MULTIPLE MYELOMA
Research Foundation

Monoclonal Gammopathy of Undetermined Significance and Smoldering Multiple Myeloma

MULTIPLE MYELOMA PRECURSOR CONDITIONS

themmrf.org

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ABOUT THE **MMRF**

The Multiple Myeloma Research Foundation® (MMRF®) is the largest nonprofit in the world solely focused on accelerating a cure for each and every multiple myeloma patient. We drive the development and delivery of next-generation therapies, leverage data to identify optimal and more personalized treatment approaches, and empower myeloma patients and the broader community with information and resources to extend their lives.

Central to our mission is our commitment to advancing access for all so that every myeloma patient can benefit from the scientific and clinical advances we pursue. Since our inception, the MMRF has raised over $600 million for research, opened over 100 clinical trials, and helped bring more than 15 FDA-approved therapies to market, which have tripled the life expectancy of myeloma patients.

To learn more about the MMRF, visit **themmrf.org**.

To speak to a patient navigator at the Patient Navigation Center, call **1-888-841-6673** or email **patientnavigator@themmrf.org**.

Accredited by:

INTRODUCTION

Patients with **multiple myeloma** typically go through an earlier phase of disease in which there are no symptoms or organ damage. This phase, which can last months or years before progressing to **symptomatic multiple myeloma**, includes conditions called **monoclonal gammopathy of undetermined significance (MGUS)** and **smoldering multiple myeloma (SMM**, also called asymptomatic myeloma). These conditions are known as **myeloma precursor conditions**. Because neither one is associated with symptoms, doctors often find them incidentally when they perform routine blood tests.

This booklet has been developed to help you better understand the myeloma precursor conditions. Words that may be unfamiliar are **bolded** and defined in the Glossary (page 9).

The information in this booklet is not intended to replace the services or advice of trained health care professionals. Please consult with your care provider regarding specific questions relating to your health, especially questions about myeloma diagnosis or treatment.

For more information about multiple myeloma and its treatment, refer to the other booklets in our Patient Toolkit, as well as the MMRF website, **themmrf.org**.

MULTIPLE MYELOMA PRECURSOR CONDITIONS

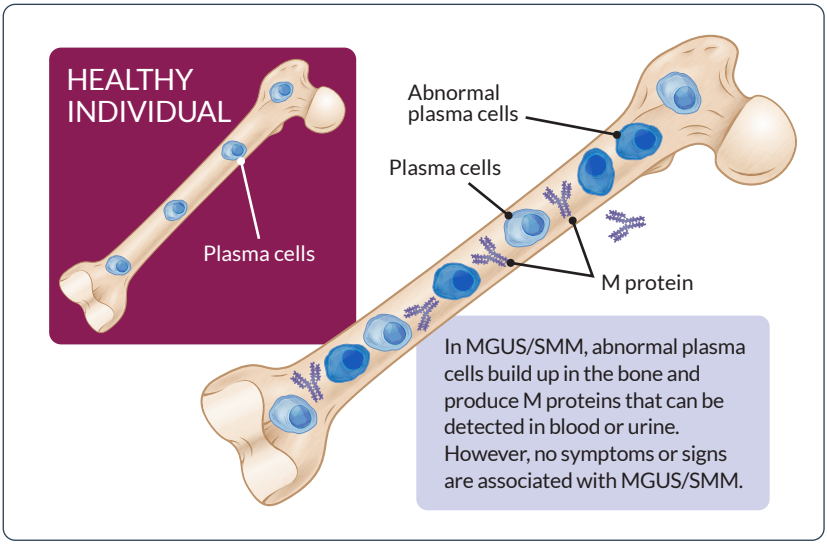
In both MGUS and SMM—as is the case in active multiple myeloma—abnormal **plasma cells** build up in the **bone marrow**. These cells produce a substance called **M protein** that can be detected in the blood or urine.

Unlike symptomatic multiple myeloma, precursor conditions produce no tumors or bone damage. They also don't cause the symptoms or signs associated with symptomatic myeloma (such as **anemia**, fractures, and kidney failure).

For an overview of precursor conditions, see the ***Multiple Myeloma Precursor Conditions*** **High-Impact Topic** video.

bit.ly/PrecursorConditions_HIT

Multiple myeloma precursor conditions.



Patients who have a myeloma precursor condition can remain undiagnosed for years. Most patients who progress to symptomatic myeloma were never diagnosed with a precursor condition.

For more information about how a diagnosis of multiple myeloma is made, refer to the companion booklet ***Multiple Myeloma Disease Overview*** and the MMRF website, **themmrf.org**.

DIAGNOSIS

If you're found to have M protein in your blood or urine, your doctor will conduct tests to see if you have MGUS, SMM, or symptomatic multiple myeloma.

The level of M protein in the blood or urine and the percentage of plasma cells in the bone marrow differ with each condition. In MGUS, there are lower amounts of both than there are in SMM.

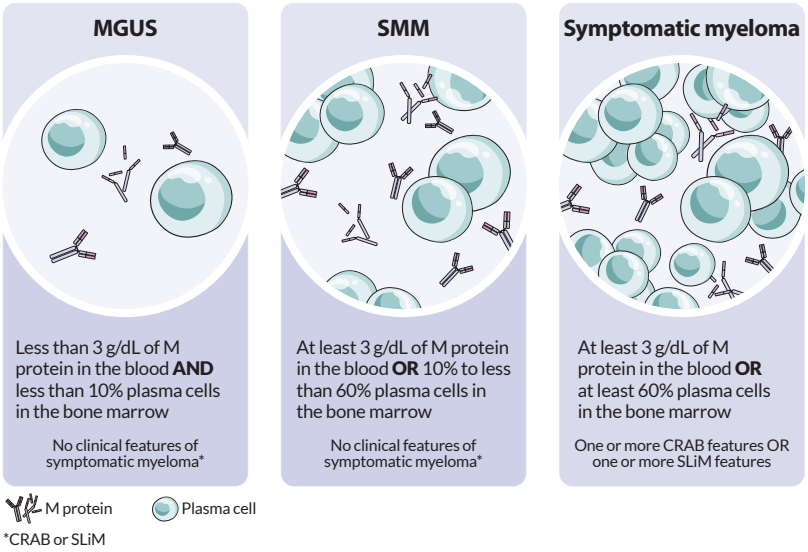
MGUS and SMM **do not** have the clinical features of symptomatic multiple myeloma, which are described with the acronym **CRAB**:

- High **C**alcium in the blood
- Kidney (**R**enal) problems
- **A**nemia (a low level of **red blood cells**)
- **B**one damage, such as holes or fractures

Another acronym, **SLiM**, describes test results that are used to measure progression to symptomatic myeloma:

- **S**ixty percent or more plasma cells in the bone marrow
- Elevated free **Light chain** ratio (a ratio of at least 100 to 1)
- More than one bone lesion (5 or more millimeters long) as determined by **Magnetic resonance imaging (MRI), positron emission tomography (PET)**, or **computed tomography (CT)**

Criteria used to identify MGUS, SMM, or symptomatic multiple myeloma.



PROGRESSION TO SYMPTOMATIC MULTIPLE MYELOMA

Multiple myeloma is the final stage of a disease process that usually begins with MGUS (which is considered **benign**), progresses to SMM, then advances to symptomatic myeloma.

The multiple myeloma disease spectrum.

MGUS

How common MGUS is varies for different people:

- It occurs in less than 1% of the general population
- It occurs in about 5% of healthy people over 50
- It's two to three times more common in the Black community for reasons that are unknown
- People who have a first-degree relative (that is, a parent, sibling, or child) with a blood cancer (not just myeloma) are at a higher risk of having MGUS
- The risk of developing MGUS increases with age

Very few people with MGUS progress to symptomatic myeloma—only about 1 patient out of 100 per year progress.

MGUS can progress to other **malignant** plasma cell diseases (**lymphoma** or **amyloidosis**), and the risk for progression increases over time. MGUS can also be associated with other diseases, including **osteoporosis**.

SMM

SMM is a stage between MGUS and symptomatic multiple myeloma. Not all patients with SMM develop symptomatic myeloma, though it's associated with a higher risk of progressing to symptomatic myeloma than MGUS is. The risk of SMM progressing to symptomatic or active myeloma gets lower over time.

The risk of SMM progressing to symptomatic multiple myeloma.

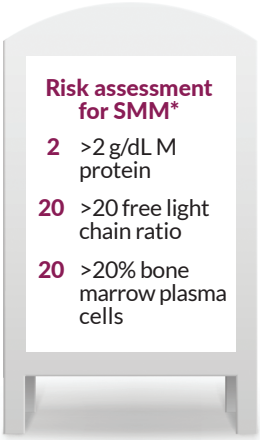
1 to 5 years after diagnosis	10 out of 100 people with SMM are likely to progress to multiple myeloma every year
5 to 10 years after diagnosis	3 out of 100 people with SMM are likely to progress to multiple myeloma every year
10 years or more after diagnosis	1 out of 100 people with SMM are likely to progress to multiple myeloma every year

HIGH-RISK SMM

Not everyone with SMM develops symptomatic myeloma. Some people have a higher chance of progressing than others. Doctors use blood and bone marrow tests to assess the risk of progressing.

When two or more risk factors are found, the likelihood of progressing is higher. This approach is known as the 2/20/20 risk **stratification model**, which is named after the values of the test results that make up the risk factors for this model.

The 2/20/20 risk-stratification model for SMM patients.



*Patients with two or more risk factors are considered high risk. This model does not include other high-risk factors (for example, genetic mutations).

In addition, several genetic **mutations** can increase the risk of progressing to symptomatic myeloma.

These mutations involve changes to the number or structure of **chromosomes** (**translocation**) and include the following:

- Missing pieces (**deletions**)
- Extra copies (**hyperdiploidy**)
- Duplications of pieces (**amplification/gain**)

Certain changes in the chromosomes are associated with higher risk of developing symptomatic myeloma. These are:

- A translocation between chromosomes 4 and 14, written as t(4;14)
- A translocation between chromosomes 14 and 16, written as t(14;16)
- Deletion of part of chromosome 17, written as del17p
- Deletion of part of chromosome 1, written as del1p
- Extra gene copies (or gain) in part of chromosome 1, written as +1q

Patients with high-risk SMM are more than seven times more likely to progress to symptomatic myeloma at 2 years than patients with low-risk SMM.

For more information about how genetic testing is used to manage myeloma, refer to the companion booklet ***Understanding Your Test Results*** and the MMRF website, **themmrf.org**.

MANAGING PRECURSOR CONDITIONS

If you're diagnosed with MGUS or SMM, your doctor will conduct regular physical exams and blood and imaging tests to see if your disease is progressing. How often you get monitored may vary depending on your risk of disease progression and where you receive care.

Monitoring myeloma precursor conditions.

If you have MGUS:	If you have SMM:	If you have high-risk SMM:
• 6 months after diagnosis • Every 1 to 3 years	• First 5 years: every 3 to 4 months • After 5 years: twice a year	• First year: every 1 to 3 months with annual imaging • After first year: every 3 to 4 months with annual imaging

MGUS AND SMM

Patients with MGUS or SMM are not treated, because neither condition is associated with organ damage or any of the symptoms associated with symptomatic myeloma. Treating patients who have a precursor condition that may not advance to symptomatic multiple myeloma could cause side effects that outweigh any benefit of treatment.

Studies are currently ongoing that are working to identify patients earlier in the myeloma disease spectrum and to understand the clinical and genetic features of precursor conditions that are associated with progression to symptomatic myeloma.

TREATING HIGH-RISK SMM

Patients with high-risk SMM might benefit from treatment to reduce the risk of progression.

Darzalex (daratumumab), a **monoclonal antibody** that is administered **subcutaneously** (that is, under the skin), is used to treat newly diagnosed myeloma and myeloma that has **relapsed** (recurred after initially responding to therapy) or is **refractory** (progressed during therapy), and it has been shown to delay progression from SMM to symptomatic myeloma.

Some doctors recommend giving Darzalex to certain patients with high-risk SMM to help delay disease progression.

If you have high-risk SMM, discuss the risks and benefits of starting Darzalex with your doctor.

Clinical trials assessing the potential benefits and risks of treatments designed to prevent progression of high-risk SMM to symptomatic myeloma are available. You should discuss with your doctor whether a clinical trial is an option for you.

Myeloma clinical trials can be found at **clinicaltrials.gov**. Or you can use the MMRF's Clinical Trial Finder (**themmrf.org/diagnosis-and-treatment/clinical-trials-and-emerging-therapies/clinical-trial-finder/**) to search for a clinical trial in your area.

The MMRF would like to thank Joshua Richter, MD, Associate Professor of Medicine, Hematology and Oncology, in the Myeloma Division at the Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai and Director of Myeloma at the Blavatnik Family Chelsea Medical Center at Mount Sinai and our patient advocate, Bob Lanza of New York, New York, for their contributions to this booklet.

GLOSSARY

amplification/gain *Chromosomal abnormality* in which a section of a chromosome is added to another chromosome

amyloidosis Disorder in which abnormal protein is deposited in organs and tissues

anemia Decrease in the number of red blood cells in the blood

antibody Protein produced by plasma cells that helps protect the body from infection and disease (also called *immunoglobulin*)

benign Not causing symptoms or damage to the body

bone marrow Soft, spongy tissue found in the center of many bones and the site of blood cell production

calcium Mineral that is important in bone formation; elevated serum levels occur when there is bone destruction

chromosomal abnormality Defect in the structure of a *chromosome*

chromosomes Thread-like structures in a living cell that contain *DNA* (genetic information)

clinical trials Studies of the safety and effectiveness of a drug using consenting human participants

computed tomography (CT) Imaging technique that uses a computer to generate three-dimensional x-ray pictures

CRAB Acronym for the following group of clinical indicators of organ damage: increased calcium level, renal (kidney) failure, anemia, bone lesions; the presence of one or more of these indicators can help establish a diagnosis of multiple myeloma

deletions *Chromosomal abnormalities* in which a segment of a chromosome is missing

DNA Genetic material of the cell, located in the chromosomes

hyperdiploidy Presence of extra copies of one or more chromosomes

immunoglobulin Protein that helps the body fight infection (also called *antibody*)

light chain The shorter of two protein chains that make up an antibody, characterized as either kappa or lambda type; light chains produced by myeloma cells are also referred to as Bence Jones proteins when they occur in the urine

lymphoma Blood cancer that develops in the lymph nodes

M protein Abnormal antibody produced by myeloma cells that is found in large quantities in the blood and urine of people with myeloma

magnetic resonance imaging (MRI) Imaging technique that uses magnetic energy to produce detailed images of bone and soft tissue

malignant Cancerous; able to grow and spread to other parts of the body

monoclonal antibody Antibody produced in a lab that is used to diagnose and treat some diseases

monoclonal gammopathy of undetermined significance (MGUS) Condition marked by M protein without symptoms that may progress to myeloma

multiple myeloma Blood cancer that develops in the bone marrow as a result of plasma cells transforming into myeloma cells

mutations Defects or errors in a gene

myeloma precursor conditions Either of two preceding phases of symptomatic multiple myeloma characterized by changes in the cells of the bone marrow but no symptoms or organ damage; see also *monoclonal gammopathy of undetermined significance (MGUS), smoldering (asymptomatic) multiple myeloma (SMM)*

osteoporosis Bone loss typically associated with old age; can occur in myeloma

plasma cells Antibody-secreting immune cells that develop from B cells; in myeloma, it is these cells that have become cancerous or abnormal

positron emission tomography (PET) Imaging technique that uses radioactive glucose to highlight cancer cells

red blood cells Blood cells that carry oxygen

refractory Not responding to therapy

relapsed Disease that progresses after initially responding to therapy

SLiM Acronym for the following group of clinical indicators of multiple myeloma: sixty percent or greater plasma cells in the bone marrow; an elevated free *light chain* ratio; MRI with more than one bone lesion; the presence of any of these indicators establishes a diagnosis of multiple myeloma

smoldering multiple myeloma (SMM) Condition that is characterized by increased M protein and slightly increased numbers of plasma cells in the bone marrow and an absence of symptoms; patients with SMM are monitored and only treated if their disease progresses; about 5% of myeloma patients have SMM

stratification model Analytical tool used to sort data, people, and objects into groups

subcutaneously Given under the skin

symptomatic multiple myeloma Multiple myeloma in which the percentage of plasma cells in the bone marrow is greater than 10% and in which the patient shows one or more CRAB symptoms (see definition at *CRAB*)

translocation *Chromosomal abnormality* in which segments of two chromosomes switch positions

NOTES

MMRF PATIENT SUPPORT AND RESOURCES

The MMRF supports the myeloma community by providing a broad range of resources for myeloma patients and their family members and caregivers. The MMRF is available to help guide you through your multiple myeloma journey every step of the way.

YOUR QUESTIONS ANSWERED

The Patient Navigation Center is available to answer your questions about disease management and treatments, help you find clinical trials, and connect you with financial and other resources.

Telephone: 1-888-841-6673
Monday—Friday, 9:00 AM to 7:00 PM ET
Email: **patientnavigator@themmrf.org**

themmrf.org/support/patient-navigation-center

CONNECT WITH AN MMRF MYELOMA MENTOR

Connect one-on-one with a trained patient and/or caregiver mentor that can share their patient journeys and experiences.

themmrf.org/support/myeloma-mentors

FIND A CLINICAL TRIAL

The MMRF Clinical Trial Finder lets you search for a clinical trial in your area.

themmrf.org/diagnosis-and-treatment/clinical-trials-and-emerging-therapies/clinical-trial-finder/

VIEW PAST PROGRAMS ON DEMAND

Access our archive of recorded Patient Summits and webcasts. Hear expert perspectives on key clinical research and the rapidly evolving myeloma treatment landscape. All available online, and free.

themmrf.org/educational-resources

SUPPORT THE MMRF

Help support the MMRF's efforts to accelerate research and find a cure! Participate in an event or donate today.

Telephone: 1-203-229-0464
Donate now/Take action: **themmrf.org/get-involved**

ATTEND A MULTIPLE MYELOMA PATIENT SUMMIT

Available in-person and virtually, MMRF Patient Summits discuss new treatments, promising clinical trials, and all the information you need to make well-informed decisions about your treatment and care.

themmrf.org/educational-resources

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I AM A:

- ☐ Myeloma Patient
- ☐ Myeloma Patient Caregiver
- ☐ Myeloma Patient Family Member (non-caregiver)
- ☐ Family/Friend of Deceased Myeloma Patient
- ☐ Healthcare Professional or Researcher
- ☐ Biopharma, Medical Device, or Healthcare Technology Industry Professional
- ☐ None of the Above

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Hours: **Mon–Fri, 9 AM–7 PM ET**

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