Eppur si muove...

La terapia nel MONDO LINFOMI

Linfoma diffuso a grandi cellule B: ottimizzazione diagnostica

ROMA, 26 MAGGIO 2022

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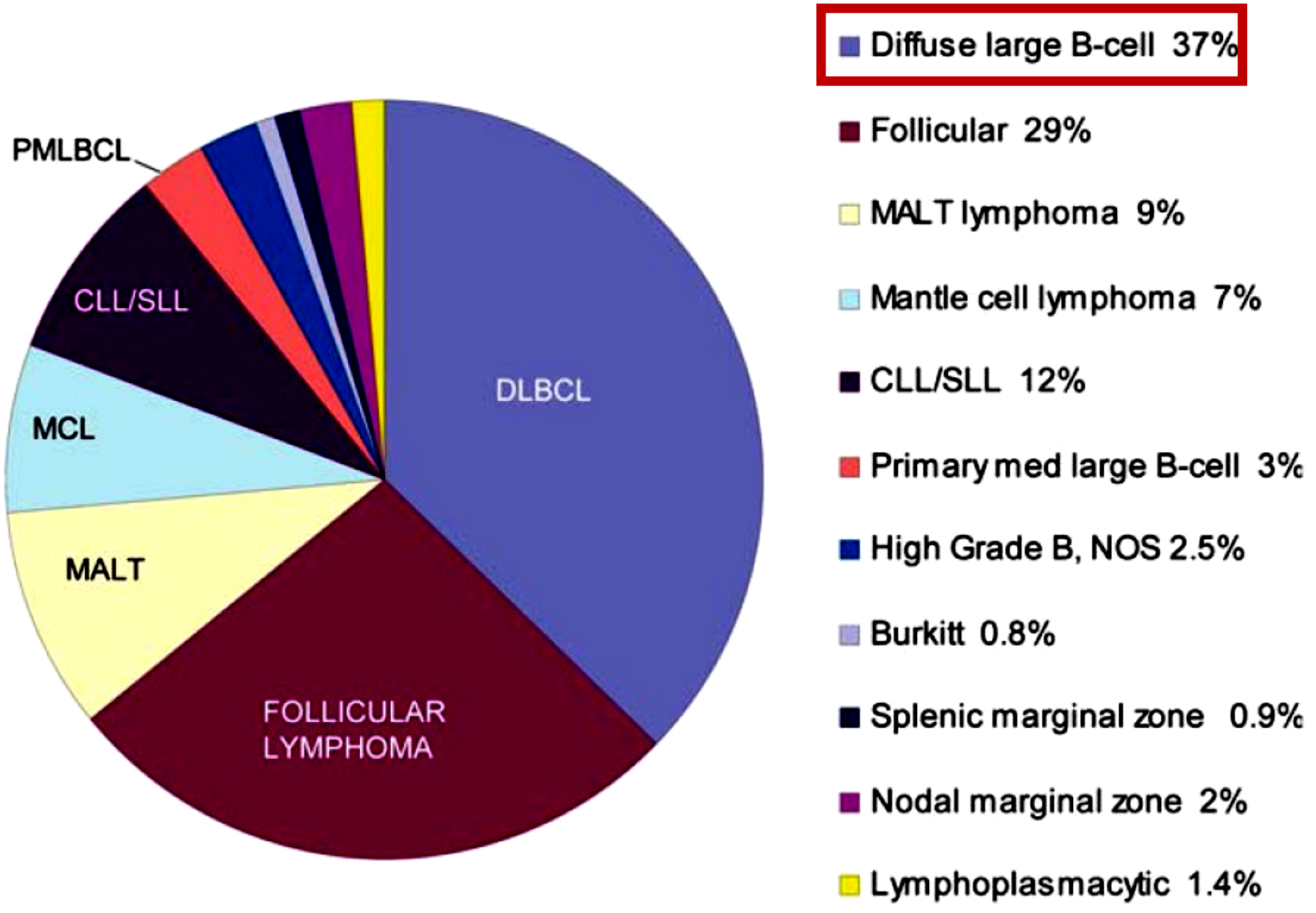
Disclosures of Stefano A. Pileri

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BeiGene						x	
Takeda						x	
Roche					x		
Diatech						x	


PMLBCL
CLL/SLL
MCL
MALT
DLBCL
FOLLICULAR LYMPHOMA
Diffuse large B-cell 37%
Follicular 29%
MALT lymphoma 9%
Mantle cell lymphoma 7%
CLL/SLL 12%
Primary med large B-cell 3%
High Grade B, NOS 2.5%
Burkitt 0.8%
Splenic marginal zone 0.9%
Nodal marginal zone 2%
Lymphoplasmacytic 1.4%

Diffuse large B-cell lymphoma: variants, subgroups and subtypes/entities

Diffuse large B-cell lymphoma, noth otherwise specified (NOS)

- Common morphologic variants
  - Centroblastic
  - Immunoblastic
  - Anaplastic
  - Other rare variants
- Molecular subgroups
  - Germinal centre B-cell-like (GCB)
  - Activated B-cell-like (ABC)

Diffuse large B-cell lymphoma subtypes

- T-cell/histiocyte-rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV-positive DLBCL, NOS
- *Large B-cell lymphoma with IRF4 rearrangements**

Other lymphomas of large B-cells

- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- ALK-positive large B-cell lymphoma
- Plasmablastic lymphoma
- HHV-8-positive DLBCL, NOS
- Primary effusion lymphoma

New provisional categories

- High grade B-cell lymphoma
  - High grade B-cell lymphoma, with *BCL2* and/or *BCL6* and *MYC* rearrangements
  - High grade B-cell lymphoma, NOS

Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)
  Germinal center B-cell subtype
  Activated B-cell subtype
Large B-cell lymphoma with 11q aberration[*] ⟸
Nodular lymphocyte predominant B-cell lymphoma[*] ⟸
T cell/histiocyte-rich large B-cell lymphoma

Primary DLBCL of the central nervous system
Primary DLBCL of the testis[*] ⟸
Primary cutaneous DLBCL, leg type
Intravascular large B-cell lymphoma
HHV-8 and EBV-negative primary effusion-based lymphoma[*] ⟸

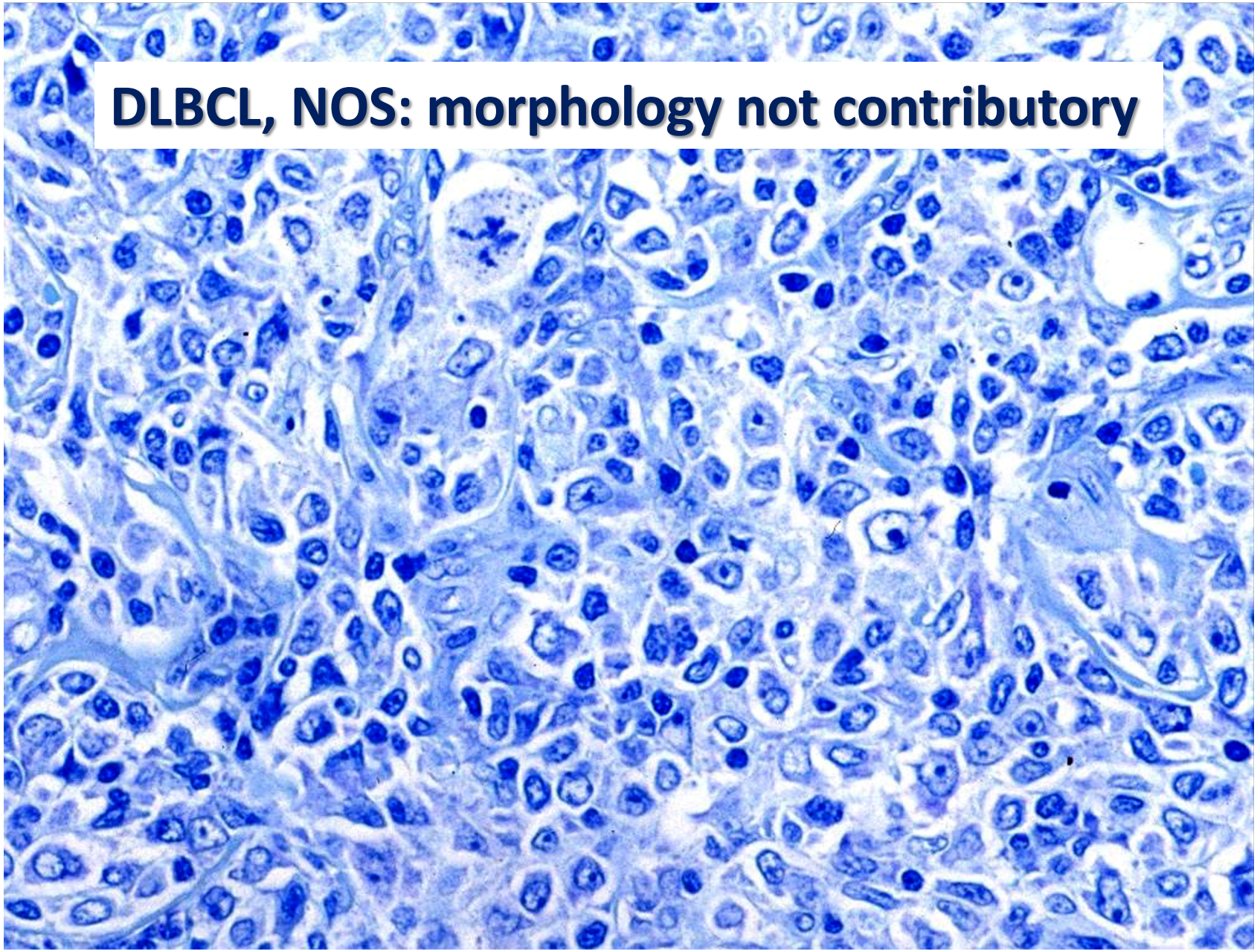
EBV-positive mucocutaneous ulcer[*] ⟸
EBV-positive DLBCL, NOS
DLBCL associated with chronic inflammation
  Fibrin-associated DLBCL
Lymphomatoid granulomatosis
EBV-positive polymorphic B-cell lymphoproliferative disorder, NOS[*] ⟸

ALK-positive large B-cell lymphoma
Plasmablastic lymphoma
HHV8-associated lymphoproliferative disorders
  Multicentric Castleman disease
  HHV8-positive germinotropic lymphoproliferative disorder
  HHV8-positive DLBCL, NOS
  Primary effusion lymphoma

Burkitt lymphoma
High-grade B-cell lymphoma, with *MYC* and *BCL2* rearrangements[*] ⟸
High-grade B-cell lymphoma with MYC and BCL6 rearrangements[*] ⟸
High-grade B-cell lymphoma, NOS

Primary mediastinal large B-cell lymphoma
Mediastinal gray-zone lymphoma[*]

DLBCL, NOS: morphology not contributory

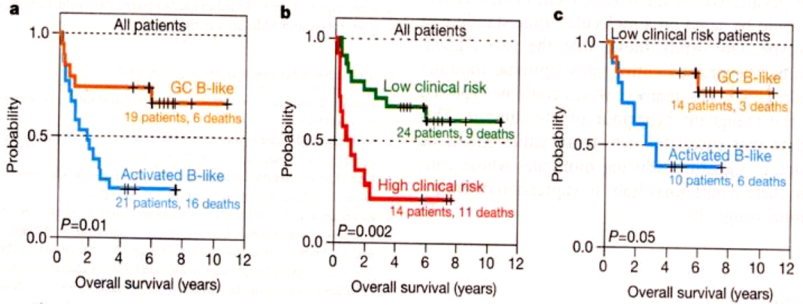


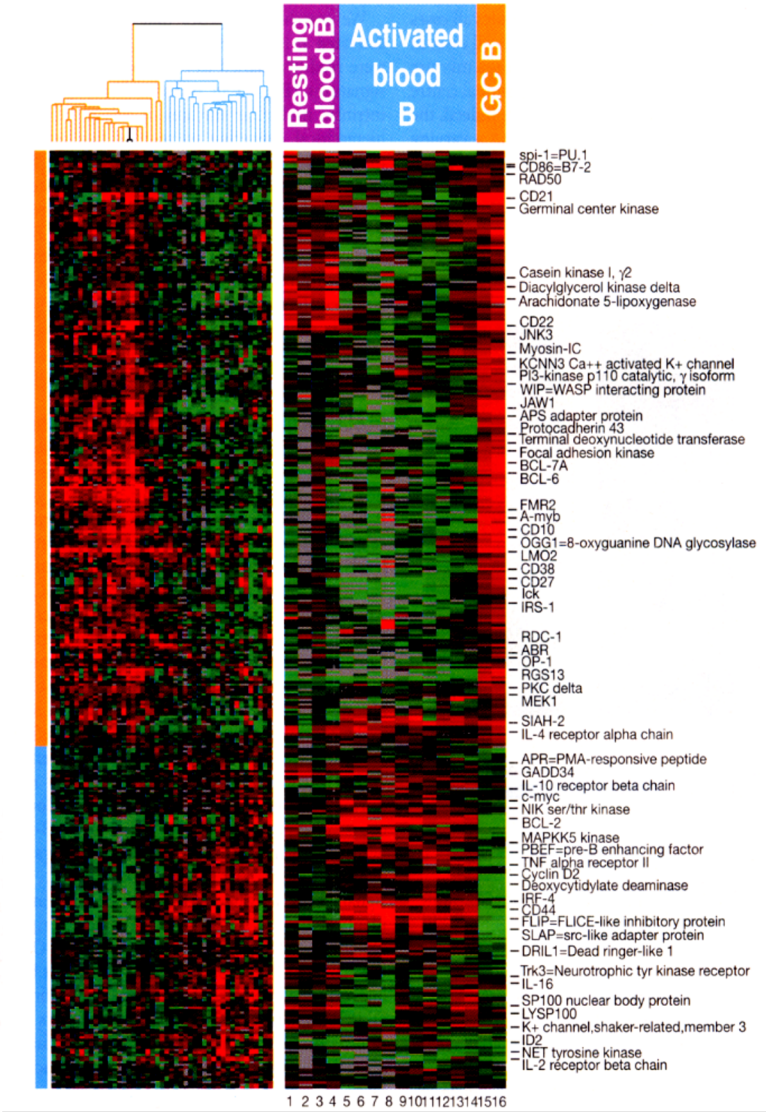
Front-MIND

Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling

Alizadeh AA et al.

Nature 2000, 403: 503-11





Original limitation:

need for fresh or frozen tissue, available in only a few patients!

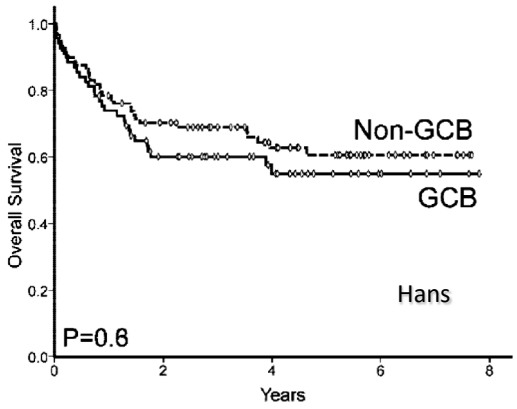
Ideally, tool to apply to FFPE samples!

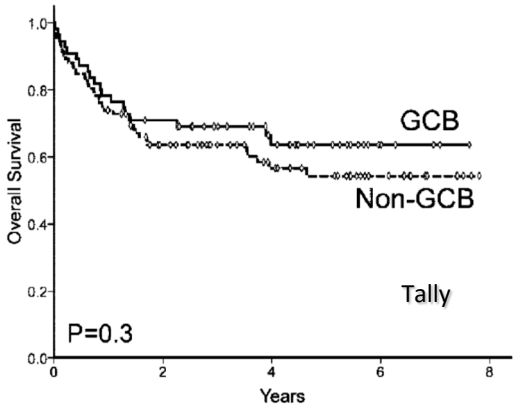
Gene-expression profiling and not immunophenotypic algorithms predicts prognosis in patients with diffuse large B-cell lymphoma treated with immunochemotherapy

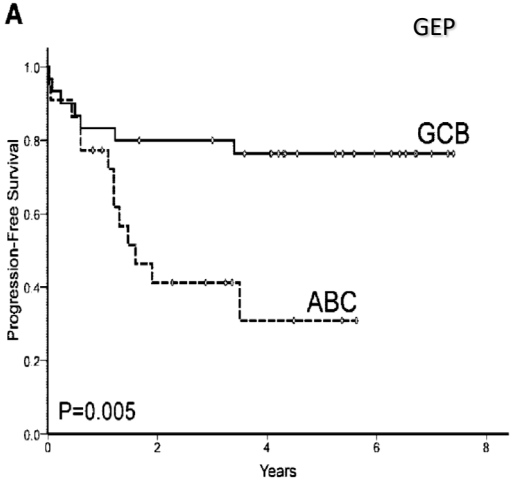
*Gonzalo Gutiérrez-García,[1] *Teresa Cardesa-Salzmann,[1] Fina Climent,[2] Eva González-Barca,[2] Santiago Mercadal,[2] José L. Mate,[3] Juan M. Sancho,[3] Leonor Arenillas,[4] Sergi Serrano,[4] Lourdes Escoda,[5] Salomé Martínez,[5] Alexandra Valera,[1] Antonio Martínez,[1] Pedro Jares,[1] Magdalena Pinyol,[1] Adriana García-Herrera,[1] Alejandra Martínez-Trillos,[1] Eva Giné,[1] Neus Villamor,[1] Elías Campo,[1] Luis Colomo,[1] and Armando López-Guillermo,[1] for the Grup per l'Estudi dels Limfomes de Catalunya I Balears (GELCAB)

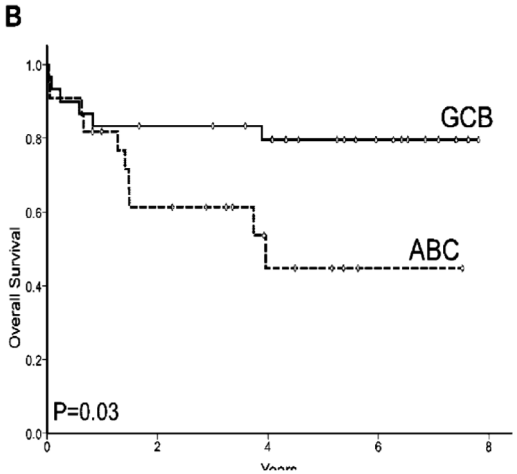
[1]Departments of Hematology and Pathology, Hospital Clínic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [2]Hospital Duran i Reynals, Hospitalet de Llobregat, Spain; [3]Hospital Germans Trias I Pujol, Badalona, Spain; [4]Hospital del Mar, Barcelona, Spain; and [5]Hospital Joan XXIII, Tarragona, Spain

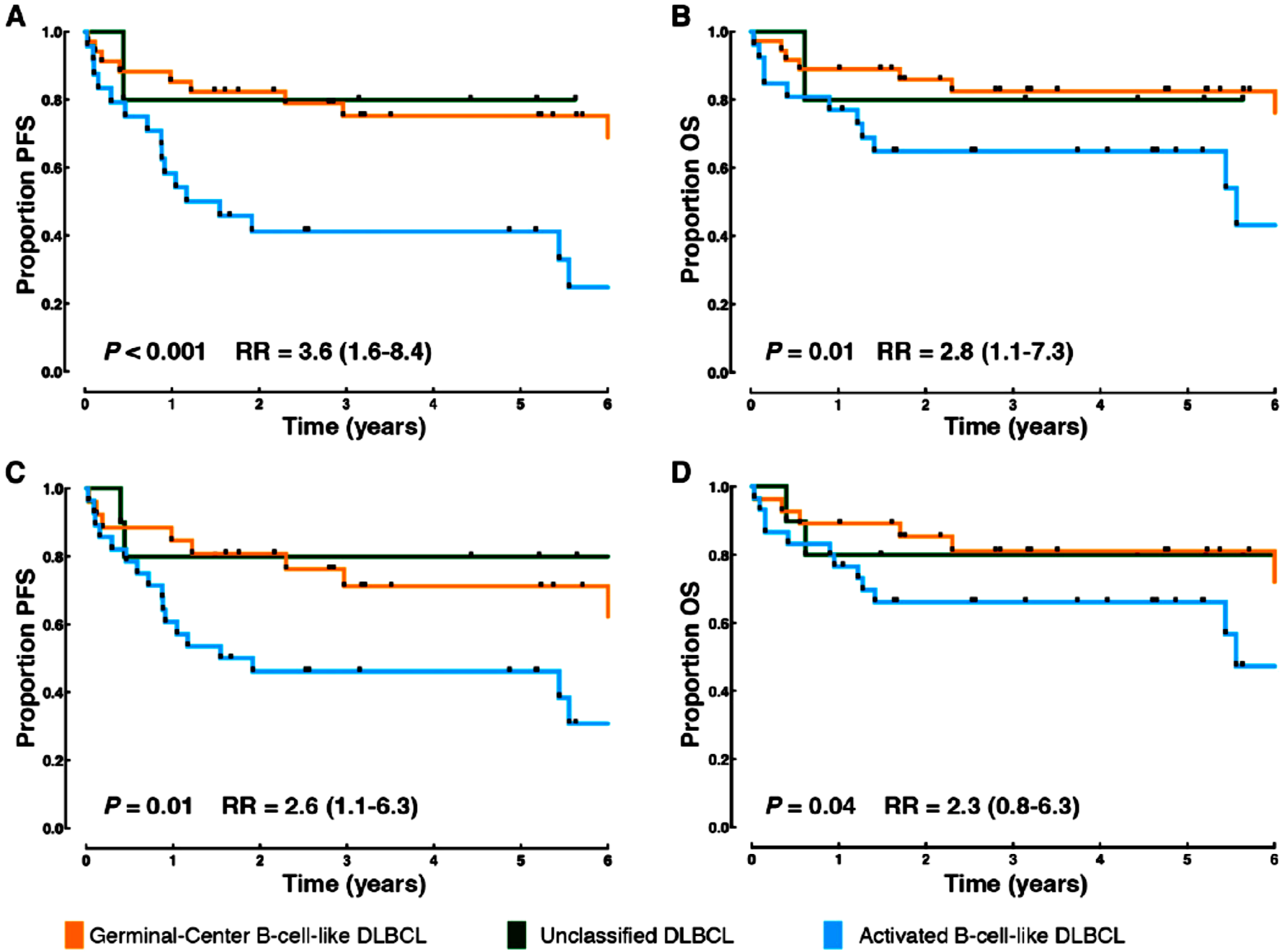
Diffuse large B-cell lymphomas (DLBCLs) can be divided into germinal-center B cell–like (GCB) and activated-B cell–like (ABC) subtypes by gene-expression profiling (GEP), with the latter showing a poorer outcome. Although this classification can be mimicked by different immunostaining algorithms, their reliability is the object of controversy. We constructed tissue microarrays with samples of 157 DLBCL patients homogeneously treated with immunochemotherapy to apply the following algorithms: Colomo (MUM1/IRF4, CD10, and BCL6 antigens), Hans (CD10, BCL6, and MUM1/IRF4), Muris (CD10 and MUM1/IRF4 plus BCL2), Choi (GCET1, MUM1/IRF4, CD10, FOXP1, and BCL6), and Tally (CD10, GCET1, MUM1/IRF4, FOXP1, and LMO2). GEP information was available in 62 cases. The proportion of misclassified cases by immunohistochemistry compared with GEP was higher when defining the GCB subset: 41%, 48%, 30%, 60%, and 40% for Colomo, Hans, Muris, Choi, and Tally, respectively. Whereas the GEP groups showed significantly different 5-year progression-free survival (76% vs 31% for GCB and activated DLBCL) and overall survival (80% vs 45%), none of the immunostaining algorithms was able to retain the prognostic impact of the groups (GCB vs non-GCB). In conclusion, stratification based on immunostaining algorithms should be used with caution in guiding therapy, even in clinical trials. (*Blood*. 2011;117(18):4836-4843)










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

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

50-gene-panel for microenvironment Ann Oncol, 2018

MF-related genes

DC-related genes

CD4⁺ T cell-related genes

STROMAL 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

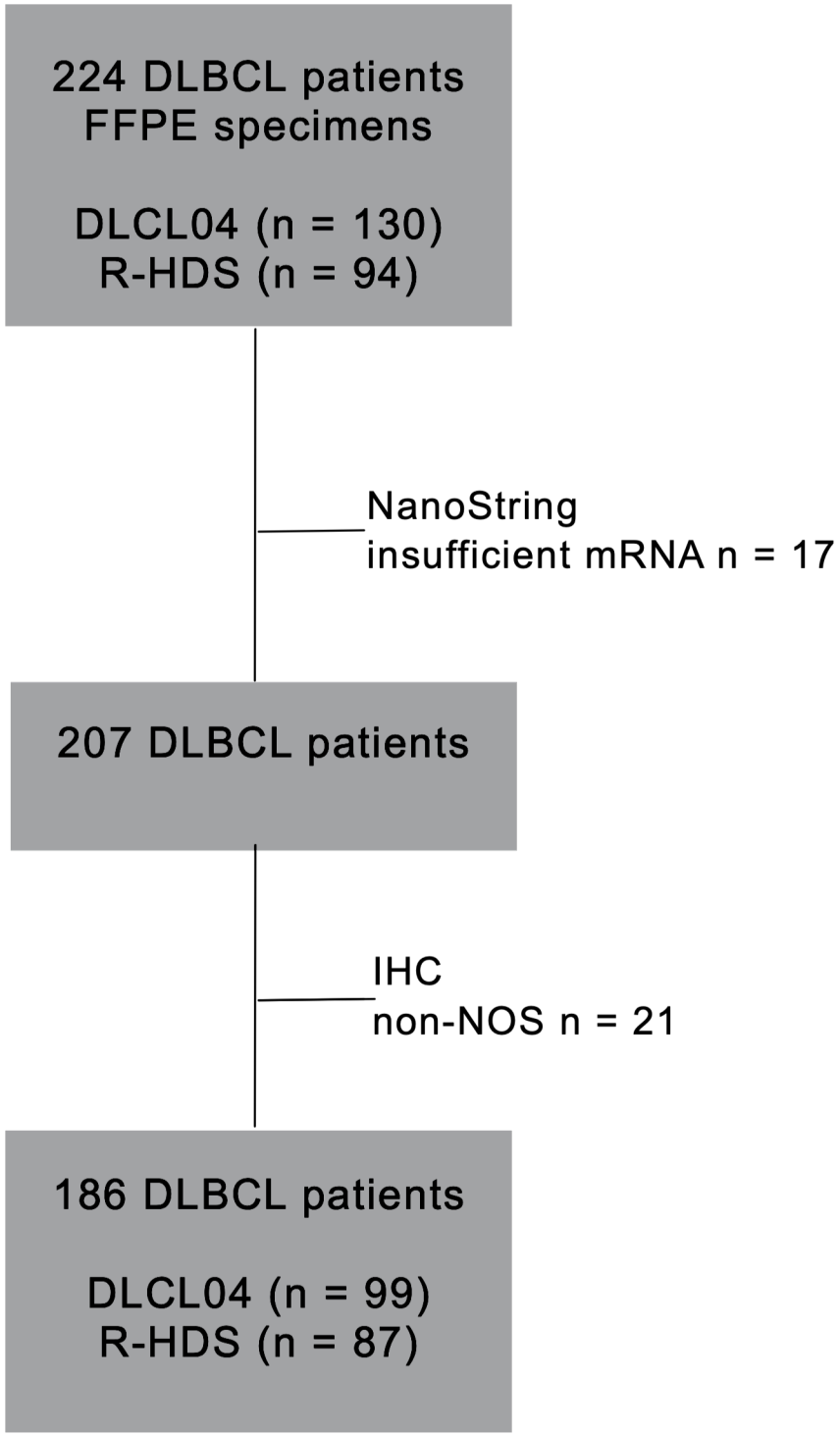
IMMUNE GENES

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),
CTS2	Cathepsin 2
HS3ST3A1	Heparan Sulfate-Glucosamine 3-Sulfotransferase 3A1
PMPCB	Peptidase, Mitochondrial Processing Beta Subunit
RAB27A	RAB27A, Member RAS Oncogene Family
SMAD1	SMAD Family Member 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]

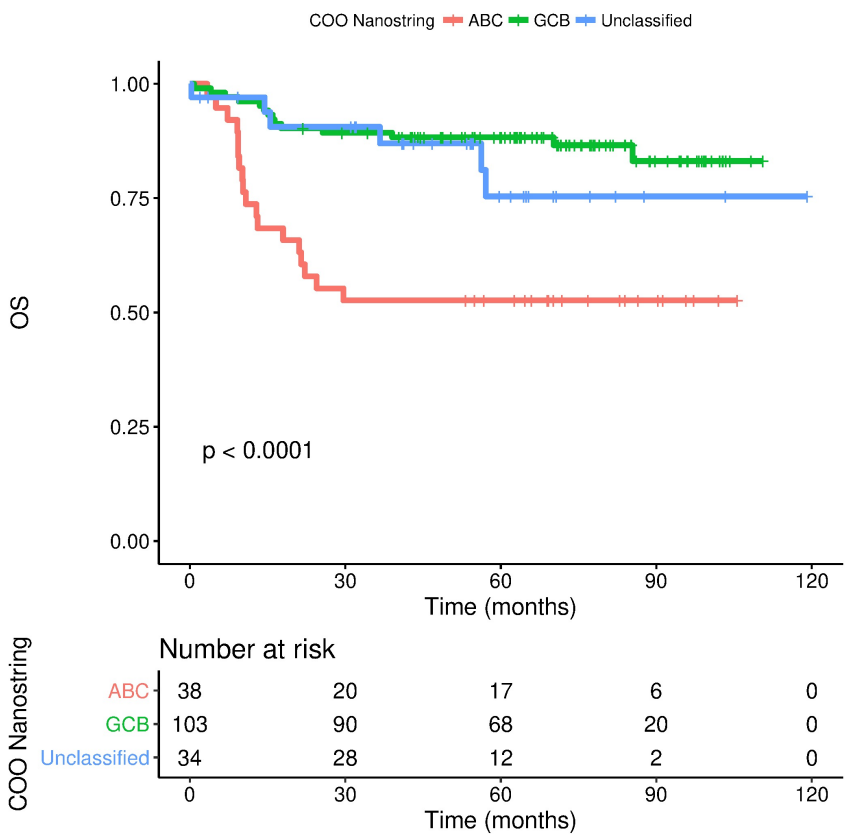

224 DLBCL patients
FFPE specimens
DLCL04 (n = 130)
R-HDS (n = 94)
NanoString
insufficient mRNA n = 17
207 DLBCL patients
IHC
non-NOS n = 21
186 DLBCL patients
DLCL04 (n = 99)
R-HDS (n = 87)

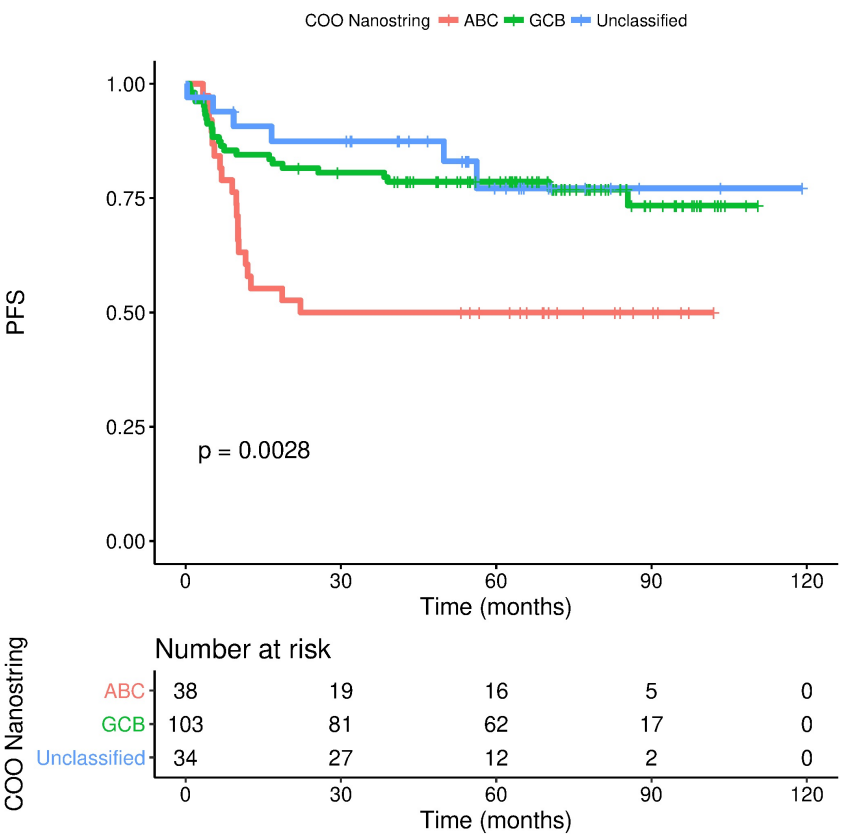
In both trials, only patients staged III-IV were enrolled, all treated with R-CHOP or R-CHOP-like therapies followed or not by Auto-SCT.

The mean age was 52 yr.s (18 – 65)

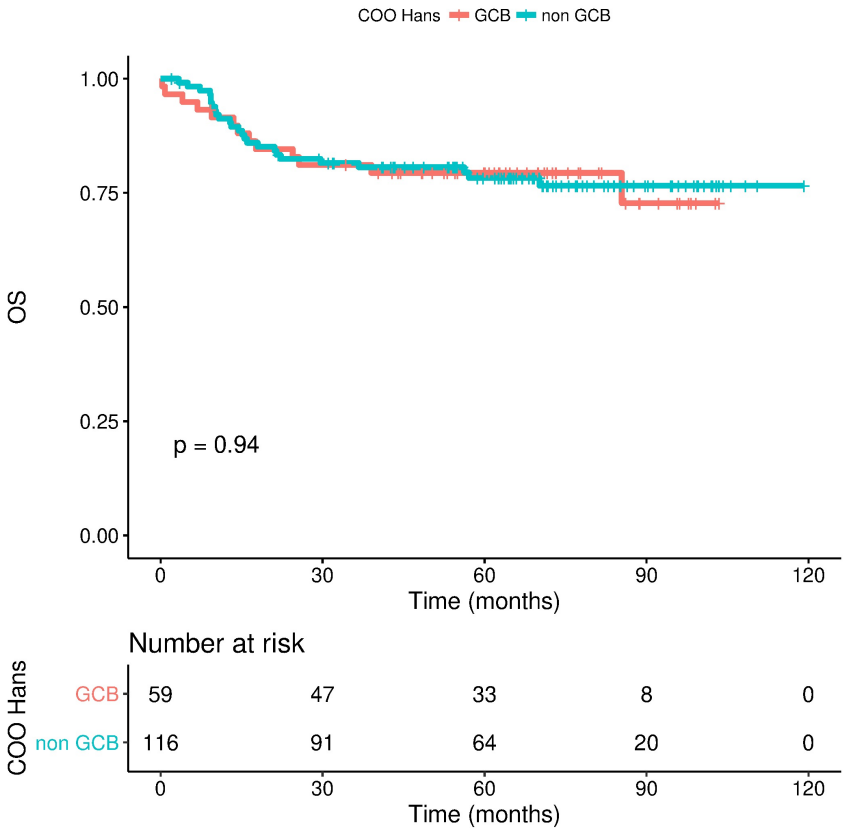
All the cases were studied by immunohistochemistry, targeted GEP and FISH (*BCL2*, *MYC* and *BCL6*).

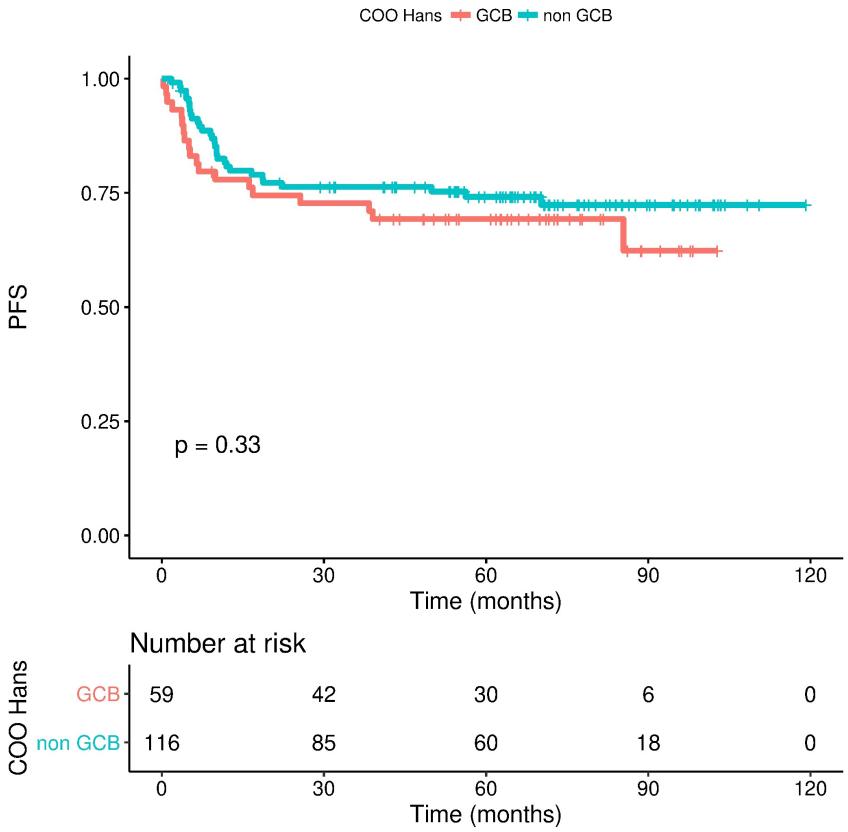
COO according to targeted GEP

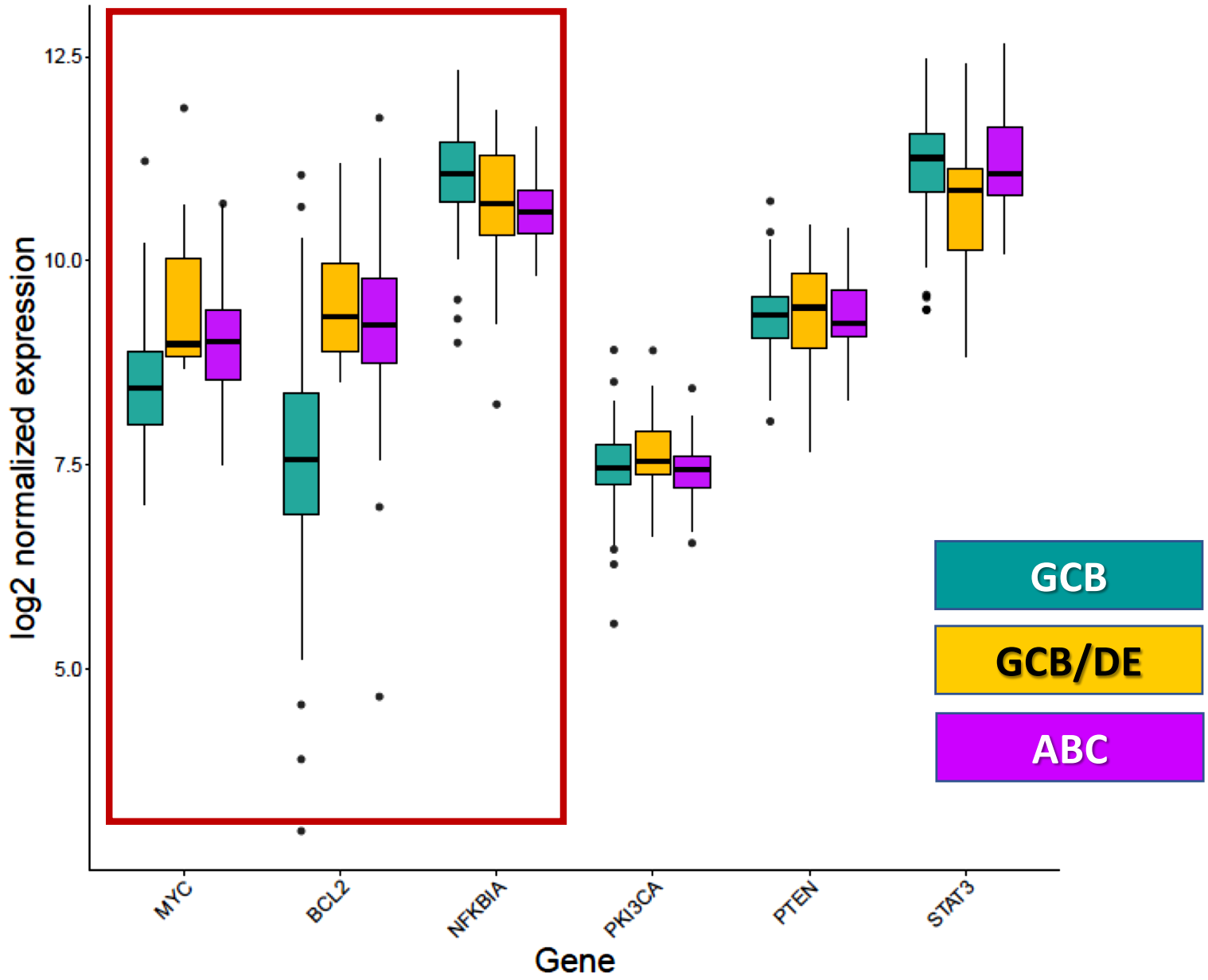


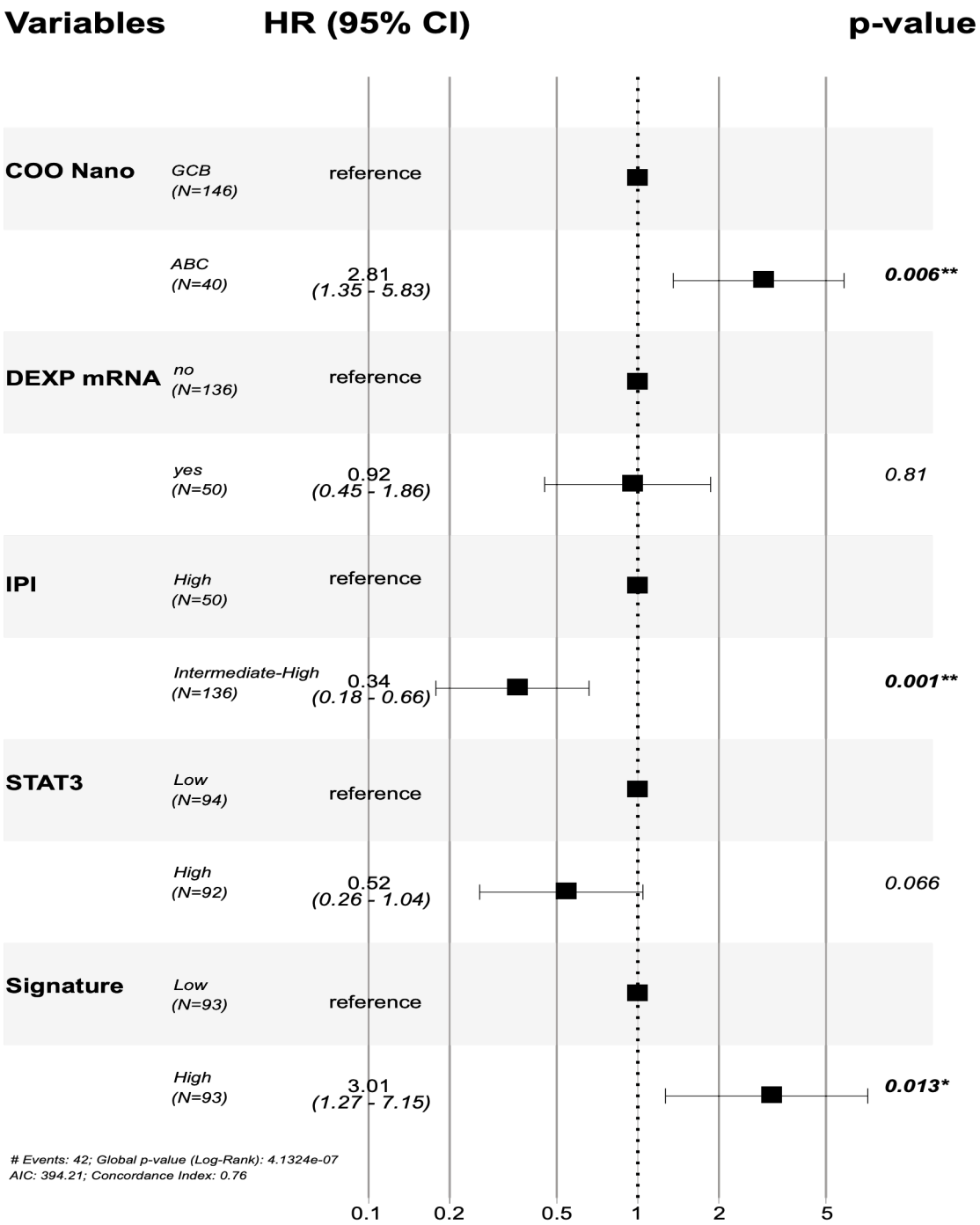


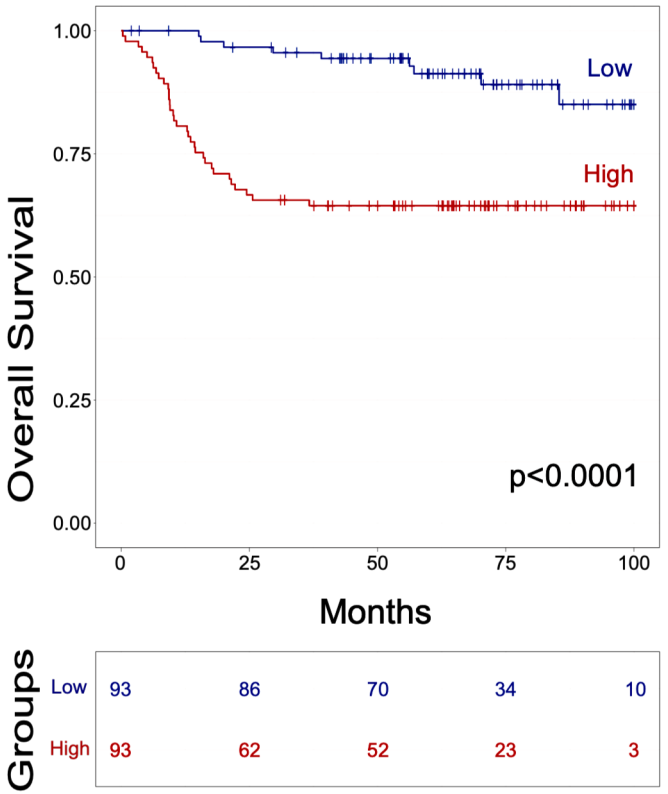
COO according to Hans' classifier





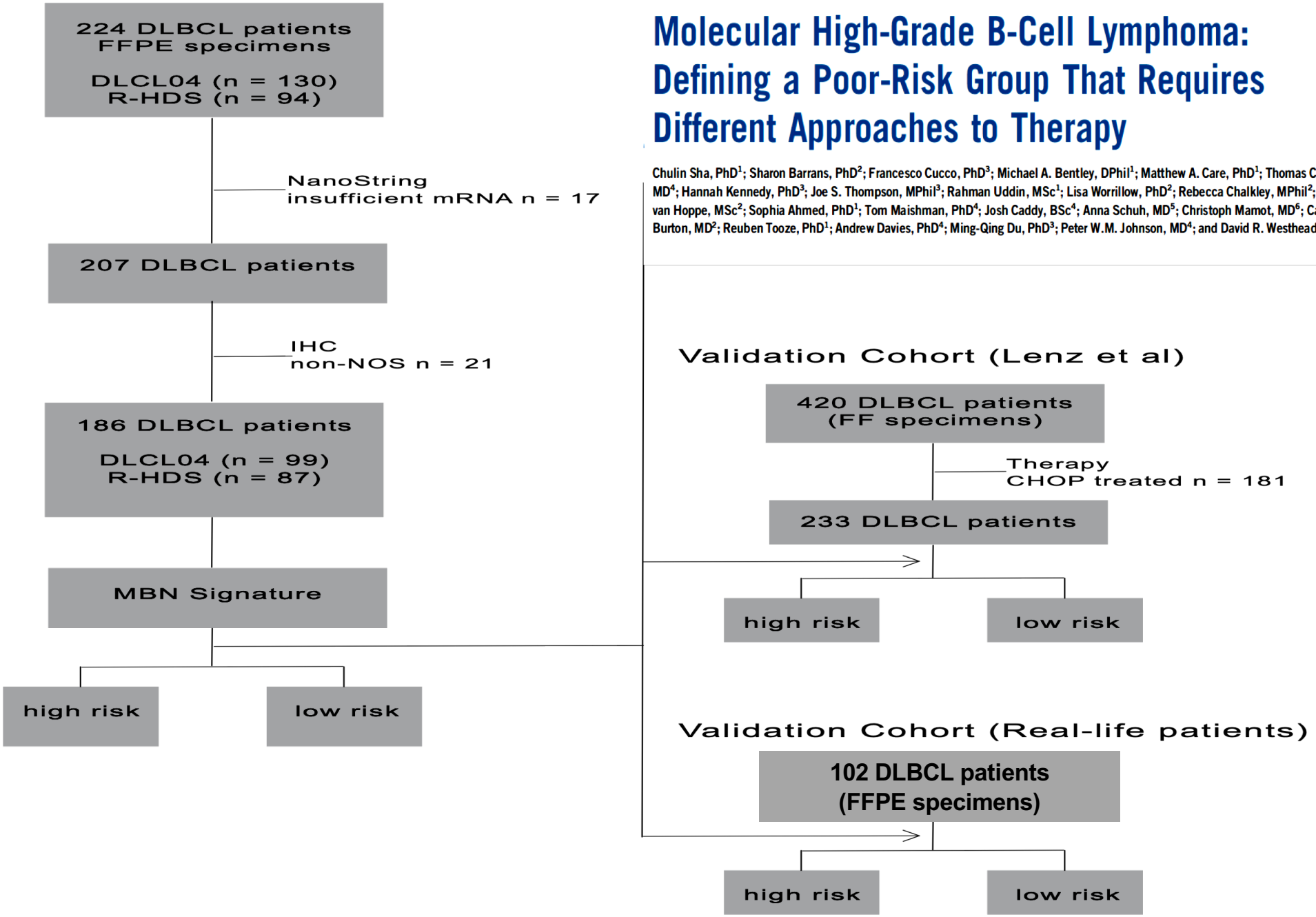

log2 normalized expression
12.5
10.0
7.5
5.0
MYC
BCL2
NFKBIA
PKI3CA
PTEN
STAT3
Gene
GCB
GCB/DE
ABC


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

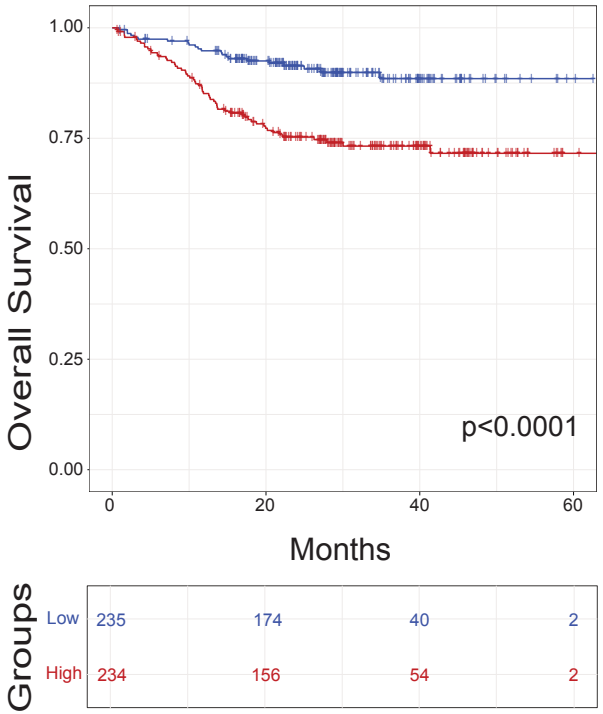

Overall Survival
1.00
0.75
0.50
0.25
0.00
Low
High
p<0.0001
0
25
50
75
100
Months
Groups
Low 93 86 70 34 10
High 93 62 52 23 3

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

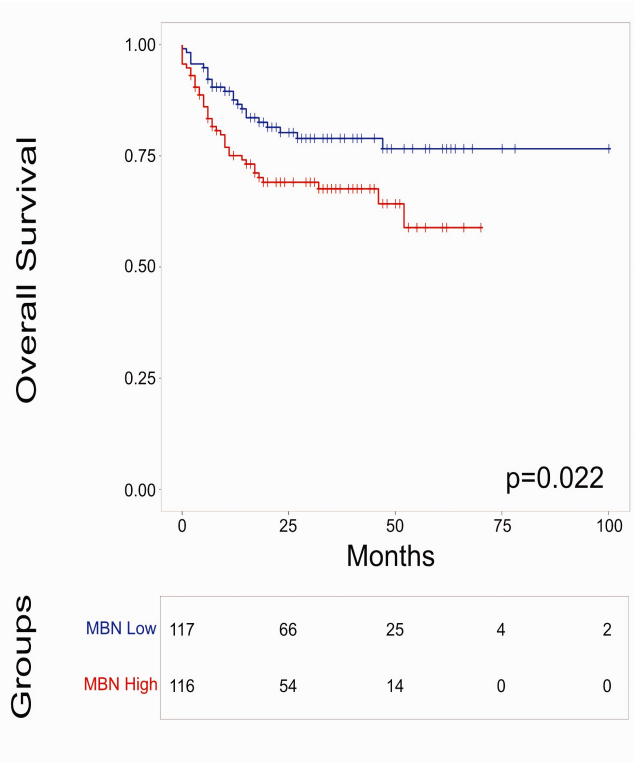
Chulin Sha, PhD[1]; Sharon Barrans, PhD[2]; Francesco Cucco, PhD[3]; Michael A. Bentley, DPhil[1]; Matthew A. Care, PhD[1]; Thomas Cummin, MD[4]; Hannah Kennedy, PhD[3]; Joe S. Thompson, MPhil[3]; Rahman Uddin, MSc[1]; Lisa Worrillow, PhD[2]; Rebecca Chalkley, MPhil[2]; Moniek van Hoppe, MSc[2]; Sophia 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]



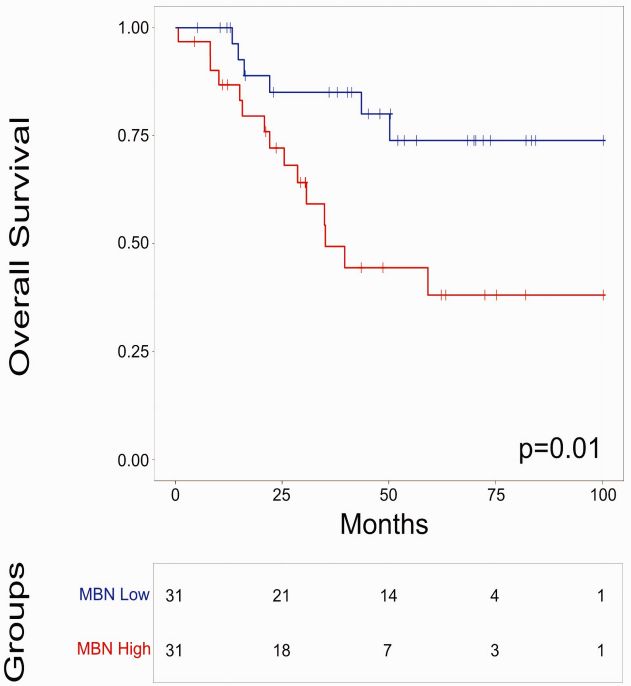
Sha's



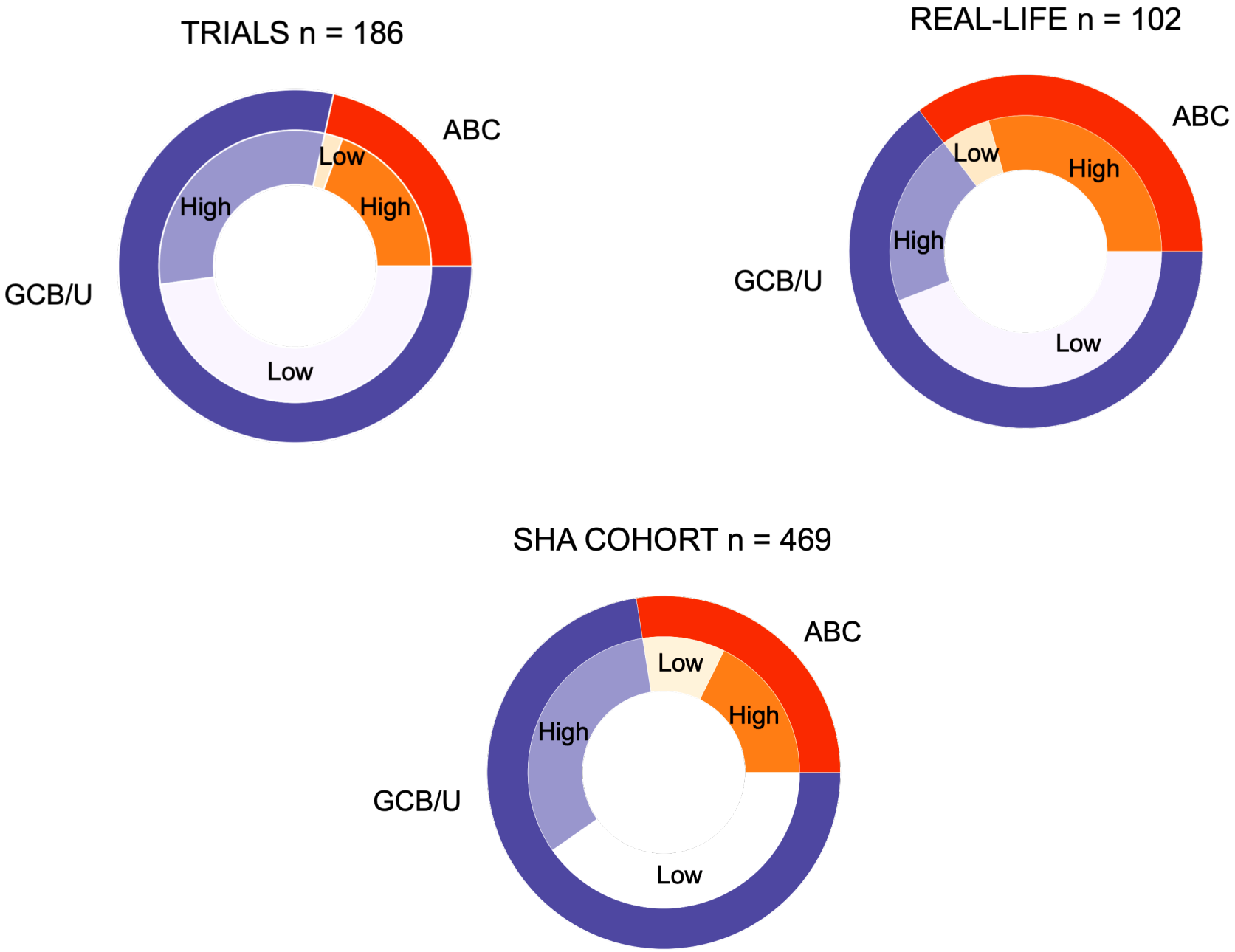
Lenz's

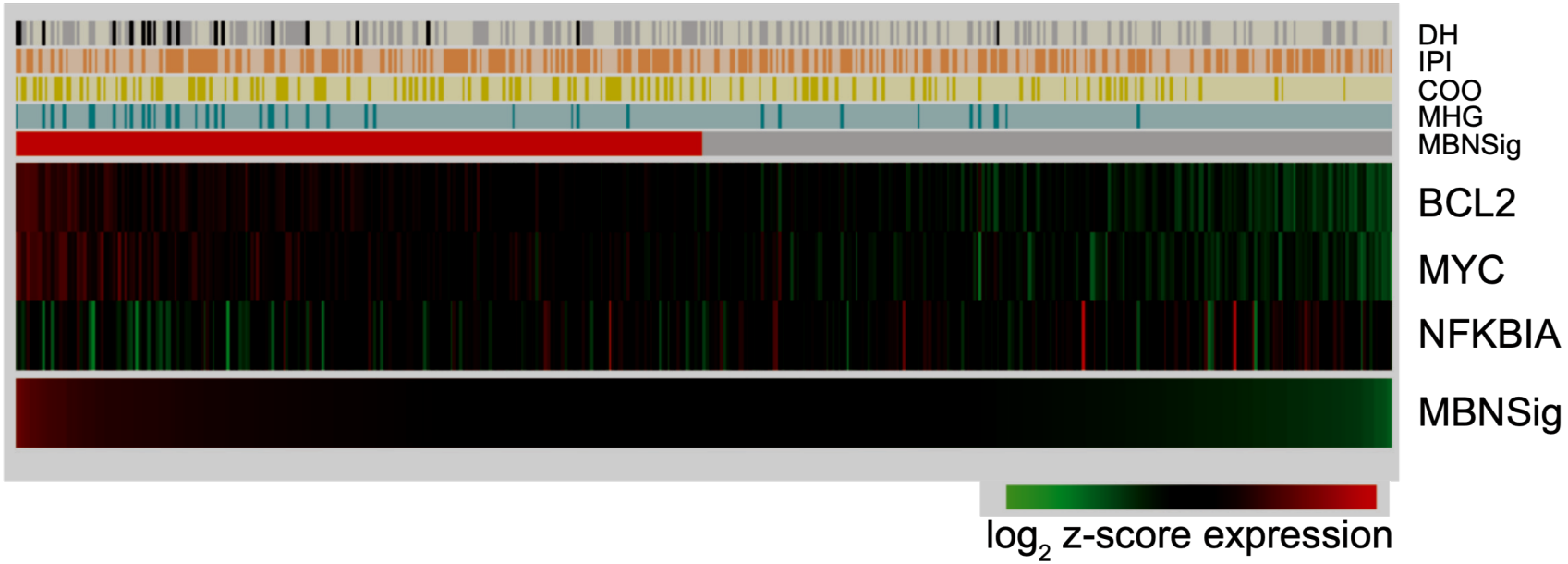


Real-life



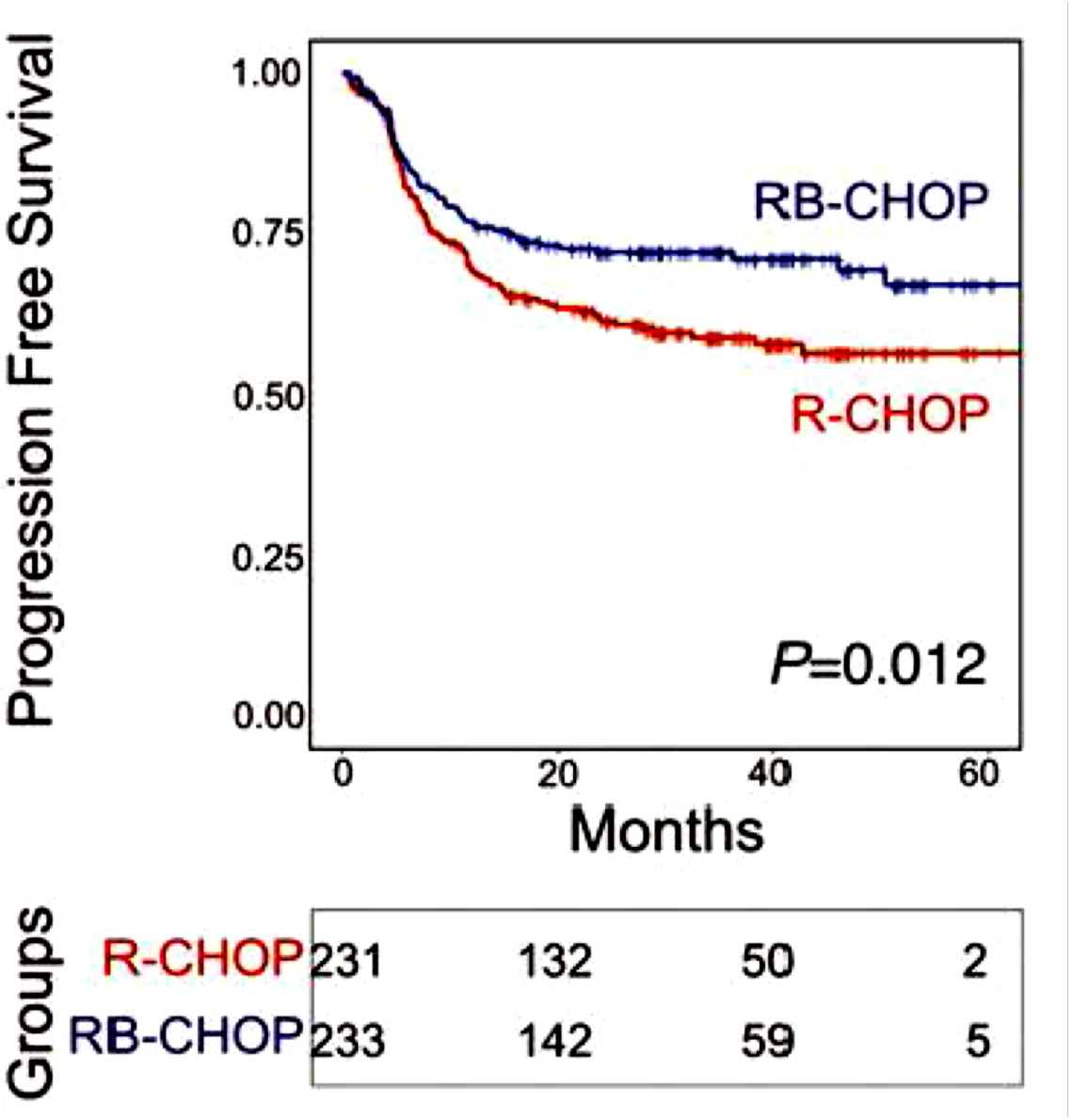
R-CHOP


TRIALS n = 186
ABC
Low
High
High
GCB/U
Low
REAL-LIFE n = 102
ABC
Low
High
High
GCB/U
Low
SHA COHORT n = 469
ABC
Low
High
High
GCB/U
Low



MBNSig	Positive	Negative	
MHG	MHG	Not MHG	
COO	ABC	Not ABC	
IPI	High	Low	
DH	Positive	Negative	NA

Patients from Sha's series with high MBN



Conclusions

- The MBN signature does implement the cell of origin (COO) determination.
- A higher risk group (enriched in genetic aberrations) can be identified among GCB/U and ABC DLBCLs.
- Potential therapeutic implications.
- Applicable to all patients at low cost!!!

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Stromal Gene Signatures in Large-B-Cell Lymphomas

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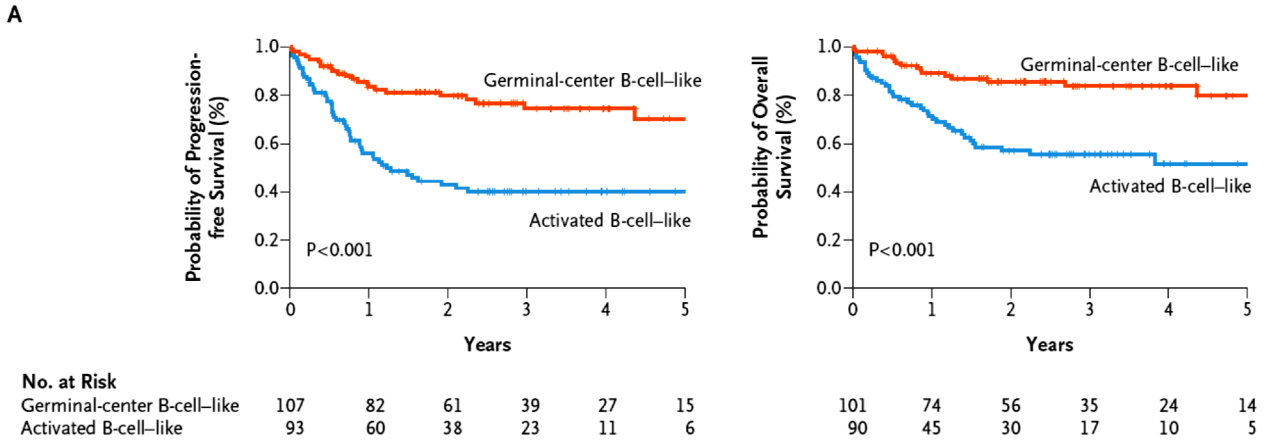
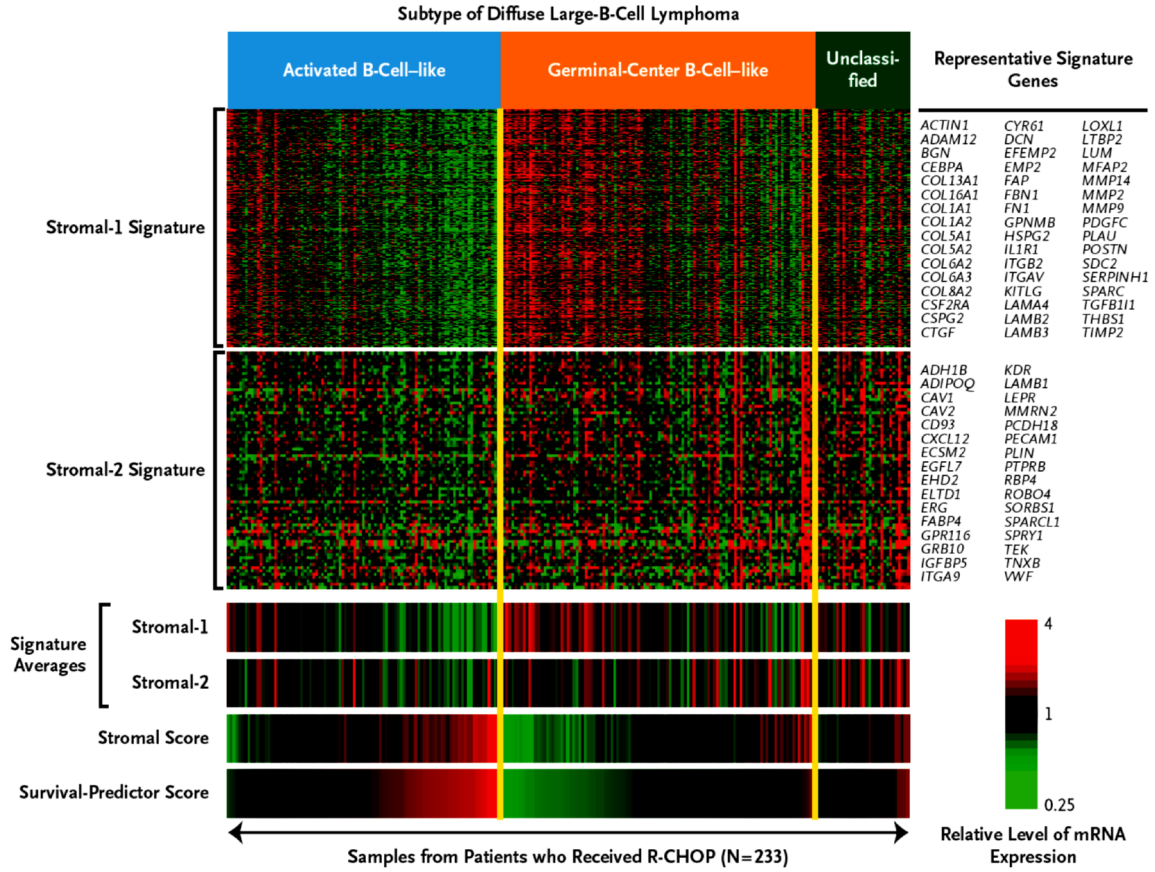




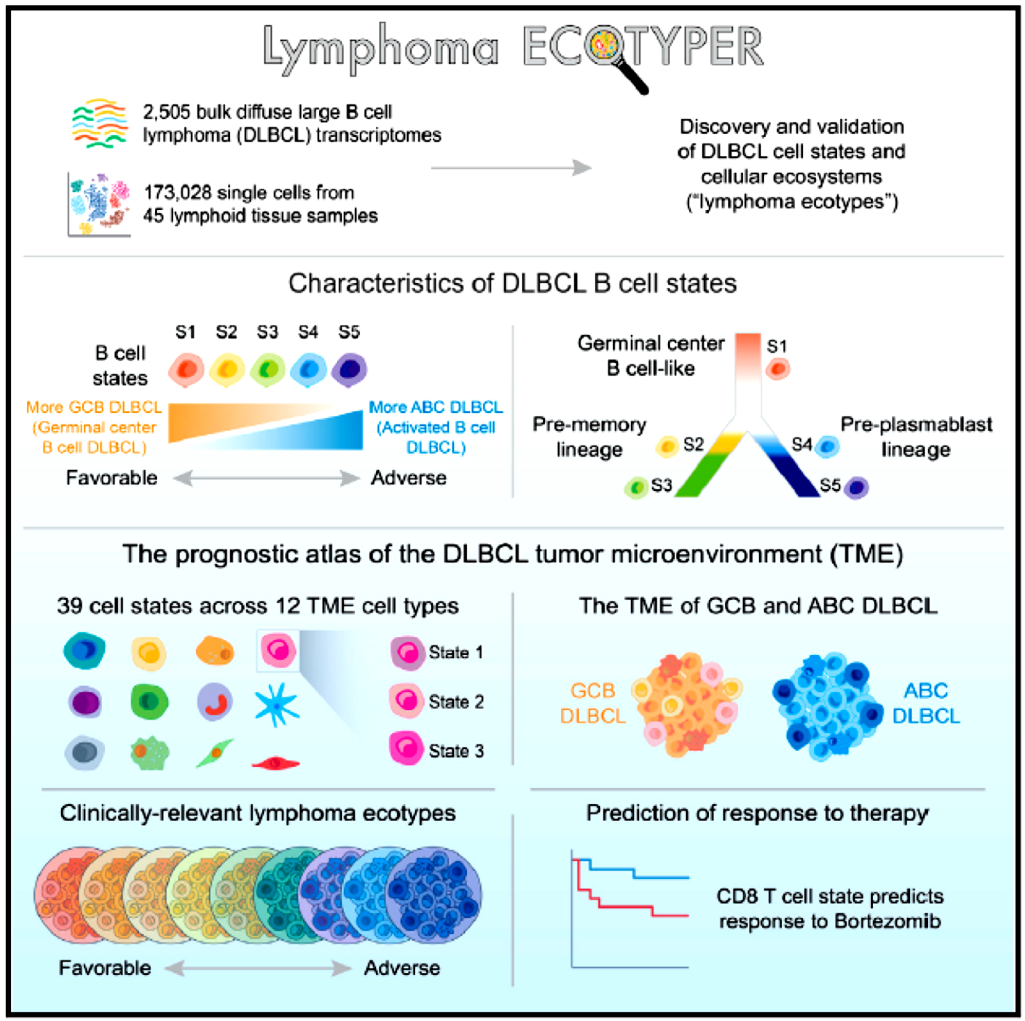
Stromal-1: Extra-cellular matrix deposition + Macrophage infiltration

Stromal-2: Angiogenic genes → Micro-vessel density

Cancer Cell

The landscape of tumor cell states and ecosystems in diffuse large B cell lymphoma

Graphical abstract



Authors

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In brief

Steen et al. implement EcoTyper, a machine-learning approach for dissecting cellular heterogeneity in the most common blood cancer, diffuse large B cell lymphoma (DLBCL). Forty-four cell states spanning malignant cells and the microenvironment are defined, uncovering a rich landscape of cellular ecosystems that extend beyond traditional DLBCL classifications, revealing new opportunities for therapy selection.

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

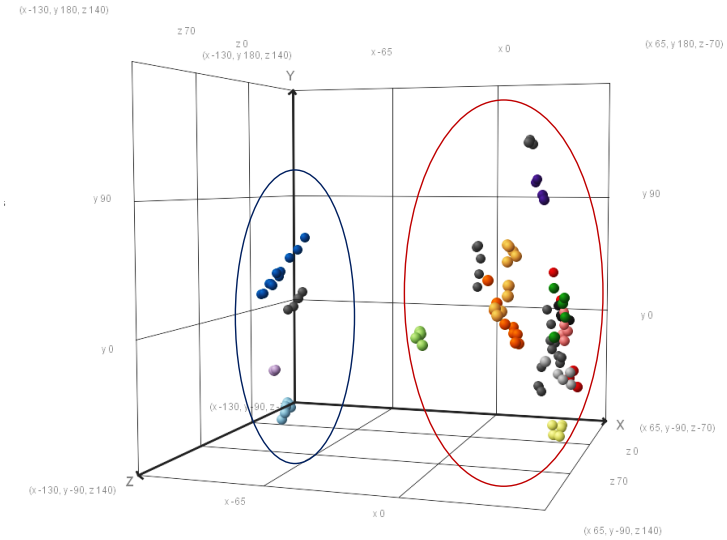
Published: 11 October 2018

CIBERSORT analysis and selection of prognostic genes

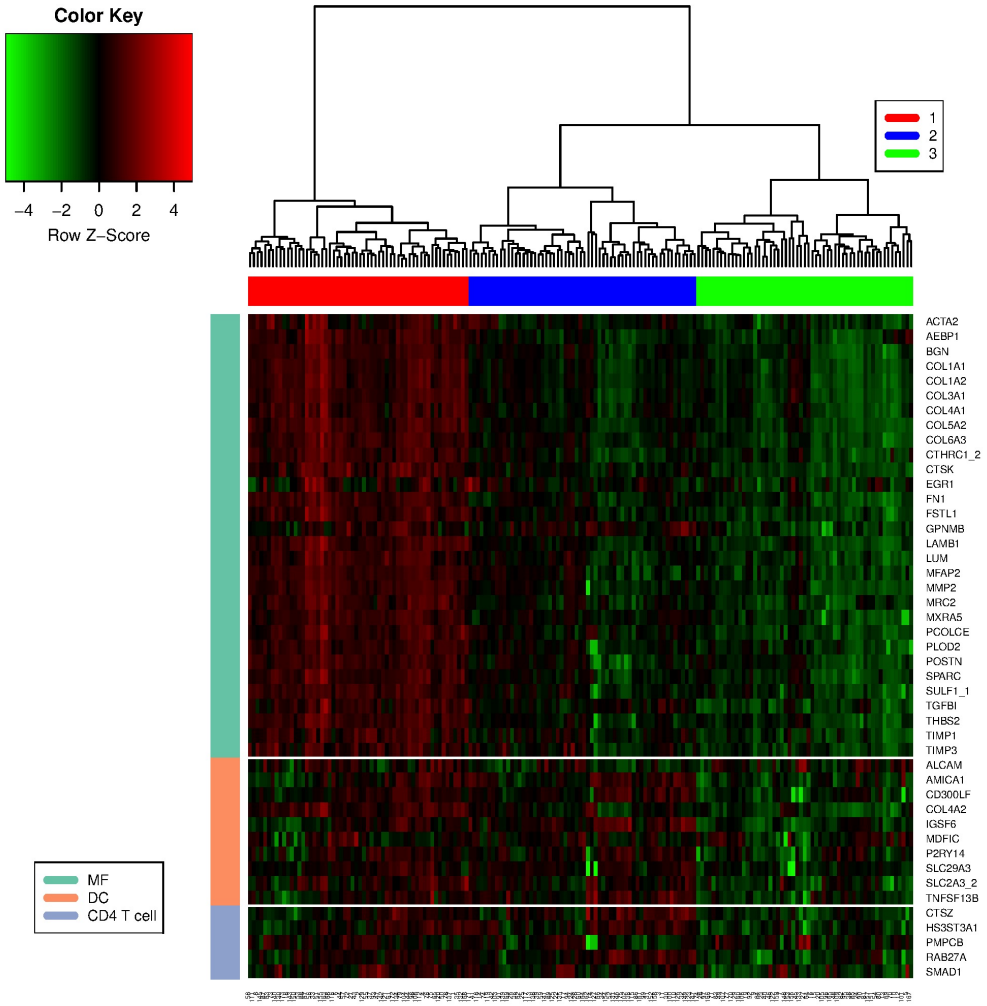
A customized signature including 1,028 genes was generated to distinguish 17 cell types of both stromal and immune origin.

- Adipocites
- CD4-T cells
- CD8-T cells
- Dendritic cells
- Eosinophils
- Lymphatic endothelial cells
- Macrophages M2
- Memory_B_cells
- Monocytes
- Myofibroblasts
- NK_activated
- NK_resting
- Naive_B
- Neutrophils
- Pericytes
- Plasmacells
- Tgamma-delta

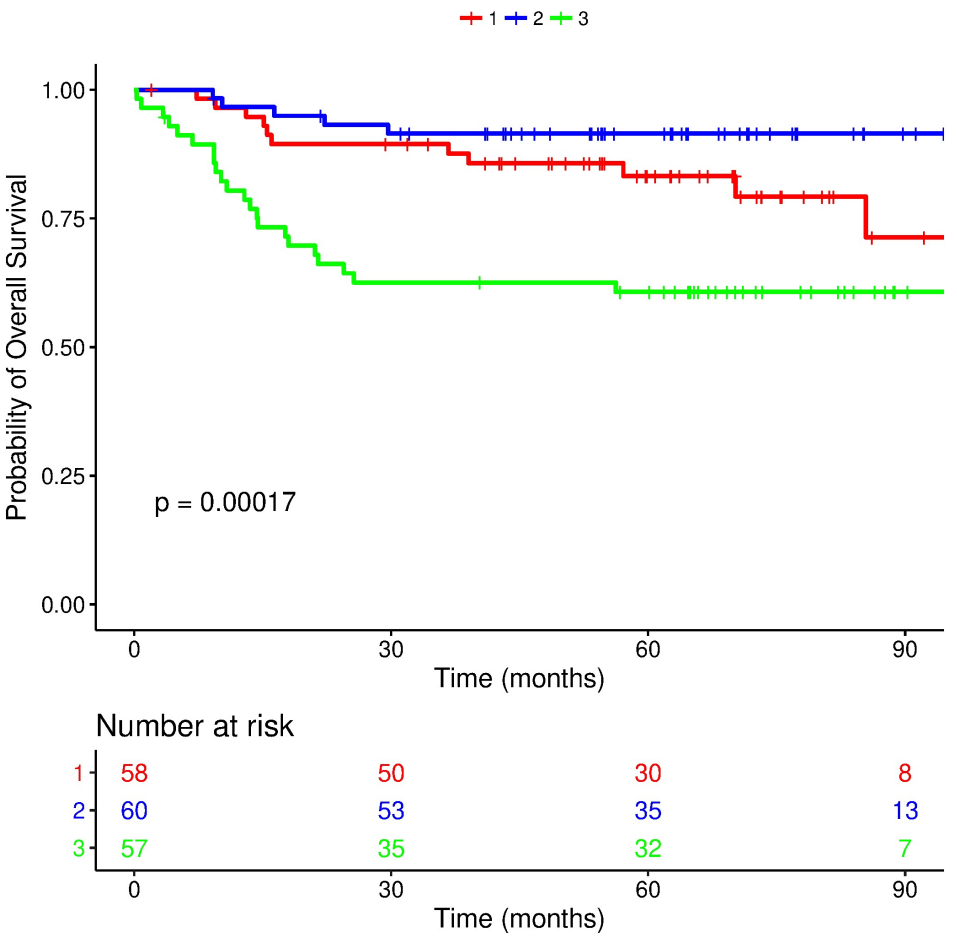
PCA



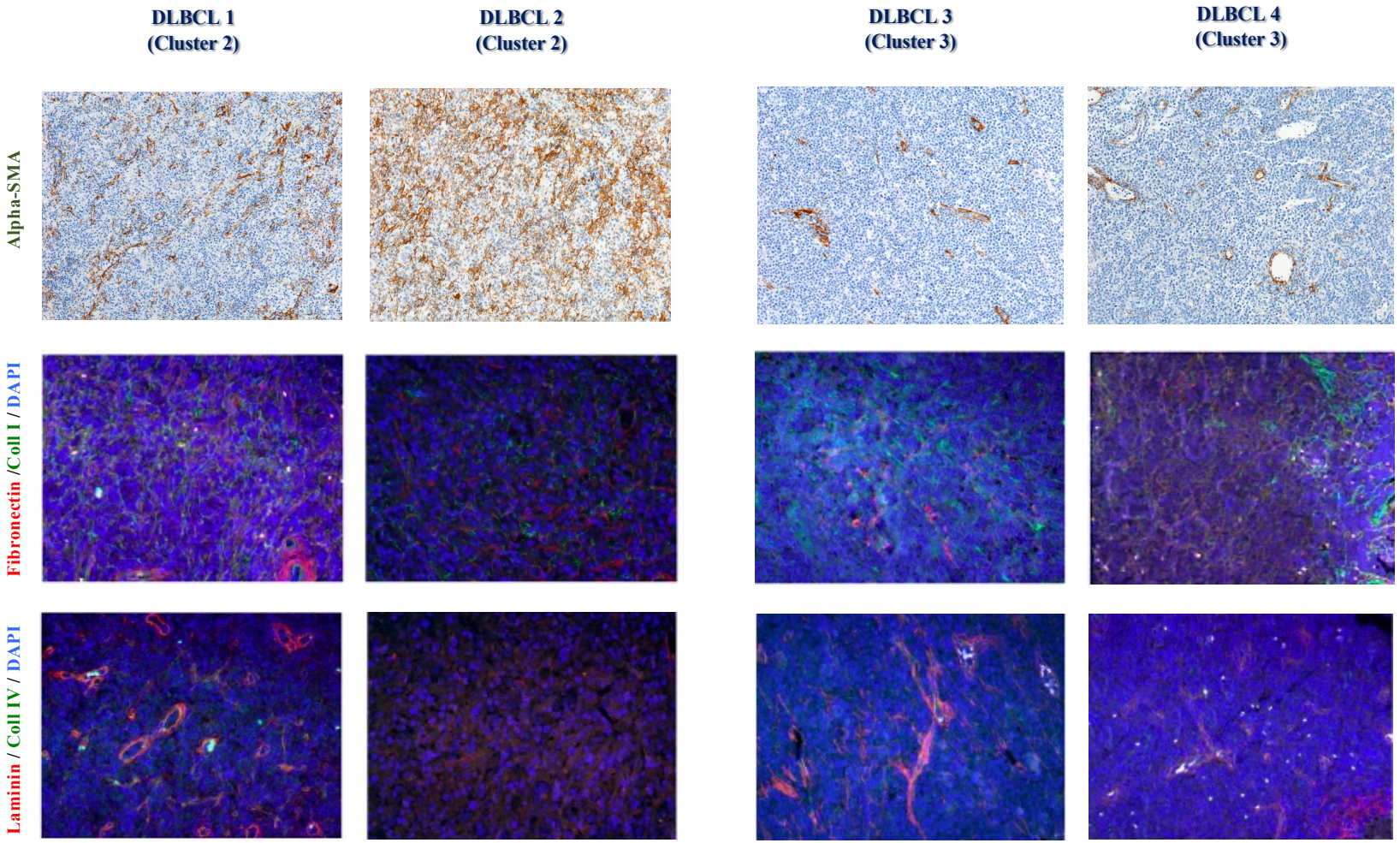
MF-related genes	*ACTA2*	Actin, alpha 2, smooth muscle
	AEBP1	AE binding protein 1
	BGN	Biglycan
	COL1A1	Collagen type I alpha 1
	COL1A2	Collagen type I alpha 2
	COL3A1	Collagen type III alpha 1
	COL4A1	Collagen type IV alpha 1
	COL5A2	Collagen type V alpha 2
	COL6A3	Collagen type VI alpha 3
	CTHRC1	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

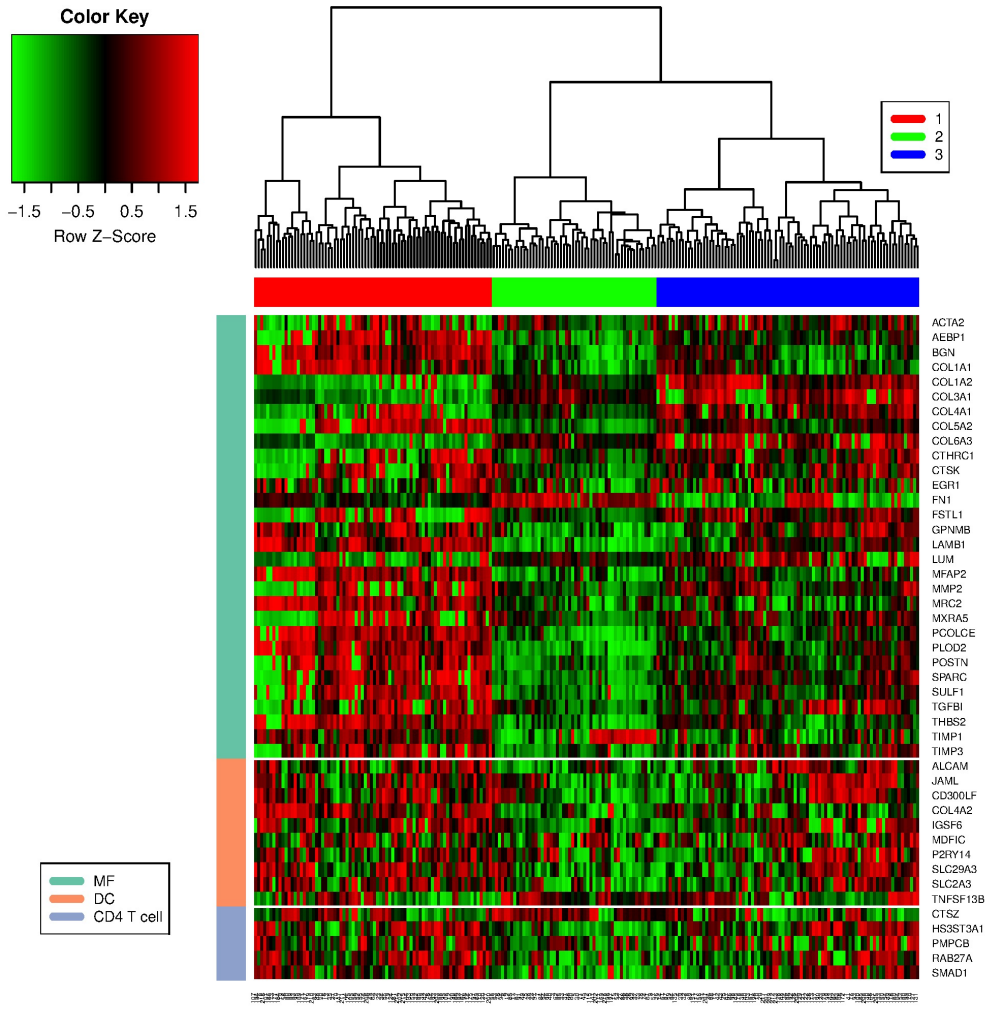


DLCL04 and R-HDS0305

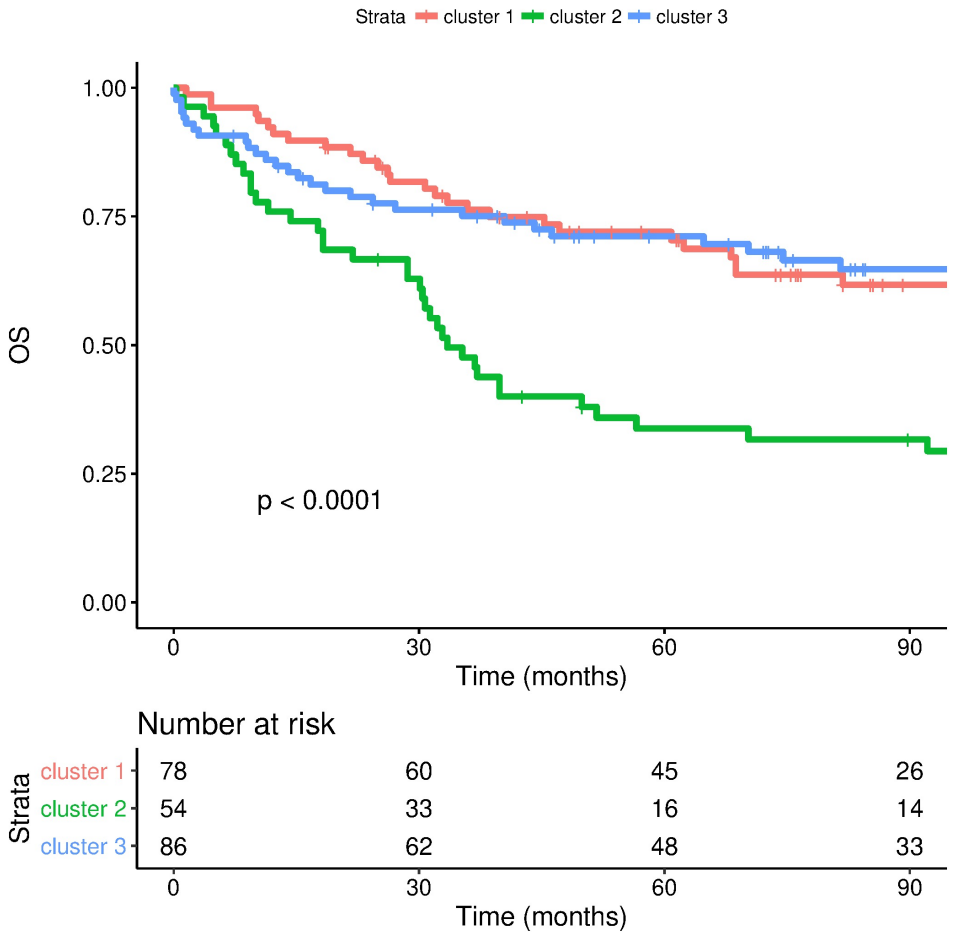


By *in situ* immunostaining we analyzed the expression of ECM proteins encoded by four of the fronting genes of the MF signature, namely Fibronectin, Collagen-I, Laminin, and Collagen-IV. However, the expression variability of these proteins does not support the use of immunohistochemistry as a reliable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

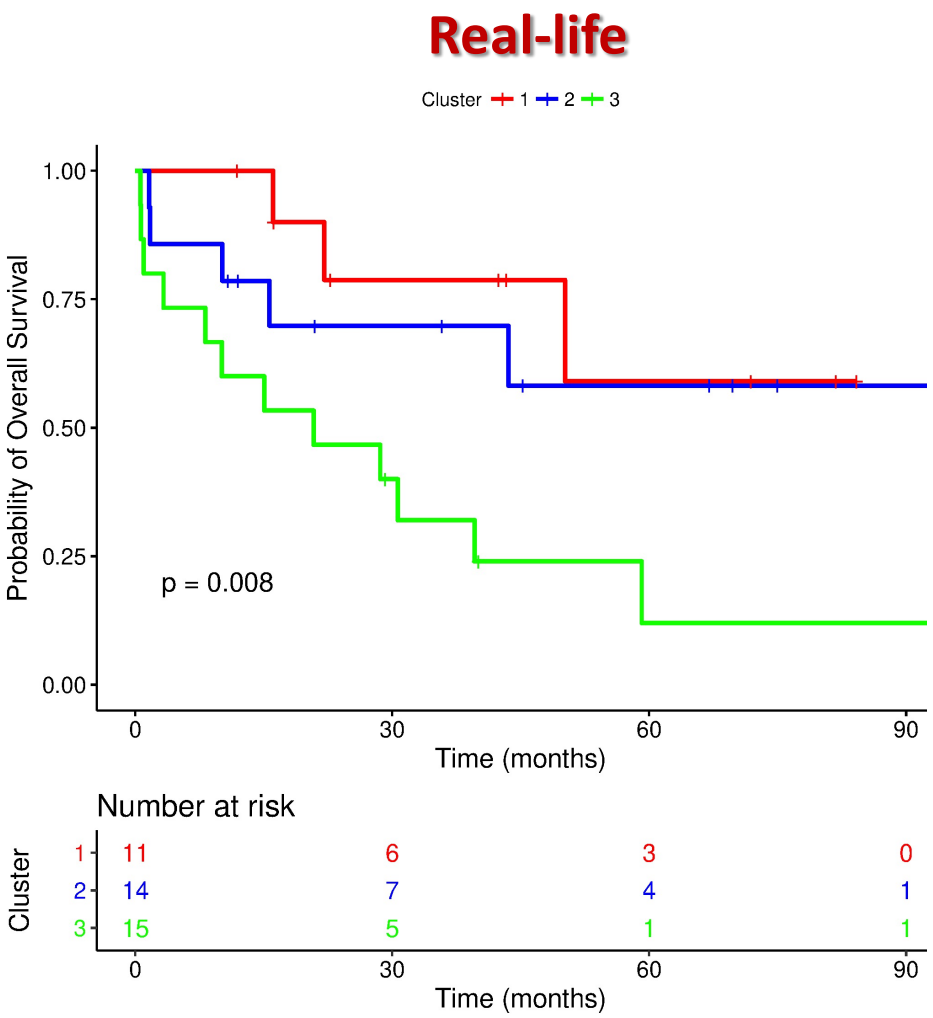


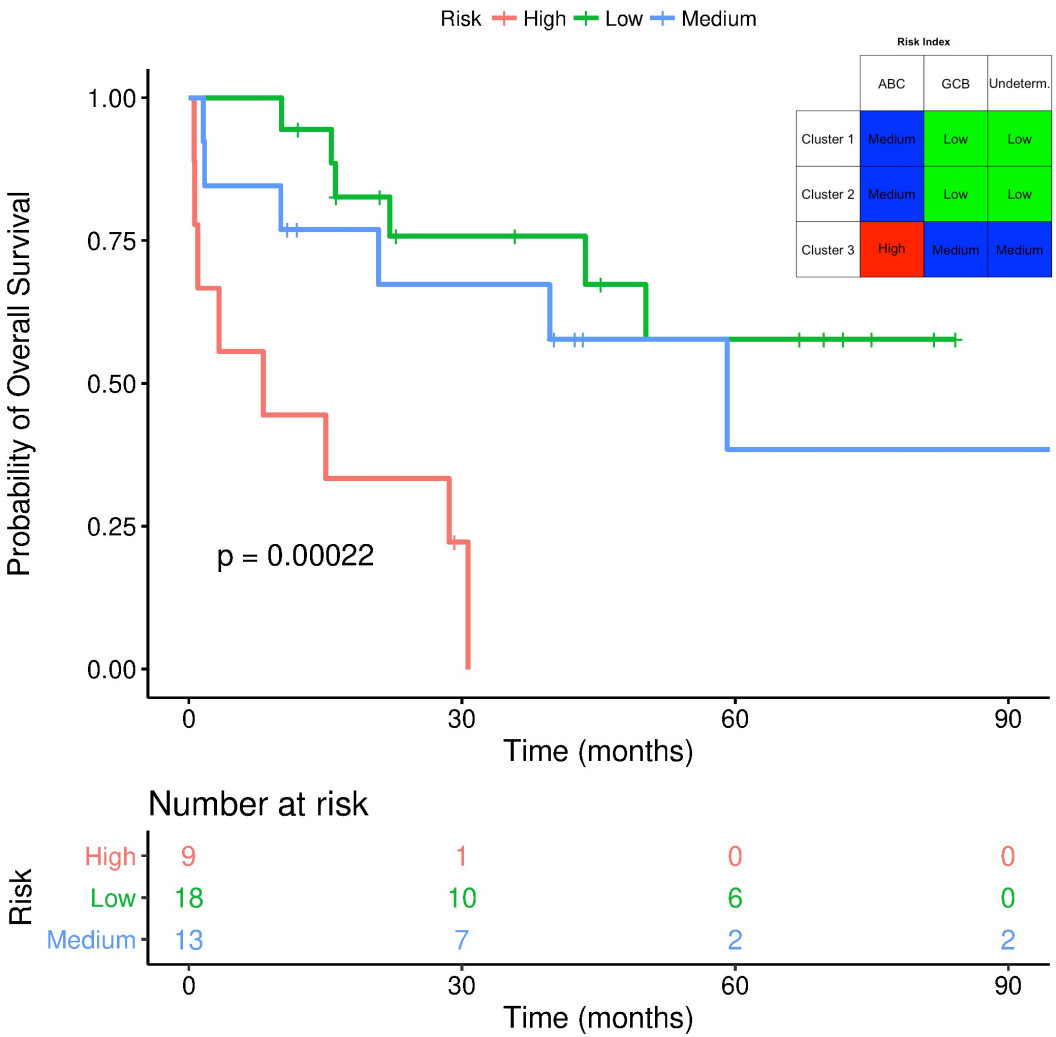

Color Key
−1.5 −0.5 0.5 1.5
Row Z−Score
1
2
3
ACTA2
AEBP1
BGN
COL1A1
COL1A2
COL3A1
COL4A1
COL5A2
COL6A3
CTHRC1
CTSK
EGR1
FN1
FSTL1
GPNMB
LAMB1
LUM
MFAP2
MMP2
MRC2
MXRA5
PCOLCE
PLOD2
POSTN
SPARC
SULF1
TGFBI
THBS2
TIMP1
TIMP3
ALCAM
JAML
CD300LF
COL4A2
IGSF6
MDFIC
P2RY14
SLC29A3
SLC2A3
TNFSF13B
CTSZ
HS3ST3A1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

Lenz' series


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 78 60 45 26
cluster 2 54 33 16 14
cluster 3 86 62 48 33
0
30
60
90
Time (months)

Real-life


Cluster 1 2 3
Probability of Overall Survival
1.00
0.75
0.50
0.25
0.00
p = 0.008
0
30
60
90
Time (months)
Number at risk
Cluster
1 11 6 3 0
2 14 7 4 1
3 15 5 1 1
0
30
60
90
Time (months)


Risk High Low Medium
Risk Index
ABC GCB Undeterm.
Cluster 1 Medium Low Low
Cluster 2 Medium Low Low
Cluster 3 High Medium Medium
Probability of Overall Survival
1.00
0.75
0.50
0.25
0.00
p = 0.00022
0
30
60
90
Time (months)
Number at risk
Risk
High 9 1 0 0
Low 18 10 6 0
Medium 13 7 2 2
0
30
60
90
Time (months)

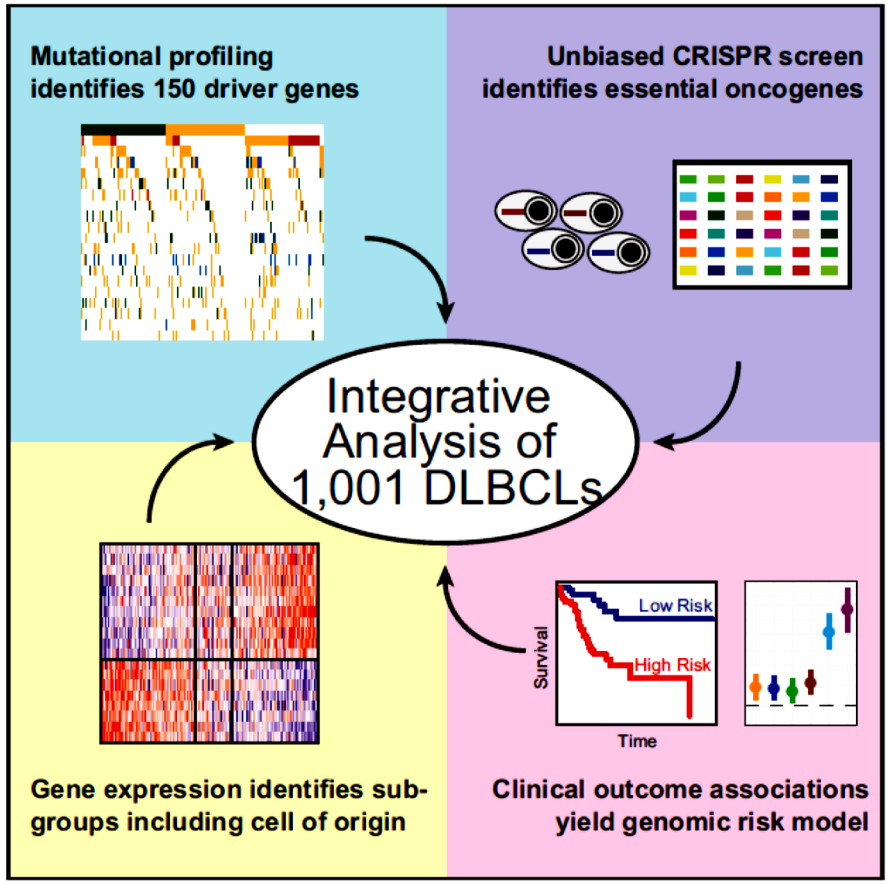
Next generation sequencing

Resource

Cell

Genetic and Functional Drivers of Diffuse Large B Cell Lymphoma

Graphical Abstract



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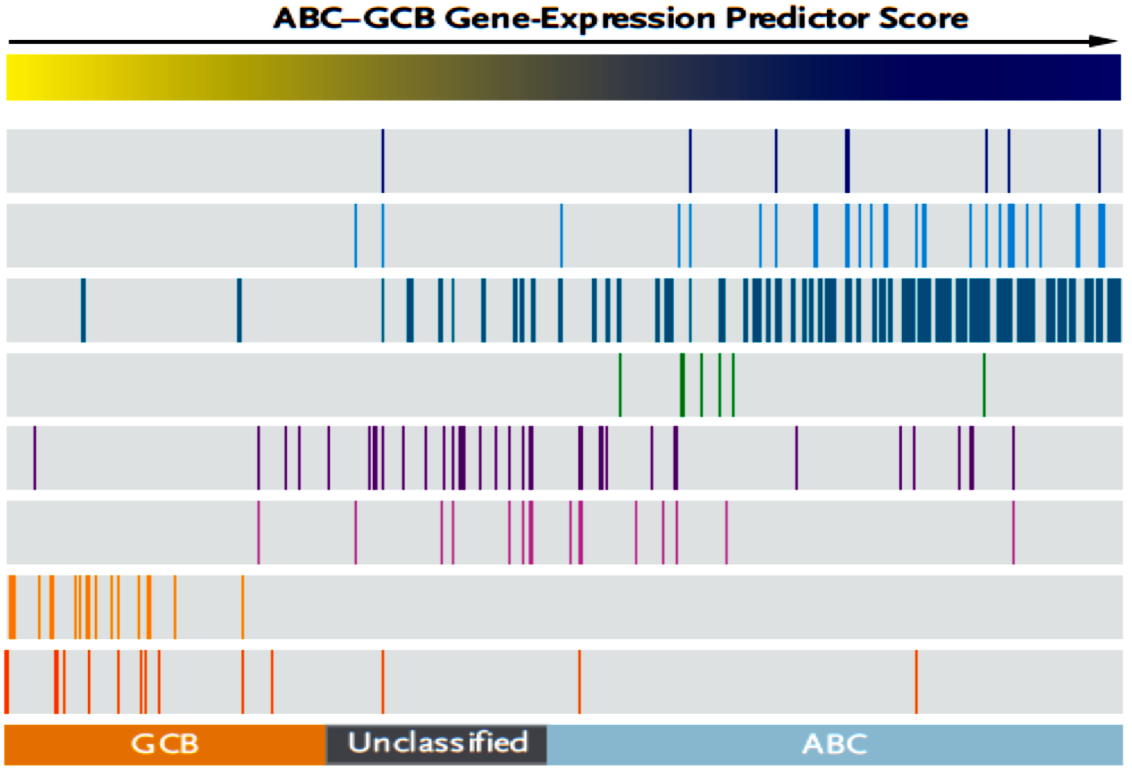
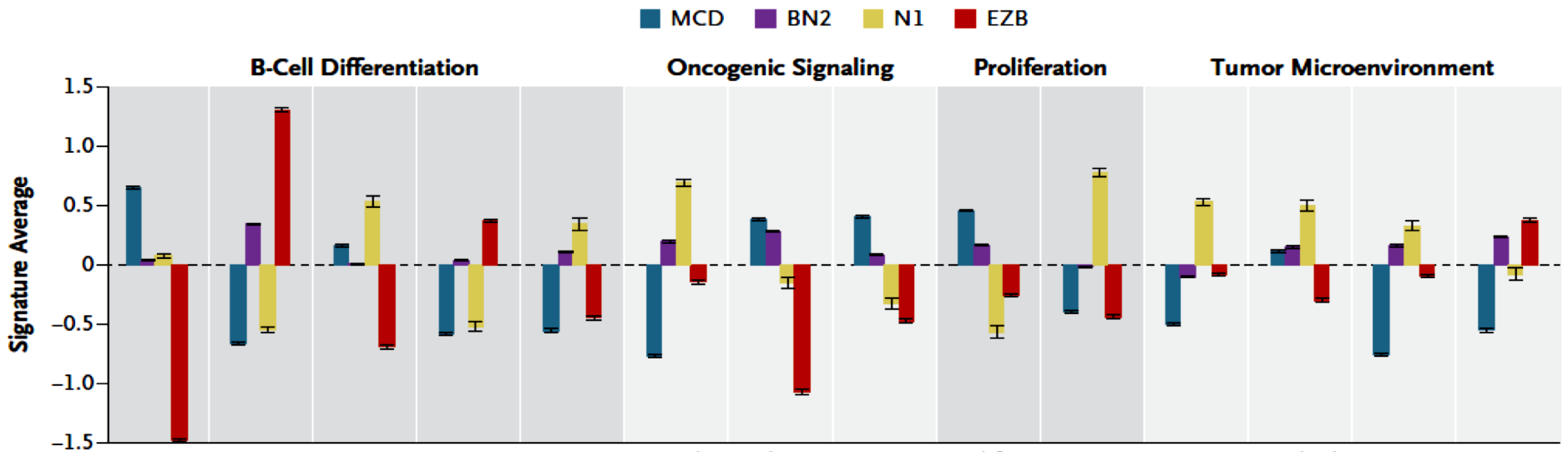
In Brief

An integrative analysis in 1,001 newly diagnosed DLBCL patients identifies 150 genetic drivers with functional characterization using an unbiased CRISPR screen in DLBCL cell lines and connects with clinical outcome.

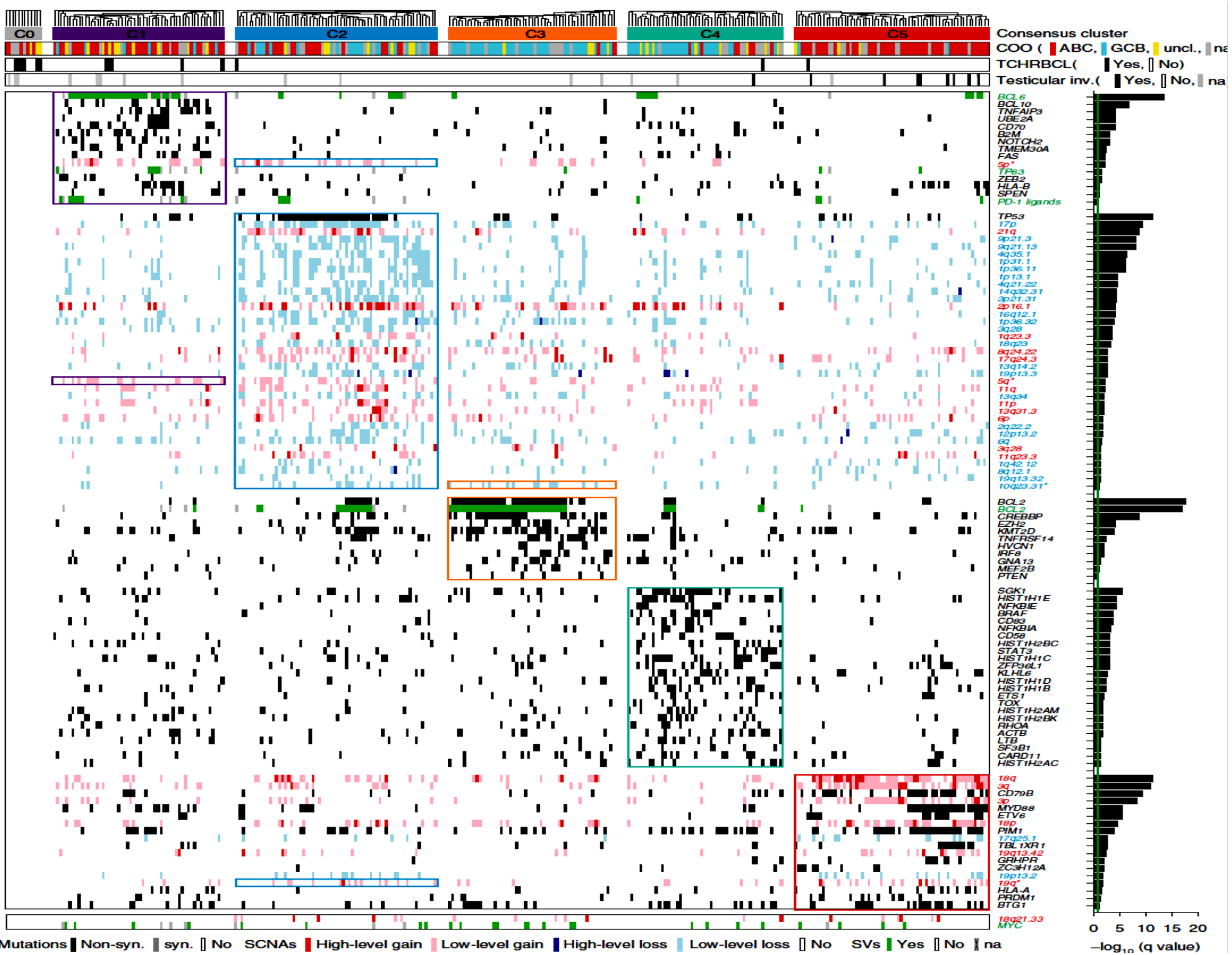
Cell *171*, 481–494, October 5, 2017

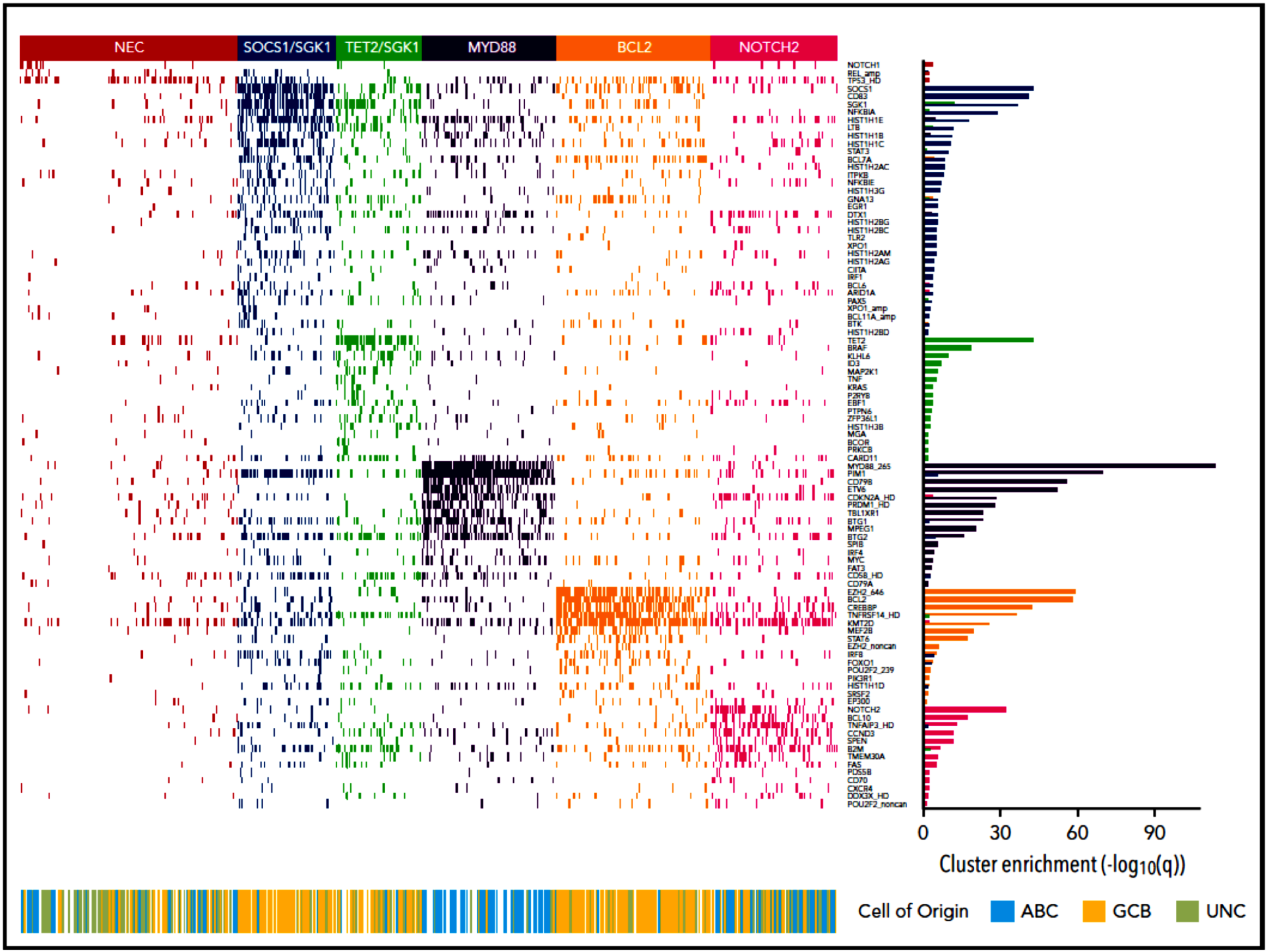
Genetic Feature	Log_{10} P Value	GCB	Unclassified	ABC
		prevalence (%)		
CD79B+*MYD88*^{L265P} double mutation	−6.4	0.6	1.7	11.5
CD79B mutation	−13.8	0.6	6.1	25.4
MYD88^{L265P} mutation	−17.0	1.2	7.8	28.8
NOTCH1 mutation	−3.8	0.0	0.9	6.1
BCL6 fusion	−4.1	11.6	33.0	18.6
NOTCH2 mutation	−5.3	3.0	20.0	6.4
BCL2 translocation	−20.4	28.0	5.2	0.7
EZH2 mutation	−12.1	22.0	5.2	1.7





Log_{10} P Value	−55.14	−36.16	−7.93	−9.00	−5.20	−11.71	−14.92	−7.33	−6.65	−6.10	−5.33	−3.16	−10.07	−6.45


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

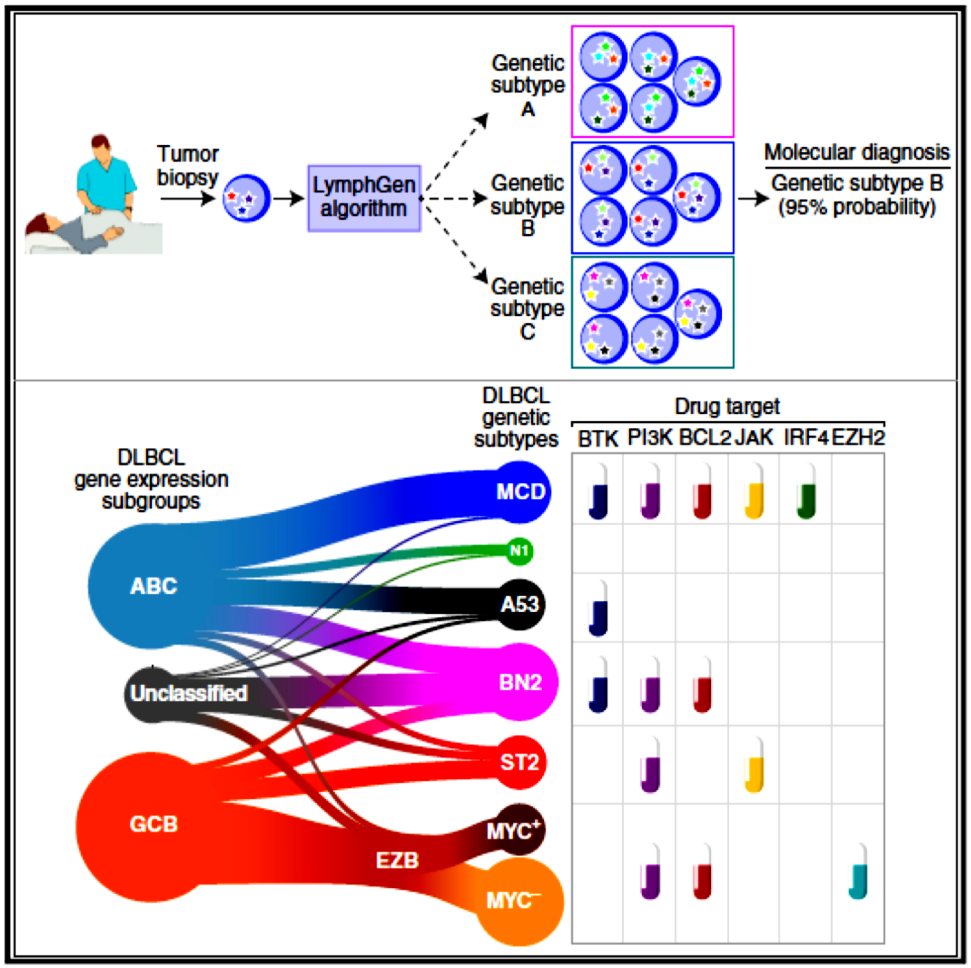

NEC
SOCS1/SGK1
TET2/SGK1
MYD88
BCL2
NOTCH2
NOTCH1
REL_amp
TP53_HD
SOCS1
CD83
SGK1
NFKBIA
HIST1H1E
LTB
HIST1H1B
HIST1H1C
STAT3
BCL7A
HIST1H2AC
ITPKB
NFKBIE
HIST1H3G
GNA13
EGR1
DTX1
HIST1H2BG
HIST1H2BC
TLR2
XPO1
HIST1H2AM
HIST1H2AG
CIITA
IRF1
BCL6
ARID1A
PAX5
XPO1_amp
BCL11A_amp
BTK
HIST1H2BD
TET2
BRAF
KLHL6
ID3
MAP2K1
TNF
KRAS
P2RY8
EBF1
PTPN6
ZFP36L1
HIST1H3B
MGA
BCOR
PRKCB
CARD11
MYD88_265
PIM1
CD79B
ETV6
CDKN2A_HD
PRDM1_HD
TBL1XR1
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
PDSS2B
CD70
CXCR4
DDX3X_HD
POU2F2_noncan
0
30
60
90
Cluster enrichment (-log10(q))
Cell of Origin
ABC
GCB
UNC

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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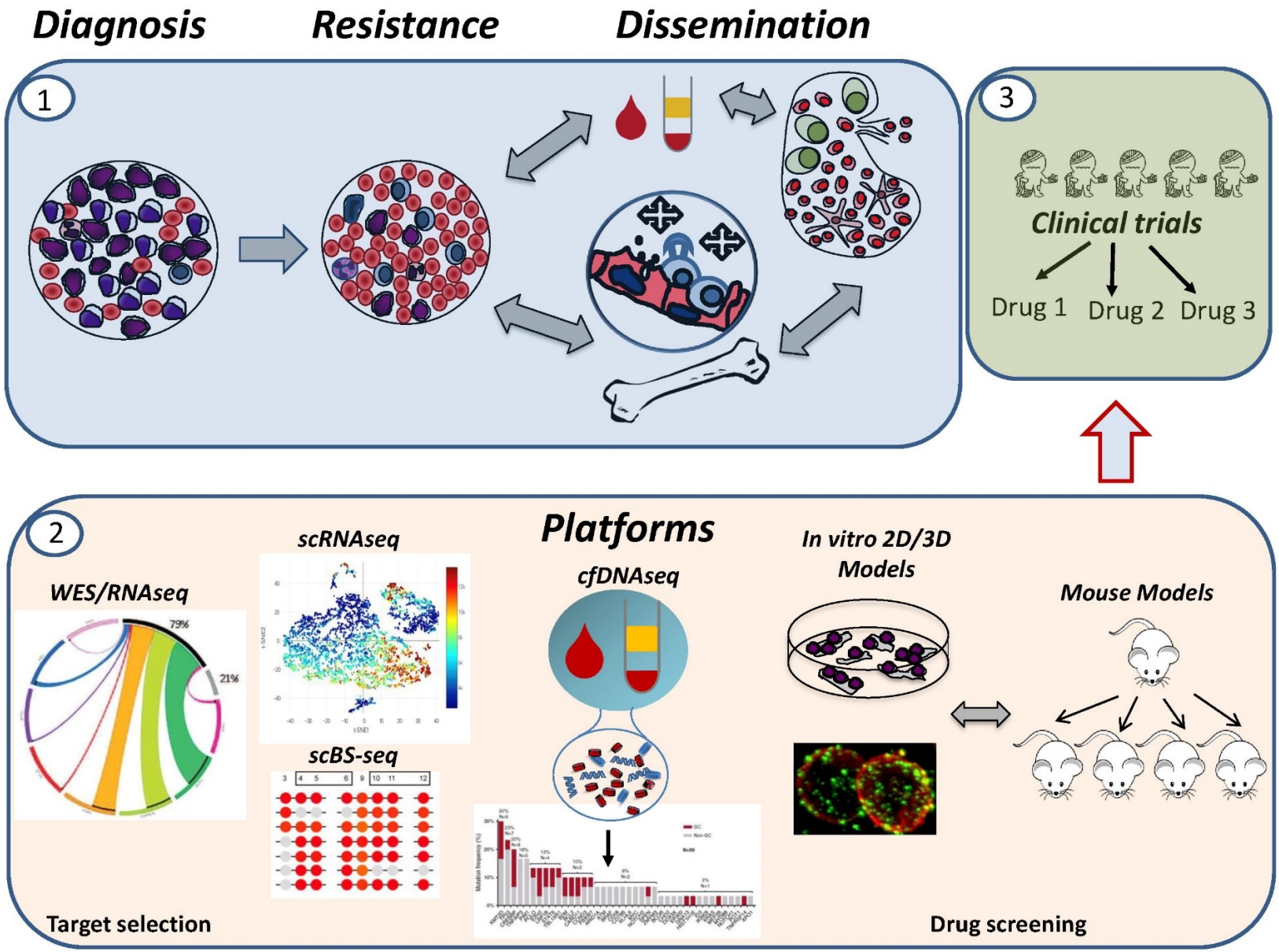
In Brief

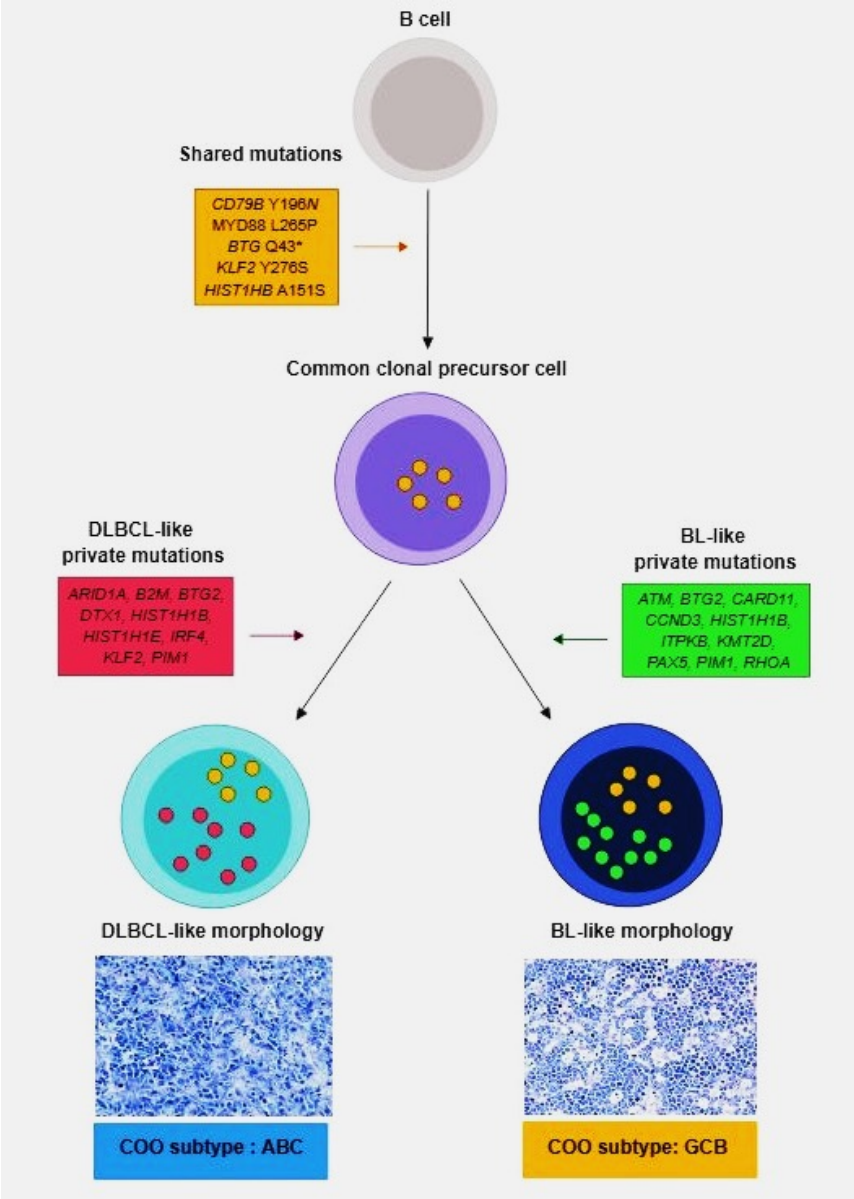
Wright et al. identify seven genetic subtypes of diffuse large B cell lymphoma (DLBCL) with distinct outcomes and therapeutic vulnerabilities. The LymphGen probabilistic classification tool that can classify a DLBCL biopsy into the genetic subtypes is developed, which could be used for precision medicine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


Diagnosis
Resistance
Dissemination
1
3
Clinical trials
Drug 1
Drug 2
Drug 3
2
Platforms
WES/RNAseq
79%
21%
scRNAseq
scBS-seq
cfDNAseq
In vitro 2D/3D Models
Mouse Models
Target selection
Drug screening

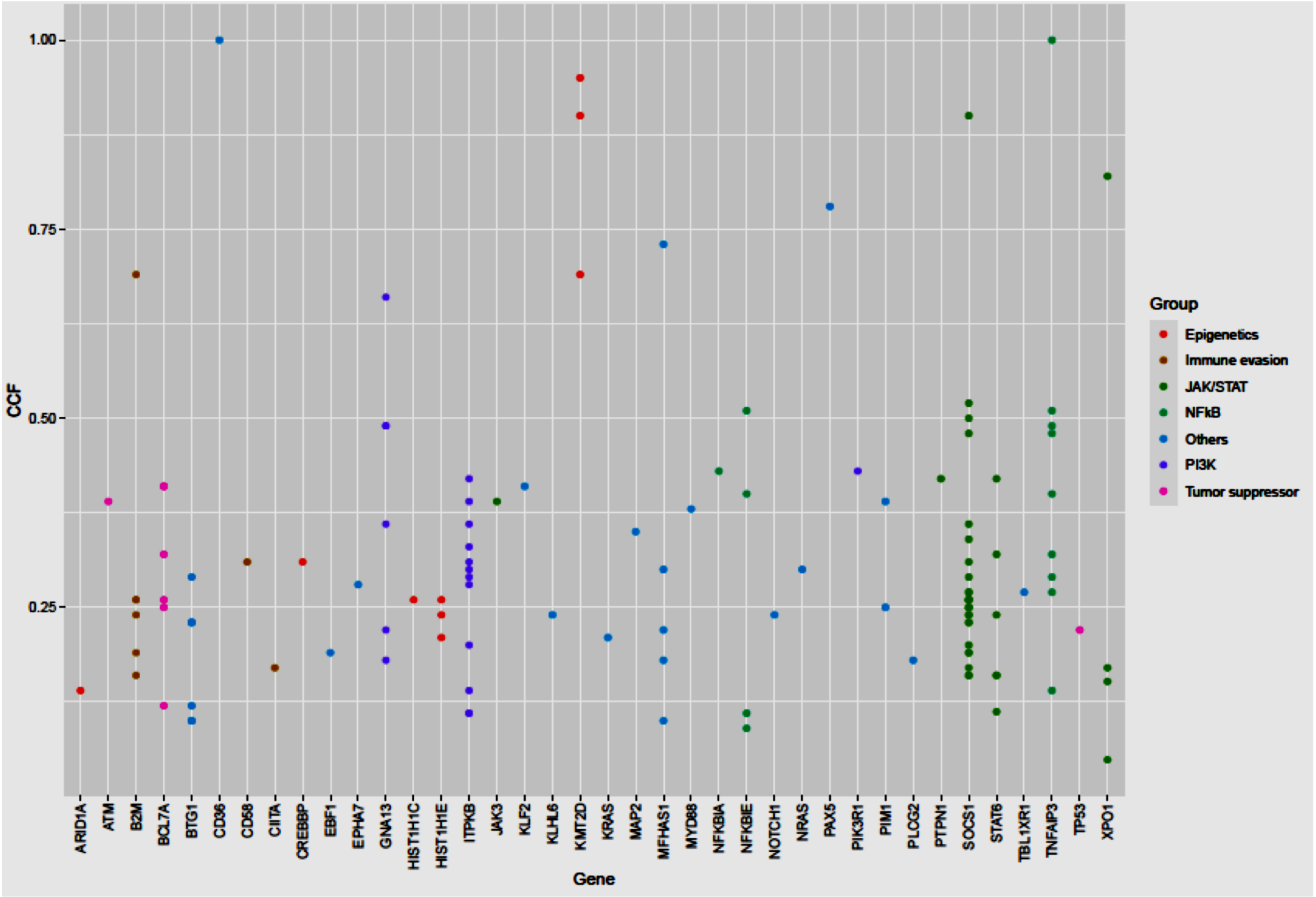
Evolutionary crossroads: morphological heterogeneity reflects divergent intra-clonal evolution in a case of high-grade B-cell lymphoma

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

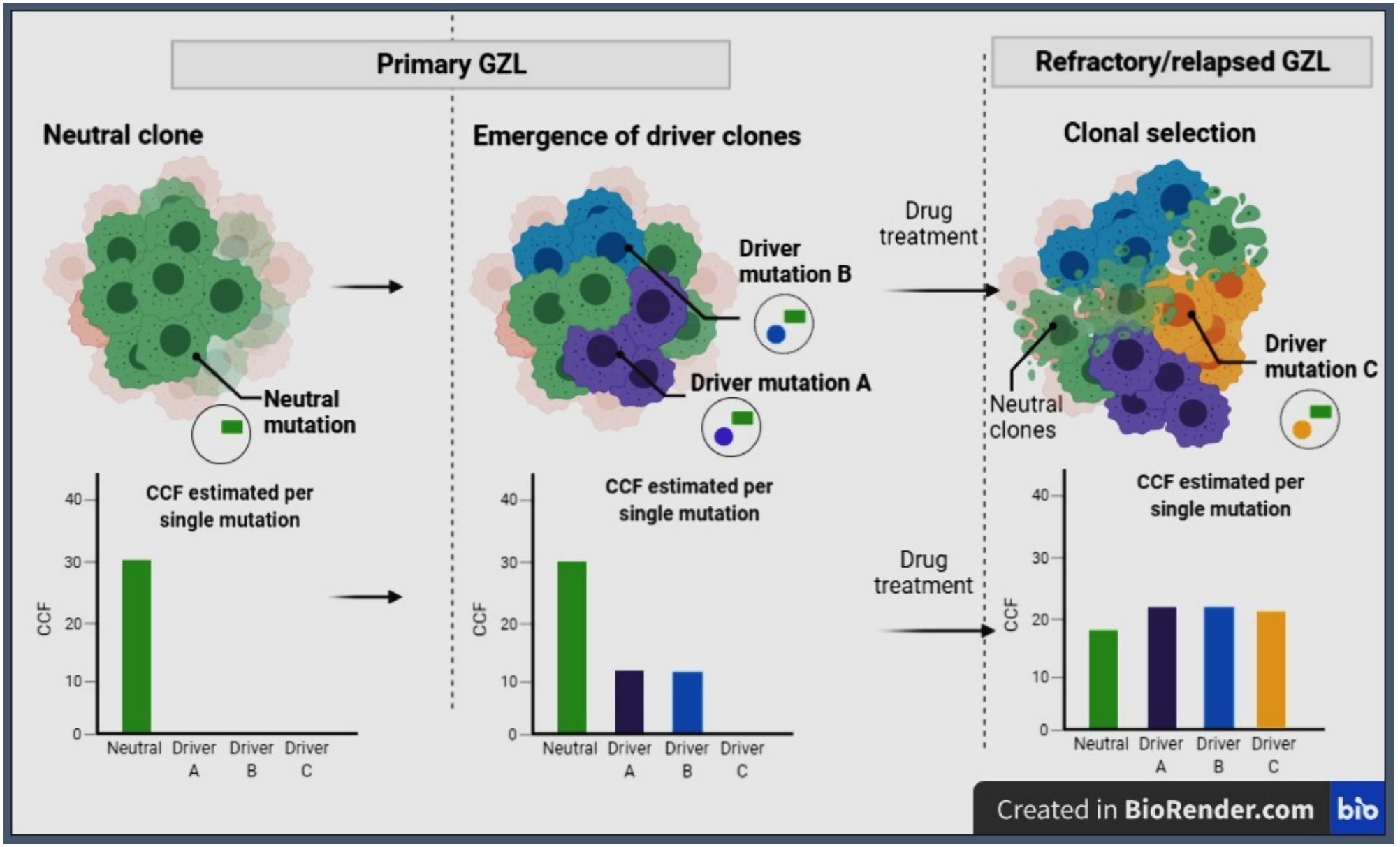
Haematologica 2020 [Epub ahead of print]

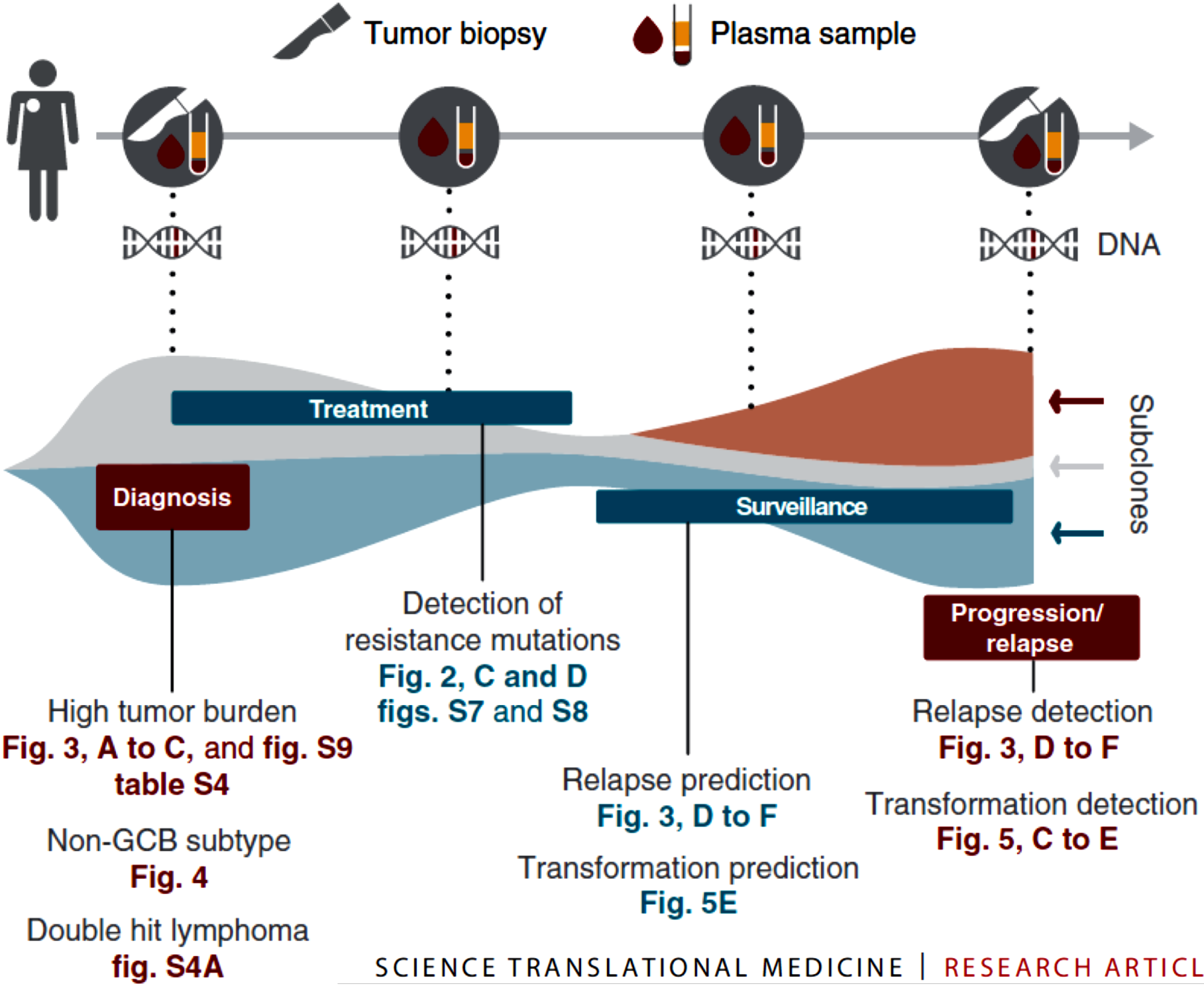


11 mediastinal GZLs (3 R/R) + 30 (EAHP Workshop)



Relapses due to subclonal selection?


Primary GZL
Refractory/relapsed GZL
Neutral clone
Emergence of driver clones
Clonal selection
Neutral mutation
Driver mutation B
Driver mutation A
Drug treatment
Neutral clones
Driver mutation C
CCF estimated per single mutation
CCF
40
30
20
10
0
Neutral
Driver A
Driver B
Driver C
Drug treatment
CCF estimated per single mutation
CCF
40
30
20
10
0
Neutral
Driver A
Driver B
Driver C
CCF estimated per single mutation
CCF
40
30
20
10
0
Neutral
Driver A
Driver B
Driver C
Created in BioRender.com
bio


Tumor biopsy
Plasma sample
DNA
Treatment
Diagnosis
Surveillance
Subclones
Progression/ relapse
Detection of resistance mutations
Fig. 2, C and D
figs. S7 and S8
High tumor burden
Fig. 3, A to C, and fig. S9
table S4
Non-GCB subtype
Fig. 4
Double hit lymphoma
fig. S4A
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

blood® 24 MARCH 2022 | VOLUME 139, NUMBER 12 1863

LYMPHOID NEOPLASIA

Molecular features encoded in the ctDNA reveal heterogeneity and predict outcome in high-risk aggressive B-cell lymphoma

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KEY POINTS

- Quantitative, mutational, and fragmentation features in the ctDNA dynamically predict treatment responses and survival.
- ctDNA captures the complete lymphoma ecosystem that extends beyond tumor biopsies, imaging, and clinical estimates.

Inadequate molecular and clinical stratification of the patients with high-risk diffuse large B-cell lymphoma (DLBCL) is a clinical challenge hampering the establishment of personalized therapeutic options. We studied the translational significance of liquid biopsy in a uniformly treated trial cohort. Pretreatment circulating tumor DNA (ctDNA) revealed hidden clinical and biological heterogeneity, and high ctDNA burden determined increased risk of relapse and death independently of conventional risk factors. Genomic dissection of pretreatment ctDNA revealed translationally relevant phenotypic, molecular, and prognostic information that extended beyond diagnostic tissue biopsies. During therapy, chemorefractory lymphomas exhibited diverging ctDNA kinetics, whereas end-of-therapy negativity for minimal residual disease (MRD) characterized cured patients and resolved clinical enigmas, including false residual PET positivity. Furthermore, we discovered fragmentation disparities in the cell-free DNA that characterize lymphoma-derived ctDNA and, as a proof-of-concept for their clinical application, used machine learning to show that end-of-therapy fragmentation patterns predict outcome. Altogether, we have discovered novel molecular determinants in the liquid biopsy that can noninvasively guide treatment decisions.


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