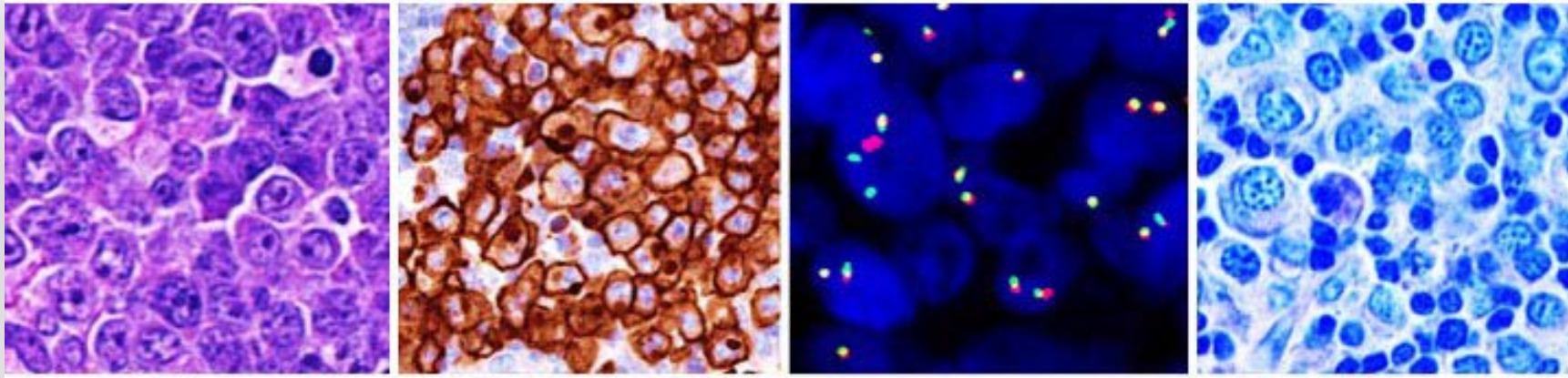


Genetik der Lymphome



Stefan Dirnhofer
Chief Physician Deputy
Head SAKK Lymphoma Pathology Reference Center
Institute of Pathology

WLAD 2021

 **University Hospital
Basel**



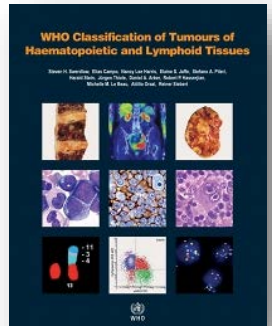


Programm

- **Einführung**
- **Genetik Grundlagen**
- **Beispiele**
- **Zusammenfassung**

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 2017

Myeloid proliferations associated with Down syndrome	169	Heavy chain diseases	237	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma	342
Transient abnormal myelopoiesis associated with Down syndrome	169	Mu heavy chain disease	237		
Myeloid leukaemia associated with Down syndrome	170	Gamma heavy chain disease	238		
		Alpha heavy chain disease	240		
9 Blastic plasmacytoid dendritic cell neoplasm	173	Plasma cell neoplasms	241	14 Mature T- and NK-cell neoplasms	345
		Non-IgM monoclonal gammopathy of undetermined significance	241	T-cell prolymphocytic leukaemia	346
10 Acute leukaemias of ambiguous lineage	179	Plasma cell myeloma	243	T-cell large granular lymphocytic leukaemia	348
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Mixed-phenotype acute leukaemia with t(9;22)(q34.1;q11.2); <i>BCR-ABL1</i>	182	Smouldering (asymptomatic) plasma cell myeloma	249	Aggressive NK-cell leukaemia	353
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Mixed-phenotype acute leukaemia, B/myeloid, not otherwise specified	184	Plasma cell leukaemia	250	Systemic EBV+ T-cell lymphoma of childhood	355
Mixed-phenotype acute leukaemia, T/myeloid, not otherwise specified	185	Plasmacytoma	250	Chronic active EBV infection of T- and NK-cell type, systemic form	358
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		Monoclonal immunoglobulin deposition diseases	254	Adult T-cell leukaemia/lymphoma	363
11 Introduction and overview of the classification of the lymphoid neoplasms	189	Primary amyloidosis	254	Extranodal NK/T-cell lymphoma, nasal type	368
		Light chain and heavy chain deposition diseases	255	Intestinal T-cell lymphoma	372
12 Precursor lymphoid neoplasms	199	Plasma cell neoplasms with associated paraneoplastic syndrome	256	Enteropathy-associated T-cell lymphoma	372
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B-lymphoblastic leukaemia/lymphoma with hypodiploidy	206	Testicular follicular lymphoma	268	Sézary syndrome	390
B-lymphoblastic leukaemia/lymphoma with t(5;14)(q31.1;q32.1); <i>IGH/IL3</i>	206	In situ follicular neoplasia	274	Primary cutaneous CD30-positive T-cell lymphoproliferative disorders	392
B-lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); <i>TCF3-PBX1</i>	207	Duodenal-type follicular lymphoma	276	Lymphomatoid papulosis	392
B-lymphoblastic leukaemia/lymphoma, <i>BCR-ABL1</i> -like	208	Paediatric-type follicular lymphoma	278	Primary cutaneous anaplastic large cell lymphoma	395
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13 Mature B-cell neoplasms	215	Diffuse large B-cell lymphoma (DLBCL), NOS	291	Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder	401
Chronic lymphocytic leukaemia/ small lymphocytic lymphoma	216	T-cell/histiocyte-rich large B-cell lymphoma	298	Peripheral T-cell lymphoma, NOS	403
Monoclonal B-cell lymphocytosis	220	Primary diffuse large B-cell lymphoma of the CNS	300	Angioimmunoblastic T-cell lymphoma and other nodal lymphomas of T follicular helper (TFH) cell origin	407
B-cell prolymphocytic leukaemia	222	Primary cutaneous diffuse large B-cell lymphoma, leg type	303	Angioimmunoblastic T-cell lymphoma	408
Splenic marginal zone lymphoma	223	EBV-positive diffuse large B-cell lymphoma, NOS	304	Follicular T-cell lymphoma	411
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Hairy cell leukaemia variant	230	Lymphomatoid granulomatosis	312	Breast implant-associated anaplastic large cell lymphoma	421
Lymphoplasmacytic lymphoma	232	Primary mediastinal (thymic) large B-cell lymphoma	314		
IgM Monoclonal gammopathy of undetermined significance	236	Intravascular large B-cell lymphoma	317		
		ALK-positive large B-cell lymphoma	319		
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		HHV8-associated lymphoproliferative disorders	325		
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		High-grade B-cell lymphoma, NOS	340		



Lymphome

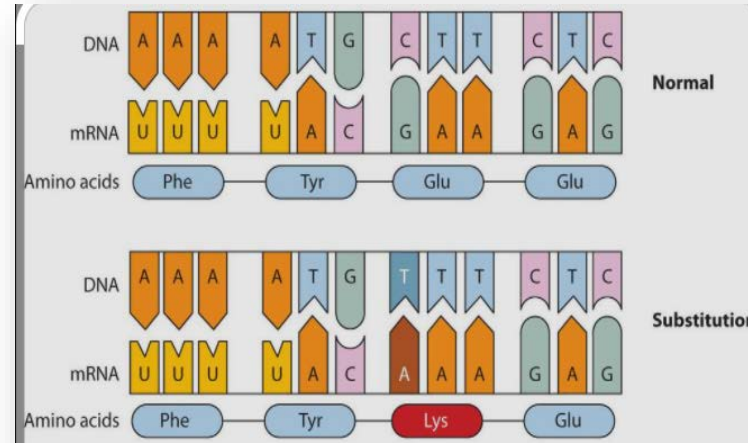
- **B-Zell – Lymphome (IgH-Rearrangement)**
- **T-Zell – Lymphome (TCR-Rearrangement)**
- **Hodgkin – Lymphome (IgH-Rearrangement)**

- **Lymphome entstehen aus B- oder T-Zellen**
- **Lymphome entstehen durch genetische Veränderungen (Mutationen)**

Genetische Aberrationen

- **Mutationen**

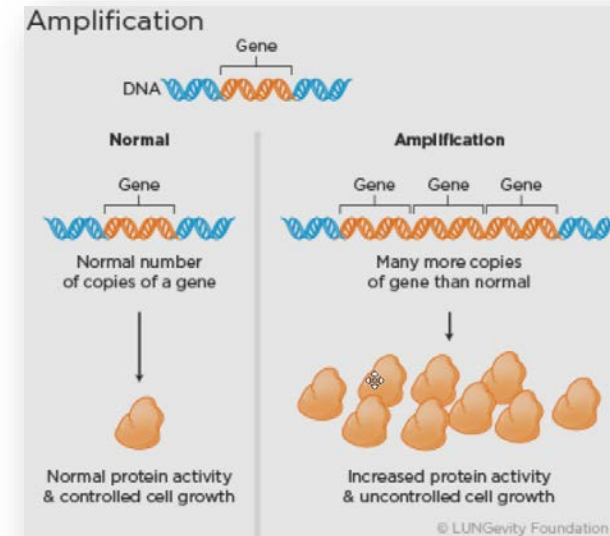
- Punktmutation
- Deletion
- Insertion
- Duplikation



- **Kopienzahlveränderungen**

(Genamplifikationen, Gendeletionen)

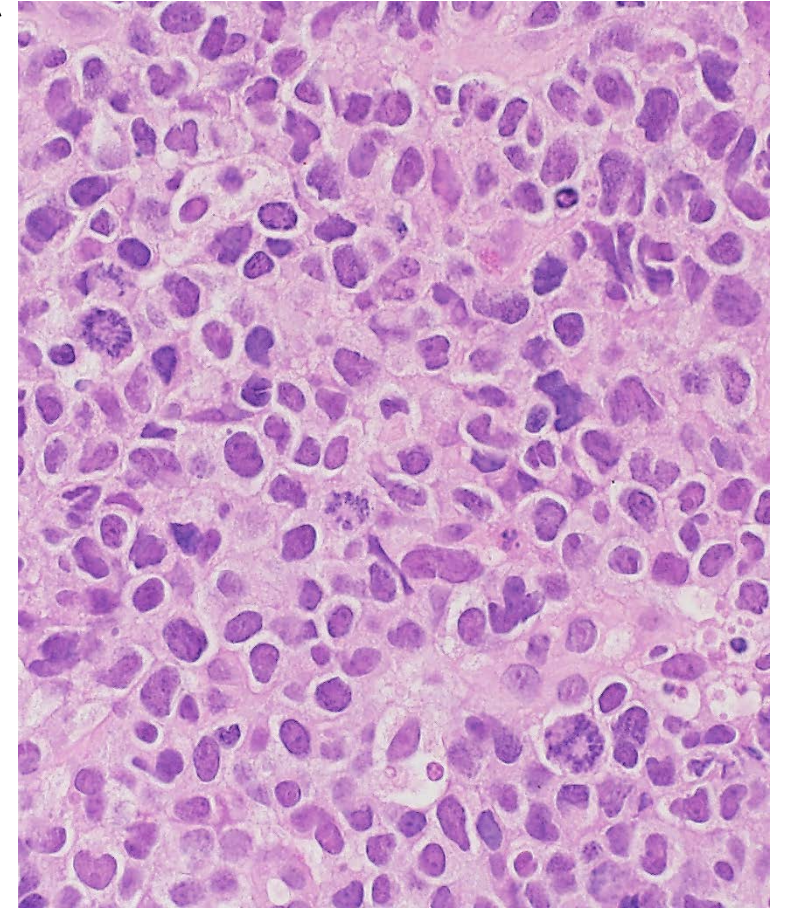
- **Translokationen**



Bedeutung der Genetik

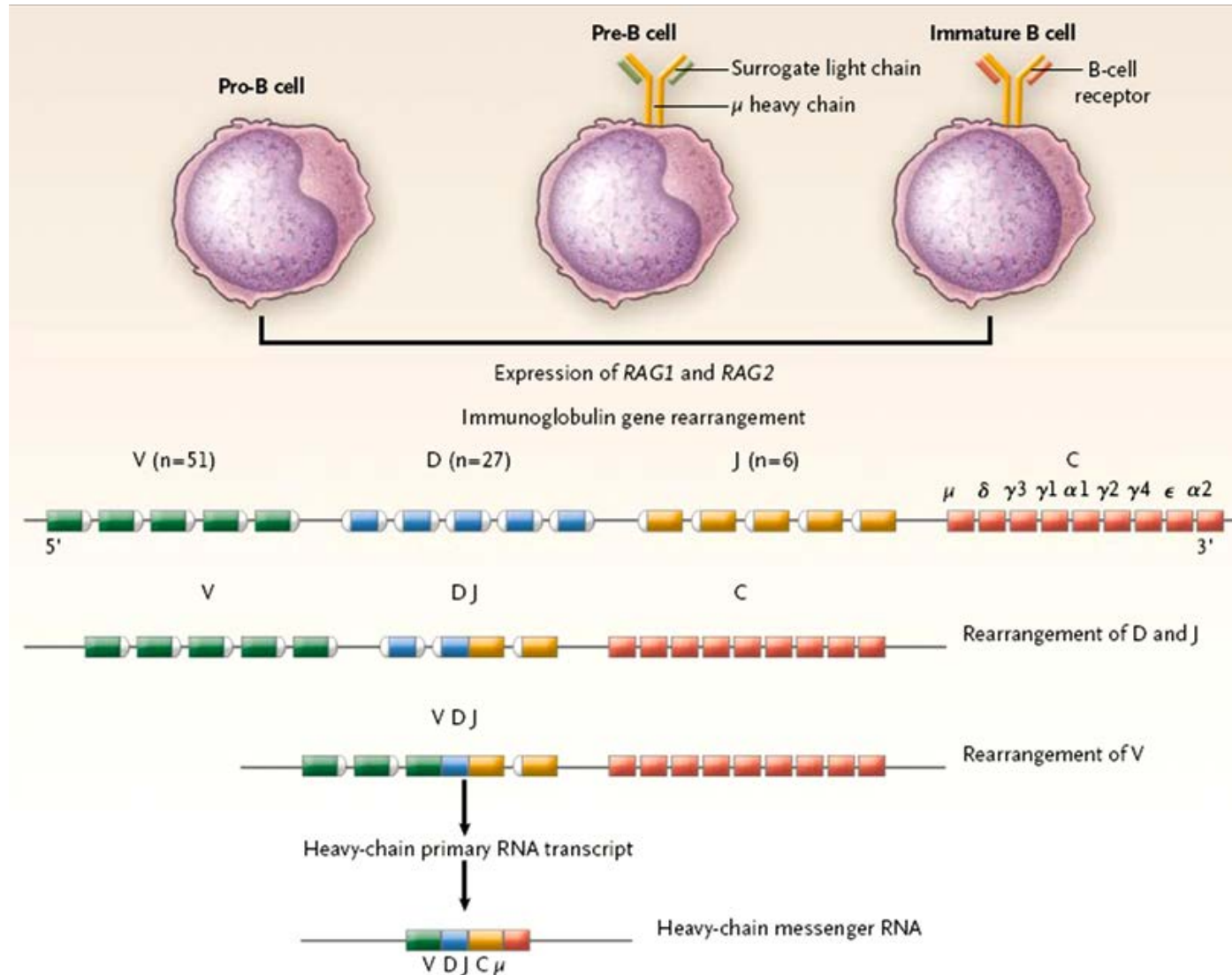
- Pathogenese der Lymphome (Krankheitsentstehung)
- **Diagnose**
- Prognose
- Therapie (Prädiktion)

Lymphknoten: reaktiv oder Lymphom?

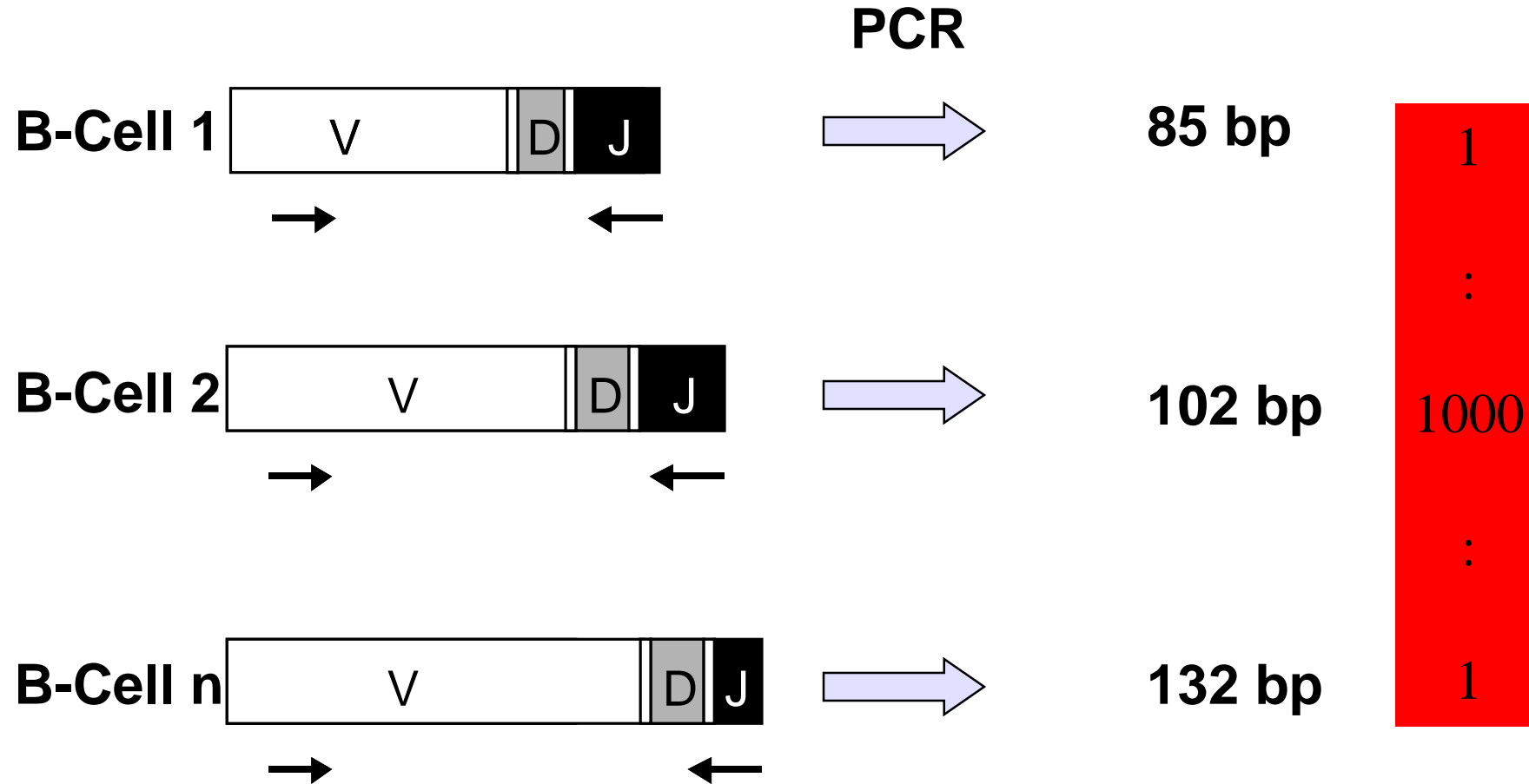


B-Zelle: Umlagerung (Rearrangement) der Immunoglobulingene

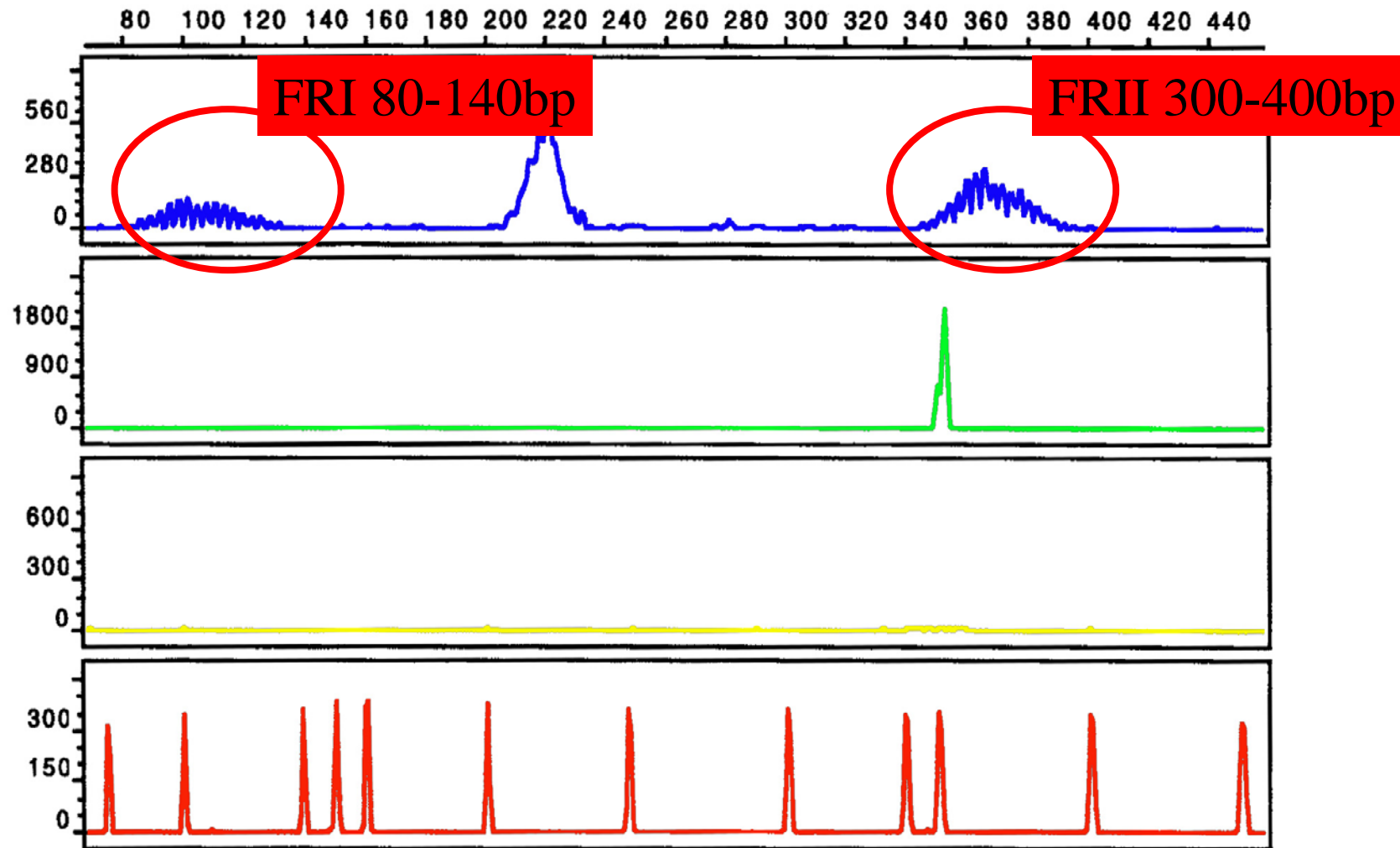
Knochenmark



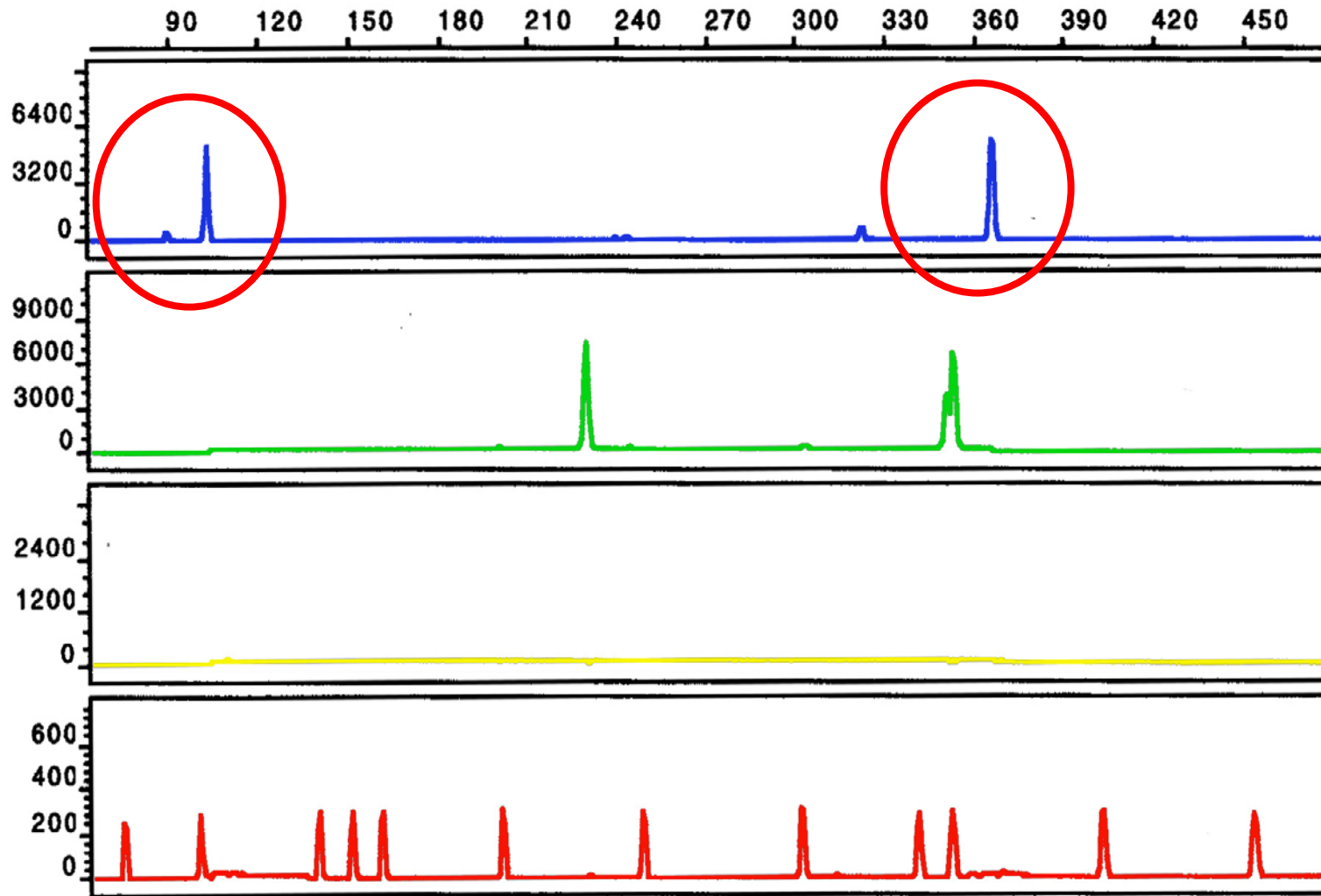
Molekulare Klonalitätsdiagnostik - PCR



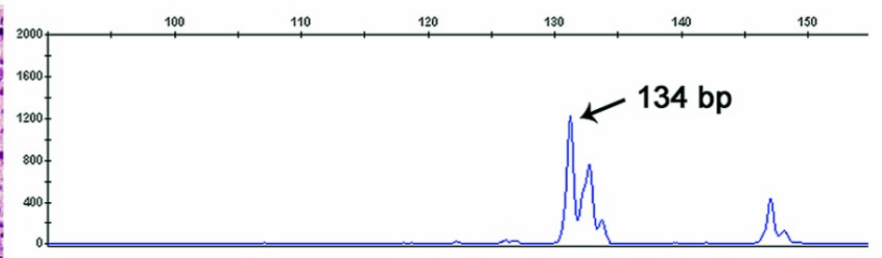
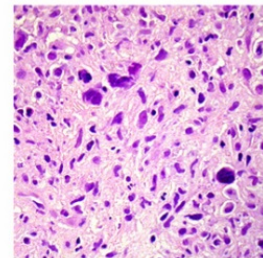
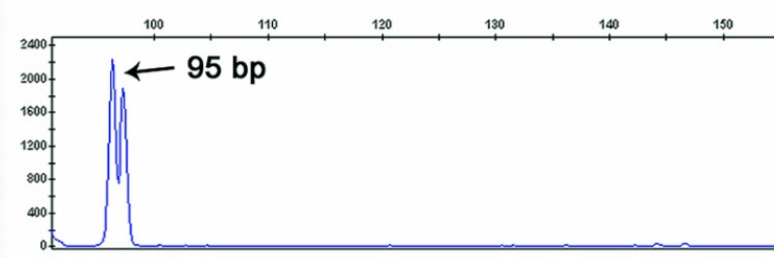
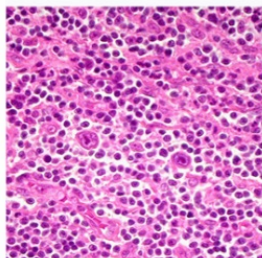
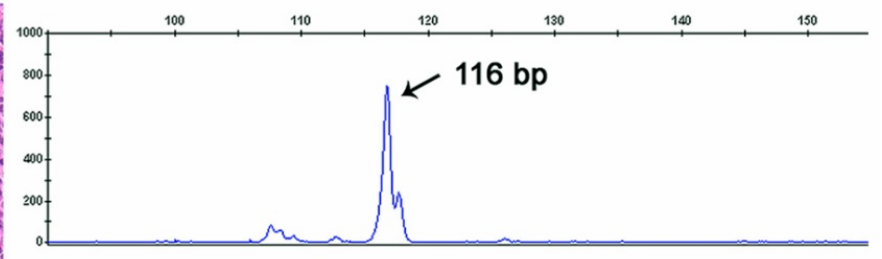
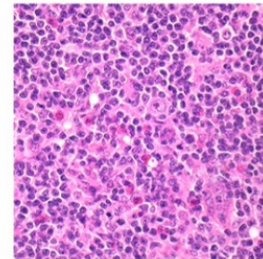
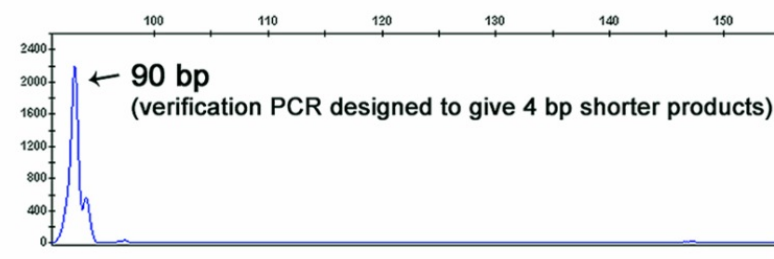
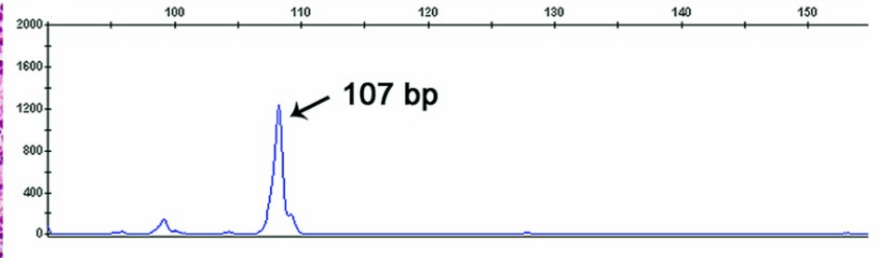
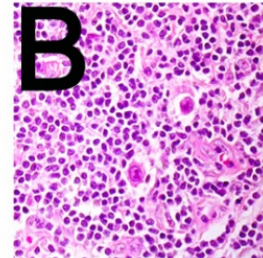
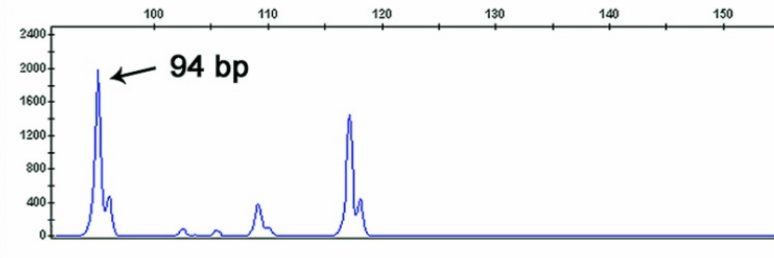
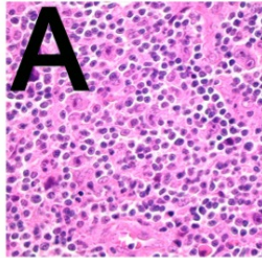
Molekulargenetische Lymphom-Diagnostik: IgH polyklonal



Molekulargenetische Lymphom-Diagnostik : IgH klonal



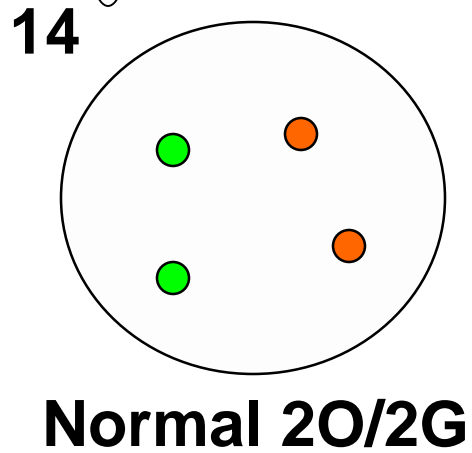
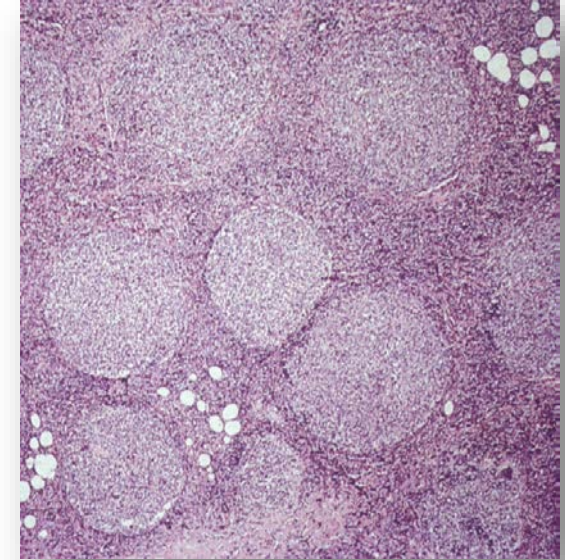
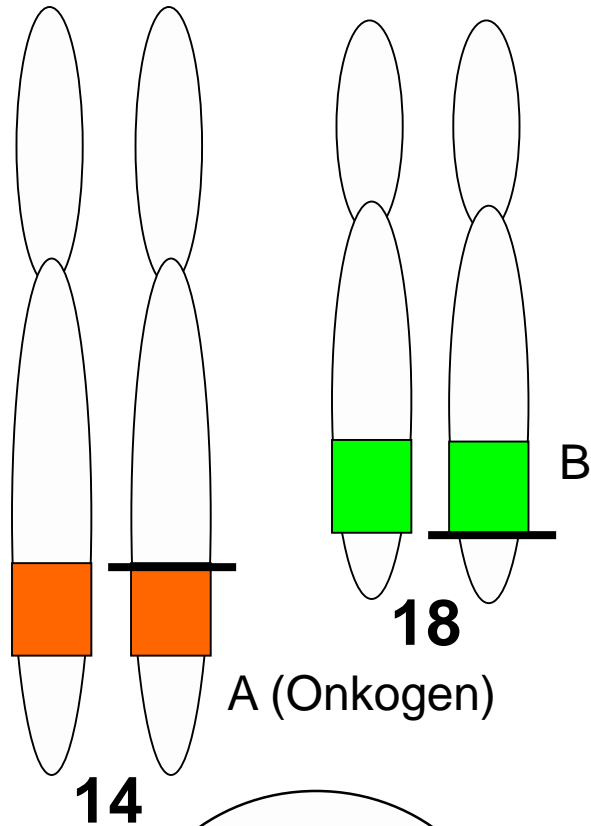
Lymphom - Rezidiv vs. (gleiche) Neuerkrankung



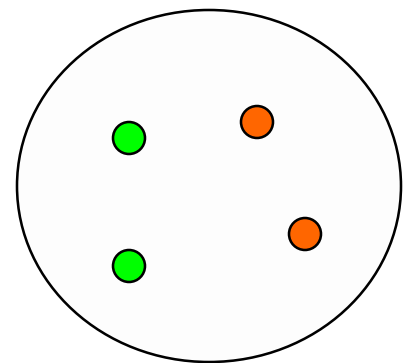
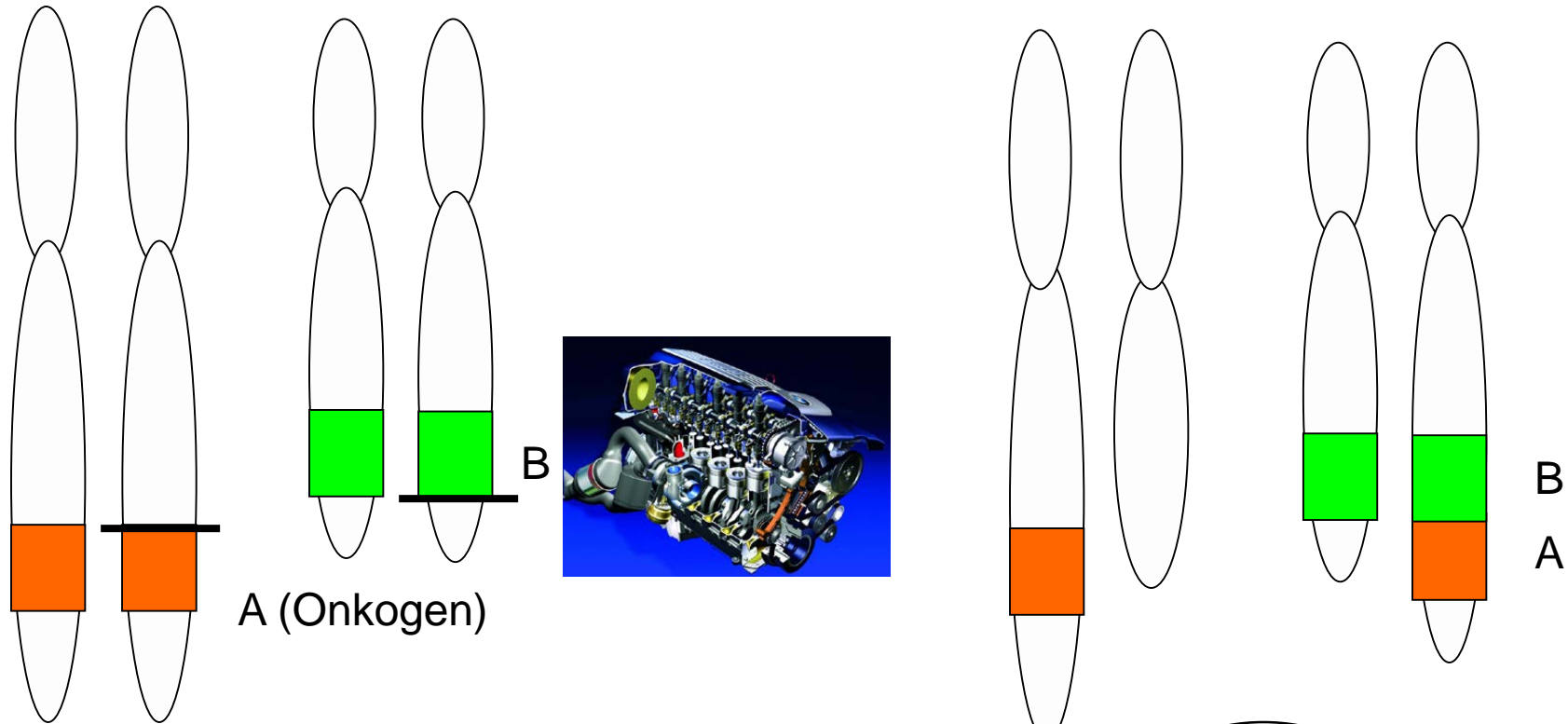
Lymphomdiagnose: Translokationen

Diagnose	Translokation	Beteiligte Gene
Follicular lymphoma	t(14;18)	IGH and BCL2
MALT lymphoma	t(11;18) t(14;18)	AP12 and MALT1 IGH and MALT1
Mantle cell lymphoma	t(11;14)	CCND1 and IGH
Burkitt lymphoma	t(8;14)	MYC and IGH
Anaplastic large cell lymphoma	t(2;5) t(2;v)	ALK and NPM ALK and div. partners

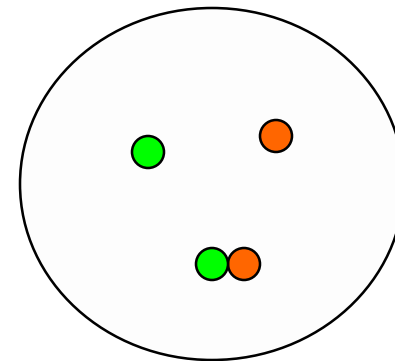
Translokationen - FISH



Translokationen - *Single-Fusion* FISH

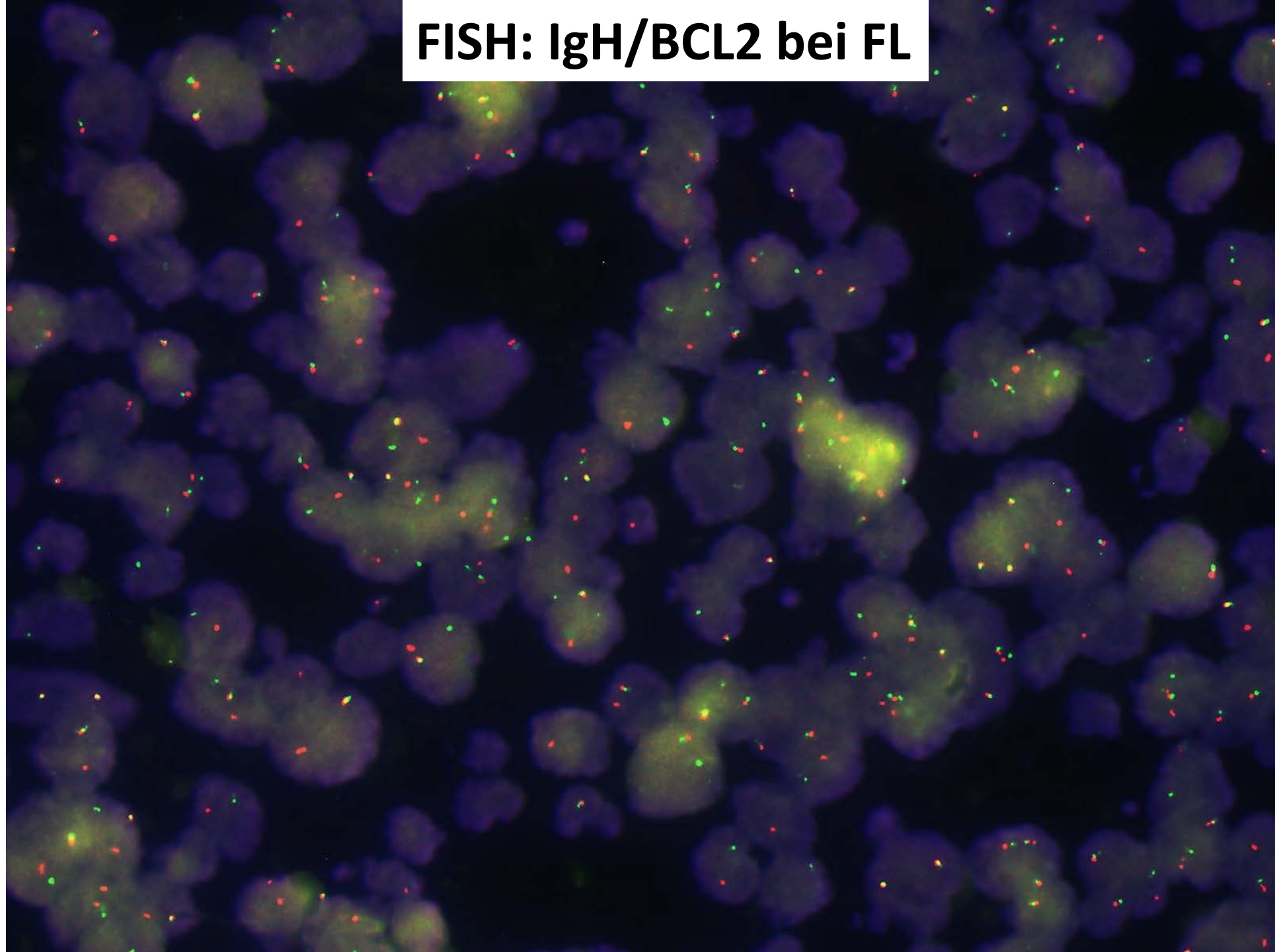


Normal 20/2G



Translokation 1O/1G/1F

FISH: IgH/BCL2 bei FL



Bedeutung der Genetik

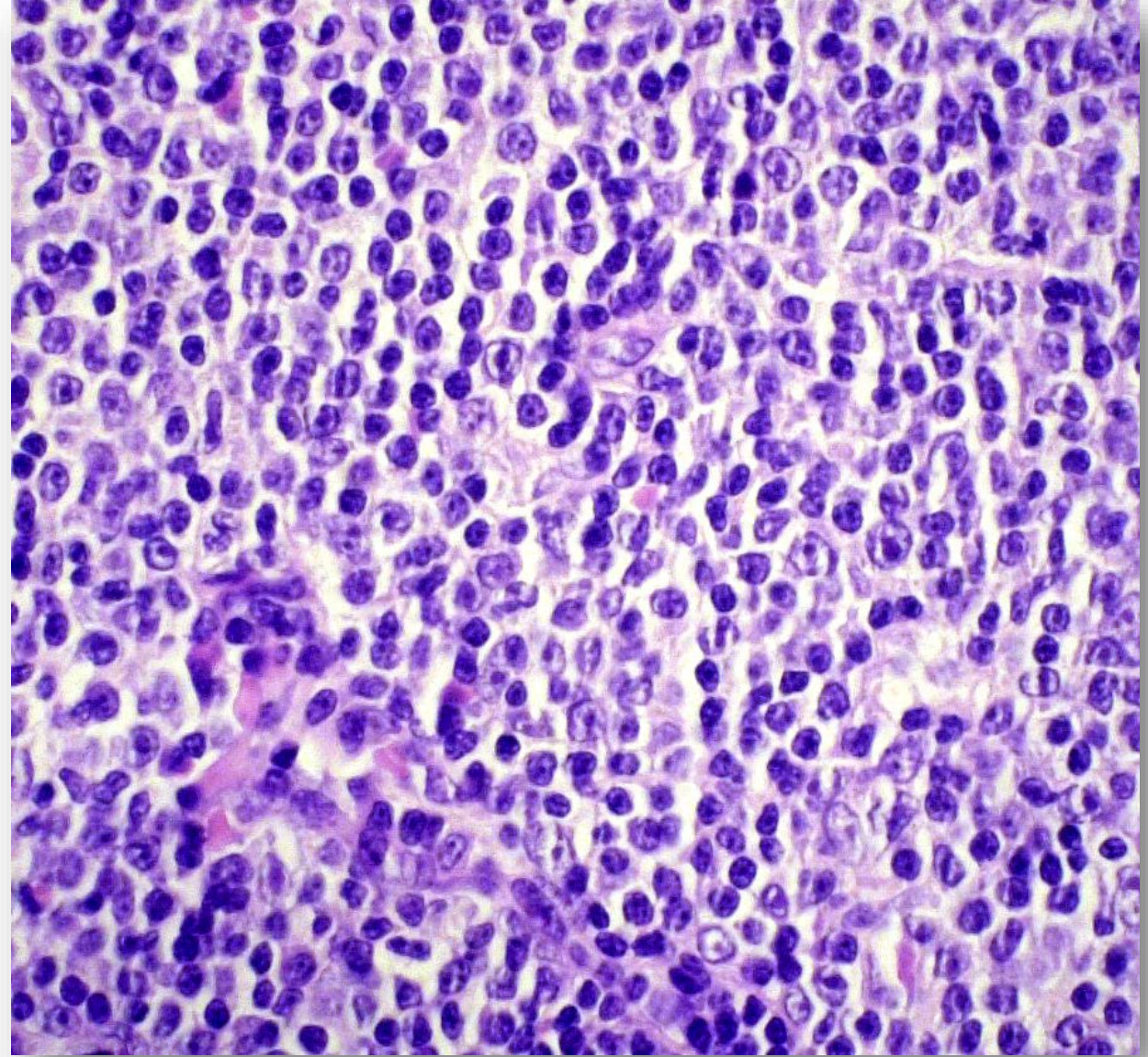
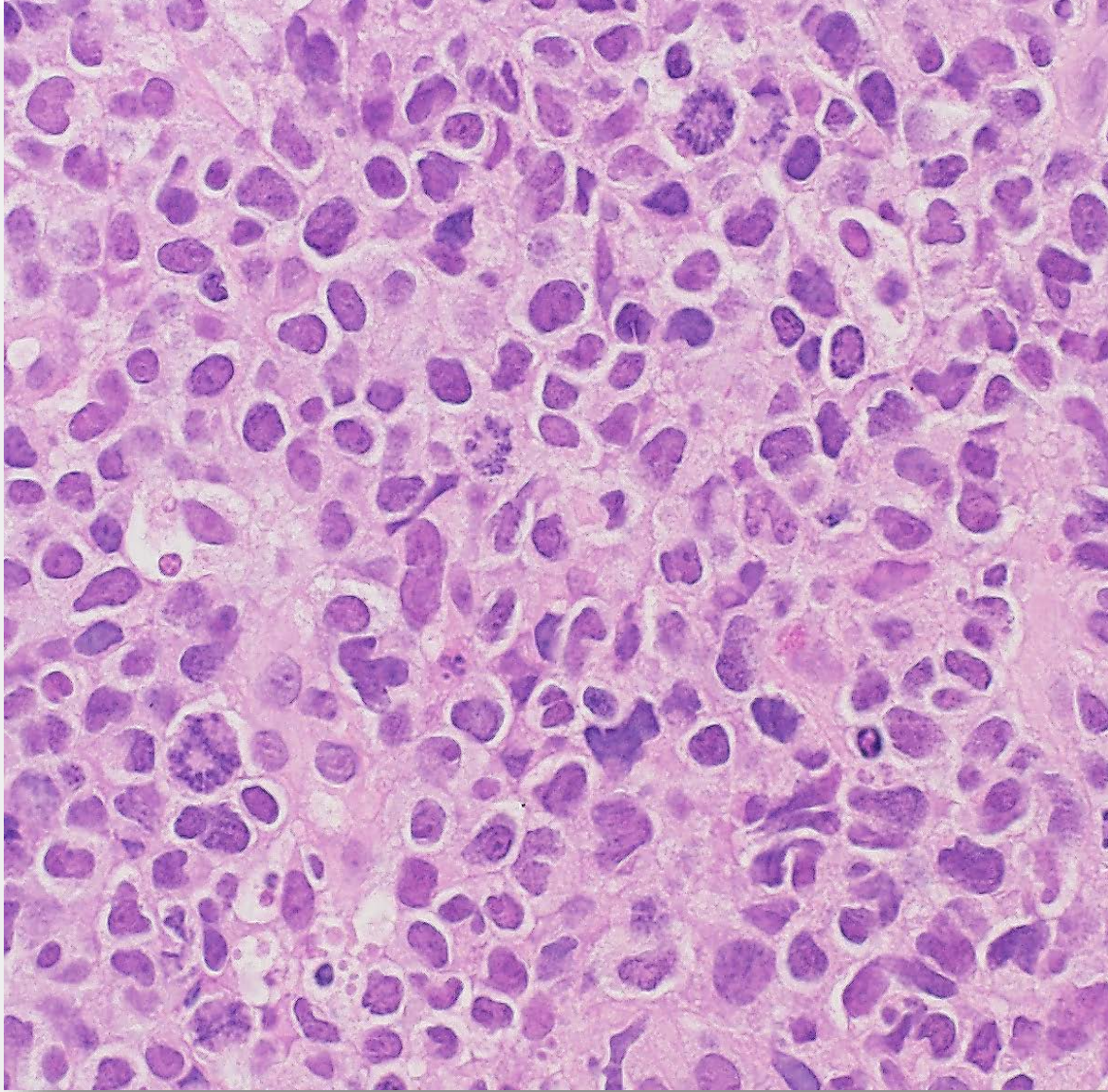
- Pathogenese der Lymphome (Krankheitsentstehung)
- Diagnose
- **Prognose**
- Therapie (Prädiktion)

THE
GOOD THE
BAD AND
UGLY



DIRECTED BY
SERGIO LEONE

Mantelzell – Lymphom (MCL)



MCL – prognostische Bedeutung von TP53mut

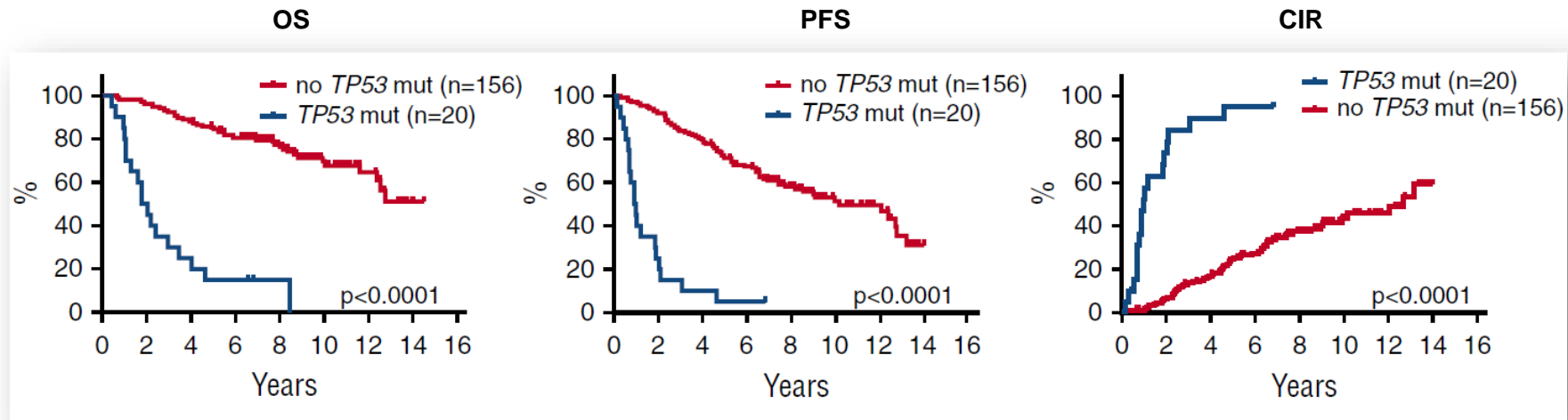


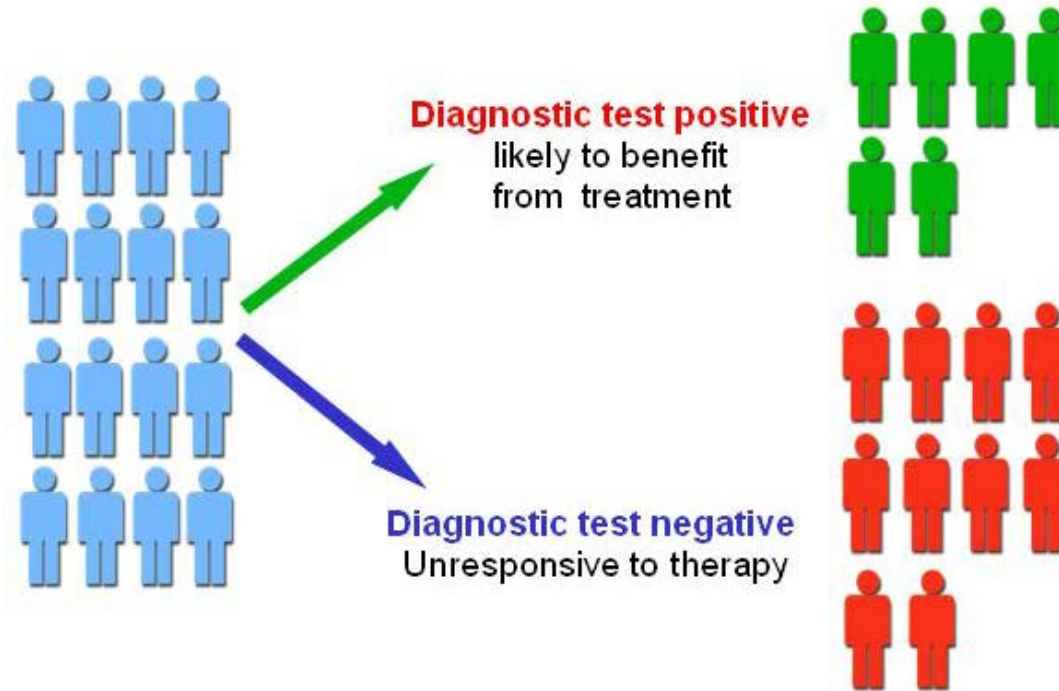
Table 2. Multivariate Cox regression analyses (n = 147)

Variables	OS			PFS			CIR		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
mut <i>TP53</i>	6.2	(2.6-14.9)	<.0001	6.8	(3.4-13.8)	<.0001	6.9	(3.3-14.5)	<.0001
mut <i>NOTCH1</i>	2.7	(0.9-8.6)	.09	2.3	(0.9-6.3)	.10	2.2	(0.7-6.5)	.17
del <i>TP53</i>	1.4	(0.7-2.8)	.37	1.5	(0.9-2.7)	.15	1.7	(0.9-3.0)	.10
del <i>CDKN2A</i>	1.3	(0.6-2.7)	.55	1.3	(0.7-2.4)	.40	1.3	(0.7-2.5)	.43
Blastoid	1.3	(0.6-2.5)	.53	0.8	(0.4-1.6)	.62	0.9	(0.4-1.7)	.65
MIPI-c high-risk*	1.8	(0.9-3.9)	.11	2.2	(1.2-4.0)	.01	2.6	(1.4-4.9)	.003
mut <i>WHSC1</i> †	0.8	(0.3-1.9)	.58	—	—	—	—	—	—

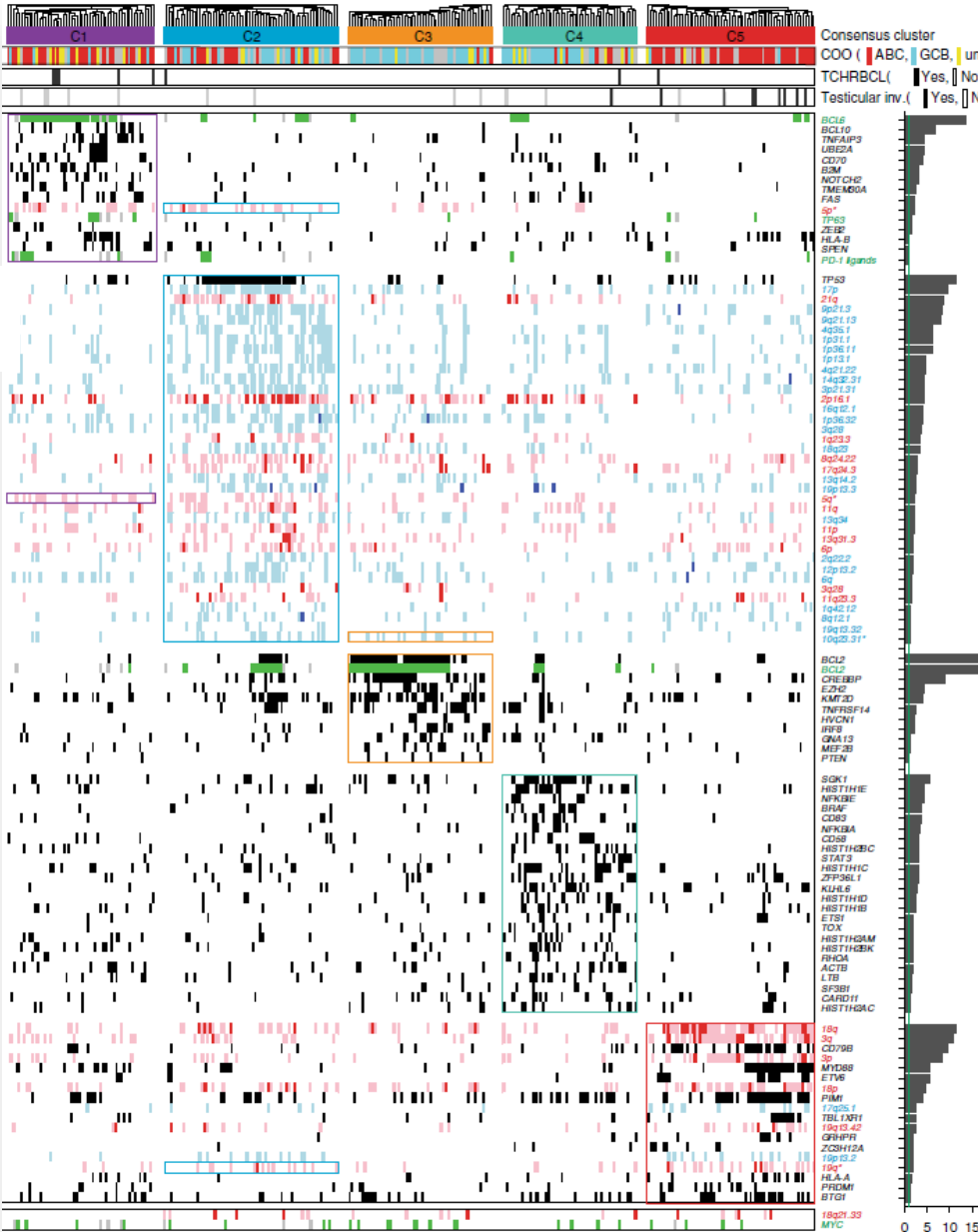
Bedeutung der Genetik

- Pathogenese der Lymphome (Krankheitsentstehung)
- Diagnose
- Prognose
- **Therapie (Prädiktion)**

Prädiktive Biomarker – Analyse für personalisierte Therapie



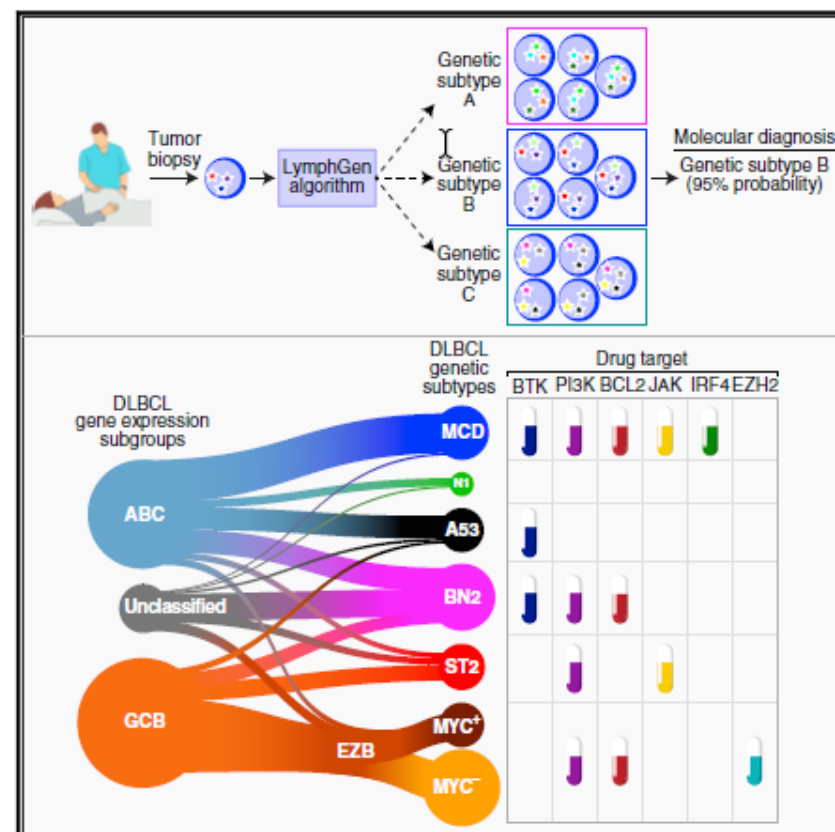
Genetik des diffus grosszelligen B-Zell Lymphoms (DLBCL)



Cancer Cell

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

Graphical Abstract



Authors

George W. Wright, Da Wei Huang,
James D. Phelan, ...,
Wyndham H. Wilson, David W. Scott,
Louis M. Staudt

Correspondence

Istaudt@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.

Optimization trial for diffuse large B-cell lymphoma

SAKK 38/19

Coordinating investigator



PD Dr. med. Anastasios Stathis
Istituto Oncologico della Svizzera Italiana (IOSI)
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Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma in adults. Around 60% of all patients with DLBCL can be cured with the standard treatment.

More trials:

Alternative chemotherapy for diffuse large B-cell lymphoma →
HD 21

Optimization of treatment for diffuse large B-cell lymphoma
HOVON 127/ SAKK 37/19

Trial with the AT...

Zusammenfassung

- **Lymphome entstehen aus genetisch veränderten B- oder T- Zellen**
- **Genetische Veränderungen erklären die Entstehung von Lymphomen**
- **Genetische Veränderungen ermöglichen eine korrekte Diagnose**
- **Genetische Veränderungen sind prognostische Biomarker**
- **Genetische Veränderungen sind Zielstrukturen für personalisierte Therapie**



The Power of Diagnostics

Pathology Basel

stefan.dirnhofer@usb.ch