Monoclonal Gammopathy Workup

Marie Vercruyssen

Belgian Haematology Society courses

04/2023

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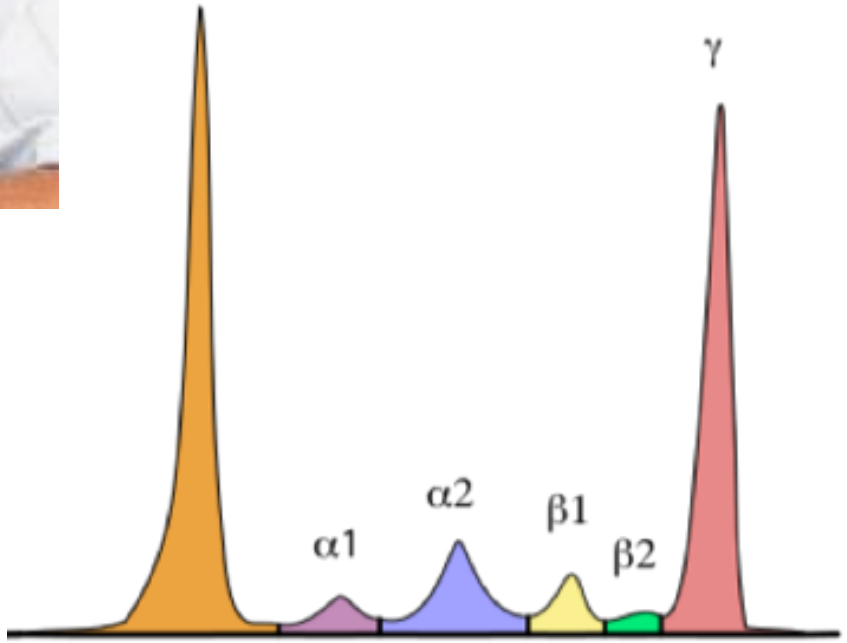
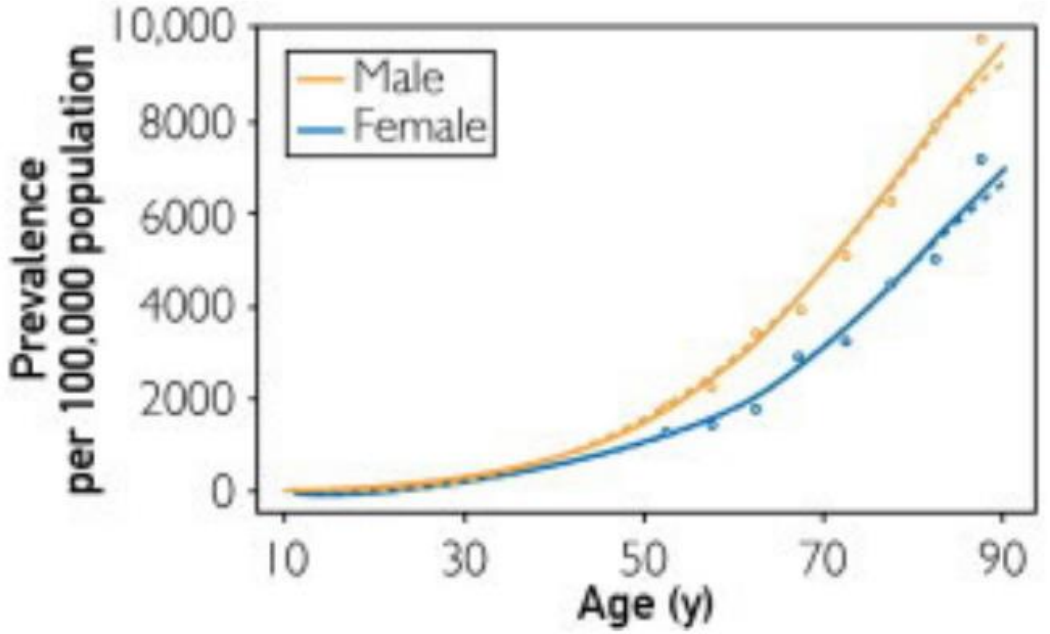


Epidemiology

- Prevalence higher with age
  - 3,2% > 50 yo
  - 5,3% > 70 yo
  - 7,5% > 85 yo
- Because of:
  - Increasing age population
  - Higher incidence!
    - **122**/100,000/year at 50 yo to **532** at 90 yo
    - < failure of immunosurveillance



Risk factors:
- Age
- Ethnic (X2-3 in Afro Americans)
- Family history of plasma cell dyscrasia

13% > 50yo!

Kyle et al. NEJM. 2006
Therneau et al. Mayo Clin. 2012
El Khoury et al. Lancet. 2022

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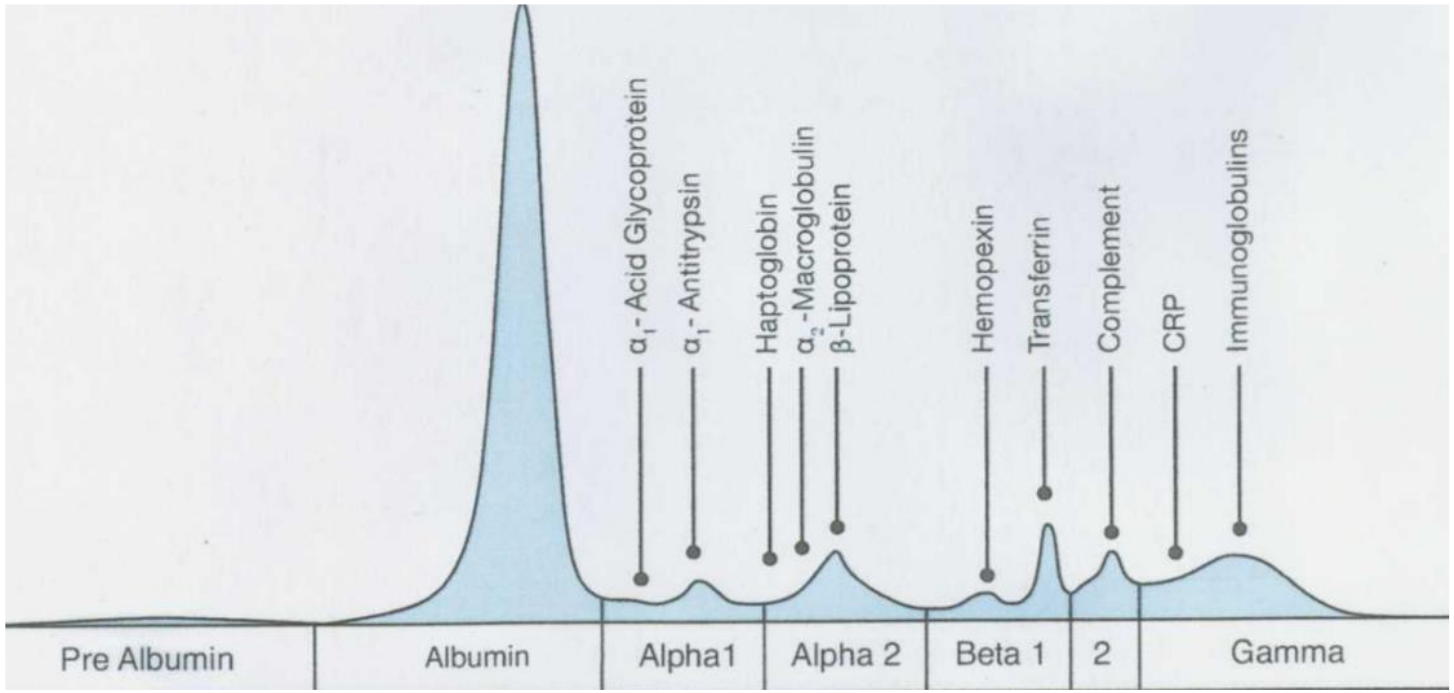
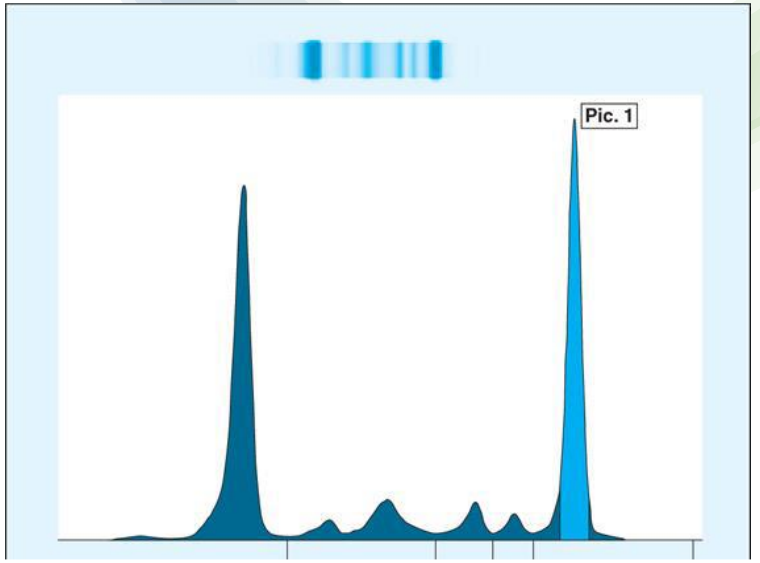
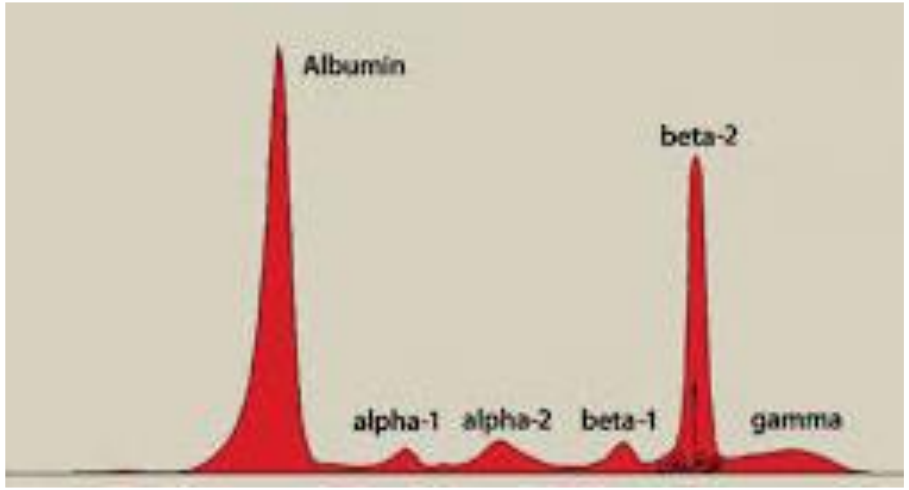
Any problem with that, Doc?

Back to basics







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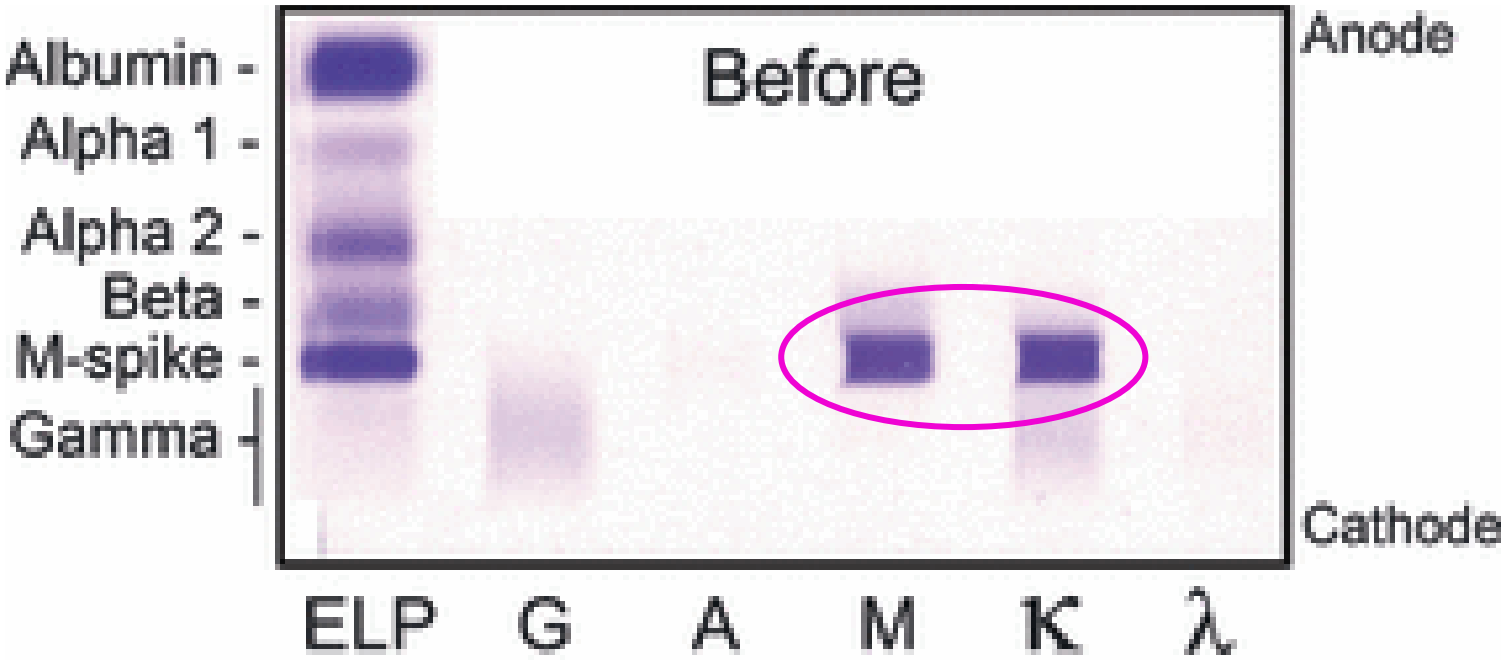

- Mostly **IgG** (65%) and **kappa** (66%)
- **IgA** 20%
- **LC** (15%)
- **Rarely**: IgD, IgM
- No secretion/production

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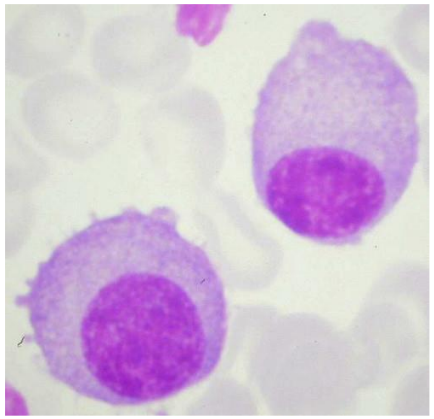

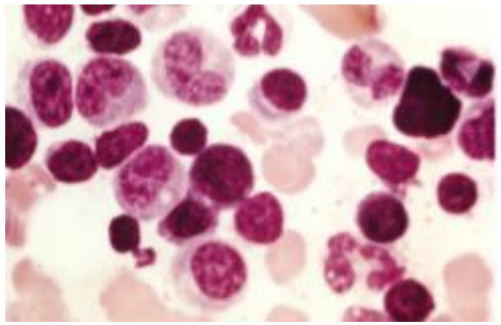

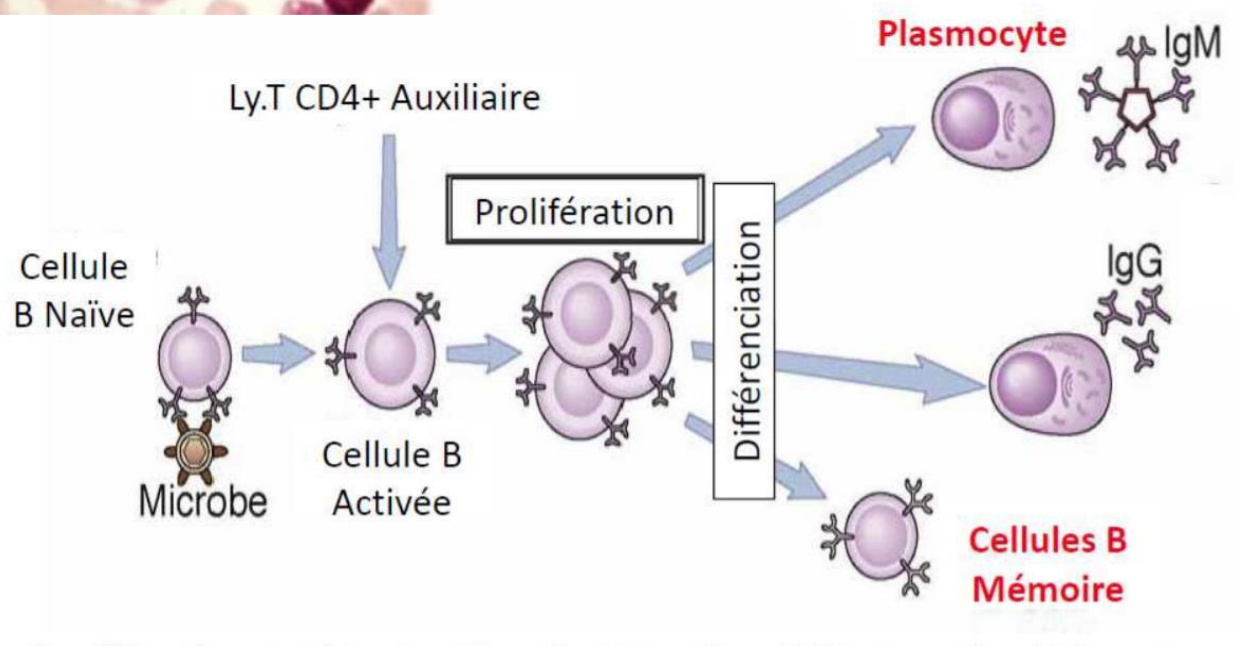

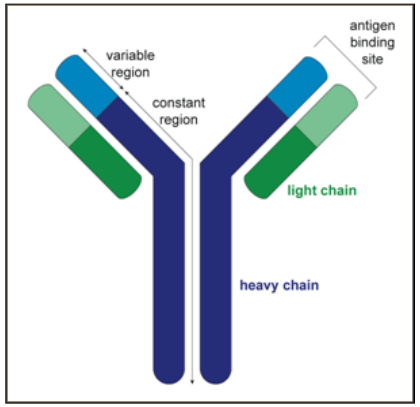

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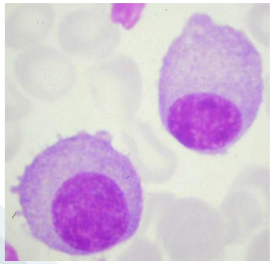

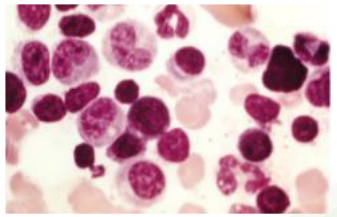

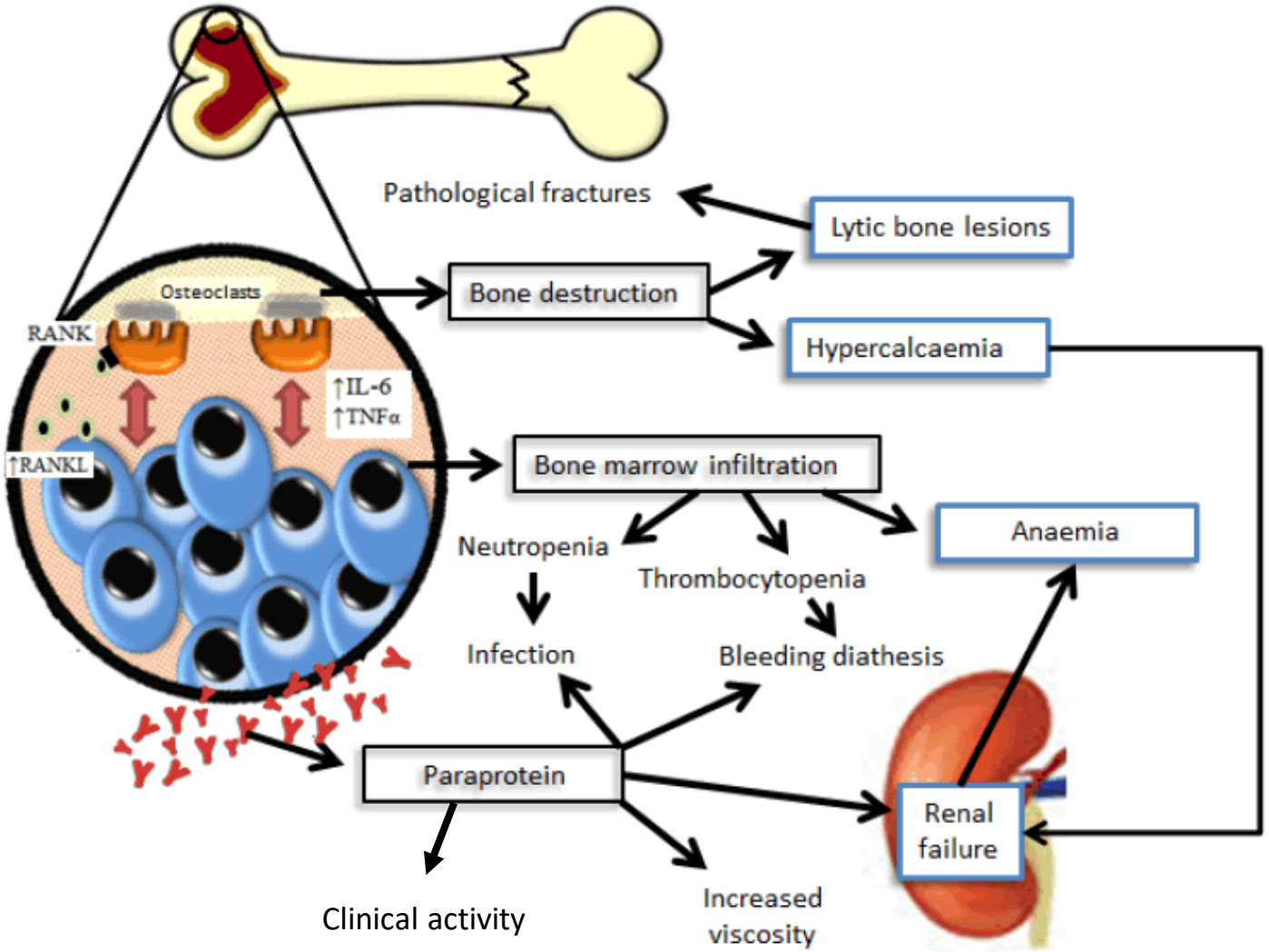

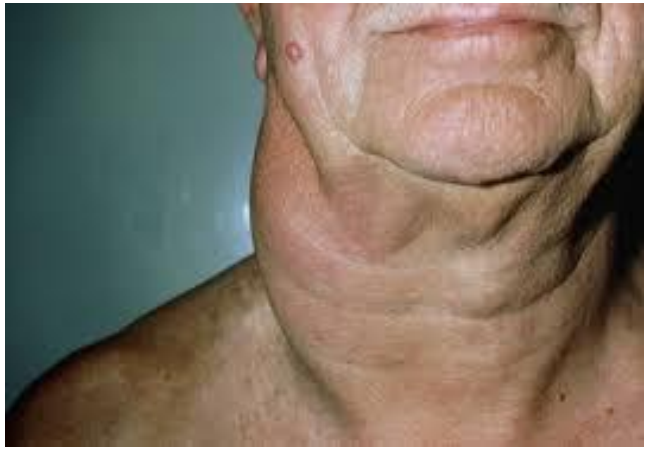

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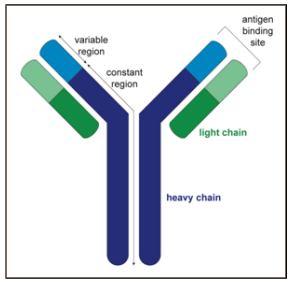

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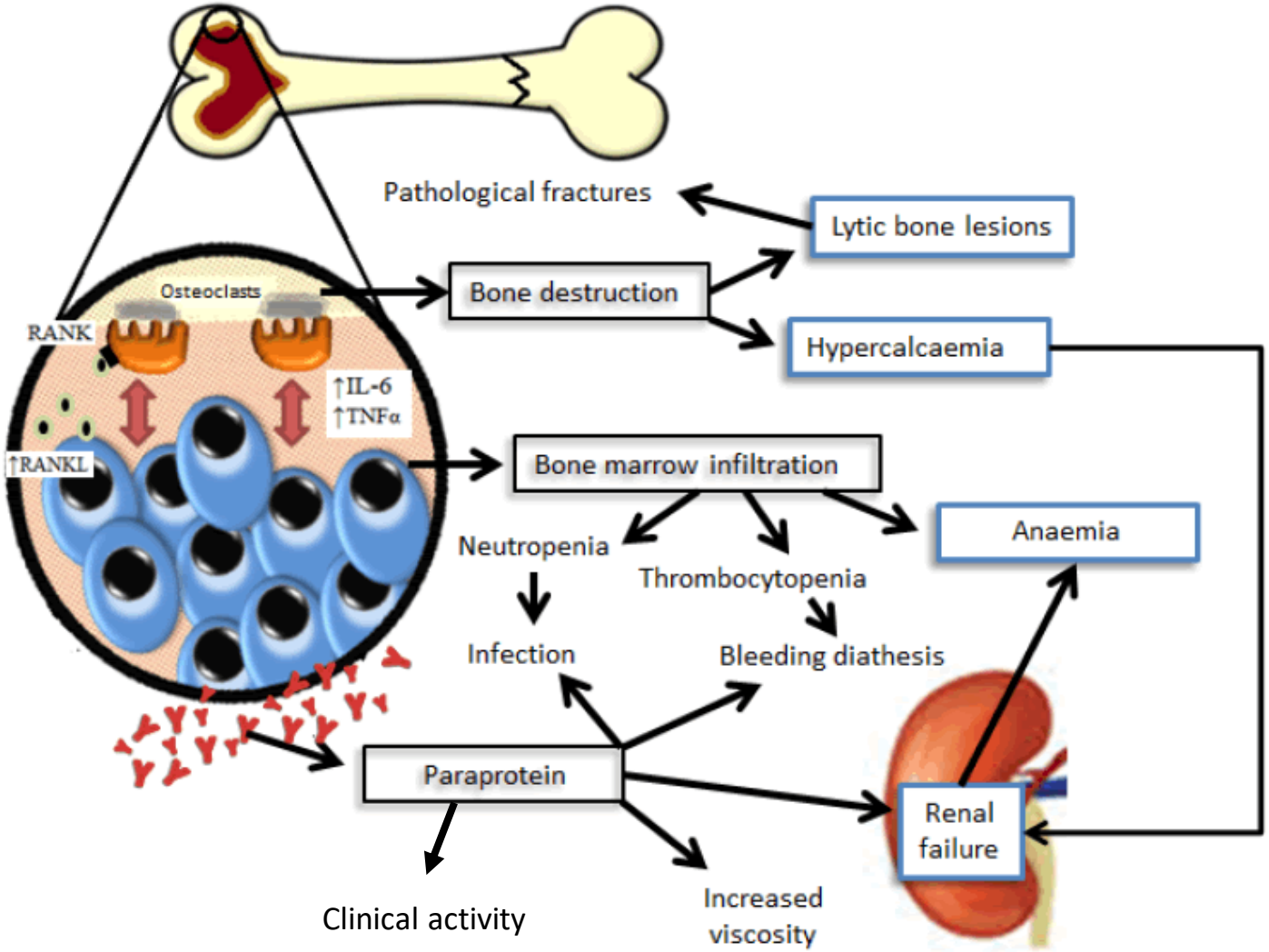

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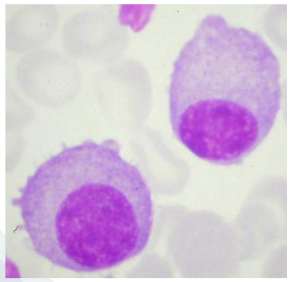

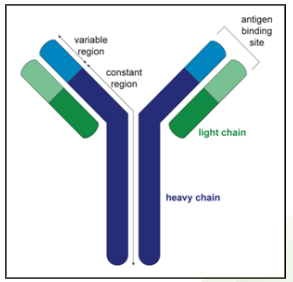

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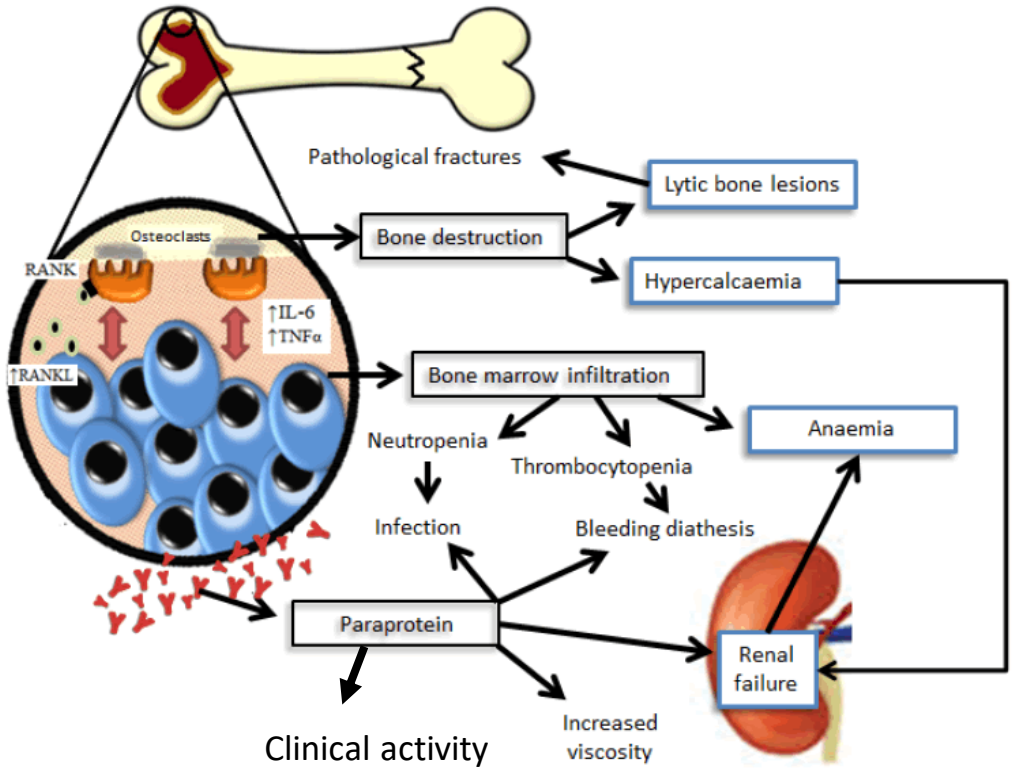


Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

★

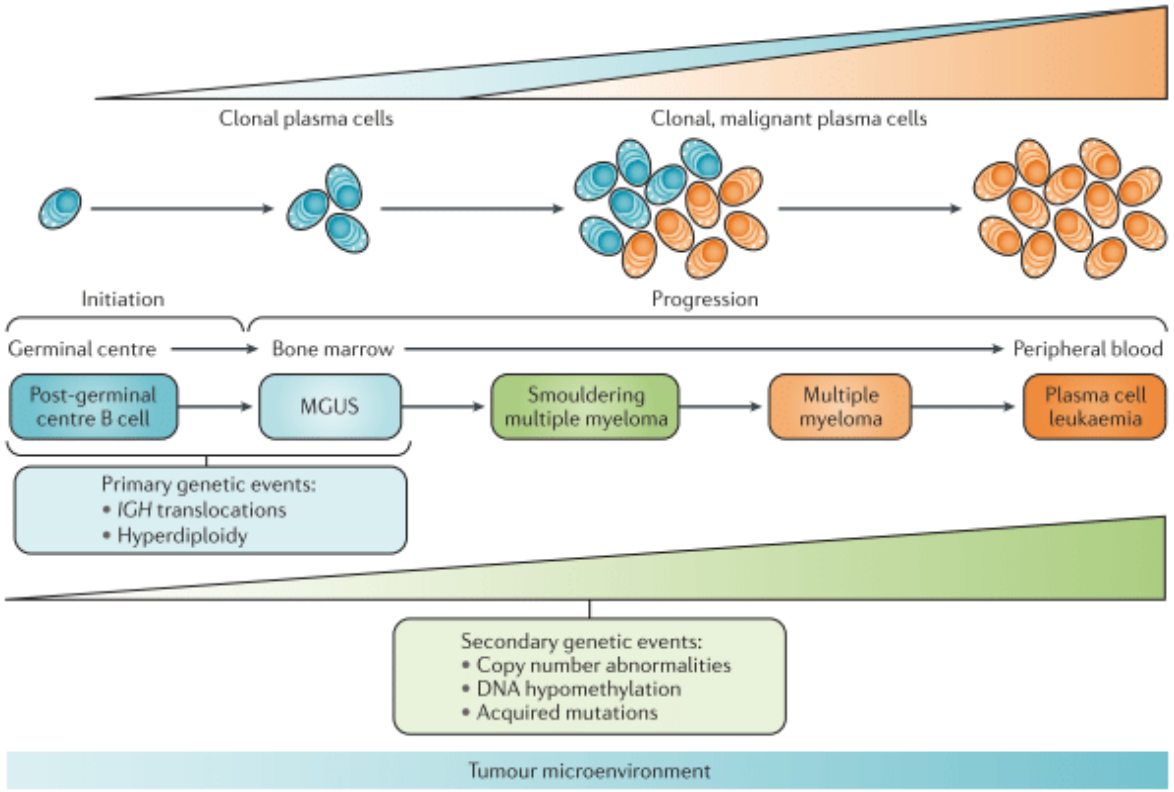
Monoclonal gammopathy of clinical significance
MGCS

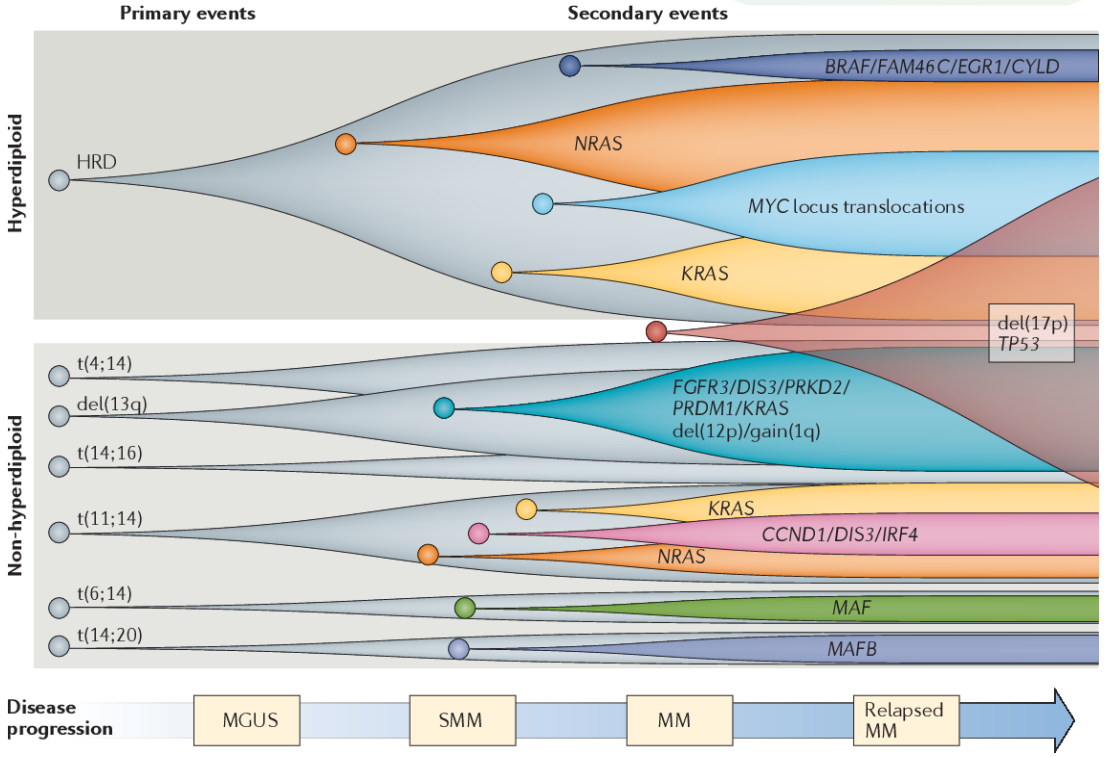
MGUS

Underlying disease

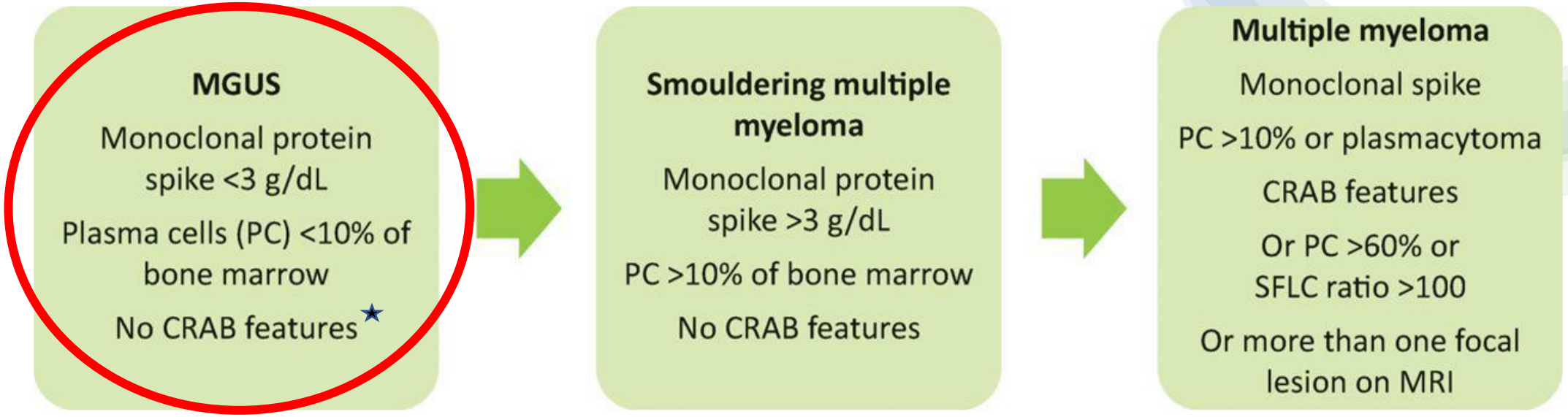
Myeloma/Waldenström

MGCS





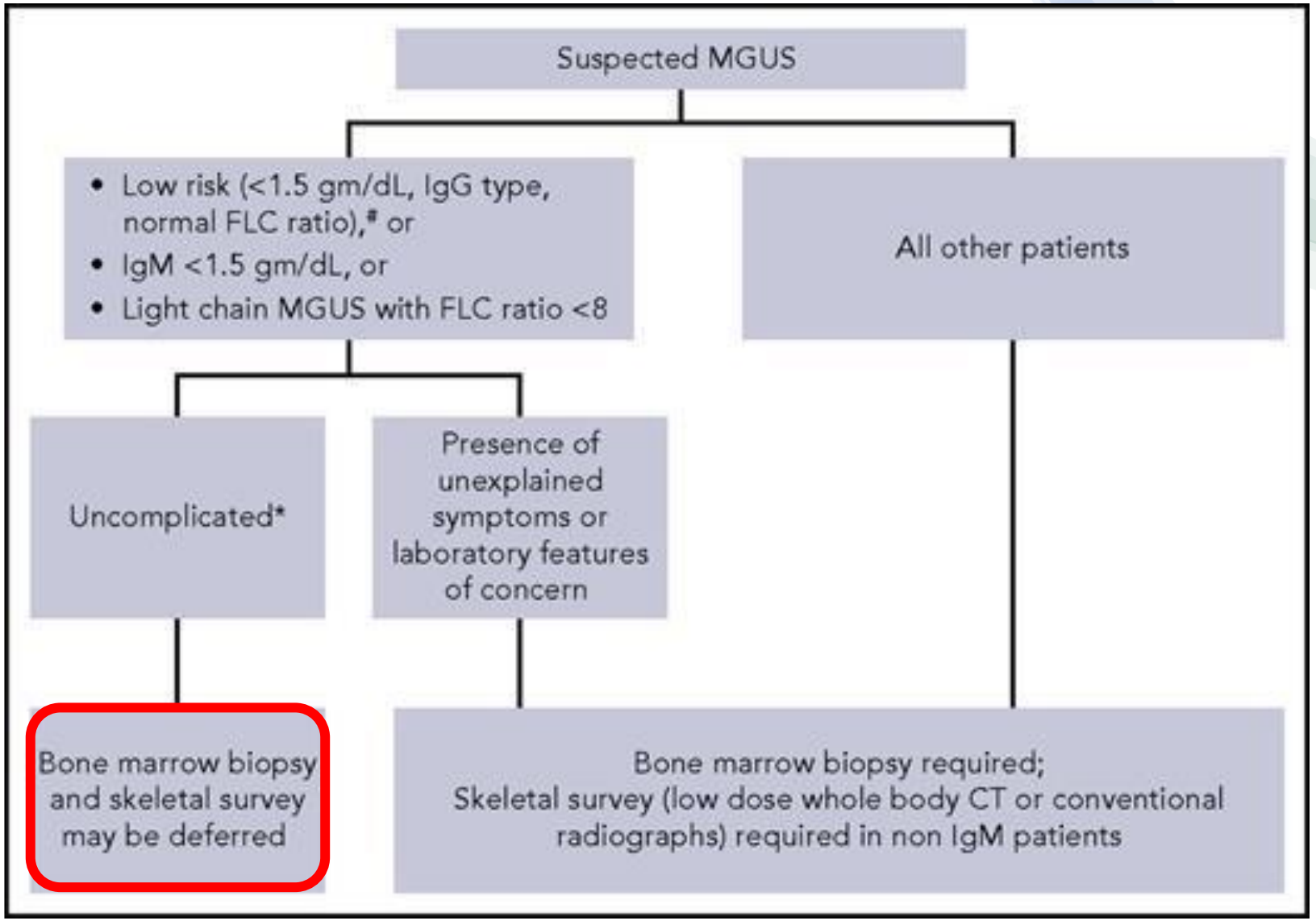
Kumar et al. Nature Reviews. 2017
Manier et al. Nature Reviews. 2016



3 RF: non-IgG, M prot > 1,5 g/dl, abnormal FLC ratio

3 RF: 58% @ 20y
2 RF: 37% @ 20y
1 RF: 21% @ 20 y
0 RF: 5% @ 20y

Atkinet al. Clin Med. 2018
Rajkumar et al.. Blood. 2018
Rajkumar et al. Blood. 2005

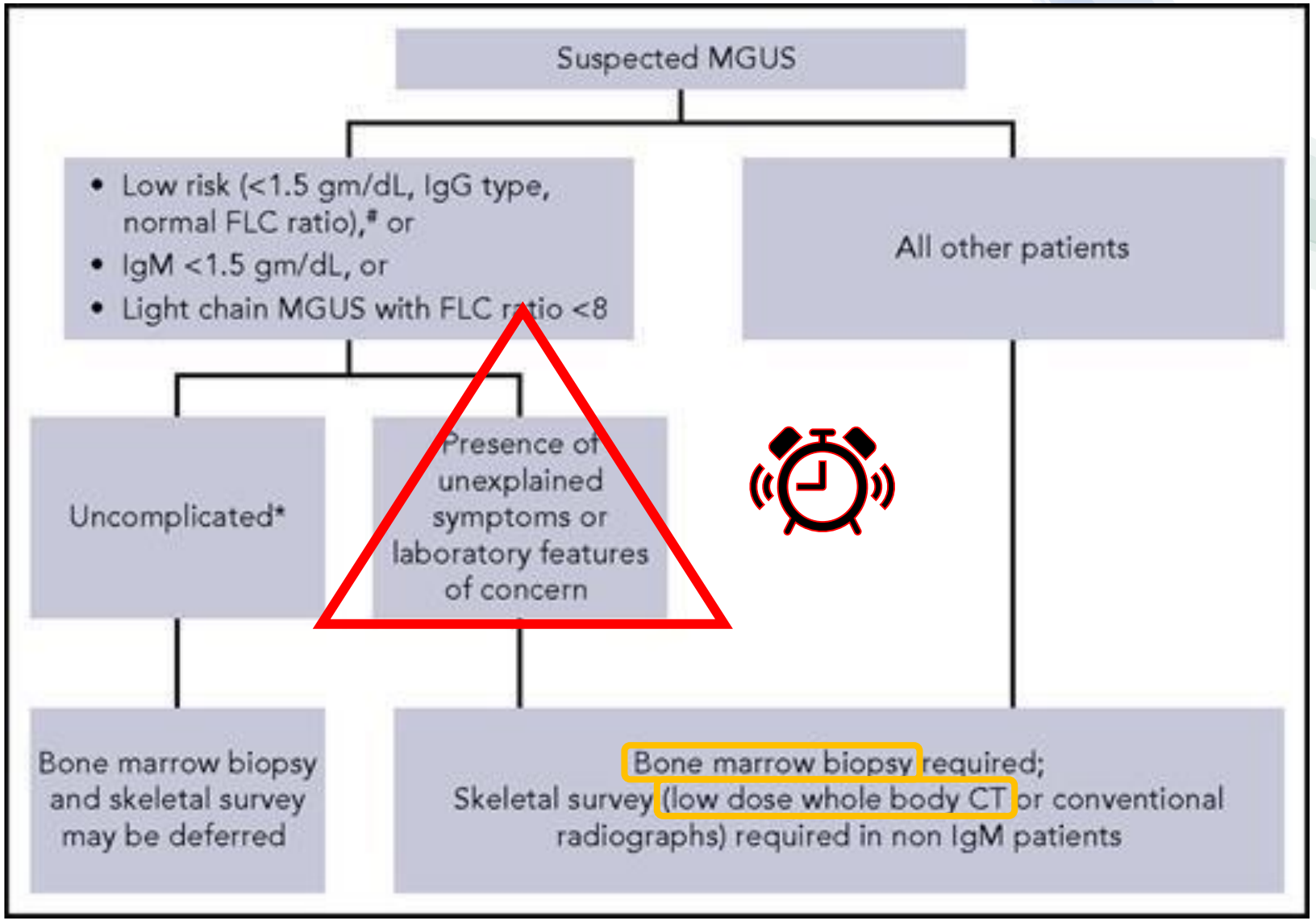


Atkinet al. Clin Med. 2018
Rajkumar et al.. Blood. 2018
Rajkumar et al. Blood. 2005

MGUS

- Infection rate 2 (X 7 MM) @ 5-10 years of FU
  - Pneumococcus/Haemophilius Influenza/Influenzae/COVID19
- Osteopenia/porosis
  - Densitometry +/- calcium/Vit D supplementation
- Thrombophilia
  - HR 3,4 @ 1 year following the diagnosis
- CV risk/morbidity?

Kristinsson et al. Haematologica. 2012
Dumontetet al. Leukemia. 2018
Raje. IMWG.2017
Melton et al. J Bone Miner Res. 2004



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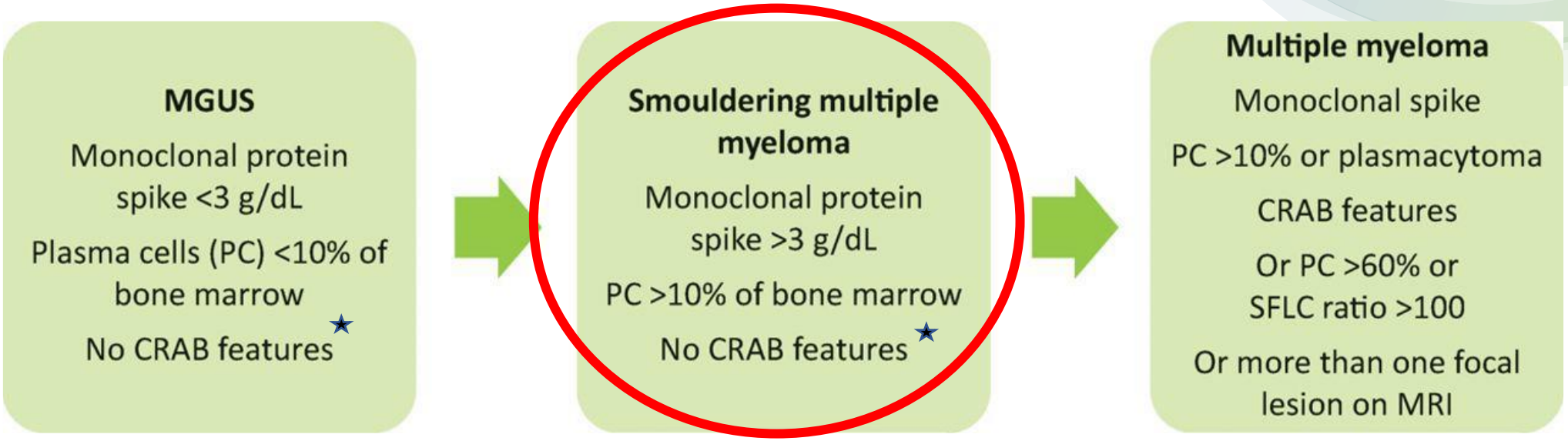
Rajkumar et al.. Blood. 2018
Rajkumar et al. Blood. 2005



3 RF: M prot ≥ 2 g/dl, BMPC ≥ 20%, FLC ratio ≥ 20
+/- cytogenetics

Atkinet al. Clin Med. 2018
Rajkumar. Lancet Oncol. 2014

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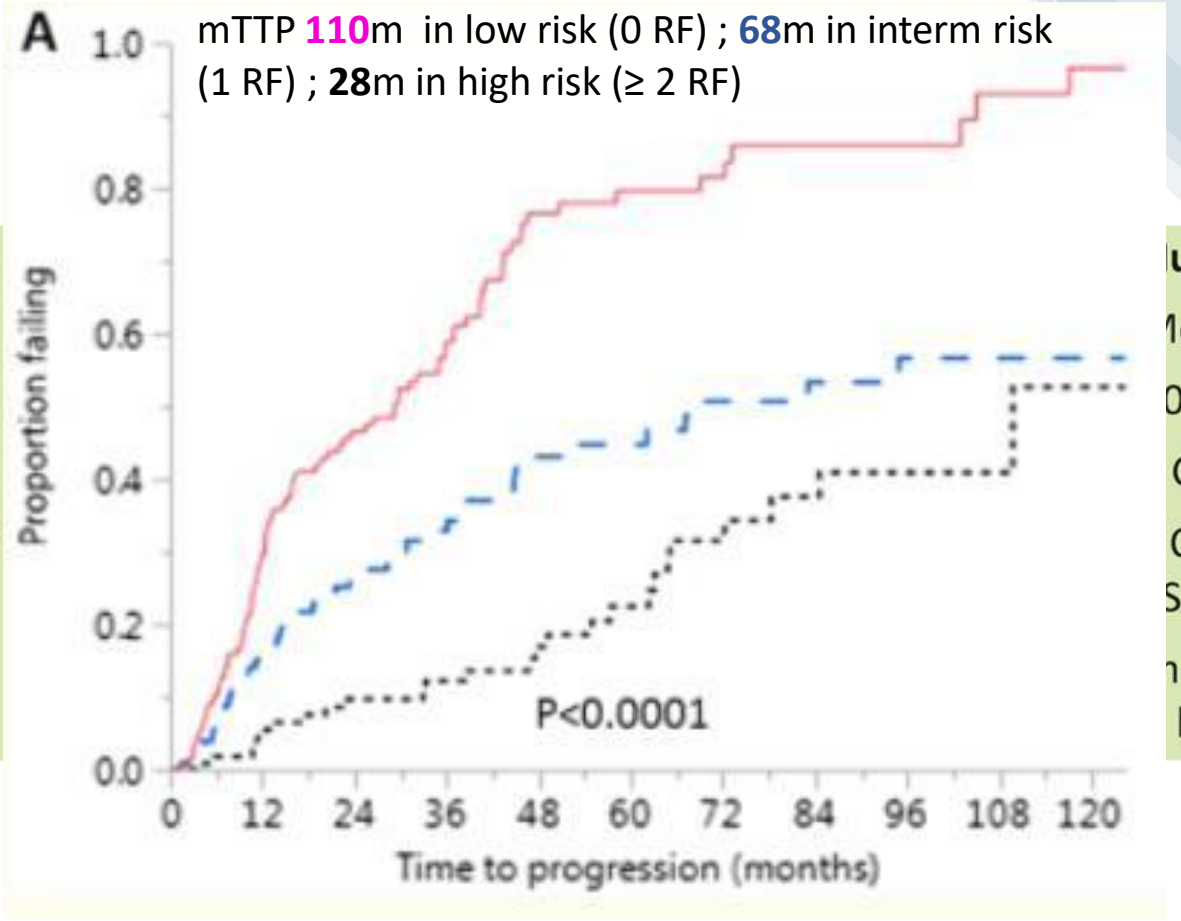
MGUS

Monoclonal protein spike <3 g/dL

Plasma cells (PC) <10% bone marrow

No CRAB features ★



ultiple myeloma

Monoclonal spike

0% or plasmacytoma

CRAB features

Or PC >60% or SFLC ratio >100

more than one focal lesion on MRI

3 RF: M prot ≥ 2 g/dl, BMPC ≥ 20%, FLC ratio ≥ 20 +/- cytogenetics

Atkinet al. Clin Med. 2018
Rajkumar. Lancet Oncol. 2014

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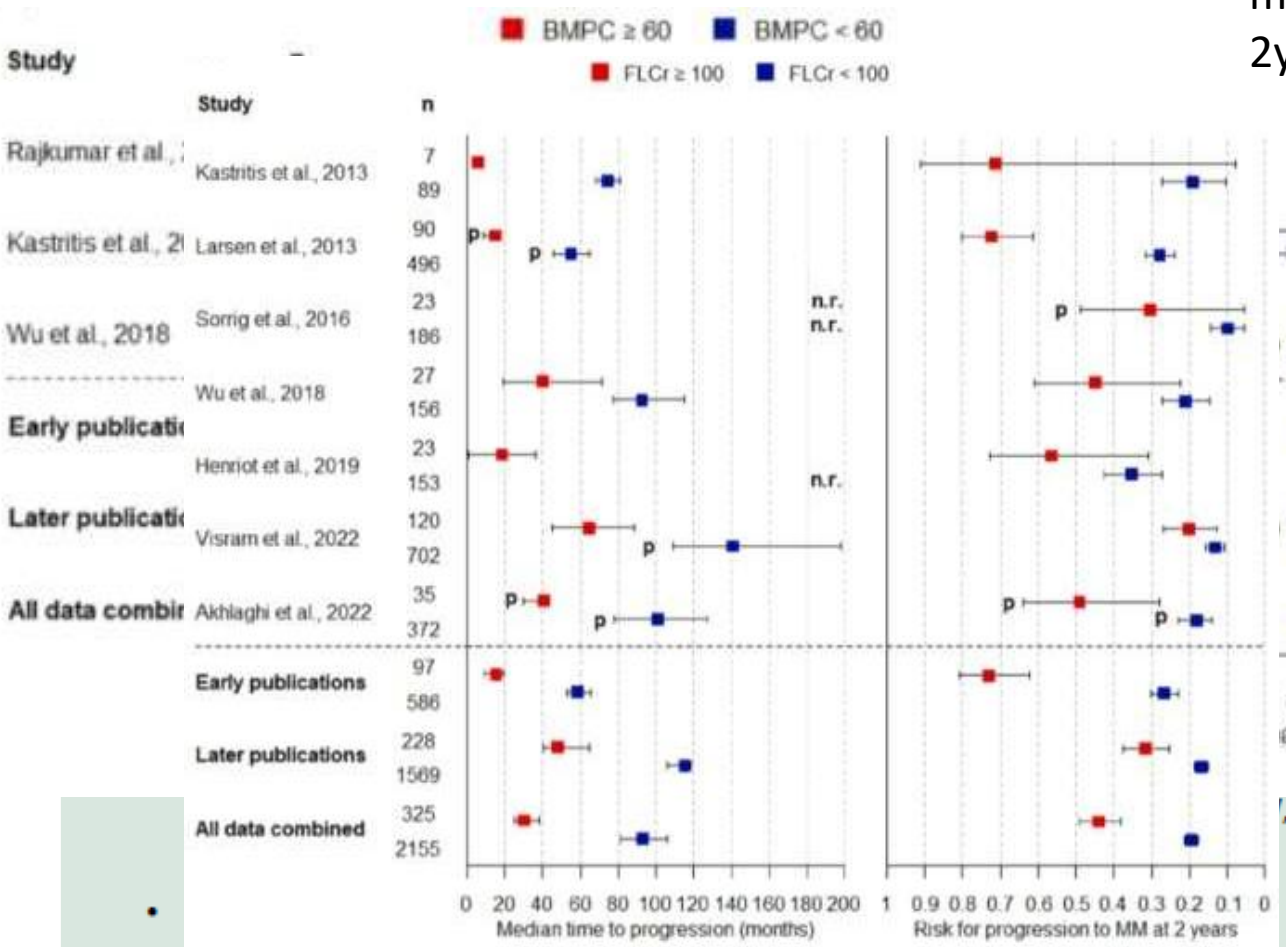
mTTP if > 60% BMPC: 9 versus 30 months!
2y risk of prog: 45 versus 86%

mTTP if FLCr > 100: 15 versus 48 months!
2y risk of prog: 32 versus 71 %



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

80% progression @2y

Multiple myeloma

Monoclonal spike

PC >10% or plasmacytoma

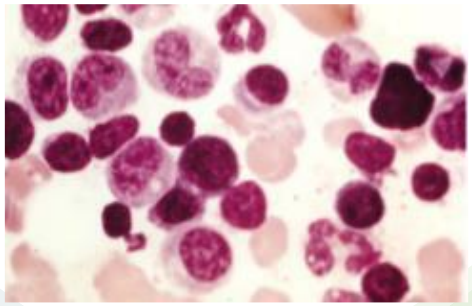
CRAB features

Or PC >60% or SFLC ratio >100

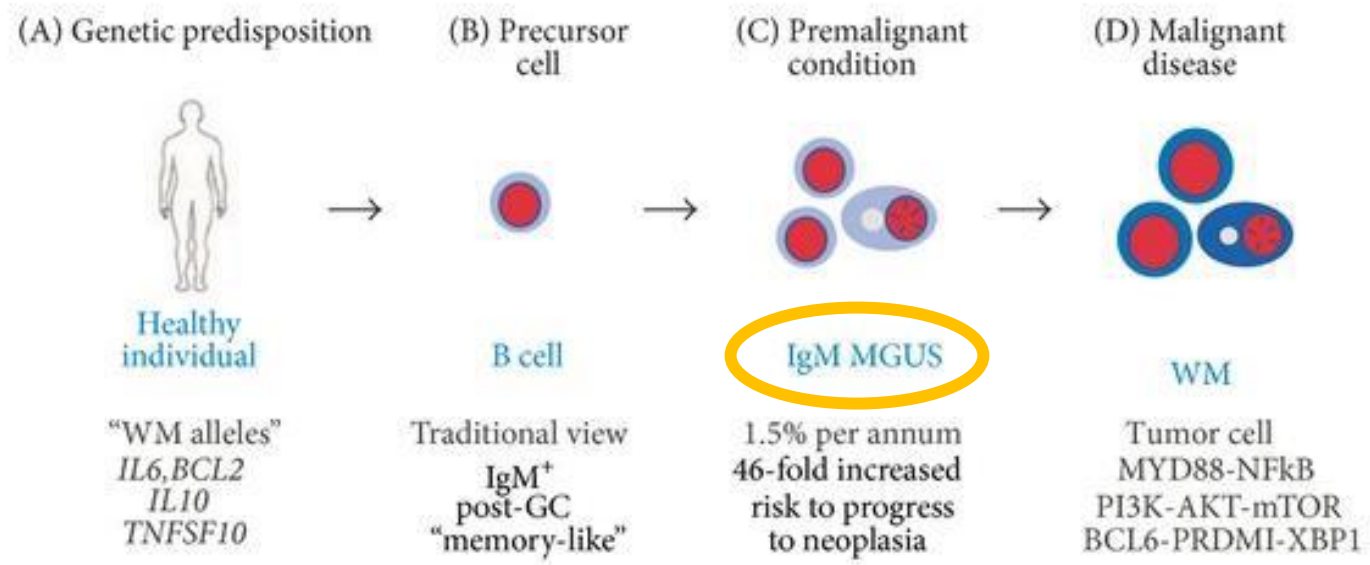
Or more than one focal lesion on MRI

MDE

Atkinet al. Clin Med. 2018
Rajkumar. Lancet Oncol. 2014
Ludwig et al. E Clin Med. 2023



IgM monoclonal gammopathy… Same story



< **3** g/dl
< **10** % LP
No sign/symptom of disease

Gertz et al. Am J of Haematology. 2018

MGUS

Underlying disease

~~Myeloma/Waldenström~~

MGCS

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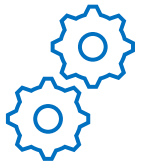
MGCS

Mechanisms of action



Organs involved

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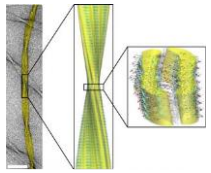
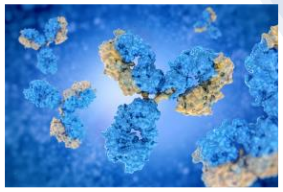
Deposition

Amyloidosis
Type I cryoglobulinemia
Fanconi
MIDD
PGNMID
Macroglobulinosis



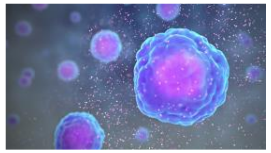


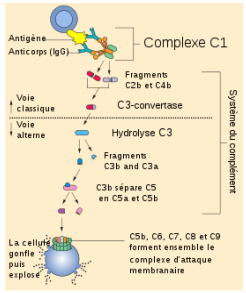
Auto-antibody activity

Neuropathy
Cold agglutinindisease
Type II cryoglobulin
Bullous skin diseases
C1 inhdeficiency
CANOMAD

Cytokine mediated

POEMS





Complement activation

C3 GN
aHUS

Unknown mecanism

Systemic Capillary Leak Synd
TEMPI
Schnitzler Synd
Scleromyxedema
Acquiredcutis laxa

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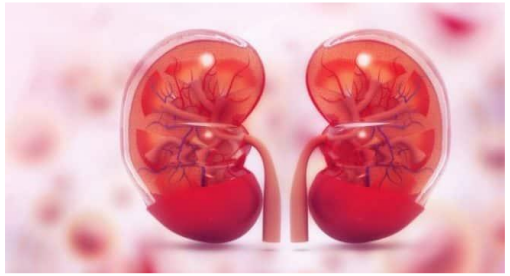

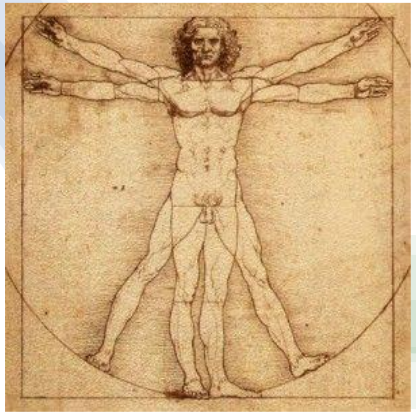

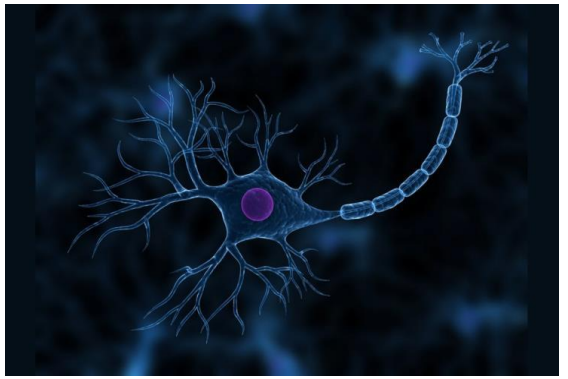

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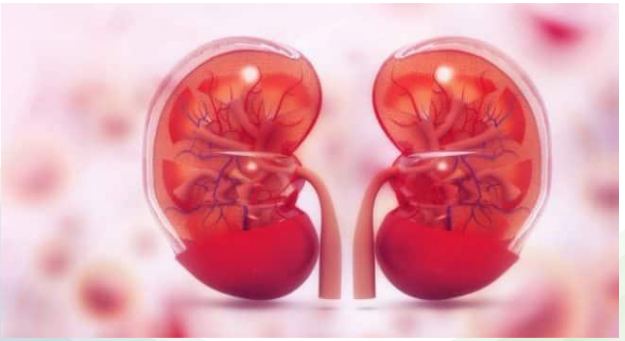


Monoclonal Gammopathy of Renal Significance
MGRS

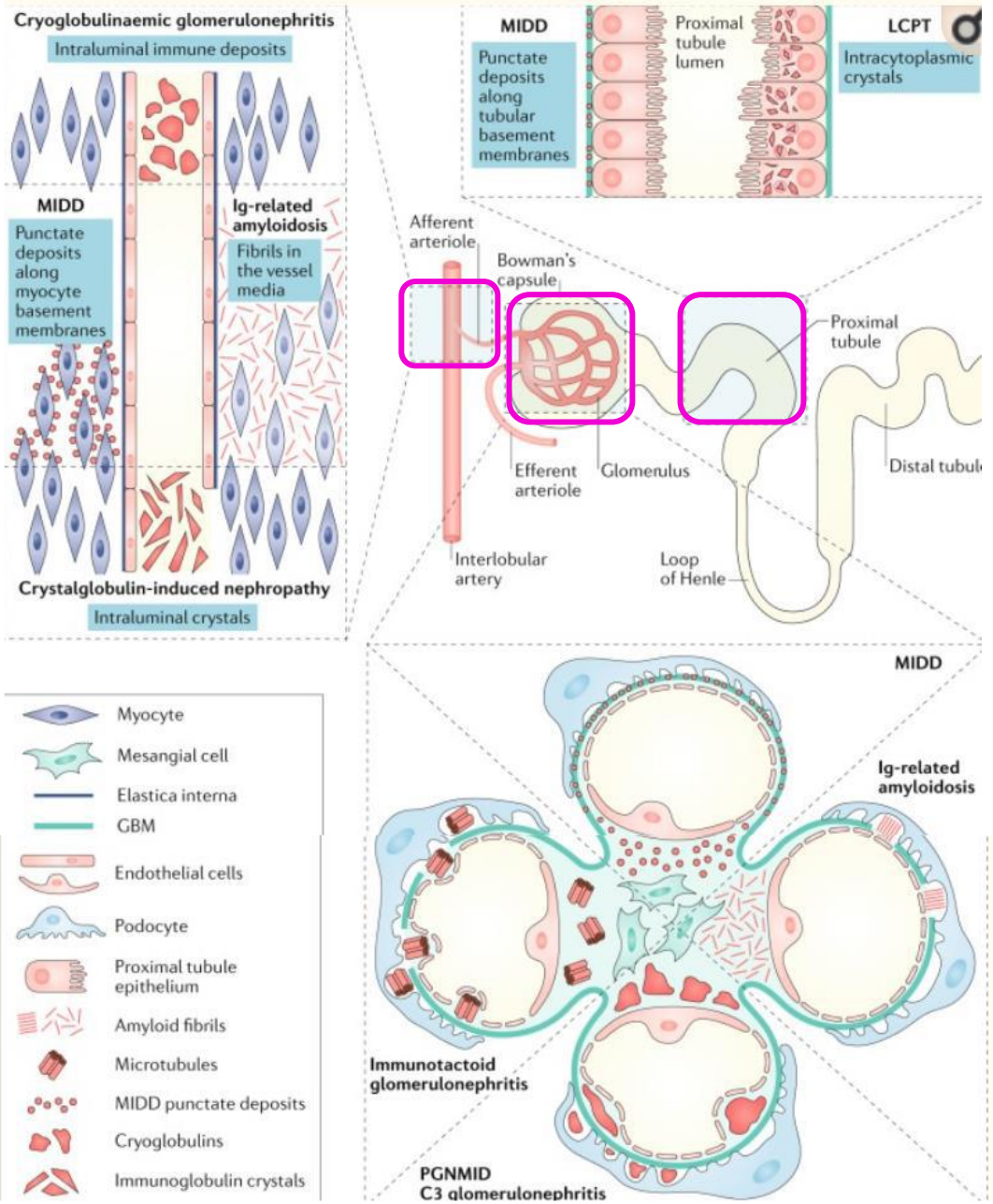
Box 1 Updated definition of MGRS

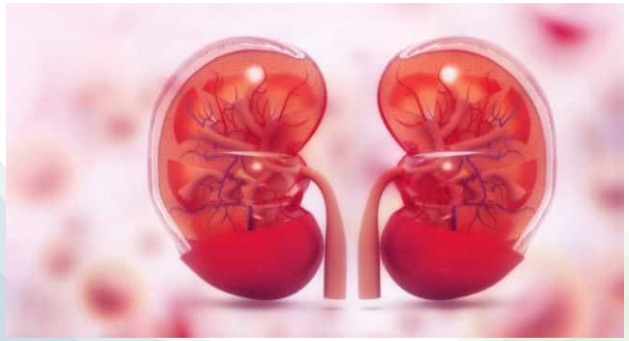
The following consensus view of monoclonal gammopathy of renal significance (MGRS) has emerged.

The term MGRS applies specifically to any B cell or plasma cell clonal lymphoproliferation with both of the following characteristics:

- One or more kidney lesions that are related to the produced monoclonal immunoglobulin
- The underlying B cell or plasma cell clone does not cause tumour complications or meet any current haematological criteria for specific therapy

Leung et al. Nat Rev Nephrol. 2019

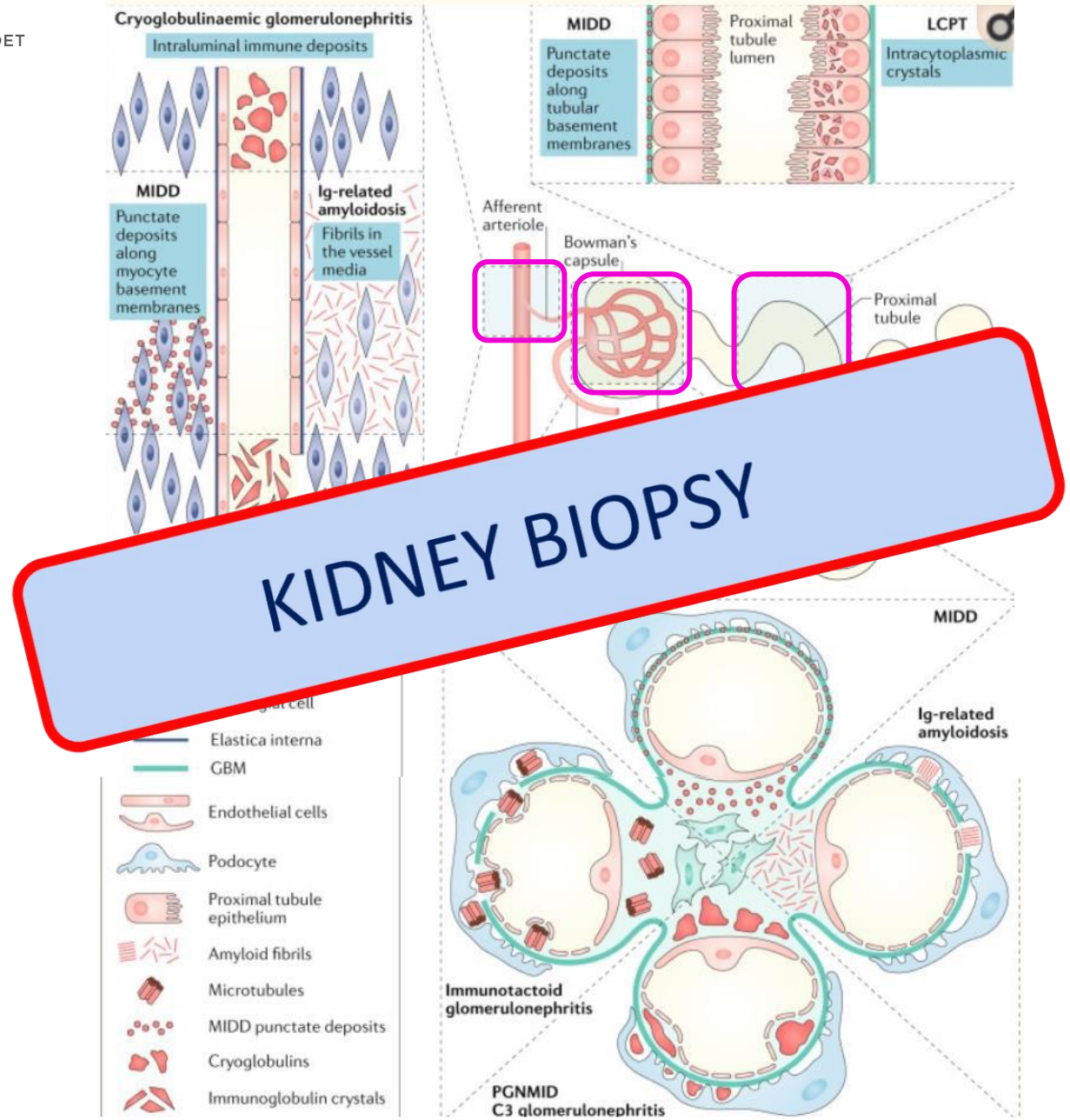


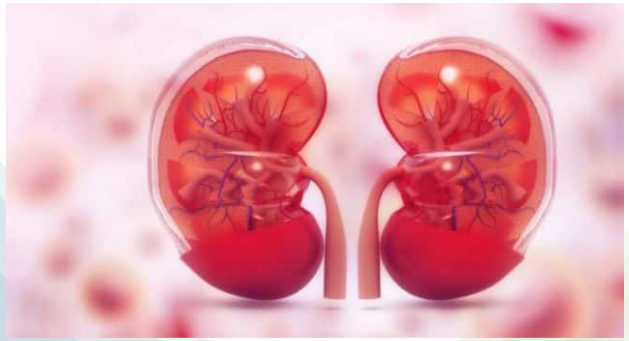


10% of MGUS – Wide spectrum

- Any kidney damage caused by monoclonal gammopathy of any kind
- **Early** regognition/treatment < limited ability to repair

Glavey et al. Blood Reviews. 2016
Leung et al. Nat Rev Nephrol. 2019



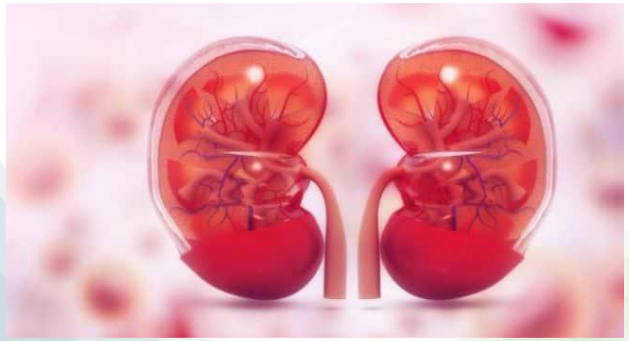


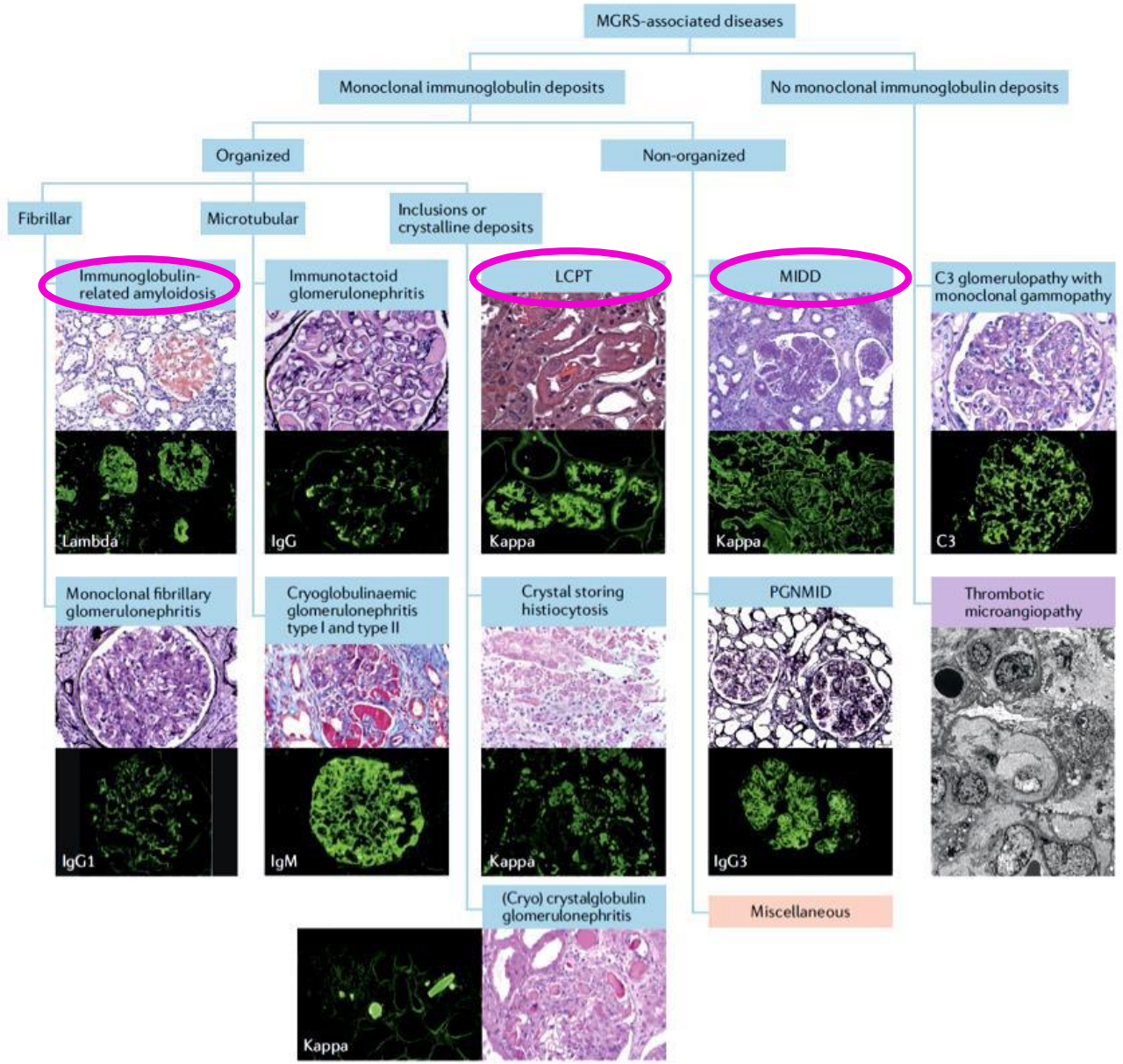
10% of MGUS – Wide spectrum

- Any kidney damage caused by monoclonal gammopathy of any kind
- **Early** regognition/treatment < limited ability to repair

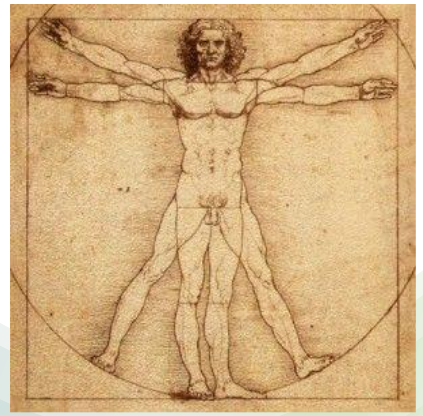
→ proteinuria/glycosuria/phosphaturia

Glavey et al. Blood Reviews. 2016
Leung et al. Nat Rev Nephrol. 2019

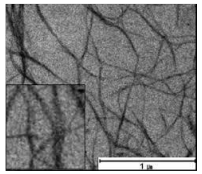




Leung et al. Nat Rev Nephrol. 2019

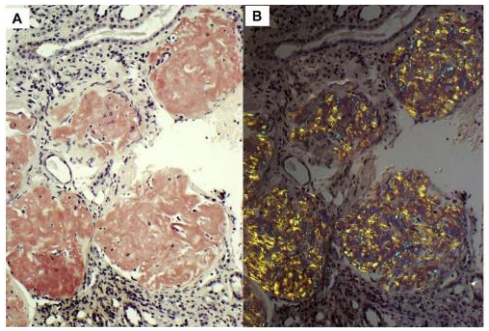


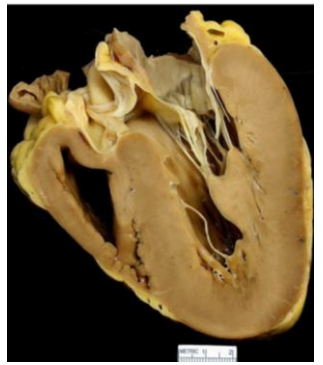
Multisystemic diseases



AL amyloidosis

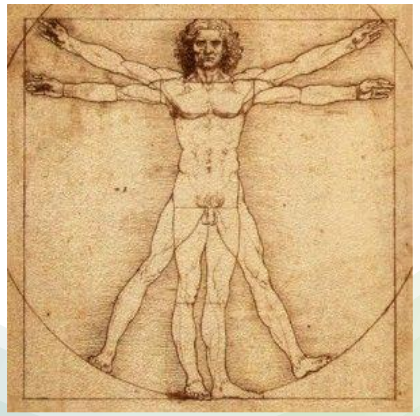
- < Amyloidogenic light chains (65-70% lambda type)
- Fibrillar deposition in virtually all organs (except CNS)
  - Mechanical + toxicity by itself → Organ dysfunction
    - Leading organs:
      - Kidney > **Albuminuria**
      - Heart > **Diastolic dyfunction**





→ screening by **proBNP/Albuminuria**

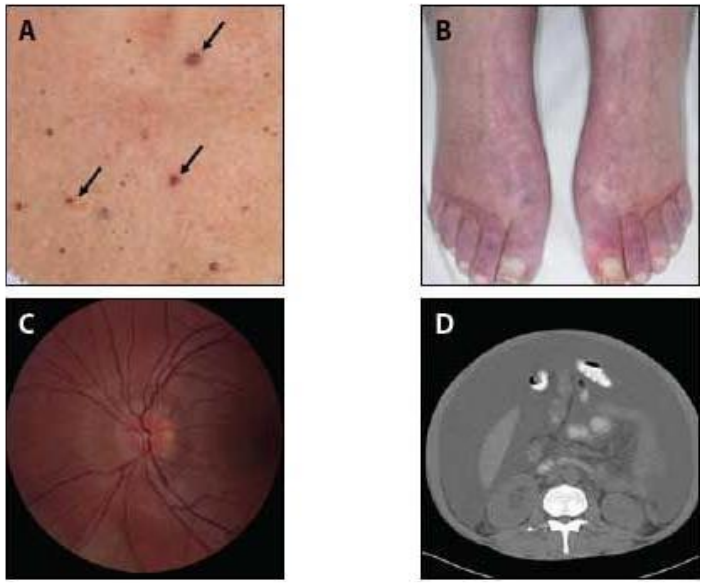
Glaveyet al. Blood Reviews. 2016
Brown et al. J Neurol. 2019

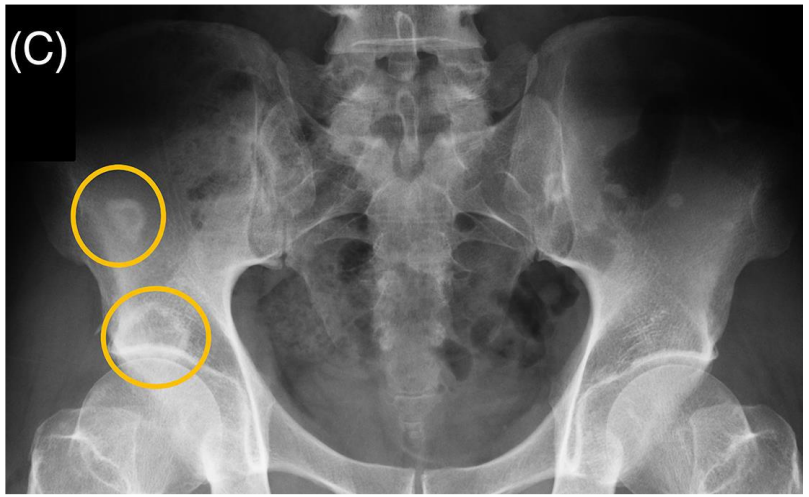


Multisystemic diseases

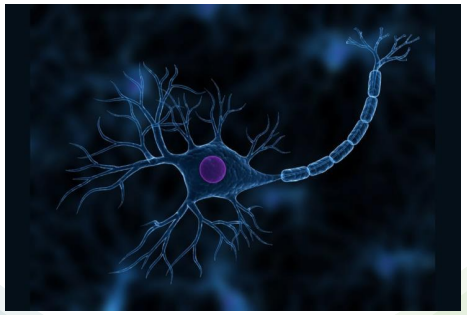
POEMS

- Polyneurpathy, organomegaly, endocrinopathy, Mprot, skin
- Other: papilloedema, extravascular overload, erythocytosis/thrombocytosis, sclerotic bone lesions
- Lambda type!! < VEGF production



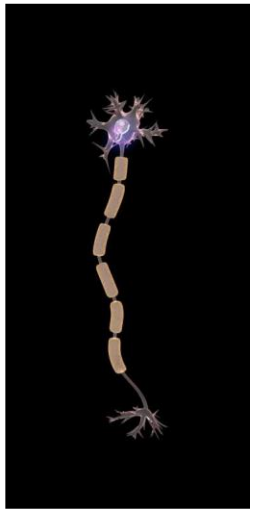


Glaveyet al. Blood Reviews. 2016
Brown et al. J Neurol. 2019



MGUS-related neuropathy

10% of MGUS!!



- IgM related (mostly kappa) - **50%**
  Demyelinating disease
  < anti MAG (50%) or anti gangliosides (GM1)

- IgA and IgG far less frequent

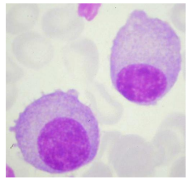
- Amyloidosis/LCDD (15-20%)
  - Axonal neuropathy!!!!
  - Mostly lambda

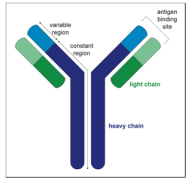
- POEMS
  - Demyelinating process

Glaveyet al. Blood Reviews. 2016
Brown et al. J Neurol. 2019

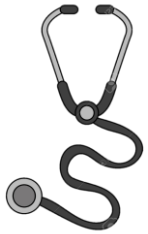
To sum up

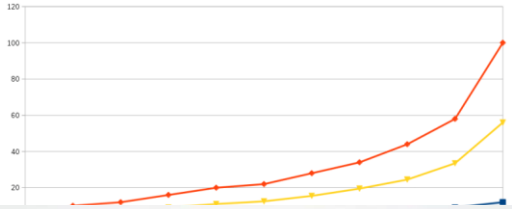
What to do with a monoclonal gammopathy?

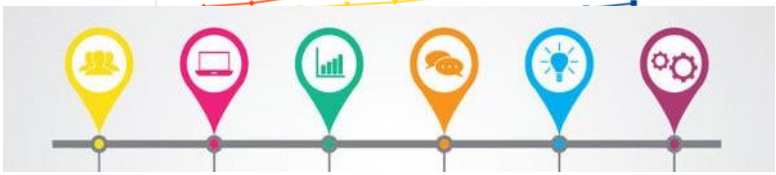




- Investigate for any sign/symptoms of disease
  - Well defined **interrogation** and **physical exam**
    - To guide explorations if needed
  - **Biological** screening
    - Mprot nature and level, FLC ratio
    - CBC, Ca++, creatininemia, proBNP
    - 24h urines
- Define the **progression risk** (Mayo Clinic)
  - +/- BM exploration, CT
- Define the **appropriate follow-up**
- **Vaccinate!**








Thanks for listening!