

# MMRF Virtual *Expert Session*: Precursor Disease

August 18, 2021



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MODERATOR

## Mary DeRome

**Multiple Myeloma Research Foundation**  
Norwalk, Connecticut



[www.theMMRF.org](http://www.theMMRF.org)



<https://www.facebook.com/theMMRF>



<https://twitter.com/theMMRF>



<https://www.youtube.com/user/theMMRF>



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## Program Support

abbvie



Bristol Myers Squibb™

cure®  
curetoday.com



Karyopharm®  
Therapeutics

janssen

Pfizer



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## VIRTUAL EXHIBIT HALL



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## Speakers



**Irene Ghobrial, MD**  
Dana-Farber Cancer Institute  
Boston, Massachusetts



**Elisabet E. Manasanch, MD**  
The University of Texas  
MD Anderson Cancer Center  
Houston, Texas



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## Virtual *Expert Session* Agenda

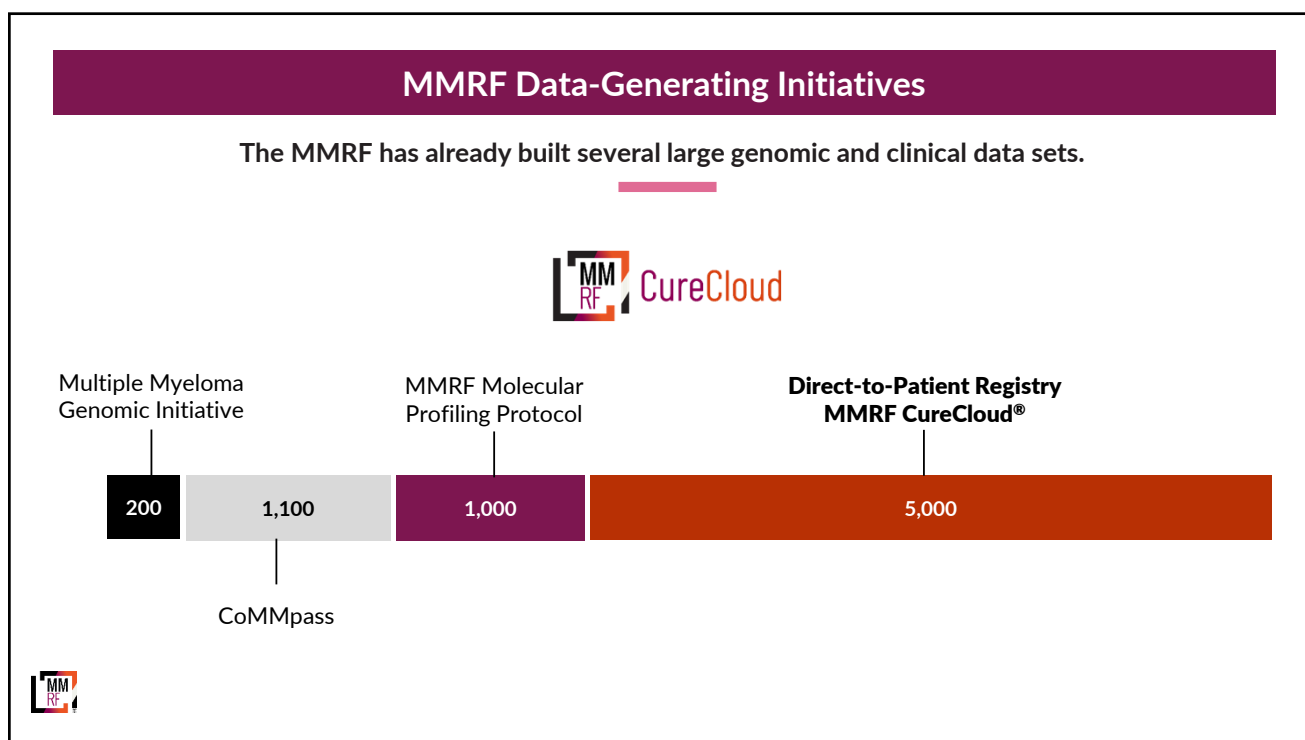
Time	Topic	Speakers
11:00 AM–11:20 AM ET	Opening Remarks	Mary DeRome
11:20 AM–11:40 AM ET	Overview of Multiple Myeloma Precursor Conditions	Elisabet E. Manasanch, MD
11:40 AM–12:05 PM ET	<i>Discussion/Questions and Answers</i>	All
12:05 PM–12:25 PM ET	Preventing Development of Active Myeloma	Irene Ghobrial, MD
12:25 PM–12:50 PM ET	<i>Discussion/Questions and Answers</i>	All
12:50 PM–1:00 PM ET	Closing Remarks	Mary DeRome



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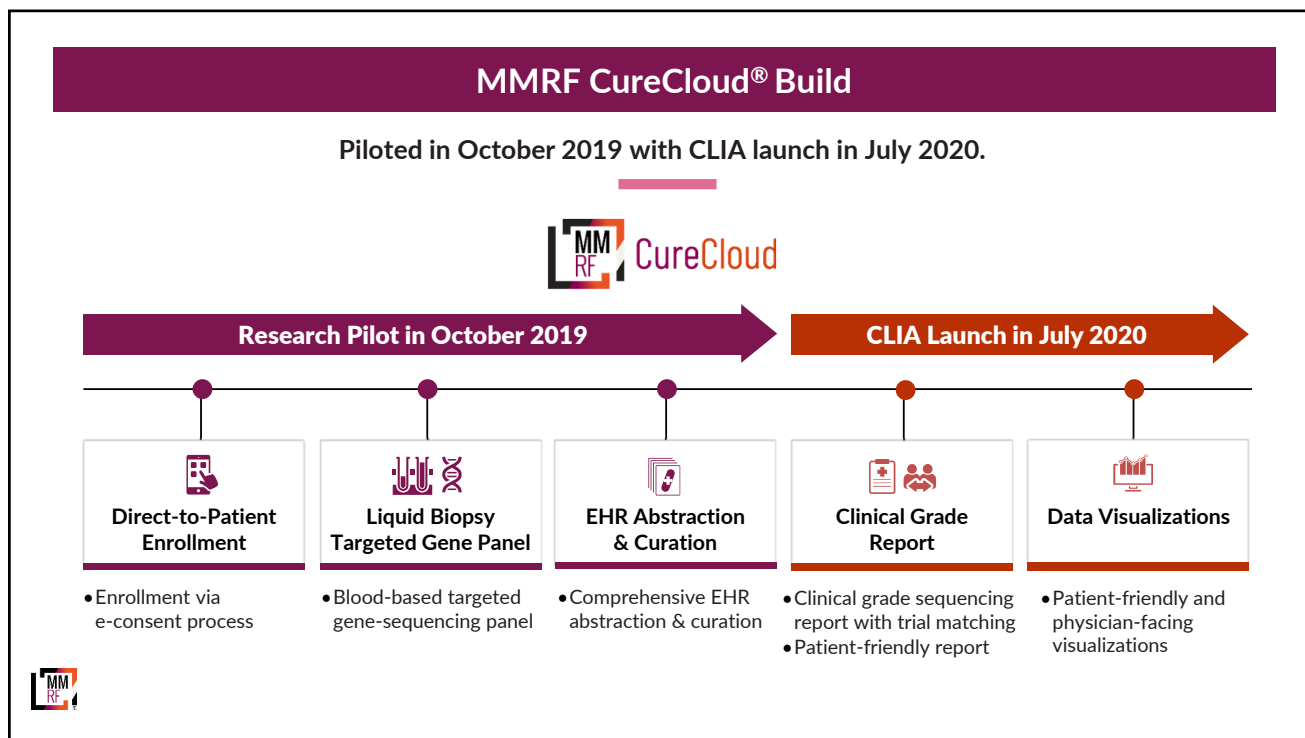


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## MMRF CureCloud®






### It starts with you.

The MMRF CureCloud® is the first research study including at-home genomic testing for myeloma patients. As a participant, you receive free tests and resources that enable more productive and informed conversations with your multiple myeloma care team.




**Genomic test**

Get a free state-of-the-art genomics test, using the first liquid biopsy for multiple myeloma.



**Personal report**

Receive a free report on the genetic variations in your multiple myeloma cells.



**Coming soon: Smarter treatment options**

You and your care team can identify more informed treatment paths based on other patient data.

Join now – visit [mmrfcurecloud.org](http://mmrfcurecloud.org) or call 1-888-841-MMRF (6673)

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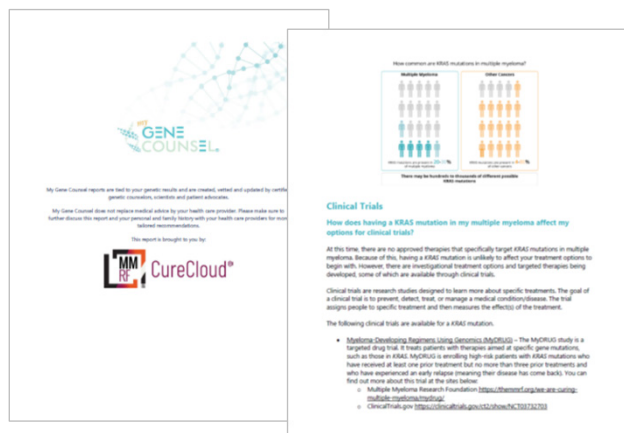
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CureCloud®

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## Personalized Reports

Personalized genomics reports designed to enhance doctor–patient communication.



The image shows a patient-facing report from MyGeneCounsel. It features a blue and white design with a network diagram. The text explains that the report is based on genetic results and is created, edited, and updated by certified genetic counselors, scientists, and patient advocates. It also mentions that the report is designed to help patients understand their genetic results and how they may affect their health. The report includes a section on clinical trials, explaining that having a KRAS mutation in multiple myeloma can affect treatment options. It lists several clinical trials that are currently recruiting patients with KRAS mutations, including the MYELOMA-1 trial, the MYELOMA-2 trial, and the MYELOMA-3 trial. The report also includes a section on the importance of genetic testing and how it can help patients understand their disease and treatment options.

MyGeneCounsel Report for Patients



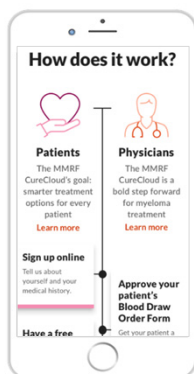
The image shows a physician-facing report from Dana-Farber Cancer Institute (DFCI). It features a white background with a blue header. The report includes patient information, a summary of the analysis, and a list of somatic alterations. The patient information section includes the patient's name, date of birth, and gender. The summary of the analysis section includes a brief overview of the patient's condition and the results of the genetic testing. The list of somatic alterations includes a table with columns for the alteration, the gene, and the frequency. The report also includes a section on the importance of genetic testing and how it can help patients understand their disease and treatment options.

DFCI Report for Physicians

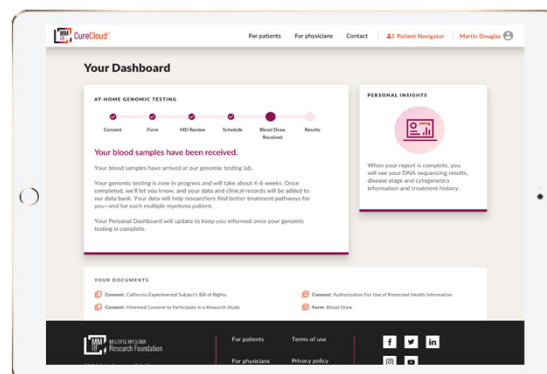
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## Patient Resources

Provide personalized insights and actionable guidance to inform more precise treatment decision-making.



Mobile & Desktop Microsite



Personalized Dashboard



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## Patient Support

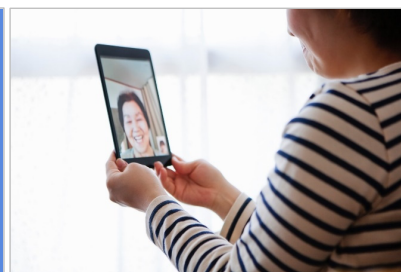
MMRF Patient Navigators are available to provide additional support; Facebook groups and Myeloma Mentors provide patients opportunities to connect with patients like them.



Patient Navigators



Facebook Groups



Myeloma Mentors



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# Thank you!



**[www.mmrfcurecloud.org](http://www.mmrfcurecloud.org)**

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## Discussion Topics

- Overview of multiple myeloma precursor conditions
- Preventing development of active myeloma



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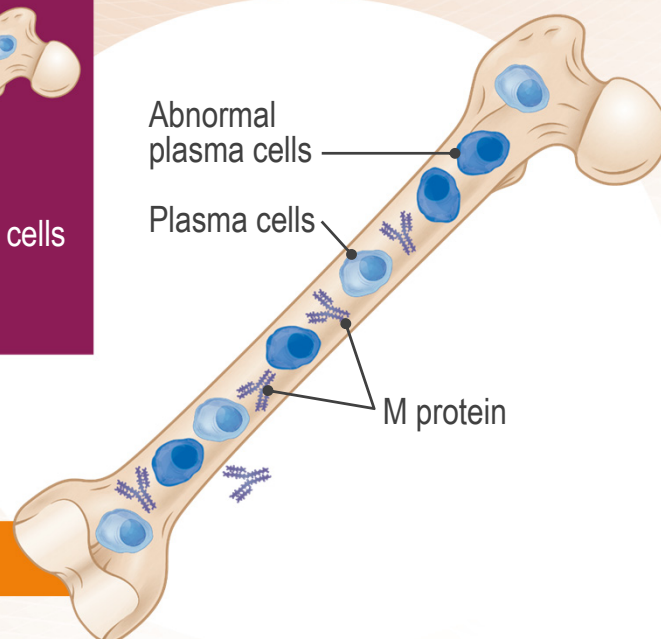
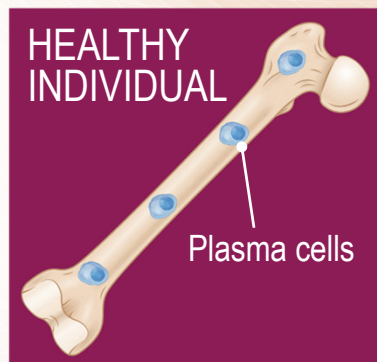


# Overview of Multiple Myeloma Precursor Conditions

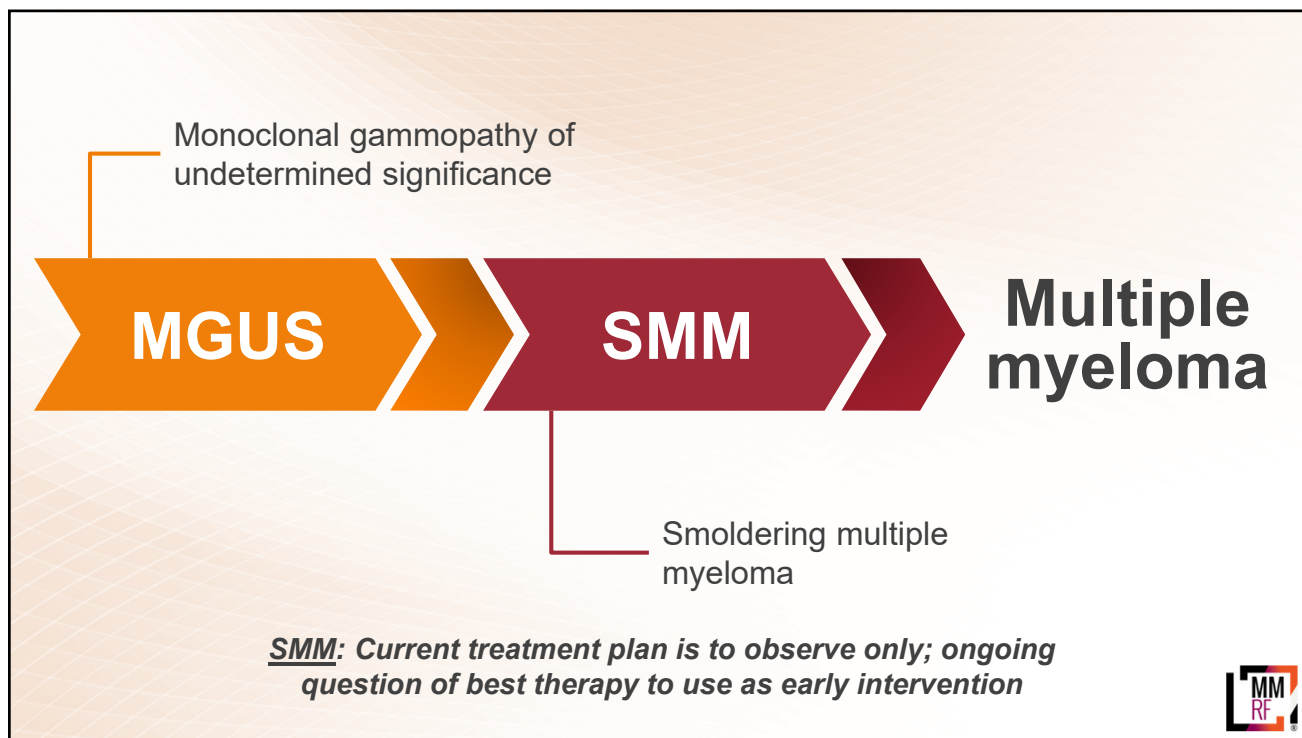
Elisabet Manasanch, MD



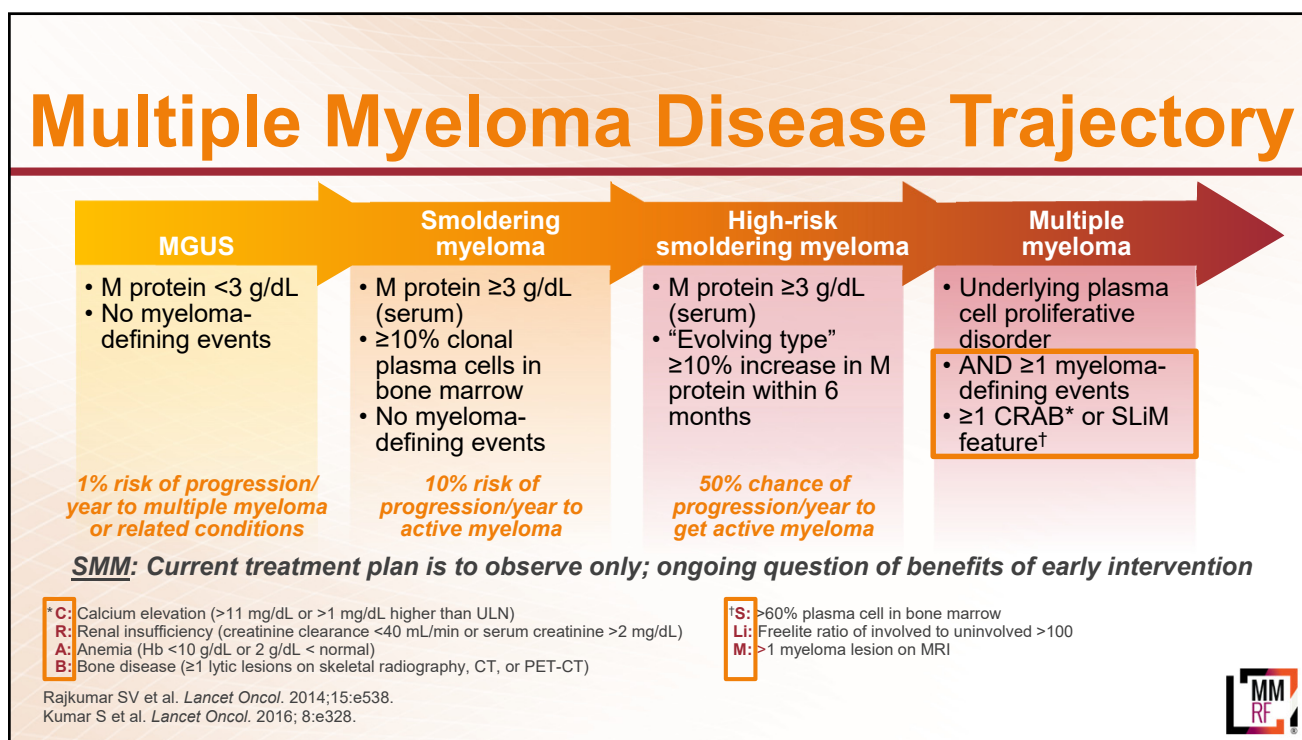
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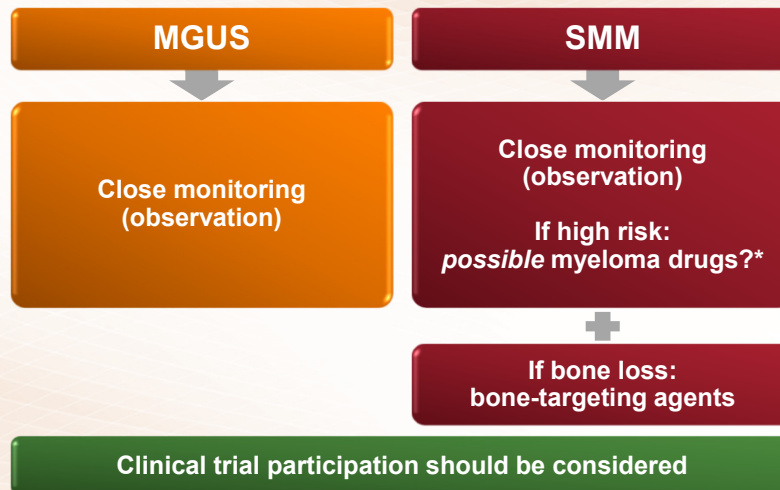


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## Overview of Treatment Approach

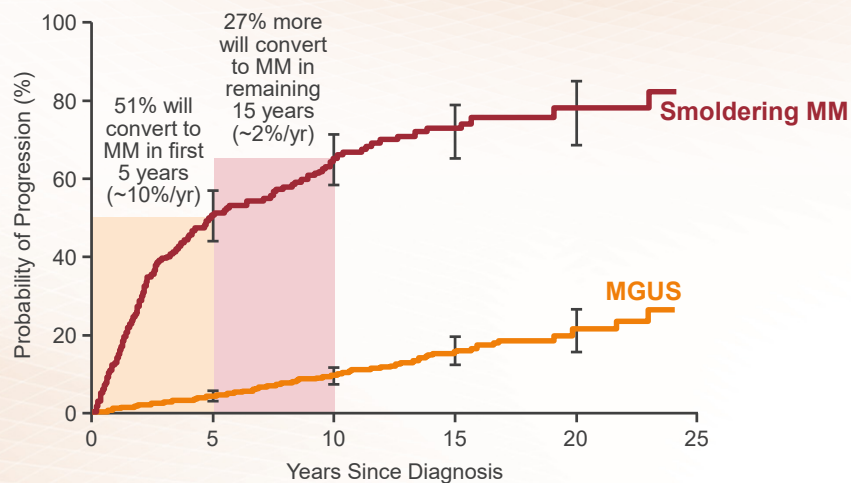


\*Promising but only available as clinical trials.



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# Smoldering Multiple Myeloma: Heterogeneous Disease

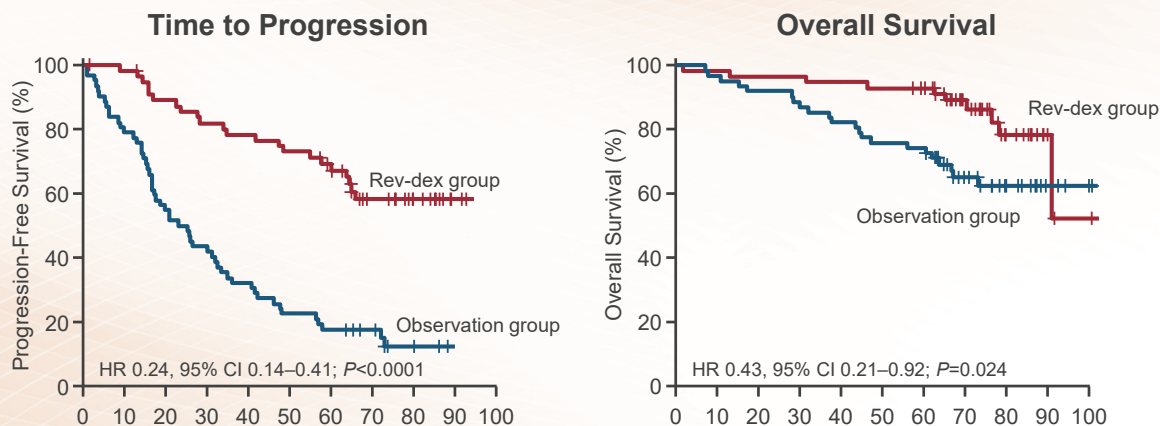


Kyle RA et al. *N Engl J Med*. 2007;356:2582.  
Greipp PR et al. *J Clin Oncol*. 2005;23:3412.



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## Phase 3 Trial of Revlimid-Dex vs Observation in High-Risk SMM

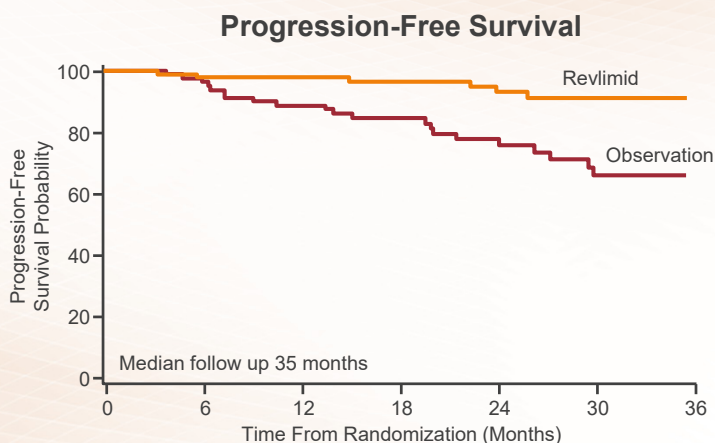


QuiRedex Trial. Mateos MV et al. *Lancet Oncol.* 2016;17:1127.



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## Revlimid vs Observation Alone in Patients With Smoldering MM



E3A06 Trial. Lonial S et al. *J Clin Oncol.* 2020;38:1126.



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## 2/20/20 Model to Identify High-Risk SMM Patients

Patients with two or more risk factors are considered high risk.

Model does not include any biological or immune factors that may account for interpatient heterogeneity.

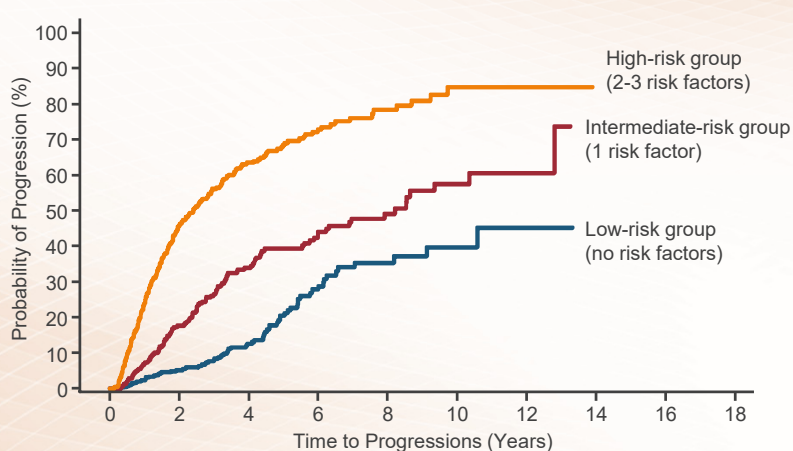
### Risk assessment for SMM

- 2** >2 g/dL protein
- 20** >20 free light chain ratio
- 20** >20% bone marrow plasma cells



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## Progression by Risk Group



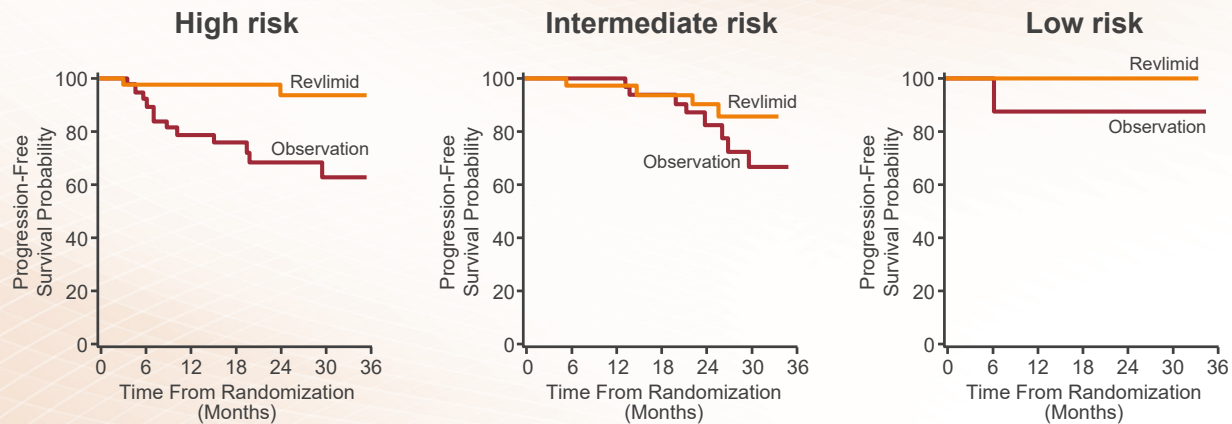
IMWG SMM Risk Stratification Model. Mateos MV et al. *Blood Cancer J.* 2020;10:102.



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## Phase 3 Progression-Free Survival by Mayo 2018 Risk Criteria



E3A06 Trial. Lonial S et al. *J Clin Oncol*. 2020;38:1126.



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## Ongoing Clinical Studies for SMM Patients

### Phases 1–3 or Observational

#### SMM patients at high risk of disease progression

- Xgeva
- Ninlaro + Revlimid + dex
- Darzalex (sc)
- Kyprolis + Revlimid + dex
- Revlimid + dex ± Kyprolis
- Kyprolis + Revlimid + Darzalex + dex (ASCENT trial)
- Revlimid + dex ± Darzalex
- **Empliciti + Revlimid + dex (E-PRISM Trial)**
- Vaccines: PVX-410, DKK1, custom-made
- **Sarclisa**

#### SMM/MGUS

- Predictors of progression (PROMISE study)
- Genomic and molecular predictors of progression (MD Anderson study)
- Darzalex
- Rifaximin
- DKK1 (dendritic cell) vaccine
- Neo-antigen personalized vaccine

*Ask your doctor about whether you are a candidate for a clinical trial.*

Trials found at [www.clinicaltrials.gov](http://www.clinicaltrials.gov)



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## Phase 2 Trial of Sarclisa in SMM Patients

Sarclisa is a monoclonal antibody  
that binds to CD38 on myeloma cells

62.5% of patients responded to treatment

- Comparable response rate to a recent phase 3 trial of Revlimid in a similar patient population (50%)

Similar binding site of Darzalex

20% of patients experienced grade 3 side effects and no grade 4

- No patients discontinued the trial due to side effects

Phase 2 study of Sarclisa in 24  
patients with SMM (majority were  
considered high risk by 2/20/20 model)

Treatment decreased patients' worries about cancer.

Analysis is ongoing.



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## Extensive Changes of the Immune Microenvironment Are Associated With Progression From Precursor Stages to MM *Prospective Observational Study Design*

Changes in immune cell  
populations and their function  
have been described as early as  
MGUS

- 2015–2019 → 100 eligible patients were included in the analysis

Study goal: Characterize immune  
dysregulation in MM precursor  
disease and describe changes in  
evolution to MM

- 41 MGUS and 59 SMM
- Median follow-up 24 months (12–48 months)






BM, bone marrow; PC, plasma cell




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THE UNIVERSITY OF TEXAS  
**MDAnderson**  
Cancer Center  
Making Cancer History®






## Extensive Changes of the Immune Microenvironment Are Associated With Progression From Precursor Stages to MM *Prospective Observational Study Results*


-  17% of SMM patients progressed to active myeloma
-  Higher risk of progression may be associated with increasing mutation rates in patients
-  Gene-expression features of both the tumor and the immune system may be used to predict risk of progression
-  Patients that progressed had different genes upregulated or downregulated when compared to non-progressors at baseline
-  Significant changes in the immune cell composition included changes in CD8 T cells, dendritic cells, NK cells, and macrophages of progressors vs non-progressors at baseline



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## Key Points

-  The classic description of SMM having an ~10% chance per year of progression to symptomatic disease is too broad a characterization of a heterogeneous group.
-  Genetic changes and mutations in the myeloma together with clinical factors can best predict progression to myeloma.
-  Genetic and mutation analysis is not yet widely available.
-  Patients with SMM should be offered treatment on clinical trials.
-  Participation in observational/interventional studies is key to finding out which patients can benefit the most from early treatment and what is the best treatment to offer early.



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## Questions & Answers



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## Preventing Development of Active Myeloma

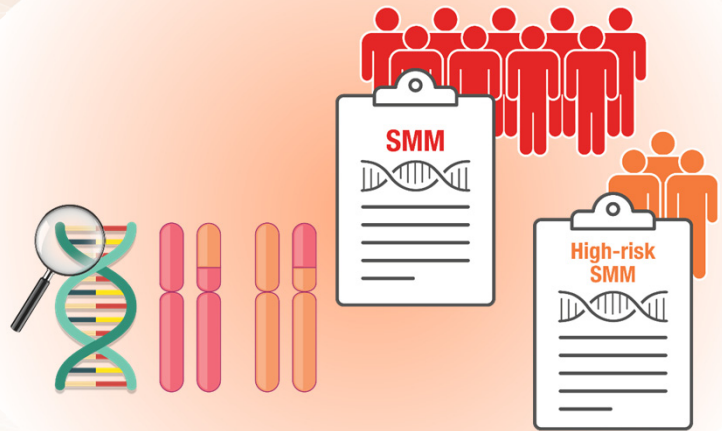
Irene Ghobrial, MD



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**Modifying current risk models using genomics to significantly improve the accuracy of identifying those at highest risk of progressing to MM**



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## Why is “precision prevention” and early detection important? And why now?



Historically, most efforts in this area have been focused on environmental causes of cancer and developing therapeutics to treat cancer.



**Advances in molecular biology (for example, genomics) enable us to better understand, predict, prevent, and detect cancers and achieve better outcomes for patients.**



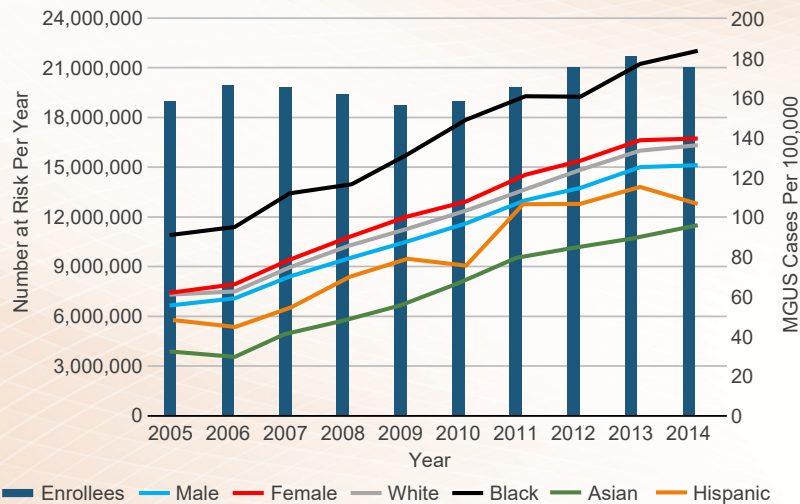
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## Detecting Multiple Myeloma Precursor Conditions

### Monoclonal Gammopathy of Undetermined Significance (MGUS)

### Smoldering Multiple Myeloma (SMM)



Go RS et al. *Leukemia*. 2016;30:1443.

- 3% of the general population at age 50 have MGUS
- This rate is 3 times higher for individuals of African descent
- This rate is 2–3 times higher for first-degree family members of myeloma patients



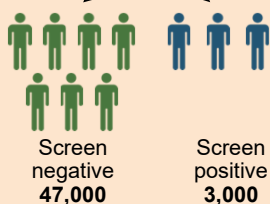
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## Changing the Multiple Myeloma Diagnosis

### Specific Aims

#### Aim 1. The PROMISE Study

Screen **50,000**  
high-risk individuals



#### Aim 2. Genomic Characteristics of MGUS/SMM

Viktor Adalsteinsson Irene Ghobrial  
Benjamin Ebert  
Gaddy Getz

#### Aim 3. Race/Obesity on Precursor Progression

Lorelei Mucci Catherine Marinac  
Tim Rebbeck

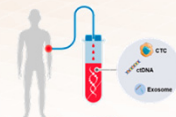
#### Aim 4. MGUS/SMM Permissive Microenvironment

Ivan Borrello  
Irene Ghobrial

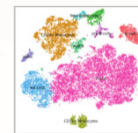
#### Aim 5. Imaging /Therapeutics For Detection/Interception

Jeremiah Johnson  
Irene Ghobrial

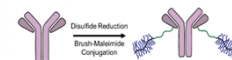
Develop novel **biomarkers** for diagnosis



Establish advanced **risk stratification**



Generate new tools to **prevent precursor progression**



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2 groups of U.S. adults, age 45-75, qualify for a free screening:

- African Americans**  
AND / OR
- People of Any Race Who Have a Parent, Sibling, or Child with:**  
**Multiple myeloma** OR one of these related conditions:
  - Monoclonal Gammopathy of Undetermined Significance (MGUS)
  - Smoldering Multiple Myeloma
  - Waldenström Macroglobulinemia

Please sign up for the study if you qualify.

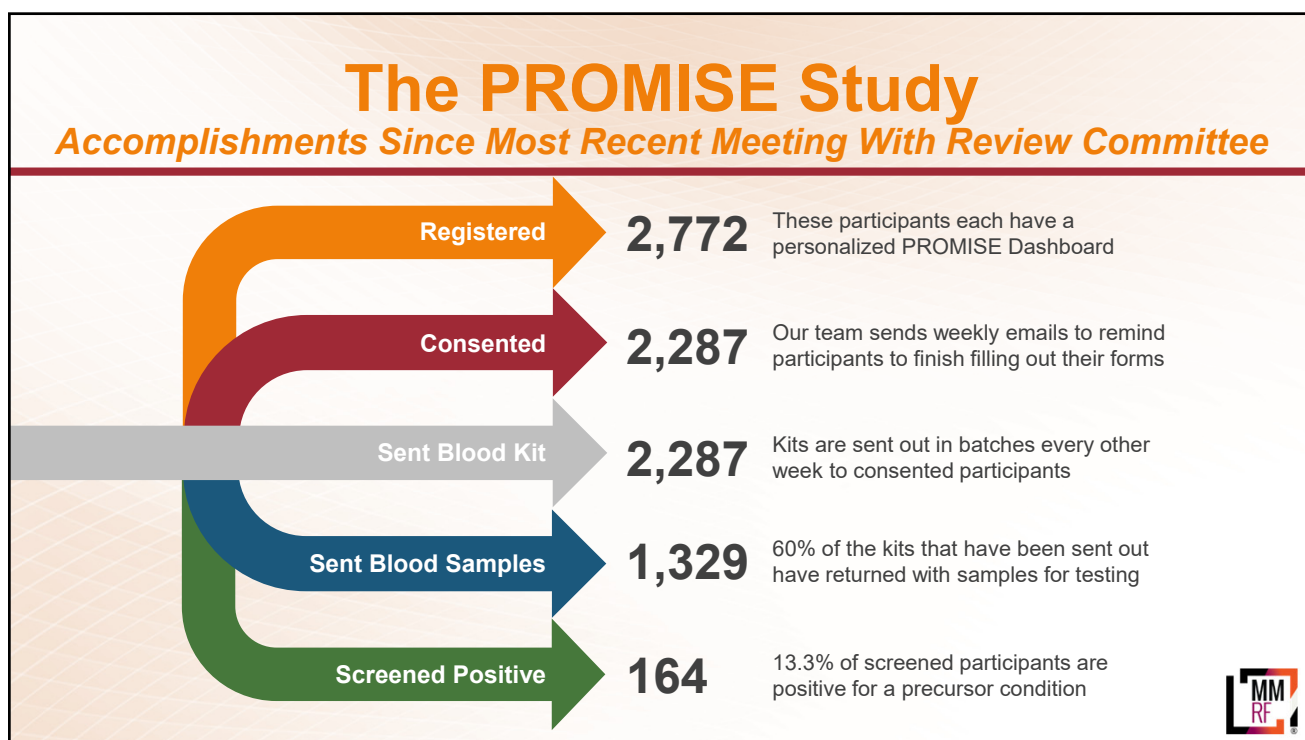
**Note:** The PROMISE study is for people who may have higher risks, but have not been diagnosed with any of these conditions.

If you have been diagnosed with one of these conditions, please visit our [PCROWD study, a sister project for people with precursor conditions](#).

PCROWD

[www.enroll.promisestudy.org/](http://www.enroll.promisestudy.org/)

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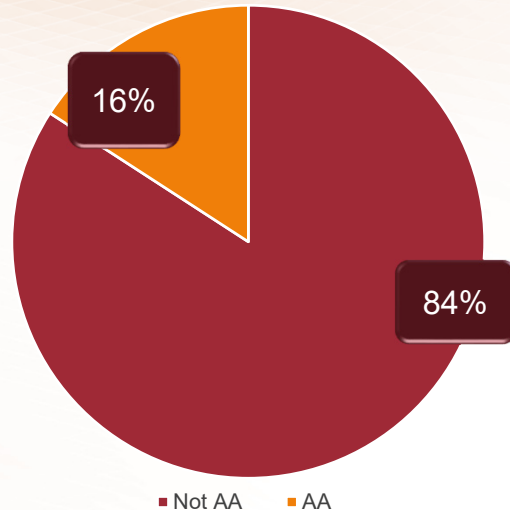
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## The PROMISE Study

*Predicting Progression of Developing Myeloma  
in a High-Risk Screened Population*

Screening individuals of African descent

- The PROMISE Study has, as of today, enrolled 15% individuals of African descent
- 13% of screened POSITIVE PROMISE participants identify as being of African descent



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## New CPOP Clinic

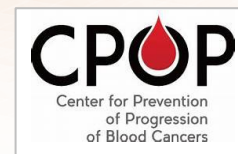
**(Center for Prevention of Progression of Blood Cancers)**

### FEATURES

**Aim and scope of clinic:** To actively study patients with precursor hematological malignancies and define mechanisms/therapies that prevent progression

**Goal:** Have DFCI be the center of excellence for early precursor hematological conditions

- Physical clinic
- Multidisciplinary
  - DFCI HM & BWH Hematology clinical staff, Medical Genetics, BWH Cardiology
- Integration of research and clinical care

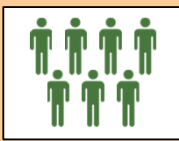


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## Our Approach

What causes progression from MGUS/SMM to MM?

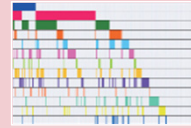


**MGUS/SMM population**

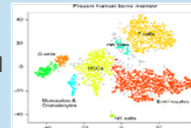
Samples of progressors and non-progressors

Genomic and epigenetic characteristics of clonal evolution from MGUS to MM

Genomic characterization

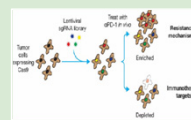


RNA seq. of BM niche



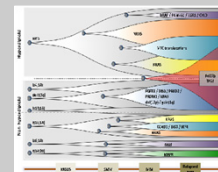
Defining the permissive tumor microenvironment in MGUS/SMM

Define the immune landscape

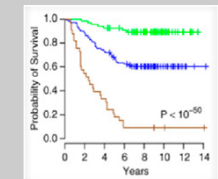


Dissecting the role of the immune microenvironment in progression from MGUS to MM

Develop novel biomarkers



Develop new therapies to prevent/delay progression



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## Defining Disease Progression Through Genomic Profiling

- Bone marrow samples from 203 SMM patients were analyzed to
  - Determine the genetic and molecular profiles that underlie disease progression
  - Improve risk stratification by identifying those at highest risk of progression compared to conventional risk assessment

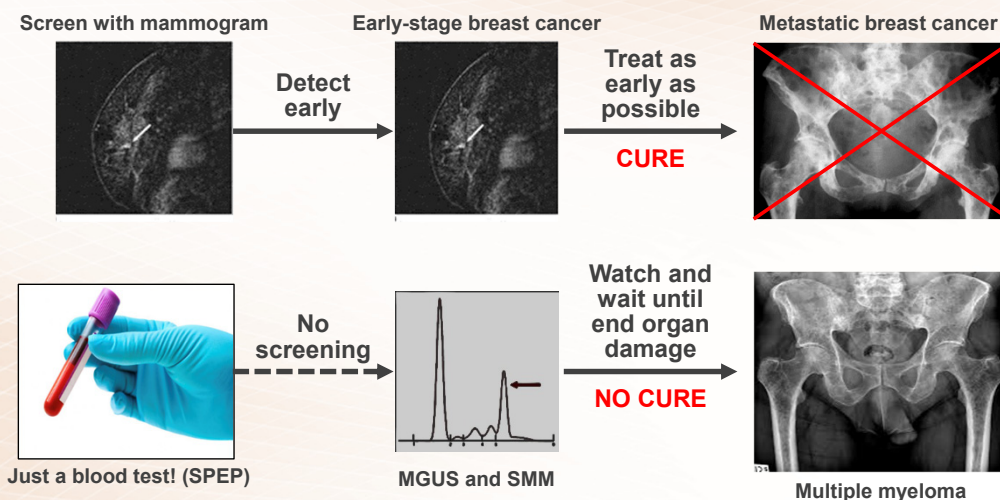
	Time to Progression (months)	
Genetic Profile	SMM Pts With	SMM Pts Without
MYC abnormality	8.4	52
MAPK pathway mutations	15	60
DNA repair mutations	19	47
≥1 DNA repair mutation	1.2 yrs	6 yrs

Bustoros M et al. Presented at the 17th International Myeloma Workshop; September 12–15, 2019. Abstract OAB-006. Manuscript under review.



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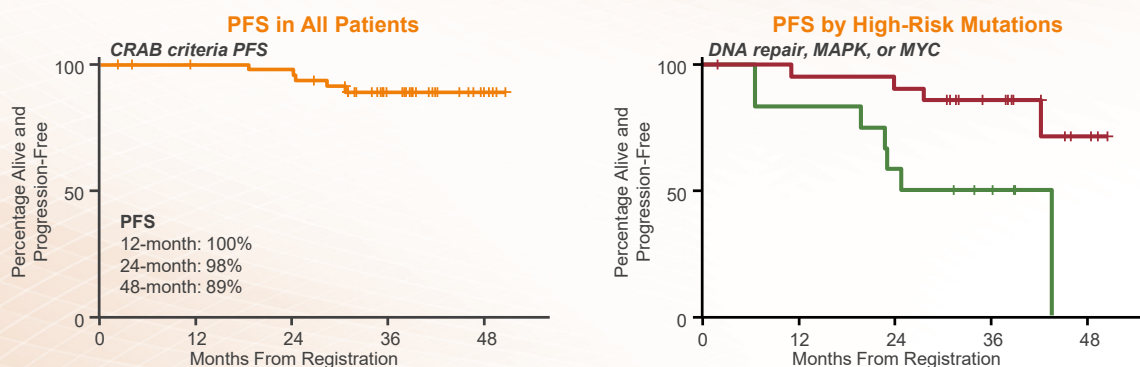
## Can intervention prevent progression in multiple myeloma?



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## Precision Intervention With Empliciti in Smoldering Myeloma

Phase 2 Trial of Combination of Empliciti, Revlimid, and Dexamethasone in High-Risk Smoldering Multiple Myeloma (With Whole-Genome Sequencing of Patient Samples)



E-PRISM Trial. Liu C-J et al. *Blood*. 2018;132: Abstract 154.



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## Questions & Answers



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## Program Support

abbvie  Bristol Myers Squibb™

cure®  Karyopharm®  
curetoday.com Therapeutics

janssen  Pfizer



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Multiple Myeloma High-Impact Topic

## MULTIPLE MYELOMA PRECURSOR CONDITIONS

Monoclonal gammopathy of undetermined significance

**MGUS** → **SMM** → **Multiple myeloma**

| Smoldering multiple myeloma

MGUS/SMM

For more information, please visit <https://themmrf.org/resources/education-programs/>

Check out our  
**NEW High-Impact  
Topic** videos

Multiple Myeloma High-Impact Topic

THE RIGHT TRACK

Multiple Myeloma High-Impact Topic

CLINICAL TRIALS

Multiple Myeloma High-Impact Topic

AUTOLOGOUS STEM  
CELL TRANSPLANT

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## COVID-19 Resources

Coronavirus & Multiple Myeloma: Click for the Latest Updates

MMRF MULTIPLE MYELOMA Research Foundation

DONATE EVENTS SIGN UP Menu

### Coronavirus (COVID-19) & Multiple Myeloma



MMRF Chief Medical Officer Speaks on COVID-19

Watch later Share

Our Chief Medical Officer, Hearn Cho, addresses important questions for multiple myeloma patients

<https://themmrf.org/2020/03/multiple-myeloma-and-the-coronavirus/>




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## MMRF Patient Resources

### EXPECT GUIDANCE.

MMRF Patient Navigation Center

- Information & Resources
- Expert Advice
- Support



MULTIPLE MYELOMA Research Foundation

### MMRF Patient Navigation Center

You and your care team will have many decisions to make along your treatment journey. The Patient Navigation Center is a space for multiple myeloma patients to connect with patient navigators – who are professionals specializing in oncology – for guidance, information, and support. Patients can connect with a patient navigator via phone, email or through one of our MMRF Facebook Groups. Whenever patients have a question, our patient navigators are here to help.

MMRF Patient Navigators include:

- Grace Allison, RN, BSN, OCN, RN-BC
- Kristen Donadio, RN, BSN
- Erin Mensching, BSN, BA, RN

### THE RIGHT TRACK™

Get on the right track for you

The MMRF's Right Track program puts you on the path to the best results for you.

Right Team	Right Tests	Right Treatment
Access experts and centers that have extensive experience treating multiple myeloma.	Get the information, tests, and precise diagnoses to make the right treatment decisions.	Work with your team to consider the best treatment plan and identify clinical trials that are right for you.

**Contact the Patient Navigation Center Today**  
Looking for guidance? We're here to help.  
Monday – Friday | 9:00am – 7:00pm ET  
Phone: 1-888-841-MMRF (6673) | Online: [TheMMRF.org/PatientNavigationCenter](https://themmrf.org/PatientNavigationCenter)

Supported By

Adaptive AMGEN Bristol Myers Squibb Genentech  
gsk Karyopharm Oncology



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Myeloma Mentors® allows patients and caregivers the opportunity to connect with trained mentors. This is a phone-based program offering an opportunity for a patient and/or caregiver to connect one-on-one with a trained patient and/or caregiver mentor to share his or her patient journeys and experiences.

No matter what your disease state—smoldering, newly diagnosed, or relapsed/refractory—our mentors have insights and information that can be beneficial to both patients and their caregivers.

**Contact the Patient Navigation Center at 888-841-6673  
to be connected to a Myeloma Mentor or to learn more.**



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## Upcoming Patient Education Events

### Save the Date

#### ***Autologous Stem Cell Transplantation for Multiple Myeloma***

Wednesday, September 22, 2021, 2:00 PM–3:00 PM ET



***Sergio A. Giral, MD***

Memorial Sloan Kettering Cancer Center  
New York, New York



***Amrita Y. Krishnan, MD***

City of Hope Medical Center  
Duarte, California

**For more information or to register, please visit  
[themmrf.org/themmrf.org/resources/education-program](https://themmrf.org/themmrf.org/resources/education-program)**



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**Thank you!**

