IgM MGUS & Smoldering WM: How Understanding Precursors can Help in Finding a Cure

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Dana-Farber
Cancer Institute

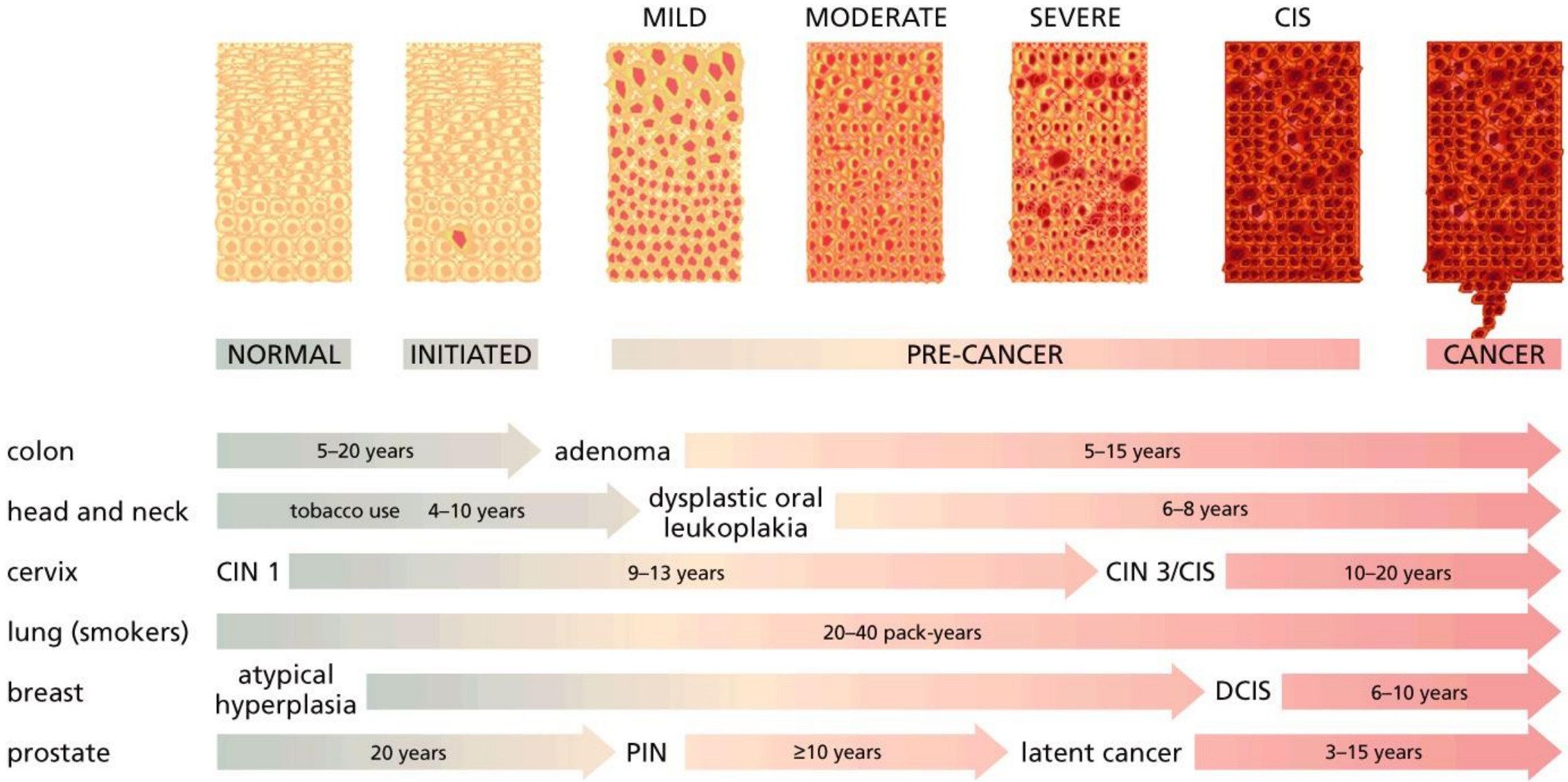
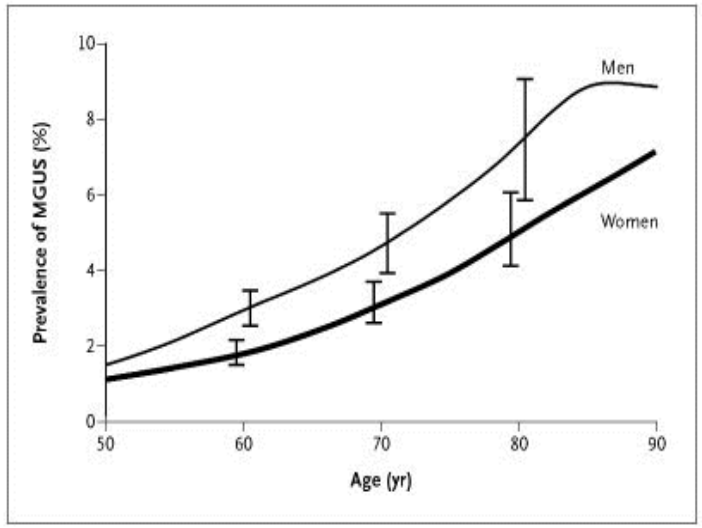
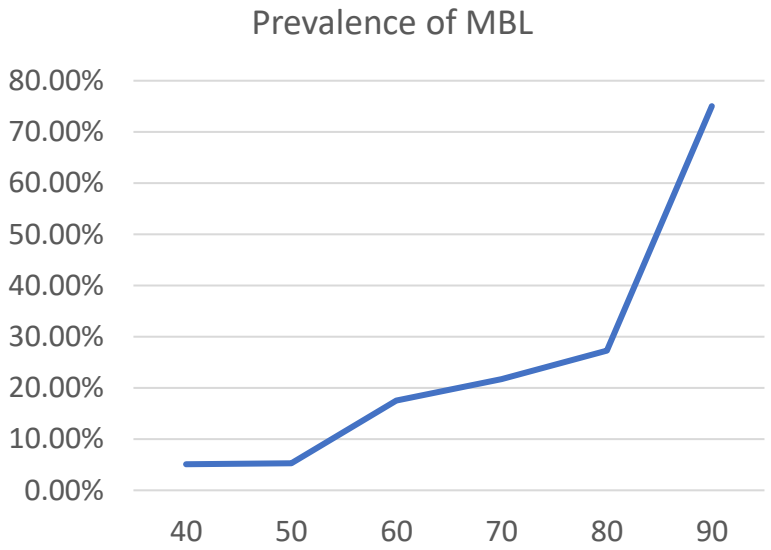
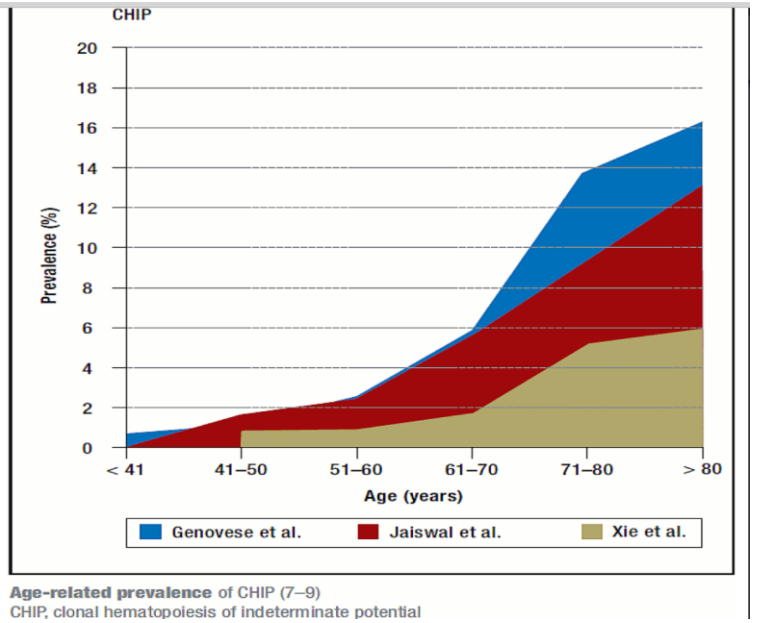


Figure 11.8a The Biology of Cancer (© Garland Science 2014)

Comparison of hematologic precursor states







Age-related prevalence of CHIP (7–9)
CHIP, clonal hematopoiesis of indeterminate potential

Incidence of monoclonal gammopathy of undetermined significance (MGUS)

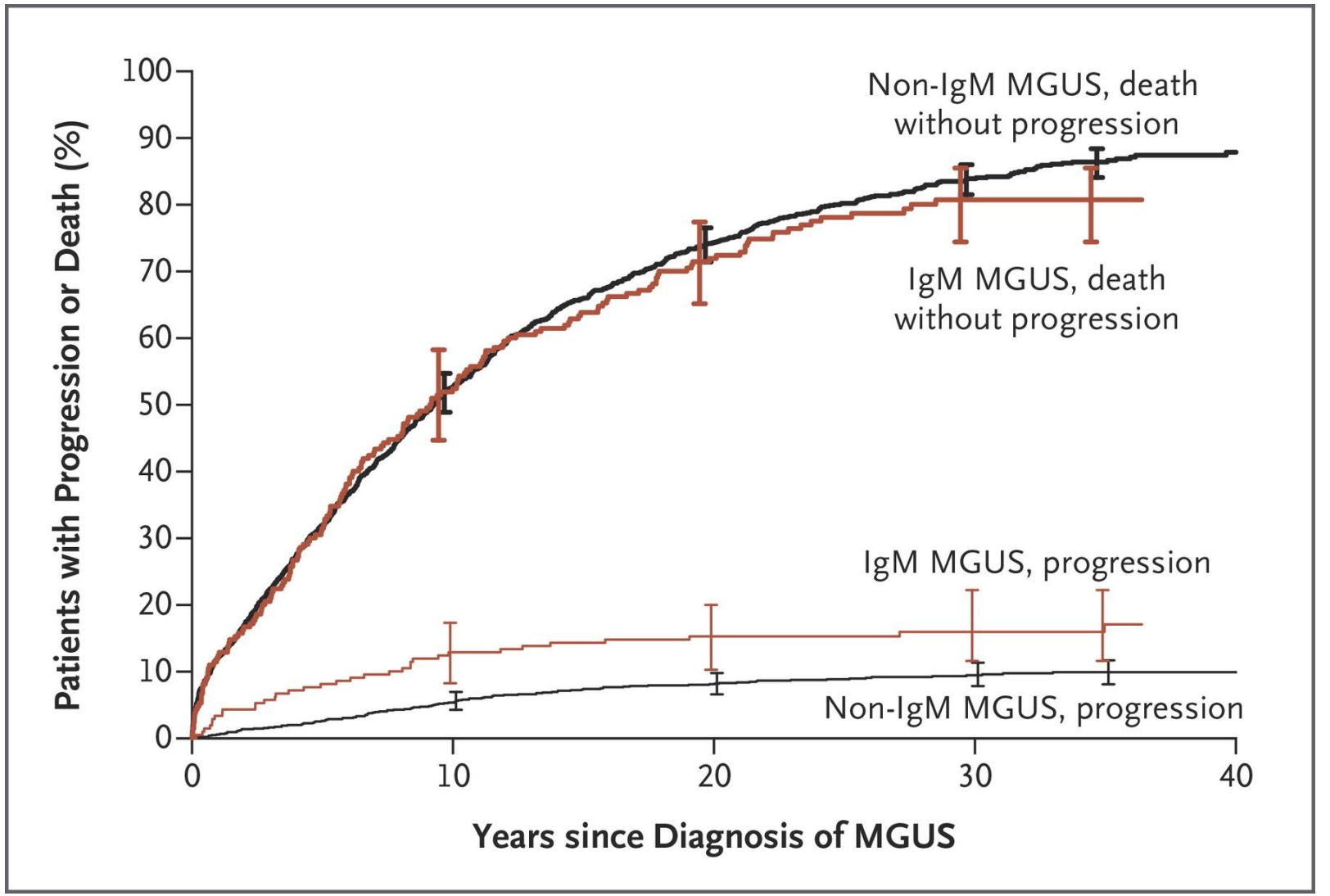
Incidence of monoclonal B cell lymphocytosis (MBL)

Incidence of mutations in preleukemic driver genes… clonal hematopoiesis of indeterminate potential (CHIP)

Kyle R et al *NEJM* 2006

Nieto WG et al *Blood* 2009

Risk of progression in IgM MGUS



Kyle et al., NEJM 2018

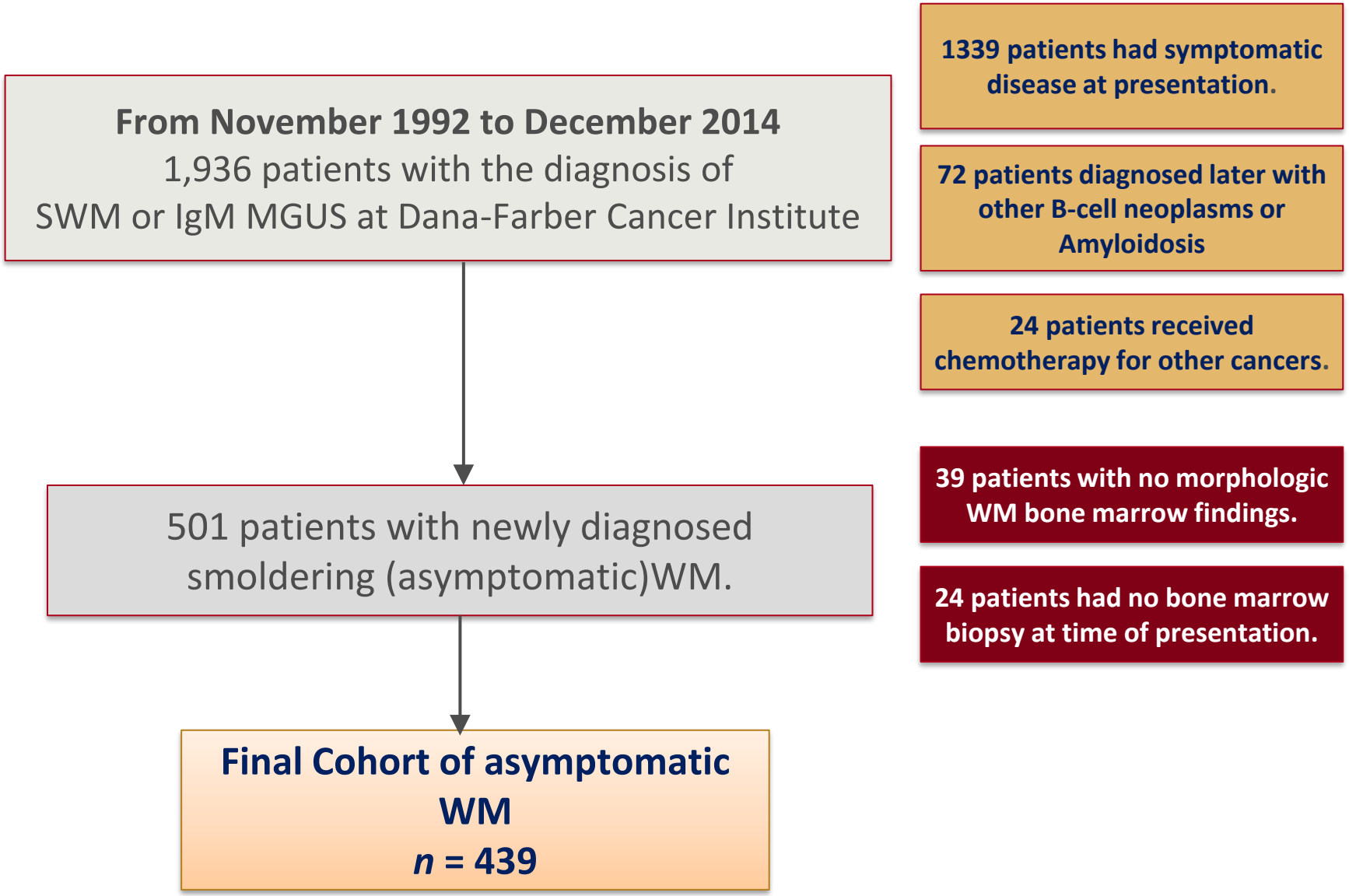
Risk of progression in IgM MGUS

Table 2. Risk and Type of Progression.*

End Point, in Entire Cohort and According to MGUS Type	Observed No. of Patients	Expected No. of Patients	Relative Risk (95% CI)
Entire cohort			
Any progression	147	22.5	6.5 (5.5–7.7)
Multiple myeloma	97	4.1	23.8 (19.3–29.1)
Non-Hodgkin's lymphoma	19	11.6	1.6 (1.0–2.6)
AL amyloidosis	14	1.6	8.8 (4.8–14.7)
Waldenström's macroglobulinemia	13	0.3	47.5 (25.3–81.3)
Chronic lymphocytic leukemia	3	4.9	0.6 (0.1–1.8)
Plasmacytoma	1	0.1	12.6 (0.3–70.2)
IgM MGUS			
Any progression	34	3.2	10.8 (7.5–15.0)
Multiple myeloma	0	0.6	0.0 (0.0–6.5)
Non-Hodgkin's lymphoma	17	1.6	10.6 (6.2–17.0)
AL amyloidosis	3	0.2	13.1 (2.7–38.1)
Waldenström's macroglobulinemia	11	<0.1	287.7 (143.6–514.7)
Chronic lymphocytic leukemia	3	0.7	4.3 (0.9–12.6)
Plasmacytoma	0	<0.1	0.0 (0.0–342.6)
Non-IgM MGUS			
Any progression	107	18.7	5.7 (4.7–6.9)
Multiple myeloma	93	3.4	27.5 (22.2–33.7)
Non-Hodgkin's lymphoma	2	9.6	0.2 (0.0–0.7)
AL amyloidosis	11	1.3	8.3 (4.2–14.9)
Waldenström's macroglobulinemia	0	0.2	0.0 (0.0–16.2)
Chronic lymphocytic leukemia	0	4.1	0.0 (0.0–0.9)
Plasmacytoma	1	0.1	15.0 (0.4–83.7)

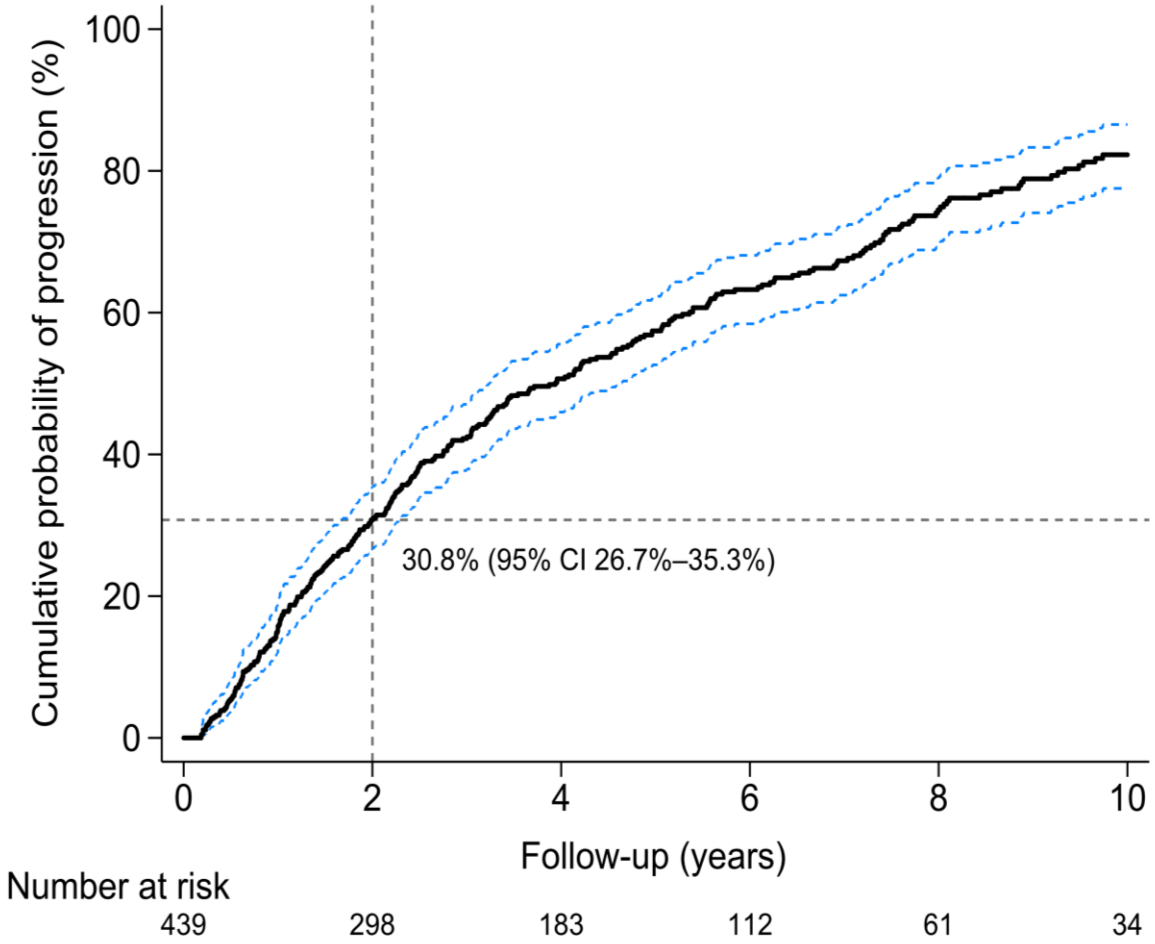
Kyle et al., NEJM 2018

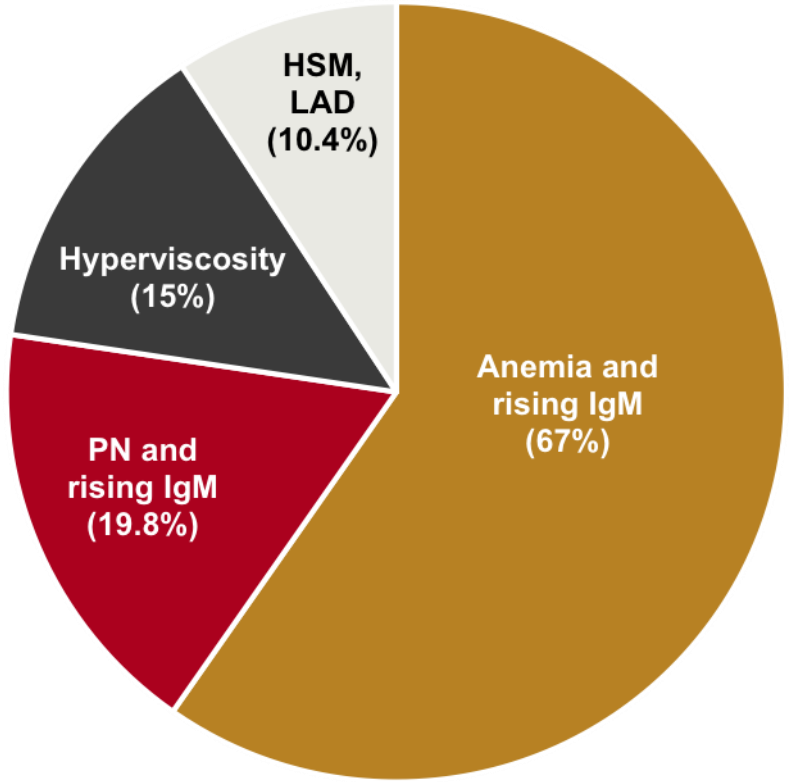
Smoldering Waldenstrom Macroglobulinemia



Bustoros et al., JCO 2019

Cumulative probability of progression among SWM patients





Indications of progression and treatment initiation

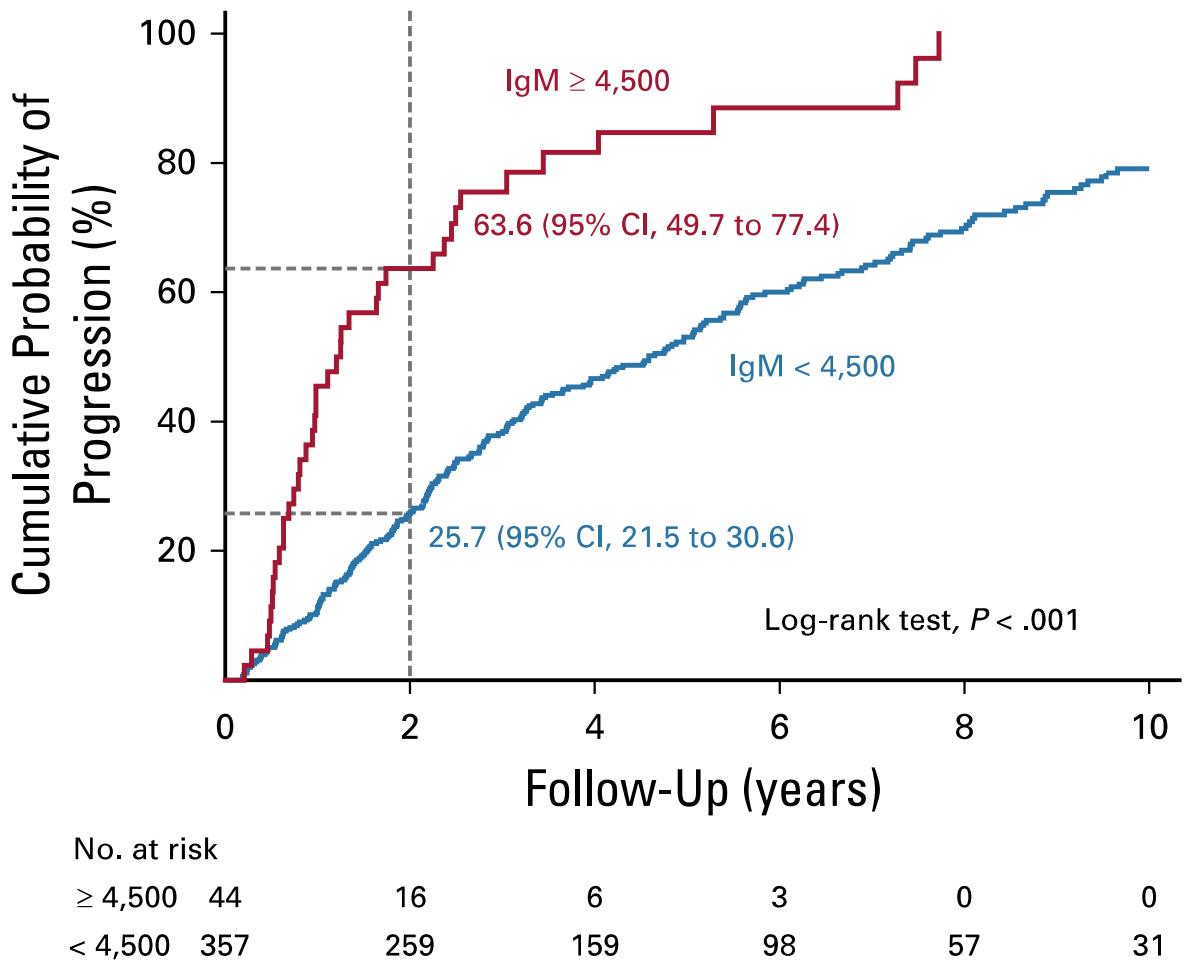
Bustoros et al., JCO 2019

Baseline patient characteristics

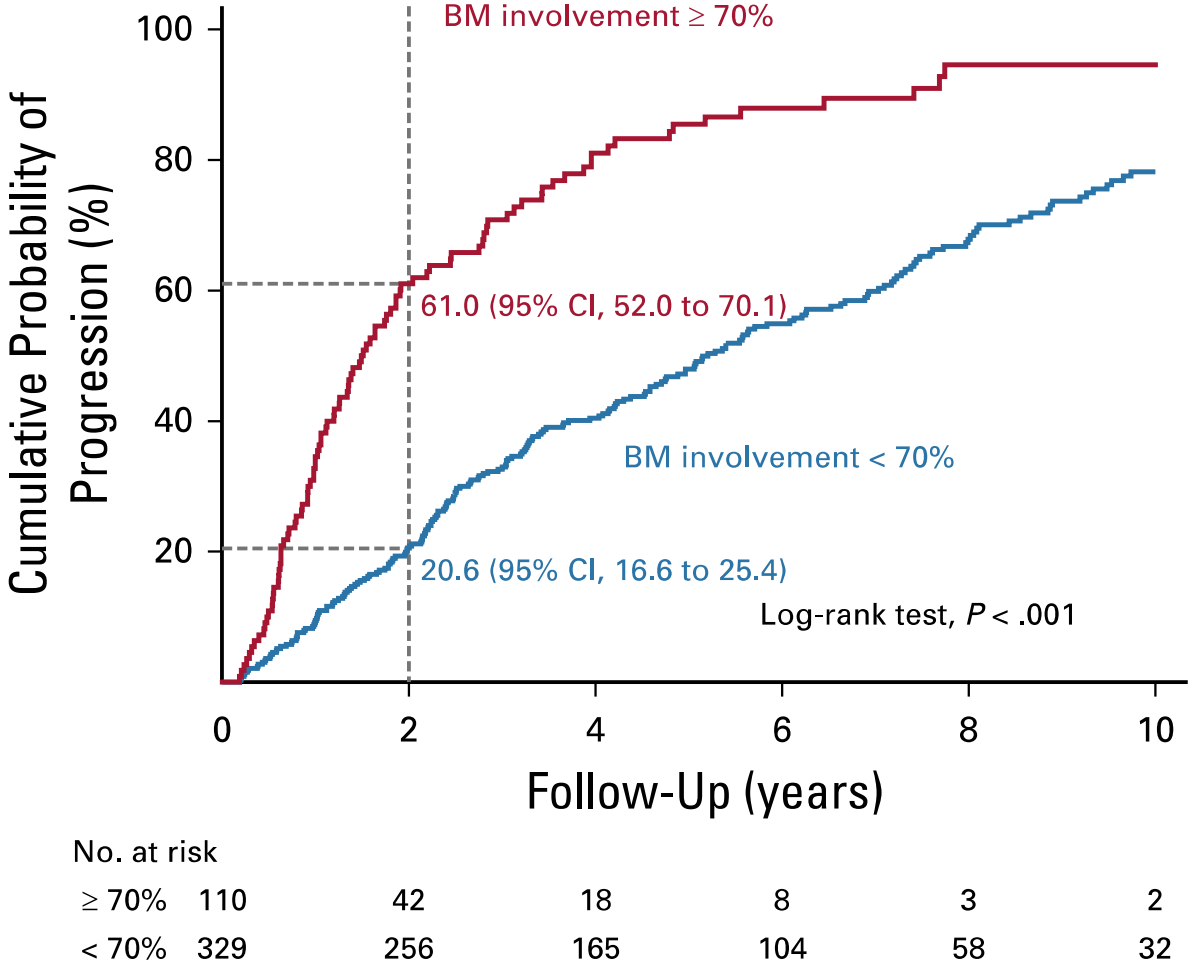
Characteristics	Total (n = 439) n	%
Median age, years (range)	61 (26–91)	
Male sex	311	62.1
Autoimmune	134	26.9
Family history for WM	42	8.4
Family history of blood cancer	95	19.0
Ashkenazi Jewish/ Eastern European	131/178	30, 41

Characteristics	Total (n = 439) Median (IQR)	%
IgM (Median)	2196 (1170–3440)	
M-protein (Median)	1.6 (0.9–2.3)	
BM involvement percentage (Median)	40 (20–70)	
≥ 70%	110	25.1
β2-microglobulin, mg/dL	2.2 (1.8–2.9)	
≥ 4.0	16	4.6
Albumin	4.1 (3.8–4.3)	
< 3.5	28	6.4
Hemoglobin	12.6 (11.6–13.3)	
< 11.5	81	18.5
Lactate dehydrogenase	138.0 (118.0–181.0)	

Risk factors for progression



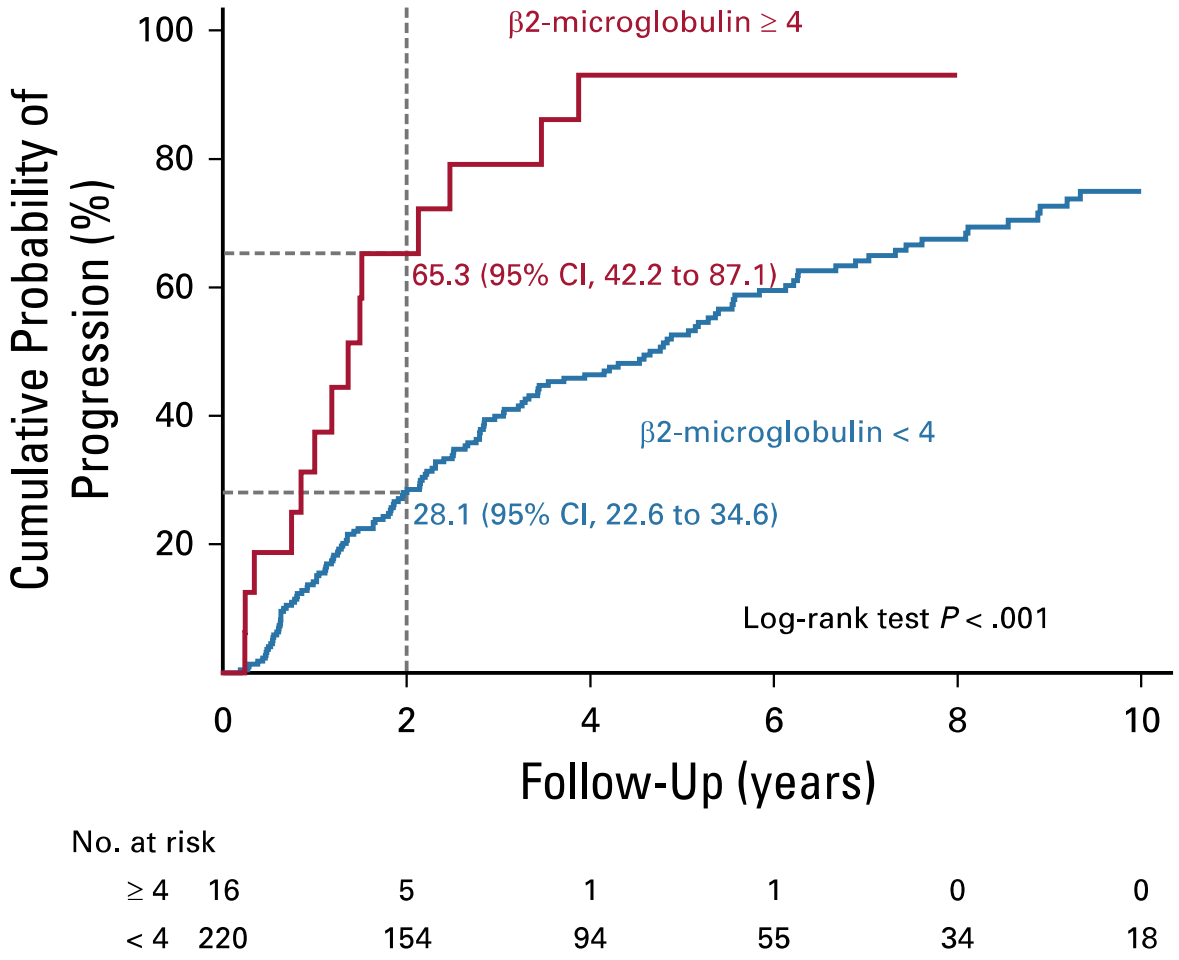
No. at risk						
≥ 4,500	44	16	6	3	0	0
< 4,500	357	259	159	98	57	31



No. at risk						
≥ 70%	110	42	18	8	3	2
< 70%	329	256	165	104	58	32

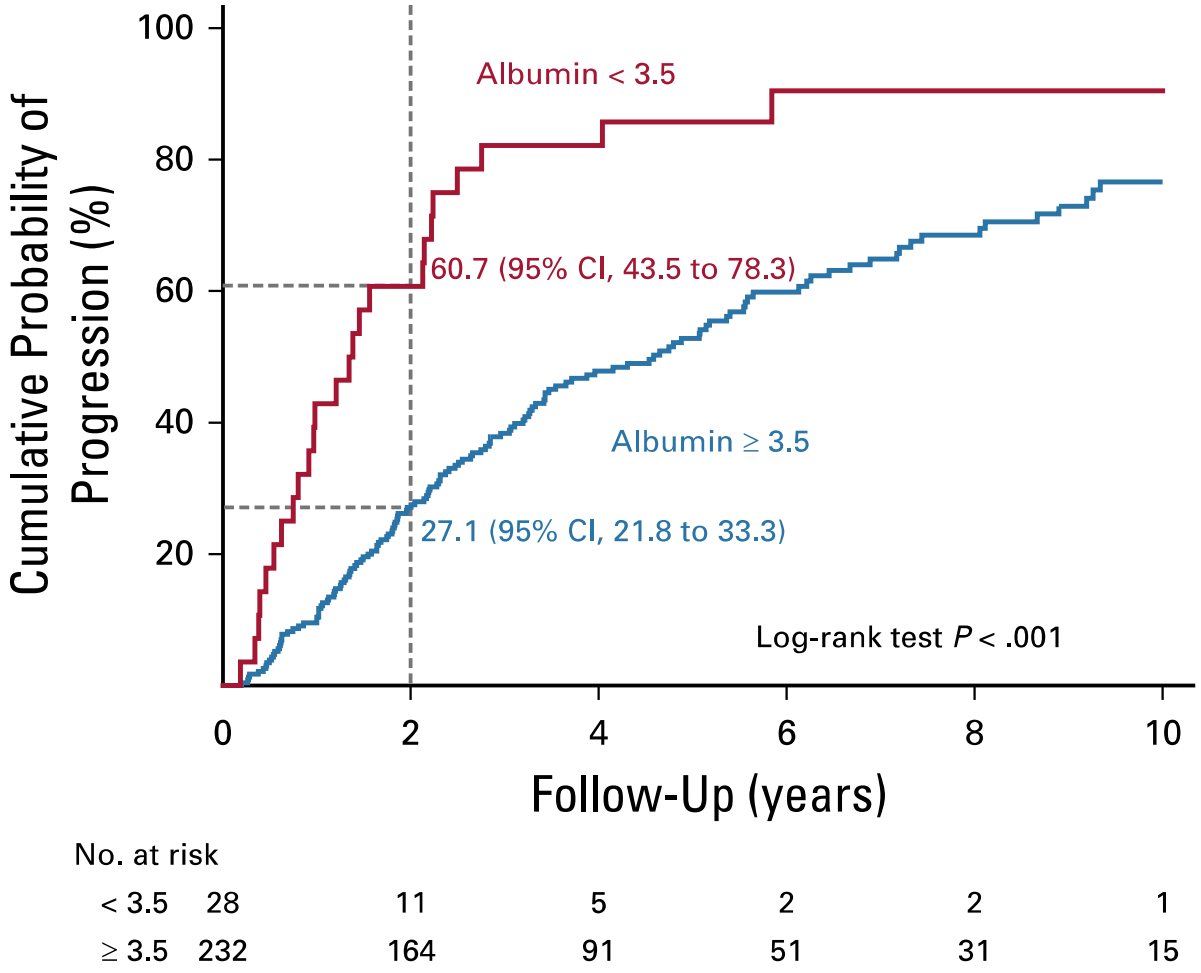
Bustoros et al., JCO 2019

Risk factors for progression



No. at risk

≥ 4	16	5	1	1	0	0
< 4	220	154	94	55	34	18

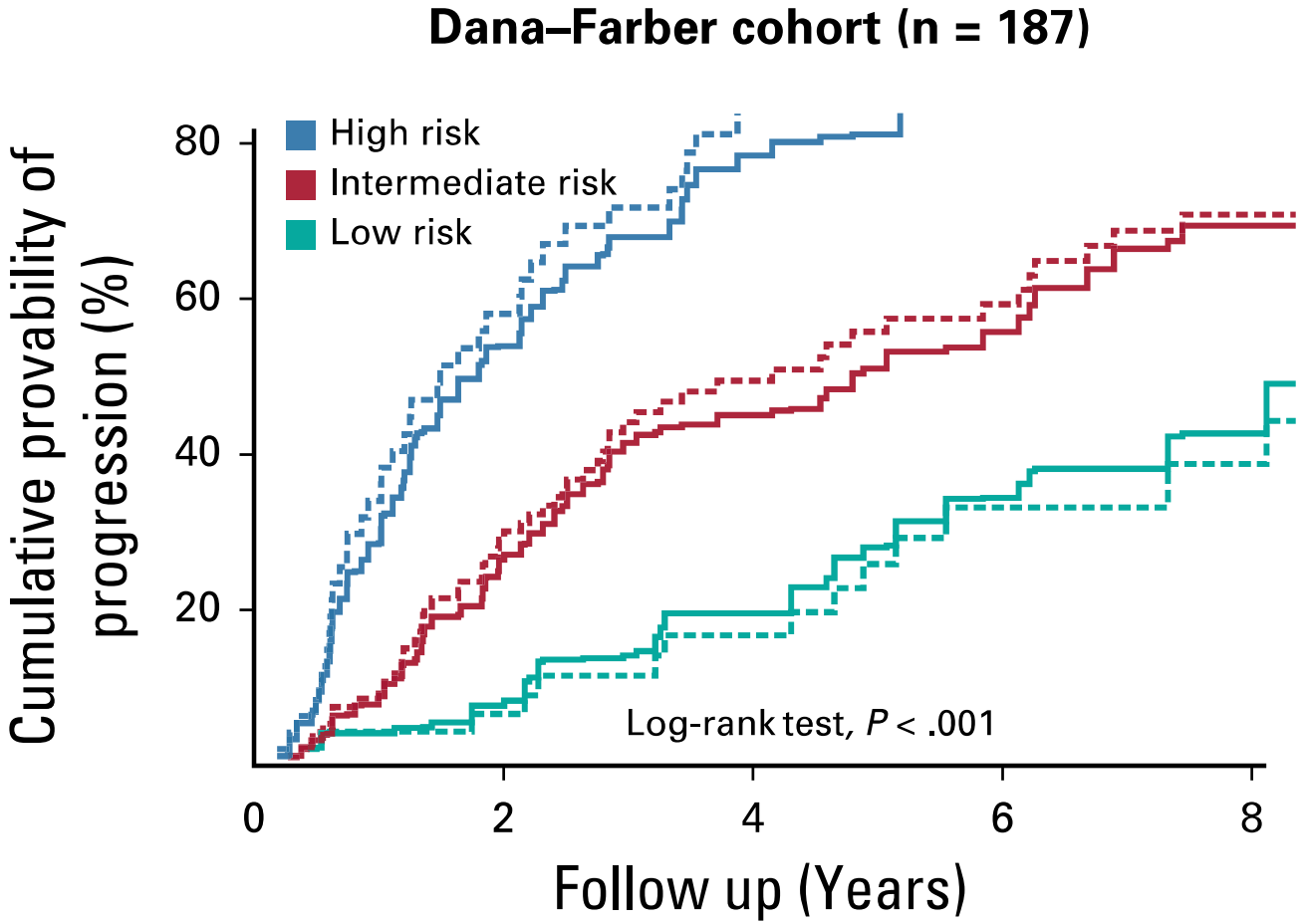


No. at risk

< 3.5	28	11	5	2	2	1
≥ 3.5	232	164	91	51	31	15

Bustoros et al., JCO 2019

A continuous proportional hazards risk model

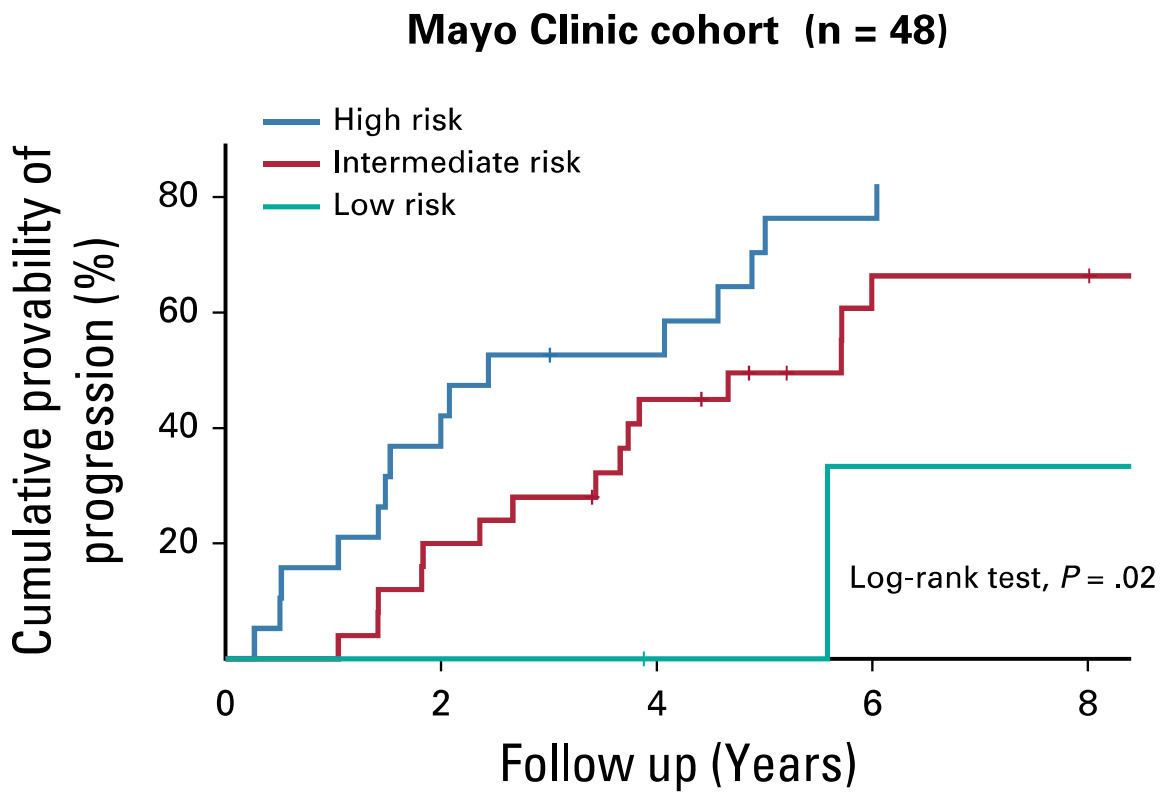


No at risk:					
High-risk:	47	19	6	1	1
Intermediate-risk:	93	66	36	22	11
Low-risk:	47	40	29	16	11

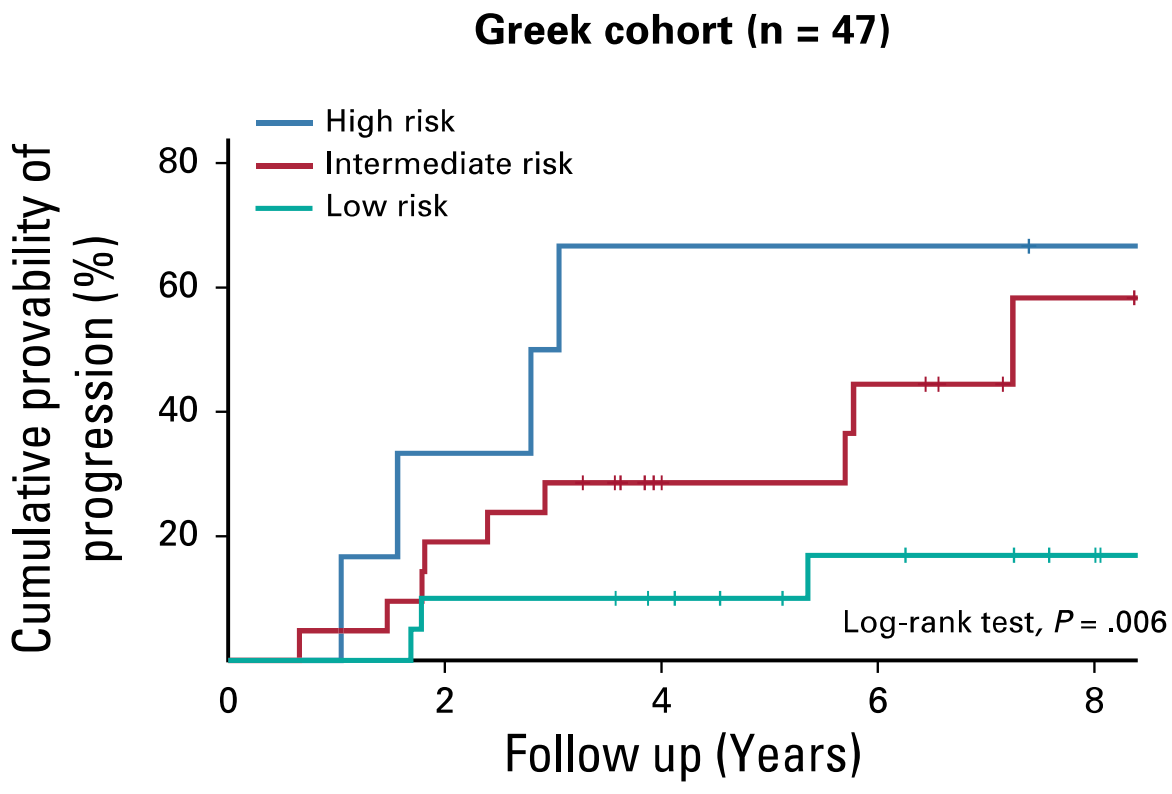
Risk group	Median time to progression
High-risk	1.9 years (95% CI 1.0 - 2.2)
Intermediate-risk	4.8 years (95% CI 2.8 - 6.2)
Low-risk	9.3 years (95% CI 5.6 - 9.4)

Bustoros et al., JCO 2019

External validation of the risk model



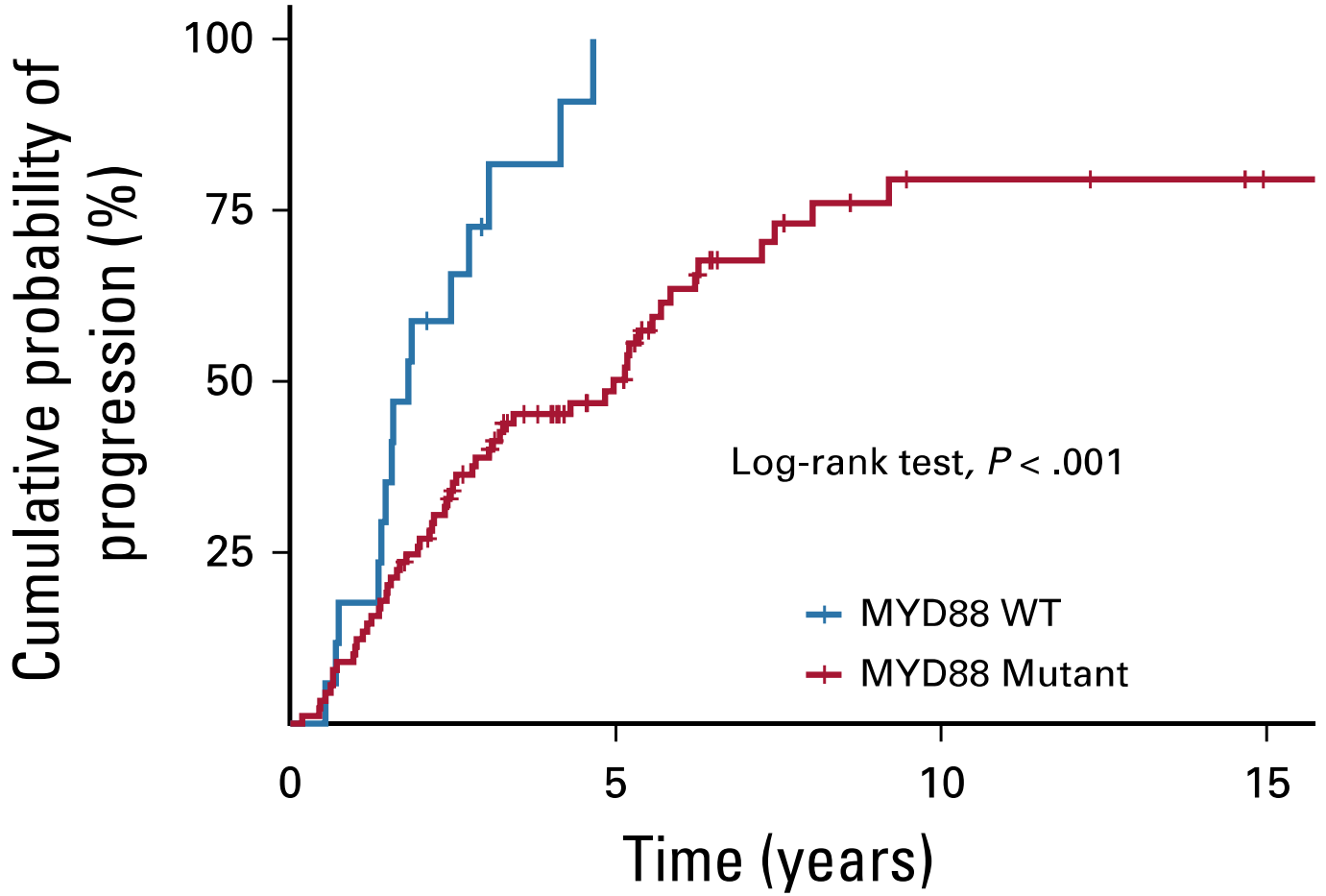
No at risk:					
High-risk:	20	12	8	4	3
Intermediate-risk:	24	19	13	6	6
Low-risk:	4	4	3	2	2



No at risk:					
High-risk:	6	4	2	2	1
Intermediate-risk:	21	17	10	7	3
Low-risk:	20	18	16	12	9

Bustoros et al., JCO 2019

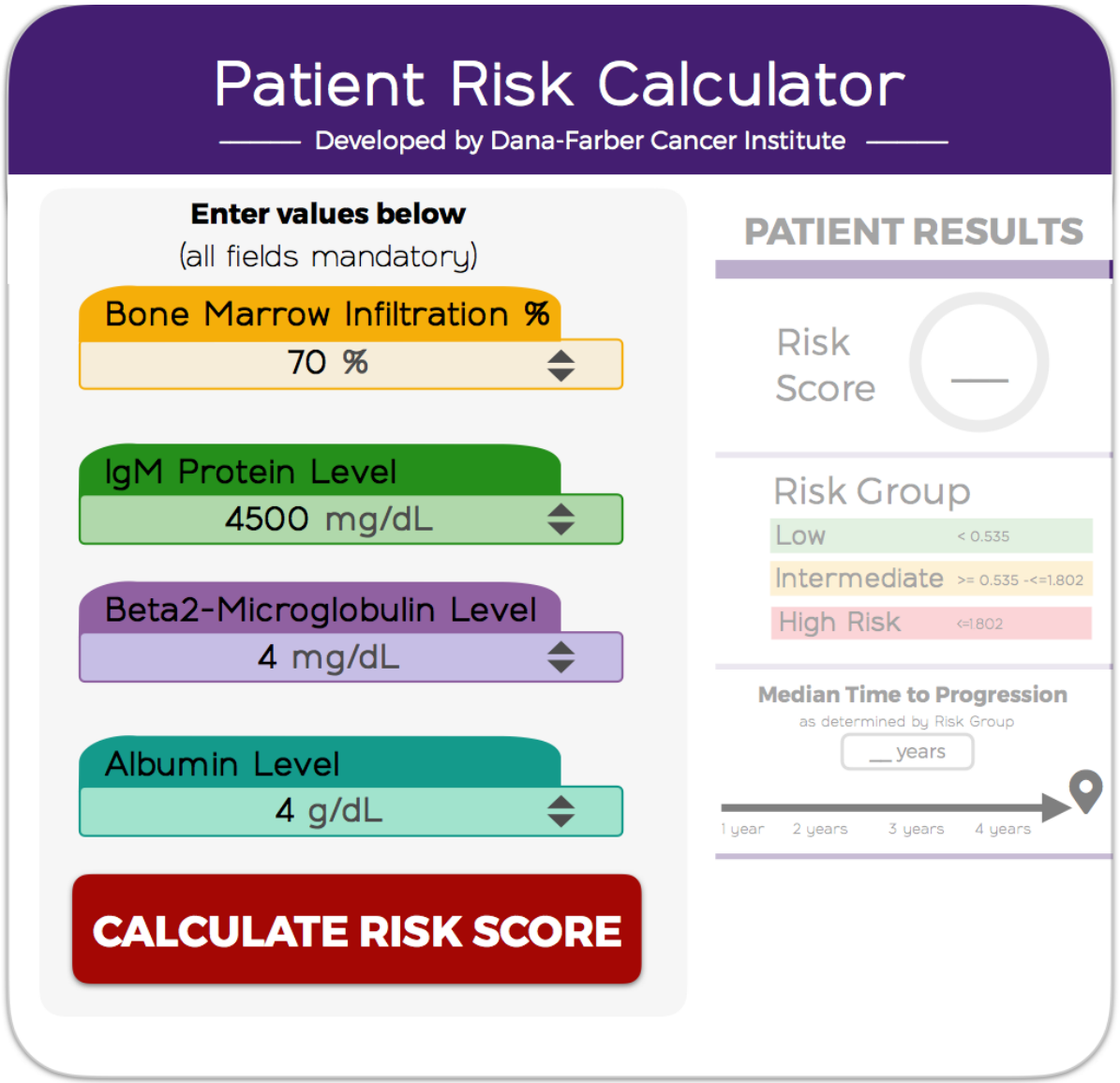
MYD88^{L265P} mutation status is a predictor of progression

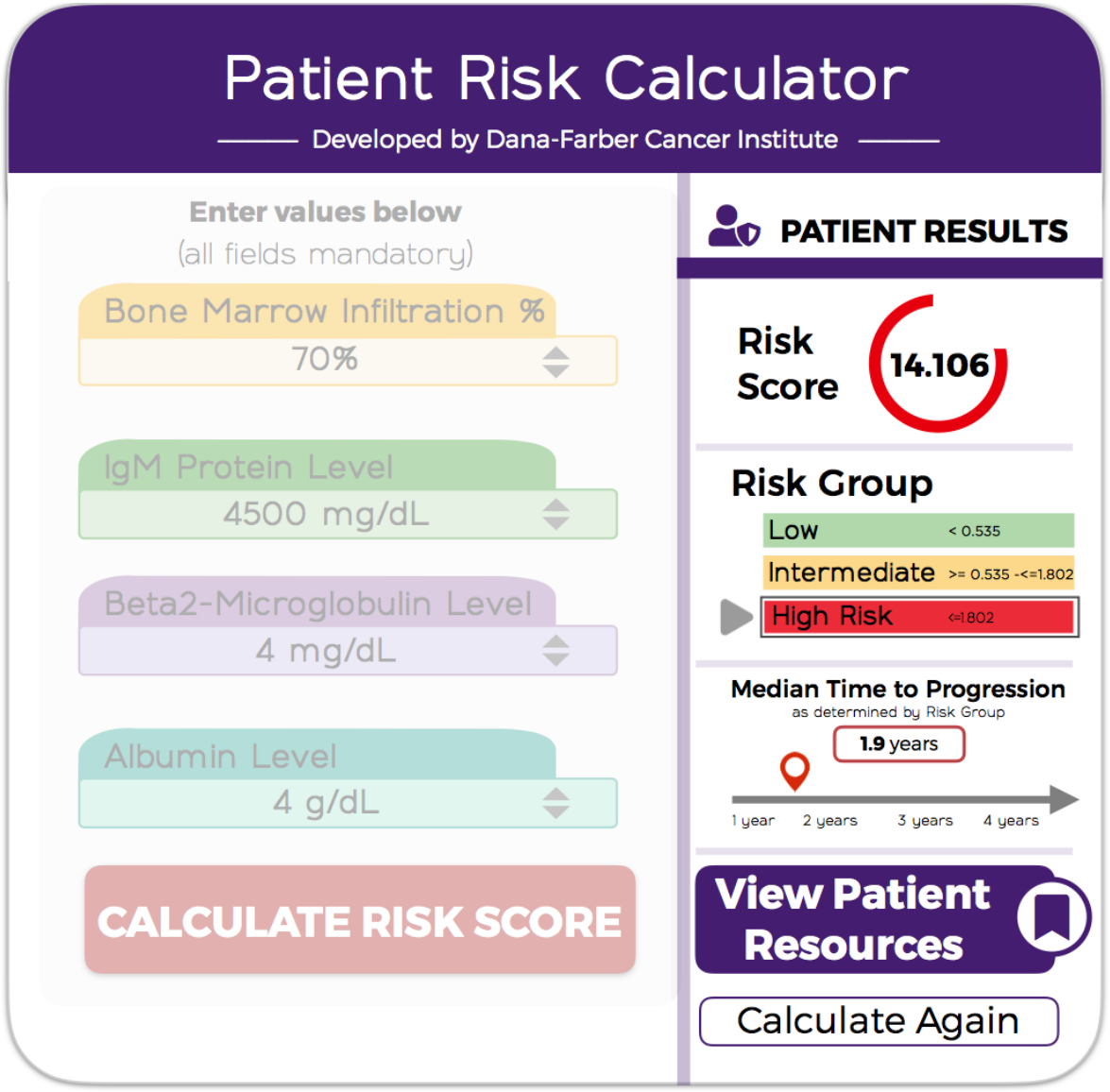


No. at risk				
MYD88 (WT)	17	0	0	0
MYD88 (Mut)	89	29	5	2

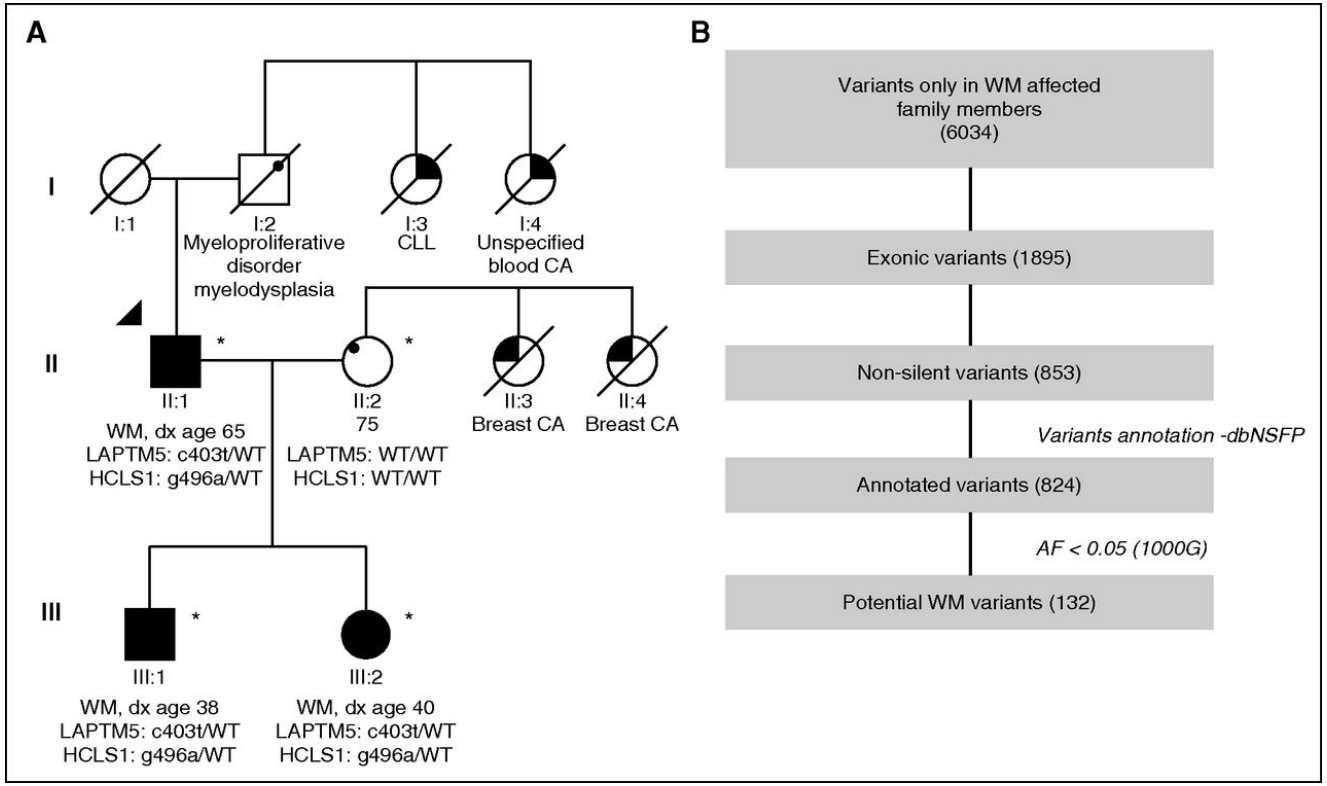
Bustoros et al., JCO 2019

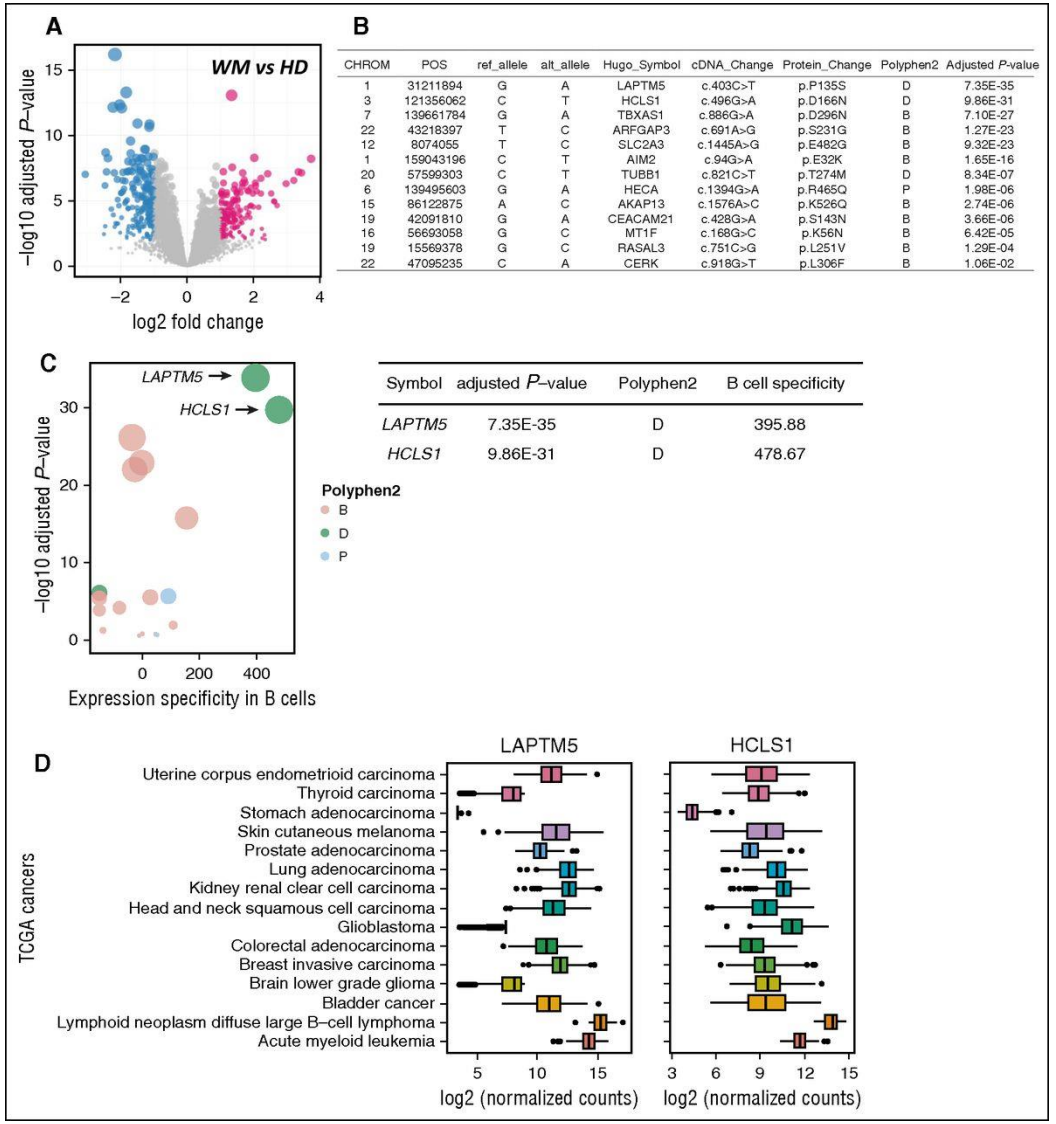
A web-based application (www.awmrisk.com)





Familial WM cases



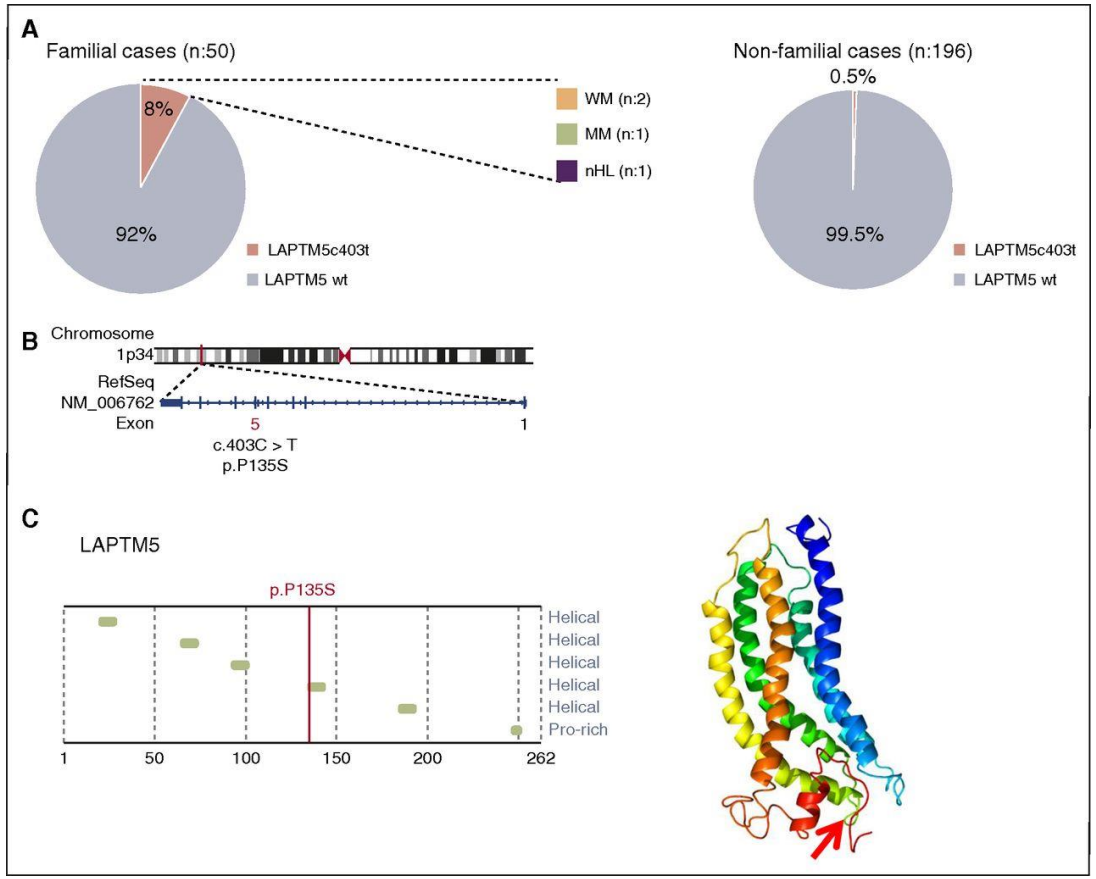


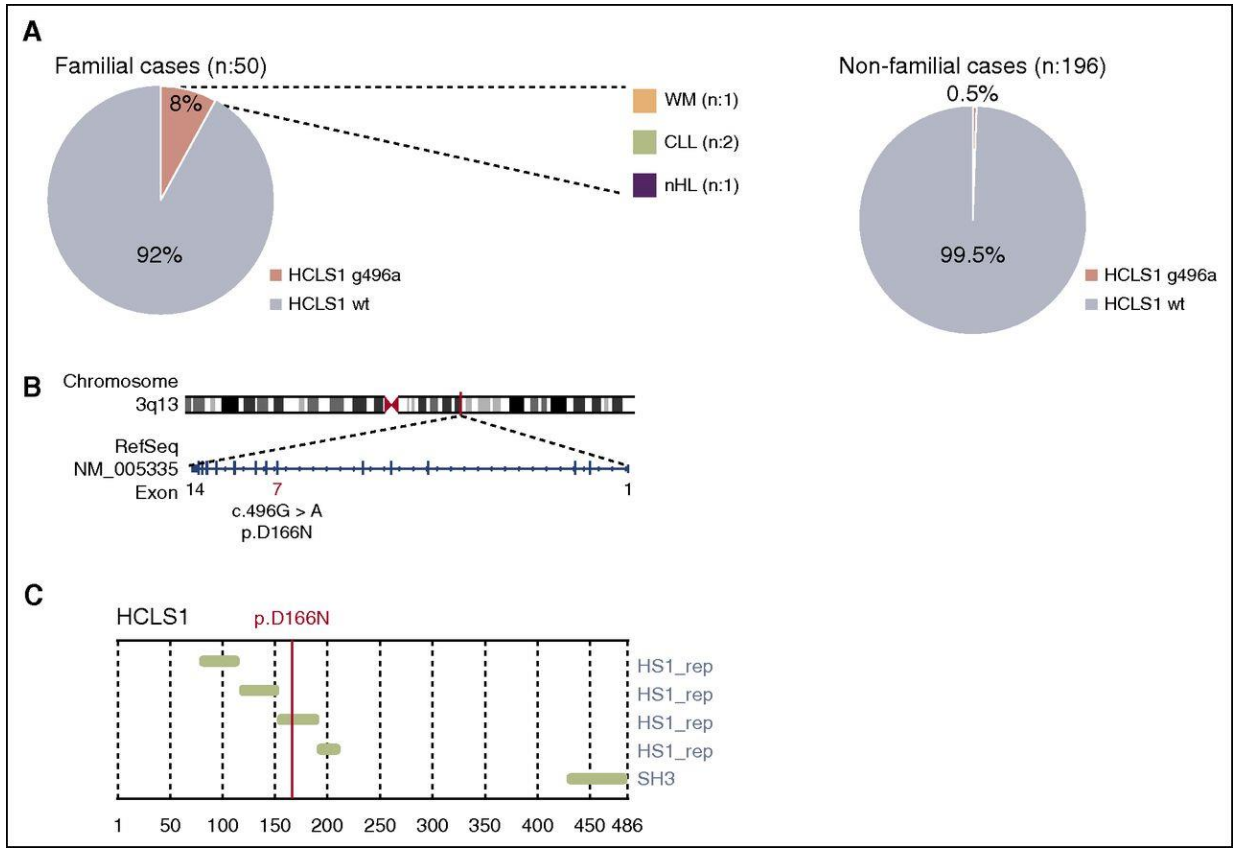
CHROM	POS	ref_allele	alt_allele	Hugo_Symbol	cDNA_Change	Protein_Change	Polyphen2	Adjusted *P*-value
1	31211894	G	A	LAPTM5	c.403C>T	p.P135S	D	7.35E-35
3	121356062	C	T	HCLS1	c.496G>A	p.D166N	D	9.86E-31
7	139661784	G	A	TBXAS1	c.886G>A	p.D296N	B	7.10E-27
22	43218397	T	C	ARFGAP3	c.691A>G	p.S231G	B	1.27E-23
12	8074055	T	C	SLC2A3	c.1445A>G	p.E482G	B	9.32E-23
1	159043196	C	T	AIM2	c.94G>A	p.E32K	B	1.65E-16
20	57599303	C	T	TUBB1	c.821C>T	p.T274M	D	8.34E-07
6	139495603	G	A	HECA	c.1394G>A	p.R465Q	P	1.98E-06
15	86122875	A	C	AKAP13	c.1576A>C	p.K526Q	B	2.74E-06
19	42091810	G	A	CEACAM21	c.428G>A	p.S143N	B	3.66E-06
16	56693058	G	C	MT1F	c.168G>C	p.K56N	B	6.42E-05
19	15569378	G	C	RASAL3	c.751C>G	p.L251V	B	1.29E-04
22	47095235	C	A	CERK	c.918G>T	p.L306F	B	1.06E-02

Symbol	adjusted *P*–value	Polyphen2	B cell specificity
LAPTM5	7.35E-35	D	395.88
HCLS1	9.86E-31	D	478.67

Roccaro et al, Blood 2016

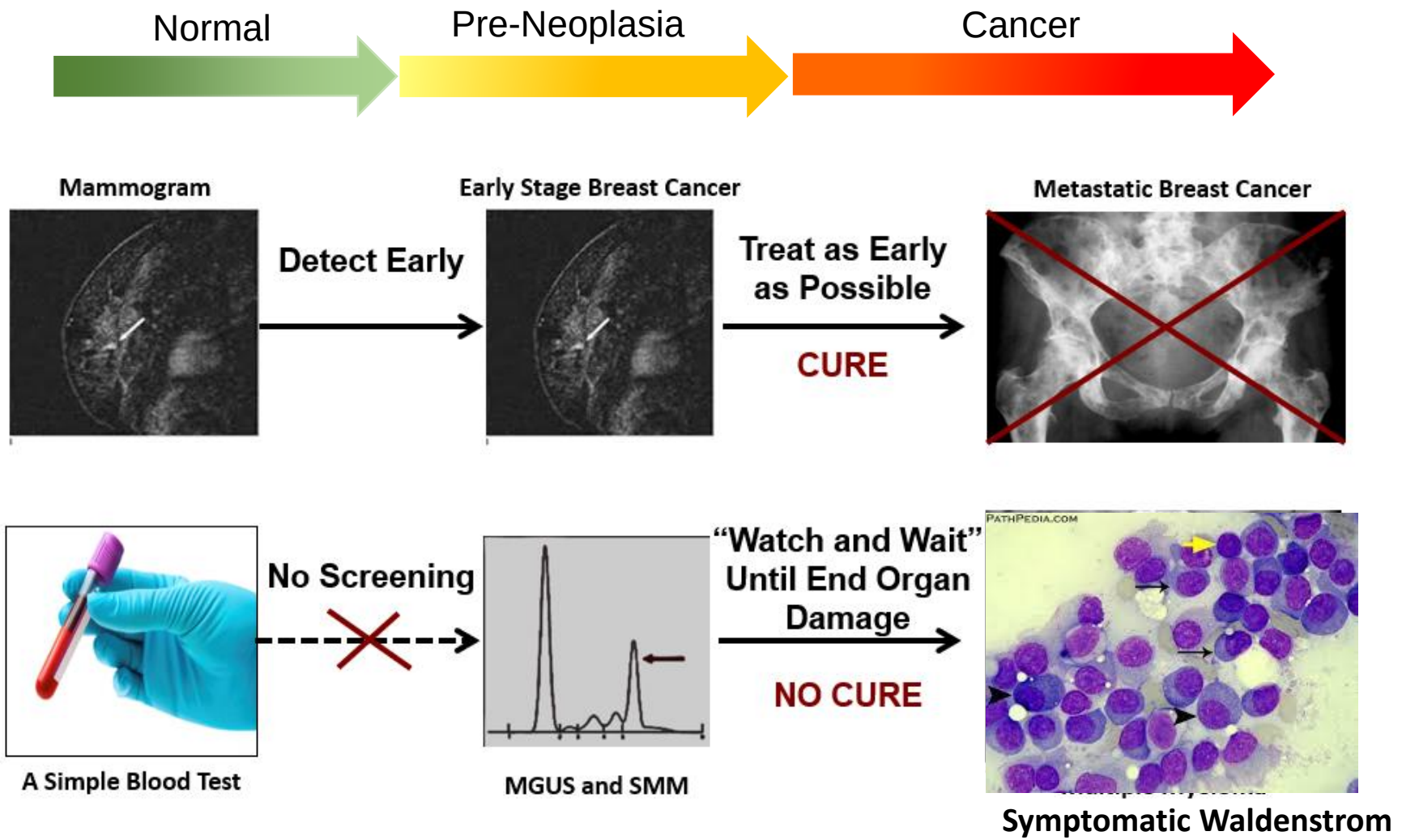
Familial WM cases





Roccaro et al, Blood 2016

Early Screening for Cancer Detection



New CPOP Clinic
(Center for Prevention of Progression of Blood Cancers)

Features

<u>Aim and scope of clinic:</u> To actively study patients with precursor hematological malignancies and define mechanisms/therapies that prevent progression.
<u>Goal:</u> 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 & clinical care**

PCROWD

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DANA-FARBER CANCER INSTITUTE

We're on a mission to stop blood cancer before it starts

Help Fight Blood Cancer

JOIN THE STUDY

Enroll Now >

PCROWD is a medical research data bank.
We study blood samples and analyze data about
early phases of blood conditions that may develop into cancer.
These early conditions are called precursor conditions

pcrowd.dana-farber.org/

THE PROMISE STUDY

Help stop Waldenström's macroglobulinemia

– before it starts.

The PROMISE Study is a collaborative research project screening individuals at higher risk for Waldenström's macroglobulinemia and multiple myeloma.

We're looking for people who DON'T HAVE CANCER, but may have higher risks.

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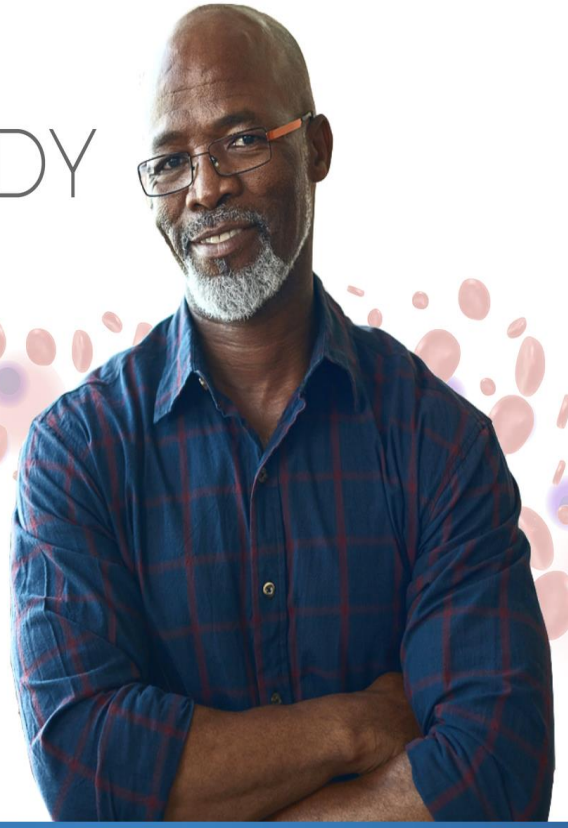
THE PROMISE STUDY

Will you join the mission to help stop myeloma before it starts?



See If You Qualify For A Free Screening

About the study

Who can join?

How do I join?

Got a question?
Offline

https://www.enroll.promisestudy.org

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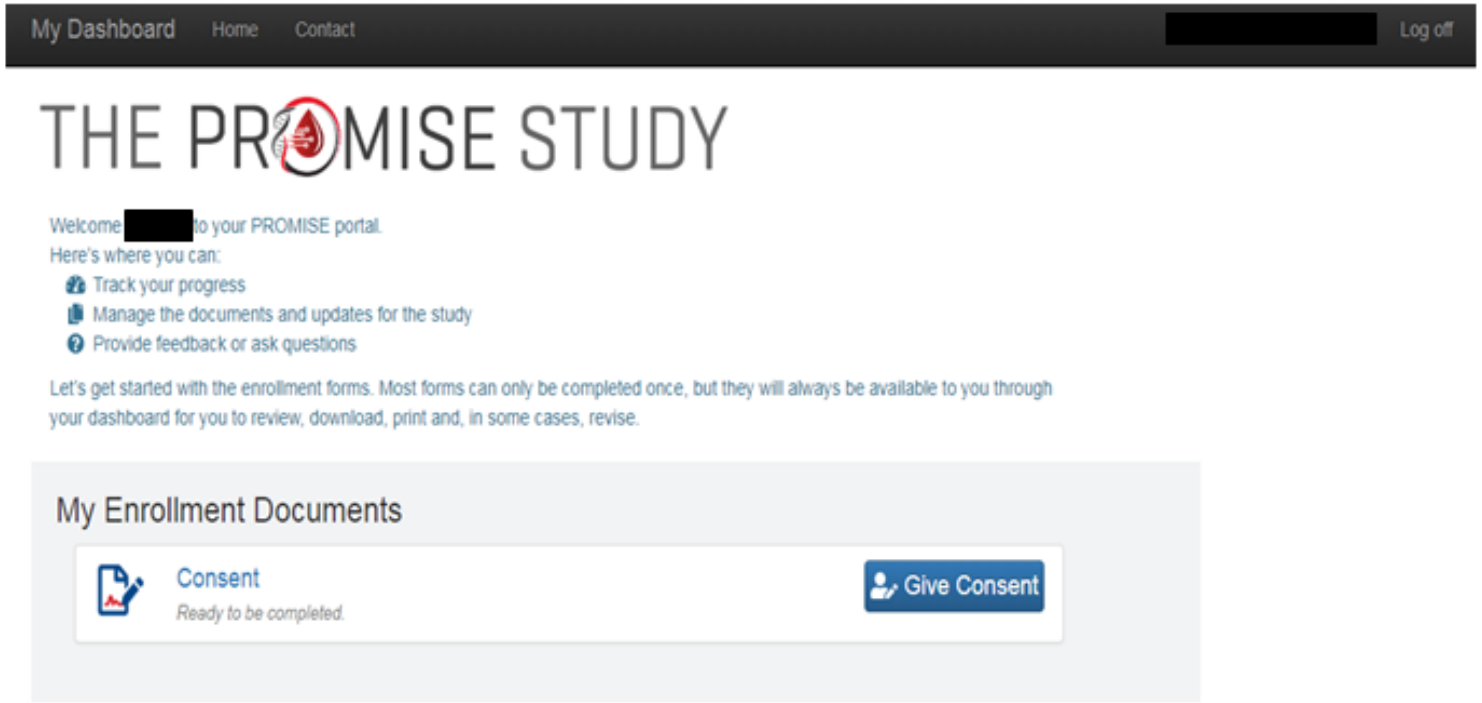
DANA-FARBER CANCER INSTITUTE PROMISE

Sign the Main Consent Form



THE PROMISE STUDY

Eligibility Criteria

Adults between 40 and 75 who are:

Individuals of African descent

Risks are 3 times higher for this group

Close Family Members

Risks are higher when a parent, sibling or child has myeloma or its precursor condition

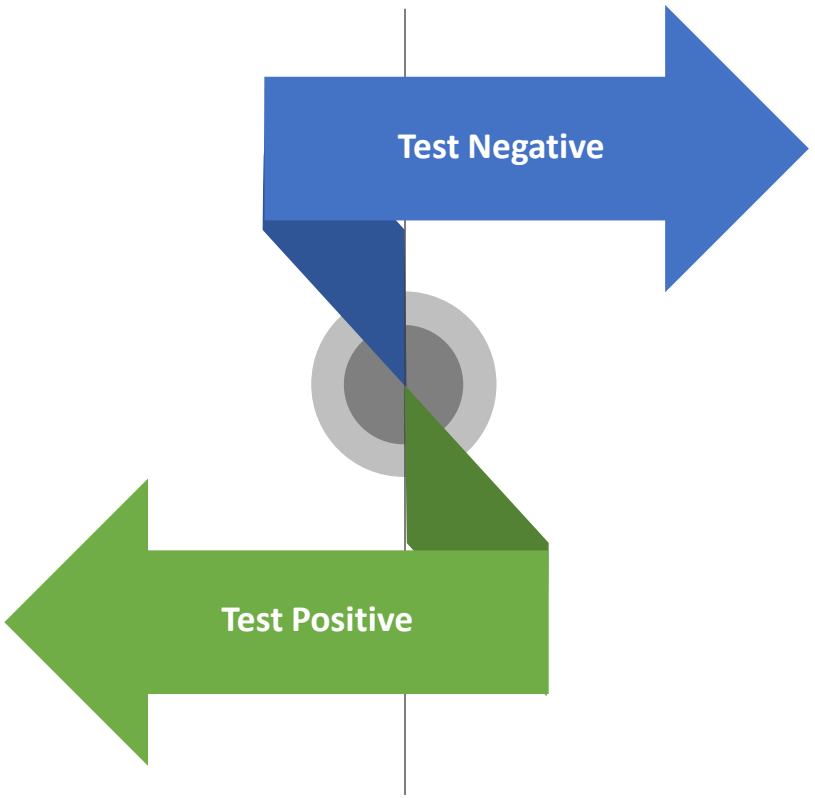
THE PROMISE STUDY

The **PROMISE** Study: Test Results

After the Mayo Clinic has tested the samples, the results are interpreted by our clinical team.

Positive Cohort

* The research nurse reaches out by phone to notify the participant and answer questions
* The participant signs the Positive Consent Form and completes their Baseline Questionnaire
* The participant finds a hematologist/oncologist for follow-up and samples are banked every few months



Negative Cohort

* Participants are notified via email of their negative result.
* Participants are asked to finish the remaining forms on their PROMISE Dashboard, notably the Baseline Questionnaire

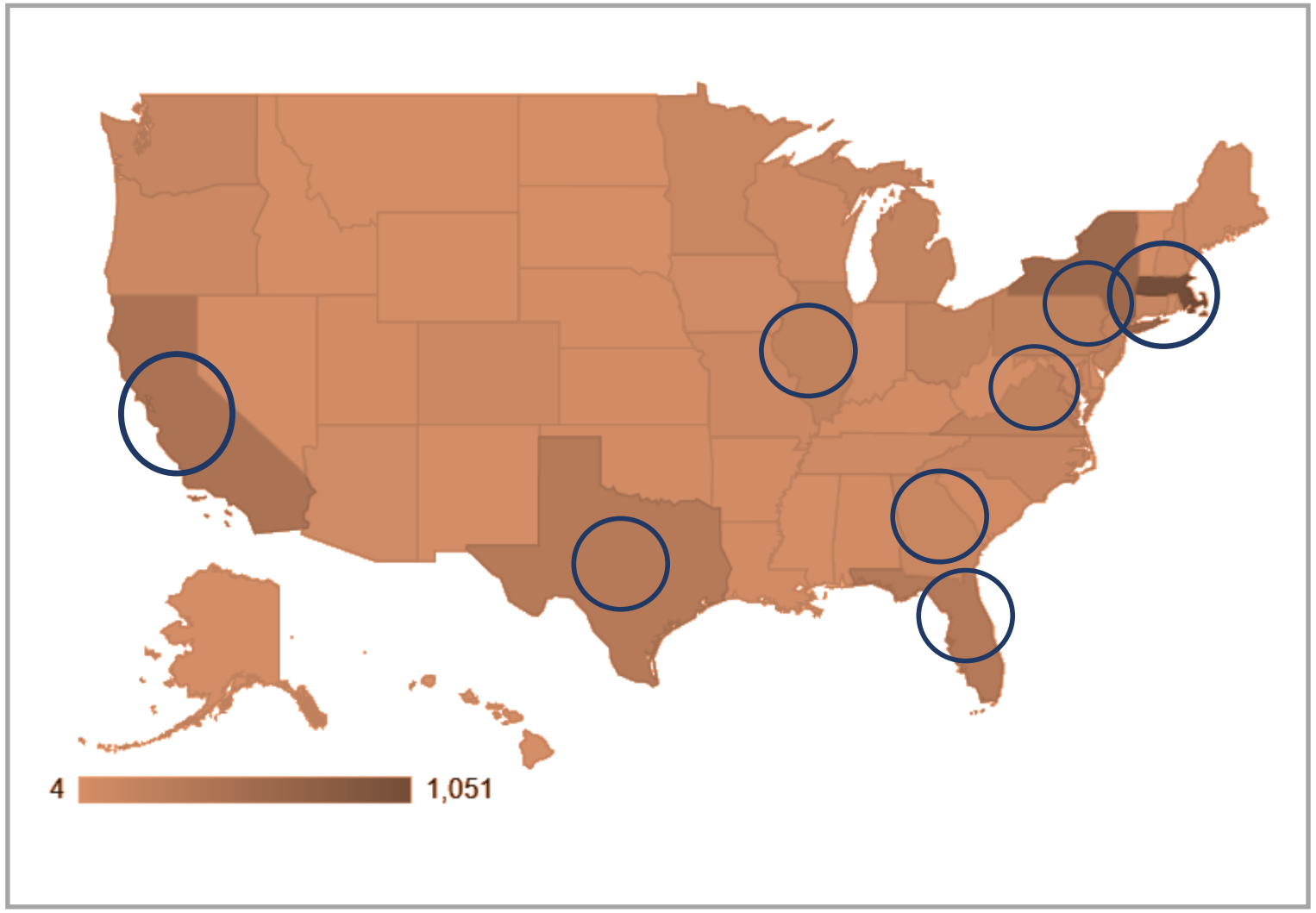
THE PROMISE STUDY

Share a Small Blood Sample

How to Use Your PROMISE Study Test Kit

Our team saw that some participants needed more information about how to use their blood draw kit, so we created a short video detailing how to repackage the blood samples.

United States WEBSITE Visitors



4,317 Unique visitors between August 2019-August 2020

9,180 Page views between August 2019-August 2020

- **12%** Massachusetts residents
- **7%** New York residents
- **8%** California residents
- **6%** Texas residents
- **6%** DC/Maryland/Virginia residents
- **5%** Florida residents
- **4%** Illinois residents
- **3%** Georgia residents

THE PROMISE STUDY

Changing the Multiple Myeloma Diagnosis

Specific Aims

Aim 1. The PROMISE Study

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

Screen Negative **47,000**

Screen Positive **3,000**

Prospective Follow-Up

Aim 2. Genomic Characteristics of MGUS/SMM

Viktor Adalsteinsson, Benjamin Ebert, Gaddy Getz, Irene Ghobrial

Aim 3. Race/Obesity on Precursor Progression

Lorelei Mucci, Tim Rebbeck, Catherine Marinac

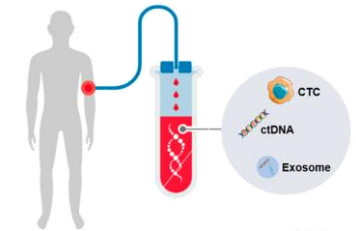
Aim 4. MGUS/SMM Permissive Microenvironment

Ivan Borrello, Irene Ghobrial

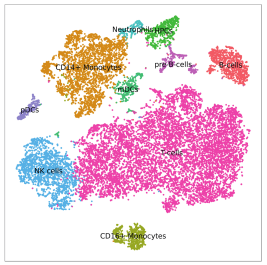
Aim 5. Imaging /Therapeutics For Detection/Interception

Jeremiah Johnson, Irene Ghobrial

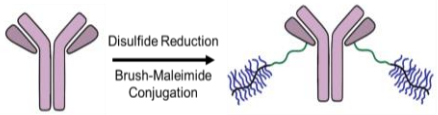
Develop novel **biomarkers for diagnosis**



Establish advanced **risk stratification**



Generate new tools to **prevent precursor progression**

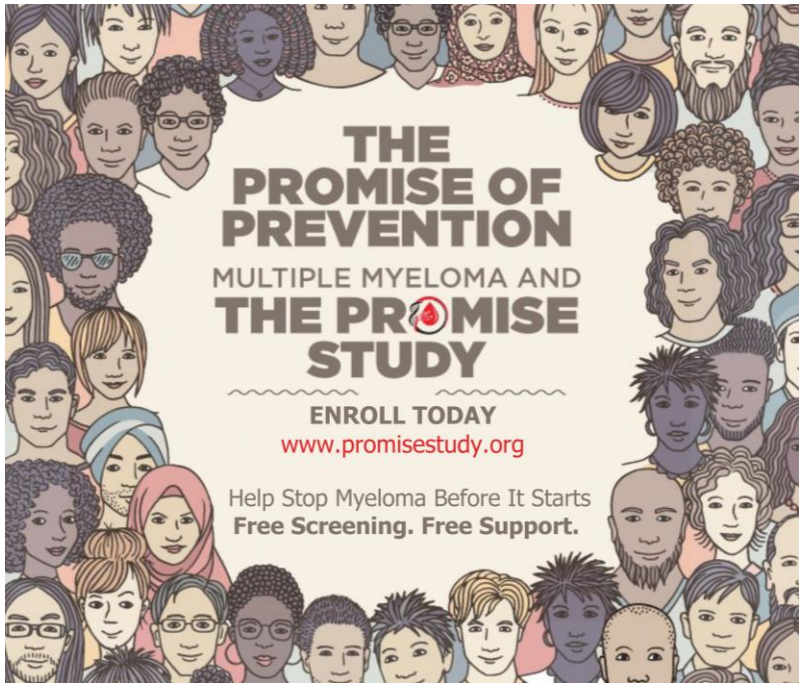


The PROMISE Study

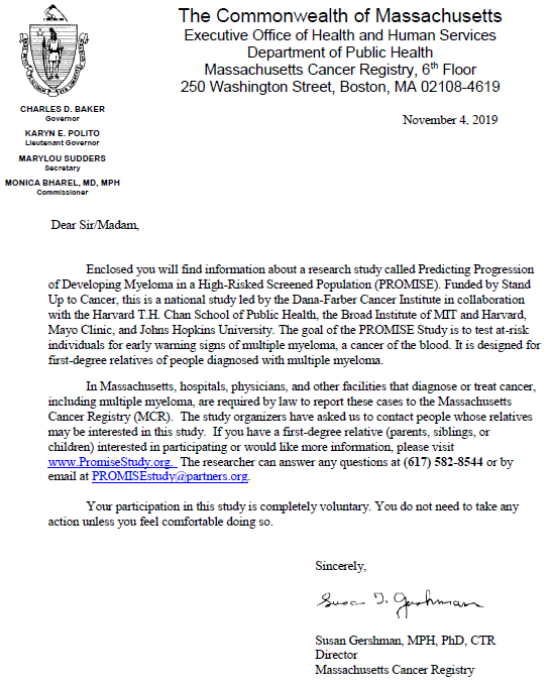
Predicting Progression of Developing Myeloma in a High-Risk Screened Population

How Does the PROMISE Study Recruit?

Virtual



Through Mail



The Commonwealth of Massachusetts
Executive Office of Health and Human Services
Department of Public Health
Massachusetts Cancer Registry, 6th Floor
250 Washington Street, Boston, MA 02108-4619

November 4, 2019

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MARYLOU SUDDERS
Secretary
MONICA BHAREL, MD, MPH
Commissioner

Dear Sir/Madam,

Enclosed you will find information about a research study called Predicting Progression of Developing Myeloma in a High-Risked Screened Population (PROMISE). Funded by Stand Up to Cancer, this is a national study led by the Dana-Farber Cancer Institute in collaboration with the Harvard T.H. Chan School of Public Health, the Broad Institute of MIT and Harvard, Mayo Clinic, and Johns Hopkins University. The goal of the PROMISE Study is to test at-risk individuals for early warning signs of multiple myeloma, a cancer of the blood. It is designed for first-degree relatives of people diagnosed with multiple myeloma.

In Massachusetts, hospitals, physicians, and other facilities that diagnose or treat cancer, including multiple myeloma, are required by law to report these cases to the Massachusetts Cancer Registry (MCR). The study organizers have asked us to contact people whose relatives may be interested in this study. If you have a first-degree relative (parents, siblings, or children) interested in participating or would like more information, please visit www.PromiseStudy.org. The researcher can answer any questions at (617) 582-8544 or by email at PROMISEstudy@partners.org.

Your participation in this study is completely voluntary. You do not need to take any action unless you feel comfortable doing so.

Sincerely,

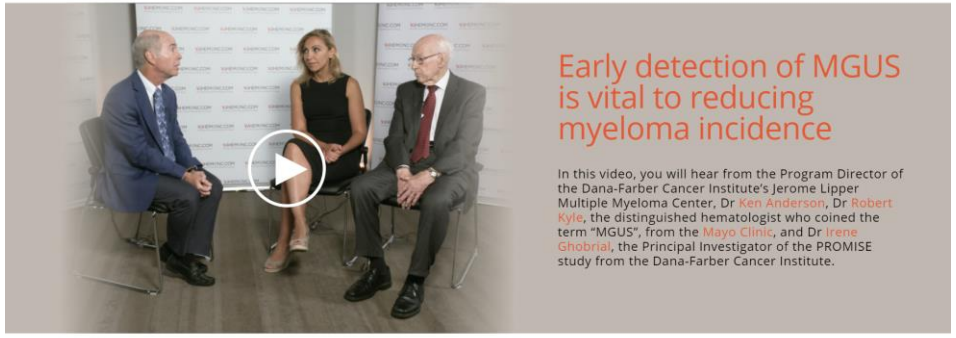
Susan Gershman, MPH, PhD, CTR
Director
Massachusetts Cancer Registry

On-The-Ground

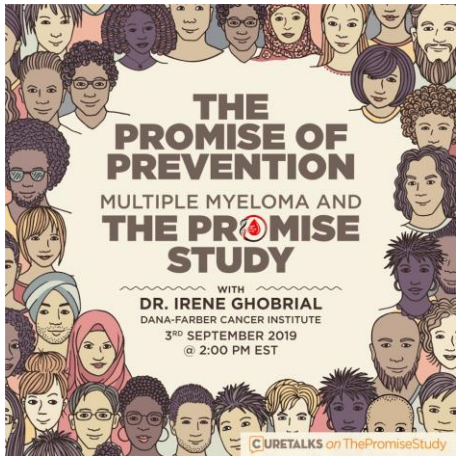
The PROMISE Study

Accomplishments Since Most Recent Meeting With Review Committee

Virtual



Interview with Dr. Bob Kyle



CureTalks Virtual Conversation

NBC 10 Health Check

Interview with Mr. Tom Brokaw

The PROMISE Study

Accomplishments Since Most Recent Meeting With Review Committee

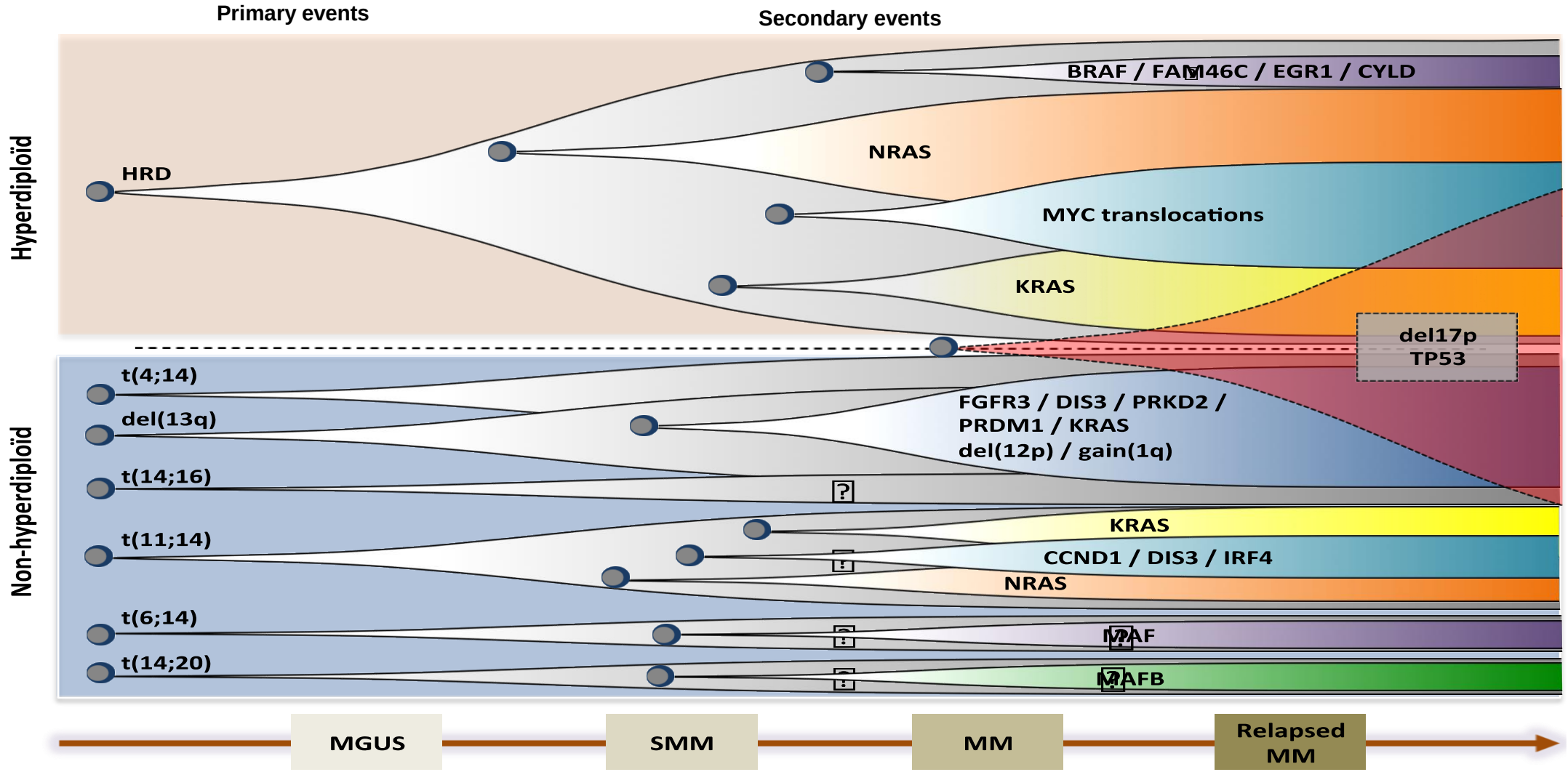
On-The-Ground

Rahway, NJ Agape Church Health Fair

Los Angeles, CA

Ayanna Pressley, MA Representative

Dissecting genomic characteristics of clonal evolution from MGUS/SMM to MM

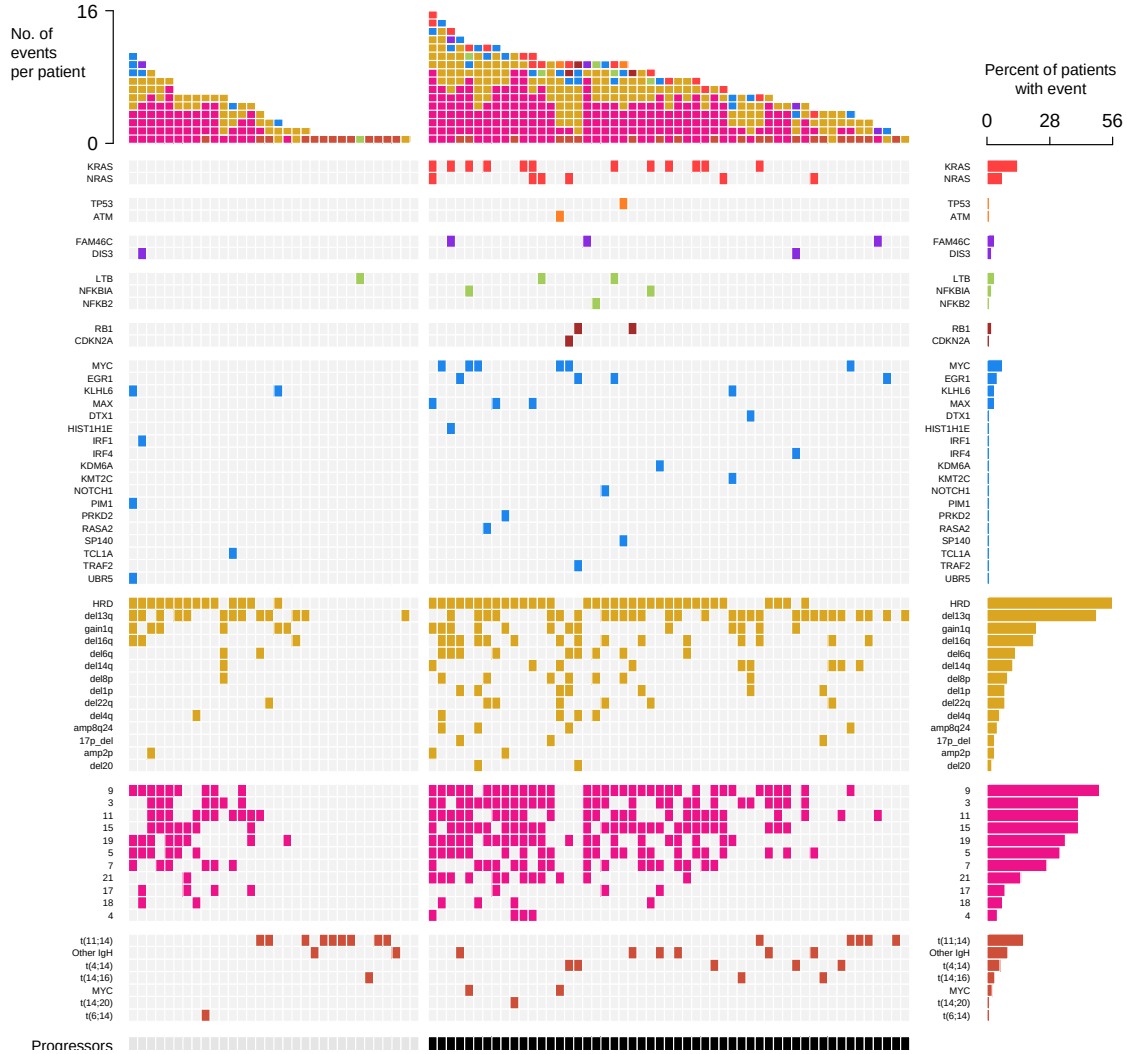


Manier, Salem, et al. *Nat Rev Clin Oncol*, 2016

Genomic Characteristics of MGUS/SMM

Dissecting genomic characteristics of clonal evolution from MGUS/SMM to MM and germline variants of high-risk individuals at risk of developing MGUS/SMM

Genomic Landscape of Progressors vs Non-Progressors (n = 85)



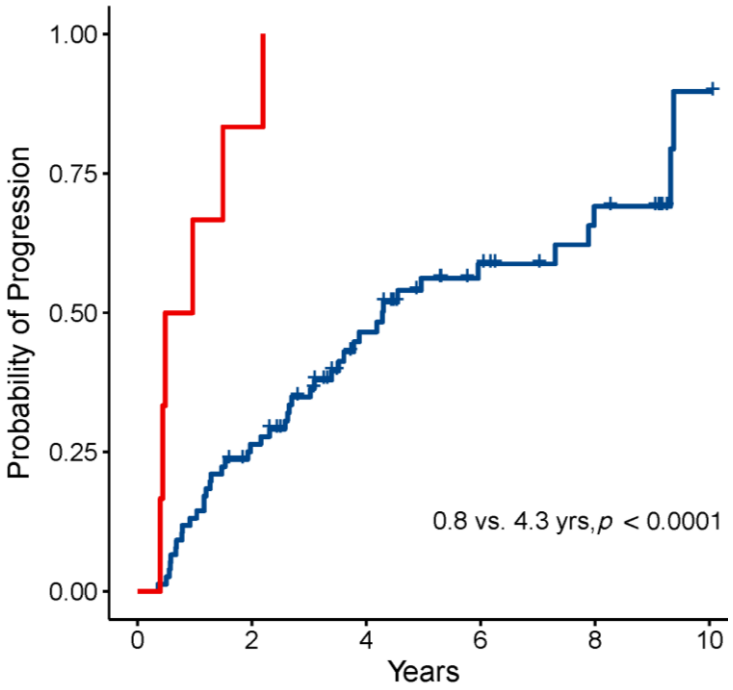
JCO in press

Genomic Characteristics of MGUS/SMM

Dissecting genomic characteristics of clonal evolution from MGUS/SMM to MM and germline variants of high-risk individuals at risk of developing MGUS/SMM

Independent Genomic Predictors of Progression from SMM to MM

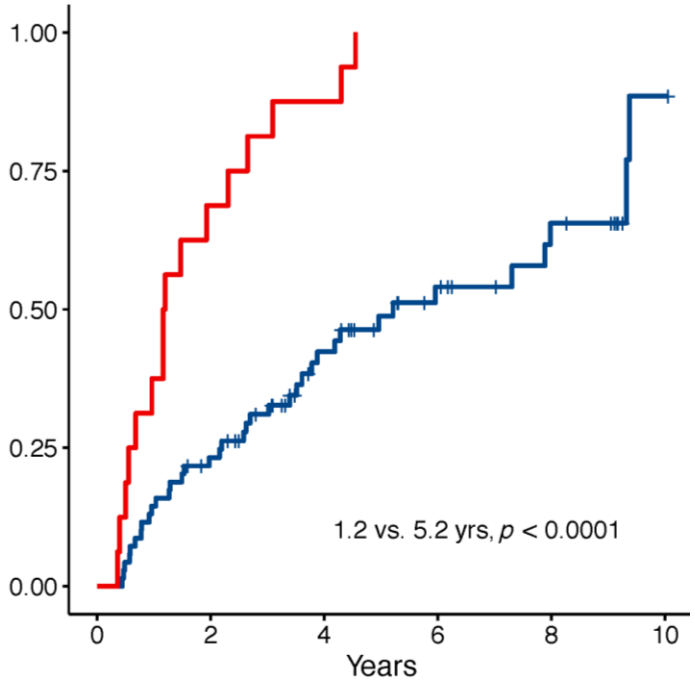
MYC alterations



Number at risk

0	76	54	30	16	9	1
1	6	1	0	0	0	0

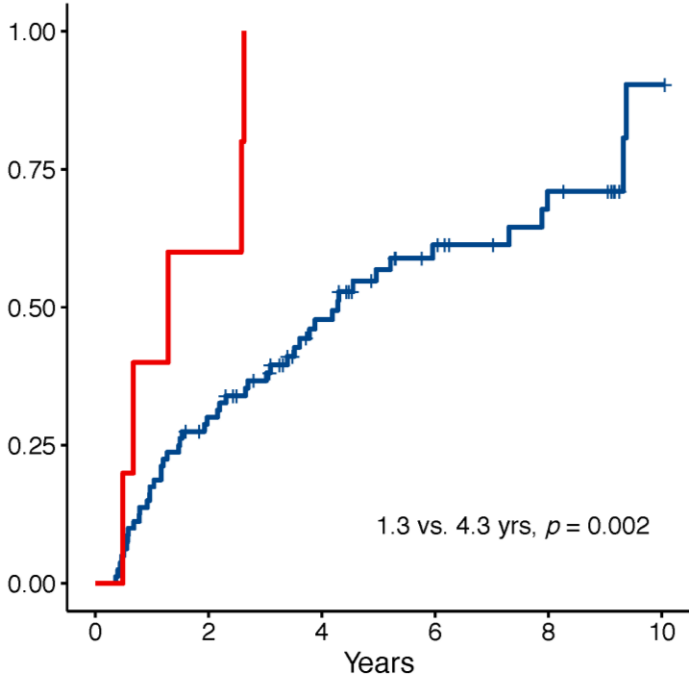
MAPK pathway mutations



Number at risk

WT	69	51	29	16	9	1
Mut	16	5	2	0	0	0

DNA repair pathway mutations



Number at risk

0	80	54	31	16	9	1
1	5	2	0	0	0	0

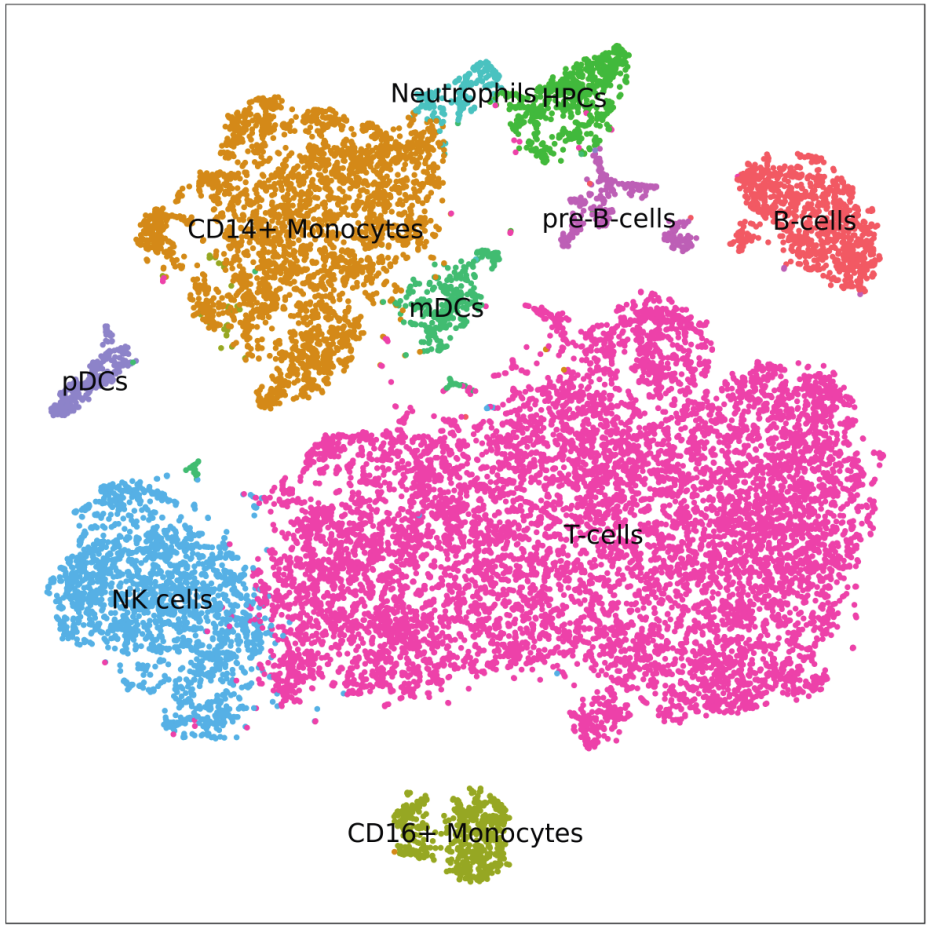
Stephen Paget, 1855–1926.
Ha elaborato alla fine del XIX secolo la teoria detta "seed and soil" (seme e terreno) per spiegare il processo di metastatizzazione. Questa teoria è tutt'ora attuale.

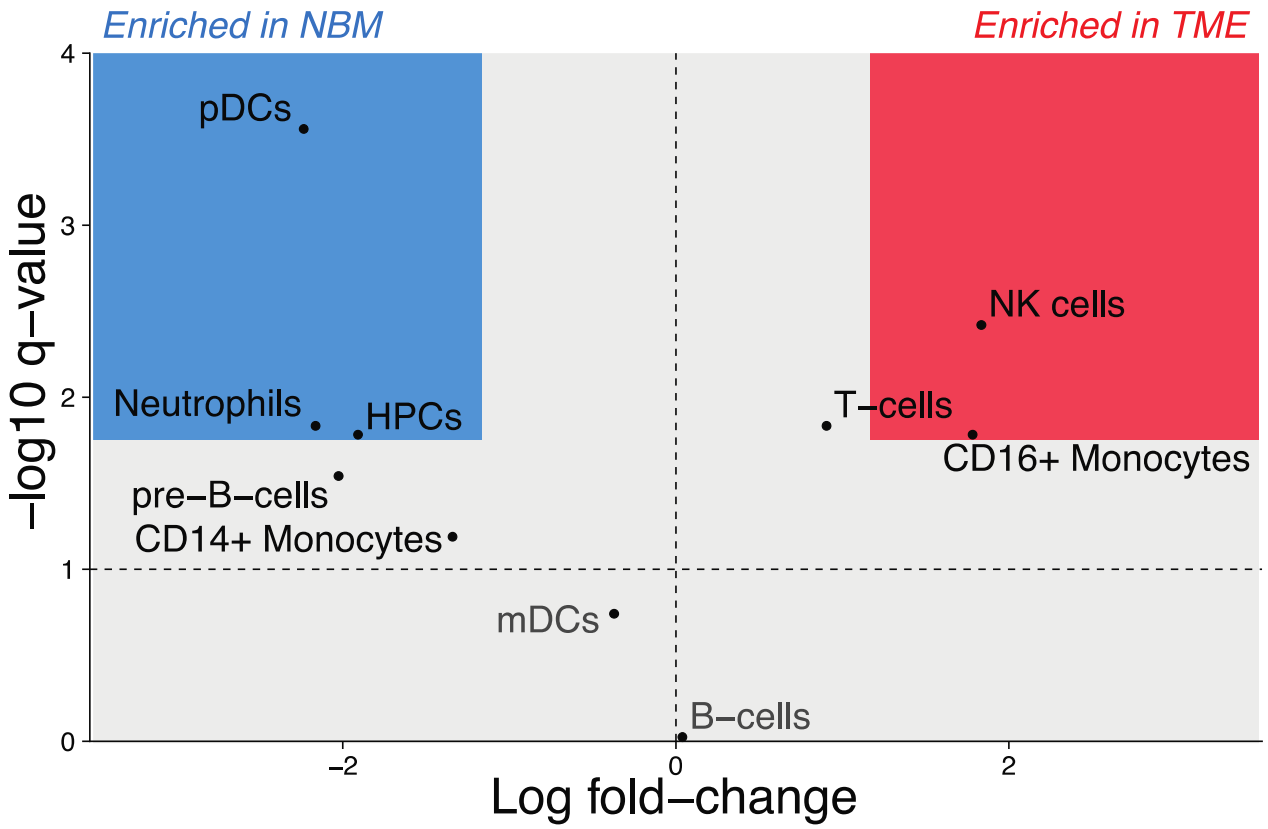
Is the bone marrow permissive to tumor progression from MGUS to MM

Hawaiian silversword developed differently in different environments

Princeton guide to Ecology

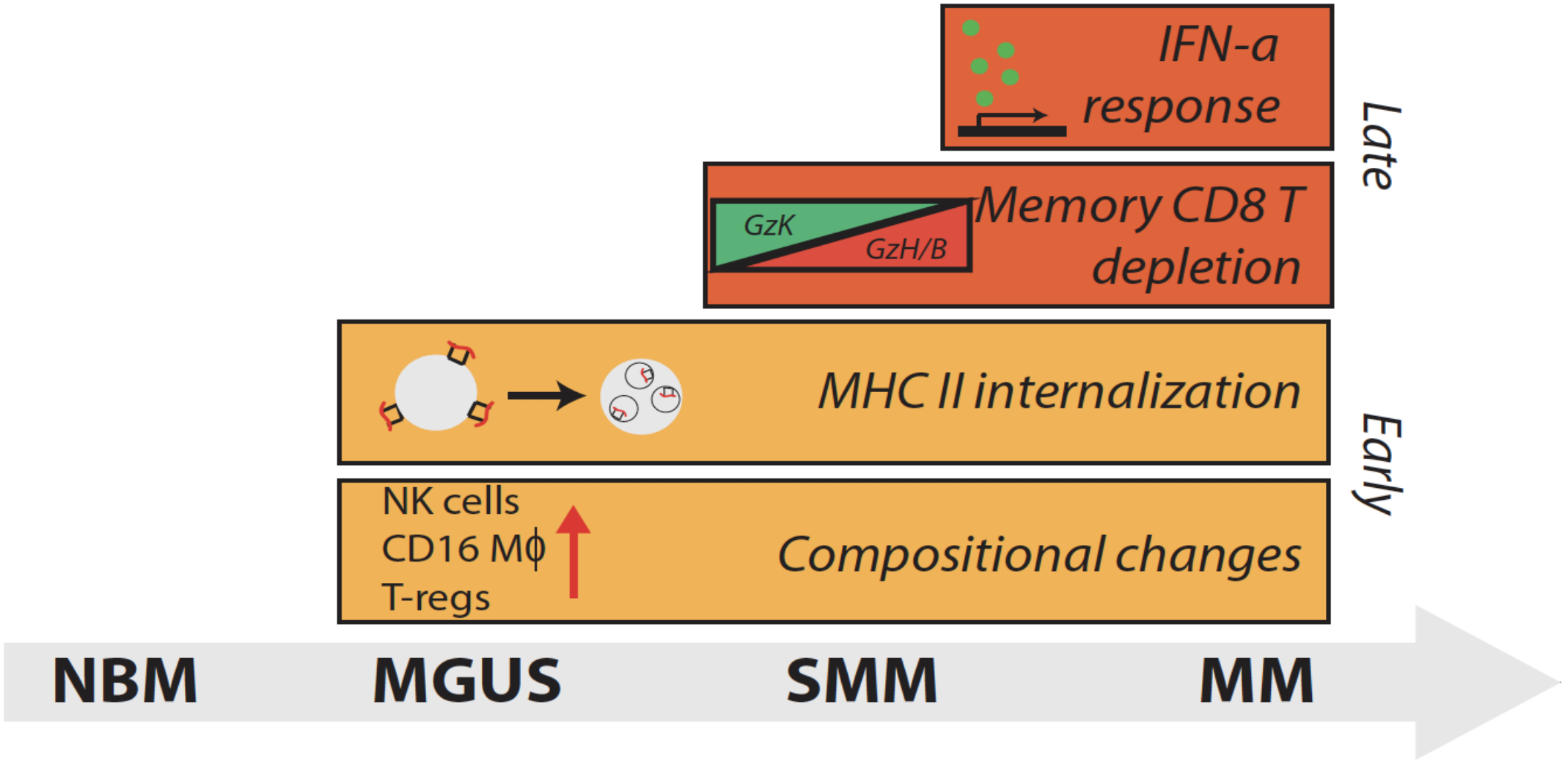
Compositional changes in MM bone marrow microenvironment





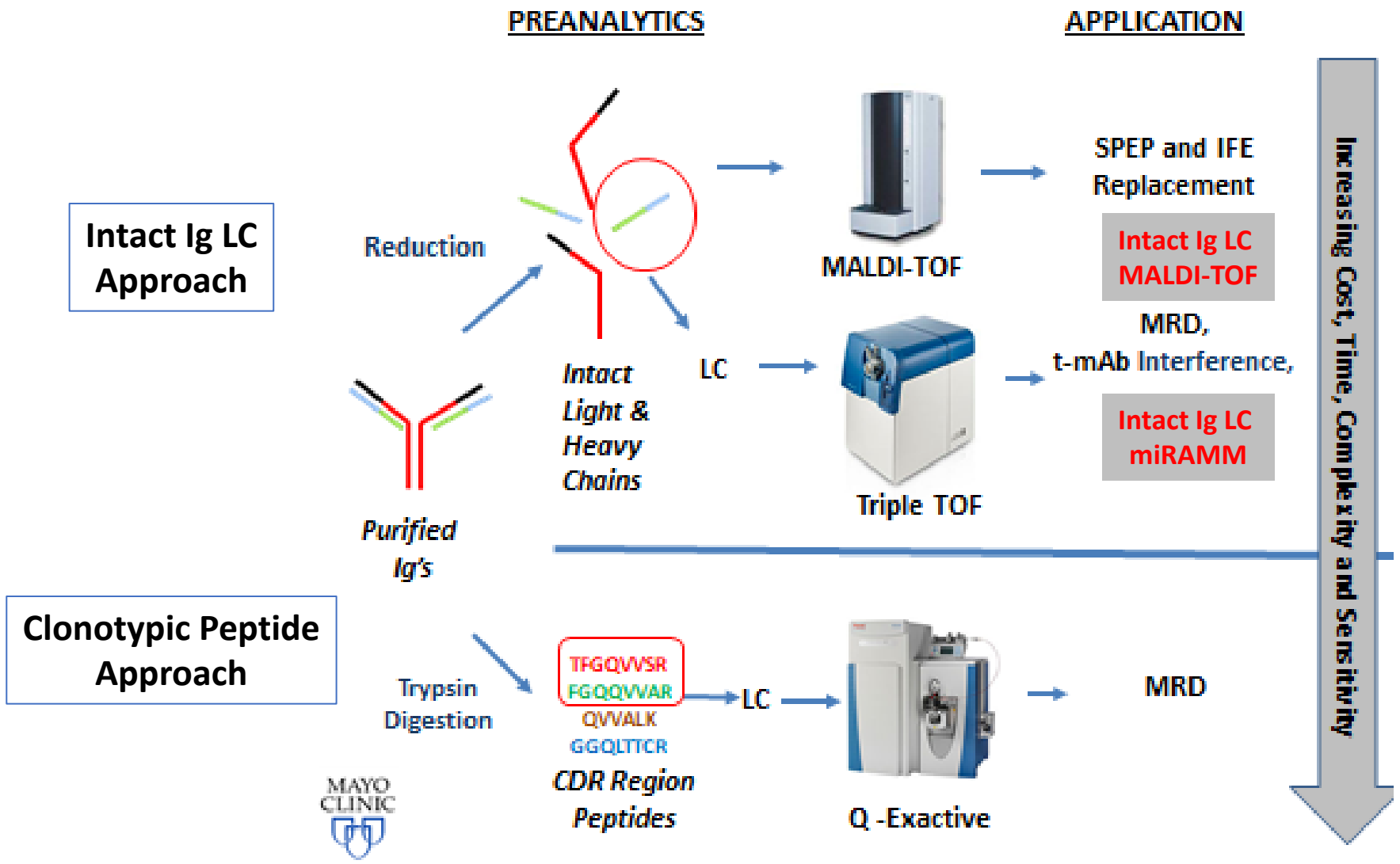
Nature Cancer, in press

Model of immune dysregulation



Nature Cancer, in press

Mass spectrometry



Mass-Fix Clinical Cohort Results

- 37,500 samples analyzed so far; 19,523 unique patient samples selected for deep analysis.

Mass-Fix Result

Type	N	Percent
No Monoclonal	12471	62.44%
Monoclonal - IgG	3094	15.49%
Can't Rule Out M-protein	1503	7.53%
Monoclonal - IgA	817	4.09%
Monoclonal - IgM	760	3.81%
mAb Drug (Dara, Elot, Isa, & Ritux)	402	2.01%
Bence Jones	302	1.51%
Light Chain Glycosylation	292	1.46%
Biclonal	287	1.44%
Monoclonal - IgD&E	25	0.13%
Heavy Chain	10	0.05%
Triclonal	9	0.05%

Mass-Fix (Isotype)

Type	N	Percent
Monoclonal - IgG	3094	58.44%
Monoclonal - IgA	817	15.43%
Monoclonal - IgM	760	14.36%

IFX Historical

Kyle (2018 Yearly Update)	
IgG	29,112 (58%)
IgM	9,022 (18%)
IgA	6,333 (12%)

Mass-Fix M-Protein

SPEP Migration	
IgA % Beta SPEP Region	37.8%
IgG % Beta SPEP Region	1.1%
IgM % Beta SPEP Region	0.98%

Background:

- The PROMISE study estimates: ~6% positive screening rate for all monoclonal gammopathies in higher risk individuals.
- Olmsted County, MN population-based study: 21,463 participants, prevalence of MGUS was 3.2% in persons ≥50 years of age.
- Prevalence of light-chain MGUS is 0·8% (95% CI 0·7–0·9) based on 18,372 samples.
- The prevalence of MGUS in persons between 40-49 years of age is 0.88%.

Kyle RA et al. N Engl J Med 2006; 354:1362-1369, Dispenzieri A. et al. Lancet , 2010, Pages 1721-1728; Landgren O. et al. Blood Cancer Journal, 2017 , page e618

Mass spectrometry assays have higher analytical sensitivity than SPEP

- M-protein can be detected by MS in most pts several years prior to diagnosis of clinical MGUS.
- When MGUS is first clinically recognized, it has likely been present in an undetected state for a median duration of >10 years.
- Prevalence of MGUS in persons ≥50 years is at least 5.1%
- During follow-up, in 300 of 16,629 MGUS-negative subjects MGUS was subsequently clinically diagnosed.

Detection of monoclonal protein using mass spectrometry assays among patients considered not to have monoclonal gammopathy of undetermined significance (MGUS) in the Olmsted Screening Study, but subsequently developed the disorder during follow-up.

	Assay type		
	Serum immunofixation	MALDI-TOF	miRAMM
Baseline samples considered negative for MGUS by serum protein electrophoresis and serum-free light-chain assay			
Number of patients tested	226	226	226
Number of patients with detectable monoclonal protein, (%)	24 (10.6)	113 (50.0)	149 (65.9)
Samples from time of clinical MGUS diagnosis			
Number of patients tested	226	226	221
Number of patients with detectable monoclonal protein, (%)	226 (100)[a]	188 (83.2)	200 (90.5)

MGUS monoclonal gammopathy of undetermined significance, *MALDI-TOF* matrix-assisted laser desorption/ionization-time of flight, *miRAMM* monoclonal immunoglobulin rapid accurate mass measurement

[a]By definition, clinical MGUS was diagnosed based on a positive serum immunofixation

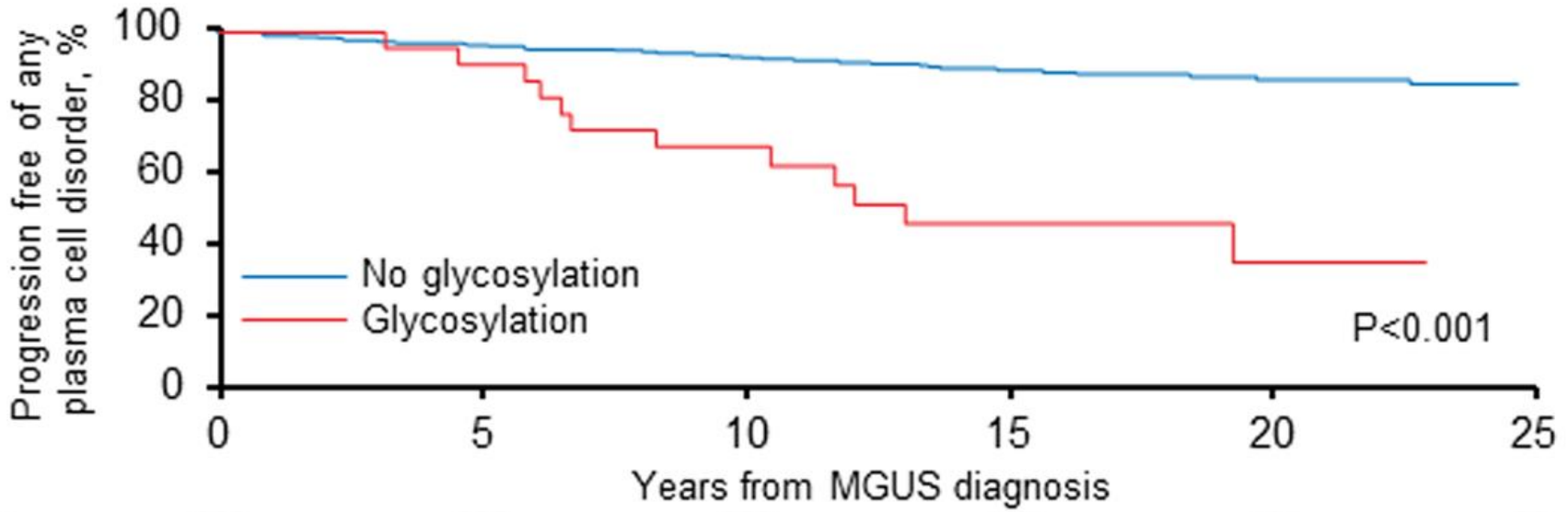
Murray D. et al. Blood Cancer J. 2019 Dec; 9(12): 102.

PROMISE data

- The prevalence of an entity seems to increase as the sensitivity of a screening technology improves.
- While SPEP was abnormal in 4.8%, M-protein was detected by LC MALDI-TOF MS/ mass-fix (MF) in 12.4% of the high-risk screening cohort.
- Prevalence of monoclonal gammopathy in the high-risk population is more than twofold higher than the prevalence in the general population.
- Additional information with respect to glycosylation of the monoclonal protein is garnered with mass-fix.

Glycosylated monoclonal/ biclonal protein	5 (2.8%)

Monoclonal LC glycosylation is a potent risk factor for progression to AL, MM, and other PCDs



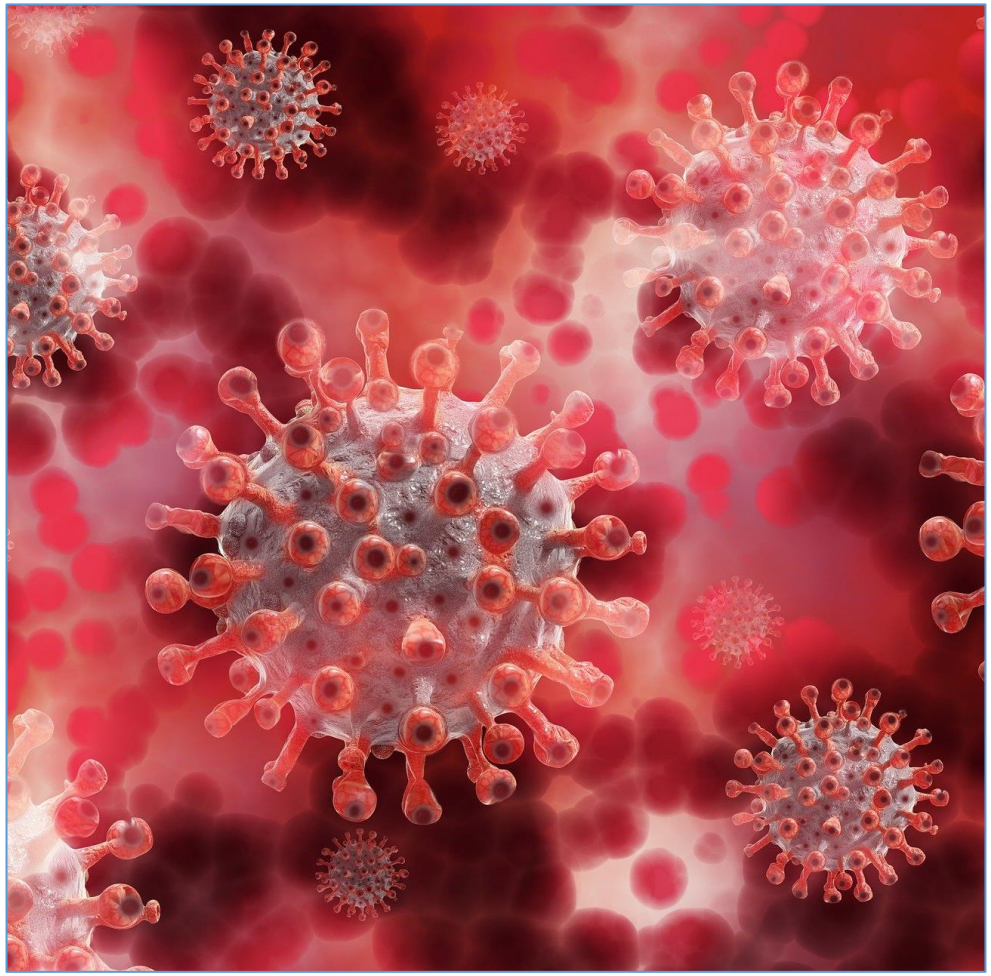
	No.	Events	5-yr rate (95% CI)	10-yr rate (95% CI)	15-yr rate (95% CI)	20-yr rate (95% CI)
No glycosylation	389	38	96.4% (94.6, 98.4)	93.1% (90.4, 95.9)	89.2% (85.6, 92.9)	86.6% (82.3, 91.1)
Glycosylation	25	12	90.7% (79.2, 100.0)	66.8% (49.4, 90.3)	44.5% (27.0, 73.5)	33.4% (15.7, 71.1)

Dispenzieri A. et al. Leukemia, June 2020

COVID-19

COVID-19 has greatly impacted the PROMISE Study:

- Screening was paused due to the pandemic
- Quest sites are COVID-19 testing locations
- On-site recruitment halted
- Urgent need for new strategies for recruitment and community outreach



THE PROMISE STUDY

IMPACT

IMmune Profiling with Antibody-based COVID-19 Testing

Dana-Farber
Cancer Institute

IMPACT

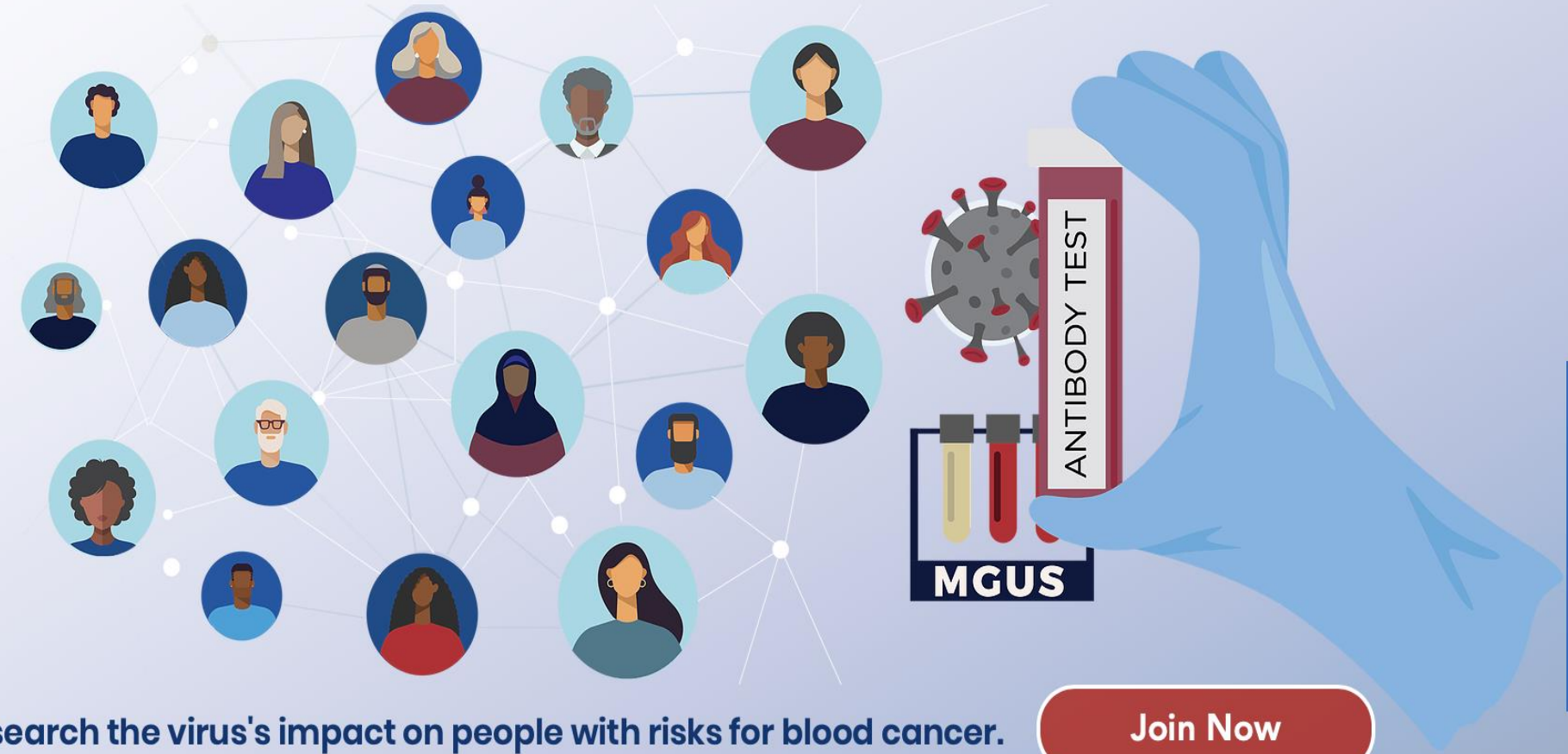
IMmune Profiling with Antibody-based COVID-19 Testing

GOAL: To evaluate the prevalence and pathogenesis of COVID19 in patients with and without a precursor hematological malignancy and define the immunological landscape of COVID19 in these patients over one year of follow-up.

- To determine the prevalence and identify the difference in pathogenesis of COVID-19 infection in an immunocompromised cohort of patients with precursor conditions to hematologic malignancies and healthy cohort
- To define the immune landscape of COVID-19 in patients with precursor hematological malignancies vs healthy individuals
- To define the long-term immune landscape and response post-infection
- To define the proteomic changes that occur in the peripheral blood of patients infected with COVID19

IMPACT

COVID-19 IMMUNE RESPONSE STUDY



Together, we'll research the virus's impact on people with risks for blood cancer.

Join Now

The IMPACT Study provides up to 1 YEAR of coronavirus antibody testing for participants in the PROMISE or PCROWD Studies.*

IMPACT

Participant consents to DFCI PROMISE or PCROWD

PROMISE

PCROWD

Participant consents to IMPACT

IMPACT COVID-19 ANTIBODY STUDY

staff order IgG SARS-CoV-2 Immunoassay through Quest Diagnostics

Quest Diagnostics

Unscreened PROMISE participant receives a PROMISE kit
(2 research tubes + 1 MM screening tube)

Screened PROMISE participant or PCROWD participant receives An IMPACT kit
(3 research tubes)

Participant has research kit tubes and immunoassay tube drawn at Quest Diagnostics or ExamOne

Quest Diagnostics

ExamOne A Quest Diagnostics Company

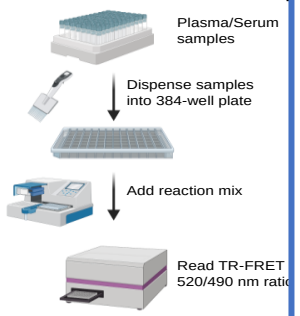
Quest FDA approve
Positive & negative results are notified

Equivocals are asked to re-screen

Research kit is shipped to DFCI

TR-FRET antibody testing or all baseline and subsequent samples

Positive and negative cases used for research questions immune cell sequencing, CYTOF, proteomics, CHIP mutations, etc.



Participants receive IMPACT kits for research blood draws at 3 months, 6 months, 1-year post-baseline

IMPACT

Unique look at individuals who have a suppressed immune systems but may not be as immunocompromised as those with more advanced hematological malignancies

Sequential samples over 1+ years allow for the comparison between pre-infection blood samples and post-infection

Diverse population of individuals who self-identify as black and/or African American

Patients harbor mutated or dysfunctional plasma cells/CHIP mutations and thus may help answer important questions about immune response in patients with vs. without precursor malignancies

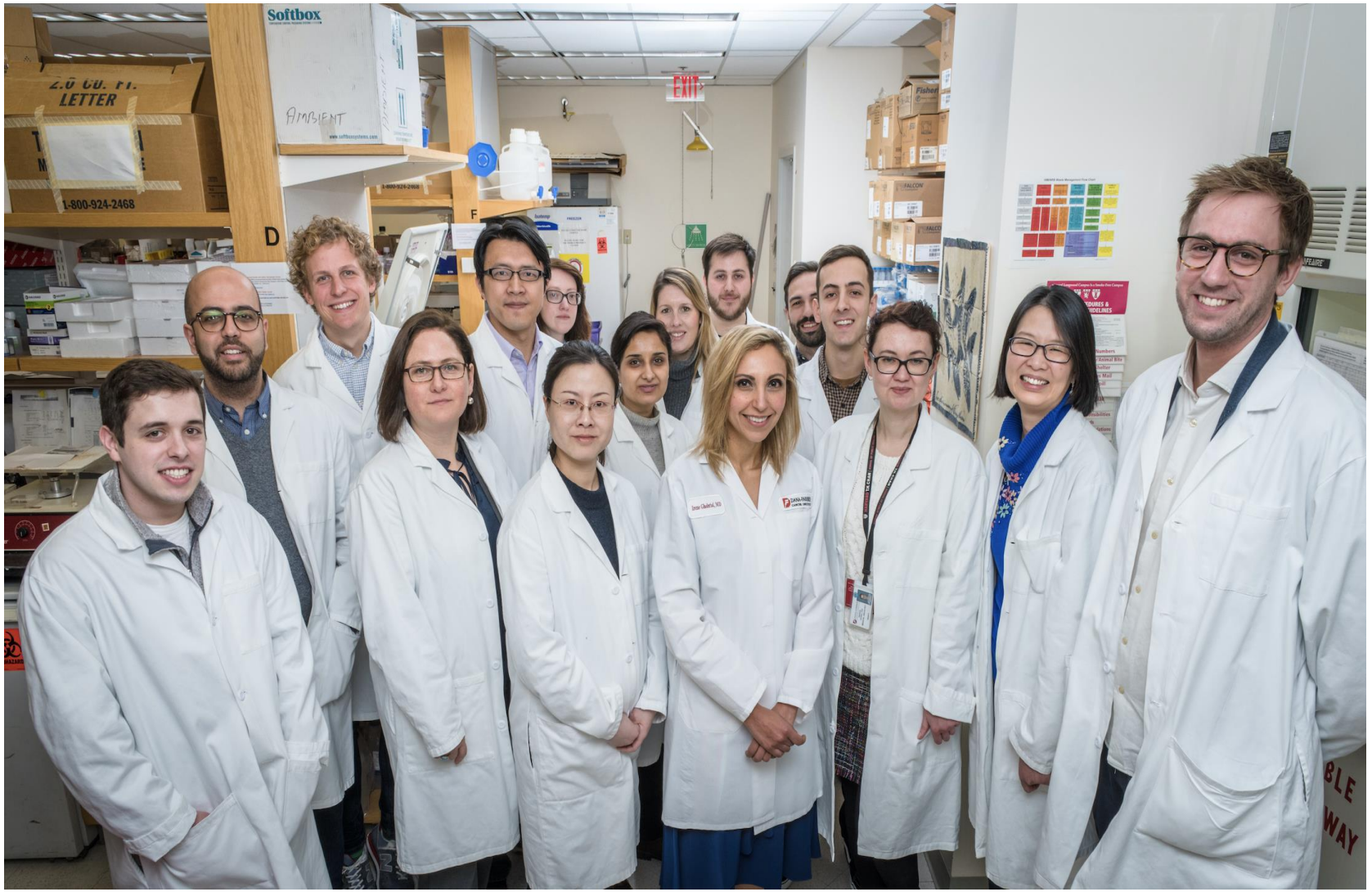
IMPACT COVID-19 ANTIBODY STUDY

Based on PROMISE and PCROWD Study populations, perceived patient interest, and accrual in similar studies, we anticipate IMPACT to enroll, at minimum,

1,000 participants over the course of 1 year

Future direction

- Can we identify MGUS and Smoldering WM early
- Can we stop this idea of watch and wait until we fall apart
- Can we start clinical trials of early interception
- Will that improve survival and prevent complications like neuropathy, hyperviscosity



Gad Getz and his team, Tim Rebbeck, Catherine Marinac, Viktor Adelsteinsson, Ken Anderson, Rob Soiffer, Nikhil Munshi, Paul Richardson, Ben Ebert.

Other collaborators: Leif Bergsagel, Marta Chesi, Bruno Paiva, Jesus San Miguel.

Dana-Farber Cancer Institute