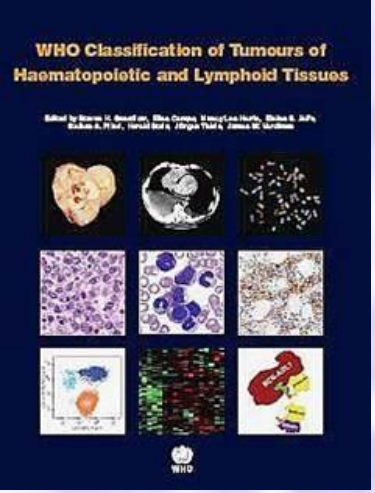


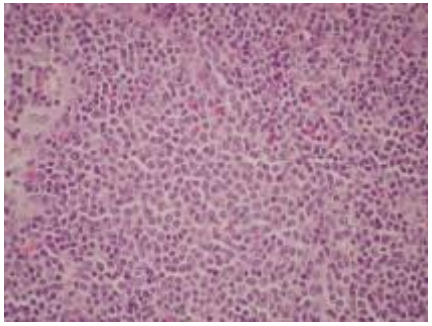
The history of lymphoma classification, the WHO 2008, and beyond!!!

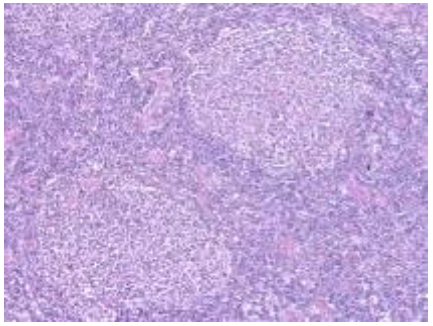
A journey from morphology to a multidisciplinary view

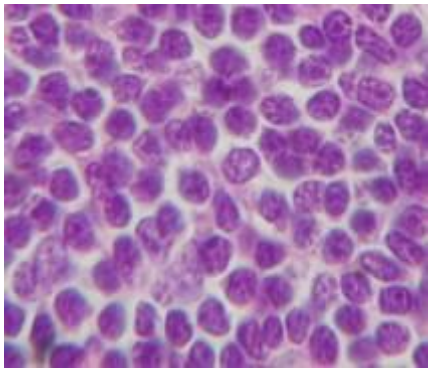
Elias Campo

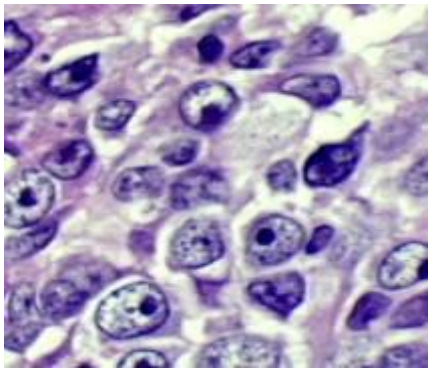
Hospital Clinic, University of Barcelona

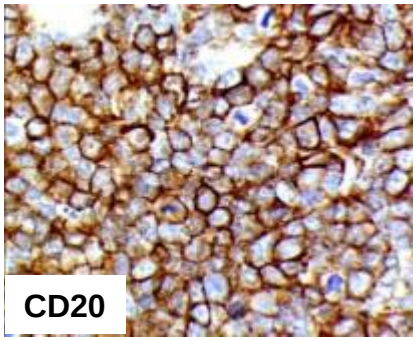
Heterogeneity of Lymphoid Neoplasms

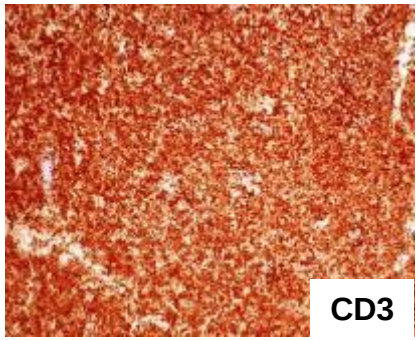


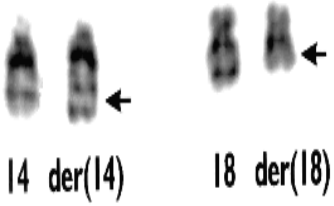


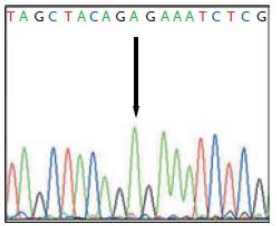


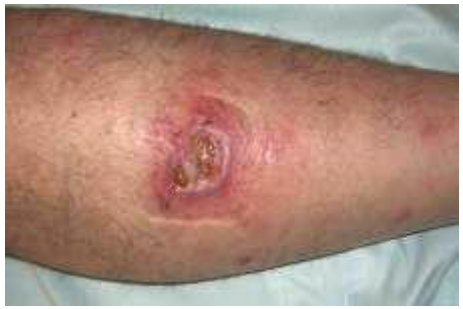


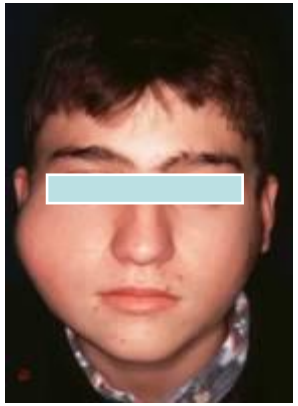


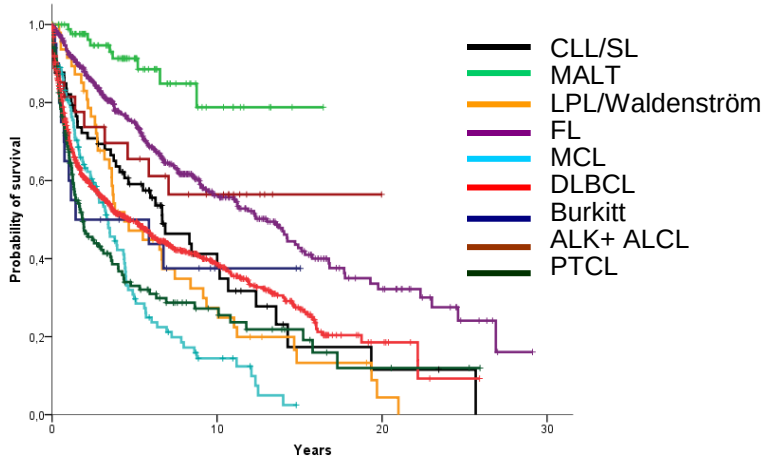








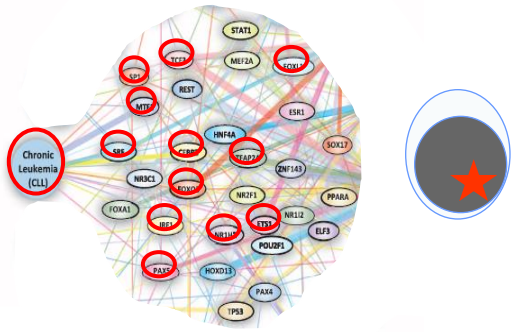




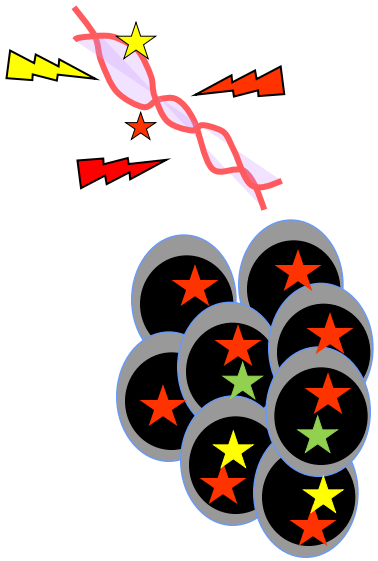
Lymphoma Pathogenesis

Integrating genetic and microenvironment interactions

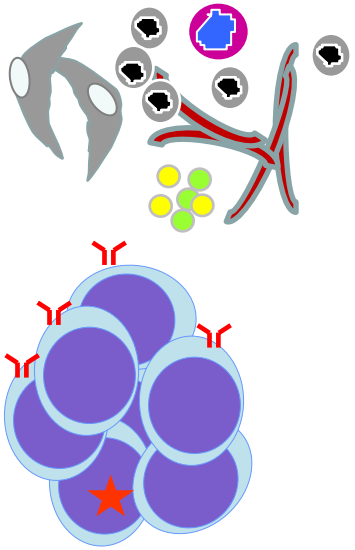
Genetic susceptibility



Somatic Genetic Alterations

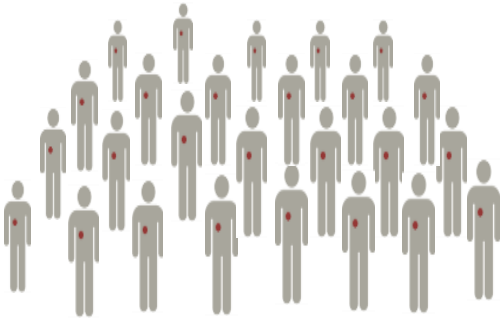


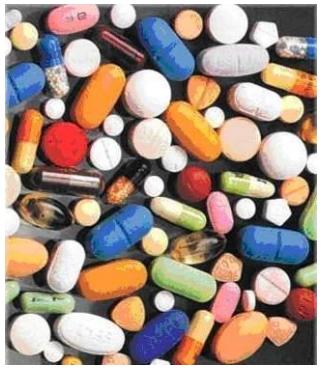
Microenvironment Interactions

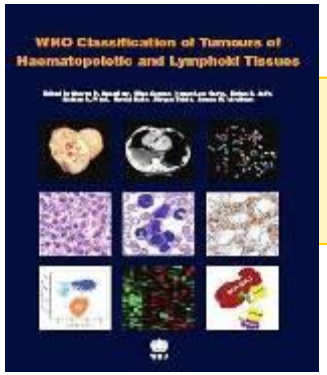


Relevance of a Precise Diagnosis

- **Epidemiological characterization**
- **Distinctive pathogenesis**
- **Clinical manifestations and evolution of the disease**
- **Different therapeutic strategies (from wait and see to very aggressive or specific target therapies)**
- **Neoplasms potentially curable**
- **Therapeutic regimens with iatrogenic risk**







WHO Classification Principles

Malignant Lymphomas as Disease Entities

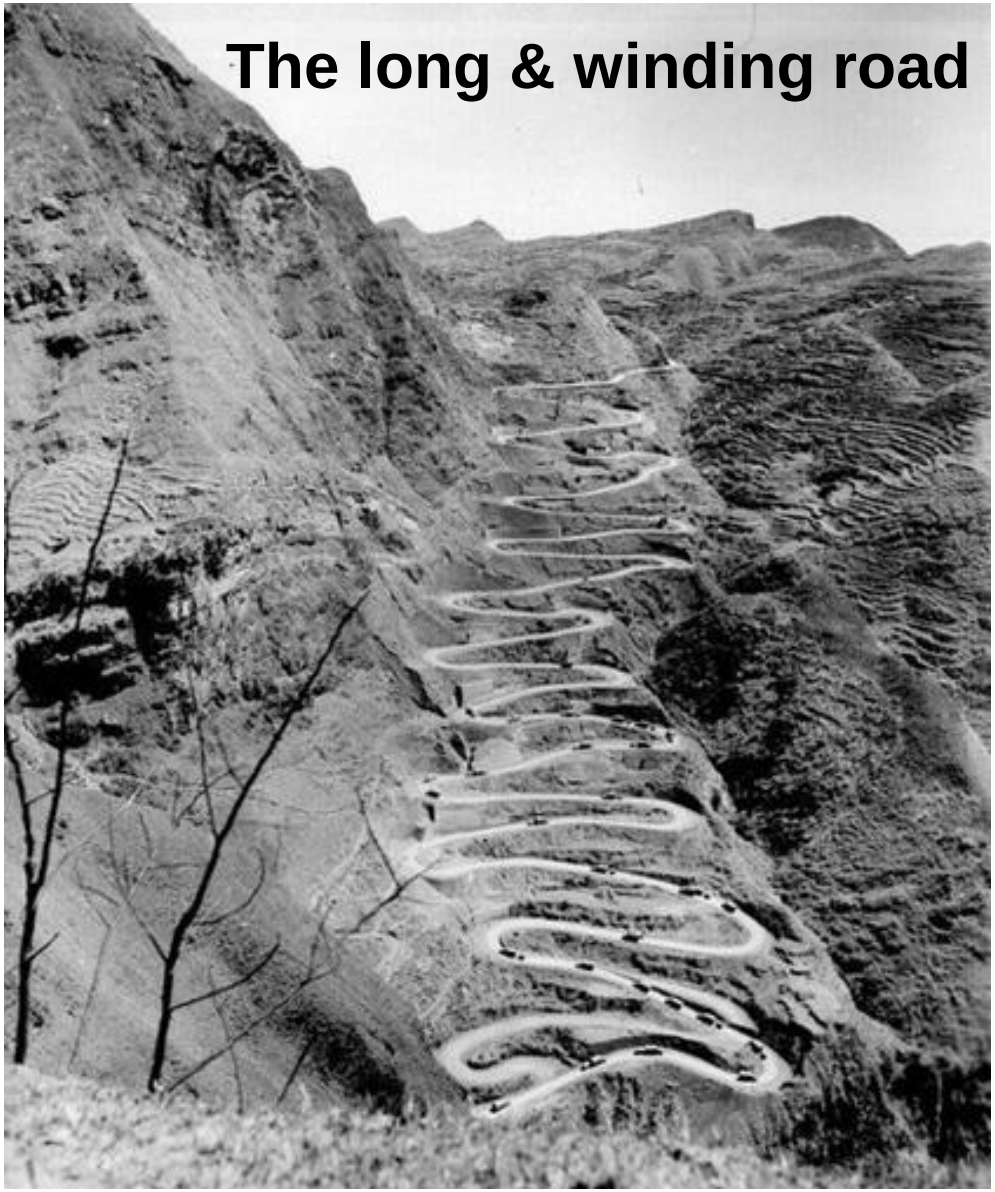
- Non-overlapping (mutually exclusive)
- Stratified according to cell lineage

Morphology
Phenotype
Genetic
Molecular alterations

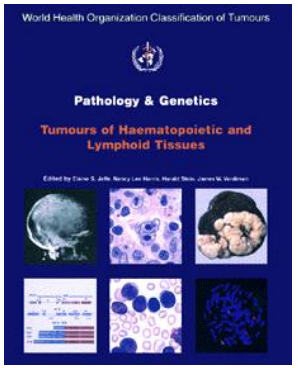
→

Epidemiology
Etiology
Pathogenesis
Clinical presentation
Evolution
Prognostic parameters
Therapy

Lymphoma Classification: The history



Courtesy of Dr S Swerdlow



Building consensus
(1994-2001)

The REAL Classificaition

The NHL Project

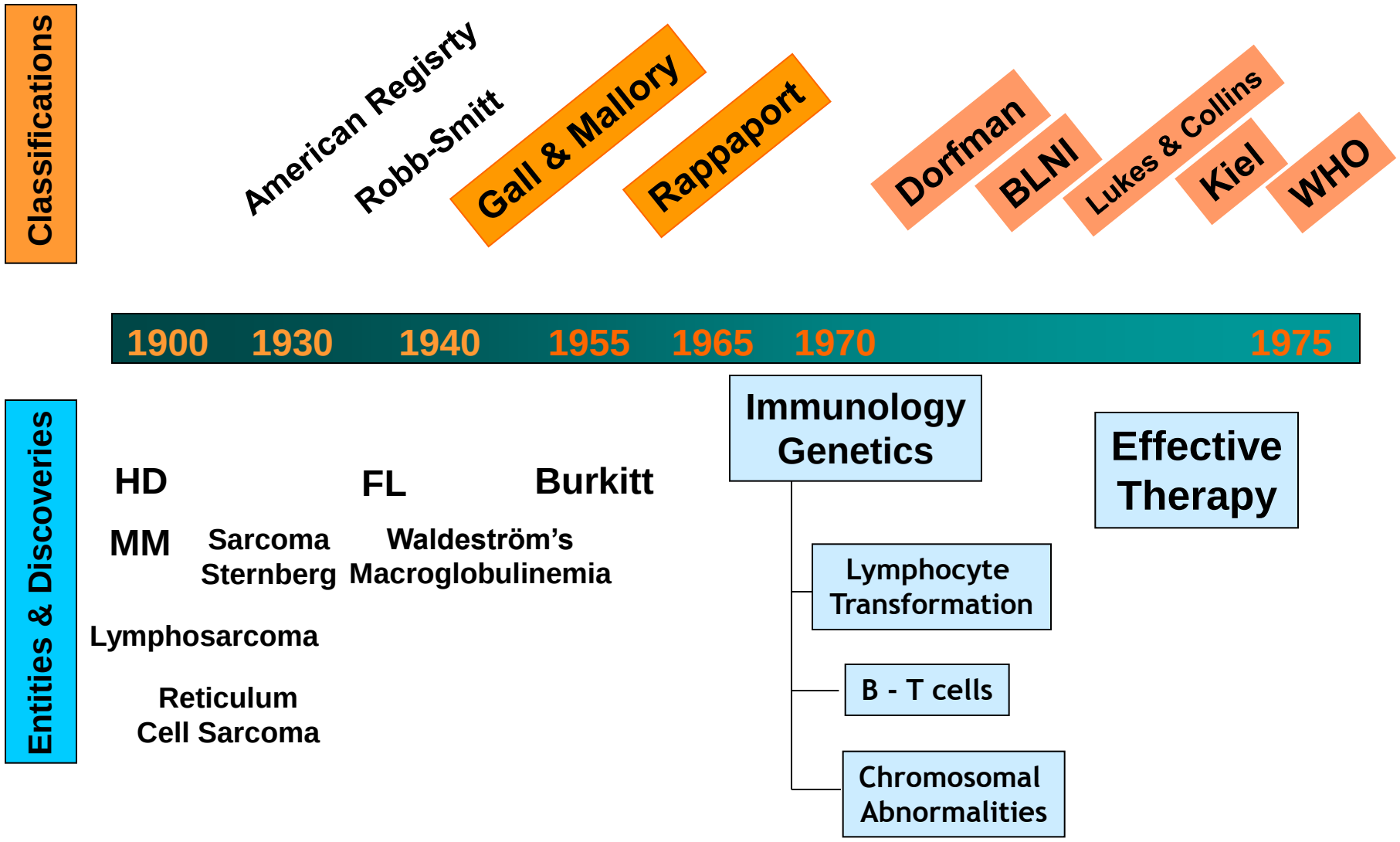
The great divide
(1975-1994)

Morphology vs Functional view

The early days
(<1975)

Morphology

Lymphoma Entities, Basic Discoveries, and Classifications



NIH Meeting in Airlie, VA (1975) of clinicians and Hematopathologists who had proposed classifications.

"No consensus"

Morphological Perspective

National Cancer Institute Sponsored Study of Classifications of Non-Hodgkin's Lymphomas

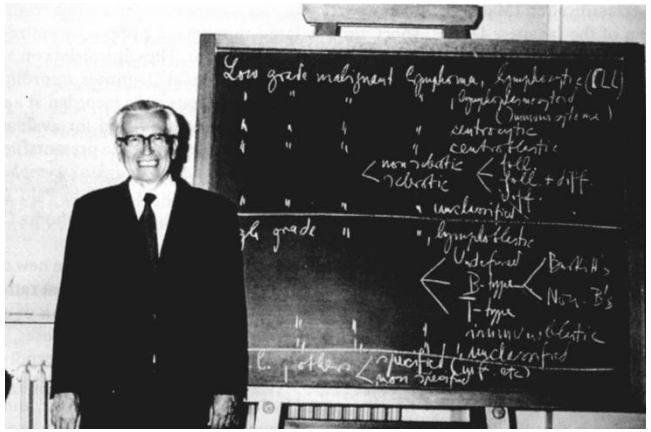
Summary and Description of a Working Formulation for Clinical Usage

THE NON-HODGKIN'S LYMPHOMA PATHOLOGIC CLASSIFICATION PROJECT*

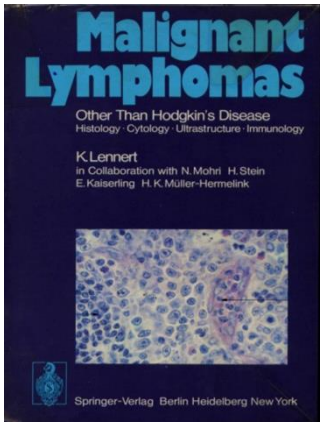
1982

Functional Perspective

Lukes, USA

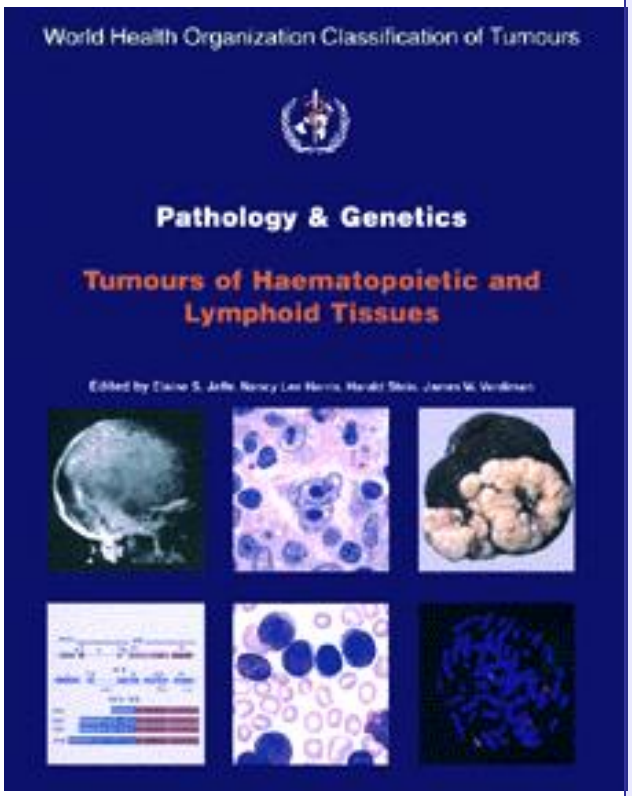


Lennert/Kiel




Poznan, Poland

WHO Classification: Hematologic Neoplasms



- **"REAL" Classification (ILSG, 1994)**
  - List of Clinicopathologic Entities
  - Cell lineage and Differentiation
  - Integration of Morphological, Immunological, Genetic, Molecular and Clinical Information
- **NHL Classification Project (1999)**
  - University of Nebraska
  - Pathologists and Clinicians of 9 Centers around the world
- **WHO Classification (2001/2008)**
  - The first true international consensus
  - European Association for Haemathopathology Society of Hematopathology,
  - Clinical Advisory Committee
  - > 100 Authors

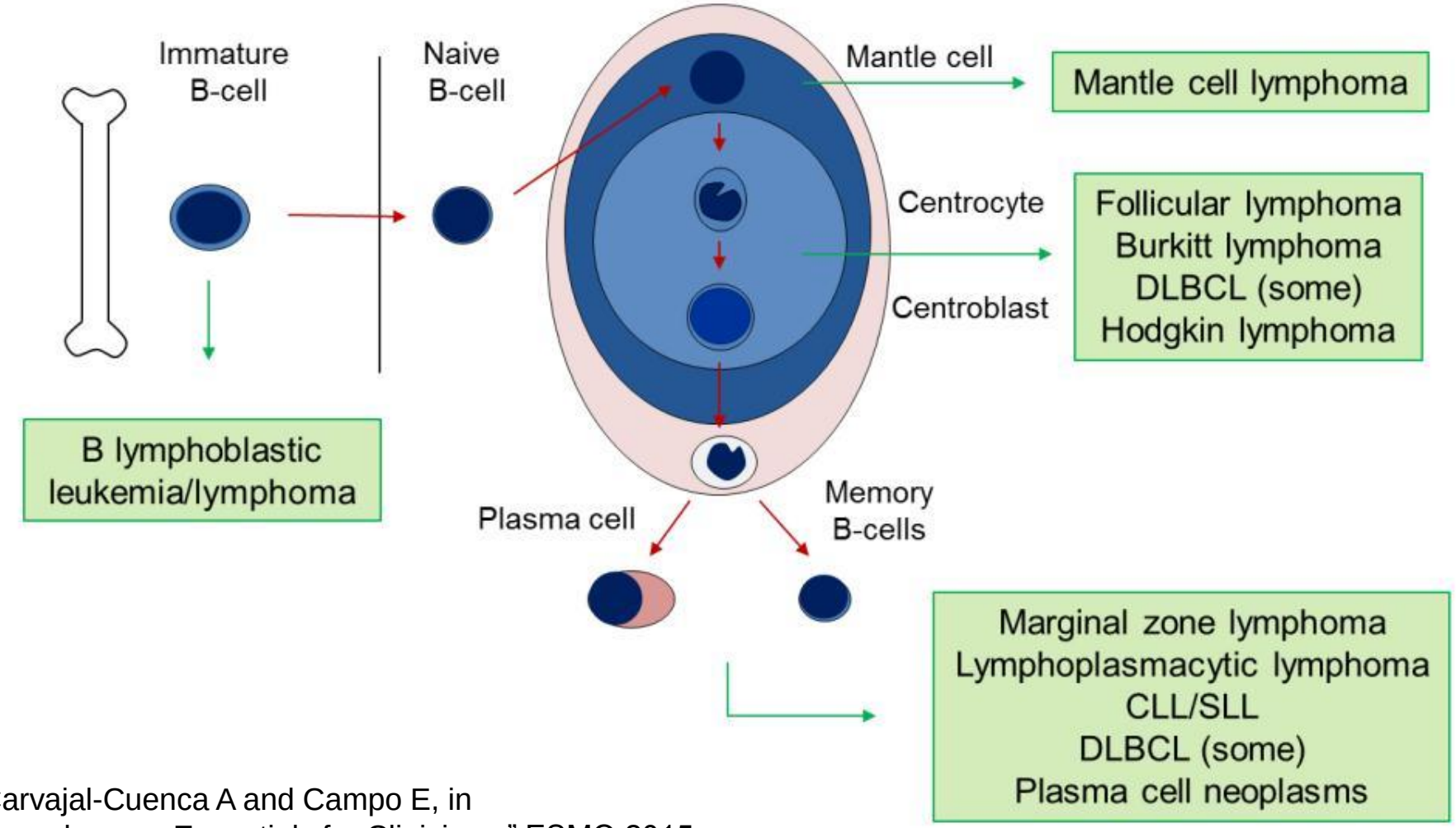
Agreement Between Referral and Final Diagnosis

Referral Diagnosis	Final Pathology Category			
	Indolent N=304	FL3 N=32	DLBCL N=299	MCL N=98
Indolent*	**296 (97%)**	4 (13%)	6 (2%)	6 (6%)
Follicular, any grade	1 (0.3%)	**29 (97%)**	1 (0.3%)	0
Diffuse large B-cell	1 (0.3%)	0	**296 (96%)**	0
Mantle cell	3 (1%)	0	1 (0.3%)	**89 (93%)**
Highly Aggressive	0	0	3 (1%)	0
Unspecified B-cell lymphoma	4 (0.2%)	0	1 (0.3%)	1 (1%)
Other Cancer	0	0	3 (1%)	0

* **CLL/SLL, FL1-2, NMZL**

LaCasce A et al J Clin Oncol 2008

Lymphomas as Malignant Counterparts of Specific Stages of Lymphocyte Maturation

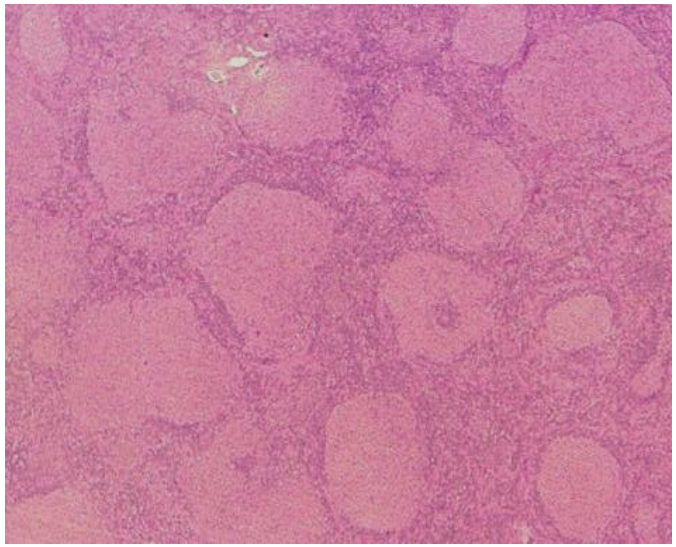


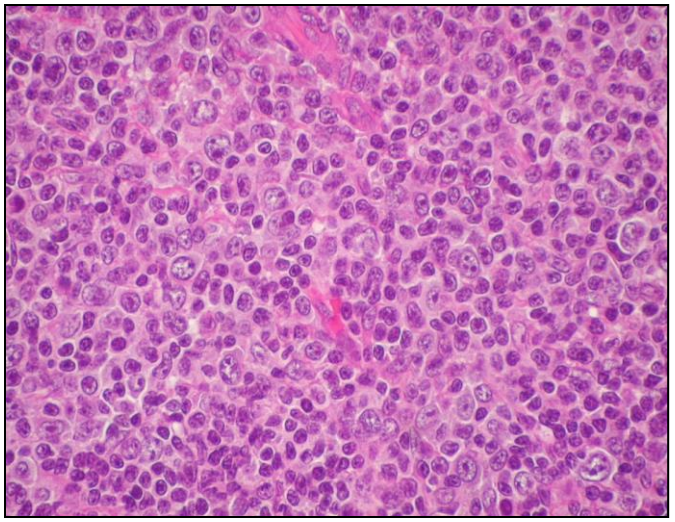
Carvajal-Cuenca A and Campo E, in
"Lymphomas: Essentials for Clinicians." ESMO 2015.

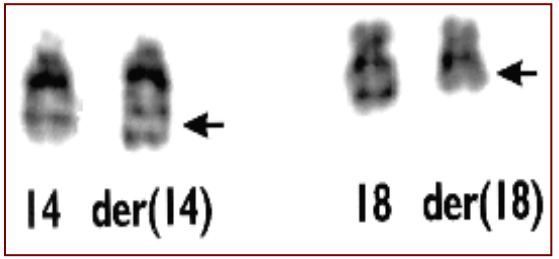
WHO Classification - 2008 and beyond

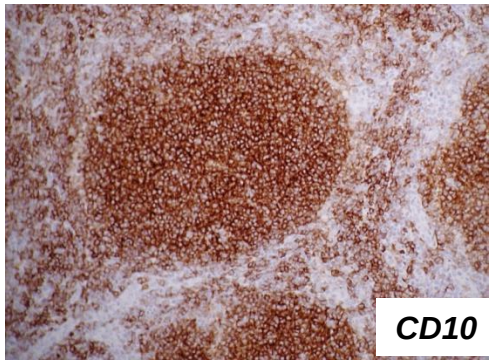
- **Diagnostic criteria**
  - **Morphology**
  - **Phenotype**
  - **Clinical Criteria**
  - **Molecular**
  - **Infectious agents**
- **Early steps in lymphoid neoplasms**
- **Categories with overlapping features between entities**
- **Introducing Precision Medicine**

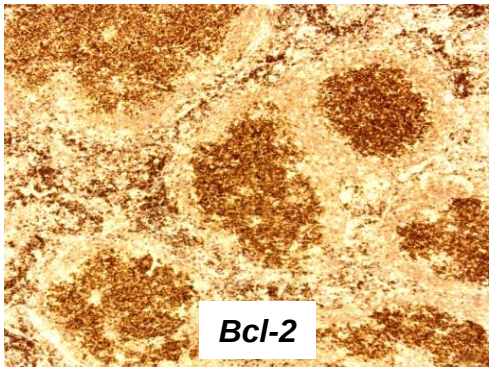
Follicular lymphoma

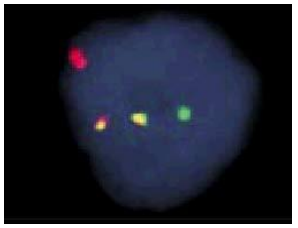










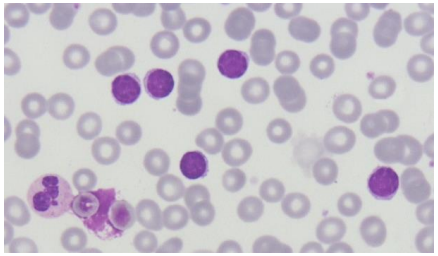


Expert Pathologist Agreement With the Consensus Diagnosis

Consensus Diagnosis	Dx 1* (%) Histology	Dx 2-1 (%)	Dx2 (%) + Phenotype	Dx 3-2 (%)	Dx 3 (%) Clinical Data
Follicular, any grade	93	1	94	0	94
Marginal zone B-cell, MALT	84	2	86	0	86
Small lymphocytic (CLL)	84	3	87	0	87
Lymphoplasmacytoid	53	3	56	0	56
High grade B-cell, Burkitt-like	47	6	53	0	53
Primary mediastinal large B-cell	51	7	58	37	85
Marginal zone B-cell, nodal	55	8	63	0	63
Mantle cell	77	10	87	0	87
Diffuse large B-cell	73	14	87	0	87
Precursor T-lymphoblastic	52	35	87	2	89
Anaplastic large T/null-cell	46	39	85	0	85
Peripheral T-cell, all types	41	45	86	0	86

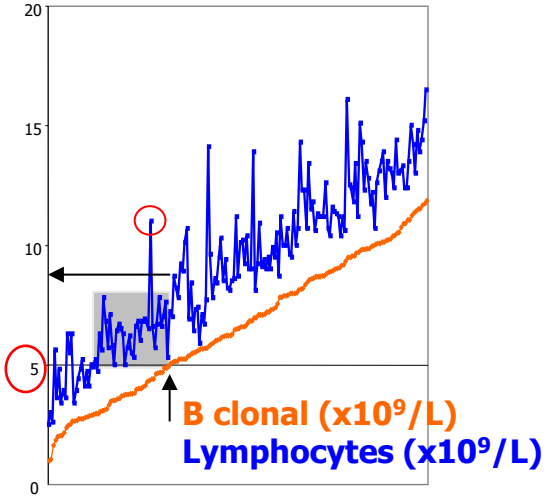
NHL project, Blood 1997; 89: 3909-3918

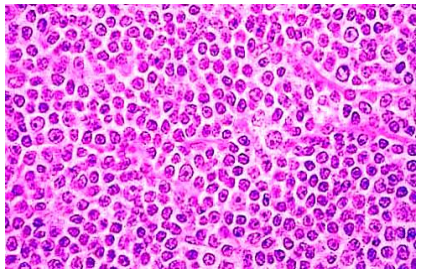
"Phenotype an numbers as diagnostic criteria"
Chronic Lymphocytic Leukemia



- **Current definitions (> 5 x10^9/L monoclonal lymphocytes with the CLL phenotype)**

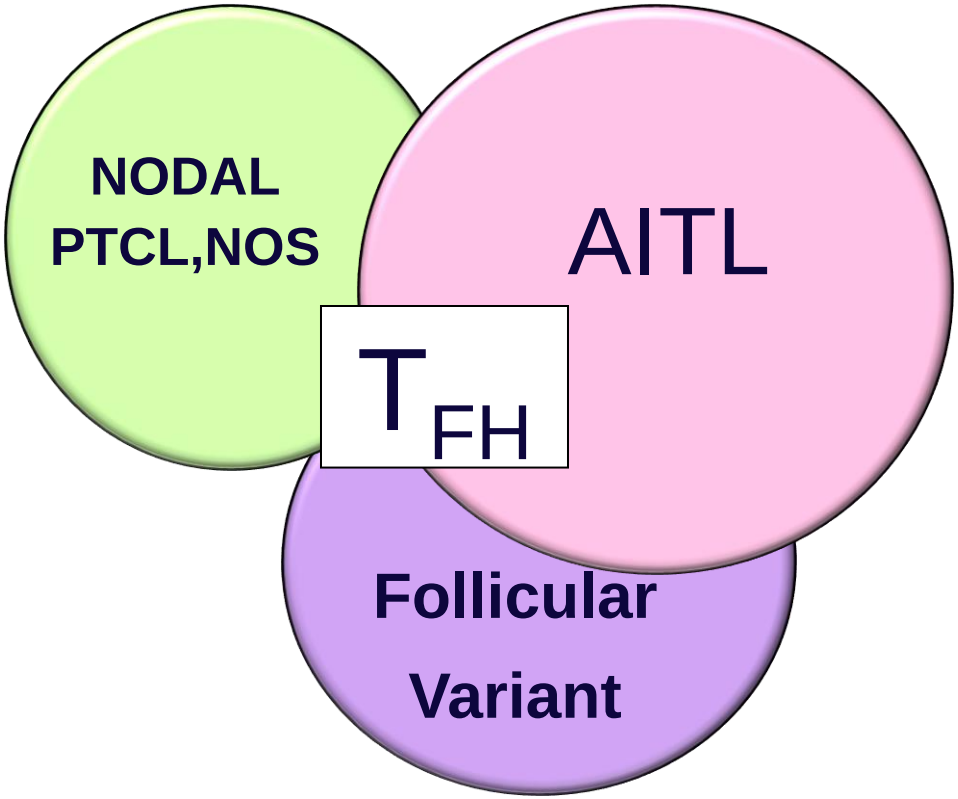
- **SLL is the same disease but restricted to tissues of non-leukemic (< 5 x10^9/L) patients without cytopenias**





WHO 2008

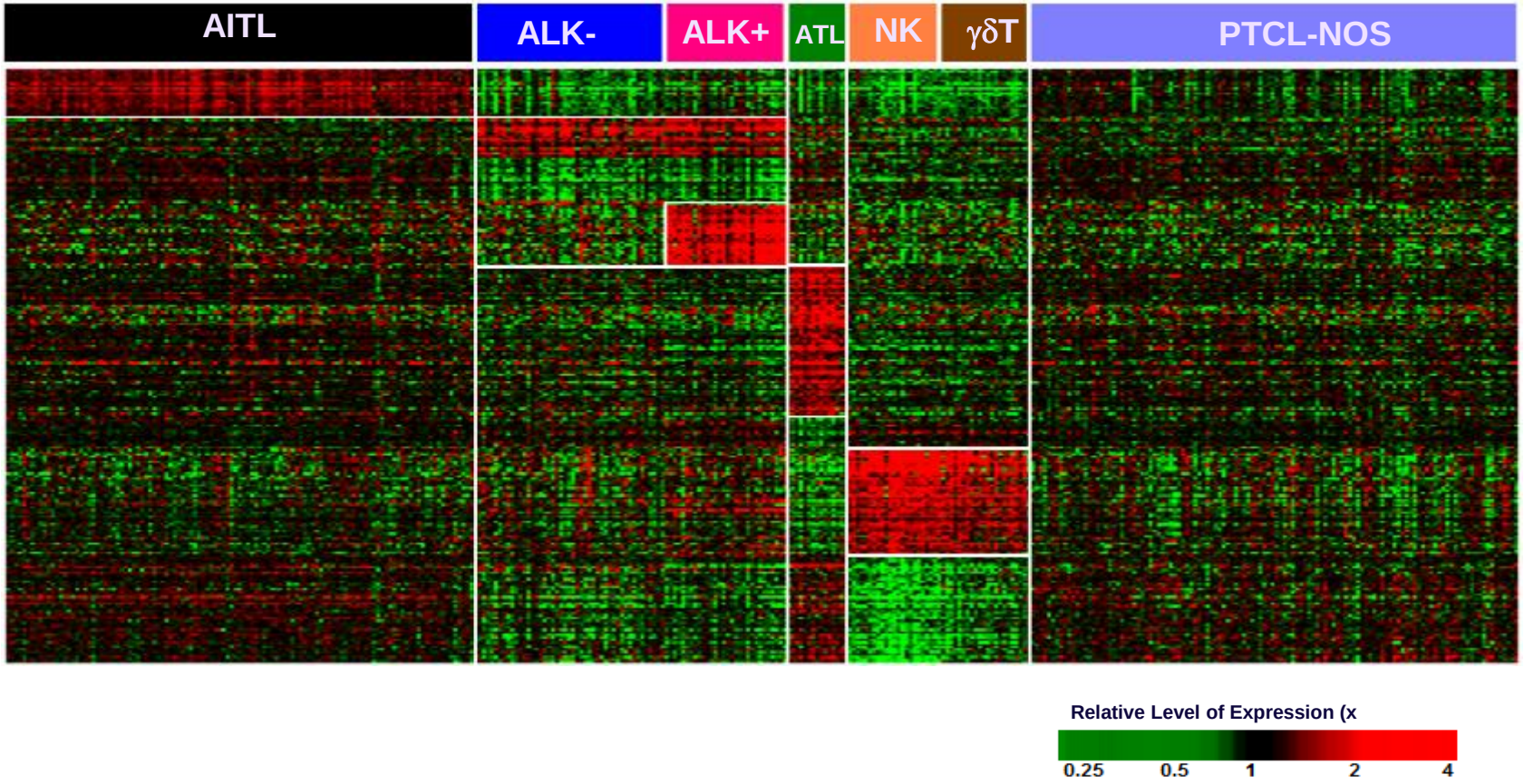
Nodal Peripheral T-cell Lymphomas of TFH Origin



- **CD10**
- **CXCL13**
- **PD1**
- **ICOS**
- **BCL6**

- Gene expression profiling and mutation analysis has helped to clarify the interrelationship among nodal T-cell lymphomas of TFH origin

Gene expression profiling allowed reclassification of 14% of PTCL, NOS as AITL

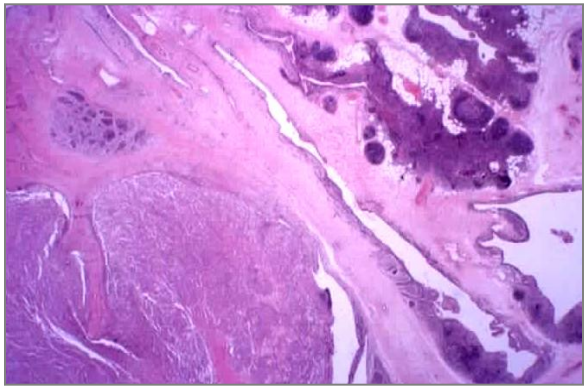


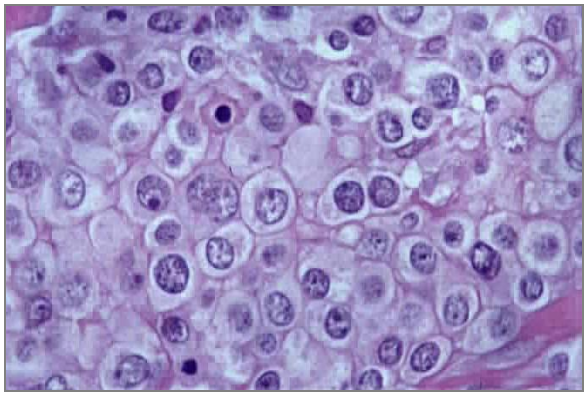
Gene expression signatures of PTCL ; Iqbal et al. *Blood 2014*

Clinical criteria in diagnosis

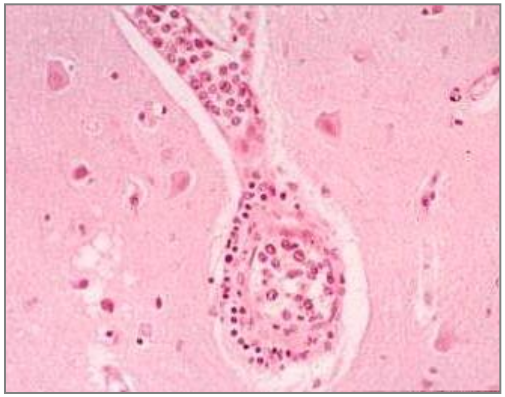
DLBCL Topographic site

Primary mediastinal

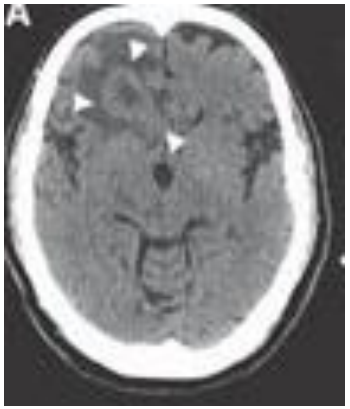


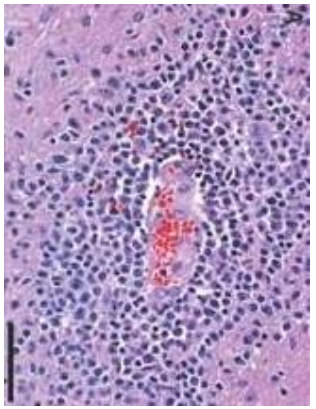


Intravascular

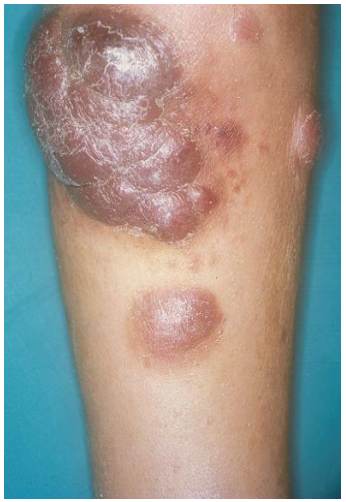


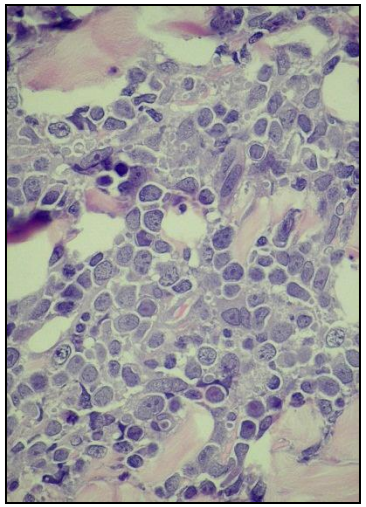
Primary CNS



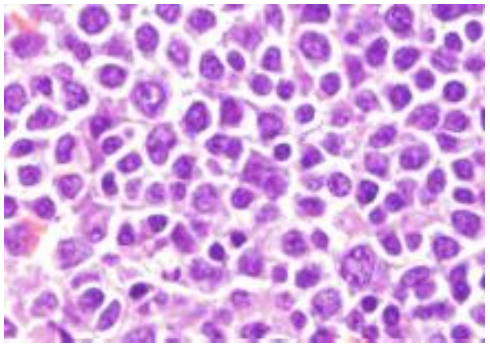


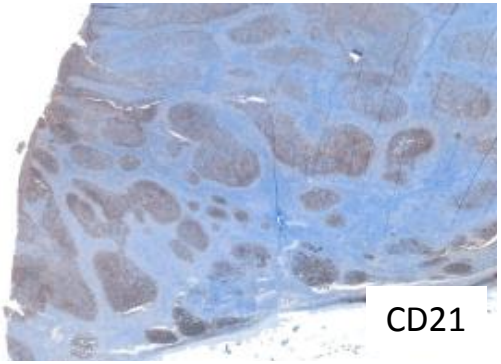
Primary cutaneous DLBCL, leg type

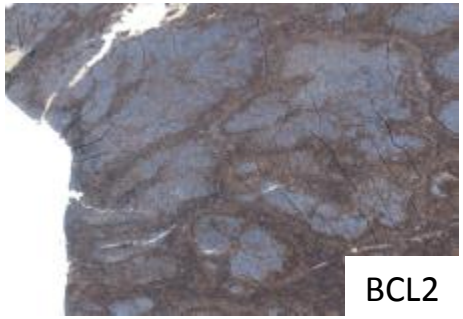




Pediatric lymphomas (come of age)
Follicular Lymphoma Pediatric Type







- Children and young adults
- Striking male predominance
- Nodal presentation, head and neck

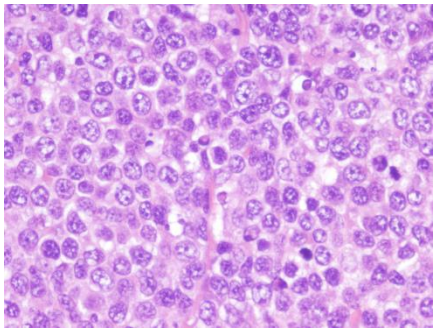
- Grade 3, blastic
- No diffuse areas
- High proliferation rate

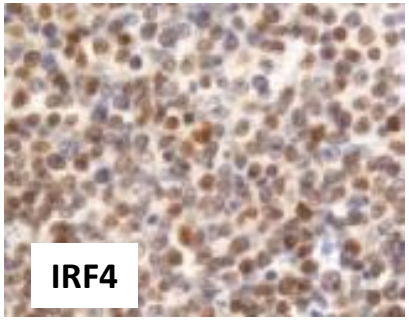
- Lack of t(14;18)

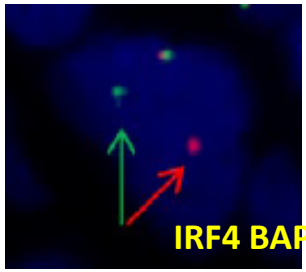
- Excellent prognosis
- Local therapy / Watch & wait recommended

Liu Q et al Am J Surg Pathol. 2013;37:333-43
Louissaint A Jr et al Blood. 2012, 120:2395-404

"Large B-cell lymphoma with IRF4 rearrangement"







- New provisional entity segregated from other pediatric FL

- Waldeyer´s ring, head and neck nodal, bowel presentation
- Most commonly in children/young adults

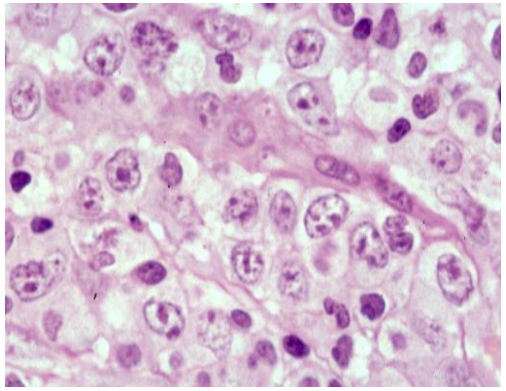
- Follicular and diffuse areas with grade 3
- Germinal center phenotype (CD10/BCL6)
- BCL2 expression but no t(14;18)

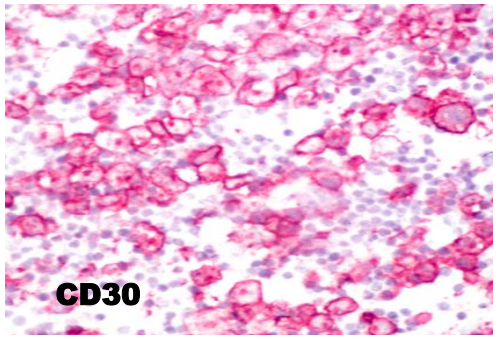
- Strong IRF4 expression and *IRF4* translocation
- Cases without the genetic alteration may be detected
- Treatment is often required

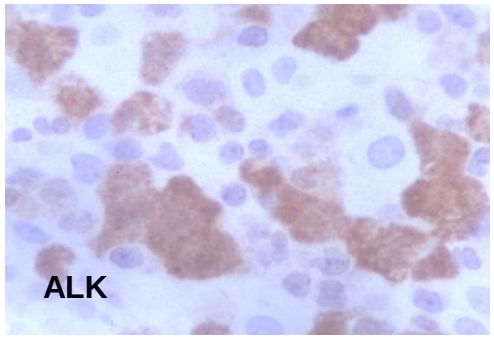
Salaverria I et al Blood 2011;118:139-47; Liu Q et al Am J Surg Pathol. 2013;37:333-43

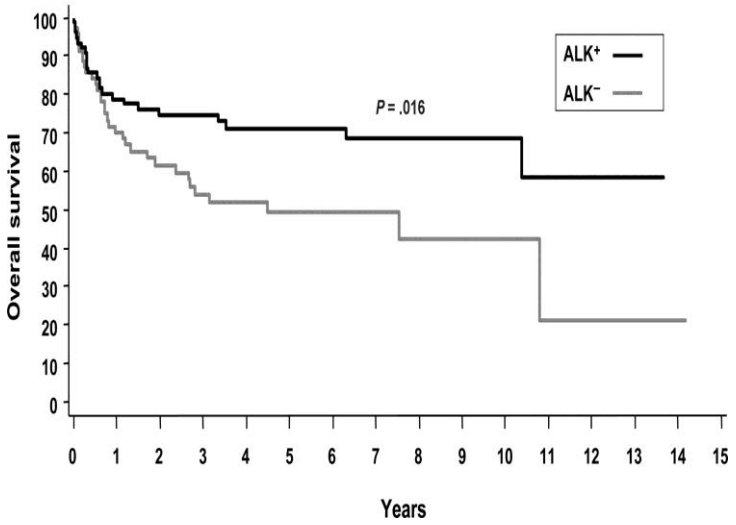
Molecular Definition of entities

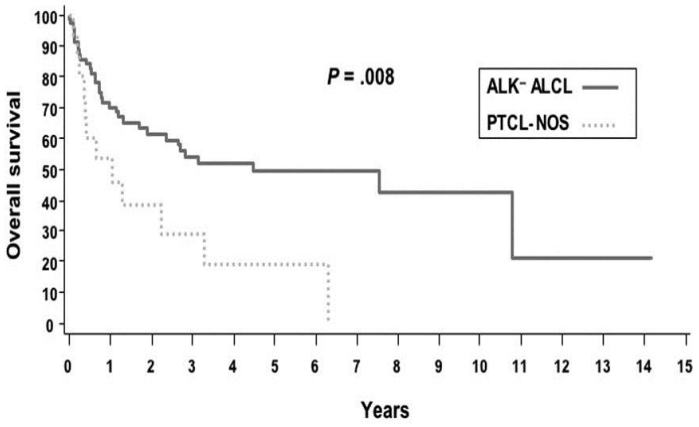
ALK + and ALK – ALCL are Different Entities

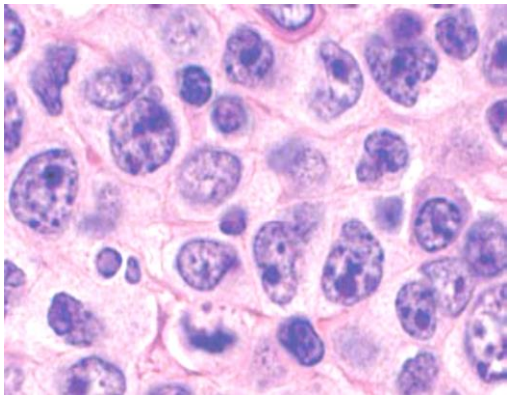


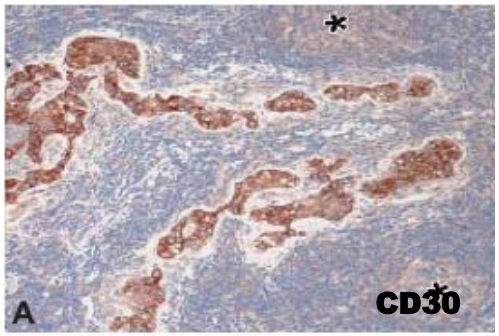


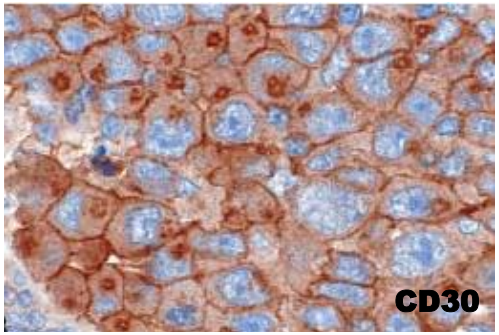






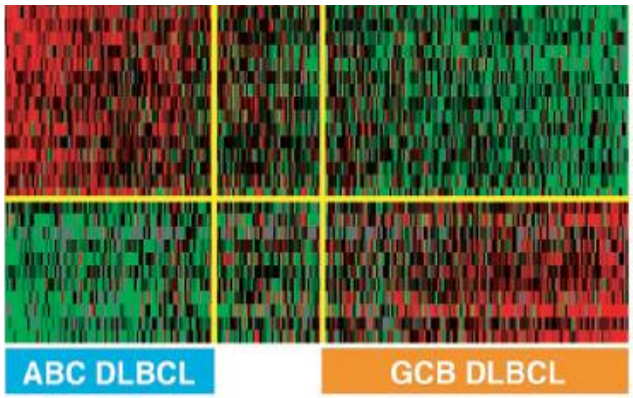




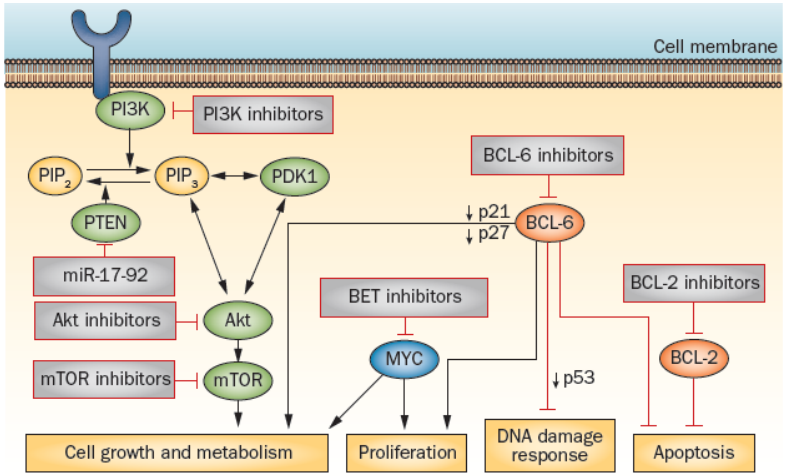


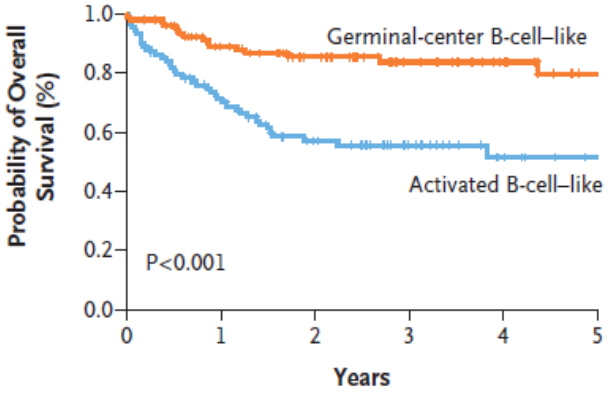
Savage K J et al. Blood 2008;111:5496-5504

Molecular Subtypes of DLBCL

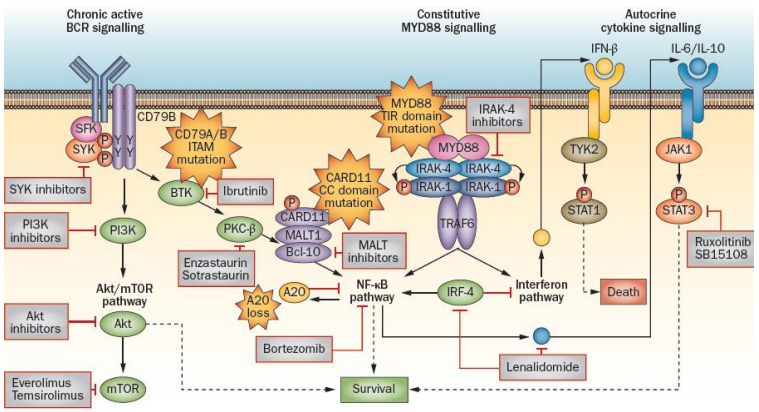


GCB



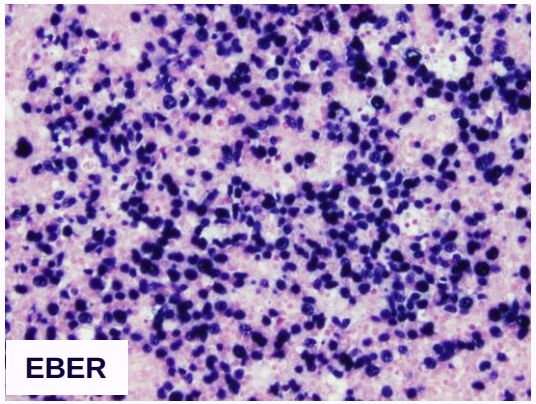


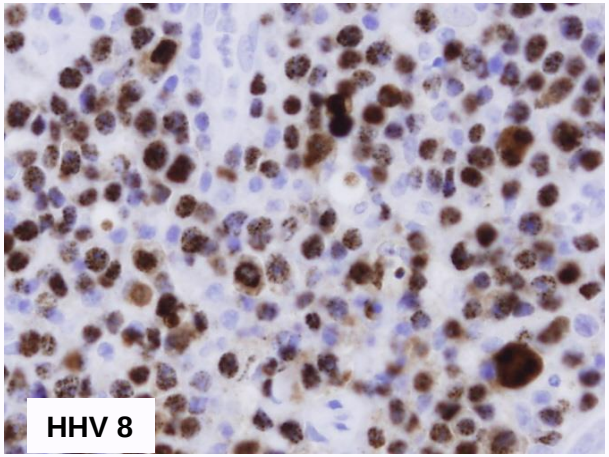
ABC



- **Acceptance (reluctantly) that, even if imperfect, IHC methods can be used for the diagnosis (Hans algorithm remains the most popular).**
- **Molecular methods for FFPE tissues on the horizon.**

Lymphoma entities related to Infectious agents





EBV+ Lymphoid neoplasms

- EBV + DLBCL of the elderly
- Extranodal NK/T-cell lymphoma, nasal type
- Epstein-Barr virus (EBV) positive T-cell lymphoproliferative diseases of childhood

HHV8+ associated lymphoid neoplasm

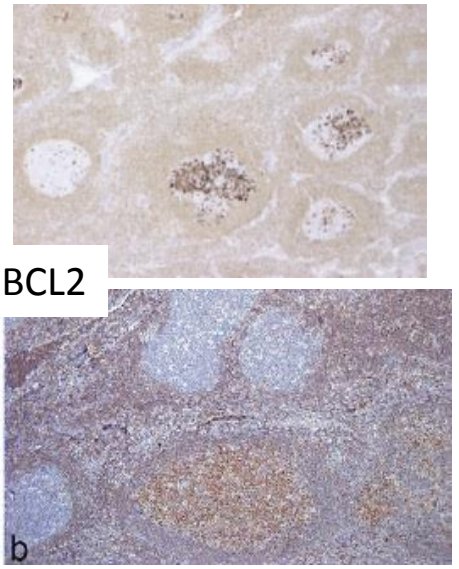
- Primary effusion lymphoma
- HHV8 positive DLBCL, NOS

Oyama T et al Am J Surg pathol 2003
Park S et al Blood 07, Hofscheier A et al Blood 2011

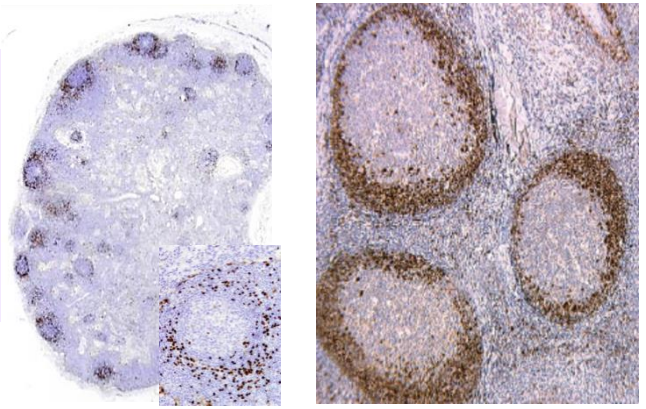
Early steps in Follicular and Mantle cell Lymphoma

"In Situ" and early involvement lesions

- **"in situ" follicular "neoplasia"**
  - Incidental finding
  - Low incidence of progression (<5%)
  - Need to exclude systemic lymphoma
- **Partial involvement by FL**
  - Stages I and II
  - 50% progress to overt FL

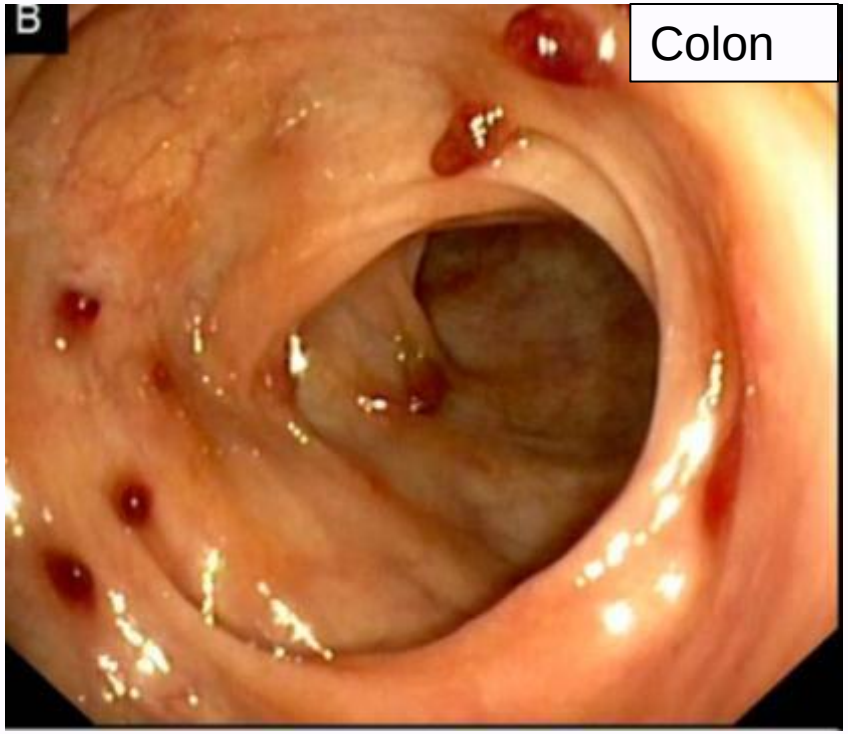


- **"in situ" mantle cell "neoplasia"**
- **Mantle zone MCL**
  - progress to overt FL



Adam P et al AJSP 2005, Carvajal-Cuenca et al Haematologica 2012
Jegalian AG et al Blood 2011
Mamessier E et al Haematologica 2014; 99: 802–810

Indolent T-cell Lymphoproliferative diseases of low malignant potential



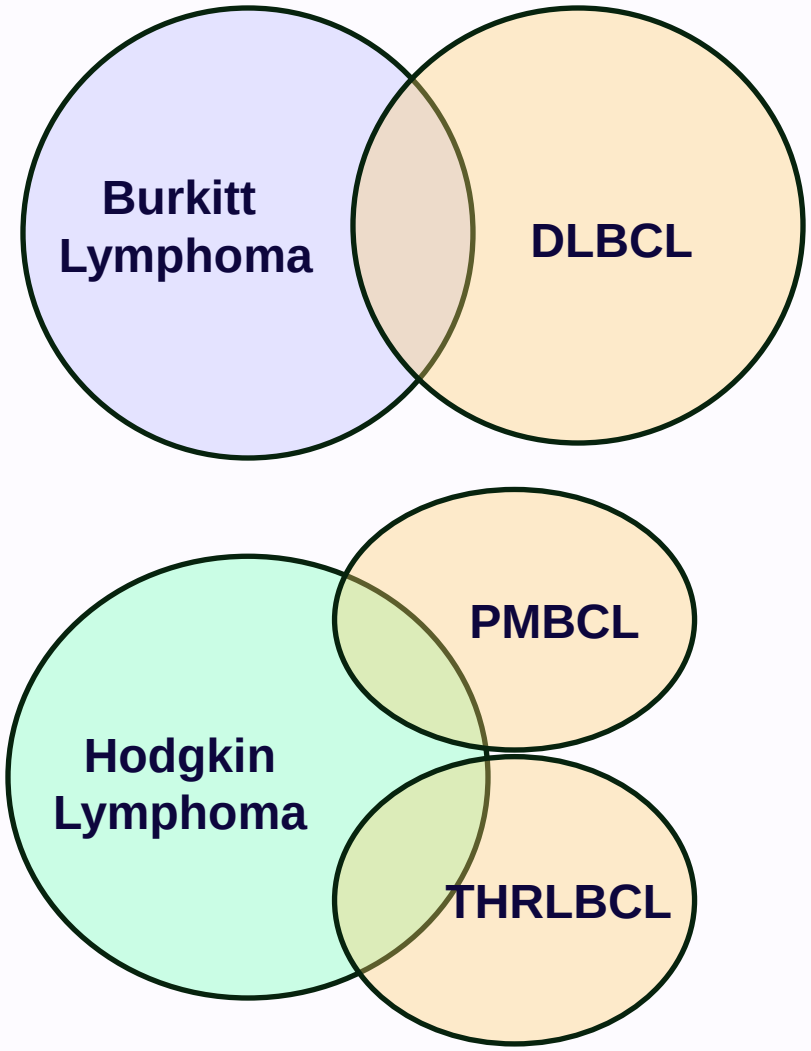
Multiple mucosal polyps
Can affect entire GI Tract

Most common in:
- small intestine
- colon

Less often:
- stomach
- oral mucosa

Perry et al., Blood 2013, Indolent T-LPD of the GI Tract

Gray Zone Lymphomas in the WHO Classification



- Recognition of biological and pathological continuum in certain entities
- Not a single criteria recognizes these categories
- Not specific entities, but working categories that need further studies
- Keep purity of well defined entities
- Challenging for clinical management. BL, HL and DLBCL protocols differ substantially

Human Genome Project

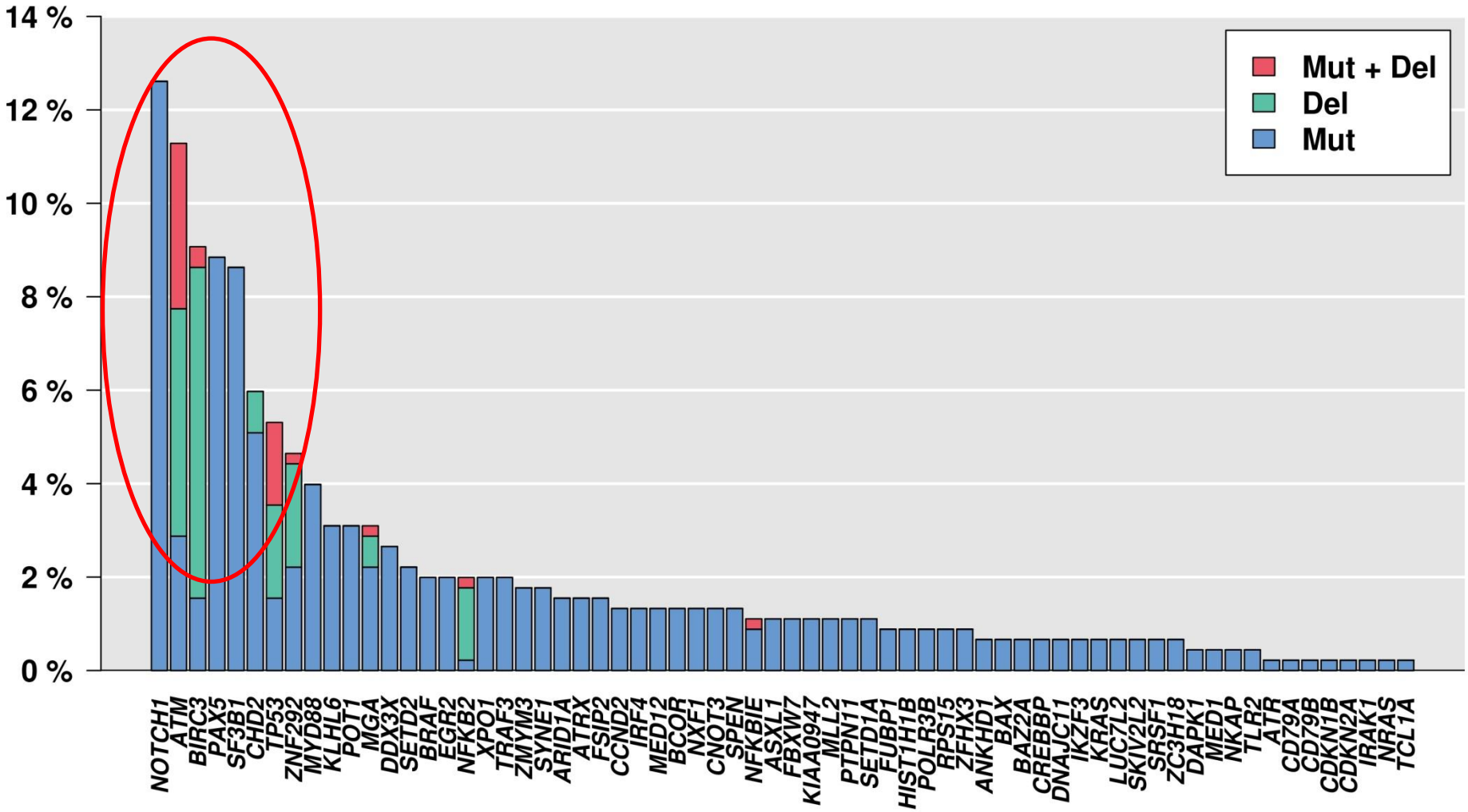
Towards a personalized medicine

Diagnostic value of somatic mutations in mature samll B-cell lymphoid neoplasms

Hairy Cell Leukemia	***BRAF* V600E**	**79-100% HCL** 4% Plasma cell myeloma 3% NHL (Other BRAF mut)
HCL-v **HCLc IGHV4-34**	***MAP2K1***	**50% HCLv** **50% HCLc IGHV4-34** 0% HCL BRAFmut
Waldenstrom M/LPL	***MYD88* L265P**	**90% WM** 29% DLBCL-ABC 6% MZL 3% CLL

Tiacci et al NEJM 2011 Ngo Nature 2011; Puente Nature 2011;
Xi L et al Blood 2012; Xu et al ASH 2011; Hunter Z et al ASH 2011;Waterfall Nat Genet 2014

Somatic Mutations and CNA in CLL and MBL (Whole genome/exome sequencing)



Puente X et al Nature 2015

Recurrently Mutated Pathways in Lymphoid Neoplasms

Pathway	U-CLL	M-CLL	MCL	FL GCB	ABC	BL	SMZL	HCL
BCR-signaling					+			
NFkB			+		+		+/-	
Chromatin Remodeling	+/-		+	+	+/-			
MLL2			+	+	+			
TLR/MYD88		+/-			+			
DNA-damage	+		+					
NOTCH1/2	+	+/-	+	+/-	+/-		+	
SF3B1	+	+/-						
ID3						+		
BRAF								+

Clinical Relevance of Mutational Profiles in Lymphoid Neoplasms

- **Diagnostic criteria to refine entities**
- **Identification of subsets of patients**
- **Prognostic and predictive significance**
- **Monitoring disease evolution: Dynamic evolution of mutational landscape**
- **Targets for therapy: Actionable mutations**

Clinical Advisory Meeting, March 31-April 1, 2014