Understanding Your Test Results

A publication of the **International Myeloma Foundation**

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Improving Lives **Finding the Cure**®

INTERNATIONAL MYELOMA FOUNDATION

Founded in 1990, the International Myeloma Foundation (IMF) is the first and largest organization focusing specifically on multiple myeloma. The IMF's reach extends to more than 525,000 members in 140 countries worldwide. The IMF is dedicated to improving the quality of life of myeloma patients while working toward prevention and a cure through our four founding principles: Research, Education, Support, and Advocacy.

RESEARCH The signature project of the IMF's Research division is the Black Swan Research Initiative®, a groundbreaking and collaborative effort to develop the first definitive cure for myeloma. Each year, the IMF also awards Brian D. Novis Grants, which promote research for better myeloma treatments, management, and practices in the field. In addition, more than 200 leading myeloma researchers comprise the IMF's International Myeloma Working Group (IMWG), a research body that has developed myeloma guidelines that are followed around the world. Finally, the IMF's Nurse Leadership Board (NLB), comprised of nurses from leading myeloma treatment centers, develops recommendations for the nursing care of myeloma patients.

EDUCATION The IMF Patient & Family Seminars and Regional Community Workshops are held around the world to provide up-to-date information presented by leading myeloma specialists and researchers directly to patients and their families. The IMF's 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 The IMF's InfoLine is staffed by information specialists who answer myeloma-related questions and provide support via phone and email to thousands of families each year. In addition, the IMF sustains a network of more than 150 myeloma 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's Advocacy team has educated and empowered thousands of individuals who make a positive impact each year on issues critical to the myeloma community. Working in the US at both federal and state levels, we lead coalitions to advocate for parity in insurance coverage. We also represent the myeloma community's interests before the US Congress and agencies such as the National Institutes of Health, the Food and Drug Administration, the Centers for Medicare and Medicaid Services, and the Veterans Administration. Outside the US, the IMF's Global Myeloma Action Network (GMAN) works to help patients gain access to treatment.

Learn more about the ways the IMF is helping to improve the quality of life of myeloma patients while working toward prevention and a cure.
Contact us at 818.487.7455 or 800.452.CURE,
or visit myeloma.org.

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What you will learn from this booklet

The IMF's *Understanding* series of booklets is designed to acquaint you with treatments and supportive care measures for **multiple myeloma** (which we refer to simply as "myeloma"). Words in **bold+blue** type are explained in the "Terms and definitions" section at the end of this booklet, as well as in a more complete compendium of myeloma-related vocabulary, the IMF's *Glossary of Myeloma Terms and Definitions*, located at glossary.myeloma.org.

Myeloma is a **cancer** that is not known to most patients at the time of diagnosis. To be empowered to play an active role in your own medical care and to make good decisions about your care with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments. The information in this booklet will help you in discussions with your healthcare team. The more information you have about resources that are available to you, the better and more fruitful that discussion will be.

The *Understanding Your Test Results* booklet outlines the various tests that are used to diagnose and monitor myeloma, and to detect **response** and **relapse**. You can better understand and cope with your myeloma if you familiarize yourself with the tests used to assess your status throughout the disease course.

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.
- 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.

Figure 1. **Sample test results**

Test	Result	Flag	Reference
HEMATOLOGY			
AUTOHEMATOLOGY - DIFFERENTIAL - MORPHOLOGY			
CBC TREAT			
WBC	**4.4**	*L*	4.5-11.0 K/UL
RBC	**3.46**	*L*	3.5-5.5 M/UL
HGB	12.3		12.0-15.0 G/DL
HCT	36.2		36.0-48.0 %
MCV	**104.6**	*H*	79.0-101.0 FL
MCH	**35.5**	*H*	25.0-35.0 PG
MCHC	34.0		31.0-37.0 G/DL
RDW-CV	15.8		11.0-16.0 %
PLT	149		140-440 K/UL
MPV	7.5		7.0-10.0 Fl
NEUT % (AUTO)	74		40-76 %
LYMPH % (AUTO)	**16**	*L*	24-44 %
MONO % (AUTO)	9		1.0-10.0 %
EOS % (AUTO)	1		0.0-3.0 %
BASO % (AUTO)	0		0-1 %
NEUT AB (AUTO)	3.22		1.9-8.8 K/UL
LYMPH AB (AUTO)	**0.69**	*L*	1.0-4.8 K/UL
MONO AB (AUTO)	0.41		0.1-0.8 K/UL
EOS AB (AUTO)	0.03		0.0-0.5 K/UL
BASO AB (AUTO)	0.02		0.0-0.1 K/UL

- 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

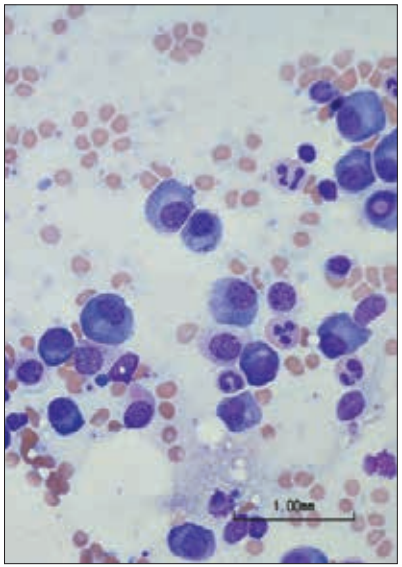
It is important for patients to educate themselves about myeloma, how it is diagnosed and monitored, and its treatments and supportive care. You can gain this understanding through many avenues: discussions with your doctors and nurses, participation in a myeloma support group (contact the IMF to help 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.

Figure 2. **Myeloma cells as seen in a bone marrow aspirate**



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.

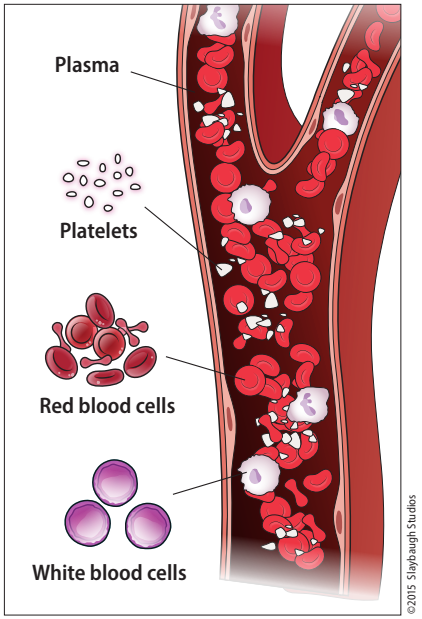
CBC results are broken down into the major headings of RBC, WBC, and platelets, with sub-categories under each major blood cell type. The sub-categories that are monitored while you are a myeloma patient are included below.

Red blood cells (RBC)

Reference range (10^{12} = 1 trillion):
males: 4.32–5.72 x 10^{12}/L
females: 3.90–5.03 x 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.

Figure 3. **Blood composition**



- ***Hemoglobin (hgb)***
  Reference range:
  males: 13.5–17.5 g/dL (135–175 g/L)
  females: 12.0–15.5 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 **C**alcium, **R**enal (kidney) dysfunction, **A**nemia, and **B**one 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%***

  Hematocrit is the volume percentage of red blood cells in the blood. Usually the percentage of RBC is about 45% for men and 40% for women. Together, low RBC, low hemoglobin, and low hematocrit indicate anemia.

White blood cells (WBC)

Reference range (10^{9} = 1 billion): ***3.5–10.5 x 10^{9}/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 x 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.

Table 1. **CBC reference ranges**

Red blood cells (RBC) males: 4.32–5.72 x 10^{12}/L (10^{12} = 1 trillion) females: 3.90–5.03 x 10^{12}/L
Hemoglobin (hgb) males: 13.5–17.5 g/dL (135–175 g/L) females: 12.0–15.5 g/dL (120–155 g/L)
Hematocrit (hct) males: 38.8%–50.0% females: 34.9%–44.5%
White Blood Cells (WBC) 3.5–10.5 x 10^9/L (10^9 = 1 billion)
Neutrophils 1.7–7.0 x 10^9/L
Platelets 150–450 x 10^9/L

Platelets

Reference range: ***150–450 x 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 pro le

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 mg/dL***

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

▶ *Serum creatinine*

Reference range: ***0.6–1.3 mg/dL***

This test is used to assess the "R" in the CRAB criteria – **R**enal (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 (mL/min = milliliters per minute):

males: 97–137 mL/min, females: 88–128 mL/min

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 m^2***

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 **C**alcium 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.

Table 2. **Comprehensive metabolic panel reference ranges**

BUN (blood urea nitrogen) 7–20 mg/dL
Serum creatinine 0.6–1.3 mg/dL
Creatinine clearance (milliliters per minute) males: 97–137 mL/min females: 88–128 mL/min
Estimated glomerular filtration rate (eGFR) 90–120 mL/min/1.73 m^2
Calcium 9–10.5 mg/dL
Total protein 6–8 g/dL

- ***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.

Tests to assess monoclonal protein

- ***Serum quantitative immunoglobulins (QIg)***
  Reference range: ***IgG: 767–1,590 mg/dL, IgA: 61–356 mg/dL***
  IgM: 37–286 mg/dL, IgD: ≤ 10 mg/dL
  IgE: ≤ 214 mg/dL *(patients ≥ 18 years old)*

  QIg testing measures the total amount of each primary **immunoglobulin** (Ig or "antibody") class (also called an "isotype") in the serum. It measures both polyclonal (normal) and monoclonal (myeloma-related) immunoglobulin, so if an increase in one of the antibody isotypes is found, further testing with electrophoresis is required to determine if the elevation is caused by the presence of monoclonal immunoglobulin protein. QIg is often the preferred way to assess IgA protein, because IgA may be difficult to quantify with electrophoresis. Note: The ranges for IgD and IgE are reported differently from those for IgG, IgA, and IgM.

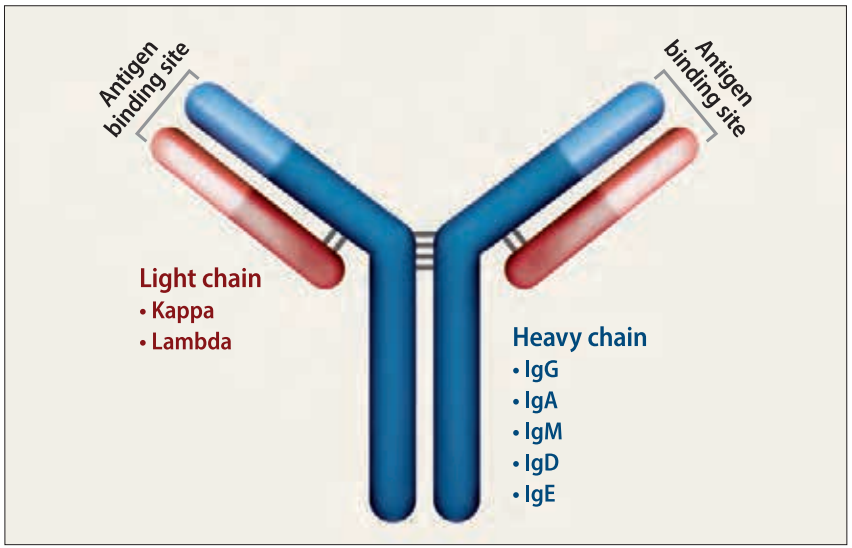
- ***Serum protein electrophoresis (SPEP)***
  Reference range: ***albumin: 3.3–5.7 g/dL, alpha-1: 0.1–0.4 g/dL***
  alpha-2: 0.3–0.9 g/dL, beta-2: 0.7–1.5 g/dL
  gamma: 0.5–1.4 g/dL

  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)."*

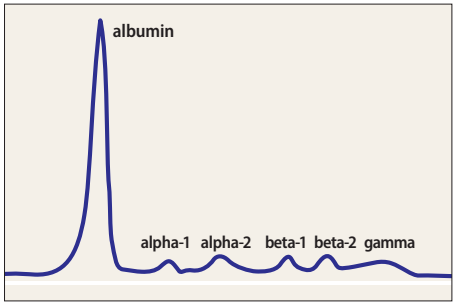
  Monoclonal immunoglobulin protein appears on the graph as a narrow spike: Because all the cells in the M-protein are identical and

Figure 4. **Structure of an immunoglobulin (antibody)**

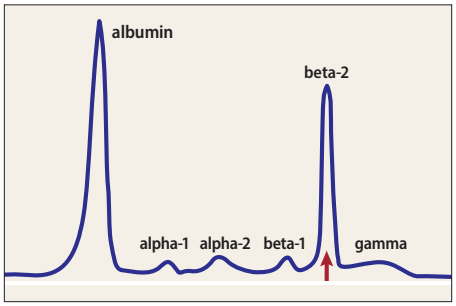


have the same electrical charge, they gravitate to the same small region and form a peak or spike on the graph. A monoclonal spike (or M-Spike) is the telltale indicator of myeloma protein in the blood, a marker for the activity of myeloma cells. By calculating the area under the curve (AUC) of the spike 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.

Figure 5. **SPEP test results**



Normal SPEP result



Abnormal result with myeloma cells producing the M-protein, creating an M-spike in the beta-2 zone

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 17.)

- ***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® (serum free light chain assay)***

  Reference range: ***Free kappa: 3.3–19.4 mg/L, Free lambda: 5.71–26.3 mg/L, Kappa/lambda 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 Freelite 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 ("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, β_2M, β2M)**
  Reference range: ***0.70–1.80 mg/L***

  The serum β2M 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, β2M can also be used to evaluate disease activity and to monitor response to treatment. A serum β2M of < 3.5 mg/L is considered stage I; a β2M ≥ 5.5 mg/L is stage III. Stage II is defined as β2M between 3.5 mg/L and 5.5 mg/L.

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

  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 (fasting blood glucose level): ***70–100 mg/dL***

  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 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-secretory myeloma, which cannot be tracked through M-protein in the blood or urine.

Figure 6. **Bone marrow biopsy**

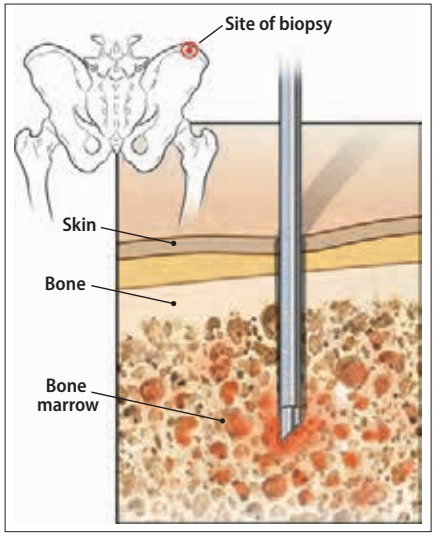
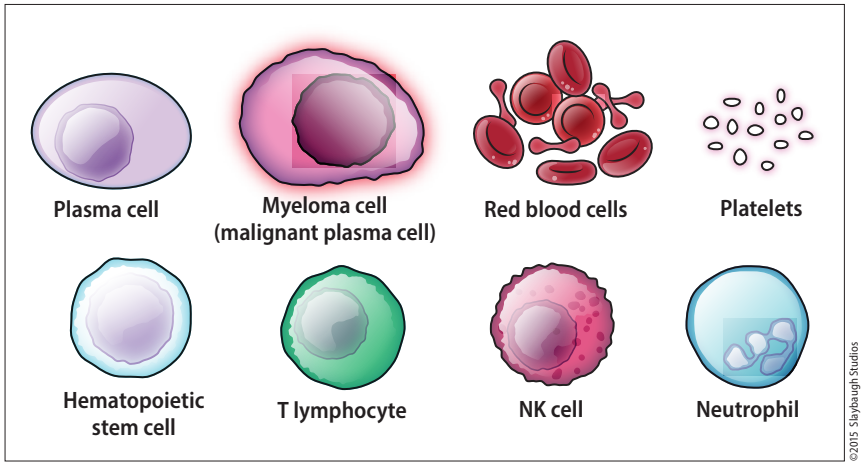


Figure 7. **Cells that play a role in myeloma**



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.

Bone marrow aspiration and core biopsy

- ***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.

  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 an ow 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 sample cells and selected antibodies are sent through a flow cytometer, which is a laser-based instrument that reads the fluorophores and identifies and sorts the myeloma cells.

The IMF's Black Swan Research Initiative® (BSRI®) has supported the development of Next-Generation Flow (NGF) cytometry, which uses many antibodies and newly designed myeloma-specific software to rapidly perform eight-color immunophenotyping of myeloma cells. NGF is a highly accurate way to detect minimal residual disease after treatment. This test is sensitive enough to identify 1 myeloma cell per approximately 1,000,000 bone marrow cells sampled.

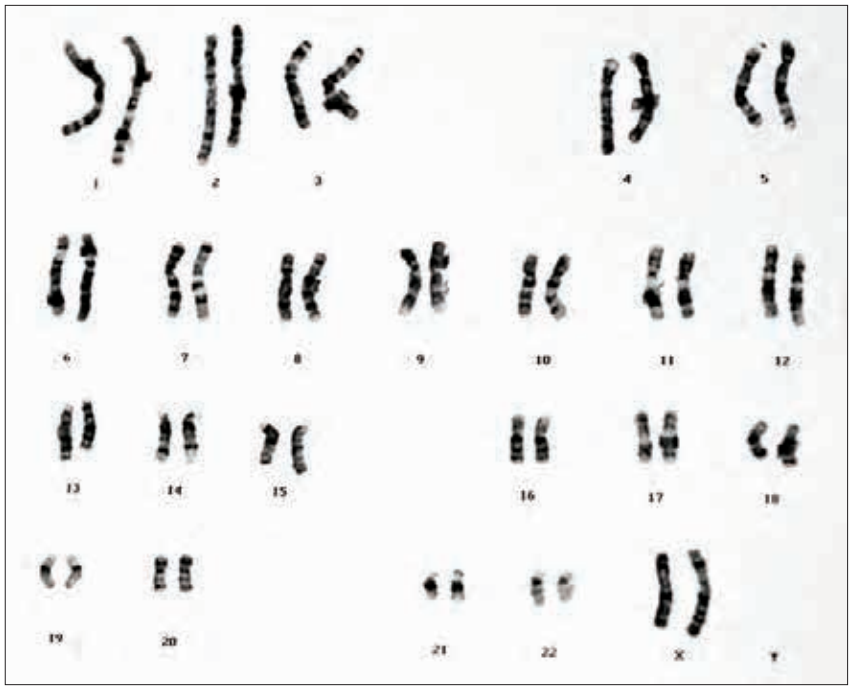
Cytogenetics

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

Figure 8. **Karyotype analysis of human chromosomes**



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.

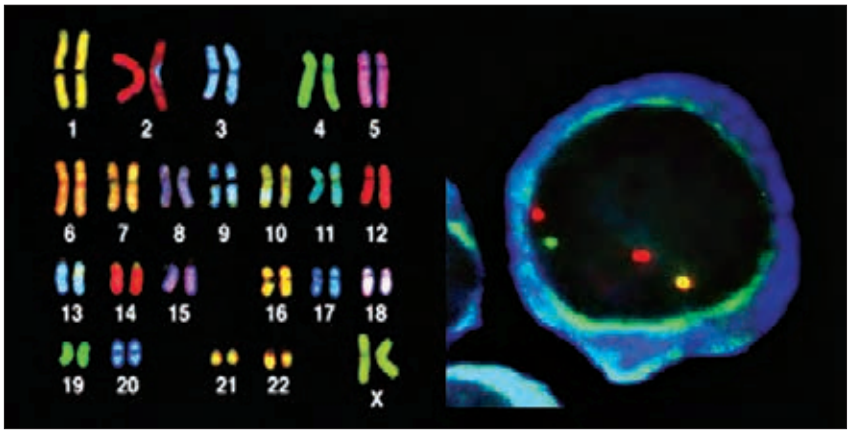
This test is particularly valuable for identifying higher-than-average-risk myeloma in patients with fewer than two copies of each chromosome (hypodiploidy) and in those whose 13th chromosome is deleted entirely during cell division (called "del 13").

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.

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



Chromosomes are made up of two **chromatids** paired in an X form, with the X shorter at the top and longer 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).
- t(14;16) (translocation of gene segments from chromosome 14 to 16).

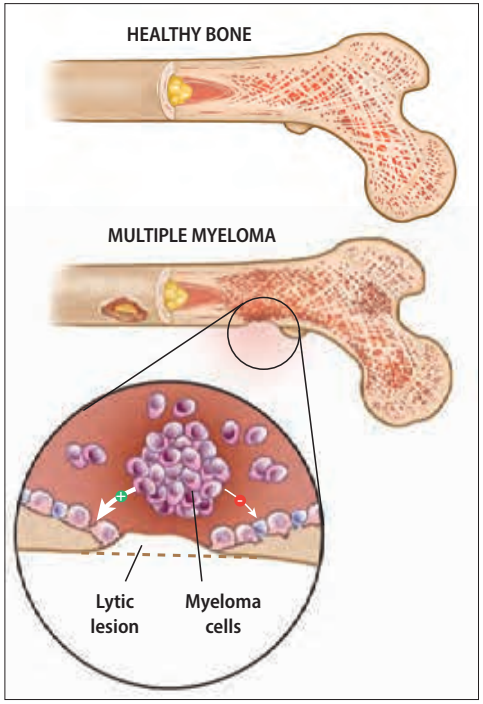
The loss of the short arm of chromosome 17 confers especially high risk because an important **tumor suppressor gene**, p53, is located there. Tumor suppressor genes, also known as "anti-**oncogenes**," control cell division and help prevent cancer cells from developing.

Because nearly all myeloma patients 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 an array 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

Figure 10. **Healthy bone compared to myeloma bone**



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 an X-ray can reveal the damage. An experimental study showed that bone loss in a lumbar vertebra can be seen on an 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 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-appearing 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 (WBMRI) or spine and pelvic MRI if WBMRI 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. In 20% to 25% of patients with negative X-ray studies, whole-body CT (WBCT) will detect destructive bone lesions.
- 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.
- WBCT is faster and more convenient than whole-body X-ray.
- Because of these advantages over conventional X-ray studies, the IMWG published "Whole-body computed tomography versus conventional skeletal survey in patients with multiple myeloma: a study of the International Myeloma Working Group" in *Blood* in August 2017, concluding that "WBCT (either computed tomography alone or as part of a positron emission tomography-CT protocol) should be considered the current standard for the detection of osteolytic lesions in MM."

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 is not as sensitive as MRI in detecting lesions outside the bone marrow in the vertebrae and pelvis.
- 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 fluorodeoxyglucose) 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).

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 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).
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 more information about myeloma and to contact the IMF InfoLine with your myeloma-related questions and concerns. The IMF InfoLine consistently provides callers with the most up-to-date and accurate information about myeloma in a caring and compassionate manner. IMF InfoLine specialists can be reached at InfoLine@myeloma.org or 818.487.7455 or 800.452.CURE.

Terms and definitions

Amyloid light-chain amyloidosis (AL amyloidosis): AL amyloidosis is a condition in which myeloma light chains crosslink with each other in a beta-pleated fashion and then are deposited in tissues and organs throughout the body, such as the heart, nerves, and kidneys, rather than being excreted by the kidneys. This condition is also known as primary amyloidosis.

Amyloidosis: A group of systemic diseases characterized by the deposition of amyloid protein in various organs and/or tissues. One type (AL amyloidosis) is related to multiple myeloma; other types include hereditary amyloidosis, AA amyloidosis, wild-type ATTR amyloidosis, ALECT2 amyloidosis, and AB2M amyloidosis. See "**Amyloid light-chain amyloidosis (AL amyloidosis)**."

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

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 can be filtered through the kidneys and pass 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. Myeloma protein heavy chains are too large to be filtered through the kidneys.

Beta-2 microglobulin (also called β2-microglobulin, β_2M, or β2M): A small protein found in the blood. High levels occur in patients with active myeloma. Low or normal levels occur in patients with early myeloma and/or inactive disease. Approximately 10% of patients have myeloma that does not produce β2M. At the time of relapse, β2M can increase before there is any change in the myeloma protein level. Factors such as viral infection can sometimes produce elevated serum β2M levels.

Bone marrow: The soft, spongy tissue in the center of bones that produces white blood cells, red blood cells, and platelets. This is the tissue within which abnormal plasma cells build up when myeloma is growing.

Bone marrow aspiration: The removal, by a needle, of a sample of fluid and cells from the bone marrow for examination under a microscope.

Cancer: A term for diseases in which malignant cells divide without control. Cancer cells can invade nearby tissues and spread through the bloodstream and lymphatic system to other parts of the body.

Cell: The basic unit of any living organism. Millions of microscopic cells comprise each organ and tissue in the body.

Chromatid: One of two identical chromosomal strands into which a chromosome splits longitudinally before cell division.

Chromosome: A strand of DNA and proteins in the nucleus of a cell. Chromosomes carry genes and function in the transmission of genetic information. Normally, human cells contain 46 chromosomes (23 pairs).

Creatinine: A small chemical compound normally excreted by the kidneys into the urine. If the kidneys are damaged, the serum level of creatinine builds up, resulting in an elevated serum creatinine. The serum creatinine test is used to measure kidney function.

Cytokine: Cytokines are proteins secreted by cells which can stimulate or inhibit growth/activity in other cells. Cytokines are produced locally (for myeloma, in the bone marrow) and circulate in the bloodstream. They are normally released in response to infection.

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 *at least* two focal lesions that are at least 5 mm in size.

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

Genetic: Inherited; having to do with information that is passed from parents to children through DNA in the genes.

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 lesion: 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 monoclone, a single malignant plasma cell. The type of myeloma protein produced is also monoclonal, a single form rather than many forms (poly-clonal). The important practical aspect of a monoclonal protein is that it shows up as a sharp spike (M-spike) on the protein 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 (myeloma 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 of the bone marrow plasma cells, white blood cells that make antibodies. The cancerous plasma cells are called myeloma cells.

Myeloma-defining event (MDE): One of three biologic markers that indicate progression to symptomatic myeloma within 18 months to 2 years. One or more of these markers indicates the need for treatment of asymptomatic (smoldering) myeloma. The MDEs are (1) the presence of 60% or more clonal plasma cells in the bone marrow, (2) more than one focal lesion at least 5 millimeters in size, and (3) a Freelite ratio greater than or equal to 100.

Neutropenia: A reduced level of neutrophils, a type of white blood cell necessary to combat bacterial infection.

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 it is damaged (mutated) by environmental exposure to carcinogens, or if it is damaged or missing because of an inherited defect. An oncogene 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 bone (SPB)**."

Platelets: One of the three major types of blood cells, the others being 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, etc., 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.

- ***Stringent complete response (sCR)*** – sCR is CR (as defined below) plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.
- ***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. VGPR 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 SPB 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: Iso 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, basophils, eosinophils, lymphocytes, and monocytes.

INTERNATIONAL MYELOMA FOUNDATION

You are not alone. The IMF is here to help.

Myeloma is a cancer that is not known to most patients at the time of diagnosis. To be empowered to play an active role in your own medical care and to make good decisions about your care with your doctor, it is vital for you to learn as much as possible about myeloma and its treatments.

The IMF produces and maintains a library of publications to help arm you with one of the most important weapons in the fight against myeloma: INFORMATION. The following is a partial list of publications available in English, and selected titles are also available in other languages.

- *Patient Handbook*
- *Concise Review of the Disease and Treatment Options*
- *Understanding Clinical Trials*
- *Understanding Dexamethasone and Other Steroids*
- *Understanding DARZALEX® (daratumumab)*
- *Understanding EMPLICITI® (elotuzumab)*
- *Understanding Fatigue*
- *Understanding High-Dose Therapy with Stem Cell Rescue*
- *Understanding the Immune System in Myeloma*
- *Understanding KYPROLIS® (carfilzomib)*
- *Understanding MGUS and Smoldering Multiple Myeloma*
- *Understanding NINLARO® (ixazomib) capsules*
- *Understanding POMALYST® (pomalidomide)*
- *Understanding REVLIMID® (lenalidomide)*
- *Understanding Treatment of Myeloma Bone Disease*
- *Understanding Treatment of Myeloma-Induced Vertebral Compression Fractures*
- *Understanding VELCADE® (bortezomib)*
- *Understanding Your Test Results*

All IMF publications and periodicals are always free of charge. Visit **publications.myeloma.org** to read, download, or order printed copies. Subscribe to IMF periodicals at **subscribe.myeloma.org** or by contacting the IMF.

As always, the IMF urges you to discuss all medical issues with your doctor, and to contact the IMF's InfoLine specialists with your myeloma questions and concerns.

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