

PRECISION DIAGNOSTICS IN LYMPHOMAS

RECENT DEVELOPMENTS AND FUTURE DIRECTIONS

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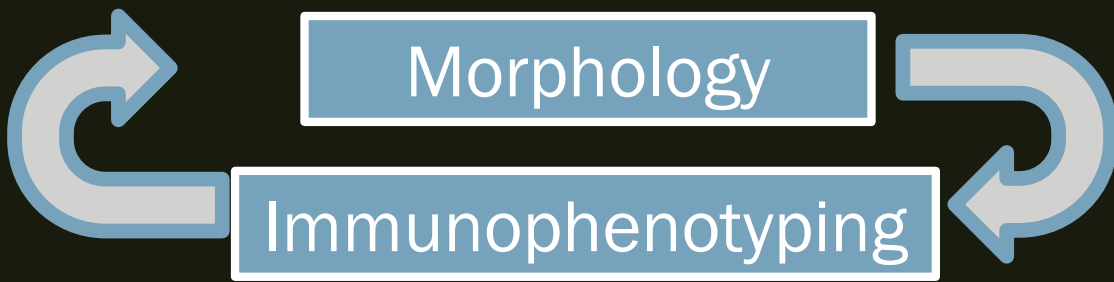
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Outline of Presentation

1. Brief introduction
2. Clinically relevant genetic aberrations in lymphomas
 - I. *Diagnostic markers*
 - II. *Prognostic markers*
 - III. *Predictive markers*
3. Assays for research vs clinical utility
4. Genomic profiling in DLBCL: what has it taught us?
5. Precision diagnostics & therapy for lymphomas

4th revised edition of the World Health Organization
Classification of Haematolymphoid Tumours:
Lymphoid Neoplasms (2016)

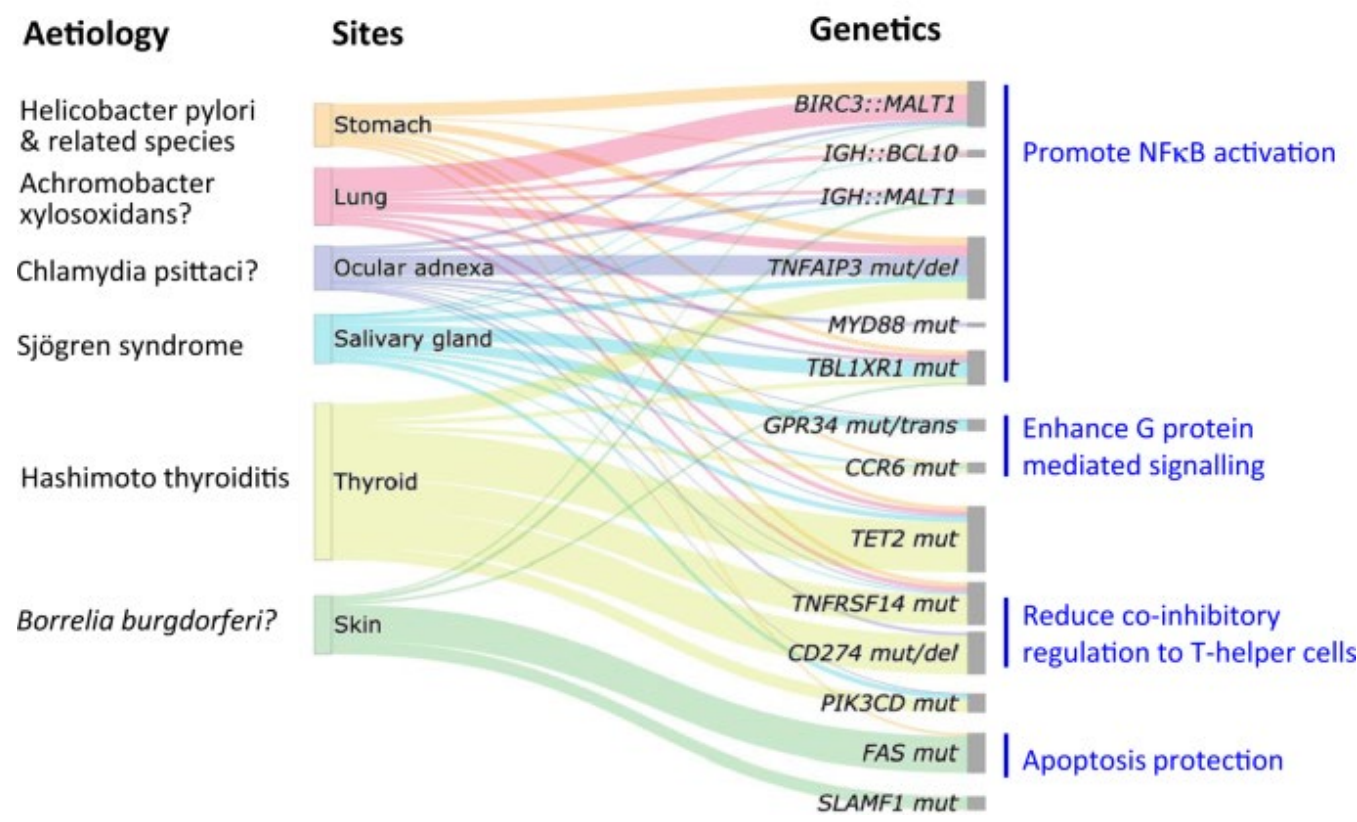
> 80 lymphoma entities



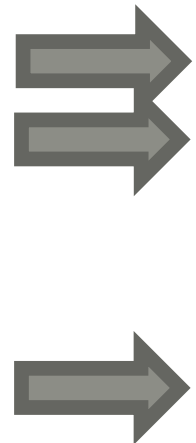
- Cytogenetics
- FISH
- PCR
- NGS
- GEP

Summary of the relationship between splenic B-cell lymphoma entities as named and defined in the WHO-HAEM4R and in WHO-HAEM5

Extranodal marginal zone lymphoma

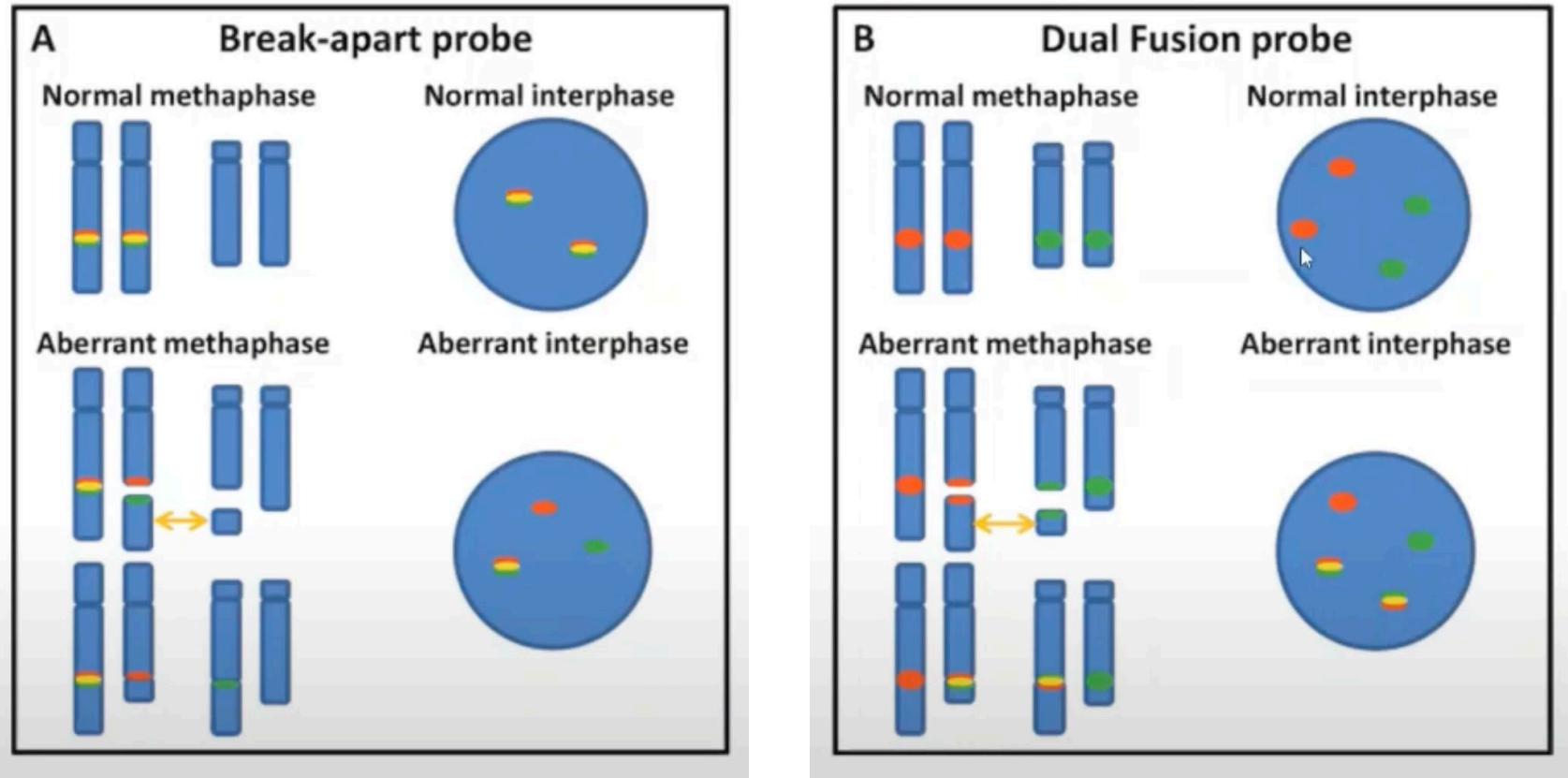


Diagnostic Markers: Chromosomal Translocations



	Genetic aberration	Genes involved	Frequency
CLL^a	del(13q) del(11q) del(17p) trisomy 12	miR15, miR16, <i>DLEU2</i> <i>ATM</i> , <i>BIRC3</i> <i>TP53</i>	35-45%* 10-20% 5-10% 10-15%
DLBCL^b	t(14;18)(q32;q21) t(3;14)(q27;q32) t(8;14)(q24;q32)	<i>IGH::BCL2</i> <i>BCL6::IGH</i> <i>MYC::IGH</i>	20-30% 25-30% 8-14%
MCL^c	t(11;14)(q13;q32)	<i>CCND1::IGH</i>	>95%
FL^d	t(14;18)(q32;q21)	<i>IGH::BCL2</i>	85-90%
BL^e	t(8;14)(q24;q32) t(8;22)(q24;q11) t(2;8)(p11;q24)	<i>MYC::IGH</i> <i>MYC::IGL</i> <i>IGK::MYC</i>	Combined >95%
ALCL^f	t(2;5)(p23;q35)	<i>ALK::NPM1</i>	84%

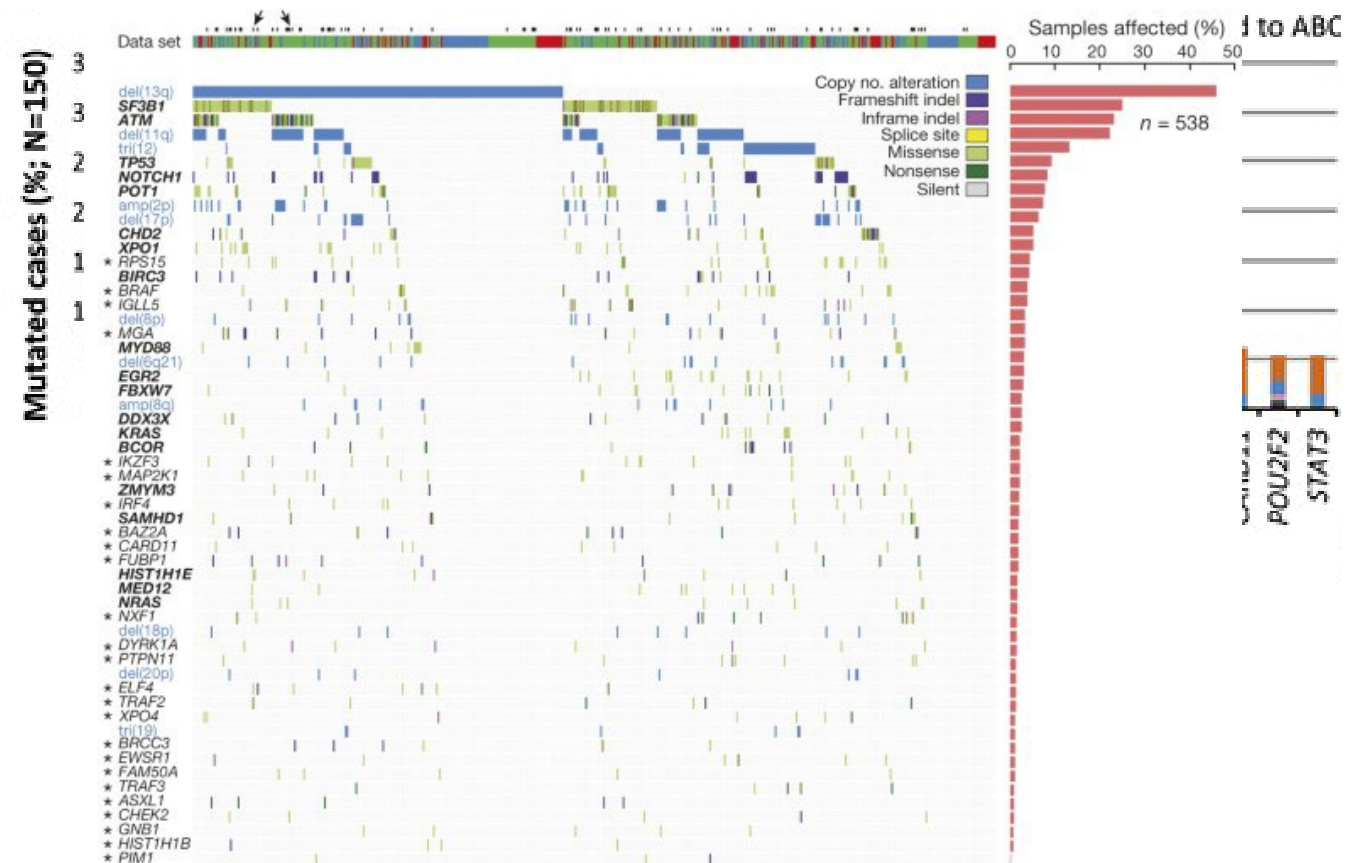
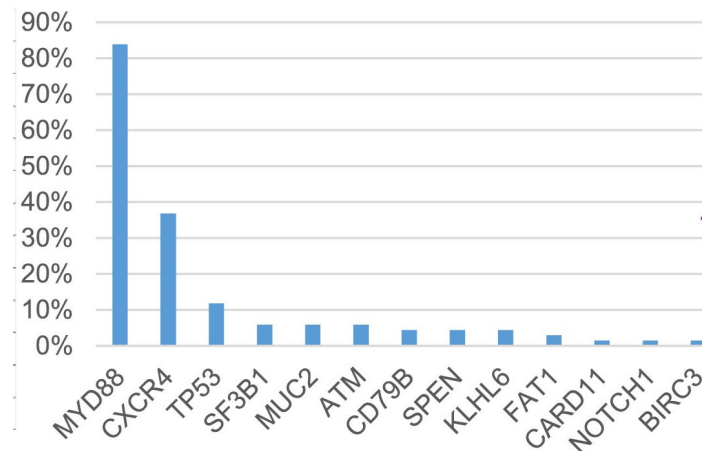
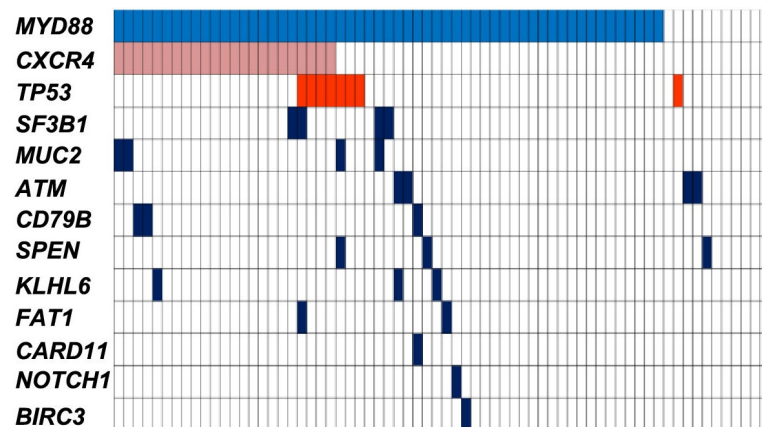
Diagnostic Markers: Chromosomal Translocations



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

Diagnostic Markers: Gene Mutations

Only a limited number of gene mutations are observed in the majority of cases within a lymphoma entity



DIAGNOSTIC MARKERS: GENE MUTATIONS

– *frequencies in
different B-cell
lymphoma
entities*

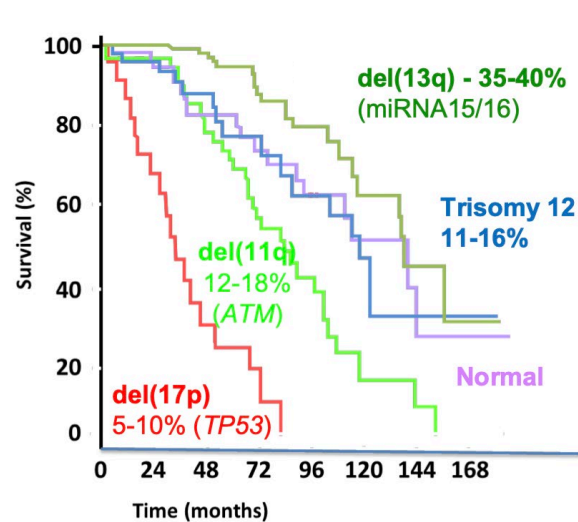
Pathway/cellular function	CLL ^a	MCL ^b	BL ^c	FL ^d	ABC-DLBCl ^e	GCB-DLBCl ^e	SMZL ^f	HCL ^g	WM ^h
B-cell receptor signaling									
CD79A/CD79B	<1%	-	-	4%	10-20%	<5%	-	-	10%
CARD11	1%	-	-	10%	10%	5%	4%	-	-
Toll-like receptor signaling									
MYD88	3%	-	5%	-	20-30%	<5%	7%	-	>90%
NF-κB signaling pathway									
TNFAIP3	-	-	-	10%	20%	<5%	8%	-	40%*
BIRC3	<3%	5-10%	-	-	-	-	5%	-	-
TRAF3	<1%	-	-	-	-	-	5%	-	-
NFKBIE	<2%	5%	-	-	<5%	<5%	2%	-	-
Notch signaling									
NOTCH1	10%	10-15%	-	-	-	-	6%	-	-
NOTCH2	<1%	5%	-	-	-	-	15-20%	-	-
Other signaling pathways									
BRAF	3%	-	-	-	4%	-	<1%	>90%	-
CXCR4	<1%	-	-	-	<10%	-	<1%	-	25%
Transcription factors									
ID3	-	-	35-60%	-	-	-	-	-	-
TCF3	-	-	10-25%	-	-	-	-	-	-
KLF2	-	-	-	-	-	-	14%	-	-
DNA repair/genomic integrity									
ATM	11%	40-50%	-	-	-	-	6%	-	-
TP53	5%	15-20%	35%	5%	10-25%	10-20%	18%	-	-
POT1	5%	<3%	-	-	-	-	<1%	-	-
Epigenetic modifiers									
TET2	<1%	<5%	-	-	5-10%	5-10%	3%	-	-
EZH2	<1%	-	-	10-20%	20%	-	<1%	-	-
IDH2	-	-	-	-	-	-	-	-	-
CREBBP	<1%	-	-	50%	40%	15-20%	6%	-	-
EP300	<1%	-	2%	10-15%	<10%	<5%	4%	-	-

DIAGNOSTIC MARKERS: GENE MUTATIONS

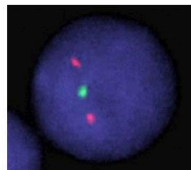
– *frequencies in
different T-cell
lymphoma
entities*

Pathway/cellular function	AITL	MF/SS	PTCL-NOS	LGL	HSTL	P-TLL	ALK-neg ALCL	NKTCL	ATLL
Co-stimulatory/TCR signaling elements									
<i>CD28</i>	11%	-	-	-	-	-	--	2%	
<i>FYN</i>	3%	-	-	-	-	-	--	3%	
<i>PLCG1</i>	12%	20%	15%	-	-	-	--	36%	
Epigenetic modifiers									
<i>TET2</i>	50-70%	-	20-48°	-	-	-	--	-	
<i>IDH2</i>	20-40%	-	-	-	-	-	--	-	
<i>DNMT3</i>	20-30%	-	10-27°	-	-	-	--	-	
JAK-STAT signaling pathway									
<i>STAT3</i>	-	-	-	35%	-	-	38%#	5-10%	22%
<i>STAT5B</i> (N642H)*	-	-	-	<5%	25%	35%	-6%	-	
<i>JAK1</i>	-	-	-	-	-	<10%	38%#	-	-
<i>JAK3</i>	-	-	-	-	-	30-40%	-20%	-	
NF-κB signaling pathway									
<i>PRKCB</i>	-	-	-	-	-	-	--	33%	
<i>CARD11</i>	-	15%	-	-	-	-	--	24%	
<i>TNFRSF1B</i>	-	6%	-	-	-	-	--	-	
Other genes									
<i>RHOA</i> (G17V)◻	60-70%	7%	18%°	-	-	-	--	<15%	
<i>DDX3X</i>	-	-	-	-	-	-	-20%	-	
<i>CCR4</i>	-	7%	-	-	-	-	--	-	

Prognostic Markers: CLL

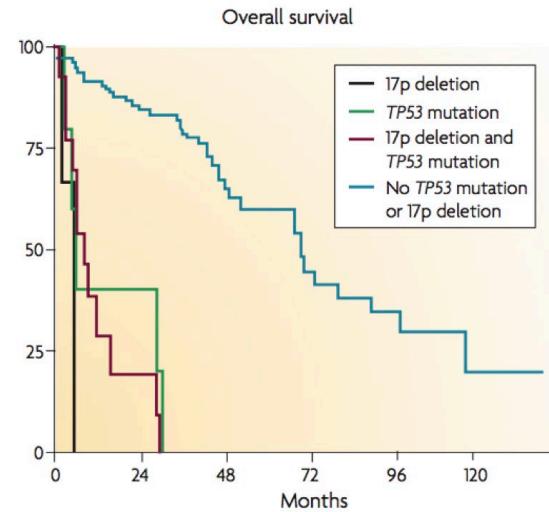


CLL-FISH

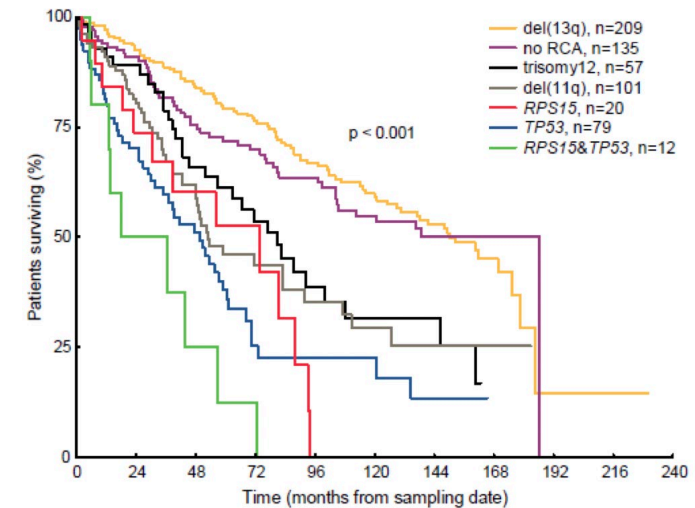
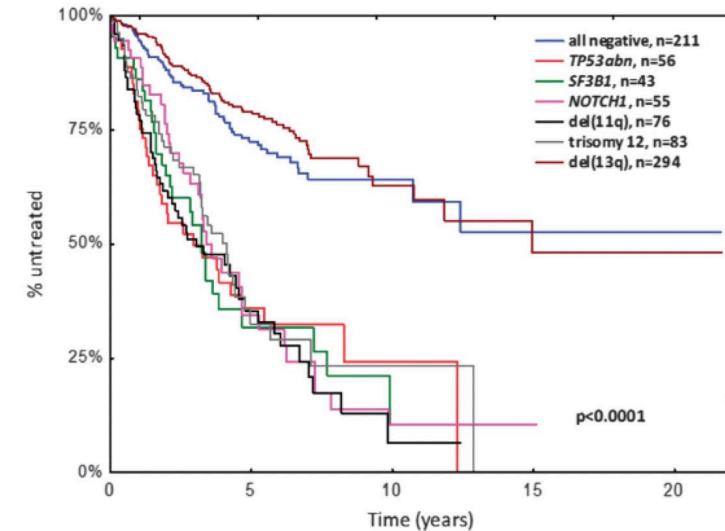
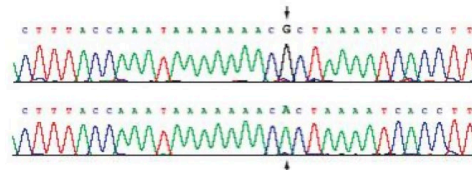


CLL-FISH and $TP53^{mut}$ analysis performed before start of therapy and at every subsequent line of treatment

$TP53^{ab}$ are included in the CLL-IPI

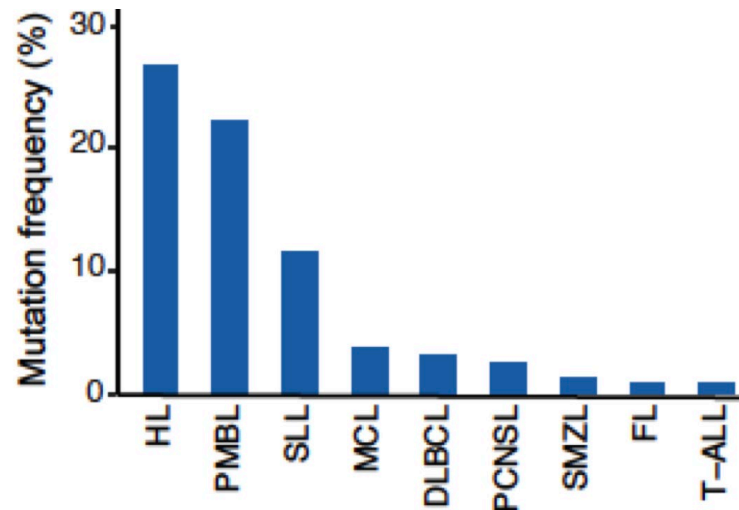


TP53 screening (exons 2-11)

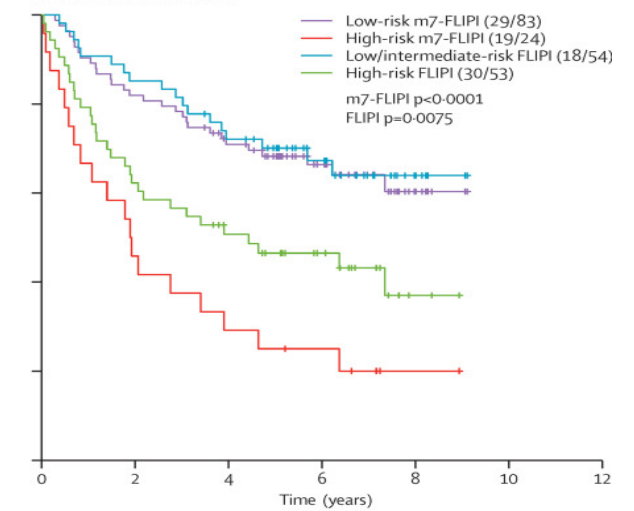
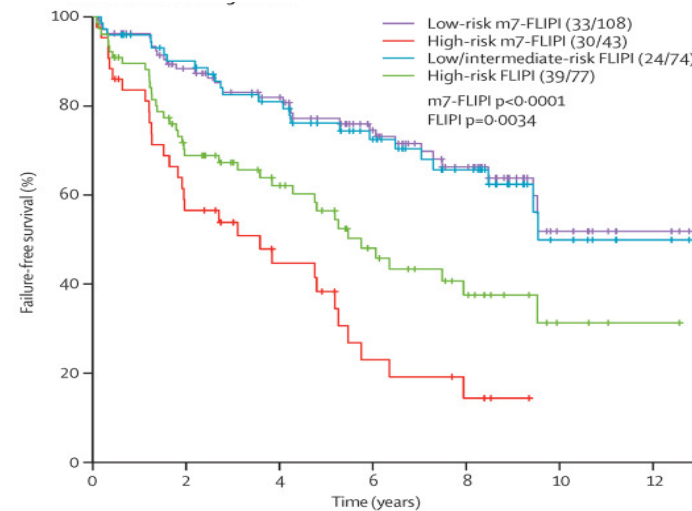
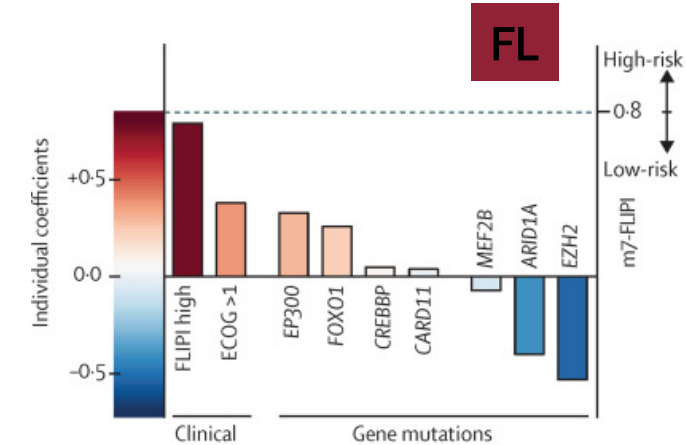
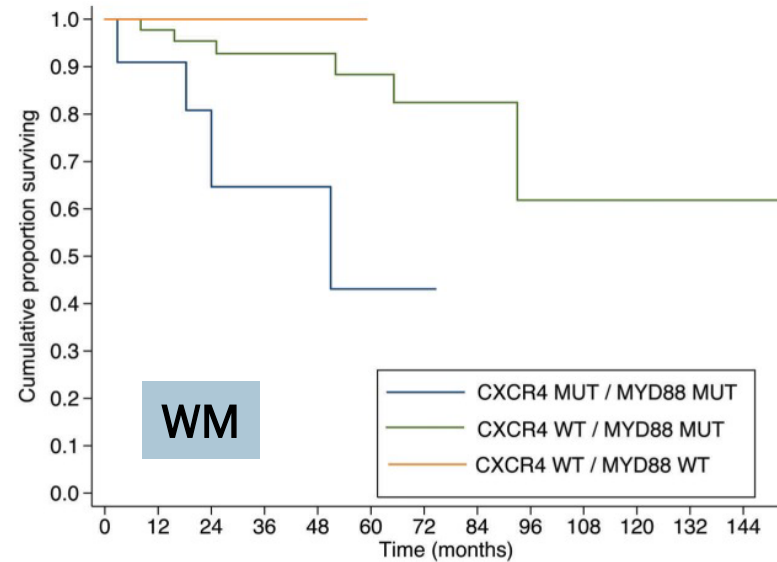
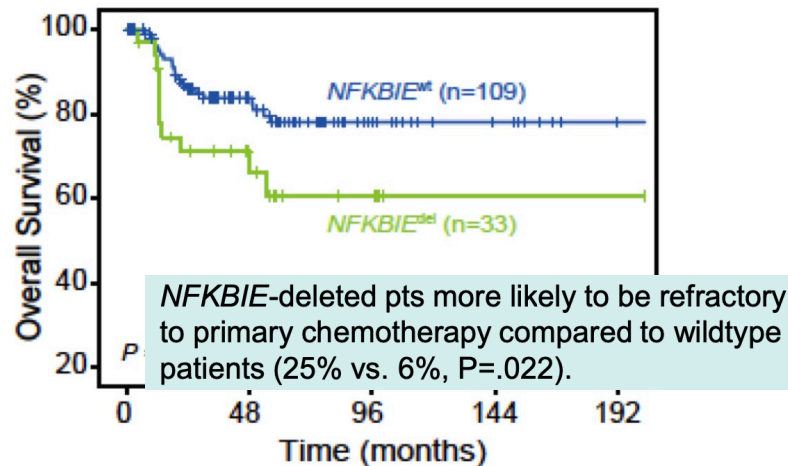


Prognostic Markers: PMBL, WM, FL

NFKBIE deletions in lymphoma



Primary mediastinal B-cell lymphomas



Prognostic Markers: Peripheral T-cell lymphomas

Not as comprehensively studied as B-cell lymphomas

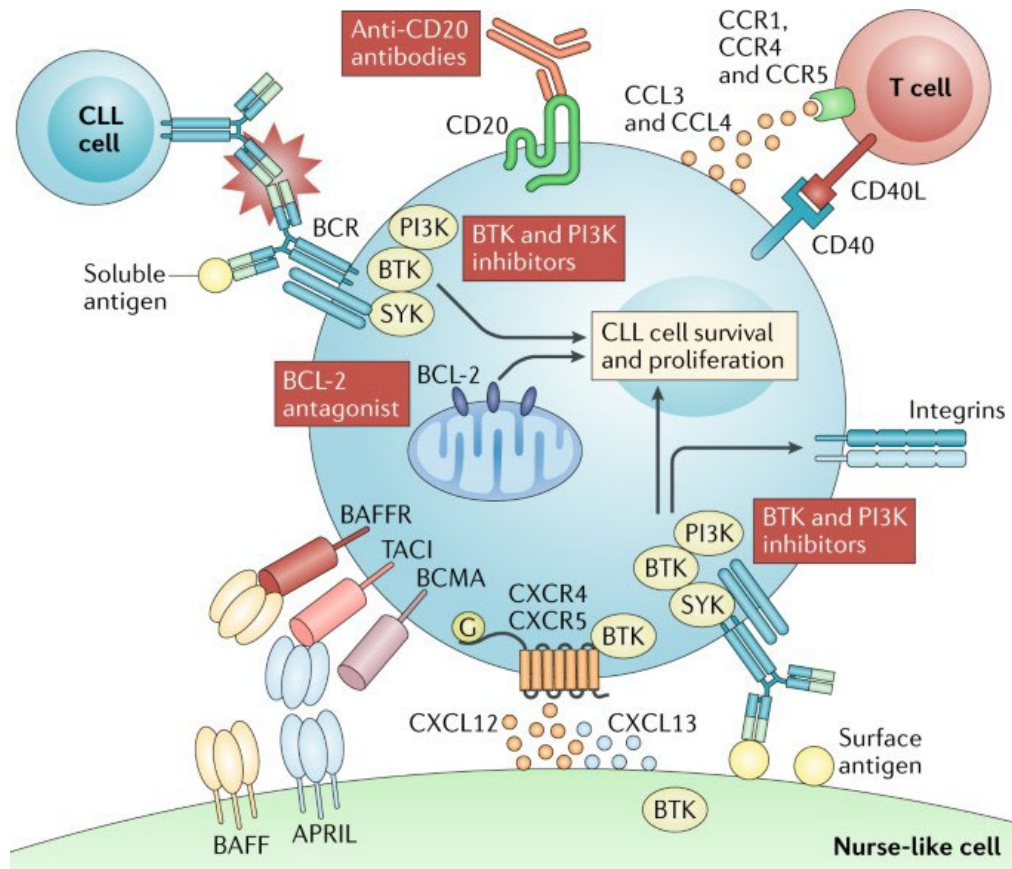
Few genes shown
to be prognostic
(to date)

1. TET2 mutations in AITL and PTCL-NOS
2. TP53 and DDX3X mutations in NK-TCL
3. Loss of PRDM1 and del(17p) in ALCL

Increasing number of genetic aberrations with prognostic impact in lymphomas but their precise role remains to be established

Predictive Markers

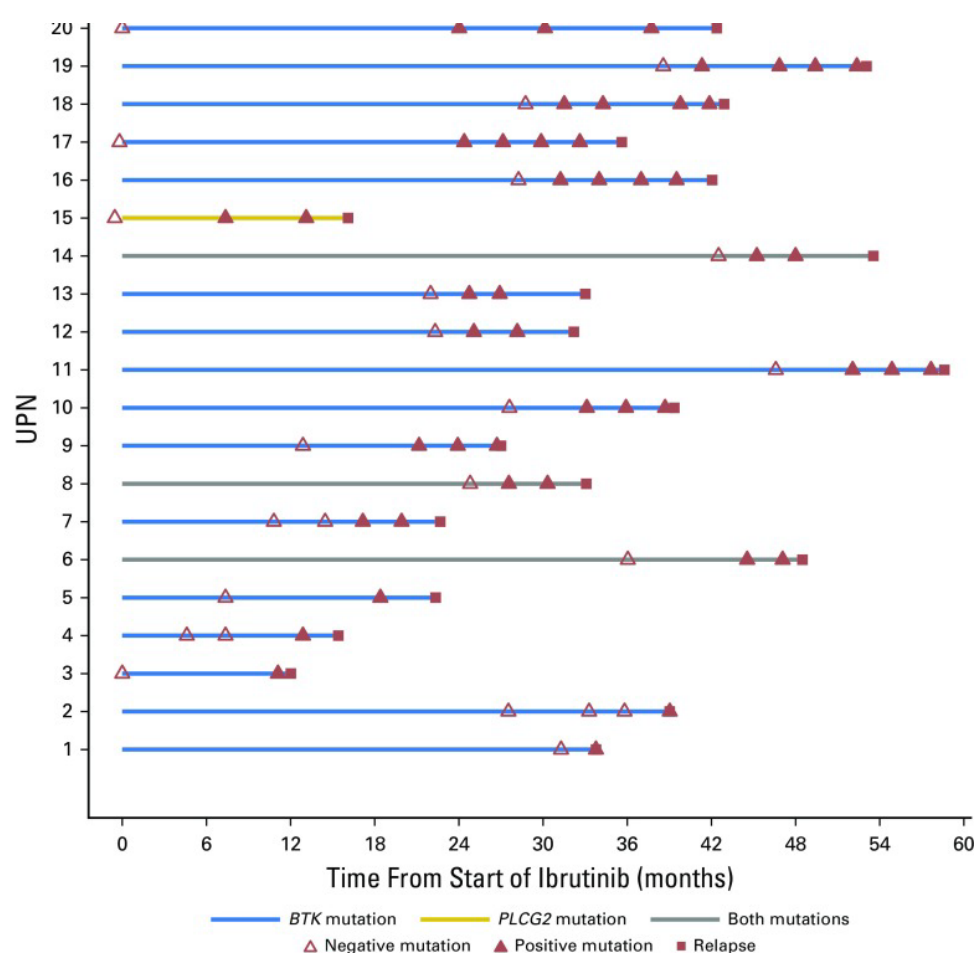
Fewer biomarkers have been translated into therapeutic management for the individual patient with lymphoma



CLL patients with aberrant TP53

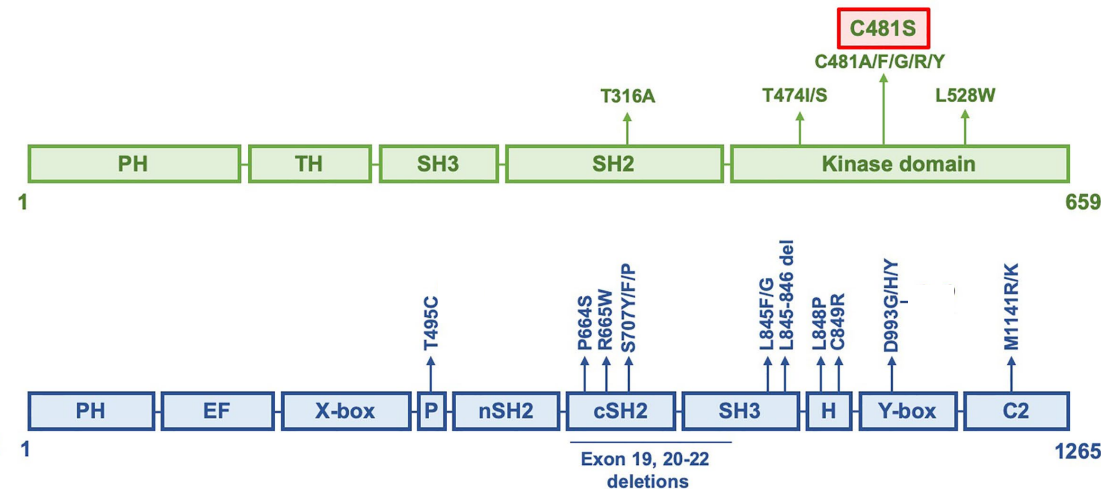
BCR inhibitors for other lymphoma subtypes

Predictive Markers: Resistance Mutations

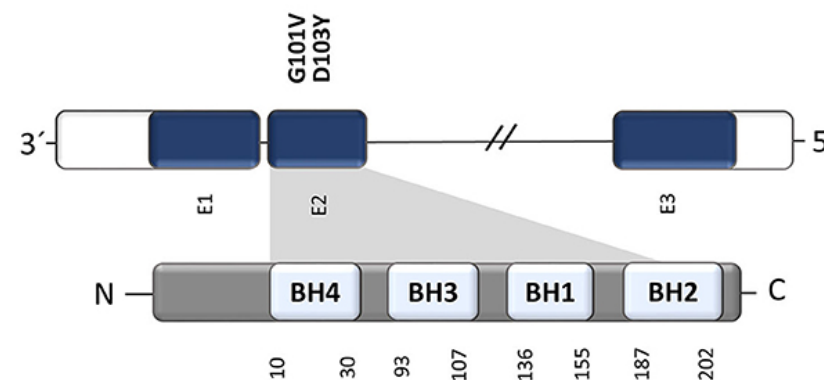


BTK
abrogated BTKI
binding capacity

PLC γ 2
GoF mutations;
BTK independent signaling



BCL2



CXCR4^{S338X} somatic mutation activates AKT and ERK, and promotes resistance to ibrutinib and other agents used in the treatment of Waldenstrom's Macroglobulinemia

Assays for research versus clinical utility

WGS & WES

Custom targeted panels

Broad-range panels

Biomarker discovery

Cytogenetics

Research arena

FISH

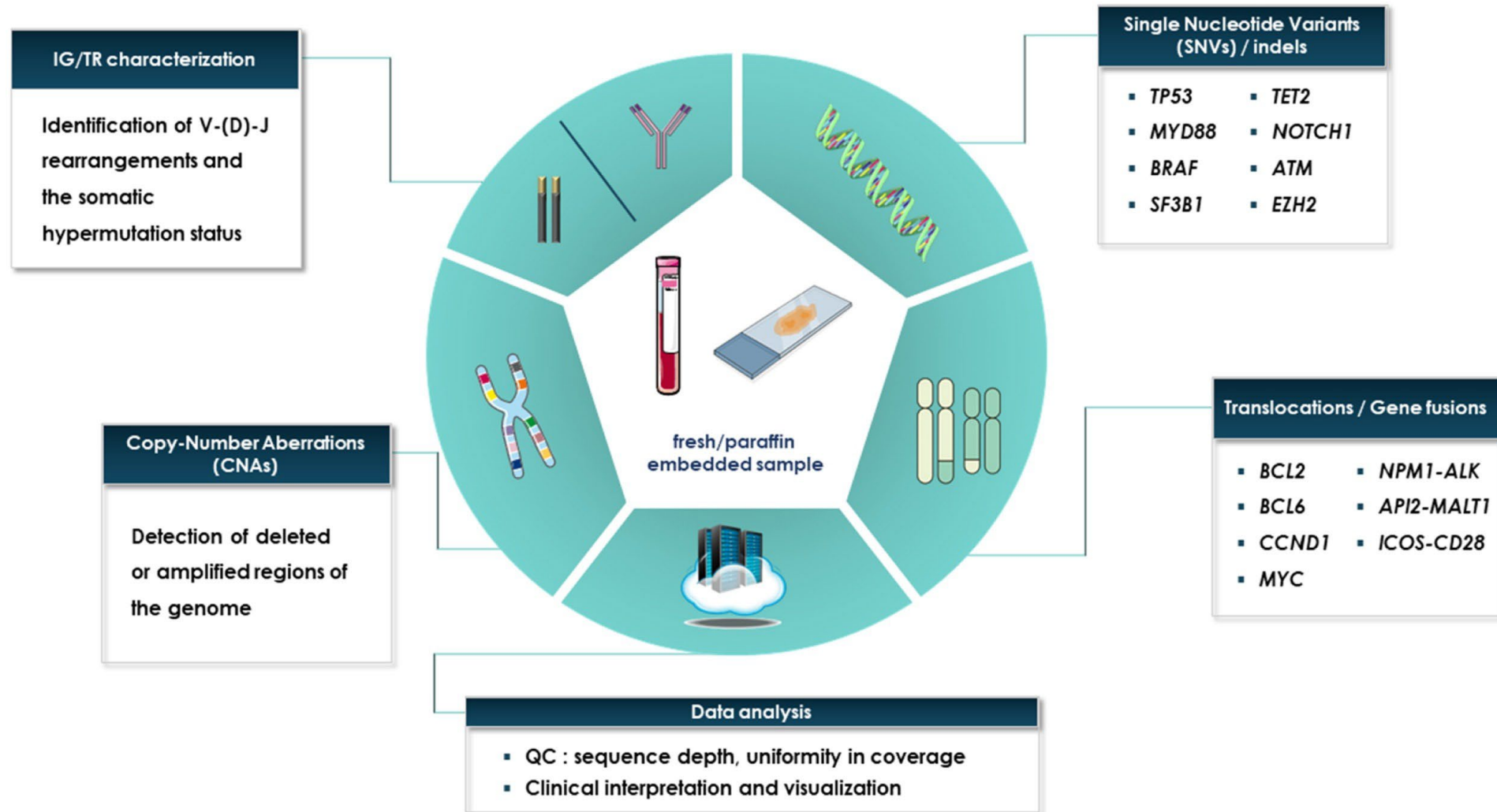
PCR

Biomarker detection

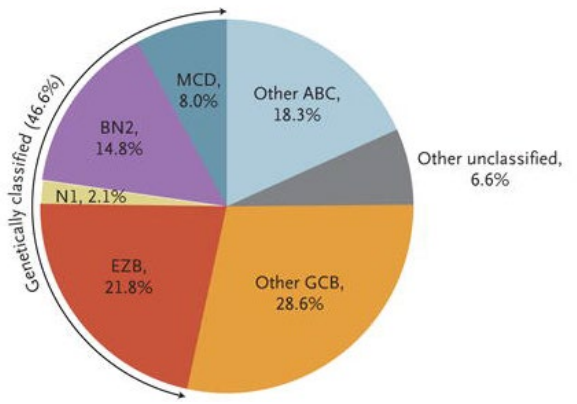
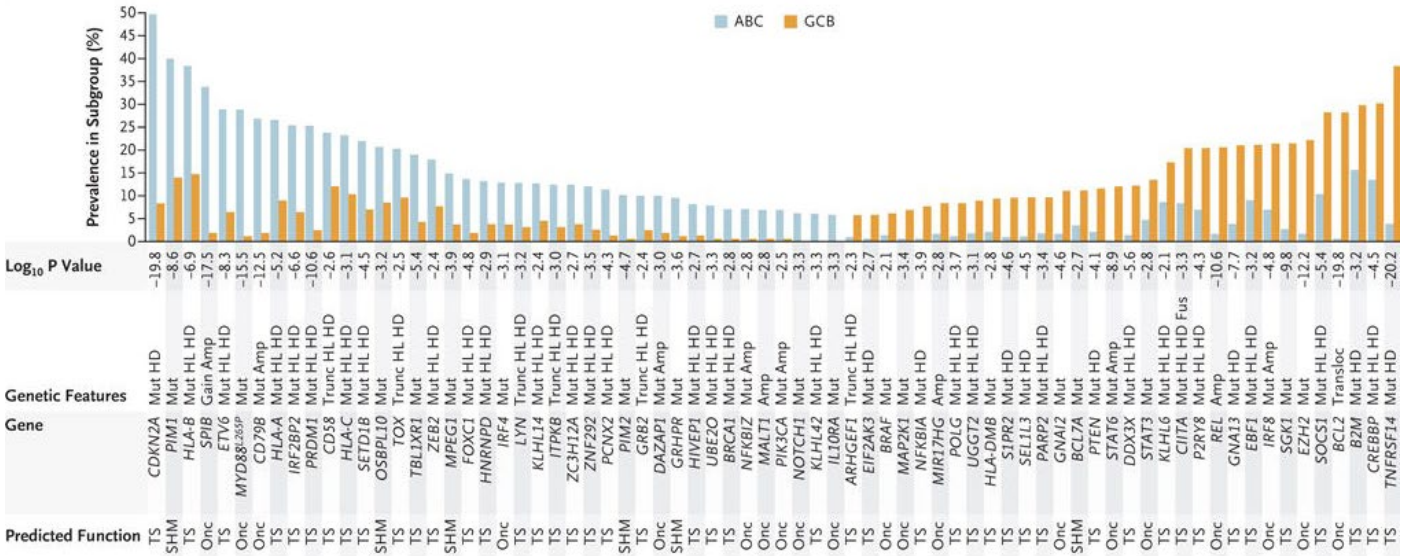
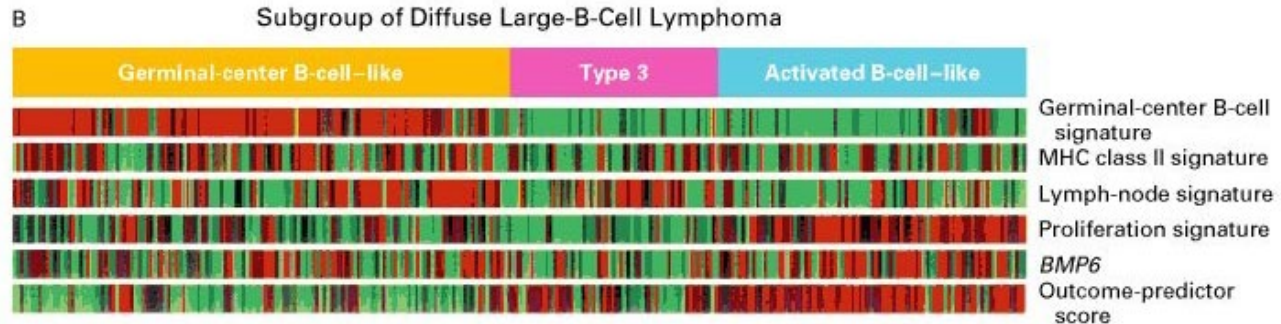
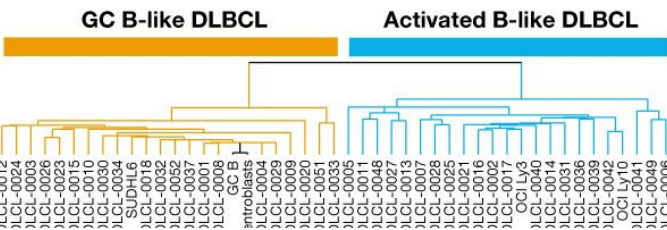
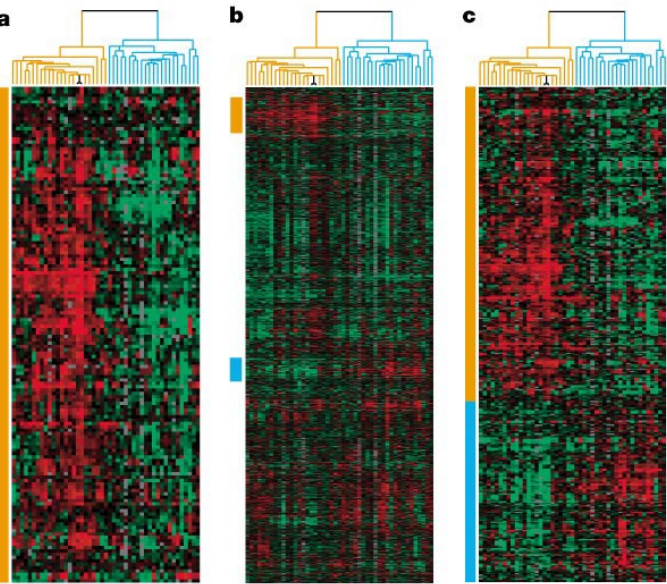


Assays for research versus clinical utility

Broad-range detection NGS panels

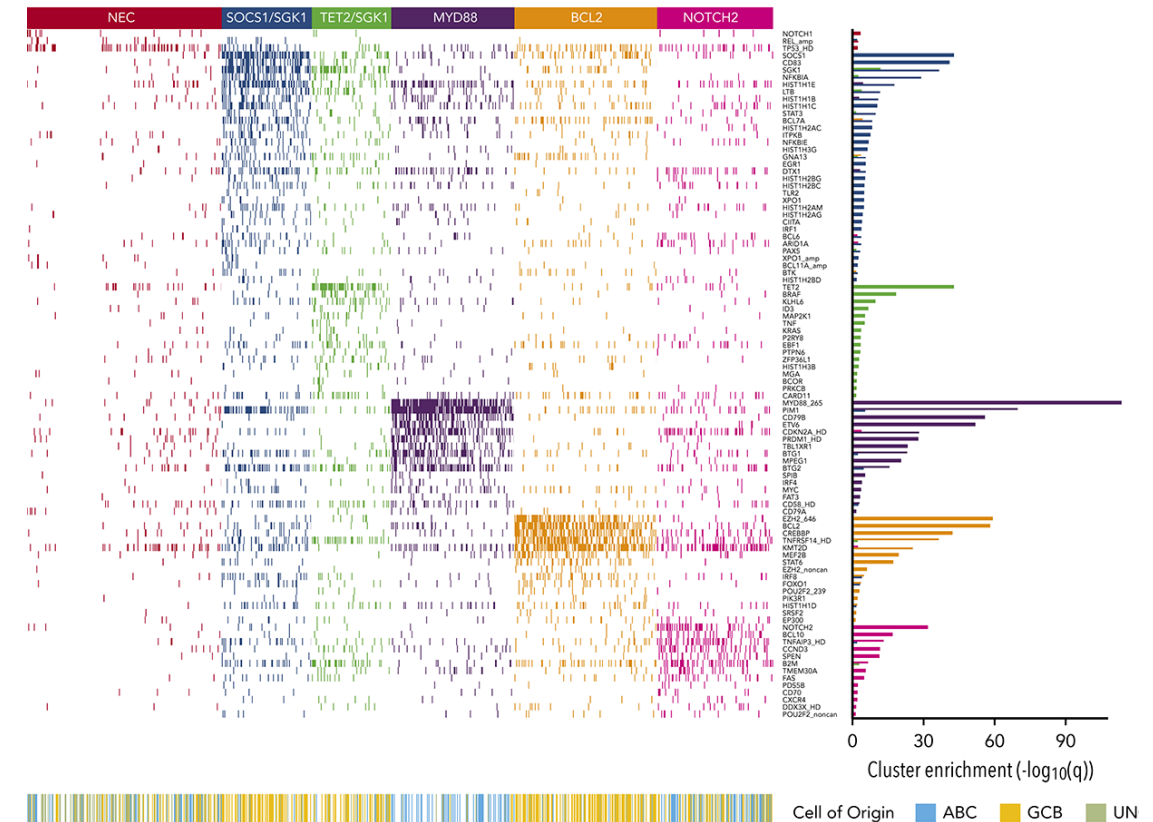
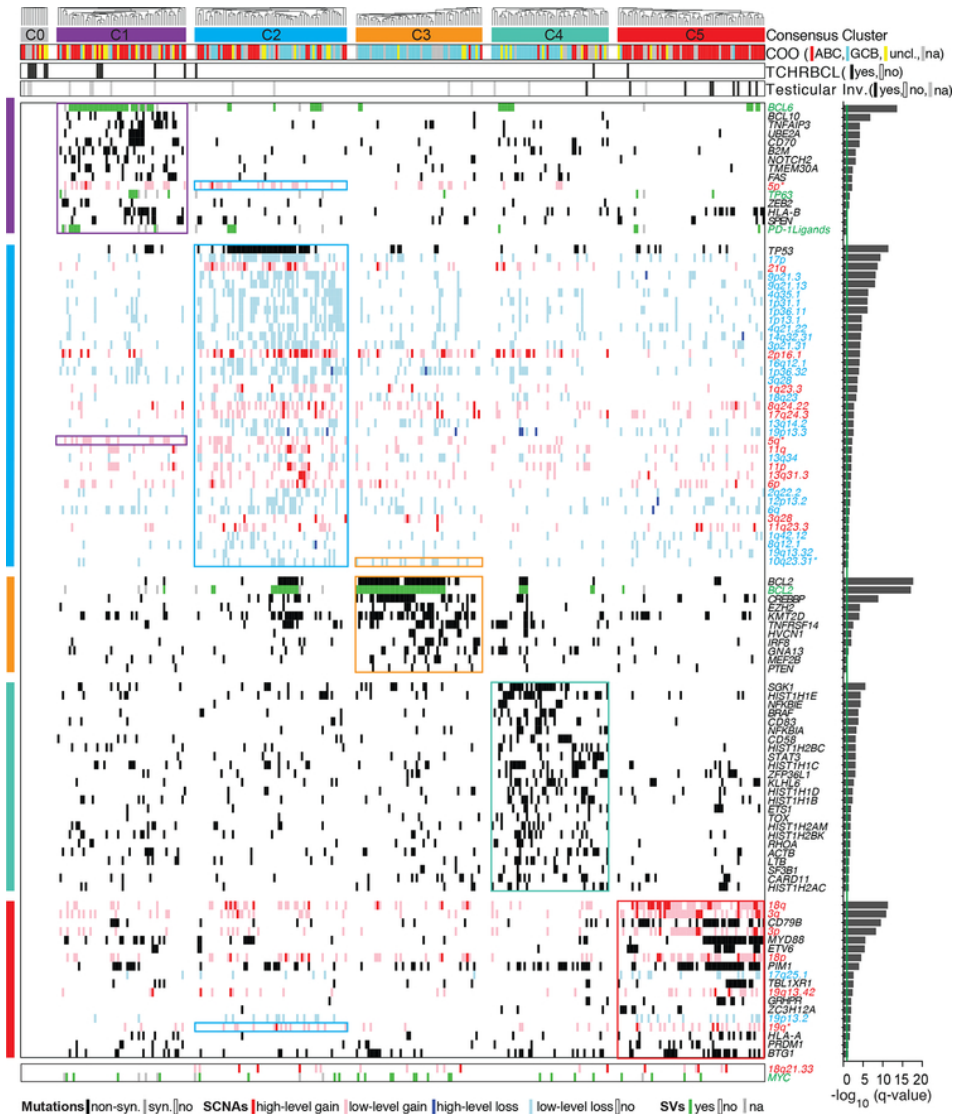


DLBCL: What has comprehensive genomic profiling taught us?



4 distinct molecular subtypes

DLBCL: What has comprehensive genomic profiling taught us?



Clinically relevant and potentially actionable molecular subtypes of DLBCL

Precision Diagnostics & Therapy for Lymphomas

Considerations, Issues and Future Directions

How can new findings be translated into clinical utility and guide therapeutic decisions?

- *List of biomarkers with predictive value for response to a given therapy is very short*
- *Prospective randomized trials*

How should we detect all these aberrations in a clinical setting?

- *cost-effectiveness/data storage*
- *turn-around times*
- *Sample material – type, availability, quality*

How can we standardize tests and reporting?

- *Harmonization of testing/coordinated uniform framework*