

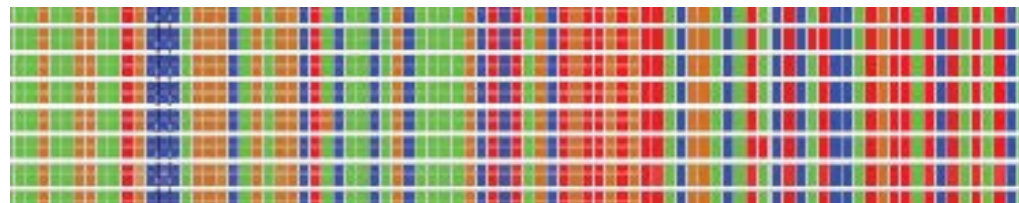
Session 5: Pre-Malignant Clonal Hematopoietic Proliferations



2017 Workshop

Molecular Genetics of Hematopoietic Neoplasms

September 7-9, 2017
Hyatt Regency Chicago
Chicago, IL



Valentina Nardi
Frank Kuo

Session 5: Pre-Malignant Clonal Hematopoietic Proliferations

- Akin to benign neoplasms in solid tumors, may represent precursors to malignancies
- 6+ entities in WHO lymphoid classification and only 1 in myeloid classification
- More widely recognized recently because of the availability of NGS-based panel testing
- Diagnostic criteria less defined
- Factors that impact risk for malignancies and other diseases are focus of research
- 27 total submitted cases (6 oral, 21 summary)
- 15 myeloid, 9 lymphoid, 3 others

Session 5: Pre-Malignant Clonal Myeloid Proliferations

- **WHO 2016**

- Transient abnormal myelopoiesis (TAM)

- **Non-WHO**

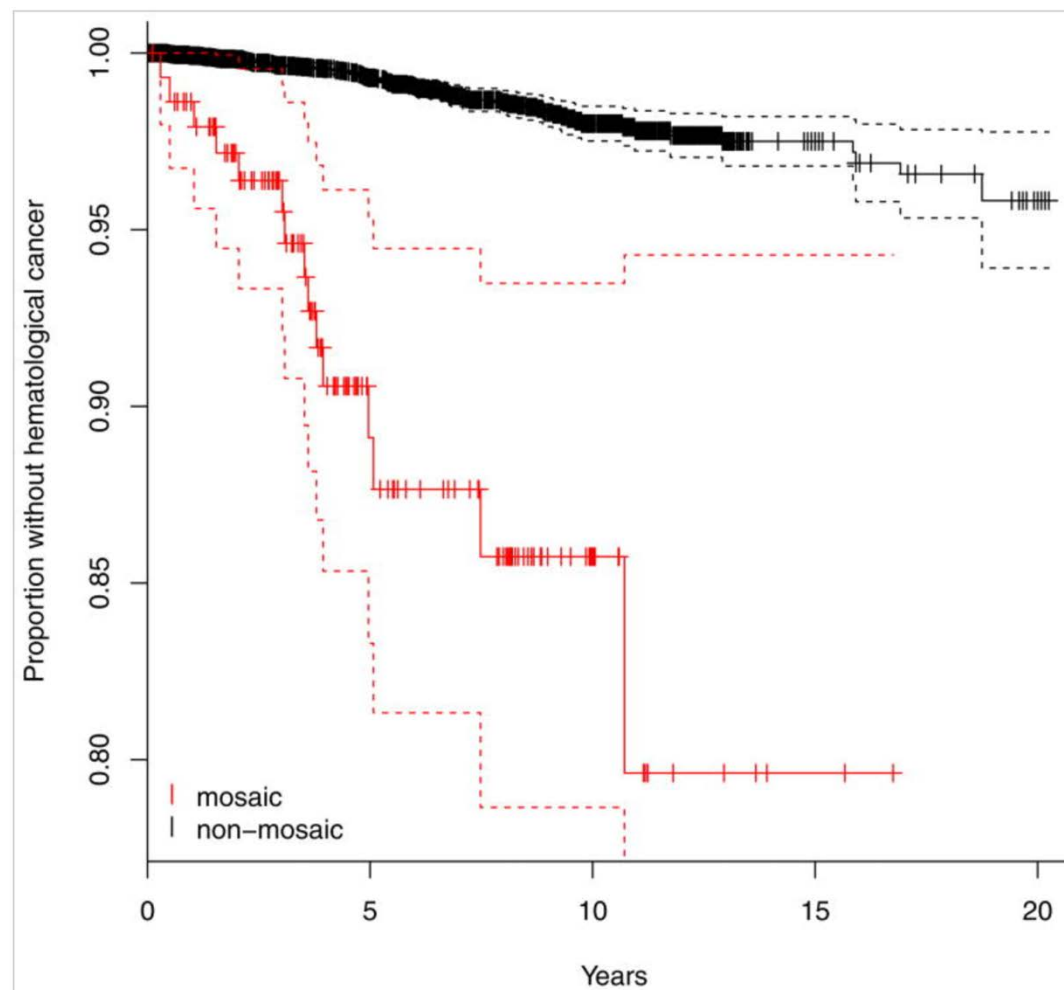
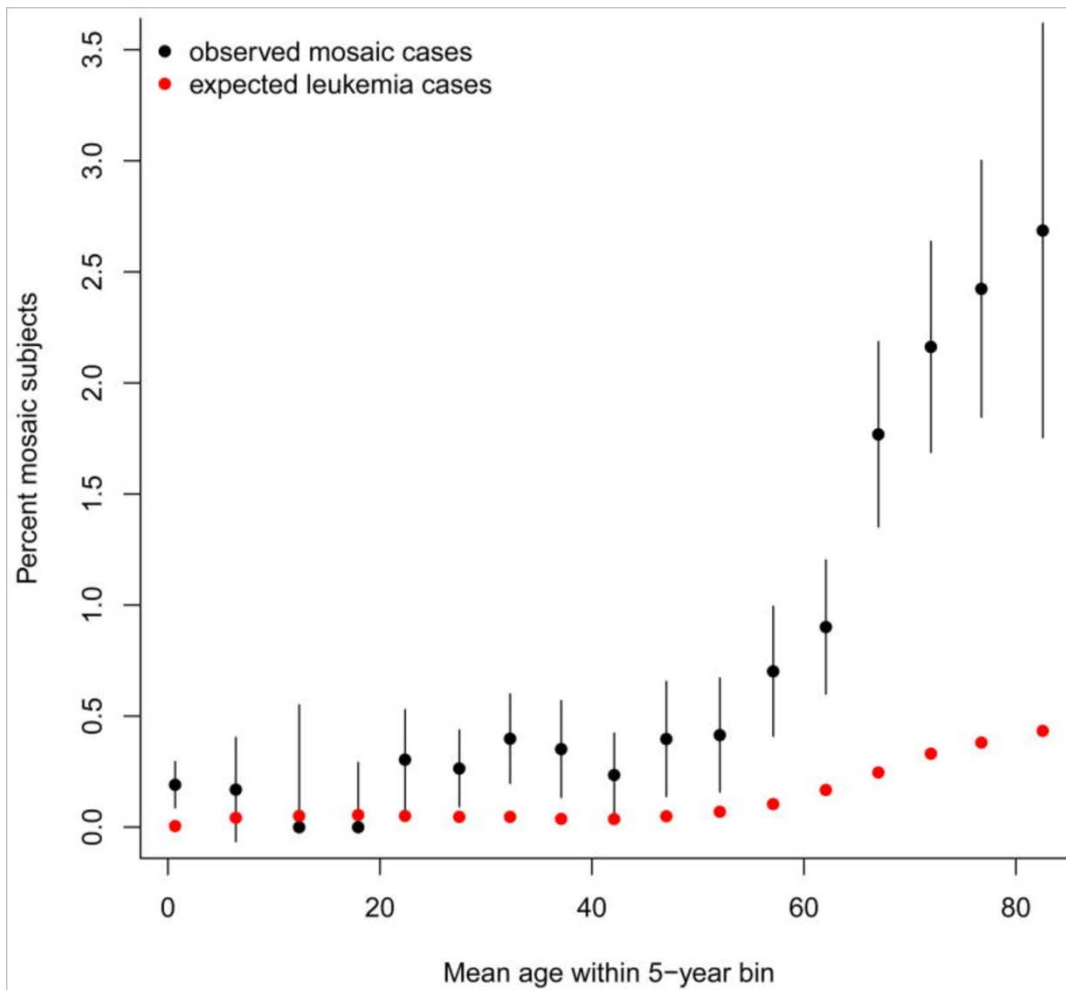
- Clonal hematopoiesis of Indeterminate Potential (CHIP)
 - **23 (T-LGL), 72 (Lung Adenocarcinoma)**
 - CHIP-like clonal marrow cytogenetic abnormality - **82 [t(3;11)], 354 [del(7q)]**
- Idiopathic Cytopenia of Undetermined Significance (ICUS) – **248**
- Clonal Cytopenia of Undetermined Significance (CCUS)
 - without progression - **47, 117, 269**
 - with progression – **50, 109, 181, 350**
 - CCUS with clonal marrow cytogenetic abnormality - **102 [-Y], 169 [aneuploid]**

	Submitter	Age	Sex		Diagnosis	time	Progression	Mutations	VAF	Karyo
269	Wood	67	M	Abnormal CBC	CCUS			ASXL1 p.G646Wfs*12, IDH1 p.R132H, KRAS p.Q61R, SRSF2 p.P95H	~40%	
50	Thompson Arildsen	35	M	Abnormal CBC	CCUS	4m	MDS-EB2	IDH1 p.R132C, NRAS p.G12D, RUNX1 p.R169Kfs*44, SRSF2 p.P95L	~40%	
350	Shanmugam	76	M	Abnormal CBC	CCUS	36m	CMML-1	SF3B1 p.K666N , RUNX1 p.Q268*, ASXL1 p.G642fs*	40% -> 45%	
47	Kwok	82	M	Abnormal CBC	CCUS			ASXL1 p.E635fs*15, ZRSR2 p.Splice, TET2 p.C1221Y	45-49%	
117	Trowell	69	F	Abnormal CBC	CCUS			SRSF2 p.P95_R102del	50%	
109	Wang	59	M	Germ cell tumor	CCUS	8m	t-MDS	TP53 exon 8 mutation	7% -> 14%	
169	Soma	?	F	B-ALL	CCUS			not done	44%?	poly?
181	Kovach	8	F	neuroblastoma	CCUS	2m	t-MDS EB2	not done	75% -> 66%	+ 21
102	Karner	67	M	DM, CKD	CCUS			not done	80%	- Y
332	Stuart	74	M	Abnormal CBC	PNH				75%	- Y
23	Raess	73	M	T-LGL	CHIP			STAT3 p.Y640F, DNMT3A p.R882C, p.E907del	4%	
72	Xia	79	F	Lung adeno	CHIP			JAK2 p.V617F	?	
82	Tang	57	M	CLL	CHIP (CMCA)				~30%	t(3;11)
354	Liu	61	M	CML	CHIP (CMCA)				20%	del(7q)
248	Loghavi	79	F	Abnormal CBC	ICUS			JAK2 p.V617F, TET2 p.Q690*, TET2 p.R1465*	<2%	

Recurrent Somatic *TET2* Mutations in Normal Elderly Individuals With Clonal Hematopoiesis

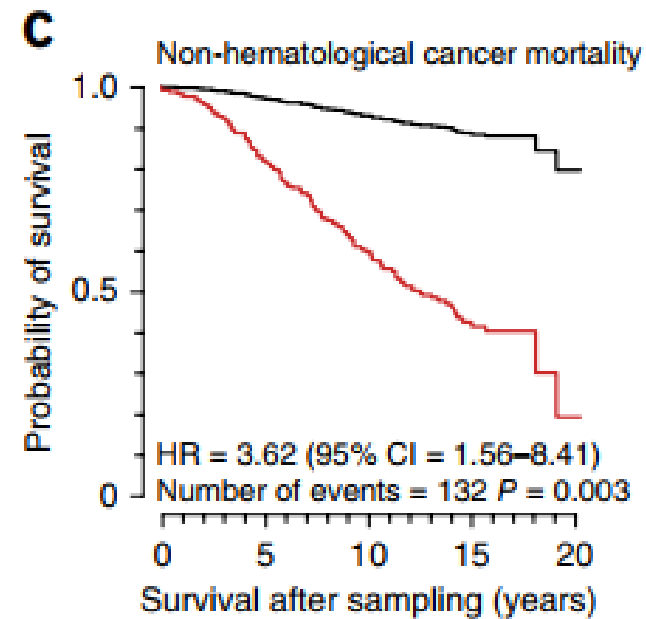
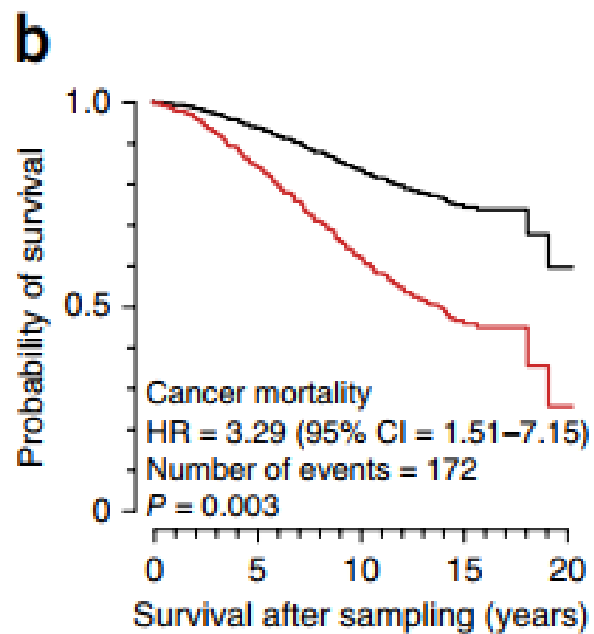
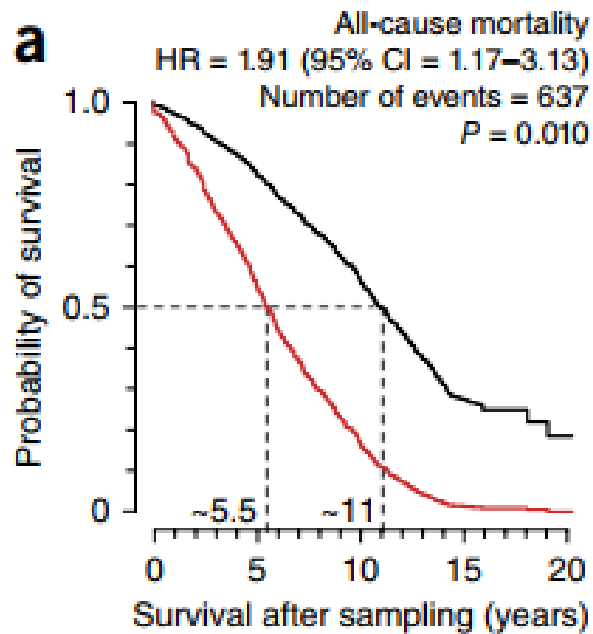
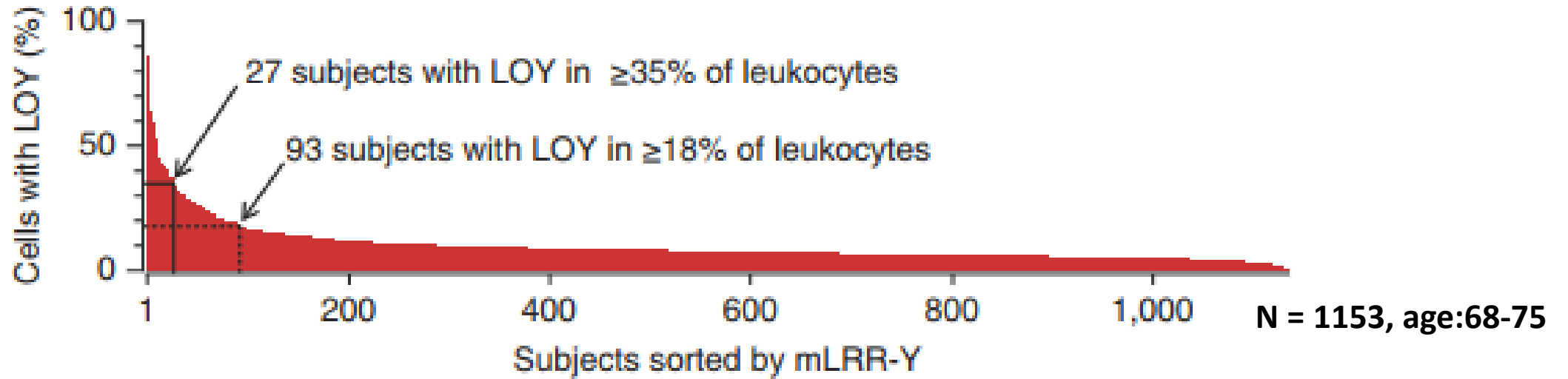
[Lambert Busque](#), [Jay P Patel](#), [Maria E Figueroa](#), [Aparna Vasanthakumar](#), [Sylvie Provost](#), [Zineb Hamilou](#), [Luigina Mollica](#), [Juan Li](#), [Agnes Viale](#), [Adriana Heguy](#), [Maryam Hassimi](#), [Nicholas Socci](#), [Parva K Bhatt](#), [Mithat Gonen](#), [Christopher E Mason](#), [Ari Melnick](#), [Lucy A Godley](#), [Cameron W Brennan](#), [Omar Abdel-Wahab](#) & [Ross L Levine](#)

Exome sequencing of three elderly females with clonal hematopoiesis, demonstrated by X-inactivation analysis, identified somatic *TET2* mutations. Recurrence testing identified *TET2* mutations in 10 out of 182 individuals with X-inactivation skewing.



SNP array, 50,000 GWAS, >5-10% clonal mosaicism

[Nat Genet.](#) 2012 May 6;44(6):642-50



Session 5: Pre-Malignant Clonal Lymphoid Proliferations

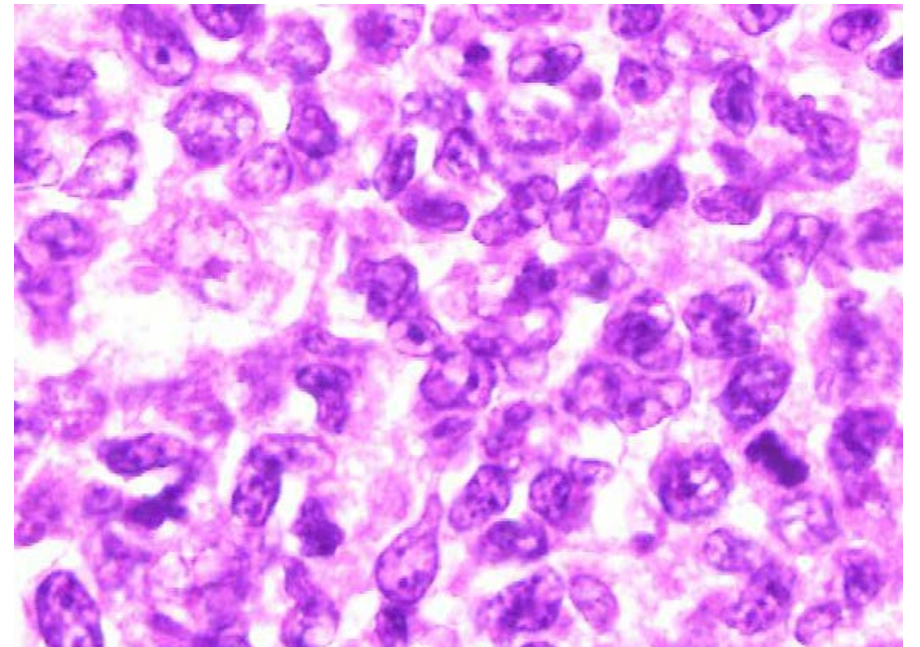
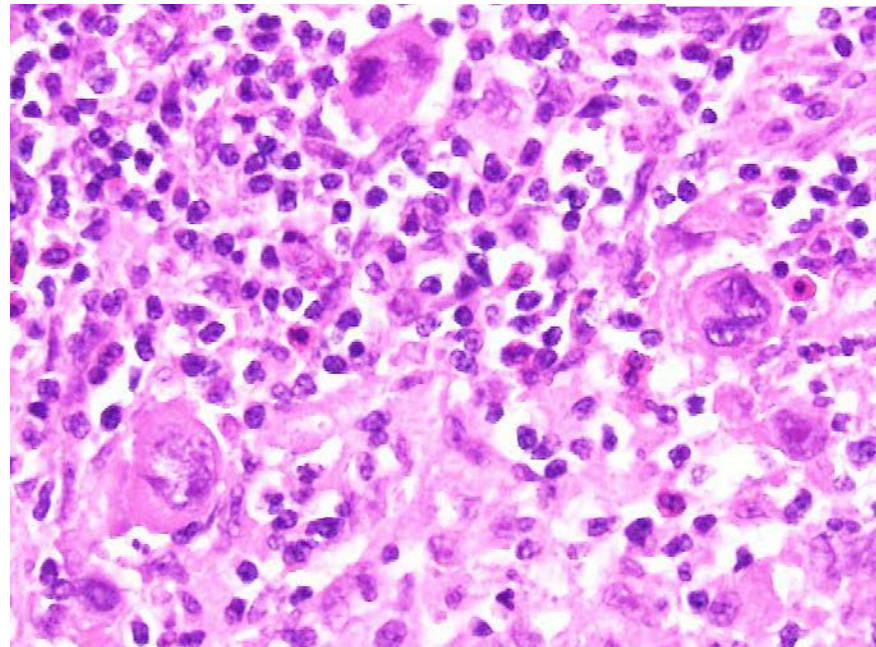
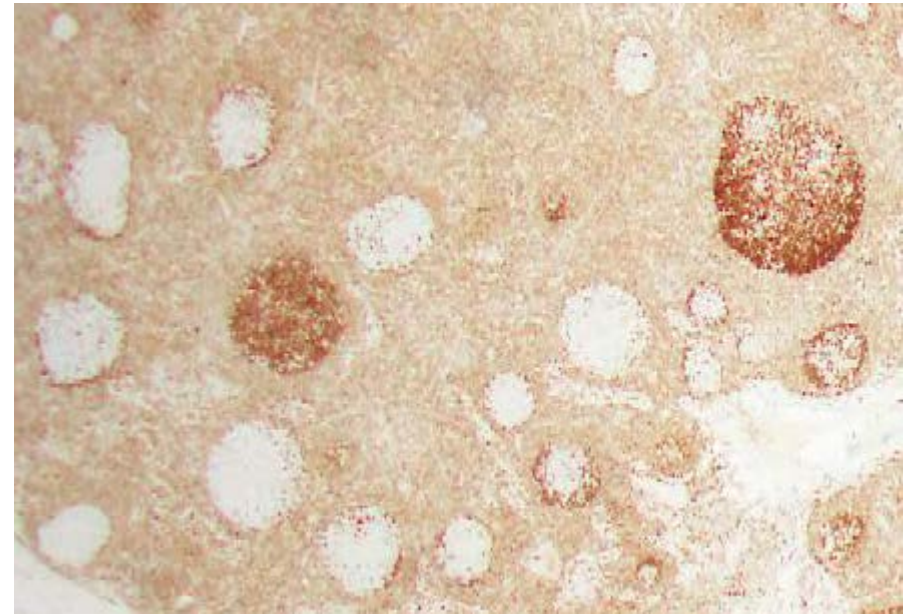
- Monoclonal gammopathy of undetermined significance (MGUS), IgM* - **70 (MCL), 254 (AML), 272, 354 (CML),**
- Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
- Monoclonal immunoglobulin deposition diseases - **63**
- In situ follicular neoplasia (ISFN) - **199 (CHL)**
- In situ mantle cell neoplasia (ISMCN) - **125 (MZL), 134 (FL)**
- Monoclonal B cell lymphocytosis (MBL)
 - CLL type, low-count
 - CLL type, high-count
 - Non-CLL type
 - tissue-based MBL of CLL type - **272**

Case 199 – **Bockelman et al**, Penn State

89 F with cervical LN

Classical HD and

In situ Follicular Neoplasia

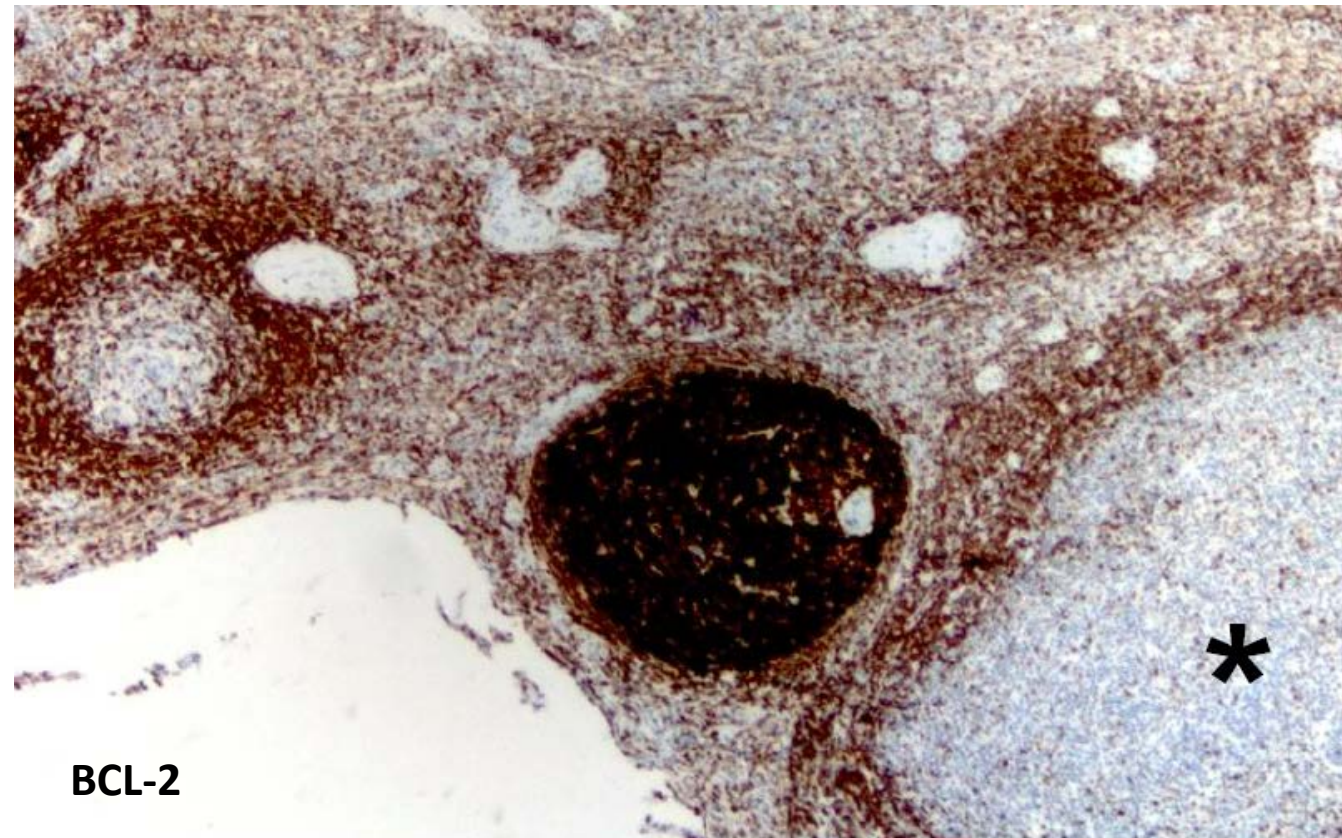
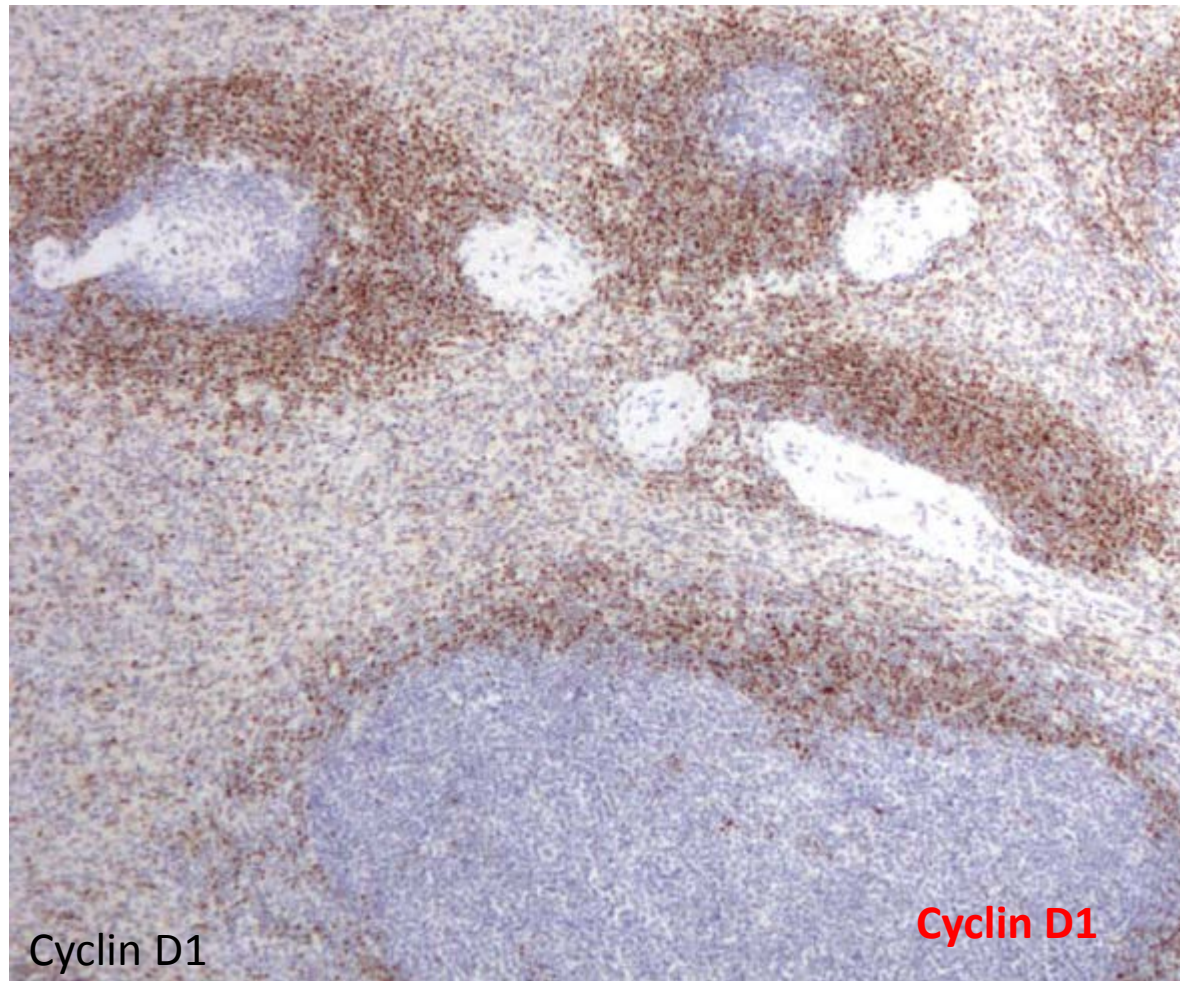


SH2017-0134 Composite and seemingly clonally related in situ follicular neoplasia and in situ mantle cell neoplasia

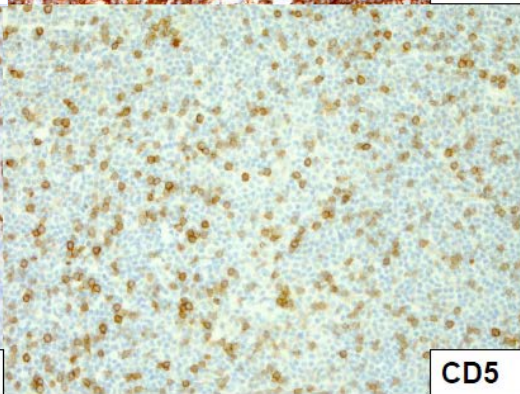
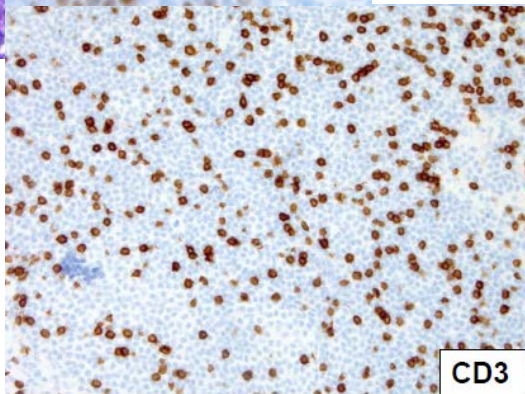
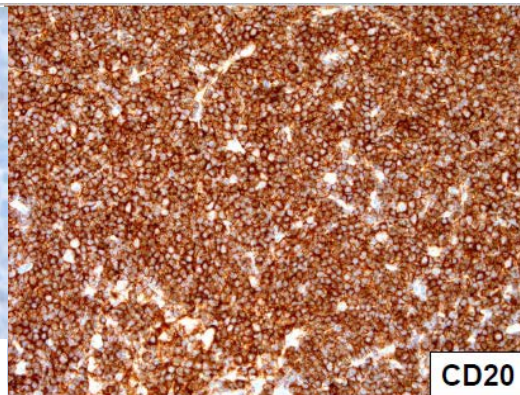
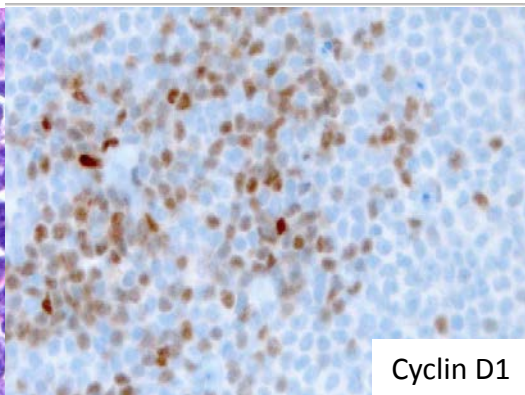
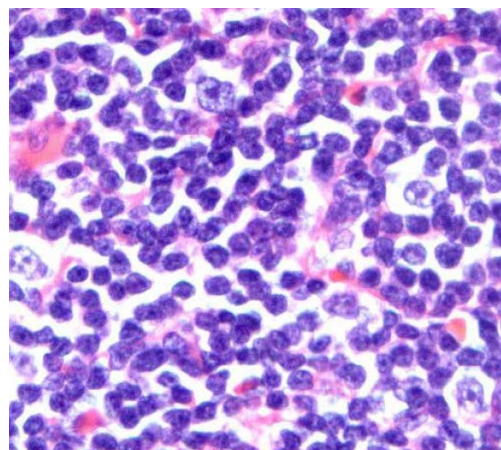
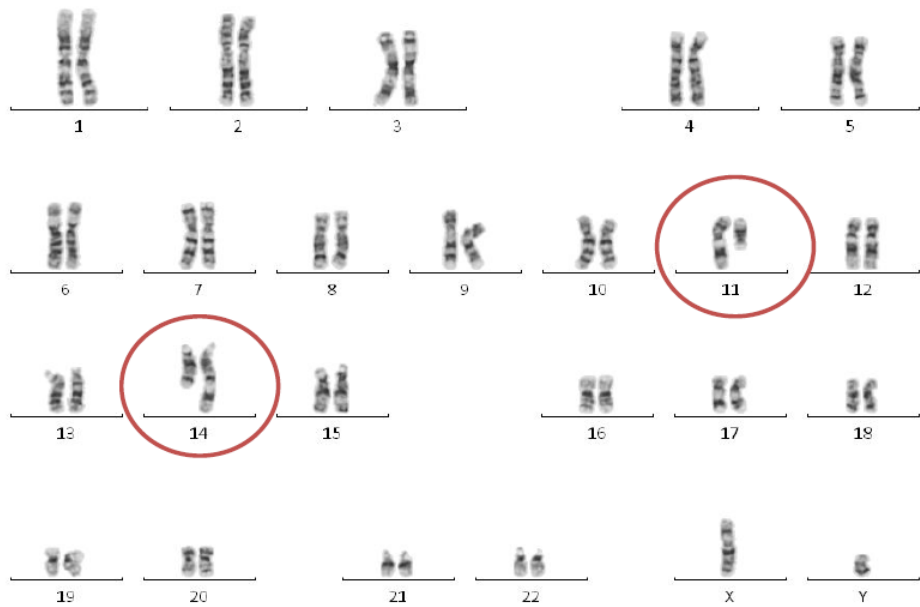
Author: Michele Bak

Additional Authors: Ellen McPhail MD, Alexander Judkins MD, Dan Arber MD, Adam Bagg MD

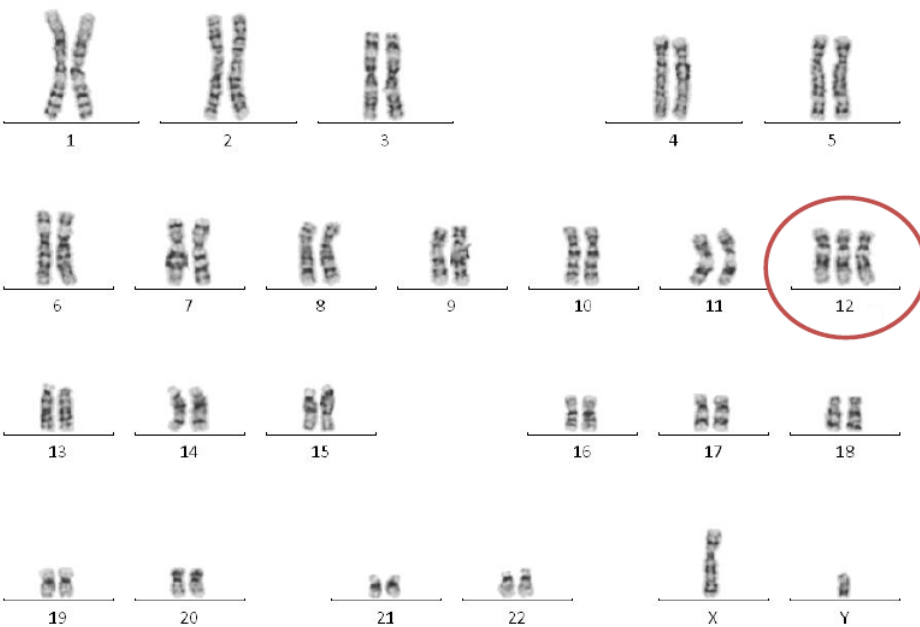
84 M with splenic masses showing involvement by follicular lymphoma. FISH positive for IGL-BCL2 rearrangement and IgH/IgK PCR+



4 out of 20 cells show 46,XY,t(11;14)(q13;q32)

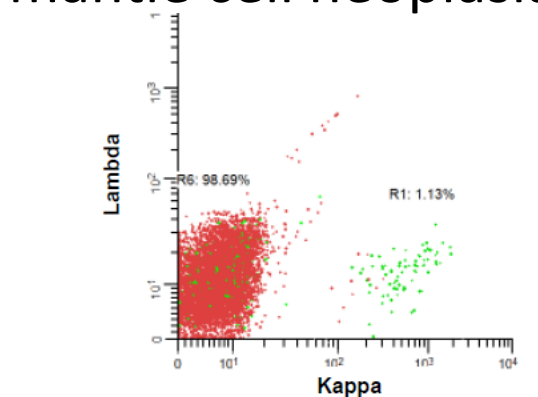
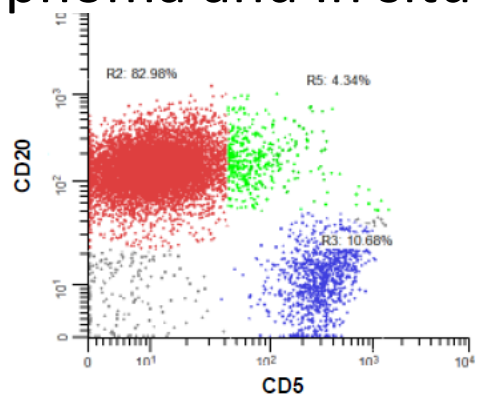


6 out of 20 cells show 47,XY,+12



Case 125 Sloan et al, Duke
58 M left inguinal LN

Marginal zone lymphoma and In situ mantle cell neoplasia



Case Number: **SH2017-0272**

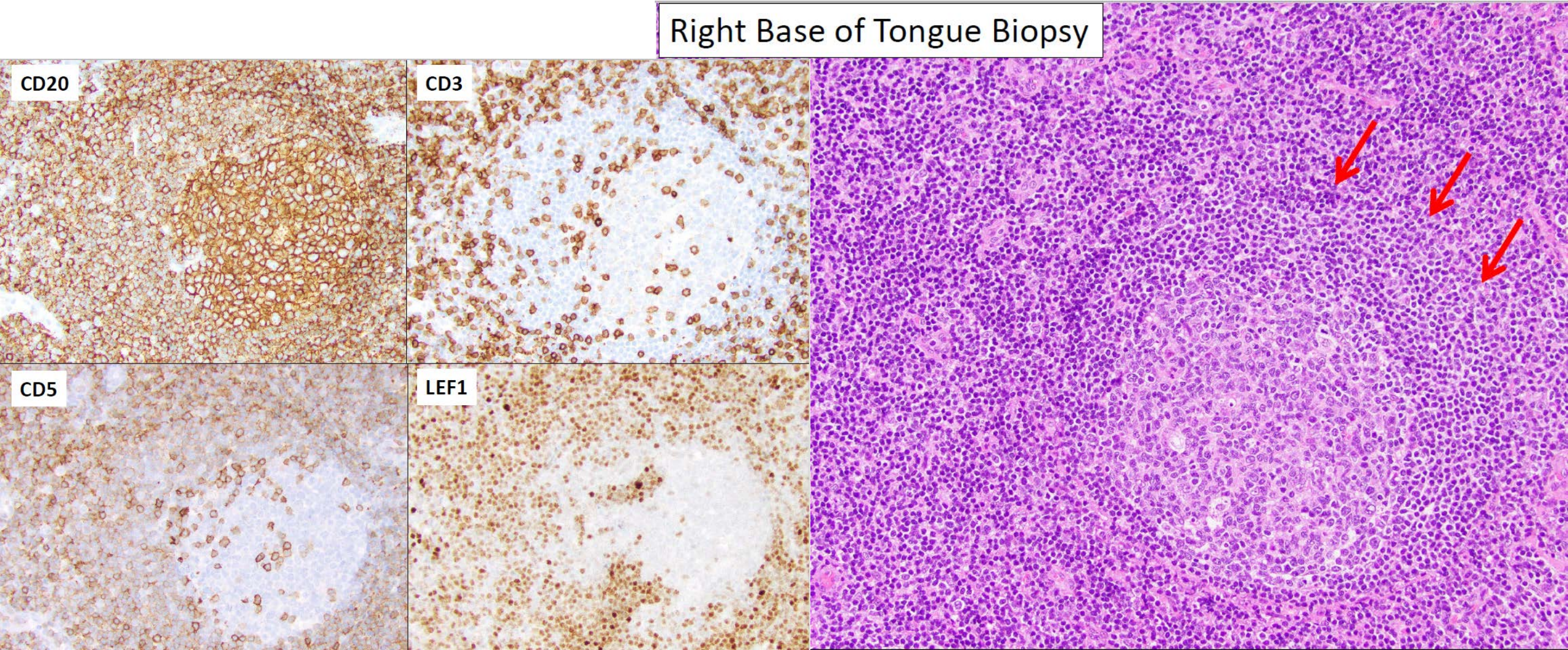
MYD88 L265P mutation in a patient with **SLL/MBL** and **IgM-MGUS**

Sarah Gibson, James Cook

University of Pittsburgh School of Medicine, Cleveland Clinic

72 M right base of tongue with tissue based monoclonal B cell lymphocytosis of CLL-type

Right Base of Tongue Biopsy

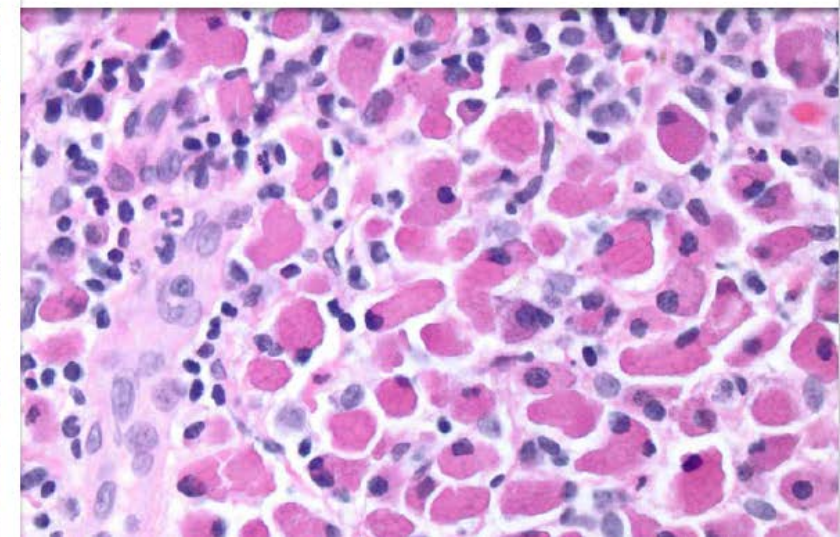
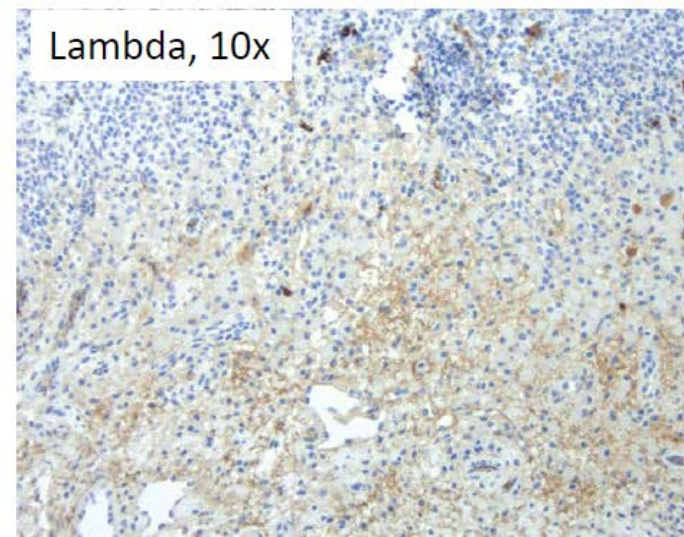
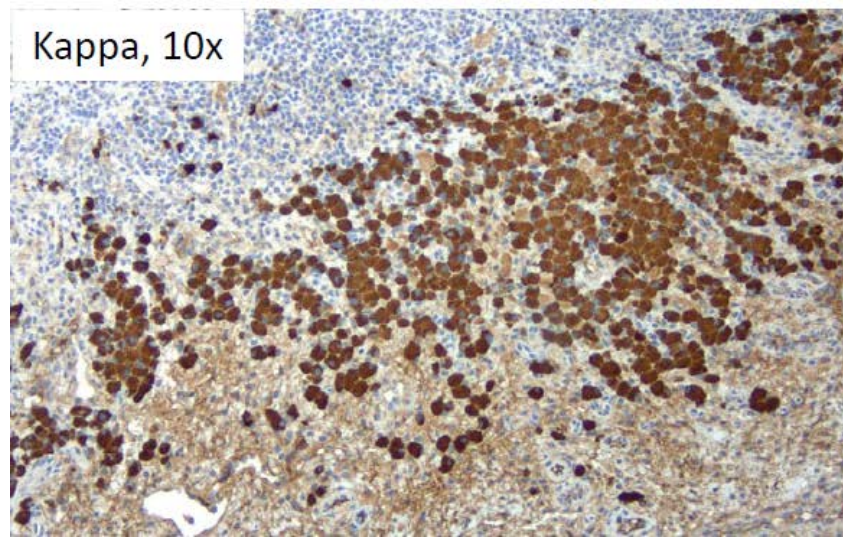
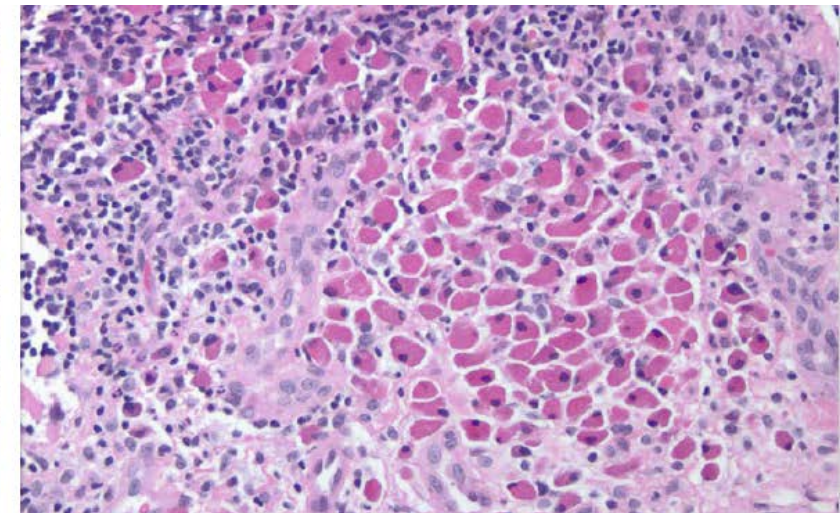
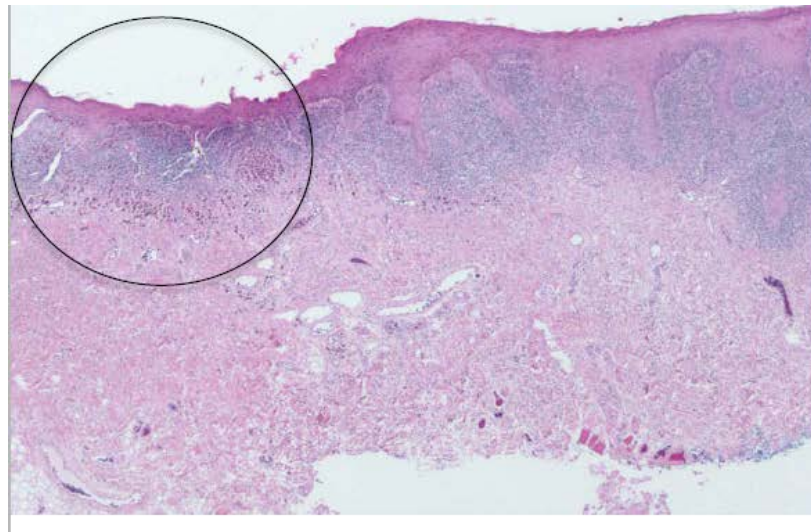


Case Number: **SH2017-0063**

Kappa monoclonal Russell body lichenoid mucositis

Lorinda Soma, Dophine Oda, Kyle Garton, Sindhu Cherian, David Wu, Kerstin Edlefsen
University of Washington Medical Center

48 year old female without significant past medical history presents with 4 month history of oral ulcerations.



#	Title	Author	Author	Proposed diagnosis	Panel diagnosis	Age	Sex	Note
76	Allopurinol Induced Pseudo-Mycosis Fungoides Resolved by High Throughput Sequencing (HTS)	Bryan	Rea	Allopurinol Induced Pseudo-mycosis Fungoides	Cutaneous atypical T-cell infiltrate (secondary to allopurinol therapy)	87	M	TCR oligoclonal
345	lymphocytic-HES, reactive (polyclonal) hypereosinophilia secondary to IL-5 over-production by T-cells with elevated IgE level.	Tania	Mendoza	lymphocytic-HES, reactive (polyclonal) hypereosinophilia secondary to IL-5 over-production by T-cells with elevated IgE level.	Hypereosinophilia, likely secondary	87	M	Spontaneously resolved
98	G-CSF Double-Edged Sword	Virginia	Knez	Acute promyelocytic leukemia, initially masked and possibly potentiated by long-term G-CSF use in the setting of chronic neutropenia.	Acute promyelocytic leukemia with PML-RARA (in a patient with prior G-CSF use)	22	F	chronic neutropenia

Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Clonal Cytopenia of Uncertain Significance (CCUS)

Idiopathic Cytopenia of Uncertain Significance (ICUS)

Myelodysplastic Syndrome (MDS)

Idiopathic Dysplasia of Uncertain Significance (IDUS)

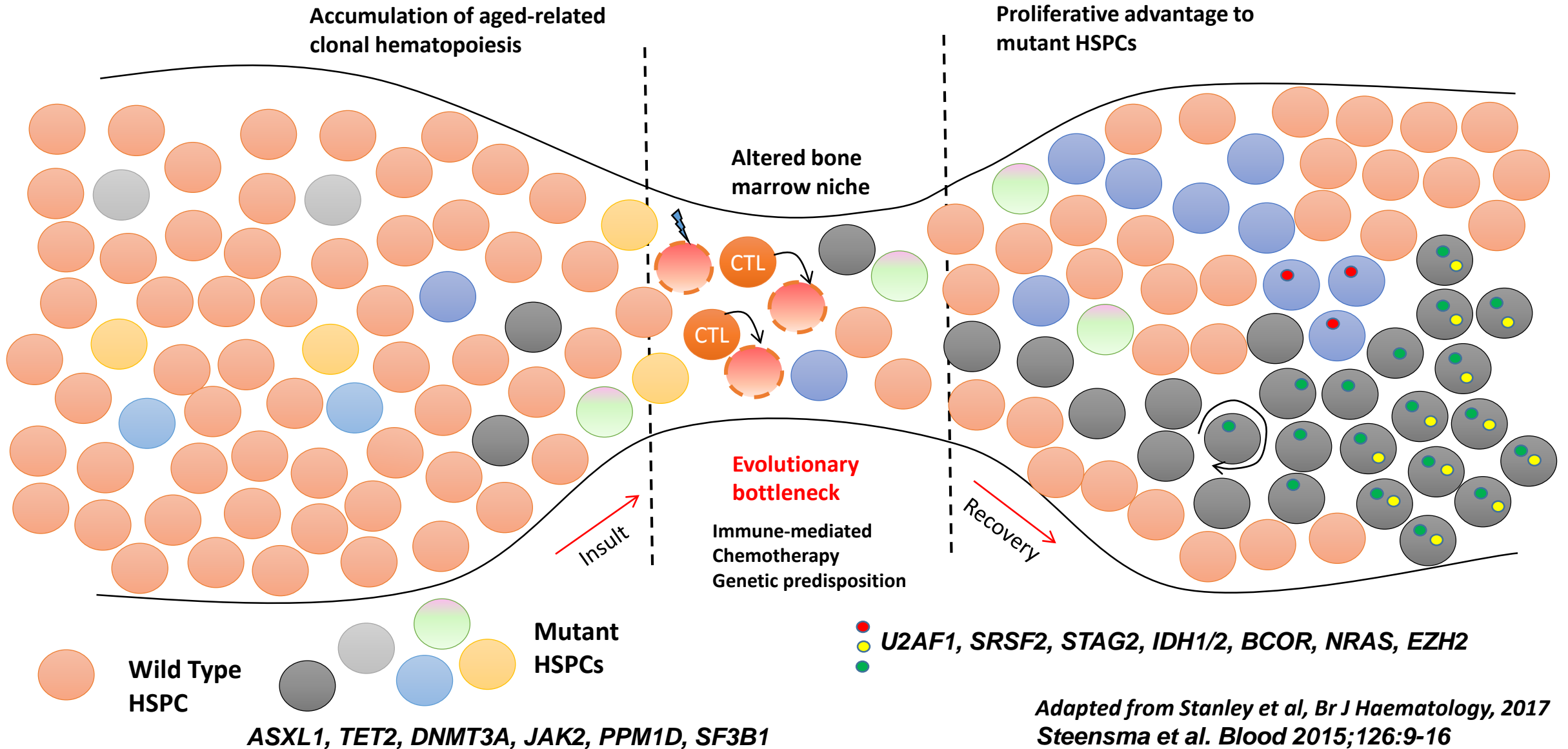
Somatic Mutation

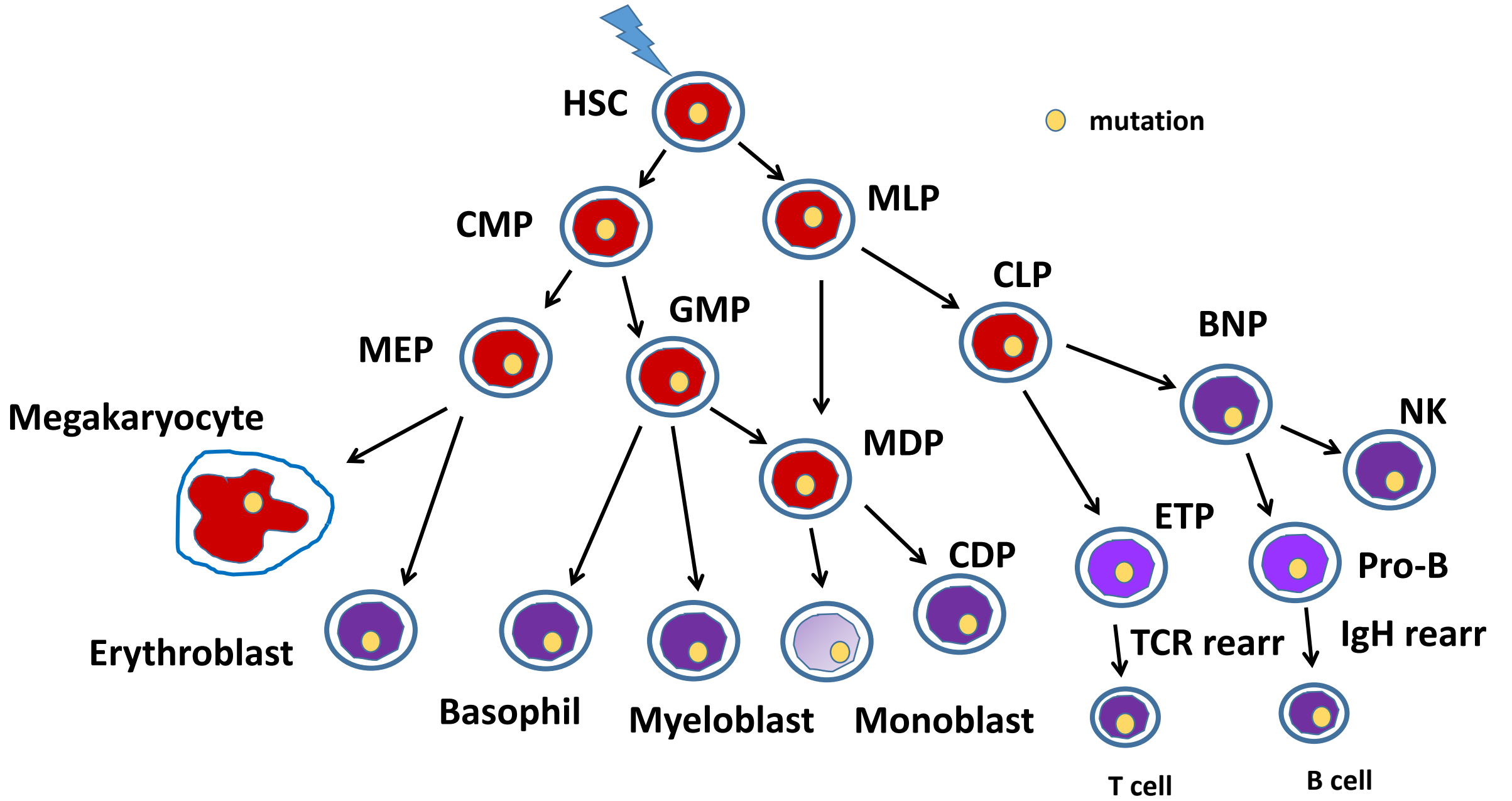
Cytopenia

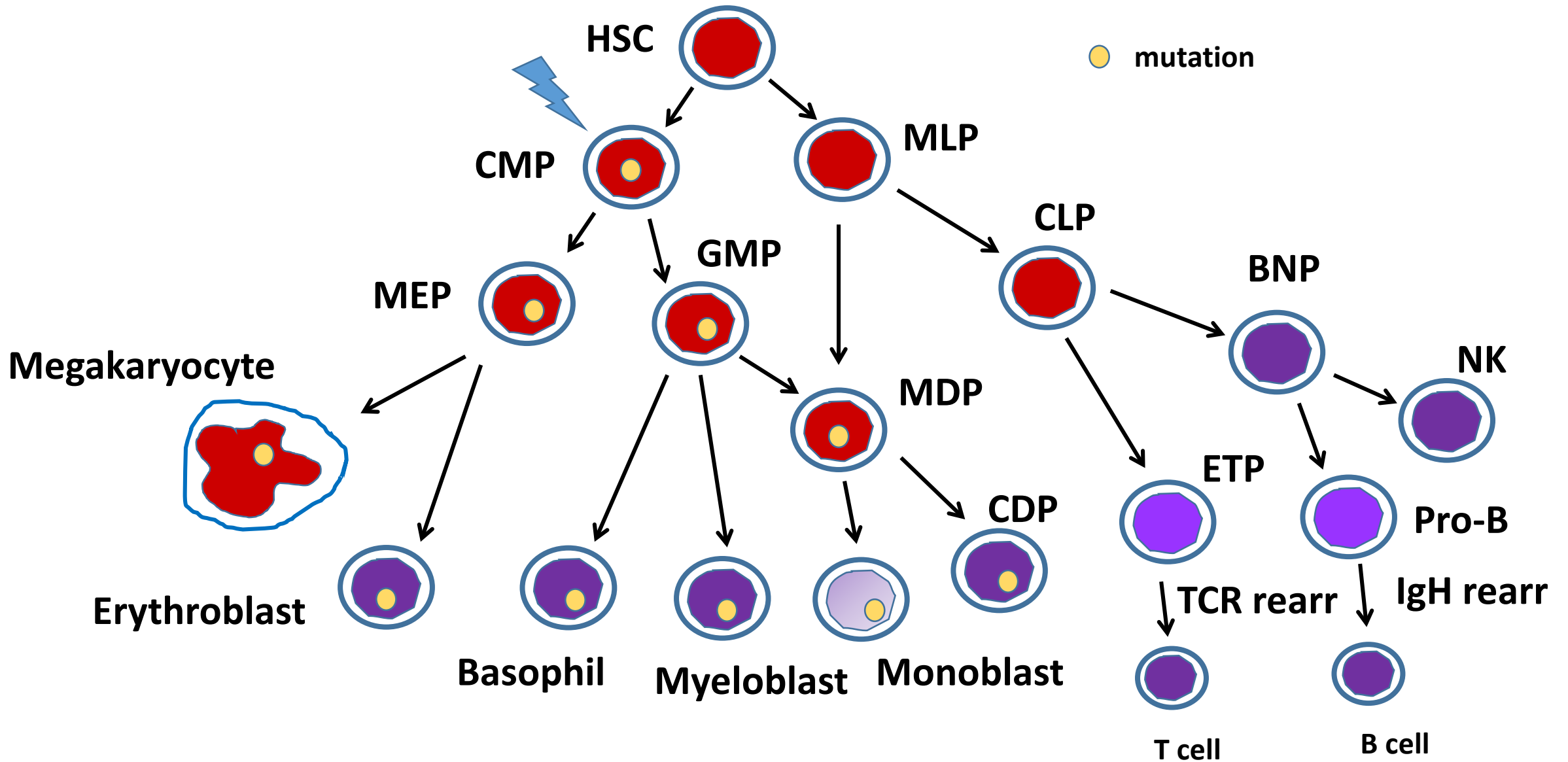
Dysplasia

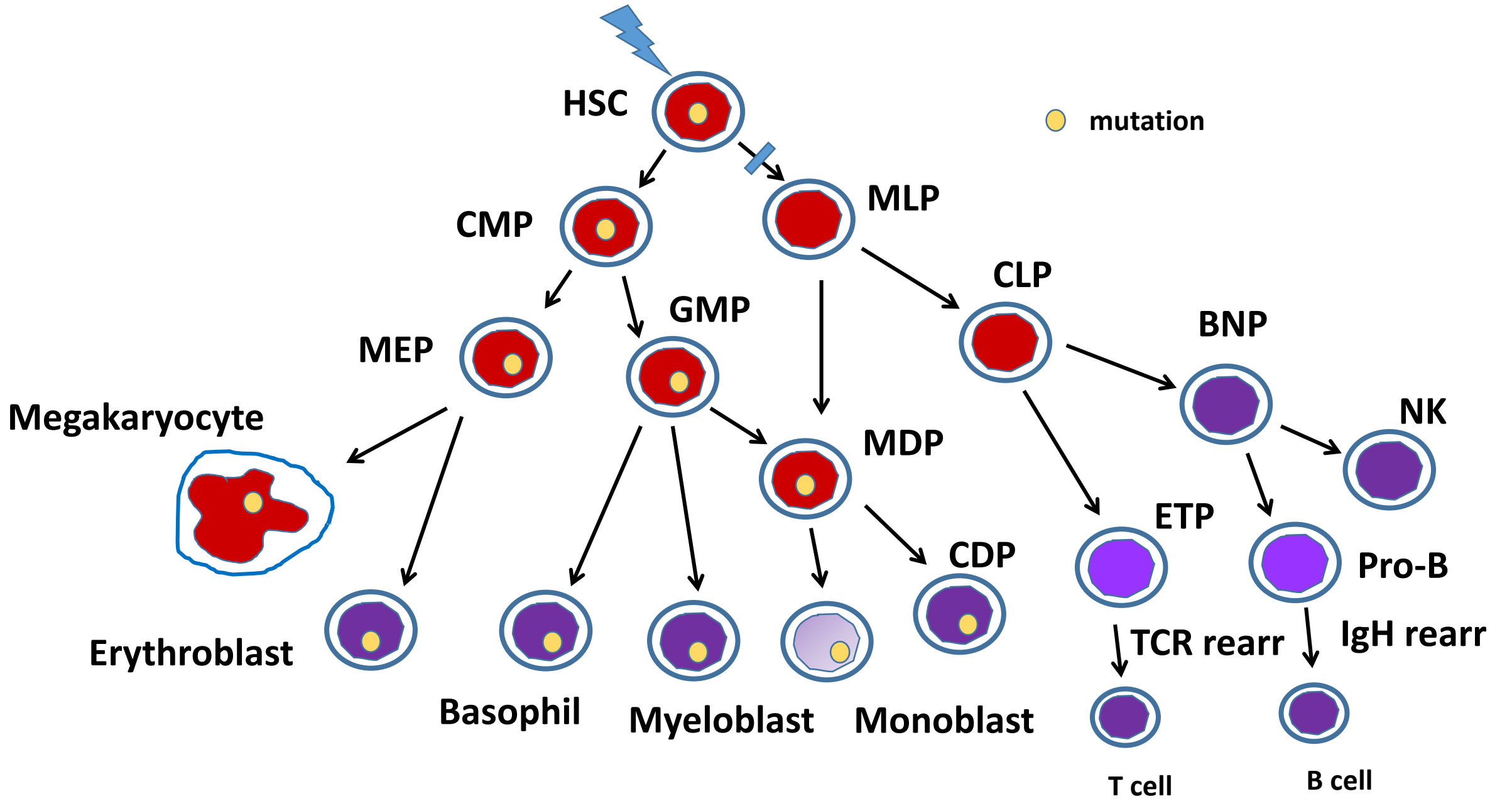
	Cytopenia	Dysplasia	CH	VAF	No. of variants	Genes	Risk
Normal	-	-	-	-	-		-
CHIP	-	-	+	>= 2% but <20%	rarely >2	<i>TET2, DNMT3A, ASXL1, SF3B1, PPM1D</i>	1%/yr
ICUS	+	-	-	-	-		low
CCUS	+	-	+	>10%	Often >1	<i>SRSF2, IDH1, NRAS, RUNX1, U2AF1, BCOR, EZH2, STAG2</i>	10%/yr
MDS	+	+	+ / -	>10%	on average >=2		-
IDUS	-	+	-	-	-		-

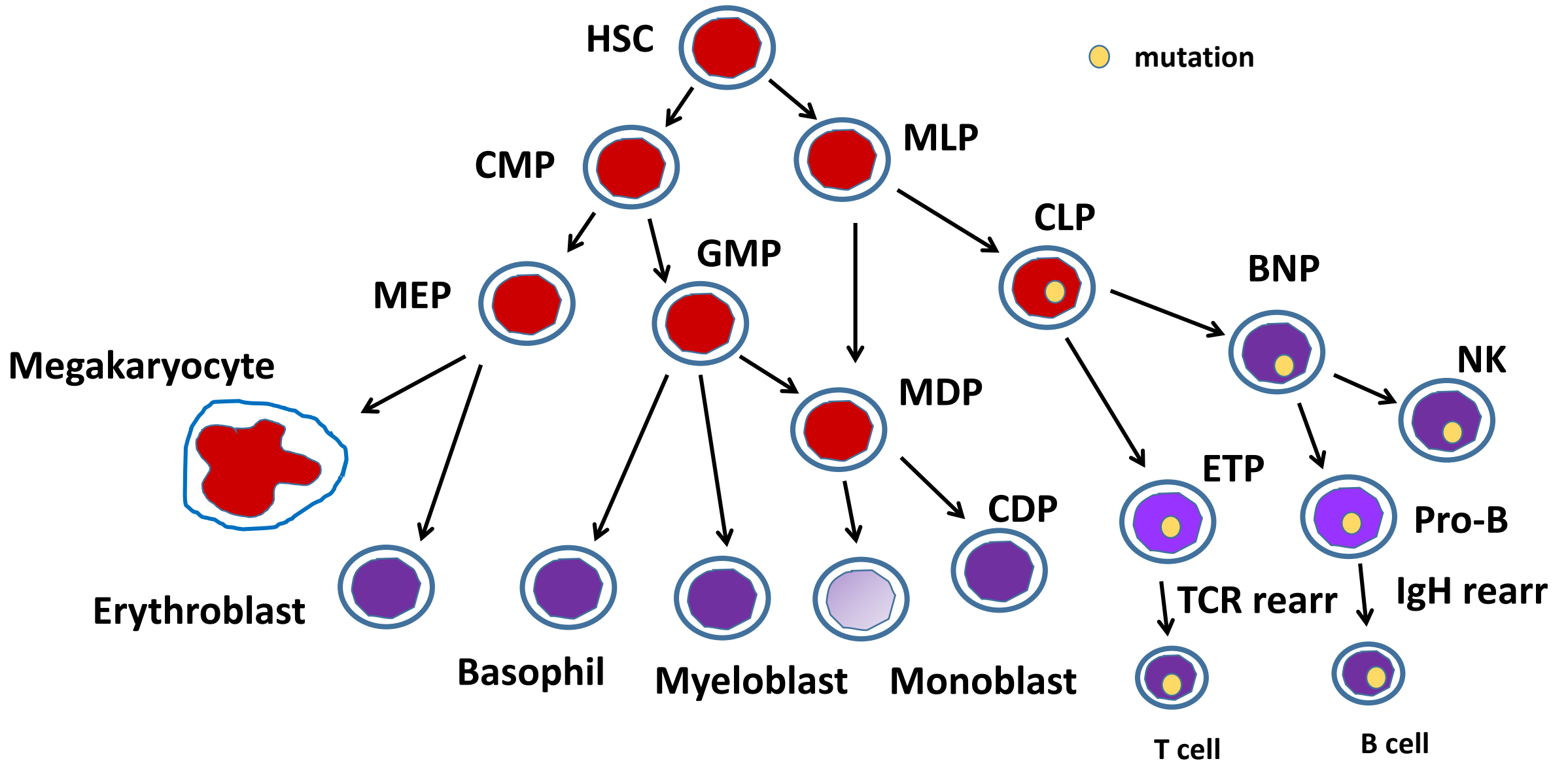
Spectrum and Evolution of Clonal Hematopoiesis











Session 5: Pre-Malignant Clonal Hematopoietic Proliferations

- How common (or rare) is CCUS? How often CCUS are under-diagnosed MDS?
- Where do mutations in CHIP occur? In a hematopoietic stem cell or a more committed progenitor cell? Does CHIP-like mutation occur in common lymphoid progenitor (CLP) cells (giving rise to “clonal” expansion of lymphoid cells prior to IgH or TCR rearrangement)?
- Will we see “monoclonal T cell lymphocytosis” and “monoclonal NK lymphocytosis” soon in the WHO?
- What is the significance of “microCHIP” (CHIP with VAF <2%)?

Thank you to all the submitters and oral presenters!