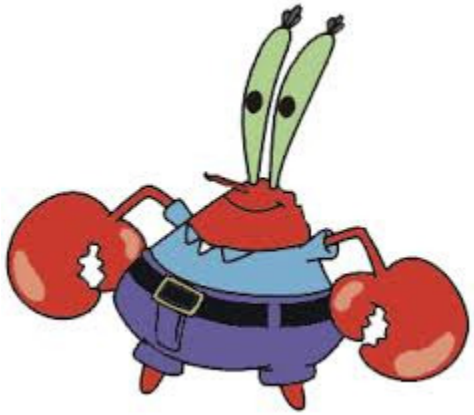
CancerCare Manitoba

Getting to Know Mr.CRAB



How to Diagnose Multiple Myeloma

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Disclosures

FINANCIAL DISCLOSURE

Grants/Research Support: Clinical trial funding from Celgene, Janssen, Onyx, Merck, Bristol Myers Squibb, Millenium

Speaker bureau/Honoraria amounts: None

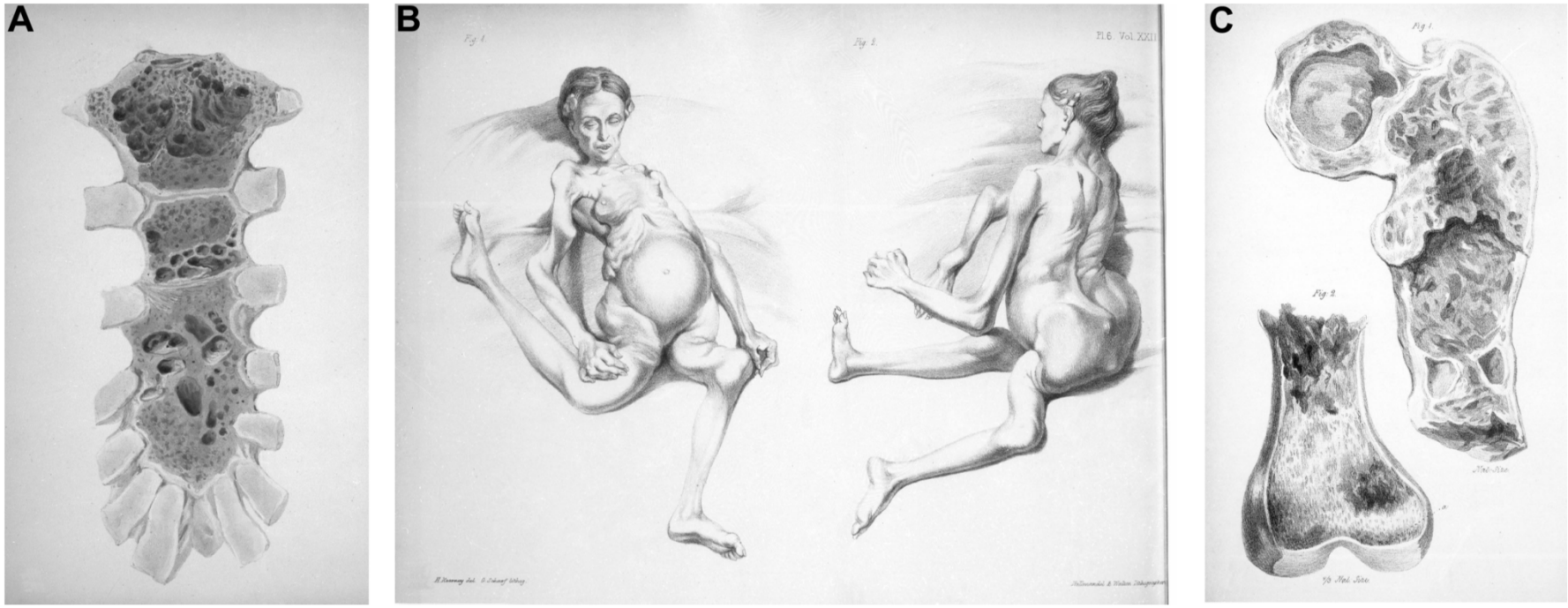
Consulting fees: None

Other: None

Objectives

By the end of this session, learners should be able to:

1) Know when to suspect a diagnosis of multiple myeloma
2) Order the appropriate initial investigations to diagnose multiple myeloma
3) Know when to refer a patient to a hematologist and identify emergency complications requiring immediate intervention



Sarah Newbury 39 female, first reported case of myeloma in 1844

III. *On a new substance occurring in the Urine of a patient with Mollities Ossium.*

By Henry Bence Jones, *M.A., F.R.S., Physician to St. George's Hospital.*

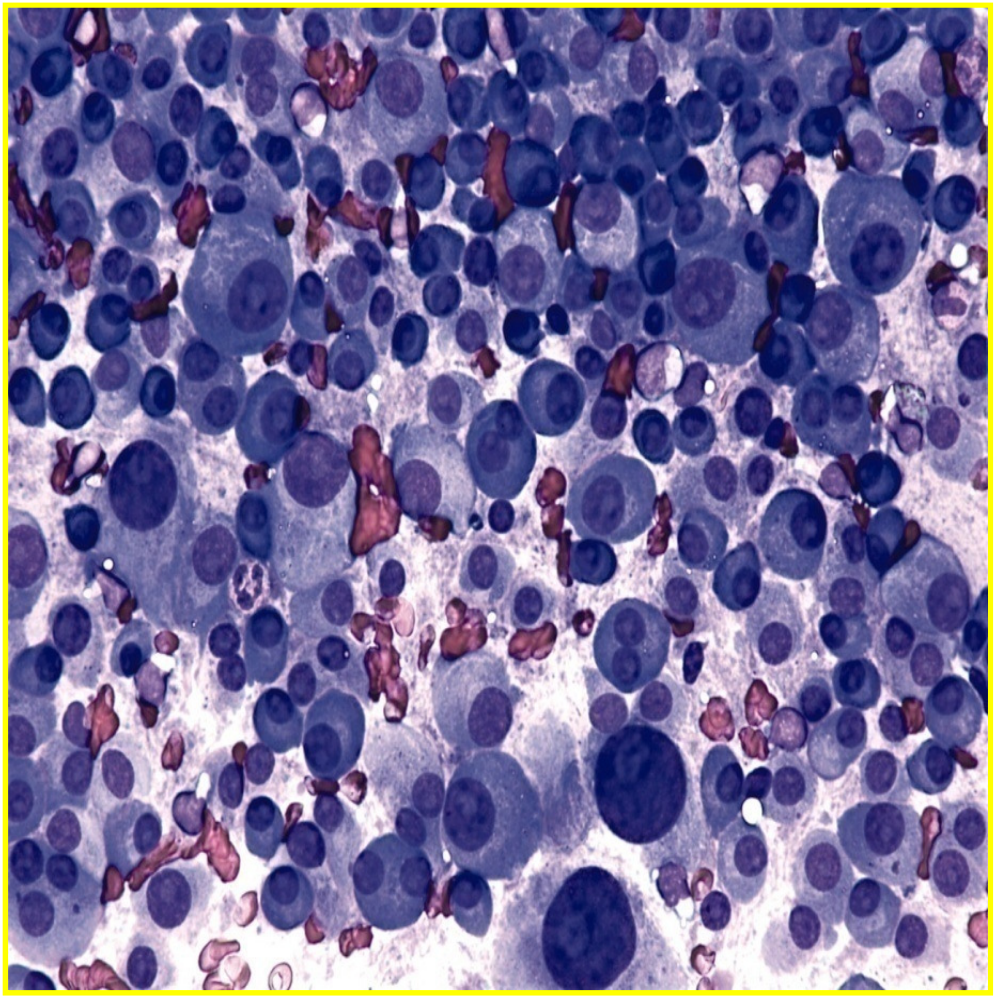
Received February 25,—Read April 22, 1847.

On the 1st of November 1845 I received from Dr. Watson the following note, with a test tube containing a thick, yellow, semi-solid substance:—"The tube contains urine of very high specific gravity; when boiled it becomes highly opake; on the addition of nitric acid it effervesces, assumes a reddish hue, becomes quite clear, but, as it cools, assumes the consistence and appearance which you see: heat reliquifies it. What is it?"

Bence Jones, Phil Trans R Soc Lond 1848

What is Multiple Myeloma?

- A bone marrow cancer characterized by uncontrolled proliferation of clonal plasma cells
- Disease manifests with CRAB symptoms
  - **C** – Hypercalcemia
  - **R** – Renal Failure
  - **A** – Anemia
  - **B** – Bone disease – lytic lesions/bone fractures



What is Multiple Myeloma?

- 1% of all cancers and 15% of hematologic malignancies
  - ~2,700 new cases in Canada in 2015 (estimated 80 new cases in Manitoba)
  - Prevalence of ~7,500 across Canada
- Median age at diagnosis of 69 years
- Incurable malignancy characterized by multiple relapses

Canadian Cancer Society Statistics 2015

FIGURE 1.2 Percent distribution of estimated new cancer cases, by sex, Canada, 2016

Males
102,900
New cases

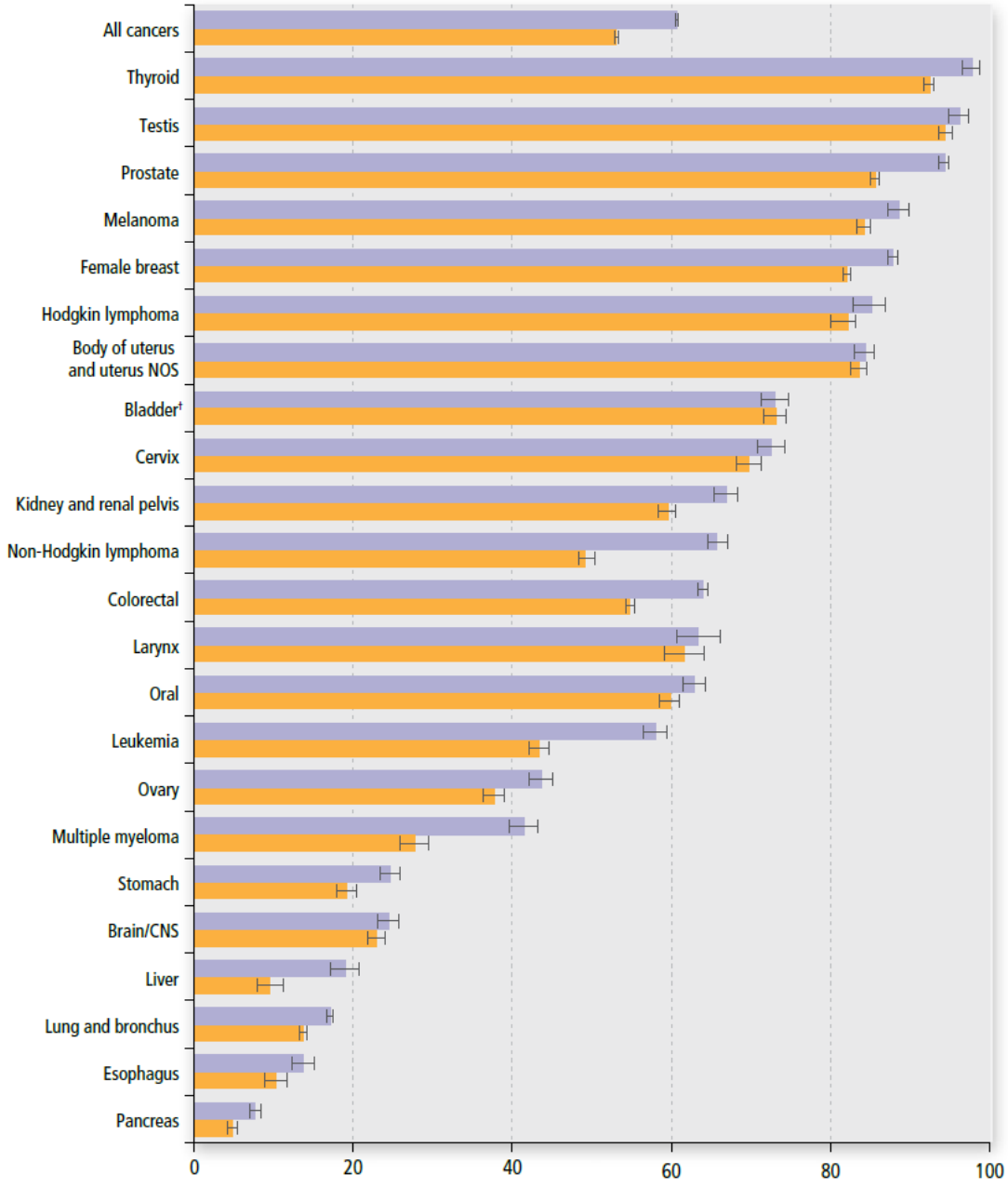
Prostate	21.0%
Colorectal	14.1%
Lung and bronchus	14.0%
Bladder	6.4%
Non-Hodgkin lymphoma	4.3%
Kidney and renal pelvis	4.0%
Melanoma	3.6%
Leukemia	3.4%
Oral	3.1%
Pancreas	2.5%
Stomach	2.1%
Esophagus	1.7%
Liver	1.7%
Brain/CNS	1.7%
Multiple myeloma	1.6%
Thyroid	1.5%
Testis	1.1%
Larynx	0.9%
Hodgkin lymphoma	0.5%
Breast	0.2%
All other cancers	10.7%

Females
99,500
New cases

Breast	25.8%
Lung and bronchus	14.1%
Colorectal	11.7%
Body of uterus and uterus NOS	6.6%
Thyroid	5.3%
Non-Hodgkin lymphoma	3.6%
Melanoma	3.1%
Ovary	2.8%
Pancreas	2.6%
Leukemia	2.4%
Kidney and renal pelvis	2.3%
Bladder	2.1%
Cervix	1.5%
Oral	1.5%
Stomach	1.3%
Brain/CNS	1.3%
Multiple myeloma	1.2%
Liver	0.6%
Esophagus	0.5%
Hodgkin lymphoma	0.5%
Larynx	0.2%
All other cancers	8.9%

Canadian Cancer Society 2016

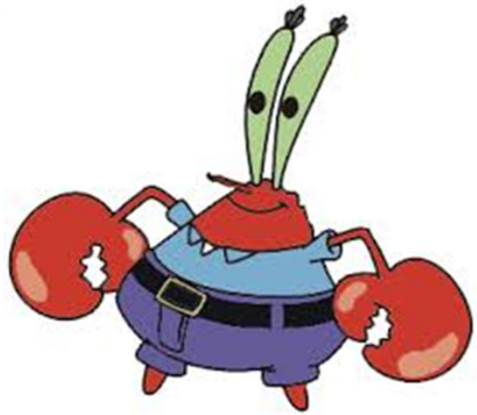
FIGURE 5.3 Five-year age-standardized net survival for selected cancers by time period, ages 15–99, Canada (excludi
2006–2008 versus 1992–1994



Canadian Cancer Society 2016

How does myeloma present?

- Study on 1027 consecutive patients referred to Mayo Clinic
  - Anemia – 73%
  - Bone pain – 58%
  - Elevated creatinine – 48%
  - Fatigue/generalized weakness – 32%
  - Hypercalcemia – 28%
  - Weight Loss - 24%



Kyle et al. Mayo Clinc Proc, 2003

Case presentation

- 73 year old female presents to family MD with a couple months history of fatigue and new low back pain
- No significant past medical history
- Physical exam unremarkable (no bony tenderness, no evidence of cord compression/neurologic compromise)
- CBC
  - Hb - 81 (previously 135 1 year ago), MCV 99.1, WBC – 9.1 (normal differential), platelets – 144
- Na 139, K 3.7, Ca – 2.58, Alb - 30,Creatinine 112 (previously in the 70s 1 year ago), urea 10.0

Case Presentation

- Questions
  - Do you think myeloma is a possibility here?
  - What investigations should you order to make the diagnosis?
  - When should you refer to hematology?

When to ORDER SPEP and how to INTERPRET RESULTS

WHEN TO ORDER AN SPEP:

- Unexplained anemia, back pain
- Osteopenia, osteolytic lesions, spontaneous fractures
- Renal insufficiency with bland urinary sediment
- Heavy proteinuria or Bence Jones proteinuria
- Hypercalcemia with normal PTH
- Hypergammaglobulinemia
- Immunoglobulin deficiency
- Unexplained peripheral neuropathy
- Recurrent infections
- Elevated ESR or serum viscosity
- Peripheral blood smear showing rouleaux

If clinical suspicion remains high for plasma cell disorder and SPEP is negative ➔ obtain serum free light chain ratio (SFLCR)

CRAB SYMPTOMS:**

C – Ca2+ >2.8
R – creatinine >177 umol/L or GFR <40mL per min
A – hemoglobin <100g/L or 20g/L below normal
B – lytic lesions
**Attributable to plasma cell disorder

OTHER SPEP RESULTS

POLYCLONAL GAMMOPATHY (reactive)

Investigate for other causes including:
- Liver disease
- Connective tissue disease I
- Infection

OLIGOCLONAL GAMMOPATHY (usually reactive)

Repeat test in 6 – 12 months if clinically indicated (see top box "When to order an SPEP")

ELEVATED FREE LIGHT CHAINS - NORMAL RATIO (reactive)

Investigate for other causes including:
- Kidney disease
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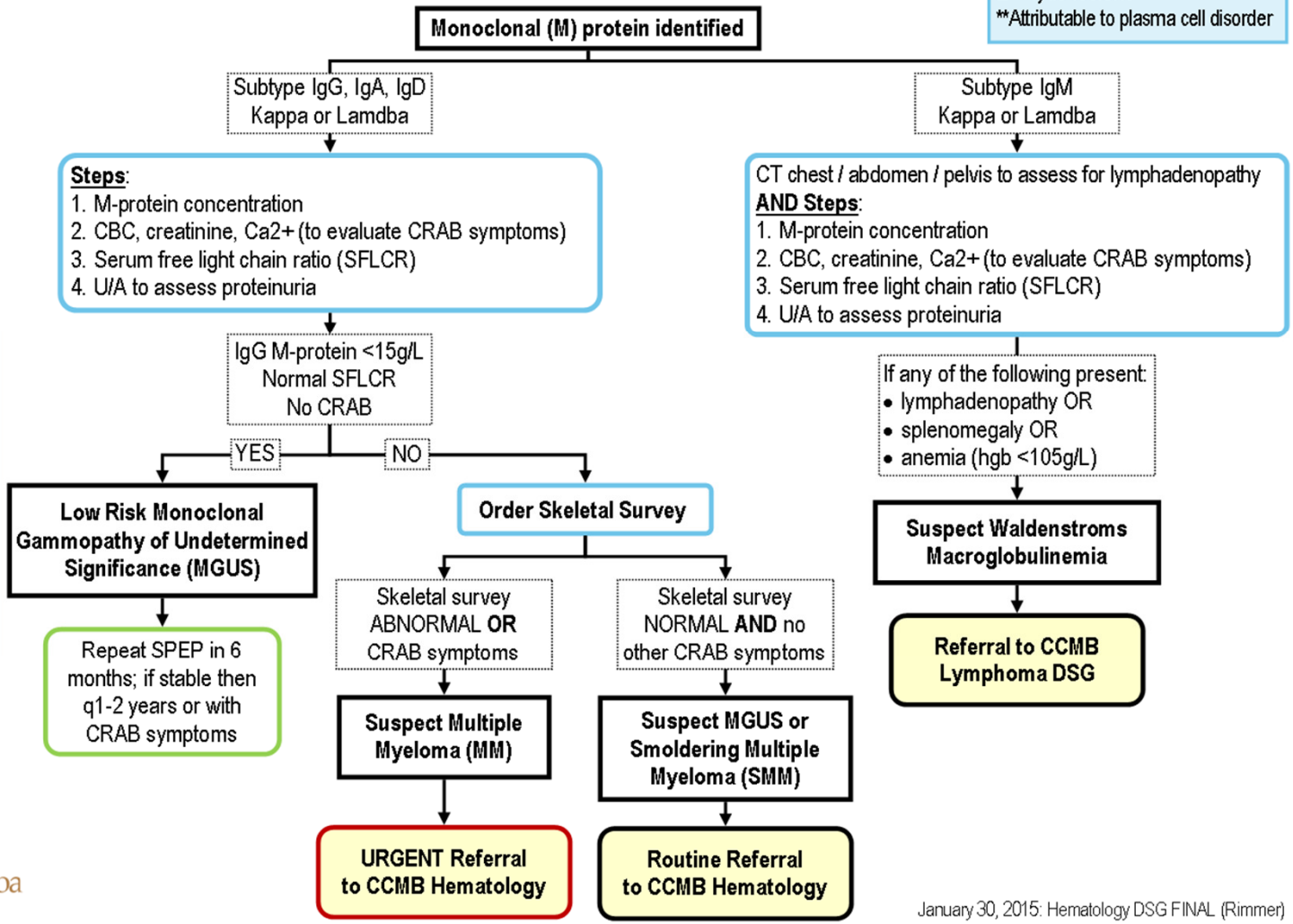

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Further Work Up

- X-ray lumbosacral spine shows L4 compression fracture
- Serum immunoglobulins
  - IgG – 4.06 g/L (low)
  - IgA – 0.3 g/L (low)
  - IgM – 0.3 g/L (low)
- Serum protein electrophoresis shows no monoclonal protein detectable
- Now What?

Monoclonal Proteins in Myeloma

- IgG – 52%
- IgA – 21%
- Light chain only – 16%
  - Seen only on UPEP or sFLC assay
- IgD – 2%
- Biclonal – 2%
- Non secretory – 3%
  - ~60% of these will be detectable using sFLC assay
- IgM – 0.5%
  - Most patients with a IgM monoclonal protein have a lymphoproliferative disorder or amyloidosis, not myeloma

Back to the case…

- Patient with lytic bone lesion and normocytic anemia
- Serum immunoglobulins
  - IgG – 4.06 g/L (low)
  - IgA – 0.3 g/L (low)
  - IgM – 0.3 g/L (low)
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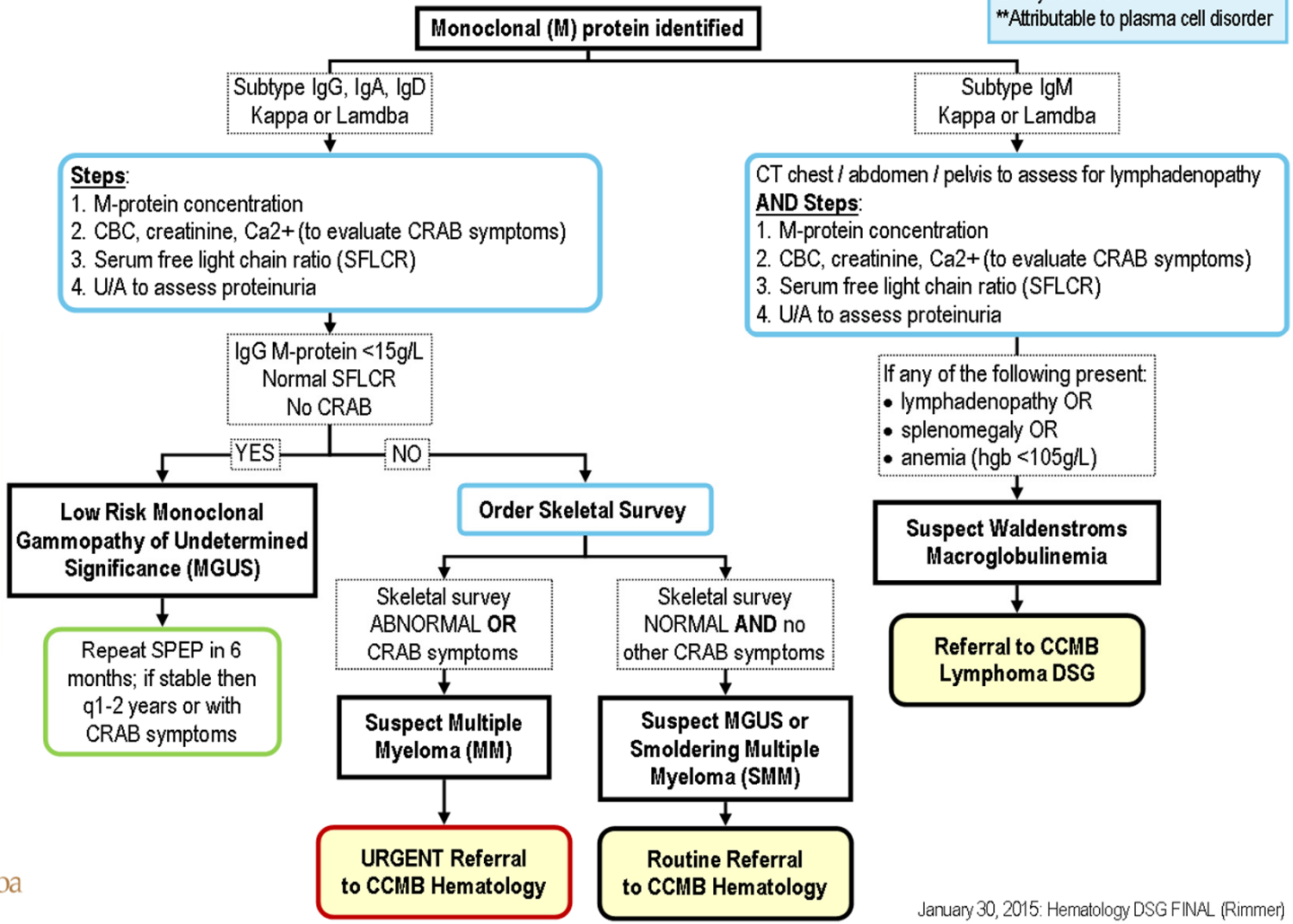

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Even Further Work Up

- 24 hour urine protein and urine protein electrophoresis
  - 4.2g/24hours proteinuria
  - Mainly consists of monoclonal lambda light chains (minimal albuminuria)
- Serum free light chain assay
  - Free kappa – 7.72 g/L
  - Free lambda – 2,224 g/L
  - Kappa/lambda ratio – 0.0034

Now What? Further Diagnostics

- Basic Investigations for Myeloma
  - CBC with differential, lytes, urea, creatinine, calcium, SPEP and UPEP with immunofixation, serum free light chain assay
  - Albumin, beta 2 microglobulin (necessary for ISS staging)
- Imaging
  - Skeletal survey in all patients
  - CT or MRI to investigate 1) pain when plain films normal, 2) extramedullary plasmactyomas, 3) neurologic compromise (cord comp)
- Bone marrow aspirate and biopsy
  - Flow cytometry
  - FISH cytogenetics – t(4;14), del17p and others (necessary for prognosis)

Who Should Do The Bone Marrow?

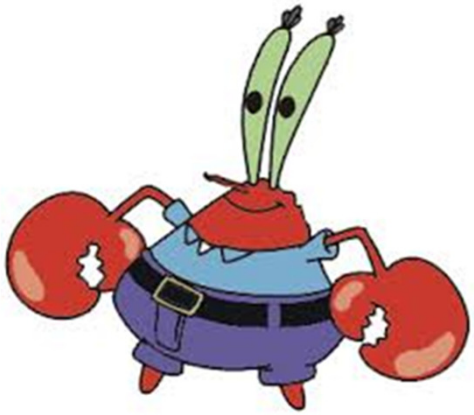
- Should be done by hematologist (or trained NP/CA/PA):
  - Higher probability of diagnostic sample due to experience
  - Availability of complex testing at tertiary care centre (flow cytometry and cytogenetics)
  - Clinical trial participation often requires bone marrow sample

Panel: Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma

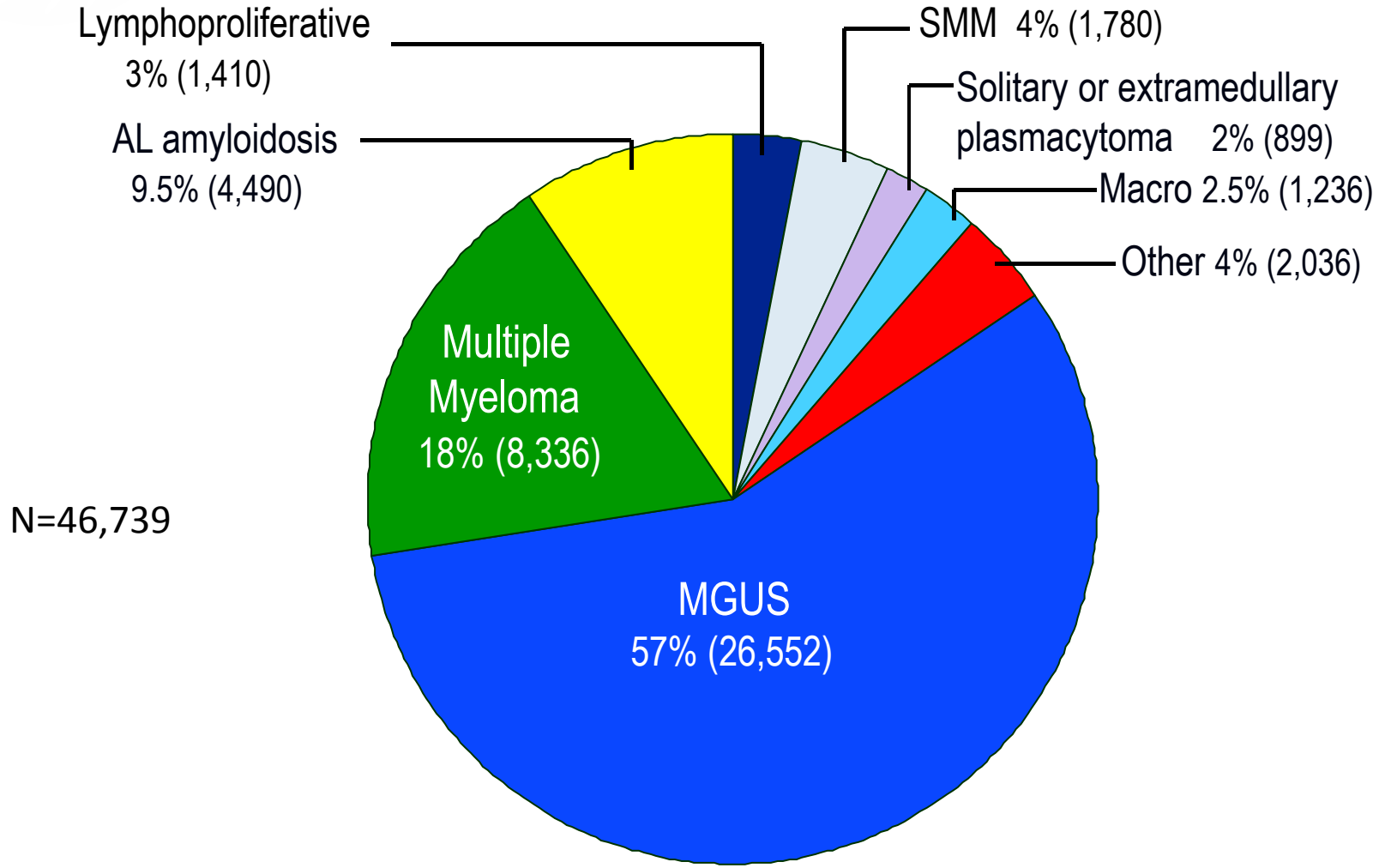
Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 µmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶



Rajkumar et al. 2014 Lancet Oncology

Monoclonal Gammopathy



N=46,739

Mayo Clinic 1960-2002

MGUS	SMM	MM
M protein in serum <30g/l **and**	M protein >30g/l **and / or**	Any level of M protein (none in non-secretory) **and**
Clonal BMPC <10% **and**	Clonal BMPC >10% **and**	Clonal BMPC >10% **and**
No myeloma related "CRAB"	No myeloma related "CRAB	Myeloma related "CRAB"
No evidence of other B cell LPD or light chain associated Amyloidosis or other tissue damage		Or : BM plasma cells >60% FLCR >100 >1 focal lesion on MRI

Rajkumar et al. 2014 Lancet Oncology

MGUS is Common

- MGUS is common especially in the elderly
  - <2% in those under 40
  - 3% in those over 50
  - 5% in those over 70
  - 7.5% in those over 85

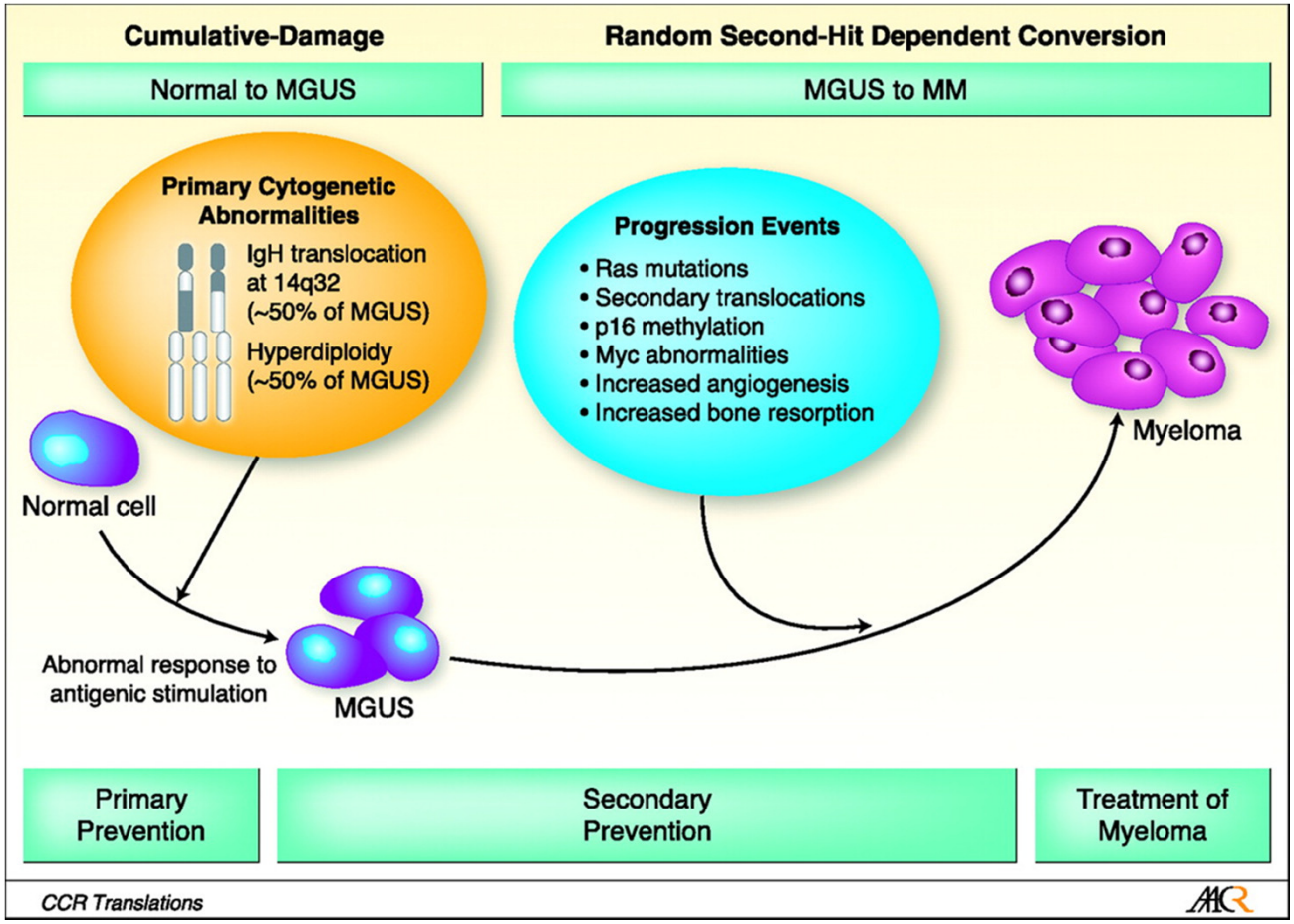
Kyle et al, NEJM 2006

Epidemiology of MGUS

- Sex: Slightly higher risk in men than women (4.0% vs 2.7% in population >50 years old)
- Race: African Americans have 3 fold higher risk compared to Caucasians
- Familial Predisposition: 1st degree relative of patients with MGUS are at higher risk (though majority of cases are sporadic)
- MGUS RR 2.8, Multiple Myeloma RR 2.9, Waldenstrom's macroglobulinemia RR 4.0, CLL RR 2.0

Landgren et al Blood. 2006
Landgren et al Blood. 2009

MGUS Progression to Myeloma



Rajkumar S V Clin Cancer Res 2009

MGUS Precedes Myeloma

- Among 77, 469 healthy adults in an American population based cancer screening study (NIH PLCO Study)
  - 71 patients later developed myeloma

Blood Draw Prior to MM Diagnosis (years)	% with MGUS
2	100%
3	98.3%
4	97.9%
5	94.6%
6	100%
7	93.3%
8+	82.4%

Landgren et al, Blood. 2009

MGUS Risk Stratification

- All patients with myeloma are thought to arise from a pre-existing MGUS BUT not all MGUS turns into myeloma (or anything)
- Overall ~1%/year risk of progression to symptomatic myeloma, AL amyloidosis, or B cell lymphoproliferative disorder

MGUS Risk Stratification

- More refined risk stratification based on 3 risk factors:
  - 1) M-protein >15g/L
  - 2) IgA or IgM M-protein
  - 3) abnormal sFLC ratio
- Risk of progression at 20 years
  - Low (0) – 5%
  - Low-intermediate (1) – 21%
  - Intermediate (2) – 37%
  - High (3) – 58%
- 70% of patients fall into the “low” risk category and therefore it is projected that >90% of those diagnosed with MGUS will NOT progress

Merlini et al ASH Educ Prog 2012

Smoldering Myeloma Risk Stratification

- Risk of progression to myeloma or AL amyloidosis 10% per year for the first 5 years, then 3% for the next 5 years then 1-2% over the next 10 years
  - Median time to progression of 4.8 years
- Risk stratify based on 3 factors
  - Bone marrow plasma cells ≥10%
  - Serum M protein ≥30g/L
  - Abnormal sFLC ratio (<0.125 or >8.0)
- Probability of progression at 5 years
  - 1 point – 25%
  - 2 points – 51%
  - 3 points – 76%

Dispenzieri et al Blood 2008

When to order an SPEP?

DIAGNOSIS

- Unexplained anemia
- Osteopenia, osteolytic lesions, spontaneous fractures
- Renal insufficiency with bland urinary sediment
- Heavy proteinuria or Bence Jones proteinuria
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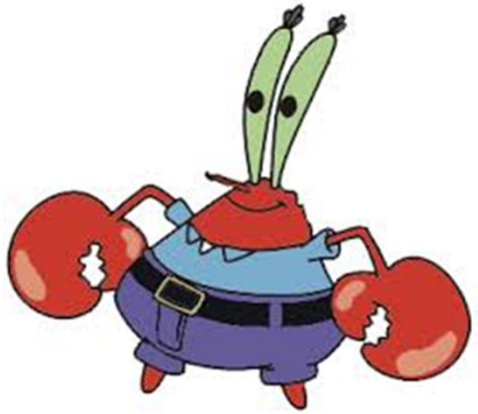
***If clinical suspicion remains high and SPEP is negative, then order a serum free light chain ratio (SFLCR)



Back to the Case

- Patient develops worsening fatigue and drowsiness
- Corrected calcium 3.58mmol/L
- Skeletal survey shows diffuse lytic bone lesions
  - “multiple lytic lesions throughout the calvarium. Small lytic lesions in the ribs as well as scapula bilaterally. Lesions in the femurs bilaterally.”

Referral to Hematology

- Outpatient Referral CCMB
  - High suspicion of myeloma (monoclonal protein on SPEP/UPEP/sFLC assay) plus:
    - One or more CRAB criteria

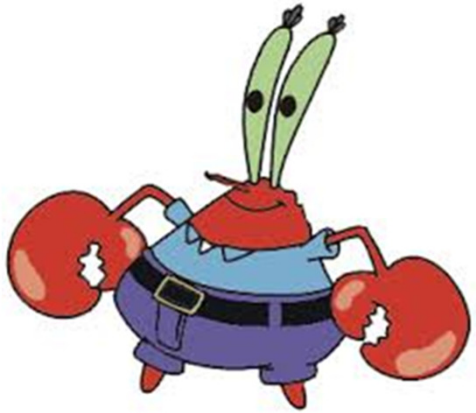
- Page Hematologist on Call
  - High suspicion of myeloma (monoclonal protein on SPEP/UPEP/sFLC assay) plus:
    - Severe hypercalcemia (calcium >3mmol/L)
    - Rapidly progressive renal failure
    - Cord compression
    - Fracture or impending pathologic fracture

Case Resolution

- Hematologist on call paged re severe symptomatic hypercalcemia
- Patient admitted to HSC
- Given IV saline and zoledronic acid to manage hypercalcemia
- Bone marrow biopsy showed 70% infiltration by clonal plasma cells (lambda light chain restricted)
- Started on chemotherapy in hospital (cyclophosphamide, bortezomib, dexamethasone)
- Discharged after 7 day stay with outpatient CCMB appts for ongoing chemo

Take Home Message

- Order an SPEP when suspecting disorders associated with monoclonal gammopathy (esp myeloma)
- If SPEP negative and still suspicious, then order UPEP and sFLC
- When monoclonal protein identified, look for Mr. CRAB
- Recognize emergent situations



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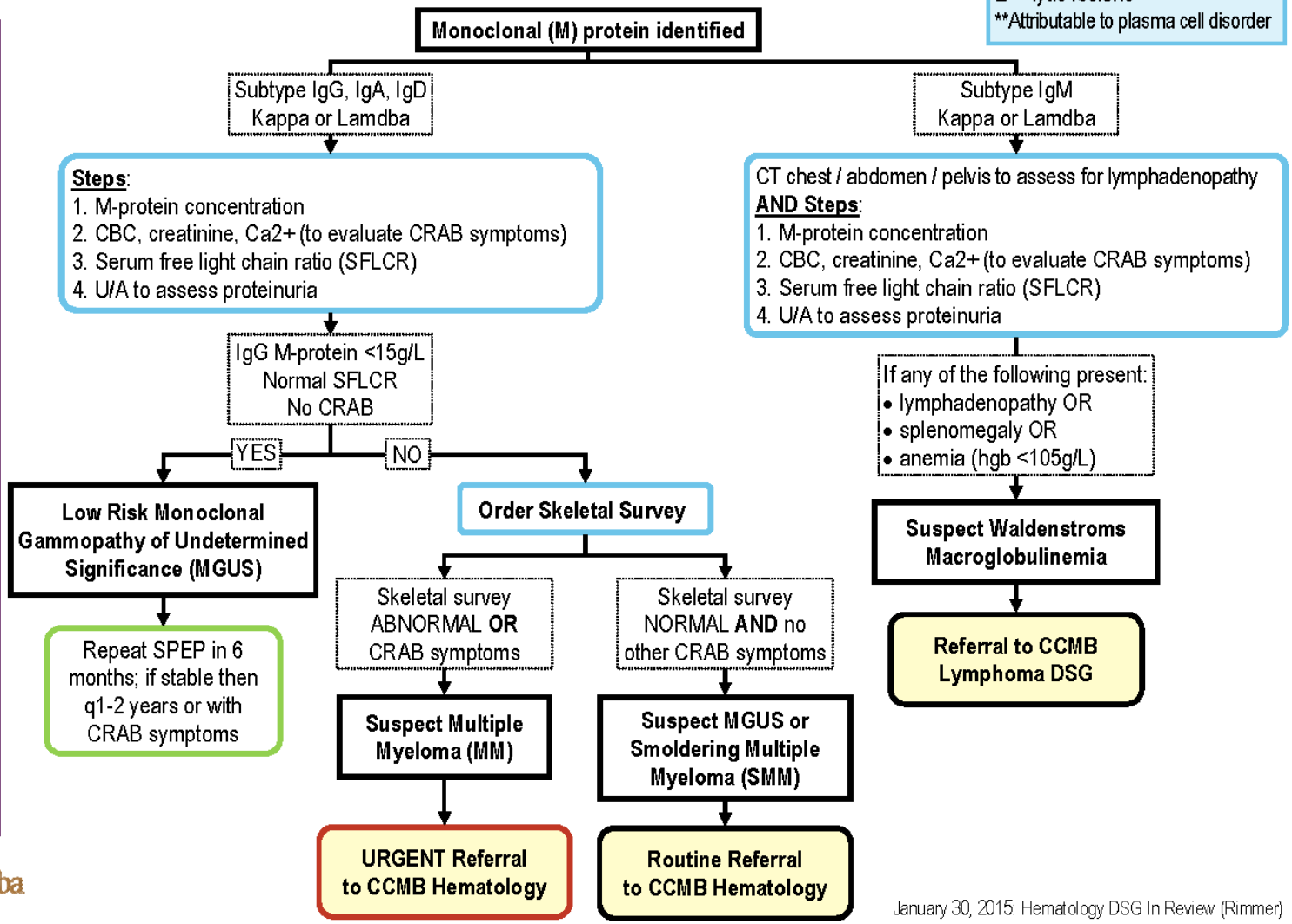

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QUESTIONS?