Paraprotein testing and monitoring

Dr Victoria Hervey

20/11/2025

Summary

- Myeloma
- Monoclonal gammopathy of undetermined significance -MGUS
- Investigations
- MGUS risk stratification
- MGUS screening iStopMM trial
- SFLC ratios
- New MGUS guidelines and pathways

Myeloma

Myeloma

- neoplastic proliferation of plasma cells producing a monoclonal immunoglobulin or light chain
  - IgG, IgA most common
  - 20% light chain only
  - IgM myeloma rare, usually associated with lymphoma
- 1-2% of all cancers. Up to 20% of all haem malignancies.
- Incidence 4.5 -7 per 100,000 per year
- Male 1.4 : 1Female
- Median age at diagnosis around 65

Myeloma common symptoms

- Anaemia – 73 %
- Bone pain – 58 % (usually central skeleton, not joints)
- Elevated creatinine – 48 %
- Fatigue/generalized weakness – 32 %
- Hypercalcemia – 28 %
- Weight loss – 24 %

CRAB criteria

- **The definition of active multiple myeloma is:**
- Clonal bone marrow plasma cells >10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following CRAB features as evidence of end organ damage
  - Hypercalcemia: serum calcium >0.25 mmol/L higher than the upper limit of normal or >2.75 mmol/L
  - Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177 micro mol/L
  - Anaemia: hemoglobin value of >20g/L below the lowest limit of normal, or a haemoglobin value <100g/L
  - Bone lesions: one or more osteolytic lesion on skeletal radiography, CT, or PET/CT.

Less common myeloma symptoms

- Hyperviscosity – headache, nosebleeds, haemorrhage, confusion, blurred vision
- Peripheral neuropathy ?additional amyloid
- Fever
- Plasmacytoma
- Spinal cord compression
- Infection – disordered immune system function +/- hypogammaglobulinaemia

Monoclonal gammopathy of undetermined significance (MGUS) definition

Monoclonal gammopathy of undetermined significance (MGUS) - definition

- a monoclonal protein (paraprotein)quantified as <30 g/L
- <10% clonal plasma cells in the bone marrow (BM)
- and the absence of features of the typical end-organ damage associated with multiple myeloma or lymphoplasmacytic malignancies

The prevalence of MGUS increases with age. Median age of 70

- 3.2% of those over 50
- 8.9%of those over 85-year olds
- Higher in patients admitted acutely to hospital compared with previous population estimates

Annual incidence of myeloma and MGUS

- The annual incidence of multiple myeloma is 4.5–7.0 per 100,000 people per year
- annual incidence of MGUS in men
  - 120 per 100,000 population at the age of 50 years and
  - 530 per 100,000 population at the age of 90 years.
- The rates for MGUS women are
  - 60 per 100,000 population at the age of 50 years and
  - 370 per 100,000 population at the age of 90 years.

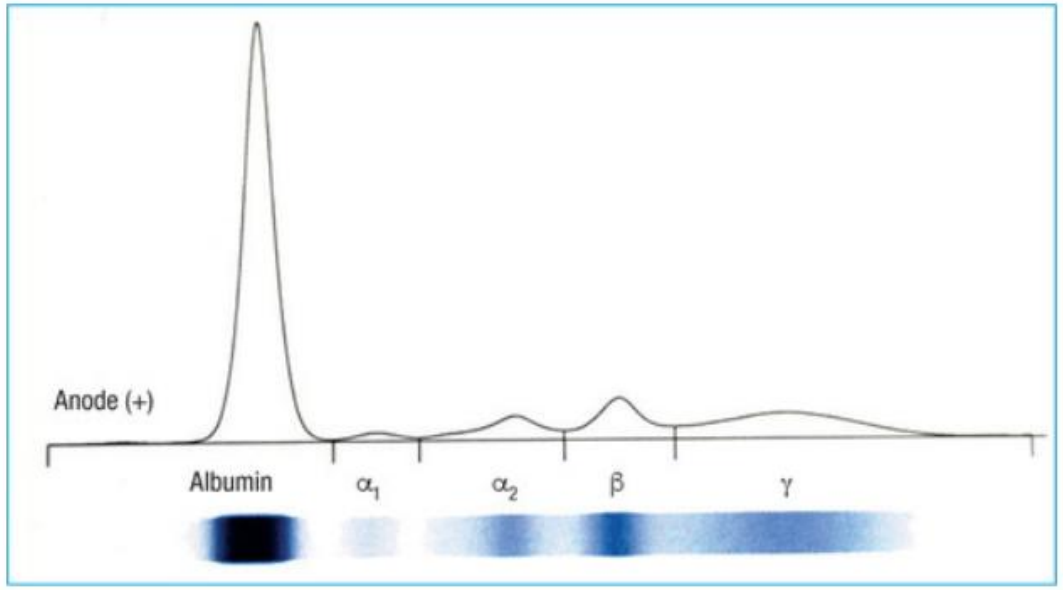
Investigations

Bloods/urine investigation for suspected myeloma

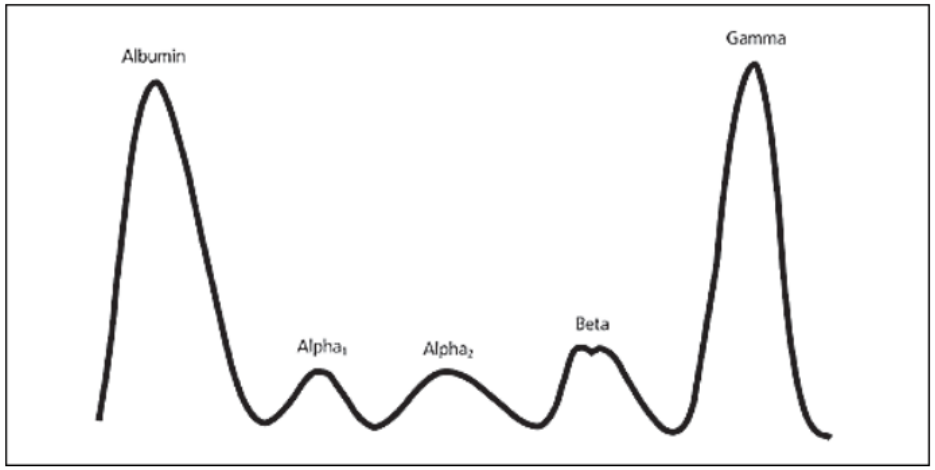
- FBE
- U+E
- LFTs (albumin and total protein)
- calcium
- Serum electrophoresis and immunofixation (to measure and type the paraprotein)
- Immunoglobulins (looking for hypogammaglobulinaemia)
- Serum free light chains
- B2 microglobulin and LDH (used in myeloma staging)
- Urine protein – amyloid, nephrotic syndrome, renal failure due to myeloma rather than other cause. Spot urine test fine for first line test
  - urinary protein:creatinine ratio >100
  - Remember ACR is testing albumin rather than all urinary protein

Serum electrophoresis

- separating proteins based on their net charge, size, and shape. The 2 major types of protein present in the serum are albumin and the globulin proteins.



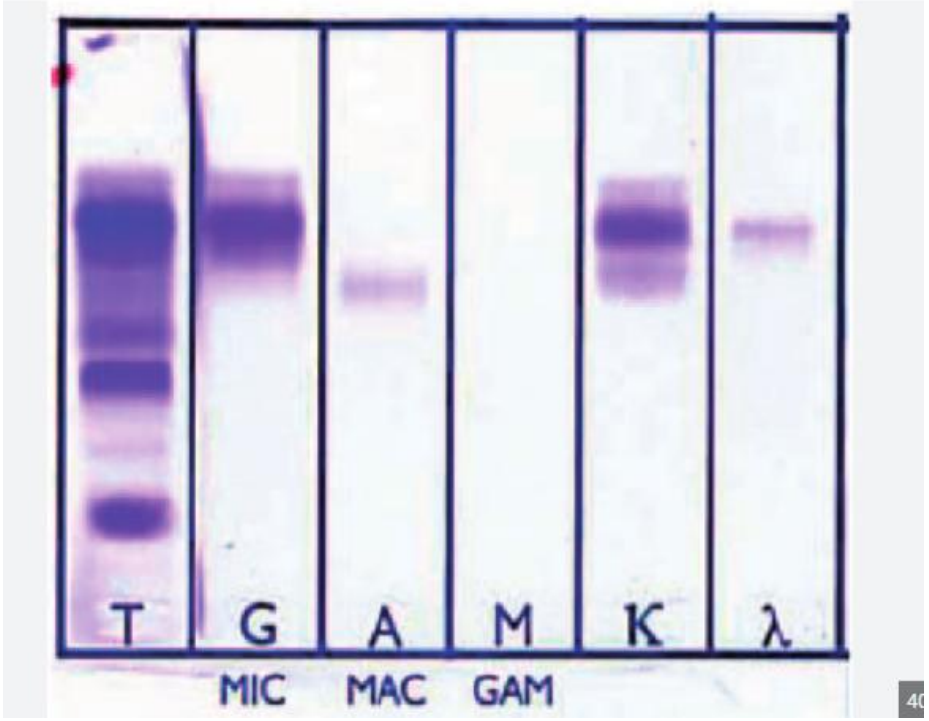
Normal SPEP. The Source



Abnormal serum protein electrophoresis pattern in a patient with multiple myeloma. Note the large spike in the gamma region.

immunofixation

- first fixing them in the gel with antibodies, then washing away all the other proteins prior to staining.



Serum free light chains

- 20% of myeloma is light chain only
- Everyone produces kappa and lambda light chains
- The ratio is the most important.

(higher range renal)

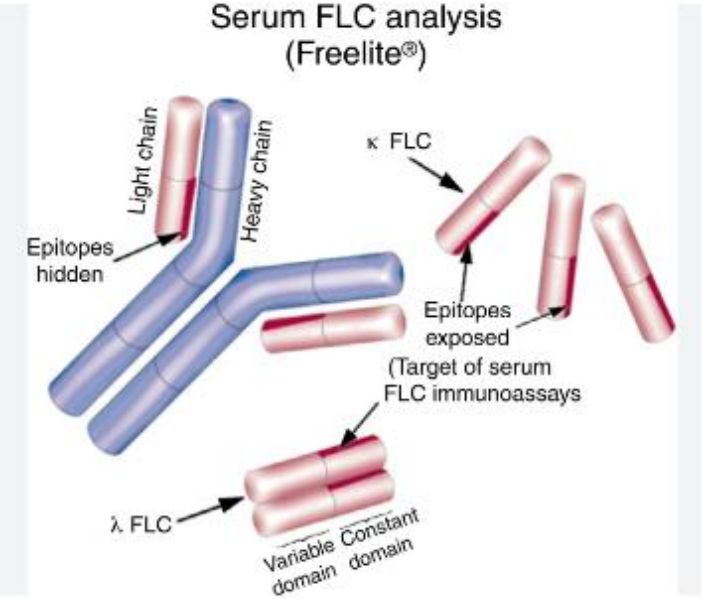


Table. Reference intervals for kappa, lambda, and FLC ratio according to kidney function

	New reference interval (2.5th to 97.5th percentile)		
Kidney function (mL/min/1.73 m²)	Kappa (mg/L)	Lambda (mg/L)	FLC ratio
eGFR 45– 59 N=4611	10.0–47.0	9.1–39.2	0.64–1.92
eGFR 30–44 N=1466	12.5–70.8	10.9–52.8	0.68–2.06
eGFR < 30 N=386	17.8–117.3	14.5–94.4	0.67– 2.17

ELECTROPHORESIS

Total Protein	66	61 - 78	g/L
EP Albumin	36 L	38 - 52	g/L
Alpha-1 Globulin	3.3	2.2 - 4.1	g/L
Alpha-2 Globulin	7.1	5.2 - 9.9	g/L
Beta 1 Globulin	4.0	3.4 - 5.8	g/L
Beta 2 Globulin	2.3	2.1 - 4.9	g/L
Gamma Globulin	13.8	6.0 - 16.0	g/L
Paraprotein CE	8.8		g/L

Paraprotein band detected in the gamma globulin region.

Comments

From the 19/8/2024 serum EPG is performed on the Sebia Cap 3 by capillary electrophoresis (CE).

There is also a second more cathodal monoclonal protein in the gamma globulin region. This monoclonal protein is too small to quantify.

ELECTROPHORESIS

Total Protein	86 H	63 - 80	g/L
EP Albumin	38	38 - 52	g/L
Alpha-1 Globulin	3.1	2.2 - 4.1	g/L
Alpha-2 Globulin	6.3	5.2 - 9.9	g/L
Beta 1 Globulin	3.5	3.4 - 5.8	g/L
Beta 2 Globulin	2.3	2.1 - 4.9	g/L
Gamma Globulin	32.9 H	6.0 - 16.0	g/L
Paraprotein CE	30.7		g/L

Paraprotein band detected in the gamma globulin region.

Comments

From the 19/8/2024 serum EPG is performed on the Sebia Cap 3 by capillary electrophoresis (CE).
Electrophoresis of serum shows a second more cathodic band in the gamma globulin region, this band is too small to quantify.

Concerning results - examples

- The only really important line is paraprotein CE and paraprotein detected

ELECTROPHORESIS

Total Protein	73	63 - 80	g/L
EP Albumin	29 L	38 - 51	g/L
Alpha-1 Globulin	5.8 H	2.2 - 4.1	g/L
Alpha-2 Globulin	13.4 H	4.9 - 8.7	g/L
Beta 1 Globulin	4.9	3.4 - 5.8	g/L
Beta 2 Globulin	6.6 H	2.1 - 4.9	g/L
Gamma Globulin	13.7	6.0 - 16.0	g/L

Electrophoresis shows mild elevation of some globulin fractions, but no discrete paraprotein band detected.

Comments

From the 19/8/2024 serum EPG is performed on the Sebia Cap 3 by capillary electrophoresis (CE).

RM

Reported on 28-Jul-25 14:18

IMMUNOFIX. PROTEINS

Immunofixation Electrophoresis

No monoclonal protein was detected.

Comments

Reactive serum electrophoresis results

- The important bit is ‘no discrete paraprotein band detected’ and no monoclonal band on immunofixation.
- The rise in globulins is reactive, similar to a raised ESR

Myeloma imaging

- If concerns about spinal cord compression or extensive spinal bone disease then MRI spine/pelvis (non-contrast)
- Otherwise CT skeletal survey – low dose CT of bones, non contrast
- Or PET scan in some situations – haematologist lead

Who should be referred to haem clinic?

- Incidental discovery of IgG lambda pp 6gl
- SFLC ratio 3
- Normal Hb, creat, calcium
- No bone pain

- How do I know if this is myeloma or MGUS
- But who will progress?
- Does everyone need monitored?
- GP or secondary care?

RAJKUMAR et al BLOOD, 1 AUGUST 2005 VOLUME 106, NUMBER 3 – Mayo clinic staging for MGUS

Risk factors for MGUS progression:

- abnormal serum kappa-lambda FLC ratio (less than 0.26 or greater than 1.65),
- high serum monoclonal protein level (greater than 15 g/L)
- non–IgG MGUS

TABLE 2 Mayo Clinic MGUS Risk Stratification Model.

Risk of progression	No. of abnormal risk factors	No of patients	Absolute risk of progression at 20 years
Low	0	449	2%
Low-intermediate	1	420	10%
High-intermediate	2	226	18%
High risk	3	53	27%

Note: The three risk factors are defined as an abnormal κ/λ FLC ratio (<0.26 or >1.65), a high serum monoclonal protein concentration (>15 g/L), and a non–IgG subtype (IgA or IgM).

Abbreviations: FLC, free light chain; Ig, immunoglobulin; MGUS, monoclonal gammopathy of undetermined significance.

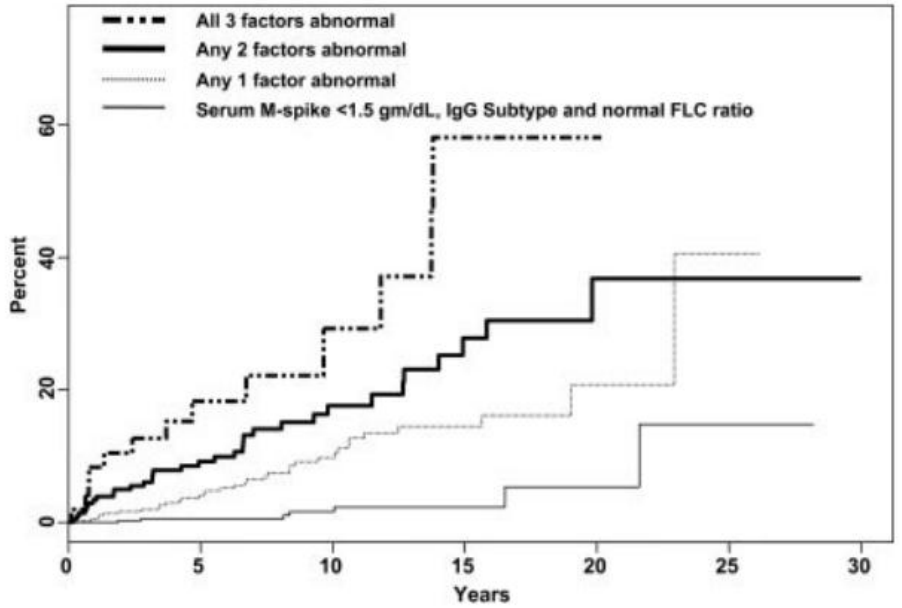


Figure 3. Risk of progression of MGUS to myeloma or related disorder using a risk-stratification model that incorporates the FLC ratio and the size and type of the serum monoclonal protein. The top curve illustrates risk of progression with time in patients with all 3 risk factors, namely an abnormal serum kappa-lambda FLC ratio (< 0.26 or > 1.65), a high serum monoclonal protein level (≥ 15 g/L), and non–IgG MGUS; the second gives the risk of progression in patients with any 2 of these risk factors; the third curve illustrates the risk of progression with one of these risk factors; the bottom curve is the risk of progression for patients with none of the risk factors.

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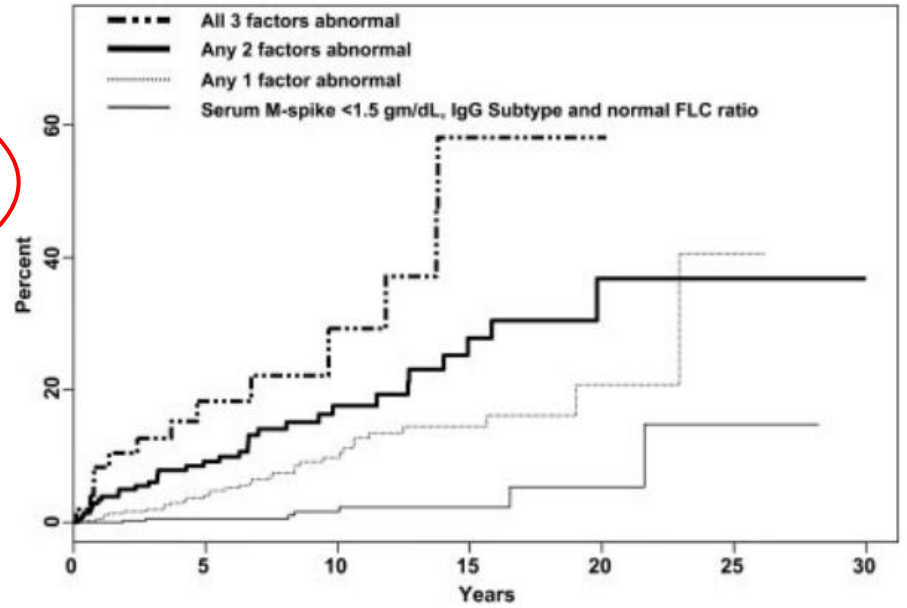

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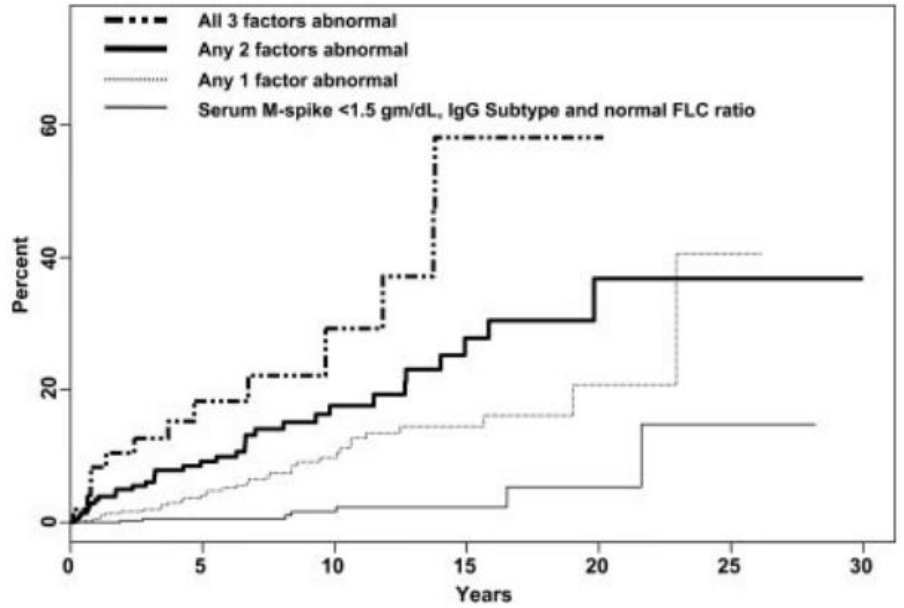

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- How do I know if this is myeloma or MGUS
- But who will progress?
- Who should be screened
- Does everyone need monitored?
- GP or secondary care?
- MGUS screening

Iceland screens, treats, or prevents multiple myeloma (iStopMM) study

The largest scientific study ever conducted in Iceland

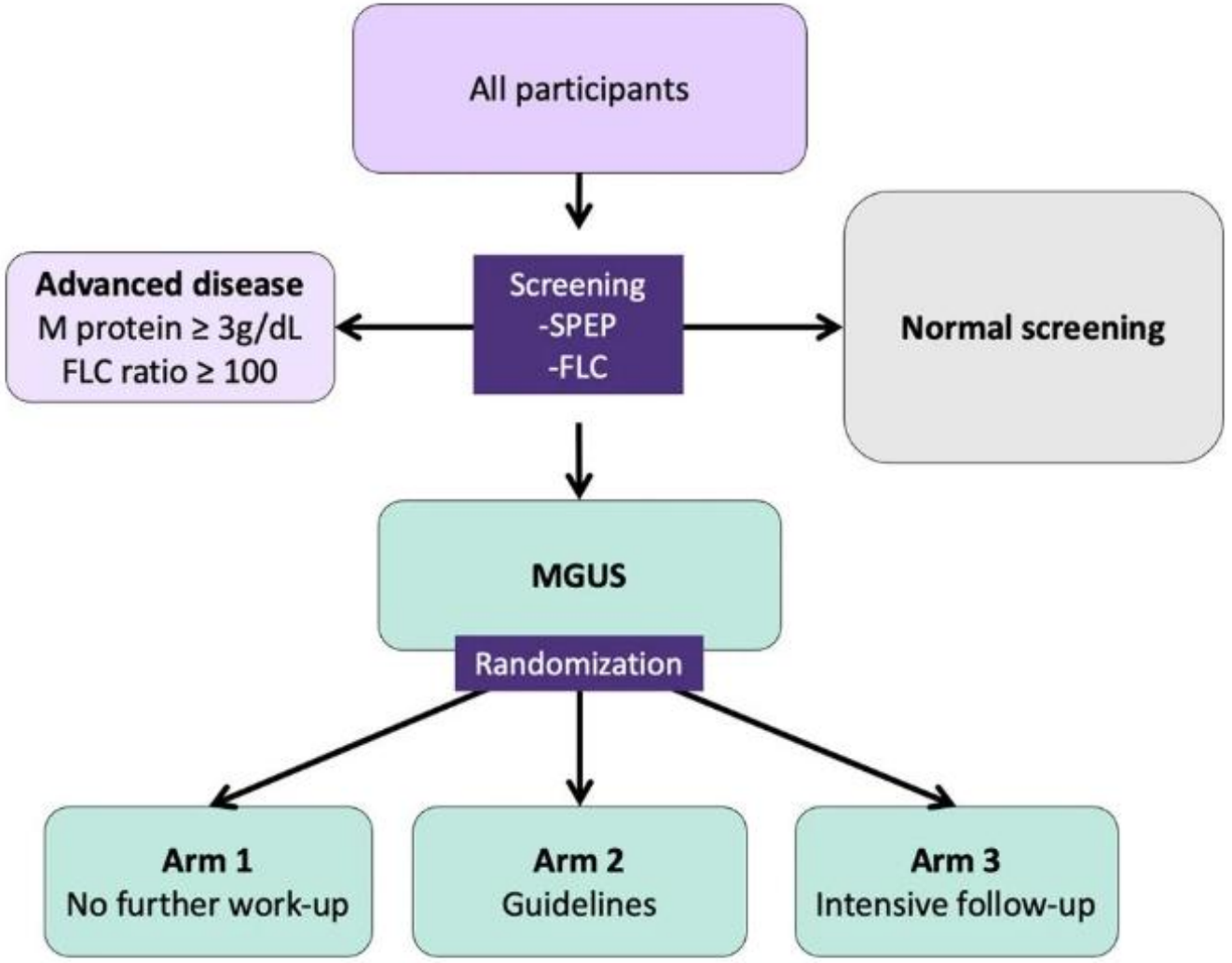
iSTOPMM

- Iceland Screens Treats or Prevents Multiple Myeloma
- All individuals living in Iceland, over age of 40 offered participation (148,704) to screen for myeloma
- 80,759 participated (53%)
- Primary endpoint of the study is 5yr OS of patients with a paraprotein receiving follow-up (arms 2 and 3) compared to those not receiving any follow-up.
- Secondary endpoints are cause-specific survival due to myeloma or other lymphoproliferative disorder, psychiatric health and well-being, and cost-effectiveness of screening.

iSTOPMM

- Eligible individuals were invited to participate in the iStopMM study born in 1975 or earlier and residing in Iceland on the 9th of September 2016, (*n* = 148,711)

2: A flowchart outlining the study design for eening and randomization of individuals with MGUS.



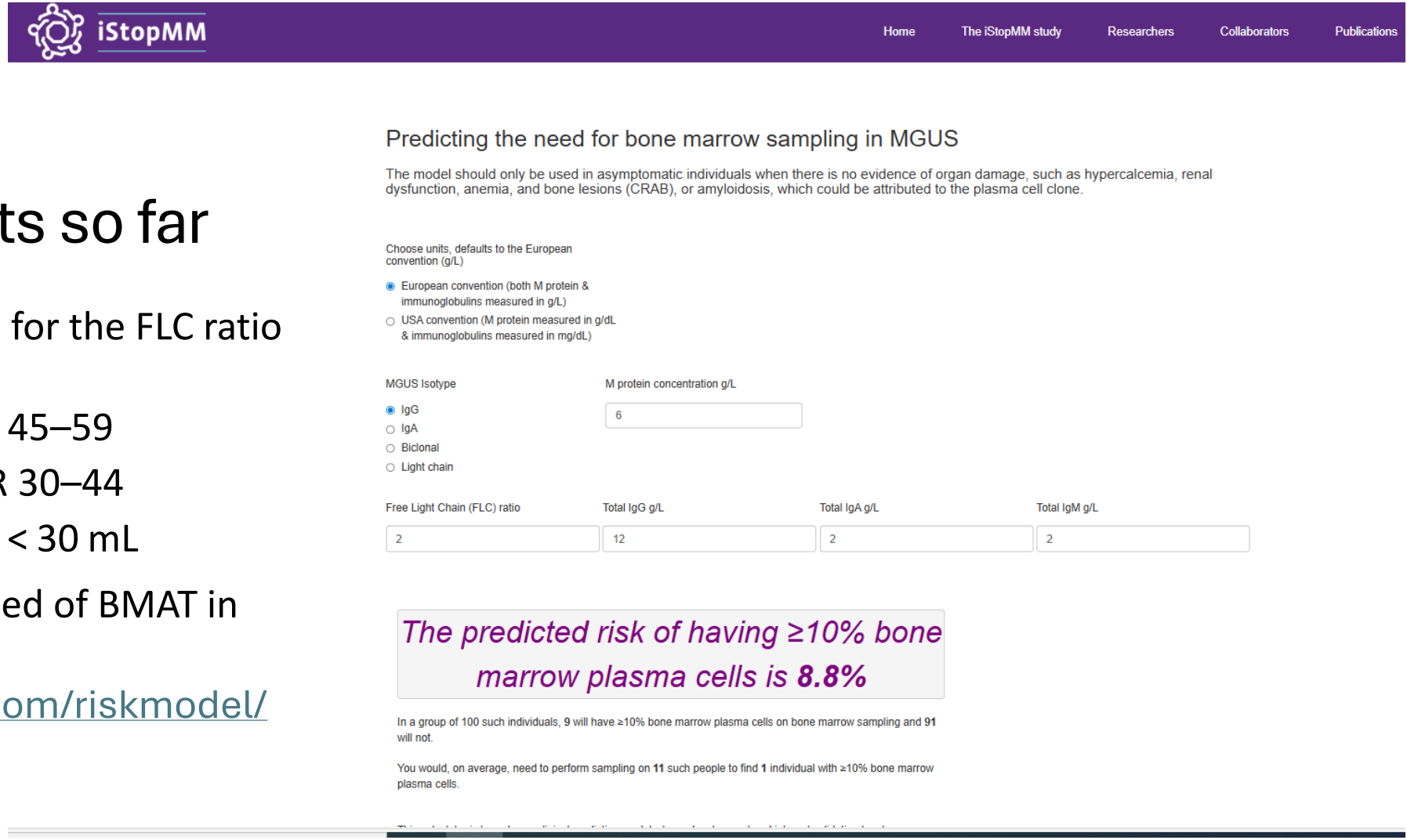
Participants with an M protein ≥3.0 g/dL or an FLC ratio ≥100 are not eligible for randomization but are all alled in for evaluation since they have, by definition, more advanced disease than MGUS[1,8,10]. Participants w th previously diagnosed MGUS cannot be randomized to arm 1, as they are aware of their MGUS status, r are thus randomized to arms 2 or 3 and will not be included in comparisons with arm 1.

investigations

Test	Arm 2–low risk and LC-MGUS	Arm 2–non-low risk	Arm 3–All
Physical exam[a]	First visit	First visit	Each visit
Blood sampling			
SPEP FLC assay	Each visit	Each visit	Each visit
CBC	First visit	Each visit	Each visit
Total calcium Albumin Creatinine	First visit	First visit	Each visit
CRP LDH ß2M	–	–	Each visit
TnT pro-BNP	–	–	Annually
Bone marrow			
Smear Biopsy	As clinically indicated	0 months Except if LC	0 and 60 months
Urine			
Protein dipstick	First visit	First visit	–
UPEP	If positive dipstick or if previously abnormal	If positive dipstick or if previously abnormal	–
Albumin/creatinine ratio	–	–	Annually
ECG	–	–	Annually
Imaging			
WB-LDCT	–	–	0 and 60 months in LC- and non-IgM
Plain X-ray of bones	As clinically indicated	First visit in LC- and non-IgM	–
CT abdomen	–	First visit to IgM	0 and 60 months in IgM
MRI of bones	–	–	–
Follow-up	Every 2–3 years	Annual	Annual

iSTOPMM outputs so far

- New reference intervals for the FLC ratio for renal failure:
  - 0.46–2.62 for eGFR 45–59
  - 0.48–3.38, for eGFR 30–44
  - 0.54–3.30 for eGFR < 30 mL
- Model to predict the need of BMAT in MGUS
  - https://istopmm.com/riskmodel/



iSTOPMM outputs so far

- MGUS seen in 2.3% in the 40-59 age group, 6.2% in the 60-79 age group, and 12.9% in the 80-103 age group.
- At 3 years, 194 patients had been diagnosed with malignancy: 9 in Arm 1, 92 in Arm 2, and 133 in Arm 3 ($P < .001$)
- 5 years from last blood sample collection will be Dec 2025 – OS data soon

Abnormal SFLC ratio

- Is it time to worry/refer?

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ONLINE ONLY ARTICLES

Excluding myeloma diagnosis using revised thresholds for serum free light chain ratios and M-protein levels

Jennifer L. J. Heaney, Alex Richter, Stella Bowcock, Guy Pratt, J. Anthony Child, Graham Jackson, Gareth Morgan, Ingemar Turesson, Mark T. Drayson

Vol. 105 No. 4 (2020): April, 2020 https://doi.org/10.3324/haematol.2019.224360

References

Central laboratory serum FLC ratios and M-protein concentrations in 3,177 newly diagnosed myeloma patients from UK clinical trials (myeloma IX and XI)

Table 1. Table 1. The percentage of myeloma patients who would be undetected at diagnosis according to various serum free light chain κ:λ ratio ranges and M-protein level thresholds.

κ:λ ratio ranges	Percentage and number of patients missed if using FLC ratio alone to detect myeloma			Percentage and number of patients missed using both FLC ratio and M-protein level		
	All patients (N=3177)	Light chain only (n=436, 13.8%)	IgG/A/M/D (n=2717, 86.2%)	M-protein <5 g/L (n=122)	M-protein < 10 g/L (n=226)	M-protein < 15 g/L (n=336)
Normal ratio range	5.2%	0	4.7%	0.4%	0.7%	0.9%
(0.26–1.65)	(172)		(148)	(12)	(23)	(29)
Extended ratio range 1	10%	0.06%	9.3%	0.5%	1.1%	1.6%
(0.15–3.36)	(319)	(2)	(293)	(16)	(35)	(49)
Extended ratio range 2	15%	0.16%	14.2%	0.5%	1.3%	2.1%
(0.08–7.41)	(478)	(5)	(449)	(16)	(40)	(65)
Proposed reference range	13.8%	0.13%	13.0%	0.5%	1.2%	2.0%
(0.1–7.0)	(438)	(4)	(410)	(16)	(38)	(62)

Patients were classified as having a normal serum free light chain (FLC) ratio according to the following reference ranges: (i) normal range for serum FLC ratio (0.26–1.65); (ii) an extended ratio range that encompassed 10% of all myeloma patients at disease presentation (0.15–3.36); (iii) an extended ratio range that encompassed 15% of all myeloma patients at disease presentation (0.08–7.41) and (iv) a proposed reference range simplified for ease of use in clinical practice (0.1-7.0) For each of these serum FLC ratio ranges, patients with a normal ratio were identified and then categorized according to myeloma type and, in the three columns on the right, according to M-protein level. Of 436 patients with only light chains, 18 had oligosecretory myeloma (immunofixation-negative in serum and urine but abnormal serum FLC ratio and FLC levels sufficient to measure response to therapy) and 24 patients (0.8% of the total 3,177 patients) were non-secretors defined by immunofixation-negative blood and urine and serum FLC ratio within the normal reference range; these were excluded from the analysis. The percentages are those of all patients with secretory disease (n=3,153).

haematologica 2020; 105:e169

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- Proposed reference range then tested on 711 MGUS cases (Turesson I, Kovalchik SA, Pfeiffer RM, et al. Monoclonal gammopathy of undetermined significance and risk of lymphoid and myeloid malignancies: 728 cases followed up to 30 years in Sweden. Blood. 2014;123(3):338-345).
- The use of the serum FLC ratio range of 0.1–7.0 in combination with an M-protein threshold of 10 g/L
  - included 97.9% of myeloma cases. The 2.1% of myeloma patients missed (n=66) included 0.8% of non-secretors
  - excluded 93.4% of MGUS cases.
  - provides 97.9% sensitivity for the detection of myeloma. This sensitivity is just 0.5% less than that achieved using the five-fold narrower range of 0.26–1.65 that has a poor specificity for myeloma
  - This risk stratification should not be used in isolation and should be applied in conjunction with clinical symptoms and other laboratory biomarkers

Can we fine tune MGUS testing and referral?

BCSH guidelines 2023

- Newly diagnosed patients with low or low-intermediate-risk MGUS do not require BM examination or imaging investigations
- Newly diagnosed MGUS patients should have repeat blood tests at 6 months after diagnosis, with annual follow-up thereafter,
  although the interval can be longer for patients with low- risk MGUS and further investigations reduced if life expectancy is short.
- Patients with high-intermediate and high-risk MGUS should be followed up in secondary care, with formal risk assessment taking place every 3 years

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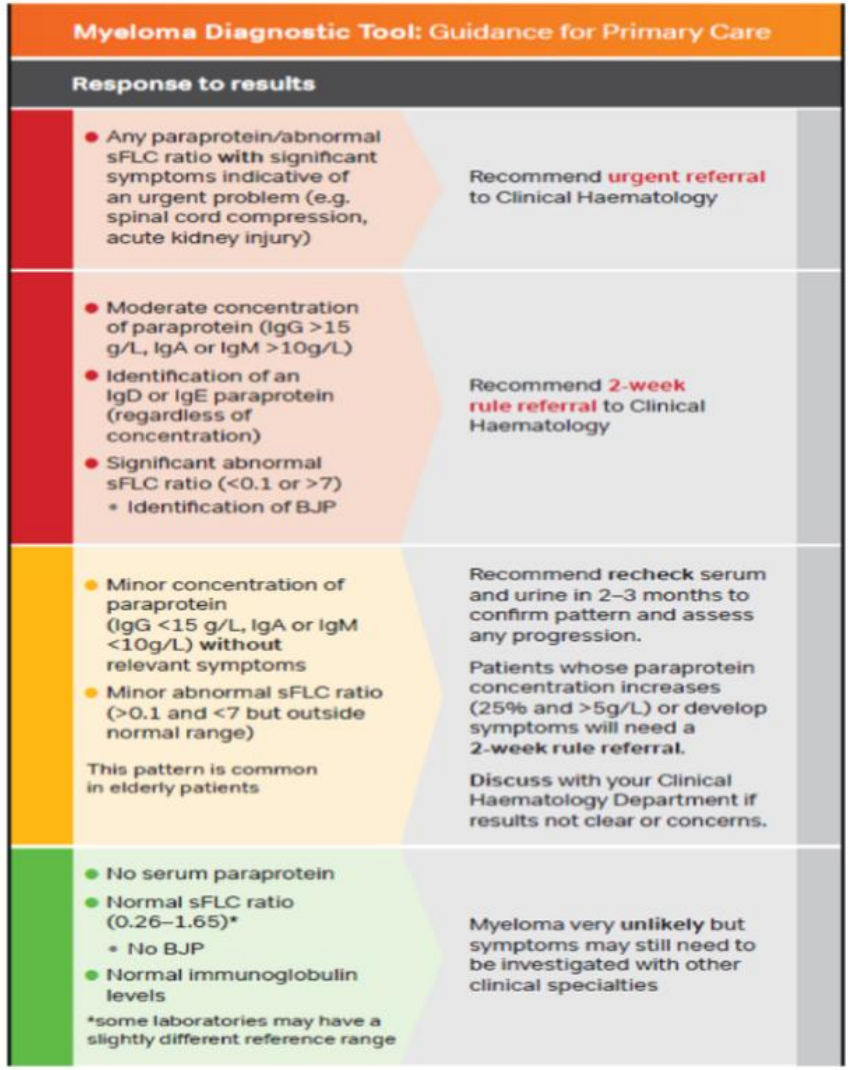
BCSH guidelines 2023

- High-intermediate and high-risk patients on the Mayo Clinic risk stratification model or those otherwise suspected of having an MM or an LPM should undergo the following investigations:
  - LDH and beta-2 microglobulin levels
  - Imaging investigations
  - Bone marrow biopsy with flow and FISH
  - Urine protein: creatinine ratio OR albumin:creatinine ratio
  - proBNP for early identification of AL amyloidosis

BCSH guidelines 2023

- applying an M-protein threshold of 10 g/L and a serum FLC ratio range (<0.1 or >7) gives high specificity and sensitivity for myeloma diagnosis. If both thresholds are exceeded that provides 98% sensitivity for the detection of myeloma and excludes 95% of MGUS cases

Myeloma UK Myeloma Diagnostic Tool, Guidance for Primary Care

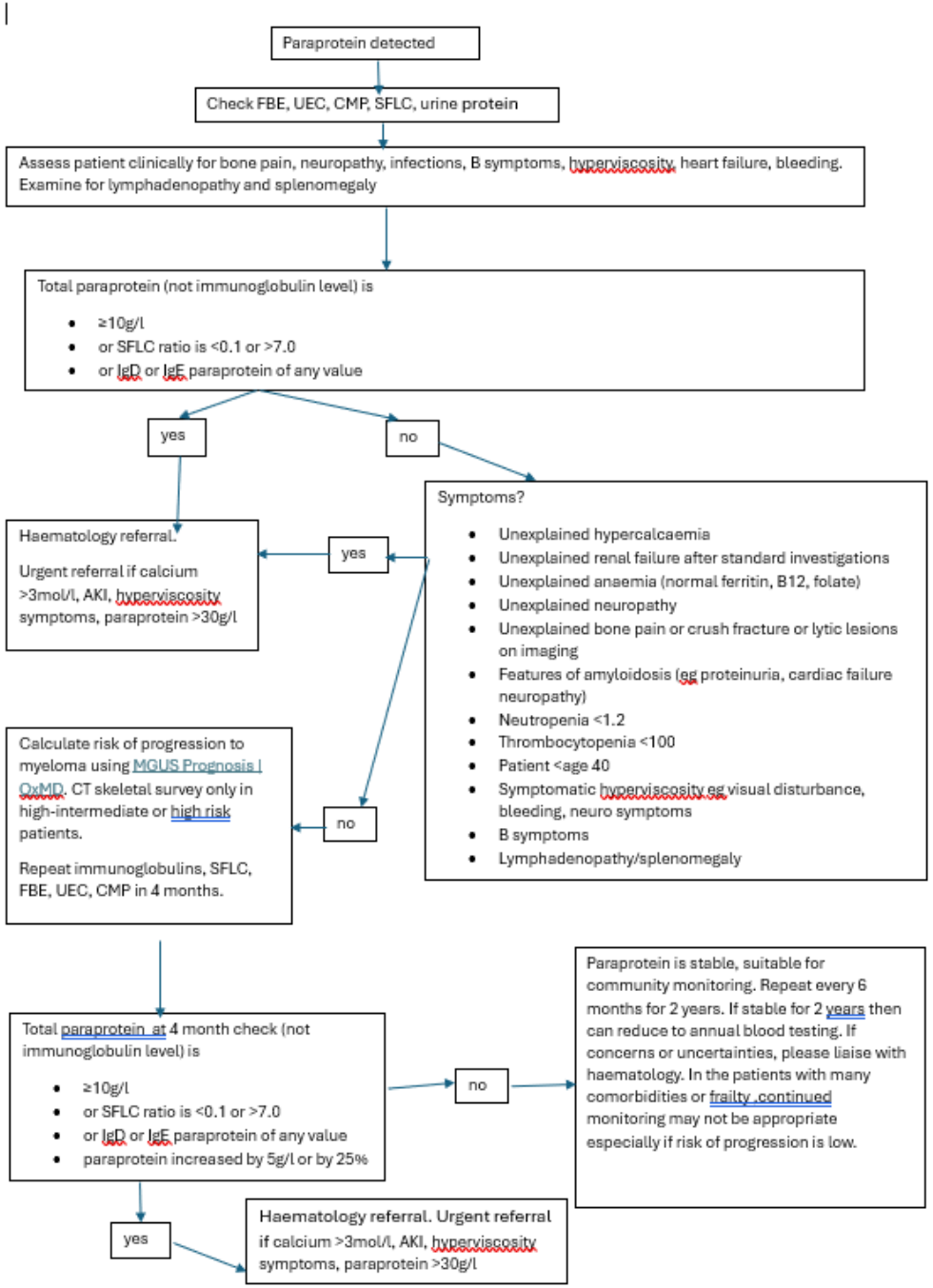


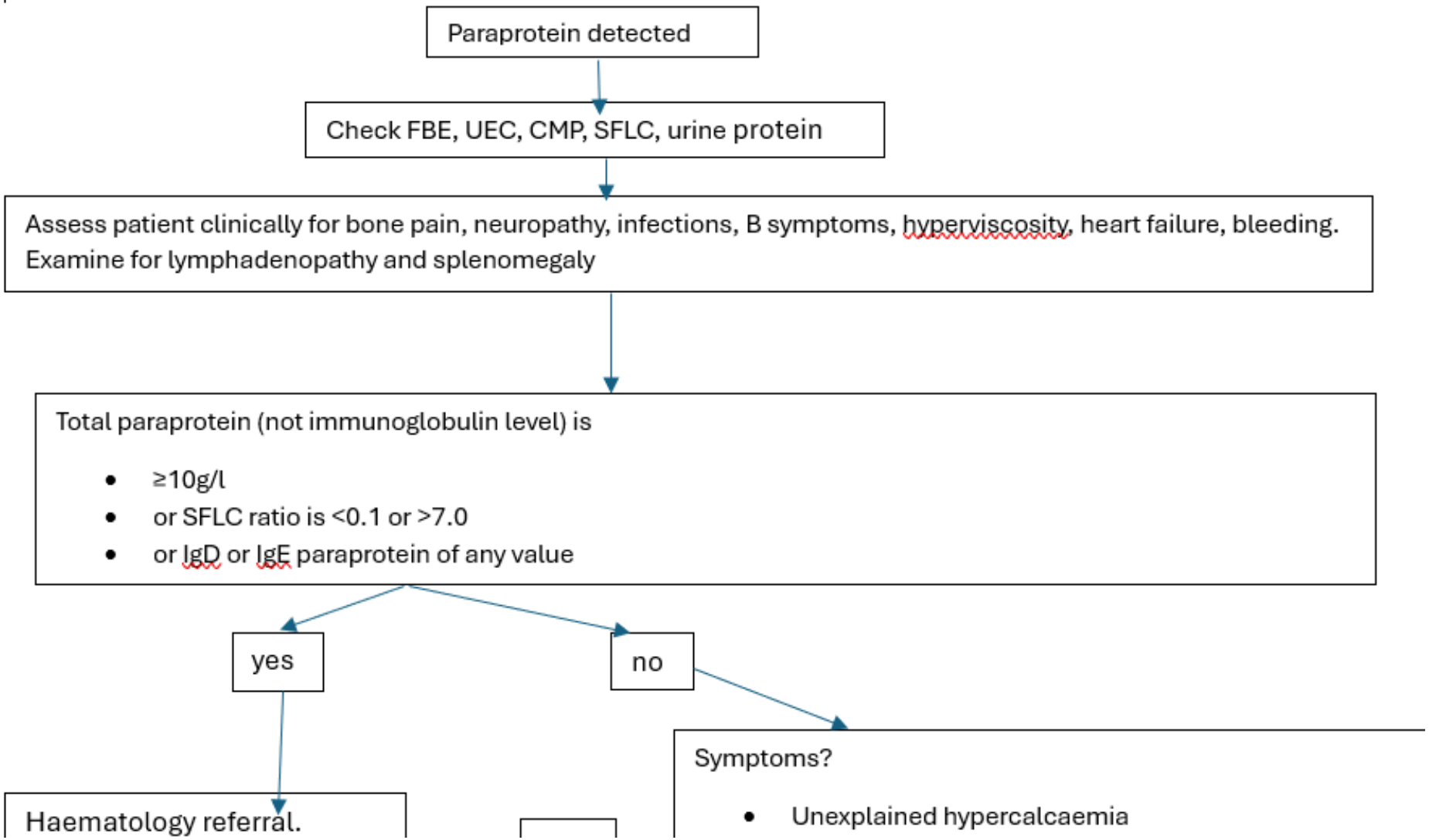
Myeloma Diagnostic Tool: Guidance for Primary Care

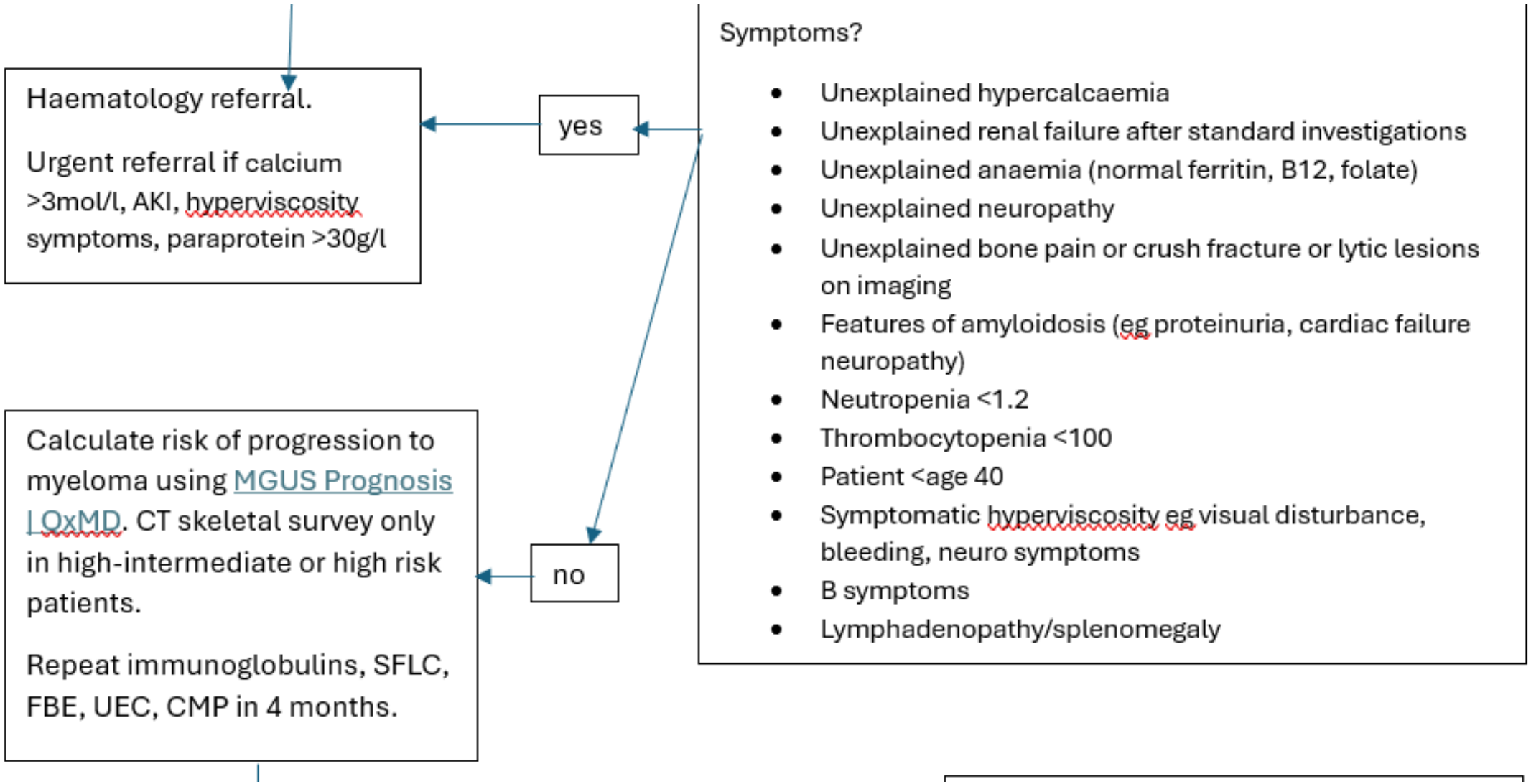
Response to results

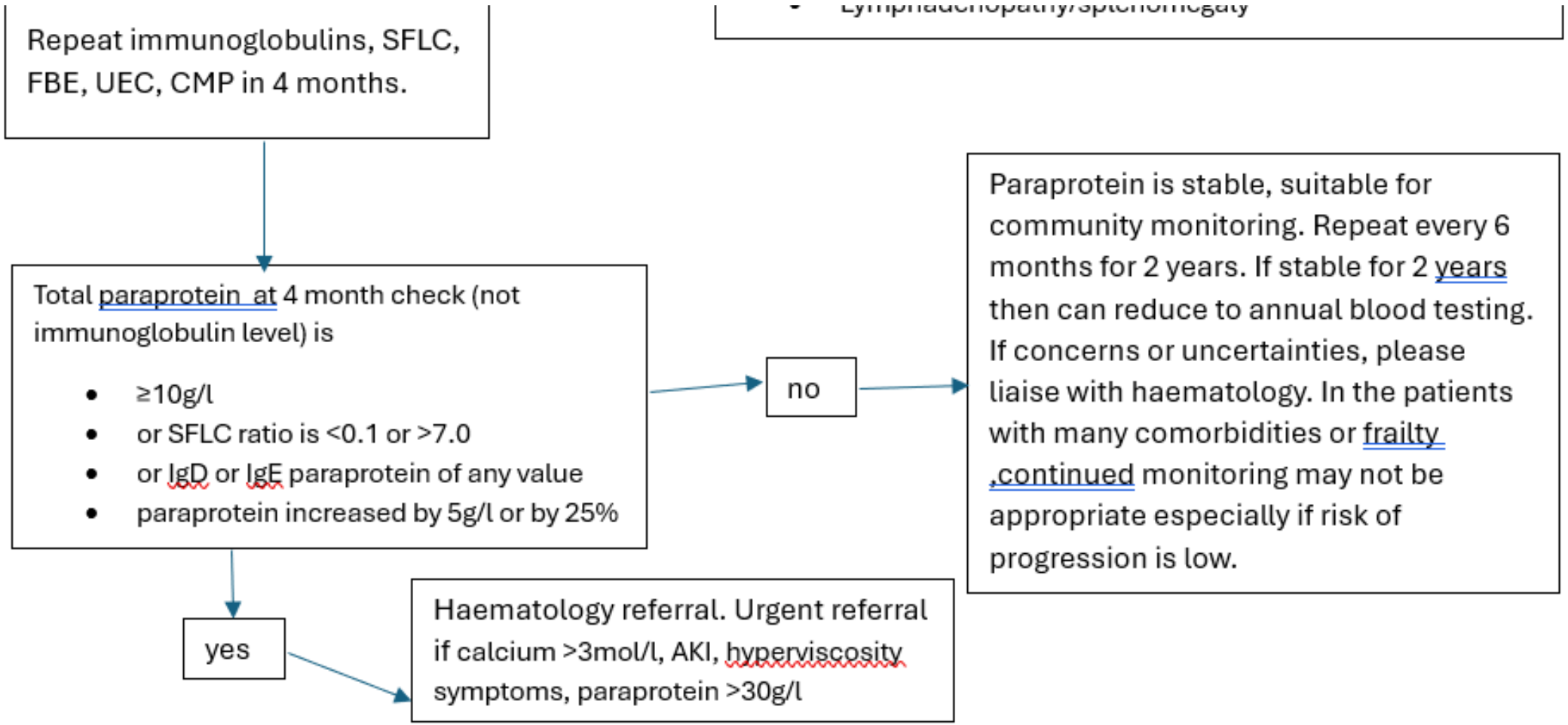
• Any paraprotein/abnormal sFLC ratio **with** significant symptoms indicative of an urgent problem (e.g. spinal cord compression, acute kidney injury)	Recommend urgent referral to Clinical Haematology
• Moderate concentration of paraprotein (IgG >15 g/L, IgA or IgM >10g/L) • Identification of an IgD or IgE paraprotein (regardless of concentration) • Significant abnormal sFLC ratio (<0.1 or >7) ◦ Identification of BJP	Recommend 2-week rule referral to Clinical Haematology
• Minor concentration of paraprotein (IgG <15 g/L, IgA or IgM <10g/L) **without** relevant symptoms • Minor abnormal sFLC ratio (>0.1 and <7 but outside normal range) This pattern is common in elderly patients	Recommend **recheck** serum and urine in 2–3 months to confirm pattern and assess any progression. Patients whose paraprotein concentration increases (25% and >5g/L) or develop symptoms will need a **2-week rule referral.** Discuss with your Clinical Haematology Department if results not clear or concerns.
• No serum paraprotein • Normal sFLC ratio (0.26–1.65)* ◦ No BJP • Normal immunoglobulin levels *some laboratories may have a slightly different reference range	Myeloma very **unlikely** but symptoms may still need to be investigated with other clinical specialties

New MGUS investigation flow chart for GPs in Tasmania




Paraprotein detected
Check FBE, UEC, CMP, SFLC, urine protein
Assess patient clinically for bone pain, neuropathy, infections, B symptoms, hyperviscosity, heart failure, bleeding.
Examine for lymphadenopathy and splenomegaly
Total paraprotein (not immunoglobulin level) is
≥10g/l
or SFLC ratio is <0.1 or >7.0
or IgD or IgE paraprotein of any value
yes
no
Haematology referral.
Symptoms?
Unexplained hypercalcaemia


Symptoms?
Unexplained hypercalcaemia
Unexplained renal failure after standard investigations
Unexplained anaemia (normal ferritin, B12, folate)
Unexplained neuropathy
Unexplained bone pain or crush fracture or lytic lesions on imaging
Features of amyloidosis (eg proteinuria, cardiac failure neuropathy)
Neutropenia <1.2
Thrombocytopenia <100
Patient <age 40
Symptomatic hyperviscosity eg visual disturbance, bleeding, neuro symptoms
B symptoms
Lymphadenopathy/splenomegaly
yes
Haematology referral.
Urgent referral if calcium >3mol/l, AKI, hyperviscosity symptoms, paraprotein >30g/l
no
Calculate risk of progression to myeloma using MGUS Prognosis | QxMD. CT skeletal survey only in high-intermediate or high risk patients.
Repeat immunoglobulins, SFLC, FBE, UEC, CMP in 4 months.


Repeat immunoglobulins, SFLC, FBE, UEC, CMP in 4 months.
Total paraprotein at 4 month check (not immunoglobulin level) is
≥10g/l
or SFLC ratio is <0.1 or >7.0
or IgD or IgE paraprotein of any value
paraprotein increased by 5g/l or by 25%
no
Paraprotein is stable, suitable for community monitoring. Repeat every 6 months for 2 years. If stable for 2 years then can reduce to annual blood testing. If concerns or uncertainties, please liaise with haematology. In the patients with many comorbidities or frailty ,continued monitoring may not be appropriate especially if risk of progression is low.
yes
Haematology referral. Urgent referral if calcium >3mol/l, AKI, hyperviscosity symptoms, paraprotein >30g/l

Tasmanian Health Pathways

- Updated to reflect this flow chart but unfortunately flow chart cannot be uploaded
- Paraproteinaemia (Monoclonal Gammopathy) and MGUS - Community HealthPathways Tasmania
- https://tasmania.communityhealthpathways.org/16173.htm
- Myeloma, MGUS and related conditions - A Guide for GPs

- Thank you