CancerCare Manitoba
ActionCancerManitoba

Blood Disorders Day 2018 FOR Health Professionals

IPEP, UPEP, we all scream for SPEP! Multiple Myeloma in 2018

Emily Rimmer MD FRCPC

May 4th, 2018

University of Manitoba
CancerCare Manitoba Community Oncology Program

Presenter Disclosure

- **Faculty / Speaker's name: Emily Rimmer**

- **Relationships with commercial interests:**
  - **Grants/Research Support:** none
  - **Speakers Bureau/Honoraria:** none
  - **Consulting Fees:** none
  - **Other:** none

Mitigating Potential Bias

- Not applicable

Objectives

1. Describe the indications for ordering an SPEP and free light chain ratio and how to interpret the results
2. Distinguish MGUS from multiple myeloma
3. Summarize current treatment options and prognosis for multiple myeloma in 2018

Referral to Hematology

Thank you for seeing this 61 year old male patient ? MGUS vs MM. In work-up for anemia (hgb 123), he was noted to have a positive SPEP subtype IgA/Kappa (attached results), normal calcium, creatinine and eGFR as well as normal skeletal survey. He feels very well, and chronic conditions of HTN and DM are well controlled.

TEST NAME	VALUE	FLAG	REFERENCE RANGES	UNITS
WBC Count	7.5		4.5 - 11.0	x10 9/L
RBC Count	3.7	L	4.0 - 5.0	x10 12/L
Hemoglobin	123	L	140 - 180	g/L
Hematocrit	0.36	L	0.40 - 0.52	L/L
MCV	96		80 - 99	fL
MCH	33		25 - 35	pg
MCHC	345		320 - 365	g/L
RDW	14.4		11.5 - 14.5	%
Platelet Count				
Platelets	238		140 - 440	x10 9/L
MPV	8.5		7.4 - 10.4	fL
Neutrophils	3.4		1.8 - 7.7	x10 9/L
Lymphocytes	3.0		1.0 - 3.3	x10 9/L
Monocytes	0.9	H	0.1 - 0.8	
Eosinophils	0.2		0.0 - 0.4	
Basophils	0.10		0.00 - 0.2	

BIOCHEMISTRY

TEST NAME	VALUE	FLAG	REFERENCE
Creatinine	60		60 - 110

URINE MONOCLONAL PROTEIN INVESTIGATION

Random sample			
Protein/Creatinine	263.3*	<25	mg/mmol
Creatinine (Urine)	3.4		mmol/L
Monoclonal free light chains - PRESENT			
Type:	Kappa		
Concentration - Trace			
Monoclonal Immunoglobulin - PRESENT			
Class/Type:	IgA / Kappa		
Concentration - Trace			
Urine Electrophoresis			

Lab # ND73233-4 Collected on 25 Apr 17 at 10:30
Your reference - PRITCHARD FARM

SERUM MONOCLONAL PROTEIN INVESTIGATION	RESULTS	REFERENCE	UNIT
Serum Total Protein	100*	60-80	g/L
Serum Albumin	35	33-45	g/L
IgG	1.95*	6.9-16.2	g/L
IgA	28.80*	0.7-3.8	g/L
IgM	0.63	0.6-2.6	g/L
Monoclonal Immunoglobulin	PRESENT		
Class/type:	IgA / Kappa		
Monoclonal Ig concentration:	30		g/L
NOTE: IgG, IgA and IgM results include normal and monoclonal Ig concentration when present.			
Monoclonal free light chains	PRESENT		
Type:	Kappa (trace amounts)		
Serum Electrophoresis			

FREE LIGHT CHAIN QUANTITATION	RESULTS	REFERENCE	UNIT
Kappa Free LC	9621.70*	3.30-19.40	mg/L
Lambda Free LC	0.82*	5.71-26.30	mg/L
Free LC Ratio	11733.78*	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.

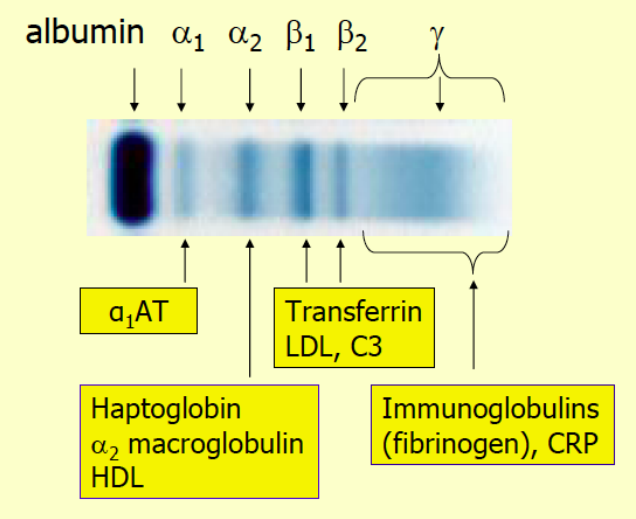
Referral to Hematology

Dear Dr. [redacted]

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

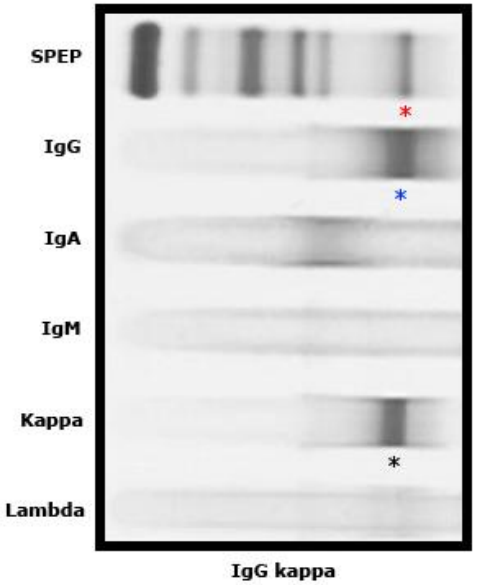
	Flags	Results	Reference Range	Units	
Total Protein (serum)	N	73	60 - 80	g/L	#
Protein Electroph-Serum					
Alb SerPl Elph-mCnc	N	42.8	38 - 54	g/L	
A1 Globulin SerPl Elph-mCnc	N	1.3	1 - 3	g/L	
A2 Globulin SerPl Elph-mCnc	N	6.7	5 - 9	g/L	
B-Globulin SerPl Elph-mCnc	N	8.9	6 - 11	g/L	
G-Globulin SerPl Elph-mCnc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

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

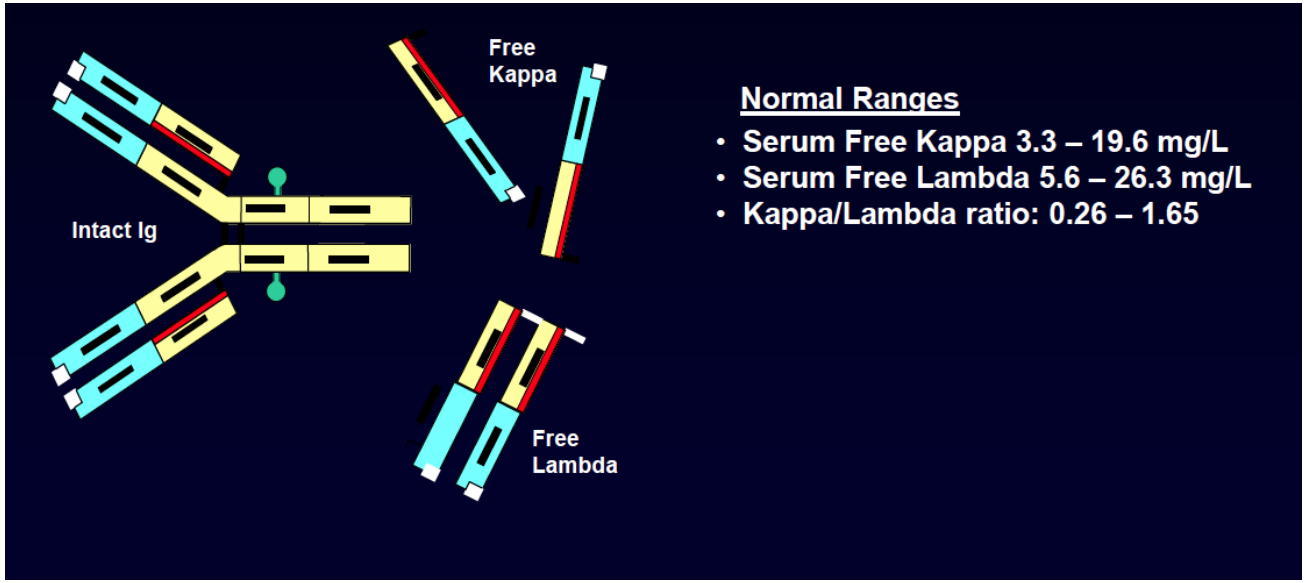
- Used to determine clonality
  - Monoclonal versus polyclonal
- Not able to quantitate the concentration of the M band
- Must be done in conjunction with the SPEP

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 Assay



Katzmann et al Clin Chem. 2002;428-44

When to order an SPEP?

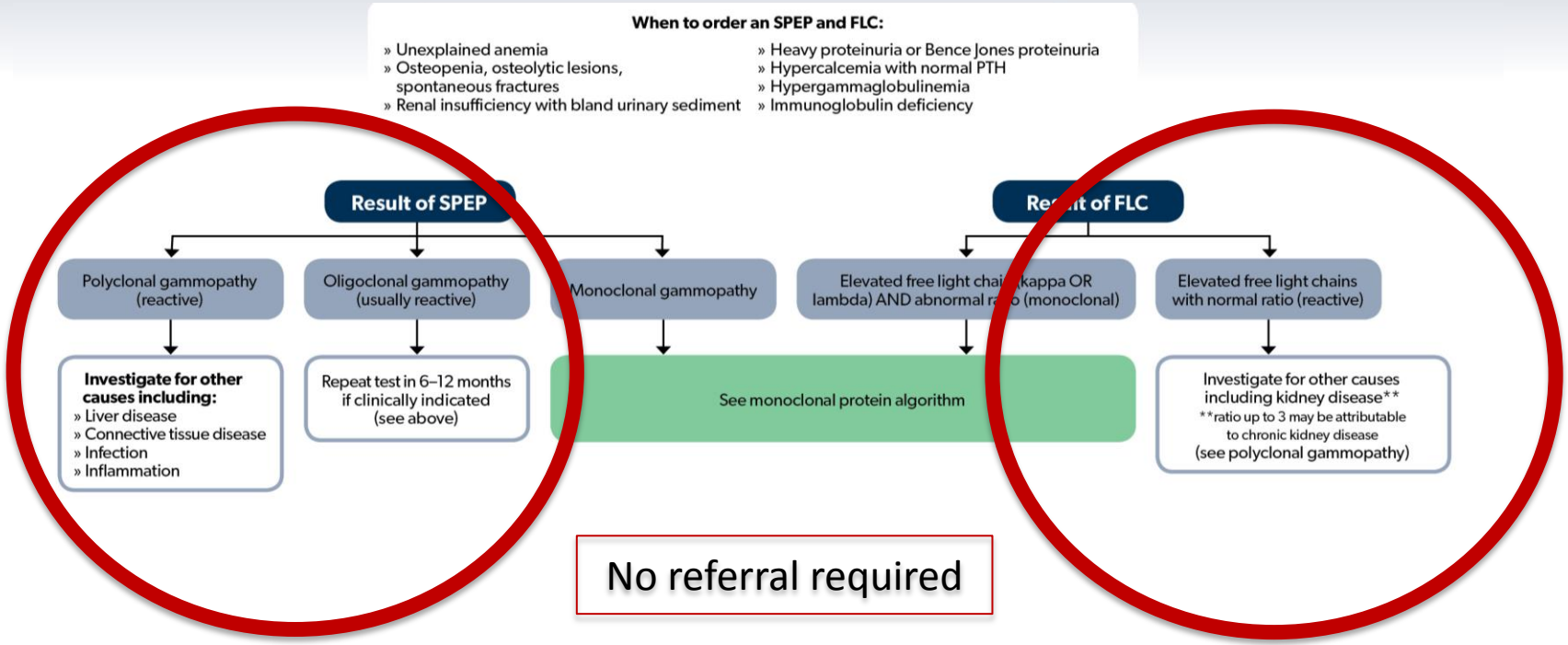
- Unexplained **anemia**, back pain
- Osteopenia, **osteolytic lesions**, spontaneous fractures
- **Renal insufficiency** with bland urinary sediment
- Heavy proteinuria or Bence Jones proteinuria
- **Hypercalcemia** with normal PTH
- Hypergammaglobulinemia
- Immunoglobulin deficiency
- Elevated ESR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

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

Take Home Message #1

Order an SPEP and FLC when you have a clinical suspicion of a plasma cell disorder

How to interpret the SPEP and FLC



SPEP = Serum Protein Electrophoresis
FLC = Free Light Chains

Referral to Hematology

Dear Dr. [redacted]

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

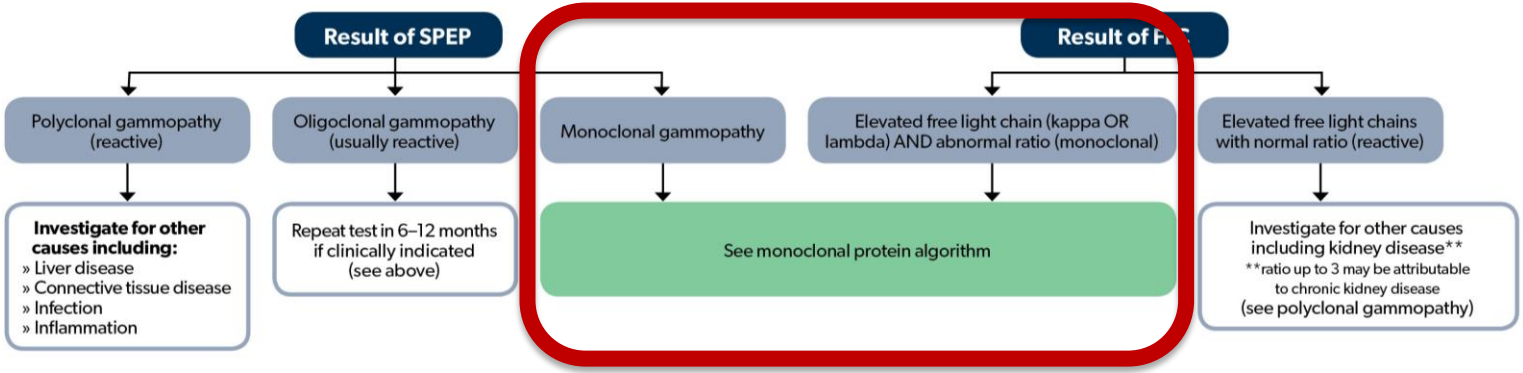
	Flags	Results	Reference Range	Units	
Total Protein (serum)	N	73	60 - 80	g/L	#
Protein Electroph-Serum					
Alb SerPl Elph-mCnc	N	42.8	38 - 54	g/L	
A1 Globulin SerPl Elph-mCnc	N	1.3	1 - 3	g/L	
A2 Globulin SerPl Elph-mCnc	N	6.7	5 - 9	g/L	
B-Globulin SerPl Elph-mCnc	N	8.9	6 - 11	g/L	
G-Globulin SerPl Elph-mCnc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

Blood Disorders Day

How to interpret the SPEP and FLC

When to order an SPEP and FLC:

- » Unexplained anemia
- » Osteopenia, osteolytic lesions, spontaneous fractures
- » Renal insufficiency with bland urinary sediment
- » Heavy proteinuria or Bence Jones proteinuria
- » Hypercalcemia with normal PTH
- » Hypergammaglobulinemia
- » Immunoglobulin deficiency



SPEP = Serum Protein Electrophoresis
FLC = Free Light Chains

Referral to Hematology

Thank you for seeing this 61 year old male patient ? MGUS vs MM. In work-up for anemia (hgb 123), he was noted to have a positive SPEP subtype IgA/Kappa (attached results), normal calcium, creatinine and eGFR as well as normal skeletal survey. He feels very well, and chronic conditions of HTN and DM are well controlled.

TEST NAME	VALUE	FLAG	REFERENCE RANGES	UNITS
WBC Count	7.5		4.5 - 11.0	x10 9/L
RBC Count	3.7	L	4.0 - 5.0	x10 12/L
Hemoglobin	123	L	140 - 180	g/L
Hematocrit	0.36	L	0.40 - 0.52	L/L
MCV	96		80 - 99	fL
MCH	33		25 - 35	pg
MCHC	345		320 - 365	g/L
RDW	14.4		11.5 - 14.5	%
Platelet Count				
Platelets	238		140 - 440	x10 9/L
MPV	8.5		7.4 - 10.4	fL
Neutrophils	3.4		1.8 - 7.7	x10 9/L
Lymphocytes	3.0		1.0 - 3.3	x10 9/L
Monocytes	0.9	H	0.1 - 0.8	
Eosinophils	0.2		0.0 - 0.4	
Basophils	0.10		0.00 - 0.2	

BIOCHEMISTRY

TEST NAME	VALUE	FLAG	REFERENCE
Creatinine	60		60 - 110

URINE MONOCLONAL PROTEIN INVESTIGATION

Random sample			
Protein/Creatinine	263.3*	<25	mg/mmol
Creatinine (Urine)	3.4		mmol/L
Monoclonal free light chains - PRESENT			
Type:	Kappa		
Concentration - Trace			
Monoclonal Immunoglobulin - PRESENT			
Class/Type:	IgA / Kappa		
Concentration - Trace			
Urine Electrophoresis			

Lab # ND73233-4 Collected on 25 Apr 17 at 10:30
Your reference - PRITCHARD FARM

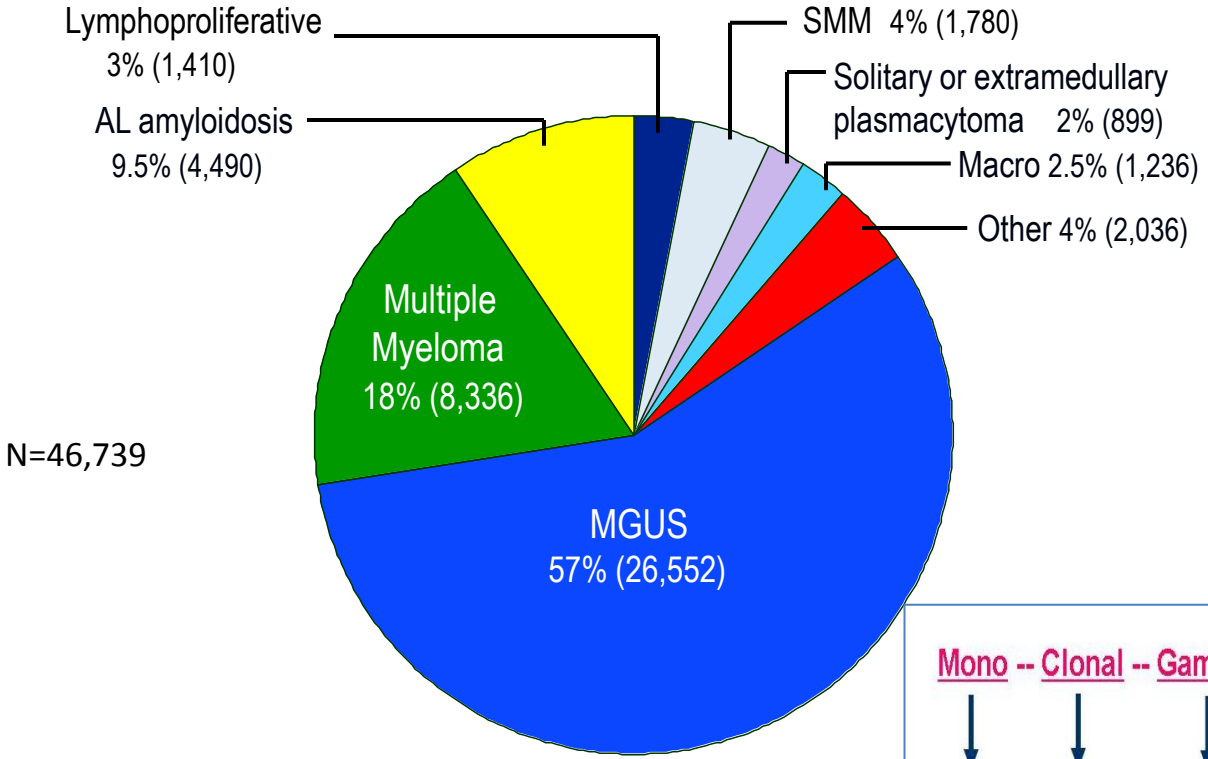
SERUM MONOCLONAL PROTEIN INVESTIGATION	RESULTS	REFERENCE	UNIT
Serum Total Protein	100*	60-80	g/L
Serum Albumin	35	33-45	g/L
IgG	1.95*	6.9-16.2	g/L
IgA	28.80*	0.7-3.8	g/L
IgM	0.63	0.6-2.6	g/L
Monoclonal Immunoglobulin	PRESENT		
Class/type:	IgA / Kappa		
Monoclonal Ig concentration:	30		g/L
NOTE: IgG, IgA and IgM results include normal and monoclonal Ig concentration when present.			
Monoclonal free light chains	PRESENT		
Type:	Kappa (trace amounts)		
Serum Electrophoresis			

FREE LIGHT CHAIN QUANTITATION	RESULTS	REFERENCE	UNIT
Kappa Free LC	9621.70*	3.30-19.40	mg/L
Lambda Free LC	0.82*	5.71-26.30	mg/L
Free LC Ratio	11733.78*	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.

Definition of Monoclonal Protein

- Monoclonal immunoglobulin secreted by an abnormally expanded clone of plasma cells that can be detected during laboratory investigation (SPEP, UPEP, serum free light chain assay)
- Can be intact immunoglobulin or free light chain
- Also known as: M-protein, paraprotein, M-spike, M-component, M-band
- Reported as g/L in Canada (eg. 5g/L), g/dL in USA (eg. 0.5g/dL)

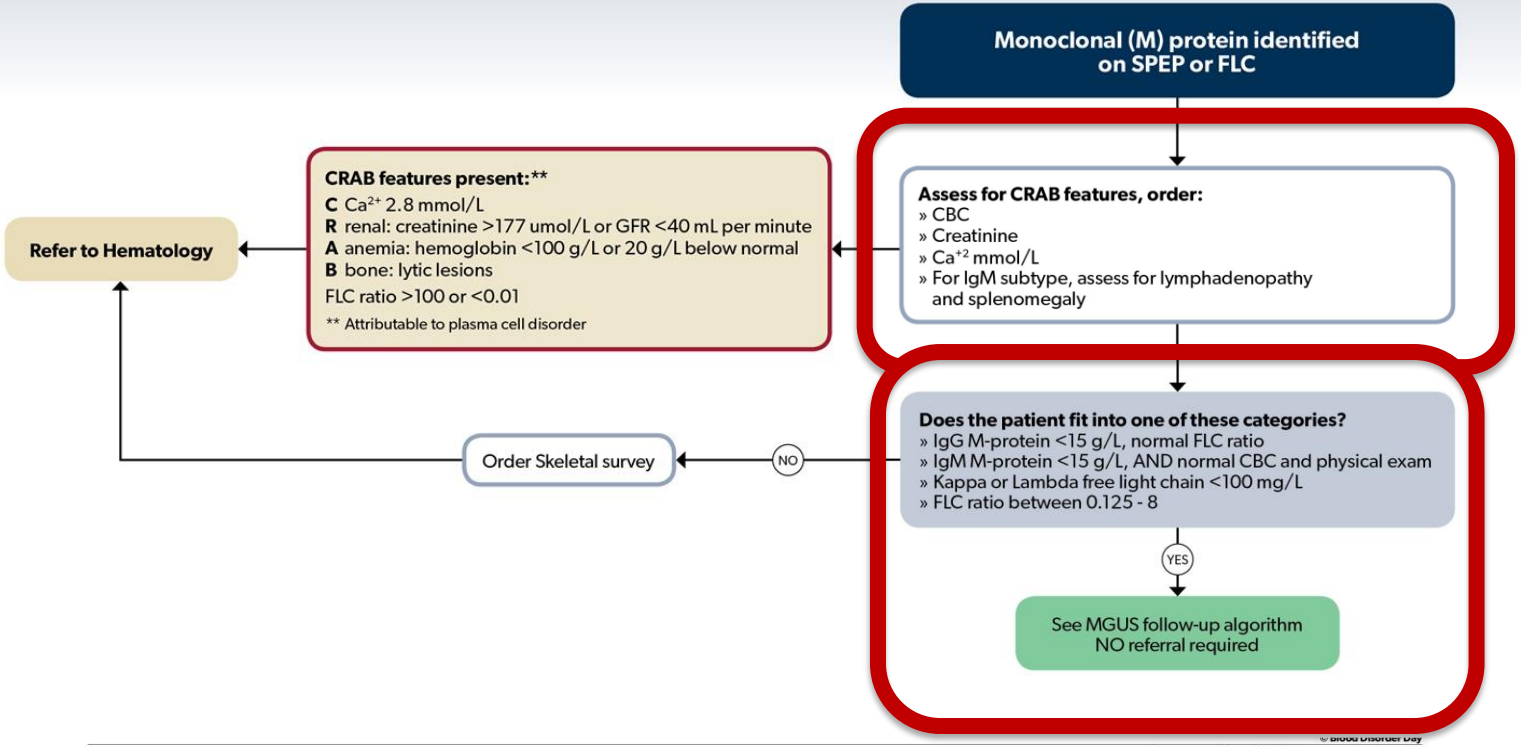


N=46,739

Mayo Clinic 1960-2002

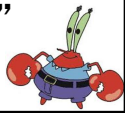
Mono -- Clonal -- Gammo ---------- Pathy
↓ ↓ ↓ ↓
One Clone gammaglobulins → Disease

Monoclonal Protein



MGUS = monoclonal gammopathy of undetermined significance
SPEP = serum protein electrophoresis
FLC = free light chain

Pathways are subject to clinical judgement and actual practice patterns may not always follow the proposed steps in this pathway.

Monoclonal Gammopathy of Undetermined Significance (MGUS)	Smoldering Multiple Myeloma	Multiple Myeloma
M protein in serum <30g/l **and**	M protein >30g/l **and / or**	Any level of M protein (none in non-secretory) **and**
Clonal Bone Marrow Plasma Cells <10% **and**	Clonal plasma cells >10% **and**	Clonal plasma cells >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; 15:e538-48

MGUS

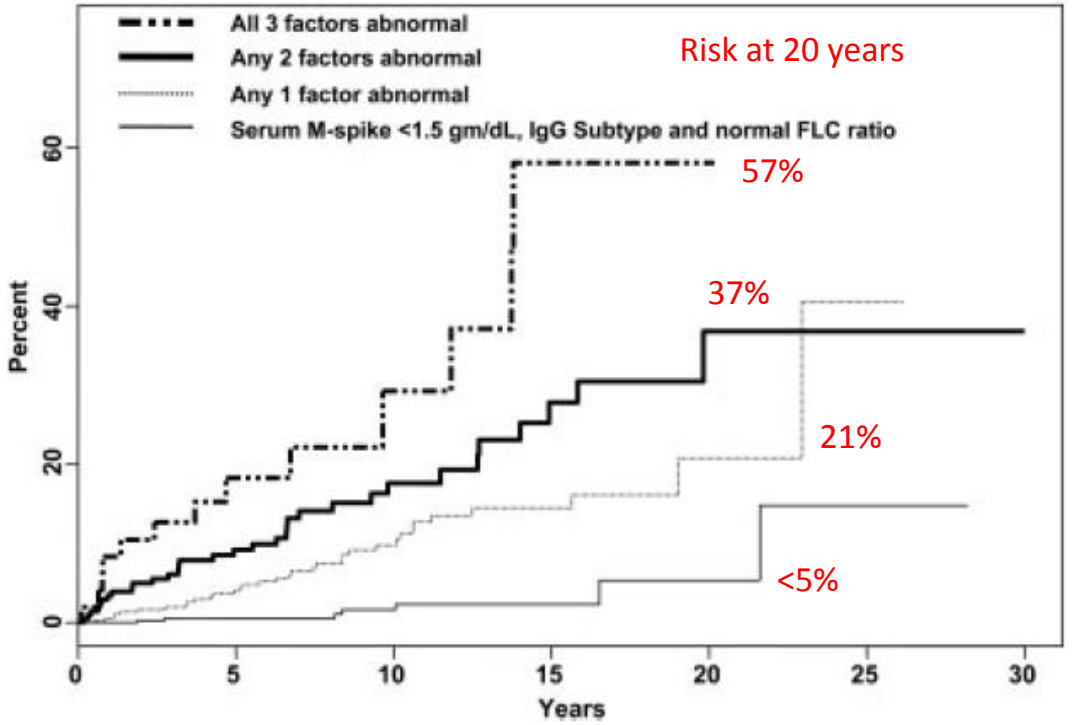
- 3% of general population >50 years old
- Increases with age
- ~50% are low-risk
- Harms of testing?
  - ~40% of patients with MGUS have anxiety, stress or fear related to diagnosis
  - Cost of follow-up

How I Manage MGUS. Go et al. Blood 2018;131:163-173

MGUS

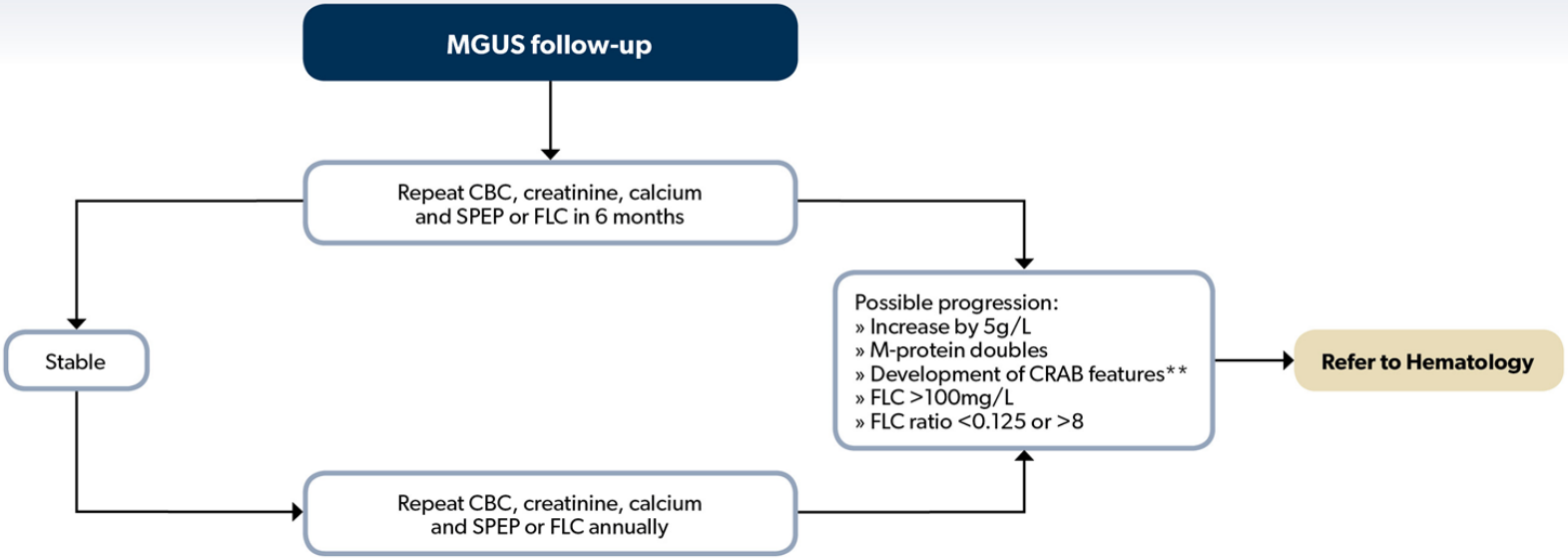
3 adverse risk factors:

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



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

MGUS Follow-up



MGUS = Monoclonal Gammopathy of Undetermined Significance
FLC = Free Light Chain

CRAB features present:**
C Ca^{2+} 2.8 mmol/L
R renal: creatinine >177 umol/L or GFR <40 mL per minute
A anemia: hemoglobin <100 g/L or 20 g/L below normal
B bone: lytic lesions
FLC ratio >100 or <0.01

** Attributable to plasma cell disorder

ANNUAL RISK OF PROGRESSION FOR MGUS SUBTYPES

Pathways are subject to clinical judgement and actual practice patterns may not always follow the proposed steps in this pathway.

MGUS Subtype	Risk	Associated disorders
IgM MGUS	1% per year	Waldenstroms macroglobulinemia
Non-IgM MGUS	0.5% per year	Multiple myeloma, plasmacytoma, amyloidosis
Light chain MGUS	0.3% per year	Light chain myeloma, amyloidosis
Low risk MGUS (IgG, <15 g/L, normal FLC)	2% lifetime risk	

Take Home Message #2

Low risk MGUS has a 2% lifetime risk of developing myeloma

Monoclonal Gammopathy of Undetermined Significance (MGUS)	Smoldering Multiple Myeloma	Multiple Myeloma
M protein in serum <30g/l **and**	M protein >30g/l **and / or**	Any level of M protein (none in non-secretory) **and**
Clonal Bone Marrow Plasma Cells <10% **and**	Clonal plasma cells >10% **and**	Clonal plasma cells >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; 15:e538-48

Referral to Hematology

Thank you for seeing this 61 year old male patient ? MGUS vs MM. In work-up for anemia (hgb 123), he was noted to have a positive SPEP subtype IgA/Kappa (attached results), normal calcium, creatinine and eGFR as well as normal skeletal survey. He feels very well, and chronic conditions of HTN and DM are well controlled.

TEST NAME	VALUE	FLAG	REFERENCE RANGES	UNITS
WBC Count	7.5		4.5 - 11.0	x10 9/L
RBC Count	3.7	L	4.0 - 5.0	x10 12/L
Hemoglobin	123	L	140 - 180	g/L
Hematocrit	0.36	L	0.40 - 0.52	L/L
MCV	96		80 - 99	fL
MCH	33		25 - 35	pg
MCHC	345		320 - 365	g/L
RDW	14.4		11.5 - 14.5	%
Platelet Count				
Platelets	238		140 - 440	x10 9/L
MPV	8.5		7.4 - 10.4	fL
Neutrophils	3.4		1.8 - 7.7	x10 9/L
Lymphocytes	3.0		1.0 - 3.3	x10 9/L
Monocytes	0.9	H	0.1 - 0.8	
Eosinophils	0.2		0.0 - 0.4	
Basophils	0.10		0.00 - 0.2	

BIOCHEMISTRY

TEST NAME	VALUE	FLAG	REFERENCE
Creatinine	60		60 - 110

URINE MONOCLONAL PROTEIN INVESTIGATION

Random sample			
Protein/Creatinine	263.3*	<25	mg/mmol
Creatinine (Urine)	3.4		mmol/L
Monoclonal free light chains - PRESENT			
Type:	Kappa		
Concentration - Trace			
Monoclonal Immunoglobulin - PRESENT			
Class/Type:	IgA / Kappa		
Concentration - Trace			
Urine Electrophoresis			

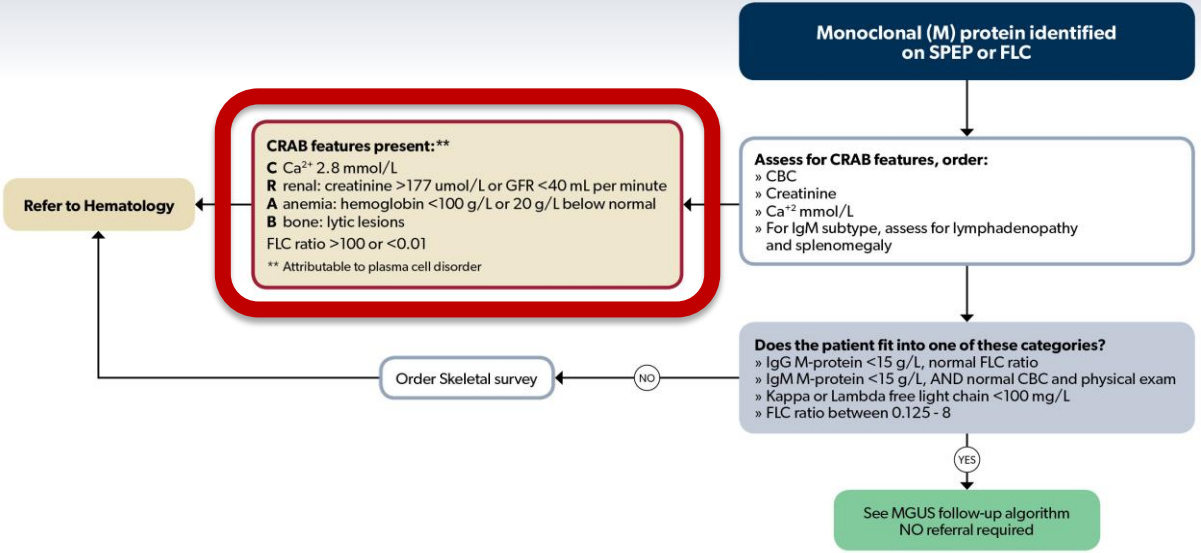
Lab # ND73233-4 Collected on 25 Apr 17 at 10:30
Your reference - PRITCHARD FARM

SERUM MONOCLONAL PROTEIN INVESTIGATION	RESULTS	REFERENCE	UNIT
Serum Total Protein	100*	60-80	g/L
Serum Albumin	35	33-45	g/L
IgG	1.95*	6.9-16.2	g/L
IgA	28.80*	0.7-3.8	g/L
IgM	0.63	0.6-2.6	g/L
Monoclonal Immunoglobulin	PRESENT		
Class/type:	IgA / Kappa		
Monoclonal Ig concentration:	30		g/L
NOTE: IgG, IgA and IgM results include normal and monoclonal Ig concentration when present.			
Monoclonal free light chains	PRESENT		
Type:	Kappa (trace amounts)		
Serum Electrophoresis			

FREE LIGHT CHAIN QUANTITATION	RESULTS	REFERENCE	UNIT
Kappa Free LC	9621.70*	3.30-19.40	mg/L
Lambda Free LC	0.82*	5.71-26.30	mg/L
Free LC Ratio	11733.78*	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.

Monoclonal Protein



MGUS = monoclonal gammopathy of undetermined significance
SPEP = serum protein electrophoresis
FLC = free light chain

What is Multiple Myeloma?

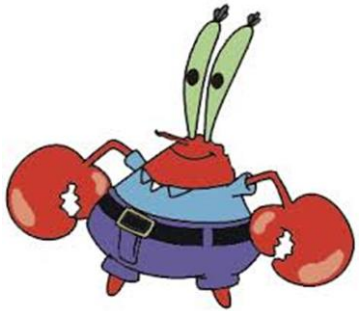
- A bone marrow cancer characterized by uncontrolled proliferation of clonal plasma cells
- Disease manifests with CRAB symptoms

1. **C** – Hypercalcemia
2. **R** – Renal Failure
3. **A** – Anemia
4. **B** – Bone disease – lytic lesions/bone fracture
5. BM plasma cells >60%, FLCR >100, >1 lesion on MRI

Rajkumar et al. 2014 Lancet Oncology; 15:e538-48

Take Home Message #3

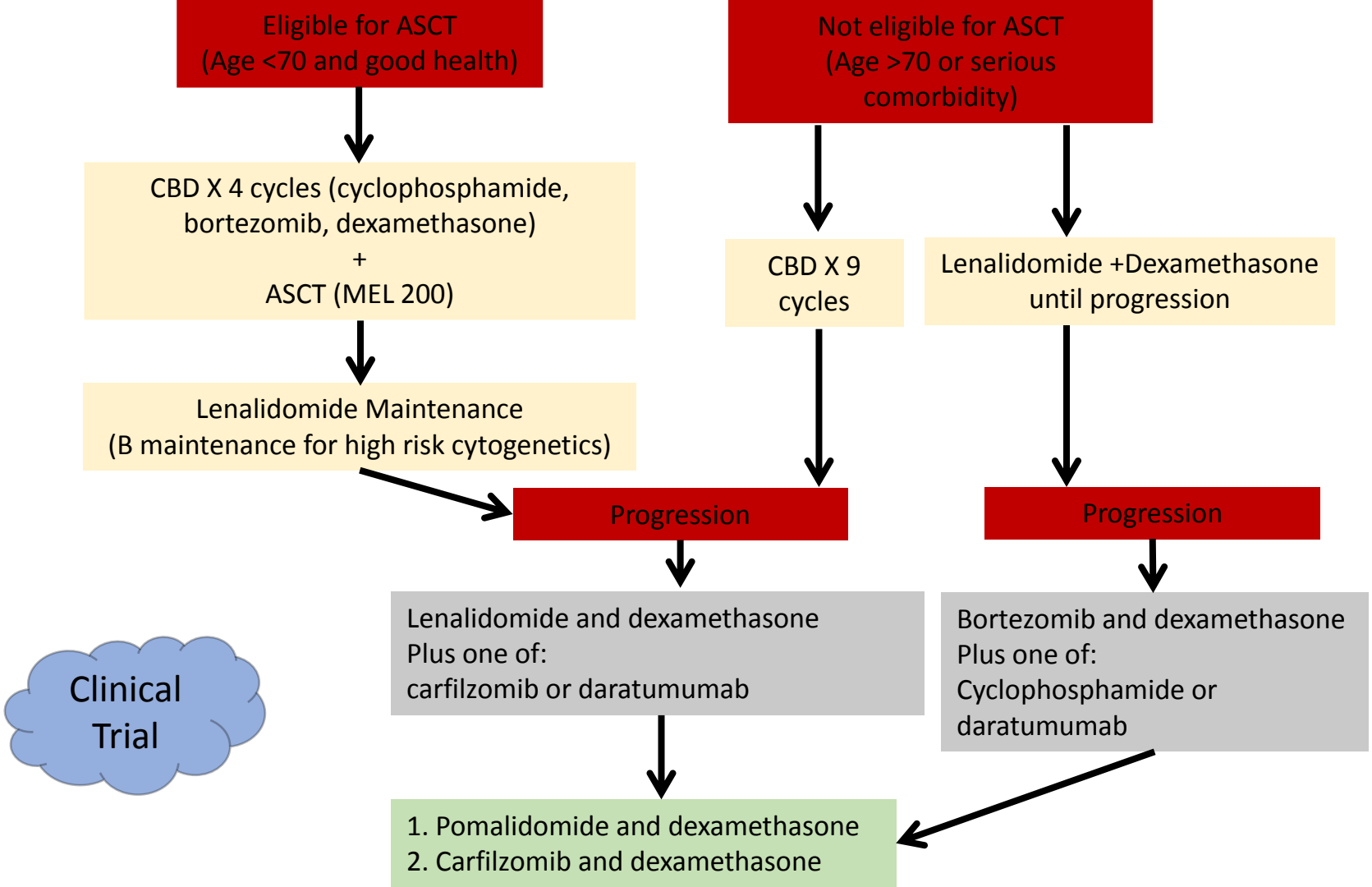
When M-protein identified, look for myeloma related CRAB features



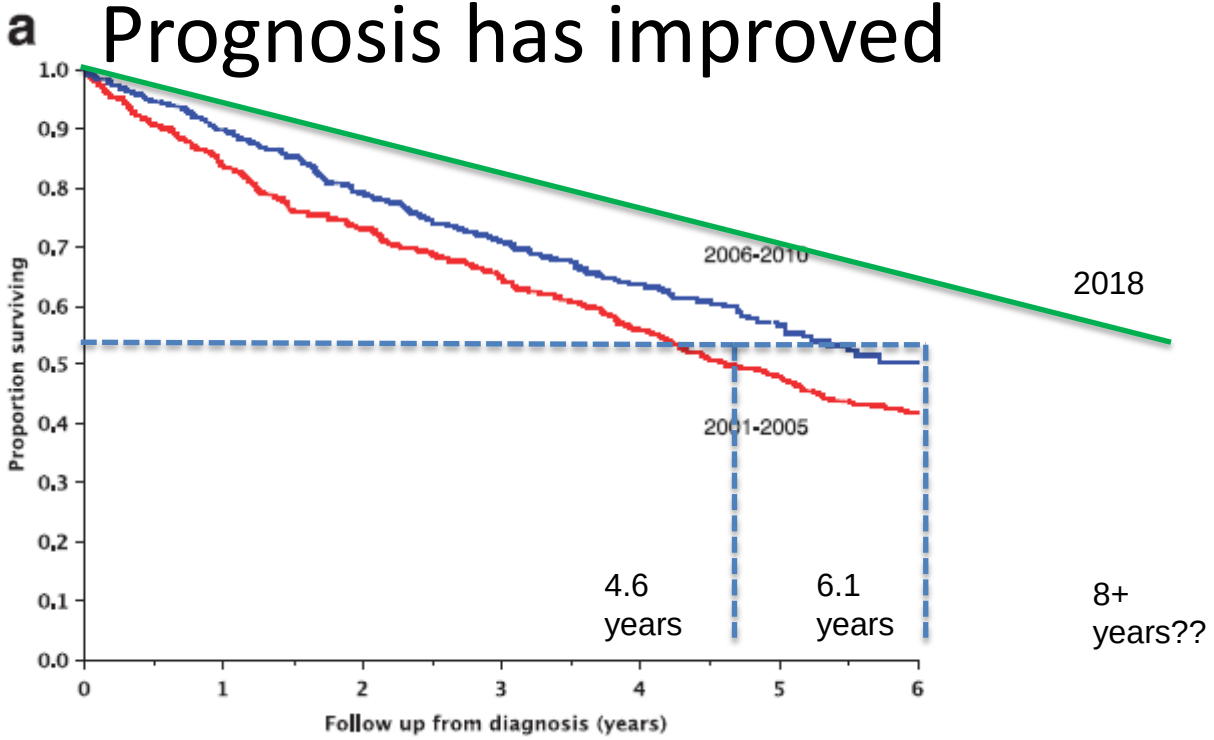
What is Multiple myeloma?

- 1% of all cancers and 15% of hematologic malignancies
  - Estimated 80 new cases per year in Manitoba
- Median age at diagnosis of 69 years
- Incurable malignancy characterized by multiple relapse

Canadian Cancer Society Statistics 2015


Eligible for ASCT
(Age <70 and good health)
Not eligible for ASCT
(Age >70 or serious comorbidity)
CBD X 4 cycles (cyclophosphamide, bortezomib, dexamethasone)
+
ASCT (MEL 200)
CBD X 9 cycles
Lenalidomide +Dexamethasone until progression
Lenalidomide Maintenance
(B maintenance for high risk cytogenetics)
Progression
Progression
Lenalidomide and dexamethasone
Plus one of:
carfilzomib or daratumumab
Bortezomib and dexamethasone
Plus one of:
Cyclophosphamide or daratumumab
Clinical Trial
1. Pomalidomide and dexamethasone
2. Carfilzomib and dexamethasone

Prognosis has improved



- Mayo clinic study of 1038 patients diagnosed with myeloma between 2001 and 2010 with a median follow up of 5.9 years
- Current estimated OS is 6-8 years

Kumar et al. Leukemia 2014;1122-28

Take Home Message #4

Survival in myeloma has improved due to advances in treatment options

Take home messages

- Order an SPEP when suspecting disorders associated with monoclonal gammopathy (esp myeloma)
- Low risk MGUS has very low risk of progression to myeloma
- When monoclonal protein identified, look for CRAB symptoms or one of the new myeloma defining events
- Survival in myeloma has improved tremendously due to new treatment options

CancerCare Manitoba
ActionCancerManitoba

Thank you

erimmer@cancercare.mb.ca

University of Manitoba

CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM