



Blood Day for Primary Care

When do I order an SPEP and how do I interpret the results?

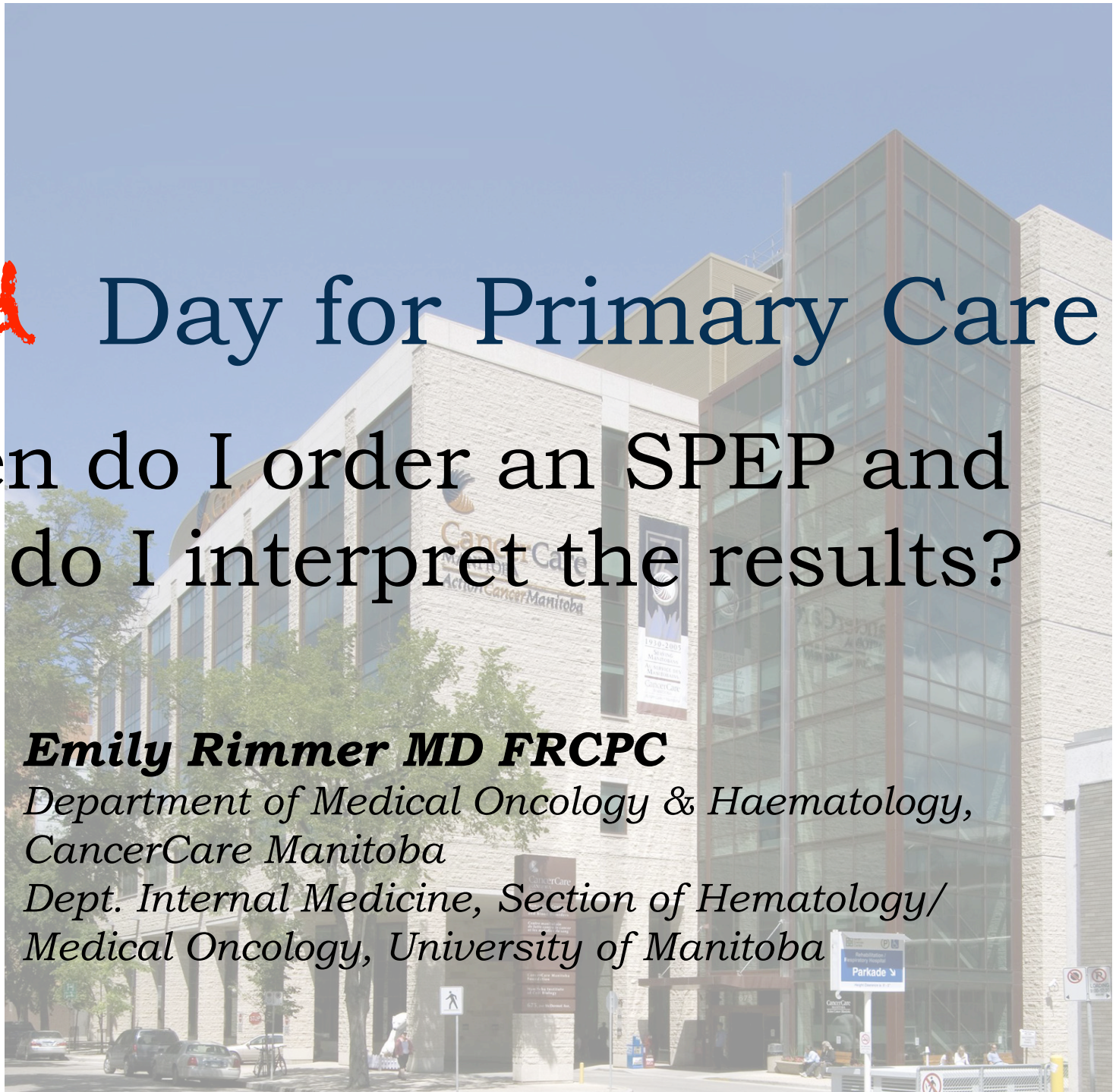
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Disclosures

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Other: None



Objectives

1. List the indications for ordering a serum protein electrophoresis (SPEP)
2. Understand the difference between a polyclonal and monoclonal gammopathy
3. Develop a logical approach to the investigation of an M-protein



Referral to Hematology

Dear Dr. [REDACTED]

Please see [REDACTED] for persistent abnormalities to SPEP, see attached.

	Flags	Results	Reference Range	Units	#
Total Protein (serum)	N	73	60 - 80	g/L	
Protein Electroph-Serum					
Alb SerPI Elph-mCnc	N	42.8	38 - 54	g/L	
A1 Globulin SerPI Elph-mCnc	N	1.3	1 - 3	g/L	
A2 Globulin SerPI Elph-mCnc	N	6.7	5 - 9	g/L	
B-Globulin SerPI Elph-mCnc	N	8.9	6 - 11	g/L	
G-Globulin SerPI Elph-mCnc	A	13.3	5 - 12	g/L	
093-5 GDML		Polyclonal gammopathy.		g/L	
Protein Electroph-Urine		No light chains noted		g/L	



Interactive question

1. What do you do next?
 - a. Investigate for multiple myeloma with CBC, creatinine, calcium, skeletal survey
 - b. Repeat test in 6 months
 - c. Investigate for reactive causes including liver disease, connective tissue diseases, infection
 - d. Order CT chest/abdo/pelvis



Referral to Hematology

Dear Cancer Care Manitoba - Intake - McCharles Unit,

I am writing to request your assessment of this patient regarding what I believe to be ██████████ ██████████ presented near the end of July, with lower back pain which had been getting worse over a two-month period. He has enjoyed very good health in the past. His only medical problem has been hypertension which has been well controlled with a combination of Ramipril 10mg daily and Hydrochlorothiazide 12.5mg daily. I did not find any dramatic findings on his physical examination. An x-ray of his lumbar spine revealed compression fractures in his lower thoracic and lumbar spine. A CT scan has also been performed and I shall enclose a copy of that report. His recent blood work has shown mild anemia, mild impairment of his renal function and elevated calcium as well as an M band on his protein electrophoresis at 1.8g/L. I do not yet have the results of his urine protein electrophoresis but will forward that result when it is available. I am also obtaining a MRI of his spine and a skeletal survey and will forward those results when available.

Thank you for seeing this patient.



Interactive question

1. What is the most likely diagnosis?
 - a. MGUS
 - b. Multiple myeloma
 - c. Diffuse large B cell lymphoma
 - d. Waldenstrom's macroglobulinemia
 - e. Chronic myeloid leukemia

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

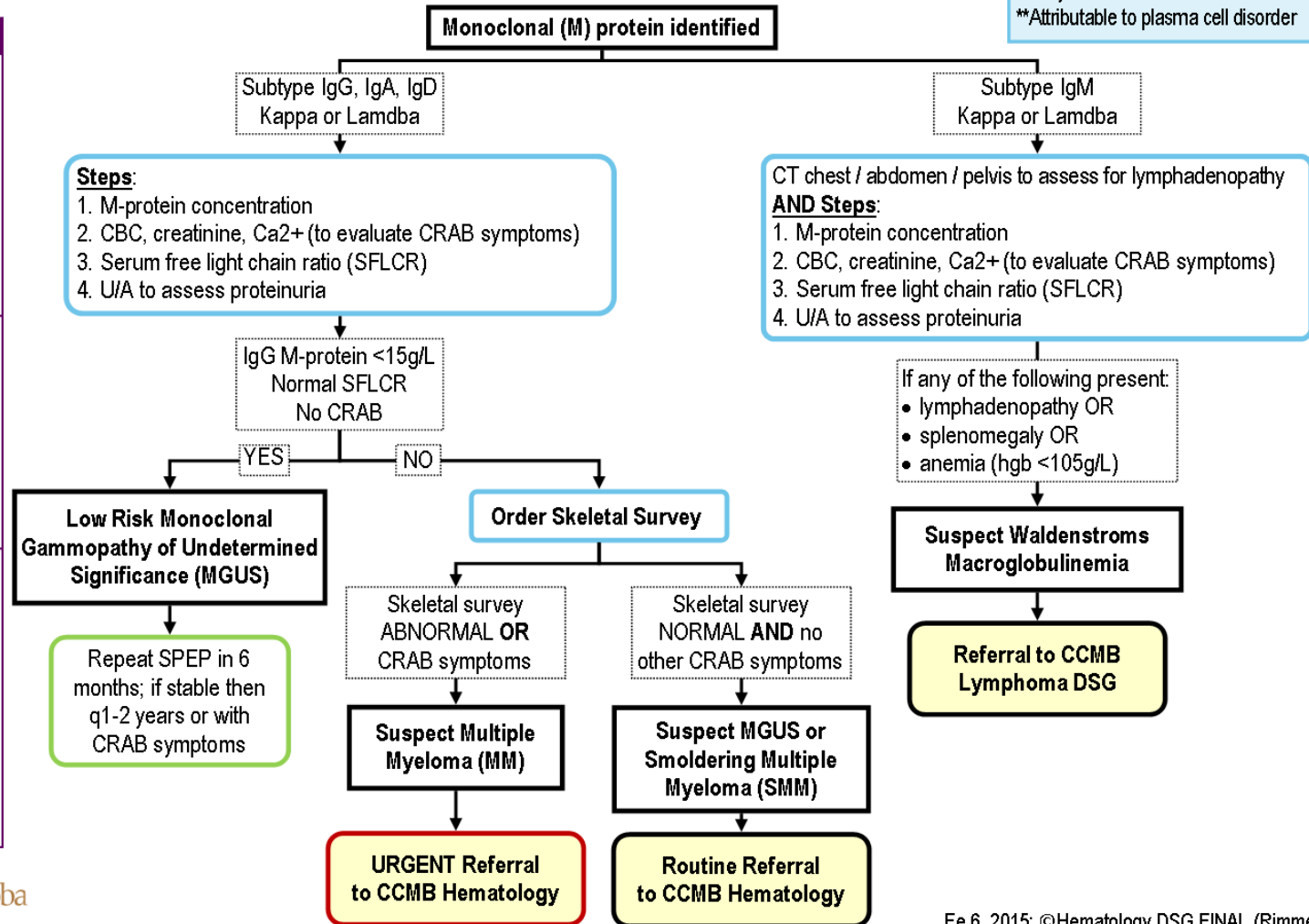
OLIGOCLONAL GAMMOPATHY (usually reactive)

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

ELEVATED FREE LIGHT CHAINS - NORMAL RATIO (reactive)

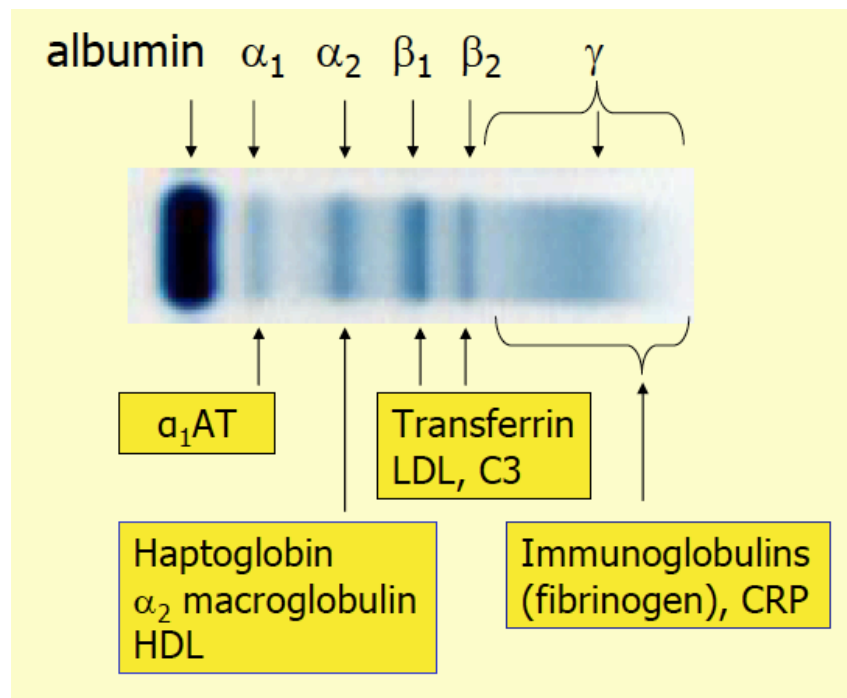
Investigate for other causes including:

- Kidney disease
- Liver disease
- Connective tissue disease
- Infection





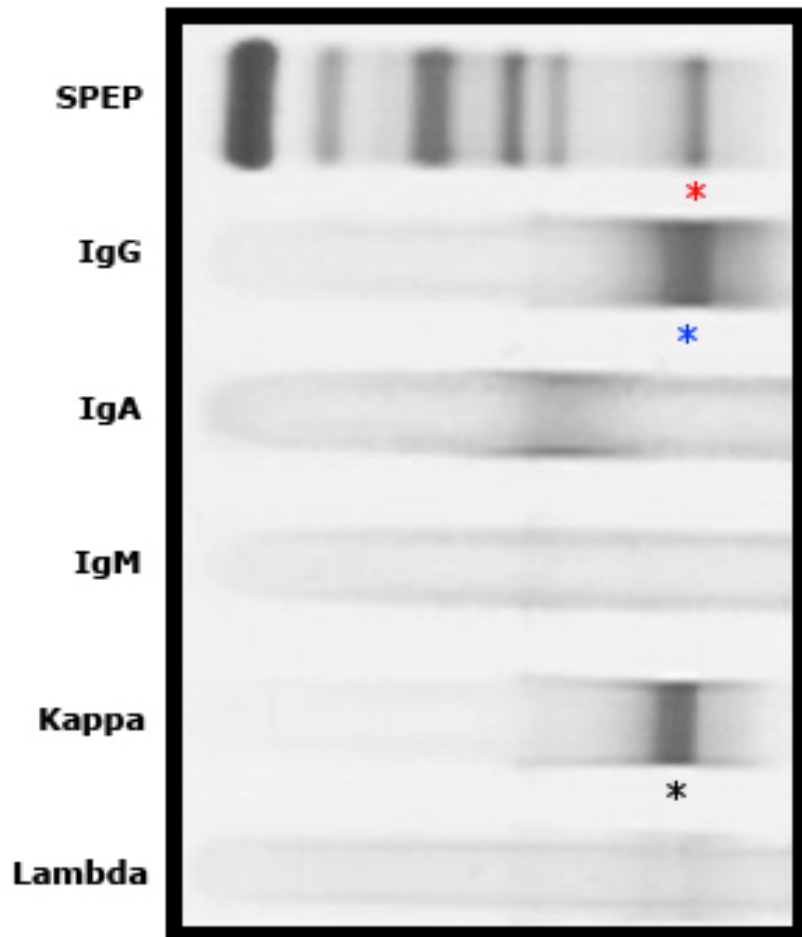
Serum Protein Electrophoresis (SPEP)



- Serum protein migrate into bands based on their size and charge
- Limitations:
 - Not sensitive when M-protein is small
 - Cannot classify type of M-protein



Serum immunofixation



IgG kappa

- Used to determine clonality
 - Monoclonal versus polyclonal
- Not able to quantitate the concentration of the M band
- Must be done in conjunction with the SPEP
 - Does not give the concentration of the M-protein



Definition of Monoclonal Protein

- Monoclonal immunoglobulin secreted by an abnormally expanded clone of plasma cells in an amount that can be detected by immunofixation of serum and/or urine/other fluids
- Also known as: M-protein, paraprotein, M-spike, M-component, M-band



Type of M-protein	Associated plasma cell disorders
Intact immunoglobulin (heavy & light chain)	Myeloma Other lymphoproliferative disorders – Waldenstrom macroglobulinemia
Light chain only	Light chain myeloma Light chain deposition disease (usually kappa) AL amyloidosis (usually lambda)
Heavy chain only	Heavy chain disease (alpha, gamma, mu) Heavy chain deposition disease



When to order an SPEP?

DIAGNOSIS

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***If clinical suspicion remains high and SPEP is negative, then order a serum free light chain ratio (SFLCR)

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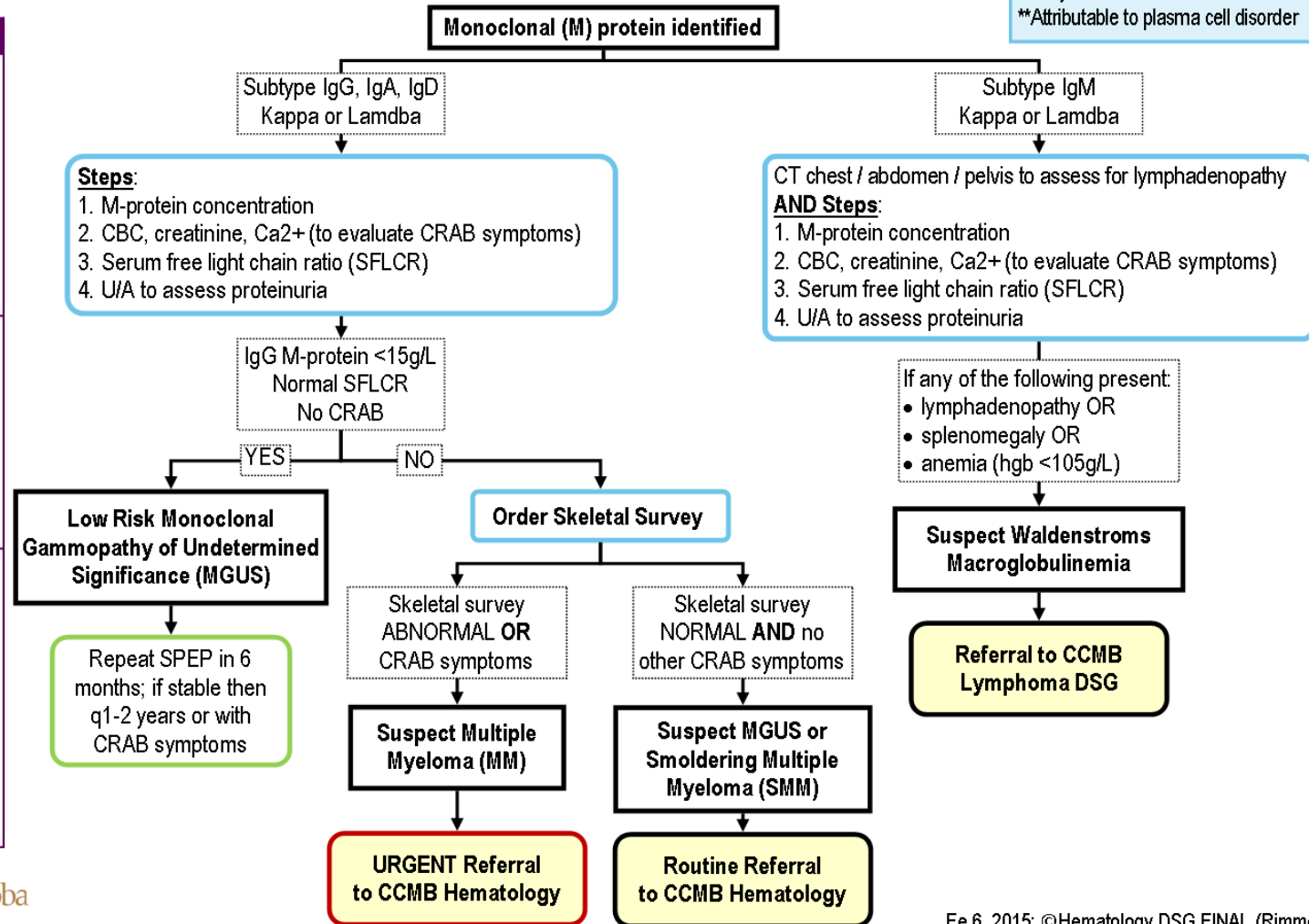
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 Repeat test in 6 – 12 months if clinically indicated (see top box "When to order an SPEP")

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 Investigate for other causes including:
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 • Liver disease
 • Connective tissue disease
 • Infection





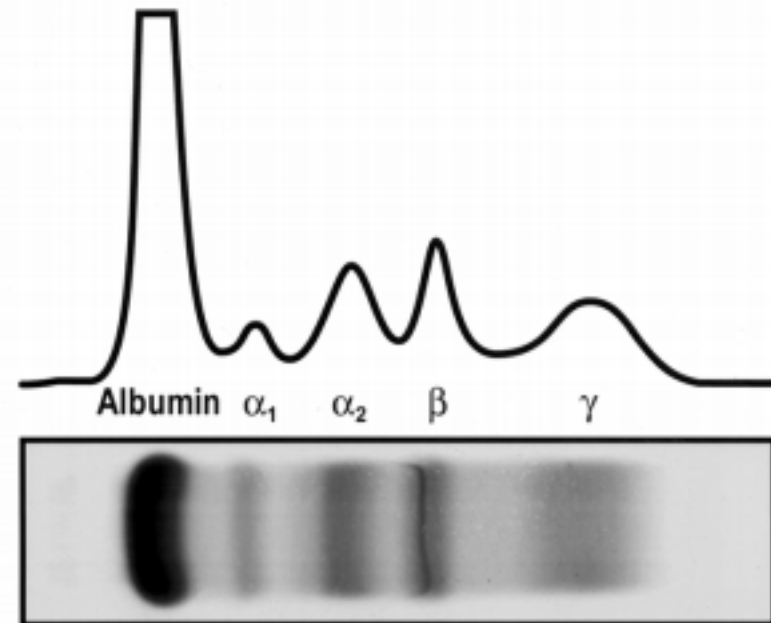
SPEP – interpretation

- Normal
 - No M protein present

RESULTS

SERUM MONOCLONAL PROTEIN INVESTIGATION

Serum Total Protein	61
Serum Albumin	34
No M protein present.	

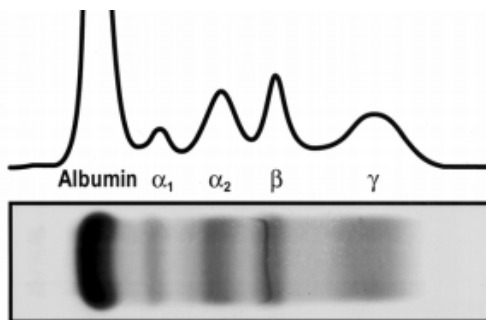




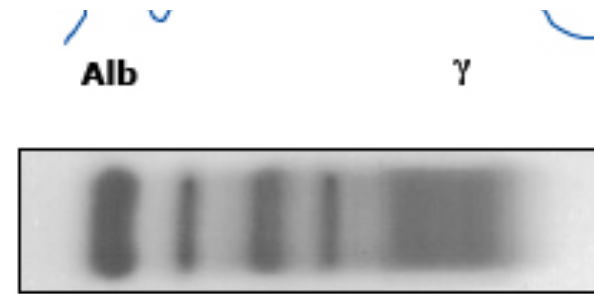
SPEP – interpretation

- Polyclonal gammopathy

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Normal

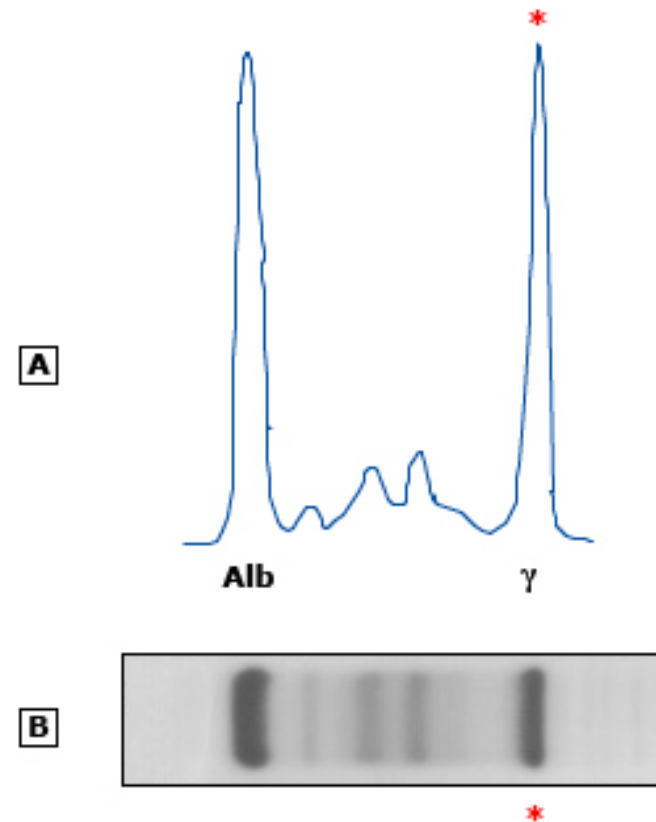


Polyclonal pattern



SPEP - Interpretation

- Monoclonal gammopathy





SPEP - Interpretation

- Monoclonal gammopathy

PROTEI	RESULTS	REF #
Total Pro		
Protein	<i>SERUM MONOCLONAL PROTEIN INVESTIGATION</i>	
Alb S	Serum Total Protein	78
A1 G	Serum Albumin	37
A2 G	IgG	16.40*
B-Glo	IgA	0.36*
G-Glo	IgM	0.22*
093-S		
IM	Monoclonal Immunoglobulin	PRESENT
SEP	Class/type:	Previous IgG / Kappa
SEP	Monoclonal Ig concentration:	14
IGG	<i>NOTE: IgG, IgA and IgM results include normal and</i>	
IGA	<i>concentration when present.</i>	
IGM		
MO	Serum Electrophoresis	



Beyond the SPEP

- If only SPEP is done – about 15% of myeloma / other disorders WILL BE MISSED because SPEP will be negative
- What can be done about this?
 - Urine Protein ElectroPhoresis (UPEP)
 - Serum free light chain ratio (SFLCR)



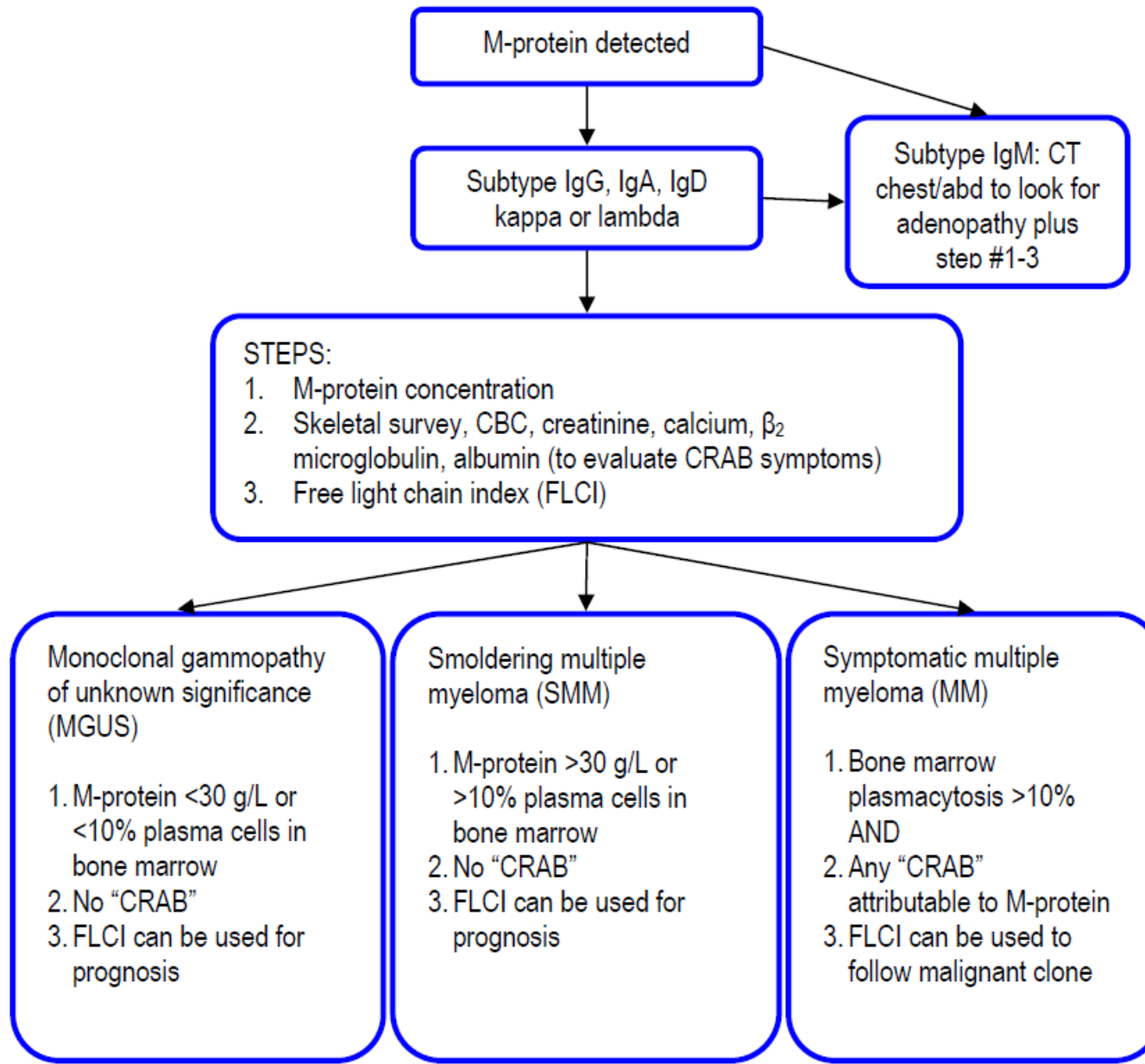
Serum free light chain index/ratio (SFLCI/R)

- Diagnosis
 - Non-secretory, oligosecretory, light chain myeloma, and amyloidosis
- Prediction of risk of progression for MGUS, smoldering myeloma, and plasmacytoma
- More sensitive than SPEP for monitoring for residual disease

RESULTS	REFERENCE	UNIT
FREE LIGHT CHAIN QUANTITATION		
Kappa Free Light Chain >4950.00*	3.3-19.4	mg/L
Lambda Free Light Chain 15.70	5.7-26.3	mg/L
Free Light Chain Ratio >315.29*	0.26-1.65	Ratio
This result should not be used in isolation for diagnosis or patient management, but rather interpreted in the context of clinical, morphologic and other laboratory findings. Please contact the laboratory with any unexpected or unexplainable results.		
Linearity limitations may affect accuracy at this detection level.		
KAPPA FREE LIGHT CHAIN [ABNORMAL] Low: 3.3 High: 19.4		53.22
LAMBDA FREE LIGHT CHAIN [ABNORMAL] Low: 5.7 High: 26.3		33.81
FREE LIGHT CHAIN RATIO [NORMAL] Low: 0.26 High: 1.65		1.57



Investigating an M-Protein





MGUS	SMM	MM
M protein in serum <30g/l <u>and</u>	M protein >30g/l <u>and / or</u>	Any level of M protein (none in non-secretory) <u>and</u>
Clonal BMPC <10% and low level of infiltration on trephine <u>and</u>	Clonal BMPC >10% <u>and</u>	Clonal BMPC >10% <u>and</u>
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; 15:e538-48



Myeloma related “CRAB”

- C = hypercalcemia (Ca >2.8mmol/L)
- R = renal failure (Cr >177) or GFR <40ml/min
- A = anemia (Hb<100 or > 20g below baseline)
- B = bony lesions (lytic lesions, plasmacytoma)

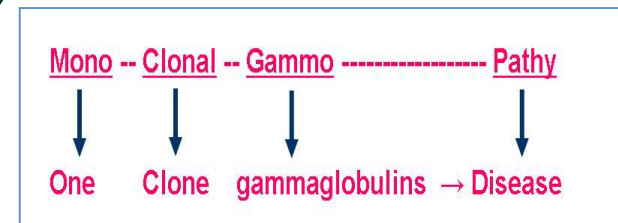
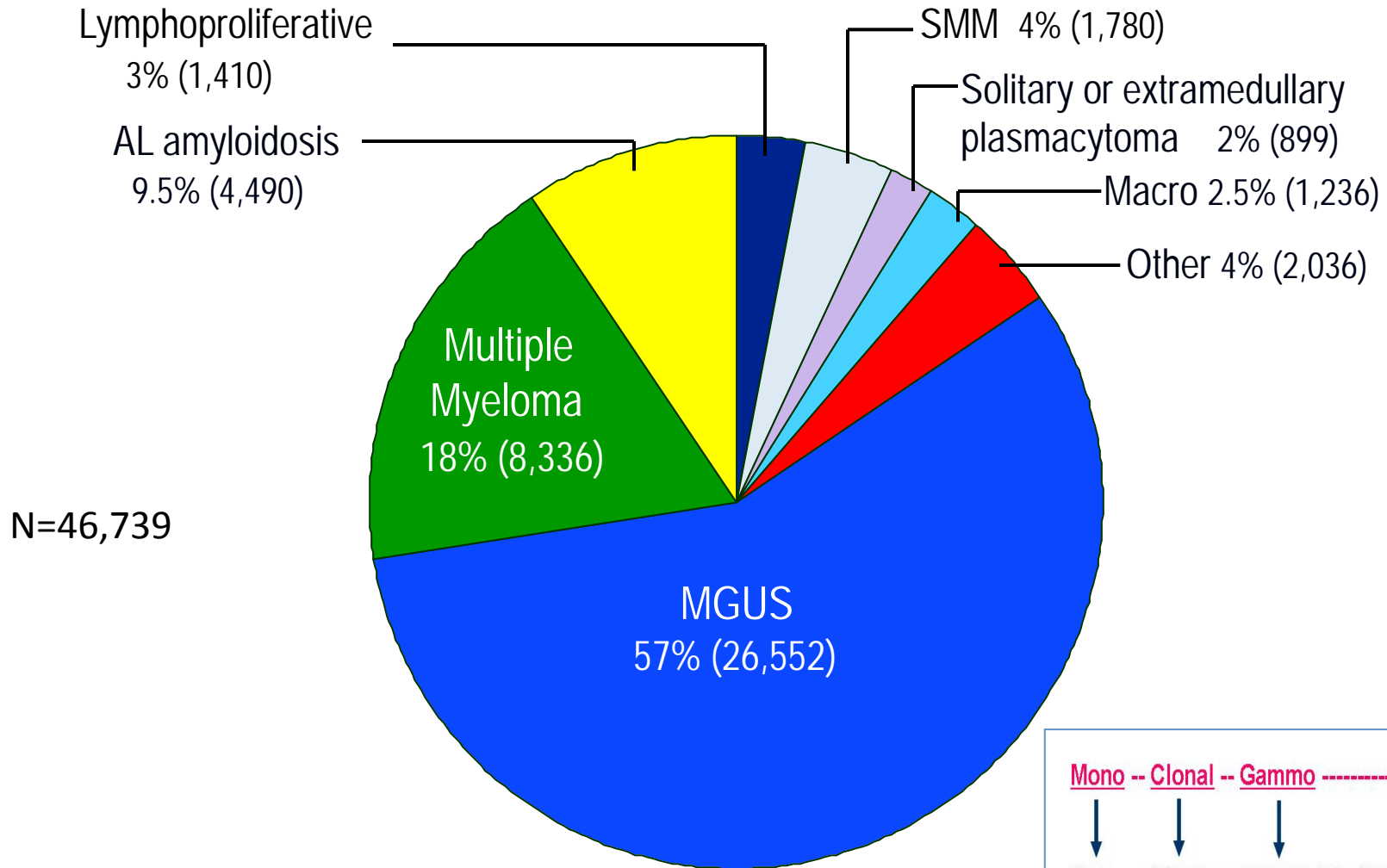
****Attributable to the plasma cell disorder

- New criteria 2014: bone marrow plasma cells >60%; involved/uninvolved SRLFR >100; >1 focal lesion on MRI

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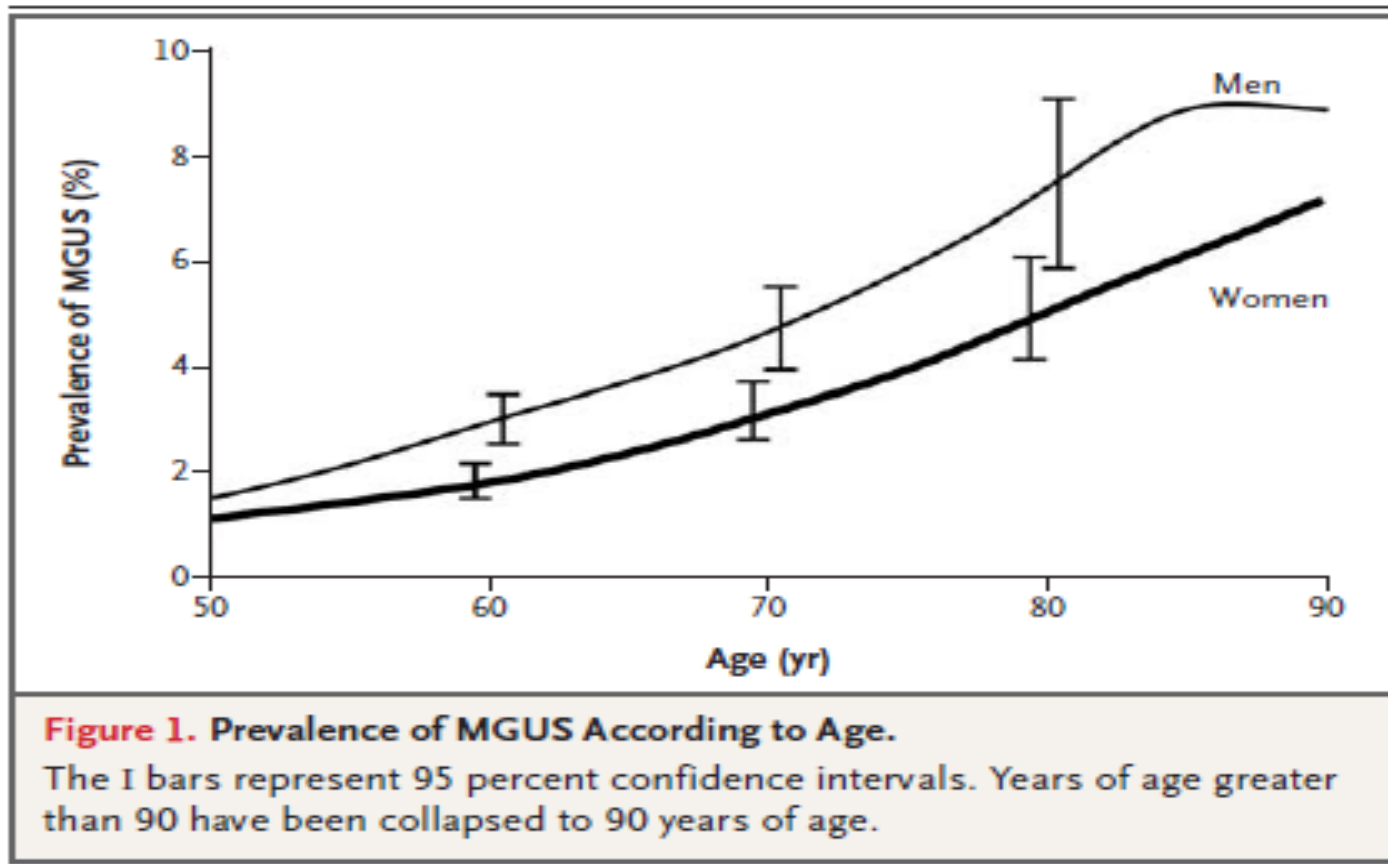
Monoclonal Gammopathy



Mayo Clinic 1960-2002



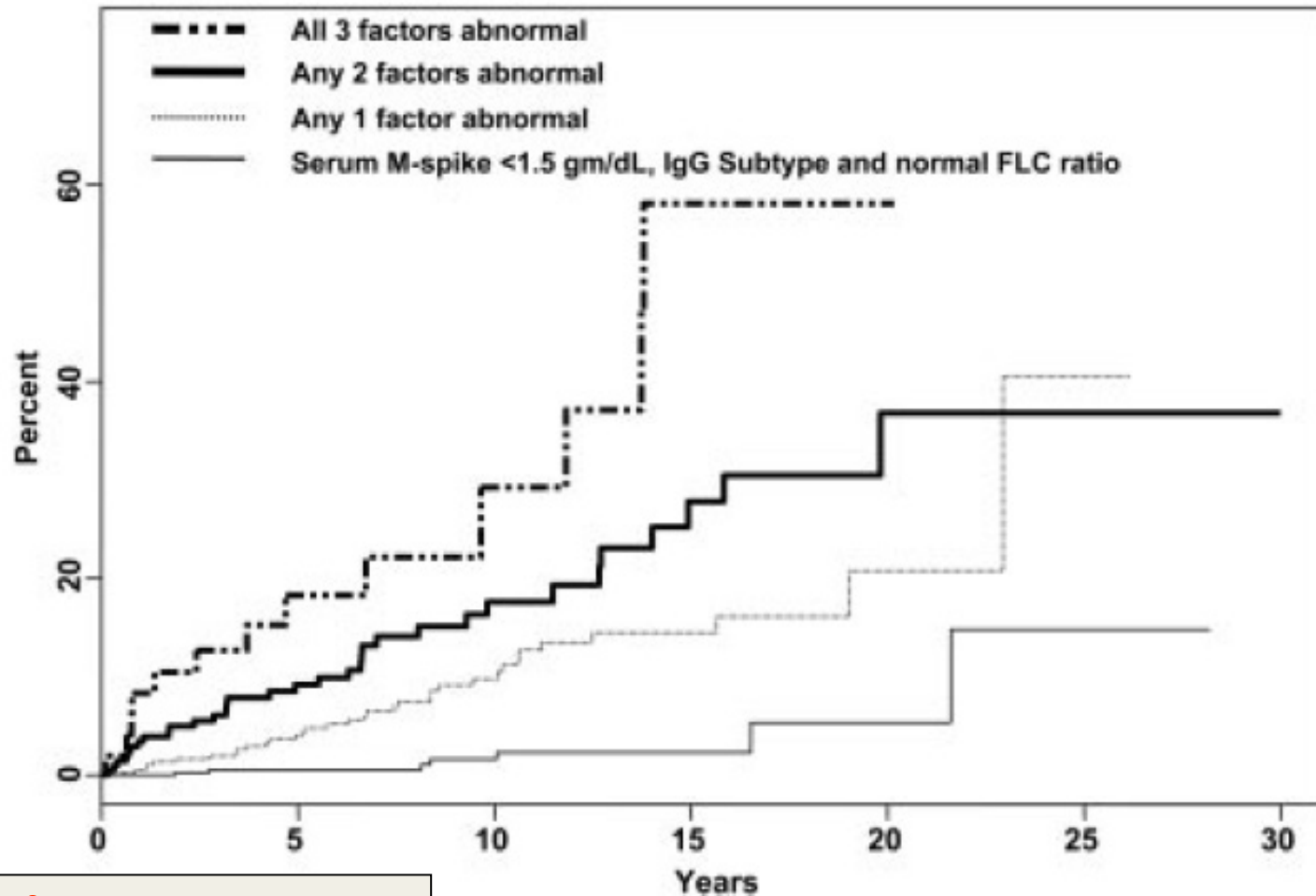
MGUS is common



Kyle et al, NEJM 2006;354:1362-9



MGUS



3 adverse risk factors:

1. M band >15g/L
2. Non-IgG subtype
3. Abnormal FLC ratio

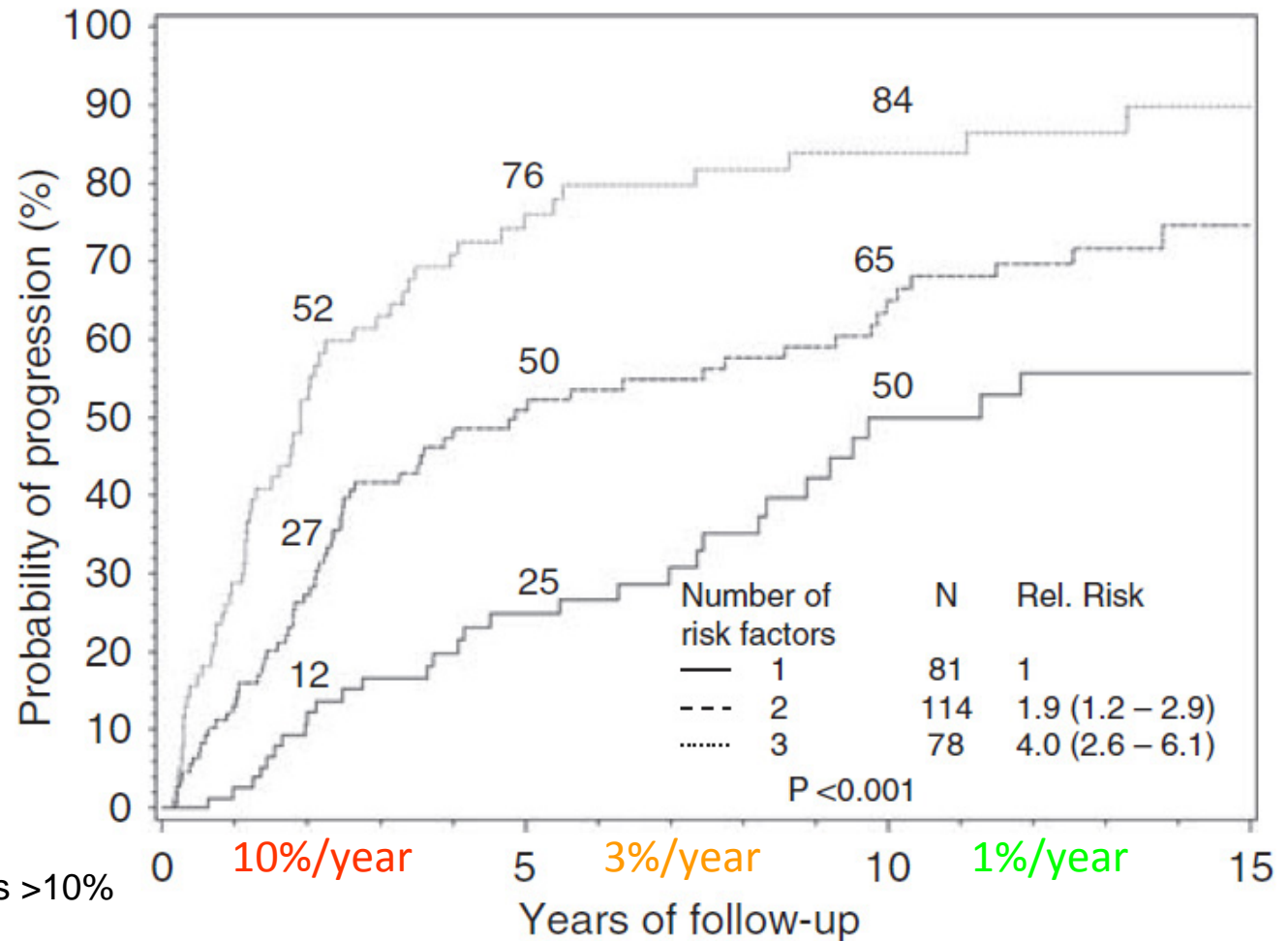
Rajkumar et al, Blood 2005;106:812-7



Smoldering myeloma



Dispenzieri et al. Blood 2008; 111:785-789



3 risk factors:

1. M band >30g/L
2. Bone marrow plasmacytosis >10%
3. FLC ratio 0.125 or >8

Figure 1 Risk stratification for smoldering multiple myeloma. The

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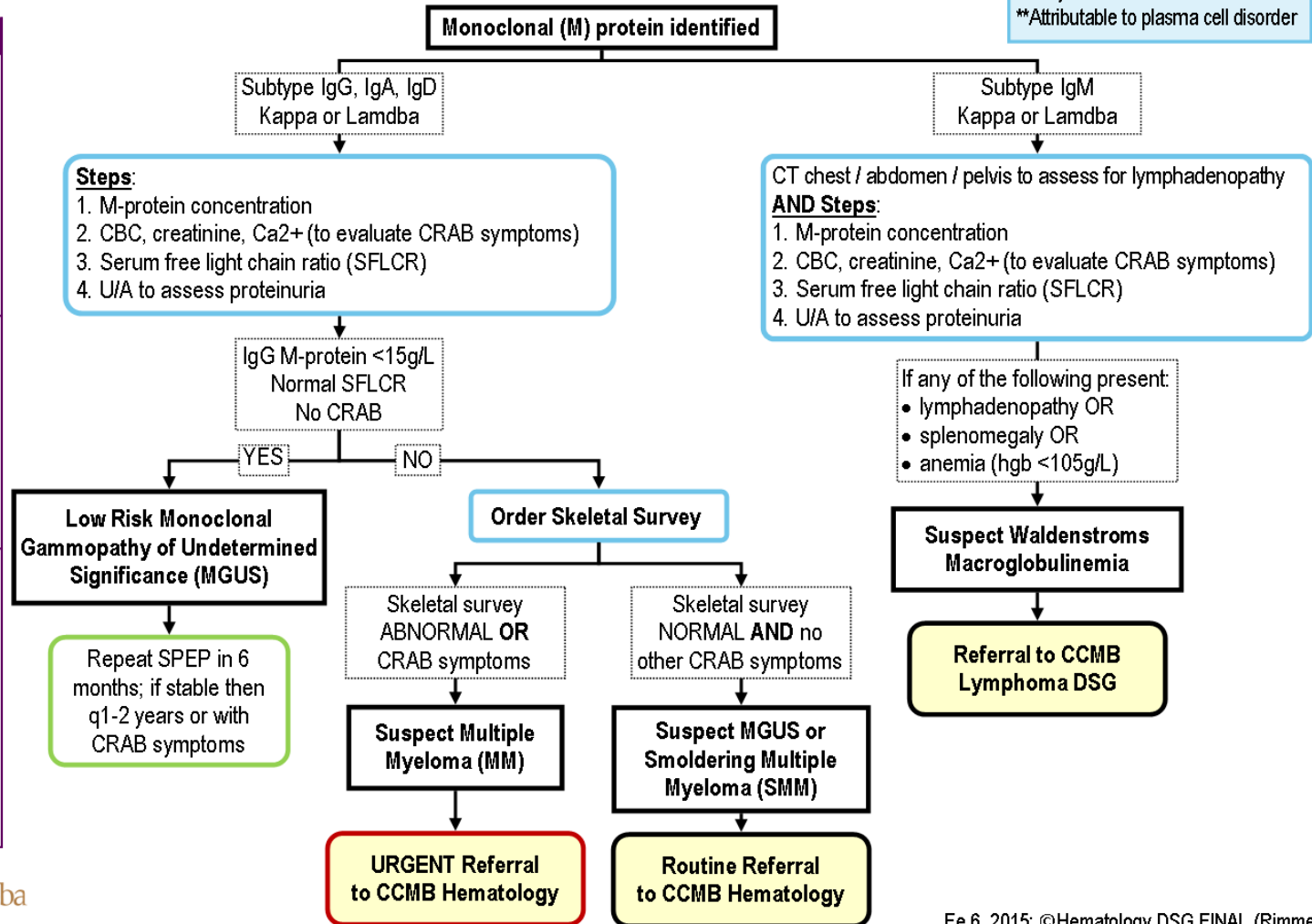
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Investigate for other causes including:

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- Liver disease
- Connective tissue disease
- Infection





Take Home Messages

- Monoclonal proteins are common
- Order an SPEP when clinically suspicious of the disorders associated with an M band
- If SPEP negative and still suspicious, then order SFLCR
- When M band identified, investigate for CRAB symptoms



When to refer to hematology

- High suspicion of multiple myeloma (CRAB or lytic lesions)
- MGUS / smoldering myeloma that is not low risk
- Include with referral: CBC, lytes, urea, creatinine, Ca²⁺, albumin, SPEP and FLC results, skeletal survey
- If skeletal survey not complete – please order



Questions?

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