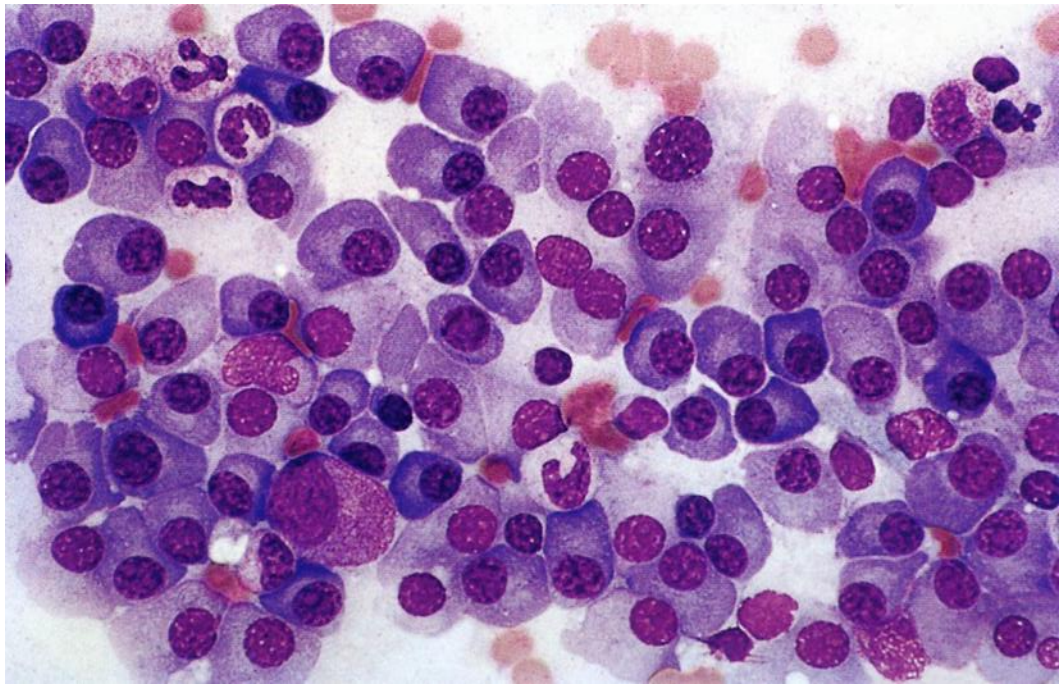
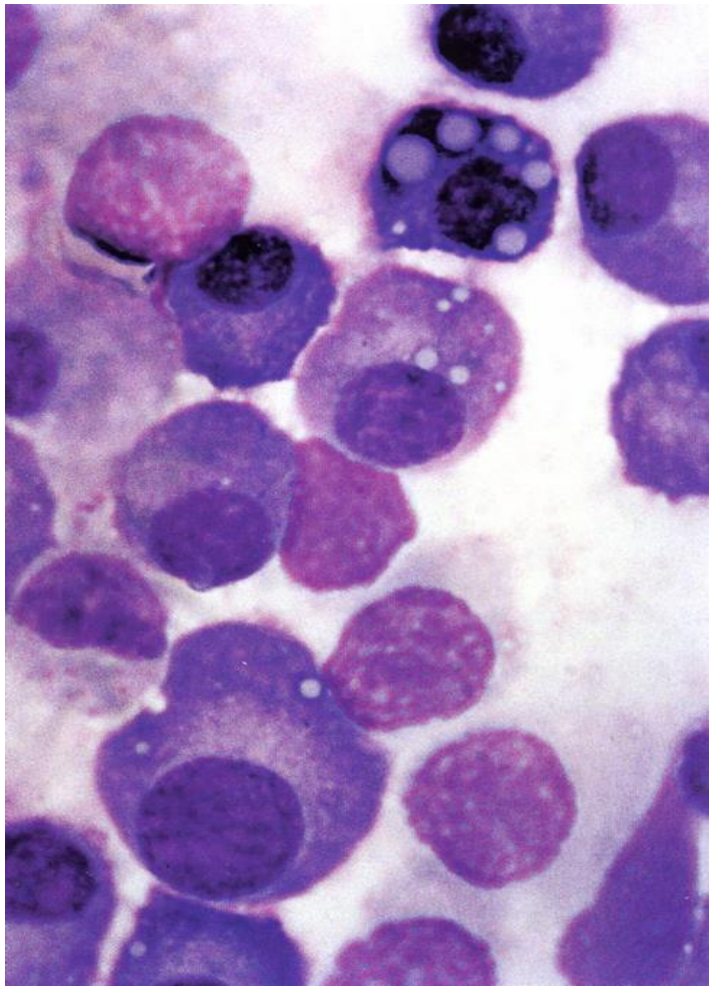
Multiple myeloma



MM: definition

- MM is a malignant disease characterised by proliferation of **clonal plasma cells** in the bone marrow and typically accompanied by the secretion of **monoclonal immunoglobulins** that are detectable in the serum or urine.



Rollig C et al. Lancet 2015; 385: 2197–208

MM and monoclonal Ig protein

- In most patients, MM is characterized by the secretion of **a monoclonal Ig protein (also known as M protein or monoclonal protein),** which is produced by the abnormal plasma cells.

- In 15–20% of patients, the MM cells secrete only monoclonal free light chains (**micromolecular MM**)

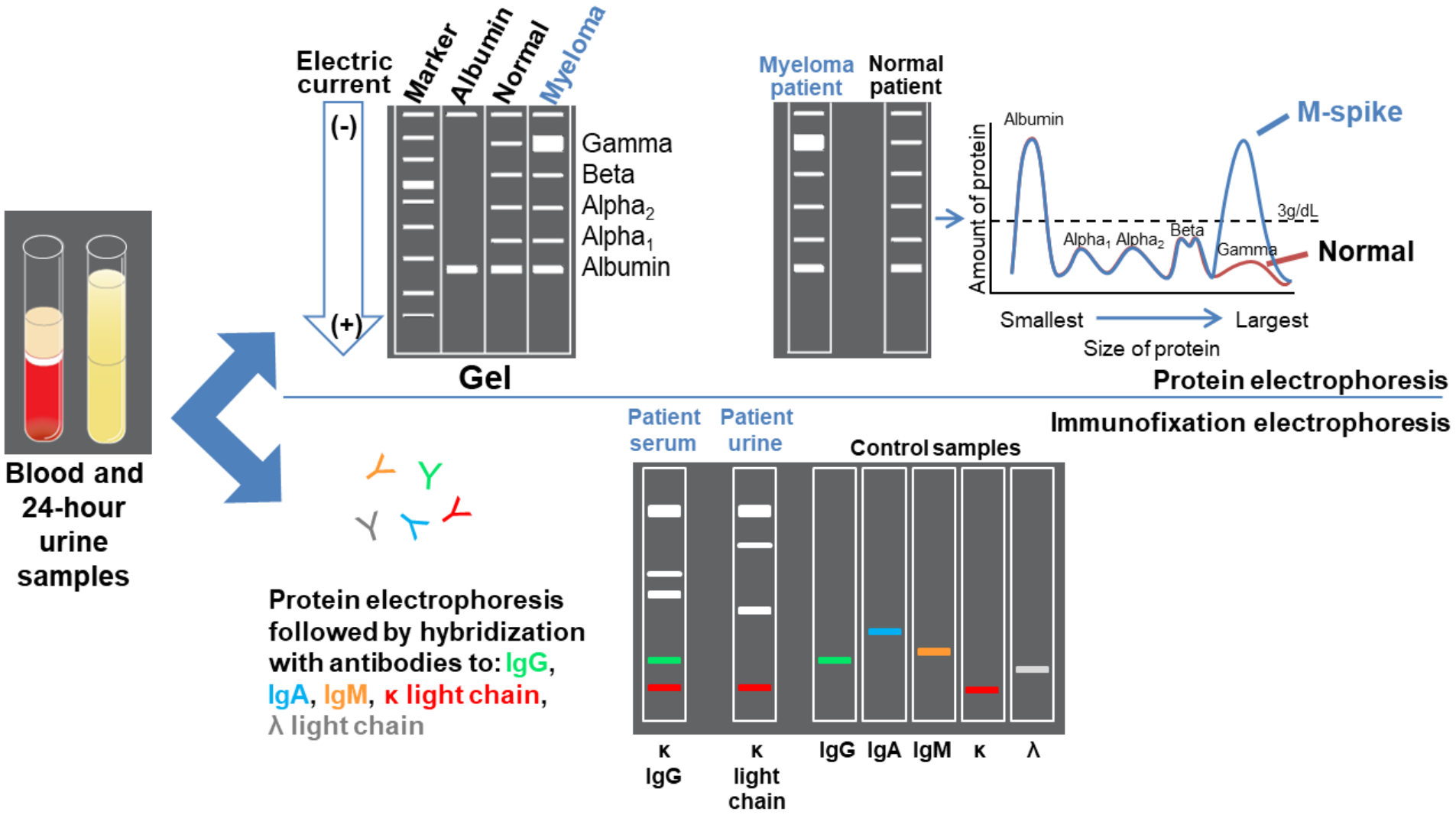
- In <3% of patients, MM cells secrete no monoclonal protein.

- IgG – 52%
- IgA – 21 %
- K or λ light chain only (Bence Jones) – 16%
- IgD – 2%
- Biclonal – 2%
- IgM – 0.5%
- Negative – 6.5%

K is the predominant light chain isotype compared with λ, by a factor of 2 to 1 with the exception that λ light chains are more common in IgD MM and MM associated with amyloidosis

Kyle. Mayo Clin Proc. 2003;78:21.

Monoclonal Gammopathies: Protein electrophoresis and immunofixation



Mayo Clinic. Test ID: PEL: Electrophoresis, Protein, Serum. Available at: www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/80085. Accessed March 2016; Lab Tests Online. Protein Electrophoresis, Immunofixation Electrophoresis.
Available at: https://labtestsonline.org/understanding/analytes/electrophoresis/tab/test. Accessed March 2016.

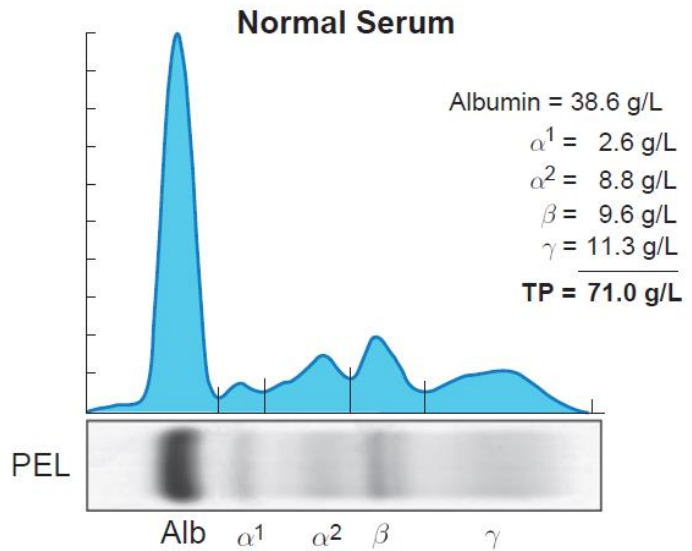


FIGURE 95.3. Images of a normal serum electrophoresis, showing the five protein components.

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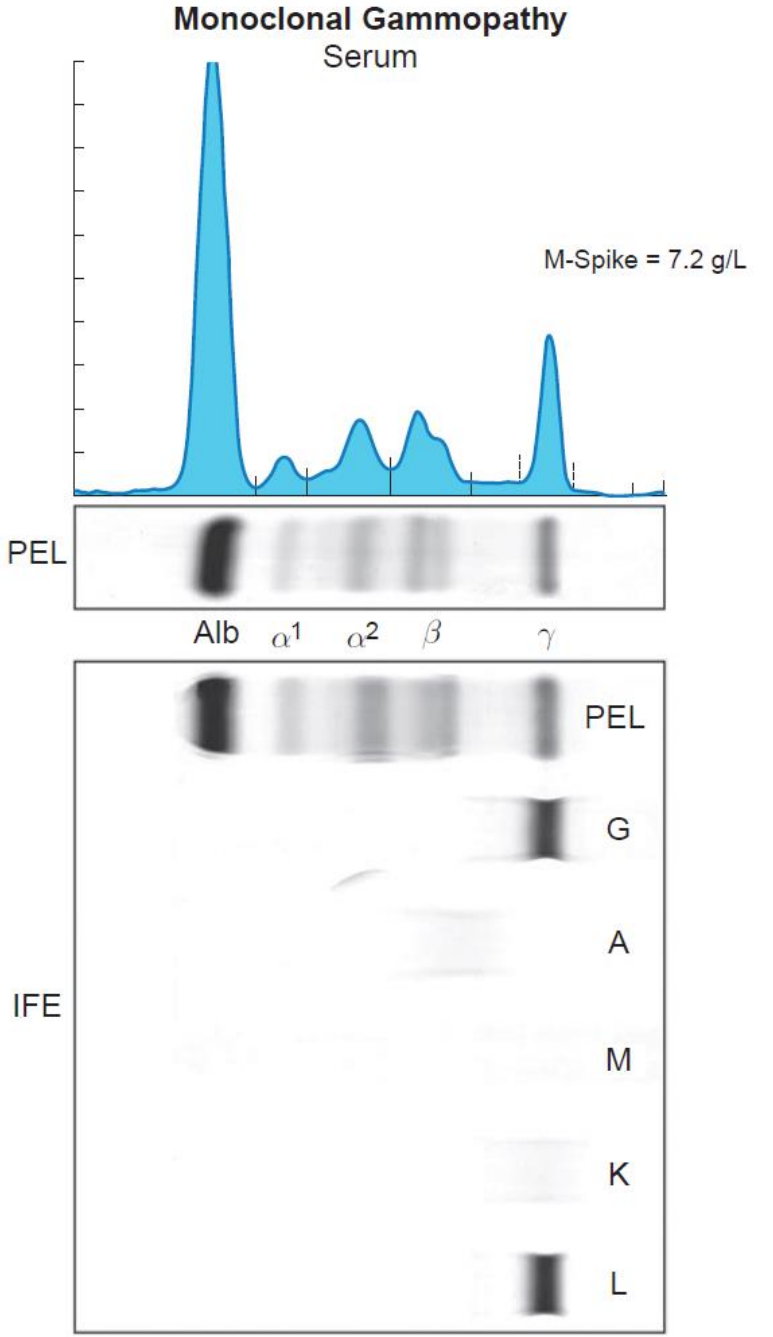

FIGURE 95.4. Images of a serum protein electrophoresis and immunofixation depicting a monoclonal protein.

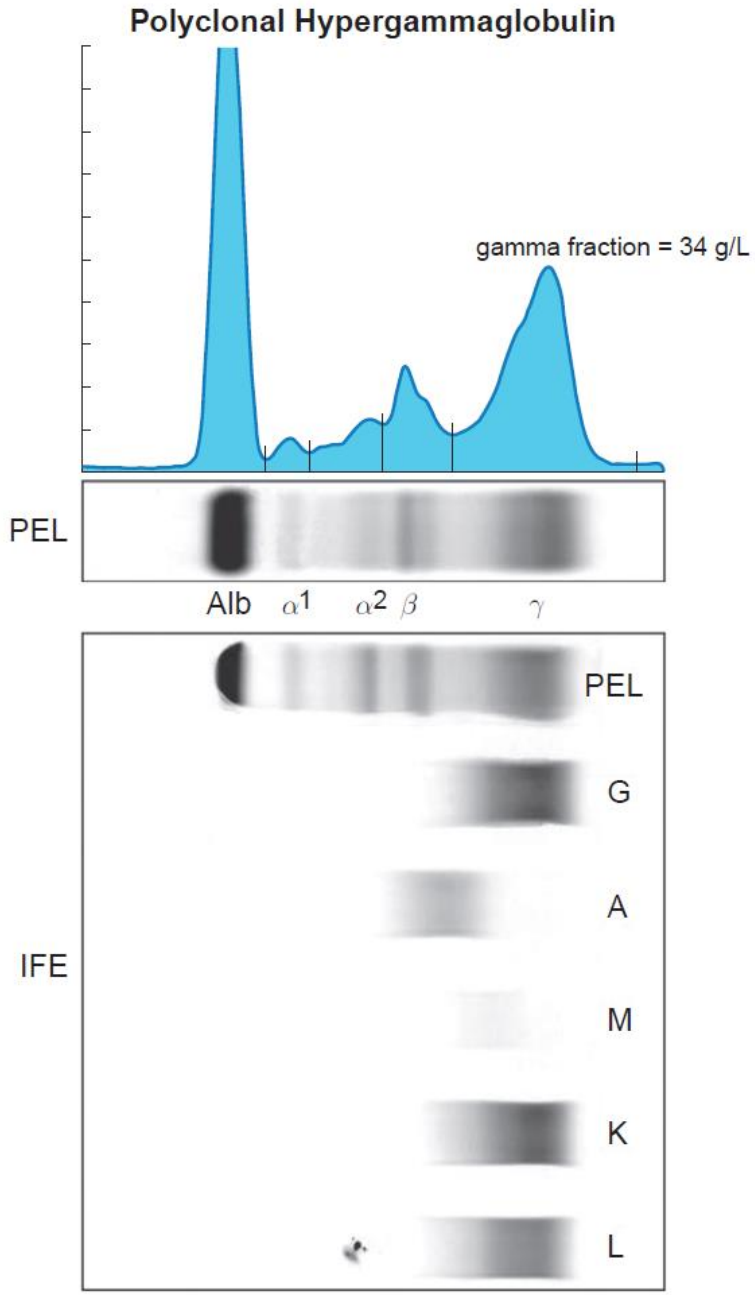

FIGURE 95.5. Images of a serum protein electrophoresis depicting a polyclonal gammopathy.

MM and monoclonal Gammopathies

- MM is part of a range of disorders referred to as the **monoclonal gammopathies**.
- Within these disorders, the most common is MGUS (Monoclonal Gammopathy of Undetermined Significance).
- MGUS is asymptomatic and consistently precedes the development of MM, with or without an identified intervening stage, referred to as **smouldering multiple myeloma** (SMM).
- Nearly 15% of patients with MGUS will progress to MM, and ~20% will progress to MM or a related condition (such as AL amyloidosis, Waldenstrom macroglobulinaemia or a lymphoproliferative disorder) over 25 years.

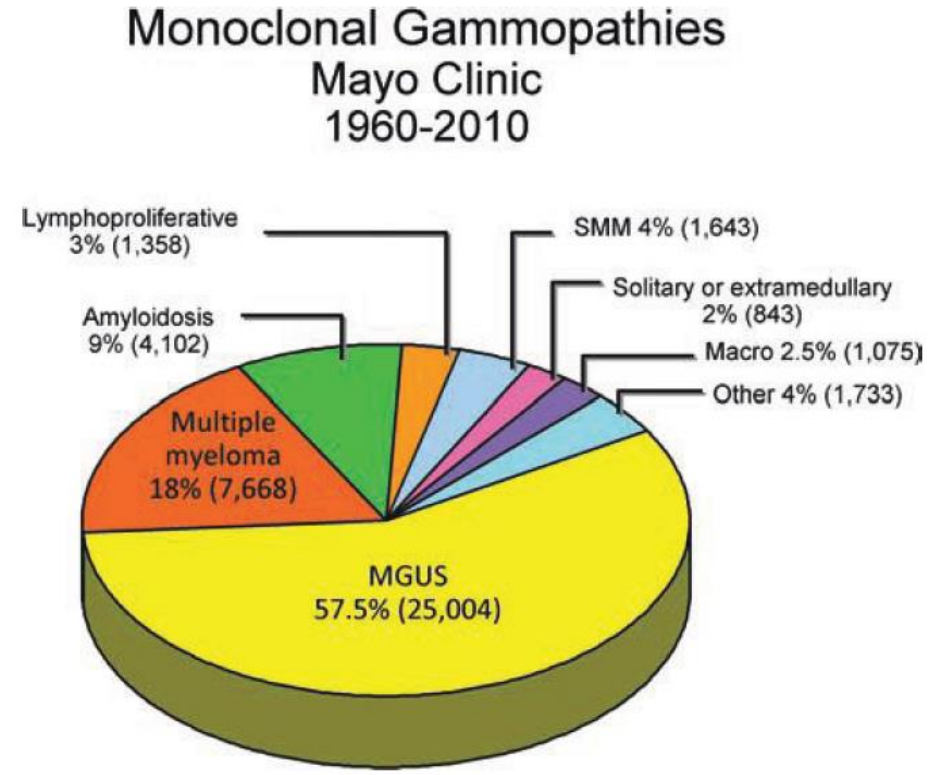

FIGURE 95.1. Distribution of monoclonal gammopathies seen at Mayo Clinic between 1960 and 2010. MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma.

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DIFFERENTIAL DIGNOSIS OF MONOCLONAL GAMMOPATHIES

IgM type
IgM MGUS (may also be biclonal)
Smoldering Waldenström macroglobulinemia
Waldenström macroglobulinemia
Other (including lymphoma and IgM MM)

Non-IgM type
Non-IgM MGUS (may also be biclonal)
SMM
MM
Plasma cell leukemia
Solitary plasmacytoma
Amyloidosis complicating a B cell neoplasm (AL)
Miscellaneous monoclonal gammopathy–associated conditions
Osteosclerotic MM with peripheral neuropathy
POEMS syndrome
Cryoglobulinemia
Peripheral neuropathy associated with MGUS
SLONM
Fanconi's syndrome
Light or heavy chain deposition disease
Castleman's disease
Scleromyxedema
Necrobiotic xanthogranuloma
Systemic capillary leak syndrome
Angioimmunoblastic lymphadenopathy with monoclonal protein
Other

MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SLONM, sporadic late onset nemaline myopathy SMM, smoldering multiple myeloma.

POEMS: polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes.
SLONM: Sporadic late-onset nemaline myopathy.

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TABLE 97.3

CLASSIFICATION OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

Type	Risk of Progression
Non-IgM MGUS[a]	1% per year risk of progression to multiple myeloma, AL amyloidosis, or related disorder
IgM MGUS[b]	1.5% per year risk of progression to Waldenström macroglobulinemia; rare patients can progress to IgM multiple myeloma
Light chain MGUS[c]	Risk of progression to light chain myeloma and AL amyloidosis. Rate of progression not defined.

IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance

[a]Almost all patients are IgG or IgA type. Occasional patients may have IgD or IgE monoclonal proteins.

[b]Note that conventionally IgM MGUS is considered a subtype of MGUS. Thus, when the term MGUS is used, in general, it includes IgM MGUS.

[c]Because light chain MGUS was only defined in 2010, studies pertaining to MGUS prior to that time do not include patients with this entity; unless otherwise specified studies since then may also not include patients with light chain MGUS.

From Rajkumar SV. Preventive strategies in monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. Am J Hematol 2012;87:453–454.

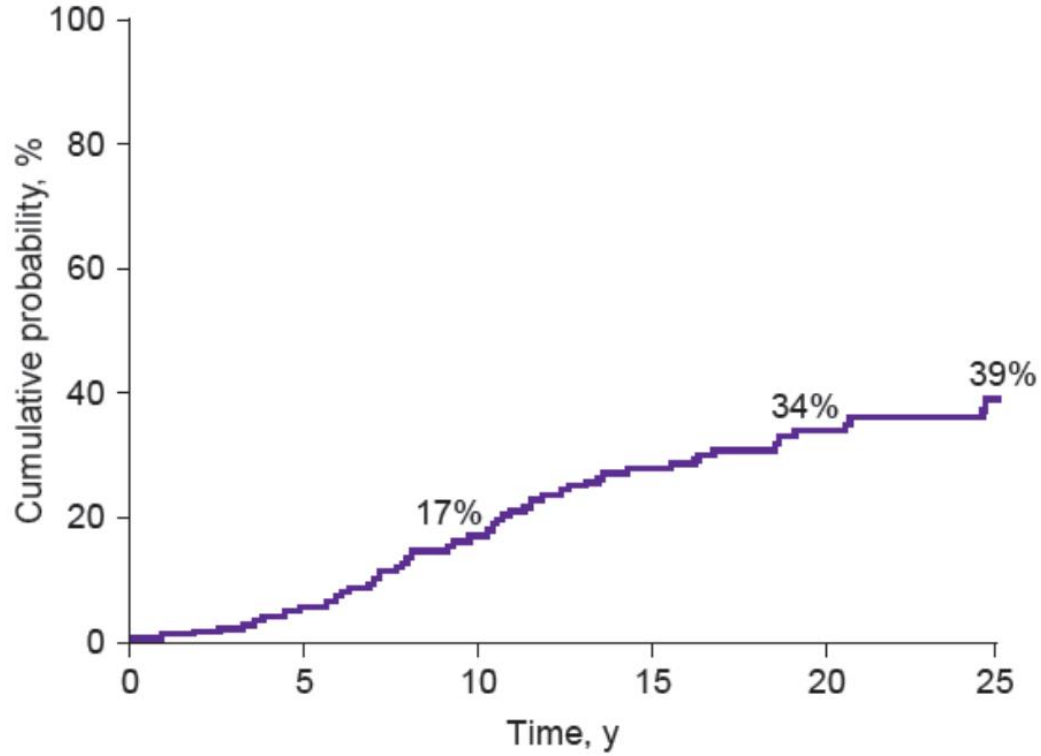


FIGURE 97.4. Actuarial analysis of incidence of multiple myeloma, macroglobulinemia, amyloidosis, or lymphoproliferative disease after recognition of monoclonal protein in 241 patients with monoclonal gammopathy of undetermined significance. (From Kyle RA, , Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Melton LJ 3rd. Long-term follow-up of 241 patients with monoclonal gammopathy of undetermined significance: the original Mayo Clinic series 25 years later. Mayo Clin Proc 2004;79:859–866.)

Risk-stratification model to predict progression of MGUS to MM or related disorders

Risk group	*No. of patients*	*Relative risk*	*Absolute risk of progression at 20 years (%)*	*Absolute risk of progression at 20 years accounting for death as a competing risk (%)*
Low-risk (serum M protein <1.5 gm/dl, IgG subtype, normal FLC ratio (0.26–1.65)	449	1	5	2
Low-intermediate-risk (any 1 factor abnormal)	420	5.4	21	10
High-intermediate-risk (any two factors abnormal)	226	10.1	37	18
High-risk (all three factors abnormal)	53	20.8	58	27

Abbreviation: MGUS, Monoclonal gammopathy of undetermined significance.
This table was originally published in *Blood*. Rajkumar SV *et al.*, Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance (MGUS) *Blood*. 2005; **106**;812–817. © the American Society of Hematology.

1. **Serum M protein < 1.5 g/dL**
2. **IgG subtype**
3. **Normal FLC ratio (0.26-1.65)**

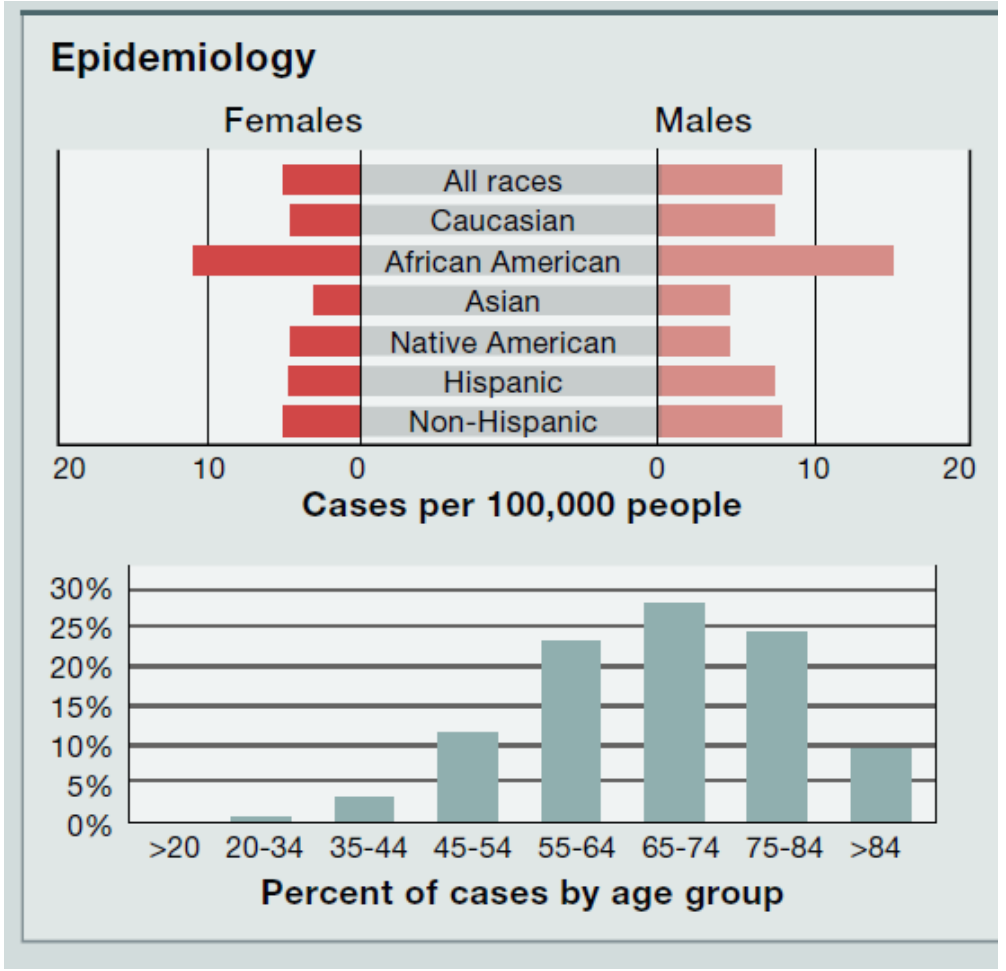
Kyle et al. Leukemia (2010) 24, 1121–1127

MM: epidemiology

- MM is the **2nd most frequent haematological malignancy** with an age-adjusted incidence of 6 per 100 000 per year in the USA and Europe.
  - The incidence is 2-3 times higher in African Americans, making it the most common haematological malignancy in this ethnic group.

- The **median age at diagnosis is 69 years**, with 75% of patients being diagnosed above the age of 55 years

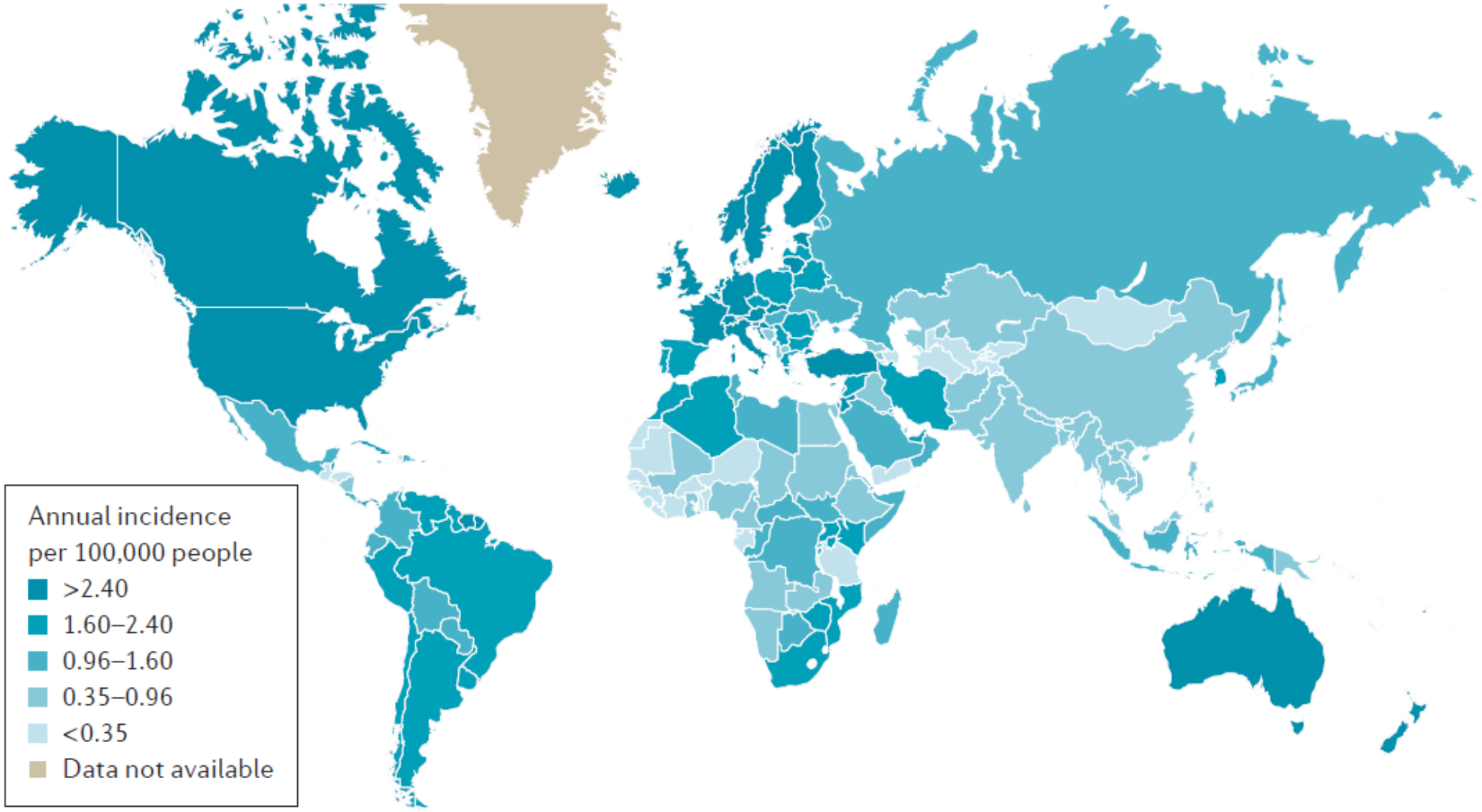
- Two of three patients are men.



Braggio E et al. Cancer Cell. 2015;28:678

Rollig C et al. Lancet 2015; 385: 2197–208

Incidence of multiple myeloma in 2012.



Kumar SK et al. Nature Reviews Disease Primers. 2017;3:1

MM: epidemiology

- Significant prevalence differences are observed between age, gender, and race, suggesting a **genetic predisposition** to MM

- With the advent of more effective therapeutic strategies and improvements in supportive care, the **median survival has increased from 3 years to 6 years in the past two decades**.

- The age-adjusted death rate for men and women between 2006 and 2010 in the USA was **3·4 in 100 000**.

Year	1975	1980	1985	1990	1999	2003	2007
5-year relative survival	26.6%	25.8%	27.0%	29.7%	33.5%	41.8%	45.1%
Increase to 1975	-	-3%	2%	12%	26%	57%	70%

Rollig C et al. Lancet 2015; 385: 2197–208

Braggio E et al. Cancer Cell. 2015;28:678

MM: Aetiology

- **The cause of MM is unknown**, although several studies have evaluated potential risk factors for this disease.
  - **Environmental and occupational exposures**.
    - Radiation (little evidence)
    - Occupational exposure (farmers: debated)
    - Exposure to hair dyes, benzene, petroleum products: little evidence
  - **Genetic factors**
    - Genome-wide association studies (GWAS) have identified multiple genetic loci associated with an increased risk of MM, in addition to loci associated with an increased mortality in diagnosed patients.
    - Several single-nucleotide polymorphisms (SNPs) that could lead to MYC activation, inferior survival or clinical presentation were also identified.

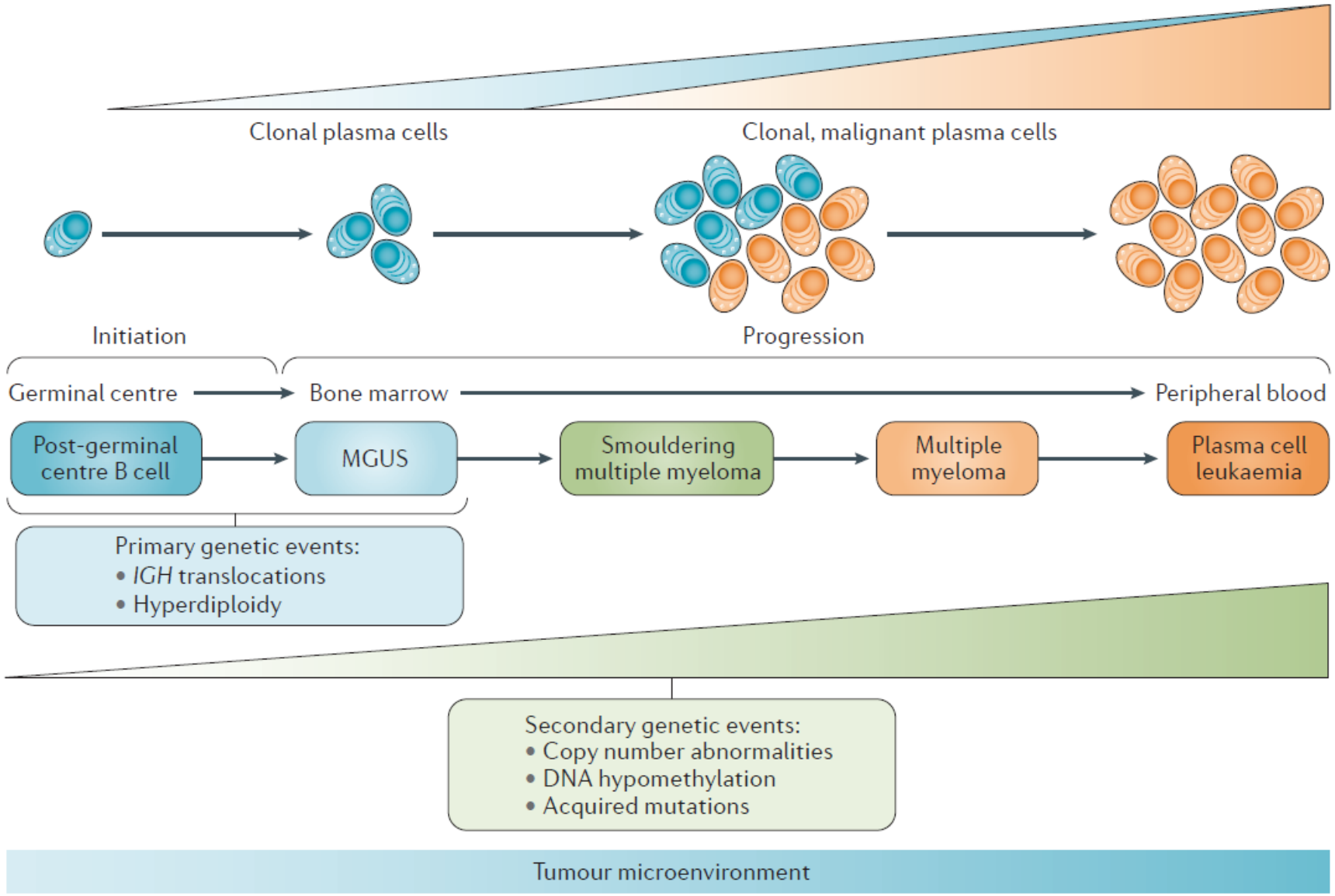
MM: pathogenesis

- MM cells are similar to long-lived, **post-germinal centre plasma cells**, and are characterised by
  - strong bone marrow dependence,
  - extensive somatic hypermutation of Ig genes,
  - absence of IgM expression.

- In most cases, MM is **preceded by a pre-malignant MGUS condition**, followed by an asymptomatic phase, called **SMM**.

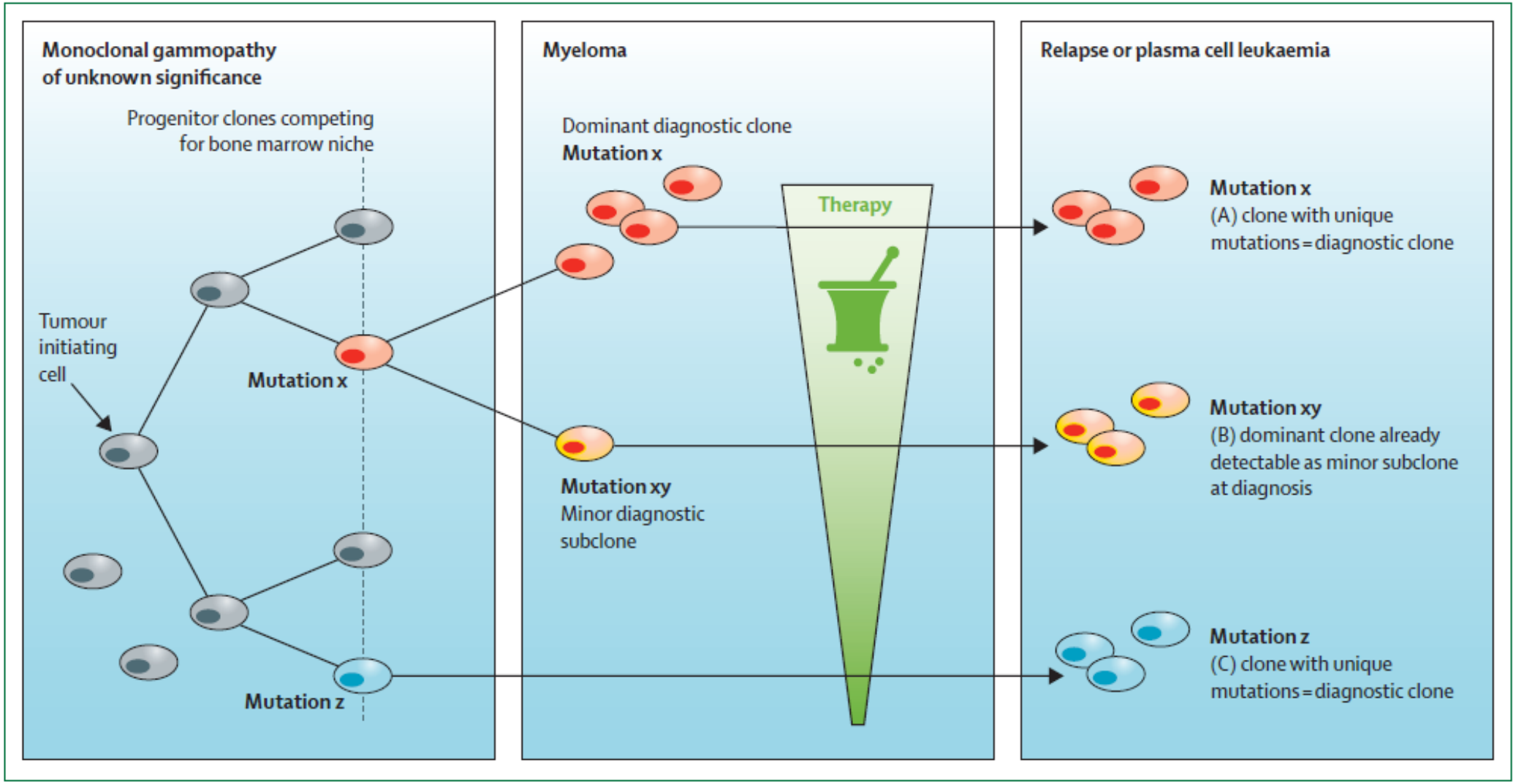
- **The risk of progression to MM is estimated 0.5%–1% per year** for the heavy chain and 0.3% for the light chain MGUS.

The development of monoclonal gammopathies



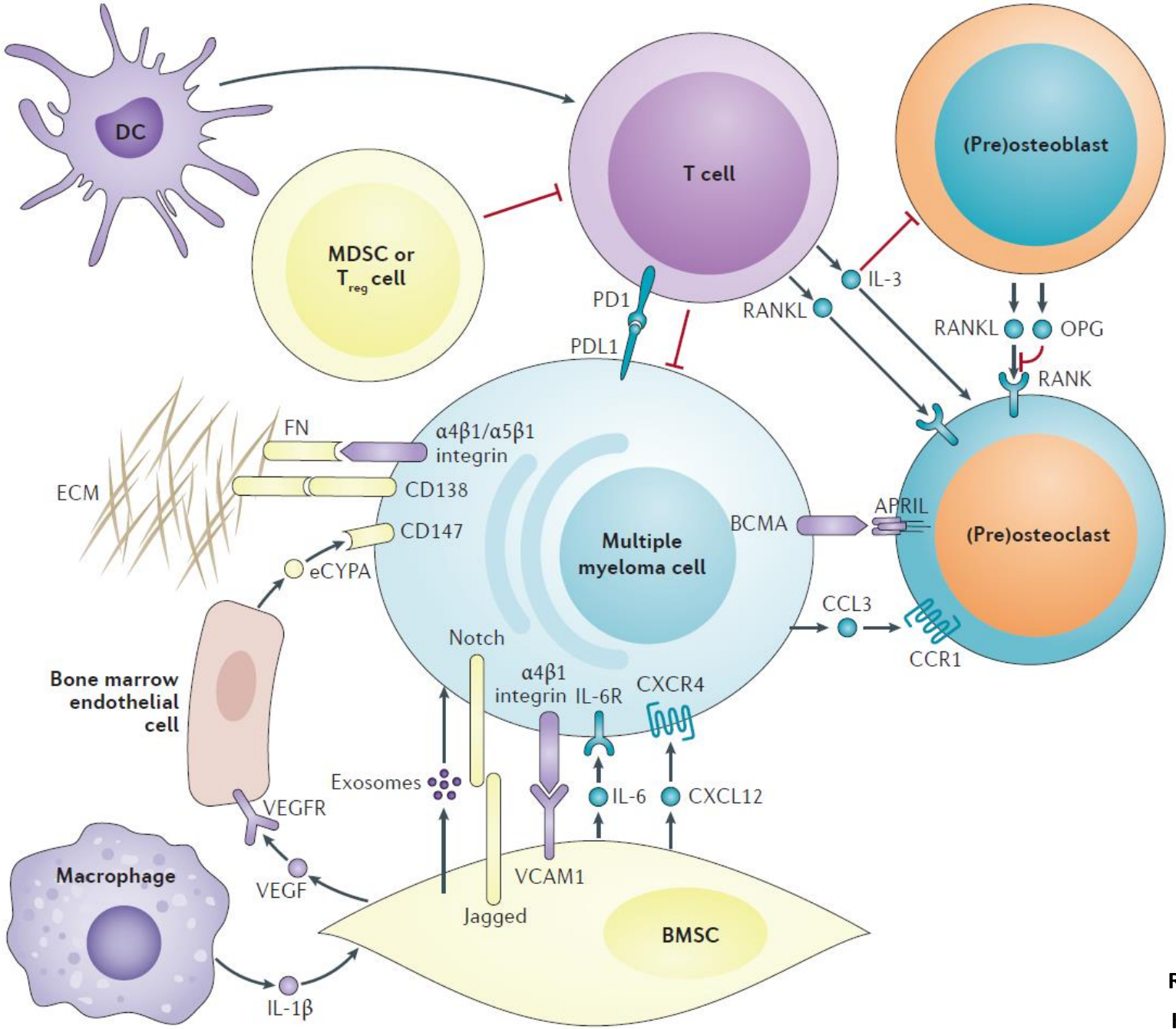
Kumar SK et al. Nature Reviews Disease Primers. 2017;3:1

Clonal composition of multiple myeloma during disease progression and therapy



Rollig C et al. Lancet 2015; 385: 2197–208

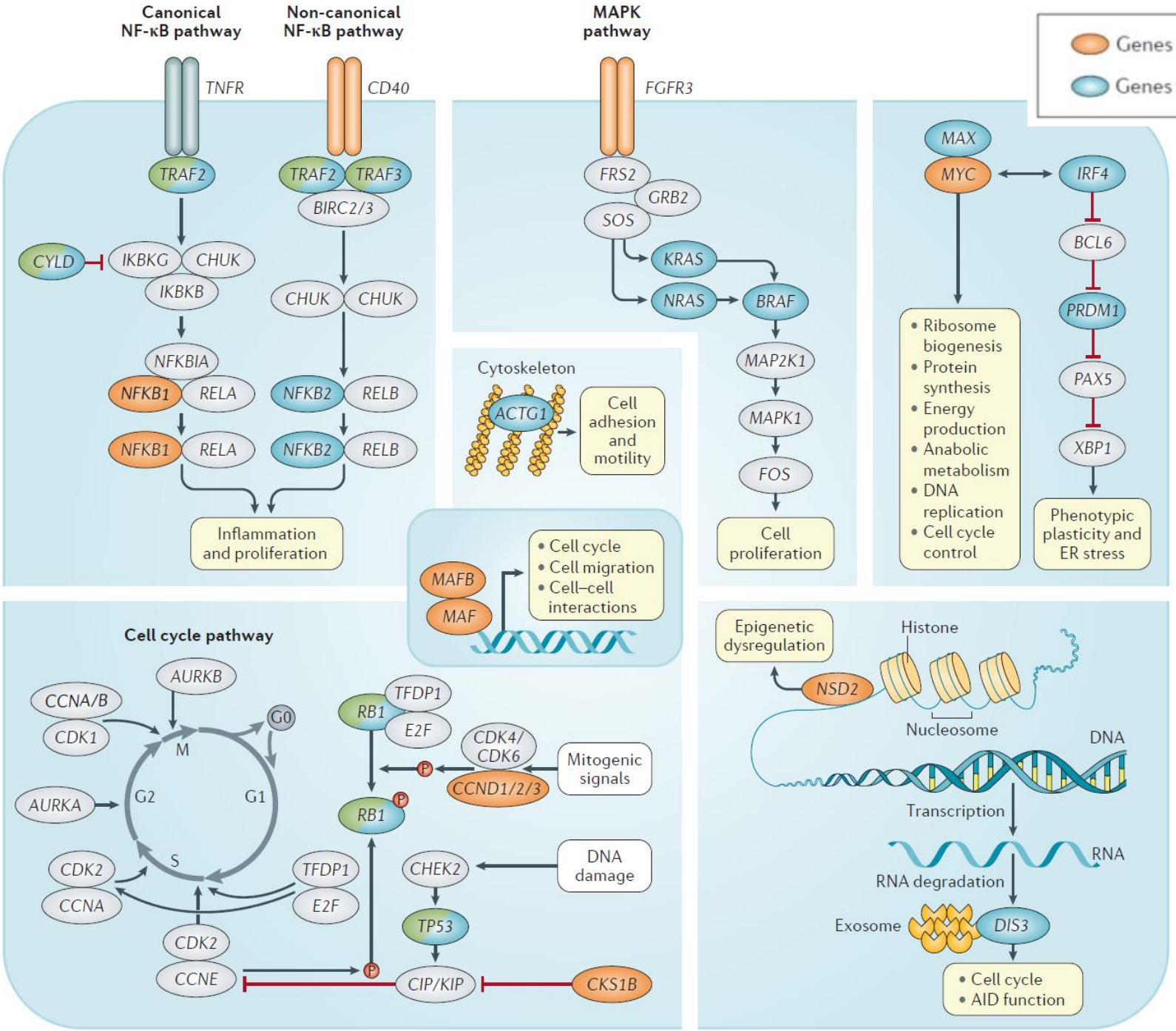
Tumour microenvironment



- **Key role of the interaction between MM cells and their bone marrow microenvironment (cell–cell and cell–matrix interactions, and growth factors and cytokines).**
- **Cellular components of the microenvironment include bone marrow stromal cells, osteoblasts, endothelial cells, and cells of the innate and adaptive immune system, including regulatory T cells.**
- **Crosstalk between MM and its microenvironment seems to be bidirectional.**

Rollig C et al. Lancet 2015; 385: 2197–208

Kumar SK et al. Nature Reviews Disease Primers. 2017;3:1

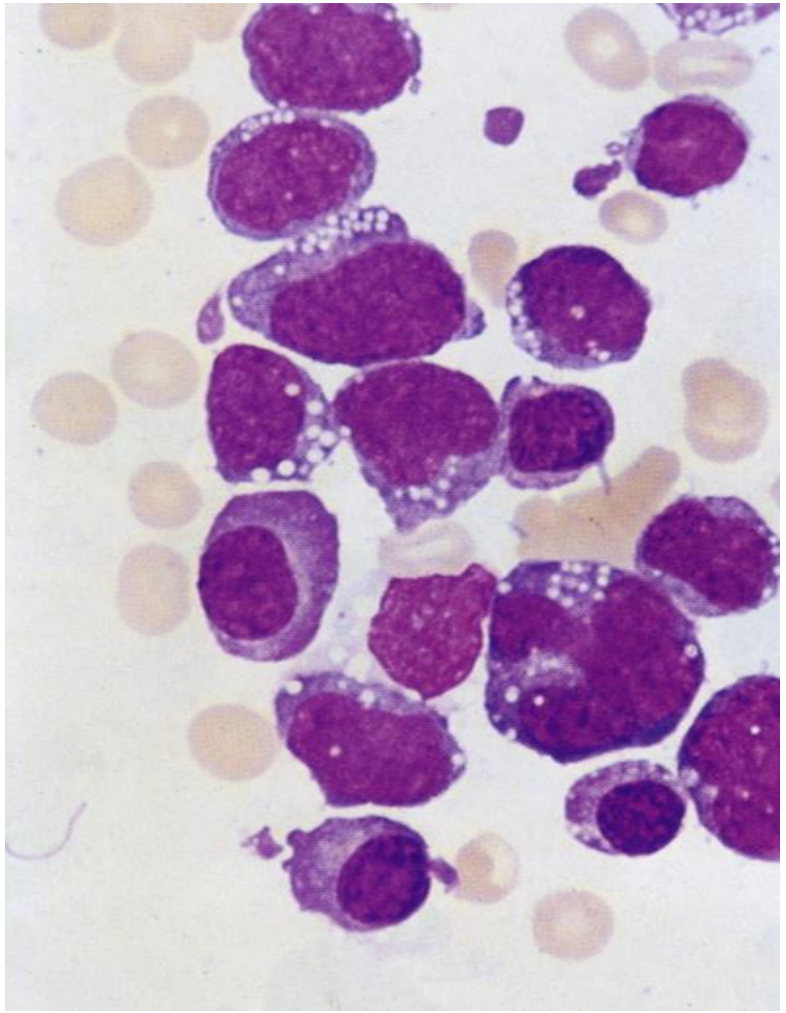


Signalling pathways affected in MM

Kumar SK et al. Nature Reviews Disease Primers. 2017;3:1

Pathobiology of end organ damage

- Once the clonal plasma cell population is created and progresses to MM, patients develop symptoms (eg, hypercalcemia, lytic bone lesions, renal dysfunction, and anemia) related to
  - the infiltration of plasma cells into the bone or other organs or to kidney
  - damage from excess light chains or monoclonal Ig



Osteolytic bone lesions

- **Osteolytic bone lesions** are the hallmark of MM.
- The pathogenesis of lytic bone lesions characteristic of MM is mediated by an **imbalance between the activity of osteoclasts and osteoblasts** with:
  - **enhanced** osteoclastic activity
  - marked **suppression** of osteoblastic activity (in contrast to other malignancies).

- As a result, MM bone lesions tend to be **purely osteolytic** and better visualized on **plain radiographs** compared with other bone metastases from solid tumors that tend to have an osteoblastic component and are better visualized on radionucleotide bone scans.

Osteolytic bone lesions

- **Increased osteolytic activity** is mediated by
  - an **increase in RANKL** (receptor activator of nuclear factor kappa-B ligand) expression by osteoblasts (and plasma cells)
  - a **reduction in the level of its decoy receptor, osteoprotegerin (OPG).**
- This leads to an **increase in RANKL/OPG ratio**, which **causes osteoclast activation** and **bone resorption**.

  - Increased levels of macrophage inflammatory protein-1 alpha (**MIP-1alpha, CCL3), IL-3, and IL-6 produced by marrow stromal cells** also contribute to the **overactivity of osteoclasts**.
  - Increased expression of **SDF-1alpha** by stromal cells and MM cells causing **osteoclast activation** by binding to **CXCR4** on osteoclast precursors.

Osteolytic bone lesions

- In addition to osteoclast activation, there is active **suppression of osteoblasts in myeloma**.

- This is most likely related to
  - increased levels of **IL-3, IL-7, and dickkopf 1 (DKK1),** which **inhibit osteoblast differentiation**.
  - MM cells express DKK1, an inhibitor of Wnt signaling.
  - An increased expression of DKK1 by these cells has been associated with presence of focal bone lesions in MM.
  - Increased IL-3 and IL-7 levels may also play a role.

Hypercalcemia

- **Hypercalcemia** appears to be a product of osteoclast activating factors such as
  - lymphotoxin,
  - interleukin-6,
  - hepatocyte growth factor,
  - receptor activator of nuclear factor kappa B ligand (RANK ligand).

Anemia

- Involvement of the bone marrow in MM can result in anemia due to
  - replacement of normal hematopoietic tissue by tumor (**myelophthisis**)
  - **disruption** of the bone marrow microenvironment.

- The common occurrence of anemia in the setting of **limited BM infiltration** suggests that MM-associated anemia is not entirely due to BM replacement by MM cells.
  - In MM, the BM contains **lower than normal numbers of hematopoietic stem and progenitor cells**.
  - This appears to be at least partially **due to changes in the BM microenvironment**.

- Elimination of MM cells and restoration of the normal BM environment may result in repopulation with these precursors and **reversal of the anemia**.

Kidney disease

- Kidney disease in patients with monoclonal gammopathies usually results from
  - the production of monoclonal Ig or Ig fragments (ie, light or heavy chains)
  - clonal proliferation of plasma cells or B cells.

- Kidney injury also result from causes unrelated to monoclonal proteins.

- **Mechanisms** of kidney injury in plasma cell malignancies can be grouped into
  - **Ig-dependent**
  - **Ig-independent**

Kidney disease

- The 3 most common forms of **Ig-dependent** kidney injury include:

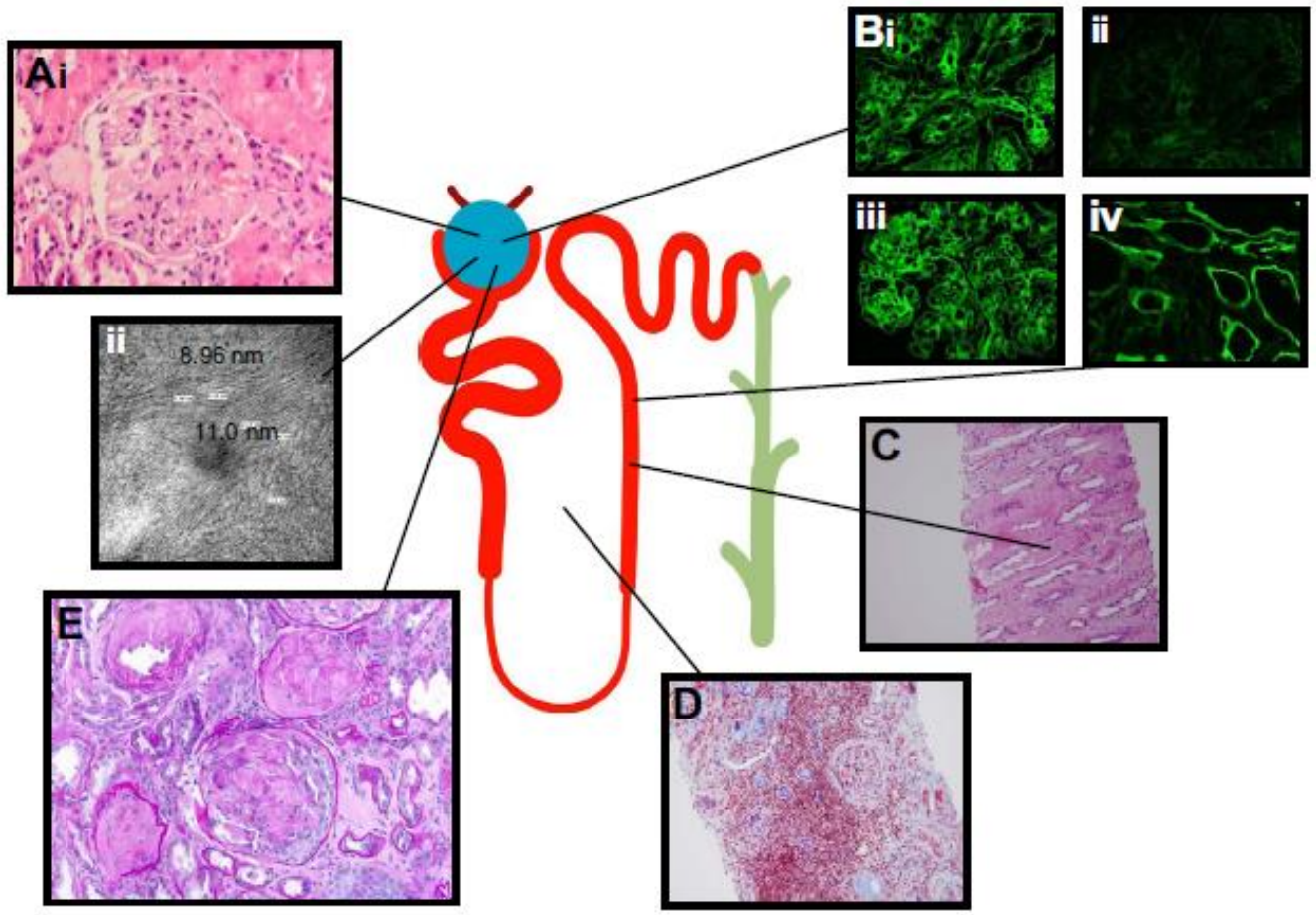
1. **cast nephropathy**, in which casts and crystals composed of filtered **monoclonal Ig** and **other urinary proteins** obstruct **distal renal tubules**, often precipitously, and typically incite an accompanying **tubulointerstitial nephritis**;

2. **AL amyloidosis**, in which primarily monoclonal light chains and other proteins together form β-pleated sheets in the **glomeruli**;

3. **monoclonal Ig deposition disease (MIDD),** in which intact or fragmented light chains, heavy chains, or both deposit along **glomerular and/or tubular basement membranes**.

Heher EC et al. Blood. 2010;116(9):1397-1404)

3 distinct syndromes account for most cases of Ig-mediated kidney disease but virtually all nephropathologic syndromes have been observed.



Heher EC et al. Blood. 2010;116(9):1397-1404)

Panel A. Amyloid fibrils consisting of monoclonal Ig and serum proteins **disrupting glomeruli architecture**.

Panel B shows MIDD. Monoclonal light chains kappa and/or heavy chains (IgG), deposit along glomerular (iii) and tubular basement membranes (iv), **altering the glomerular structure and causing dose-dependent proximal tubular toxicity.**

Panel C shows cast nephropathy. Filtered monoclonal Ig, Tamm-Horsfall, and other proteins form casts, which **obstruct tubules and collecting ducts**. Casts can rupture and result in **interstitial inflammation**.

Panel D shows interstitial inflammation. Inflammation also results from the processing of filtered monoclonal light chains, which induces NF-kB and other signaling pathwaysleading to cytokine-mediated inflammatory infiltrate and subsequent matrix deposition and fibrosis.

Panel E shows glomerular crescent. Virtually every recognized nephropathologic lesion has been described in association with paraproteinemia.

Table 1. Mechanisms of renal failure in plasma cell dyscrasias in Ig-dependent and -independent categories

Ig-dependent mechanisms	
Mechanism	**Details**
Cast nephropathy (myeloma kidney)	Risk factors include light chain myeloma with > 10 g/day of monoclonal Ig excretion, IgD myeloma, volume depletion, sepsis, medications (see "Medication toxicity" below)
MIDD	Often associated with kappa light chains. Systemic syndrome may be present.
AL amyloidosis	Often associated with nephrotic-range albuminuria and lambda light chains. Systemic syndrome may be present.
Glomerulonephritis	Membranoproliferative, diffuse proliferative, crescentic, cryoglobulinemic all recognized
Tubulointerstitial nephritis	May also result from non-Ig mechanisms.
Minimal change or membranous glomerulopathy	Albuminuria is typically present, in addition to light chain proteinuria
Henoch-Scholein purpura/IgA nephropathy	Associated with IgA myeloma
Immunotactoid and fibrillary glomerulopathy	Rare conditions
Intracapillary monoclonal deposits of IgM thrombi	Associated with Waldenström macroglobulinemia
TMA	Paraprotein causes endothelial injury with resulting TMA
Hyperviscosity syndrome	Most common with Waldenström macroglobulinemia
Ig-independent mechanisms	
Mechanism	**Details**
Volume depletion or sepsis	Can cause acute tubular necrosis and/or precipitate cast nephropathy
Hypercalcemia	Can precipitate cast nephropathy
Tumor lysis syndrome	Uric acid or phosphate nephropathy
Medication toxicity	Zoledronate: acute renal failure Pamidronate: collapsing focal segmental glomerulosclerosis Nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, loop diuretics, or IV contrast can precipitate cast nephropathy
Direct parenchymal invasion by plasma cells	Associated with advanced or aggressive myeloma
Pyelonephritis	Immunodeficiency from myeloma, deficient Ig, and chemotherapy all contribute

Ig indicates immunoglobulin; MIDD, monoclonal Ig deposition disease; TMA, thrombotic microangiopathy; and IV, intravenous.

Heher EC et al. Blood. 2010;116(9):1397-1404)

Table 1. Spectrum of neurologic complications in myeloma and related disorders.

	MGUS	Myeloma	Plasma-cytoma	Amyloi-dosis	POEMS	Walden-ström	Cryoglo-bulinemia
Compressive:							
Radiculopathy	–	✓	✓	–	–	✓	–
Spinal cord compression	–	✓	✓	–	–	–	–
Base–of–skull tumor	–	✓	✓	–	–	–	–
Carpal tunnel syndrome	–	–	–	✓	–	–	–
Infiltrative:							
Peripheral neuropathy	–	–	–	✓	–	–	–
Autonomic neuropathy	–	–	–	✓	–	–	–
Numb chin syndrome	–	✓	–	–	–	–	–
Metabolic:							
Hypercalcemia	–	✓	–	–	–	–	–
Uremia	–	✓	–	✓	✓	–	✓
Hyperviscosity	–	✓	–	–	–	✓	✓
Autoimmune, cytokine–mediated:							
Peripheral neuropathy	✓	✓	✓	–	✓	✓	✓
Vasculitic:							
Peripheral neuropathy	–	–	–	–	–	–	✓

MGUS, monoclonal gammopathy of undetermined significance.

Dispenzieri & Kyle.Best Practice & Research Clinical Haematology. 2005;18:673–688.

Common characteristics of peripheral neuropathies in plasma cell dyscrasias

	Paraprotein	Clinical symptoms	Neuropathy pattern	Electrodiagnostic findings	Pathology
MGUS (IgM)	IgM-κ	Lower extremity numbness, ataxia, tremor	Distal, symmetric, sensory	Slow MCV, markedly prolonged DML, low TLI, conduction blocks, reduced sensory potentials	Loss of myelinated fibers with evidence of remyelination; IgM antibody bound to myelin; separation of myelin lamellae
MGUS (IgG or IgA)	IgG-κ or IgA-κ	Upper and lower extremity weakness and numbness	Proximal and distal, symmetric, sensorimotor	Slow MCV, prolonged DML	Endoneurial deposits and/or possible widening of myelin lamellae
MM	IgG-κ	Heterogeneous: weakness and/or numbness of the hands and/or feet	Heterogeneous: distal, symmetric, sensory, motor, or sensorimotor	Mild slowing of MCV, mildly reduced DL, and low-absent CMAPs and SNAPs	Axonal degeneration with occasional segmental demyelination
WM	IgM κ	Lower extremity numbness, ataxia, tremor	Distal, symmetric, sensorimotor	Reduced motor amplitude, increased fibrillation potentials	IgM antibody bound to myelin; separation of myelin lamellae
POEMS	IgG-λ	Ascending weakness, tingling, and burning	Distal, symmetric, motor > sensory	Uniform slow CV, normal TLI, no conduction blocks, reduced motor amplitude, increased fibrillation potentials	Demyelination with secondary axonal degeneration; increased thickness of the basal lamina and narrowing of endoneurial vessels; uncompacted myelin
AL amyloidosis	IgG-λ or only λ	Lower extremity tingling, burning, and weakness	Distal, symmetric, sensory followed by motor, with autonomic failure	Mild slowing of MCV, mild reduction in CMAP, mildly prolonged DL; absent SNAPs; increased fibrillation potentials	Endoneurial deposition of amyloid

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CMAP, compound muscle action potential; CV, motor nerve conduction velocity; DADS, distal acquired demyelinating syndrome; DL, distal latency; DML, distal motor latencies; MCV, mean corpuscular volume; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; TLI, terminal latency index; SNAP, sensory neuron action potential.

Rosenbaum E et al. Hematological Oncology. 2017;1–12.

MM: Symptoms.

- The most common clinical manifestations of symptomatic MM are
  - anaemia,
  - infections,
  - lytic or osteopenic bone disease,
  - renal failure,

- Patients with MM might be diagnosed at an asymptomatic stage by chance.
- Generally, MM is diagnosed at an earlier stage today than in the past.

- Back pain, particularly in older patients, or unclear anaemia should prompt screening for the presence of MM.

Table 1. Symptoms and signs of multiple myeloma at presentation.

Symptom or sign	Patients (%)
Spontaneous bone pain	66
Fatigue	32
Weight loss (>20 pounds)	12
Infection and bleeding	<15
Paresthesia	5
'Tumor fever'	<1
M protein in serum or urine	97
Lytic lesions, osteoporosis, or fracture on plain radiograph	79
Hemoglobin <12 g/dL	73
Creatinine >2 mg/dL	19
Calcium >11 mg/dL	13
Viscosity >4 cP	<7

Data compiled from Kyle RA et al (2003, *Mayo Clinic Proceedings* **78**: 21–33) with permission.

MM: Clinical presentation

- Symptoms and signs present in 5 percent or less included:
  - paresthesias (5 percent),
  - hepatomegaly (4 percent),
  - splenomegaly (1 percent),
  - lymphadenopathy (1 percent), and
  - fever (0.7 percent).
  - Pleural effusion and diffuse pulmonary involvement due to plasma cell infiltration are rare and usually occur in advanced disease.

- As the use of "routine" blood work has become more common, patients are being diagnosed earlier in the disease course.

MM: Clinical presentation.

- **Extramedullary plasmacytomas** (EP) are seen in approximately 7 % of patients with MM at the time of diagnosis, and is best diagnosed by PET/CT scan;
- An additional 6 percent of patients will develop EP later in the disease course.
- the presence of EP at diagnosis is associated with inferior survival.

Clinical entities of EMM

EMM entities	Definition	Clinical presentation
Bone-related plasmacytomas	Plasmacytomas developed from the bone, arising in continuity with the bone marrow.	Tumor masses affecting the axial skeleton: ribs, vertebrae, skull, sternum, pelvis.
Extramedullary disease	Soft-tissue plasmacytoma or PC infiltration of an anatomical site distant from the bone marrow. Secondary to a hematogenous spread.	Mainly affect the liver, skin, CNS, pleural effusion, kidneys, lymph nodes, pancreas. May be triggered by invasive procedures (ie, catheter insertion, surgical scars).
PCL	Aggressive variant of myeloma characterized by the presence of circulating plasma cells (>20% and/or absolute count $>2 \times 10^9$/L).	Could be considered as EMM because of blood involvement. Extramedullary disease is also very common in PCL patients.
SP	Localized bone or extramedullary infiltration by clonal plasma cells without systemic tumor dissemination.	Bone marrow and skeletal survey are both normal. CRAB symptoms are absent. Focal radiotherapy is the treatment of choice.

CNS, central nervous system; CRAB, hypercalcemia, renal failure, anemia, bone lesions; SP, solitary plasmacytoma.

Touzeau C. Blood. 2016;127(8):971-976

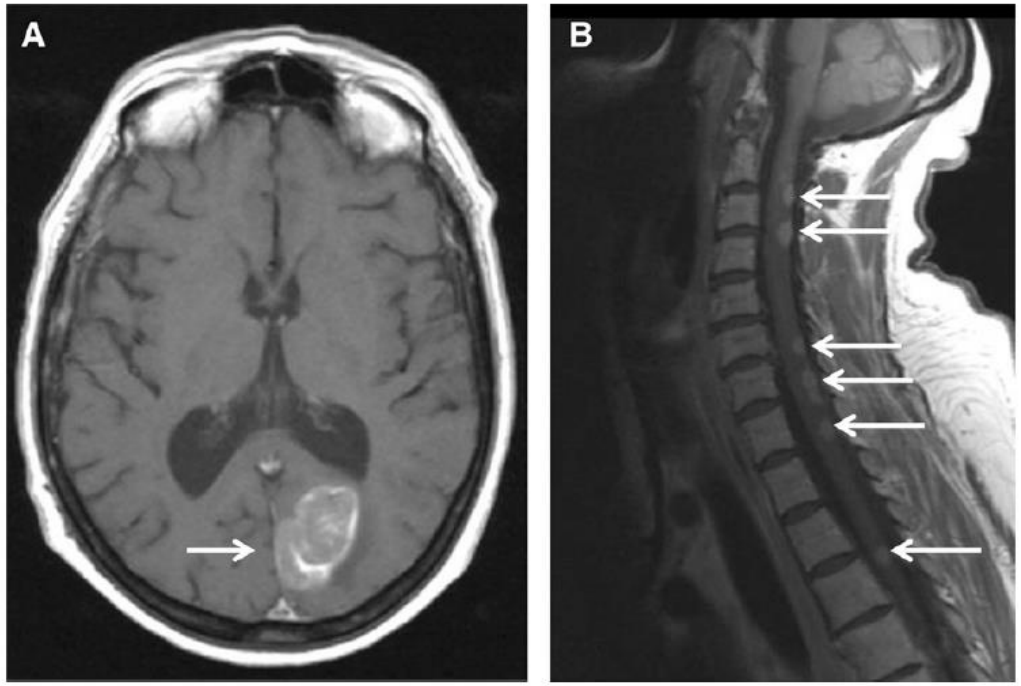
Neurologic disease

- **Radiculopathy**, usually in the thoracic or lumbosacral area, is the most common neurologic complication of MM.
- It can result from **compression** of the nerve **by a paravertebral plasmacytoma or rarely by the collapsed bone itself**.
  - **Cord compression**
    - occurs in approximately 5% of patients;
    - This set of symptoms constitutes a **medical emergency**; MRI or CT myelography of the entire spine must be performed immediately, with appropriate follow-up treatment by chemotherapy, radiotherapy, or neurosurgery to avoid permanent paraplegia.
- **Peripheral neuropathy**
    - uncommon at the time of initial diagnosis and, when present, is usually due to amyloidosis.
- **CNS involvement**
    - Intracranial plasmacytomas are rare.
    - Leptomeningeal myelomatosis is uncommon and more frequent in advanced stages

Characteristics	Summary of features
Definition	Soft-tissue plasmacytoma or PC infiltration of an anatomical site distant from the bone marrow (eg, strict extramedullary disease as defined in Table 1)
Incidence	6% to 8% in de novo patients 10% to 30% in relapsed/refractory patients
Molecular pathogenesis	$CD44^{high}$, $CD56^{low}$, CXCR4/CXCL12 Hypoxia Ras, P53, FAK mutations
Clinical characteristics	Symptoms related to organ involvement Mostly liver, skin, CNS, pleural effusion, kidneys, lymph nodes, pancreas
Biological characteristics	High LDH, anemia, thrombocytopenia High-risk gene expression profile High-risk cytogenetics (17p deletion)
Morphology	Frequent immature/plasmablastic morphology
Staging	Value of PET-CT to detect extramedullary disease CNS EMM: MRI, CSF analysis (morphology, flow cytometry, protein electrophoresis)
Prognosis	EMM is an independent adverse prognostic factor in de novo MM patients receiving intensive therapy. Few series specifically analyzed the particular outcome of EMM.

CSF, cerebrospinal fluid; CXCL, CXC chemokine ligand; CXCR, CXC chemokine receptor; FAK, focal adhesion kinase; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET-CT, positron emission tomography/computed tomography.

Extramedullary MM



MRI (T1 weighted) showing an occipital mass with leptomeningeal involvement (A, white arrow) and multiple posterior medullary lesions (B, white arrows), in a relapsed MM patient who developed progressive ataxia.

Touzeau C. Blood. 2016;127(8):971-976

Table 2. Clinical and laboratory features of plasma-cell dyscrasia-associated peripheral neuropathy.

Characteristic	MGUS	POEMS	Multiple myeloma	AL amyloidosis	Cryoglobulinemia
Peripheral neuropathy	~5%	100%	1–8%	15–20%	~25%
Sensory versus motor predominance	Sensory, ataxia (IgM) sensorimotor[a]	Predominantly motor	Sensory	Sensory, sensorimotor	Predominantly sensory
Organomegaly	−	++	+	++	++
Skin involvement	−	++	+	+	+++
Other symptoms	Asymptomatic	Edema, fatigue, endocrine abnormalities	Bone pain, fatigue, infections	Fatigue, edema, cardiomyopathy, nephrosis	Purpura, arthralgia, hepatitis, nephritis
Monoclonal heavy chain	IgM>IgG>IgA	IgG>IgA>IgM	IgG>IgA	IgG>IgA>IgM	IgM>>IgG>IgA
Monoclonal light chain	κ 65% of cases	λ>95% of cases	κ 65% of cases	λ 75% of cases	κ 75% of cases
Serum M-spike, gm/dl	<3	Usually <2	Usually>3	Usually<2	Usually<2
BM plasma cells, %	<10	Usually <5	>10	Usually <10	Usually <5
Skeletal lesions	−	+++ (sclerotic, mixed sclerotic and lytic)	+++ (lytic, osteoporotic, or fracture)	−	−
Thrombocytosis	−	++	−	+ to ++	+
Anemia	−	+	++	+	++

MGUS, monoclonal gammopathy of undetermined significance; BM, bone marrow. −, absent; +, rare, ++; occurs frequently; +++, almost always present.

[a] See also Table 3.

Dispenzieri & Kyle. Best Practice & Research Clinical Haematology. 2005;18:673–688.

Clinical presentation.

- **Coagulation abnormalities**.
  - MM can be associated with hemostatic abnormalities, either bleeding or thrombosis.
  - Bleeding/thrombosis may be present in as many as one third of patients and is related to thrombocytopenia, uremia, hyperviscosity, interference with coagulation factors and treatments.

- **Hypercalcemia**.
  - Rates of hypercalcemia at presentation have been decreasing in the last few decades, suggesting earlier diagnosis (rates from 18-30% to less than 10%)
  - Hypercalcemia often causes renal insufficiency.

Causes of hypercalcemia

Parathyroid mediated
Primary hyperparathyroidism (sporadic)
Inherited variants
Multiple endocrine neoplasia (MEN) syndromes
Familial isolated hyperparathyroidism
Hyperparathyroidism-jaw tumor syndrome
Familial hypocalciuric hypercalcemia
Tertiary hyperparathyroidism (renal failure)
Non-parathyroid mediated
Hypercalcemia of malignancy
PTHrp
Activation of extrarenal 1 alpha-hydroxylase (increased calcitriol)
Osteolytic bone metastases and local cytokines
Vitamin D intoxication
Chronic granulomatous disorders
Activation of extrarenal 1 alpha-hydroxylase (increased calcitriol)
Medications
Thiazide diuretics
Lithium
Teriparatide
Excessive vitamin A
Theophylline toxicity
Miscellaneous
Hyperthyroidism
Acromegaly
Pheochromocytoma
Adrenal insufficiency
Immobilization
Parenteral nutrition
Milk alkali syndrome

PTHrp: PTH-related peptide.

Adapted from: Khairallah W, Fawaz A, Brown EM, and El-Hajj Fuleihan G. Hypercalcemia and diabetes insipidus in a patient previously treated with lithium. Nat Clin Pract Nephrol 2007; 3:397.

Malignancies associated with hypercalcemia

Osteolytic metastases:
Breast cancer
Multiple myeloma
Lymphoma
Leukemia
Humoral hypercalcemia (PTHrP):
Squamous cell carcinomas
Renal carcinomas
Bladder carcinoma
Breast cancer
Ovarian carcinoma
Non-Hodgkin lymphoma
CML
Leukemia
Lymphoma

1,25-dihydroxyvitamin D:
Lymphoma (Non-Hodgkin, Hodgkin, lymphomatosis/granulomatosis)
Ovarian dysgerminomas
Ectopic PTH sectretion:
Ovarian carcinoma
Lung carcinomas
Neuroectodermal tumor
Thyroid papillary carcinoma
Rhabdomyosarcoma
Pancreatic cancer

Clinical manifestations of hypercalcemia

Renal
Polyuria
Polydipsia
Nephrolithiasis
Nephrocalcinosis
Distal renal tubular acidosis
Nephrogenic diabetes insipidus
Acute and chronic renal insufficiency
Gastrointestinal
Anorexia, nausea, vomiting
Bowel hypomotility and constipation
Pancreatitis
Peptic ulcer disease

Musculoskeletal
Muscle weakness
Bone pain
Osteopenia/osteoporosis
Neurologic
Decreased concentration
Confusion
Fatigue
Stupor, coma
Cardiovascular
Shortening of the QT interval
Bradycardia
Hypertension

Treatment of hypercalcemia

Intervention	Mode of action	Onset of action	Duration of action
Isotonic saline hydration	Restoration of intravascular volume Increases urinary calcium excretion	Hours	During infusion
Calcitonin	Inhibits bone resorption via interference with osteoclast function Promotes urinary calcium excretion	4 to 6 hours	48 hours
Bisphosphonates	Inhibit bone resorption via interference with osteoclast recruitment and function	24 to 72 hours	2 to 4 weeks
Loop diuretics*	Increase urinary calcium excretion via inhibition of calcium reabsorption in the loop of Henle	Hours	During therapy
Glucocorticoids	Decrease intestinal calcium absorption Decrease 1,25-dihydroxyvitamin D production by activated mononuclear cells in patients with granulomatous diseases or lymphoma	2 to 5 days	Days to weeks
Denosumab	Inhibits bone resorption via inhibition of RANKL	4 to 10 days	4 to 15 weeks
Calcimimetics	Calcium sensing receptor agonist, reduces PTH (parathyroid carcinoma, secondary hyperparathyroidism in CKD)	2 to 3 days	During therapy
Dialysis	Low or no calcium dialysate	Hours	During treatment

PTH: parathyroid hormone; RANKL: receptor activator of the nuclear factor kappa-B ligand: CKD: chronic kidney disease.
* Loop diuretics should not be used routinely. However, in patients with renal insufficiency or heart failure, judicious use of loop diuretics may be required to prevent fluid overload during saline hydration.

Data from: Shane E, Dinaz I. Hypercalcemia: pathogenesis, clinical manifestations, differential diagnosis, and management. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism (Sixth Edition). American Society of Bone and Mineral Research 2006; 179.

	Test
Blood	Serum protein electrophoresis and immunofixation Serum immunoglobulins quantitative Serum free light chain assay Total serum protein, serum albumin, creatinine, calcium, electrolytes, lactate dehydrogenase, β2-microglobulin Haemoglobin, white blood cell count, differential count, platelet count
Urine	Urine protein electrophoresis and immunofixation 24 h urine for total protein, light chains
Bone marrow	Aspirate and biopsy for plasma cell count, morphology, amyloid* Cytogenetic evaluation and fluorescence in-situ hybridisation for the detection of del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q+
Bones	Skeletal survey (conventional x-ray) or low-dose CT scan without contrast
Whole body	MRI*, PET-CT* Tissue biopsy for solitary or extraosseous plasmacytoma*

*Useful under some circumstances.

Table 1: Diagnostic workup for multiple myeloma

Rollig C et al. Lancet 2015; 385: 2197–208

Table 2. Recommendations on further examinations at diagnosis, for response assessment, during follow-up and at relapse.

Diagnostic site	Tool	Diagnosis	At response	At follow-up	At relapse
	BM cytology and biopsy to confirm plasmacytosis and monoclonality	Obligatory	Obligatory*	Not required	Obligatory**
Bone marrow	Flow cytometry	Recommended	Optional	Not required	Optional
	Cytogenetics	Obligatory	Not required	Not required	Optional
Blood	Advanced techniques: GEP, NGS	Optional	Not required	Not required	Not required
	Blood count and blood smear	Obligatory	Obligatory	Obligatory	Obligatory
	Serum electrophoresis and IF	Obligatory	Obligatory	Obligatory	Obligatory
	Serum free light chain	Recommended ***	Recommended ***	Recommended ***	Recommended ***
	Serum immunoglobulin levels	Obligatory	Obligatory	Obligatory	Obligatory
	Renal and liver function tests	Obligatory	Obligatory	Obligatory	Obligatory
	Calcium	Obligatory	Obligatory	Obligatory	Obligatory
	Lactate dehydrogenase	Obligatory	Obligatory	Obligatory	Obligatory
	Albumin, β2-microglobulin	Obligatory	Recommended	Recommended	Obligatory
Urine	Urine sample to check for proteinuria and Bence-Jones proteins	Obligatory	Obligatory	Obligatory	Obligatory
	24 h urine collection	Recommended†	Recommended†	Recommended†	Recommended†
Imaging	Low dose whole-body CT	Recommended††	Not required	When symptomatic	Recommended
	PET/CT	Optional	Optional†††	When symptomatic	Optional
	Whole-body MRI	Optional	Not required	When symptomatic	Optional

BM: bone marrow; GEP: gene expression profiling; IF: immunofixation; NGS: next generation sequencing; CT: computed tomography; PET: positron emission tomography; MRI: magnetic resonance imaging; *Obligatory for patients in complete response. **Obligatory for patients with light chain escape, oligosecretory disease, *** SFLC monitoring is obligatory for patients with light-chain disease. †Obligatory in the case of proteinuria. ††Obligatory when radiographs do not show osteolytic lesions †††PET/CT is required for confirmation of minimal residual disease negativity.

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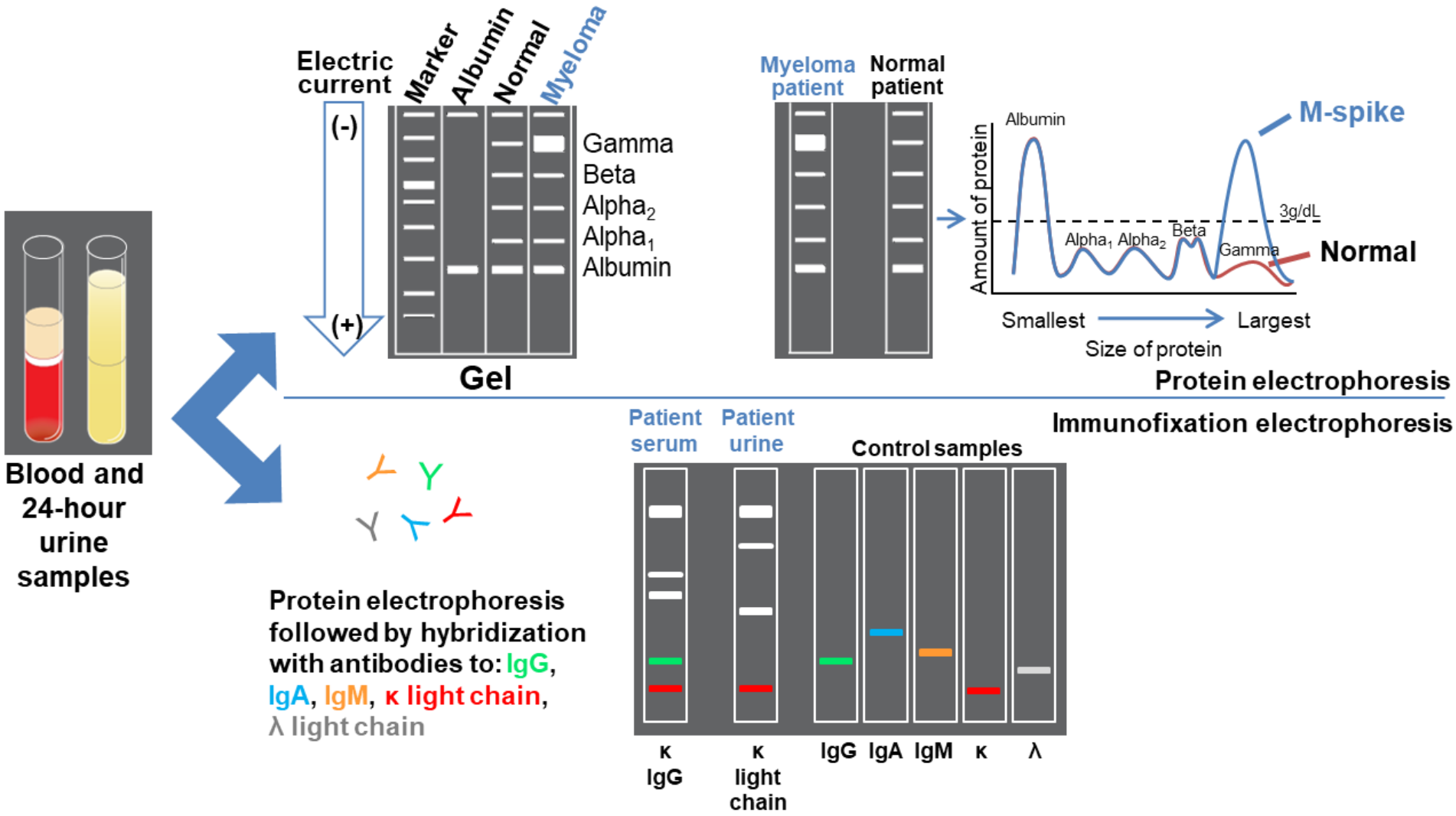
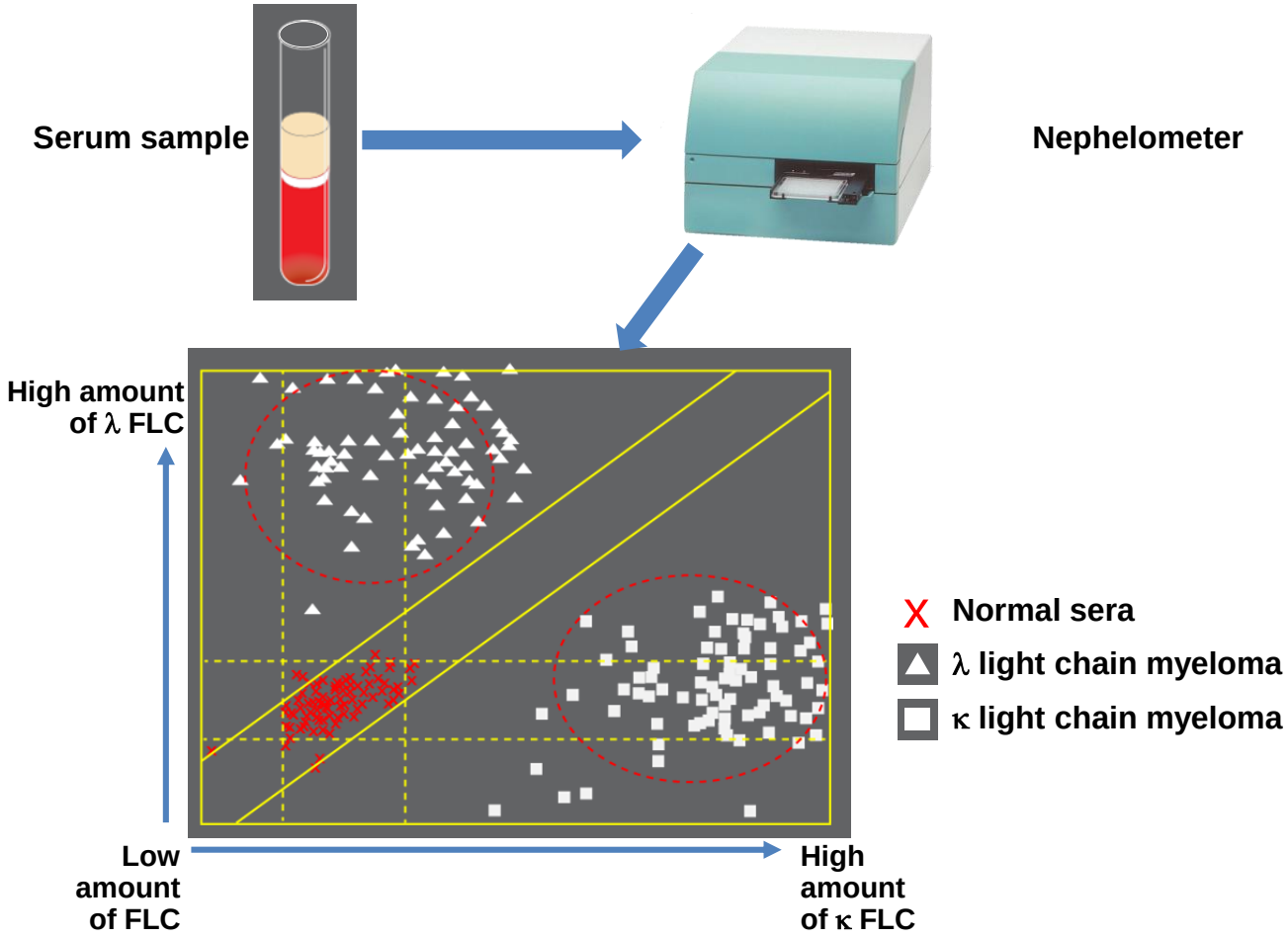
Monoclonal Gammopathies: Protein electrophoresis and immunofixation



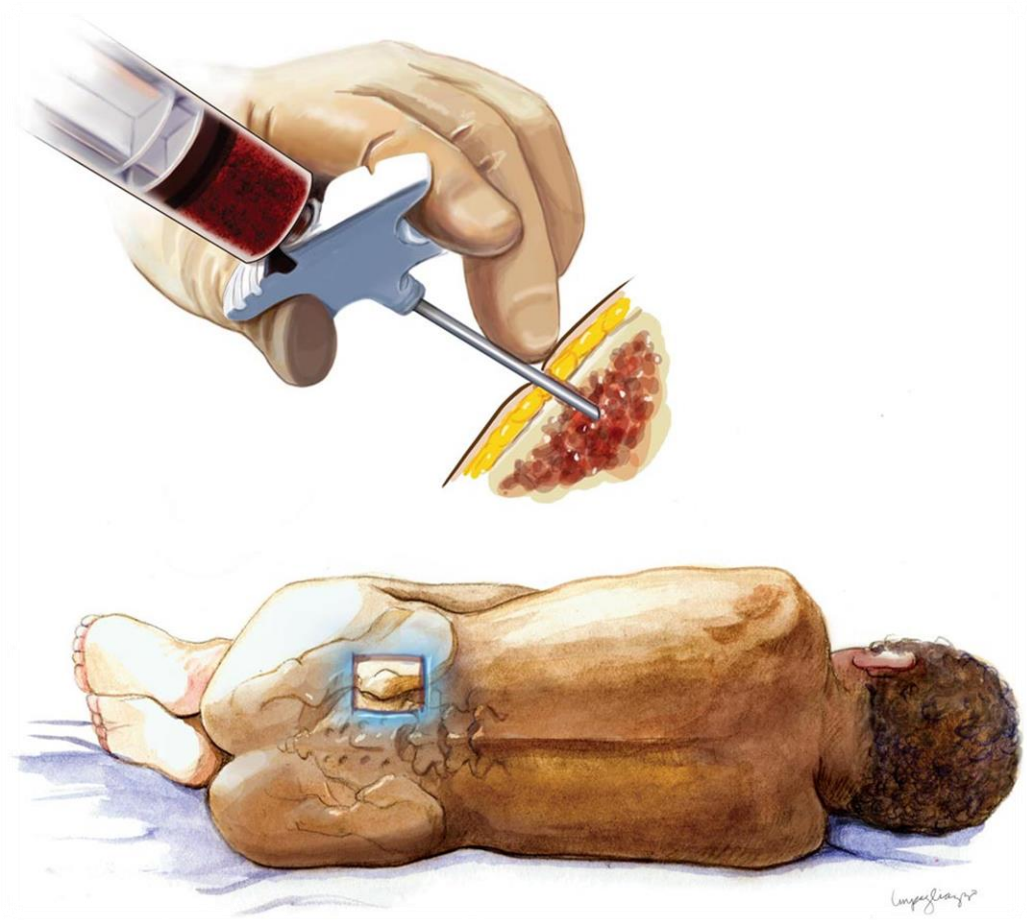
Mayo Clinic. Test ID: PEL: Electrophoresis, Protein, Serum. Available at: www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/80085. Accessed March 2016; Lab Tests Online. Protein Electrophoresis, Immunofixation Electrophoresis.
Available at: https://labtestsonline.org/understanding/analytes/electrophoresis/tab/test. Accessed March 2016.

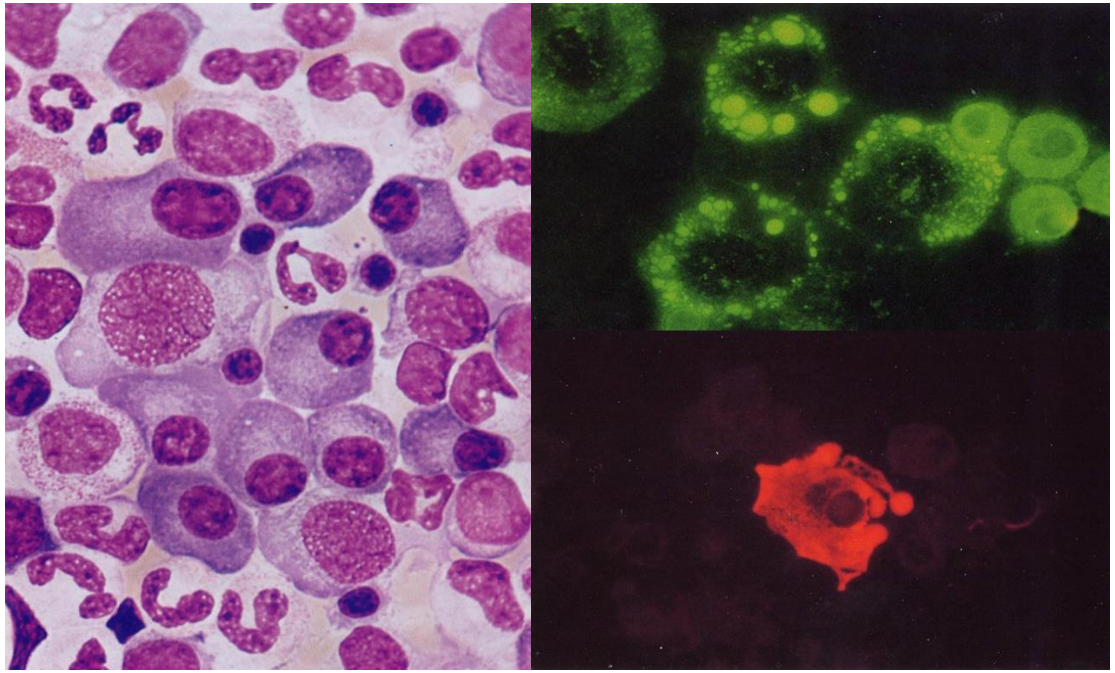
Establishing diagnosis: Free light chain assay



Bradwell. Lancet. 2003;361:489

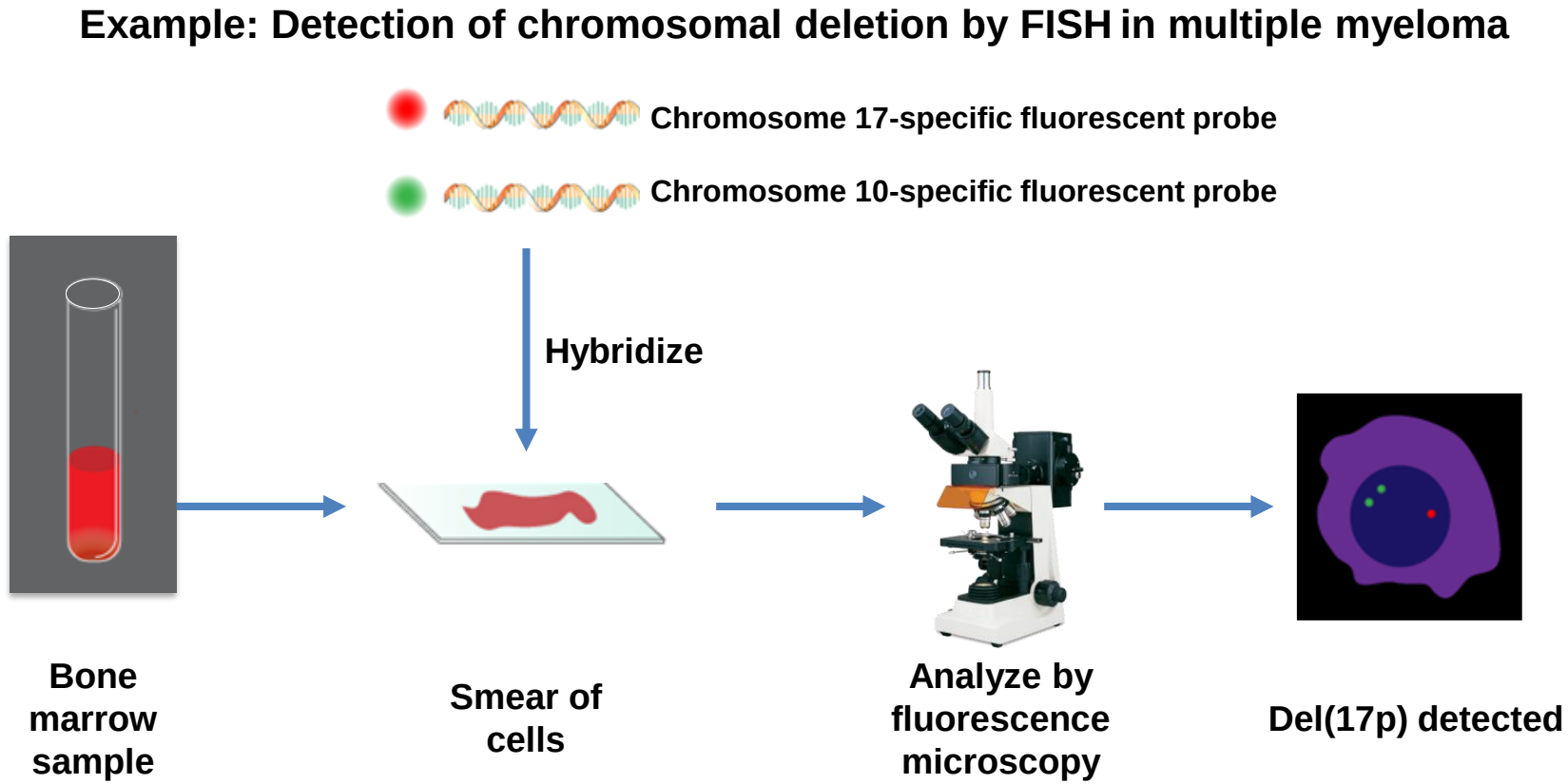
Establishing diagnosis: Bone marrow assessment





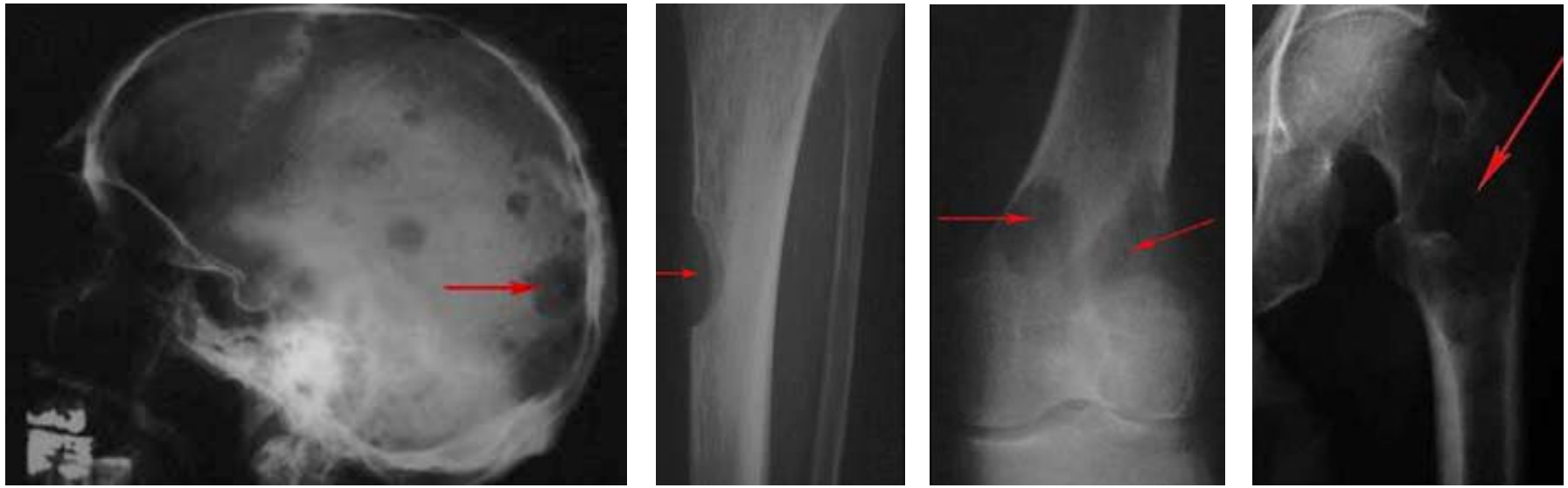
Mayo Clinic. Bone marrow biopsy and aspiration. Available at: www.mayoclinic.com/health/medical/IM01819. Accessed March 2016.

Determining prognosis: Assessment of genetic abnormalities by FISH



Adapted from O'Connor. Nature Education. 2008;1:171.

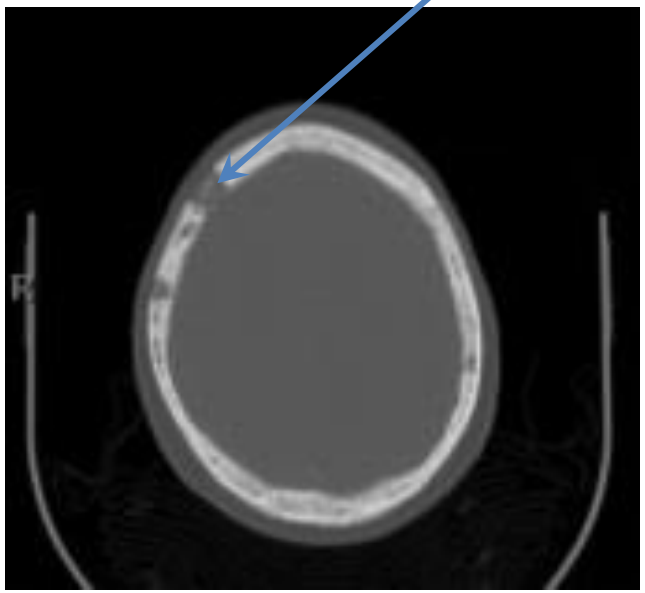
Establishing diagnosis: Skeletal survey



CT imaging and MRI are useful in the evaluation of lesions in suspected MM

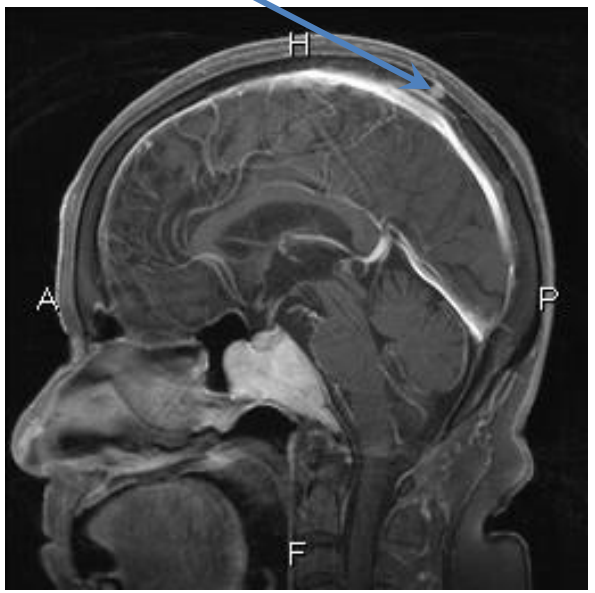
CT[1]

Bone lesion



MRI[2]

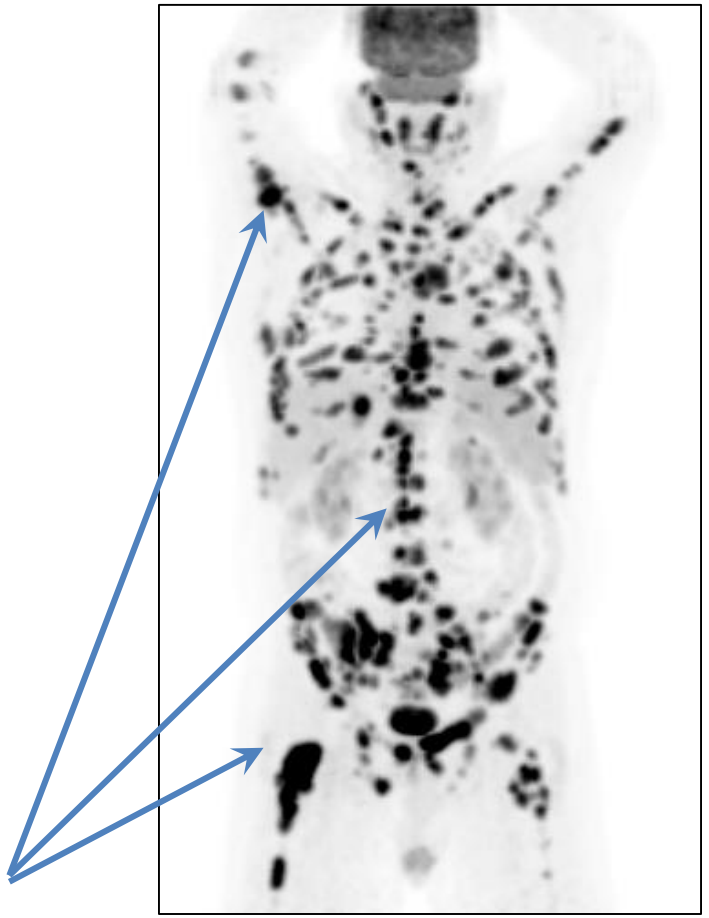
Plasmacytoma



1. Talamo. Bone lesions. Available at: http://www.myelomapennstate.net/Contents/04a-ClinManifest.htm. Accessed March 2016;
2. Terada. Cases J. 2009;2:9110.

PET

- PET provides a whole body image and shows only active MM lesions
- PET is useful in the diagnostic work-up and in determining response to treatment



Talamo. Evaluation of bone disease. Available at: http://www.myelomapennstate.net/Contents/10a-BoneDis-PET.htm. Accessed March 2016.

MM & PET

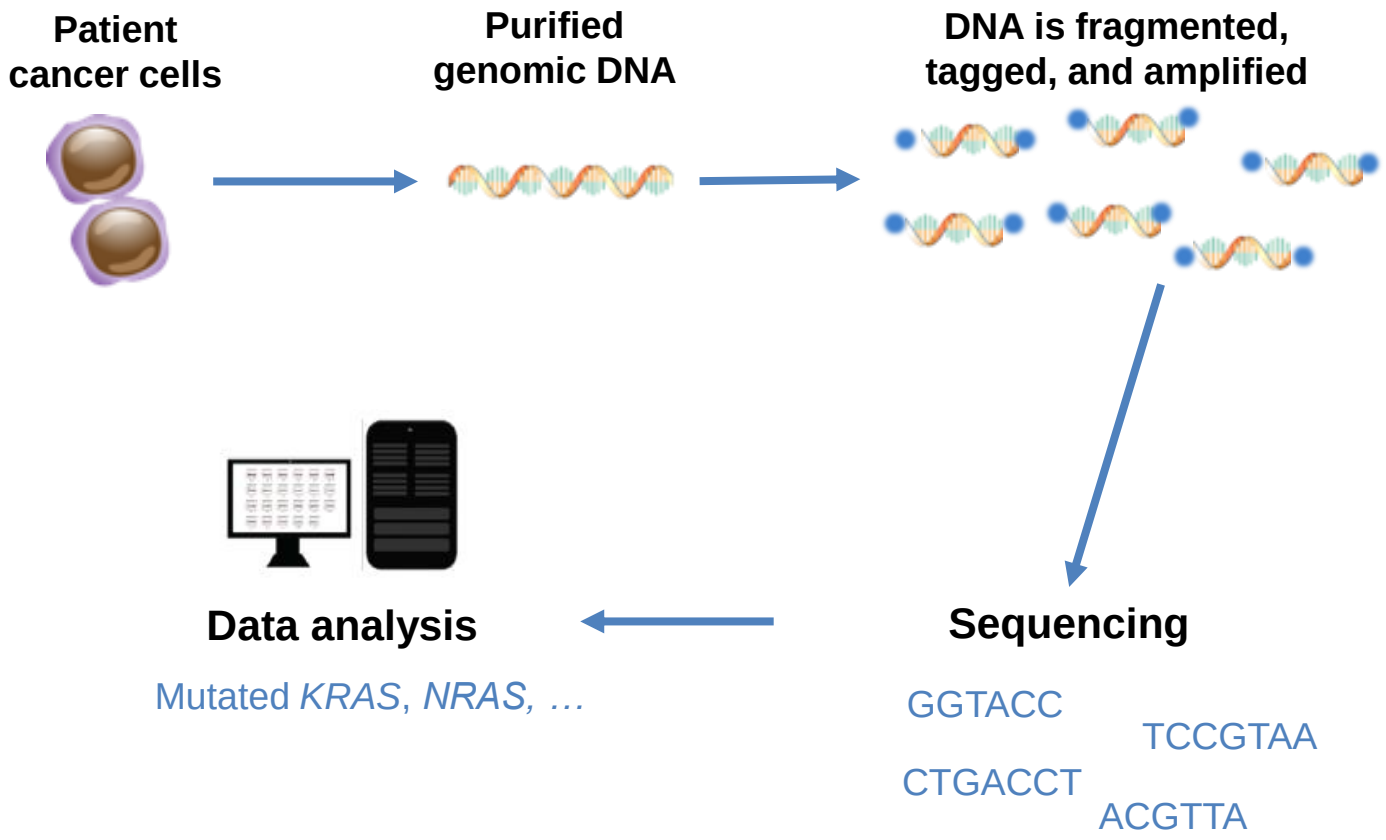
	Grade
Active multiple myeloma	
^{18}F-FDG PET/CT should be considered as part of the initial investigations in patients with newly diagnosed multiple myeloma because it provides information useful for prognostication and allows to more carefully assess the bulk of the disease, particularly in patients with extramedullary sites of the disease; assessing the bulk of the disease with ^{18}F-FDG PET/CT also applies to patients with relapsed or refractory multiple myeloma	B
In patients with newly diagnosed multiple myeloma, with or without EMD, and more than three focal lesions, ^{18}F-FDG PET/CT identifies subgroups of patients with unfavourable outcomes; controversies exist about the prognostic role of SUV_{max}	B
^{18}F-FDG PET/CT is now the preferred technique for evaluating and monitoring response to therapy; metabolic changes assessed by ^{18}F-FDG PET/CT provide an earlier evaluation of response compared with MRI	A
^{18}F-FDG PET/CT should be coupled with sensitive bone marrow-based assays as part of minimal residual disease detection inside and outside the bone marrow	B
Smouldering multiple myeloma	
Patients who meet the diagnostic criteria for smouldering multiple myeloma and have one or more lytic lesions on ^{18}F-FDG PET/CT should be defined as having multiple myeloma that requires immediate therapy	A
^{18}F-FDG PET/CT is recommended to distinguish smouldering multiple myeloma from active multiple myeloma if whole-body X-ray is negative and whole-body MRI is unavailable	A
Solitary plasmacytoma	
Patients with focal lesions on PET but without underlying lytic lesions on the CT part of ^{18}F-FDG PET/CT are at high risk of progression to active multiple myeloma	B
Patients with suspected solitary plasmacytoma, either extramedullary plasmacytoma or solitary bone plasmacytoma without symptoms or signs suggestive of cord compression, should receive ^{18}F-FDG PET/CT to unequivocally confirm the diagnosis, provided whole-body MRI is unavailable	A

^{18}F-FDG= ^{18}F-fluorodeoxyglucose. EMD=extramedullary disease. ASCT=autologous stem-cell transplantation. SUV=standardised uptake value.

Table 5: Recommendations for the use of ^{18}F-FDG PET/CT in patients with multiple myeloma and other plasma cell disorders

Cavo et al. Lancet Oncol 2017; 18: e206–17

Determining prognosis: Next-generation sequencing



Johnsen. Blood. 2013;122:3286; Kakkar Basho. Am J Hematol Oncol. 2015;11:17; Chapman. Nature. 2011;471:467.

Diagnostic criteria

- The diagnosis of MGUS, SMM and MM requires

1. the detection of serum monoclonal protein levels,

2. assessment of the bone marrow

3. Assessment of myeloma-defining events (MDEs) including
   - biomarker assessment
   - the presence or absence of CRAB features.

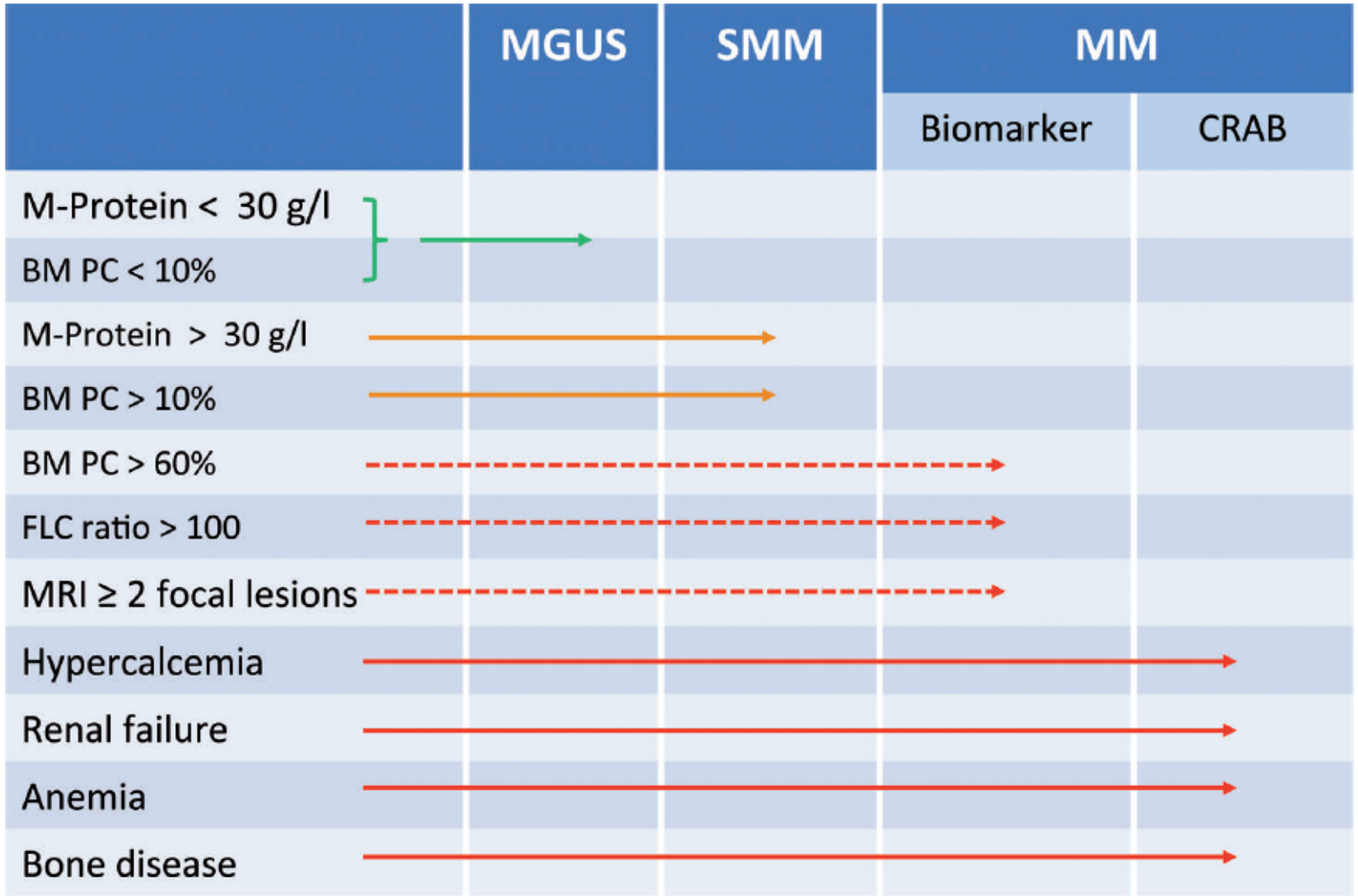


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Figure 1. The differential diagnosis between monoclonal gammopathy of undetermined significance, smoldering myeloma and multiple myeloma. The discrimination between these monoclonal gammopathies is based on: (i) the plasma cell infiltration in the bone marrow, (ii) the presence of clinical symptoms related to myeloma disease and (iii) the existence of biomarkers of disease that allow initiation of treatment. MGUS: monoclonal gammopathy of undetermined significance; SMM: smoldering multiple myeloma; MM: multiple myeloma; BM: bone marrow; PC: plasma cells; FLC: free light chain; MRI: magnetic resonance imaging.

CRAB features

- Hyper**C**alcaemia:
  - serum calcium >1 mg/ dl higher than the upper limit of normal levels (>11 mg/dl)
- **R**enal insufficiency:
  - creatinine clearance of <40 ml/min or serum creatinine >2 mg/dl
- **A**naemia:
  - Hb levels of >2 g/dl below the lower limit of normal levels (<10 g/dl)
- **B**one lytic lesions:
  - the presence of one or more lytic lesions detected by conventional radiology, CT imaging (or low-dose CT) or PET–CT

Myeloma Defining Events (MDE)*

1. CRAB features
2. A clonal bone marrow plasma cell percentage of ≥60%
3. An involved-to-uninvolved serum free light-chain ratio of ≥100
4. Two or more focal lesions on MRI (at least 5 mm in size)

- *If there is no end-organ damage, the presence of one or more biomarker is sufficient for diagnosis

Diagnostic criteria for MM

- **Both criteria must be met**

1. Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma

2. Any one or more of the myeloma defining events (MDE)

Rajkumar SV, et al. Lancet Oncol 2014;15:e538–e548.

Diagnostic criteria for Smoldering MM

- **Both criteria must be met:**

1. Serum monoclonal protein (IgG or IgA) ≥3 g/dL, or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10%–60%

2. Absence of myeloma defining events or amyloidosis

Rajkumar SV, et al. Lancet Oncol 2014;15:e538–e548.

Non-IgM MGUS

All 3 criteria must be met:

1. Serum monoclonal protein (non-IgM type) <3 g/dL
2. Clonal bone marrow plasma cells <10%
3. Absence of end-organ damage (CRAB) that can be attributed to the plasma cell proliferative disorder

Rajkumar SV, et al. Lancet Oncol 2014;15:e538–e548.

IgM MGUS

- **All 3 criteria must be met:**

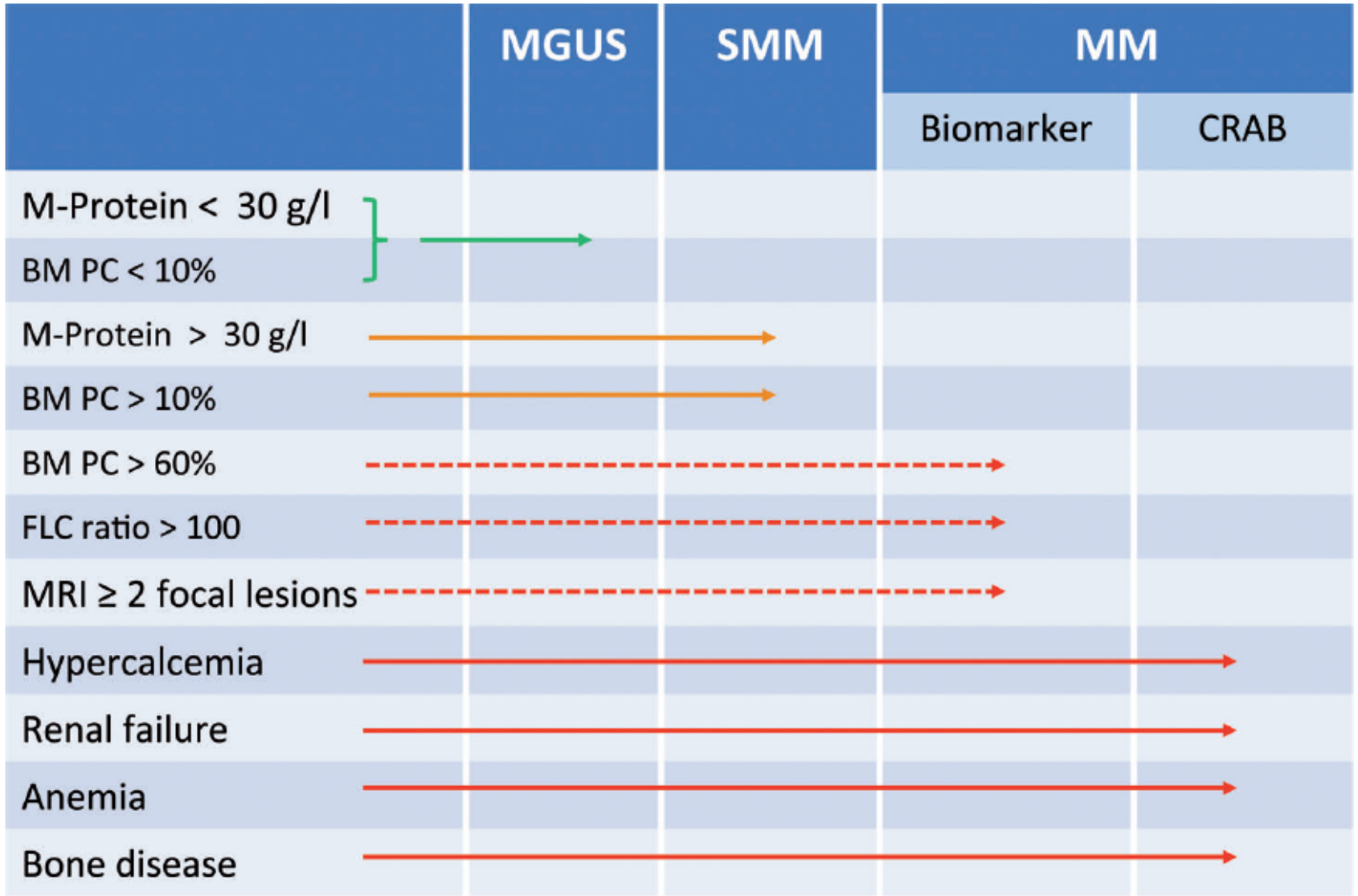
1. Serum IgM monoclonal protein <3 g/dL
2. Bone marrow lymphoplasmacytic infiltration <10%
3. No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder.

Rajkumar SV, et al. Lancet Oncol 2014;15:e538–e548.

Light Chain MGUS

- **All criteria must be met:**
  1. Abnormal FLC ratio (<0.26 or >1.65)
  2. Increased level of the appropriate involved light chain (increased k FLC in patients with ratio >1.65 and increased λ FLC in patients with ratio <0.26)
  3. No Ig heavy chain expression on immunofixation
  4. Absence of end-organ damage that can be attributed to the plasma cell proliferative disorder
  5. Clonal bone marrow plasma cells <10%
  6. Urinary monoclonal protein <500 mg/24 h

Rajkumar SV, et al. Lancet Oncol 2014;15:e538–e548.



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Solitary plasmacytoma

- **All 4 criteria must be met**
  1. Biopsy proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells
  2. Normal bone marrow with no evidence of clonal plasma cells
  3. Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion)
  4. Absence of end-organ damage (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder

Rajkumar SV, et al. Lancet Oncol 2014;15:e538–e548.

Solitary Plasmacytoma with minimal marrow involvement

- **All 4 criteria must be met**
  1. Biopsy proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells
  2. Clonal bone marrow plasma cells <10%
  3. Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion)
  4. Absence of end-organ damage (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder

Rajkumar SV, et al. Lancet Oncol 2014;15:e538–e548.

Feature	MGUS	SMM	Multiple myeloma
Serum monoclonal protein levels	<3 g per dl and	≥3 g per dl and/or	–
Clonal BMPC infiltration*	<10%	10–60%	≥10% or a biopsy-proven plasmacytoma‡
Symptomatology	Absence of CRAB features	Absence of MDE or amyloidosis	Presence of MDE

*The clonality of BMPCs has to be established by restriction of the light chain, kappa or lambda, by flow cytometry, immunohistochemistry or immunofluorescence. Assessing the infiltration of these cells into bone marrow should be done by morphology, either in the aspirate or biopsy. ‡If the BMPC infiltration is <10%, more than one lytic lesion is required to confirm a diagnosis of multiple myeloma.

Kumar SK et al. Nature Reviews Disease Primers. 2017;3:1

TABLE II. Primary Molecular Cytogenetic Classification of Multiple Myeloma

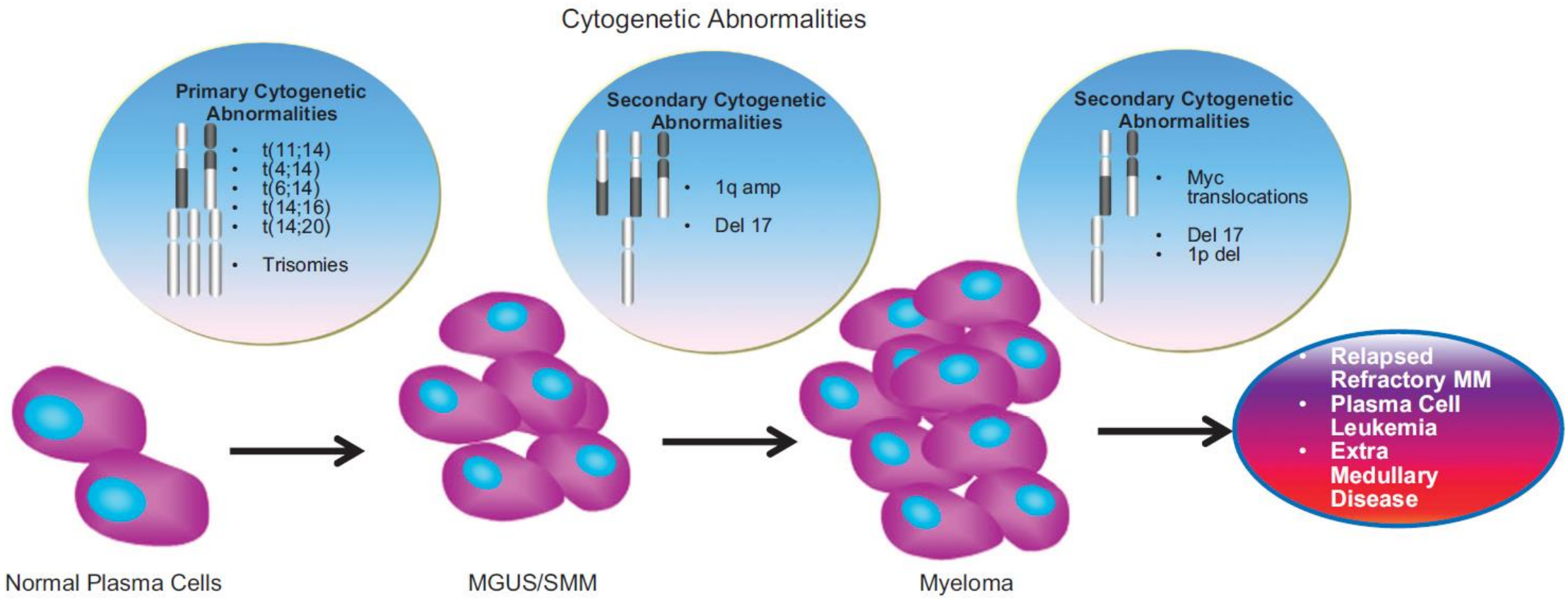
Subtype	Gene(s)/chromosomes affected[a]	Percentage of myeloma patients
Trisomic MM	Recurrent trisomies involving odd-numbered chromosomes with the exception of chromosomes 1, 13, and 21	***42***
IgH translocated MM		***30***
t(11;14) (q13;q32)	*CCND1* (cyclin D1)	15
t(4;14) (p16;q32)	*FGFR-3* and MMSET	6
t(14;16) (q32;q23)	*C-MAF*	4
t(14;20) (q32;q11)	*MAFB*	<1
Other IgH translocations[a]	*CCND3* (cyclin D3) in t(6;14) MM	5
Combined IgH translocated/trisomic MM	Presence of trisomies and any one of the recurrent IgH translocations in the same patient	***15***
Isolated Monosomy 14	Few cases may represent 14q32 translocations involving unknown partner chromosomes	***4.5***
Other cytogenetic abnormalities in absence of IgH translocations or trisomy or monosomy 14		***5.5***
Normal		***3***

Modified from Kumar S et al. Trisomies in multiple myeloma: impact on survival in patients with high-risk cytogenetics. Blood 2012; 119:2100. © American Society of Hematology.

[a] Includes the t(6;14)(p21;q32) translocation, and rarely, other IgH translocations involving uncommon partner chromosomes.

Rajkumar SV. AJH 2016;91:720-734

Cytogenetic abnormalities in MM



Trisomies, or any one IgH translocation, or combined trisomies and IgH translocations are associated with the establishment of the clone	Secondary Cytogenetic Abnormalities occur with progression; Del 17p, 1qamp, and t(4;14) associated with high risk of progression in SMM	Secondary Cytogenetic Abnormalities occur with progression; Del 17p, t(14;16) and t(14;20) associated with adverse prognosis in MM

Rajan AM. Blood Cancer Journal. 2015;5:e365.

TABLE III. Cytogenetic Abnormalities on Clinical Course and Prognosis in Multiple Myeloma

	Clinical setting in which abnormality is detected	
Cytogenetic abnormality	Smoldering multiple myeloma	Multiple myeloma
Trisomies	Intermediate-risk of progression, median TTP of 3 years	Good prognosis, standard-risk MM, median OS 7–10 years Most have myeloma bone disease at diagnosis Excellent response to lenalidomide-based therapy
t(11;14) (q13;q32)	Standard-risk of progression, median TTP of 5 years	Good prognosis, standard-risk MM, median OS 7–10 years
t(6;14) (p21;q32)	Standard-risk of progression, median TTP of 5 years	Good prognosis, standard-risk MM, median OS 7–10 years
t(4;14) (p16;q32)	High-risk of progression, median TTP of 2 years	Intermediate-risk MM, median OS 5 years Needs bortezomib-based initial therapy, early ASCT (if eligible), followed by bortezomib-based consolidation/maintenance
t(14;16) (q32;q23)	Standard-risk of progression, median TTP of 5 years	High-risk MM, median OS 3 years Associated with high levels of FLC and 25% present with acute renal failure as initial MDE
t(14;20) (q32;q11)	Standard-risk of progression, median TTP of 5 years	High-risk MM, median OS 3 years
Gain(1q21)	High-risk of progression, median TTP of 2 years	Intermediate-risk MM, median OS 5 years
Del(17p)	High-risk of progression, median TTP of 2 years	High-risk MM, median OS 3 years
Trisomies plus any one of the IgH translocations	Standard-risk of progression, median TTP of 5 years	May ameliorate adverse prognosis conferred by high risk IgH translocations, and del 17p
Isolated Monosomy 13, or Isolated Monosomy 14	Standard-risk of progression, median TTP of 5 years	Effect on prognosis is not clear
Normal	Low-risk of progression, median TTP of 7-10 years	Good prognosis, probably reflecting low tumor burden, median OS >7–10 years

FISH, fluorescent in situ hybridization; TTP, time to progression; OS, overall survival; SMM, Smoldering multiple myeloma, MM, multiple myeloma; ASCT, autologous stem cell transplantation.

Reproduced from Rajan AM, Rajkumar SV. Blood Cancer J 2015;5:e365.

Rajkumar SV. AJH 2016;91:720-734

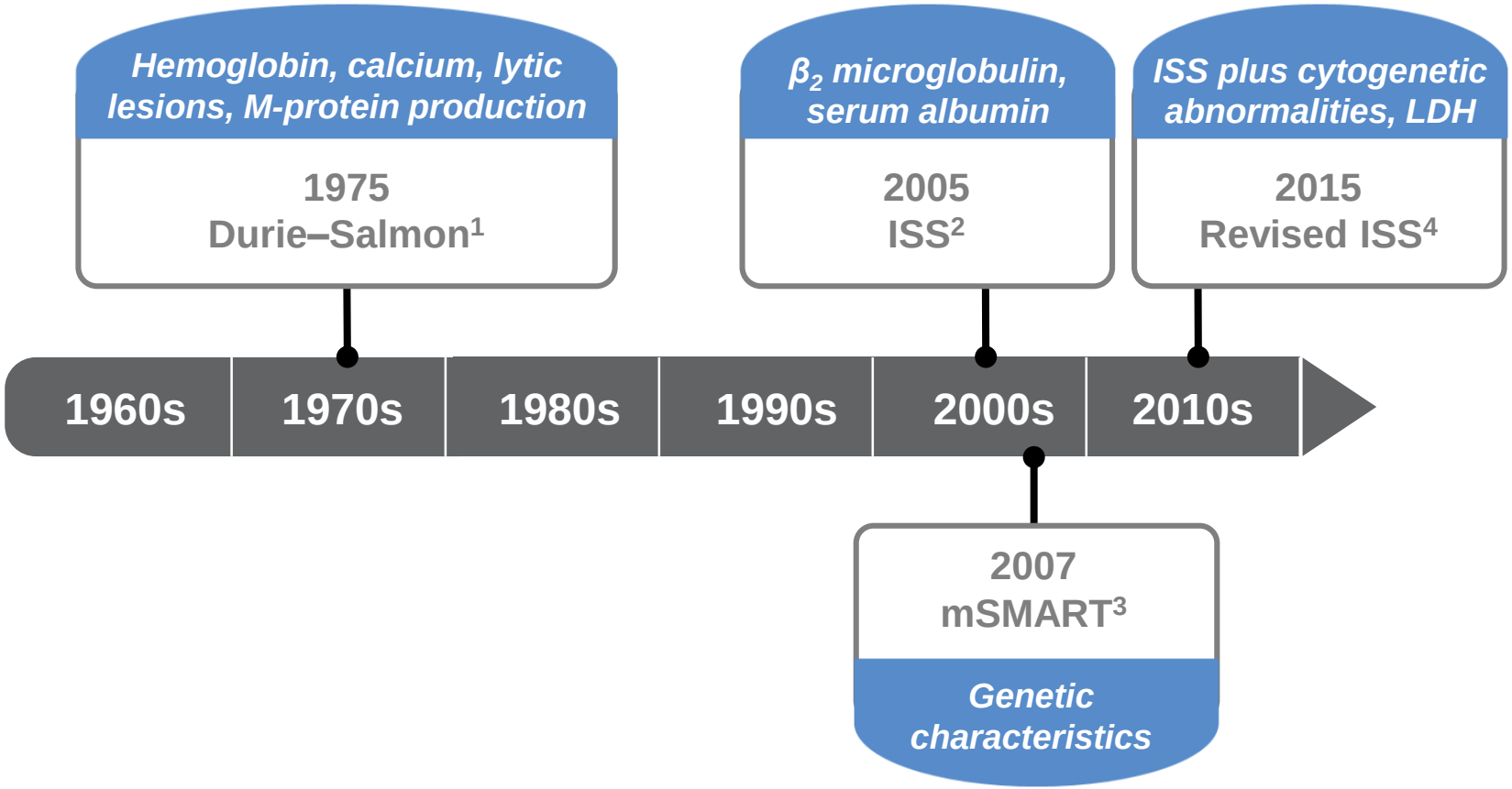
Table 3. Cytogenetic risk stratification of myeloma

Risk stratification	*Cytogenetic abnormalities*
Standard risk[a]	Trisomies
	t(11;14)
	t(6;14)
Intermediate risk[a]	t(4;14)
	Gain(1q21)
High risk	Del(17p)
	t(14;16)
	t(14;20)
	Del(1p)

Modified from Rajkumar.[1] [a]Presence of del 17p indicates high risk MM regardless of other abnormalities; gain(1q21) (without other high risk abnormalities) is considered intermediate-risk.

Rajan AM. Blood Cancer Journal. 2015;5:e365.

Staging and risk stratification has evolved with improved understanding of disease biology



1. Durie. Cancer. 1975;36:842; 2. Greipp. J Clin Oncol. 2005;23:3412;
3. Kumar. Mayo Clin Proc. 2009;84:1095; 4. Palumbo. J Clin Oncol. 2015;33:2863.

ISS, International Staging System.

Table 2 Durie-Salmon Staging System and International Staging System

	Durie-Salmon[44]		ISS[45]	
Stage	Criteria	Measured Myeloma Cell Mass (Cells × $10^{12}/m^2$)	Criteria	Median Survival
I	All of the following: 1. Hb >10 g/100 mL 2. Normal serum calcium value (≤ 12 mg/100 mL) 3. Normal bone structure (scale 0) or solitary plasmacytoma on bone x-ray 4. Low M-component production rates: a. IgG value < 5 g/100 mL b. IgA value < 3 g/100 mL c. Urine light chain M component on electrophoresis < 4 g/24 h	< 0.6 (low)	Serum β_2-microglobulin < 3.5 mg/dL and serum albumin ≥ 3.5 g/dL	62 mo
II	Fitting neither stage I nor stage III	0.6 - 1.2 (intermediate)	Not stage I or III[a]	44 mo
III	One or more of the following: 1. Hb < 8.5 g/100 mL 2. Serum calcium value > 12 mg/100 mL 3. Advanced lytic lesions (scale 3) on bone x-ray 4. High M-component production rates: a. IgG value > 7 g/100 mL b. IgA value > 5 g/100 mL c. Urine light chain M component on electrophoresis >12 g/24 h	> 1.2 (high)	Serum β_2-microglobulin ≥ 5.5 mg/dL	29 mo

[a]There are two categories for stage II: serum β_2-microglobulin < 3.5 mg/dL but serum albumin < 3.5 g/dL; and serum β_2-microglobulin 3.5 to < 5.5 mg/dL irrespective of serum albumin level.

ISS = International Staging System.

TABLE 3. Revised International Staging System for Myeloma

Stage	Frequency (% of Patients)	5-Year Survival Rate (%)
Stage I	28	82
ISS stage I (serum albumin > 3.5, serum beta-2-microglobulin < 3.5) and		
No high-risk cytogenetics		
Normal LDH		
Stage II	62	62
Neither stage I or III		
Stage III	10	40
ISS stage III (serum beta-2-microglobulin > 5.5) and		
High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] or elevated LDH		

Abbreviations: LDH, lactate dehydrogenase; ISS, International Staging System.
Derived from Palumbo et al.[33]

MM. Risk stratification

Other prognostic factors

- Circulating plasma cell numbers
- Extramedullary disease
- High plasma cell proliferative rate
- High-risk gene expression signatures (GEP70 and HOVON, among others)
- Presence of *TP53* mutations
- Renal failure
- Poor performance status
- Immunoparesis
- Plasmablastic morphology

Kumar SK et al. Nature Reviews Disease Primers. 2017;3:1

Disease management: Indication for treatment

- Patients with MGUS **do not need** treatment
- They do need regular follow-up because of the potential for progression to multiple myeloma;
- the risk of progression is only 1% per life-year.

Disease management: Indication for treatment

- Patients with SMM **have no treatment indication**
  - They should be monitored for disease progression because early treatment with conventional therapy has shown no benefit.

- The risk of progression is highest in the first 5 years and decreases subsequently.
  - The overall risk of progression is 10% per year for the first 5 years, about 3% per year for the next 5 years, and 1% per year for the next 10 years.

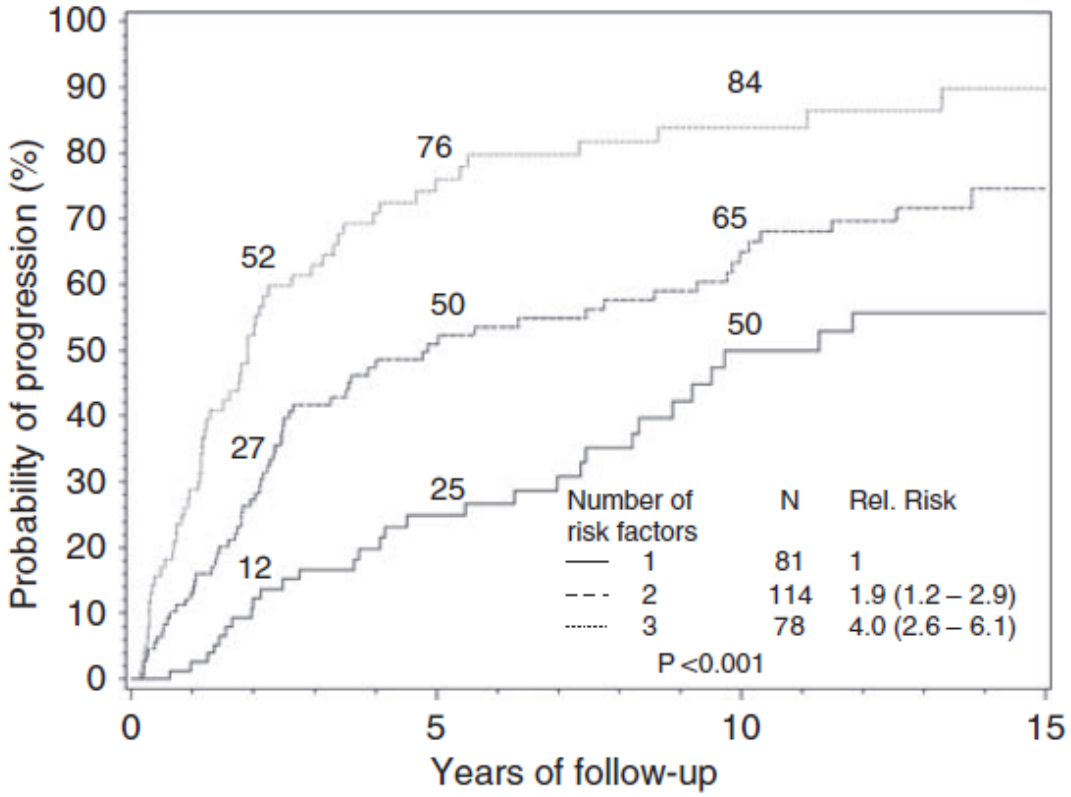
- Patients with high-risk SMM should be enrolled onto clinical trials

Risk stratification for smoldering multiple myeloma

- The model incorporates **3 risk factors**:
  1. abnormal FLC ratio
  2. Bone marrow plasma cells >10%
  3. serum M protein >3 g/dl.

- Patients with 1, 2 or 3 risk factors had **5-year progression rates** of 25, 51 and 76%, respectively.

- Corresponding **median times to progression** are 10, 5.1 and 1.9 years, respectively.

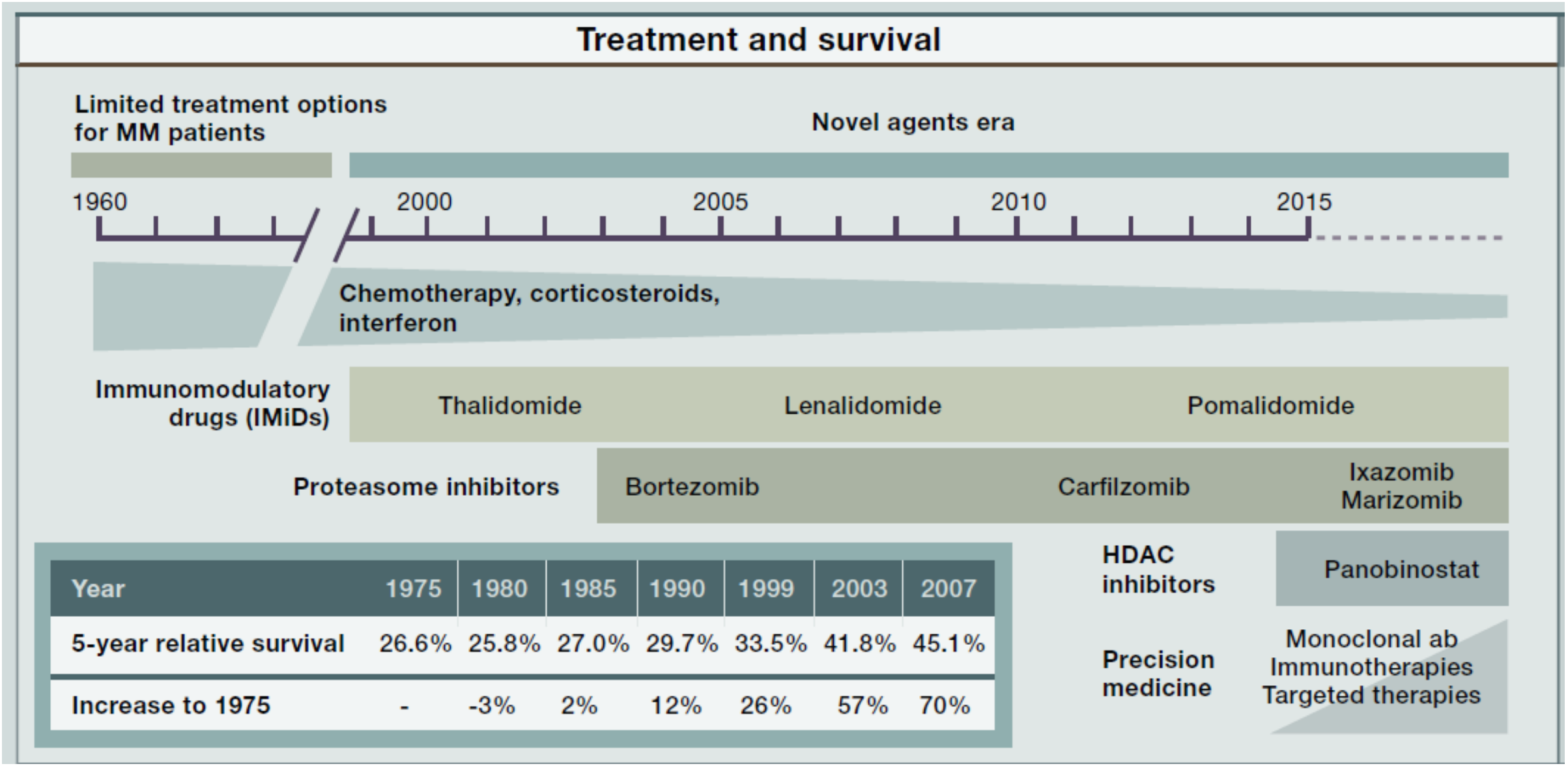


Kyle et al. Leukemia (2010) 24, 1121–1127

MM: Indication for treatment

- **Development of end-organ damage is the indication for treatment**.
  - End-organ damage is defined mainly by the CRAB criteria, which are related to a plasma cell proliferative disorder and **cannot be explained by another unrelated disease or disorder**.

- P**rogressive myeloma-induced renal insufficiency should trigger initiation of treatment** even before the creatinine threshold of 2 mg/dL (177 µmol/L) has been reached.
  - Acute renal failure due to multiple myeloma can be reversible if treated early.
  - After the confirmation of an underlying cast nephropathy, appropriate treatment should be initiated without delay.
- Once patients with renal impairment have achieved a remission, their outcomes are similar to patients with no renal insufficiency.



Year	1975	1980	1985	1990	1999	2003	2007
5-year relative survival	26.6%	25.8%	27.0%	29.7%	33.5%	41.8%	45.1%
Increase to 1975	-	-3%	2%	12%	26%	57%	70%

Braggio E et al. Cancer Cell. 2015;28:678

Box 6 | Currently used drugs in multiple myeloma

Proteasome inhibitors

- Bortezomib
- Carfilzomib
- Ixazomib

Immunomodulatory drugs

- Thalidomide
- Lenalidomide
- Pomalidomide

Monoclonal antibodies

- Daratumumab (anti-CD38)
- Elotuzumab (anti-SLAMF7 (signalling lymphocytic activation molecule family member 7))

Histone deacetylase inhibitor

- Panobinostat

Alkylating agents

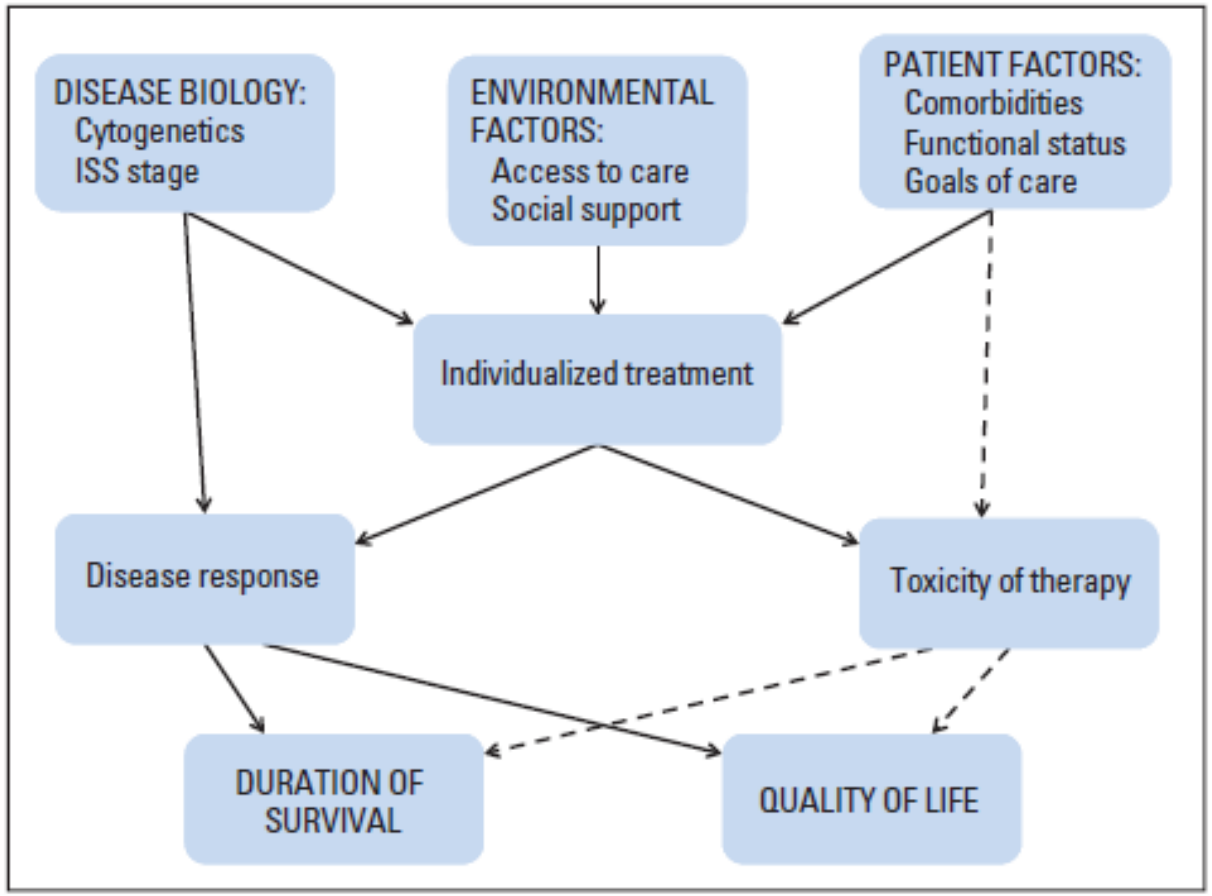
- Melphalan
- Cyclophosphamide
- Bendamustine

Others

- Dexamethasone
- Prednisone
- Cisplatin
- Etoposide
- Doxorubicin

CAR T cells

Kumar SK et al. Nature Reviews Disease Primers. 2017;3:1



Wildes TM et al. JCO. 2014;32:2531-2540.

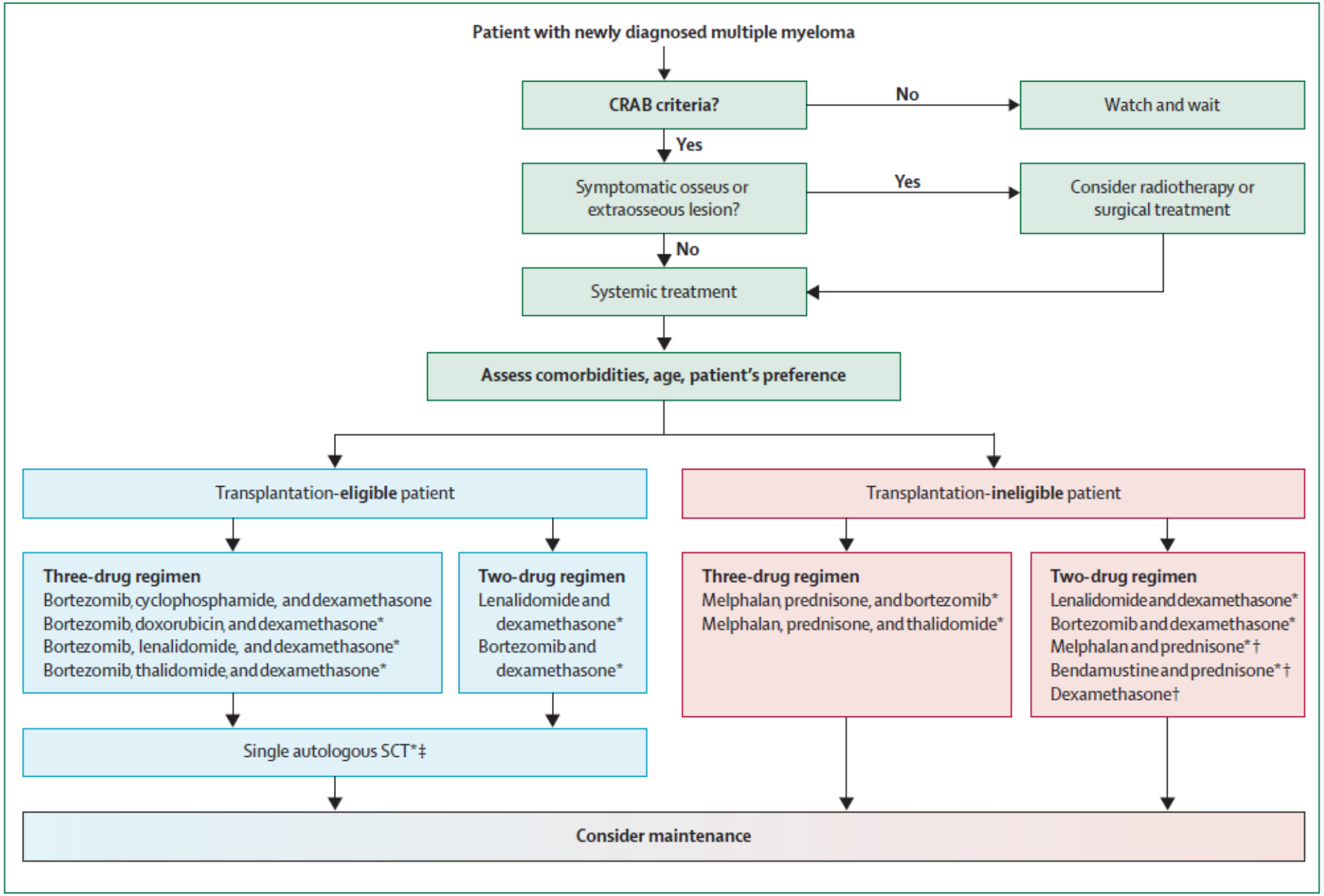
Table 5. Factors to consider in the clinical decision making for frail patients with MM

Factors	Aim
Age	To assess frailty
GA	
CRAB criteria	To start treatment
Hypercalcemia	
Renal failure	
Anemia	
Bone lesions	
Biomarkers of malignancy	
Clonal bone marrow plasma cell percentage ≥60%	
Involved/uninvolved serum free light-chain ratio ≥100	
>1 focal lesion (≥5 mm) on MRI studies	
Cardiovascular history	To choose treatment
History of diabetes	
Renal function	
Neuropathy	
Psychosocial status	
Preferences of the patient and the caregiver	

MRI, magnetic resonance imaging.

Laraocca A, Palumbo A. Blood. 2015;126(19):2179-2185.

Clinical management of patients with newly diagnosed MM



Rollig C et al. Lancet 2015; 385: 2197–208

Table 3. Response Criteria

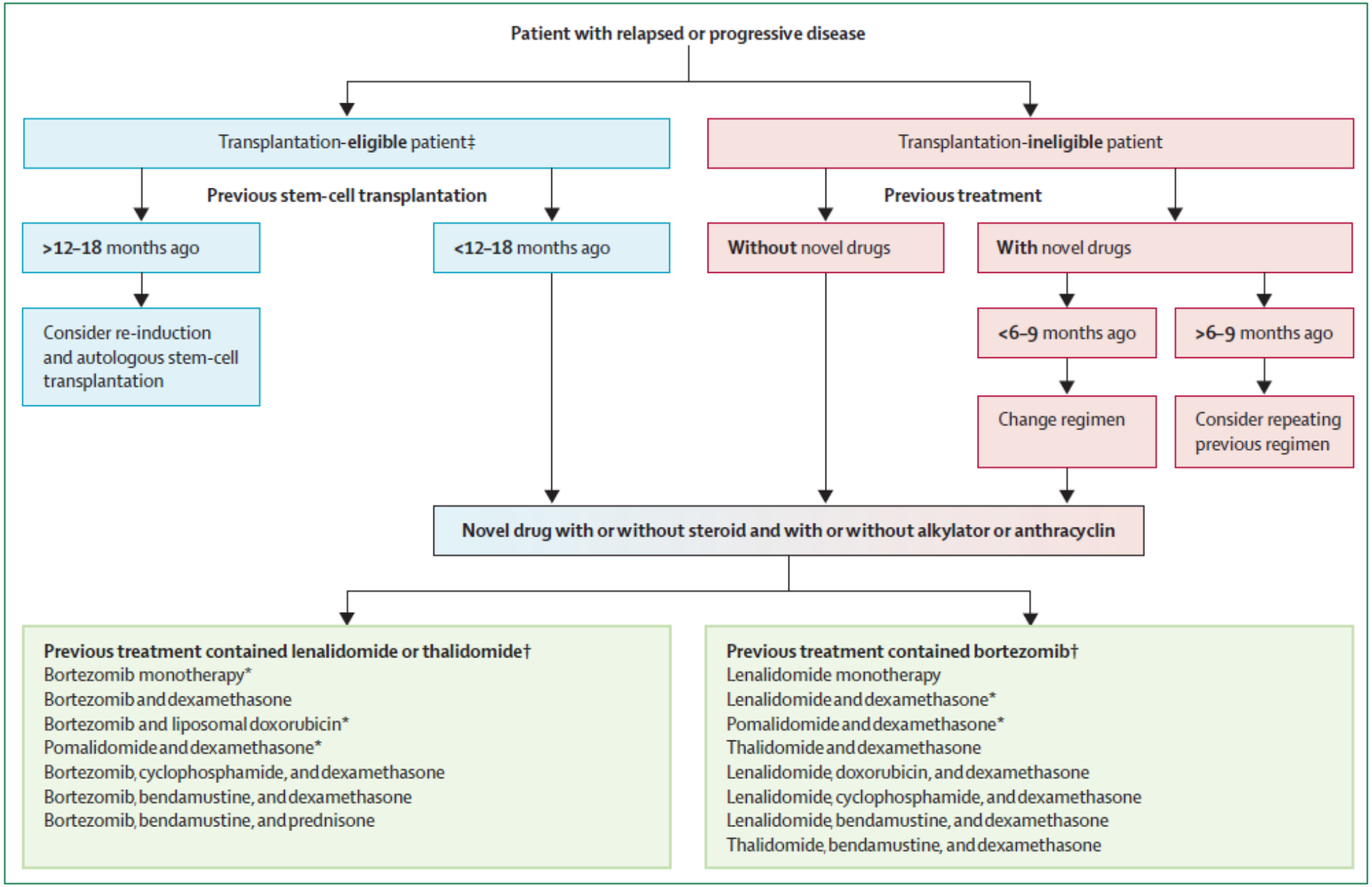
Response	Criteria
CR	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and < 5% plasma cells in bone marrow; in patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; two consecutive assessments are needed
sCR	CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or two- to four-color flow cytometry; two consecutive assessments of laboratory parameters are needed
Immunophenotypic CR	sCR as defined plus absence of phenotypically aberrant plasma cells (clonal) in bone marrow with minimum of 1 million total bone marrow cells analyzed by multiparametric flow cytometry (with > four colors)
Molecular CR	CR as defined plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5})
VGPR	Serum and urine M component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M component plus urine M component < 100 mg/24 h; in patients for whom only measurable disease is by serum FLC level, > 90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; two consecutive assessments are needed
PR	≥ 50% reduction of serum M protein and reduction in 24-hour urinary M protein by ≥ 90% or to < 200 mg/24 h If serum and urine M protein are not measurable, ≥ 50% decrease in difference between involved and uninvolved FLC levels is required in place of M protein criteria If serum and urine M protein and serum FLC assay are not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M protein, provided baseline percentage was ≥ 30% In addition, if present at baseline, ≥ 50% reduction in size of soft tissue plasmacytomas is required Two consecutive assessments are needed; no known evidence of progressive or new bone lesions if radiographic studies were performed
MR for relapsed refractory myeloma only	≥ 25% but ≤ 49% reduction of serum M protein and reduction in 24-hour urine M protein by 50% to 89% In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
SD	Not meeting criteria for CR, VGPR, PR, or PD; no known evidence of progressive or new bone lesions if radiographic studies were performed
PD	Increase of 25% from lowest response value in any of following: Serum M component with absolute increase ≥ 0.5 g/dL; serum M component increases ≥ 1 g/dL are sufficient to define relapse if starting M component is ≥ 5 g/dL and/or; Urine M component (absolute increase must be ≥ 200 mg/24 h) and/or; Only in patients without measurable serum and urine M protein levels: difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL); Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%) Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder Two consecutive assessments before new therapy are needed

NOTE. Data adapted.[8,9,30a]

Abbreviations: CR, complete response; FLC, free light chain; M, monoclonal; MR, minimal response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

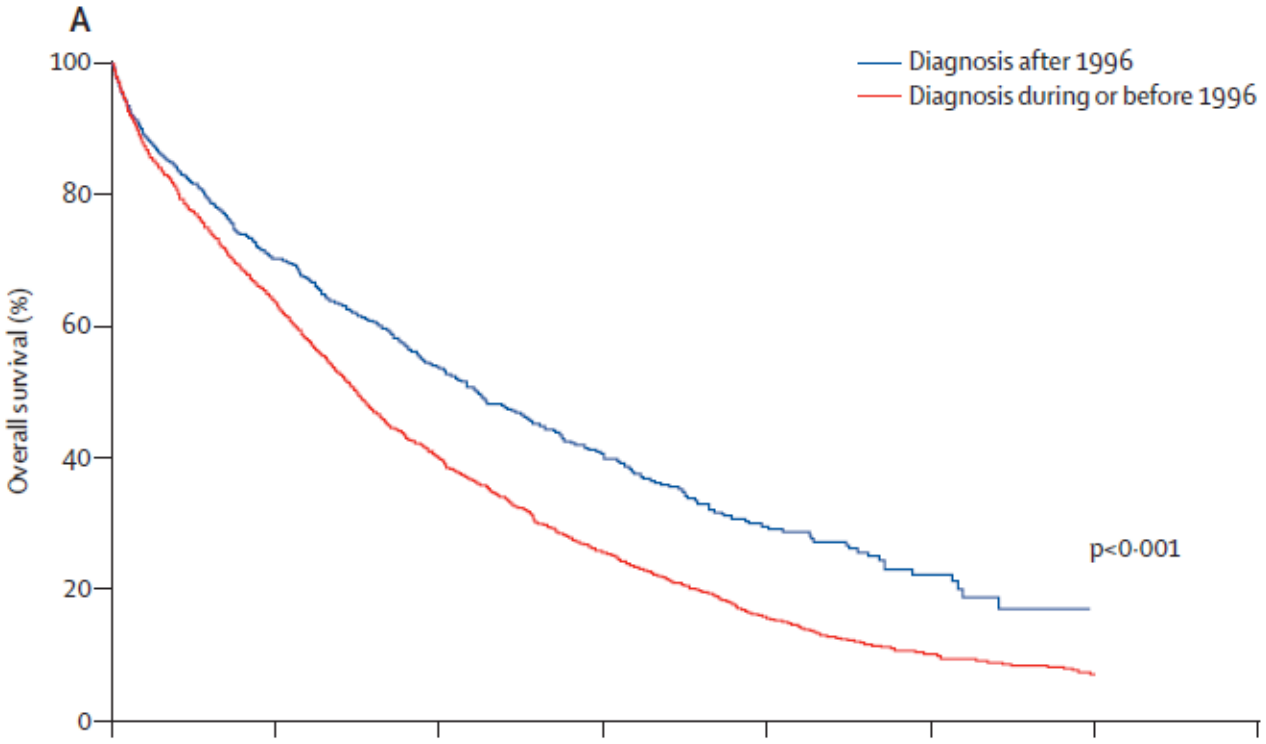
Palumbo A et al. JCO. 2014;32:587-600.

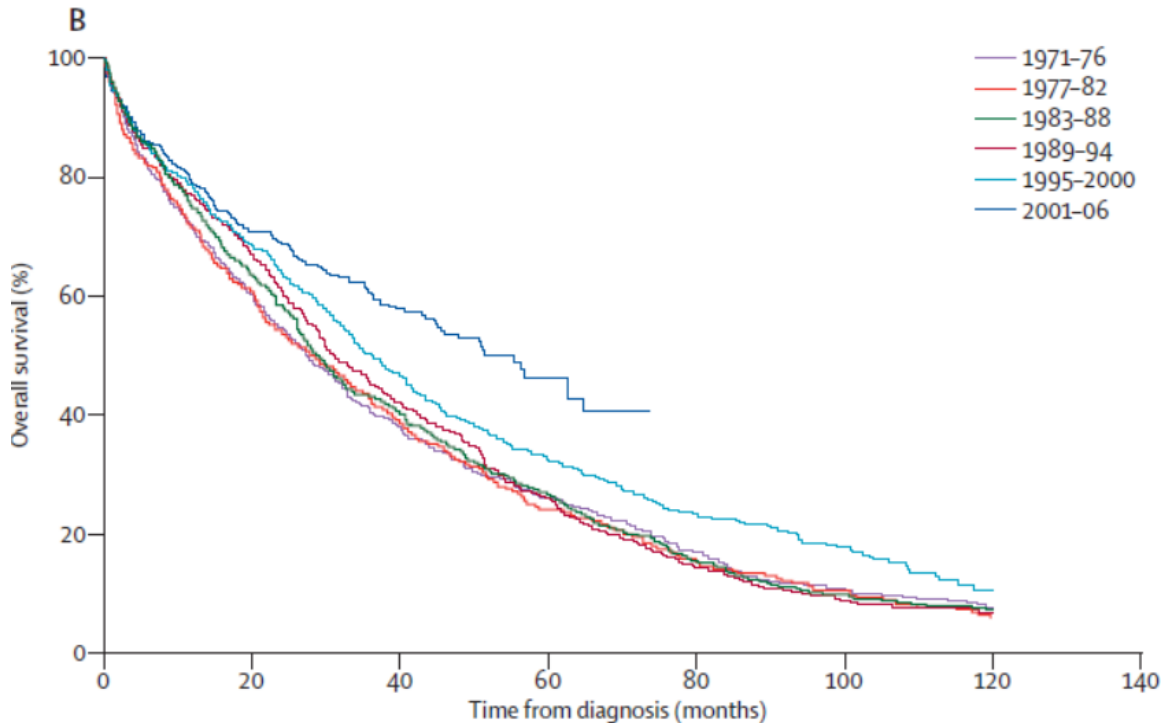
Clinical management of patients diagnosed with relapsed or progressive MM



Rollig C et al. Lancet 2015; 385: 2197–208

Overall survival after diagnosis in patients with MM





Rollig C et al. Lancet 2015; 385: 2197–208

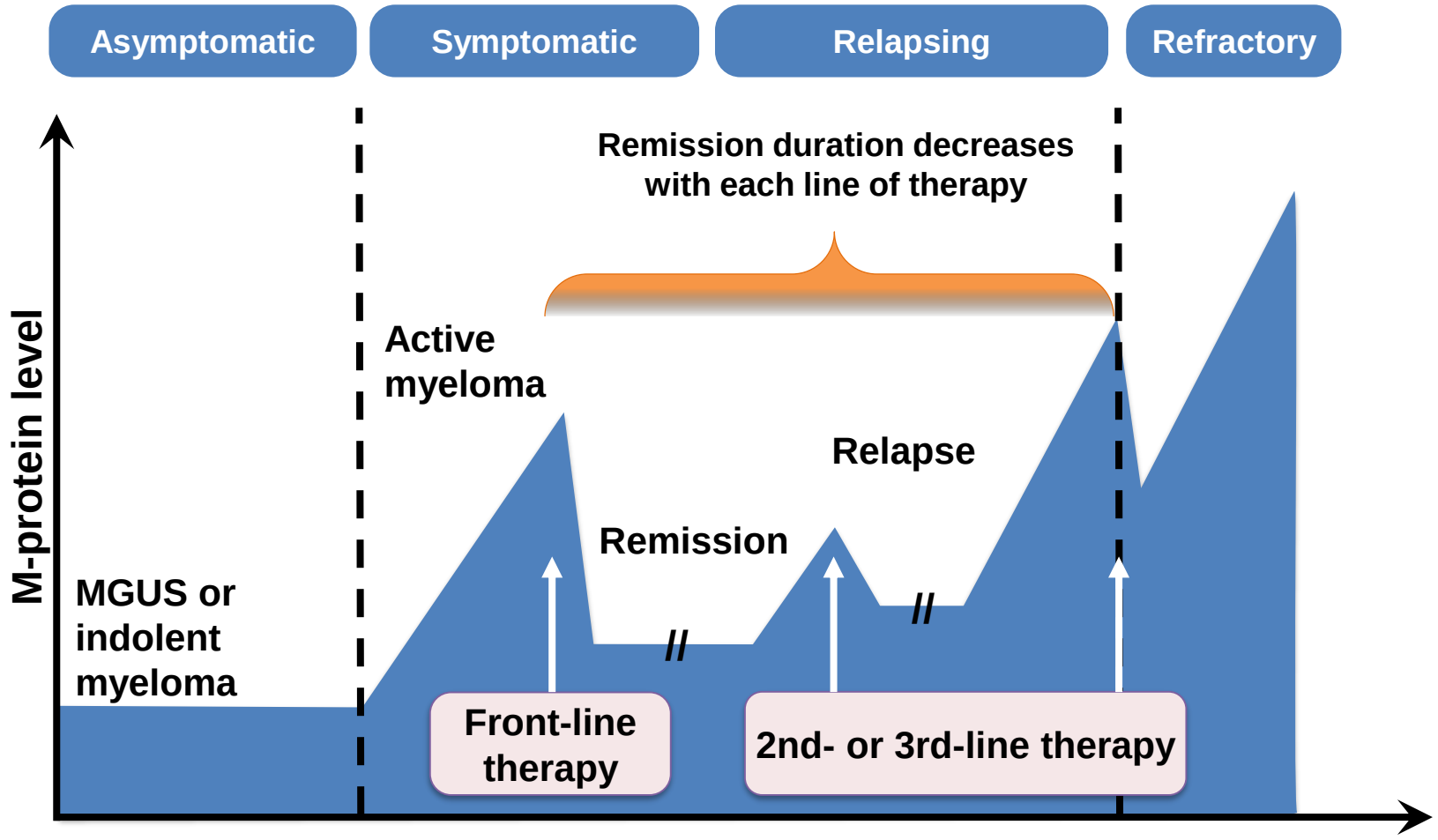
Supportive care

Symptom burden	Prevention/treatment strategy
Anemia	Blood transfusion, ESAs, iron supplementation
Thrombosis	Aspirin, LMWH, warfarin prophylaxis and treatment
Infection	Vaccination, prophylactic antivirals
Pain	Bisphosphonates, radiotherapy, surgery, pain medication
Peripheral neuropathy	Dose reduction or discontinuation, analgesics
Osteonecrosis of the jaw	Avoid invasive dental procedures during and around bisphosphonate therapy; good oral hygiene
Compression fractures	Kyphoplasty, vertebroplasty

Snowden. Br J Haematol. 2011;154:76; Mendoza. J Pain. 2012;13:564; Terpos. J Clin Oncol. 2013;31:2347.

ESA, erythropoiesis stimulating agent;
LMWH, low molecular weight heparin.

Multiple myeloma is characterized by a pattern of remission and relapse



Durie. Concise Review of the Disease and Treatment Options: Multiple Myeloma. International Myeloma Foundation, 2011/2012 edition. Available at: www.myeloma.org/pdfs/CR2011-Eng_b1.pdf. Accessed March 2016; Kumar. Mayo Clin Proc. 2004;79:867.

amyloidosis

- Disorders such as
  - nephrotic syndrome and heart failure,
  - neuropathy in non-diabetic patients,
  - left ventricular hypertrophy on echocardiography without consistent electro cardiographic evidence or low limb lead voltages,
  - hepatomegaly with normal imaging,
  - albuminuria
- should be assessed carefully to not overlook **light-chain amyloidosis** caused by free light-chain secretion.

amyloidoses

- a rare group of diseases that result from extracellular deposition of amyloid, a fibrillar material derived from various precursor proteins that self-assemble with highly ordered abnormal cross β-sheet conformation.

- Deposition of amyloid can occur
  - **in the presence of an abnormal protein**
    - (eg, hereditary amyloidosis and acquired systemic Ig light chain [AL] amyloidosis),
  - **in association with prolonged excess abundance of a normal protein**
    - (eg, reactive systemic [AA] amyloidosis and β2-microglobulin [β2M] dialysis-related amyloidosis),
  - **for reasons unknown, accompanying the ageing process**
    - (eg, wild-type transthyretin amyloidosis [ATTRwt; or senile systemic amyloidosis] and atrial natriuretic peptide amyloidosis).

Wechalekar AD et al. Lancet 2016; 387: 2641–54

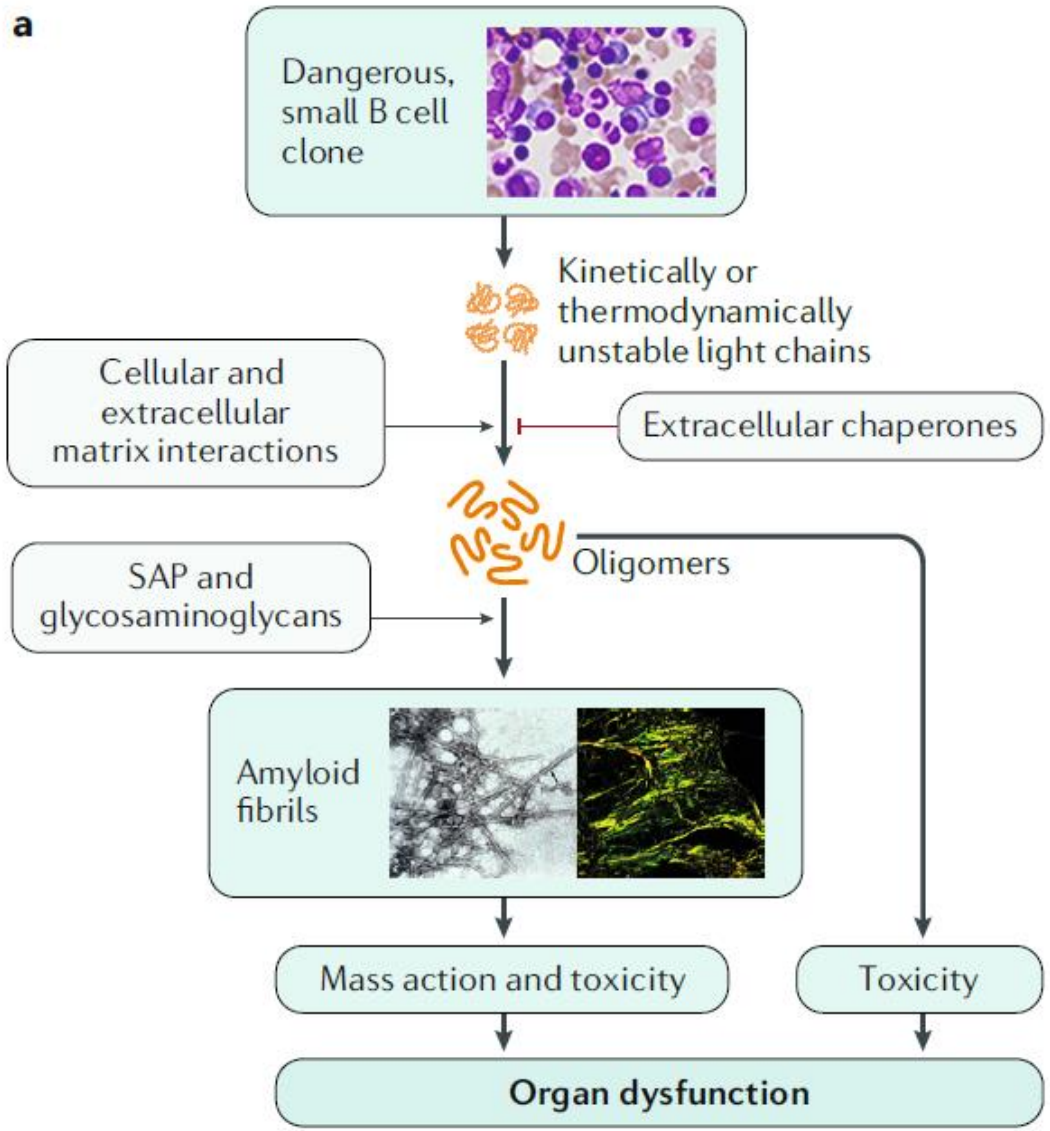
Table 1 | **Most common systemic amyloidoses**

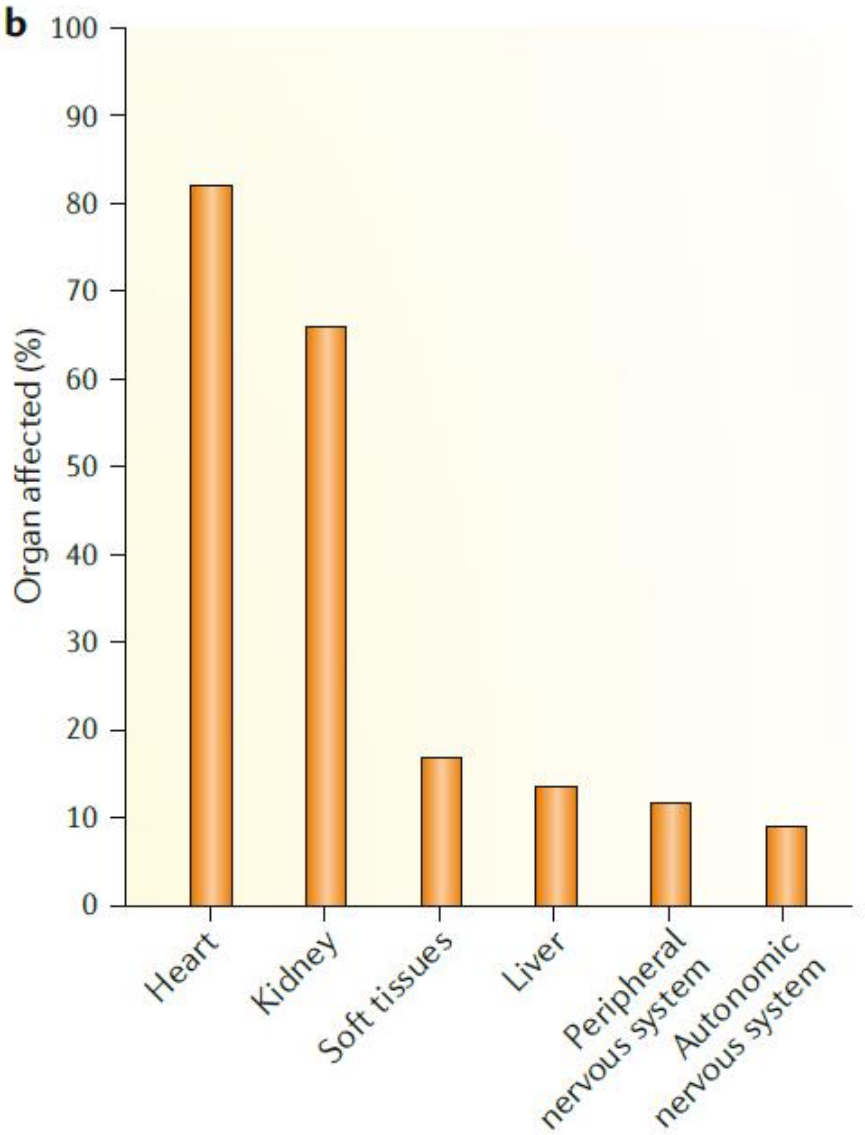
Designation[a]	Parent protein	Systemic and/or localized	Acquired or hereditary	Organs involved
AL	Immunoglobulin light chain[b]	Systemic or localized	Acquired (hereditary[c])	Heart, kidney, liver, soft tissues, peripheral nervous system (including the autonomic nervous system) and gastrointestinal tract
ATTR	Transthyretin	Systemic	Hereditary	Peripheral nervous system (including the autonomic nervous system), heart, eye, kidney and leptomeninges
		Systemic	Acquired	Heart and ligaments
AA	Serum amyloid A protein	Systemic	Acquired	Predominantly kidney, but may involve liver, gastrointestinal tract and occasionally heart, thyroid and autonomic nervous system
ALECT2	Leukocyte chemotactic factor 2	Systemic	Acquired	Kidney, liver, spleen, adrenals and lungs
AApoAI	Apolipoprotein AI	Systemic	Hereditary	Heart, liver, kidney, peripheral nervous system, testis, larynx and skin
AFib	Fibrinogen α chain	Systemic	Hereditary	Kidney, primarily, with obliterative glomerular involvement
$A\beta_2m$	β_2-microglobulin, wild type	Systemic	Acquired (haemodialysis related)	Musculoskeletal system
	β_2-microglobulin	Systemic	Hereditary	Autonomic nervous system

[a]The amyloid fibril protein is designated protein A and followed by a suffix that is an abbreviated form of the precursor protein name. For example, when amyloid (A) fibrils are derived from immunoglobulin light (L) chains, the amyloid fibril protein is AL.
[b]Rare cases of amyloidosis formed by immunoglobulin heavy chains (AH) and by heavy and light chains (AHL) have been reported.
[c]One family with mutation in the constant region of the κ light chain, with cysteine replacing serine at amino acid residue 131, has been reported[185].

Merlini et al. Nature Reviews Disease Primers 2018;4:38

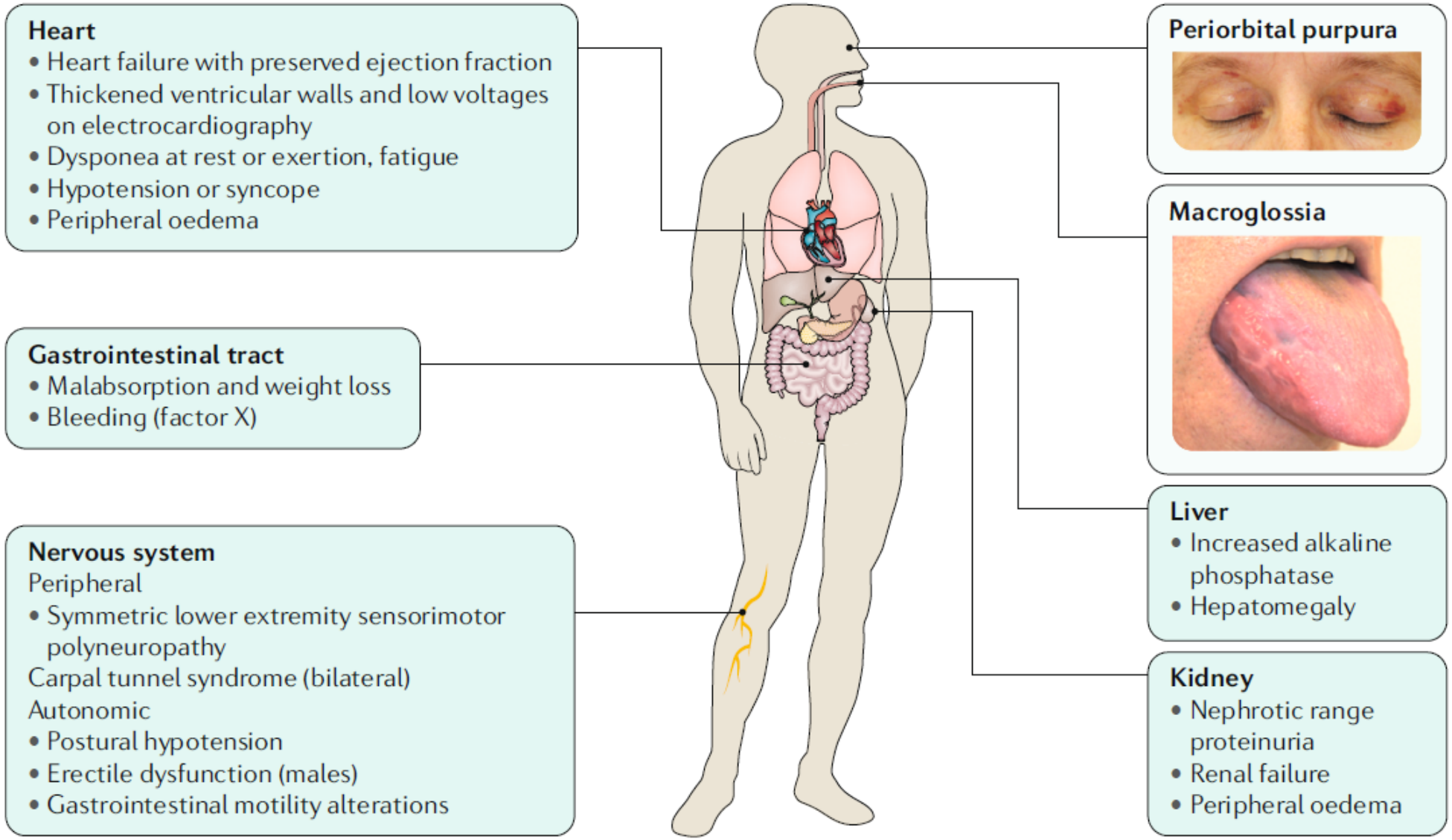
Schematic pathways involved in AL amyloid fibril formation.





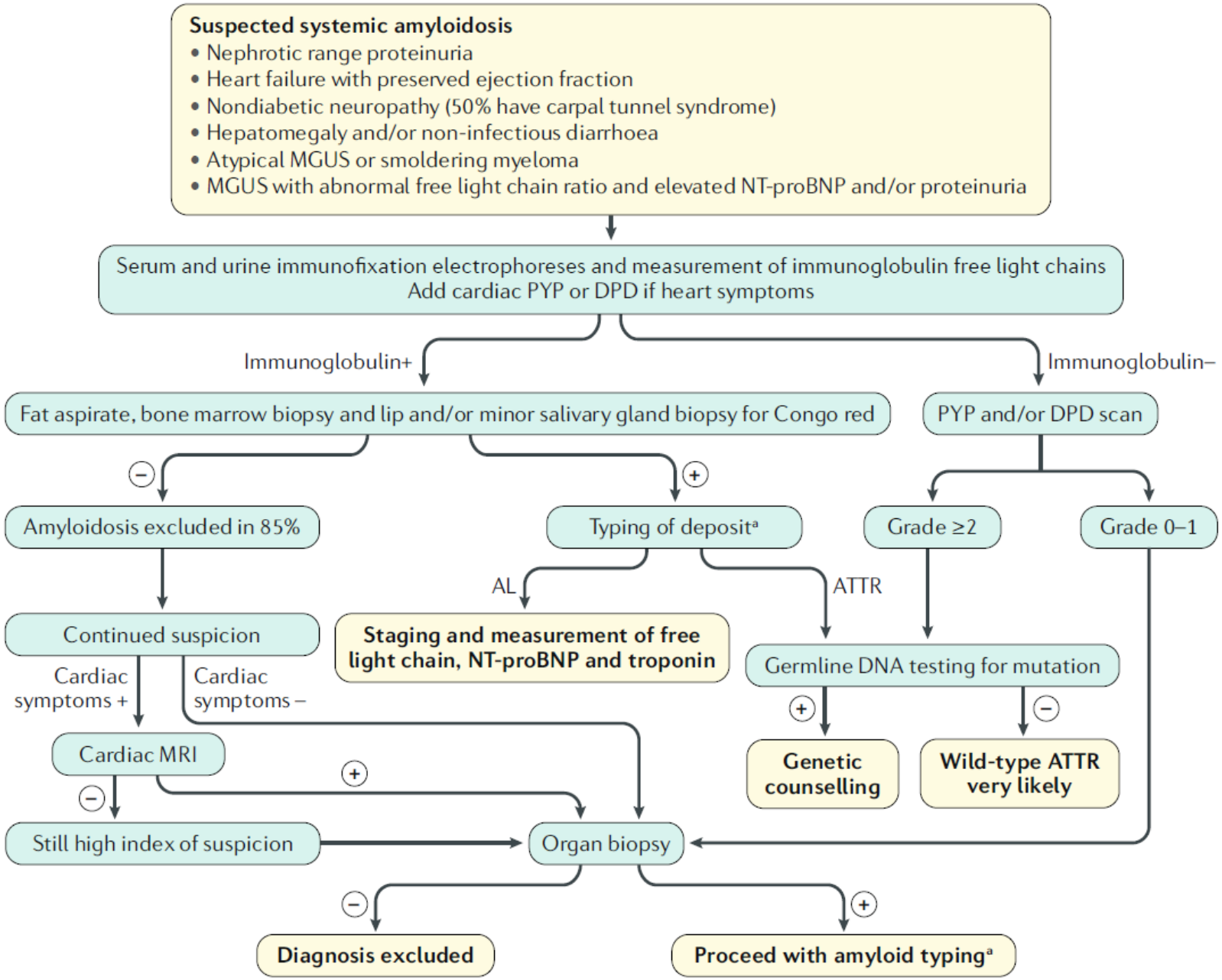
Merlini et al. Nature Reviews Disease Primers 2018;4:38

Organ involvement in systemic AL amyloidosis.



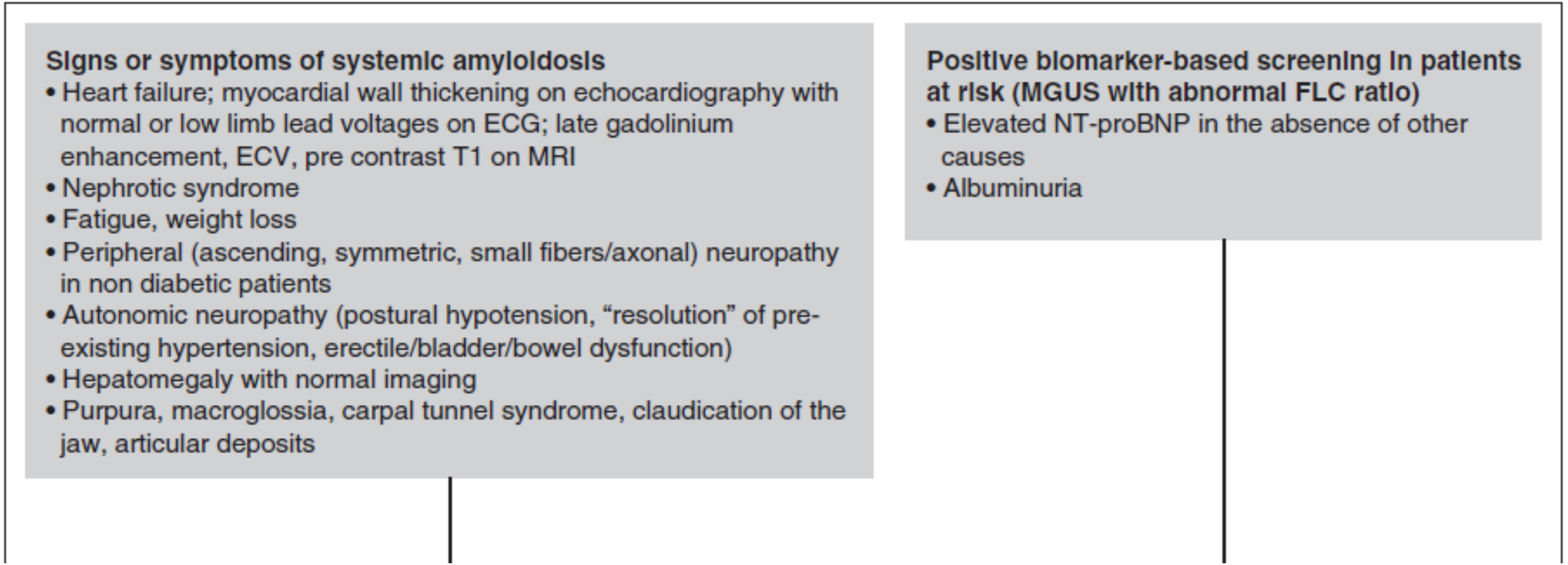
Merlini et al. Nature Reviews Disease Primers 2018;4:38

Diagnostic algorithm for systemic AL amyloidosis.



Merlini et al. Nature Reviews Disease Primers 2018;4:38

Diagnostic workup of systemic AL amyloidosis.



Paladini G, Merlini G. Blood. 2016;128(2):159-168

Diagnostic workup of systemic AL amyloidosis

Tissue biopsy
- **Abdominal fat aspirate**, and if negative
- **Salivary gland biopsy**, or
- **Organ biopsy** (beware of hemorrhagic risk, transjugular approach preferred for liver biopsy)

Identification of the plasma cell clone by serum and urine immunofixation electrophoresis and FLC measurement
Bone marrow studies including iFISH of plasma cells and skeletal survey

Unequivocal identification of amyloid type
- **Tissue typing** by mass spectrometry, immuno electron microscopy, or immunohistochemistry
- **Gene sequencing** when clinical presentation requires to rule out hereditary amyloidosis; for example transthyretin amyloidosis in patients with isolated or combined heart and peripheral nervous system involvement; apolipoprotein AI in subjects with mild liver, renal, or cardiac involvement; fibrinogen amyloidosis in patients with isolated renal involvement
- **Cardiac scintigraphy with** ^{99m}Tc-DPD or PYP can differentiate AL (mild or no uptake) from transthyretin amyloidosis (strong uptake)

Assessment of organ involvement and staging
- **Heart:** Echocardiography (with assessment of strain or MCF), NT-proBNP, troponins, ECG, Holter ECG, MRI
- **Kidney:** 24-hour urinary protein loss, eGFR
- **Liver:** Liver function tests, liver imaging (CT, US scan, MRI)

Paladini G, Merlini G. Blood. 2016;128(2):159-168

Validated staging systems for AL amyloidosis

Staging systems	Markers and thresholds	Stages	Outcomes
Standard Mayo Clinic[37]	NT-proBNP > 332 ng/L	I. No markers above the cutoff	I. Median survival 26 mo-not reached
	cTnT > 0.035 ng/mL (or cTnI > 0.01 ng/mL)	II. One marker above the cutoff	II. Median survival 11-49 mo
		III. Both markers above the cutoff	III. Median survival 4-6 mo
European staging of advanced cardiac involvement[38]	Standard Mayo Clinic stage III plus	a. No high-risk factors	a. Median survival 26 mo
	Systolic blood pressure < 100 mm Hg	b. One high-risk factor	b. Median survival 6 mo
	NT-proBNP > 8500 ng/L	c. Two high-risk factors	c. Median survival 3 mo
Revised Mayo Clinic[4,8]	NT-proBNP > 1800 ng/L	I. No markers above the cutoff	I. Median survival 94 mo
	cTnT > 0.025 ng/mL	II. One marker above the cutoff	II. Median survival 40 mo
	dFLC > 180 mg/L*	III. Two markers above the cutoff	III. Median survival 14 mo
		IV. Three markers above the cutoff	IV. Median survival 6 mo
Renal[36]	eGFR < 50 mL/min per 1.73 m^2	I. Both eGFR above and proteinuria below the cutoffs	I. 0%-3% risk for dialysis at 2 y
	Proteinuria > 5 g/24h	II. Either eGFR below or proteinuria above the cutoffs	II. 11%-25% risk for dialysis at 2 y
		III. Both eGFR below and proteinuria above the cutoffs	III. 60%-75% risk for dialysis at 2 y

cTn, cardiac troponin.

*In this study, FLC were measured with the Freelite immunonephelometric assay based on polyclonal antibodies. A novel assay, based on monoclonal antibodies (N latex FLC) has been marketed in Europe and Australia. Available data indicate that the Freelite and N latex FLC assays have comparable diagnostic sensitivity and prognostic relevance. However, the 2 tests are not interchangeable, and N latex FLC results cannot be used in the staging system.

Paladini G, Merlini G. Blood. 2016;128(2):159-168

	Number of patients	Response (%)		Median progression-free survival (years*)	Median overall survival (years)
		Clonal, % of responders (% with complete response)	Organ		
Standard chemotherapy					
Oral melphalan–dexamethasone[81,82]	46	67% (33%)	48%	3·8	5·1
Cyclophosphamide–thalidomide–dexamethasone[83]	75	74% (21%)	27%	1·7	3·4
Bortezomib[84]	70	69% (38%)	29%	At 12 months: 75%	84%
Lenalidomide–dexamethasone[85]	22	41% (–)	23%	1·6	..
ASCT					
ASCT[86]	37	67% (41%)	45%	2·7	1·8
ASCT[87]	421	.. (43%)	53%	3·4	8·4
Risk-adapted ASCT (followed by bortezomib consolidation)[88]	40	79% (58%)	70%	At 2 years: 69%	At 2 years: 82%
Novel chemotherapy combinations					
Cyclophosphamide–bortezomib–dexamethasone[89]	43	81% (65%)	46%	At 2 years: 53%	At 2 years: 98%
Cyclophosphamide–lenalidomide–dexamethasone[90]	35	60% (11%)	31%	2·4	3·1
Melphalan–lenalidomide–dexamethasone[91]	26	58% (23%)	50%	At 2 years: 54%	At 2 years: 81%
Pomalidomide–dexamethasone[92]	33	48% (3%)	15%	1·2	2·3
Ixazomib[93]	16	42% (8%)	..	..	..

*Unless otherwise specified. ..=data not available. ASCT=autologous stem cell transplant.

Table 2: **Treatment regimens for patients with AL amyloidosis**

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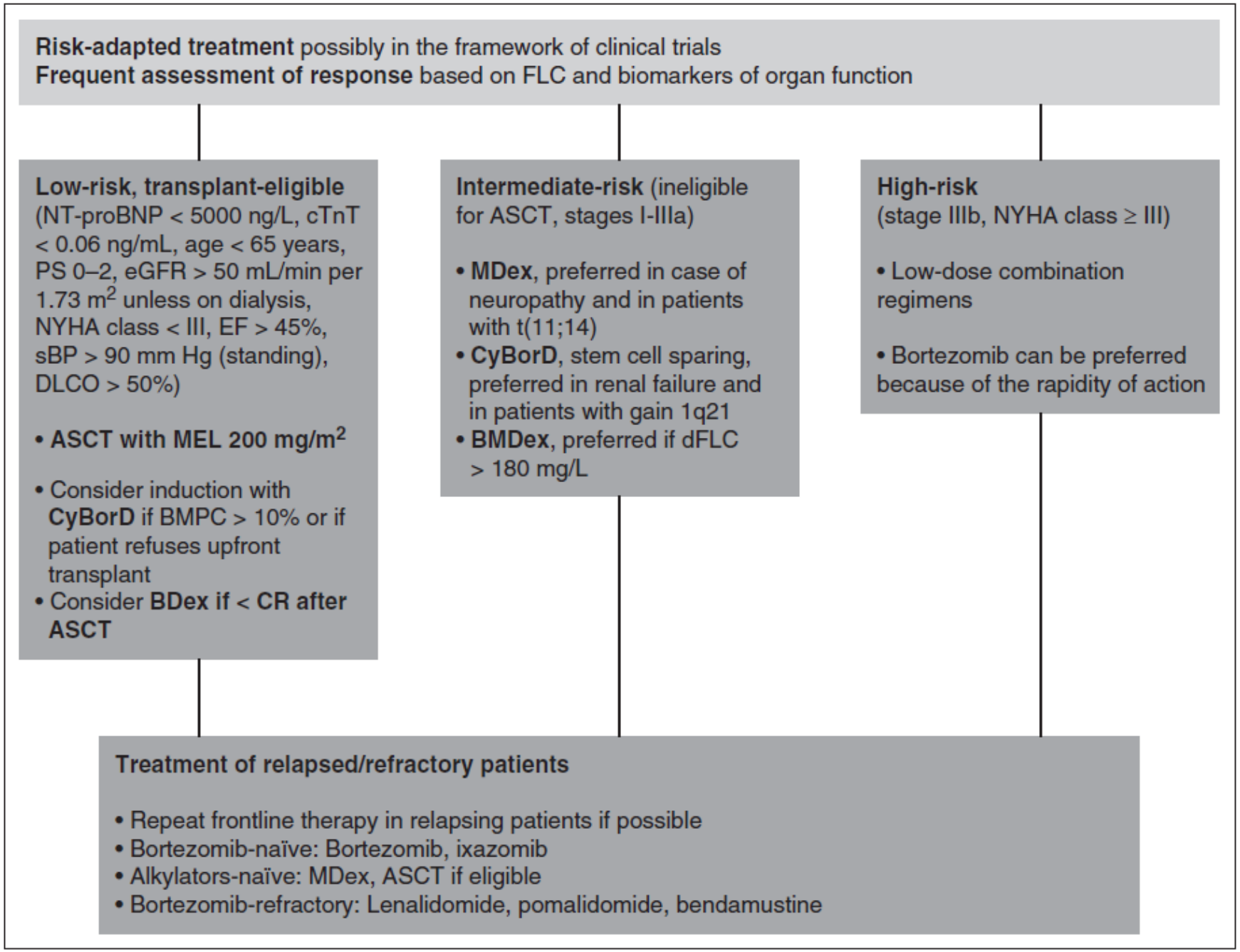
Therapeutic approach to systemic AL amyloidosis.



Paladini G, Merlini G. Blood. 2016;128(2):159-168

Outcome of AL amyloidosis treated with a selection of common upfront regimens, according to disease severity

Treatment	Disease severity	Patients	HR (CR, VGPR)	OR	Survival
ASCT[57]	Transplant eligible	1536	After 2007 71% (37%, —)	After 2007, kidney, 32%	68% at 5 y
ASCT[61]	Transplant eligible	629	— (35%, —)	—	Median, 7.6 y
MDex[63]	Treated with full-dose dexamethasone (stage IIIb 10%)	119	76% (31%, 29%)	Heart, 37%; kidney, 24%	Median, 7.3 y
	Treated with low-dose dexamethasone (stage IIIb 36%)	140	51% (12%, 20%)	Heart, 20%; kidney, 17%	Median, 1.7 y (median, 7 mo in stage IIIb)
CTD[70]	Stage IIIb 22%	69	72% (19%, 16%)	Heart, 19%; kidney, 39%	>50% at 5 y (median, 4 mo in stage IIIb)
BMDex[71]	Stage IIIb 22%	87	69% (42%, 13%)	Heart, 16%; kidney, 16%	53% at 5 y
CyBorD[73]	Stage I	30	77% (33%, 23%)	Heart, 22%	100% at 5 y
	Stages II and IIIa	128	67% (21%, 27%)	Heart, 4%	50% at 5 y
	Stage IIIb	43	42% (14%, 9%)	Overall renal response, 25%	20% at 5 y; median, 7 mo (overall, 55% at 5 y)

Larger and more recent studies were selected. Intent-to-treat responses are reported.
CR, complete response; HR, hematologic response; OR, organ response; VGPR, very good partial response; —, not available.

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Supportive therapy in systemic amyloidosis

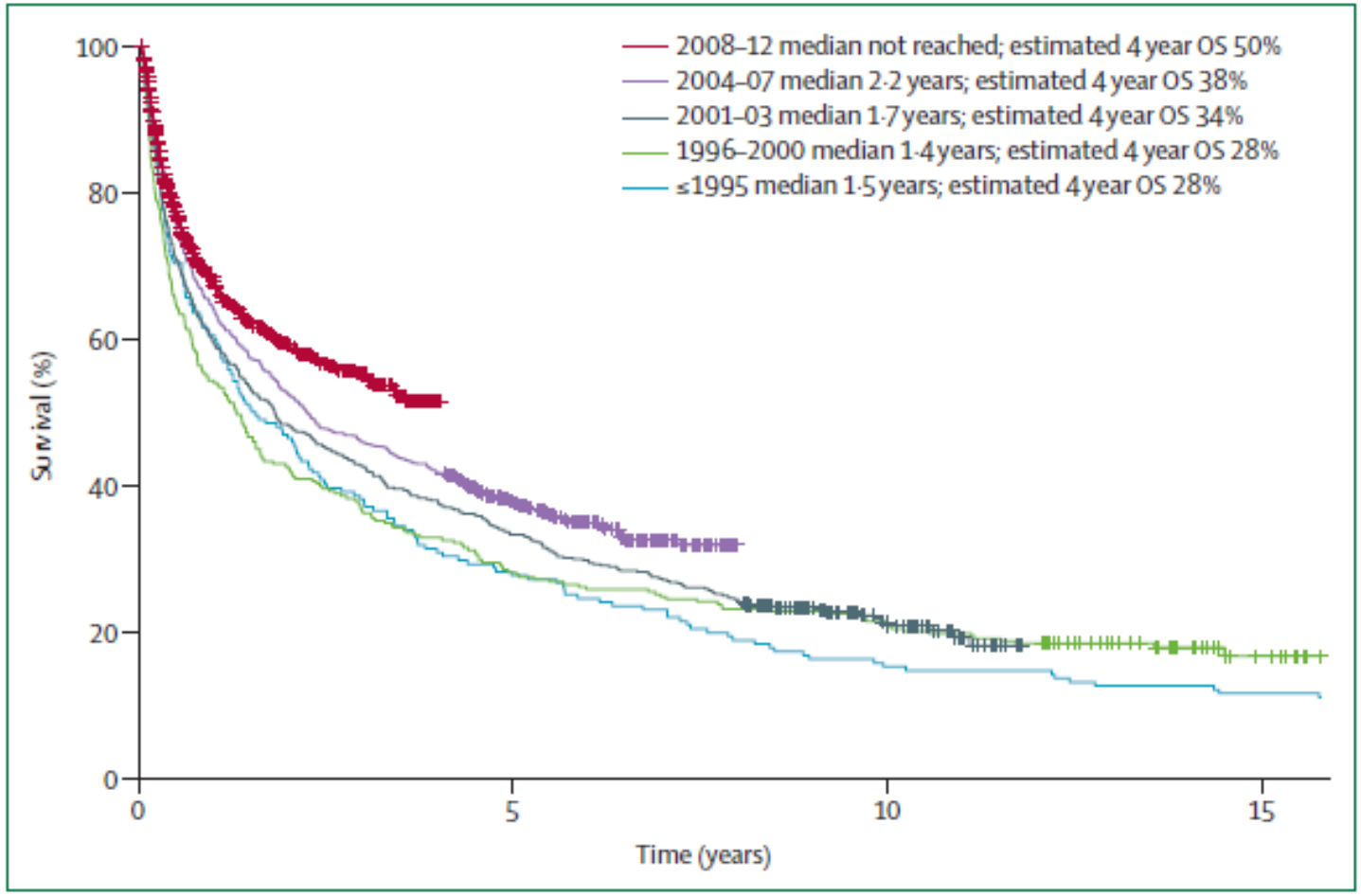
Supportive therapy

- Salt restriction.
- Diuretics (cardiac function is preload-dependent: Avoid reduction of intravascular volume).
- Patients with recurrent arrhythmic syncope may benefit from pacemaker implantation; the use of implantable ICD is controversial.
- ACE inhibitors are generally poorly tolerated because of hypotension; Use at lowest tolerated dose.
- Fitted elastic leotards and midodrine for hypotension.
- Gabapentin or pregabalin for neuropathic pain.
- Octreotide can control diarrhea.
- Nutritional support.

Organ transplant can be proposed in patients with irreversible, end-stage organ dysfunction despite CR. In young patients with isolated cardiac involvement and severe heart failure, heart transplant followed by ASCT can be considered. Left ventricular assist devices may represent a bridge to cardiac transplant.

Kaplan–Meier survival curve showing improvement over time in overall survival of patients with systemic AL amyloidosis seen at the National Amyloidosis Centre in the UK

- (n=3486)



Wechalekar AD et al. Lancet 2016; 387: 2641–54