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 health equity so that all myeloma patients can benefit from the scientific and clinical advances we pursue. Since our inception, the MMRF has raised over $600 million for research, opened nearly 100 clinical trials, and helped bring 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 for months or years before progressing to **active multiple myeloma**, includes conditions called **monoclonal gammopathy of undetermined significance (MGUS)** and **smoldering multiple myeloma (SMM**, also called asymptomatic myeloma). Together, these conditions are known as **myeloma precursor conditions**. Neither one is associated with symptoms. As a result, people often don't know that they have a precursor condition.

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).

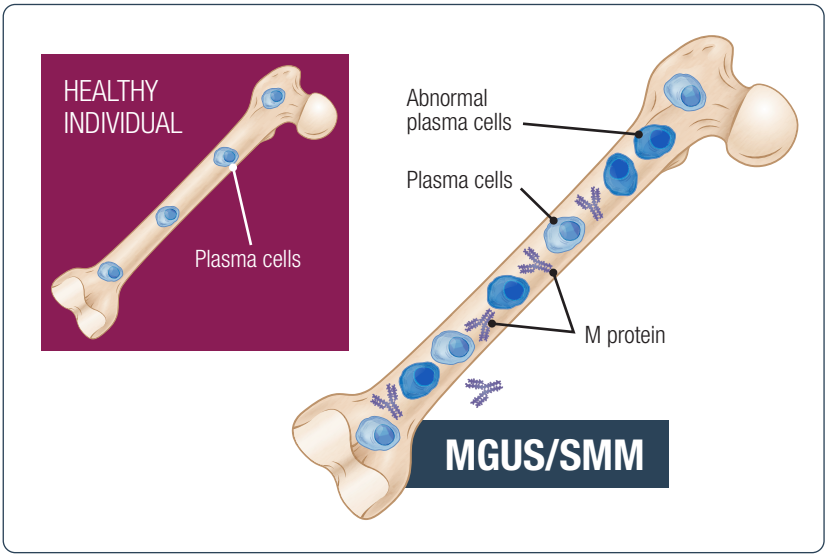
The information in this booklet is not intended to replace the services or advice of trained health care professionals. Please consult with your health care provider regarding specific questions relating to your health, especially questions about myeloma diagnosis or treatment.

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, abnormal **plasma cells** build up in the **bone marrow**. These abnormal plasma cells, which can develop into myeloma cells, produce a substance called **monoclonal protein** (or **M protein**) that can be detected in the blood or urine. Unlike active multiple myeloma, precursor conditions produce no tumors or bone damage. They also do not cause the symptoms or signs typically associated with active multiple myeloma (such as **anemia**, fractures, and kidney failure). The usual criteria used to diagnose multiple myeloma are not present.

Multiple myeloma precursor conditions.



Some patients learn that they have MGUS or SMM when M protein is detected in their blood or urine. Because most people are not screened for precursor conditions (doctors do not routinely order tests to measure M protein) and there are no symptoms associated with either condition, diagnosis of MGUS or SMM usually only happens incidentally. Most commonly, a doctor investigating another health issue (for example, problems with the kidneys, calcium levels, bones, muscles, or immune system) will happen to discover M protein in the blood or urine. Patients who have a myeloma precursor condition can remain undiagnosed for several years. Most patients who progress to active 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**.

PROGRESSION TO ACTIVE MULTIPLE MYELOMA

Multiple myeloma is a type of cancer that affects plasma cells. It is the final stage of a disease process that usually begins with MGUS and progresses to SMM before advancing to active myeloma.

The multiple myeloma disease spectrum.

MGUS occurs in less than 1% of the general population and in about 5% of healthy individuals over 50. The prevalence is two to three times higher in the Black community for reasons that are unknown. People with 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.

MGUS almost always occurs before a person develops active myeloma. It is associated with a risk of progression to active myeloma of approximately 1% per year. MGUS progresses to active multiple myeloma or another **malignant** plasma cell disease (**lymphoma** or **amyloidosis**) in about 10% of individuals with the condition at 10 years, in 18% at 20 years, in 28% at 30 years, in 36% at 35 years, and in 36% at 40 years. MGUS can also be associated with other diseases, including **osteoporosis**.

SMM is a stage between MGUS and active multiple myeloma. It is associated with a higher risk of progressing to active myeloma than MGUS is: approximately 10% per year for the first 5 years. However, progression varies among patients.

DIAGNOSIS

If you are found to have M protein in your blood or urine, your doctor will conduct tests to find out whether you have MGUS, SMM, or active multiple myeloma. Blood, urine, bone marrow, and imaging tests can help identify which condition you have.

The level of M protein in the blood or urine and the percentage of plasma cells in the bone marrow differ with each condition, with MGUS having lower amounts of both than SMM. Neither condition is associated with the clinical features characteristic of active multiple myeloma, such as elevated levels of **calcium**, renal insufficiency (kidney problems), anemia (low levels of **red blood cells**), and bone fractures or lesions (these are often referred to by doctors as the **CRAB** criteria). Additionally, neither condition meets any of the **SLiM** criteria used by doctors to diagnose active myeloma: sixty percent or more plasma cells in the bone marrow, an elevated free **light chain** ratio (>100:1), and more than one bone lesion (5 mm or larger) as determined by **magnetic resonance imaging (MRI), positron emission tomography (PET)**, or **computed tomography (CT)** scan.

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

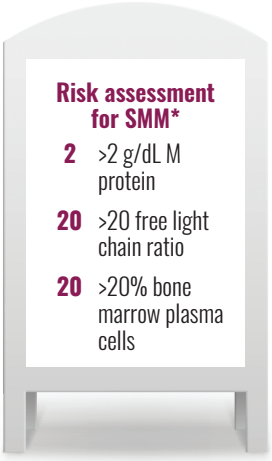
	MGUS	SMM	Active multiple myeloma
M protein	<3 g/dL in blood	≥3 g/dL in blood or ≥500 mg/24 hours in urine	≥3 g/dL in blood or ≥500 mg/24 hours in urine
Plasma cells in bone marrow	<10%	10%–60%	≥60%
Clinical features	No myeloma-defining events*	No myeloma-defining events*	One or more myeloma-defining events,* including either: • One or more CRAB features or • One or more SLiM features

*CRAB, calcium elevation, renal insufficiency, anemia, bone disease; SLiM, sixty percent or more plasma cells in the bone marrow, elevated free light chain ratio, and more than one bone lesion as determined by MRI, PET, or CT

HIGH-RISK SMM

Some patients with SMM are more likely to develop active myeloma than others. A new risk-**stratification model** has been developed to determine which patients with SMM are at high risk for progression to active myeloma. High risk is identified based on the presence of two or more specific risk factors as determined through blood and bone marrow testing. This method of assessing risk uses what is referred to as a 2/20/20 risk-stratification model, named for the key test values that define high risk.

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 any biologic or immune factors that may account for differences between patients.

In addition, there are several **chromosomal abnormalities** that may increase the risk of progressing to active myeloma. Patients with high-risk SMM have a higher risk of progressing to active myeloma at 2 years (44%) than do patients with low-risk SMM (6%).

HOW AND WHEN TO TREAT MYELOMA PRECURSOR CONDITIONS

If you're diagnosed with MGUS or SMM, the standard of care is watchful waiting. This means that your doctor will conduct regular physical exams and blood and imaging tests to determine if you have progressed to active myeloma. Treatment will only be started when progression occurs. How often you get monitored may vary depending on your risk of disease progression and where you receive care.

The reason patients with MGUS or SMM are not treated is that neither condition is associated with organ damage or any of the symptoms commonly associated with active myeloma. Furthermore, no more than half of the patients who are diagnosed with SMM progress to active myeloma within the first 5 years, and the number is even smaller for patients with MGUS. Giving myeloma treatments to patients who have a precursor condition that may not advance to active multiple myeloma could lead to side effects that outweigh any potential benefit of earlier treatment.

High-risk SMM might require treatment instead of watchful waiting. Early treatment can help delay the onset of active myeloma and increase life expectancy. If treatment is recommended, it should be done as part of a clinical trial.

If you have intermediate- to high-risk SMM, several clinical trials are available that are assessing the potential benefits of treatments designed to prevent progression to active myeloma, as well as the risks associated with them.

The latest studies are investigating whether therapy with some newer anti-myeloma drugs will be effective in preventing or delaying progression to active myeloma. You should discuss with your doctor whether a clinical trial is an option for you.

If you have normal-risk MGUS or SMM, several screening studies and observational studies are available that are being conducted 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 active myeloma.

Types of clinical studies.

	Non-interventional study	Interventional study
What is it?	Study designed to collect data on treatment and outcomes but that does not intervene in routine clinical care.	Study designed to evaluate the effectiveness, side effects, and outcomes of new potential treatments or preventative measures. Also referred to as a **clinical trial**.
Examples	**Observational study, registry, claims-based analysis**	**Randomized controlled trial, screening study**

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

MMRF PATIENT SUPPORT AND RESOURCES

The MMRF is dedicated to supporting 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

Speak to an MMRF patient navigator at the Patient Navigation Center for answers to your questions about disease management, treatments, clinical trials, and assistance with finding financial and other available resources.

Telephone: 1-888-841-6673
Monday–Friday, 9:00 AM to 7:00 PM ET
Email: **patientnavigator@themmrf.org**
Online: **themmrf.org/support/patient-navigation-center**

Connect with an MMRF Myeloma Mentor:
themmrf.org/support/myeloma-mentors

This is a phone-based program offering the opportunity for patients and/or caregivers to connect one-on-one with a trained patient and/or caregiver mentor to share their patient journeys and experiences.

FIND AND PARTICIPATE IN A CLINICAL TRIAL

Search for a clinical trial in your area or let an MMRF patient navigator help guide you through the process.

Clinical Trial Finder: **themmrf.org/resources/clinical-trial-finder**

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: Visit **themmrf.org/get-involved**

GLOSSARY

active 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*)

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*; see also *monoclonal antibody*)

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 or variation in a *chromosome*; in some people with multiple myeloma, a piece of one or more chromosomes may be missing or swapped with a piece from a different chromosome; deletion 17p and t(4;14) are examples of chromosomal abnormalities

chromosome Thread-like structure in a living cell that contains *DNA* (genetic information)

claims-based analysis Analysis of electronic health records collected during routine clinical care for information about patient–provider interactions, diagnoses, procedures, and treatments

clinical trial Interventional study of the safety and effectiveness of a therapeutic agent using consenting human participants

computed tomography (CT) Imaging technique that uses a computer to generate three-dimensional x-ray pictures (also referred to as *computerized axial tomography [CAT]*)

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

DNA Genetic material of the cell located in the chromosomes

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

interventional study Clinical study in which participants receive specific interventions that may be medical products (such as drugs or devices) or procedures

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

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

malignant Cancerous, continuing to divide

monoclonal (M) protein Abnormal antibody found in large quantities in the blood and urine of individuals with myeloma

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

monoclonal gammopathy of undetermined significance (MGUS) Condition that can occur before a patient develops or shows any symptoms of myeloma; indicated by the presence of M protein in the serum or urine, MGUS may eventually progress to active multiple myeloma

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

myeloma precursor condition A preceding phase of active 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)*

non-interventional study Clinical study designed to collect data on treatment and outcomes but that does not intervene in routine clinical care.

observational study Non-interventional study in which participants are observed over a period of time to assess health outcomes

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

plasma cell Antibody-secreting immune cell that develops from a B cell; in myeloma, it is this cell that has become cancerous or abnormal

positron emission tomography (PET) Imaging technique in which radioactive glucose (sugar) is used to highlight cancer cells

randomized controlled trial Interventional study in which a group of participants receive a treatment or procedure (also called an *intervention*) so that the effectiveness and side effects of that intervention can be compared with those seen in participants who received either no intervention (placebo) or a standard treatment

red blood cell Blood cell that carries oxygen

registry Non-interventional study that observes and records the type of clinical care provided to patients

screening study Interventional trial that evaluates new tests for detecting cancer and other health conditions in people before symptoms are present

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

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, Andrew Gordon of Harrisburg, Pennsylvania, for their contributions to this booklet.

NOTES

MMRF RESOURCES
IN PERSON OR ONLINE

Attend a Multiple Myeloma Patient Summit

Learn about standard and emerging therapies, including stem cell transplants, promising clinical trials, and more for optimal disease management. Attend a complimentary symposium for all the information you need to make well-informed decisions about your treatment and care.

To register or to view the complete calendar, visit:
themmrf.org/resources/education-programs

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, at:
themmrf.org/resources/education-programs

Find a Clinical Trial Near You

Clinical trials are critically important to developing new myeloma treatments and better understanding the biology of the disease. The more people who enroll, the faster we can find answers. Patients who enroll in clinical trials have the opportunity to be among the first to receive the newest drugs or drug combinations in development and receive close monitoring.

To find a clinical trial near you, visit:
themmrf.org/resources/clinical-trial-finder

Don’t miss out on the latest myeloma updates!

Sign up today to receive news updates and notice of educational programs.

Name: _____

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Or sign up at themmrf.org

I AM A:

- ☐ Myeloma Patient
- ☐ Myeloma Patient Caregiver
- ☐ Myeloma Patient Family Member (non-caregiver)
- ☐ Health Care Professional or Researcher
- ☐ Biopharma, Medical Device, or Health Care Technology Industry Professional

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Hours: **Mon–Fri, 9 AM–7 PM ET**

Email: **patientnavigator@themmrf.org**

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383 Main Avenue, 7th Floor, Norwalk, CT 06851

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