Diagnostic Criteria and Workup in 2021

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Mayo Clinic College of Medicine
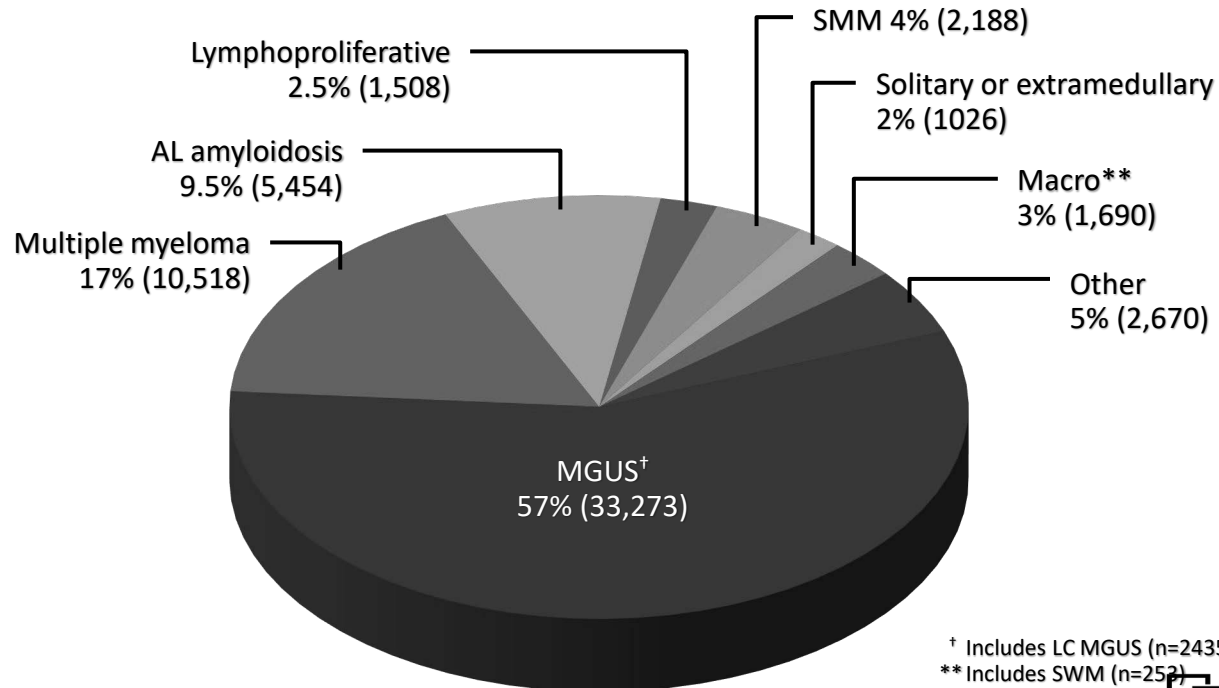**Mayo Clinic Comprehensive Cancer Center**

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DISCLOSURES

- **Research funding for clinical trials to the institution**: Celgene, Takeda, Janssen, BMS, KITE, Merck, Abbvie, Medimmune, Novartis, Roche-Genentech, Amgen, Tenebio, Carsgen

- **Consulting/Advisory Board participation**: (with no personal payments) Celgene, Takeda, Janssen, Abbvie, Genentech, Amgen, Molecular Partners and (with personal payment) Oncopeptides, Genecentrix, Cellectar.

Monoclonal Gammopathies: A spectrum

January 1, 1960 to December 31, 2018

n=58,327

SMM 4% (2,188)

Lymphoproliferative
2.5% (1,508)

Solitary or extramedullary
2% (1026)

AL amyloidosis
9.5% (5,454)

Macro**
3% (1,690)

Multiple myeloma
17% (10,518)

Other
5% (2,670)

MGUS†
57% (33,273)

$\dagger$ Includes LC MGUS (n=2435)
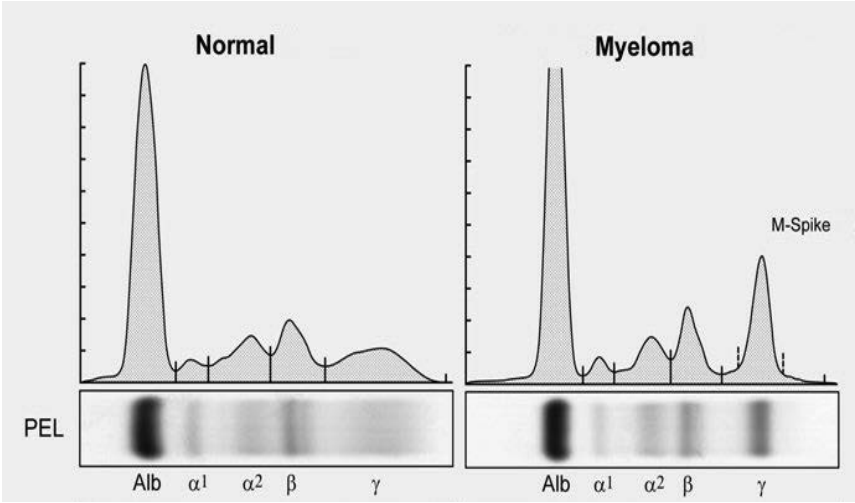** Includes SWM (n=253)

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Diagnosis of Monoclonal Gammopathy

A monoclonal protein in serum or urine

AND /OR
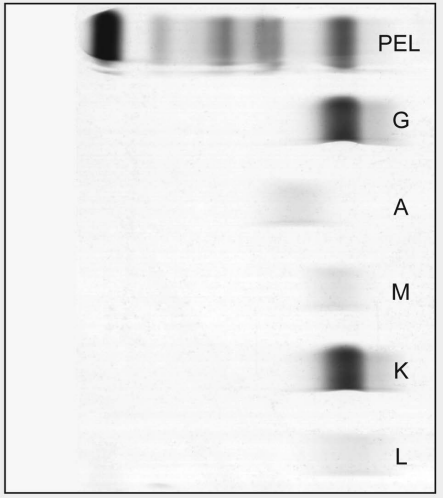
Presence of clonal plasma cells
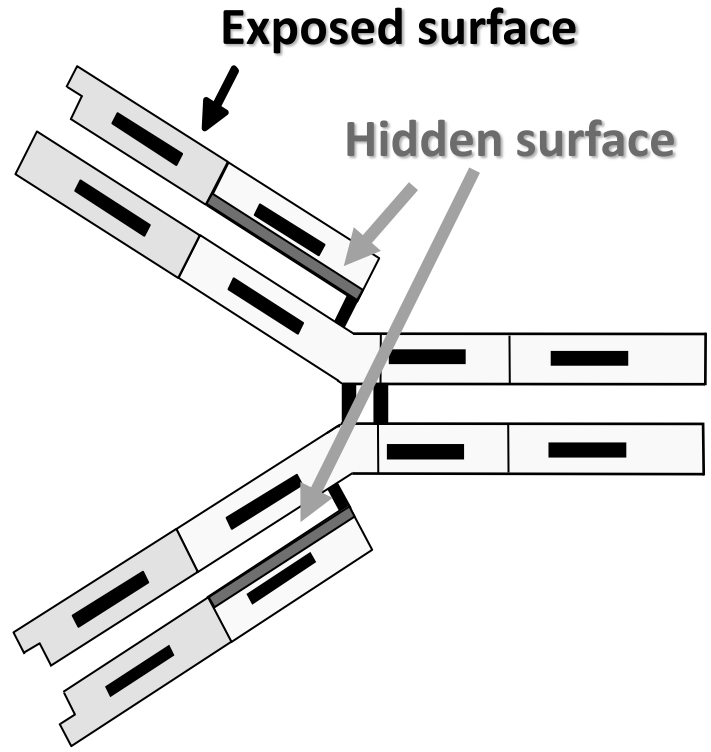
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Demonstrating Monoclonal Protein
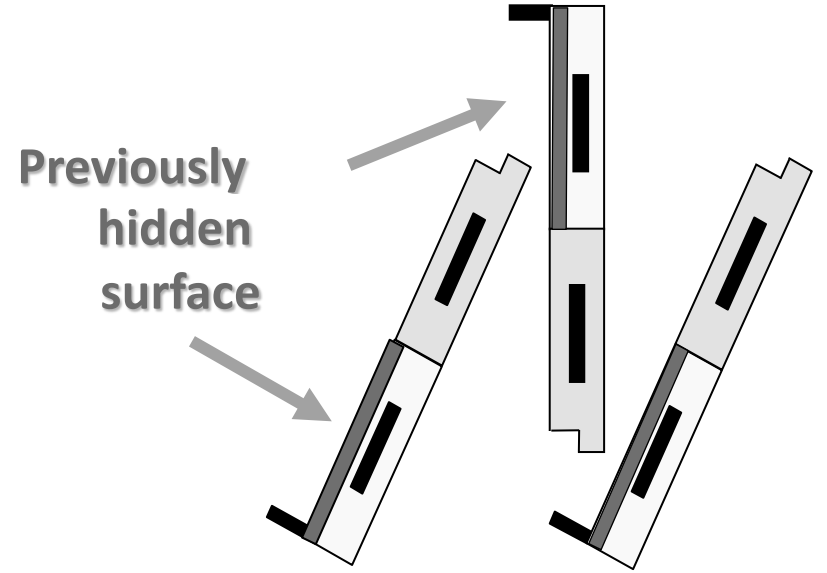

Serum or Urine Protein Electrophoresis
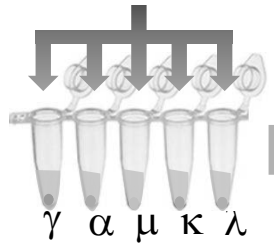
Serum or Urine Immunofixation

Intact Immunoglobulin

Exposed surface

Hidden surface

Free Light Chain Assay

Previously hidden surface

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Mass Spec: Increased sensitivity

20 uL Serum or
1 mL Urine

Incubate
Wash

Dissociate
Elute

Immunopurification
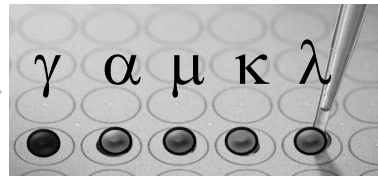
Spot on MALDI plate

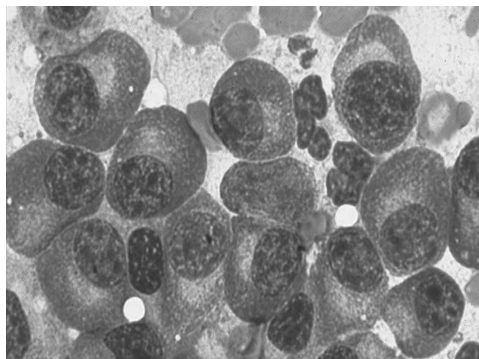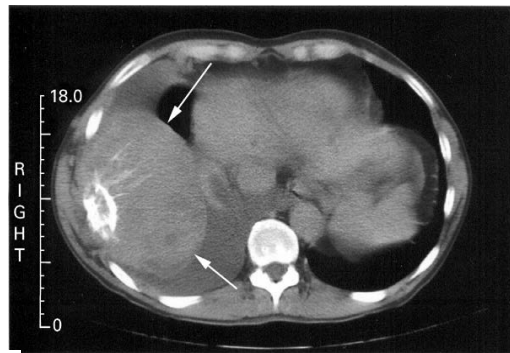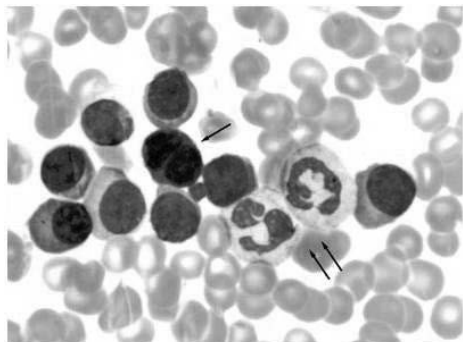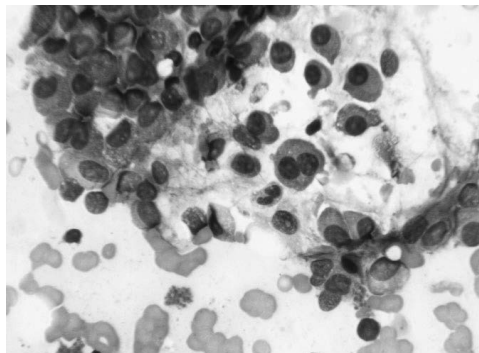Spectral Overlay & Analysis
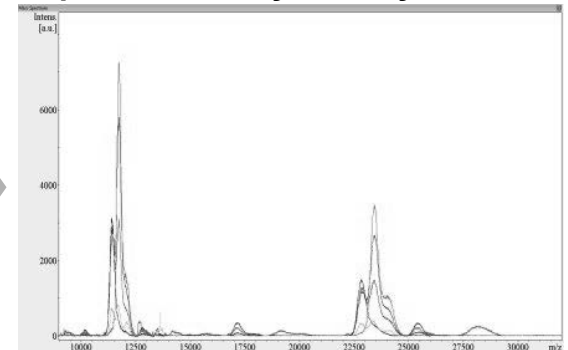
Identification
Isotype Quantitation

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Detection of Myeloma Plasma Cells
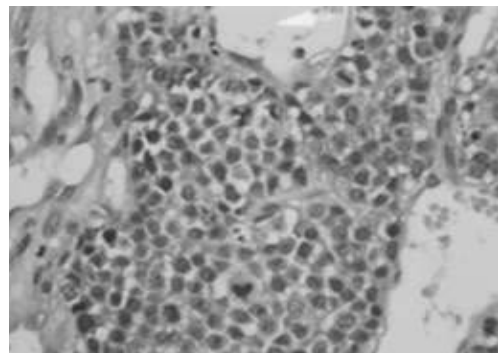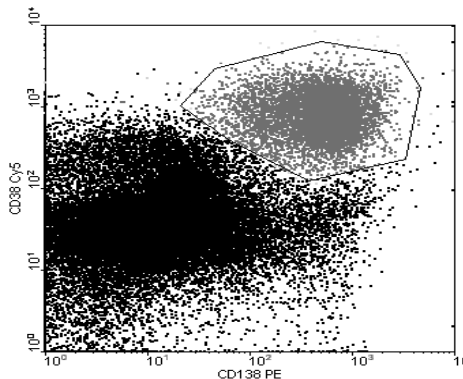
Bone marrow   Peripheral blood   Plasmacytoma

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Diagnostic approach

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                    ┌──────────────────────────────────┐
                    │  Is there a monoclonal process?  │
                    └──────────────────────────────────┘
                                     │
  ┌──────┐         ┌──────────────────────────────────┐         ┌──────┐
  │  No  │◄────────│     Clinical signs/ symptoms?     │────────►│ Yes  │
  └──────┘         └──────────────────────────────────┘         └──────┘
      │                                                              │
      │                          ┌────────────┐              ┌────────────┐
      │                          │  Uncommon  │              │   Common   │
      ▼                          └────────────┘              └────────────┘
```

No MDE (myeloma defining events)

Likely MGUS or Smoldering MM

Uncommon

- MGRS
- Ig deposition diseases
- POEMS syndrome
- Neuropathies
- Schnitzler's syndrome

Common

- Myeloma
- Amyloidosis
- Waldenstrom's

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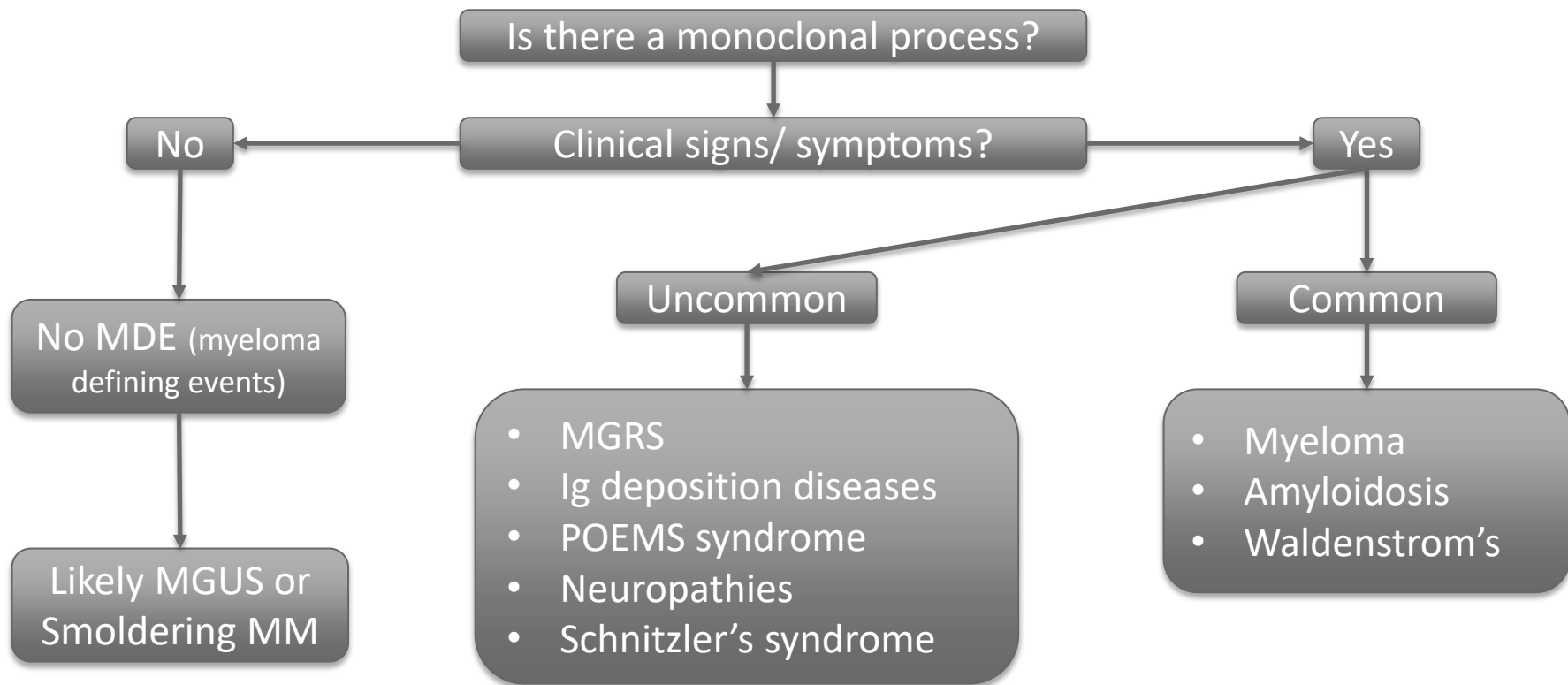
Precursor conditions

MGUS

- Serum monoclonal protein <3 g/dL

- <10 % bone marrow plasma cells

- Urinary monoclonal protein < 500 mg per 24 h

- Absence of myeloma defining events or amyloidosis

Light chain MGUS:
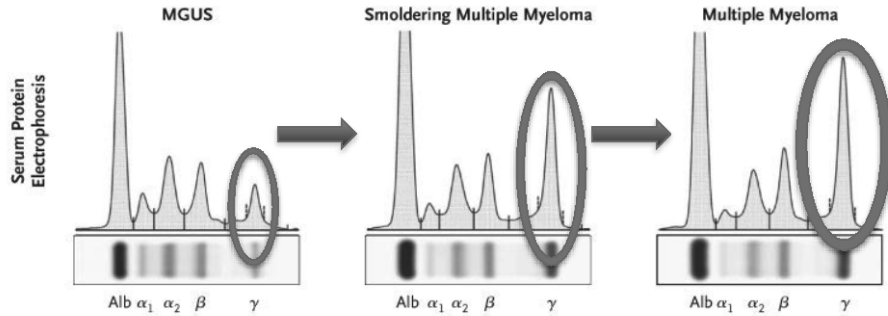
Abnormal FLC ratio (<0.26 or >1.65)

Increased level of involved light chain

No heavy chain on immunofixation

SMM

- Serum monoclonal protein (IgG or IgA) ≥3 g/dL

- Or urinary monoclonal protein ≥500 mg per 24 h

- Or clonal bone marrow plasma cells 10–59%

- Absence of myeloma defining events or amyloidosis.
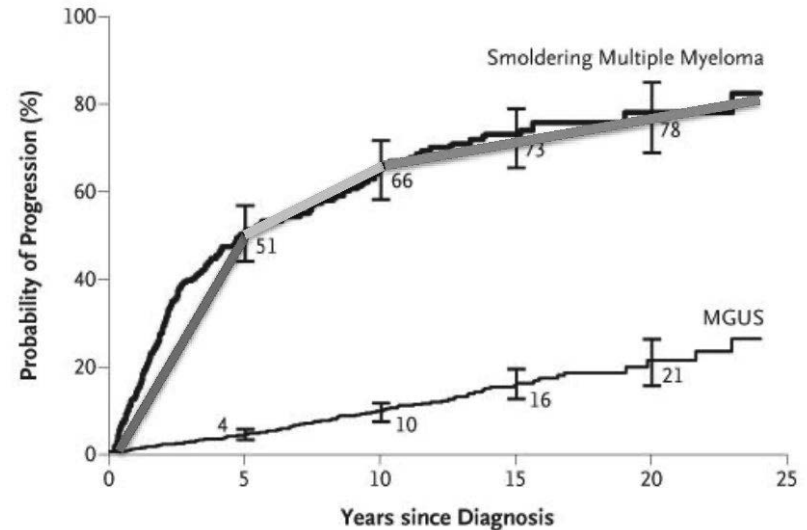
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Progression from precursors

Increasing levels of monoclonal protein

Increasing marrow plasma cell percentage

Development of End Organ Damage

Kyle et al, NEJM, Volume 356:2582-2590, June 21, 2007

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Active MM: Current Definition

Clonal BMPC ≥10% or biopsy-proven plasmacytoma <u>PLUS</u>

-<u>*Either a myeloma defining event*</u>:

C: Hypercalcemia: serum calcium >1 mg/dL higher than the upper limit of normal or >11 mg/dL

R: Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >2 mg/dL

A: Anemia: hemoglobin >20 g/L below the lower limit of normal, or a hemoglobin <100 g/L

B: Bone lesions: osteolytic lesions on x-ray, CT, or PET-CT

<u>-OR *a biomarker of early progression (≥80% risk of SMM →MM at 2 years)*</u>

- Clonal bone marrow plasma cell percentage≥60%
- Involved: Uninvolved serum free light chain ratio ≥100
- >1 focal lesions on MRI studies

Clinical interpretation important

Plasmacytoma

Solitary Plasmacytoma

- Biopsy-proven solitary lesion of bone or soft tissue with clonal plasma cells
- Bone marrow with no clonal plasma cells
- Normal imaging except for the primary solitary lesion
- Absence of end-organ damage attributable to plasma cell disorder/ MDE

Presence of clonal bone marrow plasma cells <10%

Solitary plasmacytoma with minimal marrow involvement

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Workup

Monoclonal gammopathy work up

- Serum PEP with IFE
- 24-hour urine PEP with IFE
- Serum free light chain assay
- Bone marrow aspiration and biopsy
- Bone marrow plasma cell FISH
- Plasmacytoma biopsy if required

Optional if feasible
- Plasma cell proliferation
- Peripheral blood flow for PC
- Clone ID for MRD
- PC Mutation panel
- PC gene expression signature

End organ damage/ MDE / Risk stratification work up

- Complete blood count
- Complete metabolic panel
- Serum beta-2 microglobulin, LDH
- Imaging (Whole body low dose CT or PET/CT or whole-body MRI)
- *At times*: Serum viscosity

Rule out concomitant PC disorders

- Serum NT-ProBNP, ECHO, if cardiac symptoms
- Nerve conduction studies, IL6, VEGF if neurological symptoms
- Skin biopsy – if lesions

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Conclusions

- Important to make distinction between MGUS/SMM and MM: biomarkers and end organ damage

- Advanced imaging critical for diagnostic assessment

- Precursor states with end organ damage should be identified: MGRS, neuropathy, MIDD

- Rule out concomitant amyloidosis

- Conditions with small clones and end organ effect: POEMS, other rare PCDs

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THANK YOU

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