Multiple Myeloma and disparities

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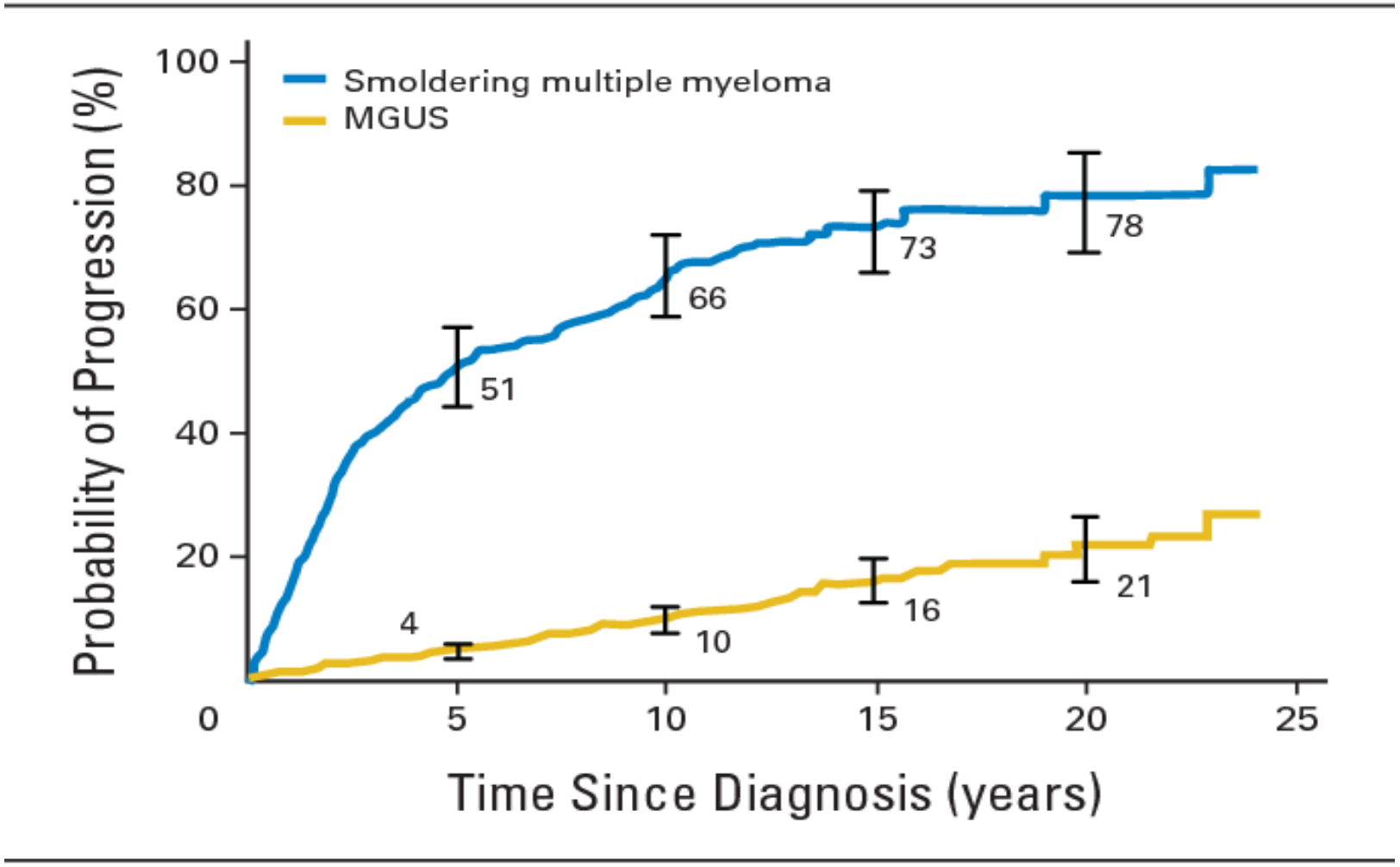
Dana-Farber Cancer Institute
Boston, MA

Dana-Farber
Cancer Institute

Multiple myeloma is always preceded by MGUS and SMM



Bladé, J., Dimopoulos, M., Rosiñol, L., Rajkumar, S.V. and Kyle, R.A., 2010. Smoldering (asymptomatic) multiple myeloma: current diagnostic criteria, new predictors of outcome, and follow-up recommendations. *Journal of clinical oncology*, *28*(4), p.690.

Myeloma is the most common blood cancer in African Americans

And the incidence is growing….

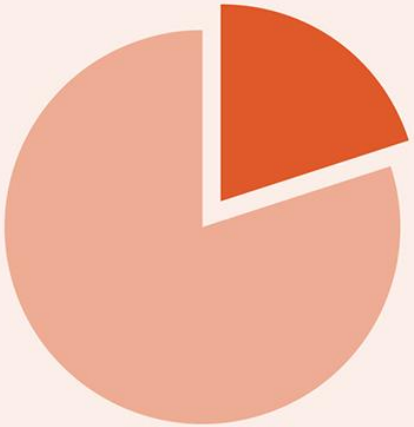
African Americans have **>2x the incidence rate** of MM compared to white Americans[1]

By 2034 it is estimated that African Americans will make up roughly **24% of the newly diagnosed** MM population[1]

African Americans currently represent about

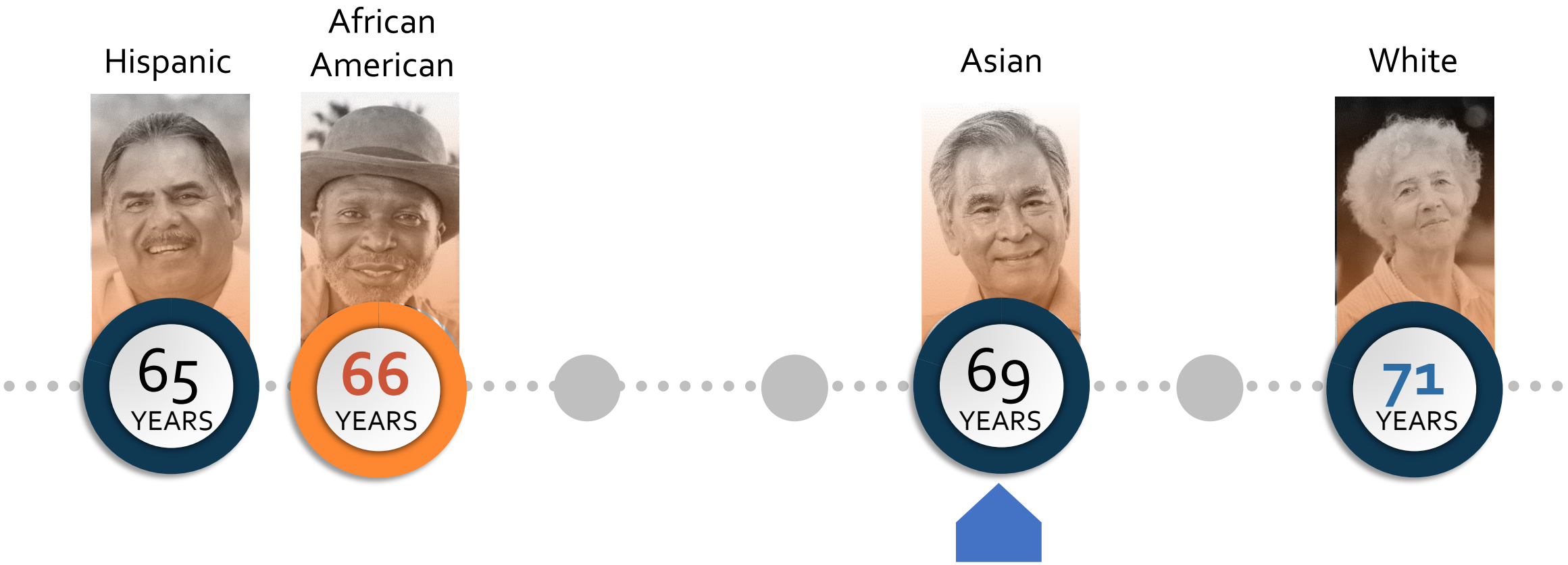
20% or 1 out of 5

patients living with multiple myeloma



[1]American Cancer Society. *Cancer Facts and Figures for African Americans 2019-2021*.

African Americans are younger at diagnosis by about 5 years



There is a **LONGER time from symptom onset** to diagnosis in African Americans

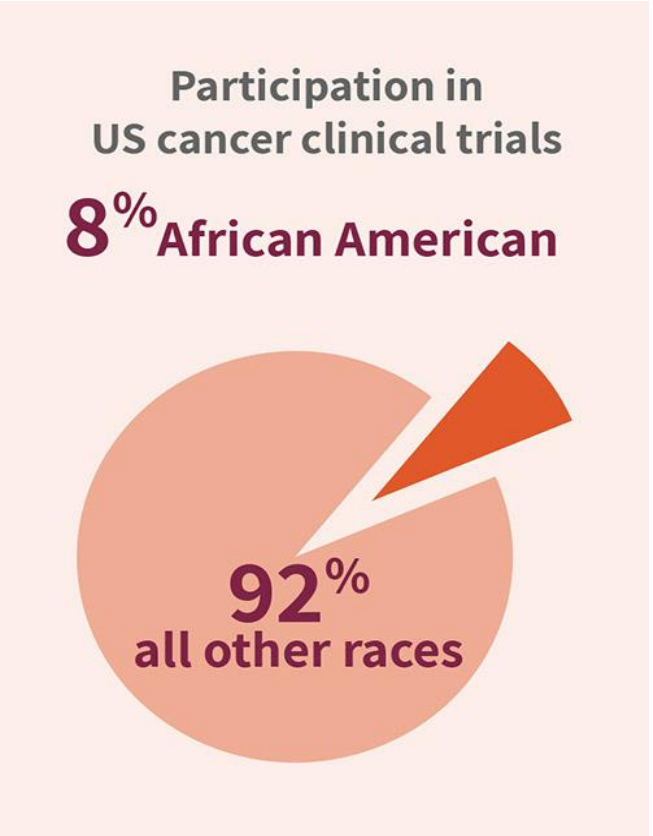
The average myeloma patient sees their primary care doctor **THREE** times with symptoms and signs consistent with MM.

- Confounding diagnoses (like diabetes), Access to diagnostics and care, Awareness in primary care providers, Timely referral to specialists…

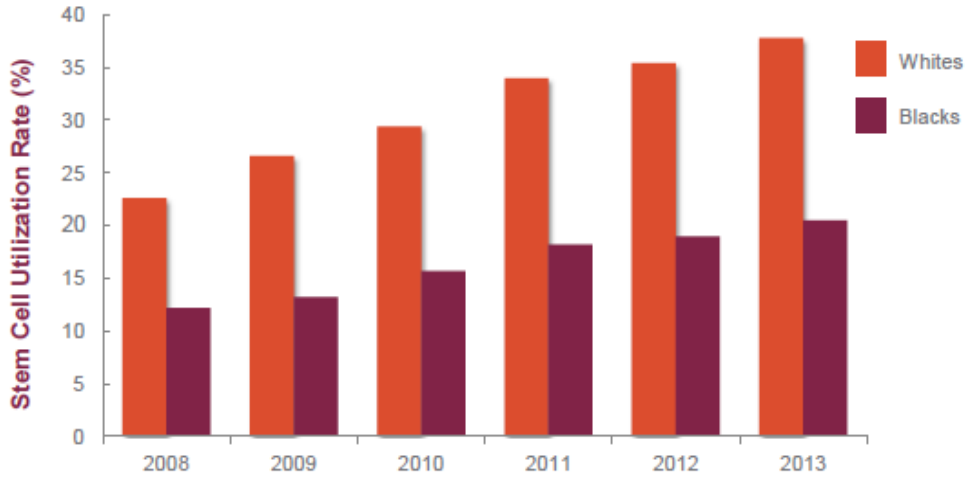
African Americans have only HALF the survival of White Americans

Huge progress in survival in MM but this has not been realized to the same extent in African Americans

Less likely to participate in clinical trials (the 4th T)



An analysis from the Center for International Blood and Marrow Transplant Research Database (CIBMTR, N=28,450) showed increased utilization differed by race



Less likely to receive the critical treatments for MM – The 3 Ts: Triplets, Transplants, and CAR T cell therapy

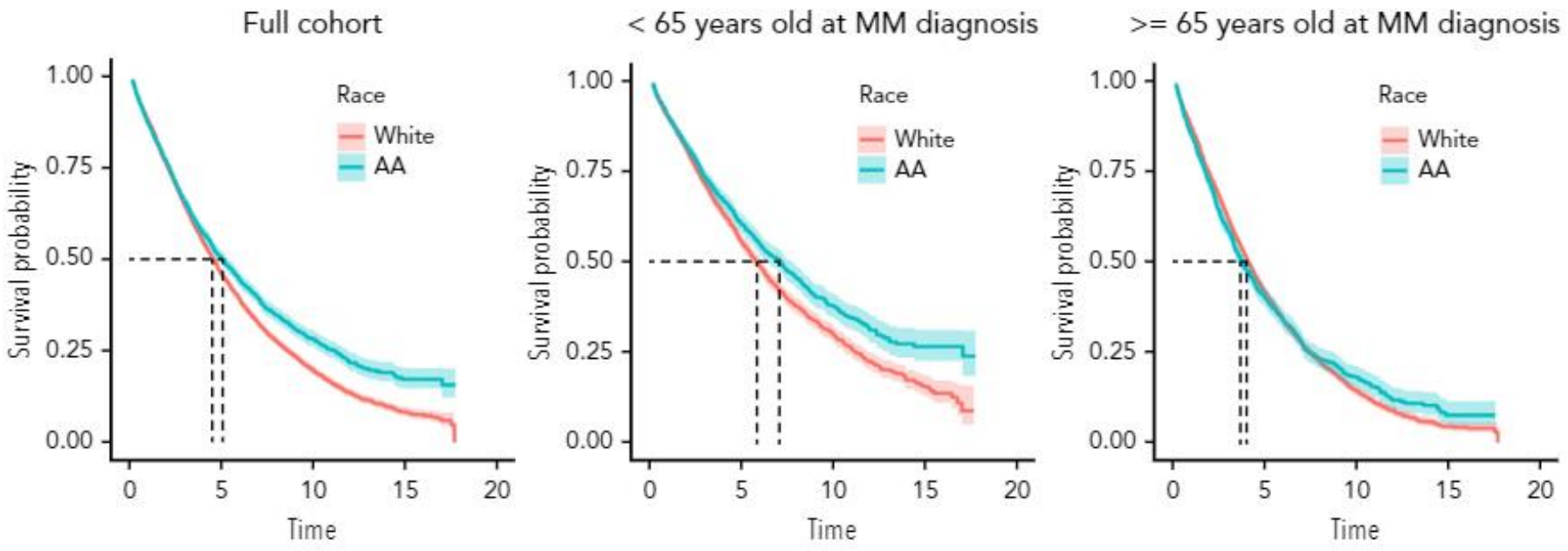
Gormley et al, Blood Cancer Discovery 2021

When African Americans receive equal access to care, their survival outcomes are equal, and at times, better than White patients

SCIENCE IN SOCIETY

Recommendations on Eliminating Racial Disparities in Multiple Myeloma Therapies: A Step toward Achieving Equity in Healthcare

Nicole Gormley[1], Lola Fashoyin-Aje[1], Trevan Locke[2], Joseph M. Unger[3], Richard F. Little[4], Ajay Nooka[5], Khalid Mezzi[6], Mihaela Popa-McKiver[7], Rachel Kobos[8], Yelak Biru[9], Tiffany H. Williams[10], and Kenneth C. Anderson[11]



Fillmore NR, et al. Blood. 2019;133:2615-2618

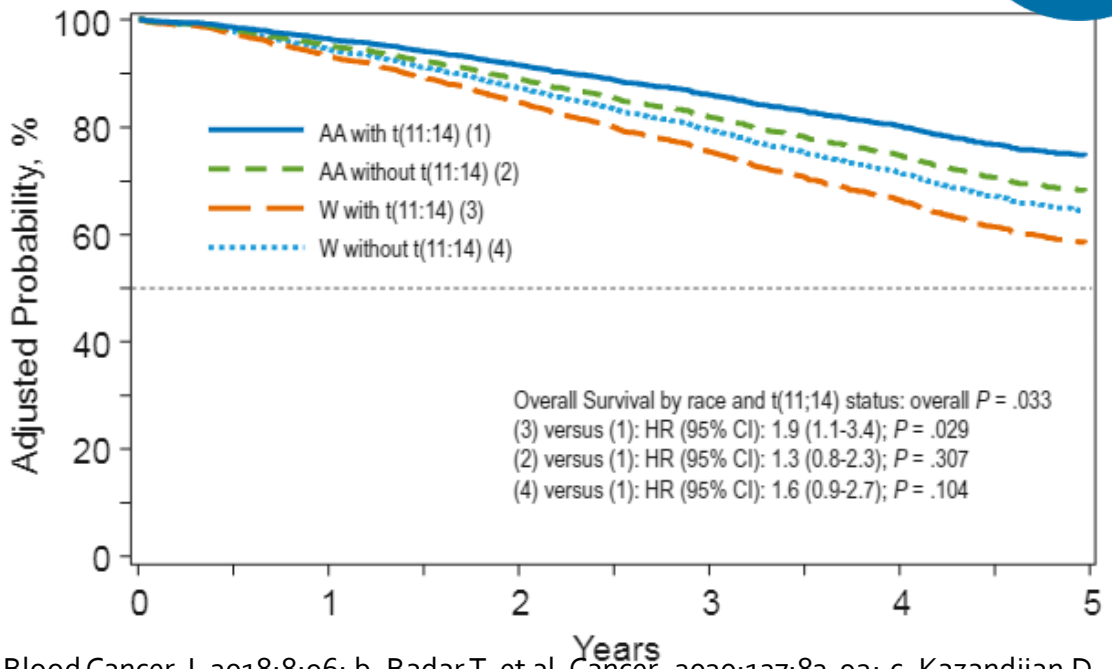
African ancestry associated with less aggressive disease

Higher prevalence of [a]:

t(11;14)

t(14;16)

t(14;20)



Lower prevalence[c]:

13q deletion

17p deletion

- Absence of 17p deletion associated with better survival among younger African Americans vs White counterparts[d]

Baughn LB, et al. Blood Cancer J. 2018;8:96; b. Badar T, et al. Cancer. 2020;127:82-92; c. Kazandjian D, et al. Blood Cancer J. 2019;9:15; d. Munjuluri A, et al. Blood. 2019;134:4388.

There are biologic differences in African Americans of lower risk disease

MM patients with the **highest levels of African ancestry** demonstrate

- a **higher** prevalence of:
  - t(11:14)
  - t(14;16)
  - t(14;20)
- a **lower** prevalence of:
  - 13q deletion
  - 17p deletion
    - However, if present in AA patients under the age of 65, median survival rate is less compared to Whites

Ailawadhi et al. (2018); Baker et al. (2013); Baughn et al. (2018); Cirstea et al. (2019); Kazandjian et al. (2019); Munjuluri (2019)

Cytogenetic differences (RVD 1000) - Emory

Cytogenetic abnormality	Caucasians (N=619)	African-American (N=352)	P-value
1q gains	111 (18.8%)	37 (10.8%)	0.001
T(11;14)	66 (11.5%)	55 (16.1%)	0.043
T(4;14)	25 (4.3%)	18 (5.3%)	0.512
T(14;16)	16 (2.8%)	10 (2.9%)	0.888
del17p	70 (12.1%)	23 (6.7%)	0.009
del13	168 (29.2%)	70 (20.5%)	0.004

Joseph et al, JCO 2020

Early detection and interception initiatives:

1

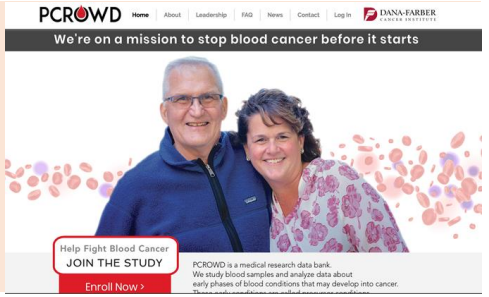
Screening Early

- Cancer screening saves lives
- A blood sample is easier than colonoscopy!
- High risk individuals have a risk of about 13% or more

2

Risk Stratification

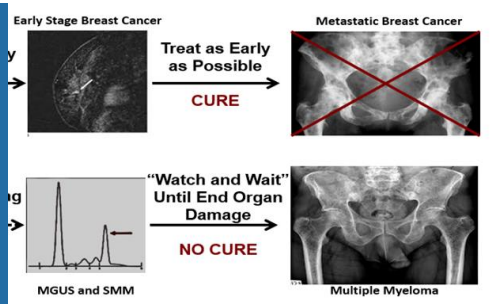
- Who is truly at risk of progression?
- Adding genomic and immune biomarkers for more precise risk assessment
- Blood instead of bone marrow



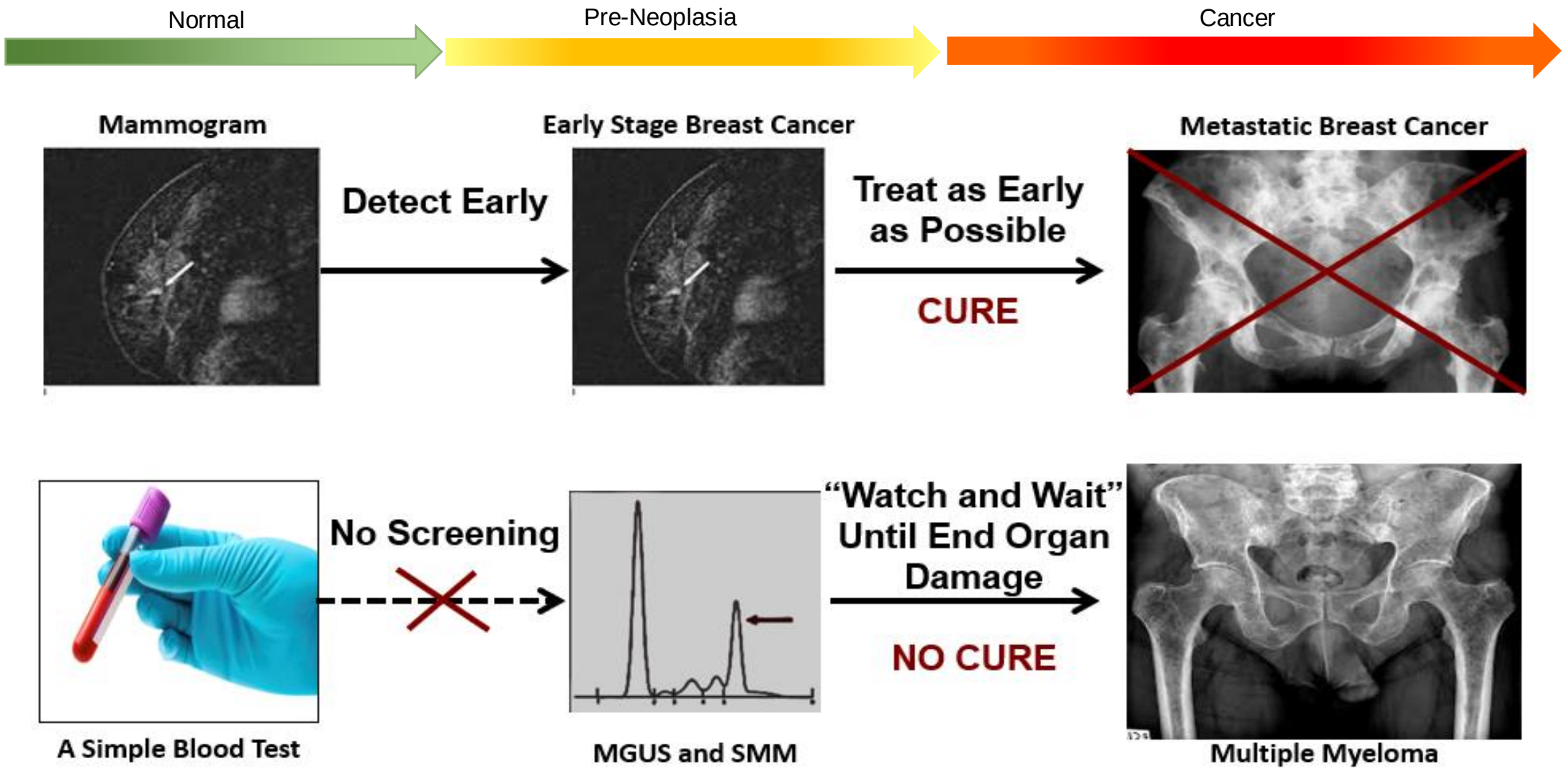
3

Early Interception

- More efficacious therapies that can cure early
- No clinical benefit of waiting until you have end organ damage
- Early use of late-stage therapies



We urgently need early detection in precursor stages of Multiple Myeloma



PROMISE

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

How do I join?

To sign up, visit:
www.PromiseStudy.org

Or you can use your phone to scan this QR code

What's involved? Participants will:

- Complete a brief survey
- Sign a consent form
- Share a small blood sample

Sign up online. No travel to Dana-Farber is required. Visit your local QUEST Diagnostics and return your kit by mail.

As a token of our appreciation, participants can request a $50 gift card.

THE PROMISE STUDY

www.enroll.promisestudy.org

ClinicalTrials.gov Identifier: NCT03689595
Current Status: Actively Recruiting
Phase: Cohort Study

www.PromiseStudy.org

PROMISE

Screen **30,000**
High-Risk Individuals

Screen Negative Screen Positive

Prospective
Follow-Up

Genetics and Genomics


Viktor Adalsteinsson


Gad Getz


Irene Ghobrial

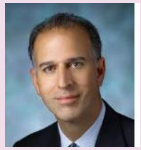
Epidemiology


Tim Rebbeck


Lorelei Mucci


Catherine Marinac

Bone Marrow Niche


Ivan Borrello

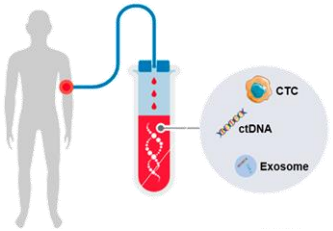

Irene Ghobrial

Imaging and Therapeutics

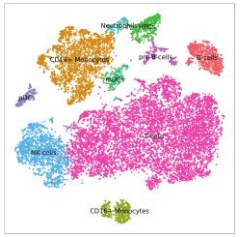

Jeremiah Johnson


Irene Ghobrial

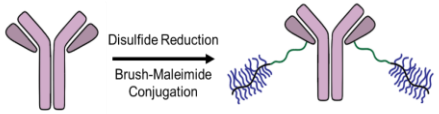
Develop novel **biomarkers for diagnosis**



Establish new **risk stratification** tools



Generate new tools to **prevent disease progression**



Dana-Farber Cancer Institute

BROAD INSTITUTE

MIT

JOHNS HOPKINS UNIVERSITY

MAYO CLINIC

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

STAND UP TO CANCER

Inclusion Criteria

Adults ≥ 30 years old who are:

African American (self-identified)

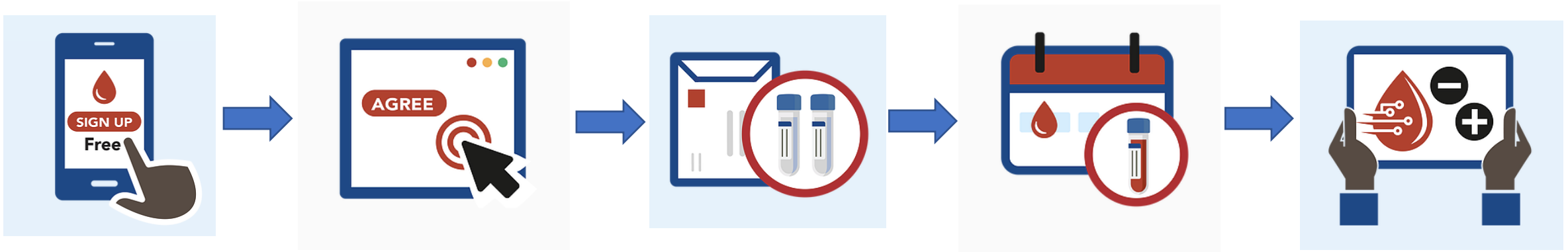
Risks are 2-3 times higher for this group

First-degree relative of a patient with a blood cancer

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

Expanded inclusion for those who are 18+ with a strong family history (2 or more 1st and/or 2nd degree relatives

How Does the PROMISE Screening Process Work?



Sign up

Accept Terms

Receive Blood Kit

Schedule Blood Draw

Receive Results

Quest Diagnostics™

THE PROMISE STUDY

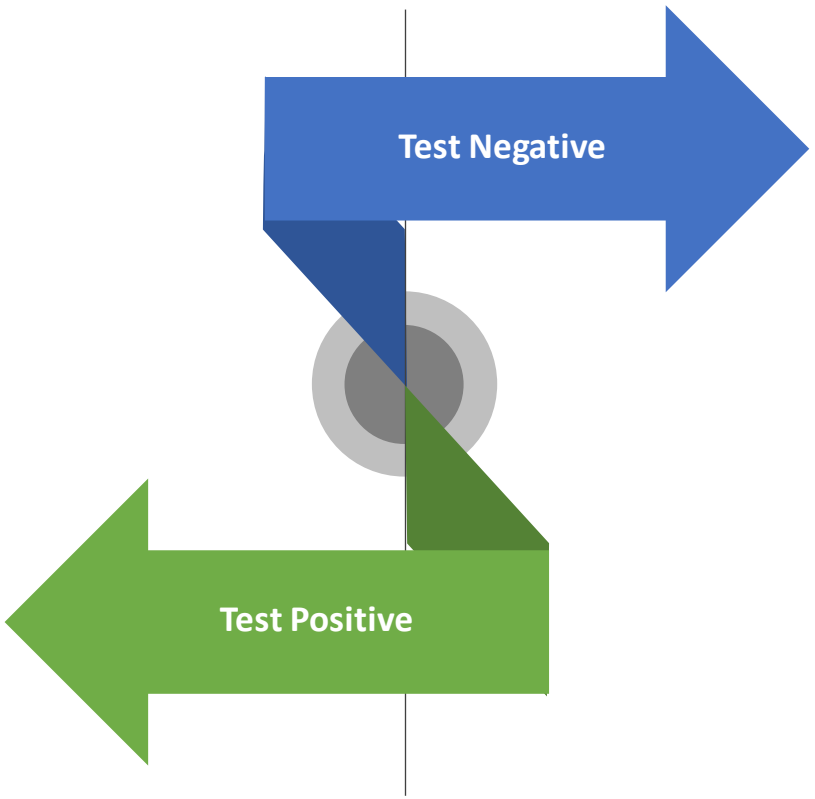
www.enroll.promisestudy.org

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

THE PROMISE STUDY

On-The-Ground

Rahway, NJ Agape Church Health Fair

Los Angeles, CA

Ayanna Pressley, MA Representative

Minority Recruitment

2022 Indiana Black & Minority Health Fair

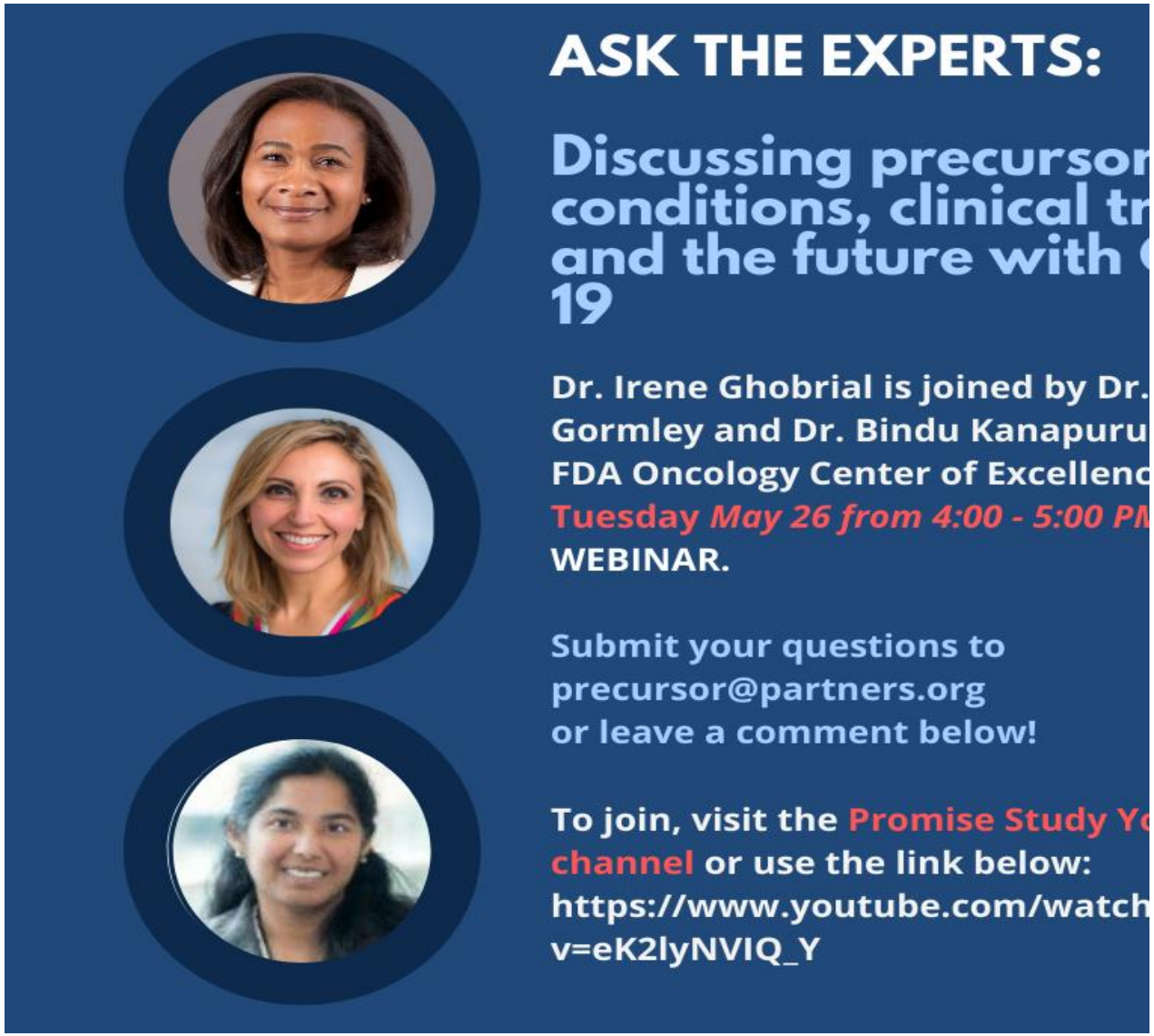
Indiana Department of Health

177 participants enrolled over 4 days

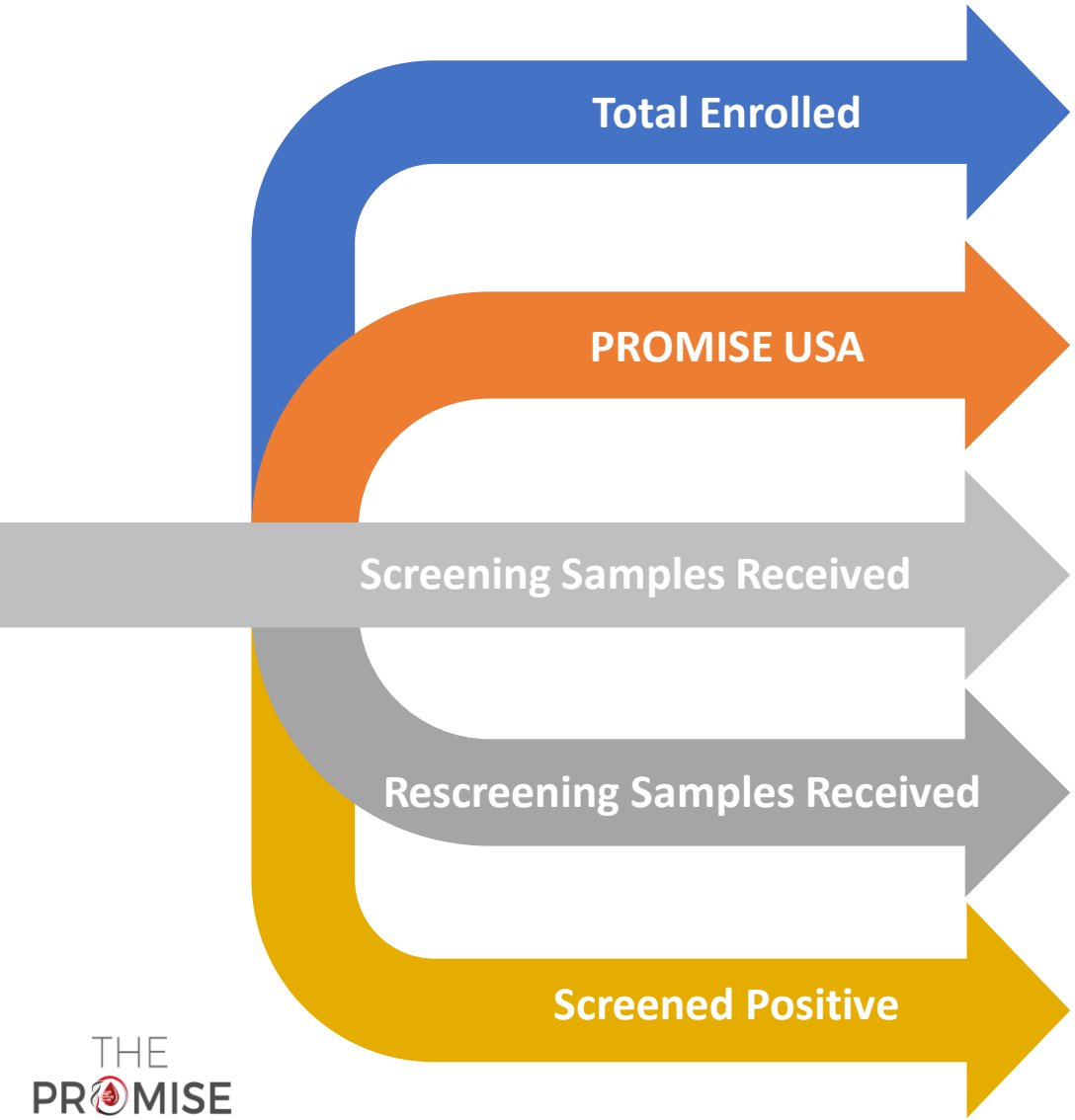
- 1 Light chain myeloma
- 21 MGUS
- 30 MGIP

THE PROMISE STUDY

COVID-era zoom educational sessions



PROMISE by the numbers



12,592 PROMISE USA, PROMISE South Africa & MGB

6,485 These participants each have a personalized PROMISE Dashboard

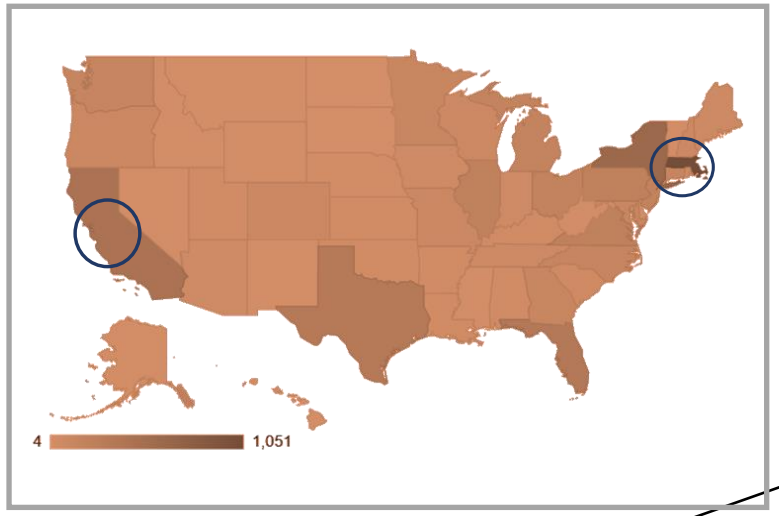
10,103 PROMISE USA, PROMISE South Africa & MGB

265 PROMISE USA

1125 12.6% positive rate

THE PROMISE STUDY

PROMISE by the numbers



12,592 Participants Enrolled

PROMISE US

PROMISE South Africa

MGB Biobank

Family history 8,653

African Descent 3,866

A look at some of PROMISE participants

A family of 9 siblings

Numerous sets of twins

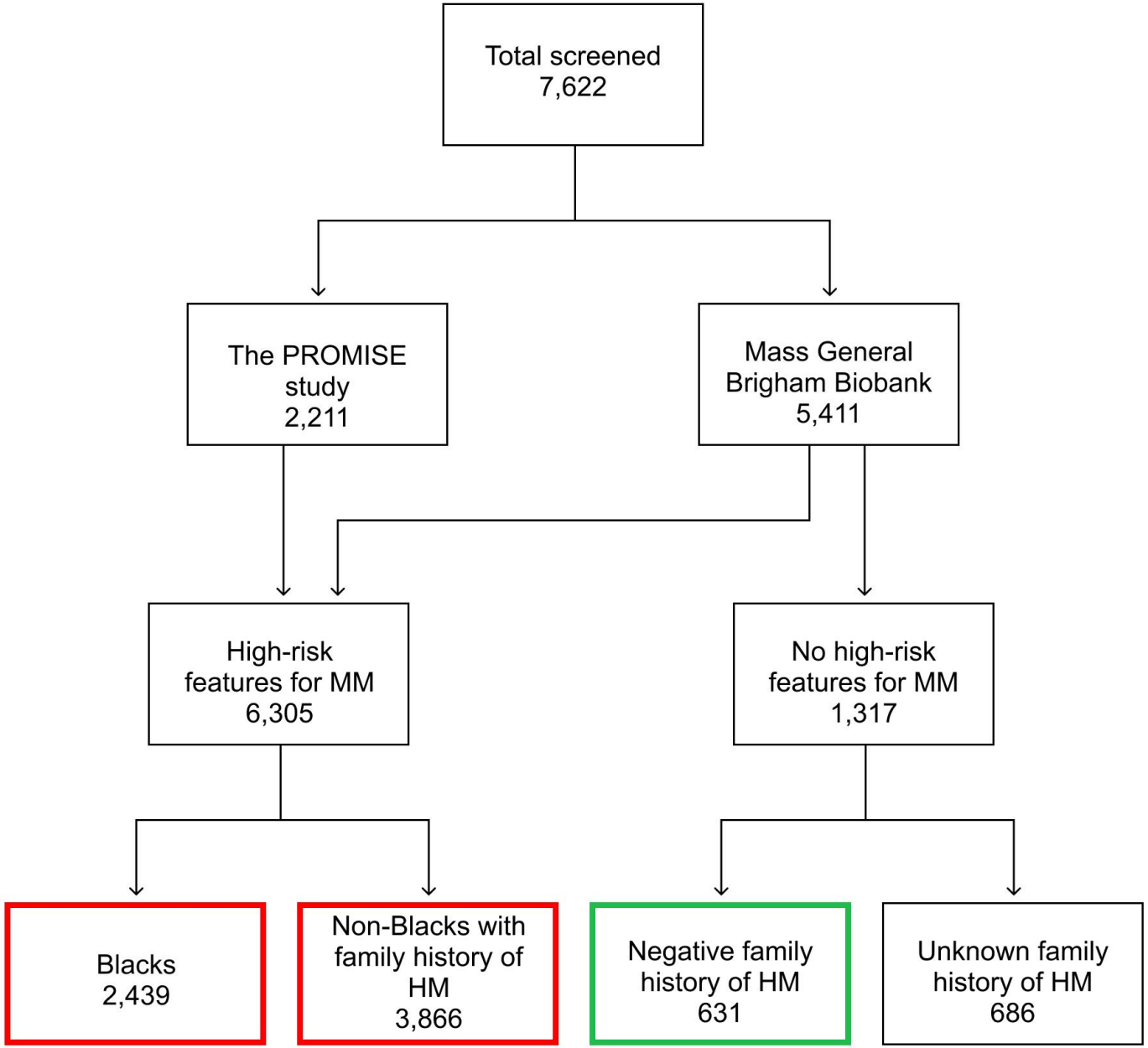
Located on the northern-most inhabited island off the coast of Alaska

A team of janitors at a public high school

THE PROMISE STUDY

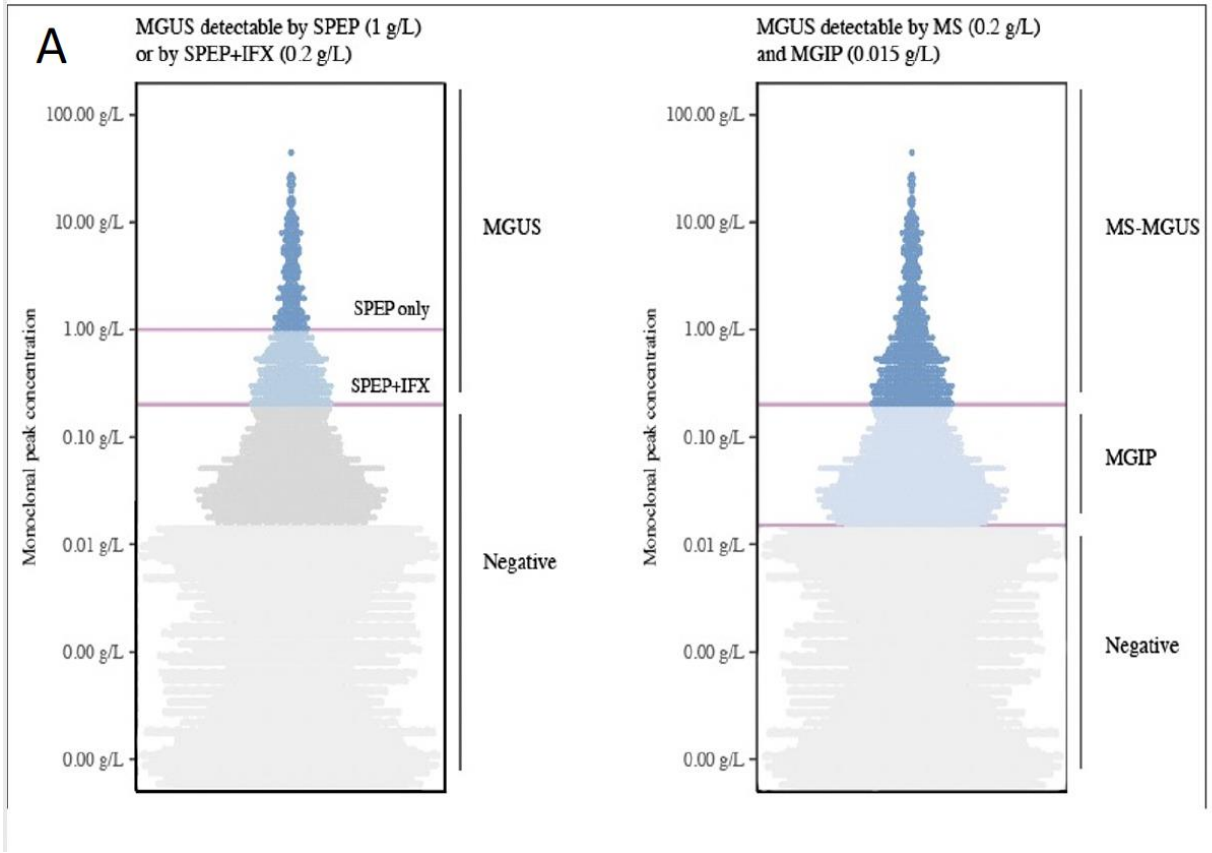
www.enroll.promisestudy.org

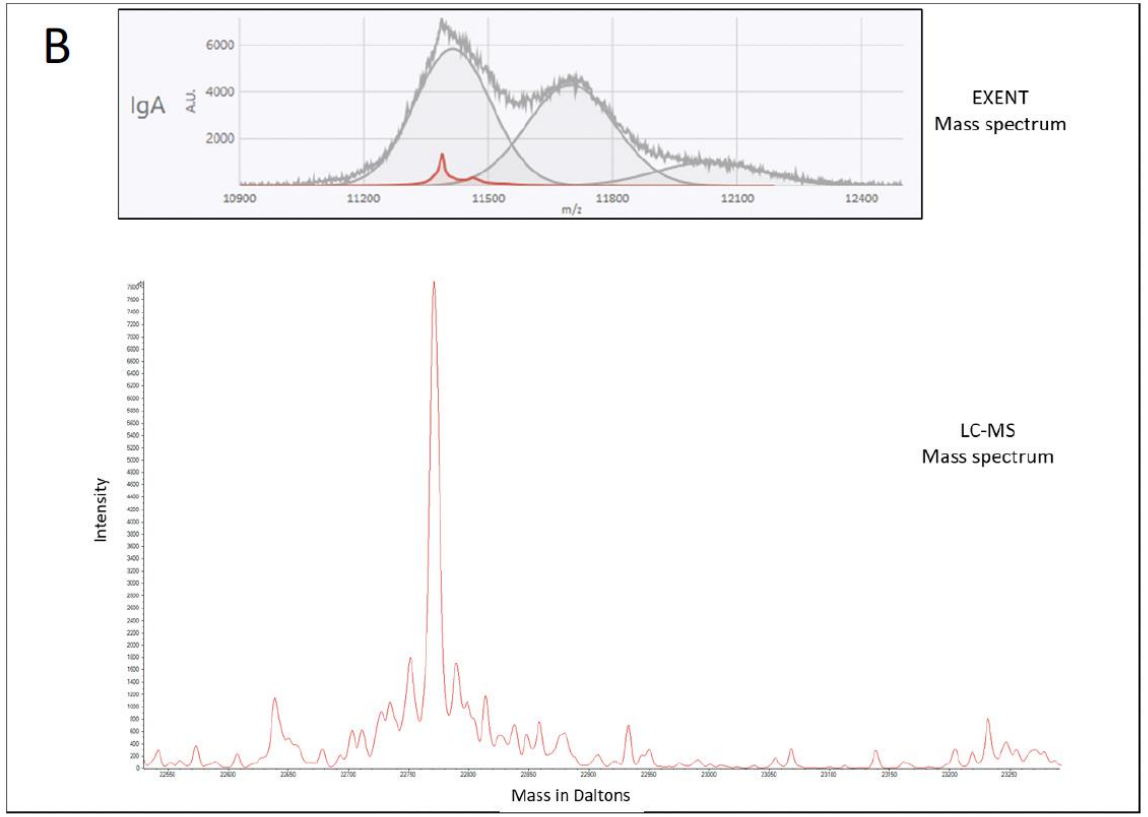
PROMISE early results: Prevalence of MGUS in a high-risk population



Elkhoury et al, Lancet Hematology 2022

Prevalence of MGUS in a high-risk population





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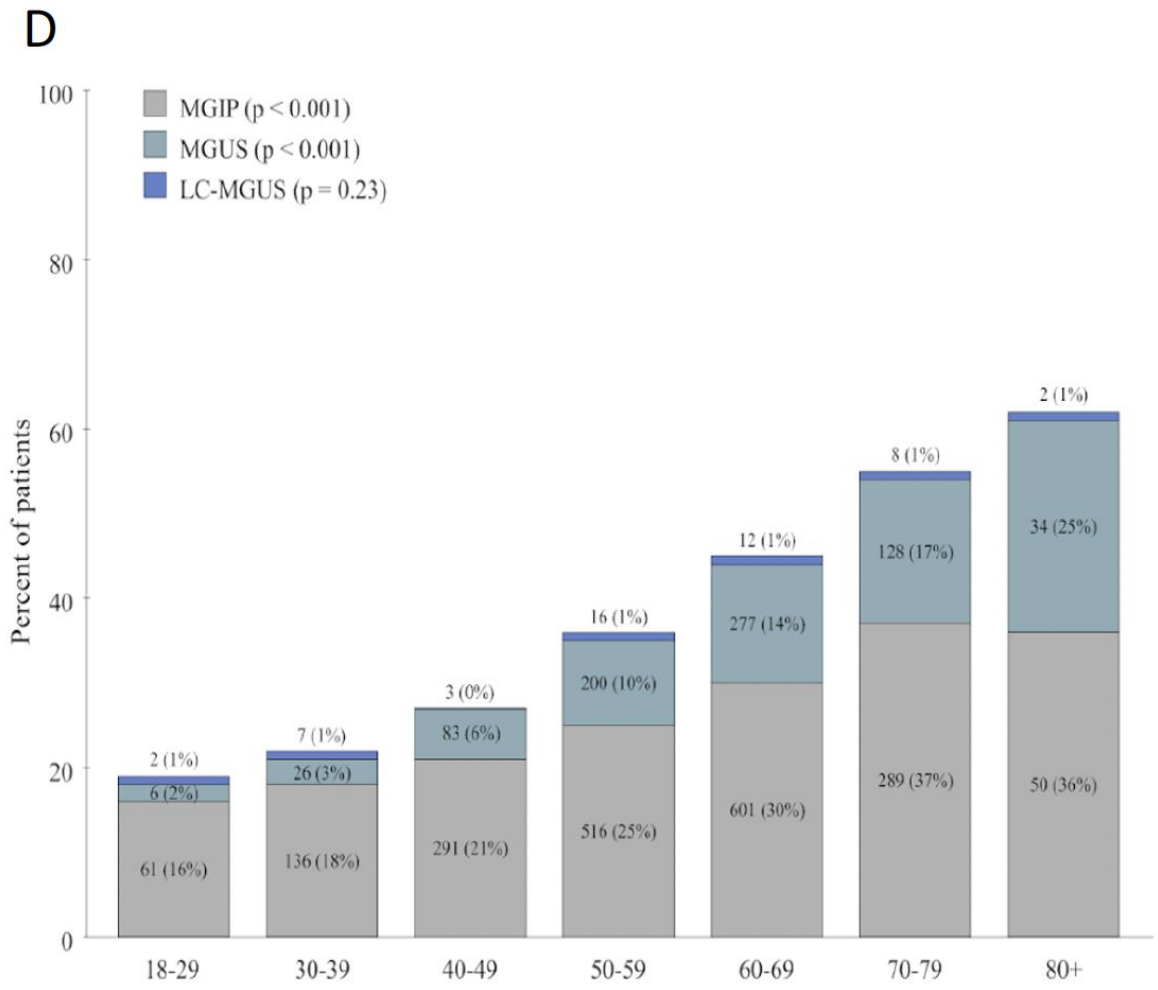
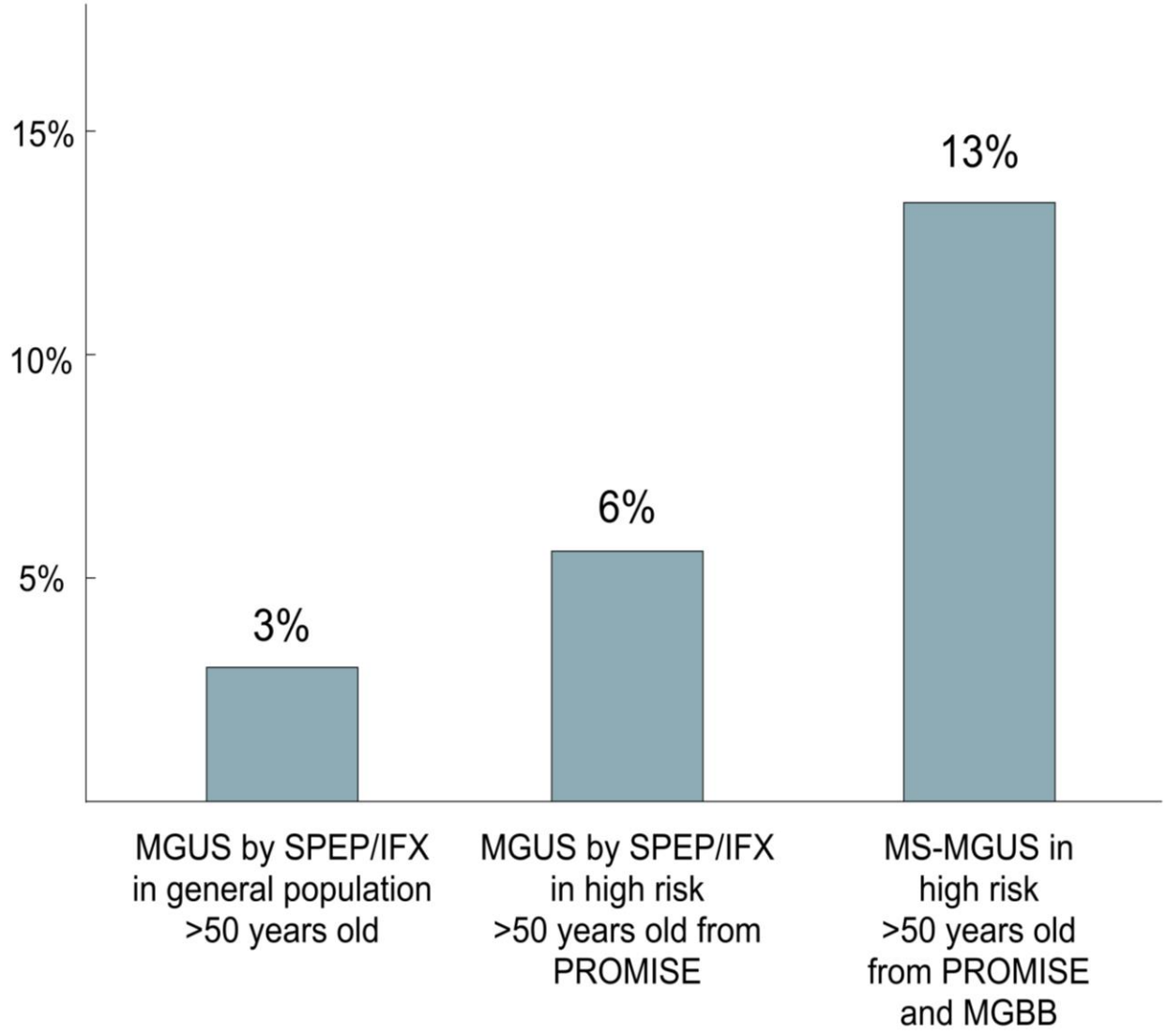
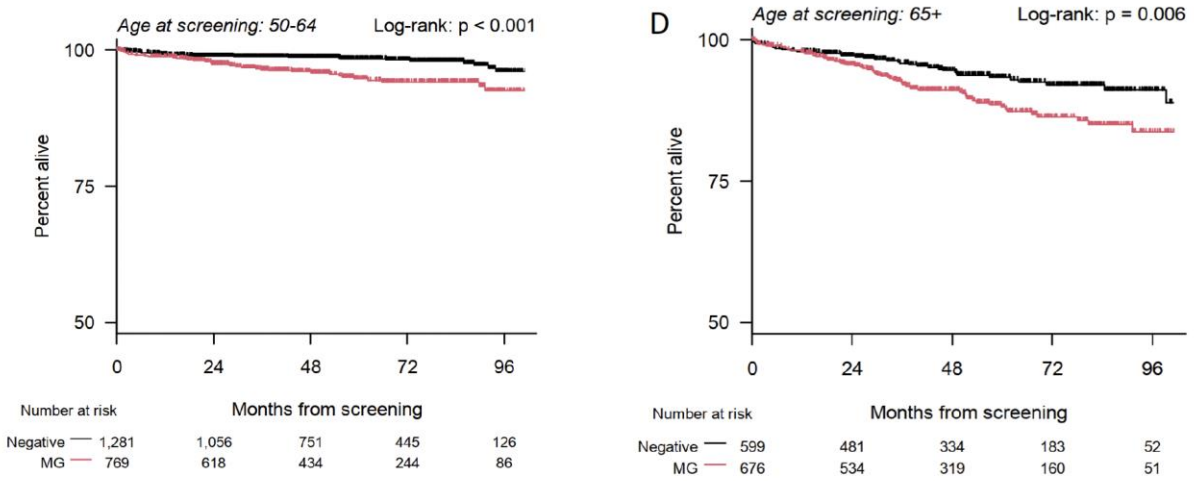
Prevalence of MGUS in a high-risk population

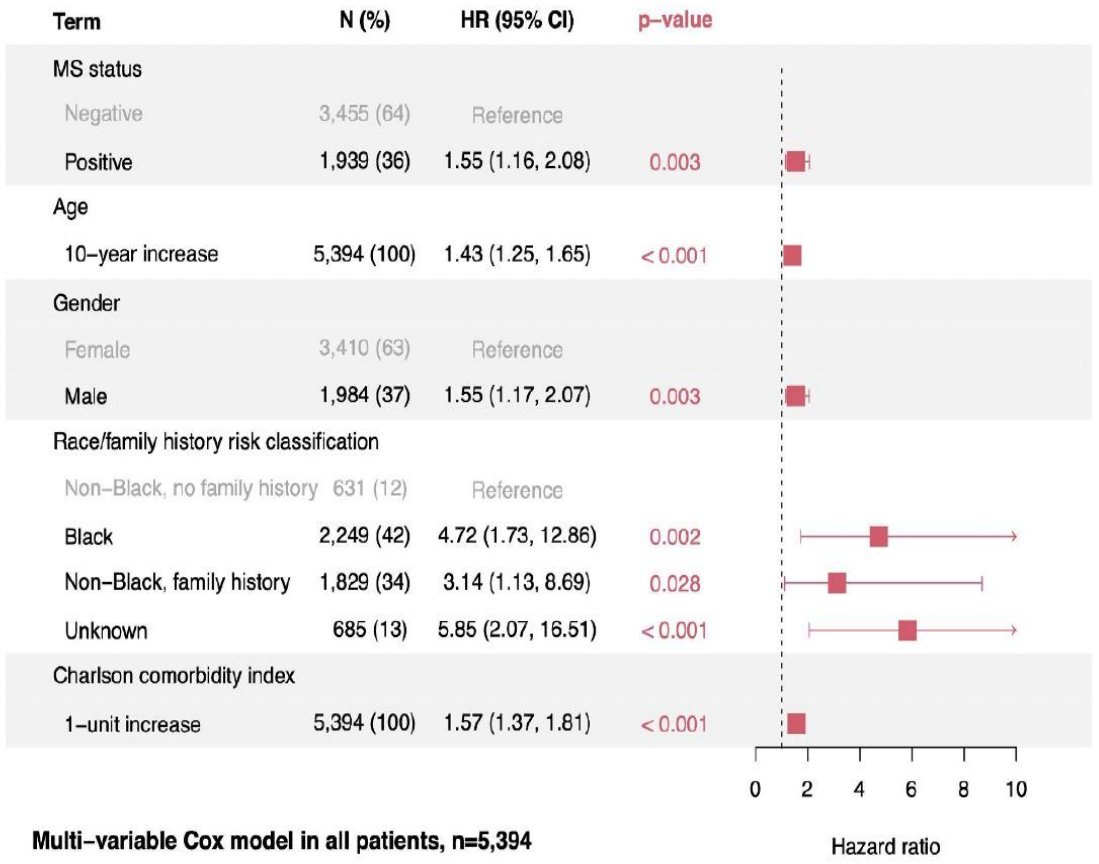




Elkhoury et al, Lancet Hematology 2022

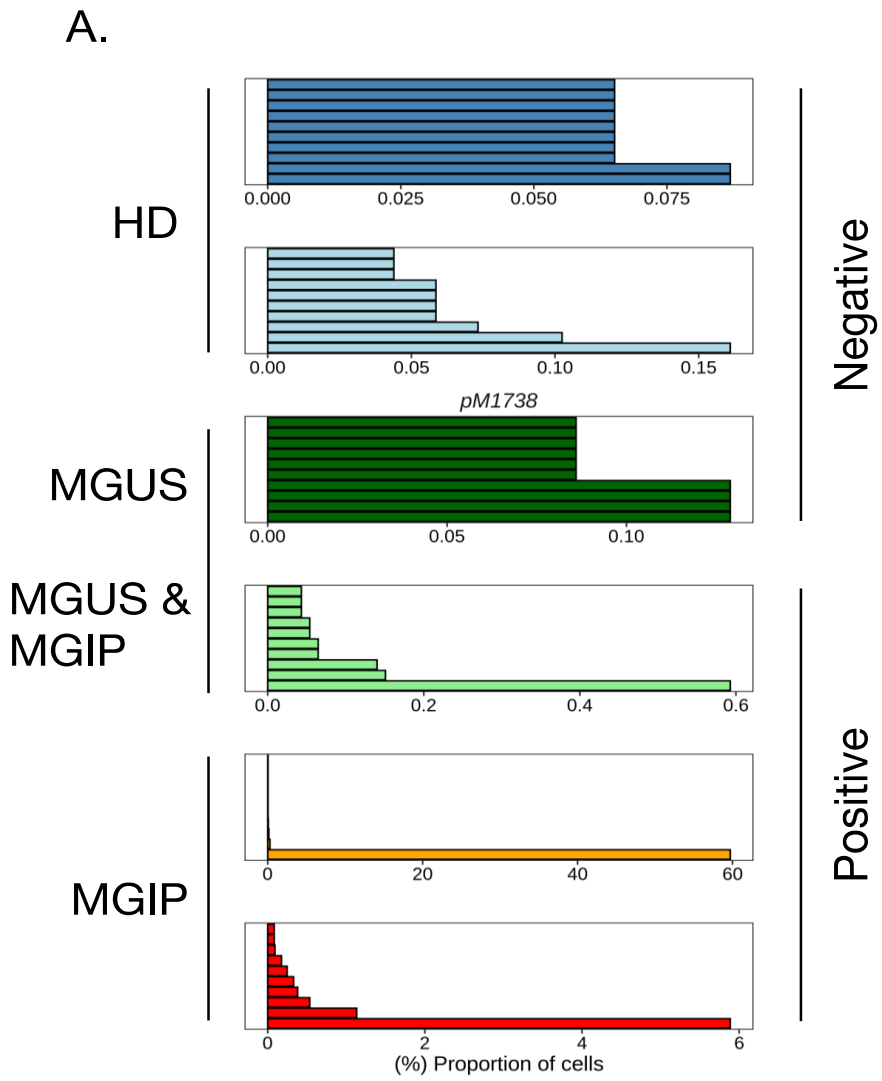
Worse overall survival and association with all cause mortality

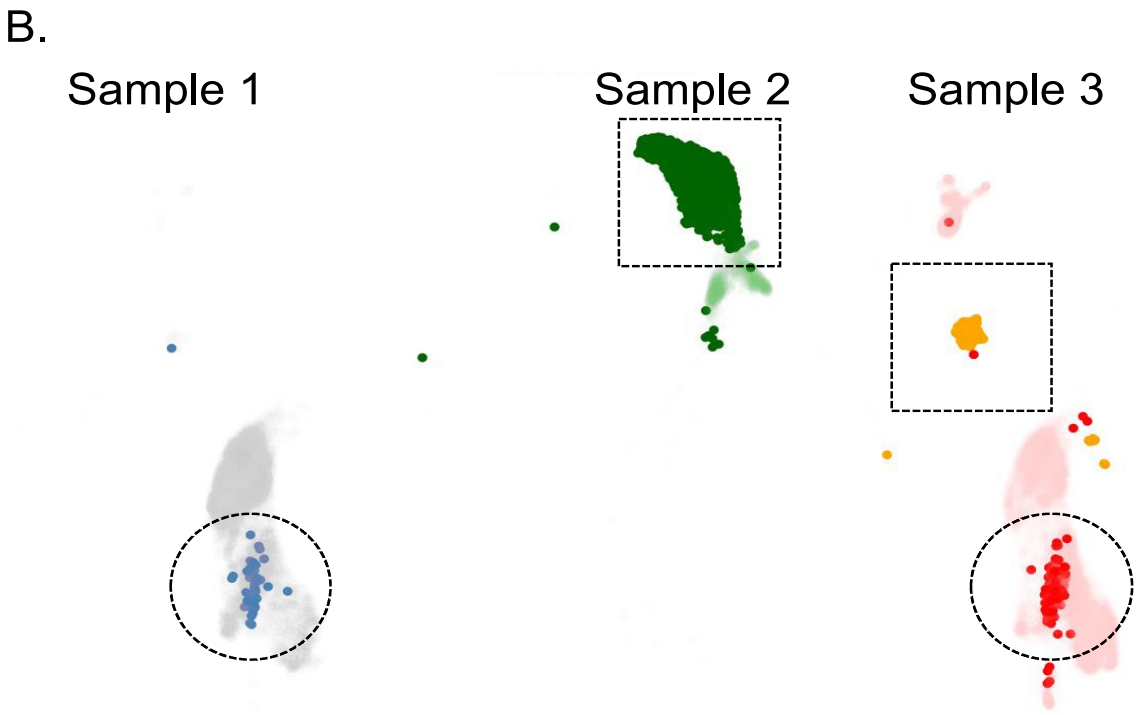


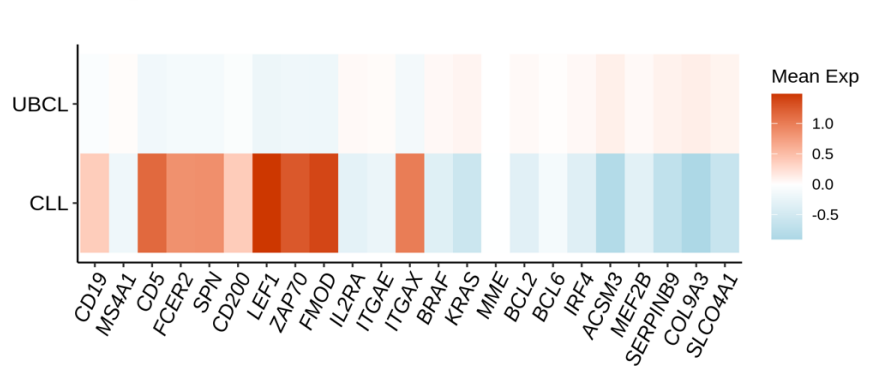


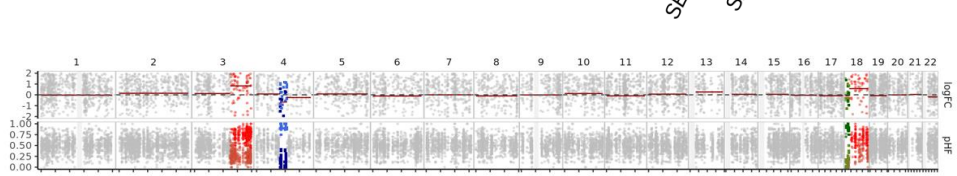
Elkhoury et al, Lancet Hematology 2022

MGIP identifies a lymphoid clone in the peripheral blood



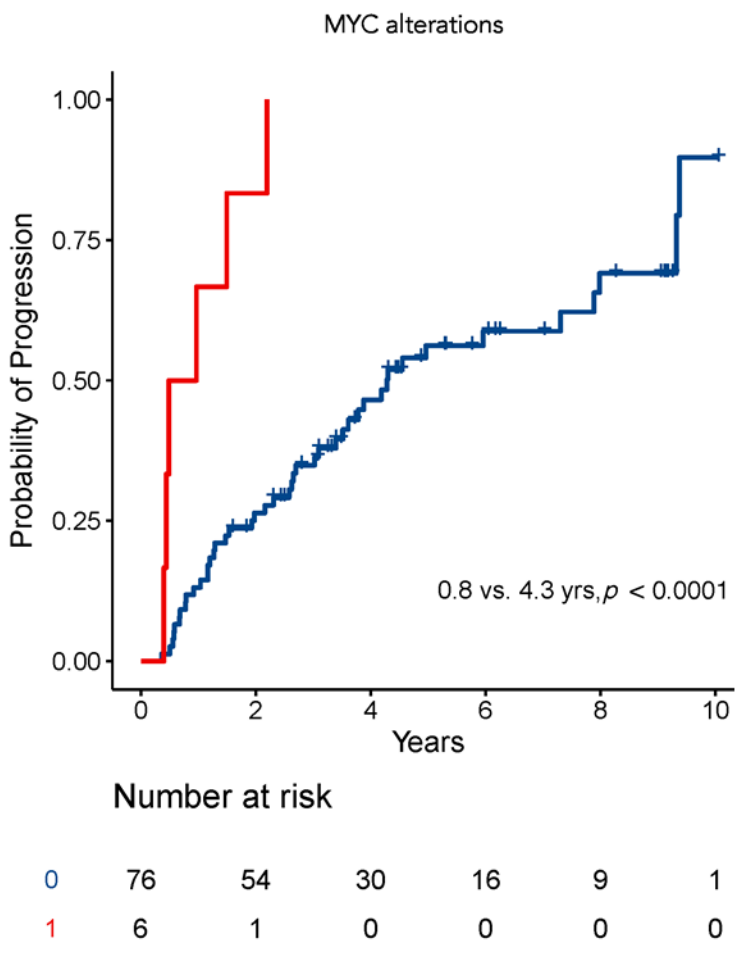


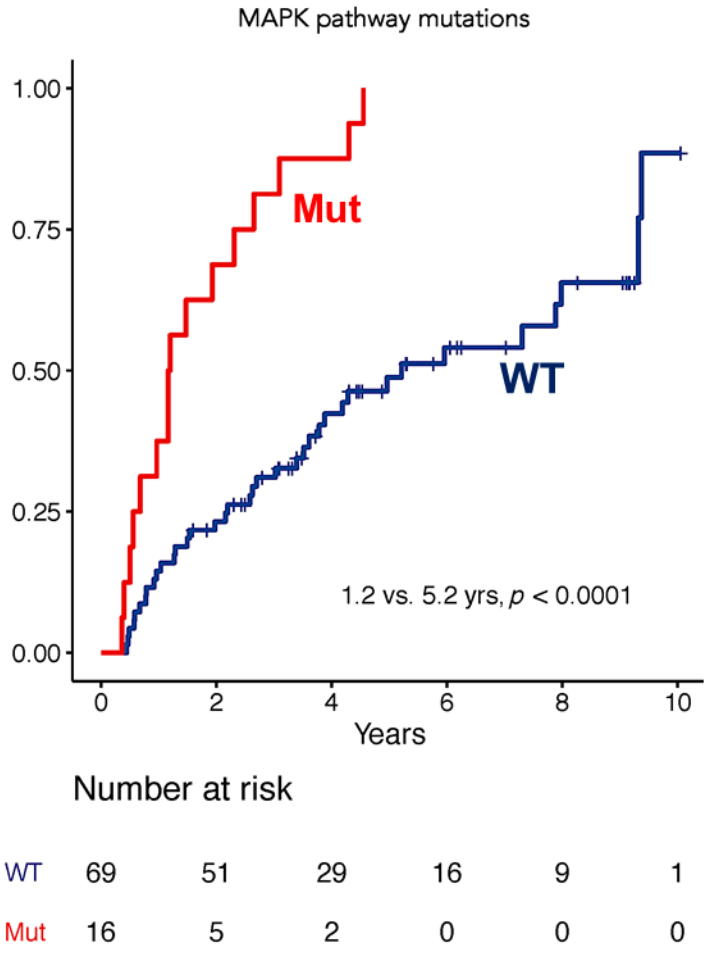


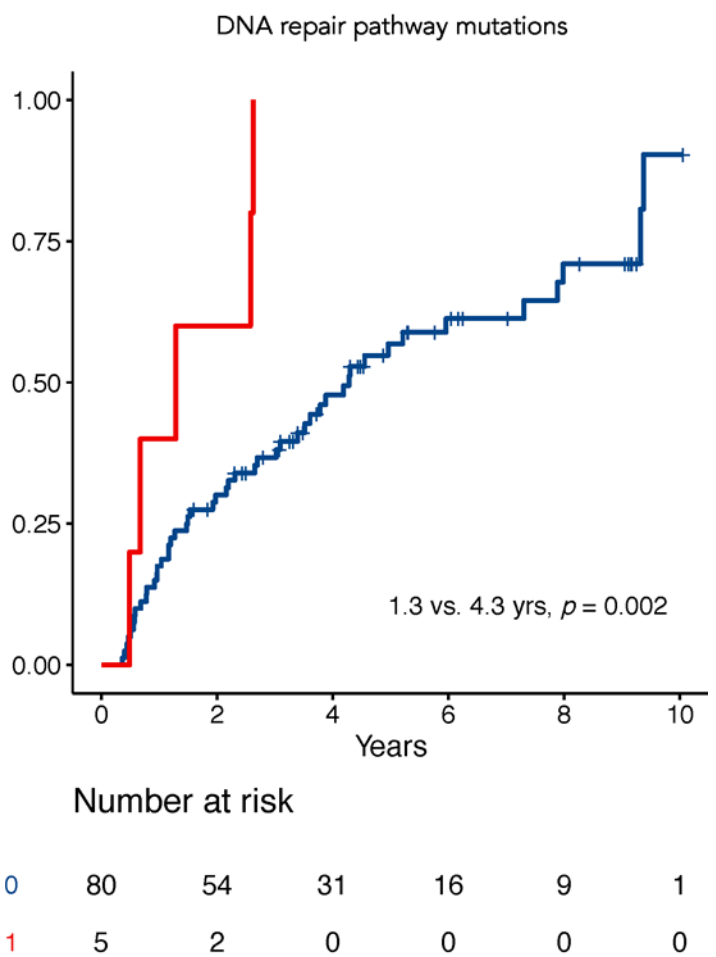


Preliminary unpublished data

Risk stratification of MGUS and SMM to predict progression to MM

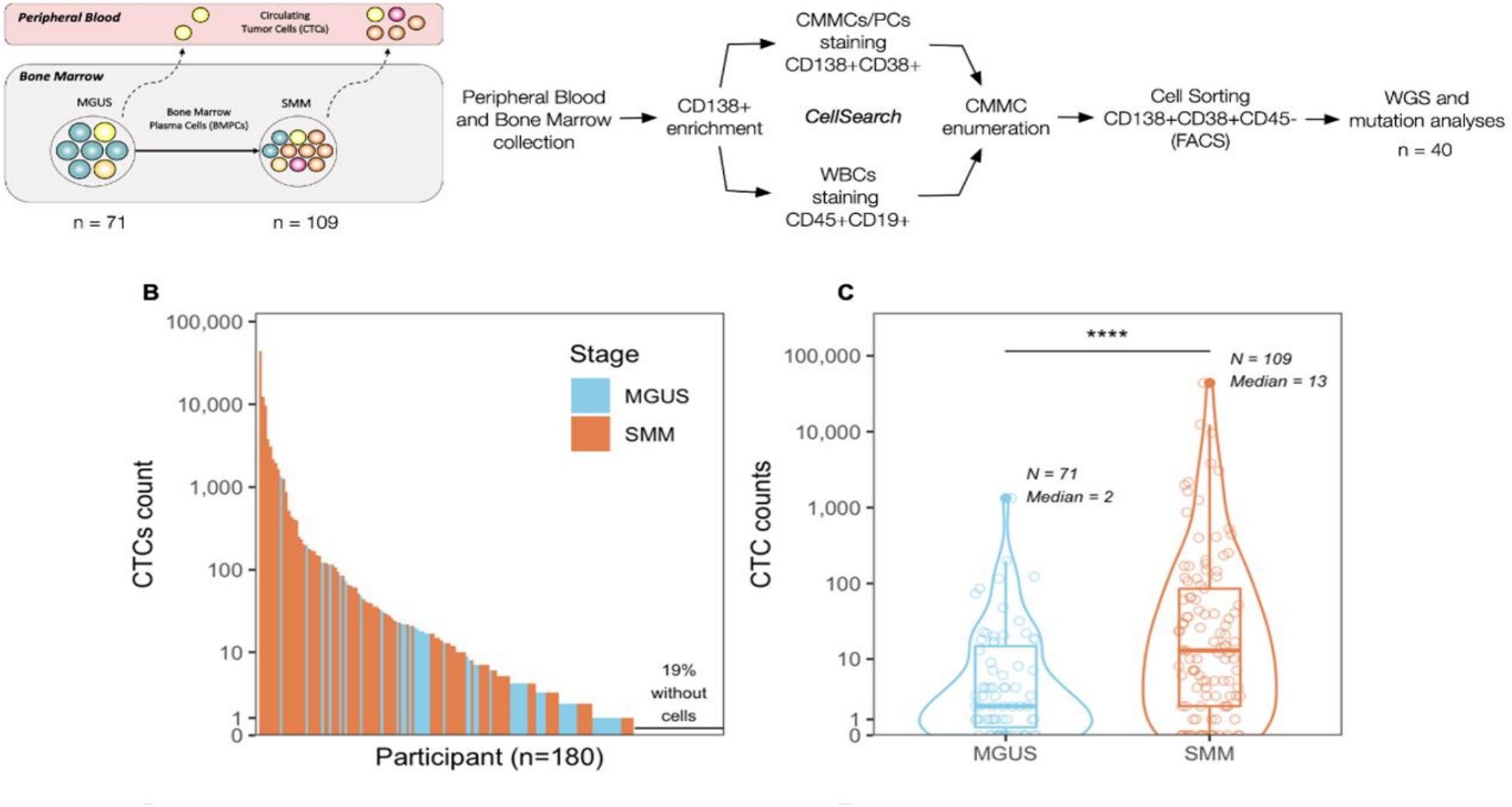






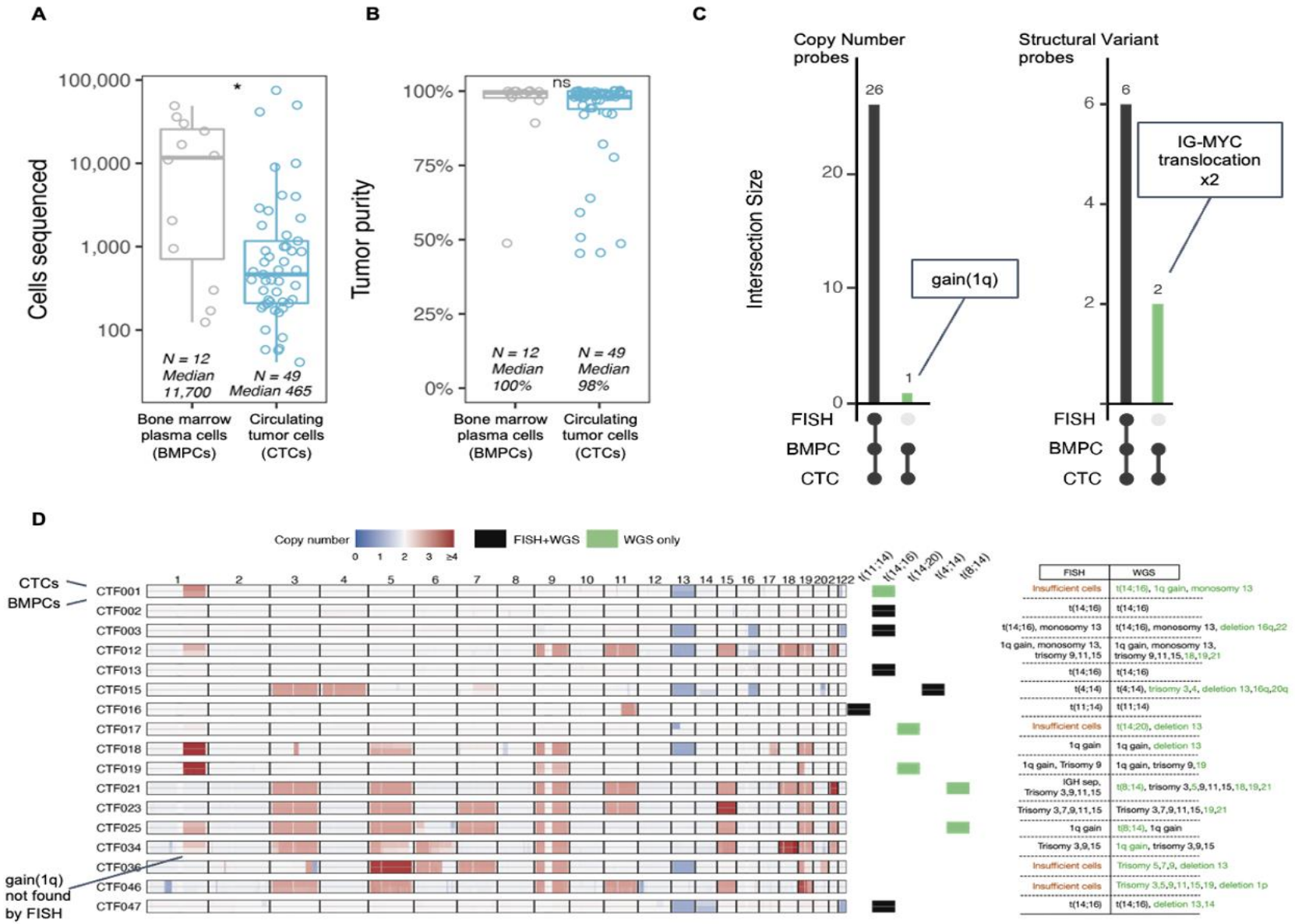
Bustoros et al, JCO 2021

MinimuMM-seq: WGS of CTCs for minimally invasive molecular characterization of clonal evolution



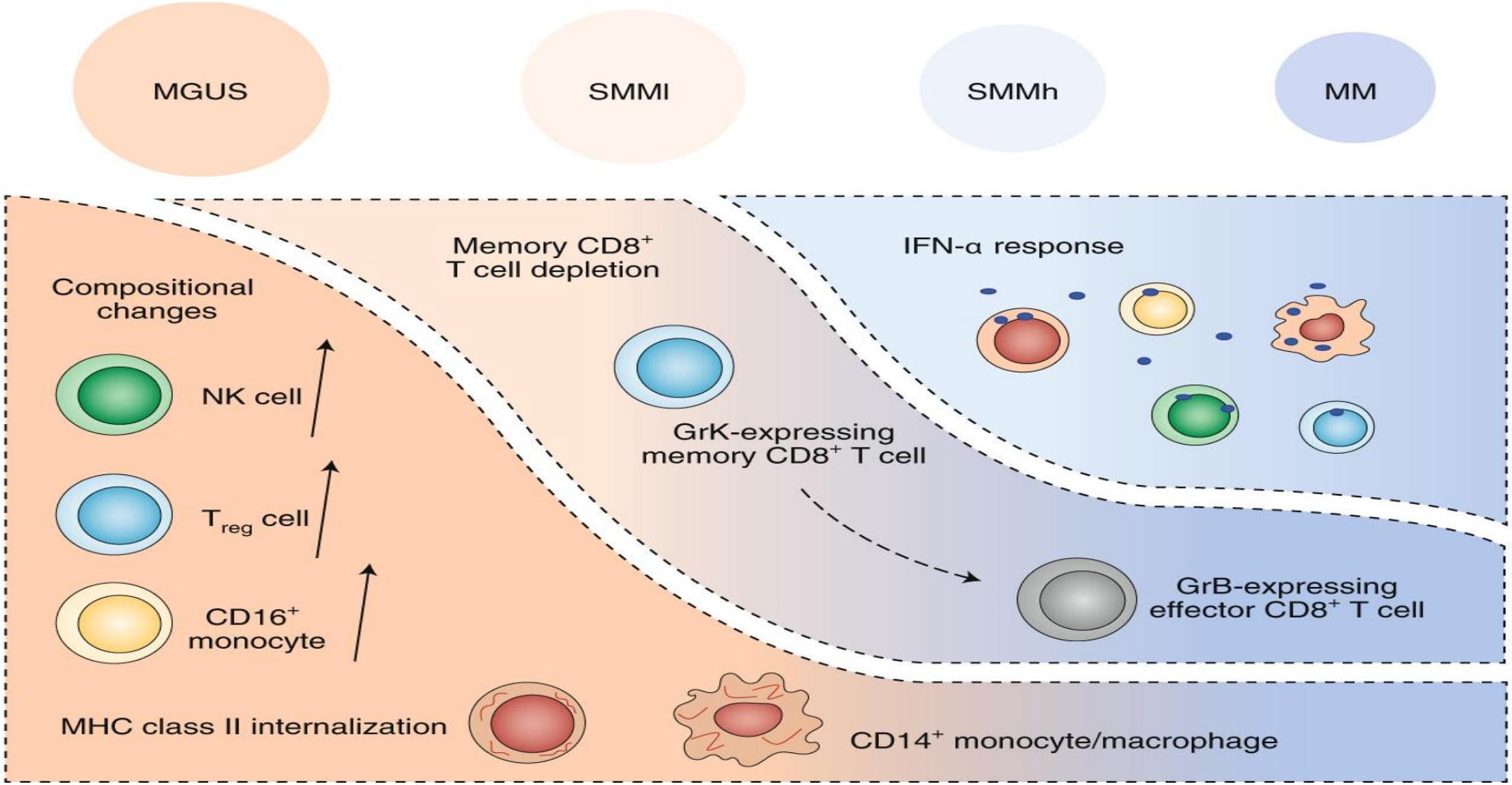
Cancer discovery, 2022

Whole genome sequencing can replace FISH



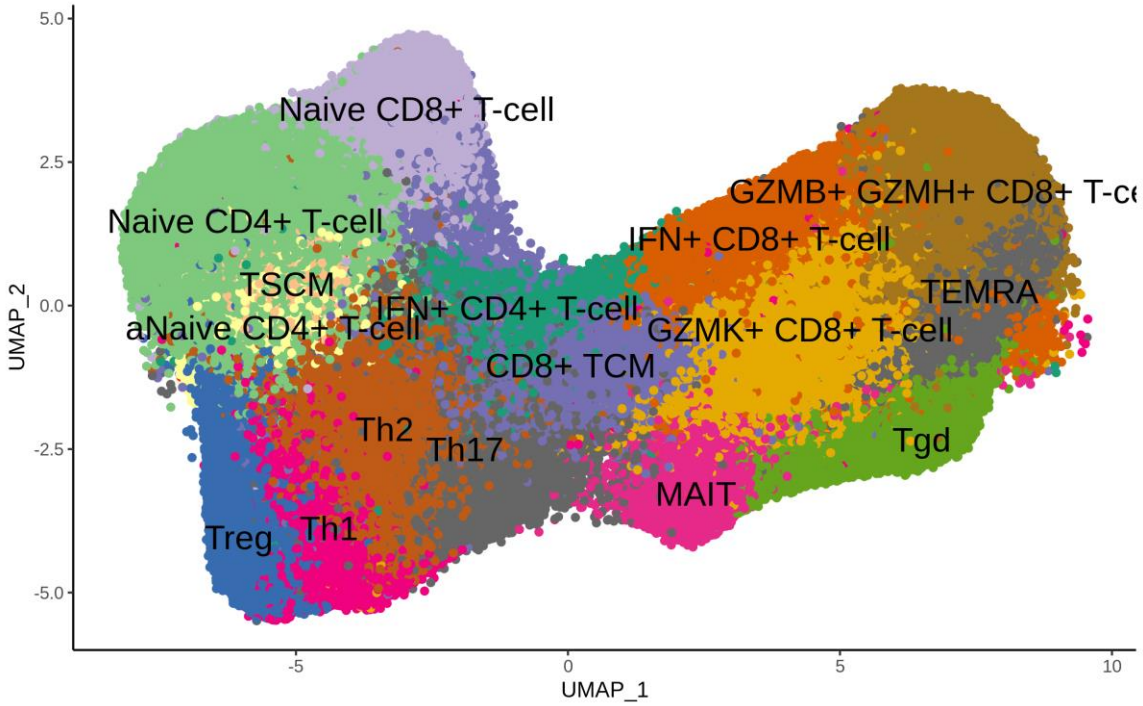
Cancer discovery, 2022

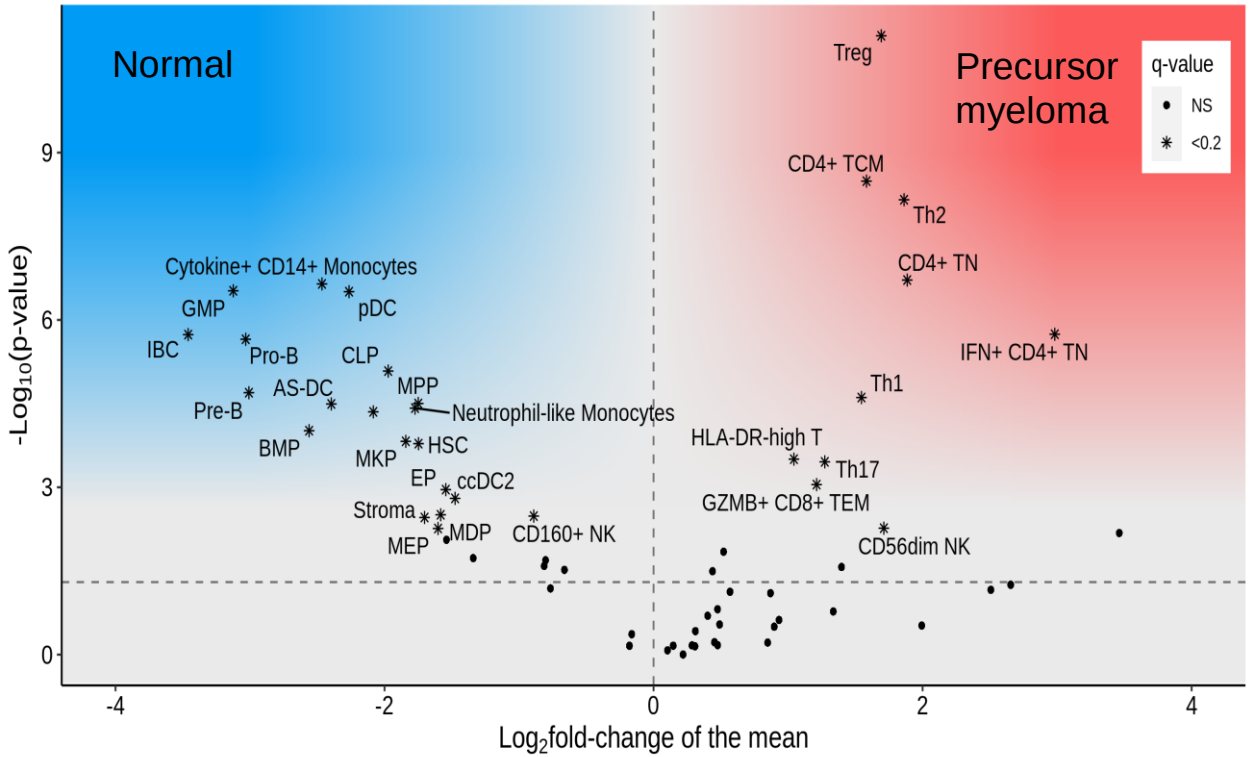
Early alterations in the immune microenvironment



Bailur et al. JCI Insight 2019
Kourelis et al. Blood Cancer J 2019
Zavidij et al. Nat Cancer 2020
Bashin et al. ASH 2020
Liu et al. Nat Comm 2021

Can we identify healthy from precursor MM by immune cell sequencing

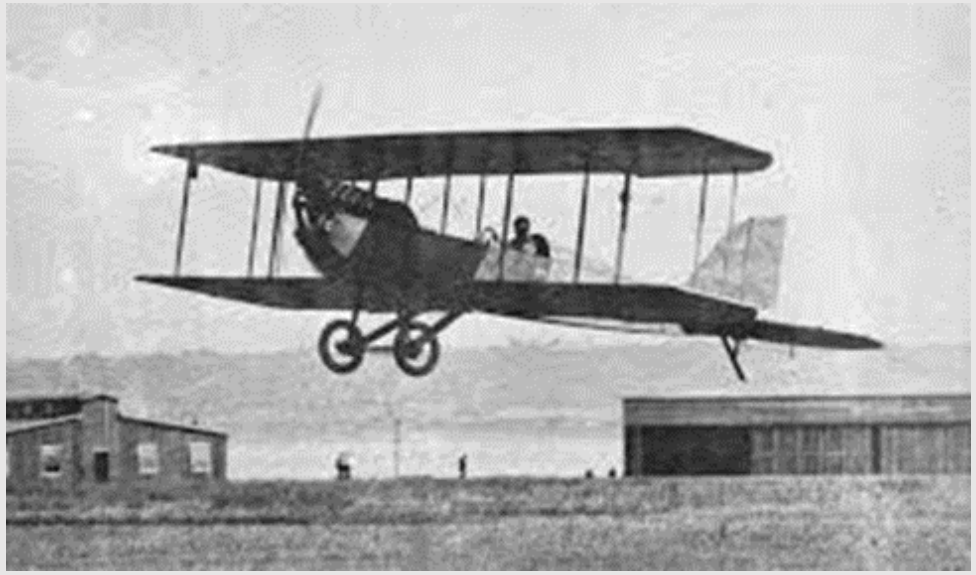




Single-cell RNA-sequencing (n=190), Healthy, MGUS and smoldering myeloma. Bone marrow and peripheral blood

Pistofidis et al. Cancer cell 2022

Our First Attempts of therapy in SMM

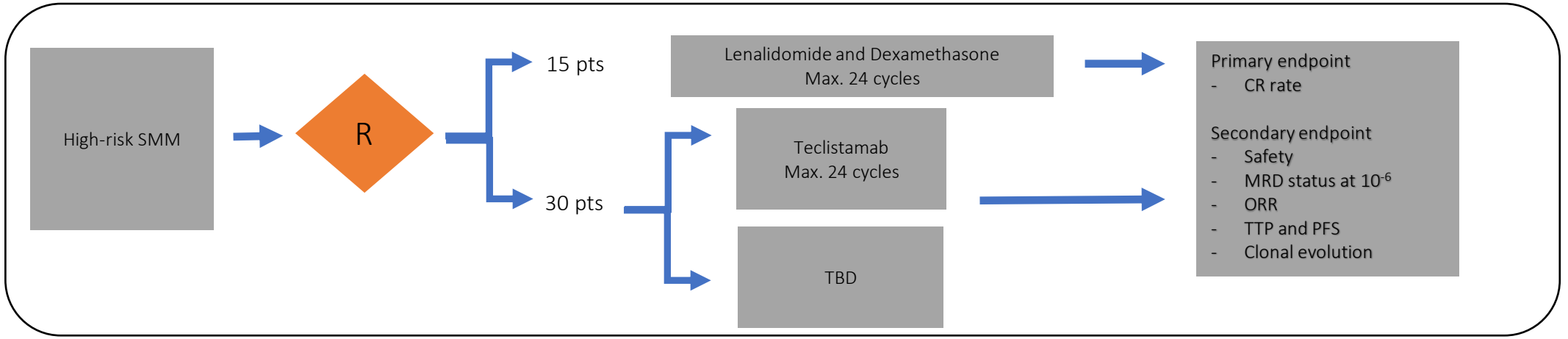


- Lenalidomide was the first proof of principle that early therapeutic intervention works in high risk SMM
- Possible immune regulation
- No overall survival benefit yet
- Cannot truly predict who had benefit and who had clonal selection and tumor resistance

Where we are heading

- Develop precision interception based on genomic/immune profile
- t11:14- venetoclax
- Vaccine therapy for MGUS
- Immunotherapy early to control the clone without the need of traditional myeloma therapy
- Identify markers of response or resistance

Immuno-PRISM (PRecision Intervention Smoldering Myeloma): A Randomized Phase II Platform Study of Select Immunotherapies for High-Risk Smoldering Myeloma



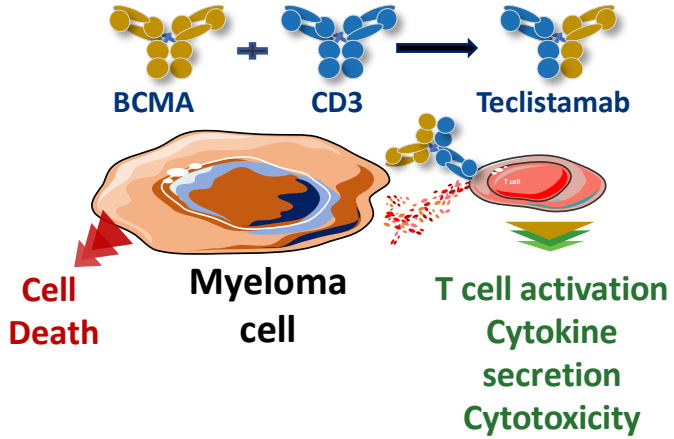
**If a participant randomized to the control arm experiences confirmed IMWG disease progression at any time during the treatment period, they may choose to receive the investigational agent for up to 24 cycles.*

Inclusion Criteria:

High risk SMM defined as having 1 of the following 2 criteria:

1. **High risk per "20-2-20" Criteria defined as presence of any two of the following:**
   - Serum M spike ≥ 2 gm/dL
   - Involved to uninvolved free light chain (FLC) ratio ≥ 20
   - Bone marrow PC% ≥ 20%

   OR **total score** of 9 using the following scoring system:
   - FLC Ratio: >10-25 = 2, >25-40 = 3, > 40 = 5
   - Serum M Protein (g/dL): >1.5-3 = 3, >3 = 4
   - BMPC%: >15-20 = 2, >20-30 = 3, >30-40 = 5, >40 = 6
   - FISH abnormality (t(4,14), t(14,16), 1q gain, or del13q = 2
2. **Presence of ≥10% BMPC and at least one of the following:**
   - **Evolving pattern**
   - **Abnormal PC immunophenotype** (≥95% of BMPCs are clonal) and reduction of. ≥1 uninvolved immunoglobulin isotype. (Only IgG; IgA and IgM will be considered)
   - **High risk cytogenetics** defined as presence of t(4;14), t(14;16), t(14;20), 17p deletion, TP53 mutation, 1q21 gain



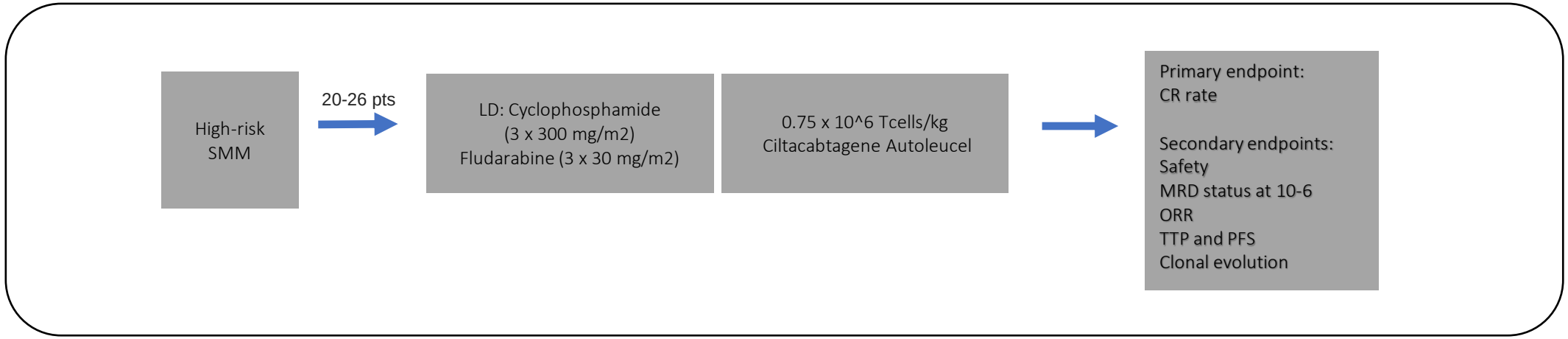
Teclistamab Dosing:

Cycle 1
- Step-up dose: days 1 and 3
- Treatment Dose: days 8, 15, 22

Cycle 2:
- Teclistamab (subcutaneous): Days 1, 8, 15 and 22

Cycle 3-24
- Teclistamab (subcutaneous): Days 1 and 15

CAR-PRISM (PRecision Intervention Smoldering Myeloma): Ciltacabtagene Autoleucel in High-Risk Smoldering Myeloma

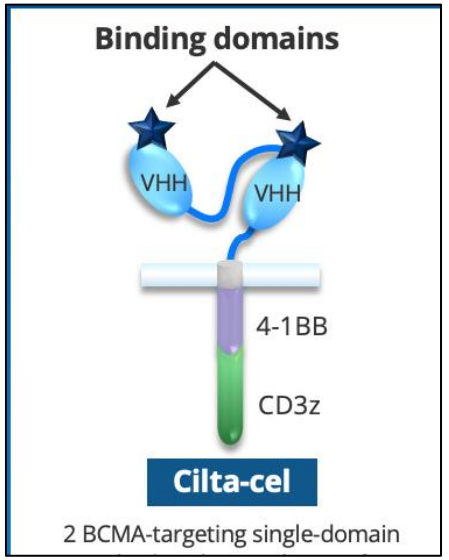


Inclusion Criteria:
High risk SMM defined as having 1 of the following 2 criteria:

1. **High risk per "20-2-20" Criteria defined as presence of any two of the following:**
   - Serum M spike ≥ 2 gm/dL
   - Involved to uninvolved free light chain (FLC) ratio ≥ 20
   - Bone marrow PC% ≥ 20%

   OR **total score** of 9 using the following scoring system:
   - FLC Ratio: >10-25 = 2, >25-40 = 3, > 40 = 5
   - Serum M Protein (g/dL): >1.5-3 = 3, >3 = 4
   - BMPC%: >15-20 = 2, >20-30 = 3, >30-40 = 5, >40 = 6
   - FISH abnormality (t(4,14), t(14,16), 1q gain, or del13q = 2

2. **Presence of ≥10% BMPC and at least one of the following:**
   - **Evolving pattern**
   - **Abnormal PC immunophenotype** (≥95% of BMPCs are clonal) and reduction of. ≥1 uninvolved immunoglobulin isotype. (Only IgG; IgA and IgM will be considered)
   - **High risk cytogenetics** defined as presence of t(4;14), t(14;16), t(14;20), 17p deletion, TP53 mutation, 1q21 gain



Cilta-Cel Dosing:

- First 3 patients at 0.5 x 10^6/kg cells
- Subsequent patients at 0.75 x 10^6/kg cells
- Stagged enrollment for first 3 patients
- Safety criteria

Dana-Farber Cancer Institute

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