Learn Your Labs

June 20, 2023

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Tech Support

1-719-234-7952

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Resources

- Resource tab includes
  - Speaker bios
  - Copy of the slide presentation
  - Exhibit Hall

Submit your questions throughout the program!

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MMRF Research Initiatives

MULTIPLE MYELOMA Research Consortium

CoMMpass Study℠

CureCloud®

For more information, visit themmrf.org

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Speakers

Joshua Richter, MD
Tisch Cancer Institute/Icahn School of Medicine at Mount Sinai
New York, New York

Craig Emmitt Cole, MD
Michigan State University
College of Human Medicine
Karmanos Cancer Institute
East Lansing, Michigan

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Blood Tests

Craig Emmitt Cole, MD
Michigan State University College of Human Medicine
Karmanos Cancer Institute
East Lansing, Michigan

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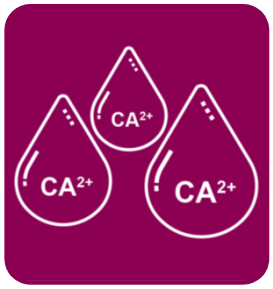
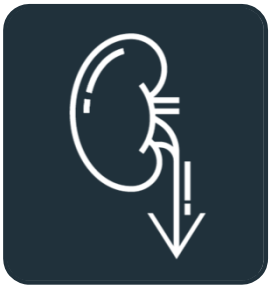
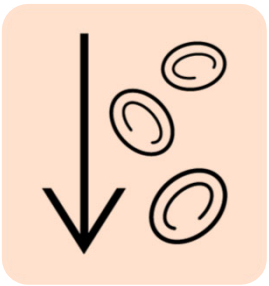
Multiple Myeloma Affects Your Bones, Blood, and Kidneys

The clinical features that are characteristic of multiple myeloma

C	R	A	B
			
High levels of **c**alcium in the blood	Decreased kidney (**r**enal) function	Low amount of red blood cells (**a**nemia)	Presence of **b**one damage

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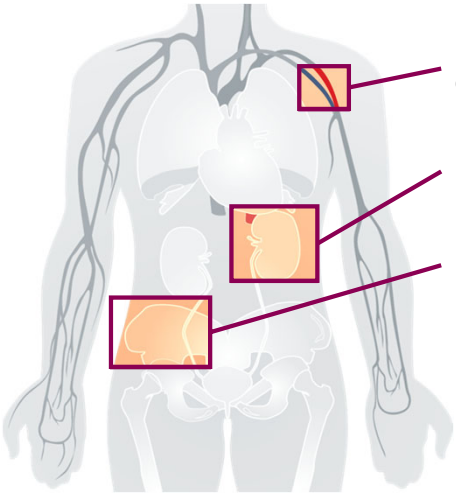
Effects of Myeloma and Common Symptoms



Low blood counts → Weakness, Fatigue, Infection

Decreased kidney function → Weakness

Bone damage → Bone pain

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

Disease presentation and myeloma-related complications after myeloma diagnosis are different in patients by race

More common in Black patients

- Hypercalcemia
- Kidney dysfunction
  - Hemodialysis
- Anemia

Less common in Black patients

- Bone fractures

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Blood, Urine, Bone Marrow, and Imaging Tests Used to Identify MGUS, SMM, or Active Multiple Myeloma

	MGUS	SMM	Active MM
M protein	<3 g/dL in blood	≥3 g/dL in blood **or** ≥500 mg/24 hrs in urine	≥3 g/dL in blood **or** ≥500 mg/24 hrs in urine
Plasma cells in bone marrow	<10%	≥10%–60%	≥60%
Clinical features	No myeloma-defining events*	No myeloma-defining events*	≥1 myeloma-defining event*, including either: • ≥1 CRAB feature ***or*** • ≥1 SLiM feature

*CRAB, calcium elevation, renal insufficiency, anemia, bone disease; SLiM, >60% plasma cells in bone marrow, free light chain involved to uninvolved ratio >100, >1 focal lesion on MRI

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

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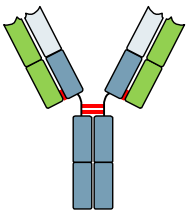
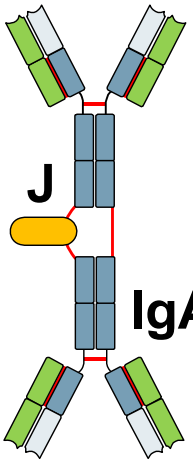
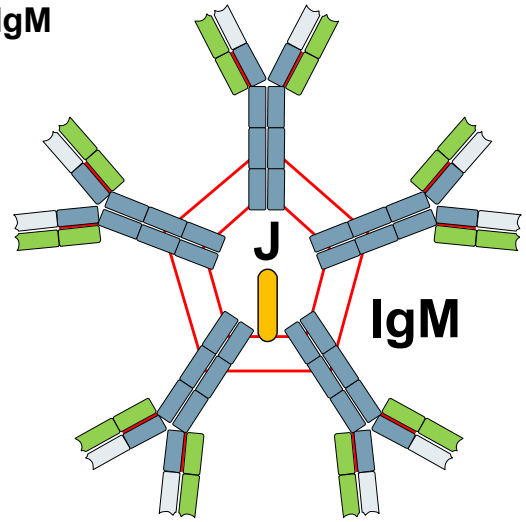
Anatomy of the Antibody

Immunoglobulin classes: IgG, IgA, and IgM



IgG





Red – disulphide links
Green – light chains
Blue – heavy chains

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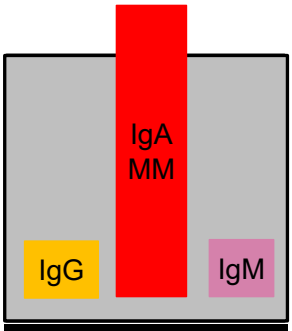
Quantitative Immunoglobulins and Immunofixation

- Quantitative serum immunoglobulins can detect *immunoparesis*
  - Quantitative immunoglobulins is a test to check the normal (uninvolved) antibody levels and the antibody produced by the myeloma plasma cells
  - Uninvolved immunoglobulins are reduced in 91% of myeloma patients
- The ***type*** of M protein is best determined by immunofixation
  - Immunofixation can also detect very small amounts of a serum and urine M-protein.
- **17% of patients with myeloma only produce light chains**
  - **We always check the M protein on the SPEP and light chains in myeloma**



Quantitative Immunoglobulins in Myeloma

Katzmann JA et al. *Am J Clin Pathol*. 1998;110:503. Dimopoulos M et al. *Blood*. 2011;117:4701. Attaelmannan M, Levinson SS. *J Clin Chem*. 2000;46:1230.

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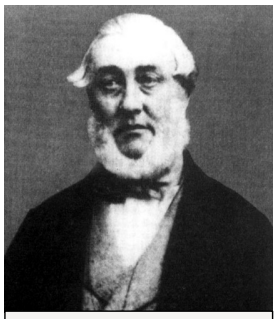
Light Chain Monoclonal Gammopathy Detection

- **17% of patients with myeloma only produce light chains**
  - **Light chain concentrations are too low to be detected by routine serum immunofixation**
  - Light chains can be found either with 24-hr urine collection for Bence Jones urine protein electrophoresis (UPEP) ***or*** a blood test for the serum light chain analysis
  - Random (spot) Bence Jones UPEP alone is **not** considered adequate screening for monoclonal gammopathies
- A sensitive assay for immunoglobulin **free light chains** (FLCs) in the blood is available
  - Several studies have shown the serum FLC test equivalent or superior to the 24-hr urine collection.
  - Ratio helps in *diagnosis*; the total FLC total value assesses response



Portrait of Henry Bence Jones @1844

NCCN Practice Guidelines Version 2.2014. Pratt G. *Br J Haematol*. 2008;141:413. Dimopoulos M et al. *Blood*. 2011;117:4701.

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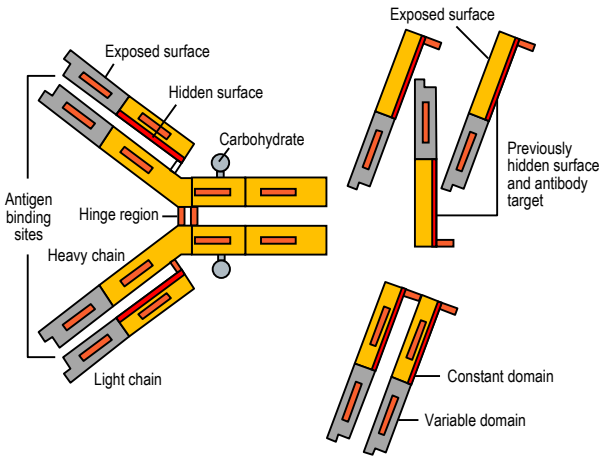
Light Chain Monoclonal Gammopathy Detection

- Serum FLC assay uses κ and λ polyclonal antibodies against specific epitopes that are hidden in intact immunoglobulins but exposed on FLCs
- FLCs independently quantify the two isotypes
- Monoclonality can be identified by the demonstration of an abnormal **ratio** of κ : λ FLCs



Hutchison CA et al. *Nat Rev Nephrol*. 2009;5:621.

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Light Chain Monoclonal Gammopathy Detection

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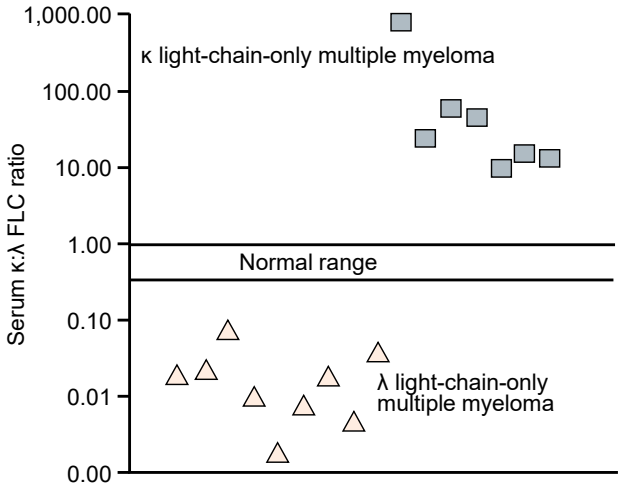

Hutchison CA et al. *Nat Rev Nephrol.* 2009;5:621.

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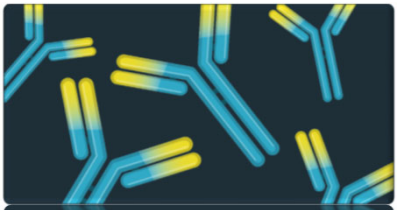
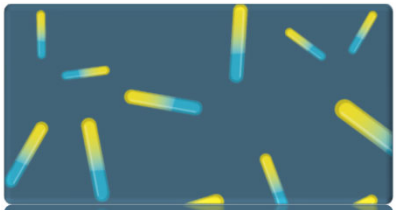
Types of Multiple Myeloma Based on Blood or Urine Tests



Intact M protein

- Named for the type of immunoglobulin and light chain pair; for example, IgG kappa (κ) or IgG lambda (λ)
- 80% of patients
- Use M protein to follow disease



Light chain only

- Also known as Bence Jones protein
- Renal failure more common in light chain multiple myeloma
- 20% of patients
- Use free light chain (κ or λ) or Bence Jones protein to follow disease

Non-secretory

- No M protein present
- 3% of patients
- Use PET scan, bone marrow biopsy, ? mass spectrometry

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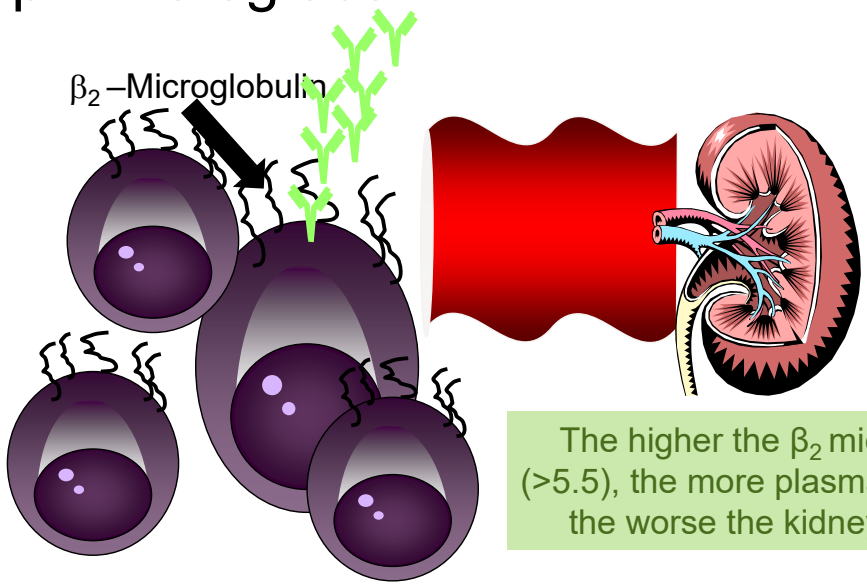
Staging Myeloma: Serum Levels of β2 Microglobulin



The higher the β_2 microglobulin (>5.5), the more plasma cells and/or the worse the kidney function.

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Diagnosing and Monitoring Myeloma: Learn Your Labs!

CBC	• Number of red blood cells, white blood cells, and platelets
CoMP	• Comprehensive panel: measure levels of albumin, calcium, and creatinine; assess function of kidney, liver, and bone status and the extent of disease
Beta-2 microglobulin	• Determine the level of a protein that indicates the presence/extent of MM and kidney function: **USED FOR STAGE**
Lactate dehydrogenase (LDH)	• Determine the level of myeloma cell production and extent of MM: **USED FOR STAGE**
Serum protein EP	• **Detect the presence and level of M protein = *how much myeloma***
Immunofixation	• **Identify the *type* of abnormal antibody proteins: IgG, IgA, κ, or λ**
Serum free light chain	• **Freelite test measures free light chains (kappa or lambda) in blood = *how much myeloma***
Urine protein EP	• **Detect Bence Jones proteins (otherwise known as myeloma light chains) in urine (*present or not present*)**
24-hr urine analysis	• **Determine the presence and levels of M protein and Bence Jones protein in the urine = *how much myeloma***

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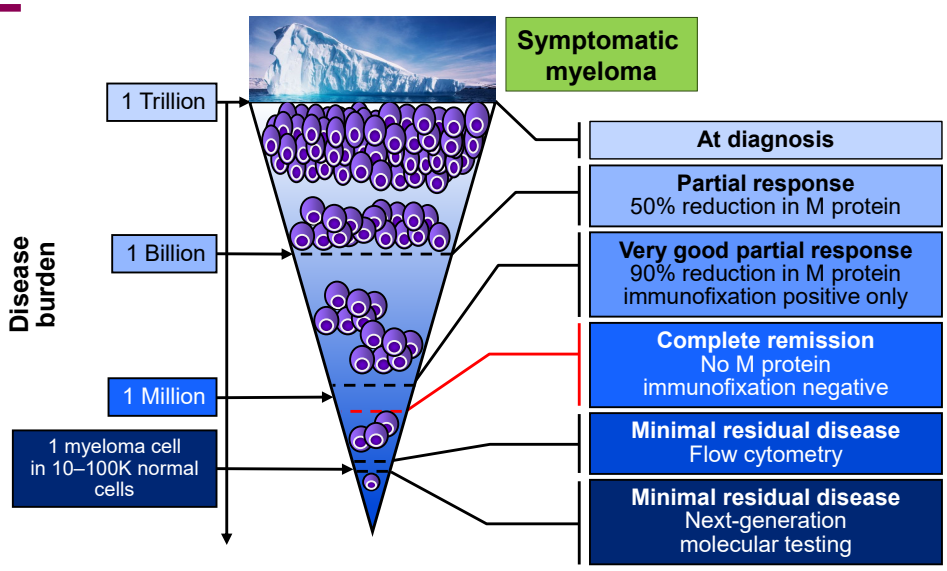
The Iceberg Model of Myeloma



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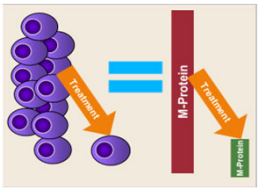
Summary

- Unlike other types of cancer, multiple myeloma is diagnosed, staged, and monitored through blood tests, x-rays, and bone marrow biopsies.
- Blood tests allow you and your doctor to not only track the myeloma but also the function of the bone marrow, kidneys, liver, immune system, and electrolytes.
- Know how to read your myeloma (M) protein level.
- Understanding and monitoring your M protein and/or free light chains will allow you to know when and how well you have responded to therapy.
- Understanding your blood work informs and empowers you!
- *You* can cope with the diagnosis of multiple myeloma by empowering yourself to learn what you need to gain control, knowledge, and support!



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Bone Marrow Biopsy and Staging

Joshua Richter, MD
Tisch Cancer Institute/Icahn School of Medicine at Mount Sinai
New York, New York

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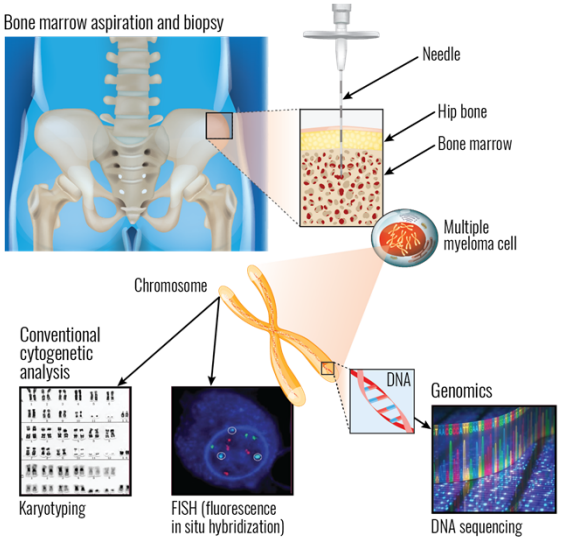
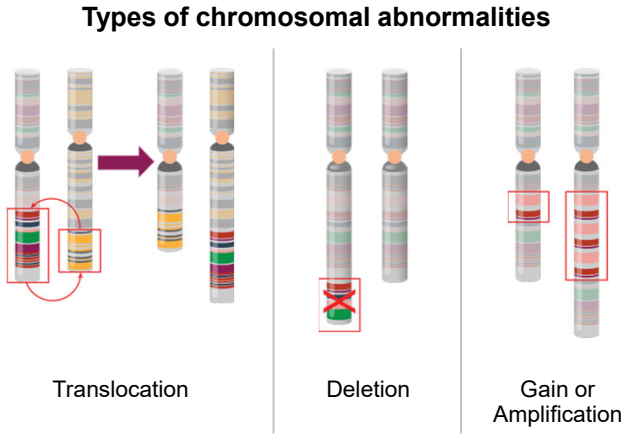
Bone Marrow Biopsy





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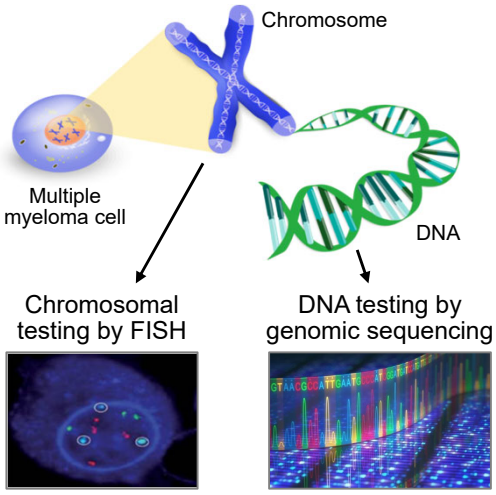
Why is genomic sequencing important in myeloma risk assessment?

- Genetic changes in myeloma cells may affect prognosis and treatment selection
- Using samples from the bone marrow—specific tests look at these genetic changes
- Some tests are used routinely and look at the ***chromosomal*** changes (FISH)
- Newer tests assess changes in the ***DNA*** (gene expression profiling and next-generation sequencing)
  - Ask your doctor if these tests are available
- All patients in the MMRF CoMMpass study had **genomic sequencing** from diagnosis to relapse. The resulting data provides detailed genetic profiles for every myeloma patient at every stage of their disease!



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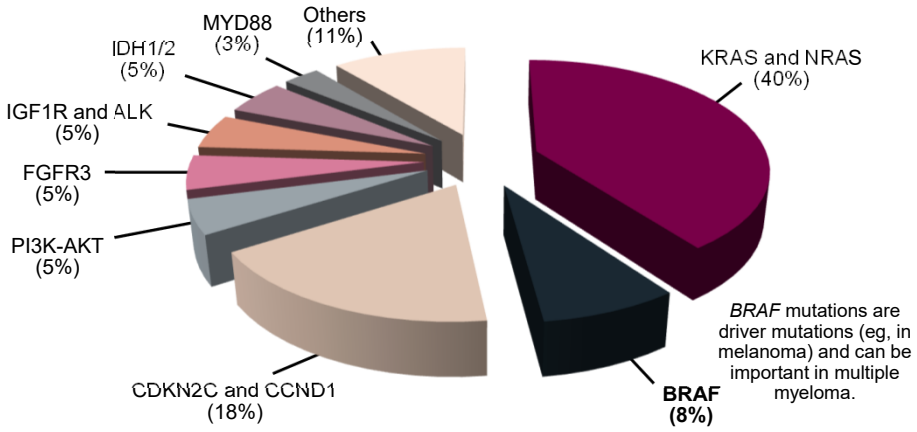
Actionable Alterations in MM

These alterations may be the Achilles' heel of myeloma cells.

Personalized medicine efforts have identified molecular alterations for which there are drugs in the clinic



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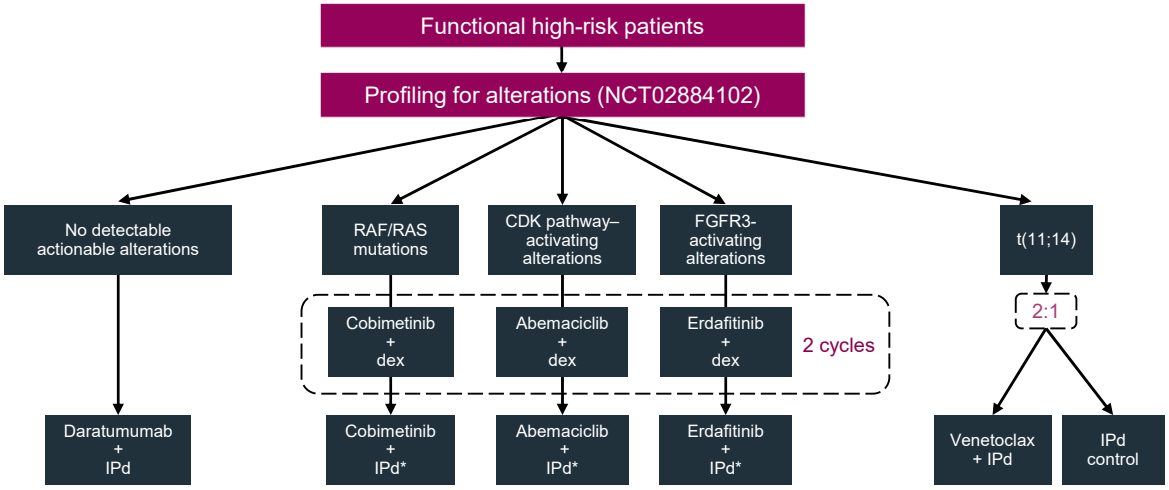
MyDRUG Trial



*Assess single-agent activity after 2 cycles: after cycle 2, add backbone to single agent

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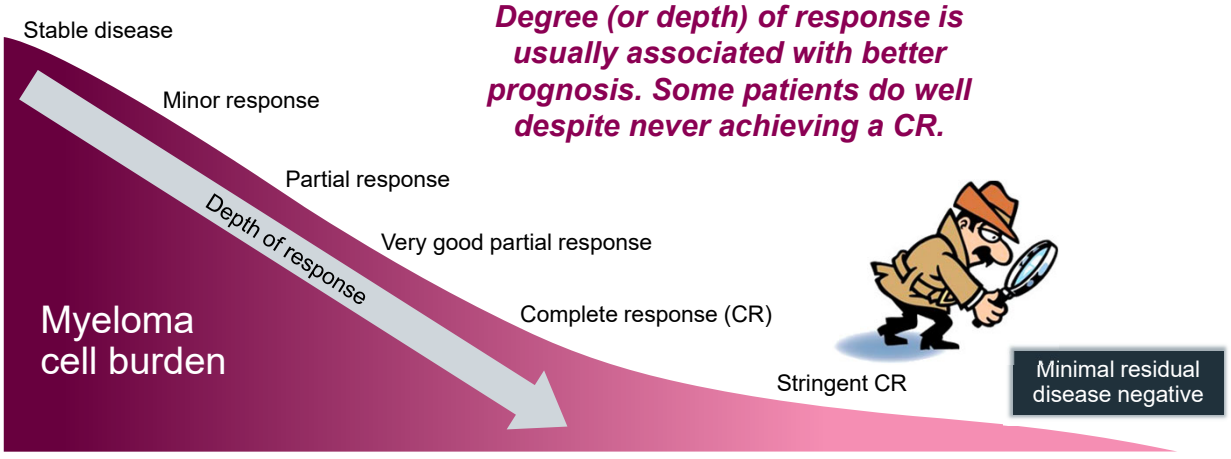
Measuring Response to Therapy



Degree (or depth) of response is usually associated with better prognosis. Some patients do well despite never achieving a CR.

ClonoSEQ is an FDA-approved next-generation sequencing (NGS) test to measure MRD in MM patients

Palumbo A et al. *J Clin Oncol*. 2014;32:587.
Kumar S et al. *Lancet Oncol*. 2016;17:e328.

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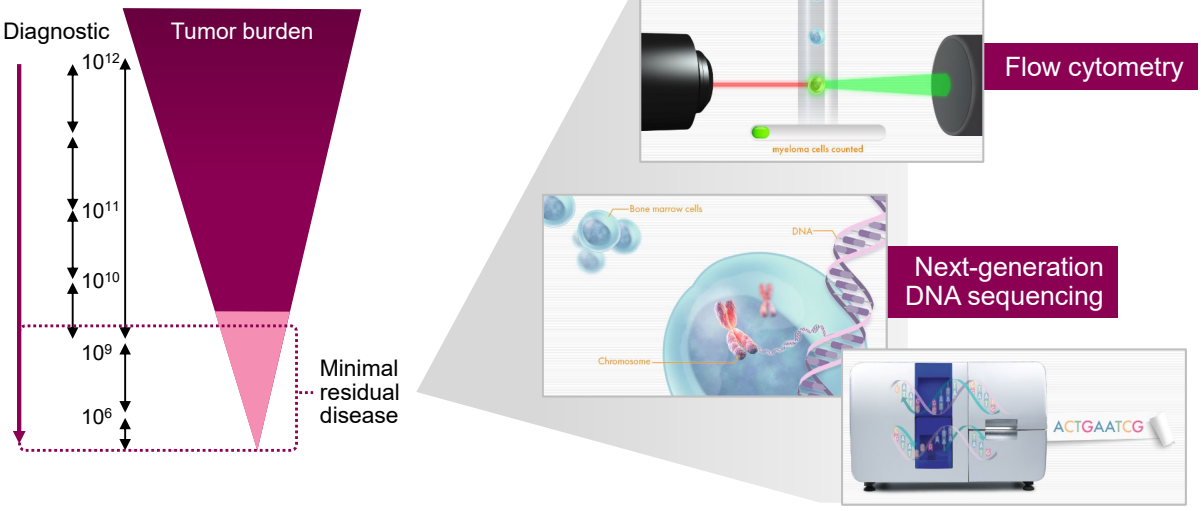
How is MRD measured?



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Techniques Available to Measure MRD in MM

	Next-generation flow (NGF)	Next-Generation sequencing (NGS)
Availability	High	Variable
Diagnostic sample	Important but not mandatory	Mandatory
Applicability	Universal (~ 100%)	High (~ 90%)
Time	2 hours	7 days
Cost	~ 250 USD	~ 700 USD
Sensitivity	10^{-5}–10^{-6}	10^{-6}
Quantitative	Yes	Yes
Fresh sample	Needed	Not needed
Patchy sample	Impacts	Impacts
Global cell characterisation	Yes	No
Standardisation	Ongoing (EuroFlow)	Yes (Adaptive)

Adapted from Paiva B et al. *Blood*. 2015;125:3059.

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Key Terms for MRD

MRD positive or MRD positivity (MRD+)

- Myeloma cells are still detectable

MRD negative or MRD negativity (MRD-)

- Myeloma cells are not detected

Sustained MRD-

- Two measurements of MRD negativity performed at least 12 months apart

Level of sensitivity can be different depending on methodology used: next-generation sequencing (NGS) or next-generation flow cytometry (NGF).

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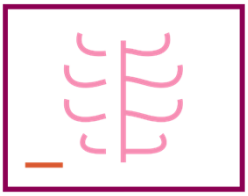
Comprehensive Response Assessment

Right now, measurement of MRD depends on counting cells in bone marrow samples

What about other areas of the body?

Imaging (with PET/CT scan) is also required to detect residual disease outside of the bone marrow



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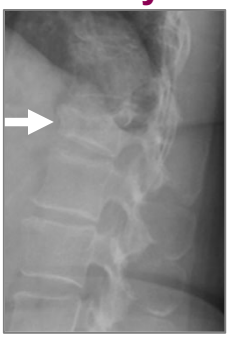
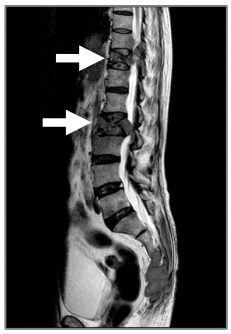
Know Your Imaging Tests!

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

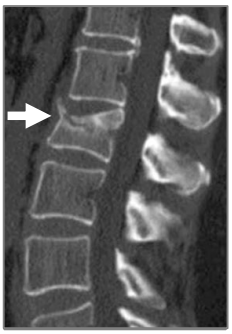
X-ray



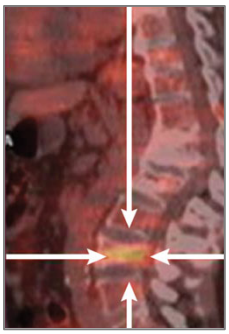
MRI



CT scan



PET scan



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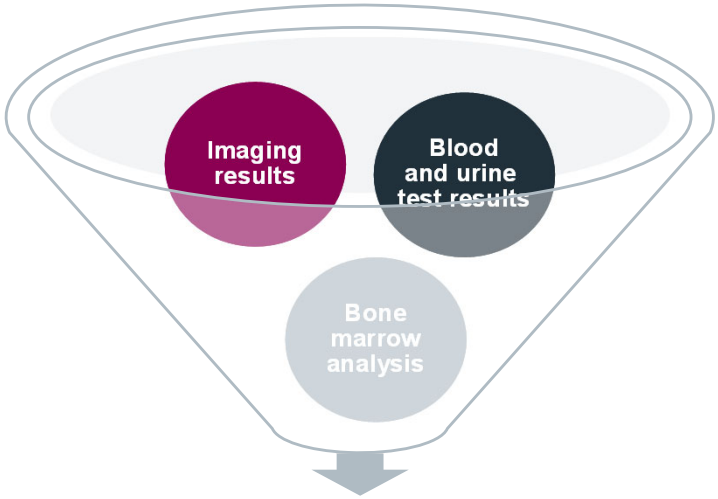
Putting the Results Together



Staging, prognosis, and risk assessment

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Multiple Myeloma Prognosis and Risk

Revised International Staging System (R-ISS)

R-ISS stage	Laboratory measurements
I	• Serum β2M level <3.5 mg/L • Serum albumin level ≥3.5 g/dL • No high-risk CA* • Normal LDH level
II	All other possible combinations
III	• Serum β2M level ≥5.5 mg/L • High-risk CA* or high LDH level

*High-risk chromosomal abnormality (CA) by FISH: del(17p) and/or t(4;14) and/or t(14;16)

Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines

High risk
- High-risk genetic abnormalities
  - t(4;14)
  - t(14;16)
  - t(14;20)
  - del 17p
  - p53 mutation
  - gain 1q
- R-ISS Stage 3
- High plasma cell S phase
- 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
- All others including:
  - Trisomies
  - t(11;14)
  - t(6;14)

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

β2M; beta-2 microglobulin; LDH, lactate dehydrogenase; GEP, gene-expression profiling

Greipp PR et al. *J Clin Oncol*. 2005;23:3412; Palumbo A et al. *J Clin Oncol*. 2015;33:2863; Mikhael JR et al. *Mayo Clin Proc*. 2013;88:360.

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Multiple Myeloma Prognosis and Risk

Many blood test and bone marrow biopsy test results can determine a patient's risk for myeloma that is aggressive (high risk) or not (standard risk) based on the R-ISS

Standard risk

- Serum β2M level <3.5 mg/L
- Serum albumin level ≥3.5 g/dL
- No high-risk chromosomal abnormality*
- Normal LDH level

All other possible combinations of the test results means that a patient is **R-ISS stage II**

High risk

- Serum β2M level ≥5.5 mg/L
- High-risk chromosomal abnormality* or high LDH level

*High-risk chromosomal abnormality by FISH: del(17p) and/or t(4;14) and/or t(14;16)

R-ISS, Revised International Staging System; β2M; beta-2 microglobulin; LDH, lactate dehydrogenase; FISH, fluorescence in situ hybridization

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Additional High-Risk Features

Disease Features

- Other cytogenetic and genetic abnormalities
- Plasma cell leukemia
- Extramedullary disease
- Renal failure

Patient Features

- Comorbidities
- Frailty

Response Features

- Lack of response to therapy
- Short first PFS

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Summary

- Bone marrow biopsies are a pain in the butt; but give us key insight into the biology of your myeloma.
- The genetic information we obtain from the biopsy can give us not only prognostic information but also guide us towards the optimal drug choice.
- Ongoing trials are looking at utilizing drugs typically used for other cancers for treating myeloma.
- Bone marrow biopsies can also let us know how deep your remission is
- There are multiple ways of staging myeloma, with the newer ones using genetic information.
- X-rays, CTs, PET scans, and MRIs are all used to stage and re-stage myeloma.

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MULTIPLE MYELOMA Research Foundation | 25th ANNIVERSARY

Questions & Answers

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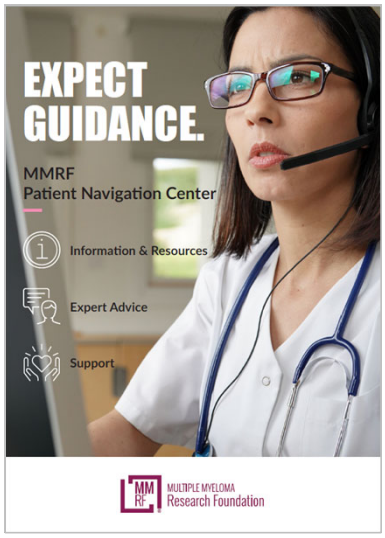
MMRF Patient Resources



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Myeloma Mentors®

Myeloma Mentors® allows patients and caregivers the opportunity to connect with trained mentors. This is a phone-based program offering an opportunity for a patient and/or caregiver to connect one-on-one with a trained patient and/or caregiver mentor to share his or her patient journeys and experiences.

No matter what your disease state—smoldering, newly diagnosed, or relapsed/refractory—our mentors have insights and information that can be beneficial to both patients and their caregivers.

Contact the Patient Navigation Center at 888-841-6673 to be connected to a Myeloma Mentor or to learn more.

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To **Learn More** & **Find Your Event today**!
www.theMMRF.org/Events

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Upcoming Patient Education Events
Save the Date

Topic	Date and Time (ET)	Speakers
Patient Summit	Saturday, June 24 9:00 AM to 3:30 PM	Peter Voorhees, MD Cindy Varga, MD Craig Cole, MD Monique Hartley-Brown, MD Jordan Robinson, PA
American Society of Clinical Oncology 2023 FAQs Livestream	Wednesday, June 28 2:30 PM to 3:30 PM	Nisha Joseph, MD Roseann Pruitt, PA-C Danielle Roberts, PA-C
Webinar: *Minimal Residual Disease*	Friday, July 14 1:00 PM to 2:00 PM	Benjamin Derman, MD Rafael Fonseca, MD

For more information or to register,
please visit **themmrf.org/resources/education-program**

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Resources

- Resource tab includes
  - Speaker bios
  - Copy of the slide presentation
  - Exhibit Hall

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Need help with travel to a clinical study?

- The MMRF has partnered with the Lazarex Cancer Foundation to help provide more equitable access to clinical studies for multiple myeloma patients
- This partnership is one facet of the MMRF's commitment to improve diversity and representation in myeloma clinical trials
- MMRF has provided $100,000 over 2 years to Lazarex to fund travel, lodging, and food for patients (and a travel companion) so that they can participate in clinical studies that are appropriate for them
- Patients are funded according to income guidelines and will be reimbursed for allowed expenses
- For more information on this program and to be connected with Lazarex, call our Patient Navigation Center at 1-888-841-6673

It's About Living
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CANCER FOUNDATION

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MMRF MULTIPLE MYELOMA Research Foundation 25th ANNIVERSARY

Thank you!

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