MULTIPLE MYELOMA
Research Foundation

MULTIPLE MYELOMA PRECURSOR CONDITIONS

Monoclonal Gammopathy of Undetermined Significance and Smoldering Multiple Myeloma

themmrf.org

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Research Foundation

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 committed over $500 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 have a preceding phase of disease in which there are changes in the **bone marrow** but no symptoms or organ damage. The diseases that occur in this phase are **monoclonal gammopathy of undetermined significance (MGUS)** and **smoldering multiple myeloma (SMM)** (also called asymptomatic myeloma), collectively known as **myeloma precursor conditions**.

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 10).

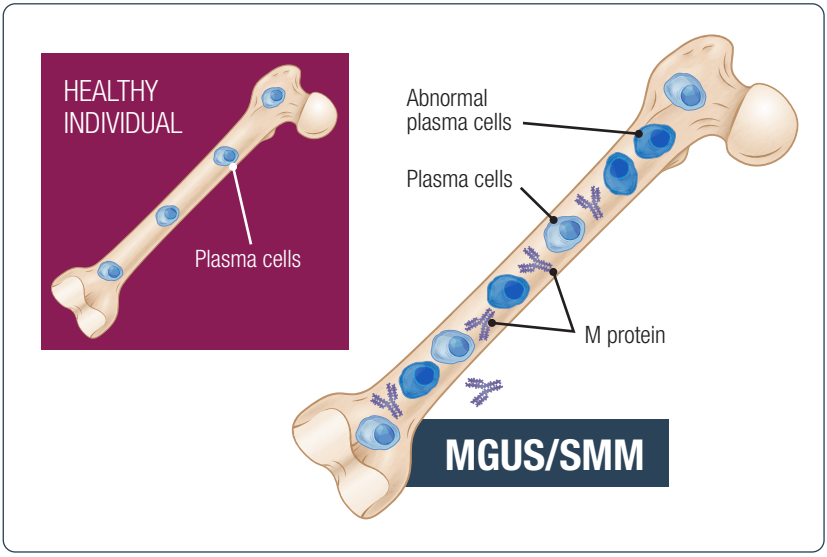
The information in this booklet is not intended to replace the services or advice of trained health care professionals. Please consult with your health care provider regarding specific questions relating to your health, especially questions about myeloma diagnosis or treatment.

For more information about multiple myeloma and its treatment, refer to the companion booklets ***Multiple Myeloma Disease Overview, Multiple Myeloma Treatment Overview, Newly Diagnosed Multiple Myeloma,*** and ***Multiple Myeloma Immunotherapy***, as well as the MMRF website, **themmrf.org**.

MULTIPLE MYELOMA PRECURSOR CONDITIONS

Almost all patients diagnosed with multiple myeloma have had a preceding phase of disease that is characterized by changes in the bone marrow. This phase can last months or years before progressing to **active multiple myeloma** and often goes undetected. Depending on the nature of these changes, this disease phase is known as monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM); collectively, these are known as myeloma precursor conditions. In both MGUS and SMM, **plasma cells** in the bone marrow grow more rapidly than normal. These rapidly growing plasma cells, which can develop into myeloma cells, produce **monoclonal protein** (or **M protein**), a substance that is detectable in the blood or urine. Both precursor conditions differ from **active multiple myeloma** in that no tumors or **osteolytic lesions** (also called lytic or bone lesions) develop, there are no symptoms or signs typically associated with active multiple myeloma (such as **anemia**, fractures, and kidney failure), and no criteria used to make a myeloma diagnosis are 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 these precursor conditions (doctors do not routinely order tests to measure M protein) and there are no signs or symptoms associated with either condition, diagnosis of MGUS or SMM usually only happens incidentally—when a doctor investigating another health issue happens to discover M protein in the blood or urine. Many patients who have one of the myeloma precursor conditions remain undiagnosed for several years.

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**).

PRECURSOR CONDITIONS AND THE RISK OF PROGRESSING TO ACTIVE MULTIPLE MYELOMA

Multiple myeloma, a cancer of the plasma cells, is part of a disease spectrum; it is the last stage of a process that generally 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. Also, if you have a first-degree relative with a blood cancer (not just myeloma), you are at a higher risk of having MGUS.

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

SMM is a stage between MGUS and multiple myeloma, and it is associated with a higher risk relative to MGUS of progression to active myeloma: 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 where on the spectrum of disease you fall—that is, whether you have MGUS, SMM, or 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 between each condition, with MGUS having lower amounts of both than SMM. Neither condition is associated with the clinical features characteristic of multiple myeloma, such as **calcium** elevation, 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 myeloma: 60% or more plasma cells in the bone marrow, an elevated free **light chain** ratio, and more than one bone lesion as determined by **magnetic resonance imaging (MRI), positron emission tomography (PET)**, or **computed tomography (CT)** scan.

*The terms *Black* and *African American* are used interchangeably in this booklet to refer to people of African descent currently residing in the U.S., regardless of their nationality or country of birth.

Blood, urine, bone marrow, and imaging tests used to identify MGUS, SMM, or active multiple myeloma.

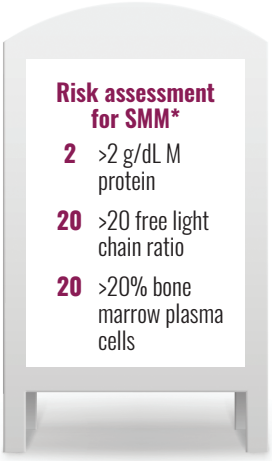
	MGUS	SMM	Active multiple myeloma
M protein	<3 g/dL in blood	≥3 g/dL in blood or ≥500 mg/24 hrs in urine	≥3 g/dL in blood or ≥500 mg/24 hrs in urine
Plasma cells in bone marrow	<10%	≥10%–60%	≥60%
Clinical features	No myeloma-defining events*	No myeloma-defining events*	≥1 myeloma-defining event*, including either: • ≥1 CRAB feature or • ≥1 SLiM feature

*CRAB, calcium elevation, renal insufficiency, anemia, bone disease; SLiM, >60% plasma cells in bone marrow; free light chain involved to uninvolved ratio >100; >1 focal lesion on MRI

HIGH-RISK SMM

Some patients with SMM are more likely to develop myeloma than others, and 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 determined 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 your risk of progressing to active myeloma. If you have high-risk SMM, you 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 have MGUS or SMM, the standard of care is watchful waiting—that is, monitoring you closely to determine if you progress to myeloma and treating you only when progression occurs. 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 myeloma. Furthermore, no more than half of SMM patients progress to myeloma within the first 5 years after diagnosis, and the number is even smaller for patients with MGUS. Additionally, administering myeloma treatments to patients who have precursor conditions that may or may not advance to multiple myeloma could lead to unwanted side effects while also yielding no benefit.

High-risk SMM may warrant treatment rather than watchful waiting and may yield the benefits of delaying the onset of active myeloma and increasing life expectancy. Treatment, if recommended at this stage, should only take place in the context of a **clinical trial**.

Fortunately, if you have normal-risk MGUS or SMM, there are several studies available. These **screening studies** and **observational studies** are being conducted to identify patients earlier in the myeloma disease spectrum and to understand the clinical and genetic features of these precursor conditions that are associated with progression to active myeloma.

Types of clinical studies

	Observational study	Interventional trial
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.
Examples	Registry Claims-based analysis	Randomized controlled trial

If you have intermediate- to high-risk SMM, several **interventional clinical trials** (that is, trials that investigate treatments) are available that are assessing the benefits of several treatments designed to prevent progression to active myeloma, as well as the risks associated with them. Early studies have shown that treatment with Revlimid prolonged the amount of time before patients with intermediate- and high-risk SMM progressed to multiple myeloma. The latest studies are investigating whether single-drug or combination therapy with some newer anti-myeloma drugs will be effective in preventing progression or lengthening the time to progression. So far, the results of these studies have been promising, and there is good reason for optimism and hope.

Patients with MGUS and SMM are typically monitored without treatment (watchful waiting) until there is evidence of disease progression. If this approach causes you anxiety, talk to your doctor about your concerns, your risk for progression, and the possibility of joining a clinical trial.

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.

The MMRF would like to thank Irene Ghobrial, MD, Lavine Family Chair of Preventative Cancer Therapy and Director of the Center for Prevention of Progression at the Dana-Farber Cancer Institute in Boston, Massachusetts, and our patient advocate, Marc Davis of Covington, Georgia, for their contributions to this booklet.

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**

Connect with an MMRF Myeloma Mentor™:
themmrf.org/resources/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**

The MMRF has partnered with Lazarex Cancer Foundation to help patients access clinical trials by helping with travel expenses. Patients who qualify will be reimbursed for out-of-pocket travel expenses for themselves and a travel companion. To learn more about this program, contact the MMRF Patient Navigation Center (1-888-841-6673 or **patientnavigator@themmrf.org**).

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

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

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

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

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 another piece from a different chromosome; deletion p13 and t(4;14) are examples of chromosomal abnormalities

clinical trial A study of the safety and effectiveness of a therapeutic agent using consenting human subjects

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

interventional trial Type of *clinical trial* 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 gammopathy of undetermined significance (MGUS) A condition that can occur before a patient develops or shows any symptoms of multiple 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 cancerous myeloma cells

myeloma precursor conditions Any of the preceding phases of multiple myeloma, called monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma (SMM), that are characterized by the amount of M protein in the blood and percentage of plasma cells in the bone marrow, but no symptoms or organ damage

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

osteolytic lesion Soft spot in the bone where bone tissue has been destroyed; appears as a hole in the bone on a standard x-ray

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

red blood cell Blood cell that carries oxygen

screening study Clinical 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) Myeloma 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; also called *asymptomatic myeloma*

stratification model An analytical tool used to sort data, people, and objects into distinct groups

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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383 Main Avenue, 5th Floor, Norwalk, CT 06851

Email: **info@themmrf.org**

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