Understanding Your Test Results
About the International Myeloma Foundation

Founded in 1990, the International Myeloma Foundation (IMF) is the oldest and largest myeloma-specific charity in the world. With more than 350,000 members in 140 countries, the IMF serves myeloma patients, family members, and the medical community. The IMF provides a wide range of programs in the areas of Research, Education, Support, and Advocacy:

**RESEARCH** The IMF is the leader in globally collaborative myeloma research. The IMF supports lab-based research and has awarded over 100 grants to top junior and senior researchers since 1995. In addition, the IMF brings together the world’s leading experts in the most successful and unique way through the International Myeloma Working Group (IMWG), which is publishing in prestigious medical journals, charting the course to a cure, mentoring the next generation of innovative investigators, and improving lives through better care.

**EDUCATION** The IMF’s educational Patient & Family Seminars, Medical Center Workshops, and Regional Community Workshops are held around the world. These meetings provide up-to-date information presented by leading myeloma specialists and researchers directly to myeloma patients and their families. Our library of more than 100 publications, for patients and caregivers as well as for healthcare professionals, is updated annually and available free of charge. Publications are available in more than 20 languages.

**SUPPORT** Our toll-free InfoLine at 800-452-CURE (2873) is staffed by coordinators who answer questions and provide support and information via phone and email to thousands of families each year. The IMF sustains a network of more than 150 support groups and offers training for the hundreds of dedicated patients, caregivers, and nurses who volunteer to lead these groups in their communities.

**ADVOCACY** The IMF Advocacy program trains and supports concerned individuals to advocate on health issues that affect the myeloma community. Working both at the state and federal level, the IMF leads two coalitions to advocate for parity in insurance coverage. Thousands of IMF-trained advocates make a positive impact each year on issues critical to the myeloma community.

Learn more about the way the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure. Contact us at 800-452-CURE (2873) or 818-487-7455, or visit myeloma.org.

---

Table of contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>What you will learn from this booklet</td>
<td>4</td>
</tr>
<tr>
<td>Blood and urine tests</td>
<td>5</td>
</tr>
<tr>
<td>Complete blood count (CBC)</td>
<td>7</td>
</tr>
<tr>
<td>Chemistry profile</td>
<td>9</td>
</tr>
<tr>
<td>Tests to assess monoclonal protein</td>
<td>11</td>
</tr>
<tr>
<td>Other useful blood tests</td>
<td>15</td>
</tr>
<tr>
<td>Bone marrow tests</td>
<td>16</td>
</tr>
<tr>
<td>Immunohistochemistry and flow cytometry of bone marrow plasma cells</td>
<td>17</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>18</td>
</tr>
<tr>
<td>FISH</td>
<td>19</td>
</tr>
<tr>
<td>Imaging studies</td>
<td>21</td>
</tr>
<tr>
<td>In closing</td>
<td>25</td>
</tr>
<tr>
<td>Terms and definitions</td>
<td>25</td>
</tr>
</tbody>
</table>
To be an informed patient, you should request and collect test results for future reference. Test results best reflect a myeloma patient’s status when followed and reviewed over time. A trend or pattern reveals more than a single test result or study. No single test is adequate to tell the whole story of a patient’s current myeloma status. Each test can be thought of as a piece of a puzzle; only when the pieces are assembled correctly can a patient and an experienced hematologist or oncologist make the proper inferences and decisions.

Test results are the most important tools that your doctor will use in order to:

- Diagnose monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), and active myeloma;
- Assess the risk of progression of MGUS or SMM to active myeloma;
- Assess the stage of your myeloma;
- Assess your genetic risk factors;
- Evaluate response to treatment;
- Monitor remission periods and determine when to start treatment again;
- Monitor for disease-related and treatment-related side effects.

Tests for myeloma patients fall into three major categories:

- Blood and urine tests
- Bone marrow tests
- Imaging studies

Other tests are used in special circumstances, such as in diagnosing and/or monitoring amyloidosis, neuropathy, and kidney or infectious complications.

These tests are beyond the scope of this booklet, and are not included.

Myeloma patients require many tests in the course of their diagnosis and treatment. Some of these tests may be used to assess other diseases or conditions that a patient has before or after the diagnosis of myeloma. Make sure you know which tests are for other medical problems, and which are for myeloma. It is always best to discuss test results with your treating physician.

### Blood and urine tests

#### Key points on laboratory test reports

##### Reference ranges
- Laboratory test results are usually reported as a quantity in relation to a “reference range” of normal results.
- The reference range is determined by sampling large numbers of healthy people. Since there is an expected variation in human biology, test results can be expected to fall within a range of values.

##### High/Low notations
- If your result is higher than the upper end of the reference range, an H (for “high”) will follow the number.
- If your result is lower than the lower end of the reference range, an L (for “low”) will follow the number (see Figure 1).
- Variation in results can occur because some tests that are not fully automated require human input; human subjectivity can affect results.
- Other factors that have nothing to do with your myeloma can affect your results as well.

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Flag</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td><strong>Autohematology - Differential - Morphology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC TREAT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td>4.4</td>
<td>L</td>
<td>4.5–11.0 K/UL</td>
</tr>
<tr>
<td>RBC</td>
<td>3.46</td>
<td>L</td>
<td>3.5–5.5 M/UL</td>
</tr>
<tr>
<td>HGB</td>
<td>12.3</td>
<td></td>
<td>12.0–15.0 G/DL</td>
</tr>
<tr>
<td>HCT</td>
<td>36.2</td>
<td></td>
<td>36.0–48.0 %</td>
</tr>
<tr>
<td>MCV</td>
<td>104.6</td>
<td>H</td>
<td>79.0–101.0 FL</td>
</tr>
<tr>
<td>MCH</td>
<td>35.5</td>
<td>H</td>
<td>25.0–35.0 PG</td>
</tr>
<tr>
<td>MCHC</td>
<td>34.0</td>
<td></td>
<td>31.0–37.0 G/DL</td>
</tr>
<tr>
<td>RDW-CV</td>
<td>15.8</td>
<td></td>
<td>11.0–16.0 %</td>
</tr>
<tr>
<td>PLT</td>
<td>149</td>
<td></td>
<td>140–440 K/UL</td>
</tr>
<tr>
<td>MPV</td>
<td>7.5</td>
<td></td>
<td>7.0–10.0 FL</td>
</tr>
<tr>
<td>NEUT % (Auto)</td>
<td>74</td>
<td></td>
<td>40–76 %</td>
</tr>
<tr>
<td>LYMPH % (Auto)</td>
<td>16</td>
<td>L</td>
<td>24–44 %</td>
</tr>
<tr>
<td>MONO % (Auto)</td>
<td>9</td>
<td></td>
<td>1.0–10.0 %</td>
</tr>
<tr>
<td>EOS % (Auto)</td>
<td>1</td>
<td></td>
<td>0.0–3.0 %</td>
</tr>
<tr>
<td>BASO % (Auto)</td>
<td>0</td>
<td></td>
<td>0–1 %</td>
</tr>
<tr>
<td>NEUT AB (Auto)</td>
<td>3.22</td>
<td></td>
<td>1.9–8.8 K/UL</td>
</tr>
<tr>
<td>LYMPH AB (Auto)</td>
<td>0.69</td>
<td>L</td>
<td>1.0–4.8 K/UL</td>
</tr>
<tr>
<td>MONO AB (Auto)</td>
<td>0.41</td>
<td></td>
<td>0.1–0.8 K/UL</td>
</tr>
<tr>
<td>EOS AB (Auto)</td>
<td>0.03</td>
<td></td>
<td>0.0–0.5 K/UL</td>
</tr>
<tr>
<td>BASO AB (Auto)</td>
<td>0.02</td>
<td></td>
<td>0.0–0.1 K/UL</td>
</tr>
</tbody>
</table>
A general rule of thumb is that if your test result is within 10%–15%, plus or minus, of where it was the previous month, the difference may not be statistically significant, but may simply be the result of normal biologic variation.

**Lab-to-lab variation**
- Reference ranges may vary from laboratory to laboratory, so make sure that you are familiar with the reference ranges at the lab (or labs) your doctors use.
- The reference ranges provided in this booklet, which are from the Mayo Clinic Reference Laboratory, are shown as examples, and may not be the same as those used at your lab(s).
- The decimal points in these examples may be in different places than where they are on your lab reports.

**Units of measurement**
- Lab results can vary depending on whether they measure grams or milligrams, liters or deciliters, and so forth.
- Make sure you know the units that are used to measure your blood and urine samples. For example, if your sample is measured in grams per deciliter (g/dL), the result will be one tenth of the result given as grams per liter (g/L).
- Some lab reports may indicate that you have 3.0 g/dL of myeloma-related monoclonal protein (or M-protein), while others may express the result as 30 g/L of M-protein.
- This does not mean that the M-protein has increased ten-fold. 3.0 g/dL = 30 g/L. The results are equivalent, but are expressed in different units.

**Note to patients in the United States:**
There is no time like the present to brush up on the metric system!

**Other variables**
Be aware that your lab results can be affected by many variables, including:
- other medications and supplements that you may be taking
- the amount and type of fluids you have consumed
- whether or not you have eaten prior to the test
- Consult with your physician to make sure there are no special instructions about medications, supplements, food, or drink prior to appointments when your blood and/or urine are collected.

**Interpreting and comparing test results**

**Patient-to-patient differences**
DO NOT COMPARE YOUR LAB RESULTS TO THOSE OF OTHER PATIENTS. Every patient’s disease is unique. One patient may have a test result and may be completely asymptomatic, while another patient with the same test result may have aggressive disease.

**Changes over time**
Myeloma is a cancer that evolves biologically, so a test that is a reliable marker for you when you are diagnosed may not be a reliable test for you later on. Conversely, a test that is not useful for you when you are diagnosed may be your most valuable assessment tool later in the disease course.

**Knowledge is power**
It is important for patients to educate themselves about myeloma, how it is diagnosed and monitored, and its treatments and supportive care. You can gain this understanding through many avenues: discussions with your doctors and nurses, participation in a myeloma support group (contact the IMF to help locate a myeloma-specific support group around the world), and the many opportunities for education offered by the IMF (website, InfoLine, publications, teleconferences, Patient & Family Seminars, and Regional Community Workshops).

Both the International Myeloma Working Group (IMWG) and the National Comprehensive Cancer Network (NCCN) provide guidelines for appropriate tests to be done throughout the myeloma disease course, from initial diagnostic workup, through monitoring of therapy, to monitoring for treatment side effects, to monitoring for relapse. At diagnosis, these tests should always be accompanied by an appointment during which your doctor takes your complete medical history, speaks with you about your health, and performs a physical exam – the “hands-on” part of diagnosing and assessing a patient.

**MGUS and SMM**
If you have been diagnosed with MGUS or SMM, the range of tests will depend upon your risk status. The IMF’s Understanding MGUS and Smoldering Multiple Myeloma booklet includes a discussion of the appropriate tests used in the diagnostic workup of these precursors to active myeloma.

**Complete blood count (CBC)**
The CBC is one of the main tests needed for diagnosing and monitoring myeloma patients. Many cases of myeloma (and its asymptomatic predecessors, MGUS and SMM) are identified as the result of blood tests routinely ordered as part of an annual medical exam, such as the CBC. The CBC is a blood test that quantifies all the cells that make up the solid parts of blood. (The liquid part of blood, in which the blood cells are suspended, is colorless, and is called serum.)

All of your blood cells – red blood cells (RBC), white blood cells (WBC), and blood-clotting cells called platelets – are made in the bone marrow, which is where myeloma grows. Both myeloma itself as well as many treatments for myeloma affect the ability of new blood cells to grow in the bone marrow. Your CBC will be watched carefully throughout your treatment course to make sure that your blood cell counts are not decreasing to dangerous levels. Sometimes, patients must have a CBC every week to make sure that a particular treatment is not taking a toll on one or more of the blood cell types.
CBC results are broken down into the major headings of RBC, WBC, and platelets, with sub-categories under each major blood cell type. The sub-categories that are monitored while you are a myeloma patient are included below.

**Red blood cells (RBC)**

*Reference Range:*
- **males:** $4.32–5.72 \times 10^{12}/L$
- **females:** $3.90–5.03 \times 10^{12}/L$

When myeloma cells are growing in the bone marrow, they interfere with the production of new blood cells, which are also made in the bone marrow. Usually the first to decrease in number in response to active myeloma are the red blood cells.

- **Hemoglobin (hgb)**
  - *Reference Range:*
    - **males:** $13.5–17.5 \text{g/dL (135–175 g/L)}$
    - **females:** $12.0–15.5 \text{g/dL (120–155 g/L)}$

Hemoglobin, the most important part of the red blood cell, transports oxygen to the organs and tissues of the body. A low hemoglobin count can be a sign of anemia, one of the CRAB criteria that are characteristic of active myeloma: elevated Calcium, Renal (kidney) dysfunction, Anemia, and Bone disease. The doctor will keep a close watch on your hemoglobin throughout your myeloma disease course, as it can be an early indicator of myeloma activity in the bone marrow.

- **Hematocrit (hct)**
  - *Reference Range:*
    - **males:** $38.8%–50.0%$
    - **females:** $34.9%–44.5%$

**White blood cells (WBC)**

*Reference Range:*
- **males:** $3.5–10.5 \times 10^{12}/L$
- **females:** $3.90–5.03 \times 10^{12}/L$

White blood cells make up the body’s immune system. They fight foreign substances that enter the body, including bacteria, viruses, and toxins. Low WBC counts can result from many types of treatment for myeloma, which can further diminish your ability to fight disease. Your WBC count will be followed carefully during your treatment for myeloma.

- **Neutrophils**
  - *Reference Range:*
    - $1.7–7.0 \times 10^{9}/L$

Neutrophils are a type of WBC that helps fight infections, particularly those caused by bacteria and fungi. A low neutrophil count is called neutropenia, a condition that results in susceptibility to infection. Your doctor will check your neutrophil count, sometimes expressed as ANC (Absolute Neutrophil Count, which measures both mature and immature neutrophils), to make sure that it is safe to give you a dose of a particular treatment.

**Platelets**

*Reference Range:*
- $150–450 \times 10^{9}/L$

Platelets are blood cells that help the blood clot and prevent bleeding. Although low hemoglobin is a more common blood-related symptom of myeloma than is a low platelet count (thrombocytopenia), some patients do have low platelets at diagnosis as a result of their myeloma. In addition, certain treatments for myeloma, in particular the proteasome inhibitors Velcade® (bortezomib), Kyprolis® (carfilzomib), and Ninlaro® (ixazomib) can also cause low platelets, resulting in severe bruising or bleeding. Your platelet count should be monitored throughout your disease course.

**Chemistry profile**

The comprehensive metabolic panel (CMP), a key test in the diagnosis and monitoring of myeloma, is given to measure various substances in the blood. Along with the CBC, it is part of a routine physical exam. Below are the individual tests from this panel that are recommended for myeloma patients by both the IMWG and the NCCN.

- **BUN (blood urea nitrogen)**
  - *Reference range:*
    - $7–20 \text{mg/dL}$

This test provides information about how well your liver and kidneys are functioning.

- **Serum creatinine**
  - *Reference range:*
    - $0.6–1.3 \text{mg/dL}$

This test is used to assess the “R” in the CRAB criteria – Renal (kidney) function. Creatinine is a waste product from the normal breakdown of muscle tissue. It is filtered through the kidneys and excreted in urine. Measurement of serum creatinine level is a useful indicator of how well your kidneys are functioning. Kidney function can be seriously affected by light chain proteins, so it's...
very important to assess kidney function at diagnosis and at regular intervals thereafter, particularly if you have Bence-Jones (light chain) protein in your urine. Kidney function can also be affected by high levels of calcium in the blood, which can result from myeloma-induced bone breakdown.

**Creatinine clearance**

Reference range:
- **males:** 97–137 mL/min
- **females:** 88–128 mL/min

(mL/min = milliliters per minute)

Creatinine clearance is the amount of blood per minute that the kidneys can make creatinine-free. The measurement of creatinine clearance helps provide information about kidney function. It requires both 24-hour urine collection and a blood sample. Creatinine clearance (and therefore kidney function) declines naturally with age, explaining the wide range of normal values. People over 60 – the vast majority of myeloma patients – may have an apparently normal serum creatinine level but have a low rate of creatinine clearance. The 24-hour urine sample provides a more accurate assessment of decline in kidney function than does the serum creatinine test.

Creatinine clearance of less than 40 mL per minute is considered a “myeloma-defining event” (MDE), that is, a sign of early active myeloma in a patient who otherwise has no CRAB features. These patients should be treated rather than merely observed for disease progression.

**Estimated glomerular filtration rate (eGFR)**

Reference range: 90–120 mL/min/1.73 m²

The eGFR is used in conjunction with the measurement of creatinine in the serum to screen for and detect kidney damage. It is estimated rather than actual because it is calculated from the serum rather than from a 24-hour urine sample. It is usually calculated automatically at the time the creatinine is measured. This test is not accurate for people who are older than 70, very overweight, very muscular, or pregnant.

**Calcium**

Reference range: 9–10.5 mg/dL

This test is used to assess the “C” in the CRAB criteria – elevated Calcium in the blood. Calcium is stored in the bones and is released as part of normal bone remodeling (the body constantly breaks down and rebuilds bone). Myeloma grows in the bone marrow, where it changes the environment inside the marrow and causes a cascade of cellular events that can result in increased bone breakdown. Increased bone breakdown results in both an increased level of calcium in the blood and an increased risk of fractures. A high blood calcium level can also damage the kidneys.

**Total protein**

Reference range: 6–8 g/dL

Total protein measures the total amount of blood protein, including two components of particular interest in myeloma: albumin and globulin. If M-protein is present in the blood, it will increase the amount of blood globulin, causing the amount of total blood protein to rise. At diagnosis, an elevated total protein should prompt a physician to order additional, more specific tests to see if the source of elevated globulin protein might be from myeloma. If you have been diagnosed and treated for active myeloma, your doctor will use more specific tests to assess the amount of M-protein in your blood and/or urine.

---

**Table 2. Comprehensive metabolic panel/chemistry profile reference ranges**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (blood urea nitrogen)</td>
<td>7–20 mg/dL</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>0.6–1.3 mg/dL</td>
</tr>
</tbody>
</table>
| Creatinine clearance                   | males: 97–137 mL/min (milliliters per minute)
                                      | females: 88–128 mL/min               |
| Estimated glomerular filtration rate   | 90–120 mL/min/1.73 m²                |
| Calcium                                | 9–10.5 mg/dL                         |
| Total protein                          | 6–8 g/dL                             |
Abnormal result with myeloma cells

Cytokines

SPEP is one of the most important tests used to assess the status of a patient’s myeloma. It measures the amount of M-protein that is made by myeloma cells. The amount of M-protein production is linked to the number and activity of myeloma cells; the more active myeloma cells, the greater the production of M-protein (except in the case of non-secretory myeloma).

SPEP separates and quantifies proteins based on their electrical charge, size, and shape. As you learned above, the two types of protein in serum are albumin and globulin. Although there is only one type of albumin, there are sub-types of globulin, usually appearing on SPEP as alpha-1, alpha-2, beta-1, beta-2, and gamma globulins. Immunoglobulin proteins are gamma globulins, and usually, M-protein produced by myeloma cells will separate out in the gamma region of the graph used to report the test results. The exception to this rule is IgA protein, which may sometimes migrate to the beta or even the alpha-2 region. If this occurs, other tests can be more useful than SPEP.

For more information, see sections on “Serum quantitative immunoglobulins (QIg)” and “Hevylite® (serum heavy + light chain isotype assay).”

Monoclonal immunoglobulin protein appears on the graph as a narrow spike: because all the cells in the M-protein are identical and have the same electrical charge, they gravitate to the same small region and form a peak or spike on the graph. A monoclonal spike (or M-Spike) is the telltale indicator of myeloma protein in the blood, a marker for the activity of myeloma cells. By calculating the area under the curve (AUC) of the spike and then calculating what percentage of the total immunoglobulin it represents, the pathologist can quantify the amount of M-protein. Once the presence and amount of an M-spike is established, the immunofixation electrophoresis (IFE) test can identify the type of heavy and light chain.

The other important component of SPEP is the result of the serum albumin measurement. Serum albumin accounts for 55% of the total protein in the clear liquid part of the blood, and is produced in the liver. When myeloma is active, it stimulates the production of certain cellular proteins (cytokines) that impede the ability of the liver to produce albumin, and the level drops. According to the revised International Staging System (R-ISS), albumin is one of two blood proteins used to predict the behavior of myeloma cells at diagnosis. (See “Beta-2 microglobulin” on page 15.)

### Urine protein electrophoresis (UPEP)

**Reference range:**
- no significant amount of globulins in the urine,
- total protein < 167 mg/24 hours,
- urine albumin < 5 mg/dL

Approximately 30% of myeloma patients have light chain protein in their urine as well as heavy chain protein in the blood. Approximately 15%–20% of patients have myeloma cells that produce only light chains and no heavy chains. Although fragments of heavy chain proteins can be found in the urine, intact heavy chains are too large to fit through the capillaries that send blood to the kidneys for filtration. Light chains, however, are so small and light in molecular weight (hence the name “light” chains) that they can easily pass through the capillaries and enter the kidneys, and from there, to the bladder and into the urine.

Patients submitting a specimen for UPEP must collect urine for 24 hours. A 24-hour specimen provides a good indication of average amounts of different proteins in the urine. Like SPEP, UPEP separates the proteins according to their size and electrical charge, and quantifies the amount of light chain protein.

### Immunofixation electrophoresis (IFE)

When an abnormal result on SPEP indicates the presence of M-protein, follow-up with IFE identifies the type of M-protein (heavy chain IgG, IgA, IgD, IgE, or IgM; kappa or lambda light chain). It does not measure the amount of M-protein, so there is no reference range. Urine IFE is performed on a 24-hour urine collection. The test result is either negative or positive for the presence of a specific type of M-protein. Serum or urine immunofixation that is negative for an M-protein is considered normal.

The IMWG Uniform Response Criteria for Multiple Myeloma define complete response (CR) to therapy as:
- Negative immunofixation on the serum and urine, and
- disappearance of any soft tissue plasmacytomas, and
- ≤ 5% plasma cells in the bone marrow.

### Freelite®

**Reference range:**
- Free kappa 3.3–19.4 mg/L
- Free lambda 5.71–26.3 mg/L
- Kappa/lamba ratio 0.26–1.65

Immunoglobulins are made up of two kinds of molecules, heavy chains and...
light chains. These heavy and light chains are usually bound together as “intact immunoglobulins.” For reasons we do not know, however, the plasma cells produce more light chains than heavy chains, and the excess, or unbound, light chains circulate freely in the blood. They are therefore called “free” light chains, and they are present in both healthy individuals and in patients with myeloma and related disorders (MGUS, SMM, amyloidosis, light chain deposition disease, and Waldenström’s macroglobulinemia).

Some patients’ myeloma cells secrete both heavy and light chains, some only heavy chains, and some only light chains. Some patients’ myeloma cells, when assessed by SPEP, appear to secrete no M-protein at all. The Free-lite test is used for patients who only secrete light chains (this is often called “Bence-Jones myeloma,” named after the doctor who first found and identified light chain protein in the urine), for patients who secrete both heavy and light chains, and for patients who secrete very low levels of protein (this is called “oligosecretory myeloma”). For more information, please read the IMF’s Understanding Freelite® and Hevylite® Tests booklet.

Some patients’ myeloma cells may secrete many more light chains at relapse than they did prior to treatment. This is sometimes called “Bence-Jones escape” or “light chain escape.” For this reason, such patients will likely be monitored after treatment using both SPEP and the Freelite assay.

The Freelite assay is also used in the diagnosis and monitoring of patients who have MGUS, a non-cancerous elevation in monoclonal protein, to assess their risk of developing active myeloma. Similarly, the Freelite test is used to monitor patients with SMM. For more information, please read the IMF’s Understanding MGUS and Smoldering Multiple Myeloma booklet.

▶ Hevylite® (serum heavy + light chain isotype assay)

*Reference range:*
- IgG kappa: 4.03–9.78 g/L
- IgG lambda: 1.97–5.71 g/L
- IgG kappa/IgG lambda ratio: 0.98–2.75
- IgA kappa: 0.48–2.82 g/L
- IgA lambda: 0.36–1.98 g/L
- IgA kappa/IgA lambda ratio: 0.80–2.04

The Hevylite assay is a laboratory blood test for measuring intact immunoglobulins. According to the FDA approval, the Hevylite assay is to be used for previously diagnosed myeloma in conjunction with other clinical and laboratory findings.

Most myeloma patients’ cancer cells secrete an immunoglobulin comprised of both a single type of heavy chain and a single type of light chain (for example, IgG heavy chains and kappa light chains). Although there is no difference in the way the various types of myeloma are treated, it’s important to know your type of heavy and light chain for monitoring purposes.

In addition to the immunoglobulin pair that your myeloma cells are making, you also have normal, intact immunoglobulin pairs circulating in your bloodstream. The Hevylite test can distinguish between the “involved” proteins – the heavy and light chain produced by the myeloma – and their “uninvolved” (i.e., normal) counterparts that have the same heavy chain isotype but are bound to a different light chain. For example, if you have IgG kappa myeloma (the “involved” heavy and light chain), then your IgG lambda heavy and light chain pairs are the normal “uninvolved” immunoglobulins. If you have IgA lambda myeloma, the normal, or “uninvolved,” paired counterpart would be IgA kappa.

This test is important for several reasons. Unlike IFE, which requires a pathologist to hold the test result up to the light to see if a faint band can be detected, Hevylite is quantified by a computer. Not only is it an accurate way to measure IgA myeloma, which often does not show up as part of the M-spike by SPEP but it is an extremely sensitive measurement of both myeloma protein and normal immunoglobulins. When Hevylite assessment reveals that normal immunoglobulin levels are suppressed, it can be an early indicator of myeloma relapse. Even when a patient is in complete remission (CR), the Hevylite test can detect extremely low levels of M-protein, indicating the presence of “minimal residual disease” (MRD).

**Other useful blood tests**

Your doctor may order other, more specialized blood tests at diagnosis and/or for monitoring your myeloma after treatment.

▶ Beta-2 microglobulin (β2-microglobulin, B2M, B2M)

*Reference range:*
- 0.70–1.80 mg/L

The serum B2M level indicates the amount and activity of the underlying myeloma. It is one of two blood proteins used in the revised International Staging System (R-ISS) to help understand the potential for the spread and aggressiveness of newly diagnosed myeloma; the other is serum albumin. In addition to its function in staging myeloma during the initial work-up, B2M can also be used to evaluate disease activity and to monitor response to treatment. A serum B2M of < 3.5 mg/L is considered stage I; a B2M ≥ 5.5 mg/L is stage III. Stage II is defined as B2M between 3.5 mg/L and 5.5 mg/L.

▶ Lactate dehydrogenase (LDH)

*Reference range:*
- 105–333 IU/L (international units per liter)

High LDH can be a sign of aggressive disease, and is therefore included in the R-ISS to help determine prognosis. LDH is an enzyme found in almost all body tissues. It plays an important role in cellular respiration, the process by which
glucose (a sugar) is converted into usable energy for cells. Although LDH is abundant in tissue cells, blood levels of the enzyme are normally low. However, when tissues are damaged by injury or disease, they release more LDH into the bloodstream. LDH rises when myeloma is actively growing.

- **C-reactive protein (CRP)**
  Increased levels of CRP indicate active myeloma and can be used as a prognostic factor. CRP is produced by the liver and released into the bloodstream within a few hours after tissue injury, the start of an infection, or another cause of inflammation.

- **Glucose**
  Reference range: 70–100 mg/dL (fasting blood glucose level)
  The level of glucose, a major source of energy for most cells, should be established before a patient starts treatment, and should be monitored carefully if you are taking dexamethasone or another glucocorticosteroid. These steroids, which are common components of myeloma treatment regimens, can cause the level of blood glucose (sugar) to rise. If not controlled, elevated blood sugar can result in diabetes.

### Bone marrow tests

Since myeloma grows in the bone marrow, the only way to examine myeloma cells and to assess their properties – how many there are, what they look like as compared to normal plasma cells, what their cellular genetics are, how rapidly they’re reproducing, which antibodies they express, if there are any myeloma cells left when a patient is in complete remission – is to remove a sample from the back of the hip (the posterior iliac crest) and perform studies on these cells. Some of these analyses can be done by a pathologist looking through a microscope, and others require sophisticated computers with customized software programs.

#### Bone marrow aspirate and biopsy

Bone marrow aspirate and biopsy are routinely performed at diagnosis, and are ordered at the doctor’s discretion after treatment (often after high-dose therapy with stem cell rescue, also known as “stem cell transplant”), annually during periods of remission, and at other points when the doctor deems it necessary to determine a patient’s status. Bone marrow biopsy is also a reliable, if invasive, way to monitor the status of patients with non-secreting myeloma, which cannot be tracked through M-protein in the blood or urine.

The bone marrow is composed of both solid and liquid matter: the solid part is a sponge-like structure consisting of a fibrous network filled with liquid; the liquid portion contains blood-making (hematopoietic) stem cells, blood cells in various stages of maturation, and such raw materials required for cell production as iron, folate, and vitamin B12. A complete bone marrow exam requires both an aspirate of the liquid portion of the marrow and a core specimen of the solid portion, which includes a piece of the bone tissue with its enclosed marrow. Although bone marrow aspiration and biopsy can be painful, there are improved needles, experienced technicians, and sedatives (and in special cases, even short-acting general anesthesia) to make the process less uncomfortable.

#### Plasma cell percentage (aspiration and/or core biopsy)

**Normal range:**

1%–2%

(Note: < 5% is CR, or complete response)

The pathologist will examine the bone marrow aspirate or core under the microscope and determine the percentage of plasma cells in the specimen. Normal bone marrow has about 2% or fewer plasma cells. The presence of 60% or more plasma cells in the bone marrow is an independent MDE (as are creatinine clearance of < 40 mL/min, Freelite ratio of more than 100, or the presence of more than one focal lesion on MRI).

Although myeloma cells don’t distribute themselves evenly throughout the bone marrow in the skeleton, the iliac crest, which is a large, hollow bone, is most often chosen as the biopsy site because it provides a fairly representative sample of how the myeloma is behaving elsewhere in the body.

#### Plasma cell morphology (aspiration and/or core biopsy)

The appearance of myeloma cells is distinct, with large nuclei that make the cells look like pimiento-stuffed olives. The appearance and number of these cells are recorded by the pathologist. Words such as “mature,” “immature,” or “atypical” are used to describe the plasma cells. Generally, “mature” cells suggest a better prognosis than “immature” or “atypical” plasma cells.

#### Specimen quality (aspiration and/or core biopsy)

This assessment reports the condition of the sample under the microscope, and helps the doctor determine how representative it is of what is going on in the bone marrow in general. Pathologists usually stipulate that the specimen should be over 1 cm in size to ensure accuracy.

### Immunohistochemistry and flow cytometry of bone marrow plasma cells

Immunohistochemistry (IHC), also called immunophenotyping, is an important tool for diagnosis and prognosis in myeloma and other hematologic malignancies. IHC is the process of detecting antigens in tissue samples by introducing antibodies that bind to them.

IHC is one of the tests used to determine stringent complete response (sCR) to therapy as defined by the IMWG Uniform...
Response Criteria. In addition to the criteria for CR, the IMWG criteria for sCR include a normal free light chain ratio and the absence of clonal plasma cells in the bone marrow by immunohistochemistry or immunofluorescence.

Immunophenotypic analysis of a myeloma patient’s bone marrow identifies myeloma protein markers, if they are present. A fluorophore, or fluorescent marker, is attached to each antibody, which glows when it finds the correct antigen on the surface of the myeloma cells. Several antibodies are usually used simultaneously; the fluorophores are given different colors (fluorochromes) for each antibody. The bone marrow biopsy specimen is placed into a special dish and allowed to grow in the laboratory. Cells are later taken from the growing sample and stained. The lab specialist uses a microscope to examine the size, shape, and number of chromosomes in the nuclei of the growing cells. The chromosomes can only be examined in this way if the cells are undergoing active cell division (the stage in cell division called “metaphase”). The stained sample is photographed to provide a “karyotype,” which shows the arrangement of the chromosomes. Certain abnormalities can be identified through the number or arrangement of the chromosomes.

**Cytogenetics**

Standard cytogenetics (karyotyping) is the assessment of the chromosomes in dividing myeloma cells after brief culture in the laboratory. Since the active growth rate of myeloma cells is usually very low (fewer than 3%, and often fewer than 1% of the cells are proliferating), this provides an incomplete assessment of any chromosomal changes present. Nonetheless, if abnormalities are noted, they are important, because they appear on the few cells that are actually growing.

This test is routinely performed on the bone marrow of newly diagnosed myeloma patients, and is sometimes repeated after treatment (especially after high-dose therapy with stem cell rescue) to see if the therapy has eliminated all the cells with chromosomal abnormalities (called “molecular complete response” or mCR), or at relapse, to help determine if it is time to resume therapy, and if so, if one therapy might be preferable to another.

The bone marrow biopsy specimen is placed into a special dish and allowed to grow in the laboratory. Cells are later taken from the growing sample and stained. The lab specialist uses a microscope to examine the size, shape, and number of chromosomes in the nuclei of the growing cells. The chromosomes can only be examined in this way if the cells are undergoing active cell division (the stage in cell division called “metaphase”). The stained sample is photographed to provide a “karyotype,” which shows the arrangement of the chromosomes. Certain abnormalities can be identified through the number or arrangement of the chromosomes.

**FISH**

Fluorescence in situ hybridization (FISH) is a newer test than standard cytogenetics. FISH is not a substitute for karyotyping, but is complementary to it. FISH is the assessment of the chromosomes of all myeloma cells in a bone marrow sample. FISH allows detection of changes whether myeloma cells are growing or not.

FISH can detect two types of chromosome abnormality: numerical and structural. It provides a way to visualize and map the genetic material in an individual’s cells, including specific genes or portions of genes. Unlike metaphase cytogenetics, FISH is not performed on cells that are actively dividing. The cells are fixed in paraffin, then fluorescent probes that bind to certain sequences of the chromosome are attached. In this way, each chromosome can be identified by a different color.

Chromosomes are made up of two chromatids paired in an X form, with the X shorter at the top and larger on the bottom. The short pieces at the top half of the X are labeled “p” and are called the “short arms” of the chromosome, and the longer pieces at the bottom are labeled “q” and are called the “long arms.” During normal cell division, the chromosomes divide in two, each single chromatid forming a duplicate of its genetic material in a new cell.

FISH is capable of detecting chromosomal translocations that can occur when pieces...
(gene sequences) of one chromatid get shifted over to the other chromatid during cell division. Translocations can be detected when the colors of the fluorescent probes appear to overlap and create secondary colors. Chromosomal deletions can be detected when a fluorophore color is absent.

FISH results have been incorporated into the revised International Staging System (R-ISS) for myeloma because they provide a powerful tool for predicting risk and survival in myeloma. The following cytogenetic abnormalities are considered to confer high risk:

- \( t(4;14) \) (translocation of gene segments from chromosome 4 to 14),
- \( 17p–, \) del 17p (deletion of the short arm of chromosome 17), and
- \( t(14;16) \) (translocation of gene segments from chromosome 14 to 16).

A translocation occurs during cell division, when instead of creating two identical, whole chromosomes, cell division imperfectly results in segments of chromosomes moving over from one member of the pair to the other. Sometimes chromosomes gain or lose segments during cell division. The loss of the short arm of chromosome 17 confers especially high risk because an important **tumor suppressor gene**, p53, is located there. Tumor suppressor genes, also known as “anti-oncogenes,” control cell division and help prevent cancer cells from developing.

Because almost all patients (86%) demonstrate deletion of all or parts of chromosome 13 by FISH analysis, deletion 13 by FISH is not considered a reliable indicator. Deletion 13, which usually occurs as part of a constellation of high-risk genetic mutations, is therefore better determined by standard cytogenetics than by FISH. Some chromosomal abnormalities have no negative prognostic impact.

Therapy choices are often related to chromosomal status. For example, regimens that contain Velcade for induction and maintenance therapy are the preferred treatment for patients with \( t(4;14) \) myeloma. Pomalyst® (pomalidomide) and dexamethasone is a less effective treatment for \( t(4;14) \), but in studies thus far, Pomalyst is more effective than Velcade for overcoming the negative impact of del 17p.

**Imaging studies**

Bone disease is characteristic of myeloma: 70%–80% of patients present with bone disease at diagnosis. In order to assess the status of a patient’s bones at diagnosis or relapse, a hematologist/oncologist has a number of available options for imaging studies. According to current IMWG criteria, none of the imaging methods is mandatory for monitoring treatment of myeloma, as long as the response can be assessed by serum and urine testing. Repeated imaging is indicated if a problem (e.g., pain or nerve compression) is likely induced by bone lesions, or in cases of relapse to exclude extramedullary (outside the bone marrow) disease. The uses, benefits, and limitations of the various types of imaging studies are explained below.

**X-ray/bone survey**

X-rays are generally the first bone study done at diagnosis to establish myeloma-caused bone damage. A full skeletal x-ray, also known as a whole-body x-ray (WBXR) survey, is performed to demonstrate loss or thinning of bone (**osteoporosis** or **osteopenia**), holes in bone (**lytic lesions**), and/or bone fractures. Doctors may use x-rays during follow-up of a patient after treatment by comparing old and new films to see if there has been bone healing or if new lesions are apparent.

Typically, x-rays are simple to do and are inexpensive. More sensitive studies are now recommended in lieu of x-rays, however, because their limitations are:

- 30% or more of the **trabecular bone** (also known as cancellous, or spongy bone; it contains the bone marrow where myeloma cells grow) must be missing before x-ray can reveal the damage. An experimental study showed that bone loss in a lumbar vertebra can be seen on x-ray only when 50%–75% of the trabecular bone has been destroyed.
- X-ray is not a sensitive study for focal lesions in the bone marrow.
- The appearance of lytic lesions may not change following

**Figure 9.** Fluorescence in situ hybridization (FISH) of a myeloma cell

**Figure 10.** Healthy bone compared to myeloma bone
therapy, even if there is no longer any active myeloma there.

- X-ray provides low visualization of the spine and pelvis.
- X-ray cannot accurately depict the cause of painful lesions in patients with myeloma.
- Because WBXR requires 20 separate films, the study is time-consuming.

**MRI (magnetic resonance imaging)**

MRI is a non-invasive study that uses magnetic energy, not radiation, to produce a detailed two- or three-dimensional image of structures inside the body. MRI scans are useful for diagnosing and monitoring myeloma because of their ability to image early focal lesions in the bone marrow. Because MRI creates images of soft tissue, it can show small clumps of myeloma in the bone marrow, plasmacytomas (tumors formed by massing of myeloma cells inside or outside the bone marrow), and compression of the spinal cord by these masses.

The IMWG recently published new guidelines on the role of MRI in the management of patients with myeloma. In these guidelines, MRI is newly defined as the gold standard for:

- imaging the spine, pelvis, and sternum;
- detection of bone marrow involvement in myeloma;
- evaluation of painful lesions and detection of spinal cord compression;
- distinguishing benign versus malignant osteoporotic vertebral fractures.

In a large comparative study of x-ray and MRI, 52% of patients had normal-looking WBXR, but had focal lesions that were apparent on MRI. In that study, MRI outperformed x-ray in imaging the spine, pelvis, and sternum, while x-ray had better performance than MRI in the ribs and long bones of the arms and legs; results were equal in the shoulders and skull.

The IMWG guidelines on MRI state that, because MRI is a more sensitive study than x-ray for focal lesions (before the appearance of lytic bone lesions), all SMM myeloma patients should undergo whole-body MRI (WB-MRI), or spine and pelvic MRI if WB-MRI is unavailable. The new IMWG diagnostic criteria specify that if a patient with SMM has more than one focal lesion on MRI that is greater than 5 mm in diameter, he or she is considered to have symptomatic myeloma requiring therapy. More than one focal lesion larger than 5 mm on MRI is another independent MDE.

Despite its advantages over x-ray, MRI also has its limitations:

- MRI is an expensive, time-consuming procedure.
- Patients who have metal implants, and patients who are claustrophobic, cannot undergo MRI.
- The contrast medium gadolinium used to enhance the MRI image may be contraindicated in myeloma patients, many of whom have some level of kidney damage.
- You must tell the radiology technician who is performing the scan about your diagnosis BEFORE you receive a dye injection into your blood.
- There is approximately a 9-month or longer lag time before an MRI will look normal after an area of myeloma has been successfully treated and is no longer active, leading to a high false-positive rate. The IMWG guidelines therefore state that the use of MRI “for the follow-up of patients, before or after different therapies, in the absence of clinical indications is not recommended.”

**CT or CAT scan (computed [axial] tomography)**

CT is a radiological study that uses x-ray technology to create a cross-sectional, three-dimensional image of the inside of the body. It is a more precise study than x-ray, and can provide clear, detailed images of bone. It has several advantages over x-rays:

- CT allows for the detection of small bone lesions that are not detectable by plain x-rays.
- CT can detect soft tissue masses that are not visible on x-ray.
- CT provides a more comprehensive assessment of fracture risk and the stability of collapsed vertebrae than x-ray.

Disadvantages of CT include:

- Like MRI, CT cannot be used for treatment monitoring because bone lesions in myeloma regress slowly or not at all, even in patients in complete remission.
- CT may require the use of contrast agents that can pose problems for myeloma patients with kidney damage.
- CT is an expensive study compared to x-ray.

Even in low-dose format, CT uses an increased level of radiation as compared to x-ray.

**PET scan (positron emission tomography)**

PET scanning is a “real-time” study that shows where, and to what extent, cancer cells are actively dividing in the body.

Before a PET scan, a patient is injected with a sugar-fluorine compound (FDG, or fluoro-deoxyglucose) that is taken up by the body’s actively multiplying cells as fuel for cell division. When the body is scanned, the areas with the highest concentration of sugar-fluorine uptake glow from positrons emitted by the fluorine, revealing “hot spots” where rapid metabolism can indicate areas of active cancer cell division. This scan covers the whole body and is very sensitive in detecting potential tumor activity. It is measured in units of Standardized Uptake Value (SUV).

818-487-7455 worldwide • 800-452-CURE (2873) toll-free in US & Canada myeloma.org
PET's advantages include its ability to:
- detect isolated focal myeloma lesions (areas of massed myeloma cells) in the bone marrow where there is no destruction of bone
- detect extramedullary (outside the bone marrow) disease
- assess the status of patients whose myeloma cells do not secrete M-protein and whose myeloma therefore cannot be assessed with standard blood and urine tests
- predict progression-free survival (PFS, or remission time) and overall survival (OS); 3 or more PET-positive lesions are an independent predictor of poorer PFS and OS.

Disadvantages of PET include the following:
- It is time-consuming and expensive.
- Because areas of infection and inflammation can also take up FDG, PET scans can produce false-positive readings for cancer.

There is some concern that skull lesions could be missed because of the normally high FDG uptake in the brain.

In the US, the Centers for Medicare and Medicaid Services (CMS) currently cover the cost of one FDG PET scan, and allow private health insurers who function as local Medicare contractors to decide whether or not to cover further PET scans. Physicians who wish to support the need for additional PET scans can do so on the basis of:
1. disease recurrence,
2. disease that is technically non-secretory (so low level that it cannot be detected by other methods), or
3. in cases where there is concern about infection or a second primary cancer.

**PET/CT**

PET/CT is a highly accurate and valuable imaging technique used in diagnosis, therapy assessment, and prognosis of myeloma. It combines PET scan with CT in areas where there is high uptake of FDG. It provides information both about past damage and current myeloma activity, thus enabling the doctor to study changes over time. Because of its sensitivity, PET/CT has been included along with Next-Generation Flow as an assessment performed in some clinical trials to establish minimal residual disease-negative (MRD-negative) status following treatment.

**Bone densitometry**

Bone density testing is useful for monitoring the effects of bisphosphonate therapy on the bones of patients who have diffuse thinning (osteopenia or the more severe condition, osteoporosis) of the outer bone cortex. It is not a useful test in assessing myeloma bone disease.

Another bone-related test that is not useful for myeloma patients is the nuclear bone scan. This test is often used at diagnosis to screen for other types of cancer that cause blastic lesions in bone (overgrowth of bone tissue) such as prostate cancer. Myeloma causes bone loss resulting in lytic lesions, which do not show up on a nuclear bone scan.

**In closing**

While a diagnosis of cancer is something you cannot control, gaining knowledge that will improve your interaction with your doctors and nurses is something you can control, and it will have a significant impact on how well you do throughout the disease course.

This booklet is not meant to replace the advice of your doctors and nurses who are best able to answer questions about your specific healthcare management plan. The IMF intends only to provide you with information that will guide you in discussions with your healthcare team. To help ensure effective treatment with good quality of life, you must play an active role in your own medical care.

We encourage you to visit myeloma.org for up-to-date information about myeloma, and to contact the IMF InfoLine with your myeloma-related questions and concerns. The IMF InfoLine consistently provides callers with the best information about myeloma in a caring and compassionate manner. IMF InfoLine specialists can be reached at InfoLine@myeloma.org, or 800-452-CURE (2873) or 818-487-7455.

**Terms and definitions**

**Amyloidosis:** A general term for a group of diseases characterized by cross-linked light chains. The light chains form rigid fibrils that are insoluble and that are deposited in various organs or tissues. Different types of amyloidoses have different signs and symptoms depending on where and in which organs the amyloid proteins are deposited.

**Anemia:** A decrease in hemoglobin contained in red blood cells that carry oxygen to the body’s tissues and organs. Anemia is usually defined as hemoglobin below 10 g/dL, with over 13–14 g/dL considered normal, and/or a decrease of ≥ 2 g/dL from the normal level for an individual.

**Antigen:** Any foreign substance (such as bacteria, a virus, toxin, or tumor) that causes the immune system to produce natural antibodies.

**Bacteria:** Single-celled microorganisms that can exist either as independent (free-living) organisms or as parasites (dependent on another organism for life). The plural of bacterium.

**Bence-Jones protein:** A myeloma monoclonal protein. The protein is composed of either free kappa or free lambda light chains. Because of their small size, Bence-Jones light chains pass freely into the urine. The amount of Bence-Jones protein in the urine is expressed in terms of grams per 24 hours. Normally, a very small amount of protein (<0.1 g/24 h) can be present in the urine, but this is albumin rather than Bence-Jones protein. The presence of any Bence-Jones protein in the urine is abnormal.

**Beta-2 microglobulin (also called β2-microglobulin, β2M, or β2M):** A small protein found in the blood. High levels occur in patients with active myeloma.
Extramedullary plasmacytoma: A tumor made up of monoclonal plasma cells that is found in soft tissue outside of the bone marrow and separate from bone.

Focal lesion: An area of irregular cells seen in the bone marrow on MRI (magnetic resonance imaging) study. In order to be considered diagnostic of myeloma, there must be more than one focal lesion that is ≥ 5 mm in size.

Gene: A specific sequence of DNA coding for a particular protein.

Heavy chain: An immunoglobulin heavy chain is the larger of two units of an antibody (immunoglobulin). There are five types of heavy chains: G, A, D, E, and M. The heavy chains most commonly made by myeloma cells are G and A.

Hematologist: A doctor who specializes in the problems of blood and bone marrow.

Immunoglobulin (Ig): A protein produced by plasma cells; an essential part of the body's immune system. Immunoglobulins attach to foreign substances (antigens) and assist in destroying them. The classes (also called isotypes) of immunoglobulins are IgG, IgA, IgD, IgE, and IgM. The non-medical word for immunoglobulin is “antibody.”

Light chain: An immunoglobulin light chain is the smaller of two units of an antibody (immunoglobulin). The light chains are bound by chemical bonds to the ends of the heavy chains, but we make extra light chains that enter the bloodstream. These are called “free light chains.” There are two types of light chains: kappa and lambda.

Lytic lesions: The damaged area of a bone that shows up as a dark spot on an x-ray when at least 30% of the healthy bone in any one area is eaten away. Lytic lesions look like holes in the bone and are evidence that the bone is being weakened.

Monoclonal: A clone or duplicate of a single cell. Myeloma develops from a single malignant plasma cell (monoclonal). The type of myeloma protein produced is also monoclonal; a single form rather than many forms (polyclonal). The important practical aspect of a monoclonal protein is that it shows up as a sharp spike (M-spike) in the serum electrophoresis test.

Monoclonal gammopathy of undetermined significance (MGUS): A category of plasma cell disorder characterized by comparatively low levels of monoclonal protein in the blood and/or urine. Bone marrow plasma cell levels are low (<10%). Myeloma-related symptoms (i.e., anemia, renal failure, hypercalcemia, and lytic lesions) are absent.

Monoclonal protein (M-protein, M-spike): An abnormal protein produced by myeloma cells that accumulates in and damages bone and bone marrow. Antibodies or parts of antibodies found in unusually large amounts in the blood or urine of myeloma patients. A monoclonal spike (M-Spike), the sharp pattern that occurs on protein electrophoresis, is the telltale indicator of M-protein in the blood, a marker for the activity of myeloma cells. See “Monoclonal.”

Multiple myeloma: A cancer arising from the plasma cells in the bone marrow. The cancerous plasma cells are called myeloma cells.

Neutropenia: A reduced level of neutrophils.

Non-secretory myeloma: Approximately 1% of myeloma patients do not have detectable M-protein in the blood (serum) and urine. Some of these patients can be successfully monitored using the serum free light chain assay; others may be monitored with bone marrow biopsy and/or PET/CT scan. Patients with non-secretory myeloma are treated in the same fashion as those with M-protein-secreting disease.

Oncogene: A gene or DNA sequence that normally directs cell growth, but which can also promote or allow the uncontrolled growth of cancer if damaged (mutated) by environmental exposure to carcinogens, or if damaged or missing because of an inherited defect. A gene that has the potential to cause a normal cell to become cancerous.

Oncologist: A doctor who specializes in treating cancer. Some oncologists specialize in a particular type of cancer.

Osteopenia: A condition in which bone mineral density is lower than normal, but not low enough to be classified as osteoporosis.

Osteoporosis: A progressive bone disease that is characterized by a decrease in bone mass and density, leading to an increased risk of fracture. Diffuse involvement of bones with myeloma produces what looks like osteoporosis on x-ray and bone density measurement.

Plasmacytoma: See “Extramedullary plasmacytoma” and “Solitary plasmacytoma of the bone (SPB).”

Platelets: One of the three major blood elements, others being the red blood cells and white blood cells. Platelets plug up breaks in the blood vessel walls and release substances that stimulate blood clot formation. Platelets are the major defense against bleeding. Also called thrombocytes.
Proteasome inhibitor: Any drug that interferes with the normal function of the proteasome, an enzyme complex responsible for breaking down and recycling unwanted proteins in both normal cells and cancer cells.

Proteins: Substances composed of amino acids. Proteins are an essential part of all living organisms, especially as structural components of body tissues such as muscle, hair, collagen, and so forth, as well as enzymes and antibodies.

Red blood cells (RBC, erythrocytes): Cells in the blood that contain hemoglobin and deliver oxygen to and take carbon dioxide from all parts of the body. Red cell production is stimulated by a hormone (erythropoietin) produced by the kidneys. Myeloma patients with damaged kidneys don’t produce enough erythropoietin and can become anemic. Myeloma patients can also become anemic because of myeloma cells’ effect on the ability of the bone marrow to make new red blood cells.

Relapse: The reappearance of signs and symptoms of a disease after a period of improvement. Patients with relapsed disease have been treated, then developed signs and symptoms of myeloma at least 60 days after treatment ended. Most clinical trials for advanced disease are for patients with relapsed and/or refractory myeloma.

Response or remission: Complete or partial disappearance of the signs and symptoms of cancer. Remission and response are interchangeable terms.

- **Complete response (CR)** – For myeloma, CR is negative immunofixation on serum (blood) and urine, and disappearance of any soft tissue plasmacytomas, and ≤ 5% plasma cells in bone marrow. CR is not the same as a cure.

- **Very good partial response (VGPR)** – VGPR is less than CR. VGPS is serum M-protein and urine M-protein detectable by immunofixation but not on electrophoresis, or 90% or greater reduction in serum M-protein, plus urine M-protein less than 100 mg per 24 hours.

- **Partial response (PR)** – PR is a level of response in which there is at least a 50% reduction in M-protein, and reduction in 24 hour urinary M-protein by at least 90% (or to less than 200 mg per 24 hours).

**Side effect:** Unwanted effect caused by a drug. Also known as adverse reaction or adverse event (AE).

Smoldering multiple myeloma (SMM): SMM is a higher level of disease than MGUS, but is still not active myeloma with CRAB features indicating organ damage. Patients with standard-risk SMM do not require treatment, but should be observed at regular intervals by a hematologist-oncologist. Patients with high-risk SMM may choose to participate in a clinical trial.

Solitary plasmacytoma of bone (SPB): A discreet, single mass of monoclonal plasma cells in a bone. The diagnosis of SBP requires a solitary bone lesion, a biopsy of which shows infiltration by plasma cells; negative imaging results for other bone lesions; absence of clonal plasma cells in a random sample of bone marrow; and no evidence of anemia, hypercalcemia, or renal involvement suggesting systemic myeloma.

**Stage:** The extent of a cancer in the body.

Thrombocytopenia: A low number of platelets in the blood. “Normal” levels vary from laboratory to laboratory. The normal level at the Mayo Clinic is 150,000–450,000. If the platelet count is less than 50,000, bleeding problems could occur. Major bleeding is usually associated with a reduction to less than 10,000.

Toxins: Poisons produced by certain animals, plants, or bacteria.

Trabecular bone: Also known as cancellous bone; the light, porous bone enclosing numerous large spaces that give it a sponge-like appearance. Trabecular bone contains marrow and blood vessels.

Tumor suppressor gene: Also called an anti-oncogene. A gene that protects a cell from one step on the path to cancer. When this gene mutates to cause a loss or reduction in its function, the cell can progress to cancer, usually in combination with other genetic changes.

Virus: A small living particle that can infect cells and change how the cells function. Infection with a virus can cause a person to develop symptoms. The disease and symptoms that are caused depend on the type of virus and the type of cells that are infected.

White blood cells (WBC): General term for a variety of cells responsible for fighting invading germs, infection, and allergy-causing agents. These cells begin their development in the bone marrow and then travel to other parts of the body. Specific white blood cells include neutrophils, granulocytes, lymphocytes, and monocytes.

**Notes**
One of the most daunting aspects of being diagnosed with multiple myeloma is learning about – and understanding – an unfamiliar disease that is quite complicated. From diagnosis to long-term survival, the 10 Steps to Better Care® will guide you through the myeloma journey:

1. Know what you’re dealing with. Get the correct diagnosis.
2. Tests you really need.
3. Initial treatment options.
4. Supportive care and how to get it.
5. Transplant: Do you need one?
6. Response Assessment: Is treatment working?
7. Consolidation and/or maintenance.
9. Relapse: Do you need a change in treatment?

Visit 10steps.myeloma.org to gain a better understanding of the disease and diagnosis, and proceed through the steps to learn the best tests, treatments, supportive care, and clinical trials currently available.

As always, the International Myeloma Foundation (IMF) urges you to discuss all medical issues thoroughly with your doctor. The IMF is here to equip you with the tools to understand and better manage your myeloma. Visit the IMF website at myeloma.org or call the IMF InfoLine at 800-452-CURE (2873) or 818-487-7455 to speak with our trained information specialists about your questions or concerns. The IMF is here to help.