



# Understanding MGUS and Smoldering Multiple Myeloma



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**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.

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**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.

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**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,  
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Improving Lives **Finding the Cure®**

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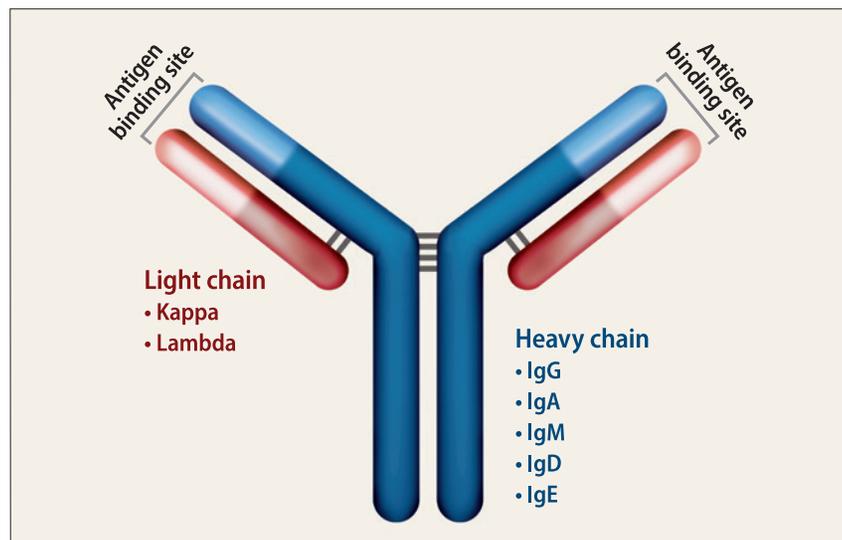
## What you will learn from this booklet

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](http://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 those discussions will be.

This booklet discusses monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). MGUS is not cancer or a disease. SMM is not active myeloma. However, both MGUS and SMM may be precursors to active disease, and it is therefore important to understand if, when, and how active myeloma might evolve and which monitoring or interventions are appropriate.

**Figure 1. Structure of an immunoglobulin (antibody)**



## Monoclonal gammopathy of undetermined significance

### What is MGUS?

MGUS (pronounced "EM-gus") is a term coined in 1978 by Professor Emeritus Robert A. Kyle of the Mayo Clinic in Rochester, Minnesota. The term MGUS describes a **benign** and **asymptomatic** condition that is characterized by an excess of **monoclonal protein (myeloma protein, M-protein, M-spike)**, a type of blood protein made by immune system cells called **plasma cells**. MGUS is not cancer or a disease.

### What are plasma cells?

Plasma cells develop from **white blood cells** called **B cells (B lymphocytes)** and are a key part of the **immune system**. Plasma cells make **antibodies** to proteins or molecules that the body recognizes as foreign (not part of the body). In medical language, the particular foreign protein that reacts with or binds to the antibody is called an **antigen** (a word coined from the two words "antibody" and "generator"). Examples of antibody-generating foreign materials (antigens) are bacteria, viruses, parasites, fungi, and toxins.

In the normal immune response, B cells mature into plasma **cells** in the **bone marrow**, where they produce antibodies (or in medical language, **immunoglobulins** or "Ig") to fight the invading antigen. Human beings make five types of heavy chain immunoglobulins: **IgG, IgA, IgD, IgE**, and **IgM**. Attached to the heavy chains are one of two types of immunoglobulin light chains: kappa ( $\kappa$ ) or lambda ( $\lambda$ ).

Under normal circumstances, these antibodies attach to specific invader antigens and, together with other immune system cells, disable and destroy the antigen and/or associated infectious agent or cell. Antibodies that arise from plasma cells in a normal immune response are called "polyclonal," because they derive from many different plasma cells and are capable of attacking a wide range of antigens.

### What is monoclonal protein?

MGUS represents the expansion and persistence of a single clone of abnormal plasma cells producing an antibody against a single antigen. The single type of antibody secreted by the clone of identical plasma cells is known as a "monoclonal antibody," "monoclonal protein," or "M-protein." M-protein is abnormal and is not usually a fully functional antibody. However, sometimes such antibodies do react with and bind to normal body antigens to become "auto-antibodies." Many **autoimmune diseases**, such as lupus, psoriasis, rheumatoid arthritis, and diabetes type 1, are caused by auto-antibodies.

## How is MGUS detected?

MGUS may be detected during a routine physical exam. If there is an increased level of protein in the blood or urine, tests should be ordered to determine the cause of this increase. Serum protein **electrophoresis** (SPEP) and/or urine protein electrophoresis (UPEP) and **immunofixation electrophoresis (IFE)** tests indicate the presence of M-protein. For more information about the tests used to identify and quantify M-protein, see the IMF publication *Understanding Your Test Results*.

## Is there more than one type of MGUS?

MGUS can arise from either lymphoid cells or plasma cells, and these two cell types of MGUS are biologically different. The lymphoid type produces only IgM-type M-protein and accounts for about 15% of all MGUS. This type of MGUS, should it progress, becomes **Waldenström's macroglobulinemia (WM)** or lymphoma. The plasma cell type of MGUS can progress to become myeloma or other related plasma cell disorders (including **amyloidosis** and **light chain deposition disease**). This booklet focuses on the plasma cell type of MGUS, which comprises 85% of all MGUS cases.

## What is the incidence of MGUS?

MGUS occurs in 3%–4% of the population over the age of 50; **incidence** increases with age. It is highly likely that many people have MGUS and never know it. Current data demonstrate that myeloma is consistently preceded by MGUS, although only one-fifth of cases of MGUS actually develop into a malignancy.

## What are the diagnostic criteria for MGUS?

The diagnostic criteria for MGUS are:

- Less than 3 grams/deciliter (g/dL) of M-protein in the serum (the liquid part of the blood).
- Fewer than 10% monoclonal plasma cells in the bone marrow.
- No **CRAB criteria**, which define active myeloma: elevated **C**alcium, **R**enal (kidney) damage, **A**nemia, or **B**one disease.

## What is the risk that MGUS will progress to active myeloma?

The risk of progression of MGUS to active malignancy was studied at great length by Dr. Kyle, who determined that it occurs at a rate of only 1% per year, and that only 20% of people with MGUS ever develop myeloma or another malignant condition.

The 2010 publication by the International Myeloma Working Group (IMWG), *Monoclonal Gammopathy of Undetermined Significance (MGUS) and Smoldering (Asymptomatic) Multiple Myeloma: IMWG Consensus Perspectives – Risk Factors for Progression and Guidelines for Monitoring and Management*, establishes criteria for MGUS that is at low, intermediate, and high risk of progression to myeloma.

The three criteria for low-risk MGUS are:

- M-protein less than 1.5 g/dL (or 15 g/L).
- IgG-type M-protein.
- Normal **free light chain** (FLC) ratio (number of kappa chains divided by the number of lambda chains; the result should be close to 1.65).

Low-intermediate-risk MGUS is defined as having one of the risk factors, that is, more than 1.5 g/dL of M-protein, a type of M-protein other than IgG, or an abnormal FLC ratio.

High-intermediate-risk MGUS is defined as having two of the risk criteria.

MGUS at high risk of progression has all three of the risk criteria.

For more information about free light chains and the test used to quantify them, see the IMF publication *Understanding Freelite® and Hevlyte® Tests*.

Researchers have developed some understanding of the biologic events that take place when MGUS develops into myeloma, but they do not yet know what triggers the progression in certain patients and not in others or how to prevent it. Researchers continue to seek answers to these questions. Although only one-fifth of patients with MGUS will develop myeloma or another malignancy, all cases of myeloma are preceded by MGUS.

## What is the diagnostic process for MGUS?

### All newly diagnosed MGUS

The IMWG consensus on management of a patient newly diagnosed with MGUS recommends that a hematologist/**oncologist** perform a complete history and physical exam to check for symptoms that may suggest myeloma or amyloidosis. Lab tests should include complete blood count (CBC), serum calcium and **creatinine** levels, and a test to identify if urine protein is present. If protein in the urine (proteinuria) is found, UPEP and IFE tests are indicated.

### Low-risk MGUS

Patients with low-risk MGUS do not require a baseline bone marrow biopsy or a skeletal X-ray survey (or other bone imaging study) if the clinical exam,

CBC, serum creatinine, and calcium values suggest MGUS. SPEP should be repeated 3–6 months after the MGUS is discovered. Time is an important factor in the diagnosis of MGUS: Your hematologist/oncologist must evaluate the status of your health and of your protein level in the months after diagnosis to see if there is any change.

A bone marrow biopsy is always required if the patient has unexplained **anemia**, evidence of kidney dysfunction, **hypercalcemia**, bone lesions, or a suspicion of AL amyloidosis. Patients should be followed with a repeat SPEP within 3–6 months and, if stable, can be followed at intervals of 1–2 years at the doctor’s discretion, barring any change in health or any suggestion of symptoms.

### Intermediate-risk or high-risk MGUS

Patients with intermediate- or high-risk MGUS should have a bone marrow aspirate and biopsy at baseline, and genetic studies should be done on the bone marrow sample.

If the patient has IgM-type M-protein, a **computerized axial tomography (CAT or CT) scan** of the abdomen should be performed to check for lymph node enlargement. **Lactate dehydrogenase (LDH)**, **beta-2 microglobulin (β2M)**, and **C-reactive protein (CRP)** levels should be determined if there is evidence of myeloma or WM. If these tests are within normal ranges, patients can be followed with SPEP and CBC in 6 months, and then annually for life or until any changes occur, at which point more frequent and/or additional testing may be required.

### Is there treatment for MGUS?

In rare cases, if an MGUS patient has an underlying, pre-existing infection, treating the infection may cause the MGUS to remit, but this is not typical. Historically, MGUS patients have not been treated outside the context of clinical trials, which have evaluated such non-medicinal interventions as green tea extract, omega-3 fatty acids, and curcumin (a component of the spice turmeric), and such medical interventions as zoledronic acid (a **bisphosphonate** used to prevent skeletal breakdown), anakinra (an interleukin-1 antagonist), clarithromycin + prasterone (an antibiotic + a dietary supplement used to correct **dehydroepiandrosterone [DHEA]** deficiency), and celecoxib (a **nonsteroidal anti-inflammatory drug**). None of these interventions prevented the progression of MGUS to myeloma.

As of the date of this writing, currently open and soon-to-open MGUS clinical trials include both non-interventional measures (such as genetic studies, tissue banking, and screening studies) and treatment trials. One of these planned treatments uses the experimental **dendritic cell** DKK1

vaccine, an immune-based therapy, to attempt to trigger an immune response against the abnormal plasma cells. Because a relationship between obesity and myeloma has been established, another of the planned interventional studies will treat patients with high levels of epicardial fat (fat deposits around the heart) with a drug that is given for weight loss, liraglutide. An interventional study for high-risk MGUS and low-risk SMM that is currently recruiting participants uses an approved myeloma therapy, the **monoclonal antibody** Darzalex® (daratumumab), to see if early intervention can prevent patients from developing active myeloma.

## Possible complications of MGUS

### Peripheral neuropathy

MGUS, though defined as asymptomatic, does sometimes cause medical problems. In approximately 10% of patients, the low-level M-protein can cause **peripheral neuropathy (PN)**. IgM-type MGUS is the most common type of monoclonal gammopathy associated with PN, but IgA and IgG monoclonal gammopathies can also cause PN. If you are experiencing any feelings of numbness or tingling in your extremities, be sure to report this to your doctor so that appropriate steps can be taken. Your doctor may want to discuss the use of supplements that help protect nerve tissue or may want to send you to a neurologist for a consultation and/or for treatment of the PN.

### Skeletal complications

Patients with MGUS and SMM are at a higher risk for **osteoporosis** and for fractures of the hip and vertebrae than the general population. These patients should be aware of the potential risk to bone health and should inform their primary care physicians and other specialists they see that they have been diagnosed with MGUS.

### Infections

MGUS patients are more than twice as likely as the general population to develop bacterial or viral infections because they have reduced production of polyclonal (normal) immunoglobulins, and therefore have diminished immune response. Patients who have an M-protein level of more than 2.5 g/dL have the highest risk of infection, although the risk is increased even among MGUS patients with less than 0.5 g/dL of M-protein. MGUS patients should take logical precautions to reduce the risk of infection, such as careful hand hygiene, annual flu vaccination, and avoidance of contact with friends and family members who have contagious illnesses.

## Smoldering multiple myeloma

### What is SMM?

Smoldering multiple myeloma (SMM), a term coined in 1980 by Professor Emeritus Philip Greipp of the Mayo Clinic, describes an asymptomatic intermediate stage between MGUS and active myeloma. It reflects a higher level of plasma cells in the bone marrow and a higher level of M-protein in the blood than does MGUS. Like MGUS, SMM causes no damage to the kidneys, red blood cells, or bones. In other words, it causes no CRAB criteria, defined as high calcium level in the blood due to bone loss (“C”), renal or kidney insufficiency (“R”), anemia (“A”), and bone damage (“B”).

### How is SMM detected?

SMM may be detected during a medical exam or may be diagnosed in an asymptomatic patient who has been followed for MGUS. The amount of M-protein in the blood and/or urine and of plasma cells in the bone marrow may increase to the point that they are in the range of SMM rather than MGUS.

### Is there more than one type of SMM?

SMM is not a single entity but rather a spectrum of different stages of disease, including at least three distinct possibilities:

1. MGUS with an increased but stable number of **tumor** cells.
2. Minimally progressive myeloma without damage to the bones, red blood cells, or kidneys (also called “end-organ” damage).
3. Moderately progressive myeloma, but with end-organ damage that is not yet detectable.

This new understanding of the biology and behavior of SMM enables doctors to avoid treating patients who do not need to be treated, but to intervene promptly in the case of patients who are at very high risk of progression to myeloma.

### What are the diagnostic criteria for SMM?

The IMWG definition of SMM is:

- M-protein greater than or equal to 3 g/dL, and/or
- Greater than or equal to 10% monoclonal plasma cells in the bone marrow, and
- Absence of CRAB criteria.

As with MGUS, the hematologist’s judgment and experience are crucial in making this diagnosis, and in differentiating SMM from MGUS and from active myeloma. A primary consultation or second opinion with a myeloma specialist is recommended.

### What is the risk that SMM will progress to cancer?

Dr. Kyle’s research established that the risk of progression of SMM to MM is 10% per year for the first five years, 3% per year for the next five years, and then 1% per year for the next decade. A substantial proportion of SMM patients remain free of progression for long periods of time (50% do not progress in the first five years after diagnosis, and approximately 30% are free of progression after 10 years).

Risk factors for progression of SMM to active myeloma include the amount of M-protein, the presence and number of **focal lesions** seen on **magnetic resonance imaging (MRI)**, the number of plasma cells in the bone marrow, and the ratio of involved (monoclonal) to uninvolved (normal, or polyclonal) light chains.

New diagnostic criteria have been established for active myeloma to include “ultra-high-risk SMM” that is at 80% or greater risk of progression to active myeloma within two years. This new, broader definition of myeloma is set forth in the “International Myeloma Working Group Updated Criteria for the Diagnosis of Multiple Myeloma,” published in 2014 in *The Lancet*. The IMWG determined that it was imperative to develop these new criteria, called **myeloma-defining events (MDE)**, to prevent patients with very early disease from developing end-organ damage. The criteria that determine if a patient with early disease should be treated or not can be established with three widely available tests (bone marrow biopsy, Freelite® assay, and MRI), and are:

- Bone marrow that is 60% or more monoclonal plasma cells.
- A ratio of involved (myeloma-related) to uninvolved (normal) free light chains of 100 or higher.
- More than one focal lesion in the bone marrow that is greater than 5 mm in size seen on MRI.

If an asymptomatic patient has any one of these three criteria, he or she should be treated for active myeloma.

### How is risk of progression defined in SMM?

When the International Myeloma Working Group updated the criteria for diagnosing myeloma, the segment of “ultra-high-risk” SMM patients were in effect removed from the pool of SMM patients and moved into the active myeloma category. This prompted the need to re-evaluate those patients left in the SMM category and to distinguish who among them was at high risk, intermediate risk, and low risk of progression to active disease. The Mayo Rochester group undertook this analysis, and published their results in *Blood Cancer Journal* in June, 2018.

Statistical analysis of multiple variables among 471 patients with smoldering myeloma seen at the Mayo Clinic revealed that the following three criteria were most associated with short time to progression from smoldering to active myeloma:

- a level of M-protein in the blood > 2 g/dL,
- a percentage of plasma cells in the bone marrow > 20%, and
- a free light chain ratio (the number of monoclonal light chains divided by the number of normal light chains) > 20.

The researchers at Mayo Clinic proceeded to construct a risk stratification system based on the data for patients who had none, one, or two–three of these “2/20/20” criteria. Patients who had none of the risk factors for progression had a median time to progression of 109.8 months and were assigned to the low-risk group. Those who had one risk factor had a median time to disease progression of 67.8 months and were assigned to the intermediate-risk group. Those with two or three risk factors (little difference in time to progression was evident with either two or three) had a median time to progression of 29.2 months and were assigned to the high-risk group.

Further refinements to these “2/20/20” criteria are the addition of two high-risk chromosomal abnormalities, 1q+ and 13q-. If either or both of these abnormalities are found by FISH testing of myeloma cells, the risk of disease progression is increased.

### What is the diagnostic process for SMM?

For an asymptomatic patient with M-protein of at least 3 g/dL, the diagnostic process includes SPEP, CBC, and measurement of calcium and creatinine values. Twenty-four-hour urine collection for electrophoresis and immunofixation should be performed at diagnosis and in 2 to 3 months after the initial recognition of SMM. A baseline bone marrow biopsy and skeletal survey are mandatory. MRI of the spine and pelvis are highly recommended. Skeletal X-rays are no longer the standard of care in the diagnostic process of SMM and suspected myeloma since they only pick up bone lesions after approximately 30% of the **cancellous bone** has been destroyed. Whole-body low-dose CT or MRI of the spine and pelvis are not only more sensitive studies, but they are better able to predict for more rapid progression to symptomatic myeloma. If lab test and imaging results are normal, the studies should be repeated every 4–6 months for one year, and, if still stable, evaluation can be lengthened to every 6–12 months.

Thus, SMM patients are carefully monitored at regular intervals. As with MGUS, these intervals are based on the patient’s status and the doctor’s

judgment. Routinely they are shorter intervals than those for MGUS patients, because the risk of progression is higher for SMM than for MGUS. Good communication is essential between patients with SMM and their physicians, as this can be a diagnosis that causes a great deal of anxiety. It is not an easy thing to hear that you have a very early stage of cancer, but that you are simply going to be monitored and not treated yet. It is imperative that you are seen by an experienced hematologist and that you report any and all changes in your health to your doctor and the other members of your healthcare team. Many patients across the disease spectrum, from MGUS to active myeloma, find it helpful to seek some psychological support as well.

### Is there treatment for SMM?

The IMF’s Black Swan Research Initiative® funded a project known as iStopMM® (Iceland Screens, Treats, Or Prevents Multiple Myeloma). This large population study and clinical trial was launched in November 2016. iStopMM is designed to screen approximately 140,000 residents of Iceland who are over 40 years of age for evidence of previously undetected MGUS, SMM, or active myeloma. This is the largest population-based screening study for myeloma and its earlier disease precursors that has ever been conducted. Not only will iStopMM allow researchers to observe patterns of occurrence, but they will be able to better understand disease biology and to identify the genes that drive disease progression. Moreover, monitoring patients with MGUS for many years will demonstrate which prognostic tests are most reliable as indicators of disease progression and which patients benefit most from early intervention. Patients with high-risk SMM will be invited to participate in a treatment trial.

Also with the support of the IMF’s Black Swan Research Initiative, two clinical trials – one in Spain with three years of data and one in the US – are being conducted to attempt to cure patients with high-risk SMM:

- Data from the Spanish trial, dubbed CESAR, were presented at the 2018 American Society of Hematology (ASH) meeting, and demonstrated that after a median follow-up of 17 months, 97% of the patients were alive and 94% were free of progression. The CESAR protocol includes Kyprolis® (carfilzomib) + Revlimid® (lenalidomide) + dexamethasone (KRd) induction, followed by high-dose therapy with autologous stem cell transplant (HDT-ASCT), consolidation with KRd, and maintenance with Rd.
- The US trial, called ASCENT, combines KRd with the monoclonal antibody Darzalex® (daratumumab) for 12 cycles followed by two years of maintenance therapy with Kyprolis and Darzalex. The trial is currently enrolling patients at nine sites across the US.

There are many other clinical trials for patients with both standard-risk and high-risk smoldering myeloma offering a wide range of treatments, but outside of clinical trials, there are no current standardized treatment options for SMM. “Ultra-high-risk” SMM is now considered early active myeloma and should be treated as newly diagnosed myeloma.

If you are interested in pursuing a clinical trial for SMM, you should discuss this option with your doctor and weigh the pros and cons carefully. You and your doctor must have a good understanding of the relative risk of progression in your case and of the potential risks and benefits of treatment, including the psychological aspects of treatment versus observation.

## Possible complications of SMM

Complications of SMM are the same as those of MGUS. Please see the “Possible complications of MGUS” section.

## 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](http://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](mailto: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, a protein 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  $\geq 2$  g/dL from the normal level for an individual. Over 13–14 g/dL is considered normal.

**Antibody:** A protein produced by white blood cells called plasma cells in response to an antigen that enters the body. The medical term for antibody is “immunoglobulin.”

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

**Asymptomatic:** Producing no signs or symptoms.

**Asymptomatic myeloma:** Myeloma that presents no signs or symptoms of disease; early-stage myeloma. Also called “**Smoldering multiple myeloma (SMM)**.”

**Autoimmune disease:** A condition that occurs when the immune system abnormally creates antibodies to a normal body part. Common autoimmune diseases include type 1 diabetes, celiac disease, inflammatory bowel disease, multiple sclerosis, psoriasis, and rheumatoid arthritis.

**B cells (B lymphocytes):** White blood cells that are part of the natural immune system. Some B cells develop into plasma cells in the bone marrow and are the source of antibodies.

**Benign:** Not cancerous; does not invade nearby tissue or spread to other parts of the body.

**Beta-2 microglobulin (also called  $\beta 2$ -microglobulin,  $\beta_2M$ , or  $\beta 2M$ ):**

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  $\beta 2M$ . At the time of relapse,  $\beta 2M$  can increase before there is any change in the myeloma protein level. Factors such as viral infection can sometimes produce elevated serum  $\beta 2M$  levels.

**Bisphosphonate:** A type of drug that protects against osteoclast activity (bone breakdown) and binds to the surface of bone where it is being resorbed or destroyed.

**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.

**C-reactive protein (CRP):** A protein made in the liver that increases in amount when there is inflammation throughout the body.

**Calcium:** A mineral found mainly in the hard part of bone matrix (hydroxyapatite). If produced or released in excess, it can build up in the bloodstream. See “**Hypercalcemia**.”

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

**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.

**Computerized axial tomography (CAT or CT) scan:** A test using computerized X-rays to create three-dimensional images of organs and structures inside the body. In myeloma, used to detect small areas of bone damage or soft tissue involvement.

**CRAB criteria:** An elevated level of **C**alcium in the blood, **R**enal damage, **A**nemia or low red blood cell count, and **B**one damage are criteria used to diagnose myeloma along with “**Myeloma-defining event (MDE)**.”

**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.

**Dehydroepiandrosterone (DHEA):** The hormone DHEA is produced in the adrenal gland and, in turn, helps produce other hormones, including testosterone and estrogen. Natural DHEA levels peak in early adulthood and then slowly fall with aging.

**Dendritic cell:** Also called “professional antigen-presenting cells,” dendritic cells bring antigens from pathogens that enter the body to other immune system cells for recognition and destruction.

**Electrophoresis:** A laboratory test in which a patient’s serum (blood) or urine proteins are subjected to separation according to their size and electrical charge. For myeloma patients, electrophoresis of the blood or urine allows both the calculation of the amount of myeloma protein via serum or urine electrophoresis (SPEP or UPEP), as well as the identification of the type of M-spike for each patient (immunoelectrophoresis, IFE). Electrophoresis is used as a tool both for diagnosis and for monitoring.

**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.

**Free light chain:** An immunoglobulin (antibody) light chain is the smaller of two units that make up an antibody. There are two types of light chain: kappa and lambda. A light chain may be bound to a heavy chain or it may be unbound, or free. Free light chains circulate in the blood and are small enough to pass into the kidneys, where they may be filtered out into the urine or may stick together and block up the kidney’s tubules.

**Hypercalcemia:** A higher than normal level of calcium in the blood. In myeloma patients, it usually results from bone breakdown with release of calcium from the bone into the bloodstream. This condition can cause a number of symptoms, including loss of appetite, nausea, thirst, fatigue, muscle weakness, restlessness, and confusion. See “**Calcium**.”

**IgG, IgA:** The two most common types of myeloma. The G and the A refer to the type of heavy chain protein produced by the myeloma cells. The myeloma protein, which is an immunoglobulin, consists of two heavy chains, (for example, of a G type) combined with two light chains, which are either kappa or lambda. The terms “heavy” and “light” refer to the size or molecular weight of the protein, with the heavy chains being larger than the light chains.

**IgD, IgE:** Two types of myeloma that occur less frequently. See “**IgG, IgA**.”

**IgM:** Usually associated with Waldenström’s macroglobulinemia. In rare cases, IgM can be a type of myeloma.

**Immune system:** The body’s defense system from pathogens and foreign substances destroys infected and malignant cells, and removes cellular debris. The immune system includes white blood cells and organs and tissues of the lymphatic system.

**Immunofixation electrophoresis (IFE):** An immunologic test of the serum or urine used to identify proteins. For myeloma patients, it enables the doctor to identify the M-protein type (IgG, IgA, kappa, or lambda). The most sensitive routine immunostaining technique, it identifies the exact heavy- and light-chain type of M-protein.

**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.”

**Incidence:** The number of new cases of a disease diagnosed each year.

**Lactate dehydrogenase (LDH):** An energy-producing enzyme that is present in almost all of the tissues in the body. LDH levels in the bloodstream rise in response to cell damage. LDH may be used to monitor myeloma activity.

**Light chain deposition disease:** A type of monoclonal gammopathy that is characterized by deposition of immunoglobulin light chains in various organs, most frequently in the kidneys.

**Magnetic resonance imaging (MRI):** A diagnostic imaging test that uses magnetic fields and radio waves, not ionizing radiation, to produce detailed two- or three-dimensional images of organs and structures inside the body. MRI gives very fine resolution of soft tissues, especially encroachments on the spinal cord, but is less accurate for bone lesions.

**Monoclonal:** A clone or duplicate of a single cell. Myeloma cells are derived from a “monoclonal,” a single malignant plasma cell in the bone marrow. 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) on the protein electrophoresis test.

**Monoclonal antibody:** An antibody manufactured in a lab rather than produced in the human body. Monoclonal antibodies are specifically designed to find and bind to cancer cells and/or immune system cells for diagnostic or treatment purposes. Monoclonal antibodies can be used alone, or they can be used to deliver drugs, toxins, or radioactive material directly to tumor cells.

**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.

**Nonsteroidal anti-inflammatory drug (NSAID):** A drug used to reduce fever, swelling, and pain.

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

**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.

**Peripheral neuropathy (PN):** A feeling of numbness, tingling, burning, and/or pain in the hands, feet, lower legs, and/or arms.

**Plasma cells:** Special white blood cells that produce antibodies (immunoglobulins). Myeloma is a cancer of the plasma cells. Malignant plasma cells are called myeloma cells. In myeloma, malignant plasma cells produce abnormal antibodies that lack the ability to fight infection. These abnormal antibodies are the monoclonal protein, or M-protein, that functions as a tumor marker for myeloma. The presence of malignant plasma cells in the bone marrow can lead to organ and tissue damage (anemia, kidney damage, bone disease, and nerve damage).

**Tumor:** An abnormal mass of tissue that results from excessive cell division. In myeloma, a tumor is referred to as a plasmacytoma.

**Waldenström’s macroglobulinemia (WM):** A rare type of indolent lymphoma that affects plasma cells. Excessive amounts of IgM protein are produced. Not a type of myeloma.

**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 bone marrow and then travel to other parts of the body. Specific white blood cells include neutrophils, basophils, eosinophils, lymphocytes, and monocytes.



## 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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