Primary Care Management Pathway
Monoclonal Gammopathy of Underdetermined Significance (MGUS)

Background

Primary care management pathways are being developed by specialist and primary care groups to support the management of common, non-urgent conditions for which long wait times to specialty care currently exist. The pathways will help identify patients with high-risk features and facilitate early referral to specialists as needed.

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic state where a low level of monoclonal protein is detectable in the blood or urine. MGUS is estimated to affect approximately 3% of the general population >50 years of age, 5% of those age >70 years, and 9% of those age >85 years (1). People with MGUS have a low risk of conversion to symptomatic myeloma, estimated at approximately 1% per year (2–4). MGUS can be further sub-classified into risk categories including low, intermediate and high risk.

Defining MGUS [5]

- An asymptomatic state with no CRAB* features attributable to the monoclonal protein
- Serum monoclonal protein <30g/L on serum protein electrophoresis (SPEP)
- Urine monoclonal protein <500mg in 24-hour collection on urine protein electrophoresis (UPEP)
- Bone marrow plasma cells <10% (if completed)

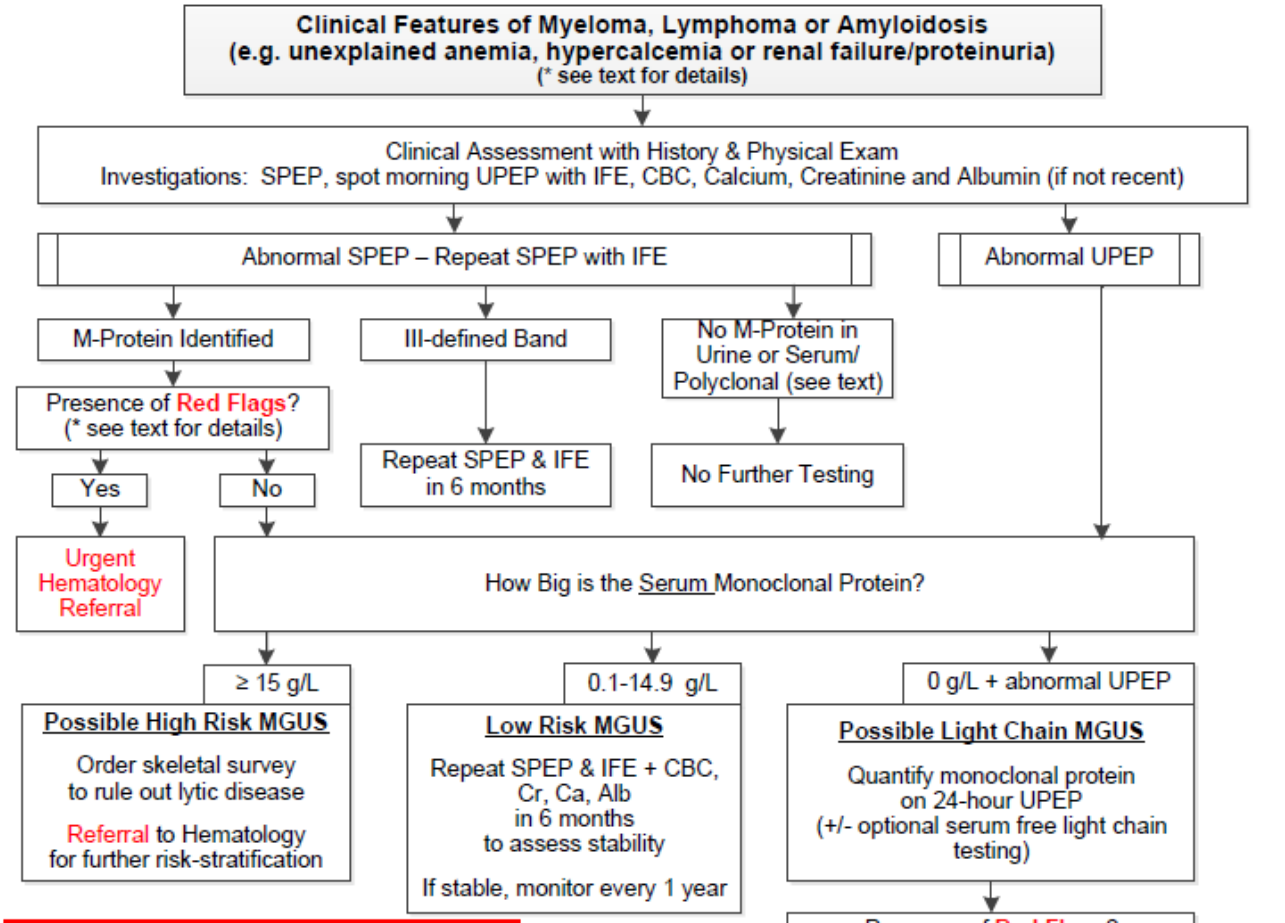
*__C__alcium with corrected serum calcium >2.75mmol/L; __R__enal failure with creatinine >177umol/L; __A__nemia with hemoglobin less than 100g/L; __B__one disease with lytic disease on skeletal survey

- The Clinical “CRAB” features include
  - C – calcium – hypercalcemia, corrected serum Ca >2.75mmol/L
  - R – renal failure with Cr >177umol/L
  - A – Anemia with Hgb less than 100g/L
  - B – bone disease – with lytic disease on skeletal survey (SS)

Patient information

It is possible that your patient and/or their family member may express a desire for additional information about the primary care management pathway and their role or experience throughout the process of being on a pathway. Additional information for patient education has been provided in “Appendix B – Patient Information”.

Primary Care Management Pathway – Clinical Flow Diagram
Monoclonal Gammopathy of Underdetermined Significance (MGUS)



*** Red Flag Features Include Any Of The Following:**

- Hemoglobin <100 g/L
- Calcium >2.75 mmol/L
- eGFR <45 ml/min/1.72m^2
- Lytic bone lesions
- Urine M-protein >500 mg/24 hours
- sFLC ratio >8 or <0.125

Referral Contact Details
For emergency referrals, contact Hematologist through KHSC Switchboard 613-549-6666, press 8 – ask to speak to **attending** Hematologist about a **pathway patient**
Fax # 613-533-6855
Referral form: www.https://kingstonhsc.ca/refer

Do you have a question regarding a patient on the pathway?
Contact Hematologist through KHSC Switchboard 613-549-6666, press 8 – ask to speak to **attending** Hematologist about a **pathway patient**

Please consider eConsult if there are questions about patients who do not meet pathway criteria for a referral.
eConsult is available to practitioners registered with the eConsult service: https://otnhub.ca.

Abbreviations:
M-protein = monoclonal protein; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; IFE = immune fixation; SFLC = serum free light chain

Appendix A – Expanded Detail

What is a monoclonal protein?

A monoclonal protein (M-protein) is a monoclonal immunoglobulin secreted into the blood stream or urine by a clonal plasma cell in the bone marrow. Monoclonal proteins can be a whole immunoglobulin (including heavy and light chain components, e.g. IgG kappa) or just the light chain component (e.g. kappa).

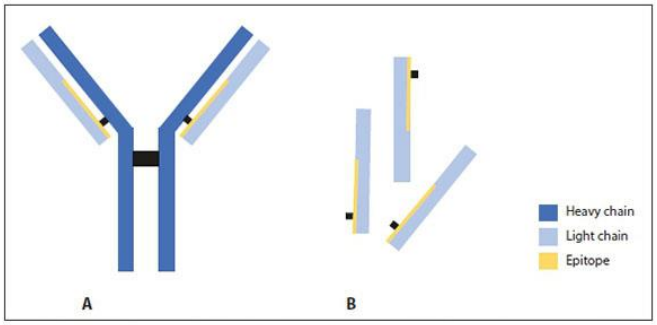


Fig. 1 (A). IgG antibody with both heavy and light chains. When the light chain is bound to the heavy chain the free light-chain (FLC) epitope is hidden and therefore unable to bind in the serum FLC immunoassay. (B) FLCs. When dissociated from its heavy chain counterpart, an epitope is exposed that allows binding in the serum FLC assay.

Image: Houston et al. 2019 (6)

Defining Polyclonal Gammopathy

Polyclonal gammopathy or hypergammaglobulinemia refers to the over production of more than one class or type of immunoglobulins. Common causes include: acute or chronic inflammation, autoimmune disorders, solid organ-malignancies, and liver disease. Investigations should be focused around determining the underlying cause of these reactive findings. Polyclonal gammopathy itself is not a disease and does not progress to multiple myeloma.

When should we test for the presence of monoclonal proteins?

Testing for monoclonal proteins should be pursued when an M-protein related disorder such as myeloma, lymphoma, or amyloidosis is suspected. These diagnoses may be

suspected in the presence of unexplained anemia, hypercalcemia, or unexplained renal failure/proteinuria (see KidneyWise toolkit, Ontario Renal Network). Do *not* screen the general population for monoclonal proteins.

When testing for the presence of a monoclonal protein, order a serum protein electrophoresis **(SPEP)** and a **morning spot urine protein electrophoresis (UPEP) with immunofixation**, as well as a complete blood count **(CBC)**, **calcium**, **albumin**, and **creatinine** if not done recently. If the SPEP is abnormal, then repeat **SPEP with immunofixation (IFE)** in order to confirm the M-protein type and amount.

What is Multiple Myeloma?

Multiple myeloma is a malignancy arising from clonal plasma cells in the bone marrow. It evolves from an asymptomatic state, MGUS. Myeloma is a symptomatic state characterized by at least one of the following: anemia, renal failure, bone disease and associated hypercalcemia. Based on the updated 2014 International Myeloma Working Group (IMWG) recommendations, the diagnosis of multiple myeloma is based on the presence of *any* high-risk biomarkers (acronym SLIM) or clinical features (acronym CRAB).[5] The timely diagnosis of multiple myeloma is essential in order to limit or avoid irreversible end-organ damage including renal failure and fractures.

The high-risk "SLIM" biomarkers include
- SL – serum free light chain ratio of 100 or greater
- I – imaging – more than one lytic lesion ≥ 5mm on MRI
- M – marrow – bone marrow plasma cell percentage 60% or greater

Which of my patients with MGUS will progress to myeloma?

Generally, MGUS is a low-risk condition with a rate of progression to myeloma of around 1% per year. However, a subset of higher-risk patients, who may benefit from closer monitoring, can be identified. Individuals with a large amount of monoclonal protein have a higher risk of progression. For example, patients with a monoclonal protein >25g/L have a 50% risk of progression to myeloma at 20 years. Patients with IgA and IgM M-proteins also have a higher risk of progression at about 1-3% per year.

MGUS can be further sub-classified into risk categories. [7]

	Number of risk factors*	Risk of progression at 20 years (%)
Low Risk	0	5
Low-intermediate Risk	1	21
Intermediate-high Risk	2	37
High Risk	3	58

**Risk factors: MP >15g/L, abnormal FLC ratio, non-IgG type MP (e.g. IgA, IgM)*
MP monoclonal protein, FLC free light chain
Serum free light chain testing is optional; patient will need to pay if done at private laboratories.

I confirmed a diagnosis of MGUS in my patient, now what?

- Explain the diagnosis of MGUS to your patient:
  "This is a common condition that exists in the general population and becomes more common as we age. Monoclonal gammopathy of undetermined significance is not a cancer, but it may put you at higher risk of developing a cancer in the future (approximately 1% per year). Monitoring for MGUS and screening for myeloma will now become part of your routine cancer screening just like screening for colon cancer, etc."
- Assess the patient & repeat blood work in 6 months to assess stability.
- If the blood work is stable (e.g. less than 20% change in the M-protein on SPEP), then repeat bloodwork every 1 year as indicated per algorithm.
- If **RED FLAGS** arise at any time, please refer urgently to Hematology.
- If the M-protein rises to above 15g/L, please refer to Hematology for further risk-stratification (additional blood tests and/or bone marrow biopsy may be considered).

Investigations to conduct at diagnosis on MGUS pathway if indicated

	Required in …
Complete blood count, calcium, albumin, creatinine. serum protein electrophoresis, urine protein electrophoresis with immune fixation (spot sample), physical examination for lymphadenopathy and hepatosplenomegaly	All
Serum protein electrophoresis with immune fixation	Those with an abnormal serum protein electrophoresis where not reflexively tested
24-hour urine protein electrophoresis	Those with abnormal urine protein electrophoresis AND no detectable serum monoclonal protein
Serum free light chain testing	Those interested in full risk stratification and with ability to pay (optional)
Skeletal survey x-rays	Those with serum monoclonal protein >15g/L or clinical features of concern (i.e. bone pain)

Abdominal/pelvis ultrasound	Those requiring work up for renal impairment or concern of pathology on physical exam
Urine albumin to creatinine ratio	Those being worked up for renal impairment

Investigations to complete for follow-up on MGUS pathway if indicated

	Required in …
Complete blood count, calcium, albumin, creatinine, serum protein electrophoresis with immune fixation, physical examination for lymphadenopathy and hepatosplenomegaly	All
Urine protein electrophoresis with immune fixation (spot sample)	Those with abnormal urine protein electrophoresis AND no detectable serum monoclonal protein
Additional investigations	Those with emerging clinical indications

When should I refer my patient with MGUS to a Hematologist?

1. If any of the following **RED FLAG** symptoms are present:

   ⇒ Hemoglobin <100g/L
   ⇒ Unexplained hypercalcemia, corrected serum Ca >2.75mmol/L
   ⇒ Deterioration in kidney function
      - eGFR <45 ml/min/1.73m2 and decline of > 5 ml/min/1.73m2 within 6 months in absence of self-limited illness
         - eGFR must be repeated in 2-4 weeks to confirm persistent decline
      - Proteinuria: Urine ACR >60mg/mmol
   ⇒ Presence of lytic bone lesions incidentally noted on x-rays
   ⇒ Unexplained bone pain
   ⇒ Lymphadenopathy or hepatosplenomegaly
   ⇒ Urine monoclonal protein >500mg/24 hours
   ⇒ sFLC ratio >8 or <0.125

2. If M-protein is >15g/L, recommend referral for further risk stratification

**Serum free light chain testing is optional; patient will need to pay if done at private laboratories.*

When should I stop MGUS monitoring?

Discontinuation of MGUS follow-up can be considered for patients with a life expectancy of <5 years and among those >80 years old, consistent with screening guidelines for other common cancers. (11)

The present work is based on expert opinion and the following clinical guidelines:

1. International Myeloma working Group (IMWG) consensus perspectives risk factors for progression and guidelines for monitoring and management (8)
2. UK Myeloma Forum (UKMF) and Nordic Myeloma Study Group (NMSG): guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS) (9)
3. The clinical relevance and management of monoclonal gammopathy of undetermined significance and related disorders: recommendations from the European Myeloma Network (10)
4. How I manage monoclonal gammopathy of undetermined significance (11)

Appendix B – Patient Information

PLEASE NOTE: THE FOLLOWING INFORMATION IS MEANT TO BE GIVEN TO THE PATIENT, EITHER AS A HANDOUT OR IN CONVERSATION WITH THEIR PRIMARY CARE PROVIDER.

WHAT IS MGUS?

MGUS stands for monoclonal gammopathy of undetermined significance. This is a common condition that exists in the general population and becomes more common as we age. MGUS is not a cancer, but it may put you at higher risk of developing a cancer in the future (approximately 1% per year). Monitoring for MGUS and screening for myeloma will now become part of your routine cancer screening just like screening for colon cancer, etc.

HOW WILL MY DOCTOR FOLLOW MY CONDITION?

Your family doctor will follow you with a clinical assessment and investigations (including blood work and urine tests) every 1 year.

YOU ARE ENROLLED ON AN MGUS CLINICAL PATHWAY. WHAT DOES THIS MEAN?

The MGUS clinical pathway was developed by family doctors, hematologists and other specialists at Kingston Health Sciences Centre to help with the screening and monitoring of people with MGUS. Clinical pathways are an evidence-based tool for common conditions seen frequently by family doctors. They pathways ensure that patients receive standardized care for their conditions. Clinical pathways help identify patients with high risk features and facilitate early referral to specialists as needed. They also identify patients with low risk disease who can be monitored by their family doctors.

Appendix C – Endnotes

1. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, et al. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med. 2006 Mar;354(13):1362–9.
2. Kyle RA, Larson DR, Therneau TM, Dispenzieri A, Kumar S, Cerhan JR, et al. Long-Term Follow-up of Monoclonal Gammopathy of Undetermined Significance. N Engl J Med. 2018;378(3):241–9.
3. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med. 2002 Feb;346(8):564–9.
4. Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med. 2007 Jun;356(25):2582–90.
5. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. The Lancet Oncology. 2014.
6. Houston BL, Rimmer E, Zarychanski R, Seftel M. Laboratory testing in the evaluation of a monoclonal protein: A practical framework for interpretation. South African Med Journal; Vol 109, No 10 [Internet]. 2019 Sep 30; Available from: http://www.samj.org.za/index.php/samj/article/view/12741
7. Rajkumar SV, Kyle RA, Therneau TM, Melton III LJ, Bradwell AR, Clark RJ, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. Blood [Internet]. 2005 Aug 1;106(3):812–7. Available from: https://doi.org/10.1182/blood-2005-03-1038
8. Kyle RA, Durie BGM, Rajkumar S V., Landgren O, Blade J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia. 2010;24(6):1121–7.
9. Bird J, Behrens J, Westin J, Turesson I, Drayson M, Beetham R, et al. UK myeloma forum (UKMF) and nordic myeloma study group (NMSG): Guidelines for the investigation of newly detected M-proteins and the management of monoclonal gammopathy of undetermined significance (MGUS). Br J Haematol. 2009;147(1):22–42.
10. van de Donk NWCJ, Palumbo A, Johnsen HE, Engelhardt M, Gay F, Gregersen H, et al. The clinical relevance and management of monoclonal gammopathy of undetermined significance and related disorders: Recommendations from the European Myeloma Network. Haematologica. 2014;99(6):984–96.
11. Go RS, Vincent Rajkumar S. How i manage monoclonal gammopathy of undetermined significance. Blood. 2018;131(2):163–73.