
NM_003929.2	RAB7L1	3324	203	
NM_174908.3	CCDC50	8421	306	
NM_015361.3	R3HDM1	4722	1099	
NM_017706.4	WDR55	2580	383	
NM_020701.3	ISY1	3778	285	
NM_014607.3	UBXN4	4018	508	
NM_030961.2	TRIM56	4723	755	
NM_000902.3	MME	5643	750	
NM_001284275.1	SERPINA9	1661	435	*
NM_024701.3	ASB13	2736	278	
NM_018717.4	MAML3	7086	1138	
NM_002221.3	ITPKB	6162	946	
NM_001080416.3	MYBL1	5192	752	
NM_004230.3	S1PR2	3589	353	
NM_020529.2	NFKBIA	1579	371	
NM_139276.2	STAT3	4978	770	
NM_000314.6	PTEN	8718	403	*
NM_006218.2	PKI3CA	3724	1068	

26-gene-panel for COO & key-genes Haematologica, 2020

224 DLBCL patients
FFPE specimens

DLCL04 (n = 130)
R-HDS (n = 94)

NanoString
insufficient mRNA n = 17

207 DLBCL patients

IHC
non-NOS n = 21

186 DLBCL patients

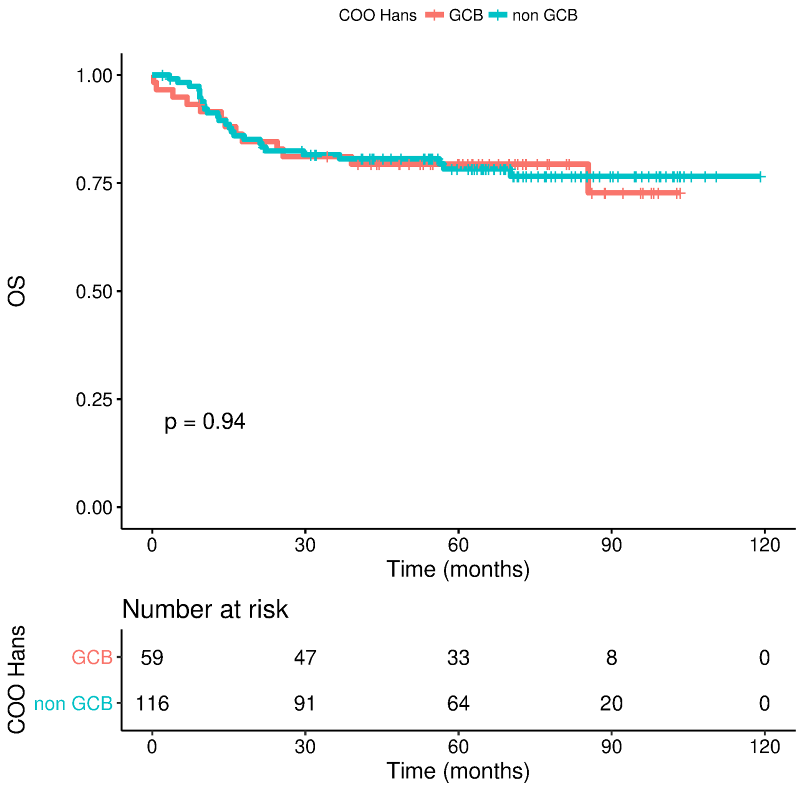
DLCL04 (n = 99)
R-HDS (n = 87)

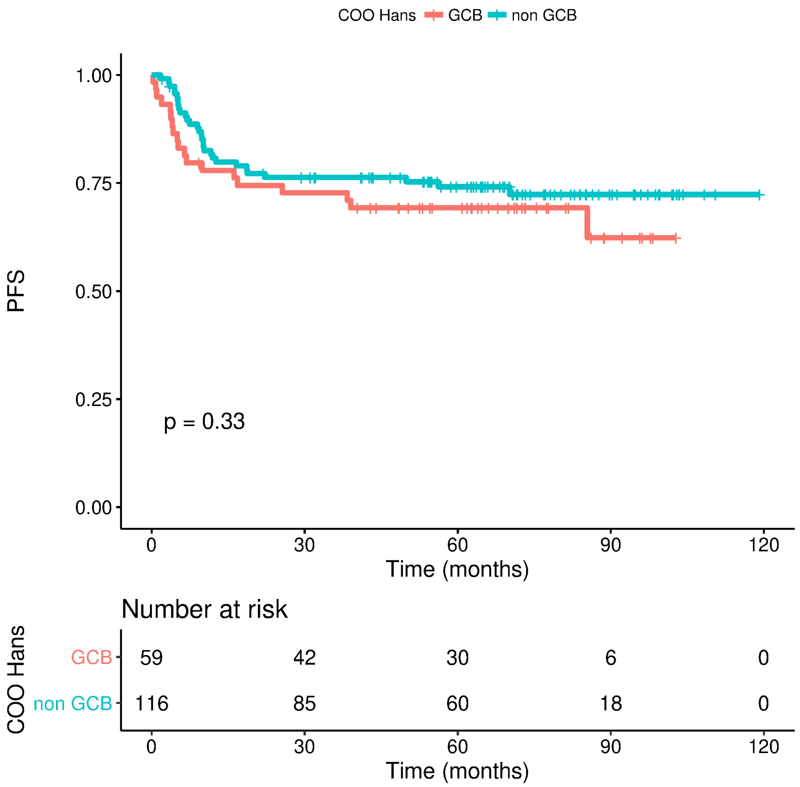
In both trials, only patients staged III-IV were enrolled, all treated with R-CHOP or R-CHOP-like therapies followed or not by Auto-SCT.

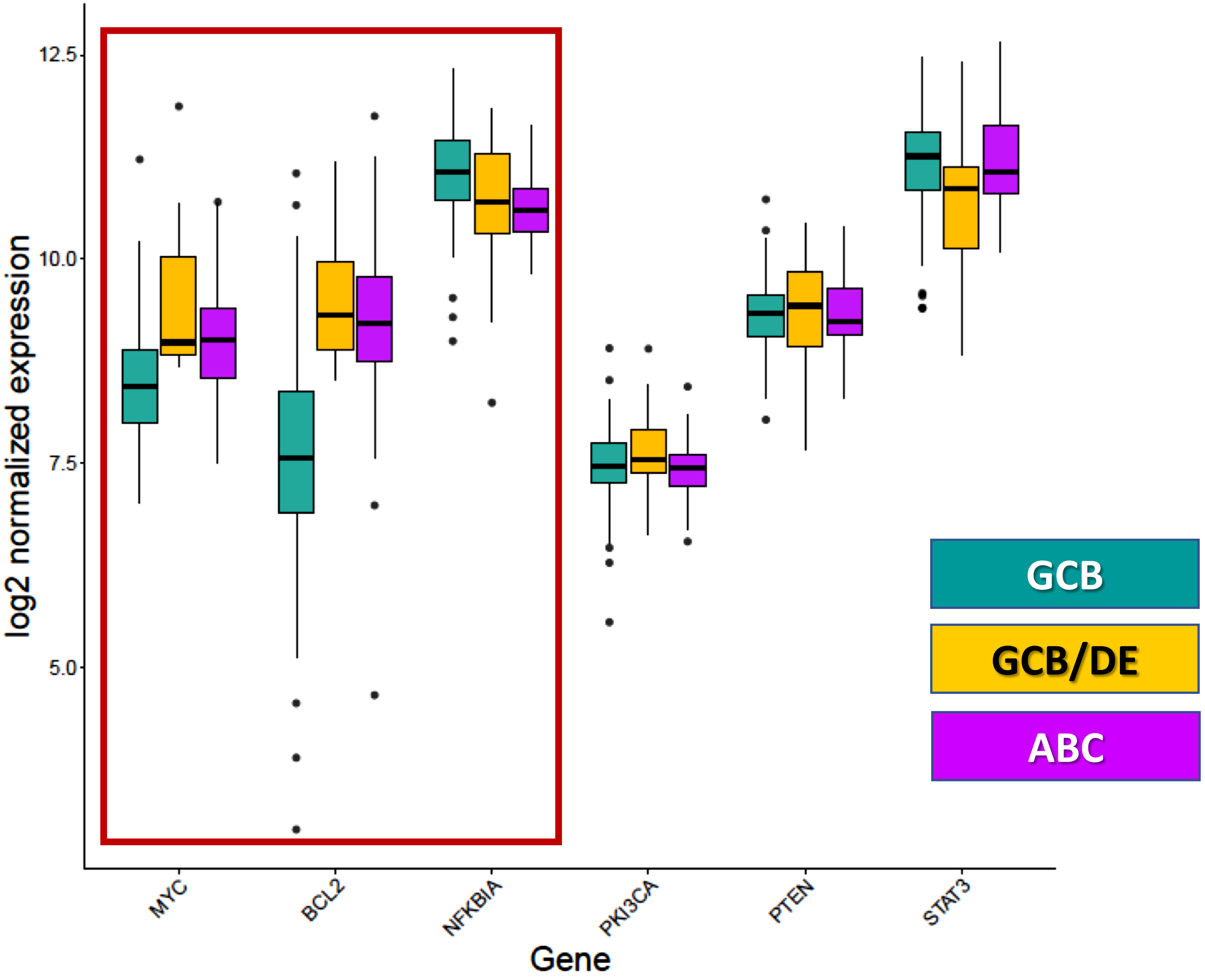
The mean age was 52 yr.s (18 – 65)

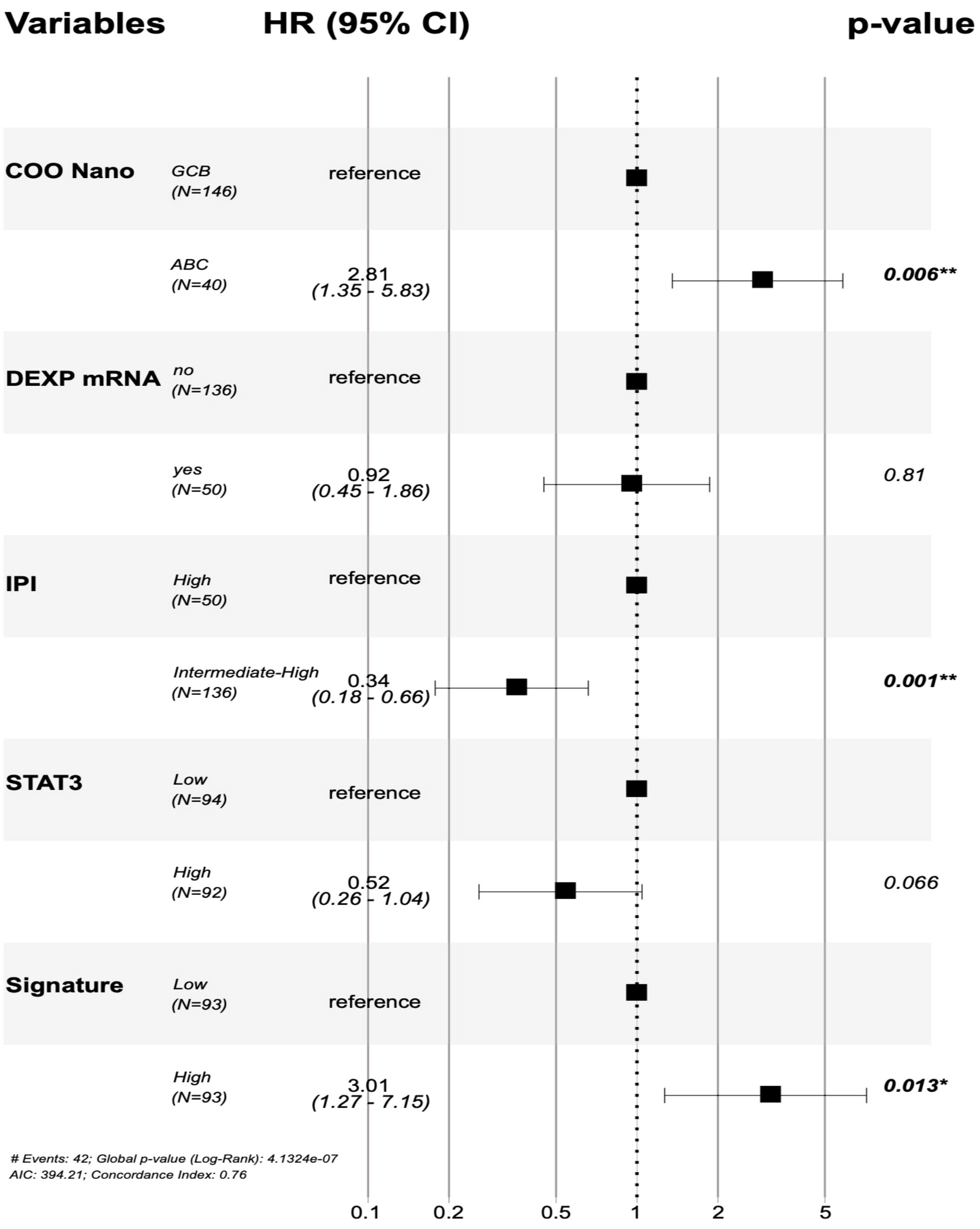
All the cases were studied by immunohistochemistry, targeted GEP and FISH (*BCL2*, *MYC* and *BCL6*).

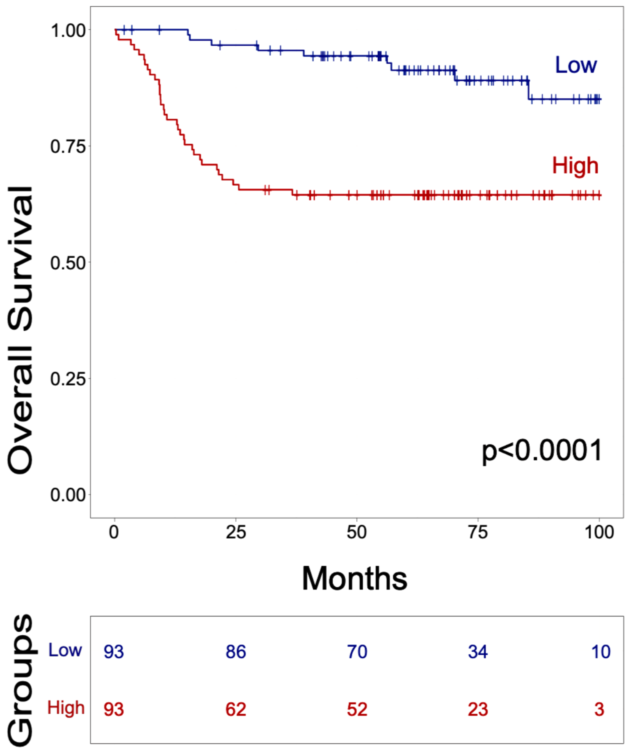
COO according to Hans' classifier

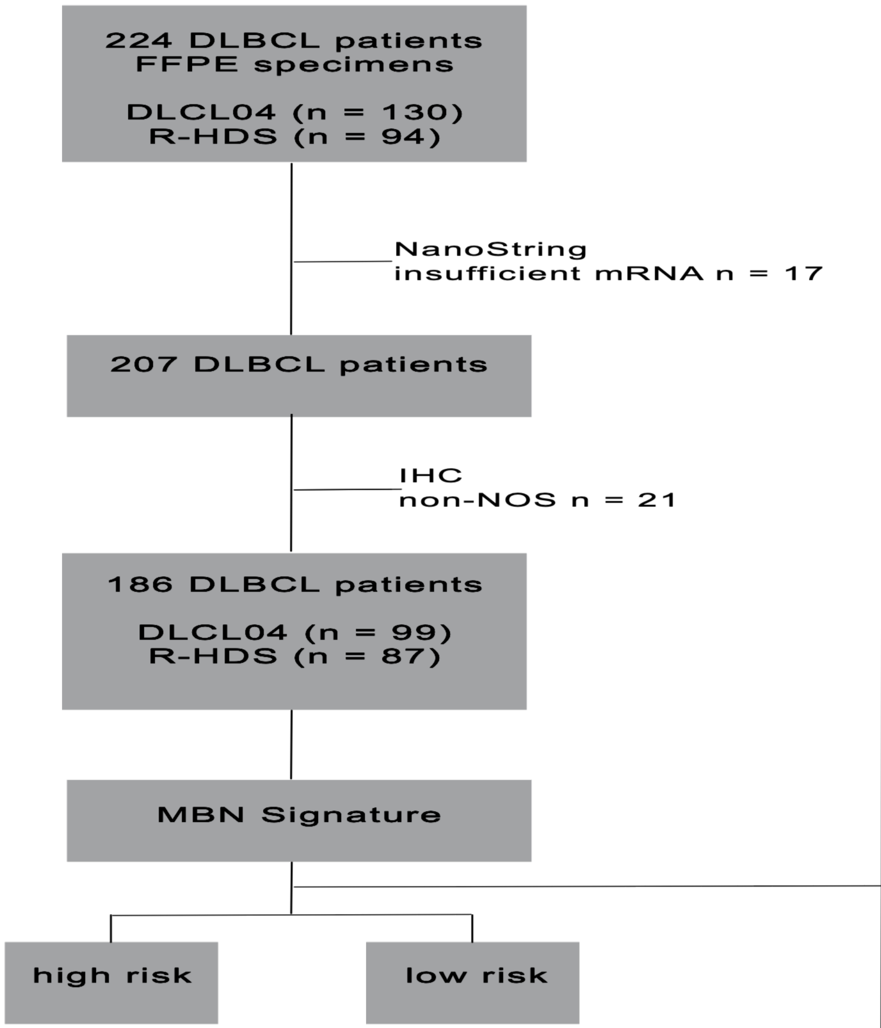





12.5
10.0
7.5
5.0
log2 normalized expression
MYC
BCL2
NFKBIA
PKI3CA
PTEN
STAT3
Gene
GCB
GCB/DE
ABC


Variables
HR (95% CI)
p-value
COO Nano
GCB (N=146)
reference
ABC (N=40)
2.81 (1.35 - 5.83)
0.006**
DEXP mRNA
no (N=136)
reference
yes (N=50)
0.92 (0.45 - 1.86)
0.81
IPI
High (N=50)
reference
Intermediate-High (N=136)
0.34 (0.18 - 0.66)
0.001**
STAT3
Low (N=94)
reference
High (N=92)
0.52 (0.26 - 1.04)
0.066
Signature
Low (N=93)
reference
High (N=93)
3.01 (1.27 - 7.15)
0.013*
Events: 42; Global p-value (Log-Rank): 4.1324e-07
AIC: 394.21; Concordance Index: 0.76
0.1
0.2
0.5
1
2
5


Overall Survival
1.00
0.75
0.50
0.25
0.00
Low
High
p<0.0001
0
25
50
75
100
Months
Groups
Low 93 86 70 34 10
High 93 62 52 23 3



224 DLBCL patients
FFPE specimens

DLCL04 (n = 130)
R-HDS (n = 94)

NanoString
insufficient mRNA n = 17

207 DLBCL patients

IHC
non-NOS n = 21

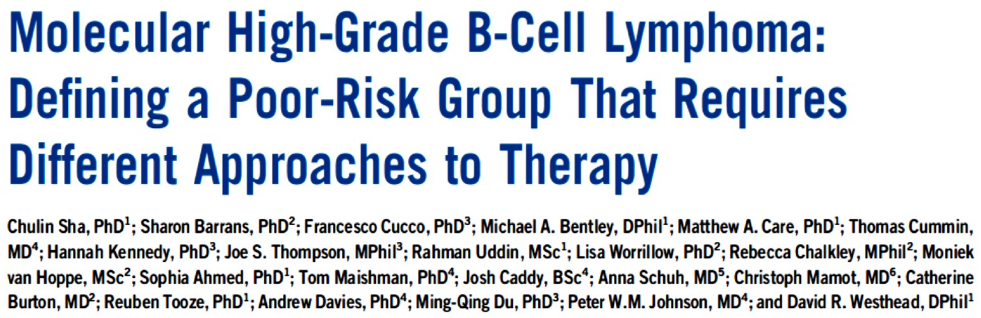
186 DLBCL patients

DLCL04 (n = 99)
R-HDS (n = 87)

MBN Signature

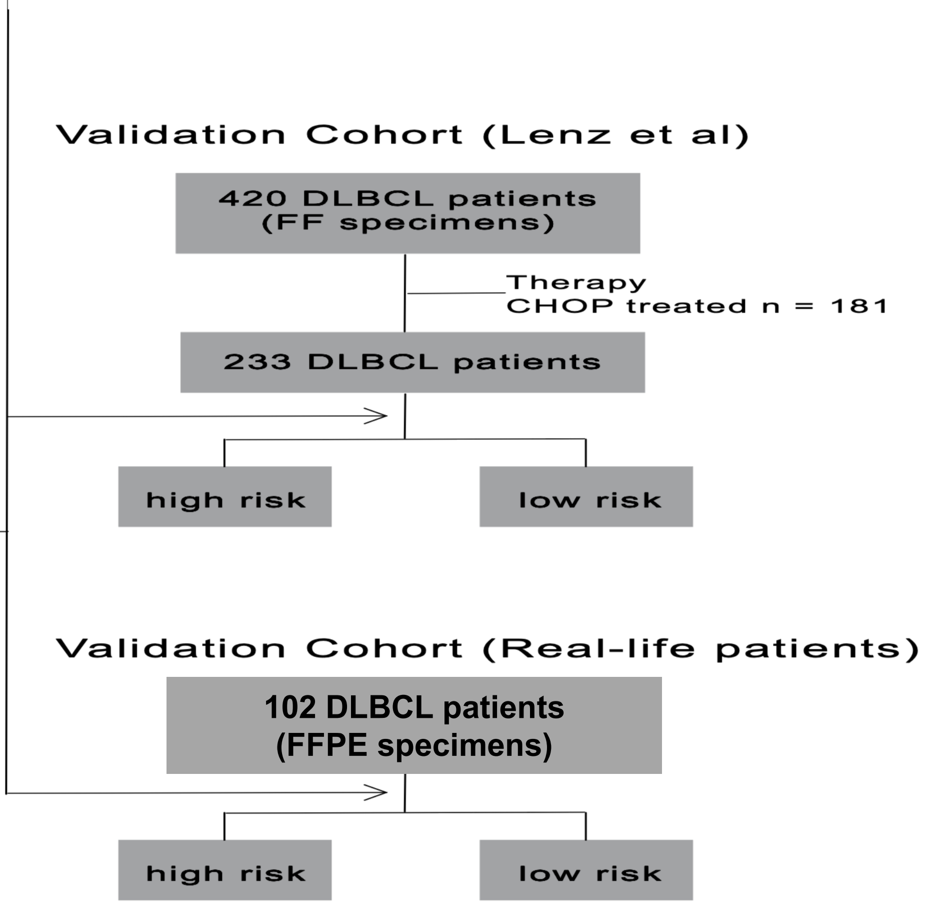
high risk

low risk



Molecular High-Grade B-Cell Lymphoma: Defining a Poor-Risk Group That Requires Different Approaches to Therapy

Chulin Sha, PhD[1]; Sharon Barrans, PhD[2]; Francesco Cucco, PhD[3]; Michael A. Bentley, DPhil[1]; Matthew A. Care, PhD[1]; Thomas Cummin, MD[4]; Hannah Kennedy, PhD[3]; Joe S. Thompson, MPhil[3]; Rahman Uddin, MSc[1]; Lisa Worrillow, PhD[2]; Rebecca Chalkley, MPhil[2]; Moniek van Hoppe, MSc[2]; Sophia Ahmed, PhD[1]; Tom Maishman, PhD[4]; Josh Caddy, BSc[4]; Anna Schuh, MD[5]; Christoph Mamot, MD[6]; Catherine Burton, MD[2]; Reuben Tooze, PhD[1]; Andrew Davies, PhD[4]; Ming-Qing Du, PhD[3]; Peter W.M. Johnson, MD[4]; and David R. Westhead, DPhil[1]



Validation Cohort (Lenz et al)

420 DLBCL patients
(FF specimens)

Therapy
CHOP treated n = 181

233 DLBCL patients

high risk

low risk

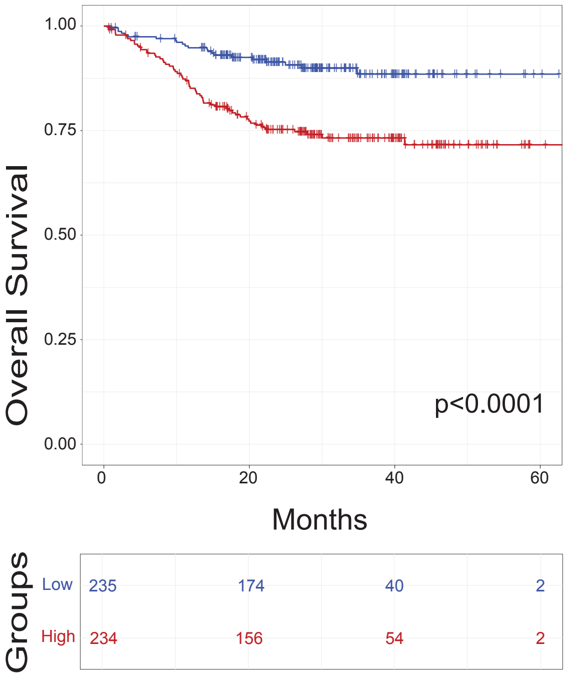
Validation Cohort (Real-life patients)

102 DLBCL patients
(FFPE specimens)

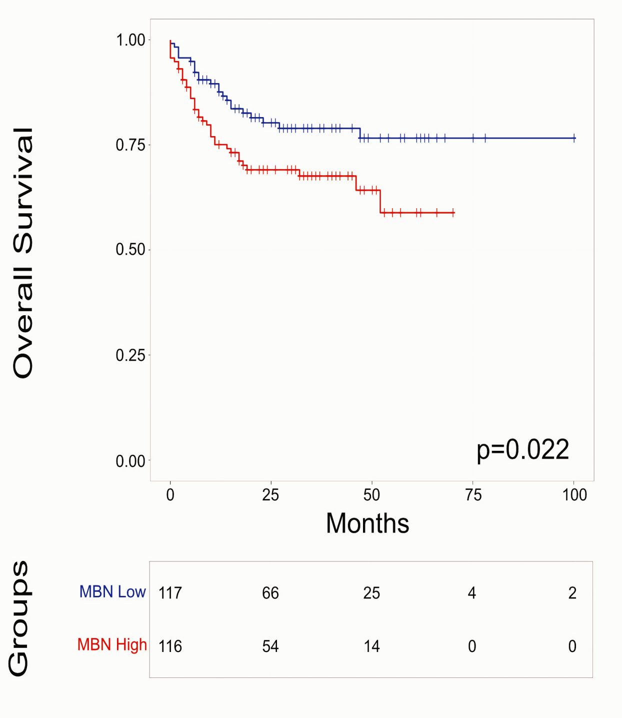
high risk

low risk

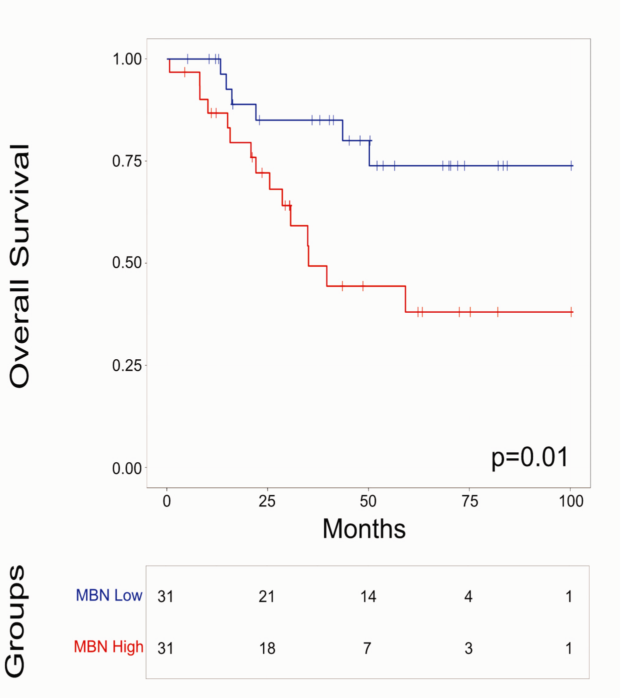
Sha’s



Lenz’s

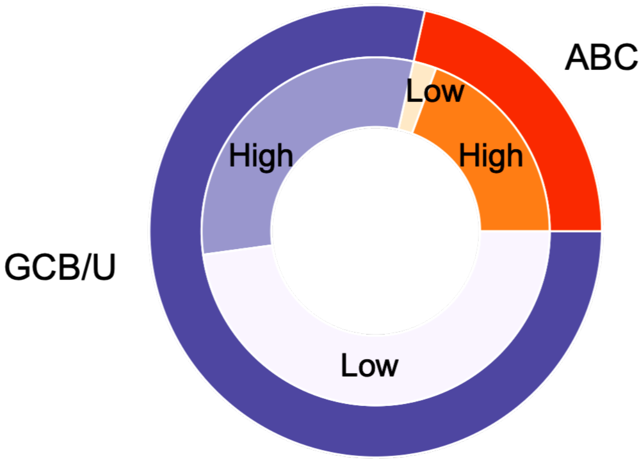


Real-life

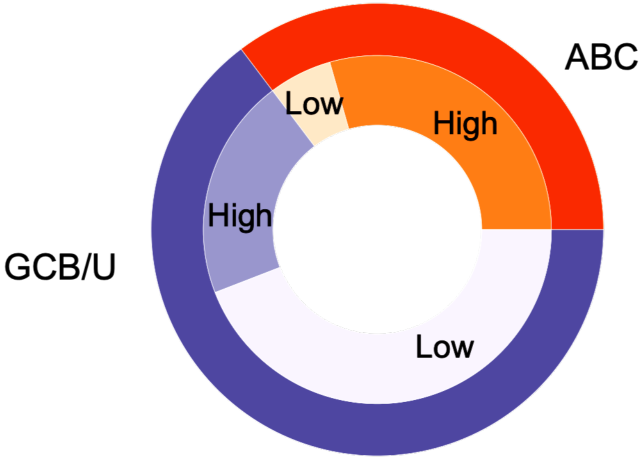


R-CHOP

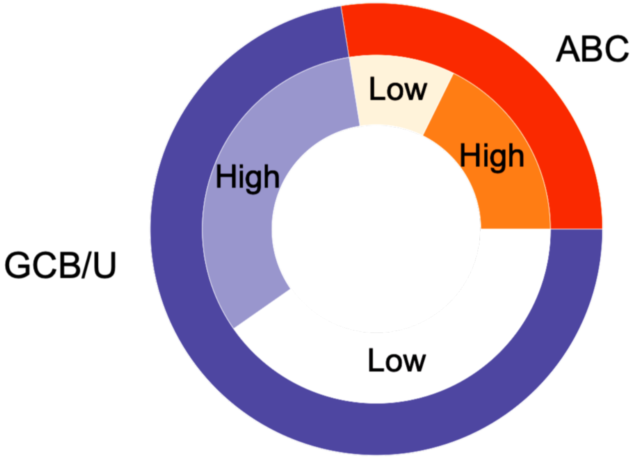
TRIALS n = 186

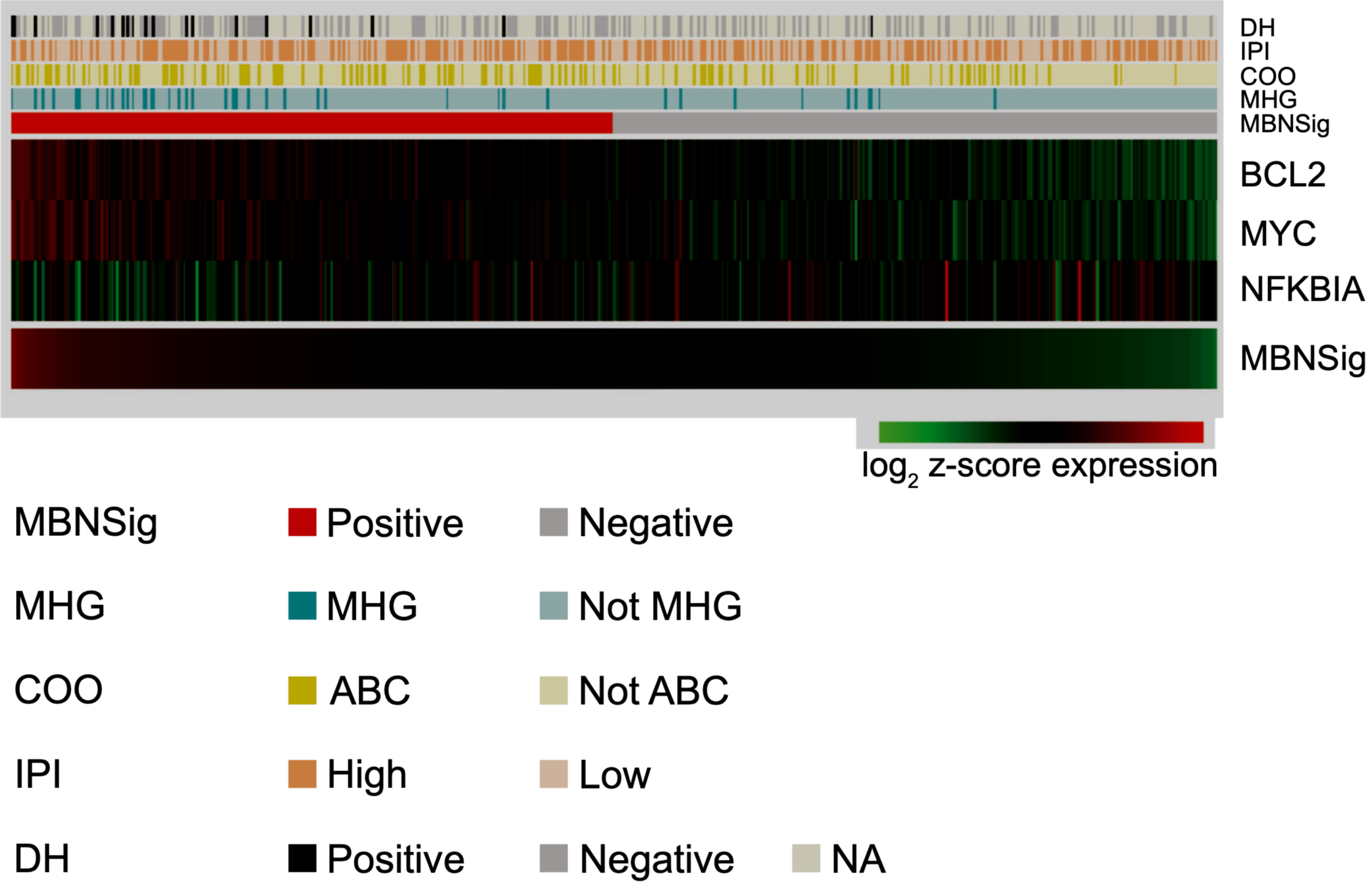


REAL-LIFE n = 102



SHA COHORT n = 469



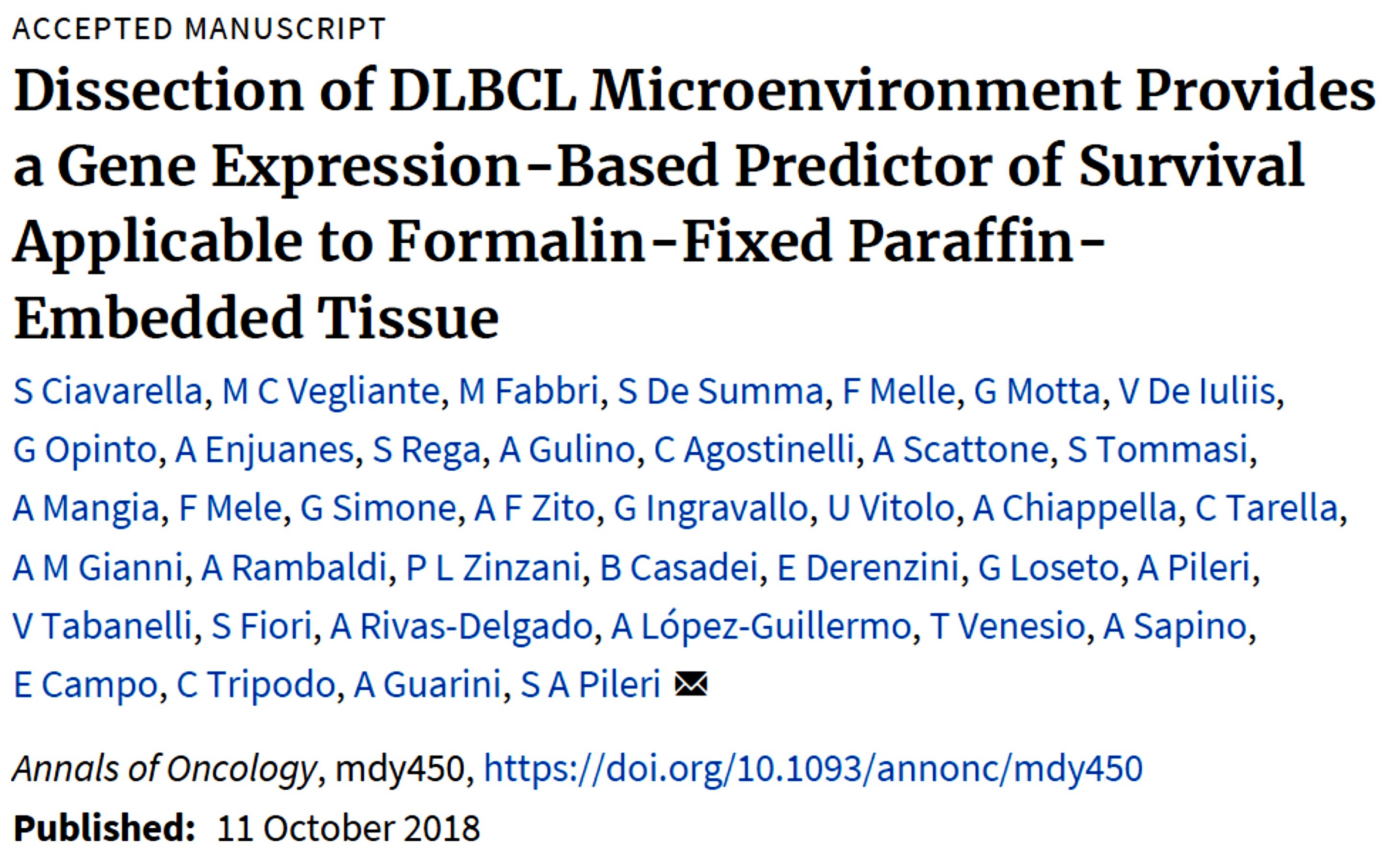

DH
IPI
COO
MHG
MBNSig
BCL2
MYC
NFKBIA
MBNSig
log$_2$ z-score expression
MBNSig
Positive
Negative
MHG
MHG
Not MHG
COO
ABC
Not ABC
IPI
High
Low
DH
Positive
Negative
NA

Longitudinal expression profiling identifies a poor risk subset of patients with ABC-type diffuse large B-cell lymphoma

Submitted 18 March 2022; accepted 25 July 2022; prepublished online on *Blood Advances* First Edition 10 August 2022; final version published online 6 March 2023.

Findlay Bewicke-Copley,[1] Koorosh Korfi,[1] Shamzah Araf,[1] Brendan Hodkinson,[2] Emil Kumar,[1] Thomas Cummin,[3] Margaret Ashton-Key,[4] Sharon Barrans,[5] Suzan van Hoppe,[5] Cathy Burton,[5] Mohamed Elshiekh,[6] Simon Rule,[7] Nicola Crosbie,[8] Andrew Clear,[9] Maria Calaminici,[9] Hendrik Runge,[10] Robert K. Hills,[11] David W. Scott,[12] Lisa M. Rimsza,[13] Geetha Menon,[14] Chulin Sha,[15] John R. Davies,[15] Ai Nagano,[1] Andrew Davies,[3] Daniel Painter,[16] Alexandra Smith,[16] John Gribben,[9] Kikkeri N. Naresh,[6] David R. Westhead,[15] Jessica Okosun,[9] Andrew Steele,[17] Daniel J. Hodson,[10] Sriram Balasubramanian,[17] Peter Johnson,[3] Jun Wang,[1,*] and Jude Fitzgibbon[1,*]

Microenvironment (ME)



ACCEPTED MANUSCRIPT

Dissection of DLBCL Microenvironment Provides a Gene Expression–Based Predictor of Survival Applicable to Formalin-Fixed Paraffin-Embedded Tissue

S Ciavarella, M C Vegliante, M Fabbri, S De Summa, F Melle, G Motta, V De Iuliis, G Opinto, A Enjuanes, S Rega, A Gulino, C Agostinelli, A Scattone, S Tommasi, A Mangia, F Mele, G Simone, A F Zito, G Ingravallo, U Vitolo, A Chiappella, C Tarella, A M Gianni, A Rambaldi, P L Zinzani, B Casadei, E Derenzini, G Loseto, A Pileri, V Tabanelli, S Fiori, A Rivas-Delgado, A López-Guillermo, T Venesio, A Sapino, E Campo, C Tripodo, A Guarini, S A Pileri ✉

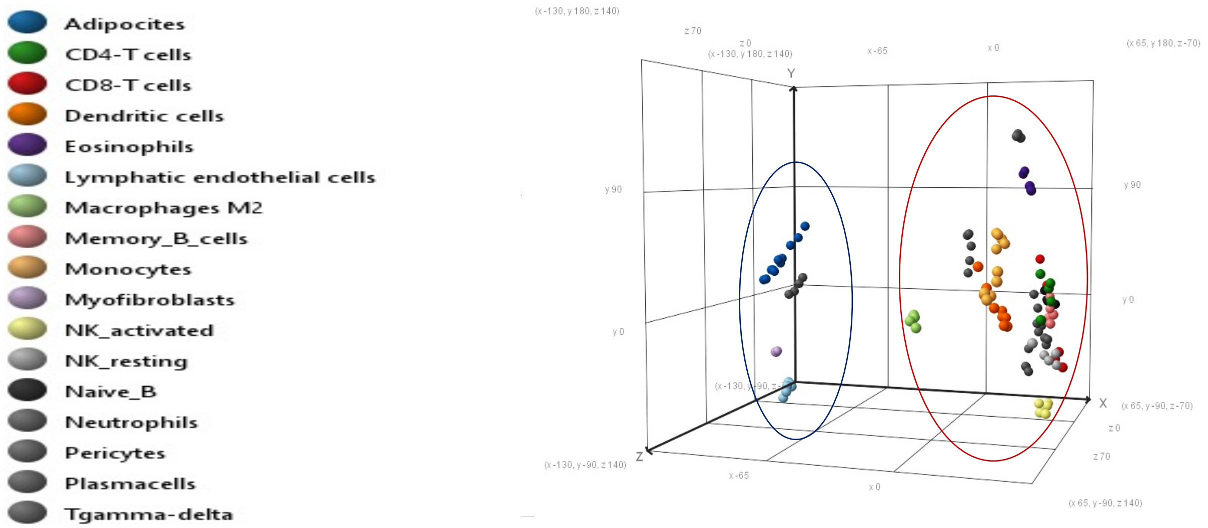
Annals of Oncology, mdy450, https://doi.org/10.1093/annonc/mdy450

Published: 11 October 2018

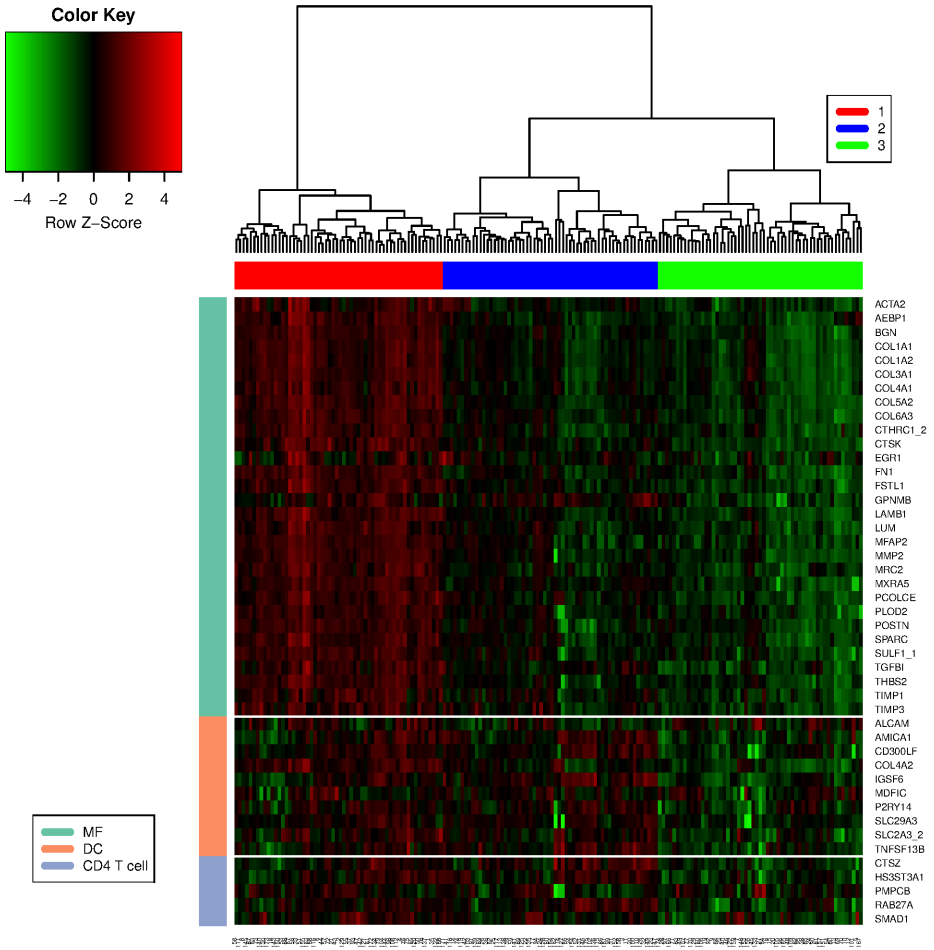
CIBERSORT analysis and selection of prognostic genes

A customized signature including 1,028 genes was generated to distinguish 17 cell types of both stromal and immune origin.

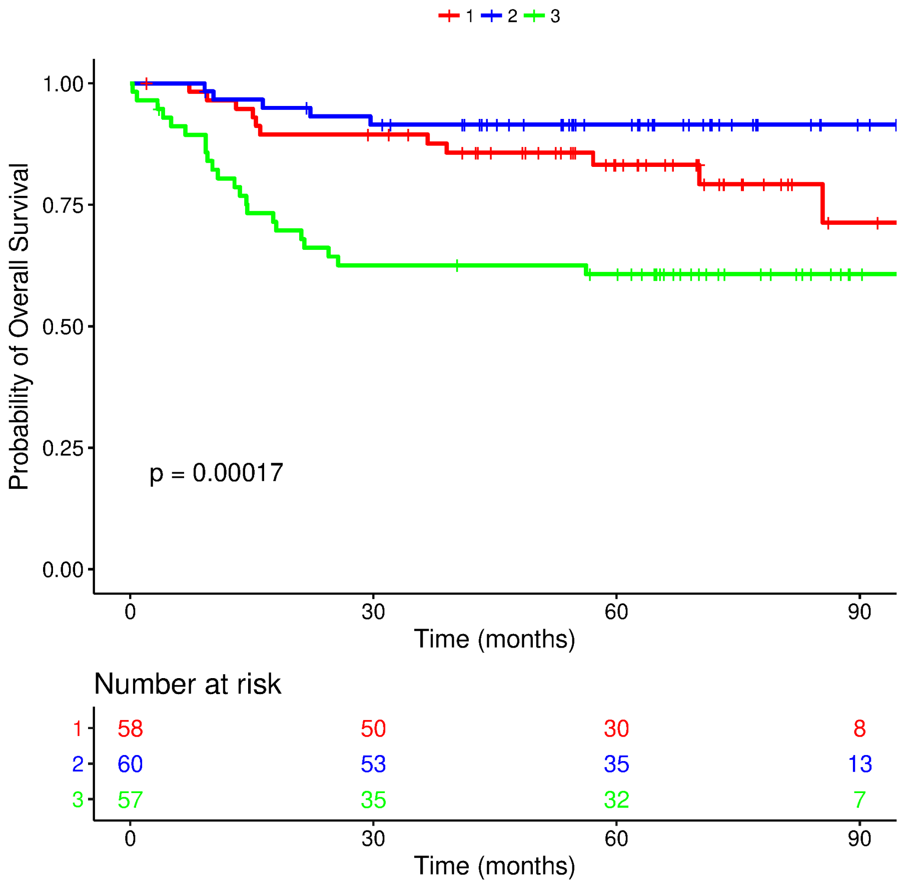
PCA



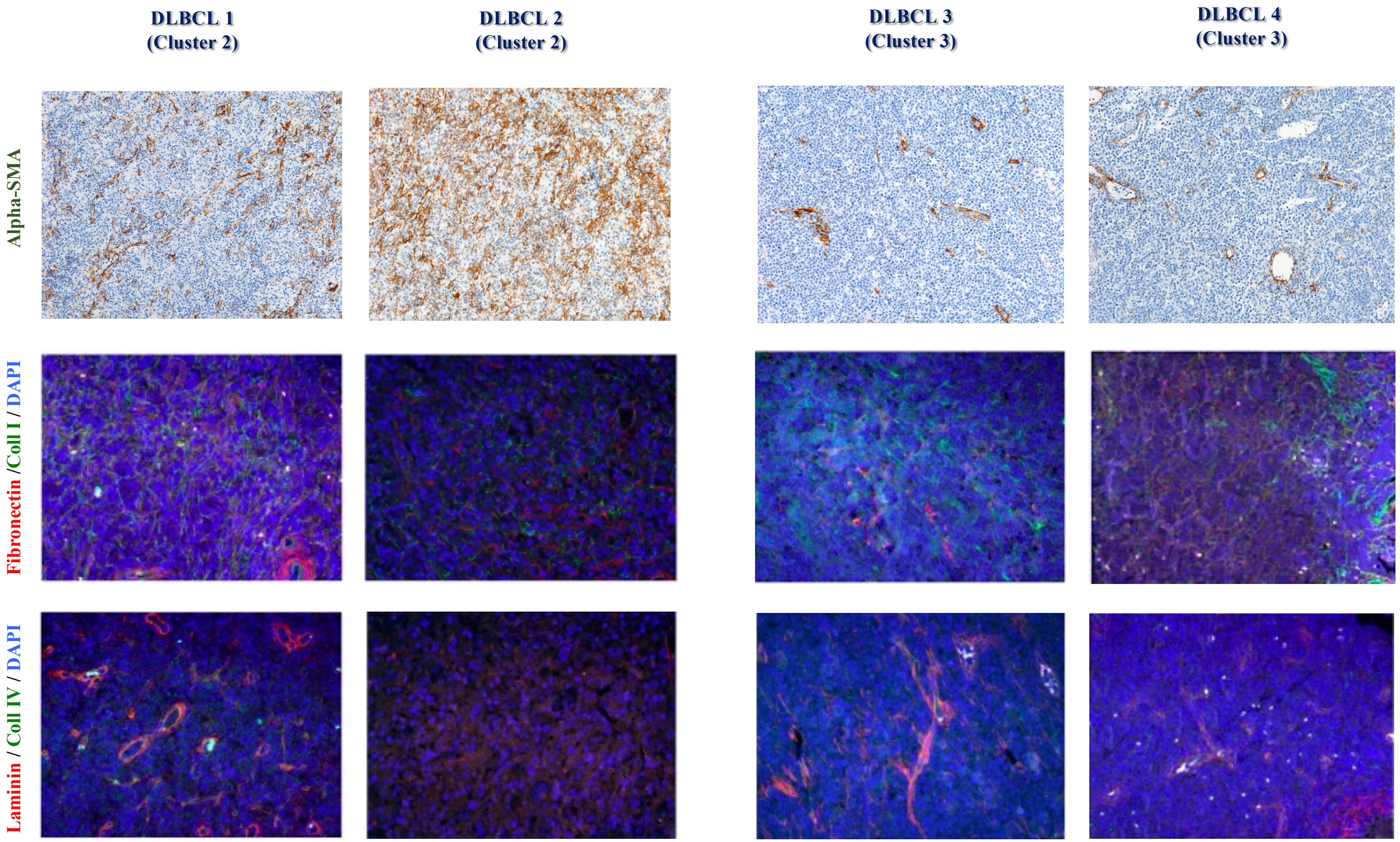
MF-related genes	*ACTA2*	Actin, alpha 2, smooth muscle
	AEBP1	AE binding protein 1
	BGN	Biglycan
	COL1A1	Collagen type I alpha 1
	COL1A2	Collagen type I alpha 2
	COL3A1	Collagen type III alpha 1
	COL4A1	Collagen type IV alpha 1
	COL5A2	Collagen type V alpha 2
	COL6A3	Collagen type VI alpha 3
	CTHRC1	Collagen triple helix repeat containing 1
	CTSK	Cathepsin K
	EGR1	Early growth response 1
	FN1	Fibronectin 1
	FSTL1	Follistatin like 1
	GPNMB	Glycoprotein nmb
	LAMB1	Laminin subunit beta 1
	LUM	Lumican
	MFAP2	Microfibrillar associated protein 2
	MMP2	Matrix metallopeptidase 2
	MRC2	Mannose receptor, C type 2
	MXRA5	Matrix-Remodelling Associated 5
	PCOLCE	Procollagen C-endopeptidase enhancer
	PLOD2	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2
	POSTN	Periostin, osteoblast specific factor
	SPARC	Secreted protein acidic and cysteine rich
	SULF1	Sulfatase 1
	TGFBI	Transforming growth factor beta induced
DC-related genes	*ALCAM*	Activated leukocyte cell adhesion molecule
	AMICA1	Adhesion molecule, interacts with CXADR antigen 1
	CD300LF	CD300 molecule-like family member F
	COL4A2	Collagen, type IV, alpha 2
	IGSF6	Immunoglobulin superfamily, member 6
	MDFIC	MyoD Family Inhibitor Domain Containing
	P2RY14	Purinergic receptor P2Y, G-protein coupled, 14
	SLC29A3	Solute carrier family 29 (nucleoside transporters), member 3;
	SLC2A3	Solute carrier family 2 (facilitated glucose transporter),
CD4$^+$ T cell-related genes	*CTSZ*	Cathepsin Z
	HS3ST3A1	Heparan Sulfate-Glucosamine 3-Sulfotransferase 3A1
	PMPCB	Peptidase, Mitochondrial Processing Beta Subunit
	RAB27A	RAB27A, Member RAS Oncogene Family
	SMAD1	SMAD Family Member 1



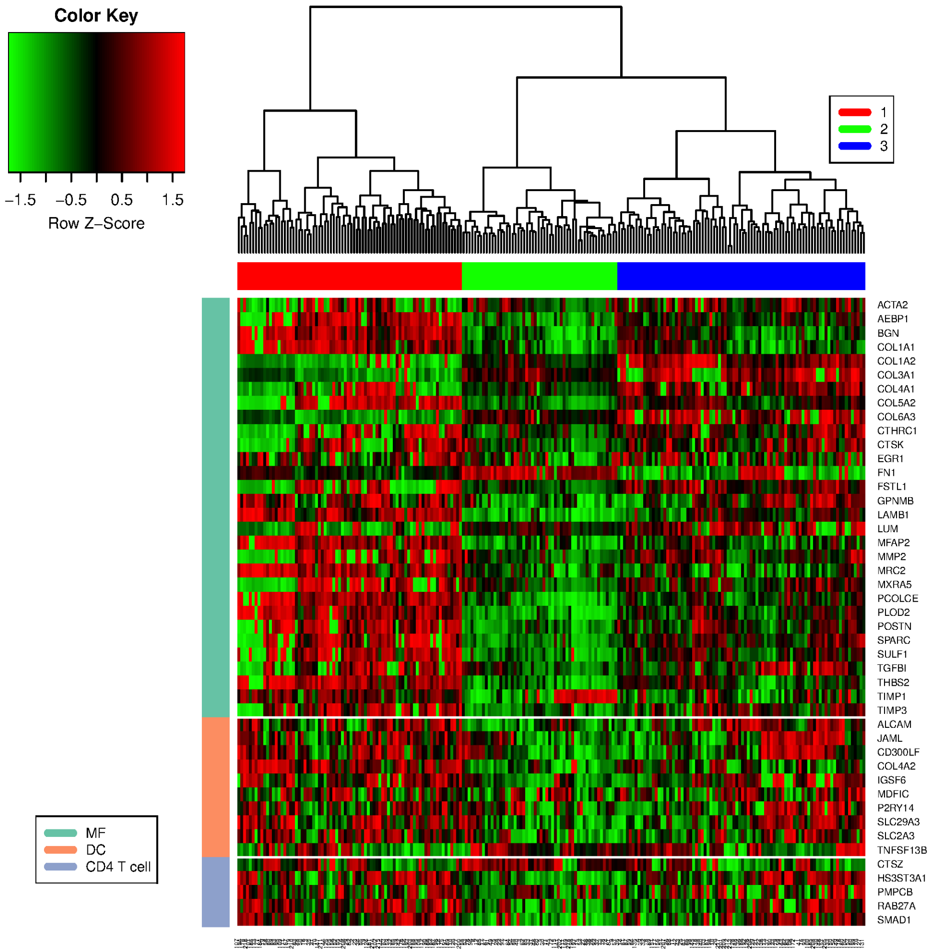
DLCL04 and R-HDS0305

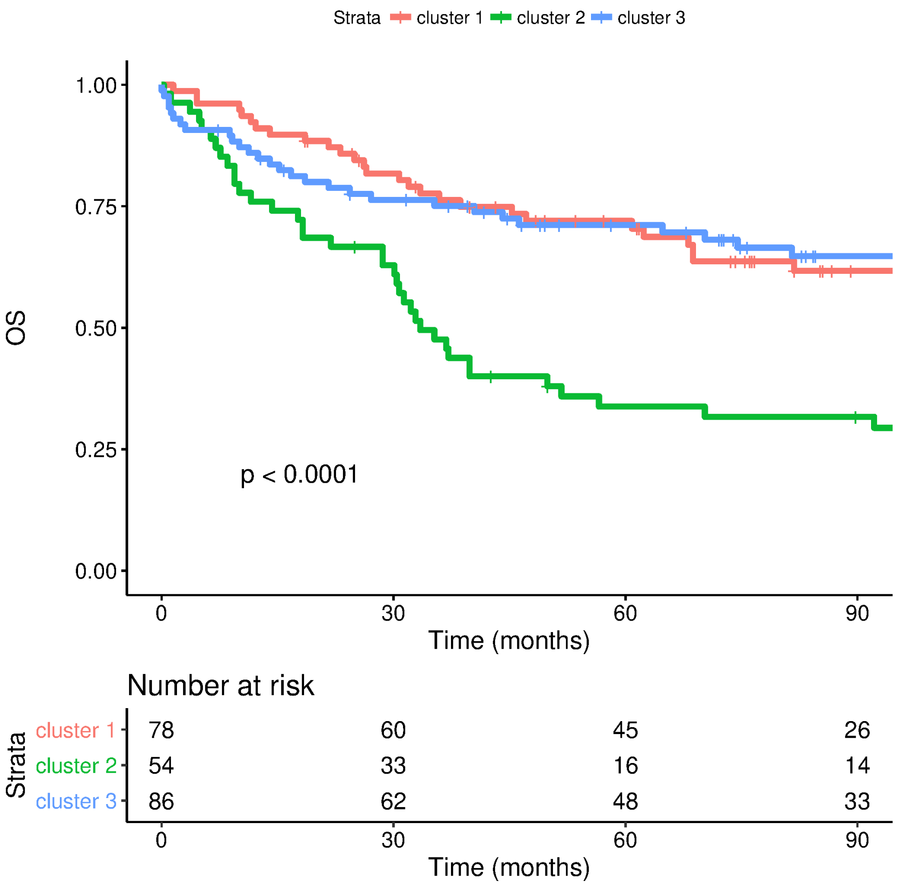


By *in situ* immunostaining we analyzed the expression of ECM proteins encoded by four of the fronting genes of the MF signature, namely Fibronectin, Collagen-I, Laminin, and Collagen-IV. However, the expression variability of these proteins does not support the use of immunohistochemistry as a reliable assay to provide insight on the prognostic gene expression patterns of DLBCL microenvironment determinants.

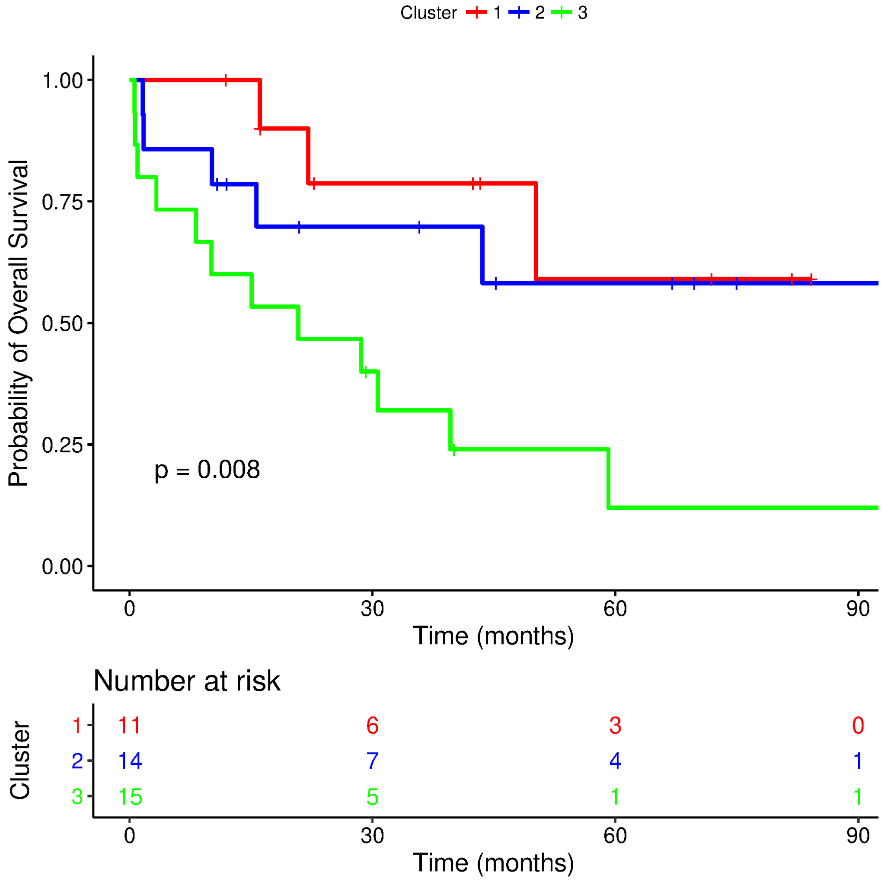


Lenz' series

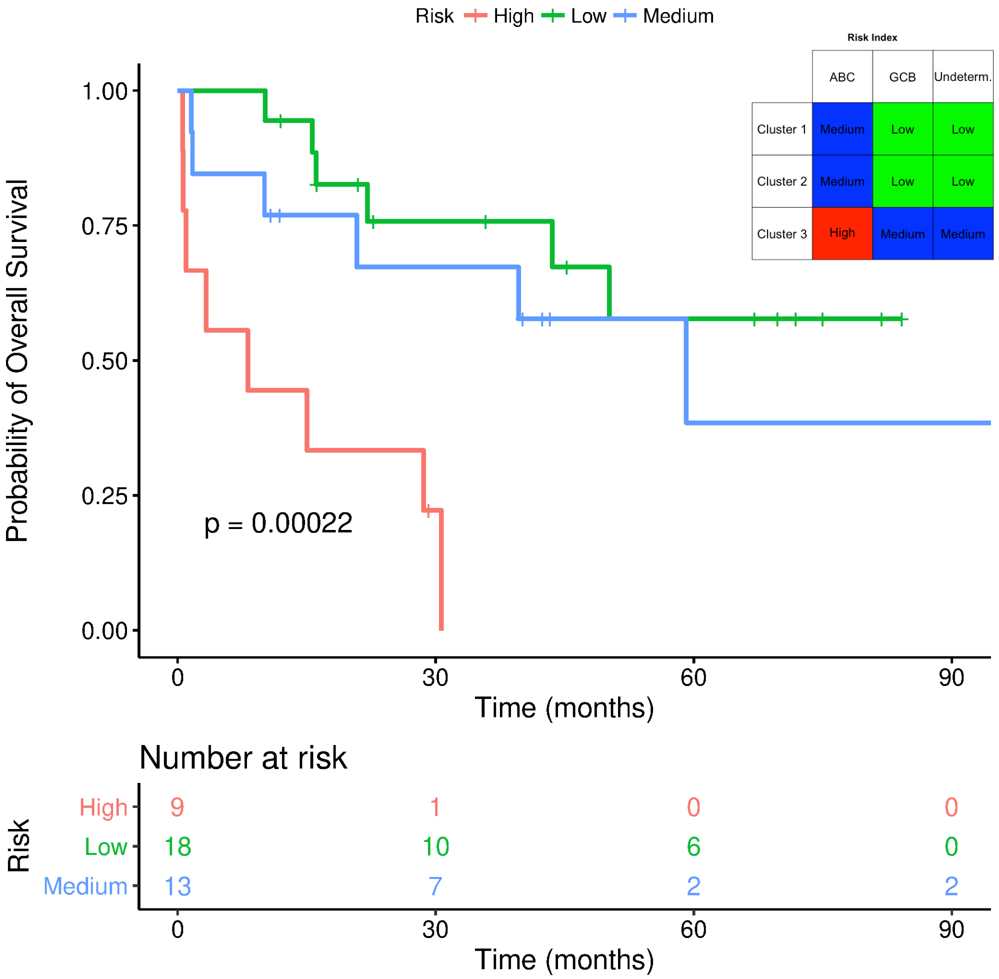

Color Key
−1.5
−0.5
0.5
1.5
Row Z−Score
1
2
3
ACTA2
AEBP1
BGN
COL1A1
COL1A2
COL3A1
COL4A1
COL5A2
COL6A3
CTHRC1
CTSK
EGR1
FN1
FSTL1
GPNMB
LAMB1
LUM
MFAP2
MMP2
MRC2
MXRA5
PCOLCE
PLOD2
POSTN
SPARC
SULF1
TGFBI
THBS2
TIMP1
TIMP3
ALCAM
JAML
CD300LF
COL4A2
IGSF6
MDFIC
P2RY14
SLC29A3
SLC2A3
TNFSF13B
CTSZ
HS3ST3A1
PMPCB
RAB27A
SMAD1
MF
DC
CD4 T cell


Strata
cluster 1
cluster 2
cluster 3
OS
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
30
60
90
Time (months)
Number at risk
Strata
cluster 1
cluster 2
cluster 3
78
60
45
26
54
33
16
14
86
62
48
33
0
30
60
90
Time (months)

Real-life



Cluster	0	30	60	90
1	11	6	3	0
2	14	7	4	1
3	15	5	1	1



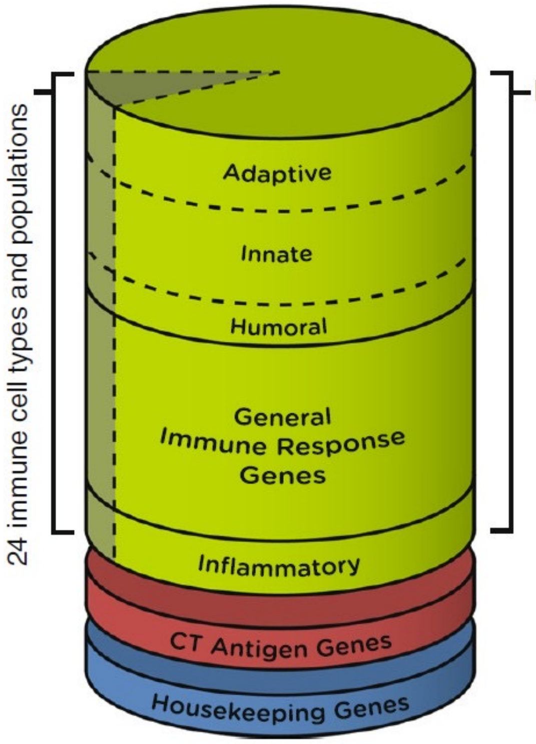
Risk	0	30	60	90
High	9	1	0	0
Low	18	10	6	0
Medium	13	7	2	2

Risk Index

	ABC	GCB	Undeterm.
Cluster 1	Medium	Low	Low
Cluster 2	Medium	Low	Low
Cluster 3	High	Medium	Medium

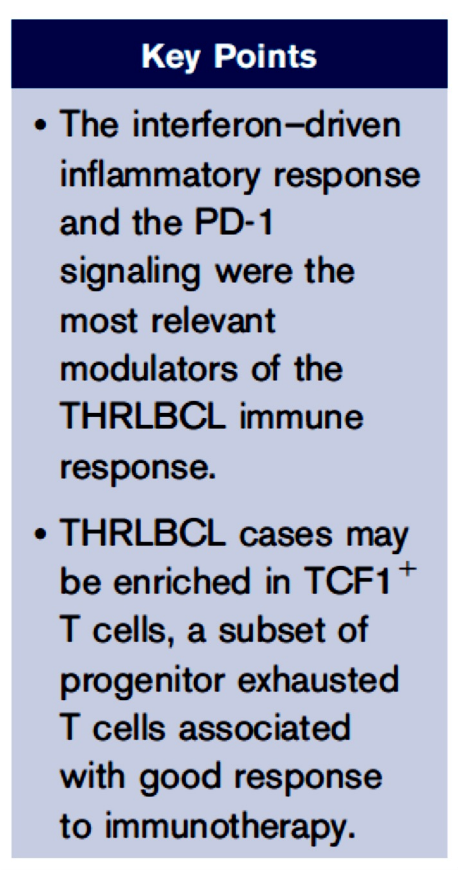
PanCancer Immune Profiling Panel (PCIP)

- A multiplexed gene expression approach to profiling cancer immunology
  - Quantify infiltrating immune cells in a tumor microenvironment
  - Assess immunological activity and response to therapeutic intervention
  - Identify tumor-specific antigens



Immune response categories:
- B cell functions
- T cell functions
- NK cell functions
- antigen processing
- adhesion
- cell cycle
- chemokines
- complement
- cytokines
- interleukins
- leukocyte functions
- marcrophage functions
- microglial functions
- pathogen defense
- senescence
- TLR
- TNF super family
- transporter functions

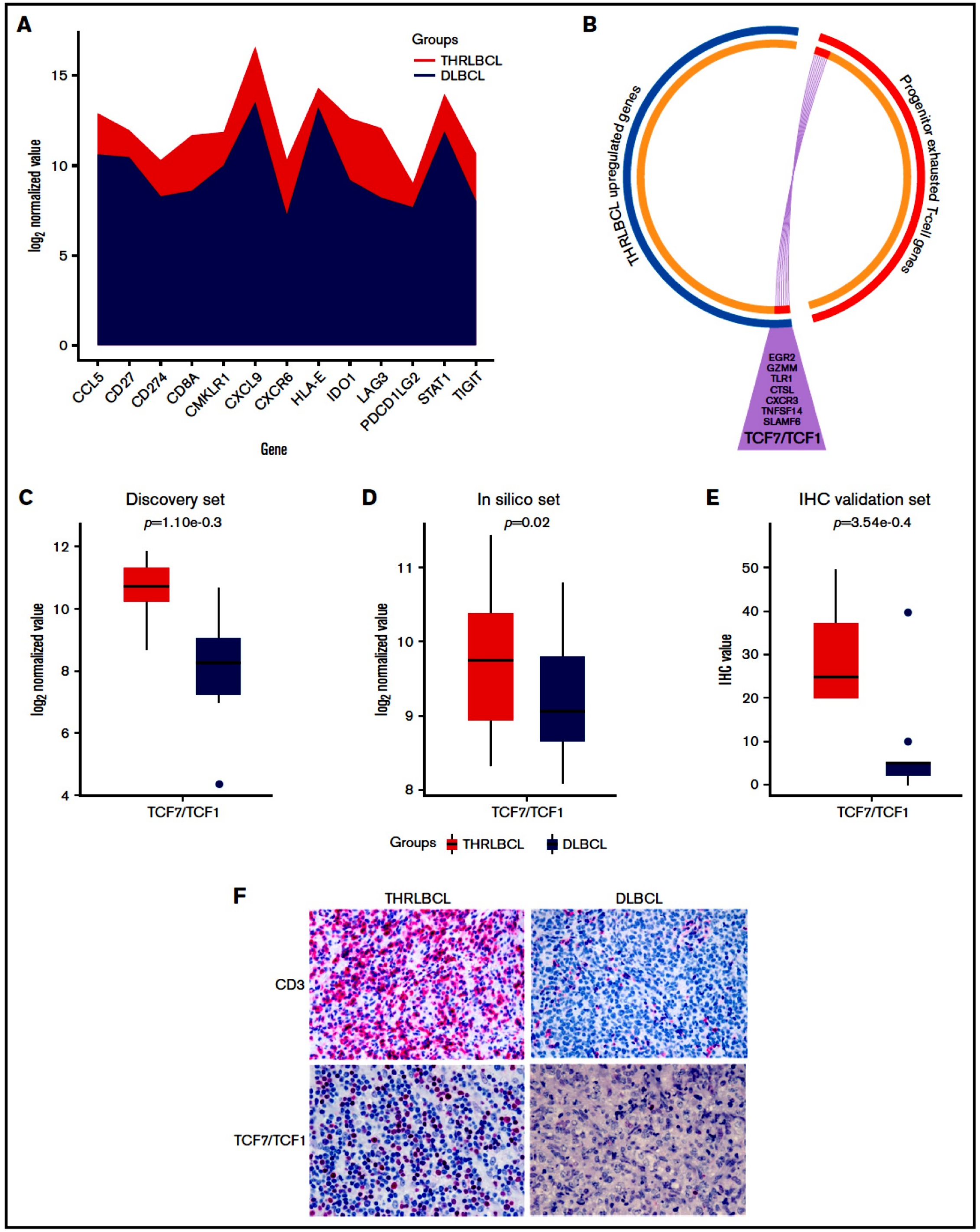
Discovery set: 12 THRBCLs vs. 10 DLBCLs, NOS

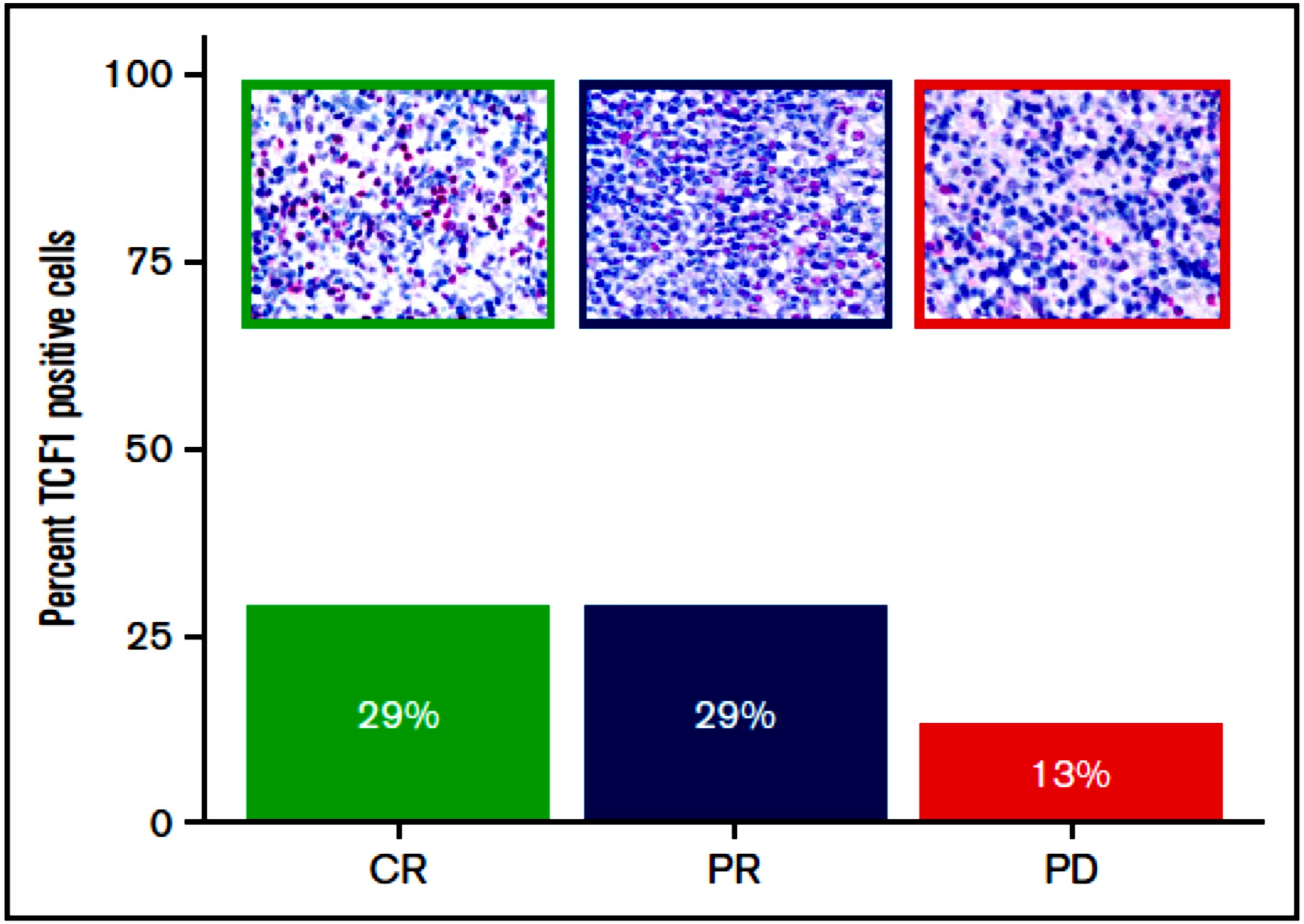


Key Points

- The interferon–driven inflammatory response and the PD-1 signaling were the most relevant modulators of the THRLBCL immune response.
- THRLBCL cases may be enriched in TCF1$^+$ T cells, a subset of progenitor exhausted T cells associated with good response to immunotherapy.

***In silico*: 31 THRBCLs vs. 473 DLBCLs, NOS**
IHC: 15 THRBCLs vs. 26 DLBCLs, NOS




Percent TCF1 positive cells
100
75
50
25
0
29%
29%
13%
CR
PR
PD

Spatial-omics for Every Spatial-scale

RNA and Protein

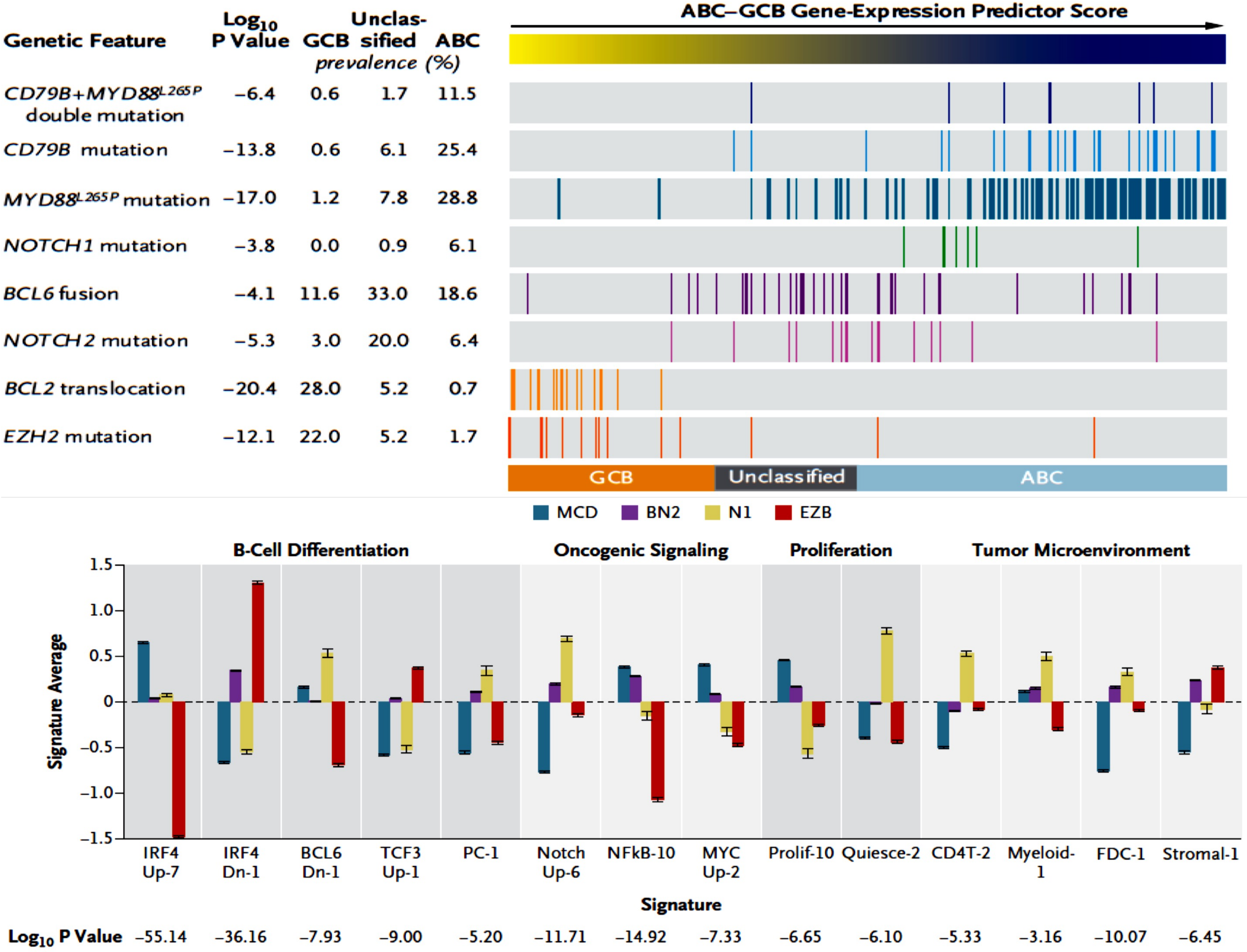
GeoMx DSP

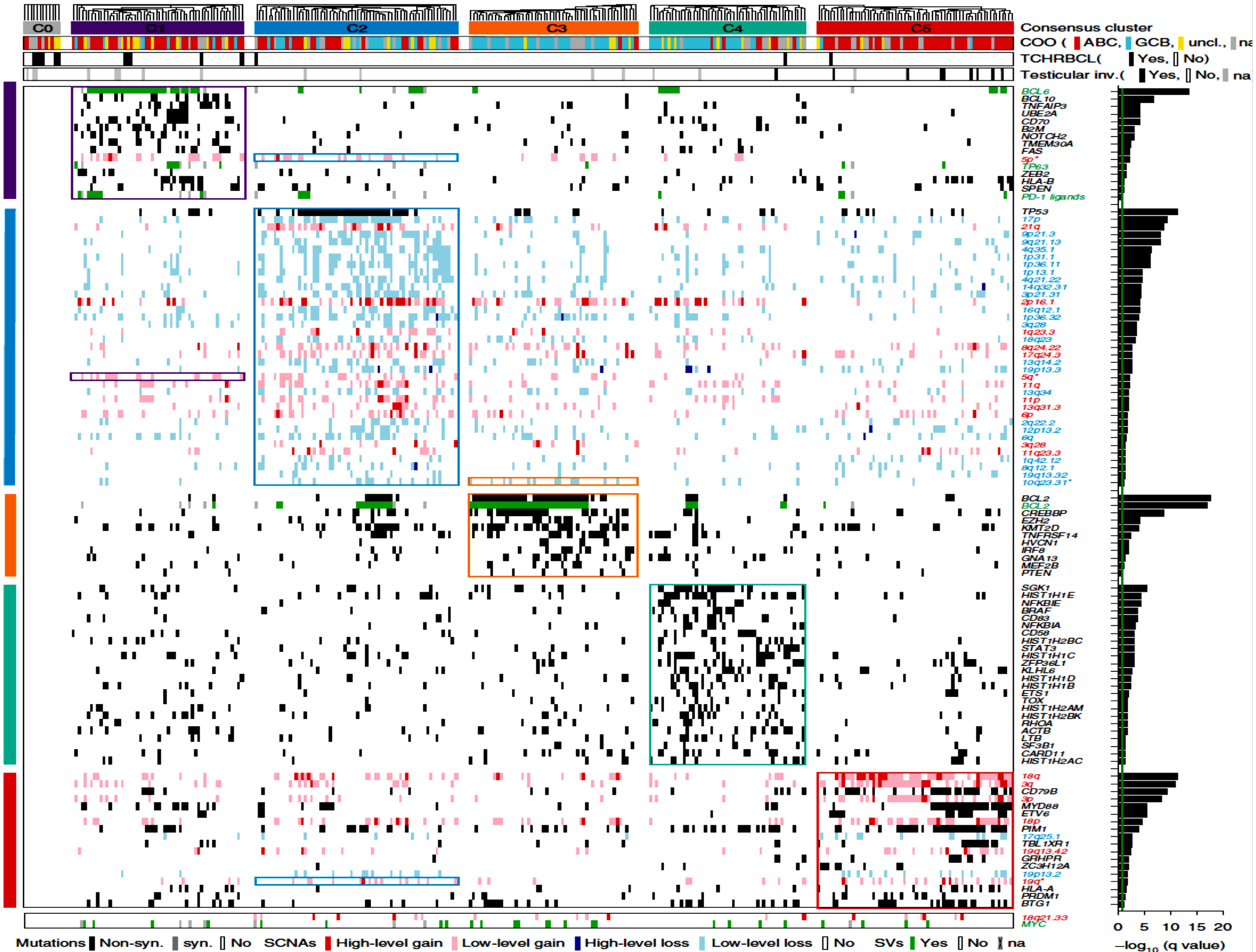
- Whole Transcriptome
- High Throughput
- Single Phenotype
- Unbiased Molecular Profile
- Difference Between Samples

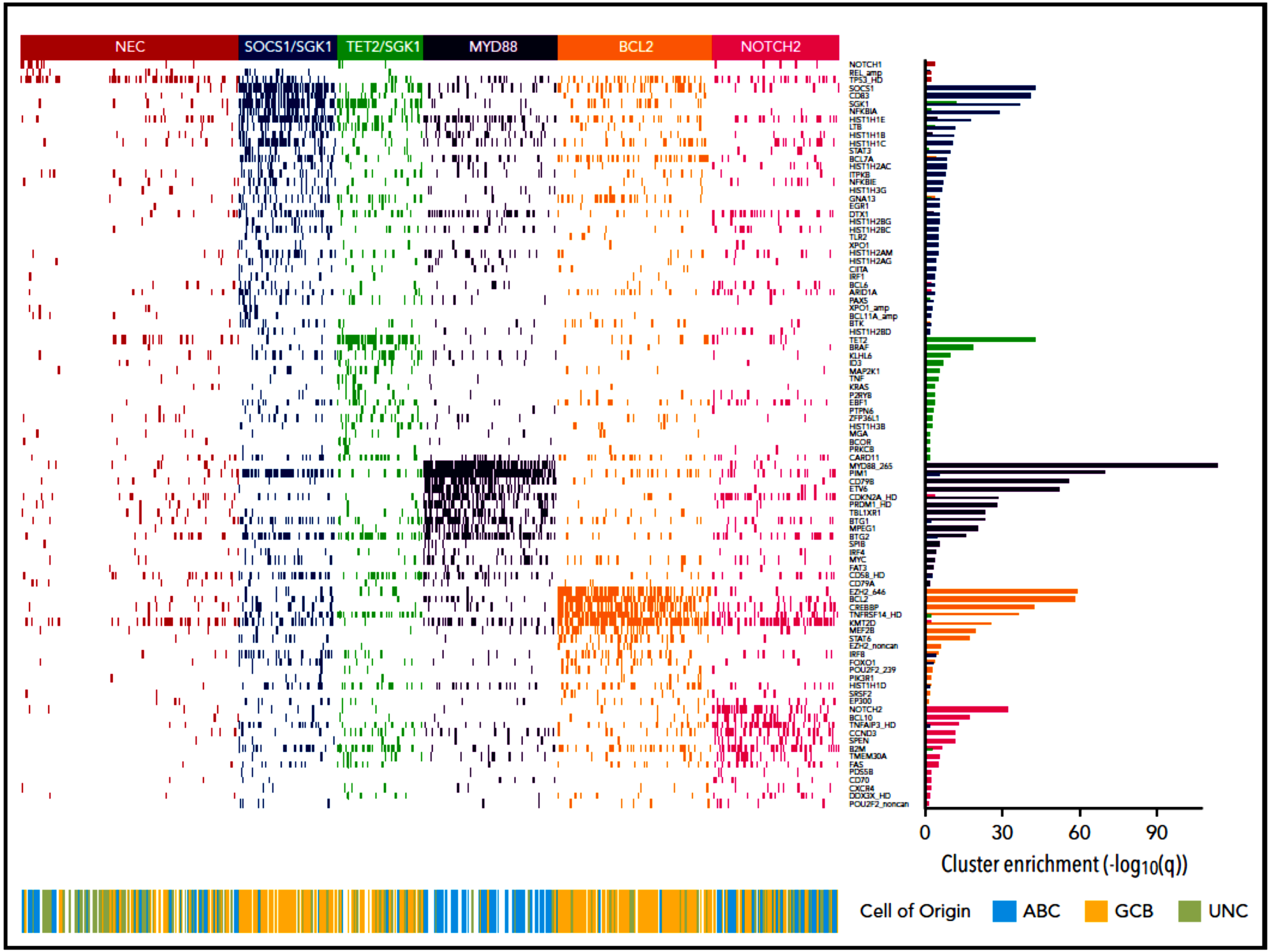
- Single-Cell Resolution
- Entire Tissue Section
- High Multiplexing
- Comprehensive Cell Type Map
- Difference Between Cell Type and Cell State

CosMx SMI

Next generation sequencing (NGS)




C0
C1
C2
C3
C4
C5
Consensus cluster
COO (ABC, GCB, uncl., na
TCHRBCL(Yes, No)
Testicular inv.(Yes, No, na
BCL6
BCL10
TNFAIP3
UBE2A
CD70
B2M
NOTCH2
TMEM30A
FAS
5p*
TP63
ZEB2
HLA-B
SPEN
PD-1 ligands
TP53
17p
21q
9p21.3
9q21.13
4q35.1
1p31.1
1p36.11
1p13.1
4q21.22
14q32.31
3p21.31
2p16.1
16q12.1
1p36.32
3q28
1q23.3
18q23
8q24.22
17q24.3
13q14.2
19p13.3
5q*
11q
13q34
11p
13q31.3
6p
2q22.2
12p13.2
6q
3q28
11q23.3
1q42.12
8q12.1
19q13.32
10q23.31*
BCL2
BCL2
CREBBP
EZH2
KMT2D
TNFRSF14
HVCN1
IRF8
GNA13
MEF2B
PTEN
SGK1
HIST1H1E
NFKBIE
BRAF
CD83
NFKBIA
CD58
HIST1H2BC
STAT3
HIST1H1C
ZFP36L1
KLHL6
HIST1H1D
HIST1H1B
ETS1
TOX
HIST1H2AM
HIST1H2BK
RHOA
ACTB
LTB
SF3B1
CARD11
HIST1H2AC
18q
3q
CD79B
3p
MYD88
ETV6
18p
PIM1
17q25.1
TBL1XR1
19q13.42
GRHPR
ZC3H12A
19p13.2
19q*
HLA-A
PRDM1
BTG1
18q21.33
MYC
0
5
10
15
20
−log10 (q value)
Mutations Non-syn. syn. No SCNAs High-level gain Low-level gain High-level loss Low-level loss No SVs Yes No na


NEC
SOCS1/SGK1
TET2/SGK1
MYD88
BCL2
NOTCH2
NOTCH1
REL_amp
TP53_HD
SOCS1
CD83
SGK1
NFKBIA
HIST1H1E
LTB
HIST1H1B
HIST1H1C
STAT3
BCL7A
HIST1H2AC
ITPKB
NFKBIE
HIST1H3G
GNA13
EGR1
DTX1
HIST1H2BG
HIST1H2BC
TLR2
XPO1
HIST1H2AM
HIST1H2AG
CIITA
IRF1
BCL6
ARID1A
PAX5
XPO1_amp
BCL11A_amp
BTK
HIST1H2BD
TET2
BRAF
KLHL6
ID3
MAP2K1
TNF
KRAS
P2RY8
EBF1
PTPN6
ZFP36L1
HIST1H3B
MGA
BCOR
PRKCB
CARD11
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PIM1
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ETV6
CDKN2A_HD
PRDM1_HD
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BTG1
MPEG1
BTG2
SPIB
IRF4
MYC
FAT3
CD58_HD
CD79A
EZH2_646
BCL2
CREBBP
TNFRSF14_HD
KMT2D
MEF2B
STAT6
EZH2_noncan
IRF8
FOXO1
POU2F2_239
PIK3R1
HIST1H1D
SRSF2
EP300
NOTCH2
BCL10
TNFAIP3_HD
CCND3
SPEN
B2M
TMEM30A
FAS
PDS5B
CD70
CXCR4
DDX3X_HD
POU2F2_noncan
0
30
60
90
Cluster enrichment (-log10(q))
Cell of Origin
ABC
GCB
UNC

Table 2: Genomic subtypes of DLBCL

Wright 2020[30]	Chapuy 2018[29]	Lacy 2020[31]	Hallmark drivers	COO	% of cases	Outcome 5 yr OS (%)	Putative related small cell lymphoma
MCD	C5	MYD88	MYD88/CD79B	ABC	9-14-21	40-42	
BN2	C1	NOTCH2	tBCL6/ NOTCH2	GCB/ABC Unclassified	16-19	48-67	MZL
EZB-MYC-	C3	BCL2	EZH2 tBCL2	GCB	13-18	63-82	FL
EZB-MYC+			EZH2/tMYC	GCB/DZ	6	48	
A53	C2		TP53 Aneuploidy	All	7-21	63	
ST2	C4	SOCS1/SGK1 TET/SGK1	SOCS1/TET/ SGK1	GCB	5-17	65-84	NLPBL
N1			NOTCH1	ABC	2	27	CLL
UNCLASS		UNCLASS		Unclass, GCB,ABC	27-37	66	

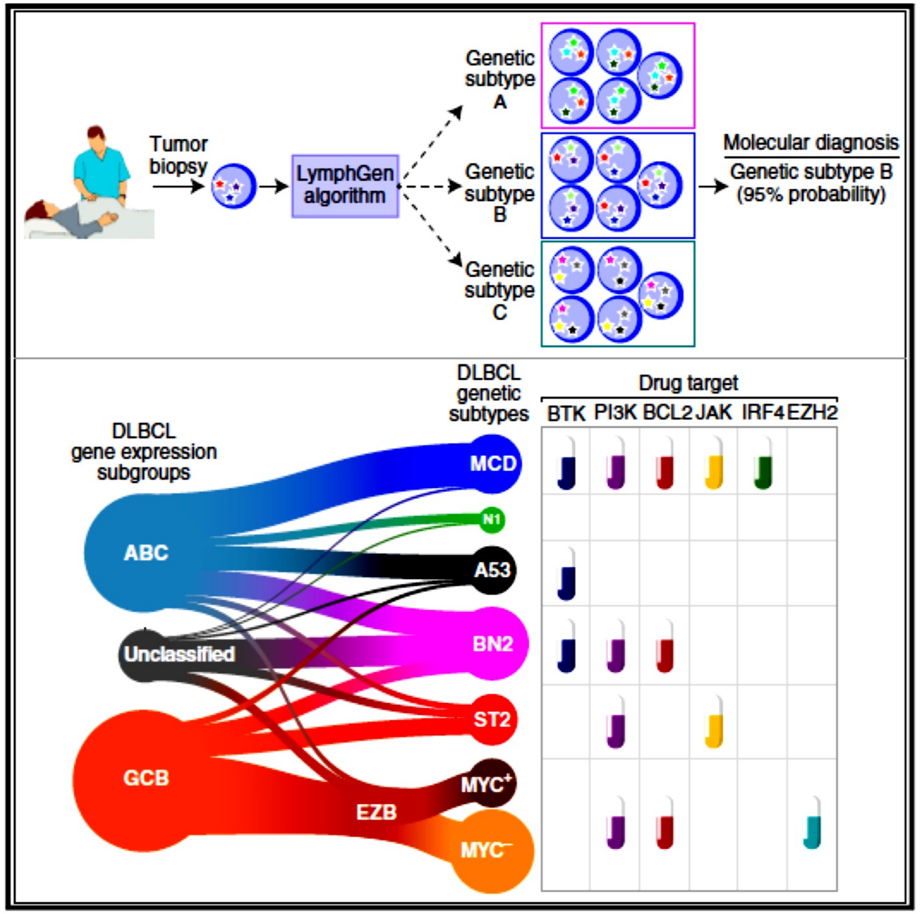
ABC: Activated B-cell type; GCB: Germinal center B-cell type; DZ: Dark zone signature; CLL: Chronic lymphocytic leukemia; FL: Follicular lymphoma, MZL: Marginal zone lymphoma; NLPBL: Nodular lymphocyte predominant B-cell lymphomat; t: Translocation

Article

Cancer Cell

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

Graphical Abstract



Authors

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Correspondence

lstaudt@mail.nih.gov

In Brief

Wright et al. identify seven genetic subtypes of diffuse large B cell lymphoma (DLBCL) with distinct outcomes and therapeutic vulnerabilities. The LymphGen probabilistic classification tool that can classify a DLBCL biopsy into the genetic subtypes is developed, which could be used for precision medicine trials.

American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

DLBCL associated NOTCH2 mutations escape ubiquitin-dependent degradation and promote chemo-resistance

Tracking no: BLD-2022-018752R1

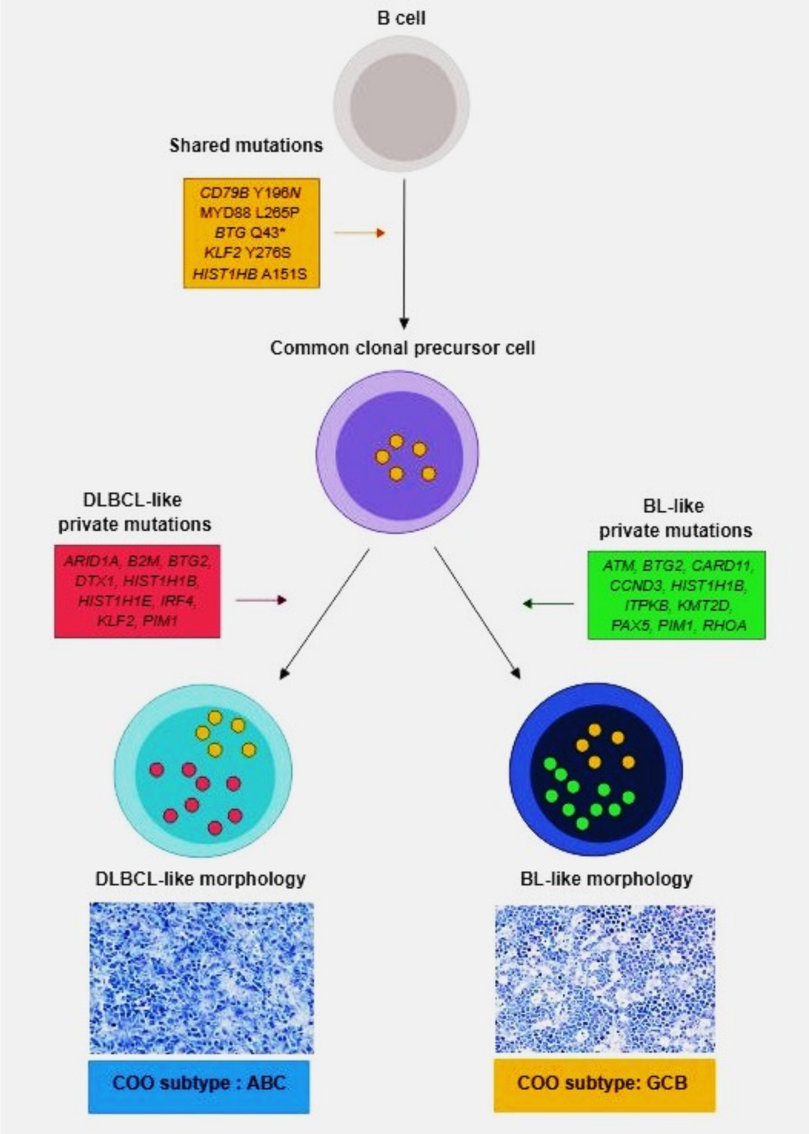
Nan Zhou (University of Pennsylvania, United States) Jaewoo Choi (University of Pennsylvania, United States) Grant Grothusen (University of Pennsylvania, United States) Bang-Jin Kim (University of Pennsylvania, United States) Diqiu Ren (University of Pennsylvania, United States) Zhendong Cao (University of Pennsylvania, United States) Qinglan Li (University of Pennsylvania, United States) Yiman Liu (University of Pennsylvania, United States) Arati Inamdar (University of Pennsylvania, United States) Thomas Beer (The Wistar Institute, United States) Hsin-Yao Tang (The Wistar Institute, United States) Eric Perkey (University of Pennsylvania, United States) Ivan Maillard (University of Pennsylvania, United States) Roberto Bonasio (University of Pennsylvania, United States) Junwei Shi (University of Pennsylvania, United States) Marco Ruella (University of Pennsylvania, United States) Liling Wan (University of Pennsylvania, United States) Luca Busino (University of Pennsylvania, United States)

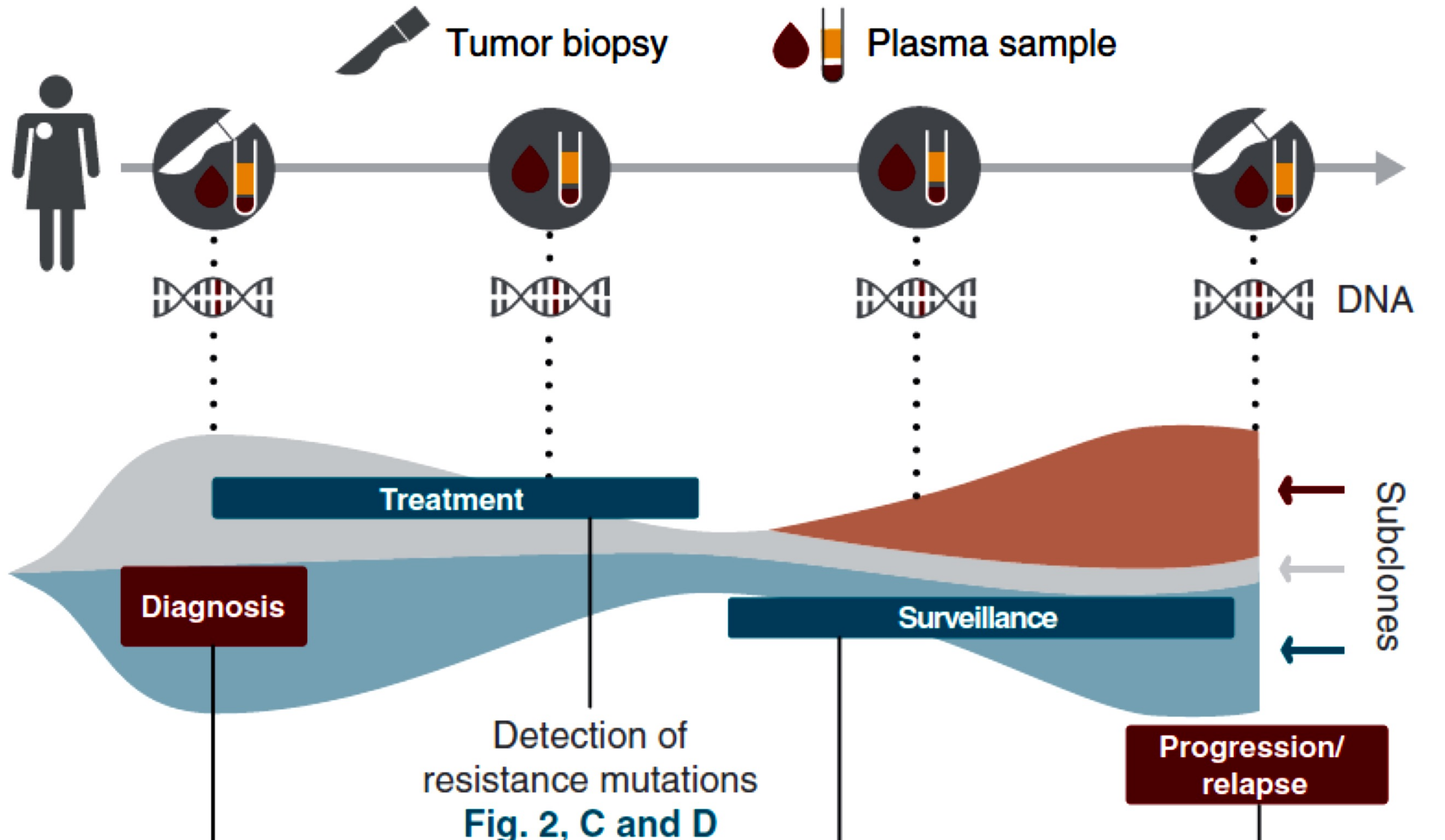

Covaris
ME220
HOME
HISTORY
ABOUT
Edit
New
Run
Pause
Samples
A
B
C
D
E
F
G
H
Process
System Status
Motion Control
Water Works
On
Off
Creation Notes
Covaris
ME220
Covaris

Evolutionary crossroads: morphological heterogeneity reflects divergent intra-clonal evolution in a case of high-grade B-cell lymphoma

by Valentina Tabanelli, Federica Melle, Giovanna Motta, Saveria Mazzara, Marco Fabbri, Chiara Corsini, Elvira Gerbino, Angelica Calleri, Maria Rosaria Sapienza, Ignazio Abbene, Viviana Stufano, Massimo Barberis, and Stefano A. Pileri

Haematologica 2020 [Epub ahead of print]





High tumor burden
Fig. 3, A to C, and fig. S9
table S4

Non-GCB subtype
Fig. 4

Double hit lymphoma
fig. S4A

Detection of resistance mutations
Fig. 2, C and D
figs. S7 and S8

Relapse prediction
Fig. 3, D to F

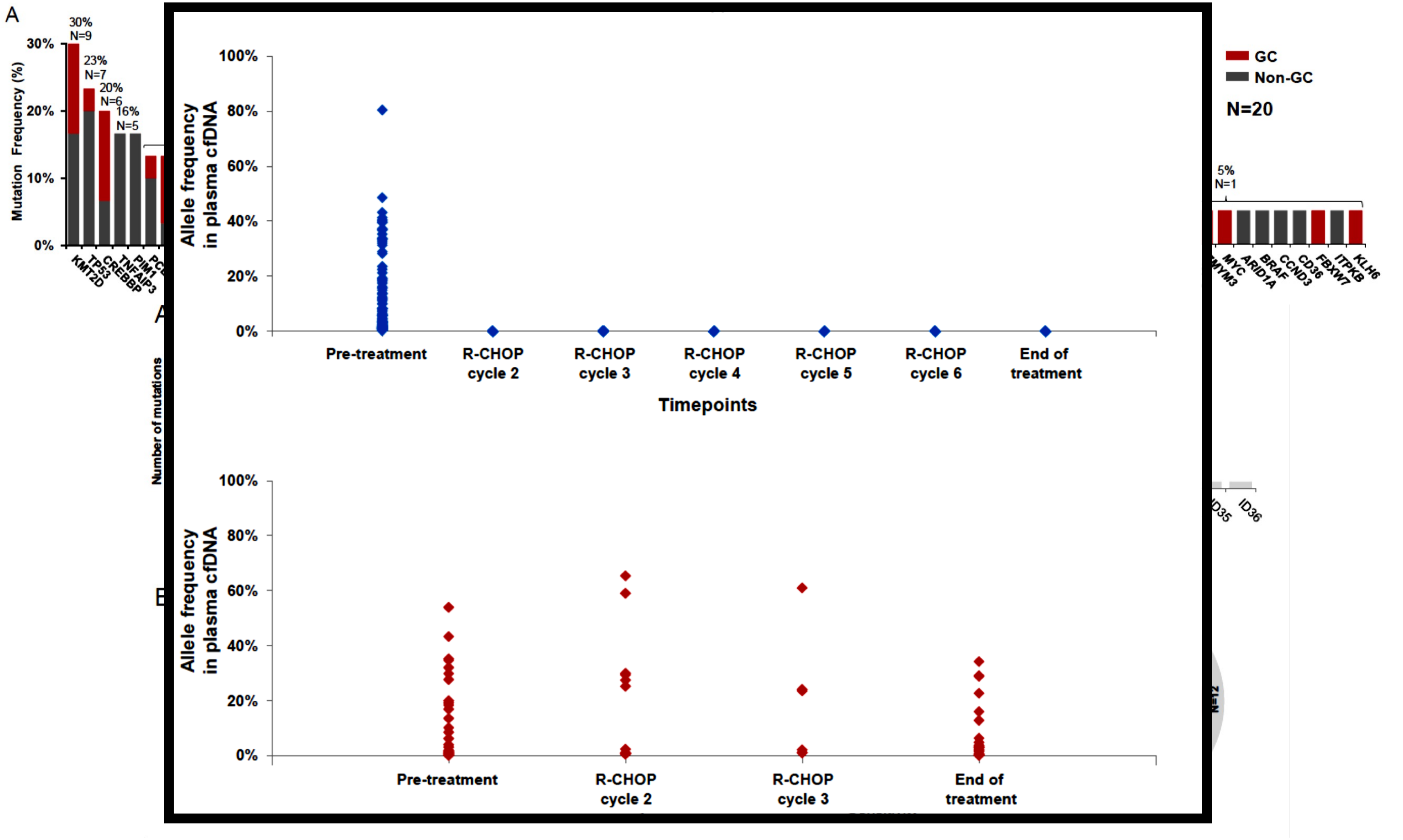
Transformation prediction
Fig. 5E

Relapse detection
Fig. 3, D to F

Transformation detection
Fig. 5, C to E

Rossi et al, Blood 2017

DIFFUSE LARGE B-CELL LYMPHOMA GENOTYPING ON THE LIQUID BIOPSY




ngiyabonga
рахмат
danke
謝謝
spas
teşekkür ederim
Баярлалаа
mersi
kia ora
barka
welalin
tack
mahalo
tapadh leat
спасибо
faafetai lava
vinaka
blagodaram
dank je
misaotra
matondo
paldies
grazzi
спасибі
kiitos
dankie
thank you
gracias
хвала
nanni
nandri
dhanyavad
mauruuru
asante
manana
bedankt
bayarlalaa
gracie
hvala
koszonom
dankon
aciu
obrigada
murakoze
tenki
enkosi
djiere dieuf
tau
mochchakkeram
akun
дякую
mamnun
dziękuję
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grafias ago
gràcies
sulpay
go raibh maith agat
chokrane
sobodi
dekuji
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sukriya
kop khun krap
taiku
arigatô
takk
dakujem
trugarez
obrigado
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madloba
ありがとう
tanemirt
grazie
didi
najis tuke
terima kasih
rahmet
dhanyavadagalu
shukriya
merce
мерси
kam sah hamnida
rahmat
ευχαριστώ
diolch
xiexie
merci
তোমাকে ধন্যবাদ
감사합니다