P1027:Appropriate Antibody Test Requesting and Interpretation in Primary Care is Key to Improving Timely Diagnosis Of Myeloma

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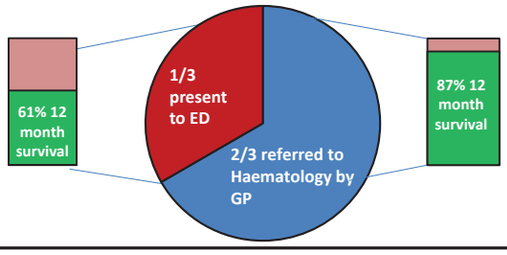
What is Myeloma? What is the problem?

Multiple myeloma is a plasma cell tumour that causes bone lesions, hypercalcaemia, anaemia, renal failure and susceptibility to infection. Survival has improved dramatically in recent years but myeloma patients experience some of the longest times to diagnosis of all cancers with a median diagnostic interval from first symptom of 163 days in the UK. However due to difficulties in test interpretation, there are many unnecessary referrals made to secondary care. (Lyratzopoulos 2012), (Howell 2017).

Route to Diagnosis and Impact on Prognosis *(Atkin 2021) (Figure: Lodwick 2021)*



Diagnosing Myeloma is Difficult: Presenting symptoms in multiple myeloma are non-specific and this causes significant diagnostic delay. The TEAMM trial collected presenting symptoms and fall in performance status in 6 months prior to myeloma diagnosis from 977 patients at trial entry. 3 major symptom categories predominated: back pain (37.8%), other pain (31%), systemic symptoms (27.8%). Most symptoms had a low positive predictive value for myeloma diagnosis. Patients with advanced renal failure had more systemic symptoms while patients with fractures had more back pain. *(Drayson 2021)*

Back pain Including neck pain	**Anaemia**	**Abnormal blood results – myeloma related**	**Bleeding or thrombosis**	**Other pain symptoms**
Renal Unspecified AKI CKD AKI on CKD Proteinuria	**Respiratory symptoms** Shortness of breath Cough Hoarse voice Abnormal chest x-ray	Hypercalcaemia Raised total protein Raised ESR **Gastrointestinal (GI) symptoms** Abdominal pain Vomiting Nausea Constipation Diarrhoea	Epistaxis Haematuria Bruising Haemoptysis PE or DVT Gum bleeding	Chest pain (including rib pain) General pain Limb pain (hip) Limb pain (shoulder) Limb pain (leg) Limb pain (arm) Joint pain Joint pain (knee) Limb pain (groin) Face pain Foot pain Hand pain Limb pain Radicular pain
Systemic symptoms Fatigue Weight loss Generally unwell Anorexia Sweats (including night sweats) Collapse/dizziness Reduced exercise tolerance Falls Low mood Weight gain	**GI symptoms** pain Vomiting Nausea Constipation Diarrhoea Altered bowel habit Dyspepsia GI bleeding Dysphagia Jaundice Unspecified 'GI symptoms' **Urological symptoms** Urinary frequency Bladder outflow problems Nocturia Reduced urine output Urgency	**Abnormal blood results - non-specific** Unspecified abnormal blood result Neutropenia Pancytopenia Thrombocytopenia B12 deficiency High PSA Hyperkalemia Hypernatremia Hyperparathyroidism Hypogammaglobulinaemia Leucopenia Low albumin Low total protein Raised ferritin Raised inflammatory markers Thrombocytosis	**Infection** Lower respiratory infection UTI Fever 'Recurrent' (site not specified) Upper respiratory infection Cellulitis 'Viral' Tooth **Systemic symptoms** Fatigue Weight loss Generally unwell Anorexia Sweats (including night sweats) Collapse/dizziness Reduced exercise tolerance Falls Low mood Weight gain	**Other pain symptoms** Chest pain (including rib pain) General pain Limb pain (hip) Limb pain (shoulder) Limb pain (leg) Limb pain (arm) Joint pain Joint pain (knee) Limb pain (groin) Face pain Foot pain Hand pain Limb pain Radicular pain
Neurological symptoms Symptoms of spinal cord compression* Headache Confusion Visual disturbance Carpal tunnel				

Interpretation of the Tests is Complicated and Leads to unnecessary referrals

All SFLC tests received by our Clinical Immunology Service from primary care to the Queen Elizabeth hospital Birmingham between May 2017 and May 2018 were assessed.

Inconsistent laboratory antibody requests and difficulties in the interpretation of these results in myeloma and monoclonal gammopathy of undetermined significance (MGUS) patients is associated with long delays to diagnosis, increased morbidity and mortality and inappropriate urgent cancer referrals as shown by the data below. There is need to better define the normal ranges and provide clear guidance on interpretation. *(Lodwick 2018)*

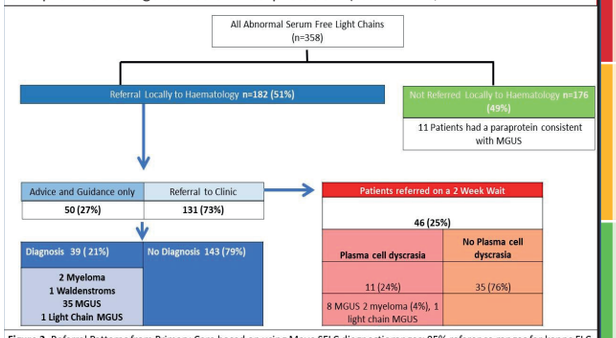


Figure 2. Referral Patterns from Primary Care based on using Mayo SFLC diagnostic ranges: 95% reference ranges for kappa FLC 3.3-19.4 mg/L and lambda FLC 5.7-26.3 mg/L and 100% ref range for KLR 0.26–1.65 mg/L

We need to improve primary care requesting of tests, and improve guidelines and interpretation to decrease Unnecessary and Expensive secondary care referrals.

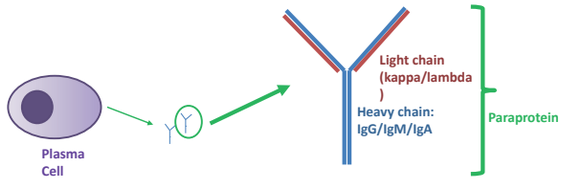
When to Test For Myeloma? Red flags:

1. Non specific new bony pain
2. Multiple visits with gradual decline
3. Unexplained Anaemia
4. Hypercalcaemia
5. New acute renal failure
6. Recurrent or Persistent infections
7. Spontaneous fractures
8. Generally unwell/fatigue, weight loss, suspicion of underlying cancer
9. Unexplained peripheral neuropathy

What are the tests you are requesting?

- Serum Free light chains
- Immunoglobulins
- Serum Protein Electrophoresis

Approx price £50 for all 3 tests



A Practical Approach to Myeloma Test interpretation:

1. **Is the Kappa/Lambda light chain RATIO abnormal?** Many pathologies cause raised light chains, but if it is polyclonal i.e both Kappa and lambda are raised, the ratio remains normal. In myeloma only the ratio is important as it implies that a plasma cell clone is producing just one type of Immunoglobuin i.e. it is monoclonal.
2. **Polyclonal Causes of Raised Light chains i.e. raised light chains with a normal ratio:**
   - Chronic infection (osteomyelitis, endocarditis, HIV, EBV)
   - Inflammation, IgG4 related disease
   - Autoimmune (RA, SLE, Sjogren)
   - Neoplasm (lung, liver, gastric, rare T cell lymphomas)
   - Liver disease (cirrhosis, chronic hepatitis)

These Simple antibody test can identify myeloma patients earlier but also identifies the hundred-fold more common condition MGUS.

No of people living in the UK	**67,081,000 people** *(2021 uk census)*
No of people living the Uk aged >50 years	**24.9 million people**
3% of people aged >50yrs have a paraprotein	**749,970 people**
1% of the people with a paraprotein develop myeloma per year	**7,499 people**

Paraprotein >10 g is significant

We have developed New Extended Normal Thresholds, and Guidelines to Simplify Diagnosis and Interpretation, and reduce inappropriate, expensive urgent referrals

We have examined samples from 3177 newly diagnosed myeloma patients and 711 MGUS patients and used different M-protein level thresholds combined with different KLR ranges to distinguish myeloma from MGUS without loss of sensitivity for identifying patients that need urgent referral for myeloma diagnosis. **Applying an M-protein threshold of 10 g/L and/ or a kappa lambda ratio <0.1 or >7.0 excludes 93.4% of MGUS cases and provides 98% sensitivity for detection of myeloma**