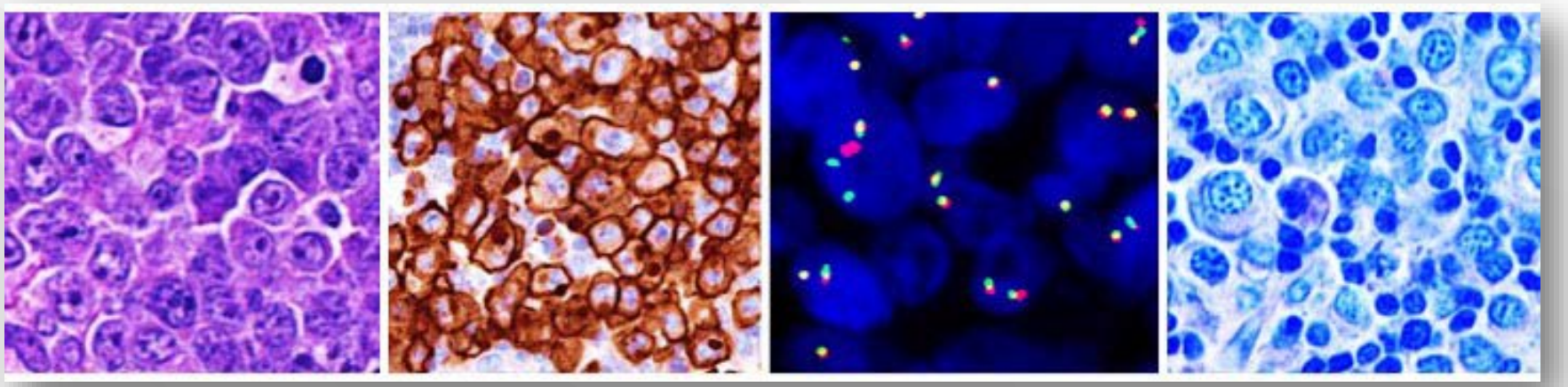
Genetik der Lymphome



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

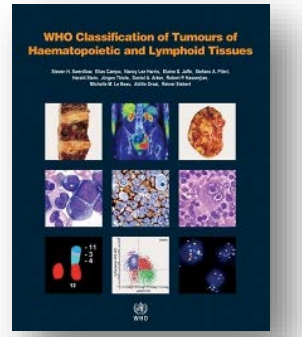
University Hospital Basel

WLAD 2021

Programm

- Einführung
- Genetik Grundlagen
- Beispiele
- Zusammenfassung

WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 2017



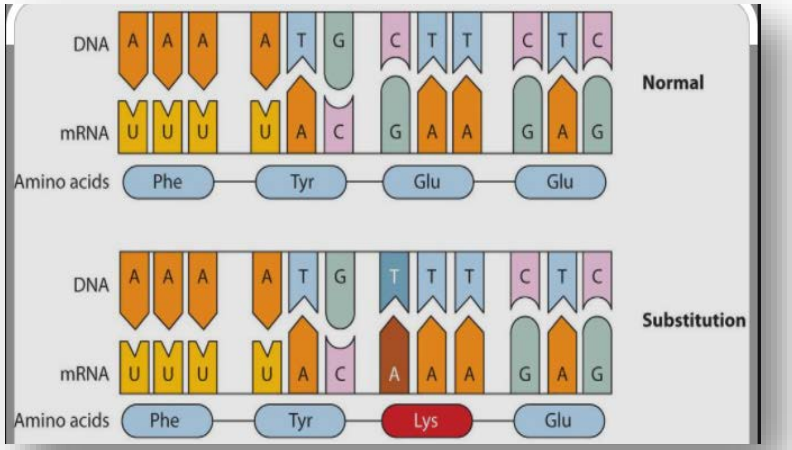
Lymphome

- **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)**

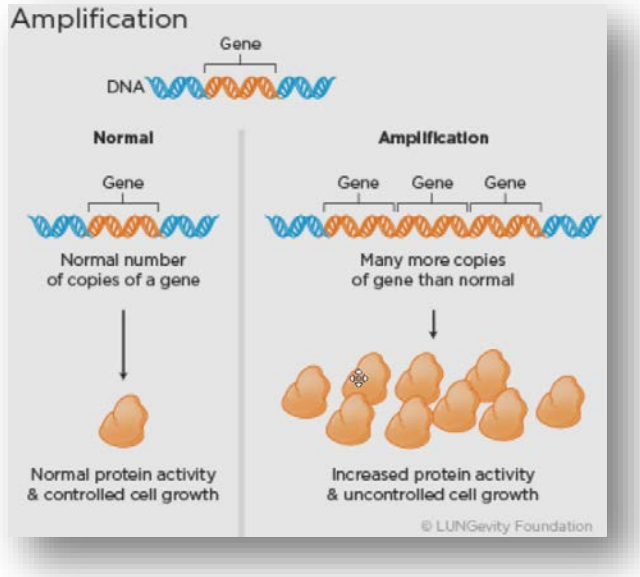
Genetische Aberrationen

- **Mutationen**
  - Punktmutation
  - Deletion
  - Insertion
  - Duplikation



- **Kopienzahlveränderungen**

  (Genamplifikationen, Gendeletionen)

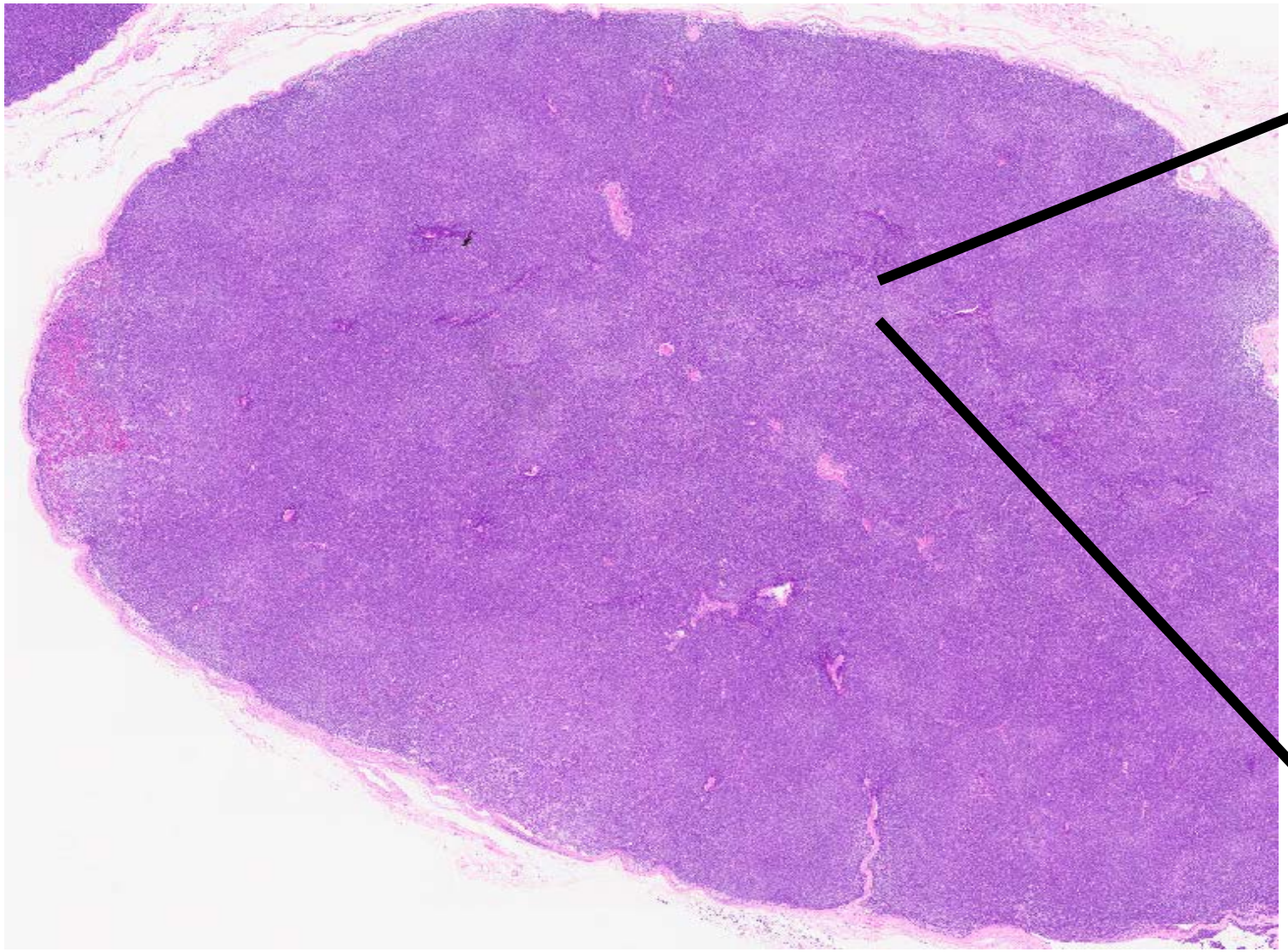


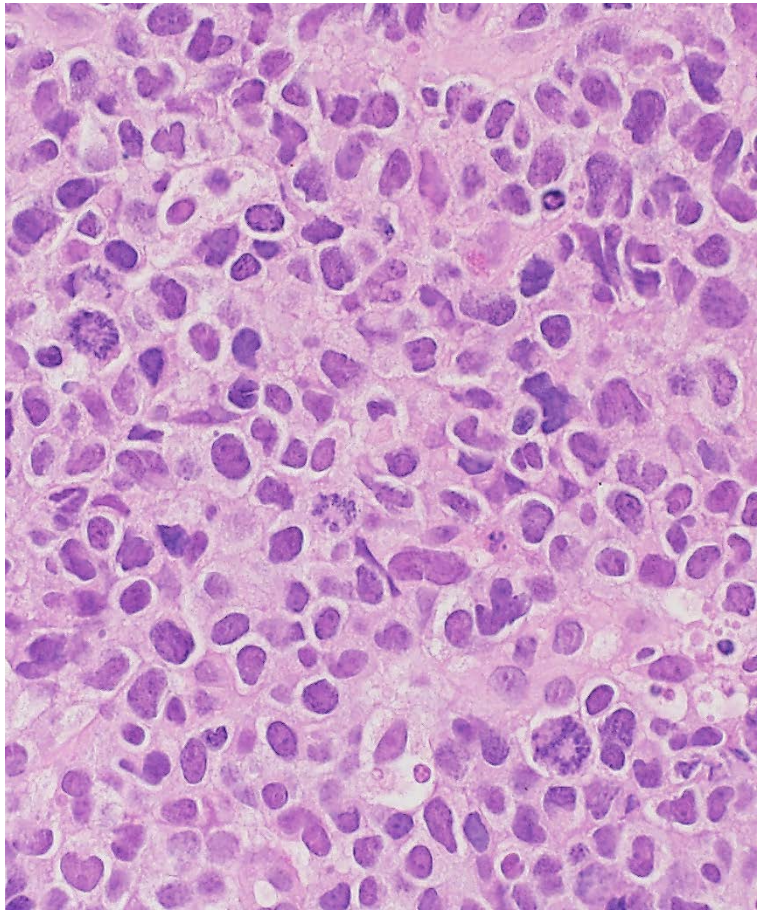
- **Translokationen**

Bedeutung der Genetik

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

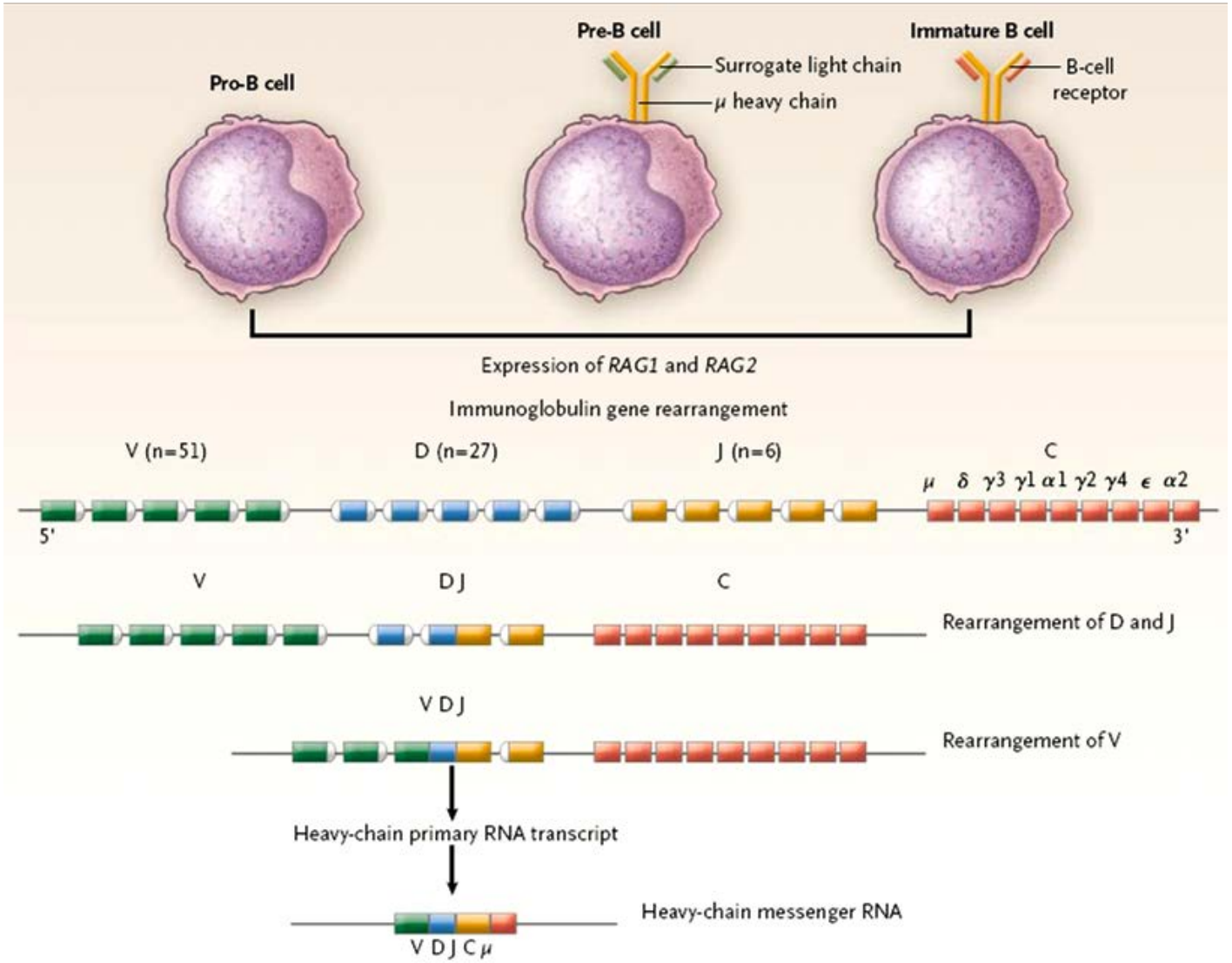
Lymphknoten: reaktiv oder Lymphom?



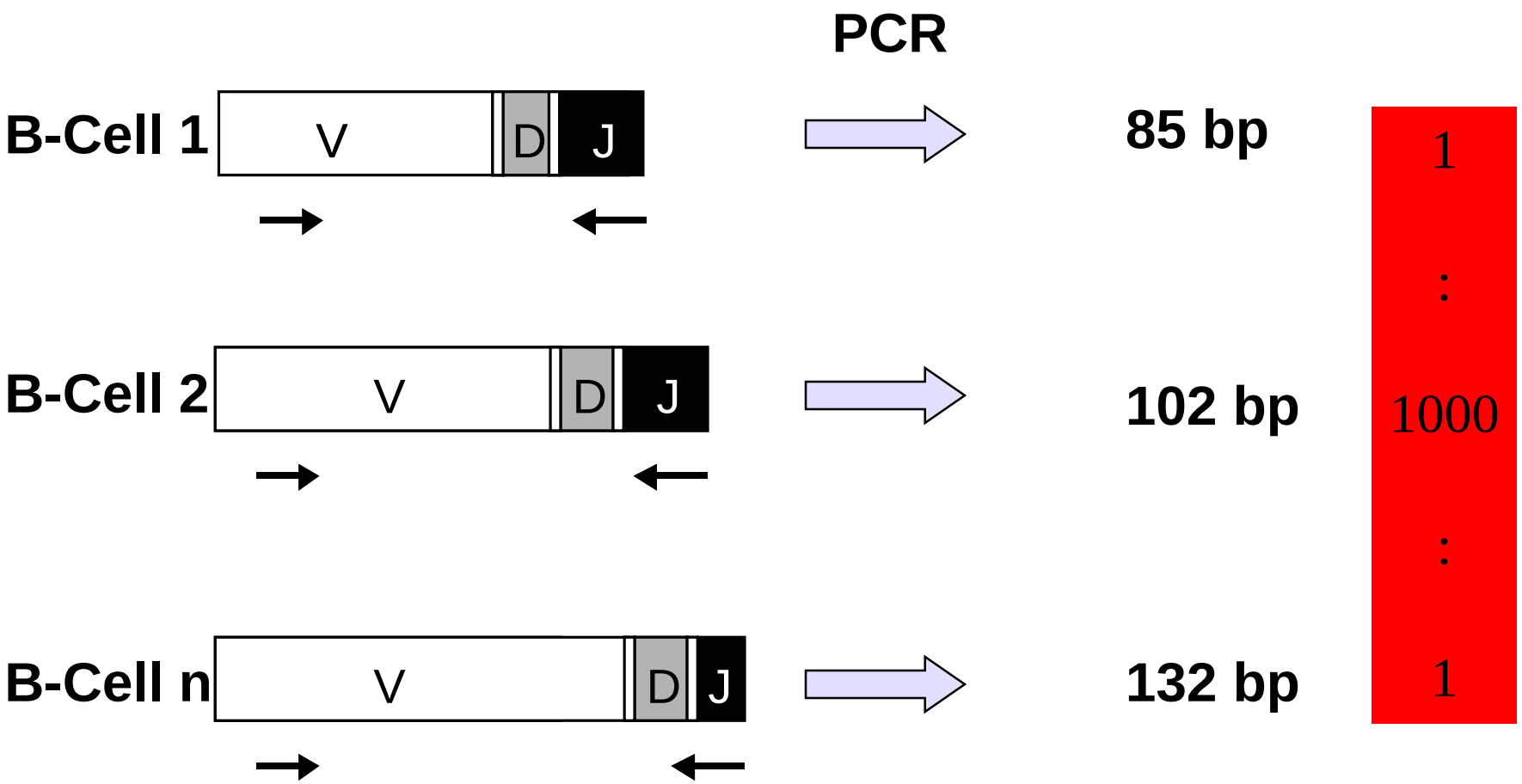


B-Zelle: Umlagerung (Rearrangement) der Immunoglobulingene

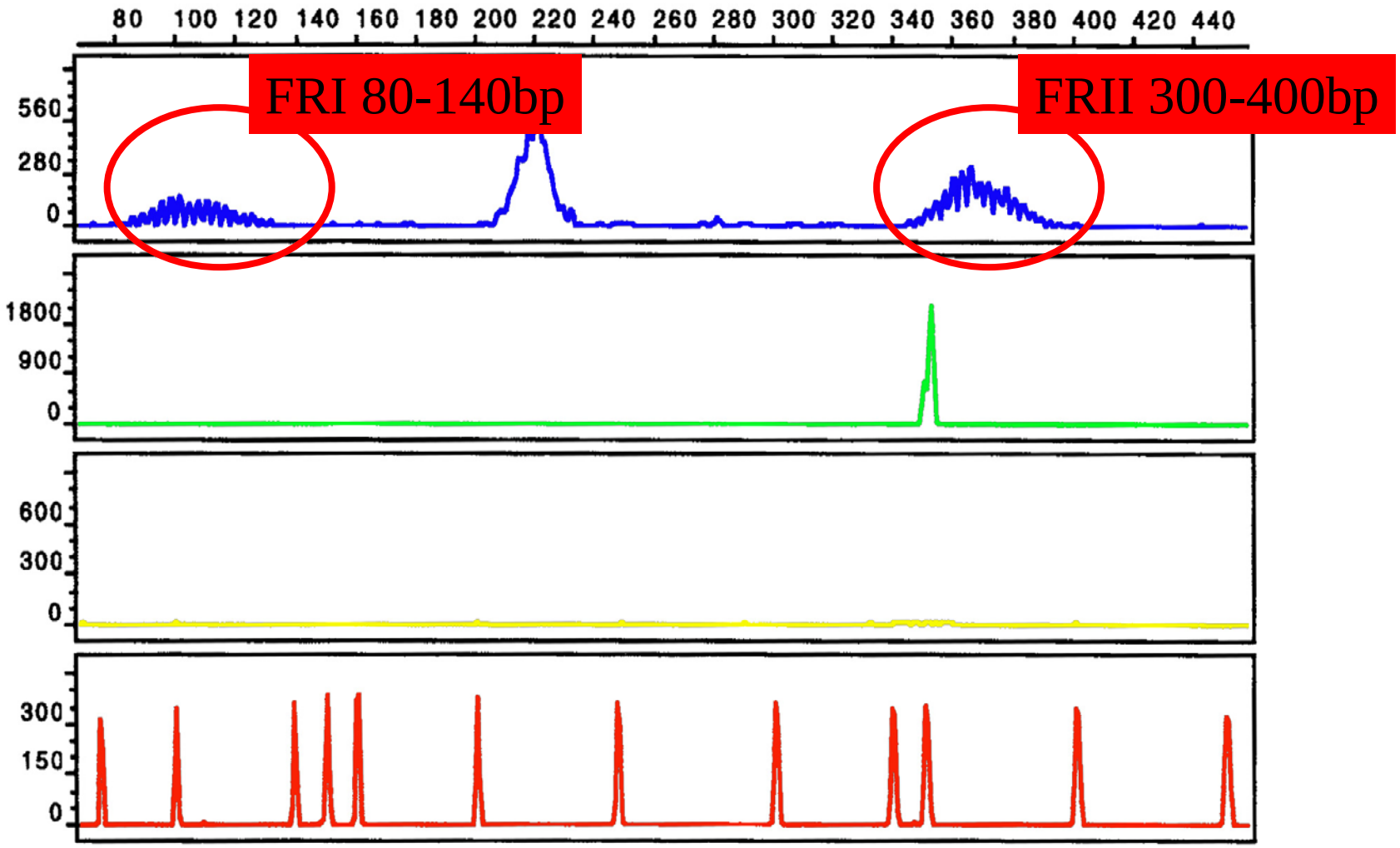
Knochenmark



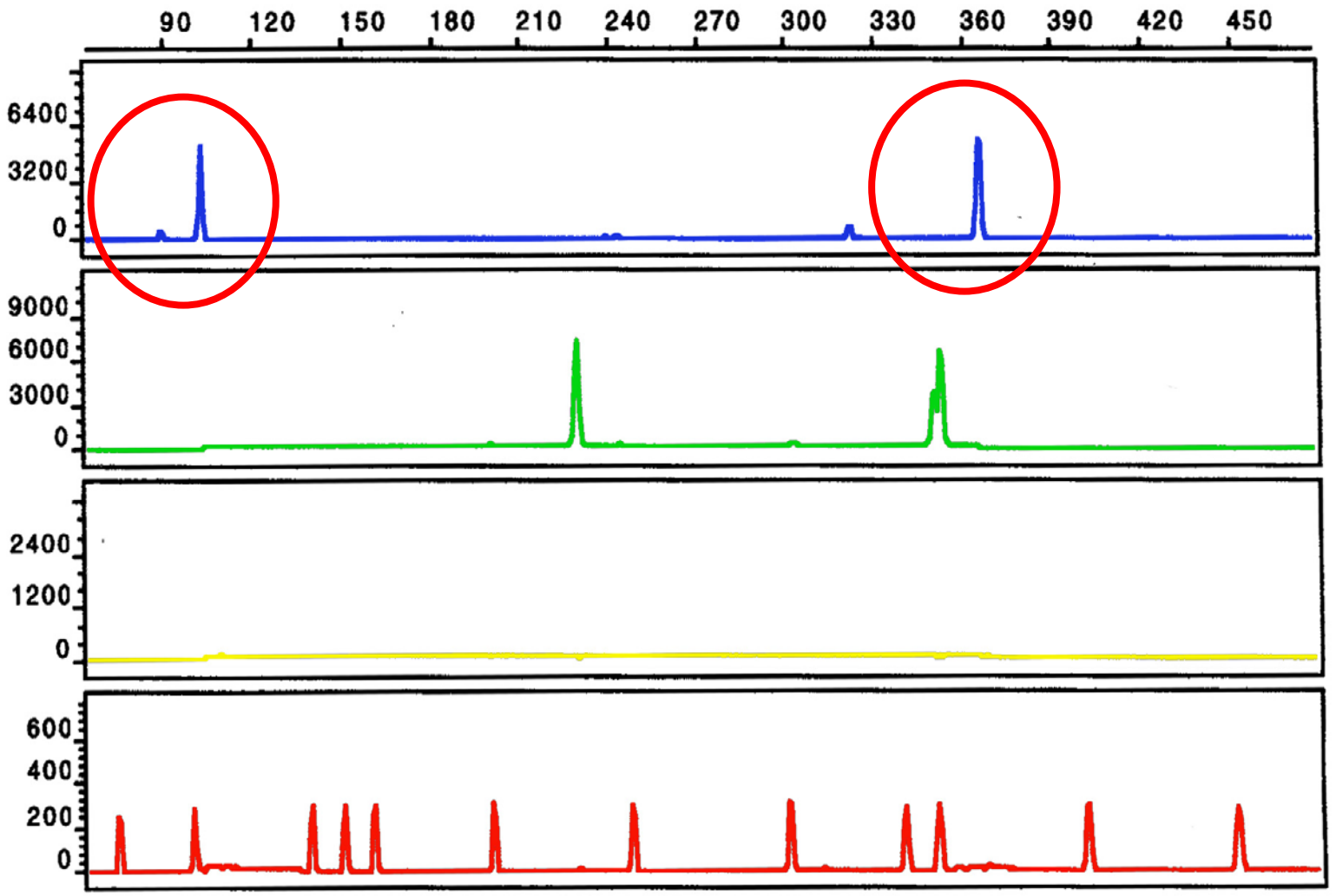
Molekulare Klonalitätsdiagnostik - PCR



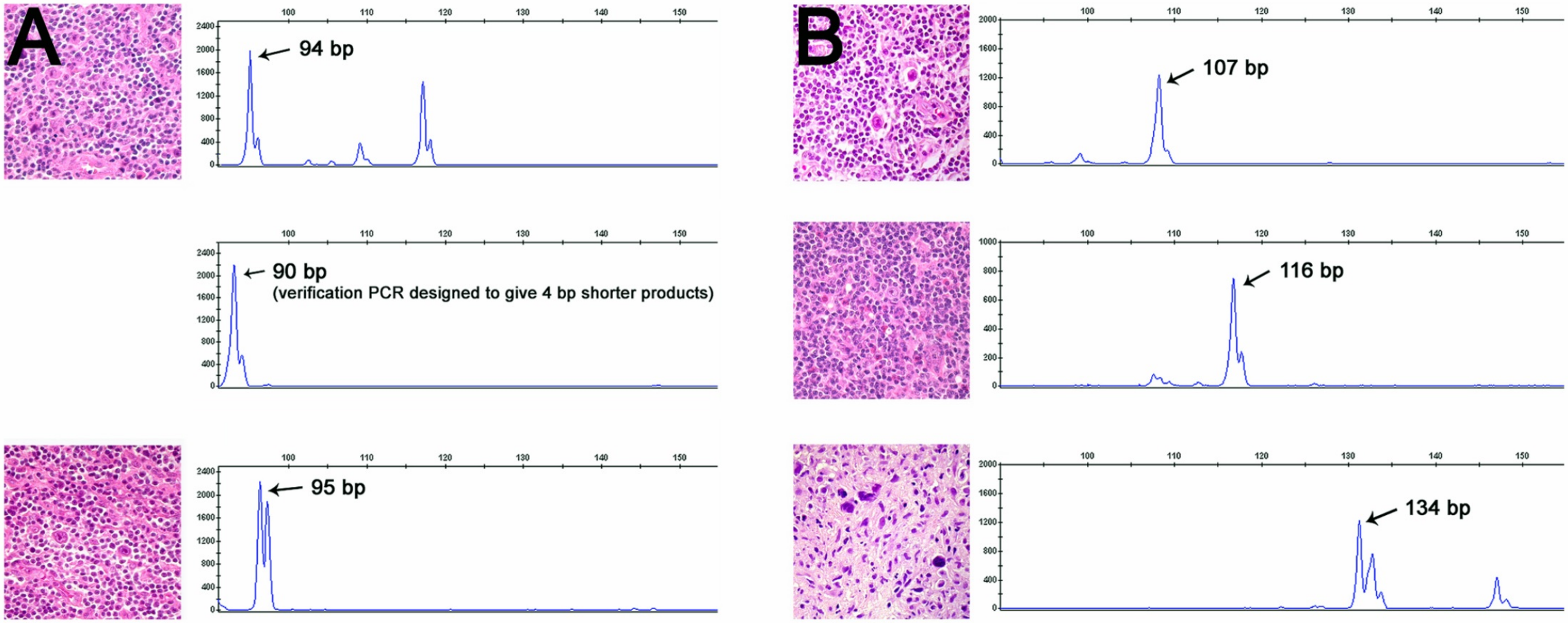
Molekulargenetische Lymphom-Diagnostik: IgH polyklonal



Molekulargenetische Lymphom-Diagnostik : IgH klonal



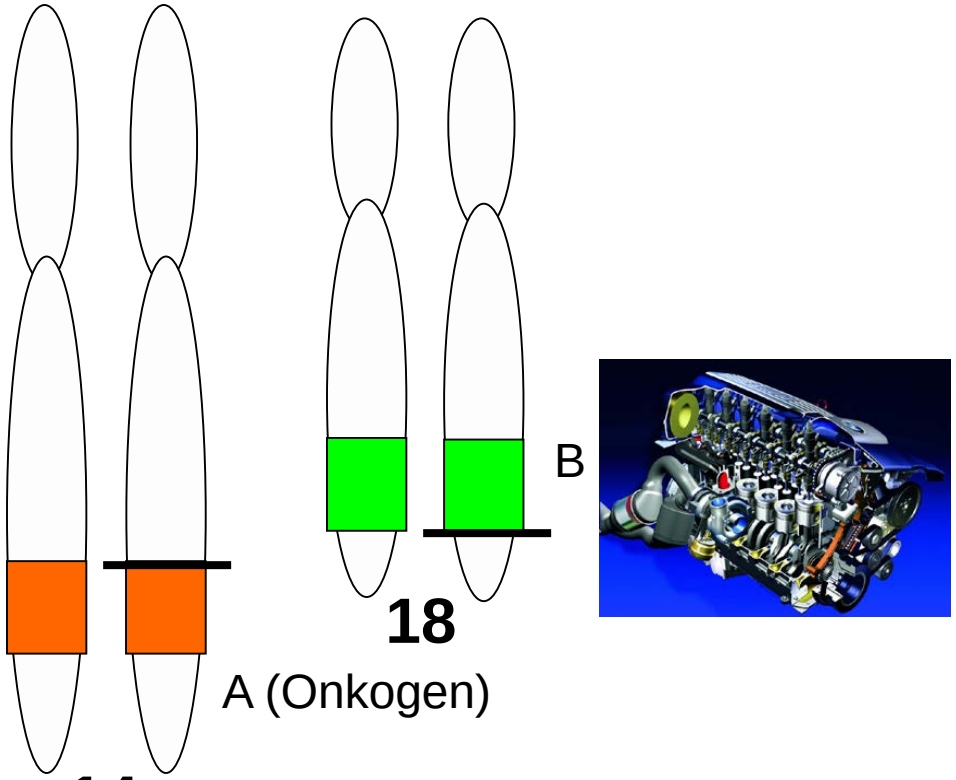
Lymphom - Rezidiv vs. (gleiche) Neuerkrankung

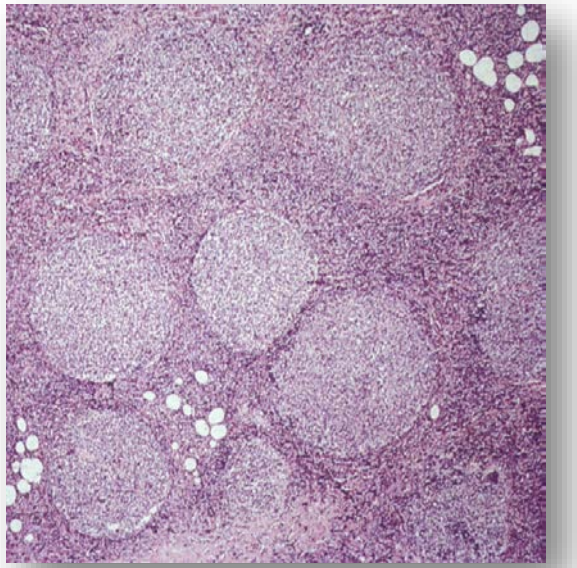


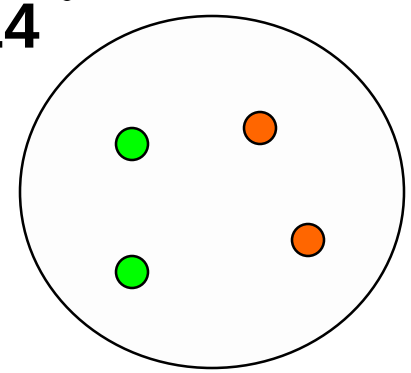
Lymphomdiagnose: Translokationen

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

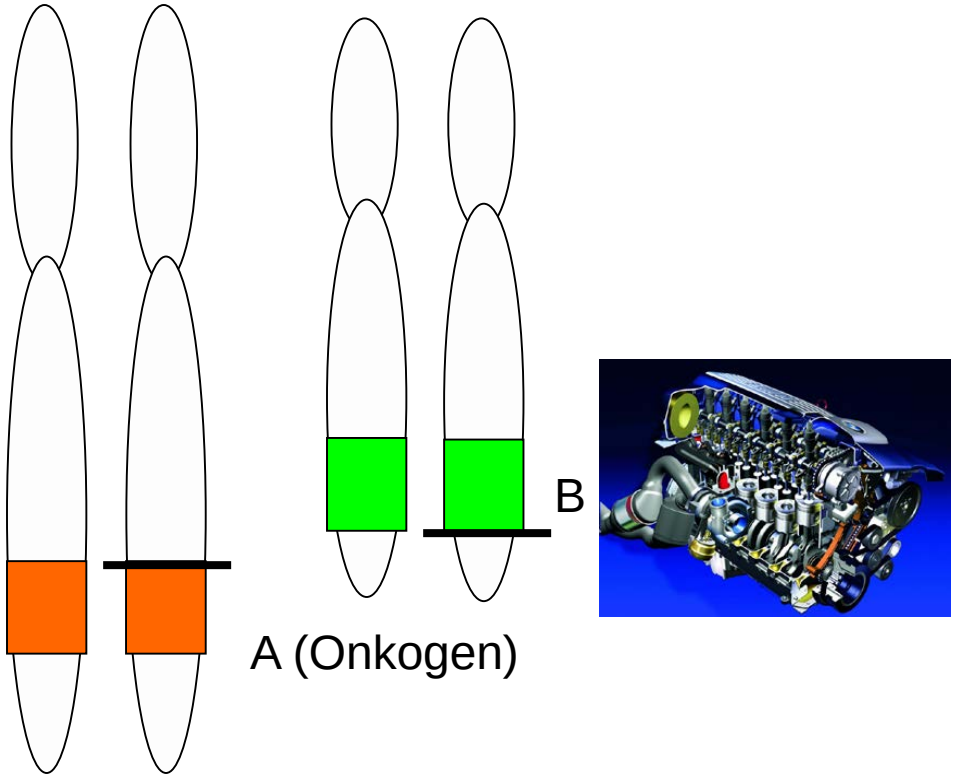


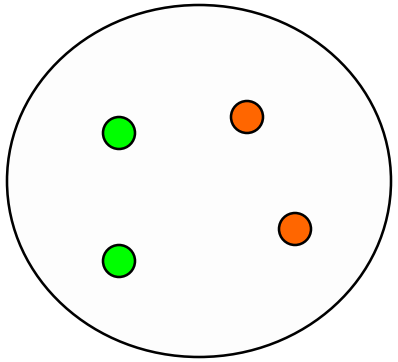




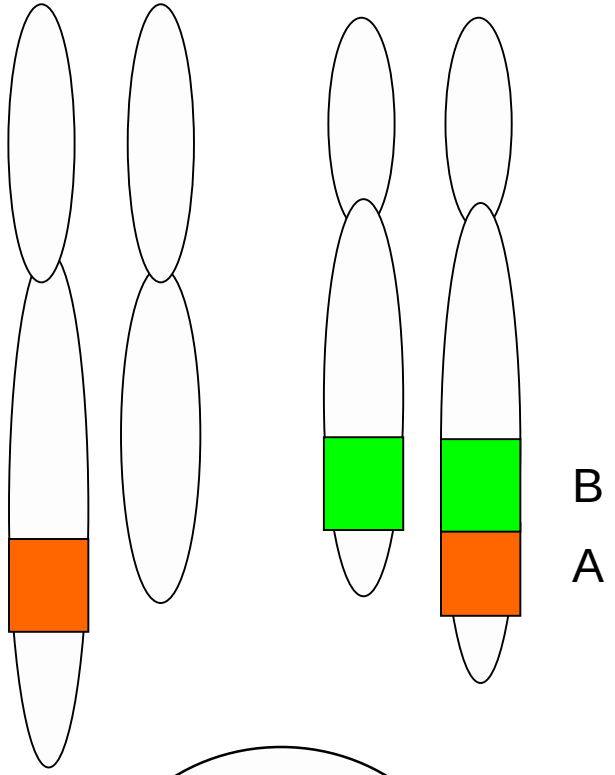
Normal 2O/2G

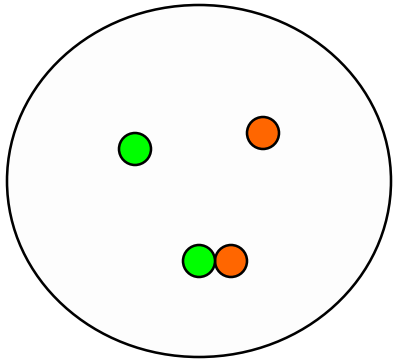
Translokationen - *Single-Fusion* FISH





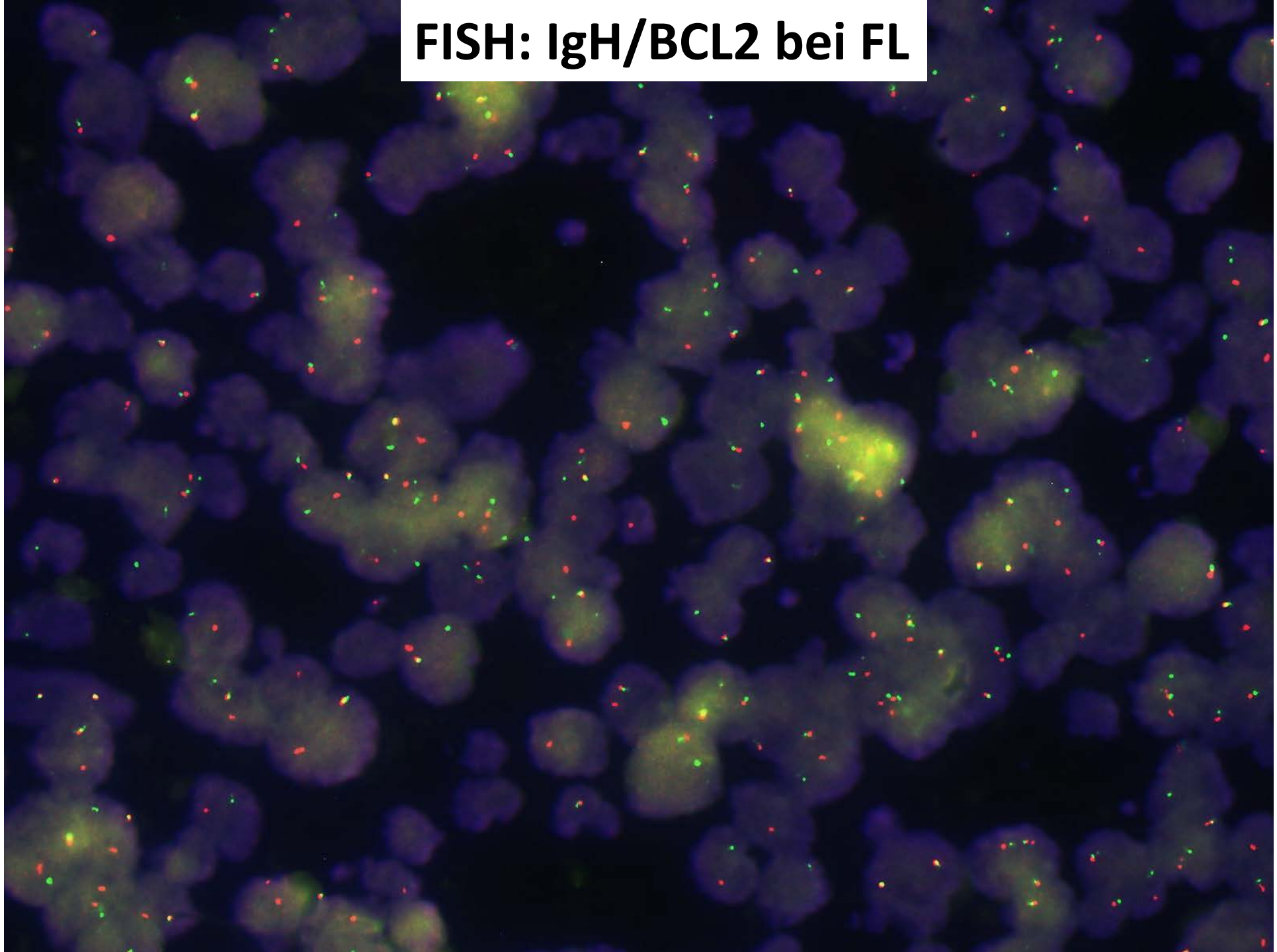
Normal 2O/2G





Translokation 1O/1G/1F

FISH: IgH/BCL2 bei FL

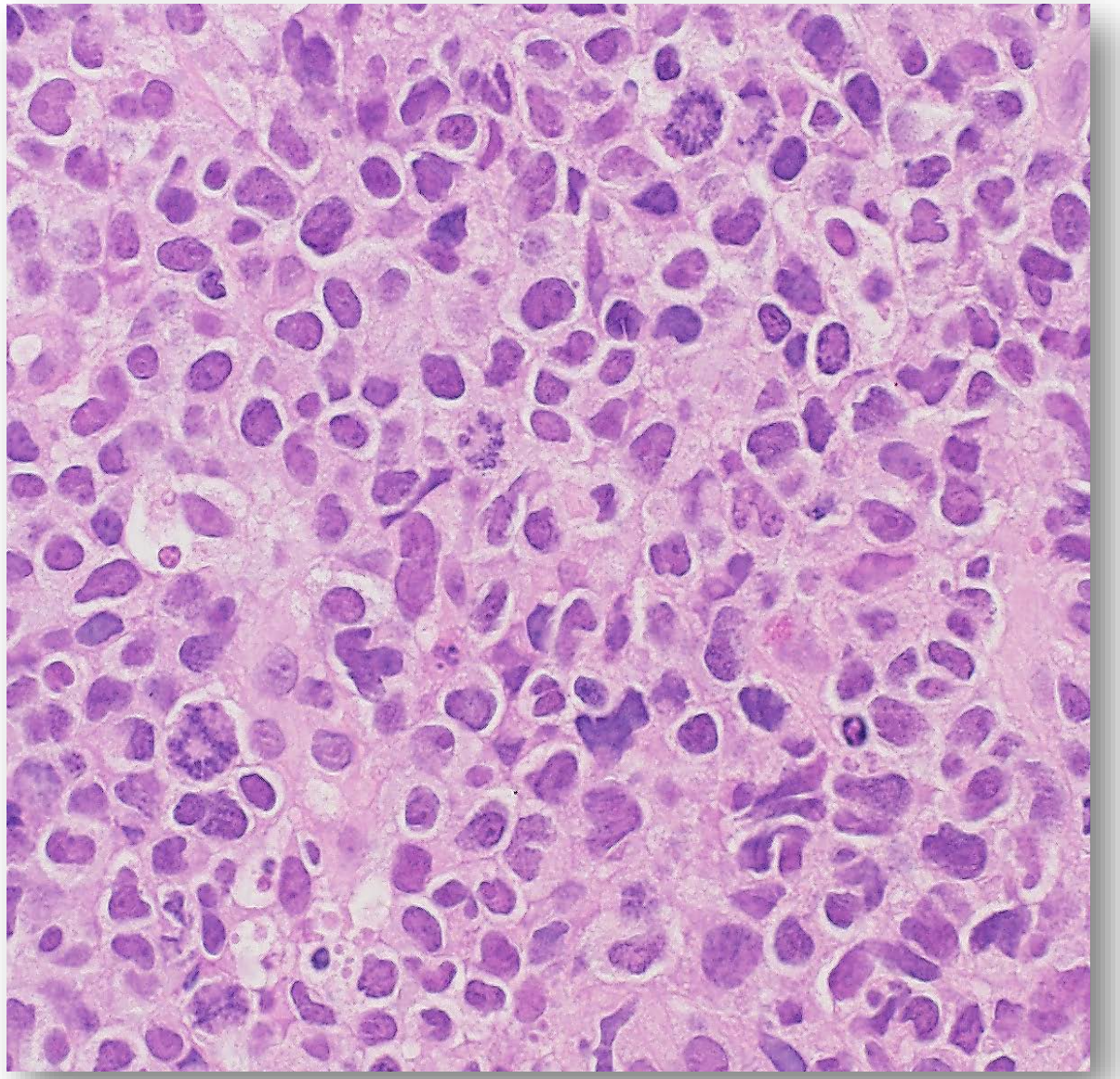


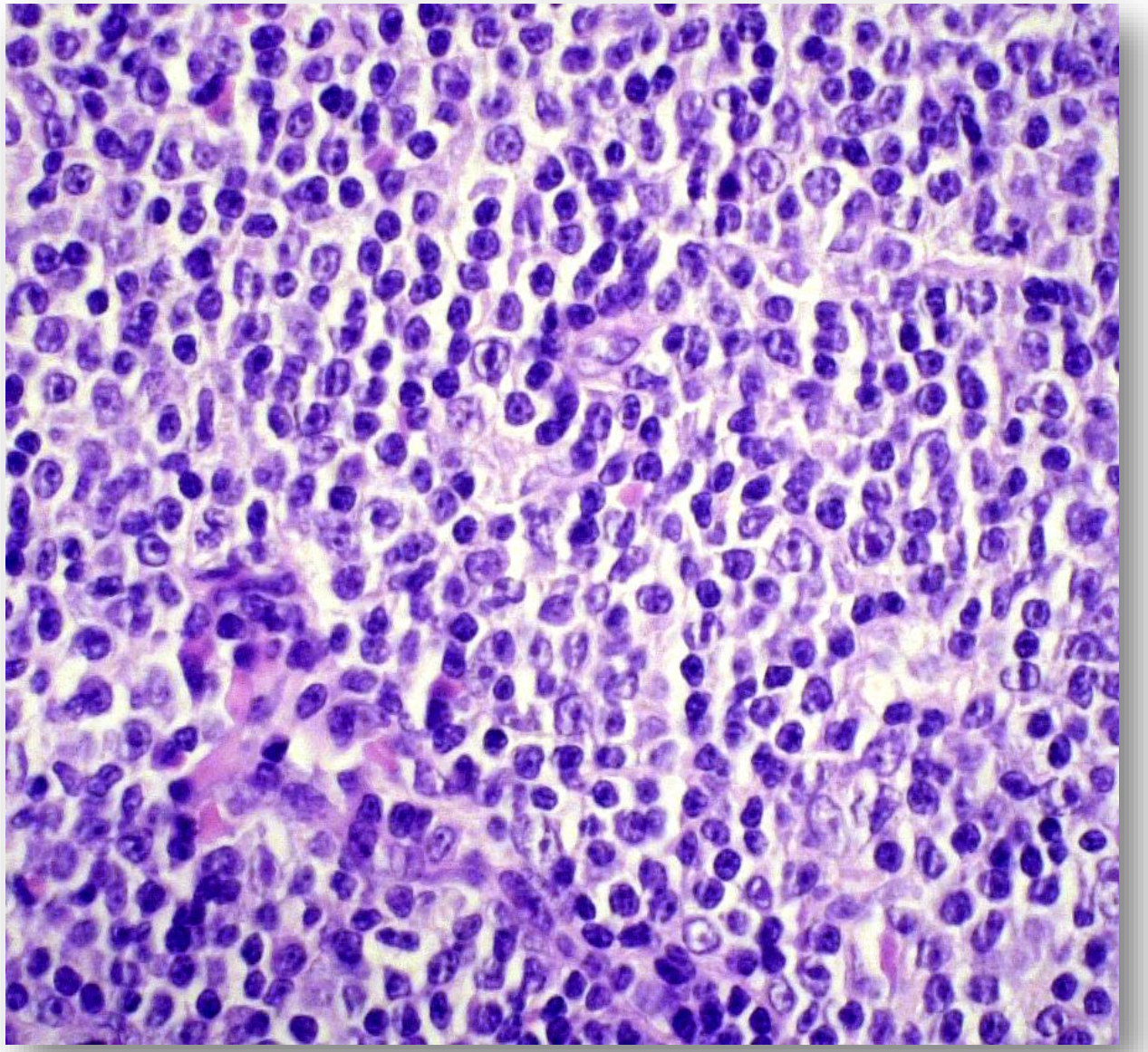
Bedeutung der Genetik

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


THE GOOD
THE BAD
AND
THE UGLY
DIRECTED BY
SERGIO LEONE

Mantelzell – Lymphom (MCL)





MCL – prognostische Bedeutung von TP53mut

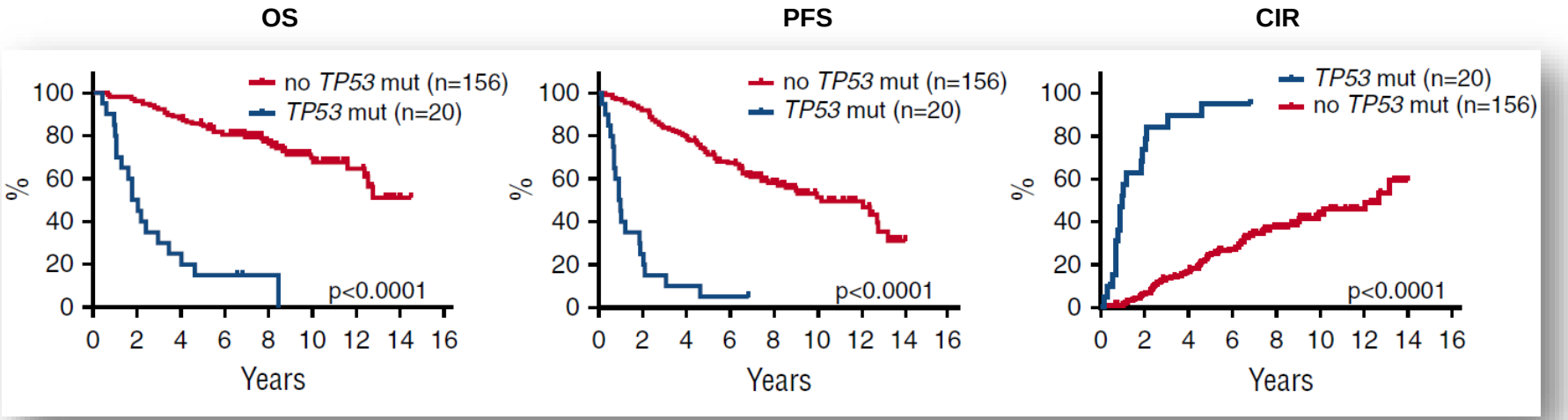


Table 2. Multivariate Cox regression analyses (n = 147)

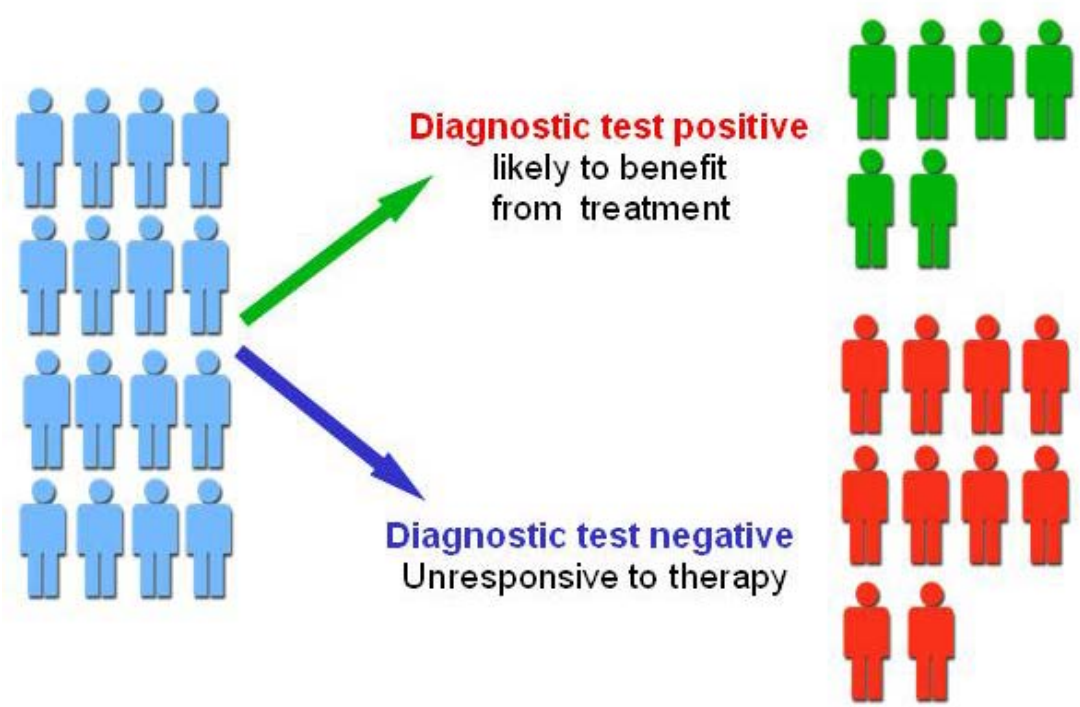
	OS			PFS			CIR		
Variables	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
mut *TP53*	6.2	(2.6-14.9)	<.0001	6.8	(3.4-13.8)	<.0001	6.9	(3.3-14.5)	<.0001
mut *NOTCH1*	2.7	(0.9-8.6)	.09	2.3	(0.9-6.3)	.10	2.2	(0.7-6.5)	.17
del *TP53*	1.4	(0.7-2.8)	.37	1.5	(0.9-2.7)	.15	1.7	(0.9-3.0)	.10
del *CDKN2A*	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 *WHSC1*†	0.8	(0.3-1.9)	.58	—	—	—	—	—	—

Ekselung et al. Blood 2017

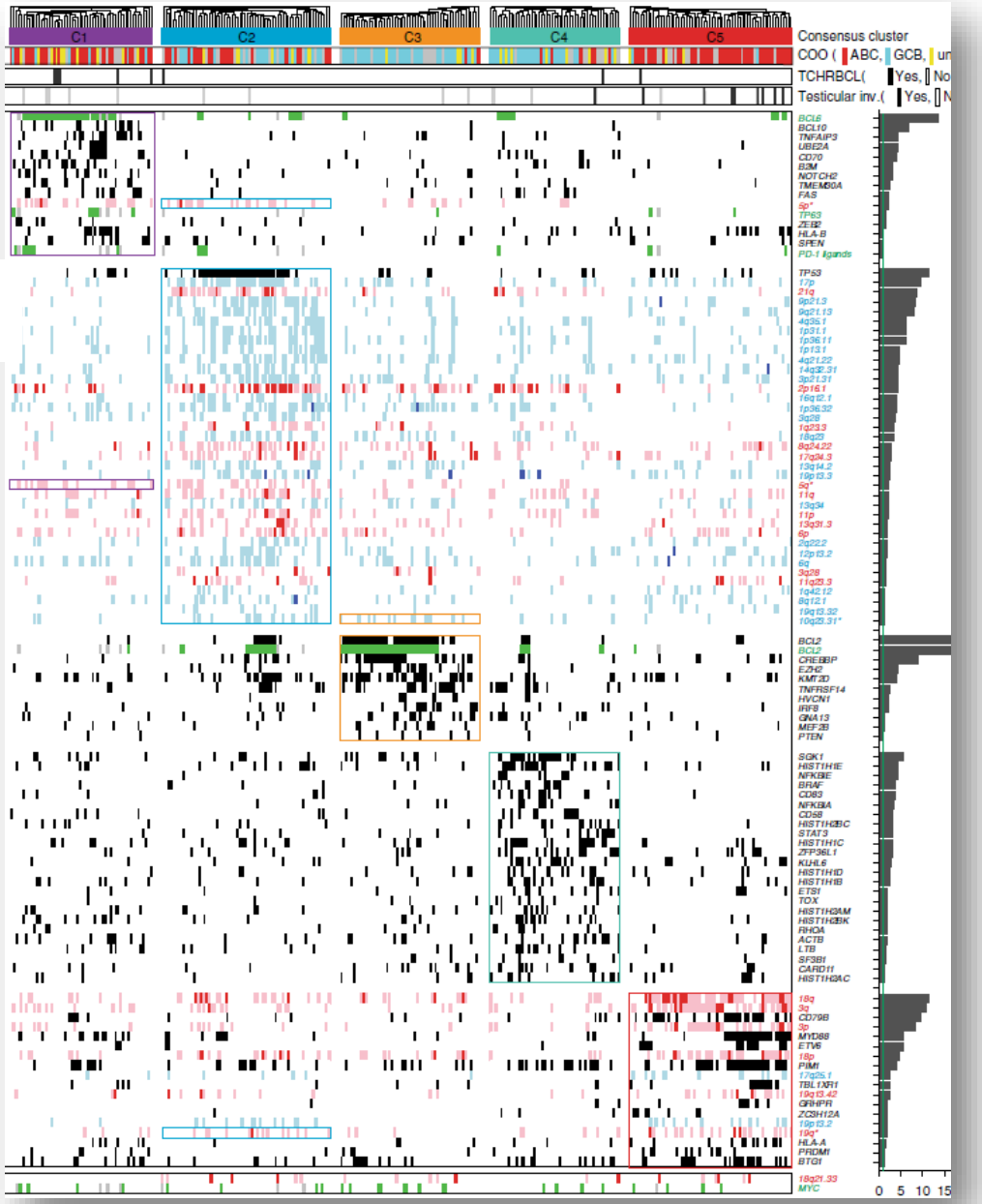
Bedeutung der Genetik

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

Prädiktive Biomarker – Analyse für personalisierte Therapie



Genetik des diffus grosszelligen B-Zell Lymphoms (DLBCL)



Chapuy et al; Nature Medicine 2018

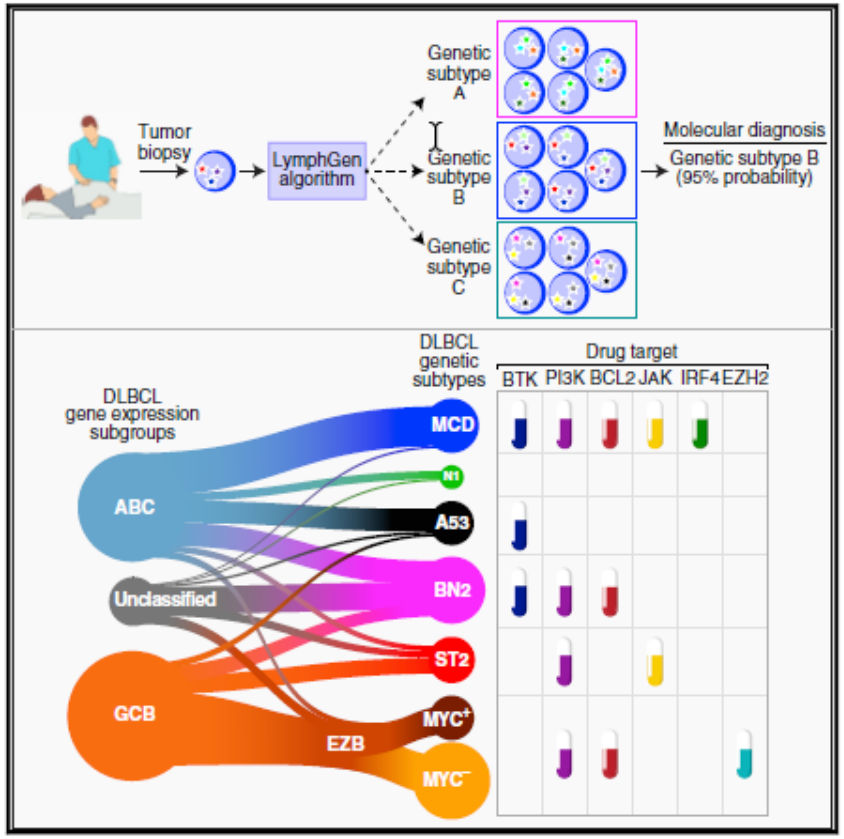
Cancer Cell

Article

2020

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

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.

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Optimization trial for diffuse large B-cell lymphoma

SAKK 38/19

Coordinating investigator

PD Dr. med. Anastasios Stathis
Istituto Oncologico della Svizzera Italiana (IOSI)
+41 91 811 89 31

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 cher
lymphoma →
HD 21

Optimization of
HOVON 127/ SAKK 37/

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

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