Recogniz… n… primary care

When to worry?!

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Disclosures

- None

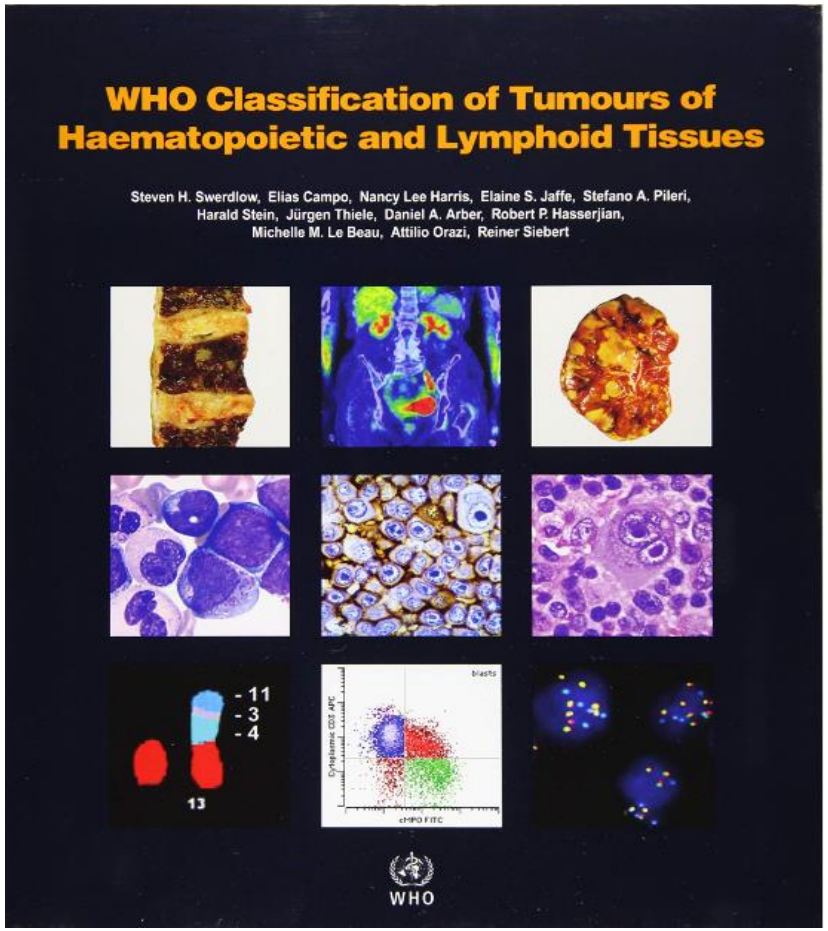
Objectives

1. Describe hematopoiesis and **clonal hematopoiesis** in the context of **hematologic malignancies**

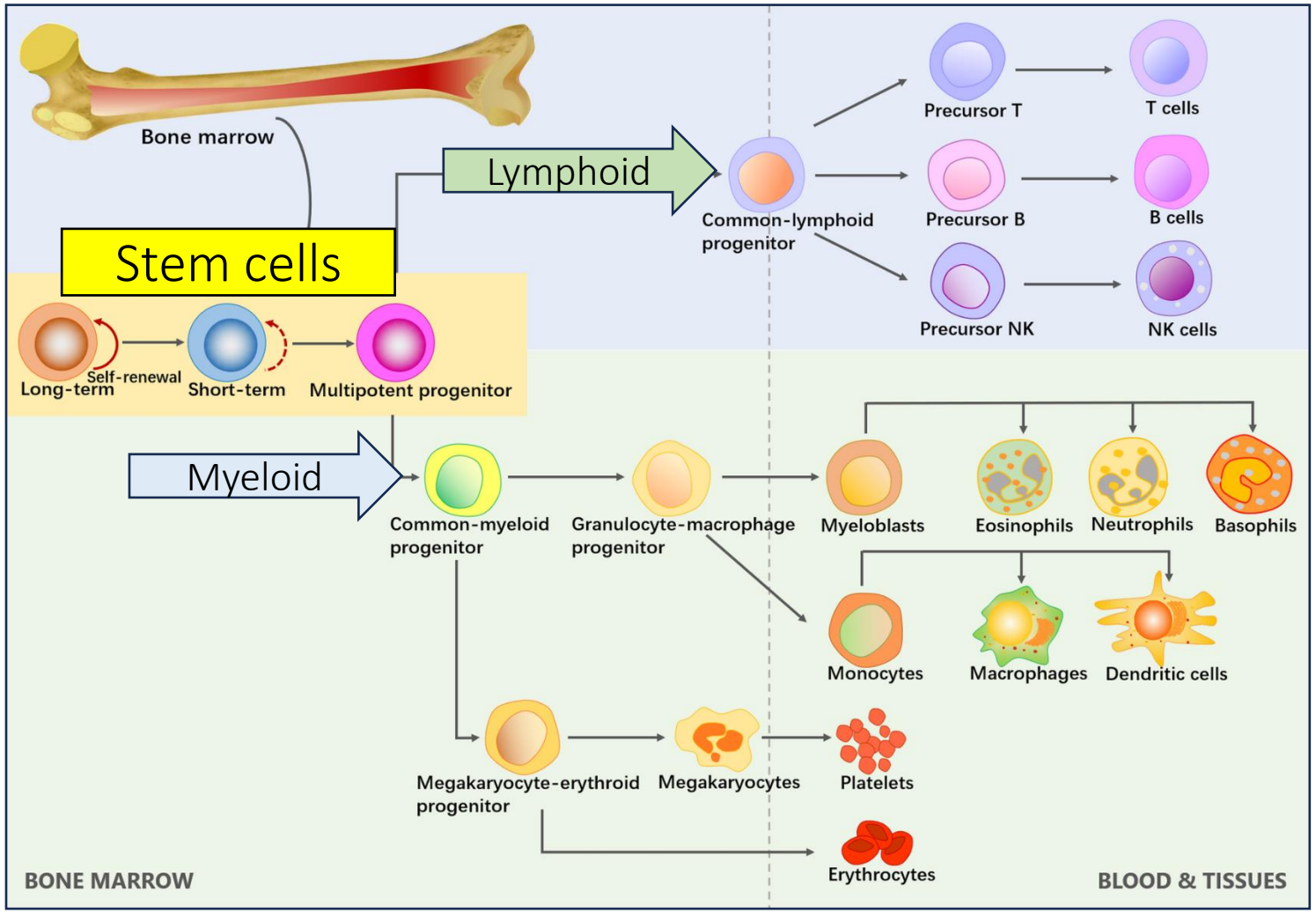
2. Differentiate between **MGUS and myeloma**, recognizing when to worry

3. Review worrisome vs. non worrisome features in cases of **low blood counts** and **high blood counts**

Absolutely NOT the objective



Normal hematopoiesis



T cells

B cells → Plasma cells

Neutrophils

Eosinophils

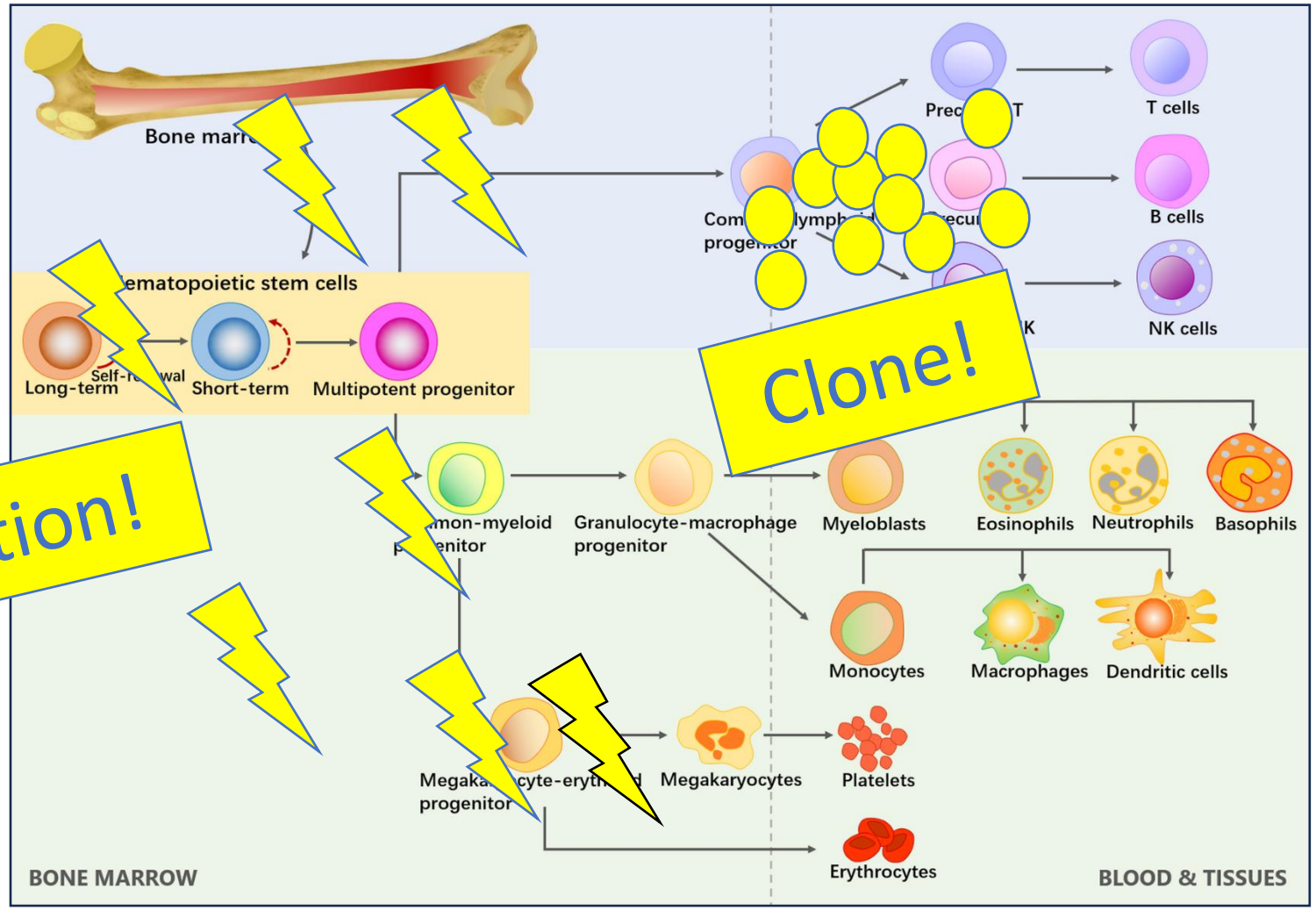
Basophils

Monocytes

Platelets

Red cells

Not normal (**clonal**) hematopoiesis

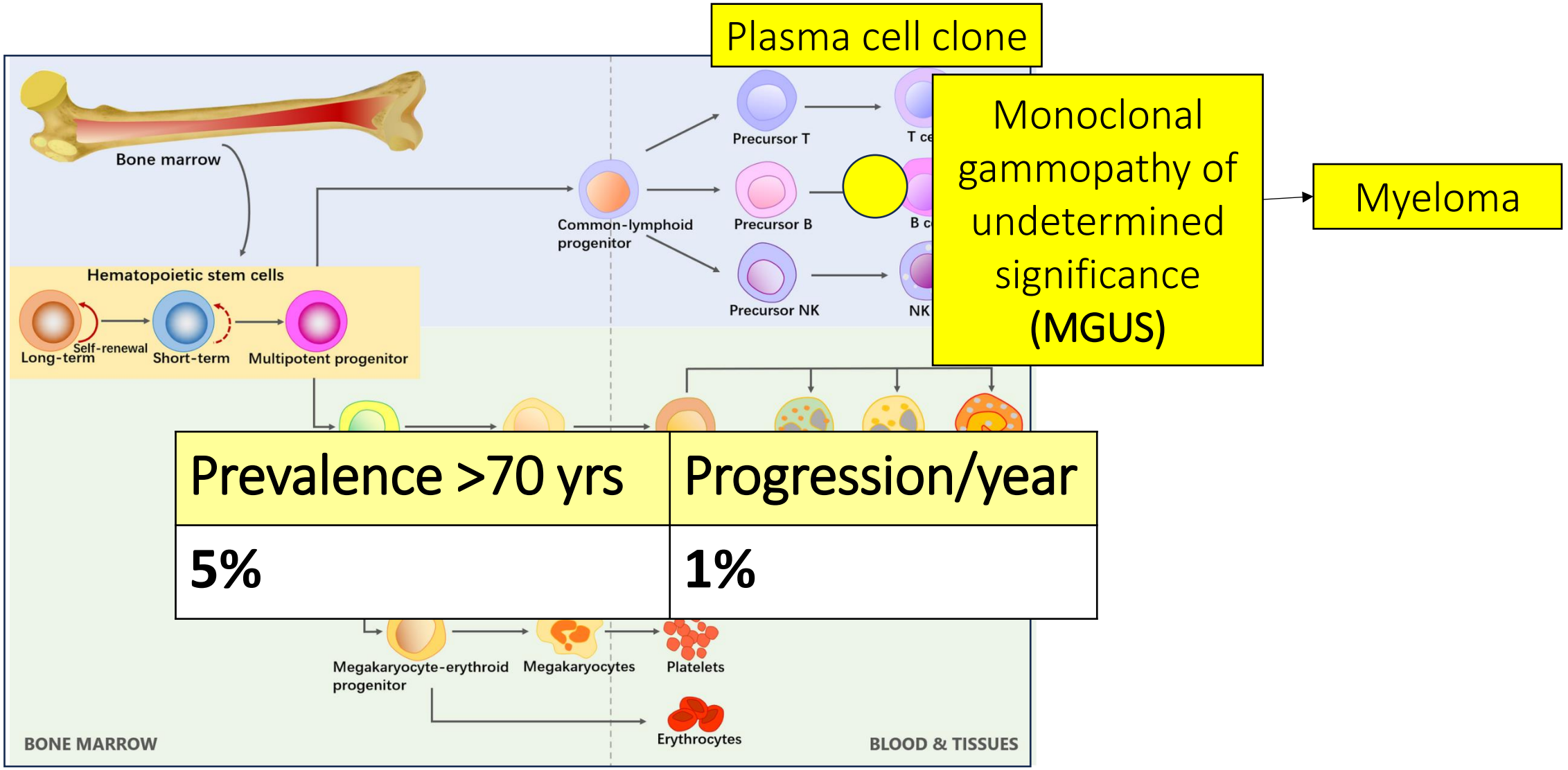


Mutation!

Clone!

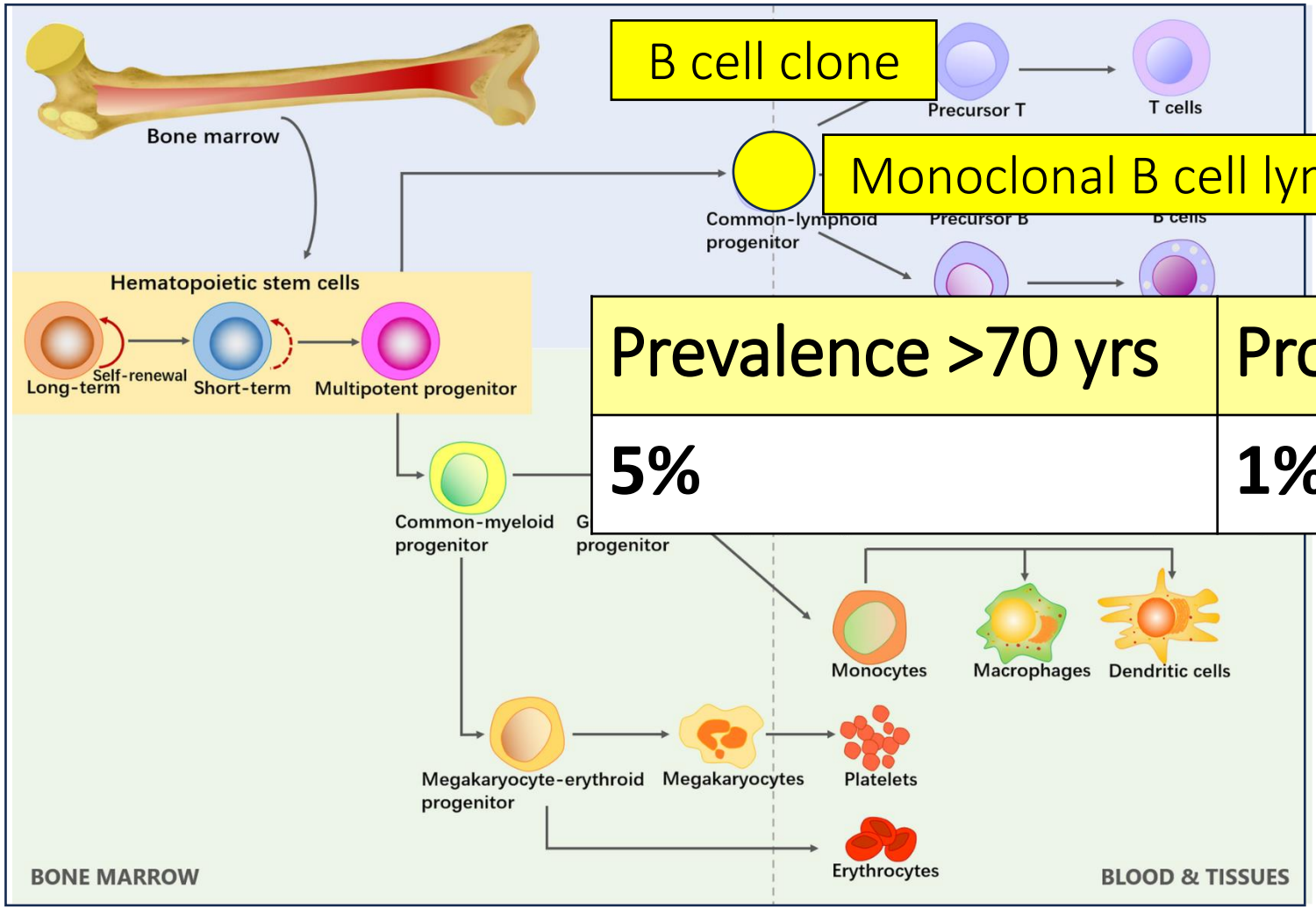
Maybe cancer!

3 **clones** that may matter



Prevalence >70 yrs	Progression/year
5%	**1%**

3 **clones** that may matter

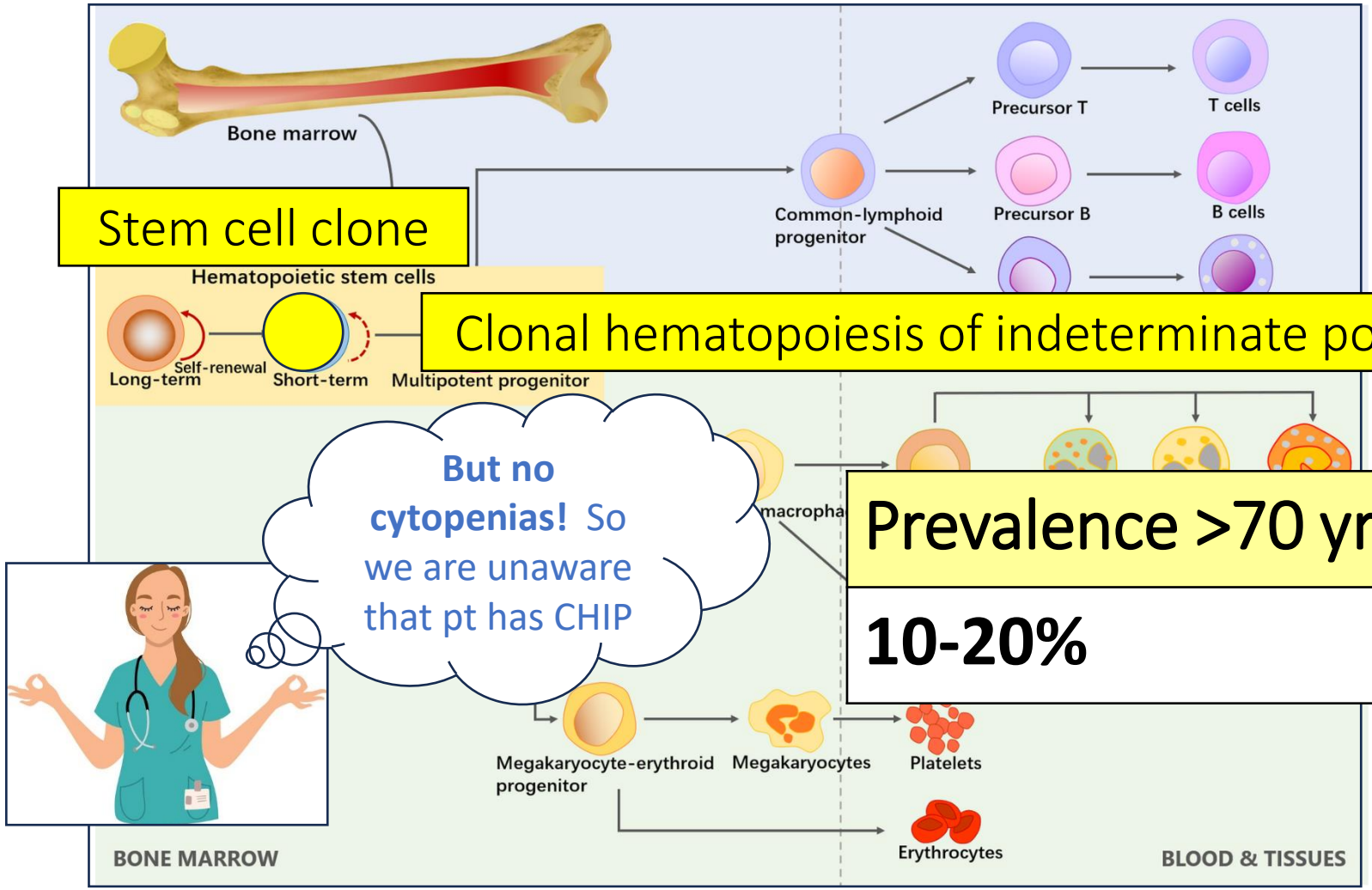


B cell clone

Monoclonal B cell lymphocytosis **(MBL)** → CLL

Prevalence >70 yrs	Progression/year
5%	**1%**

3 **clones** that may matter

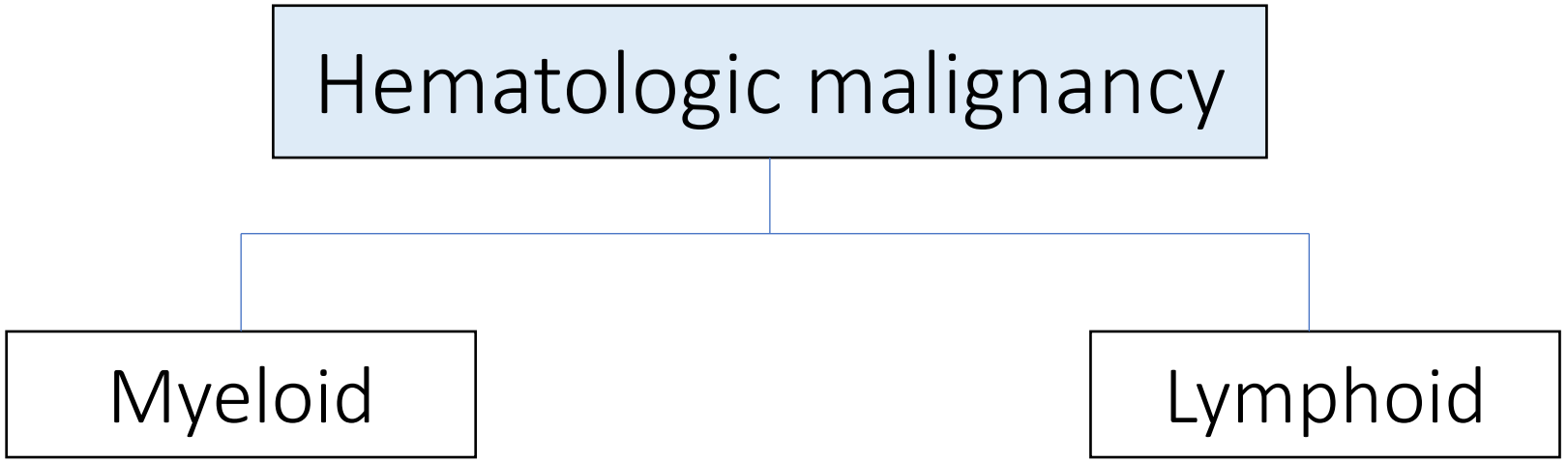


Clonal hematopoiesis of indeterminate potential (CHIP) → MDS,AML

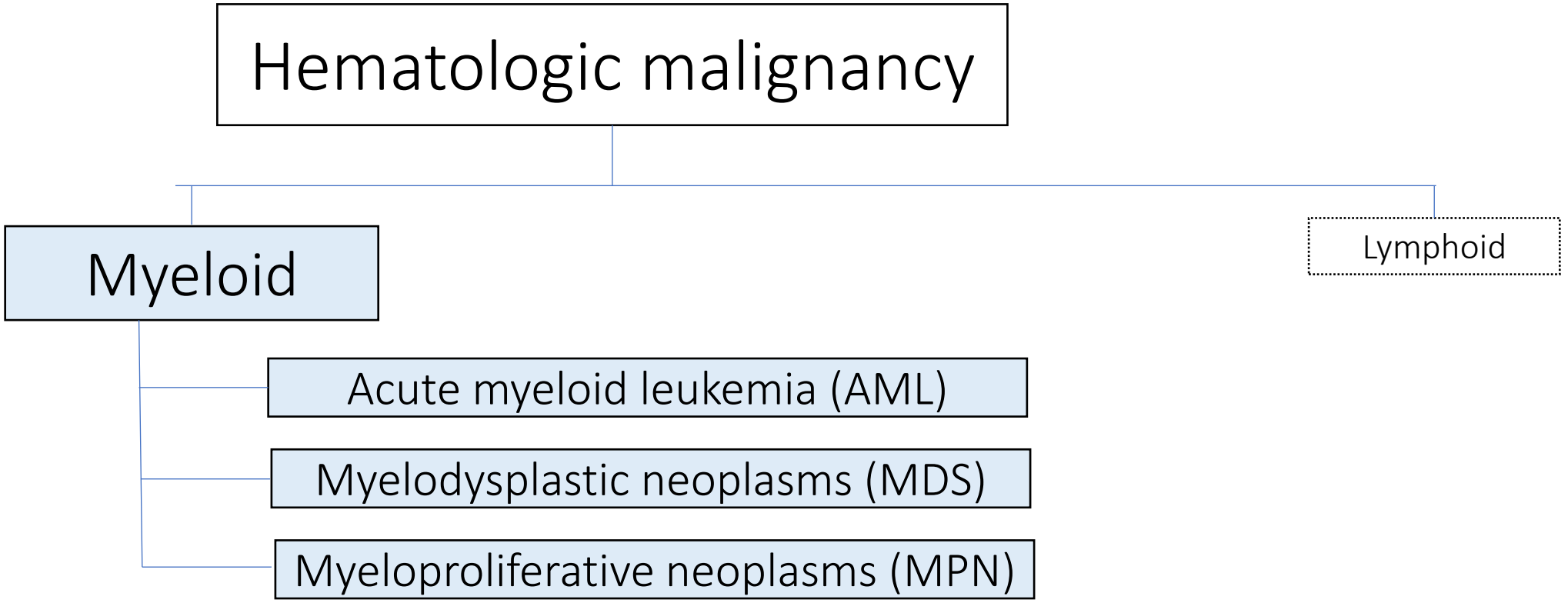
But no cytopenias! So we are unaware that pt has CHIP

Prevalence >70 yrs	Progression/year
10-20%	**0.5-1%**

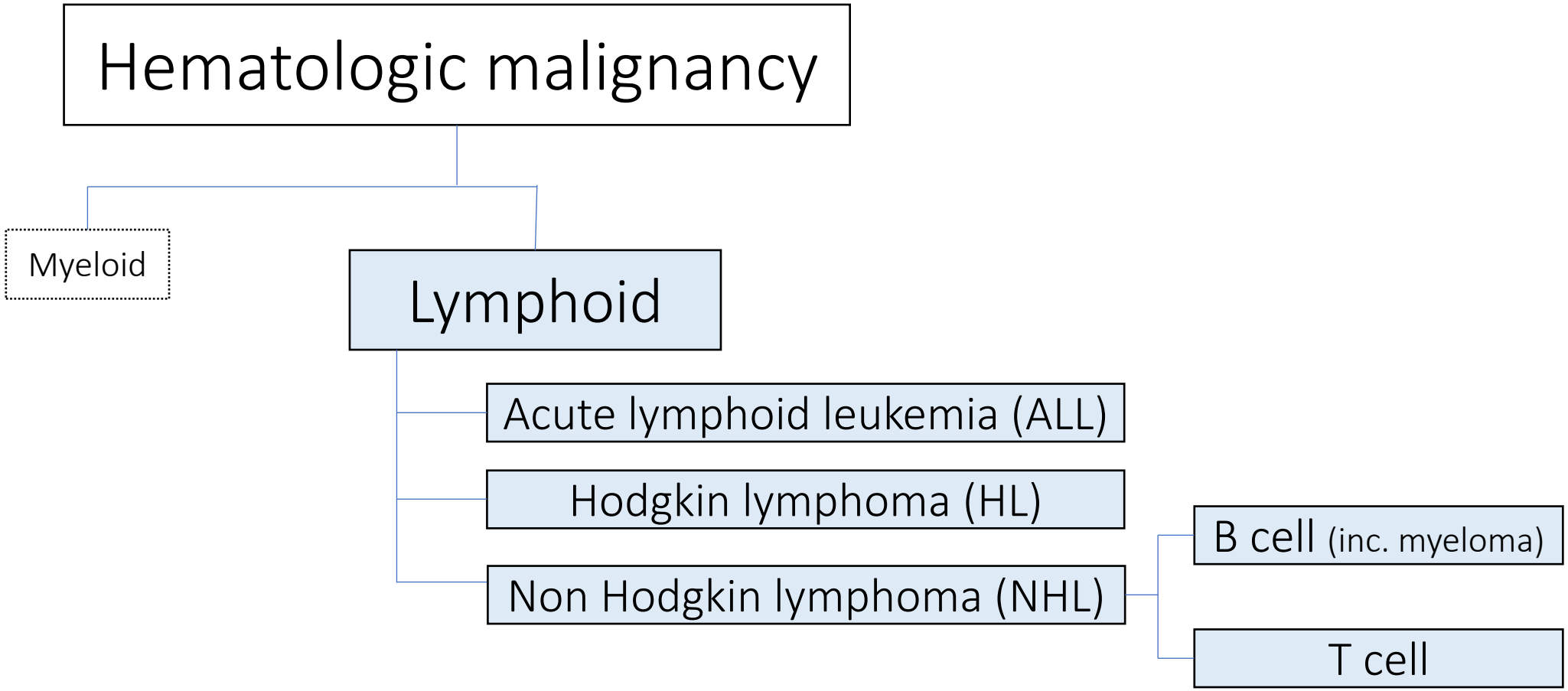
Overview



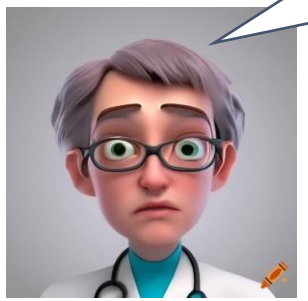
Overview


Hematologic malignancy
Myeloid
Lymphoid
Acute myeloid leukemia (AML)
Myelodysplastic neoplasms (MDS)
Myeloproliferative neoplasms (MPN)

Overview

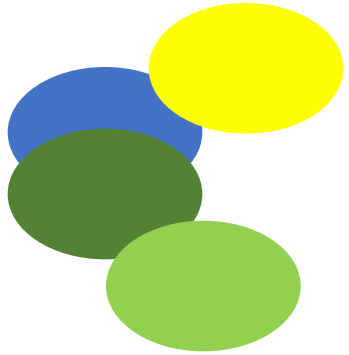

Hematologic malignancy
Myeloid
Lymphoid
Acute lymphoid leukemia (ALL)
Hodgkin lymphoma (HL)
Non Hodgkin lymphoma (NHL)
B cell (inc. myeloma)
T cell

When to worry?



MGUS vs myeloma (or lymphoma)

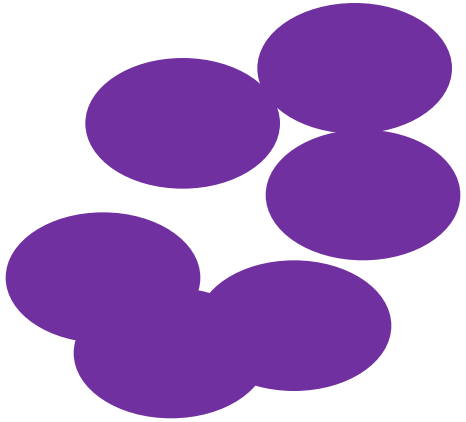
Plasma cells

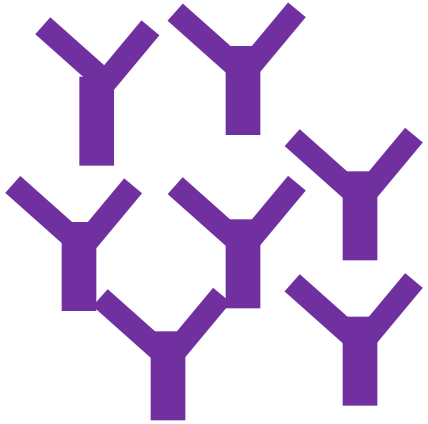


Normal polyclonal plasma cells

Normal polyclonal antibodies

Normal and good job



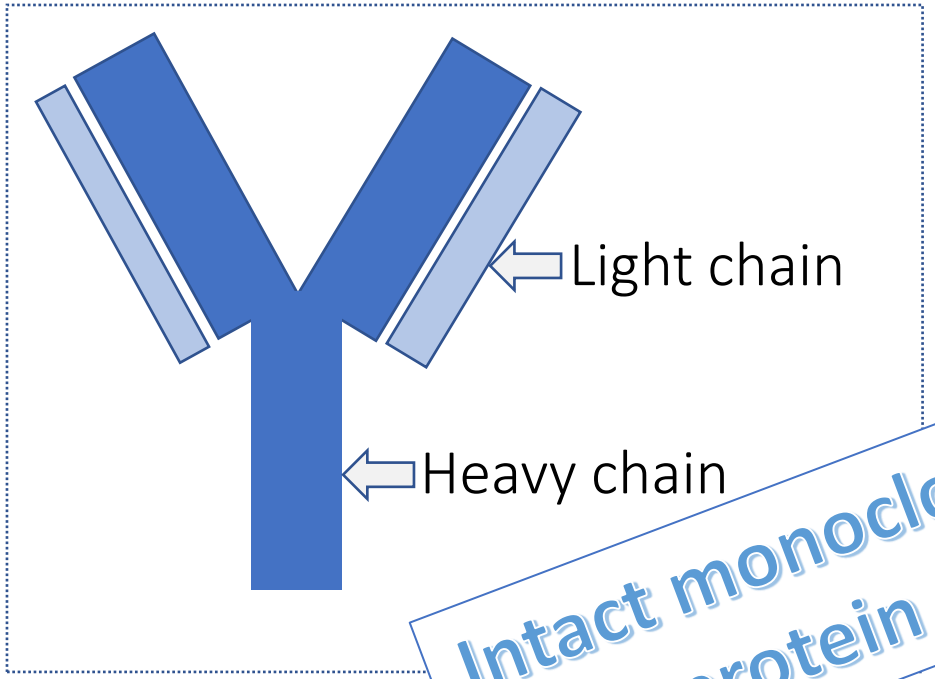


Abnormal **clonal** plasma cells

Abnormal **monoclonal** PROTEIN!

No job, just mischief

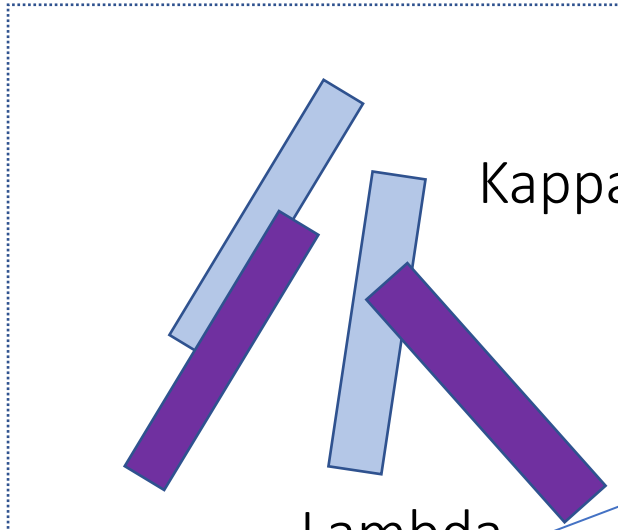
Monoclonal proteins



Intact monoclonal protein

IgG
IgA
IgM
IgD
IgE

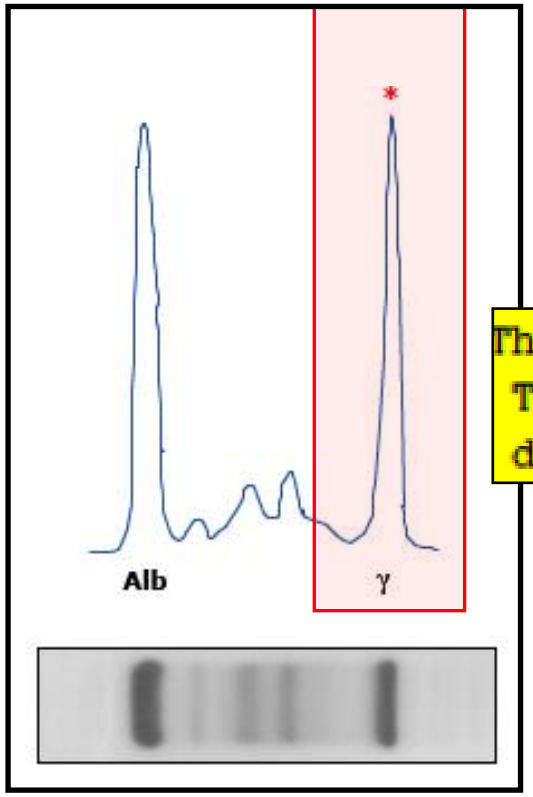
Kappa
Lambda



Monoclonal free light chain

SPEP and immunofixation

SPEP



SPEP tells you:

1. **Size** of protein (please note: **GRAMS**/litre)
2. Whether or not it is **monoclonal**

And…the information is in the **comment!**

There is a dense monoclonal band (approx. 48 g/L) in the gamma region. This will be investigated by immunofixation. Gamma globulins are decreased. Reviewed by Dr D Li,

SPEP and immunofixation

Immunofixation

Immunofixation tells you:

1. Heavy and light chain **isotype**

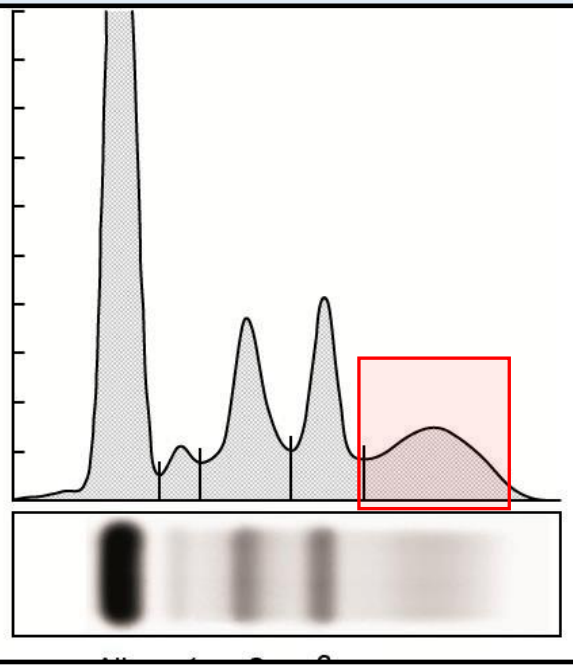
And…the information is in the **comment!**

Comment:

Large monoclonal IgG kappa band in the gamma region **in serum.**

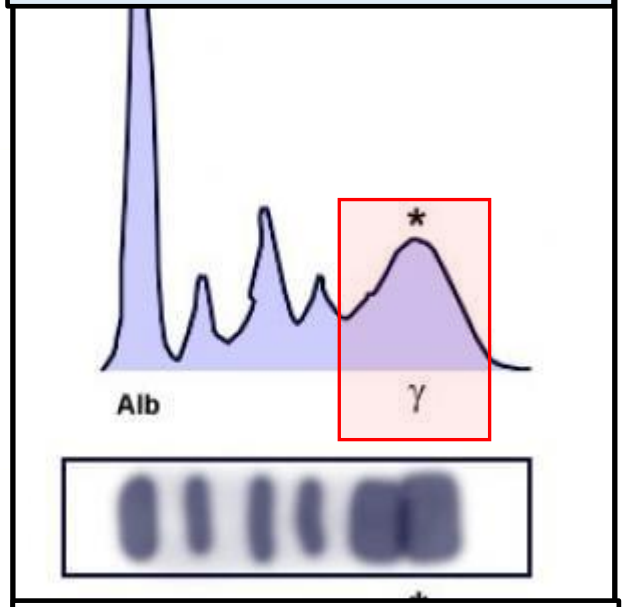
To worry or not to worry? (about hematologic malignancy)

Normal

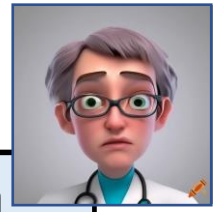


Nothing to worry about!

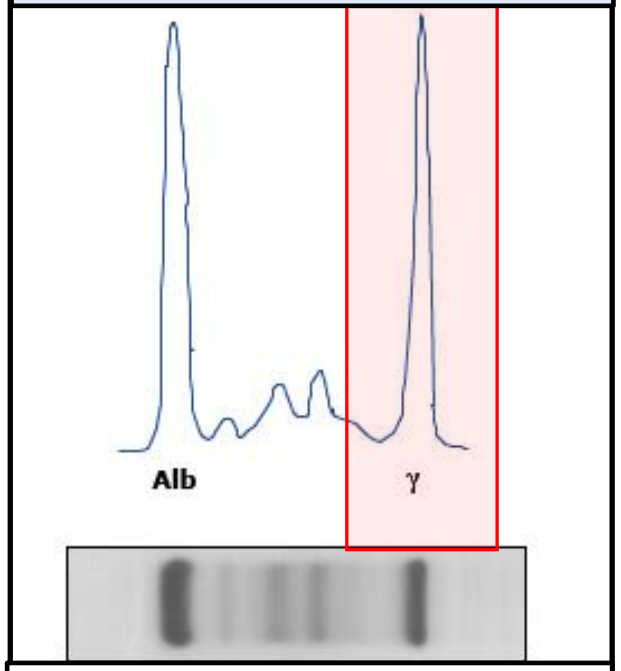
Polyclonal hypergammaglobulinemia



Do not ignore, but **almost never** heme malignancy



Monoclonal protein

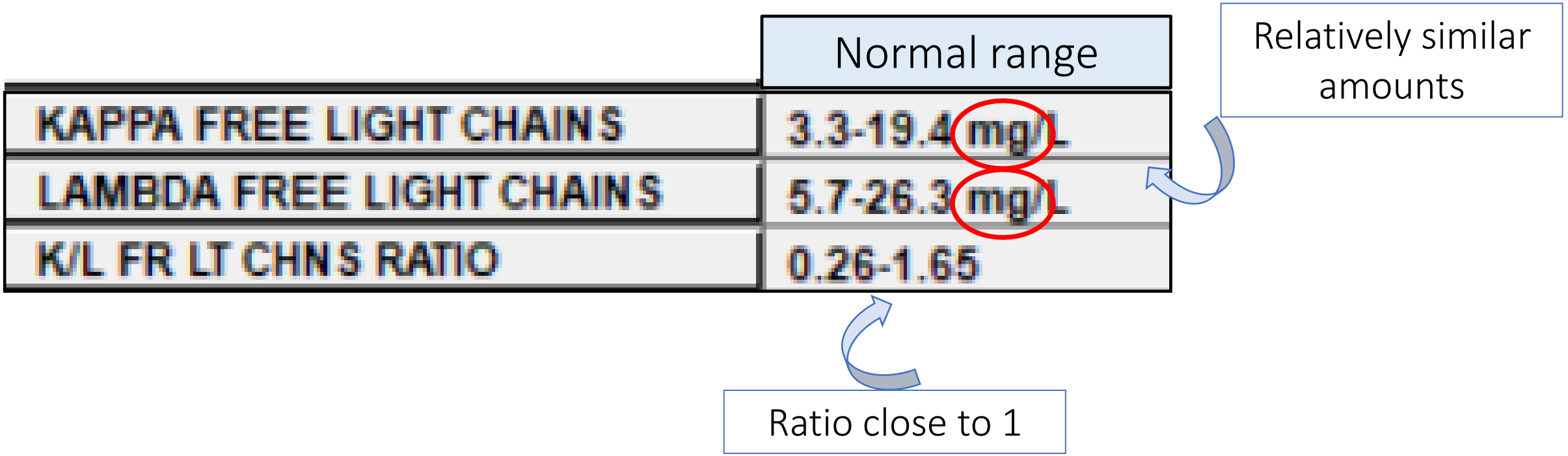


This could be myeloma or lymphoma!

To remember:

- With SPEP and immunofixation, the answer is in the **comment!**
- These tests detect M proteins in the **GRAM**/L range, ie. will miss small monoclonal free light chains (**MILLIGRAM**/L range)
- **Polyclonal** hypergammaglobulinemia almost never means hematologic malignancy

Free light chain assay



If one light chain isotype is high, **ratio** will be skewed = **clonality!**

Abnormal free light chain assays?

Monoclonal **kappa** free light chains

KAPPA FREE LIGHT CHAINS	3.3-19.4 mg/L	595.0 h
LAMBDA FREE LIGHT CHAINS	5.7-26.3 mg/L	2.4 l
K/L FR LT CHNS RA	0.26-1.65	247.92 h

Yes, worry!

Monoclonal **lambda** free light chains

KAPPA FREE LIGHT CHAINS	3.3-19.4 mg/L	1.4 l
LAMBDA FREE LIGHT CHAINS	5.7-26.3 mg/L	16608.4 h
K/L FR LT CHNS RATIO	0.26-1.65	See Detail @a7

Abnormal free light chain assays?

Mild polyclonal hypergammaglobulinemia

KAPPA FREE LIGHT CHAINS	3.3-19.4 mg/L	25.6 h
LAMBDA FREE LIGHT CHAINS	5.7-26.3 mg/L	29.2 h
K/L FR LT CHNS RATIO	.26-1.65	0.88

Normal

Not worrisome!

Mild kappa excess

KAPPA FREE LIGHT CHAINS	3.3-19.4 mg/L	40.4 h
LAMBDA FREE LIGHT CHAINS	5.7-26.3 mg/L	25.7
K/L FR LT CHNS RATIO	0.26-1.65	1.57

Normal

What about UPEP?

- UPEP (cheap!) and free light chain assay (not cheap!) measure the same thing (monoclonal free light chains), with FLC assay being more sensitive

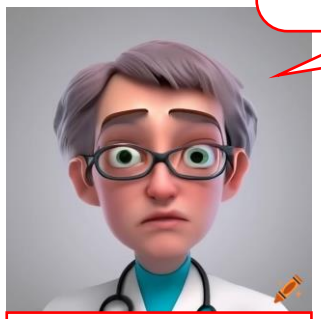
- Abnormal free light chain assay values are part of diagnostic criteria for myeloma, not true for UPEP results

- Free light chain assay provides good quantitative information and is very useful for **monitoring** myeloma as well

To remember:

- The free light chain assay is only abnormal if the **ratio** is abnormal
- Free light chains are present in small (**MILLIGRAM**/L) amounts
- Almost 20% of myelomas secrete monoclonal free light chains only, **can be missed with SPEP**

We can’t talk about myeloma without talking about…



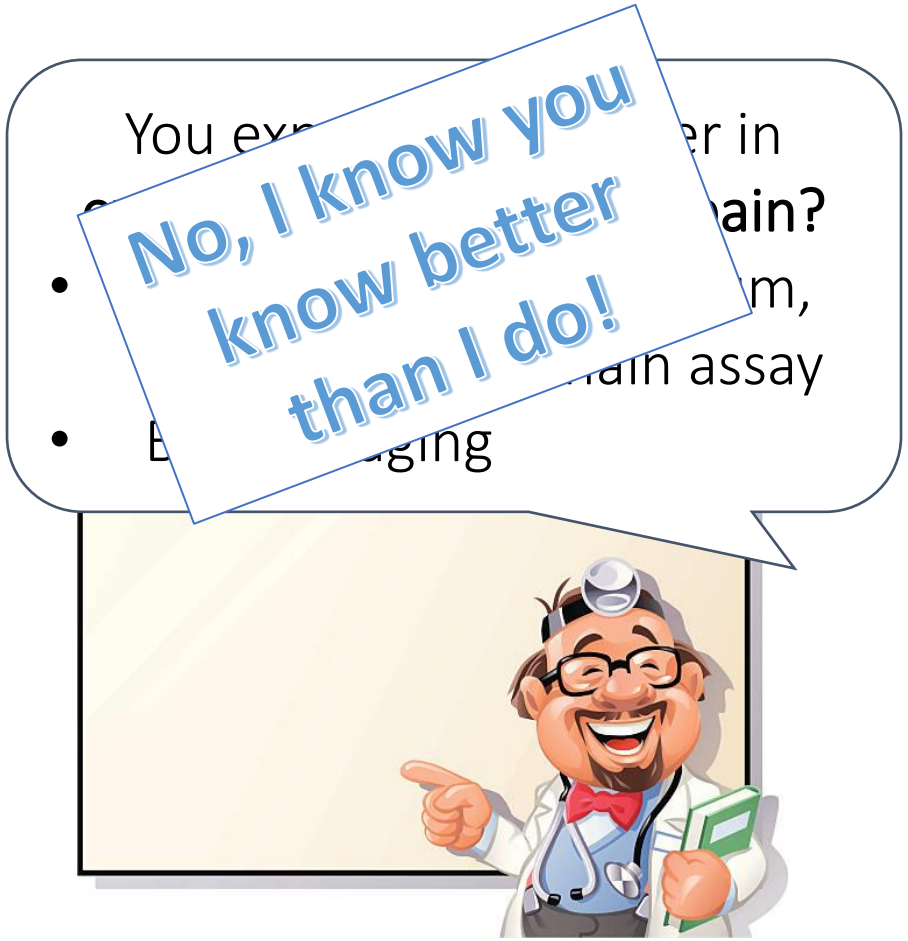
Ahhh! This patient has myeloma!

ME

Another patient with back pain…

YOU

Really?



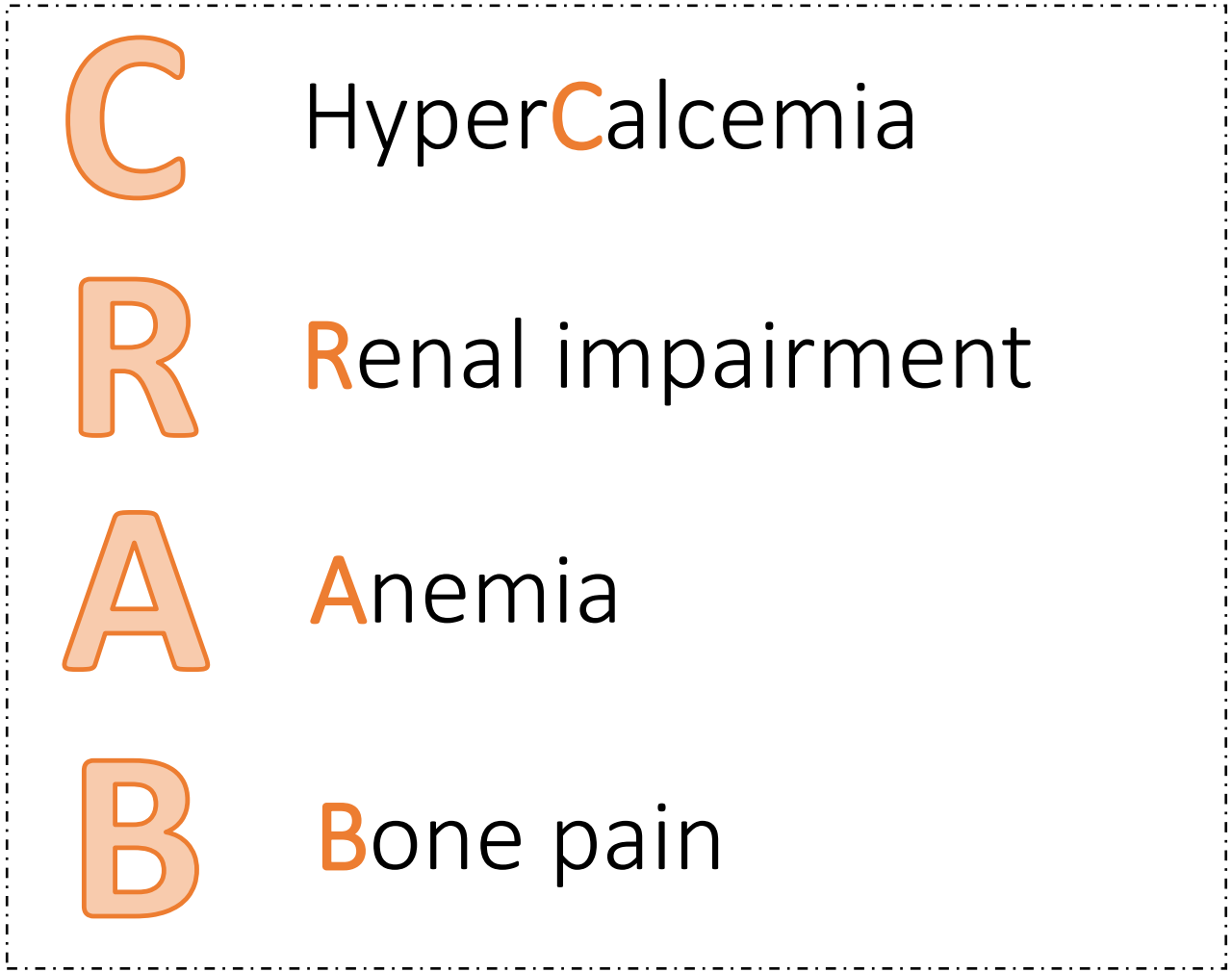
Guideline for the
Evidence-Informed Primary Care Management of **Low Back Pain**

If cancer or infection is suspected, order the appropriate blood tests. In the absence of red flags, no laboratory tests are recommended.

For acute low back pain (no red flags), diagnostic imaging tests, including X-ray, computed tomography (CT), and magnetic resonance imaging (MRI) are not indicated.

The complaint I hear from myeloma patients is **repeated visits** with back pain before diagnosis

CRAB criteria for myeloma



To worry or not to worry?

Case 1

- 67 y old with osteoporosis
- Feeling perfectly well
- SPEP: 2.3 M-protein
- UP
- CBC
- Calcium normal
- Creatinine normal

MGUS

Case 2

- 67 y old with no medical problems
- Fatigued, 10 lb weight l ip pain
- SPEP: 78 g/L
- UPEP K chains
- Hb 100, WBC 3.5
- Calcium 2.8
- Creatinine 150

Myeloma

MGUS vs. myeloma

Elective referral

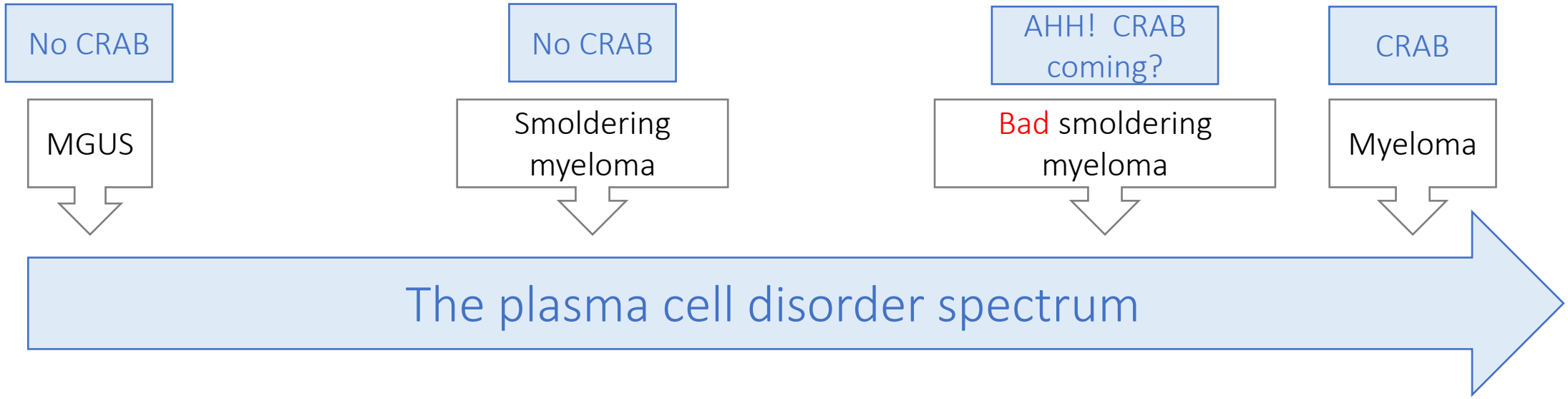
Urgent referral!

	MGUS	Myeloma
Frequency	Common	Uncommon
Category	Clonal, premalignant	Clonal, malignant
Symptoms	No symptoms	Bone pain! Unwell.
CRAB	No CRAB	Yes CRAB
M protein size	<30 g/L	Any size, usually big
Bone marrow plasma cells	<10%	>10%

To remember:

- If the M protein is **>30 g/L**, this is **NOT MGUS**
- With **myeloma**, the M protein can be **ANY SIZE**

A bit of a more sophisticated view



- **"Ultra high risk"** smoldering myeloma
- Risk of progression of > 80% over 2 yrs
- Certain defining features = **SLiM criteria**

Which brings us to SLiM CRAB

There is a bit more to myeloma than CRAB…

SLiM CRAB

S Bone marrow clonal plasma cells **>**Sixty%

Li Light chain ratio >100, with involved light chain >100 mg/L

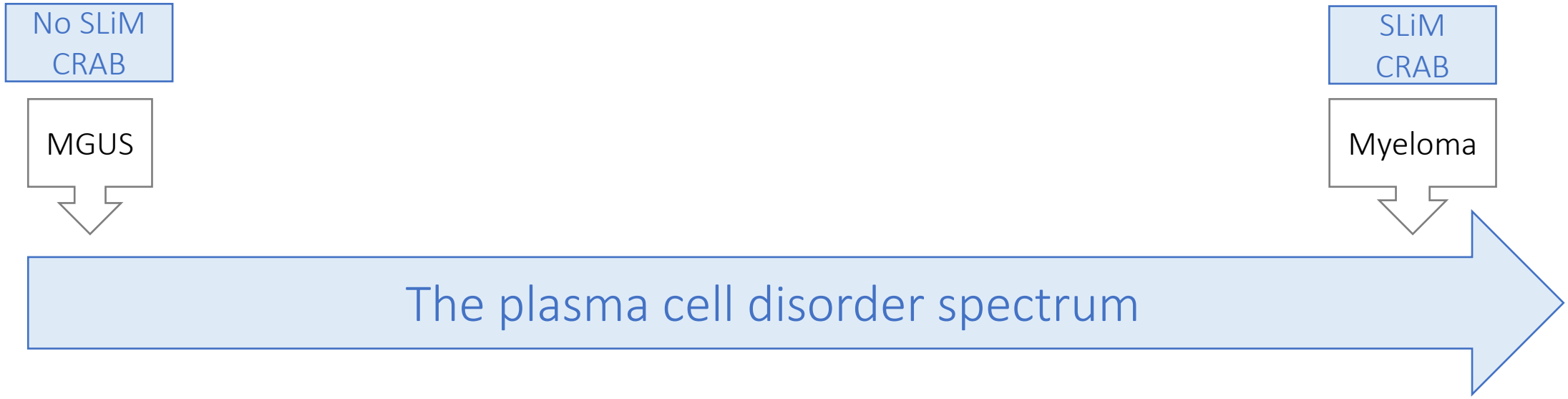
M >1 bone lesion on whole body MRI

Such high risk for progression to CRAB, now part of diagnostic criteria for myeloma. **Just treat.**

SLiM criteria in your office

Light chain ratio >100, with involved light chain >100 mg/L

Today’s view, MGUS vs. myeloma



To worry or not to worry?

Case 3

- 67 yr old with no medical problems
- Fatigued, 10 lb weight loss, hip pain
- SPEP: 78 g/L IgG K
- FLC assay, ratio 4
- Hb , plts 100, WBC 3.5
- Calcium 2.8
- Creatinine 150

IgG K myeloma

Case 4

- 67 yr old with foot numbness
- Otherwise perfect pain
- SPEP:
- FLC ratio 1000
- CBC
- Calcium normal
- Creatinine normal

K light chain myeloma

To worry about what?

Case 5

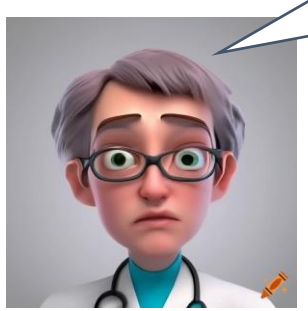
- 67 y old with no medical problems
- Fatigued, 10 lb weight loss
- SPEP: 78 g/L IgM protein
- FLC assay: K [illegible], L [illegible], ratio 4
- Hb 105 g/L, plts 100, WBC 3.5
- Calcium normal
- Creatinine normal

Lymphoplasmacytic lymphoma/ Waldenstrom's macroglobulinemia

To remember:

- If the M protein is **IgM,** think **LYMPHOMA,** not myeloma
- Big IgM M proteins can cause **hyperviscosity**

When to worry?



Low blood counts

To worry or not to worry?

Case 6

- 67 y old with no ma… roblems
- Pre… weight loss … in neck
- CBC… is normal except Hb 111 g/L

Think LYMPHOMA!

“B symptoms”

1. Fevers >38 deg C
2. Weight loss > 10% over 6 m
3. **Drenching** night sweats

To worry or not to worry?

(about hematologic malignancy)

Case 7

- 67 y old with no medical problems
- Presents with fatigue
- Hb 67 g/L
- MCV 60
- Platelets normal
- WBC normal

Microcytic anemia

T halassemia

A nemia of chronic disease/inflammation

I ron deficiency

L ~~ead poisoning~~

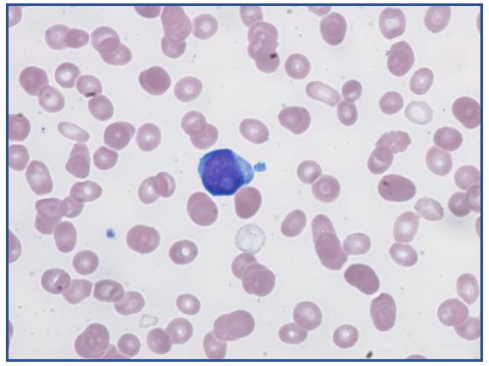
S ~~ideroblastic anemia~~

Isolated microcytic anemia is almost NEVER a hematologic malignancy!

To worry or not to worry?

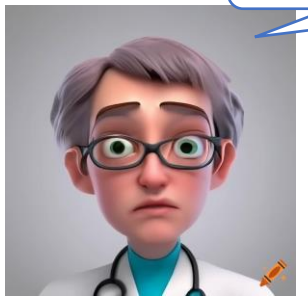
Case 8

- 67 y old with no medical problems
- Fatigued, possible weight loss
- Hb 107 g/L
- MCV 102
- Plts 150
- WBC 4



Hemepath blood film comment:
"Rare circulating **blast**"

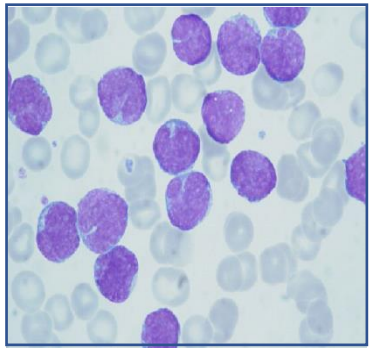
Blasts are NEVER normal



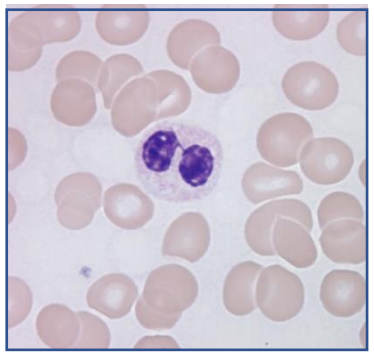
To remember:

- Blasts are NEVER normal
- By definition - >20% blasts = acute leukemia
- *Almost always* mean **hematologic malignancy**
  - Acute leukemia
  - Advanced MDS
  - Advanced MPN

Other bad things on blood films

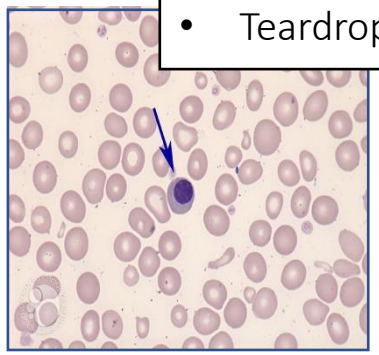


Circulating lymphoma cells



Dysplasia (=MDS)

- Left shifted white cells
- Nucleated red cells
- Teardrops



Leukoerythroblastosis (=marrow fibrosis)

To remember:

- The hematopathologist comment on the blood film can be very helpful
- Can be obvious worrisome findings even without major cytopenias

To worry or not to worry?

(about hematologic malignancy)

Case 9

- 67 y old with lupus on no meds
- Feeling perfectly
- Hb 120
- M
- Plt
- WBC 1, neutrophils 0.1

Immune neutropenia

Case 10

- 67 y old with no medi problems
- Feeling quit igue
- Hb
- M
- Plts
- WBC trophils 1.8

Early MDS or indolent lymphoma

To remember:

- The degree of cytopenia(s) does not *always* correlate with concern
- Although severe and/or multiple cytopenias are generally more concerning
- Early MDS or indolent lymphomas can present in healthy patients with mild cytopenias

Cytopenia red flags

History

- B symptoms
- Unexplained bone pain
- Recurrent or persistent bacterial infections
- Bleeding manifestations
- Abdominal discomfort, early satiety
- Lumps

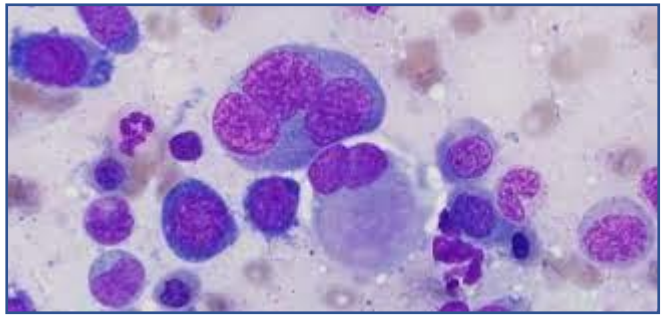
Physical exam

- Looking unwell
- Lymphadenopathy
- Splenomegaly
- Bruising, petechiae

Bloodwork hints

- Multiple cytopenias
- Anemia not microcytic
- Low reticulocytes
- Worrisome blood film
- No obvious “benign” explanation
  - E.g. low ferritin
- Other “malignant” results
  - E.g. monoclonal protein

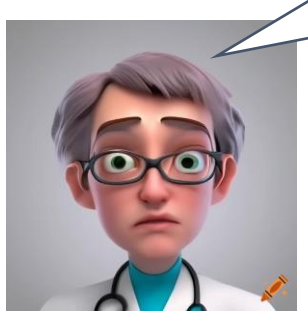
Myelodysplastic syndromes



What is MDS?

- **A hematologic malignancy!**
- A form of bone marrow failure so **blood counts are low**
- May have **dysplastic changes** on blood film
- A **spectrum** from asymptomatic to almost acute leukemia
- All can evolve to acute leukemia
- Bone marrow biopsy is required for diagnosis
- Treatments vary, tailored to how bad the disease is

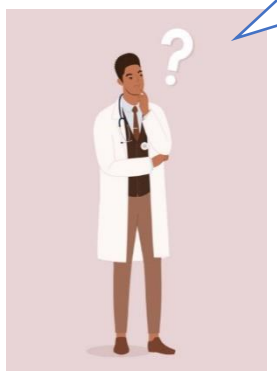
When to worry?



High blood counts

Always the first question for leukocytosis!

What is the differential? To answer the question – is this myeloid or lymphoid?



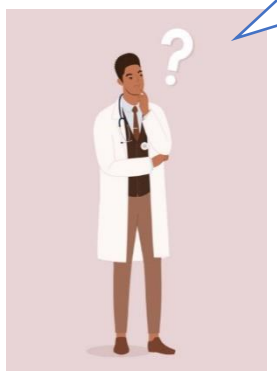
This patient has a **myeloproliferative neoplasm**!

WBC	87.2
RBC	3.55
Hemoglobin	110
Hematocrit	0.32
MCV	91
MCH	31.0
MCHC	340
RDW	14.5
Platelets	223
Neutrophils	77.6
Lymphocytes	4.4
Monocytes	3.5
Eosinophils	0.0
Basophils	0.0
Granulocytes Immature	1.7

High WBC

Always the first question for leukocytosis!

What is the differential? To answer the question – is this myeloid or lymphoid?



WBC	**155.4**
RBC	**3.29**
Hemoglobin	**83**
Hematocrit	**0.28**
MCV	85
MCH	25
RDW	**15.2**
Platelets	**147**
MPV	**8.9**
Neutrophils	4.4
Lymphocytes	**144.3**
Monocytes	**6.3**
Eosinophils	0.1
Basophils	0.1
Granulocytes Immature	**0.3**

High WBC

This patient has a **lymphoma**!

To worry or not to worry?

Case 11

- 67 y old with DM2, d… …mia, HTN, smoker, obesit…
- Mul…
- H…
- M…
- WB…
- Plate…
- Last CB… …188

Increased Hb d/t volume depletion, sleep apnea & smoking

Case 12

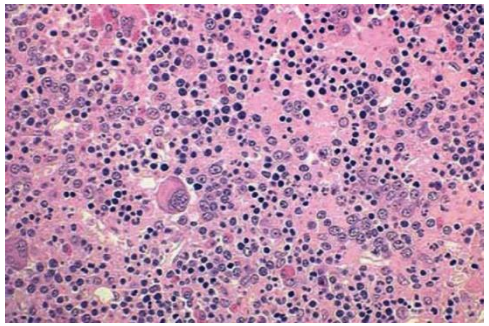
- 67 y old with no medica… …oblems
- Presents with P…
- Hb 16…
- …
- W… …phils 18
- Plt…
- Last CBCD 2 y ago - slightly elevated counts

Polycythemia vera

Myeloproliferative neoplasms

What are MPNs?

- A group of **hematologic malignancies!**
- Feature **bone marrow proliferation** so **blood counts are high***
- For some the big concern is **increased thrombosis** (ET, PV)
- All can evolve to myelofibrosis with low blood counts
- All can evolve to acute leukemia
- Bone marrow biopsy is required for diagnosis, but special blood tests can be supportive (**JAK2 mutation** – a driver mutation in MPNs, **Philadelphia chromosome** – mandatory for CML diagnosis)
- Treatments vary widely



Essential thrombocythemia (ET)
Polycythemia Vera (PV)
Myelofibrosis (MF)
Chronic myeloid leukemia (CML)

Essential thrombocythemia

WBC	6.9
RBC	**5.28**
Hemoglobin	146
Hematocrit	**0.46**
MCV	87
MCH	28
RDW	**16.2**
Platelets	**967**
MPV	10.4
Differential; Manual	
Neutrophils	5.0
Lymphocytes	1.2
Monocytes	0.5
Eosinophils	0.1
Basophils	0.0

Normal WBC

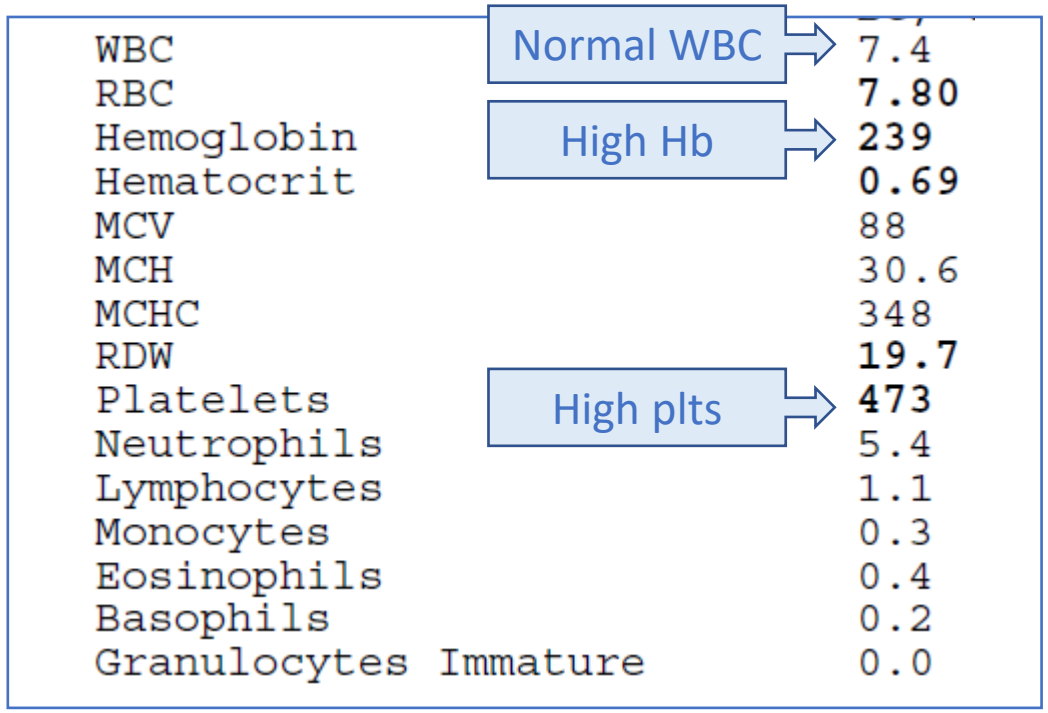
Normal Hb

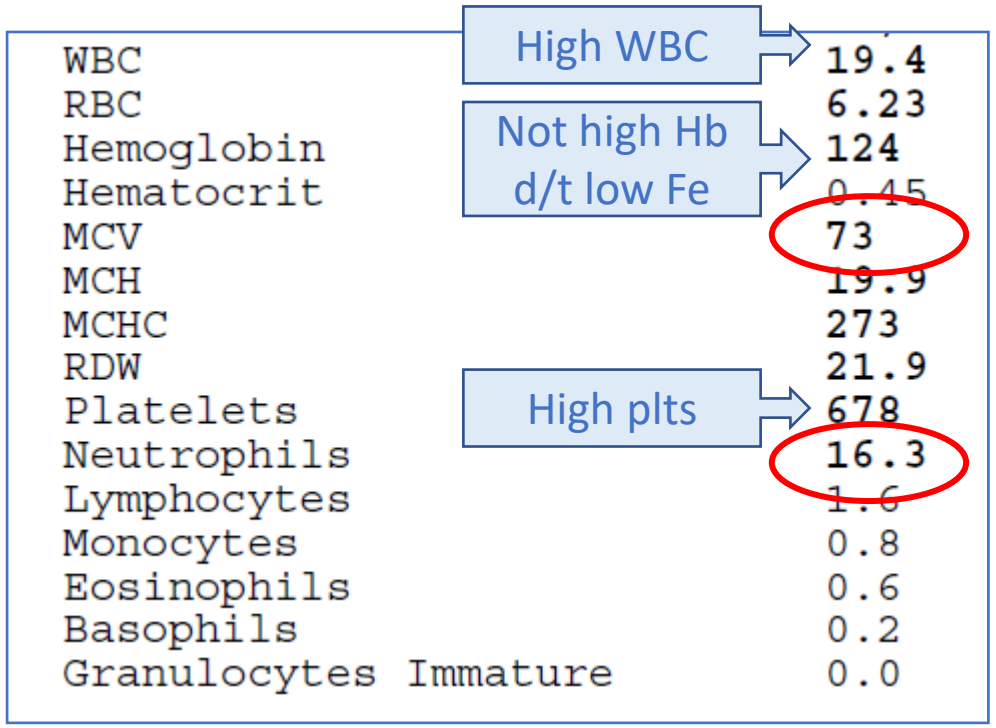
High plts

Pattern:

- **Isolated** thrombocytosis
- No reactive cause of thrombocytosis
- 50% JAK2 mutation positive

Polycythemia vera

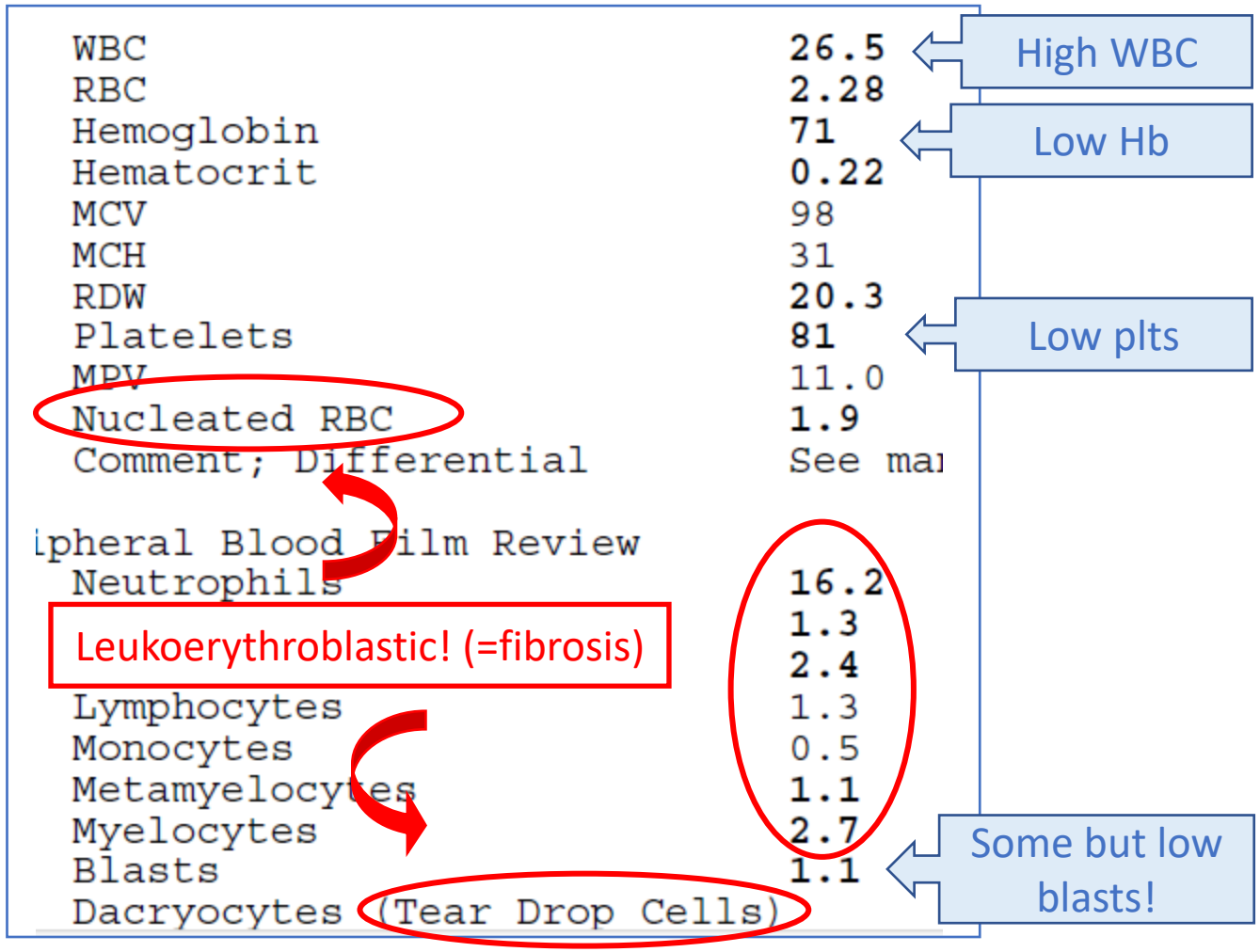




Pattern:

- Yes high Hb, but often **PANCYTOSIS** (beware Hb not being high due to low iron)
- Almost all JAK2 mutation positive
- Low erythropoietin level

Myelofibrosis



Pattern:

- Depends on how bad fibrosis is
- **Anemia is universal**
- White cells can be high (maturing white cells, **NOT lots of blasts**), normal or low
- Platelets can be high, normal or low
- Leukoerythroblastic blood film
- 50% JAK2 mutation positive

Chronic myeloid leukemia (chronic phase)

WBC	187.6
RBC	2.88
Hemoglobin	86
Hematocrit	0.26
MCV	91
MCH	30
RDW	20.6
Platelets	922
MPV	12.3
Neutrophils	130.6
Lymphocytes	5.1
Monocytes	0.0
Eosinophils	0.0
Basophils	0.0
Granulocytes Immature	0.0
Nucleated RBC	0.1
Metamyelocytes	11.8
Myelocytes	38.8
Blasts	1.3

Very high WBC

Low Hb

High plts

Some but low blasts!

Pattern:

- High WBC, consists of maturing white cells, **NOT lots of blasts**
- Often at least mild anemia
- Platelets variable, often high
- Philadelphia chromosome positive [(t(9;22) or BCR:ABL rearrangement]

You can order!

And erythropoietin level on standard requisition

CANCER GENETICS AND GENOMICS LABORATORY

MYELOID TESTING

BC CANCER
DEPT. OF PATHOLOGY AND LABORATORY MEDICINE
ROOM 3307 - 600 WEST 10TH AVENUE
VANCOUVER BC V5Z-4E6

604-877-6000 EXT 67-2094
FAX: 604-877-6294
MON-FRI 8:30AM-4:30PM
WWW.CANCERGENETICSLAB.CA
CANCERGENETICSLAB@BCCANCER.BC.CA

Myeloproliferative Neoplasm	□ *BCR::ABL1* t(9;22) FISH □ Karyotype for MF or CMML (BM only)	**Single-gene testing** □ query *JAK2* V617F MPN

For lymphoma with circulating lymphoma cells, can order "flow cytometry for lymphoma" on standard requisition. With LN, can refer to surgeon for LN biopsy

To remember:

- For high counts, the higher the more worrisome
- Each MPN has a different pattern
- For **MPNs**, you can order **Philadelphia chromosome**, **JAK2 mutation** and **erythropoietin** testing
- For **lymphomas**, you can order **flow cytometry, CT scans,** can **refer to surgeon** for **lymph node biopsy**

MGUS vs. myeloma (or lymphoma)

pearls

1. Keep doing your best with back pain! (so as to not miss myeloma)
2. If an M- protein is **> 30 g/L**, this is **not MGUS**
3. **Myeloma** can have **any size** of an M protein (yes, usually big)
4. Without UPEP or FLC assay, will **miss ~20%** of myelomas
5. With FLC assays, only significantly abnormal **ratios** matter
6. A **very abnormal** FLC assay **diagnoses myeloma** (involved light chain >100, ratio >100)
7. Remember **SLiM CRAB** for myeloma diagnosis
8. **IgM** M-proteins mean **lymphoma**, not myeloma
9. **Polyclonal** hypergammaglobulinemia is NOT worrisome for heme malignancy

Low blood counts pearls

1. **Not** every anemia is iron deficiency
2. Isolated **microcytic** anemias almost **never** mean hematologic malignancy
3. The **degree** of cytopenia does **not always** correlate with concern
   (yes, severe or multiple cytopenias more concerning)
4. Healthy patients with mild cytopenias may have early MDS or indolent lymphoma
5. Look at the **blood film comment** for worrisome findings
6. Think about the **red flags** for cytopenias

High blood counts pearls

1. With **leukocytosis**, you must look at the WBC **differential** (to answer the question - is this an MPN or a lymphoma)
2. A **very high** hemoglobin does **not always mean polycythemia vera** (relatively common finding with smokers, metabolic problems, sleep apnea, diuretics)
3. Each **MPN** has a **specific pattern**
4. For **MPNs,** you can order testing for **Philadelphia chromosome** (CML), **JAK2 mutation** (PV, ET, MF), **erythropoietin level** (low in PV)
5. For **lymphomas**, you can order flow cytometry, CT scans (and ref to surgery for lymph node biopsy of course!)

Top 3 “misses”!

Blaming anemia on iron deficiency when the patient is not iron deficient

Misinterpreting free light chain assay results

Missing myeloma related back pain

Thank you and questions?