MULTIPLE MYELOMA 101

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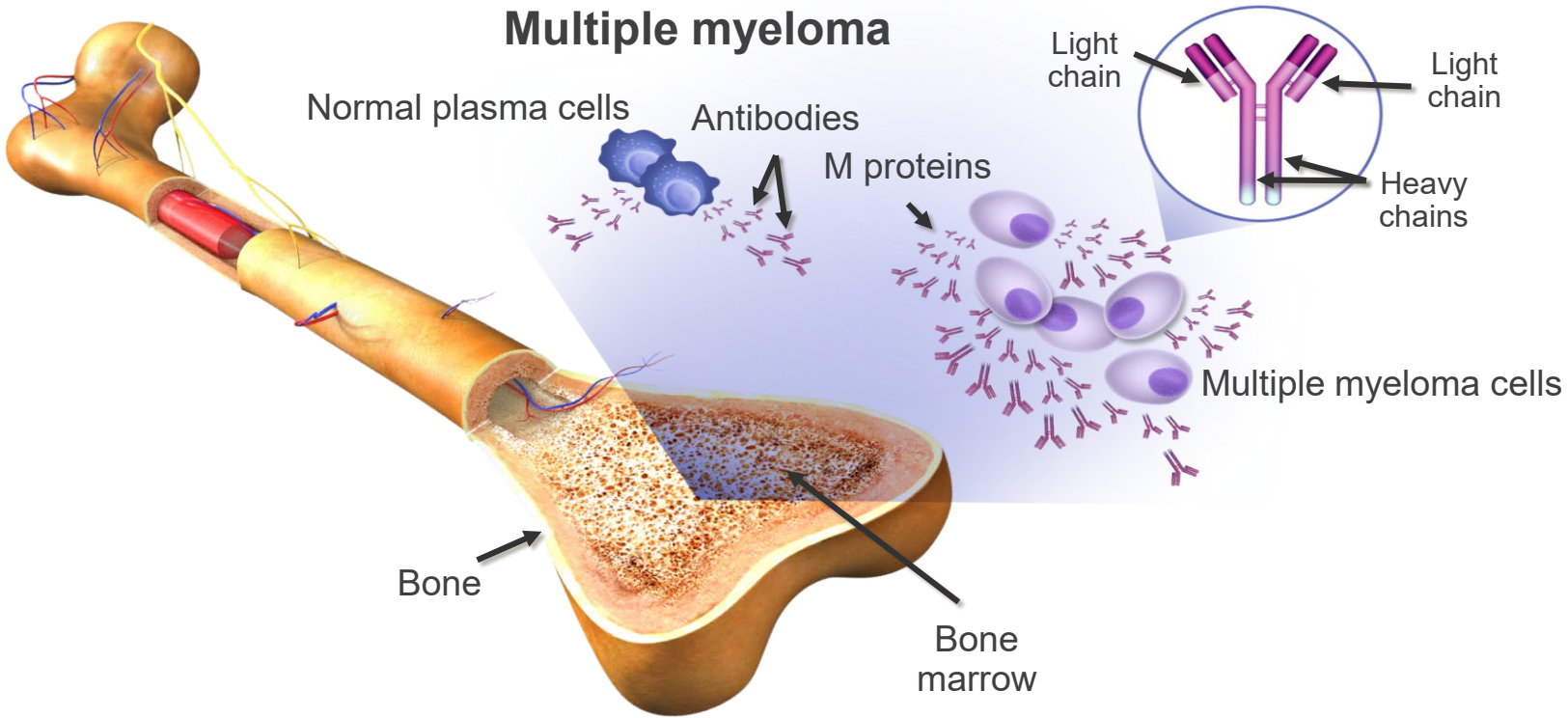
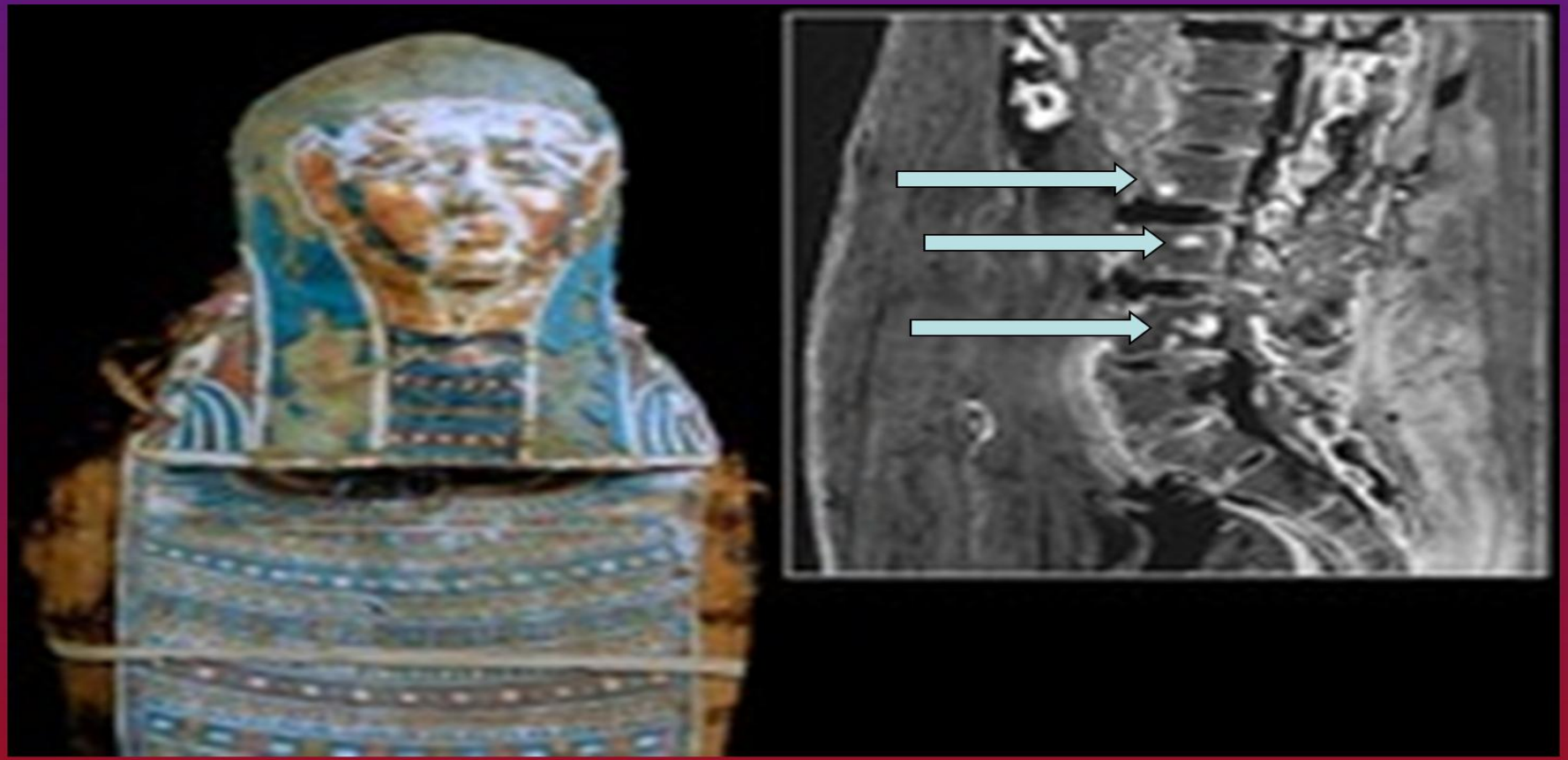
Providing Extraordinary Care

What is multiple myeloma?

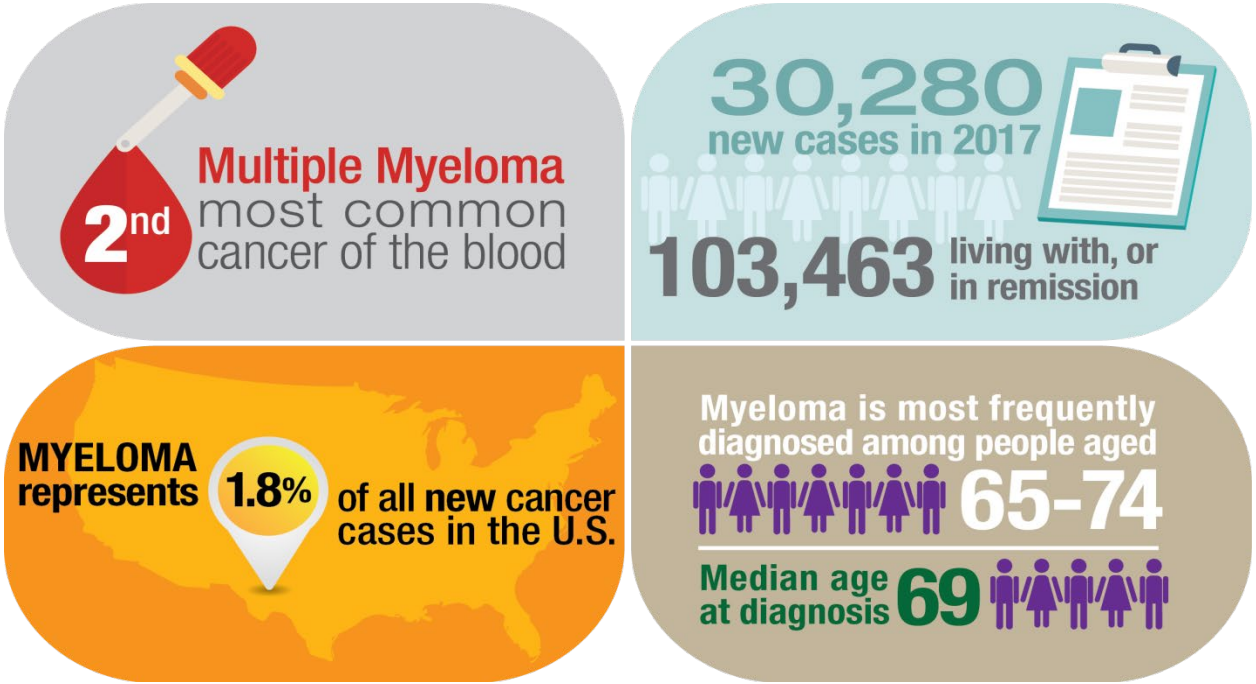


Myeloma in Mummies



Ancient affliction. A high-resolution CT scan of the lumbar spine region of a 2150-year-old Egyptian mummy revealed small, round lesions.

How common is multiple myeloma?



SEER Cancer Stat Facts: Myeloma. National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/statfacts/html/mulmy.html

MM: Epidemiology

- 30,280 new cases/year
- 11,240 deaths/year
- 104,000 patients alive with MM/year
- Median age 70 years
- Slowly increasing incidence
- Males > Females (57:43)
- 1.8% of all malignancies
  - 10% of all hematologic malignancies
  - 20% in African-Americans

Etiology: Risk Factors for MM

- Chronic exposure to low-dose ionizing radiation (? Radon)
- Occupational exposure (e.g. chemical)
- Genetic factors-increase MGUS risk in families
- Chronic antigenic stimulation (eg, recurrent infections and drug allergies)
- Agent orange, 9/11 exposure
- Ultimately, we do not know why patients develop MM

Small inherited risk

- Landgren et al First degree relatives of 4488 Swedish MGUS pts had increased relative risk of:
  - MGUS 2.84 (1.45-5.57)
  - WM 4.94 (1.32-18.46)
  - MM 2.87 (1.92-4.27)
  - CLL 2.05
  - No increased risks of NHL, HD
  - Incidence in African Americans 17.4

Monoclonal Gammopathy of Undetermined Significance (MGUS)

- 3.5% of all 50 year olds
- ~10% of 80 year olds
- Dysregulation of normal immune system
- BENIGN

Prevalence of Monoclonal Gammopathy of Undetermined Significance (MGUS) in Men and Women by Age (1A) and by race and ethnicity (1B)

Figure 1A

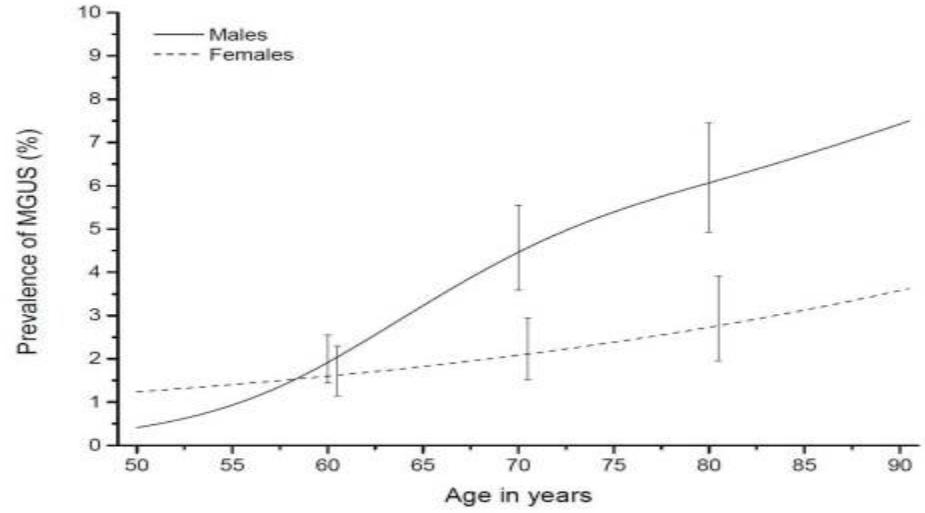
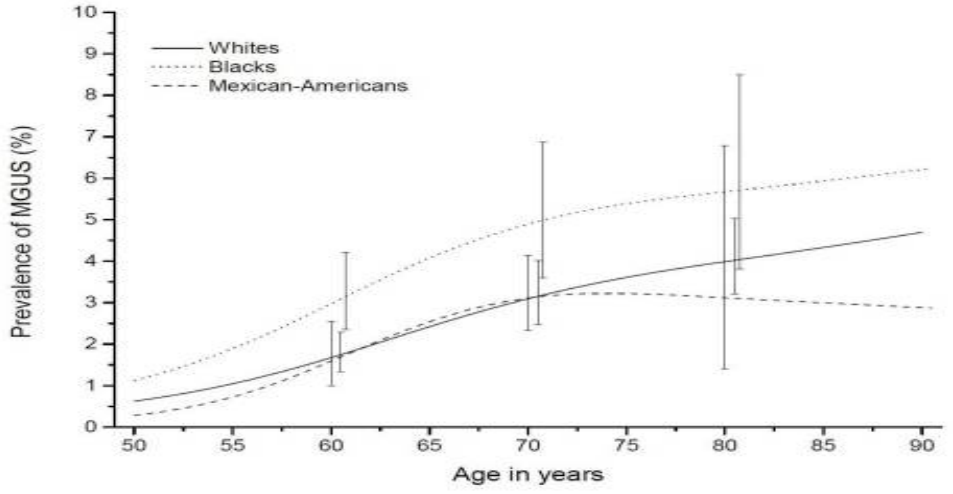


Figure 1B



ALL MGUS IS NOT CREATED EQUAL

Risk Factors for Potential Malignancy

- Type of paraprotein (e.g. IgG)
- Amount of paraprotein (> 1.5 g)
- Free light chain ratio (0.26 to 1.65)

Risk at 20 years ranges

- 5% (no risk factors)
- 27% (two risk factors)
- 58% (three risk factors)

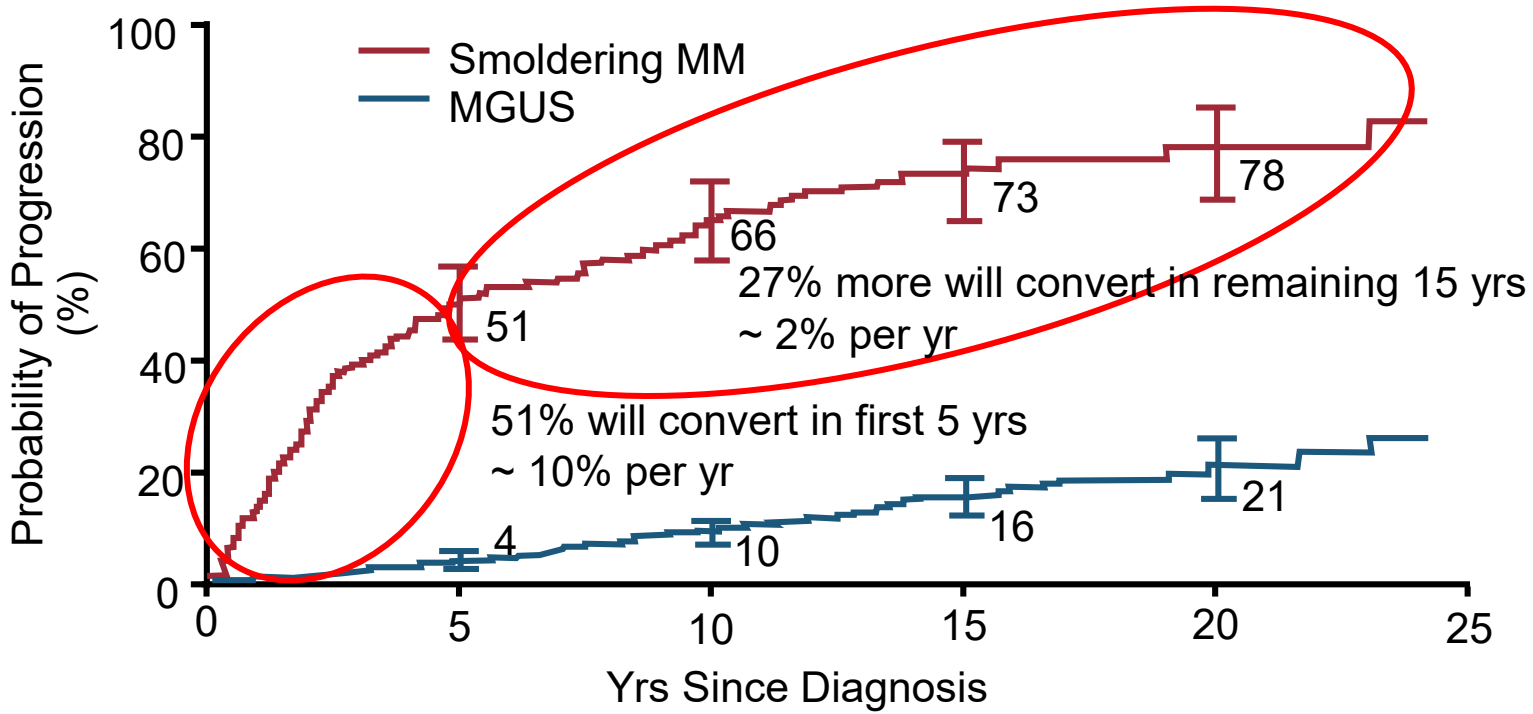
Smoldering Myeloma

Smoldering Myeloma

- No symptoms; no related organ/tissue impairment
- New criteria for smoldering myeloma[1]
- 10% to 20% of newly diagnosed myeloma[2]
- Can remain indolent for yrs
- Progression rate: ~ 50% at 5 yrs[3]
  - Progression rate in high-risk subgroup: 80% at 2 yrs[4]

1. Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548. 2 Kyle RA. ASCO Connection. 2012. 3. Kyle RA, et al. Br J Haematol. 2007;139:730-743. 4. Mateos MV, et al. N Engl J Med. 2013;369:438-447.

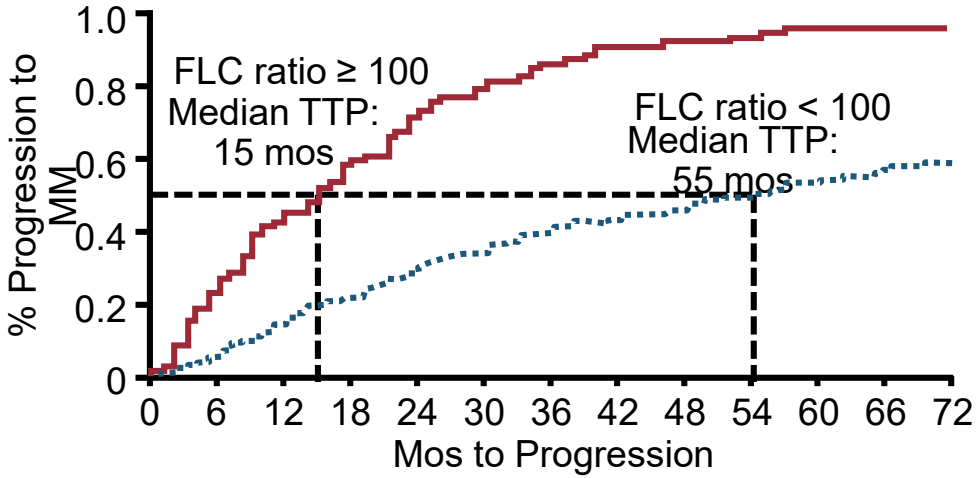
Smoldering Multiple Myeloma



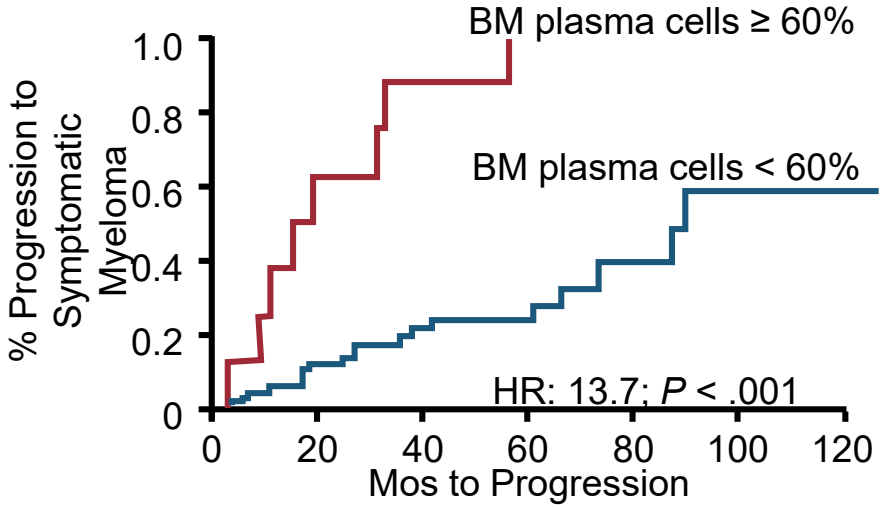
Kyle RA, et al. N Engl J Med. 2007;356:2582-2590. Greipp PR, et al. J Clin Oncol. 2005;23:3412-3420.

Biomarkers to Predict Risk of Progression

FLC ratio ≥ 100 predicts risk ($P < .0001$)



Clonal plasma cells in BM predicts risk ($P < .001$)



Larsen JT, et al. Leukemia. 2013;27:941-946. Kastritis E, et al. Leukemia. 2013;27:947-953.

Updated IMWG Criteria for Diagnosis of Multiple Myeloma

MGUS

- M protein < 3 g/dL
- Clonal plasma cells in BM < 10%
- No myeloma defining events

Smoldering Myeloma

- M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine)
- Clonal plasma cells in BM ≥ 10% to 60%
- No myeloma defining events

Multiple Myeloma

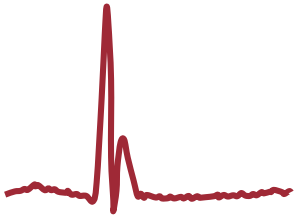
- Underlying plasma cell proliferative disorder
- AND 1 or more myeloma defining events
- ≥ 1 CRAB* feature
- Clonal plasma cells in BM ≥ 60%
- Serum free light chain ratio ≥ 100
- > 1 MRI focal lesion

*C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET-CT)

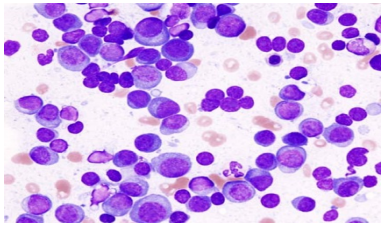
Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-e548.

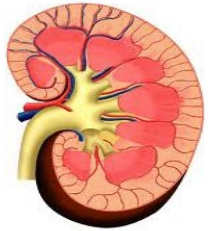
MM: Clinical Manifestations

Series of genetic mutations, translocations, normal cell turns malignant
Hallmarks of myeloma: CRAB (also known as myeloma defining events)

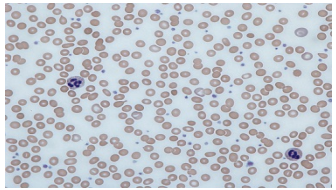


C = Hypercalcemia





R = Renal Complications



A = Anemia

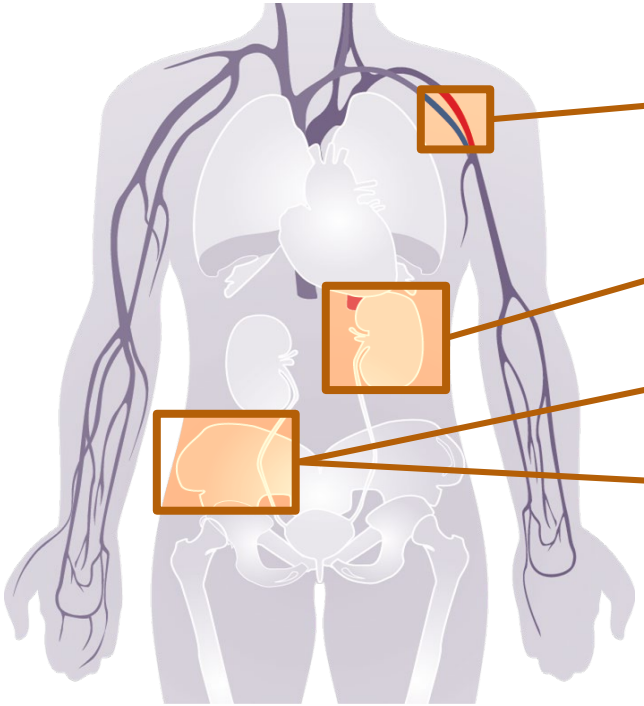
Recurrent infections*

B = Bone Disease

* Not an MDE, yet relatively common

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

Effects of Myeloma and Common Symptoms



Low blood counts →
- Weakness
- Fatigue
- Infection

Decreased kidney function → Weakness

Bone damage → Bone pain

Bone turnover →
- Loss of appetite
- Weight loss

About 10% to 20% of patients with newly diagnosed myeloma do not have any symptoms.

Multiple Myeloma Symptoms, Side Effects, and Complications. https://themmrf.org/multiple-myeloma/symptoms-side-effects-and-complications/. Accessed February 19, 2019.
Campbell K. *Nurs Times*. 2014;110:12.
Kyle R et al. Mayo Clin Proc. 2003;78:21.

Diagnostic Workup

Lab tests:

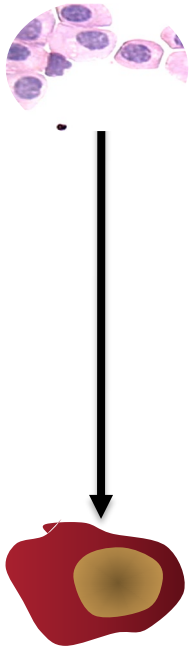
- Serum protein electrophoresis (SPEP)
- Urine protein electrophoresis (UPEP)
- Complete metabolic panel (CMP)
- CBC + differential
- Plasma ratio of free kappa/lamba light chains
- Monoclonal protein analysis (MPA)

Bone marrow biopsy:

- FISH, cytogenetics, and gene expression profiling (GEP)

Imaging:

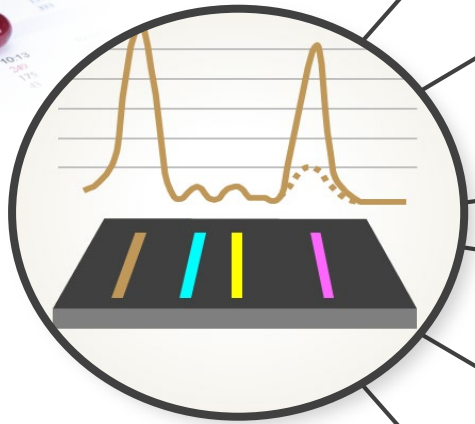
- Skeletal survey
- MRI, CT
- PET scan ± MRI, CT



Ghobrial IM, et al. Blood. 2014;124:3380-3388. Rajkumar SV, et al. Lancet Oncol. 2014;15:e538-3548. Faiman B. Clin Lymphoma Myeloma Leuk. 2014;14:436-440.

Diagnosing Myeloma: Learn Your Labs!

Blood tests

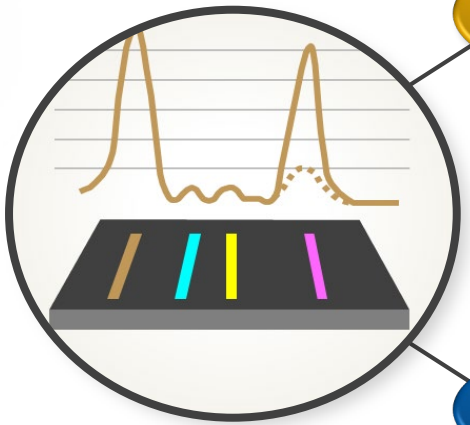


- **CBC**
  - Number of red blood cells, white blood cells, and platelets
- **CMP**
  - Measure levels of albumin, calcium, lactate dehydrogenase (LDH), blood urea nitrogen (BUN), and creatinine. Assess function of kidney, liver, and bone status and the extent of disease.
- **B2M**
  - Determine the level of a protein that indicates the presence/extent of MM and kidney function
- **SPEP**
  - Detect the presence and level of M protein
- **IFE**
  - Identify the type of abnormal antibody proteins
- **SFLC**
  - Freelite® test measures light chains (kappa or lambda)

CBC, complete blood count; CMP, complete metabolic panel; B2M; beta-2 microglobulin; SPEP, serum protein electrophoresis; IFE, immunofixation electrophoresis; SFLC, serum free light chain assay

Diagnosing Myeloma: Learn Your Labs!

Urine tests



UPEP

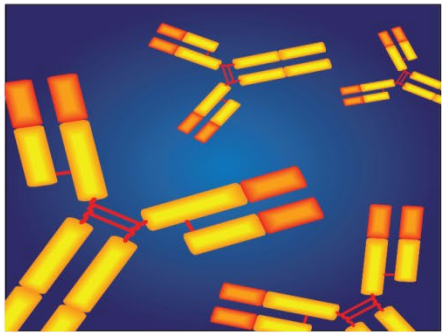
- Detect Bence Jones proteins (otherwise known as myeloma light chains)

24-hr Urine Analysis

- Determine the presence and levels of M protein and Bence Jones protein

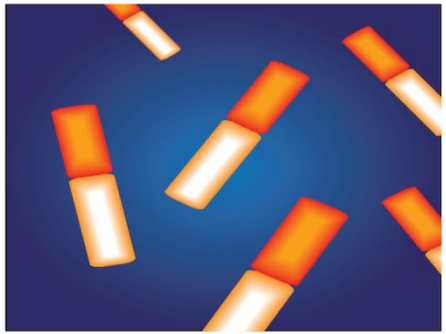
UPEP, urine protein electrophoresis

Types of Monoclonal Protein (M Protein) in Multiple Myeloma



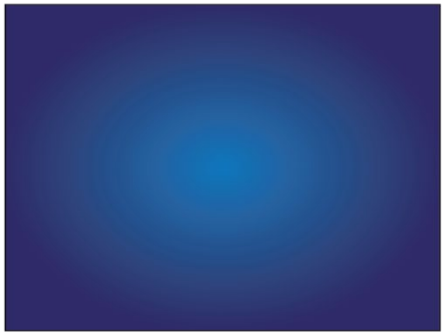
Intact immunoglobulin

- For example:
  - IgG+kappa
  - IgG+lambda
  - IgA+kappa
  - IgA+lambda
  - etc…
- 80% of myeloma cases



Light chain only

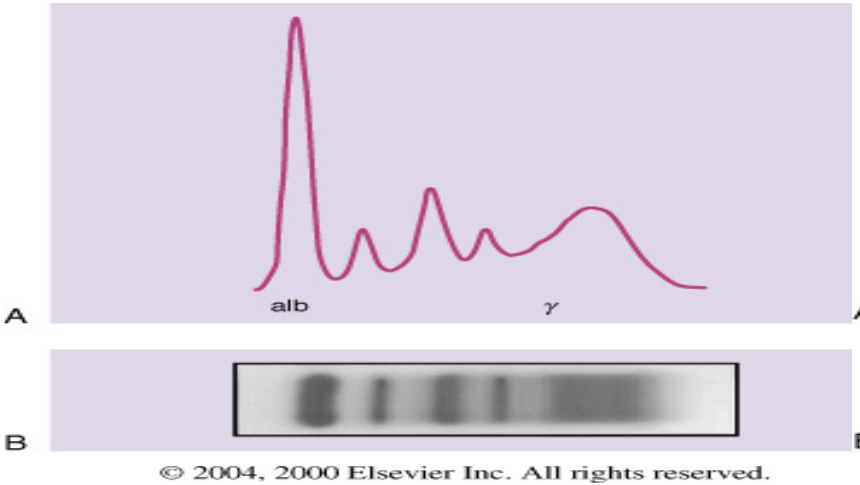
- Also known as Bence Jones protein
- 20% of all myeloma cases
- Renal failure more common in light chain multiple myeloma; creatinine >2 mg/dL in 1/3 of cases

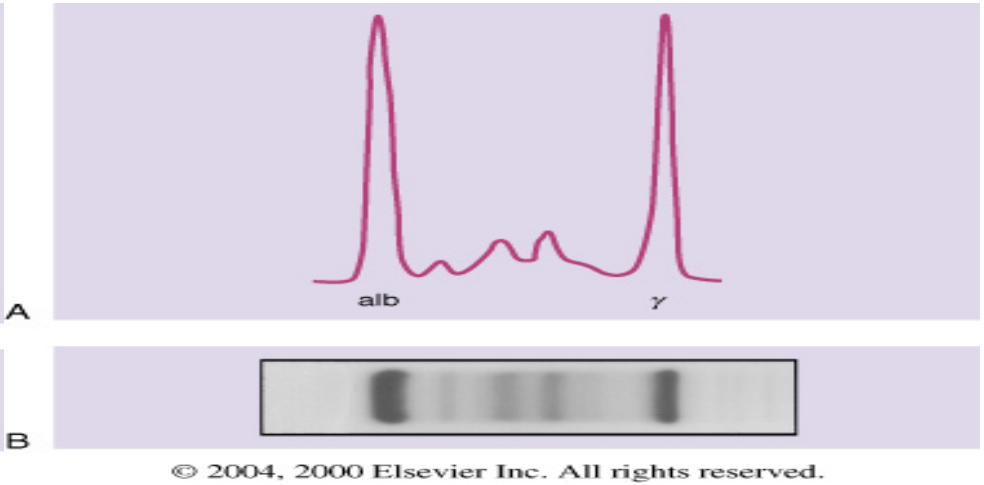


Non-secretory

- No monoclonal protein present
- 3% of cases of multiple myeloma

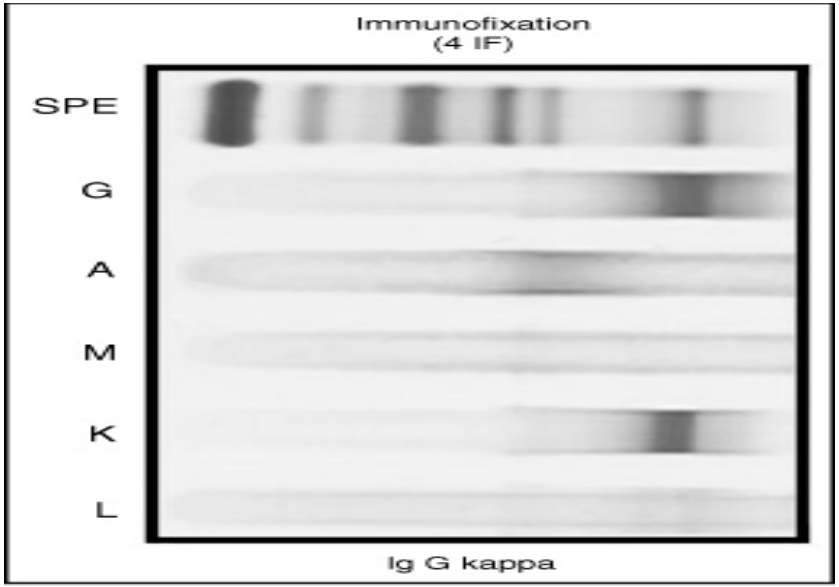
Monoclonal Protein—M Spike



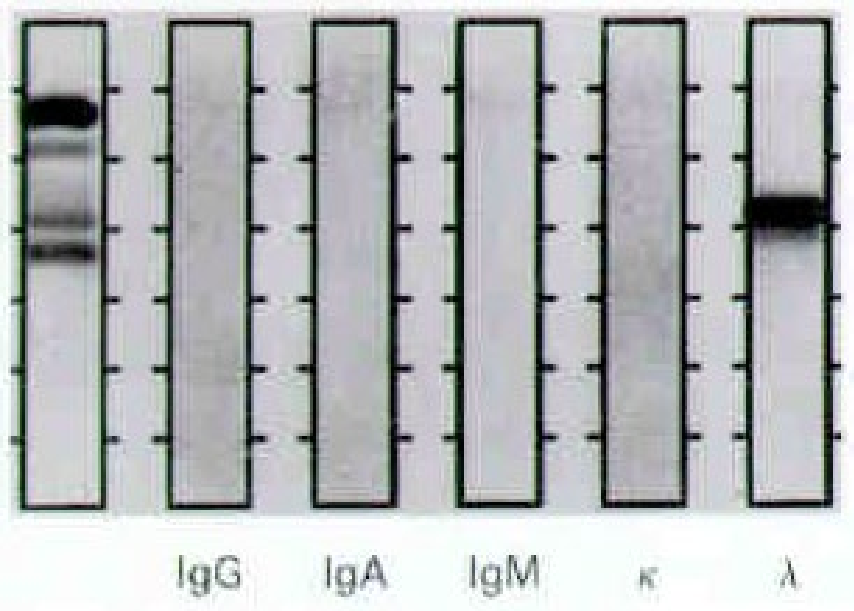


- Amount/type of M protein varies among patients (IgG, IgA 80% of cases)
- Abnormal M protein (immunoglobulin [Ig]) loses immune function and adheres and binds to tissues

Immunofixation to Determine Type of Monoclonal Protein



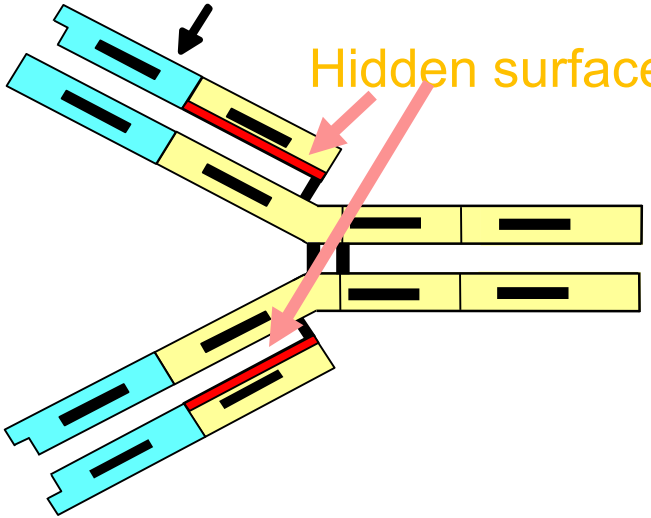
IgG kappa M protein



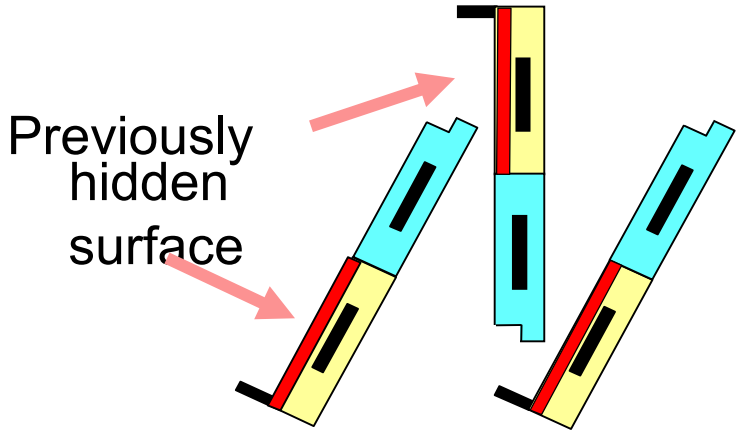
Lambda Light Chains

Kyle RA and Rajkumar SV. Cecil Textbook of Medicine, 22nd Edition, 2004

Intact Immunoglobulin



Free Light Chain



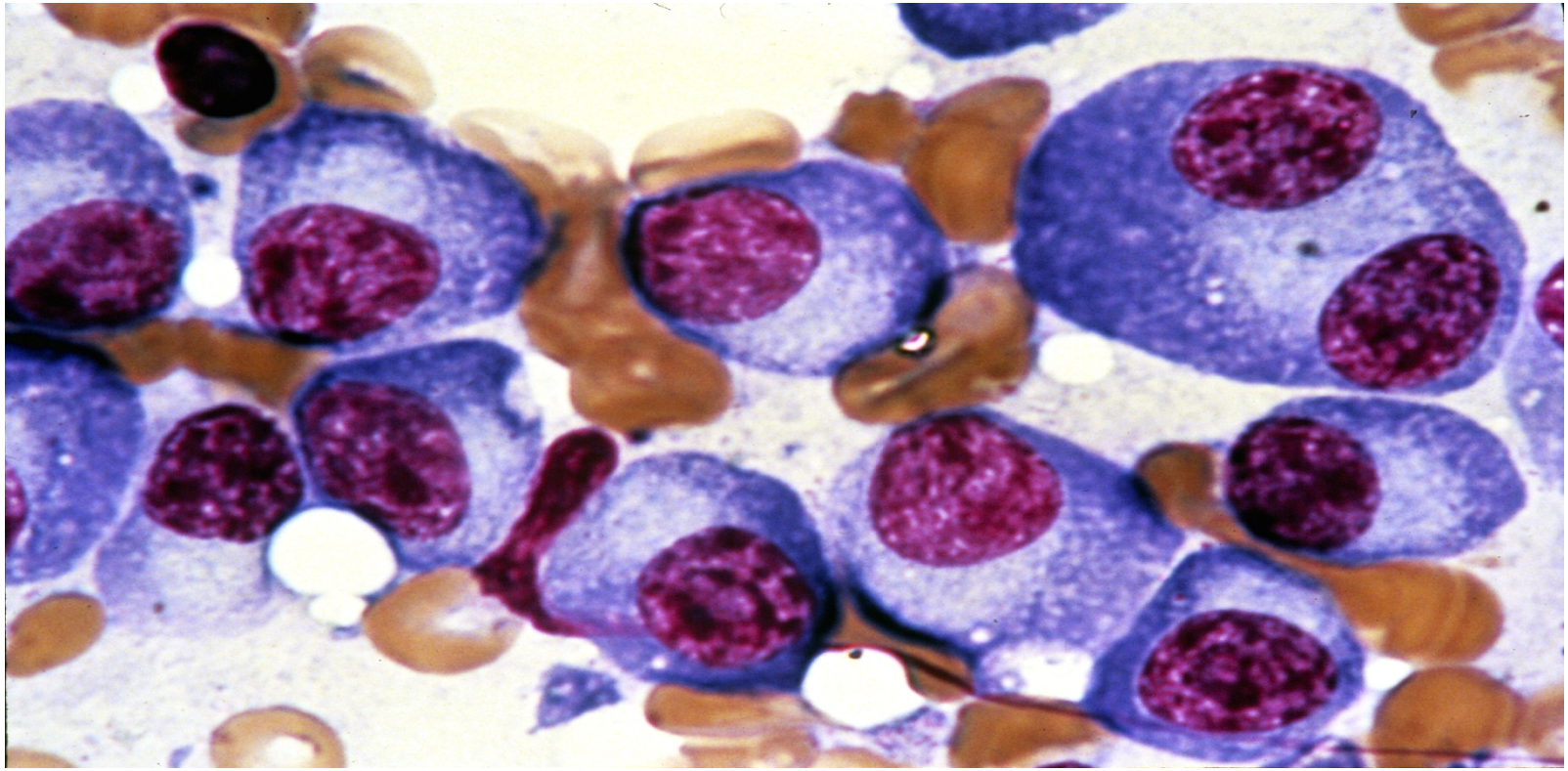
FLC reference range:

κ 3.3 – 19.4 mg/L

λ 5.7 – 26.3 mg/L

κ/λ ratio 0.26 - 1.65

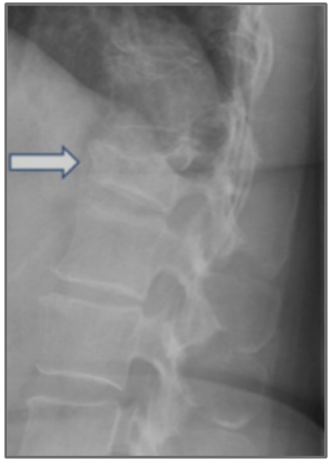
Myeloma Cells



Diagnosing Myeloma: Know Your Imaging Tests!

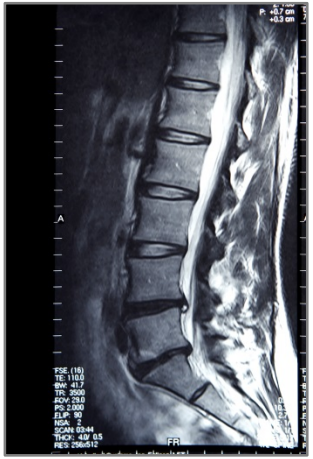
Assess changes in the bone structure and determine the number and size of tumors in the bone

X-ray

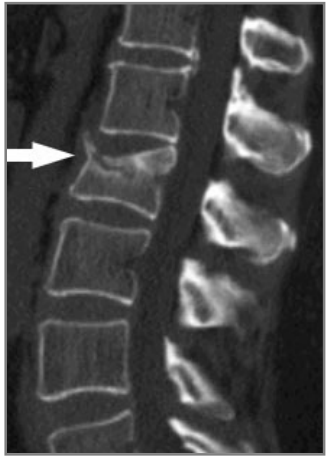


Conventional x-rays reveal punched-out lytic lesions, osteoporosis, or fractures in 75% of patients.

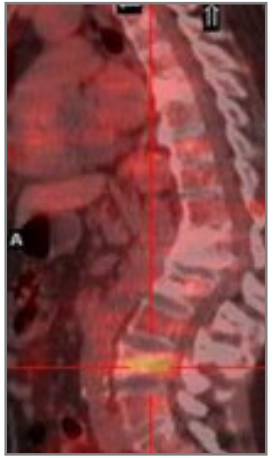
MRI



CT scan

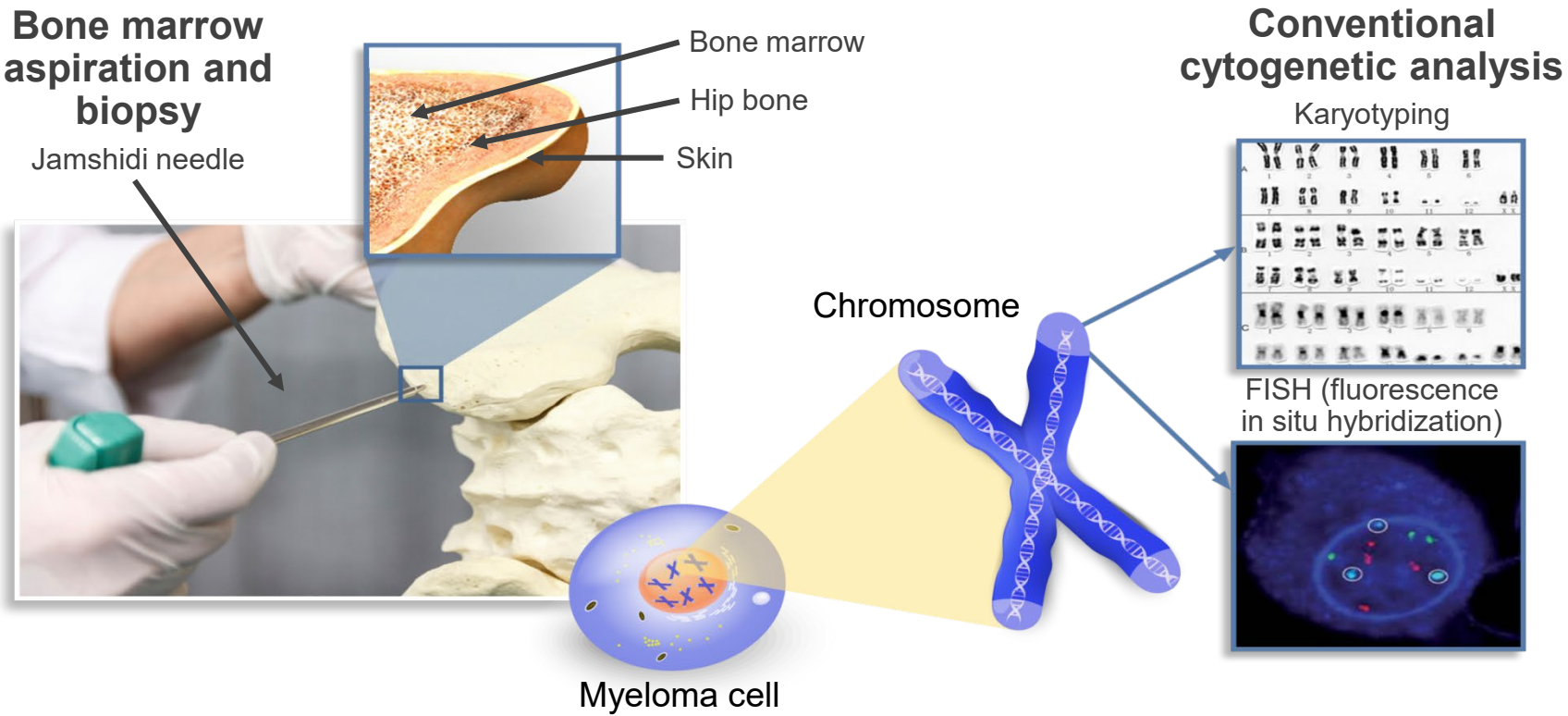


PET scan



MRI and PET/CT appear to be more sensitive (85%) than skeletal x-rays for the detection of small lytic bone lesions.

Diagnosing Myeloma: Know Your Bone Marrow Tests!



How aggressive is my myeloma?

High Risk

- High-risk genetic abnormalities[a,b]
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - Del 17p
  - p53 mutation
  - Gain 1q
- RISS Stage 3
- High plasma cell S-phase[c]
- GEP: high-risk signature

- Double-hit myeloma: any two high-risk genetic abnormalities
- Triple-hit myeloma: three or more high-risk genetic abnormalities

Standard Risk[a]

- All others including:
  - Trisomies
  - t(11;14)[d]
  - t(6;14)

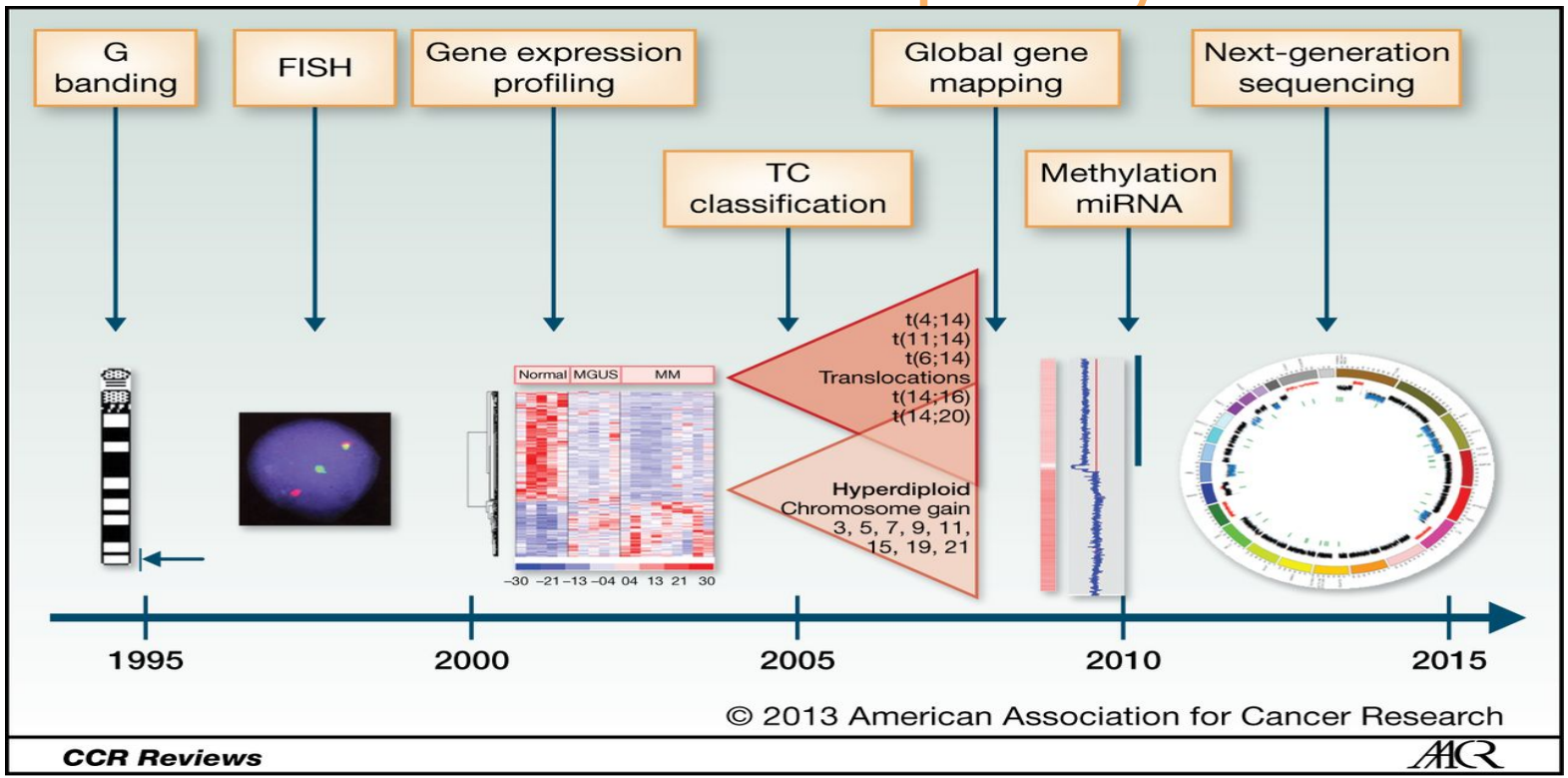
Currently cannot predict with great certainty all high-risk patients.

Based on the Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013

[a]Trisomies may ameliorate; [b]By FISH or equivalent method; [c]Cut-offs vary; [d]t(11;14) may be associated with plasma cell leukemia

Mikhael JR et al. *Mayo Clin Proc*. 2013;88:360.

Technological advances in detecting biomarkers in multiple myeloma



REVISED- International Staging System (ISS):Prognostic Groupings

Stage	Criteria
Stage I	Serum β_2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL Standard risk cytogenetics Normal LDH
Stage II	Not R-ISS stage I or stage III
Stage III	Serum β_2-microglobulin ≥ 5.5 mg/L and high risk cytogenetics by FISH or high LDH [t(4;14), t(14;16), 17p]

Greipp et al. *J Clin Oncol*. 2005;23(15):3412; Palumbo et al J Clin Onco Aug 2015l

Know the Diagnosis
Key Items That Define the Diagnosis

MGUS

- M protein <3 g/dL
- Clonal plasma cells in BM <10%
- No myeloma-defining events

1% risk of progression/year to multiple myeloma or related conditions

Smoldering Myeloma

- M protein ≥3 g/dL (serum) or ≥500 mg/ 24 hrs (urine)
- Clonal plasma cells in BM ≥10%–60%
- No myeloma-defining events

10% risk of progression/year to active myeloma

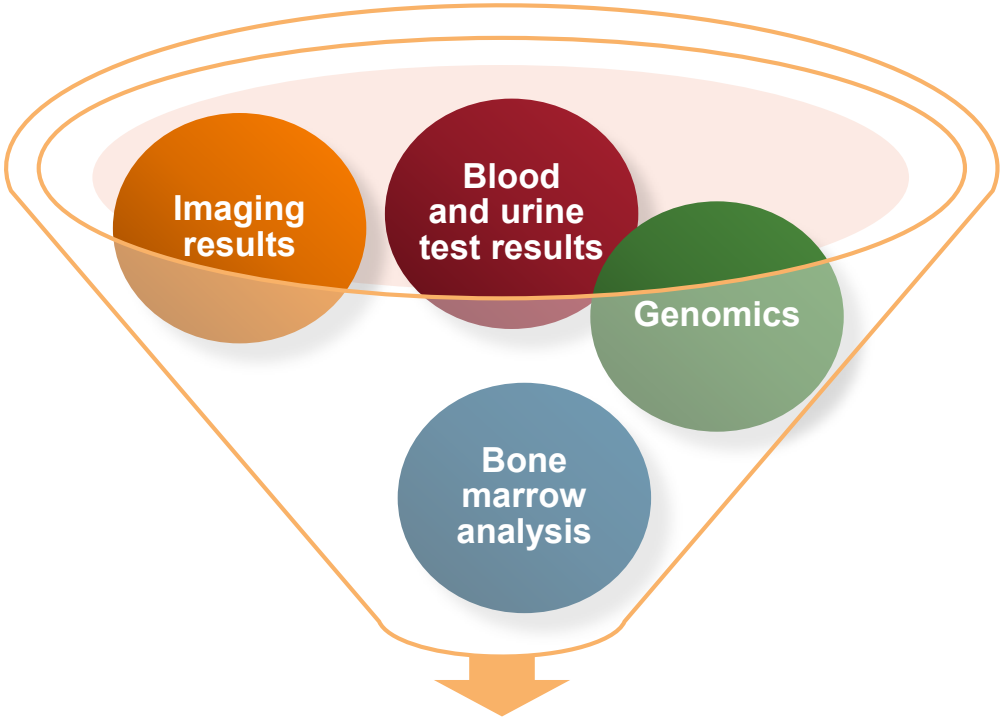
Multiple Myeloma

- Underlying plasma cell proliferative disorder
- AND ≥1 myeloma-defining events
- ≥1 CRAB* feature
- Clonal plasma cells in BM ≥60%
- Serum free light chain ratio ≥100
- >1 MRI focal lesion

*__C:__ Calcium elevation (>11 mg/dL or >1 mg/dL higher than ULN)
__R:__ Renal insufficiency (creatinine clearance <40 mL/min or serum creatinine >2 mg/dL)
__A:__ Anemia (Hb <10 g/dL or 2 g/dL < normal)
__B:__ Bone disease (≥1 lytic lesions on skeletal radiography, CT, or PET-CT)

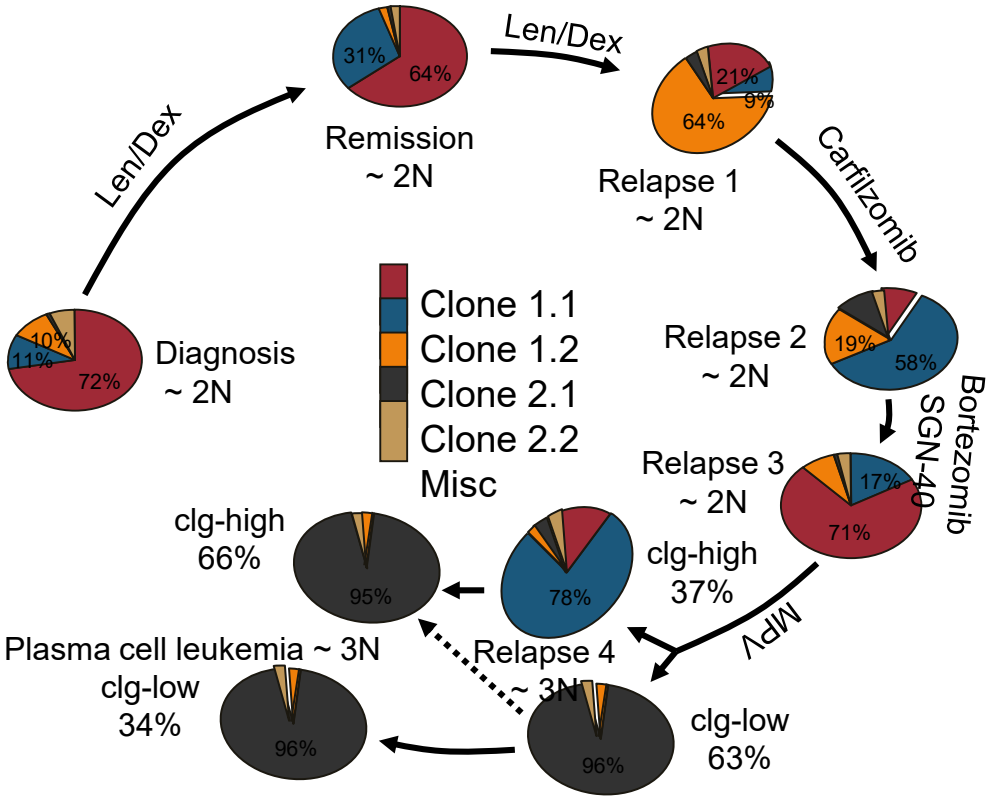
Rajkumar SV et al. *Lancet Oncol*. 2014;15:e538.

Putting the Results Together



Staging, and Prognosis

Clonal Evolution and Clonal Competition



Keats JJ, et al. Blood. 2012;120:1067-1076.

Multiple clones may be present at the time of diagnosis

The predominant clone may change over time, especially after treatment rounds

Hypothesis: effective treatment reduces or eliminates the dominant clone; however, other clones can still exist

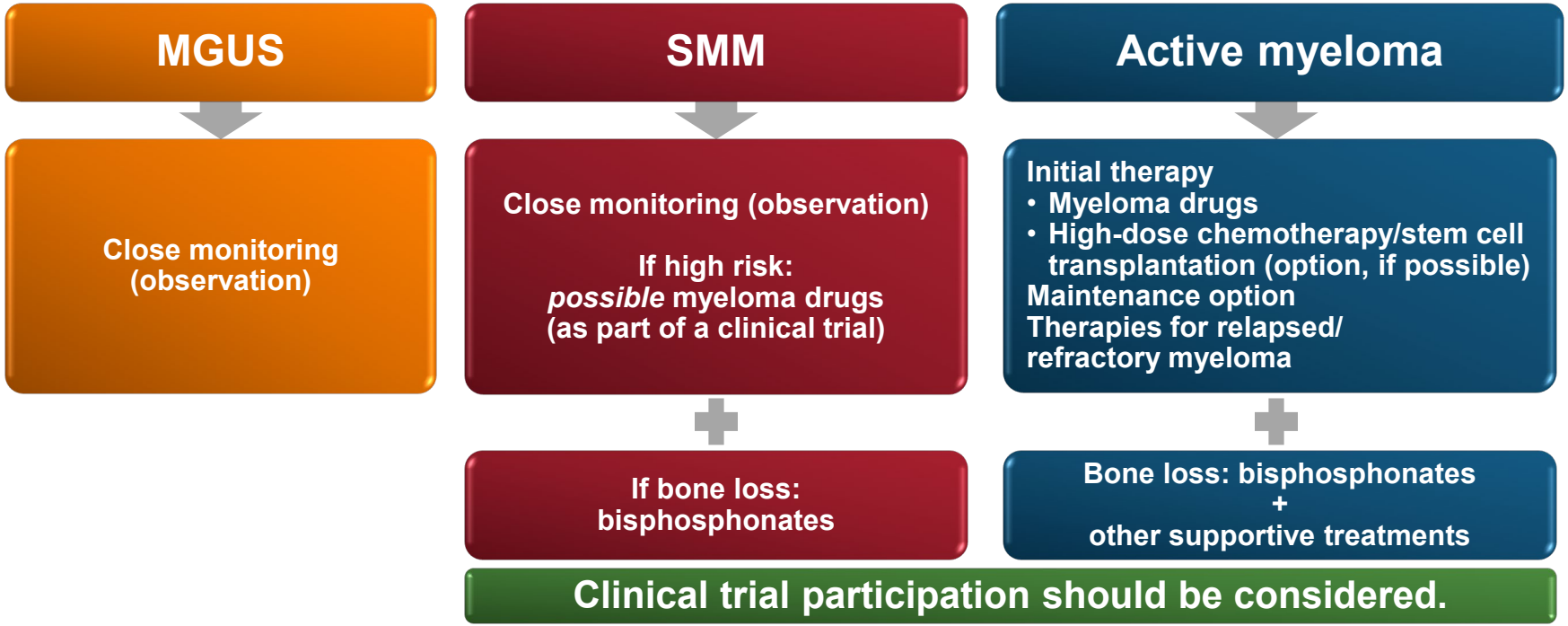
Relapse can occur when:

Existing clone no longer has to compete for space with the formerly dominant clone

Acquires additional mutation(s) providing a growth and/or survival advantage

Treatment Overview

Overview of Treatment Approach



History of Treatment

- 1844: Rhubarb and infusions of orange peel for Sarah Newbury
- 1845: Phlebotomy, then leeches for maintenance therapy (William McBean)
- 1947: Urethane reported by Alwall
- 1958: Blohkin reports sarcolysin (melphalan) in 3 of 6 patients
- 1962: Bergsagel expands use of melphalan
- 1962: Maas report on prednisone

First Randomized Trial in MM

- A controlled trial of urethane treatment in multiple myeloma. Holland JR, Hosley H, Scharlau C, Carbone PP, Frei E 3rd, Brindley CO, Hall TC, Shnider BI, Gold GL, Lasagna L, Owens AH Jr, Miller SP.

- Randomized 83 patients with treated or untreated multiple myeloma to receive *urethane* or a placebo consisting of a cherry- and cola-flavoured syrup.
- No difference was seen in objective improvement or in survival in the two treatment groups. In fact, the urethane-treated patients died earlier

Blood 1966; 27: 328-342

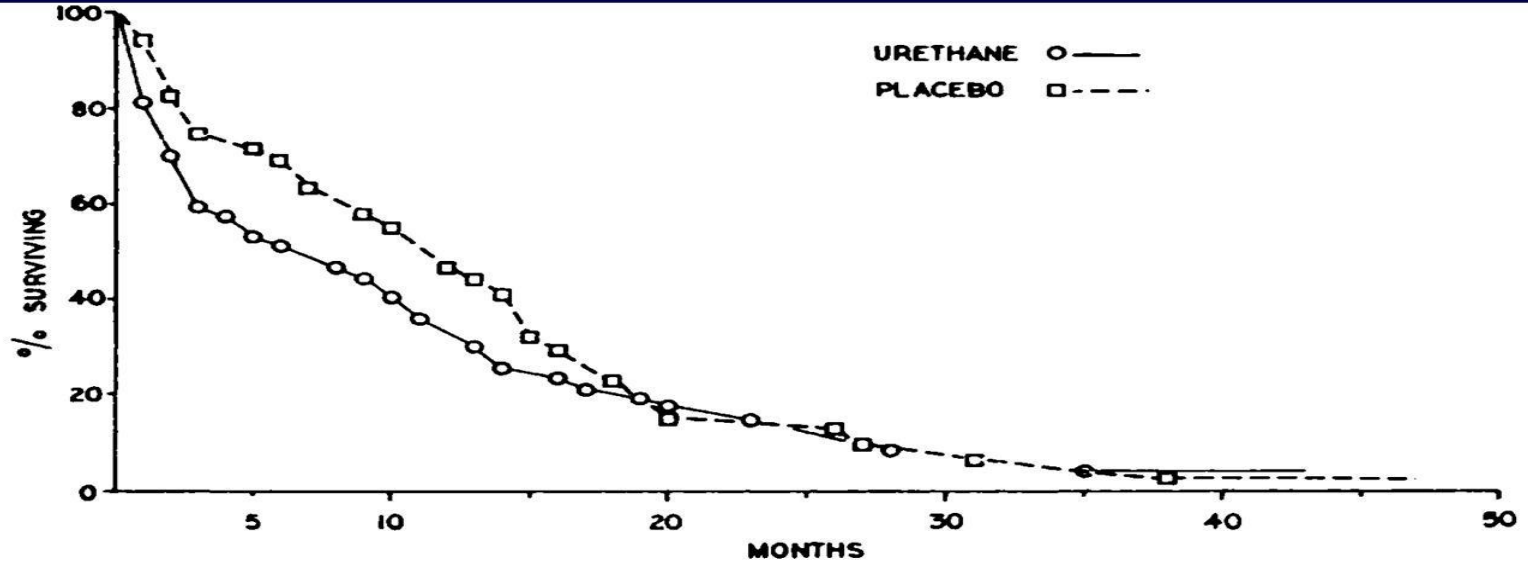


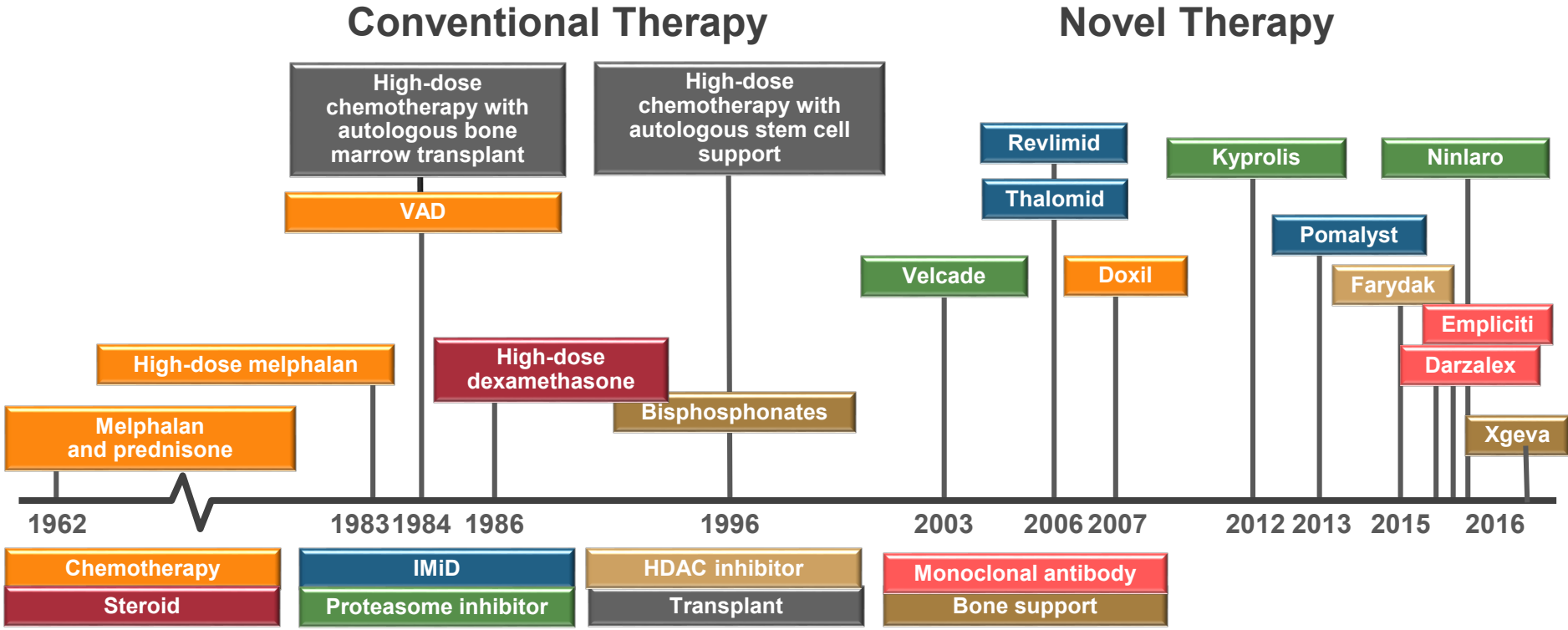
Fig. 1.—Survival from onset of treatment plotted by life table method in patients with multiple myeloma according to treatment category.

Table 7.—*Median Survival from Onset of Treatment of Patients with Multiple as Influenced by Prior and Present Treatment*

	Median Survival, Months		
	A	B	C
Urethane	8	8	5
Placebo	15	10.5	12

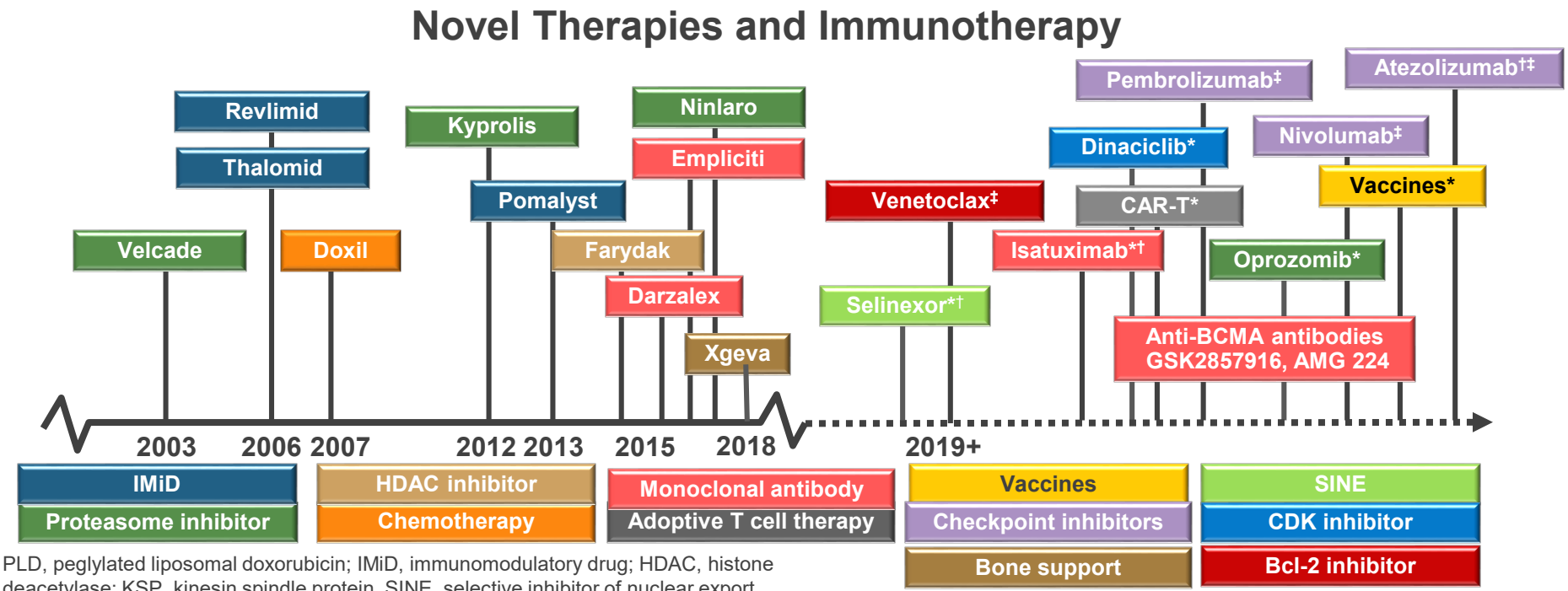
A = Prior urethane.
B = Other prior treatment.
C = No prior treatment.

Evolution of Multiple Myeloma Treatment: 11 New Drugs Approved in ≤15 Years



VAD, vincristine, doxorubicin, dexamethasone; IMiD, immunomodulatory drug; HDAC, histone deacetylase.

Continuing Evolution of Multiple Myeloma Treatment: New Classes and Targets



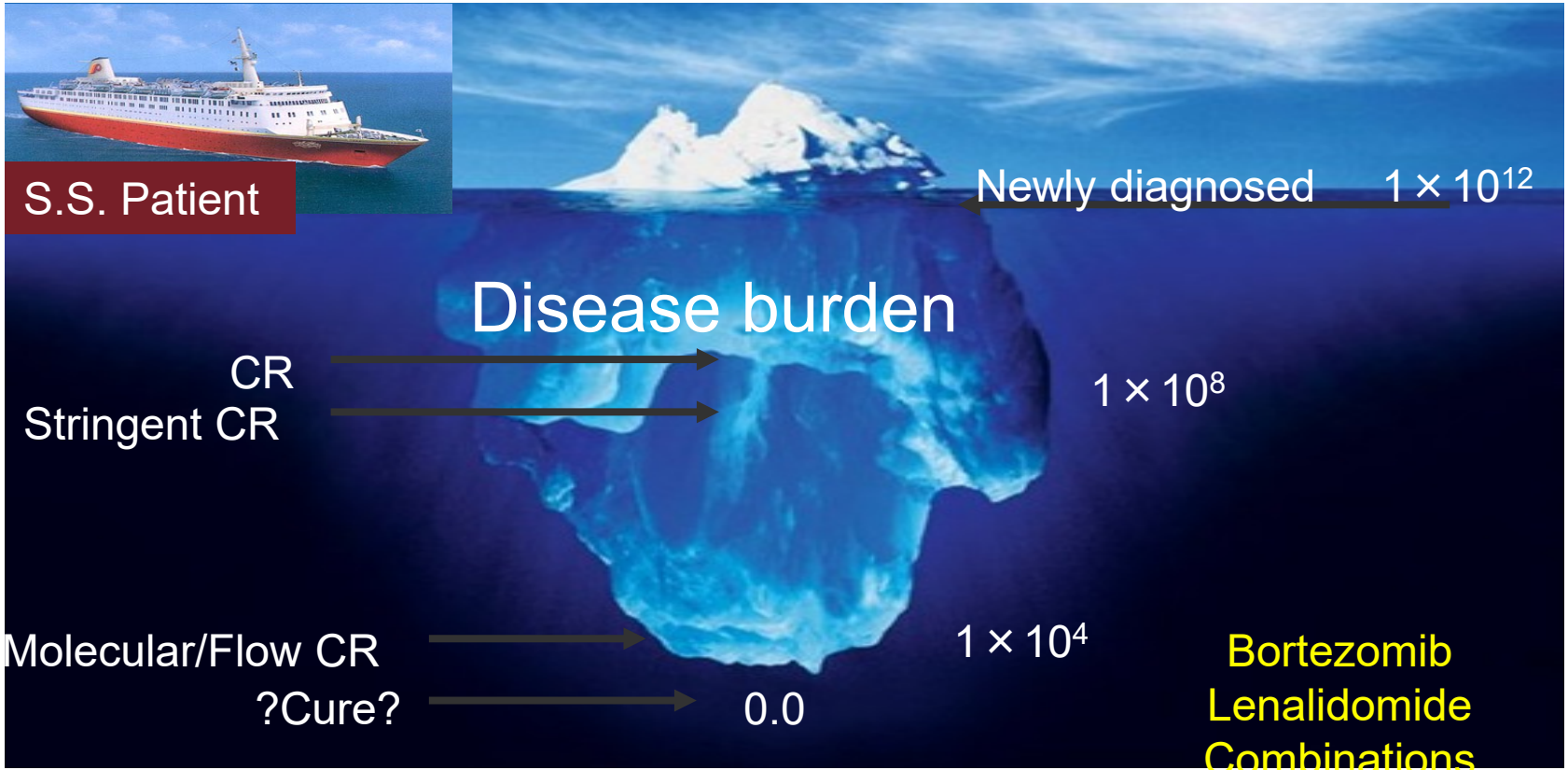
PLD, peglylated liposomal doxorubicin; IMiD, immunomodulatory drug; HDAC, histone deacetylase; KSP, kinesin spindle protein, SINE, selective inhibitor of nuclear export
*Not yet FDA-approved; only available in clinical trials
†Treatments studied in MMRC trials
‡FDA-approved for a non-MM indication

Measuring Response to Therapy

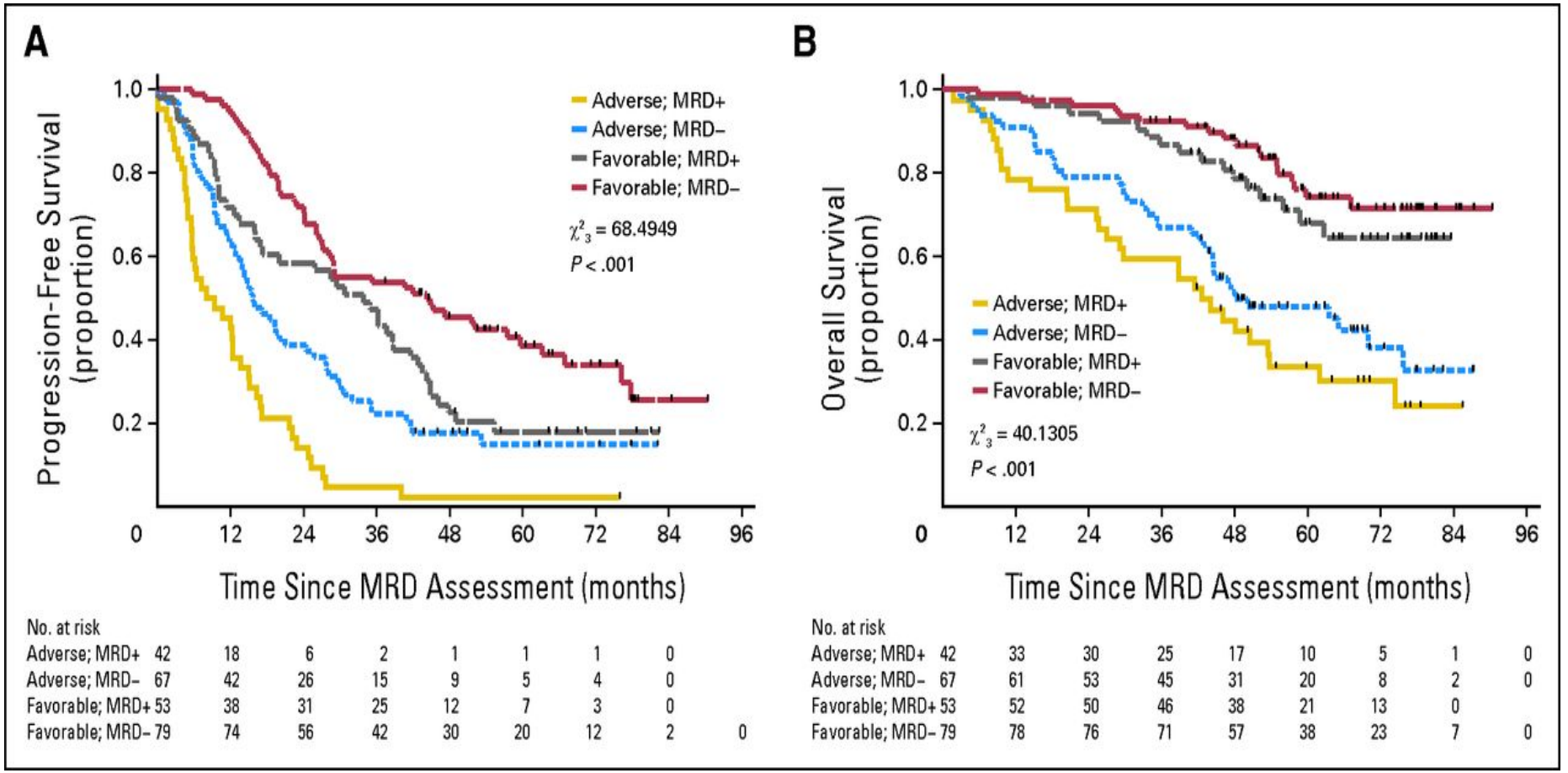
Response Type	Abbreviation	Tests						
		M-Protein Reduction		Immunofixation	Bone Marrow			Freelite
		Blood	Urine		PC	Immuno-fluorescence	Other	
Complete response	CR	0	0	Negative	<5%	—	—	—
Stringent complete response	sCR	0	0	Negative	<5%	Negative	—	Normal
Very good partial response	VGPR	>90%	<100 mg/24 hrs	—	—	—	—	—
Partial response	PR	>50%	>90%	—	—	—	—	—
Stable response	SD	Does not meet criteria for response or progressive disease						
Progressive disease	PD	An increase of 25% in M-protein; an increase of 10% in bone marrow plasma cells						

e (or depth) of response is usually associated with better prognosis. Some patients do well despite never

Getting to Minimal Residual Disease (MRD): New Definitions for CR



Minimal Residual Disease (MRD)



Key Considerations for Optimal Disease Management

1. Laboratory and imaging tests, tissue banking, and diagnosis
2. Staging and prognosis
3. Obtain a second opinion
4. Know the standard of care
5. Consider clinical trials

Myeloma 101: Summary

- Multiple myeloma can have numerous effects on the body.
- Genomics is growing and may lead to personalized treatments.
- Survival improving because of new drugs and new combinations of drugs.
- Treatment paradigm will continue to change with the approval of additional novel agents.

Be an informed and empowered patient!