Should we screen for precursor conditions

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Conflict of Interest

• IMG is a consultant for Janssen, Pfizer, Sanofi, BMS, Takeda, GSK, Binding Site.
Pre-malignant conditions are very common and affect millions of people.

Cancer centers and industry have been focusing largely on improving survival for late-stage cancers.

Patients are diagnosed by chance when they have symptoms.

Early detection can disrupt cancer diagnosis, care delivery, and survival.

Early intervention on premalignant precursors can prevent cancer altogether.

We can change the cancer experience if we can find it early at a curable stage.
The opportunity

Heme malignancies
MGUS/CHIP/MBL
1% per year
Smoldering myeloma/MDS
10% per year
Myeloma/AML/CLL
The screening imperative for multiple myeloma

S. Vincent Rajkumar says there is enough evidence to begin testing, and treating, people at high risk of the disease much earlier.
Cancer screening saves lives

Normal → Pre-Neoplasia → Cancer

Mammogram
Detect Early
Early Stage Breast Cancer
Treat as Early as Possible
CURE

Metastatic Breast Cancer

No Screening
A Simple Blood Test

MGUS and SMM
“Watch and Wait” Until End Organ Damage
NO CURE

Multiple Myeloma

Dana-Farber Cancer Institute
Early therapeutic interventions prolong survival in SMM

Lenalidomide plus Dexamethasone for High-Risk Smoldering Multiple Myeloma

María-Victoria Mateos, M.D., Ph.D., Miguel-Teodoro Hernández, M.D., Pilar Giraldo, M.D., Javier de la Rubia, M.D., Felipe de Arriba, M.D., Ph.D., Lucía López Corral, M.D., Ph.D., Laura Rosiñol, M.D., Ph.D., Bruno Paiva, Ph.D., Luis Palomera, M.D., Ph.D., Joan Bargay, M.D., Àlvar Oriol, M.D., Felipe Prosper, M.D., Ph.D., Javier López, M.D., Ph.D., Óscar Olavarria, M.D., Ph.D., Nuria Quintana, M.D., José-Luis García, M.D., Joan Bladé, M.D., Ph.D., Juan-José Lahuerta, M.D., Ph.D., and Jesús-F. San Miguel, M.D., Ph.D.

Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

Sagar Lonial, MD; Susanna Jacobus, MSCE; Rafael Fonseca, MD; Matthias Weiss, MD; Shaji Kumar, MD; Robert Z. Orlowski, MD, PhD; Jonathan L. Kaufman, MD; Abdulrahem M. Yacoub, MD; Francis K. Buadi, MD; Timothy O'Brien, MD; Jeffrey V. Matous, MD; Daniel M. Anderson, MD; Robert V. Emmons, MD; Anuj Mahindra, MD; Lynne L. Wagner, PhD; Madhav V. Dhodapkar, MBBS; and S. Vincent Rajkumar, MD

A

No. at Risk
Treatment group 57 57 48 38 20 14 0
Observation group 62 49 32 21 11 3 0

Hazard ratio for progression, 0.18
P<0.001

Progression-Free Survival Probability

Time from Randomization (Months)

Numbers at Risk
Lenalidomide 90 83 81 72 55 42 31
Observation 92 77 67 56 34 26 19
The number of people who can be saved by early detection

3-5% of the general population at age 50 have MGUS

This rate is 2-3 times higher for individuals of African descent

This rate is 2 times higher for first-degree family members of myeloma patients

About 15 million people in the US

Prevalence of Monoclonal Gammopathy of Undetermined Significance

MGUS and SMM lead to MM

Published in Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2010

Smoldering (asymptomatic) multiple myeloma: current diagnostic criteria, new predictors of outcome, and follow-up recommendations.

J. Bladé, M. Dimopoulos, L. Rosiñol, S. V. Rajkumar, R. Kyle
Efforts of screening for MM

https://doi.org/10.1038/s41408-021-00480-w

Iceland screens, treats, or prevents multiple myeloma (iSTOPMM): a population-based screening study for monoclonal gammopathy of undetermined significance and randomized controlled trial of follow-up strategies

Sæmundur Rögnvaldsson1, Thorvardur Jon Love1, Sigrun Thorsteinsdottir1,2, Elín Ruth Reed1, Jón Þórir Óskarsson1, Íris Pétursdóttir1, Guðrún Ásta Sigurðardóttir1, Brynjar Viðarsson3, Páll Torfi Önundarson1,3, Bjarni A. Agnarsson1,3, Margrét Sigurðardóttir3, Ingunn Þorsteinsdóttir3, Ísleifur Ólafsson3, Ásðís Rósa Þórdardóttir1, Elías Eyþórsson3, Ásbjörn Jónsson3, Andri S. Björnsson4, Gunnar Þór Gunnarsson1,5, Runólfur Pálsson1,3, Ólafur Skúli Indriðason1,3, Gauti Kjartan Gíslason1, Andri Ólafsson1, Guðlaug Katrín Hákonardóttir1, Manje Brinkhuis1,
The PROMISE study

I promise to be there when he becomes a champion...

www.promisestudy.org
Nationwide Study of Myeloma Screening and Prevention: PROMISE

Screen 30,000 High-Risk Individuals

Screen Negative 26,100

Screen Positive 3,900

Prospective Follow-Up

Develop novel biomarkers for diagnosis

Establish new risk stratification tools

Generate new tools to prevent disease progression

Genetics and Genomics
- Viktor Adalsteinsson
- Gad Getz
- Irene Ghobrial

Epidemiology
- Tim Rebbeck
- Lorelei Mucci
- Catherine Marinac

Bone Marrow Niche
- Ivan Borrello
- Irene Ghobrial

Imaging and Therapeutics
- Jeremiah Johnson
- Irene Ghobrial

Screen Negative 26,100

Screen Positive 3,900

Prospective Follow-Up
Eligibility Criteria

2 groups of U.S. adults, age 40-75, qualify for a free screening:

1. African Americans
   AND / OR
2. People of Any Race Who Have a Parent, Sibling, or Child with:
   Multiple myeloma, another blood cancer, OR one 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.
How does the PROMISE screening process work?

1. Sign up
2. Accept Terms
3. Receive Blood Kit
4. Schedule Blood Draw
5. Receive Results
National and International PROMISE

>5600 accrued to date

South Africa, Kenya, Israel
PROMISE partners with the MGB BioBank

- 123,000 individuals
- 20% non-White
- 50,000 GWAS or exome sequencing data

PROMISE inclusion criteria applied to MGB: 4,446 samples into PROMISE
- 2,373 individuals self-identify as Black/African American > 30 years
- 1,868 participants who reported to have a first-degree family relative diagnosed with a hematologic malignancy >30 years to be screened
MALDI-TOF Mass spec is sensitive and specific

Stacked mass spectra from MALDI-TOF MS and confirmatory LC-MS of monoclonal light chains observed in the heavy chain (blue trace) and the monoclonal light chains observed in the light chain (pink trace) in a sample from a PROMISE study participant.
No Increase in Cancer Worry after Screening Positive

Cancer worry assessed pre- and post-screening using 4-item scale adapted from the Lerman Breast Cancer Worry Scale

- Cancer worry assessed after receiving a diagnosis of MGUS was not significantly different than cancer worry pre-screening (paired t-test p-value=0.52)
No Difference in Quality of Life Between Positive and Negative Participants

**Quality of Life** assessed post screening using the RAND 36-item Short Form Health Survey (SF-36)

- No significant differences observed between screen-positive vs screen-negative participants for any of the following sub-scales (all p>0.2)
  - Physical functioning
  - Role limitations due to physical health
  - Role limitations due to emotional problems
  - Energy/Fatigue
  - Emotional well-being
  - Social functioning
  - Pain
  - General health
Argument for screening for myeloma

- Early therapeutic intervention can improve PFS/prevents CRAB morbidity
- Early detection of MGUS can help identify those at risk of developing MM
- Screening of high-risk individuals can show a high prevalence rate >10%
- Screening is sensitive and specific
- The cost of yearly follow up is significantly lower than the cost of active therapy of MM with comorbidities (renal failure, fractures, etc)
- No evidence of increased worry or change in QOL
A Message from our Promise Participants

www.promisestudy.org