Case 3

Multi-Institutional Hematopathology Interesting Case Conference

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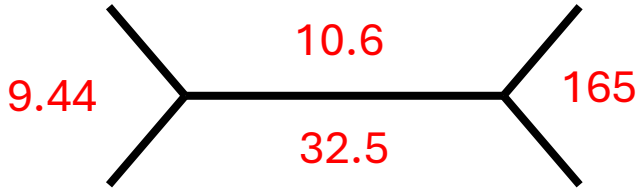
PGY-5

History

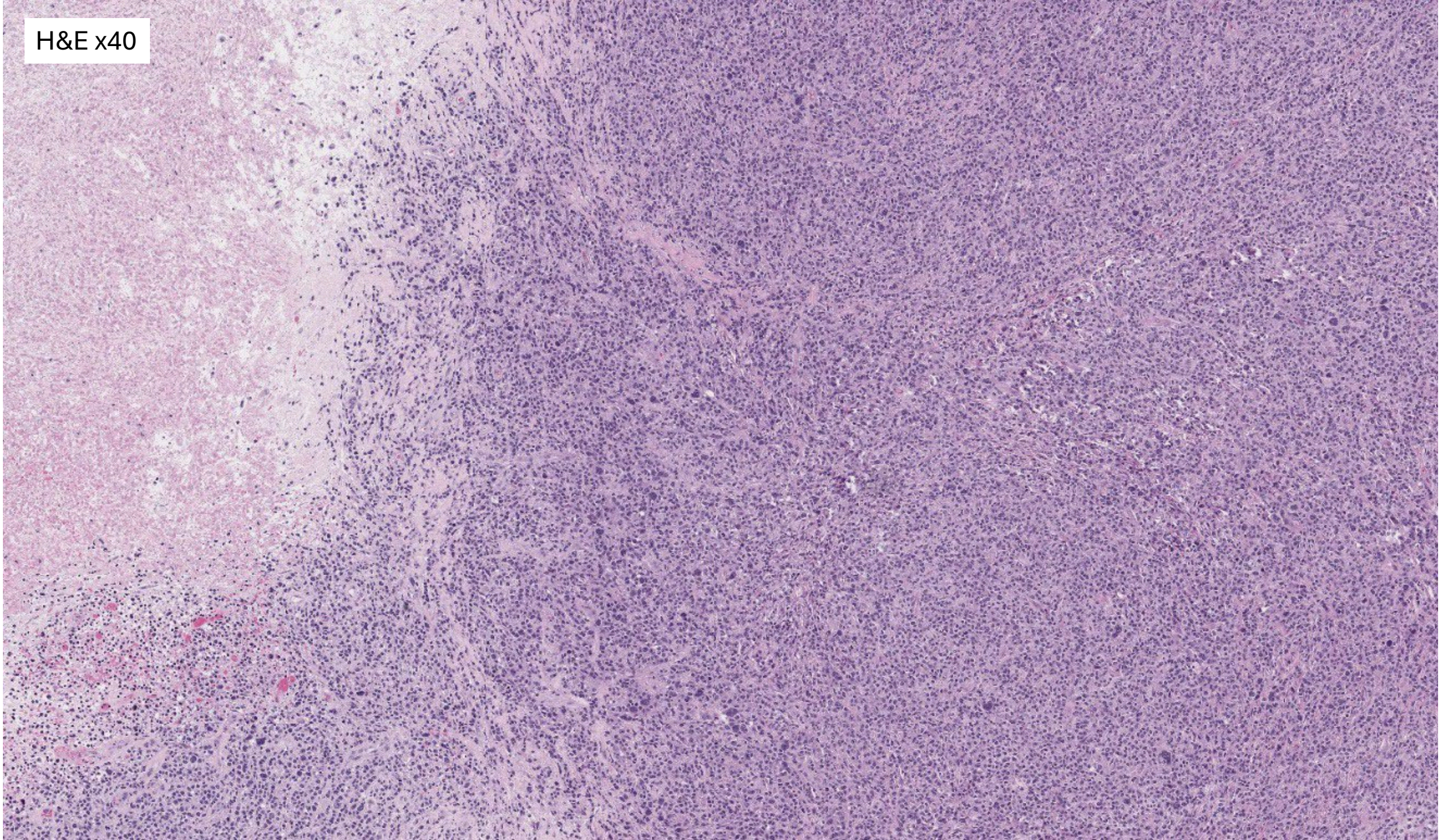
- 82-year-old man
- Previously diagnosed B-cell lymphoma from an outside hospital, treatment unknown
- Presenting with visible right neck lymphadenopathy and 30-40 lb weight loss over the course of one year
- Lymph node biopsy performed

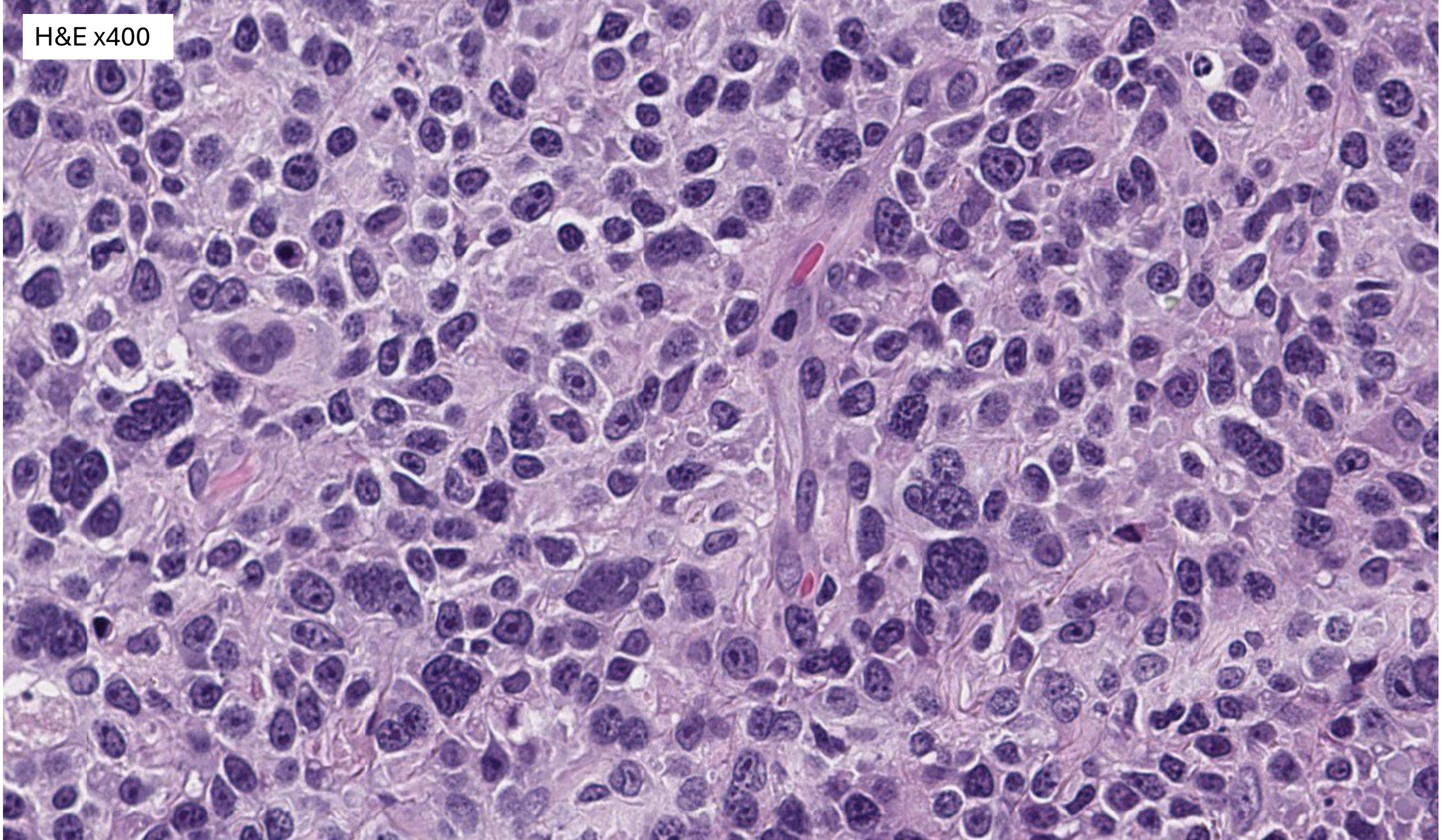


MCV: 101.9 fL

Differential:
Neutrophil: 87.5%
Lymphocytes: 3.4%
Monocytes: 7.8%
Eosinophils: 0.5%
Basophils: 0.3%

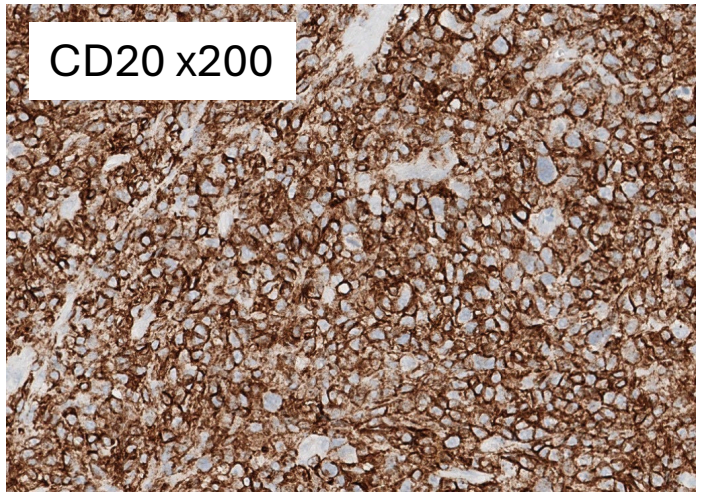
LDH: 280 U/L

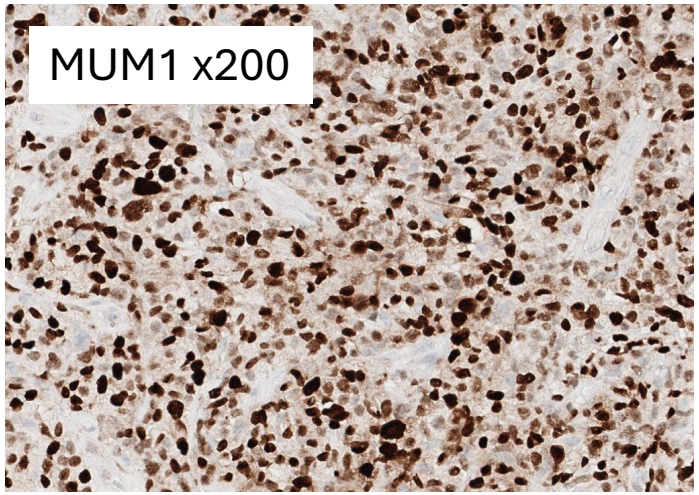

H&E x40

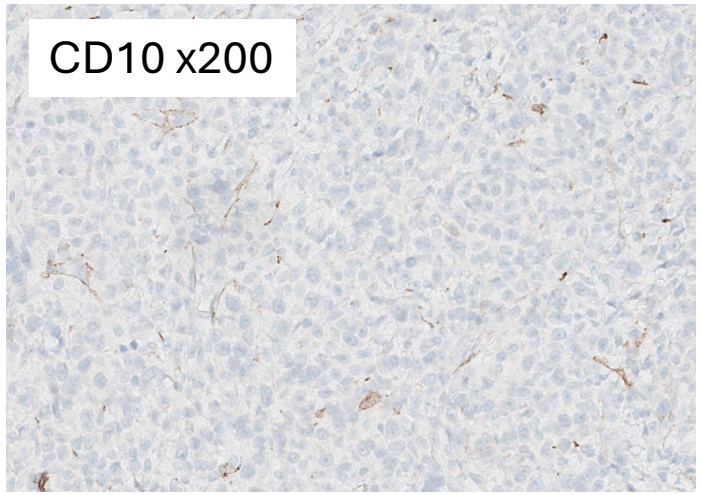

H&E x400

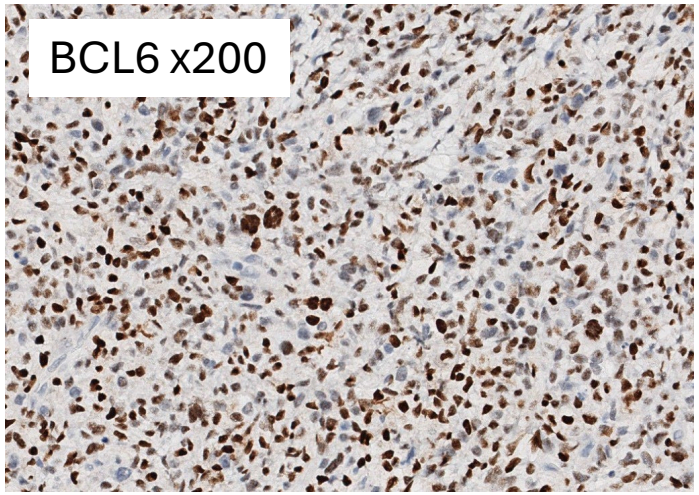
Immunophenotype

Marker	B-cell lymphoma
CD19	+
CD20	+
PAX5	+
CD5	-
CD10	-
BCL6	+
MUM1	+
BCL2	+ (greater than 90%)
C-MYC	+ (greater than 40%)
Cyclin D1	-
TdT	-
EBER ISH	-
KI-67	70-80%









FISH for Aggressive B-cell Lymphoma

	Result	Reference Range
BCL6 Rearrangement	2%	(0-9%)
MYC Rearrangement	5%	(0-11%)
t(8;14)(q24.21;q32.33) *IGH::MYC*	3%	(0-7%)
BCL2 Rearrangement	71%	(0-5%)

B-cell lymphoma NGS Results

- Pathogenic mutations detected:
  1. ***B2M***: c.289G>T; p.Glu97* (81%)
  2. ***KMT2D***: c.11800C>T; p.Gln3934* (55%)
  3. ***TP53***: c.376-2_382delinsCCT; p.? (67%)
- Variants of unknown clinical significance detected:
  1. ***ARID1A***: c.4918A>G; p.Thr1640Ala (13%)
  2. ***ATM***: c.4564G>C; p.Gly1522Arg (3%)
  3. ***BCL2***: Multiple variants in ***BCL2*** were detected (NM_000633.2)
     c.-2G>A; p.? (24%)
     c.66_67delinsAT; p.Lys22_Leu23= (48%)
     c.95C>T; p.Ala32Val (48%)
     c.103G>A; p.Val35Met (48%)
     c.175C>G; p.Pro59Ala (52%)
     c.179C>T; p.Ala60Val (25%)
     c.386G>A; p.Arg129His (8%)
     c.403G>A; p.Glu135Lys (26%)
     c.493G>A; p.Glu165Lys (54%)
  4. ***KMT2D***: c.176+3A>T; p.? (31%)
  5. ***PIM1***: c.140G>C; p.Ser47Thr (29%)
  6. ***TNFRSF14***: c.325C>T; p.Arg109Trp (80%)

Final Diagnosis

- Diffuse large B-cell lymphoma, NOS
  - Cell of origin (Hans classifier): non-Germinal center

- Can we subclassify more?

Molecular subclassification

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

George W. Wright,[1] Da Wei Huang,[2] James D. Phelan,[2] Zana A. Coulibaly,[2] Sandrine Roulland,[2] Ryan M. Young,[2] James Q. Wang,[2] Roland Schmitz,[2] Ryan D. Morin,[3] Jeffrey Tang,[3] Aixiang Jiang,[3] Aleksander Bagaev,[4] Olga Plotnikova,[4] Nikita Kotlov,[4] Calvin A. Johnson,[5] Wyndham H. Wilson,[2] David W. Scott,[6] and Louis M. Staudt[2,7,*]

- Proposed molecular subclassification of DLBCL (3 independent studies)
- Diffuse large B cell lymphoma (DLBCL) consists of seven genetic subtypes

LymphGen	Modified HMRN	Harvard	Main Genetic Alterations	COO	Clinical Outcome	Related Lymphoma
MCD	**MYD88**	**C5**	*MYD88*^{L265P}, *CD79B*, *PIM1*, *ETV6*, *CDKN2A*	ABC	Poor	Primary CNS lymphoma, Primary testis lymphoma
EZB	**BCL2**	**C3**	*BCL2*-R, *EZH2*, *CREBBP*, *KMT2D*, *TNFRSF14*	GCB	Good	Follicular lymphoma
EZB-MYC+	**BCL2-MYC**				Poor	Double hit lymphoma
BN2	**NOTCH2**	**C1**	*BCL6*-R, *NOTCH2*, *BCL10*, *SPEN*, *CD70*, *TNFAIP3*	ABC, GCB, UC	Intermediate	Marginal zone lymphoma
ST2	**TET2/SGK1**	**C4**	*TET2*, *SGK1*, *KLHL6*, *BRAF*	GCB	Good	Nodular lymphocyte predominant Hodgkin lymphoma
	SOCS1/SGK1		*SOCS1*, *SGK1*, *CD83*, *NFKBIA*, *NFKBIE*, *STAT3*	GCB	Very good	Primary mediastinal B cell lymphoma
Other	NEC	**C0**				
N1	**NOTCH1**	NA	*NOTCH1*, *ID3*	ABC	Poor	Chronic lymphocytic leukaemia
A53	NA	**C2**	*TP53*, aneuploidy	Mixed	Intermediate	

Cutmore et al. 2022 (PMID: 36788062)

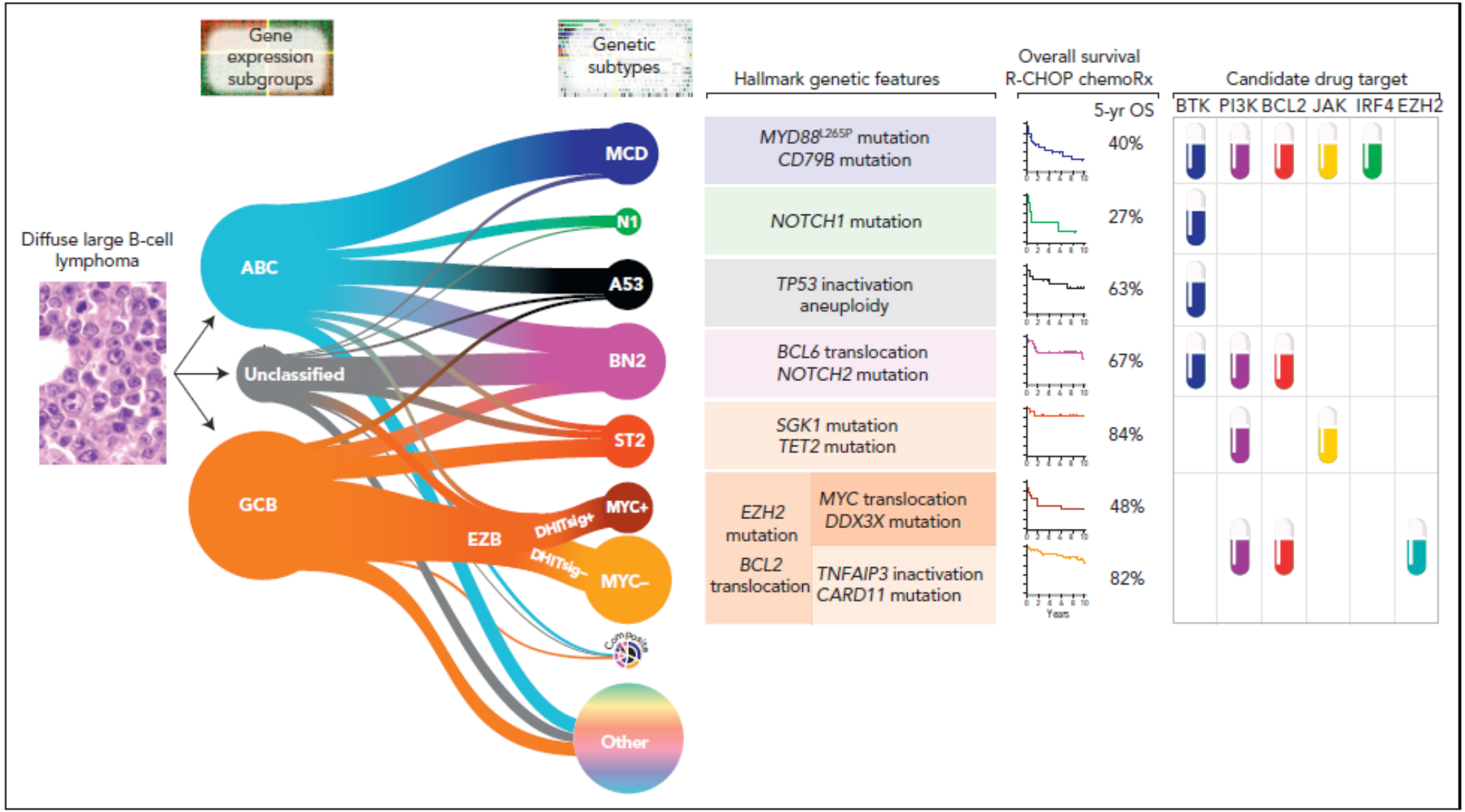
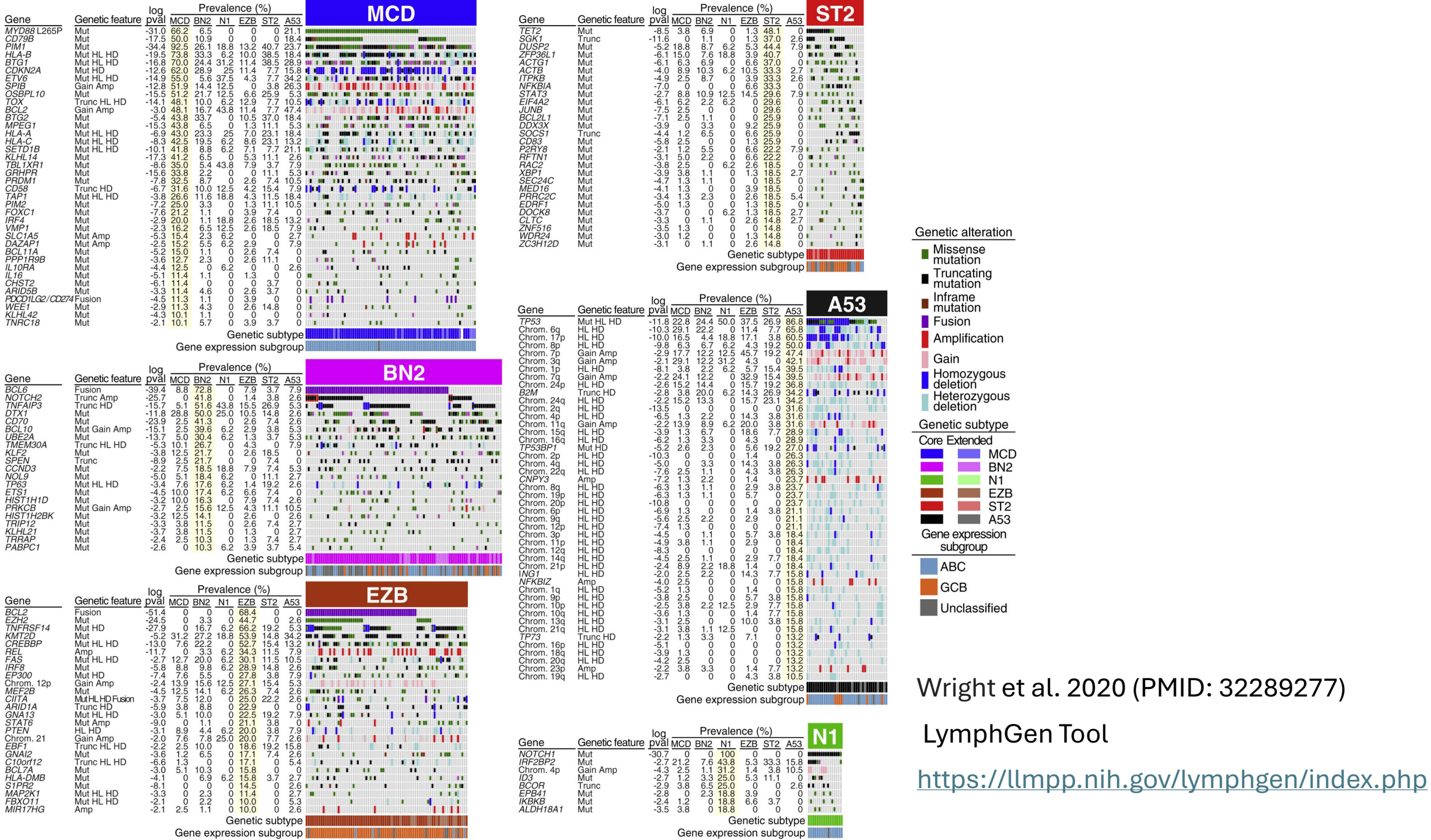


Figure 3. Genetic subgroups of DLBCL illustrated using the LymphGen algorithm. The relationships between COO and the probabilistic assignments to genetics-based subgroups are shown. The size of the subgroup circles approximates the proportions of patients in each group, with the prevalence based on Schmitz et al,[185] adjusted for a population-based distribution of COO subgroups. Tumors assigned with high confidence to ≥2 subgroups are assigned to the composite group, while ~37% of tumors are not assigned to any subgroup with sufficient confidence (other). The hallmark genetic features are those frequent within that subgroup but are not required for that assignment. OS following R-CHOP chemoimmunotherapy along with inferred drug targets are shown. GCB, germinal center B-cell–like.

de Leval et al. 2022

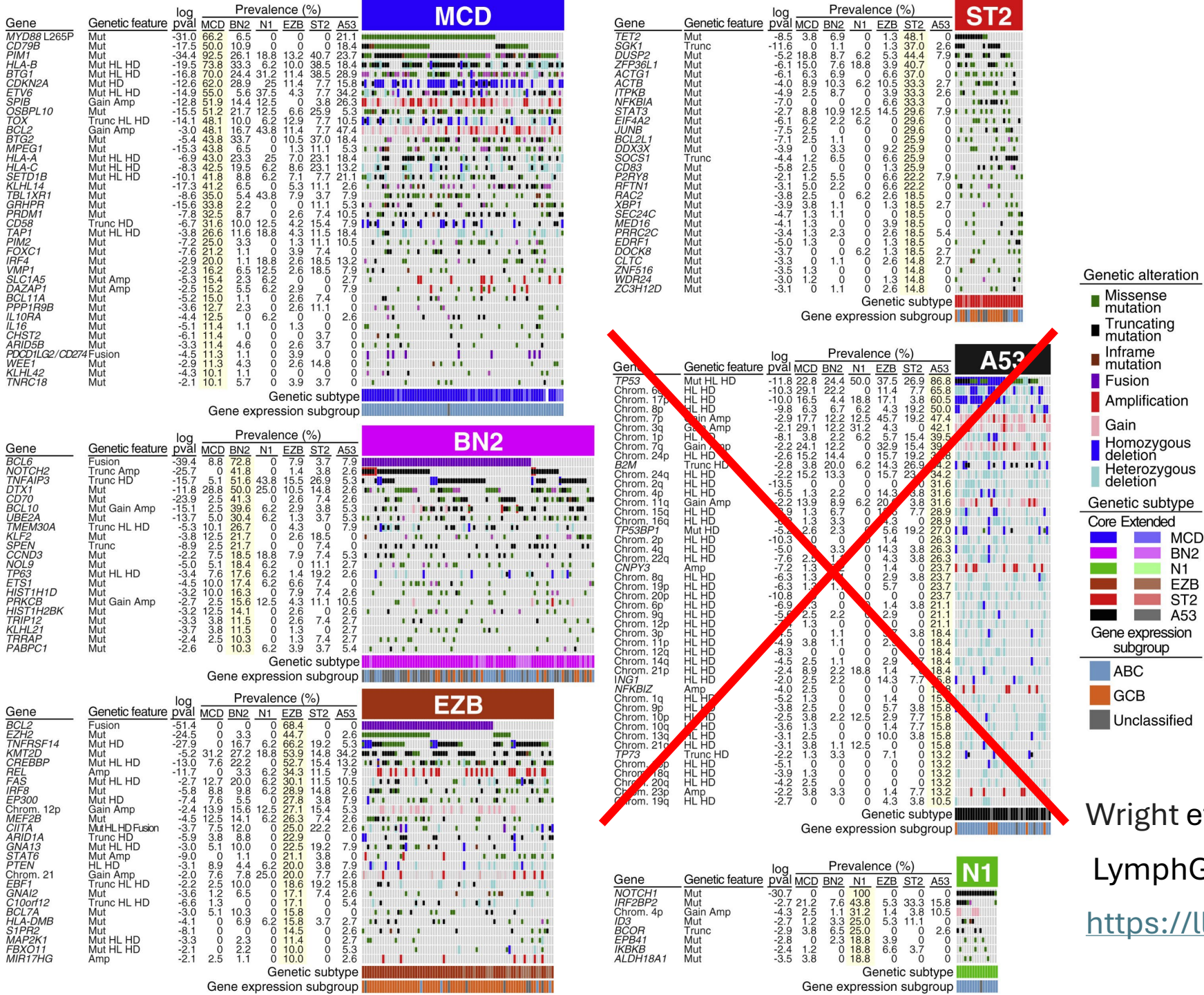
PMID: 36001803



Wright et al. 2020 (PMID: 32289277)

LymphGen Tool

https://llmpp.nih.gov/lymphgen/index.php



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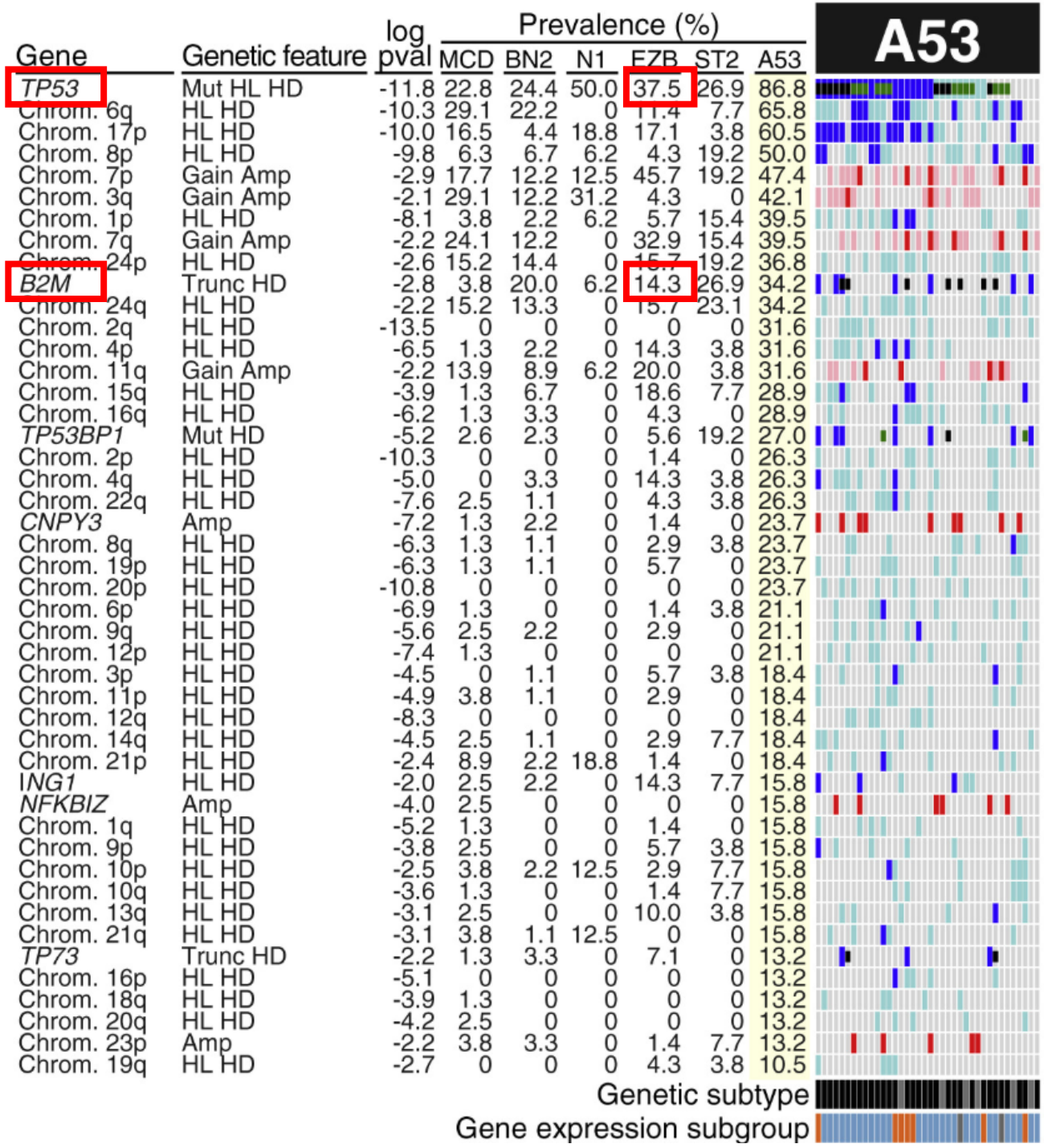
Using the LymphGen Tool (2.0)

- 98% confidence that this belonged to the

Gene	Genetic feature	log pval	Prevalence (%) MCD	BN2	N1	EZB	ST2	A53
BCL2	Fusion	-51.4	0	0	0	68.4	0	0
EZH2	Mut	-24.5	0	3.3	0	44.7	0	2.6
TNFRSF14	Mut HD	-27.9	0	16.7	6.2	66.2	19.2	5.3
KMT2D	Mut	-5.2	31.2	27.2	18.8	53.9	14.8	34.2
CREBBP	Mut HL HD	-13.0	7.6	22.2	0	52.7	15.4	13.2
REL	Amp	-11.7	0	3.3	6.2	34.3	11.5	7.9
FAS	Mut HL HD	-2.7	12.7	20.0	6.2	30.1	11.5	10.5
IRF8	Mut	-5.8	8.8	9.8	6.2	28.9	14.8	2.6
EP300	Mut HD	-7.4	7.6	5.5	0	27.8	3.8	7.9
Chrom. 12p	Gain Amp	-2.4	13.9	15.6	12.5	27.1	15.4	5.3
MEF2B	Mut	-4.5	12.5	14.1	6.2	26.3	7.4	2.6
CIITA	Mut HL HD Fusion	-3.7	7.5	12.0	0	25.0	22.2	2.6
ARID1A	Trunc HD	-5.9	3.8	8.8	0	22.9	0	0
GNA13	Mut HL HD	-3.0	5.1	10.0	0	22.5	19.2	7.9
STAT6	Mut Amp	-9.0	0	1.1	0	21.1	3.8	0
PTEN	HL HD	-3.1	8.9	4.4	6.2	20.0	3.8	7.9
Chrom. 21	Gain Amp	-2.0	7.6	7.8	25.0	20.0	7.7	2.6
EBF1	Trunc HL HD	-2.2	2.5	10.0	0	18.6	19.2	15.8
GNAI2	Mut	-3.6	1.2	6.5	0	17.1	7.4	2.6
C10orf12	Trunc HL HD	-6.6	1.3	0	0	17.1	0	5.4
BCL7A	Mut	-3.0	5.1	10.3	0	15.8	0	0
HLA-DMB	Mut	-4.1	0	6.9	6.2	15.8	3.7	2.7
S1PR2	Mut	-8.1	0	0	0	14.5	0	2.6
MAP2K1	Mut HL HD	-3.3	0	2.3	0	11.4	0	2.7
FBXO11	Mut HL HD	-2.1	0	2.2	0	10.0	0	5.3
MIR17HG	Amp	-2.1	2.5	1.1	0	10.0	0	2.6


Gene
Genetic feature
log pval
Prevalence (%)
MCD
BN2
N1
EZB
ST2
A53
A53
TP53 Mut HL HD -11.8 22.8 24.4 50.0 37.5 26.9 86.8
Chrom. 6q HL HD -10.3 29.1 22.2 0 11.4 7.7 65.8
Chrom. 17p HL HD -10.0 16.5 4.4 18.8 17.1 3.8 60.5
Chrom. 8p HL HD -9.8 6.3 6.7 6.2 4.3 19.2 50.0
Chrom. 7p Gain Amp -2.9 17.7 12.2 12.5 45.7 19.2 47.4
Chrom. 3q Gain Amp -2.1 29.1 12.2 31.2 4.3 0 42.1
Chrom. 1p HL HD -8.1 3.8 2.2 6.2 5.7 15.4 39.5
Chrom. 7q Gain Amp -2.2 24.1 12.2 0 32.9 15.4 39.5
Chrom. 4p HL HD -2.6 15.2 14.4 0 15.7 19.2 36.8
B2M Trunc HD -2.8 3.8 20.0 6.2 14.3 26.9 34.2
Chrom. 24q HL HD -2.2 15.2 13.3 0 15.7 23.1 34.2
Chrom. 2q HL HD -13.5 0 0 0 0 0 31.6
Chrom. 4p HL HD -6.5 1.3 2.2 0 14.3 3.8 31.6
Chrom. 11q Gain Amp -2.2 13.9 8.9 6.2 20.0 3.8 31.6
Chrom. 15q HL HD -3.9 1.3 6.7 0 18.6 7.7 28.9
Chrom. 16q HL HD -6.2 1.3 3.3 0 4.3 0 28.9
TP53BP1 Mut HD -5.2 2.6 2.3 0 5.6 19.2 27.0
Chrom. 2p HL HD -10.3 0 0 0 1.4 0 26.3
Chrom. 4q HL HD -5.0 0 3.3 0 14.3 3.8 26.3
Chrom. 22q HL HD -7.6 2.5 1.1 0 4.3 3.8 26.3
CNPY3 Amp -7.2 1.3 2.2 0 1.4 0 23.7
Chrom. 8q HL HD -6.3 1.3 1.1 0 2.9 3.8 23.7
Chrom. 19p HL HD -6.3 1.3 1.1 0 5.7 0 23.7
Chrom. 20p HL HD -10.8 0 0 0 0 0 23.7
Chrom. 6p HL HD -6.9 1.3 0 0 1.4 3.8 21.1
Chrom. 9q HL HD -5.6 2.5 2.2 0 2.9 0 21.1
Chrom. 12p HL HD -7.4 1.3 0 0 0 0 21.1
Chrom. 3p HL HD -4.5 0 1.1 0 5.7 3.8 18.4
Chrom. 11p HL HD -4.9 3.8 1.1 0 2.9 0 18.4
Chrom. 12q HL HD -8.3 0 0 0 0 0 18.4
Chrom. 14q HL HD -4.5 2.5 1.1 0 2.9 7.7 18.4
Chrom. 21p HL HD -2.4 8.9 2.2 18.8 1.4 0 18.4
ING1 HL HD -2.0 2.5 2.2 0 14.3 7.7 15.8
NFKBIZ Amp -4.0 2.5 0 0 0 0 15.8
Chrom. 1q HL HD -5.2 1.3 0 0 1.4 0 15.8
Chrom. 9p HL HD -3.8 2.5 0 0 5.7 3.8 15.8
Chrom. 10p HL HD -2.5 3.8 2.2 12.5 2.9 7.7 15.8
Chrom. 10q HL HD -3.6 1.3 0 0 1.4 7.7 15.8
Chrom. 13q HL HD -3.1 2.5 0 0 10.0 3.8 15.8
Chrom. 21q HL HD -3.1 3.8 1.1 12.5 0 0 15.8
TP73 Trunc HD -2.2 1.3 3.3 0 7.1 0 13.2
Chrom. 16p HL HD -5.1 0 0 0 0 0 13.2
Chrom. 18q HL HD -3.9 1.3 0 0 0 0 13.2
Chrom. 20q HL HD -4.2 2.5 0 0 0 0 13.2
Chrom. 23p Amp -2.2 3.8 3.3 0 1.4 7.7 13.2
Chrom. 19q HL HD -2.7 0 0 0 4.3 3.8 10.5
Genetic subtype
Gene expression subgroup

Conclusion

- Molecular classification is expected to replace cell-of-origin subclassification
- LymphGen's results can inform the design and interpretation of clinical trials for DLBCL
- Currently, can be used for prognosis
- In the future, expected to affect management

References

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