Understanding your Myeloma Labs
By monitoring your labs you can prevent end organ damage and significant disease.
Multiple Myeloma is a type of cancer of plasma cells.
Plasma cells produce proteins called **immunoglobulins**

- Immunoglobulins are **proteins that attach to foreign substances entering the body**, ○ **Helping fight infections**
- There are many different types and they are specialized for different things.
Multiple Myeloma and Monoclonal Proteins

- Myeloma, secretes abnormal immunoglobulins of only one type that cannot properly fight infections.

- They are called **Monoclonal Proteins**
  - Also called M-protein, M-spike, and other names.

- **Crowding out** the other antibodies and other components of the immune system.
  - Making too much of one type reduces the ability to create a wide spectrum of immunoglobulins to fight infections.

- As Myeloma cells grow, they start **Crowding out the other Blood cells** in the bone marrow.

Top: Normal Bone Marrow; Bottom: Multiple Myeloma Bone Marrow
MGUS is a precursor of Myeloma

Diagnosed with the following

<table>
<thead>
<tr>
<th>Serum monoclonal protein $&lt;3 \text{g/dL}$</th>
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<tbody>
<tr>
<td>Clonal bone marrow plasma cells $&lt;10%$</td>
</tr>
<tr>
<td><strong>Absence</strong> of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (<strong>CRAB</strong>) that can be attributed to the plasma cell proliferative disorder</td>
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</table>
Smoldering Myeloma is another precursor closer to Myeloma

Diagnosed with the following

<table>
<thead>
<tr>
<th>Serum monoclonal protein $\geq 3\text{ g/dL}$, or urinary monoclonal protein $\geq 500\text{ mg per 24 h}$</th>
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<tbody>
<tr>
<td>Clonal bone marrow plasma cells $10\text{-}60%$</td>
</tr>
<tr>
<td><strong>Absence</strong> of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder, or amyloidosis</td>
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</table>
Multiple Myeloma

Diagnosed with ≥10% plasma cells, and

**Presence** of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder

Or any of the following:
- ≥60% plasma cells in the bone marrow
- Free light chain (FLC) ratio ≥100 (with involved FLC level ≥100 mg/L)
- Extramedullary disease
- More than one focal lesion on MRI ≥ 5mm
CRAB

- **Calcium:** serum calcium >11 mg/dL
- **Renal insufficiency:** creatinine clearance (eGFR) <40 mL per minute or serum creatinine >2 mg/dL
- **Anemia:** hemoglobin value <10 g/dL
- **Bone lesions:** one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography-CT (PET-CT)
R-ISS Myeloma Staging

- Measured only at the time of diagnosis of active Multiple Myeloma
- The experts already knew that high levels of Beta 2 microglobulin and low albumin levels were indicators of higher risk myeloma. This staging system was updated as myeloma researchers learned more about high-risk genetic features and high levels of LDH.
- The Revised International Staging System was last updated in 2015.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>Serum albumin $\geq$ 3.5 g/dL, Serum beta-2-microglobulin $&lt;3.5,\text{mg/L}$, No high-risk cytogenetics, and Normal serum lactate dehydrogenase level</td>
</tr>
<tr>
<td>Stage II</td>
<td>Not fitting Stage I or III</td>
</tr>
<tr>
<td>Stage III</td>
<td>Serum beta-2-microglobulin $&gt;5.5,\text{mg/L}$, and High-risk cytogenetics [$t(4;14)$, $t(14;16)$, or $\text{del}(17p)$] or elevated serum lactate dehydrogenase level</td>
</tr>
</tbody>
</table>

This staging system is only a guide for your doctor on how to treat your myeloma, and does not fully predict the evolution of the disease.
M-Spike Tests

- **Serum/Urine Protein Electrophoresis (SPEP/UPEP)** are tests used to find and quantify abnormal proteins.
  - The abnormal protein produced by the Myeloma, is known by several different names, including *Monoclonal Immunoglobulin*, *M protein*, *M spike*, *paraprotein*, and others.
- **Immunofixation** shows the exact type of the antibody that is abnormal.
- **A normal result** = 0 g/dL or negative.
When treated with a monoclonal antibody, like Darzalex, this antibody will be shown in the electrophoresis and Immunofixation studies as a little M spike.
Free Light Chains

- This test measures the free light chains, **Kappa and Lambda**
- It is important to know your **myeloma subtype** in order to monitor the relevant light chain.
- **Kappa reference values**: 3.3 to 19.4 mg/L
- **Lambda reference values**: 5.71 to 26.3 mg/L

Reference values may vary from lab to lab.
About 25% of myeloma patients will have NEGATIVE SPEP (no M-Spike), but will have a POSITIVE light chain.
Free Light Chains in the blood can help detect an early progression or relapse.
Light Chain Ratio (in Multiple myeloma)

- **The Ratio** is the balance between the kappa and lambda light chains.
- **With a normal creatinine** (< 2 mg / dL): reference values are 0.26 – 1.65.
- **With a elevated creatinine** (≥ 2 mg / dL): reference values are 0.37 – 3.1.

Reference values may vary from lab to lab
Light Chain Ratio (in Multiple myeloma)

- If Kappa/Lambda Ratio is **above 8** or **less than 0.125** it is considered a significant **abnormality** that needs to be investigated.

- People who have **kidney problems** often have **higher levels** of light chains at baseline.
### Immunoglobulins (Heavy chains)

Reference values may vary from lab to lab

<table>
<thead>
<tr>
<th>Immunoglobulin</th>
<th>Range</th>
<th>Unit</th>
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<tbody>
<tr>
<td>Immunoglobulin A</td>
<td>68 - 378</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Immunoglobulin G</td>
<td>768 - 1632</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Immunoglobulin M</td>
<td>60 - 263</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Immunoglobulin D</td>
<td>&lt; or ≤ 10</td>
<td>mg/dl</td>
</tr>
<tr>
<td>Immunoglobulin E</td>
<td>&lt; or ≤ 214</td>
<td>mg/dl</td>
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**The myeloma subtype**

Defined by the M-Spike immunofixation, and the highest results in the free light chain and immunoglobulins testing, composed like this:

**Heavy chain (if any) + Light chain + Phase**

Examples:
- IgG Kappa MGUS
- Kappa light chain only Smoldering Myeloma
- IgA Lambda Multiple Myeloma
Complete Blood Count

Because multiple myeloma crowds out bone marrow, it can cause several kinds of blood deficiencies such as:

- **Anemia**, a shortage of red blood cells shown on the **Hemoglobin**,
- **Thrombocytopenia**, a shortage of **Platelets**,
- **Leukopenia**, a shortage of **White Blood Cells** (leukocytes),
  - Neutropenia, a shortage of **Neutrophils**, and
  - Lymphopenia, a shortage of **Lymphocytes**.

<table>
<thead>
<tr>
<th>White Blood Cell count (WBC)</th>
<th>Hemoglobin (HGB)</th>
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<tbody>
<tr>
<td>3.2 - 10.6 k/ul</td>
<td>12.1 - 15.9 g/dl</td>
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<table>
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<tr>
<th>Platelets</th>
<th>Lymphocyte Absolute Count</th>
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<tr>
<td>150 - 440 k/ul</td>
<td>0.8 - 3.1 k/ul</td>
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<table>
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<tr>
<th>Absolute Neutrophils Count (ANC)</th>
<th>Reference values may vary from lab to lab</th>
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<tbody>
<tr>
<td>1.3 - 7 k/ul</td>
<td></td>
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Comprehensive Metabolic Panel

Chemistry panels are run regularly during and after treatment to check your body's normal functions.

**Albumin.** One of the most abundant proteins in humans. Diminished by the monoclonal proteins.

**High Calcium.** Caused by bone destruction done by MM,

- It may result in severe constipation and loss of appetite, weakness, drowsiness, and confusion.

Elevated **Serum Creatinine** or Low **eGFR** may indicate poor hydration or possible kidney damage.

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<th>Albumin</th>
<th>Calcium</th>
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<tr>
<td>3.5 - 4.7 g/dl</td>
<td>8.4 - 10.2 mg/dl</td>
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<table>
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<tr>
<th>Creatinine (Serum/Blood)</th>
<th>eGFR (Estimated glomerular filtration rate) / Creatinine Clearance</th>
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<tr>
<td>0.52 - 1.08 mg/dl</td>
<td>&gt;60 ml/min</td>
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<table>
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<th>Glucose</th>
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<td>64 - 128 mg/dl</td>
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Plasma Cell Percentage

- The percentage in the bone marrow core biopsy will be a major determinant of the classification of the type of disorder.
  - **Normal** = <5%
  - **MGUS** = <10% + Absence of end-organ damage
  - **Smoldering myeloma** = 10-60% + Absence of end-organ damage
  - **Multiple myeloma** = >10% + Evidence of end-organ damage, or ≥60%

- Stains may be performed to highlight the different cell types present (IHC or Immunohistochemistry).
  - **CD138** is an antibody stain that marks plasma cells and aids in enumeration.
Bone marrow genetics tests

- A Plasma cell is like a police department,
- it will have a nucleus/bookshelf with all the rulebooks/chromosomes of how the department should behave, we have 46 chromosomes in each cell, and
- the rules written inside them are the DNA.
Bone marrow genetics tests

- **Myeloma cell** is a police department that is not working well.
- The **rulebooks or rules may have mistakes** or mutations,
  - there may be rules or parts of books missing duplicated, or with other kinds of aberrant changes.
- These **mutations** may vary from cell to cell and from person to person, and might change over time.
- And they may **help or hinder** the progression of the myeloma.
Mayo clinic genetic risk stratification for multiple myeloma (mSMART)

- **Standard Risk**
  - Trisomies, t(11;14) and t(6;14).
  - 75% of newly diagnosed patients.

- **High risk**
  - Del(17p), t(4;14), t(14;16), t(14;20), Amplification 1q (4 or more copies), p53 mutation, R-ISS Stage III, High-risk signature by GEP, or High Plasma Cell S-phase.
  - 25% of newly diagnosed patients.
  - **One hit**
    - Only one high-risk factor
  - **Double hit**
    - Two high-risk factors
  - **Triple Hit**
    - Three or more high-risk factors

This staging system is only a guide for your doctor on how to treat your myeloma, and does not fully predict the evolution of the disease.

- **Used only in active Multiple Myeloma**
- It was designed for physicians external to Mayo.
- And helps to classify the most common genetic features that can occur in myeloma cells.
- Last updated in 2018.
Flow Cytometry

- Flow cytometry is a test used on both blood samples and bone marrow samples to identify “markers” on the cell's surface and may give us targets for the use of immunotherapies, like monoclonal antibodies.
- Cells are passed in front of a laser beam which causes them to give off light. Groups of cells can be separated and counted.
Flow Cytometry in a normal plasma cell

The most common immunophenotype (expected immune markers) of normal Plasma Cells may be described as:

- CD38, CD138, CD19, CD20, CD27 predominantly bright positive, and
- Polytypic cytoplasmic immunoglobulin, this means that they express both Kappa and Lambda immunoglobulin.
Flow Cytometry in a myeloma cell

The typical immunophenotype (expected immune markers) of myeloma cells shows several deviations from the normal pattern,

- with some substances that are expected negative with positive results (CD56, CD81, CD117, etc.), some others that are expected positive with negative results, and
- **Monoclonal** cytoplasmic immunoglobulin, this means that they express only **Kappa or Lambda** immunoglobulin.
Summary

- Know what type of myeloma you have.

- Keep your labs up to date!

- Monitor your labs (especially the Myeloma Markers).

- Keep learning! We have multiple resources at [HealthTree University](http://HealthTreeUniversity).
Thank you!

If you need assistance, contact our team at:

support@healthtree.org

+1 800-709-1113

HealthTree Cure Hub
FOR MULTIPLE MYELOMA