



# FDA-AACR Workshop to Examine Underrepresentation of African Americans in Multiple Myeloma Clinical Trials

Thursday, February 13, 2020

Washington Marriott at Wardman Park, Washington, D.C.

 Join the conversation with #MyelomaDiversity 

**Kenneth C. Anderson, M.D.**

Director, Jerome Lipper Multiple Myeloma Center,

Dana-Farber Cancer Institute;

Kraft Family Professor of Medicine Harvard Medical School

**Consultant:** Celgene, Bristol Myers Squibb, Millennium-Takeda,  
Sanofi-Aventis, Janssen, Gilead, Precision Biosciences, Tolero

**Scientific Founder:** Oncopep, C4 Therapeutics

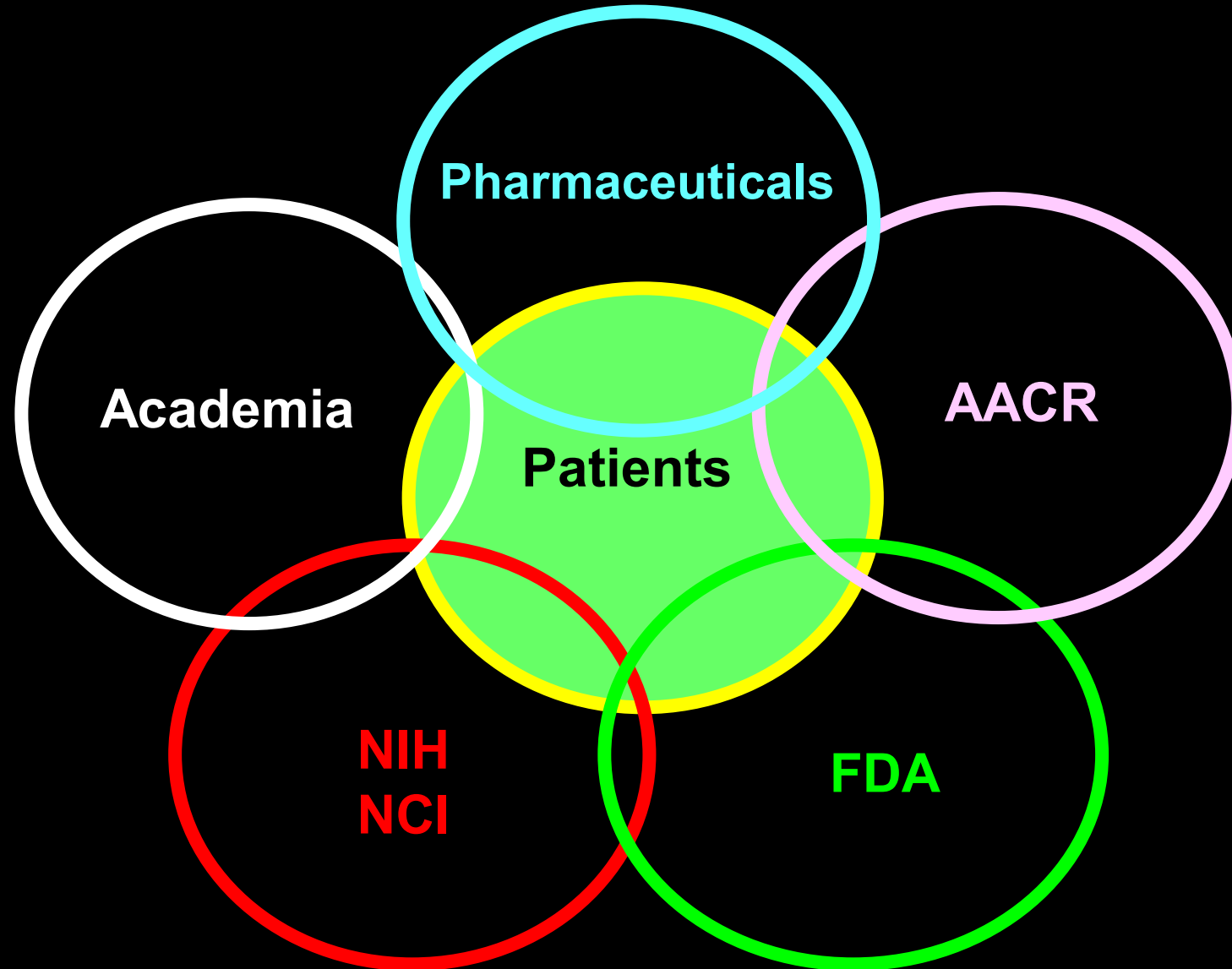
# MULTIPLE MYELOMA

- Monoclonal protein with excess BM plasma cells
- Associated with hypercalcemia, renal dysfunction, anemia, bone disease, hyperviscosity, recurrent infections, neuropathy
- High incidence in African Americans, Pacific Islanders
- Mean age 62 years men, 61 years women
- MGUS (all patients), irradiation or petroleum products, farmers, paper producers, furniture manufacturers, wood workers at risk
- Associated with second cancers in 10% cases

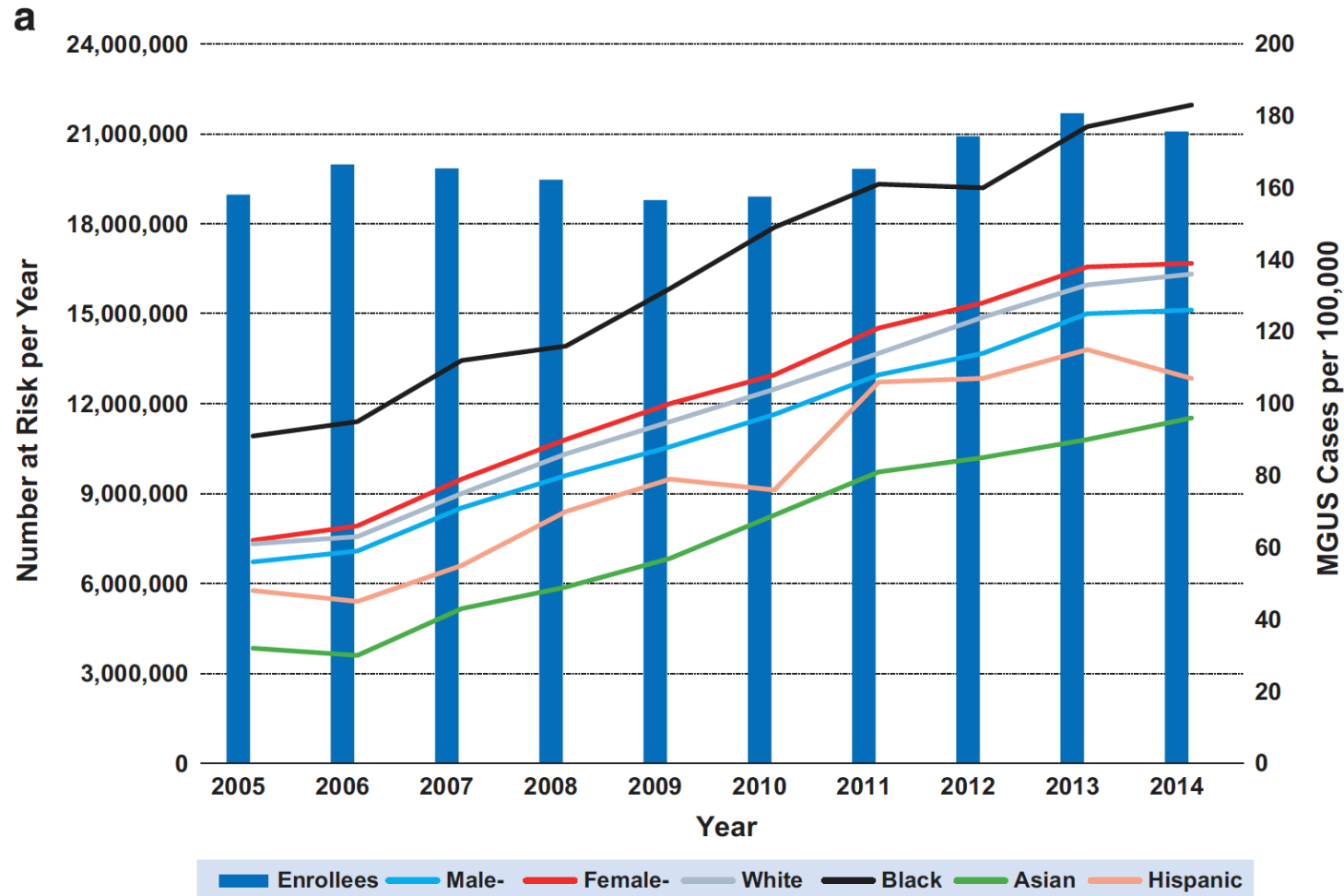
- **Proteasome inhibitors:** bortezomib, carfilzomib, ixazomib;  
**immunomodulatory drugs:** thalidomide, lenalidomide, pomalidomide;  
**HDAC inhibitor:** panobinostat; **monoclonal antibodies:** elotuzumab and daratumumab; **nuclear transport inhibitor:** selinexor
- **Target MM in the BM microenvironment**, alone and in combination, to overcome conventional drug resistance in vitro and in vivo
- Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy
- **26 FDA approvals and median patient survival prolonged 3-4 fold, from 3 to at least 8-10 years, and MM is a chronic illness in many patients.**



# MULTIPLE MYELOMA IS A COLLABORATIVE MODEL FOR RAPID TRANSLATION OF NOVEL AGENTS FROM BENCH TO BEDSIDE



# MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE (MGUS)



- 3% of population at age 50
- Increases with age
- 3 times more common in AA
- Younger age for AA
- 3 times more in familial cases

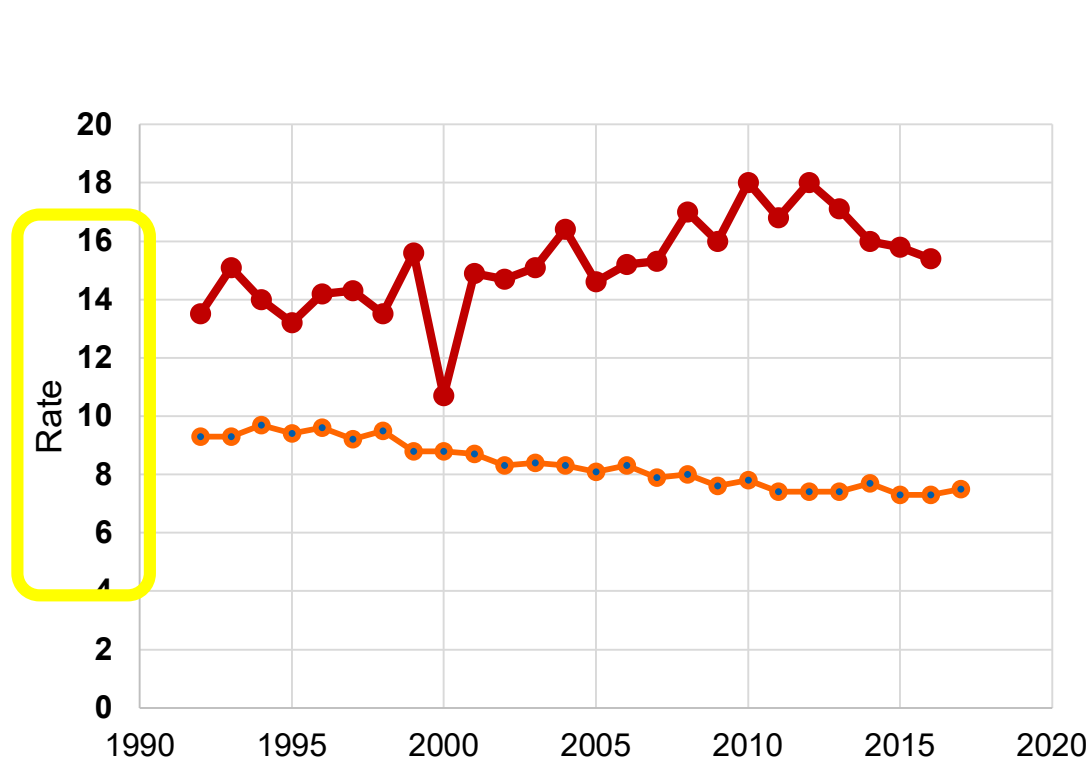
# EXAMINE UNDERREPRESENTATION OF AFRICAN AMERICANS IN MULTIPLE MYELOMA CLINICAL TRIALS

- Incidence rates higher in African Americans than whites:
  - 15.9 vs 7.5 cases per 100,000, respectively
- Mortality higher in African Americans than in whites:
  - 5.6 vs 2.4 deaths per 100,000, respectively
- SEER: 1973-2005: African Americans higher OS, but 5 year relative survival rates increased for whites (26.3% to 35%,  $p < 0.005$ ), but not African Americans (31% to 34%)

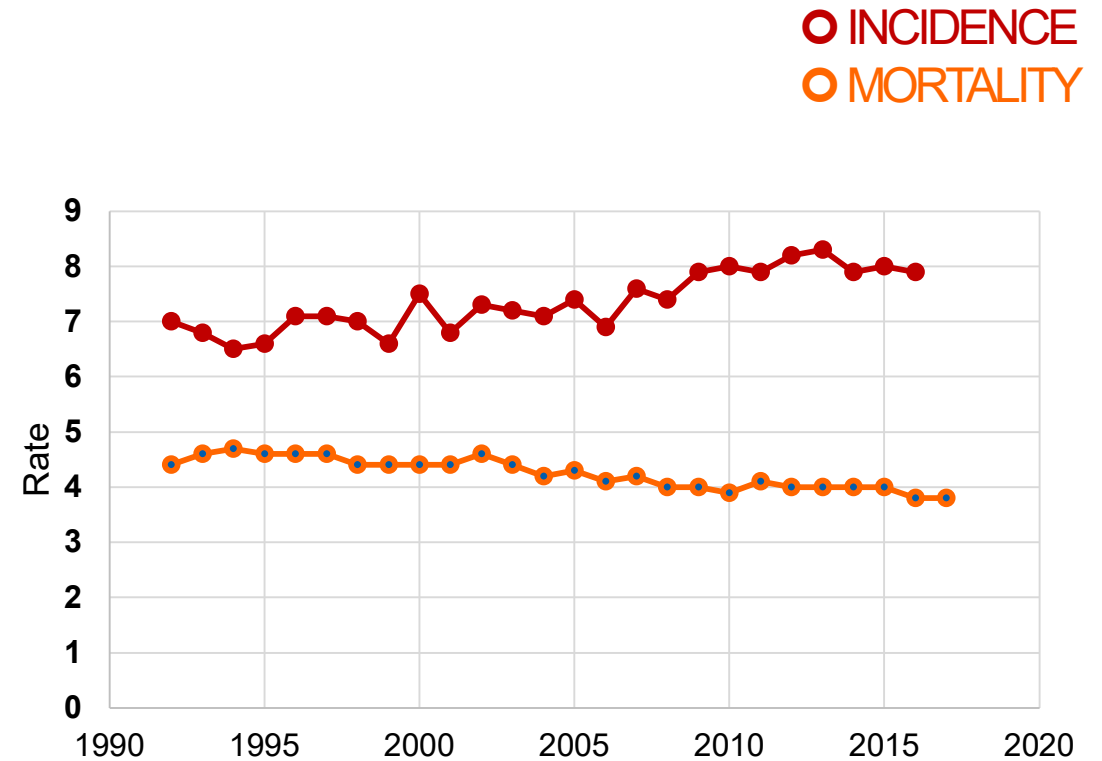
De Sanctis et al CA Cancer J 2019; 69: 211-13.  
Waxman et al Blood 2010; 116: 5501-6.

# MULTIPLE MYELOMA INCIDENCE AND MORTALITY IN MEN

Mortality is decreasing similarly for black men and white men.



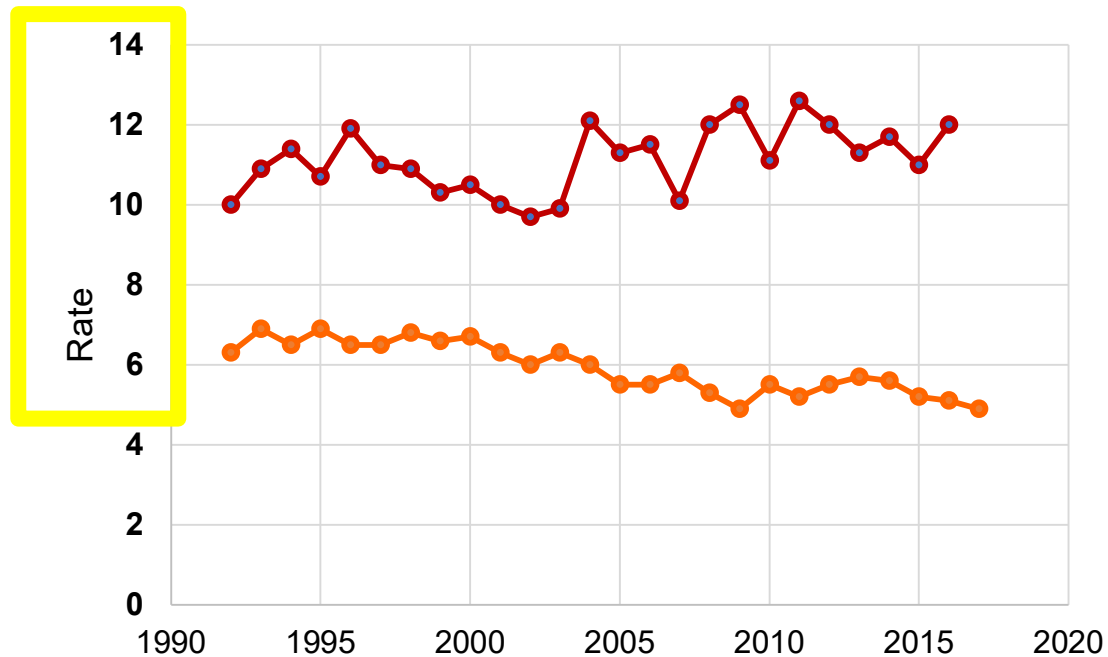
Black men



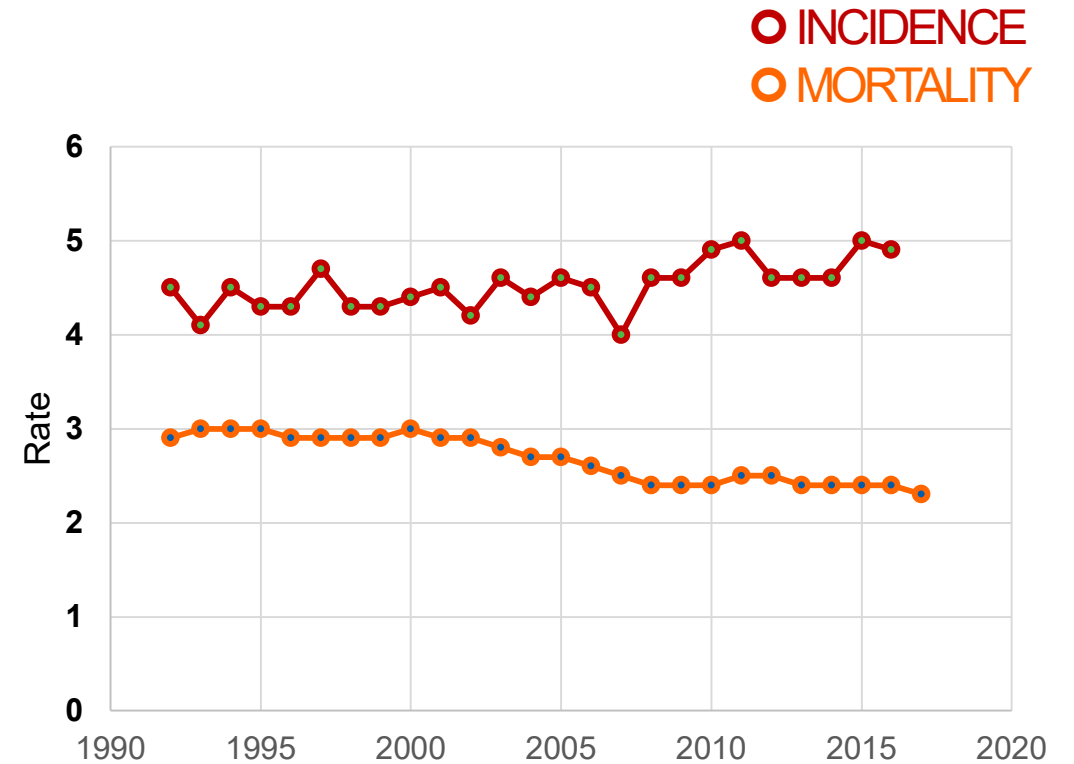
White men

# MULTIPLE MYELOMA INCIDENCE AND MORTALITY IN WOMEN

Mortality is decreasing similarly for black women and white women.



Black women



White women

- African Americans more commonly have IgH translocations than European ancestry: t(11:14), t(14:16), t(14:16)
- African Americans less likely than whites to have TP53/17p deletions

- 2003 - 2017 FDA New Drug Applications in myeloma:
  - Low rates of African American patient enrollment in pivotal (4.5%) and international (1.8%) trials
- 2002 - 2011 Cooperative Group clinical trials:
  - 13% African American patient enrollment, compared to 16.5% for prior 10 years. Most does not include novel agents or stem cell transplant.
- NB: African American patients treated with novel agents in FDA approval trials or in Veterans Administration Hospital system have similar or even improved outcome.

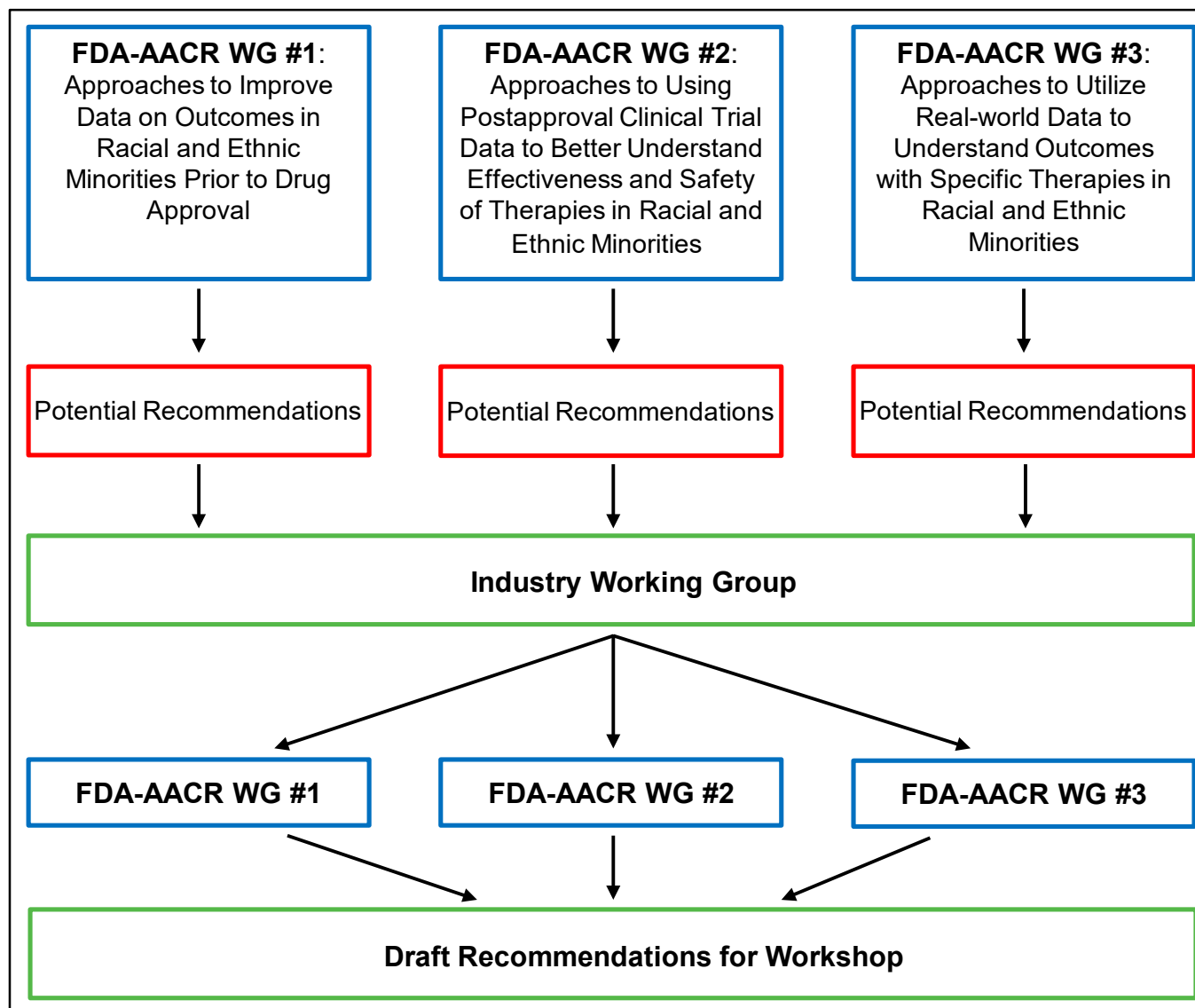
Ailawadhi et al Blood CA J 2018; Pulte et al Blood Advances 2018; Fillmore et al Blood 2019; 2615-17.

# EXAMINE UNDERREPRESENTATION OF AFRICAN AMERICANS IN MULTIPLE MYELOMA CLINICAL TRIALS

- African Americans are 13% of US population and 20% myeloma patients, but clinical trials to date have not characterized either efficacy or safety in these patients.



# WORKING GROUPS



FDA and AACR partnered on this workshop, forming working groups of experts to develop recommendations for improving and understanding data on outcomes and effectiveness of multiple myeloma therapies in African Americans in preapproval, postapproval, and real-world settings.

## ■ FDA

- **Lola A. Fashoyin-Aje, MD, MPH**, Acting Deputy Director, Division of Oncology 3, Office of Oncologic Diseases, CDER, FDA
- **Nicole J. Gormley, MD**, Acting Director, Division of Hematologic Malignancies 1, Office of Oncologic Diseases, CDER, FDA
- **Paul G. Kluetz, MD**, Deputy Director, Oncology Center of Excellence, FDA

## ■ AACR

- **Kenneth C. Anderson, MD, FAACR**, Program Director, Jerome Lipper Multiple Myeloma Center and LeBow Institute for Myeloma Therapeutics, Dana-Farber Cancer Institute; Kraft Family Professor of Medicine, Harvard Medical School

# AGENDA

## SESSION I: STATE OF THE SCIENCE & CLINICAL IMPLICATIONS

SESSION COCHAIR: KENNETH C. ANDERSON, MD

|          |                                                                                                                                                                                                                           |
|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 8:15 AM  | <b>Overview of “FDA-AACR Workshop to Examine Under-representation of African Americans in Multiple Myeloma Clinical Trials”</b><br>Lola A. Fashoyin-Aje, MD, MPH, & Nicole Gormley, MD, U.S. Food and Drug Administration |
| 8:35 AM  | <b>FDA analysis of multiple myeloma trials supporting approval</b><br>Laura Fernandes, PhD, & Bindu Kanapuru, MD, U.S. Food and Drug Administration                                                                       |
| 8:55 AM  | <b>Evaluation of characteristics and outcomes of multiple myeloma patients from an EHR-derived database</b><br>Kathleen Maignan, MSN, NP, Flatiron Health                                                                 |
| 9:15 AM  | <b>Scope of the issue: Discovery science, differences in clinical features, prognostic factors, differential outcomes</b><br>Nikhil C. Munshi, MD, Dana-Farber Cancer Institute                                           |
| 9:35 AM  | <b>Biology and genomic differences of multiple myeloma</b><br>Shaji K. Kumar, MD, Mayo Clinic Cancer Center                                                                                                               |
| 9:55 AM  | <b>Increasing minority accrual in myeloma clinical trials: Emory experience and lessons learned</b><br>Ajay K. Nooka, MD, Winship Cancer Institute of Emory University                                                    |
| 10:15 AM | <b>BREAK</b>                                                                                                                                                                                                              |

**SESSION II: APPROACHES TO IMPROVE DATA ON OUTCOMES IN RACIAL AND ETHNIC MINORITIES  
PRIOR TO DRUG APPROVAL  
SESSION CHAIR: CRAIG E. COLE, MD**

**10:35 AM**      **Overview of Working Group 1 Recommendations**  
Craig E. Cole, MD, Michigan State University Breslin Cancer Center

**10:50 AM**      **PANEL DISCUSSION AND AUDIENCE INPUT**

**Moderator:**      Craig E. Cole, MD, Michigan State University Breslin Cancer Center

**Panelists:**      Vishal Bhatnagar, MD, U.S. Food and Drug Administration

                 Ruemu E. Birhiray, MD, Hematology Oncology of Indiana

                 Yelak Biru, Patient Advocate

                 Mihaela Popa McKiver, MD, PhD, Bristol-Myers Squibb

                 Khalid Mezzi, MD, MBA, Amgen

**11:50 AM**      **LUNCH BREAK (ON YOUR OWN)**

# AGENDA

## SESSION III: APPROACHES TO USING POST-APPROVAL CLINICAL TRIAL DATA TO BETTER TO UNDERSTAND EFFECTIVENESS AND SAFETY OF THERAPIES IN RACIAL AND ETHNIC MINORITIES

SESSION CHAIR: RICHARD F. LITTLE, MD

**12:55 PM**      **Overview of Working Group 2 Recommendations**  
Richard F. Little, MD, National Cancer Institute

### **1:10 PM**      **PANEL DISCUSSION AND AUDIENCE INPUT**

**Moderator:**      Richard F. Little, MD, National Cancer Institute

**Panelists:**      Bindu Kanaparu, MD, U.S. Food and Drug Administration  
Sikander Ailawadhi, MD, Mayo Clinic Cancer Center Jacksonville  
Wan-Jen Hong, MD, Genentech  
Rachel Kobos, MD, Janssen Pharmaceuticals  
Shaji K. Kumar, MD, Mayo Clinic Cancer Center  
Angela X. Qu, MD, PhD, Parexel  
Tiffany H. Williams, Patient Advocate

**2:10 PM**      **BREAK**

**SESSION IV: APPROACHES TO UTILIZE REAL-WORLD DATA TO UNDERSTAND OUTCOMES  
WITH SPECIFIC THERAPIES IN RACIAL AND ETHNIC MINORITIES  
SESSION CHAIR: JOSEPH M. UNGER, PHD, MS**

**2:30 PM**      **Overview of Working Group 3 Recommendations**  
**Joseph M. Unger, PhD, MS**, Fred Hutchinson Cancer Research Center

**2:45 PM**      **PANEL DISCUSSION AND AUDIENCE INPUT**

**Moderator:**      **Joseph M. Unger, PhD, MS**, Fred Hutchinson Cancer Research Center  
**Panelists:**      **Kunthel By, PhD**, U.S. Food and Drug Administration  
                         **Daniel Auclair, PhD**, Multiple Myeloma Research Foundation  
                         **Ruthanna Davi, PhD**, Acorn AI  
                         **Irene M. Ghobrial, MD**, Dana-Farber Cancer Institute  
                         **Kathleen Maignan, MSN, NP**, Flatiron Health  
                         **William A. Wood, MD**, UNC Lineberger Comprehensive Cancer Center

# AGENDA

## SESSION V: CONCLUSIONS & FUTURE DIRECTIONS

### 3:45 PM PANEL DISCUSSION AND AUDIENCE INPUT

**Moderator:** Kenneth C. Anderson, MD, FAACR, Dana-Farber Cancer Institute

**Panelists:** Lola A. Fashoyin-Aje, MD, MPH, U.S. Food and Drug Administration

Nicole Gormley, MD, U.S. Food and Drug Administration

Irene M. Ghobrial, MD, Dana-Farber Cancer Institute

Mihaela Popa McKiver, MD, PhD, Bristol-Myers Squibb

Joseph Mikhael, MD, Med, FRCPC, FACP, International Myeloma Foundation; TGen

Edith P. Mitchell, MD, Sidney Kimmel Cancer Center at Thomas Jefferson University

Tiffany H. Williams, Patient Advocate

### 4:45 PM Summary and Wrap-up

Kenneth C. Anderson, MD, FAACR, Dana-Farber Cancer Institute

### 4:55 PM Closing Remarks

Paul G. Kluetz, MD, U.S. Food and Drug Administration

### 5:00 PM ADJOURN

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JOIN THE CONVERSATION

# #MyelomaDiversity



@AACR

@FDAOncology

# PHOTOGRAPHY

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# Session I

## State of the Science and Clinical Implications

# **OVERVIEW OF FDA-AACR WORKSHOP AND WORKING GROUPS TO EXAMINE UNDER-REPRESENTATION OF AFRICAN AMERICANS IN MULTIPLE MYELOMA CLINICAL TRIALS**

Lola Fashoyin-Aje, MD,MPH and Nicole Gormley, MD  
Office of Oncologic Diseases  
U.S. Food and Drug Administration

# Outline

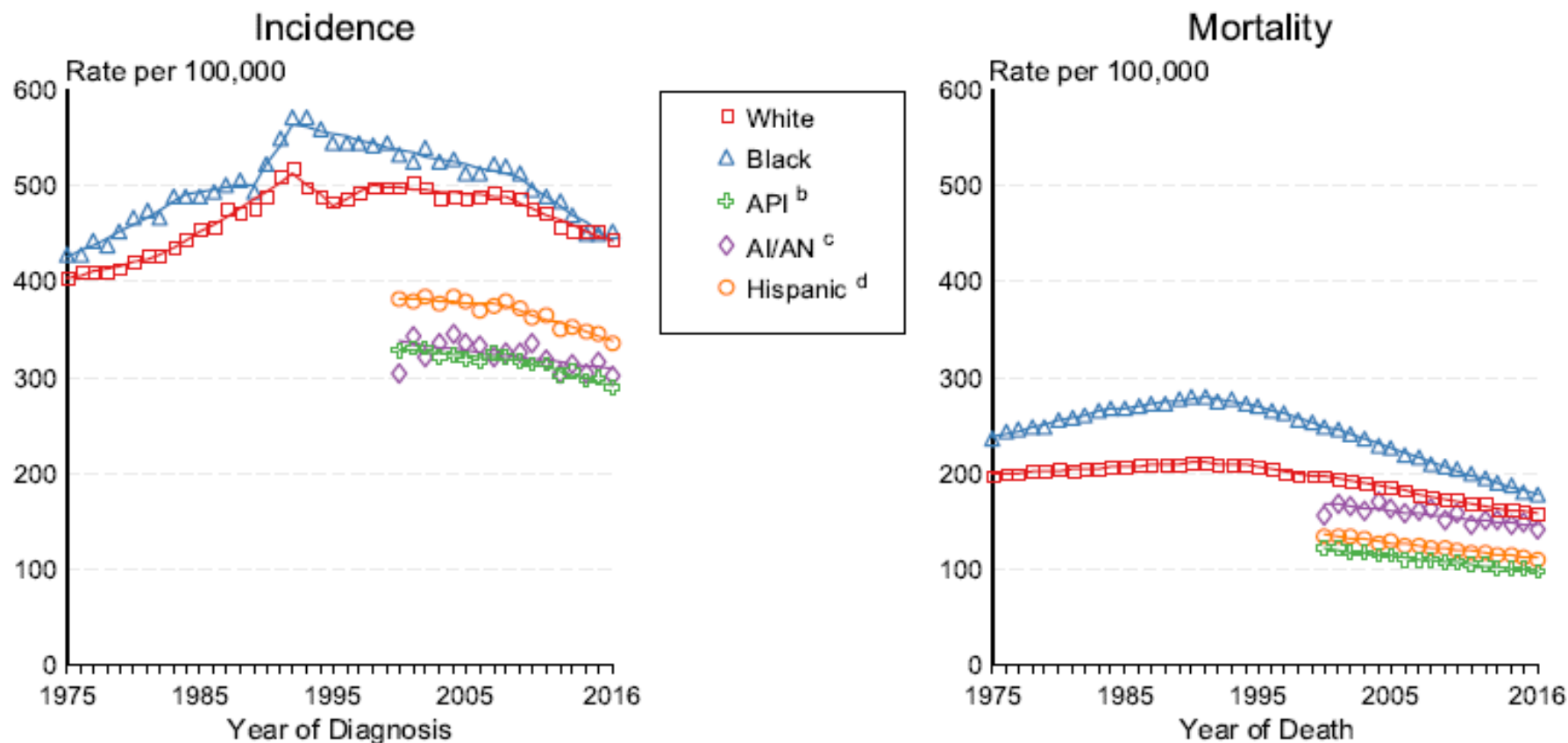
## PART 1

- Introduction (disparities, clinical trials in oncology)
- Racial/ethnic representation in cancer clinical trials (CTs)
- FDA's regulatory framework
- Progress to date/future directions

## PART 2

- Multiple Myeloma (MM) Epidemiology and outcomes
- Representation in MM trials
- FDA-AACR pre-Workshop Working groups

# Cancer Outcomes by Race/Ethnicity



# Factors Contributing to Cancer Disparities

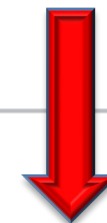
- Patient Factors
  - Risk factors (smoking, excess body weight, alcohol, physical inactivity, etc.,)
  - Bias, mistrust
  - Socioeconomic status
  - Geographic location
- Structural Factors
  - Access to care (geographic location, insurance coverage, lack of cultural competency, language barriers, etc.,)
  - Access to quality care (screening, prevention, survivorship, **clinical trials**, etc.,)

# Clinical Trials in Oncology Care

- Critical for advancing science of cancer care by
  - Evaluating safety and effectiveness of new therapeutics
  - Informing re appropriate use of therapies (sequencing, dosage, organ impairment, etc.,)
  - Comparing standards of care
  - Providing alternative treatment when no (effective) treatments exist
- Some potential limitations of CTs
  - Study population may differ from general population with the disease
    - Demographics (race/ethnicity, age)
    - Eligibility criteria (Comorbidities, performance status, organ function, etc.,)
  - For global trials: regional differences in:
    - available therapies, practice patterns, quality of care during treatment
    - etiologic risk factors (e.g., liver cancer, head and neck cancer, etc.,)
  - Size of trial (i.e., not broad representation, limited analyses of outcomes in relevant subgroups)



## CLINICAL TRIAL ENROLLMENT PATTERNS FOR MULTIPLE STUDIES IN THE LITERATURE<sup>1</sup>



|                                           | TRIAL<br>UNAVAILABLE | INELIGIBLE | NOT ENROLLED | ENROLLED |
|-------------------------------------------|----------------------|------------|--------------|----------|
| Academic Centers                          |                      |            |              |          |
| Average rate <sup>2</sup>                 | 41.4%                | 24.3%      | 19.5%        | 14.8%    |
| Community Centers                         |                      |            |              |          |
| Average rate <sup>2</sup>                 | 59.9%                | 15.7%      | 17.9%        | 6.3%     |
| Combined                                  |                      |            |              |          |
| Adjusted rate <sup>3</sup><br>All studies | 56.2%                | 17.4%      | 18.2%        | 8.0%     |

<sup>1</sup> Adapted from Unger et al., 2018, in press

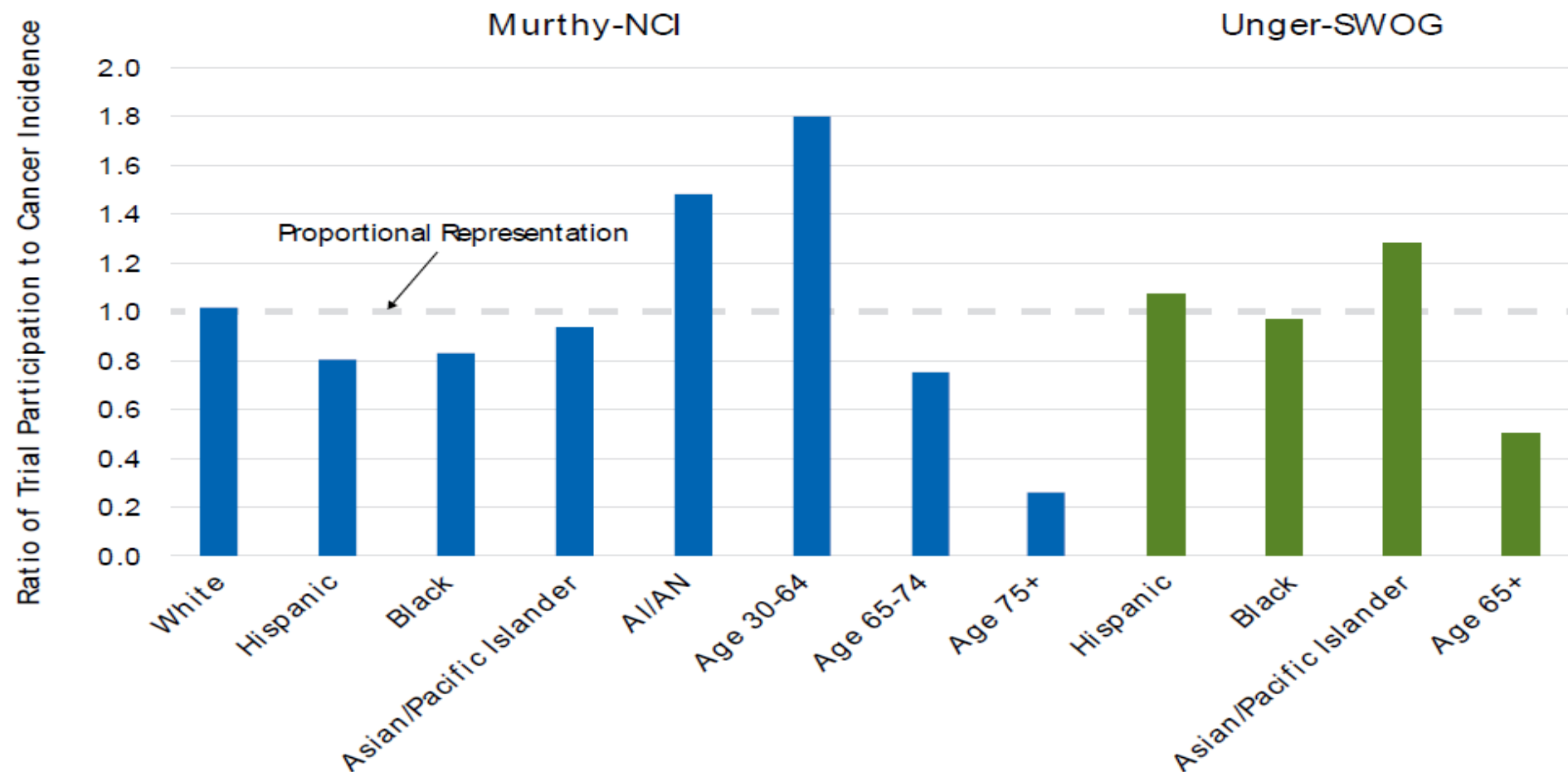
<sup>2</sup> Calculated using a weighted average based on study size

<sup>3</sup> Based on multiple sources, we estimated that approximately 80% of patients receive their care in community-based cancer centers. Thus the overall average rate was weighted at a ratio of 4:1 based on average estimates from community/academic centers

Sources: Academic [34, 118, 139, 207], Community [109, 110, 111]

**Source:** Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer: A Landscape Report. April 2018.

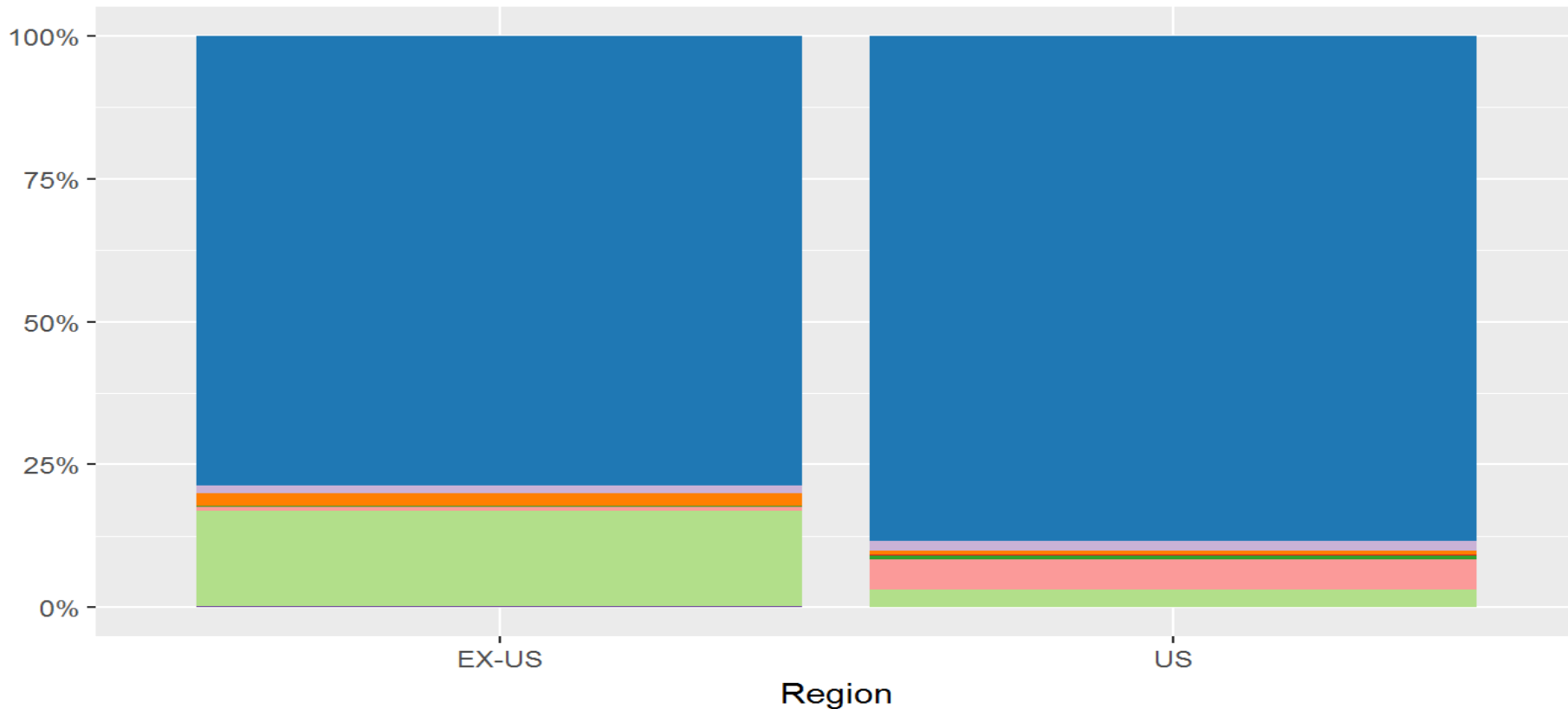
## DEMOGRAPHIC REPRESENTATION IN NCI TRIALS



Sources: Murthy (2004) Participation in Cancer Clinical Trials, JAMA; Unger (2006) Impact of the Year 2000 Medicare Policy Change on Older Patient Enrollment to Cancer Clinical Trials, JCO  
 AI/AN = American Indian/Alaska Native

**Source:** Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer: A Landscape Report. April 2018.

# FDA Analysis: Racial composition in trials supporting the US approval of anti-cancer new molecular entities: 2011- 2016

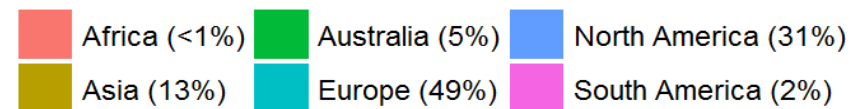
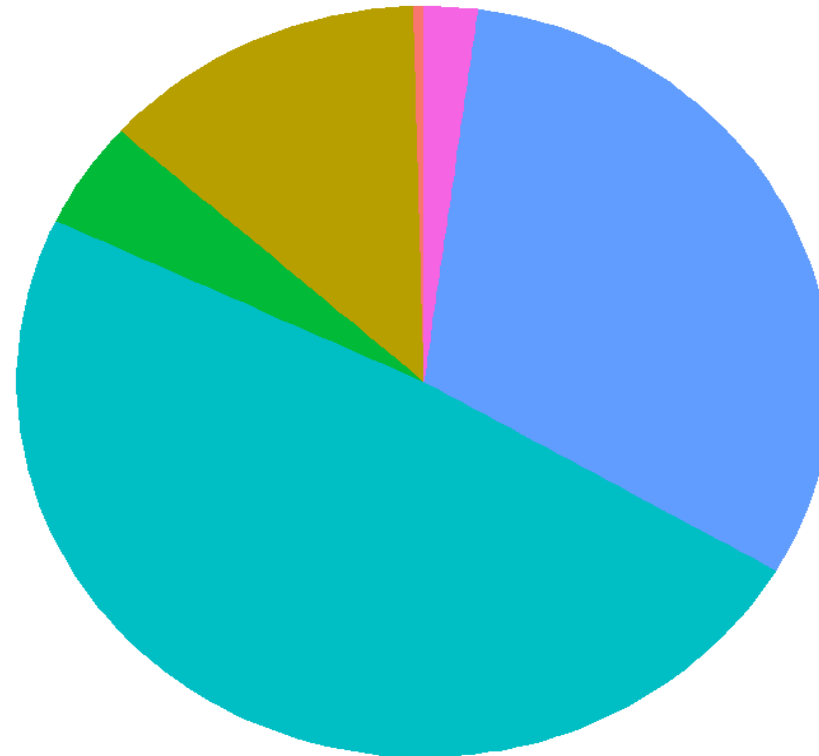


# FDA Analysis



| Race                              | EX-U.S.<br>n= 17104 (%) | U.S.<br>n= 6319(%) | Overall<br>n= 23423(%) |
|-----------------------------------|-------------------------|--------------------|------------------------|
| American Indian Or Alaskan Native | 49/17104(0.3)           | 8/6319(0.1)        | 57/23423(0.2)          |
| Asian                             | 2831/17104(16.6)        | 187/6319(3)        | 3018/23423(12.9)       |
| Black Or African American         | 124/17104(0.7)          | 342/6319(5.4)      | 466/23423(2)           |
| Hispanic                          | 23/17104(0.1)           | 38/6319(0.6)       | 61/23423(0.3)          |
| Native Hawaiian Or Other PI       | 3/17104(0)              | 11/6319(0.2)       | 14/23423(0.1)          |
| Non-Hispanic                      | 1/17104(0)              | NA                 | 1/23423(0)             |
| Not Reported                      | 379/17104(2.2)          | 38/6319(0.6)       | 417/23423(1.8)         |
| Other                             | 241/17104(1.4)          | 114/6319(1.8)      | 355/23423(1.5)         |
| White                             | 13453/17104(78.7)       | 5581/6319(88.3)    | 19034/23423(81.3)      |

# Regional Representation



# Considerations to relevant to CT enrollment

- Changing landscape in conduct of clinical trials (implications for diversity in CTs)
  - NCI/NCI-funded cooperative groups/academic centers- Patient advocacy- Pharmaceutical companies
  - Different mandates for representation in CTs (NIH vs FDA regs)
- Innovations in CT designs: Big randomized CT –replaced by smaller, smarter trials
  - Smaller overall numbers of patients, homogeneity in patient population
- Better understanding of molecular underpinnings of cancer: molecularly defined subsets of a disease (anatomically/histological-based definitions of cancer to hundreds of small diseases: rare subsets)
- Patients want/need faster access to promising drugs
- Increasing globalization of CTs

The FDA does not have the regulatory or statutory authority to require that sponsors include demographic subgroups as participants in clinical trials.

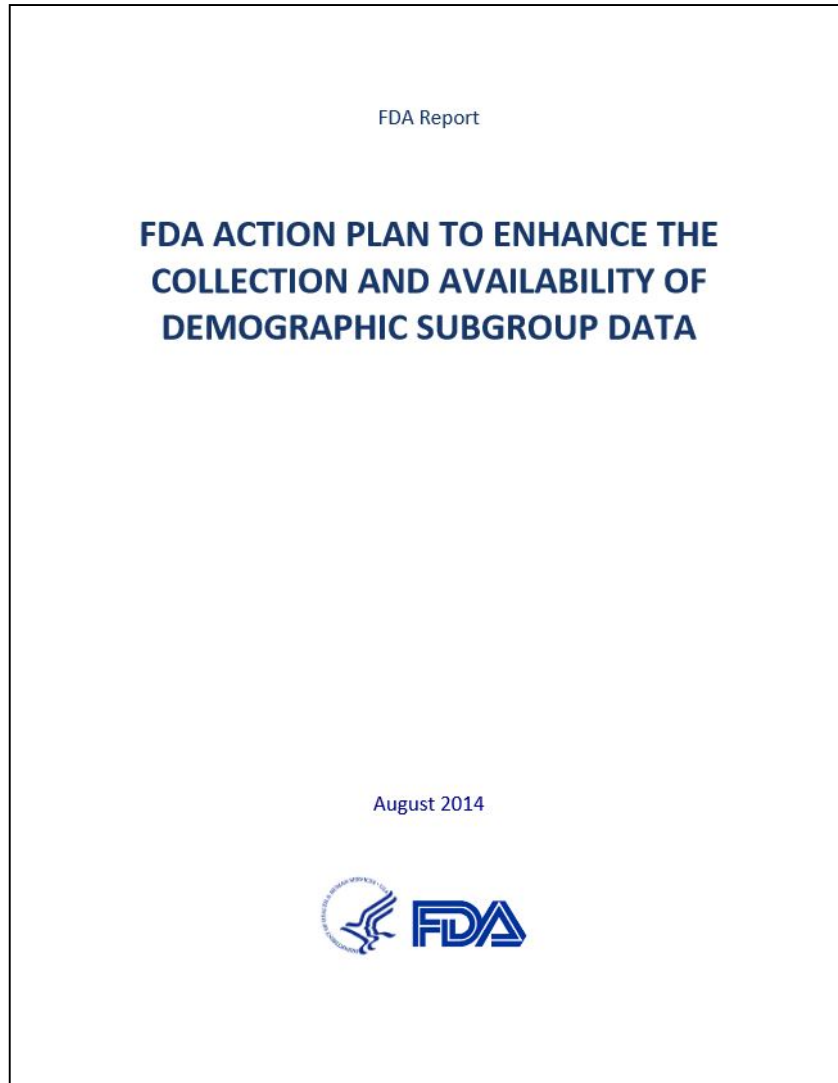
# Collection of Race/Ethnicity Data in Clinical Trials



- **1998-** “Demographic Rule” Regulation (21 CFR 314.50 and 21 CFR 312.33)
  - NDAs must include information by gender (sex), age and race for trial participation, safety and effectiveness;
  - IND Annual Reports must tabulate the # of participants by gender (sex), age and race.
  - No requirement for specific numbers /proportion of CT enrollees
  - Race and ethnicity- self-reported
- **1999-** ICH E5 Ethnic Factors in the Acceptability of Foreign Clinical Data
  - “Ethnically sensitive” bridging studies necessary to extrapolate from one region to another
- **2005-** FDA Guidance on Data Collection of Race and Ethnicity Data in Clinical Trials
  - FDA regulations require sponsors to present a summary of safety and effectiveness data by demographic sub-groups for age, gender and race/ethnicity based on OMH Directive 15 and census
- **2012-** FDA Safety and Innovation Act of 2012- mandated that FDA review the adequacy of its existing regulations and processes, develop a report addressing the extent to which demographic subgroups are included in applications submitted to FDA and develop an Action Plan based on the findings to advance clinical trial diversity



# FDASIA Section 907 Action Plan



## Three overarching priorities:

- Improve the completeness and quality of demographic subgroup data collection, reporting and analysis (**Quality**)
- Identify barriers to subgroup enrollment in clinical trials and employ strategies to encourage greater participation (**Participation**)
- Make demographic subgroup data more available and transparent (**Transparency**)

*Contains Nonbinding Recommendations*

## **Collection of Race and Ethnicity Data in Clinical Trials**

### **Guidance for Industry and Food and Drug Administration Staff**

Document issued on October 26, 2016

For questions about this document, contact the FDA Office of Minority Health at 240-402-5084 or [omh@fda.hhs.gov](mailto:omh@fda.hhs.gov).

U.S. Department of Health and Human Services (HHS)  
Food and Drug Administration (FDA)  
Office of the Commissioner (OC)  
Office of Minority Health (OMH)  
Office of Women's Health (OWH)  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Center for Devices and Radiologic Health (CDRH)

October 2016  
Clinical Medical

## **Clinically Relevant Enrollment**

Participants who reflect the demographics for clinically relevant populations (age, gender, race, ethnicity)

A plan to address inclusion of clinically relevant subpopulations submitted to Agency no later than end-of Phase 2 meeting

Inadequate participation and/or data analyses from clinically relevant subpopulations can lead to insufficient information pertaining to medical product safety and effectiveness for product labeling.

For potential race/ethnicity differences relevant to the evaluation of the medical product intended for the treatment of disease/condition, consider:

Prevalence, diagnosis & treatment patterns, previous subgroup in past studies for indication, any clinically meaningful subgroup differences in safety and efficacy

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# Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry

## *DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ebla Ali-Ibrahim, 301-796-3691, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

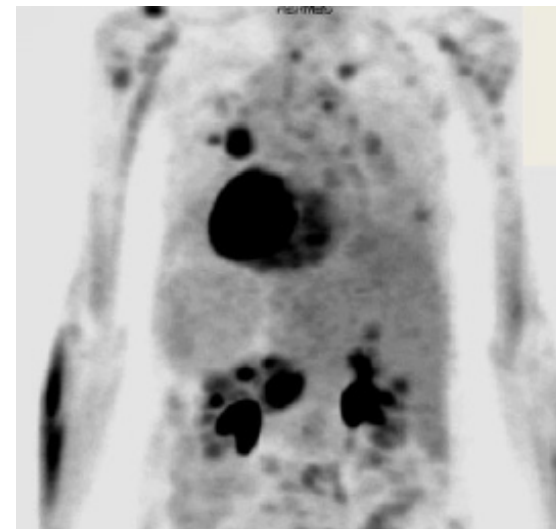
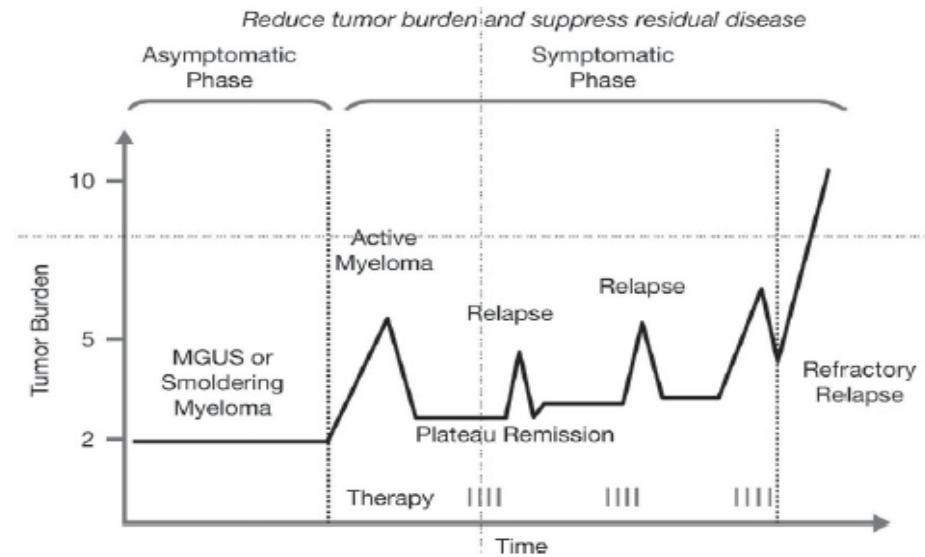
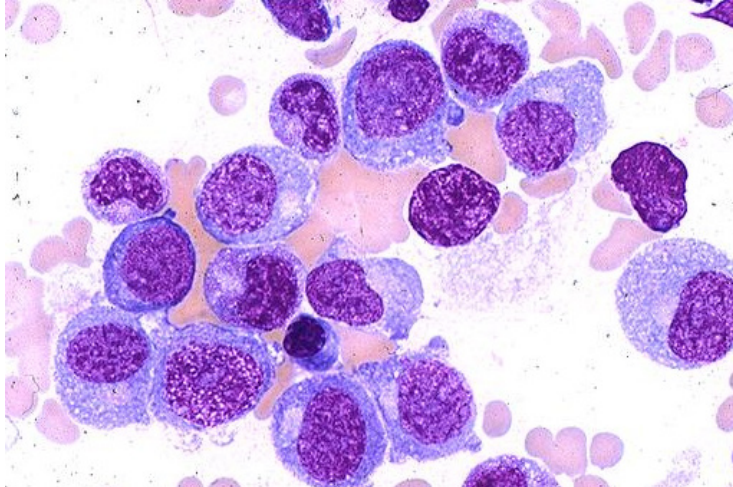
June 2019  
Clinical/Medical

- Broadening eligibility criteria and avoid unnecessary exclusions from CTs
- Eligibility criteria and trial recruitment so that CT participants better reflect population likely to use the drug if approved
- Applying the recommendations for broadening eligibility criteria to CTs for drugs intended to treat rare diseases/conditions
- **Recommendations:**
  - Inclusive trial practices
  - Trial designs and methodological approaches
  - Decrease practices that are burdensome to patients
  - Adopt enrollment & retention practices to enhance inclusiveness
  - Expanded access

# Progress to date/future directions

- **Promoting Transparency/Raising awareness**
  - Drug Trials Snapshot
    - provides information about the sex, age, race and ethnicity of clinical participants for recently approved drugs
  - 2016- Year of Diversity in Clinical Trials
    - FDA Office of Minority Health (& Health Equity) clinical trial diversity campaign
  - Engagement to facilitate research/policy/advocacy efforts improve CT participation
    - Oncology Center of Excellence (OCE) Project Community
- **External Collaborations (Research, Policy)**
  - Eligibility criteria, health equity, uses of real world data (RWD), etc.,
  - FDA-wide Broad Agency Announcement (BAA)- OCE soliciting requests for health equity in oncology trials
- **Innovations in CT delivery**
  - Decentralized CTs (Pragmatic trials)

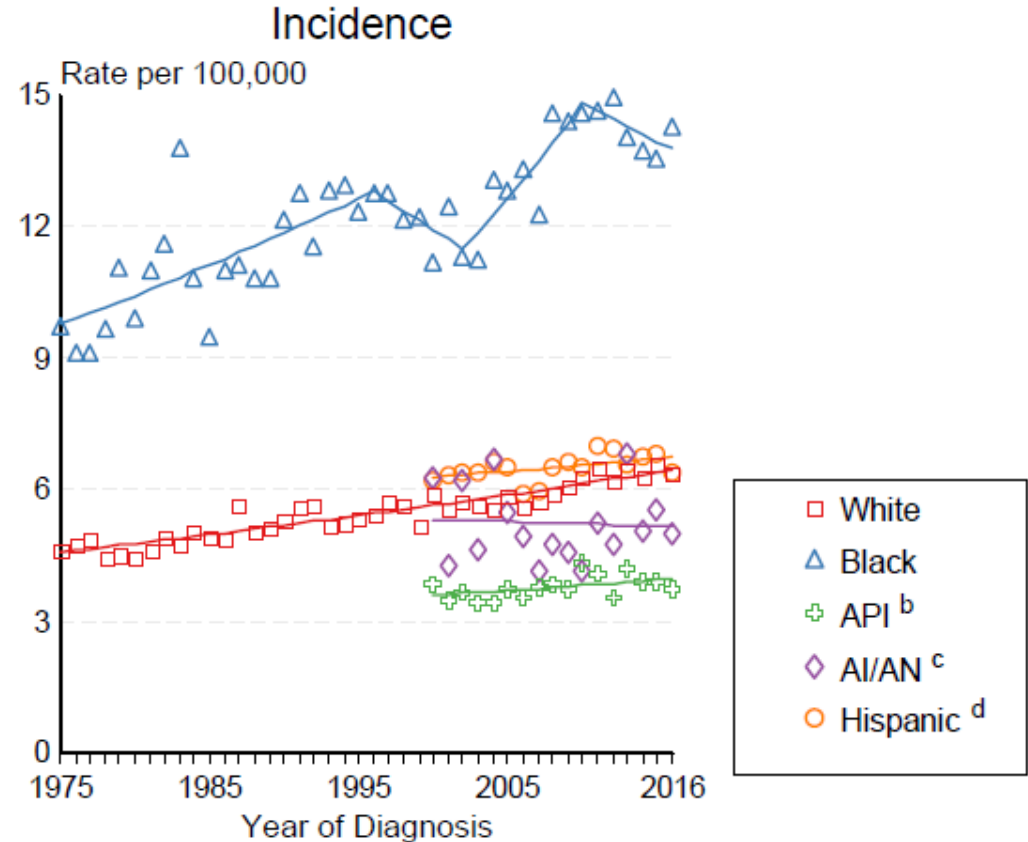
# Multiple Myeloma Clinical Course



Borello Leuk Rsch 2012  
Ghobrial Blood 2012

# Multiple Myeloma Epidemiology

- Estimated 32,110 new cases and 12, 960 deaths from MM in 2019



Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Myeloma

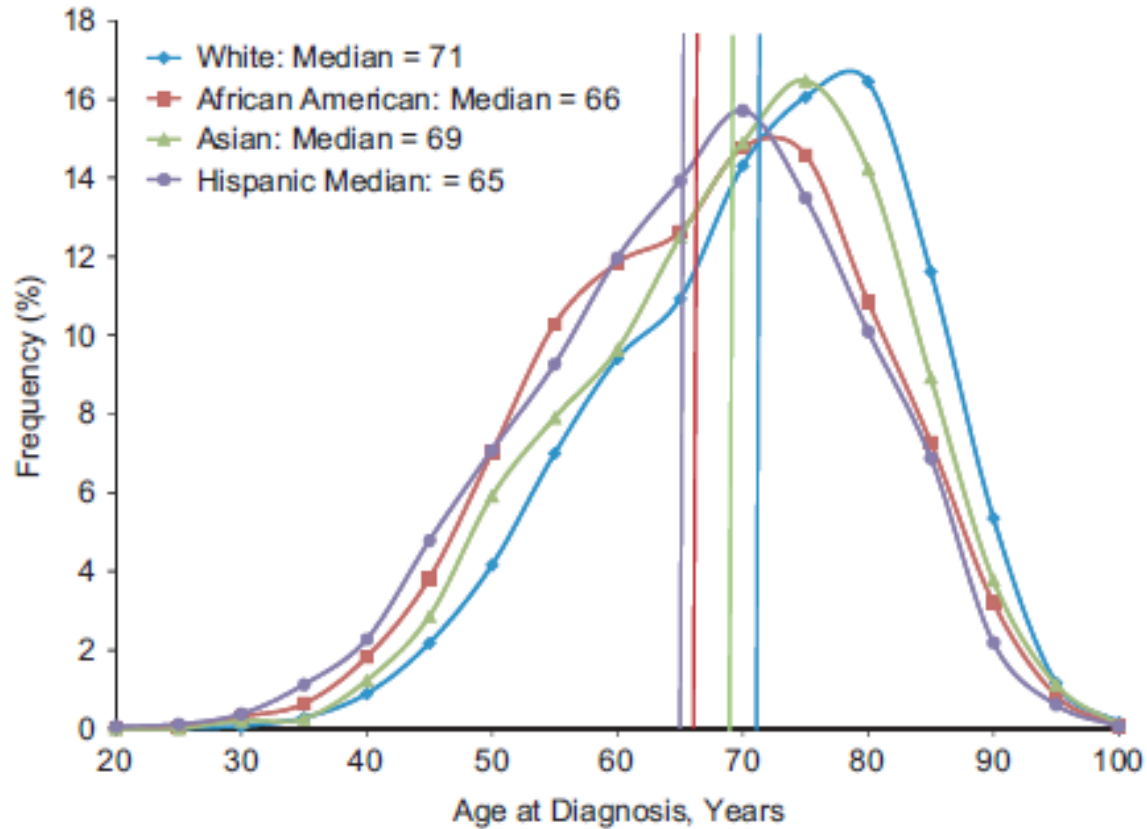
| MALE |                                 | FEMALE |
|------|---------------------------------|--------|
| 8.7  | All Races                       | 5.6    |
| 8.1  | White                           | 4.9    |
| 16.3 | Black                           | 11.9   |
| 4.9  | Asian / Pacific Islander        | 3.0    |
| 6.0  | American Indian / Alaska Native | 5.0    |
| 8.2  | Hispanic                        | 5.5    |
| 8.8  | Non-Hispanic                    | 5.6    |

Howlader N et al. SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. Bethesda, MD, [https://seer.cancer.gov/csr/1975\\_2016/](https://seer.cancer.gov/csr/1975_2016/), based on November 2018 SEER data submission, posted April 2019

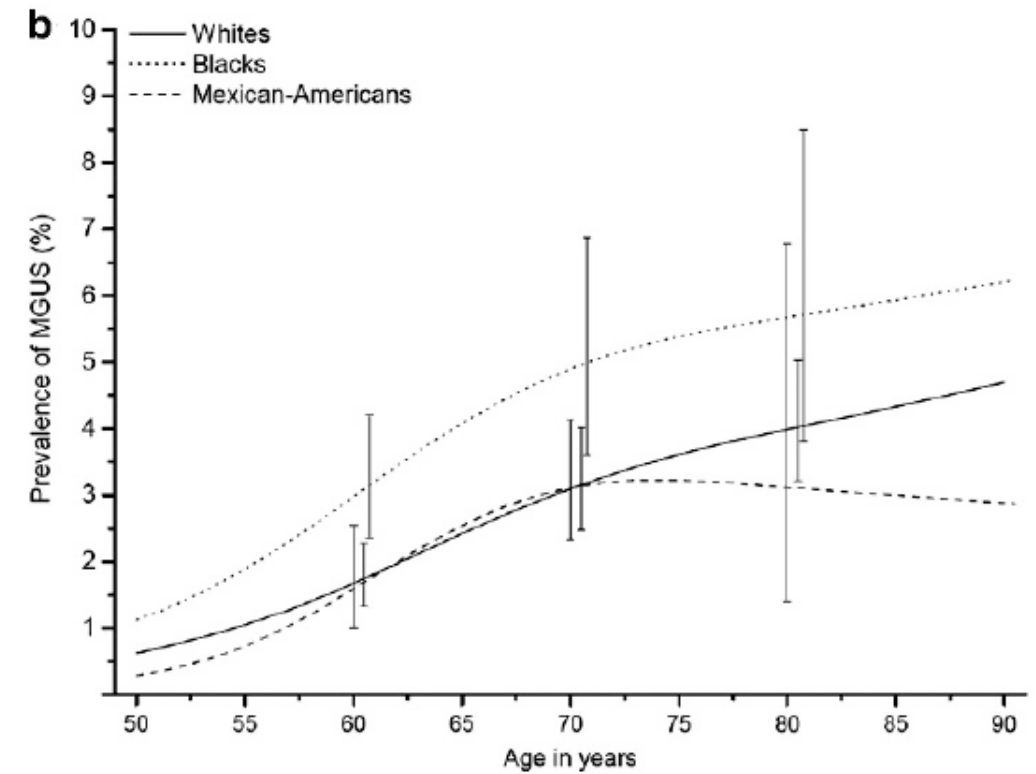
# Multiple Myeloma Epidemiology



Median Age at Diagnosis



MGUS Development



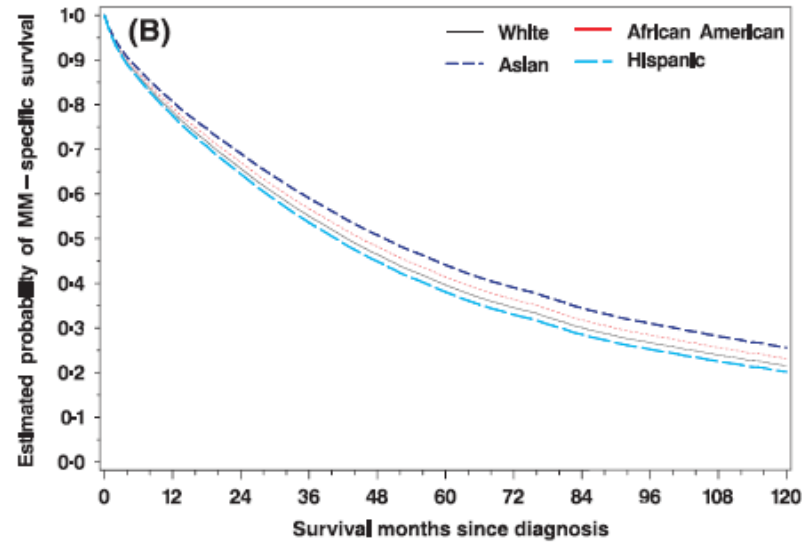
Ailawadhi BJH 2012  
Landgren Leukemia 2014



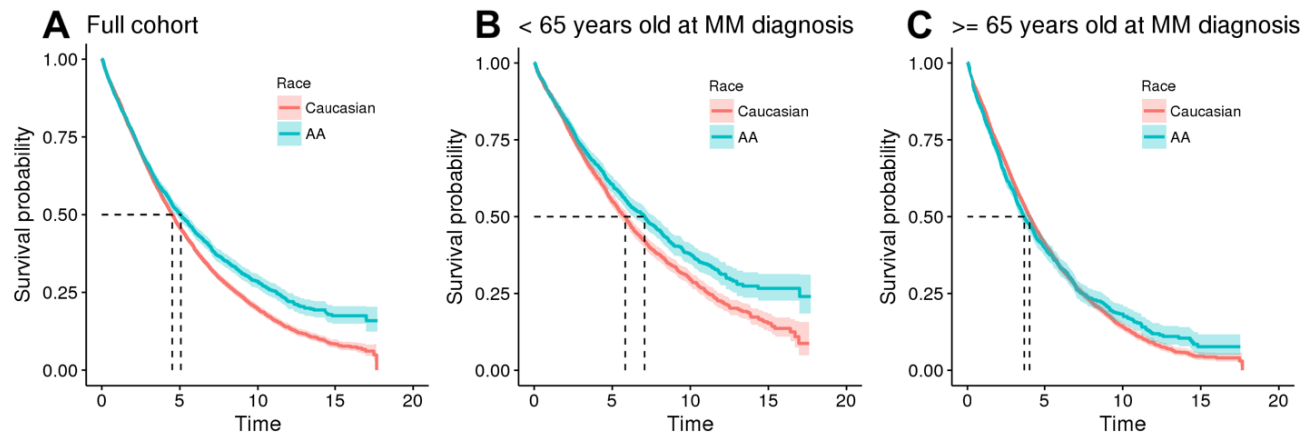
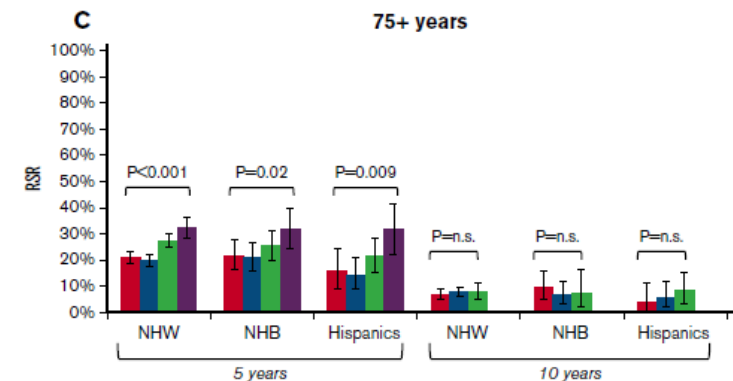
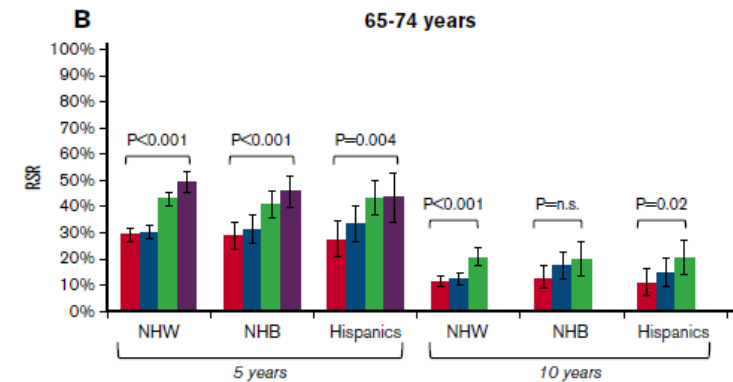
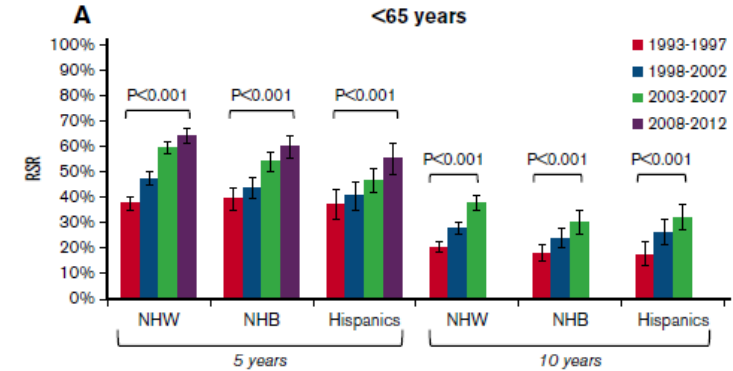
# Multiple Myeloma Outcomes by Race



## Myeloma Specific Survival



## Relative Survival Rates



Ailawadhi BJH 2012  
Filmore Blood 2019  
Costa Blood Advances 2017



# Multiple Myeloma Cytogenetics



**Table 4 Cytogenetic abnormalities by ancestry**

|                                 | African descent (N = 120) | European descent (N = 235) | Other (N = 526) | Total (N = 881) | p value |
|---------------------------------|---------------------------|----------------------------|-----------------|-----------------|---------|
| Abnormality by Ancestry         |                           |                            |                 |                 |         |
| <i>Abnormality</i>              |                           |                            |                 |                 |         |
| t(11;14), t(14;16), or t(14;20) | 61 (50.8%)                | 77 (32.8%)                 | 180 (34.2%)     | 318 (36.1%)     | 0.008   |
| t(4;14)                         | 8 (6.7%)                  | 20 (8.5%)                  | 44 (8.4%)       | 72 (8.2%)       | 0.862   |
| t(6;14)                         | 1 (0.8%)                  | 4 (1.7%)                   | 9 (1.7%)        | 14 (1.6%)       | 0.862   |
| Other IgH                       | 8 (6.7%)                  | 24 (10.2%)                 | 54 (10.3%)      | 86 (9.8%)       | 0.739   |
| Trisomy no IgH                  | 37 (30.8%)                | 97 (41.3%)                 | 203 (38.6%)     | 337 (38.3%)     | 0.464   |
| All Other                       | 5 (4.2%)                  | 13 (5.5%)                  | 36 (6.8%)       | 54 (6.1%)       | 0.739   |
|                                 | African descent (N = 120) | European descent (N = 235) | Other (N = 526) | Total (N = 881) | p value |
| Trisomy by Ancestry             |                           |                            |                 |                 |         |
| Any Trisomy                     |                           |                            |                 |                 | 0.066   |
| No Trisomy                      | 62 (51.7%)                | 91 (38.7%)                 | 229 (43.5%)     | 382 (43.4%)     |         |
| Trisomy                         | 58 (48.3%)                | 144 (61.3%)                | 297 (56.5%)     | 499 (56.6%)     |         |

P values are based on the comparison of the indicated abnormality (versus otherwise) compared to individuals  $\geq 80.0\%$  African ancestry, individuals with  $< 0.1\%$  African (excluding Asian ancestry) and all others individuals (3-group test) and are adjusted to control the false discovery rate (FDR) using the method of Benjamini and Hochberg

# FDA Analysis of multiple myeloma trials



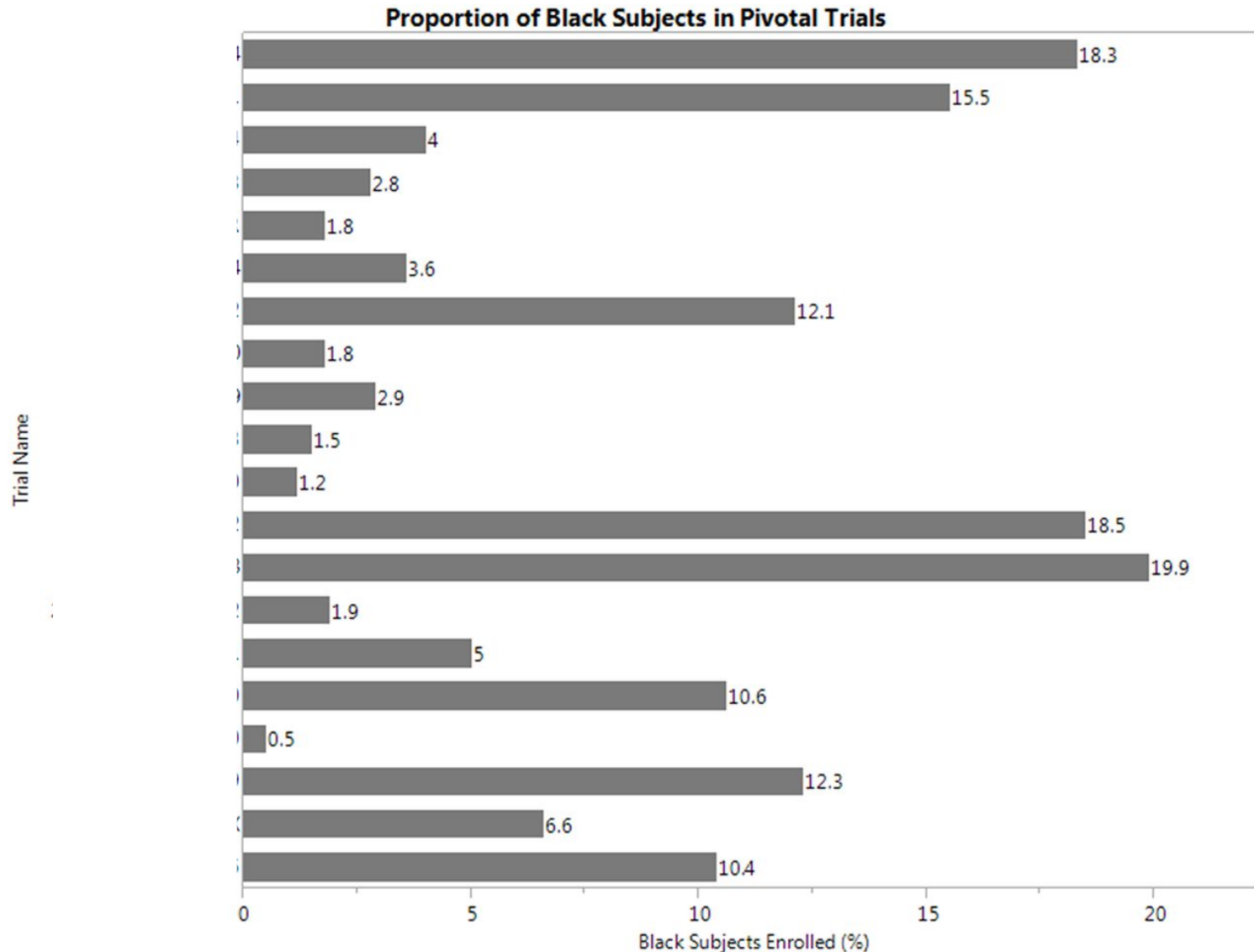
- Methods
  - Reviewed the FDA database for NDA/BLA applications submitted between 2003 and 2017
  - Applications reviewed for baseline demographic data, including age, race and country
  - Intention-to treat populations from individual trials included in the analysis
  - Analysis was conducted only on pivotal trials that included race data

# FDA Analysis of multiple myeloma trials



- Results:
  - 23 trials were submitted for approval during this time period
  - 20 of the trials included information on race
  - Median enrolled percentage of blacks was 4.5%
    - Range 0.5% to 19.9% of the trial population
  - Trials with higher U.S enrollment had better enrollment of blacks
    - Median percentage of blacks was 10.5%

# FDA Analysis of multiple myeloma trials



# FDA-AACR Working Groups



- Working Group 1: Approaches to Improve Data in Racial and Ethnic Minorities Prior to Drug Approval
- Working Group 2: Approaches to Using Post-Approval Clinical Trial Data to Better Understand Effectiveness and Safety of Therapies in Racial and Ethnic Minorities
- Working Group 3: Approaches to Utilize Real-World Data to Understand Outcomes with Specific Therapies in Racial and Ethnic Minorities

# FDA-AACR Working Groups



- Working Group 1: Approaches to Improve Data in Racial and Ethnic Minorities Prior to Drug Approval
  - Aims:
    - To identify and prioritize strategies to obtain data on racial/ethnic minorities to inform FDA's assessment of safety and efficacy prior to approval of a new therapeutic for the treatment of multiple myeloma. These data could be sourced from the registrational clinical trial(s), supportive clinical trials in the marketing application, or other data/studies which inform the use of the therapeutic in racial/ethnic minorities (e.g., pharmaco-metric studies or small cohort studies).
    - To evaluate what amount of information is sufficient to have confidence in our assessment of safety and effectiveness of antimyeloma therapies in racial and ethnic minorities.

# FDA-AACR Working Groups



- Working Group 2: Approaches to Using Post-Approval Clinical Trial Data to Better Understand Effectiveness and Safety of Therapies in Racial and Ethnic Minorities
  - Aims:
    - To identify strategies to better understand drug-specific outcomes (i.e., safety and effectiveness) in racial/ethnic minorities once the drug has been approved.
    - To consider strategies to obtain data from post-approval clinical trials, sponsored by various stakeholders, including any strategies that may facilitate access to these data. This may include industry sponsored trials or cooperative group trials that evaluate the use of the therapeutic in racial/ethnic minorities. Additionally, these trials may provide further evidence of the safety and effectiveness of the therapeutic in a setting (e.g., community centers) that more closely reflects the experience of patients in the U.S.

# FDA-AACR Working Groups



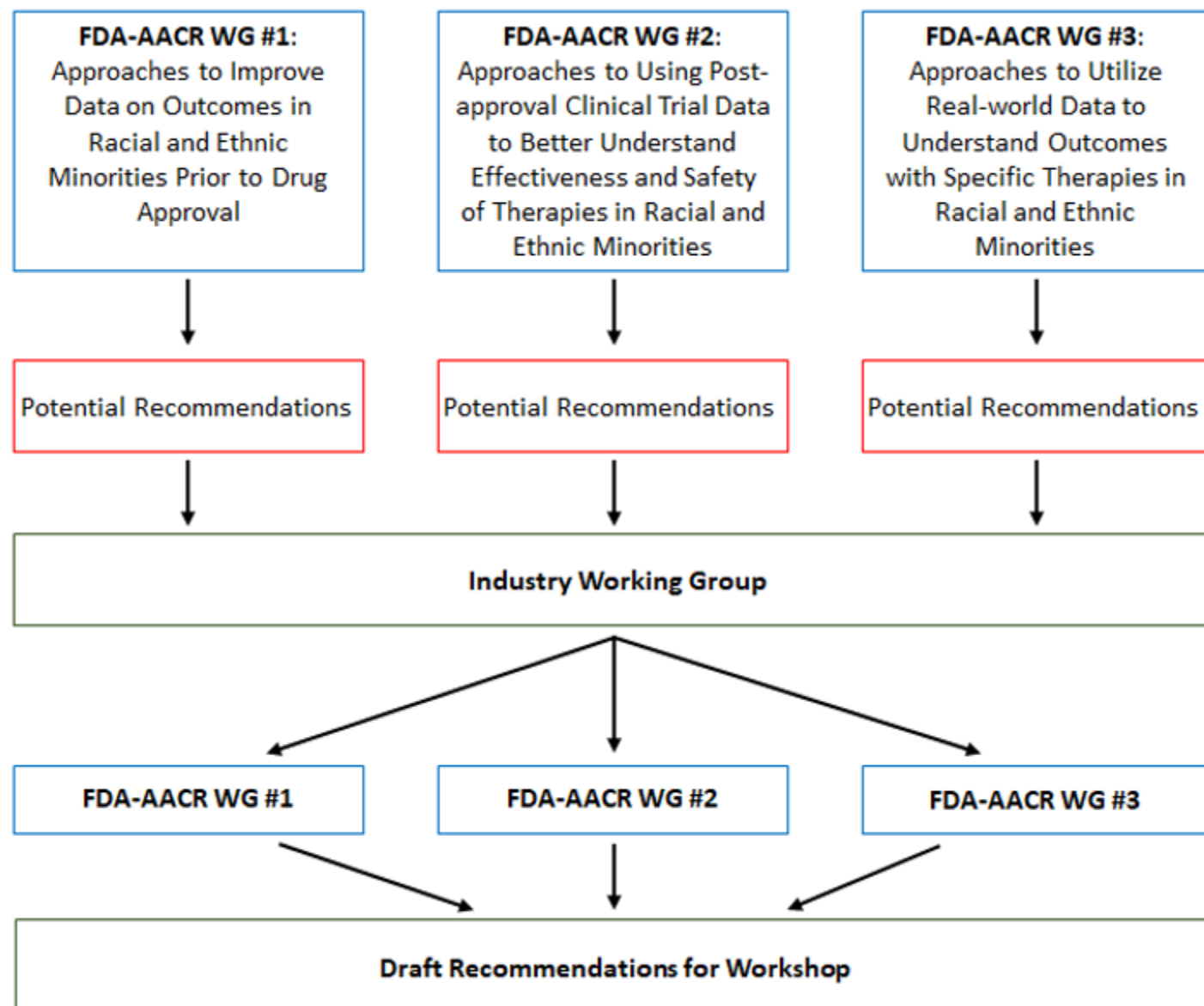
- Working Group 3: Approaches to Utilize Real-World Data to Understand Outcomes with Specific Therapies in Racial and Ethnic Minorities
  - Aims:
    - To consider real-world data (e.g., data derived from electronic health records, product or disease registries, claims and billing data, patient generated data, etc.) that may be used to inform our understanding of the effectiveness and safety of approved drugs in racial/ethnic minorities.
    - To evaluate data sources that may be leveraged for this purpose, including any operational issues that must be addressed to facilitate use of these data sources.



# AACR Industry Working Group



- AACR Industry Working Group
  - Aim: Provide feedback and industry insight on potential recommendations developed by FDA-AACR working groups examining issues around the under-representation of African Americans in multiple myeloma clinical trials



# Thank you

- AACR
  - Margaret Foti
  - Jon Retzlaff
  - Sarah Martin
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- FDA Staff
  - Rick Pazdur
  - Paul Kluetz
  - Bindu Kanapuru
  - Andrea Baines
  - Laura Fernandes
  - Yuan Li Shen
  - Vishal Bhatnagar
  - Kunthel By
  - Rachel Ershler
  - Richardae Araojo
  - Angela James
  - Dianne Spillman
  - Christine Lee
  - Lola Lua
  - Dianne Pulte
  - Anuradha Ramamoorthy
  - Sonia Swayze

# Biology and Genetic Differences in Myeloma

*Shaji Kumar, M.D.*

*Professor of Medicine*

*Chair, Myeloma, Amyloid, Dysproteinemia Group*

*Mayo Clinic*



**Scottsdale, Arizona**



**Rochester, Minnesota**

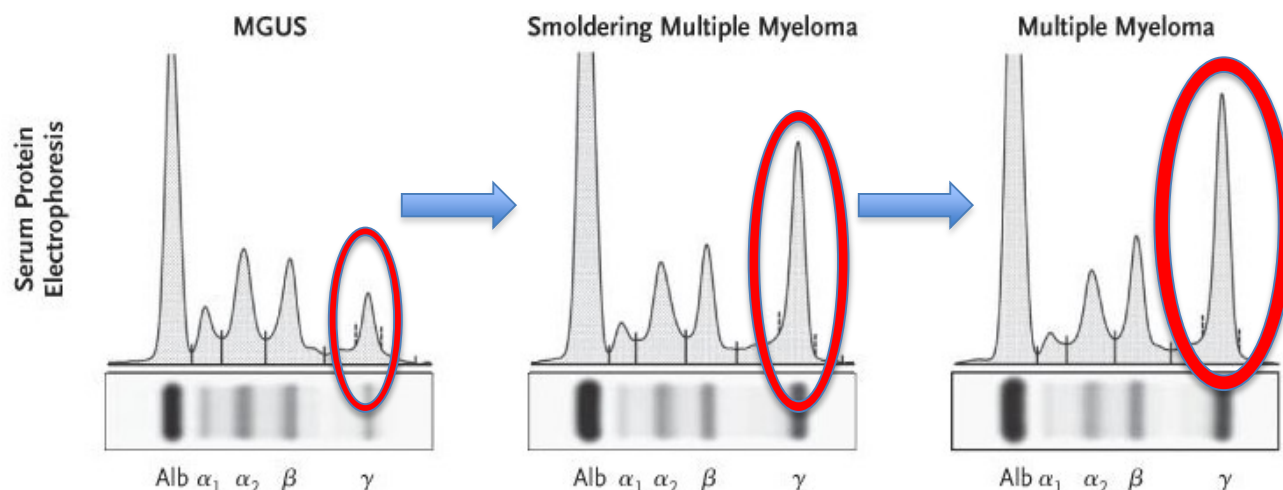


**Jacksonville, Florida**

# Disclosures

- Research funding for clinical trials to the institution: Celgene, Takeda, Janssen, BMS, Sanofi, KITE, Merck, Abbvie, Medimmune, Novartis, Roche-Genentech, Amgen
- Consulting/Advisory Board participation: Celgene, Takeda, Janssen, KITE, Merck, Abbvie, Medimmune, Genentech, Amgen Oncopeptides, Adaptive.

# Monoclonal gammopathies: a spectrum



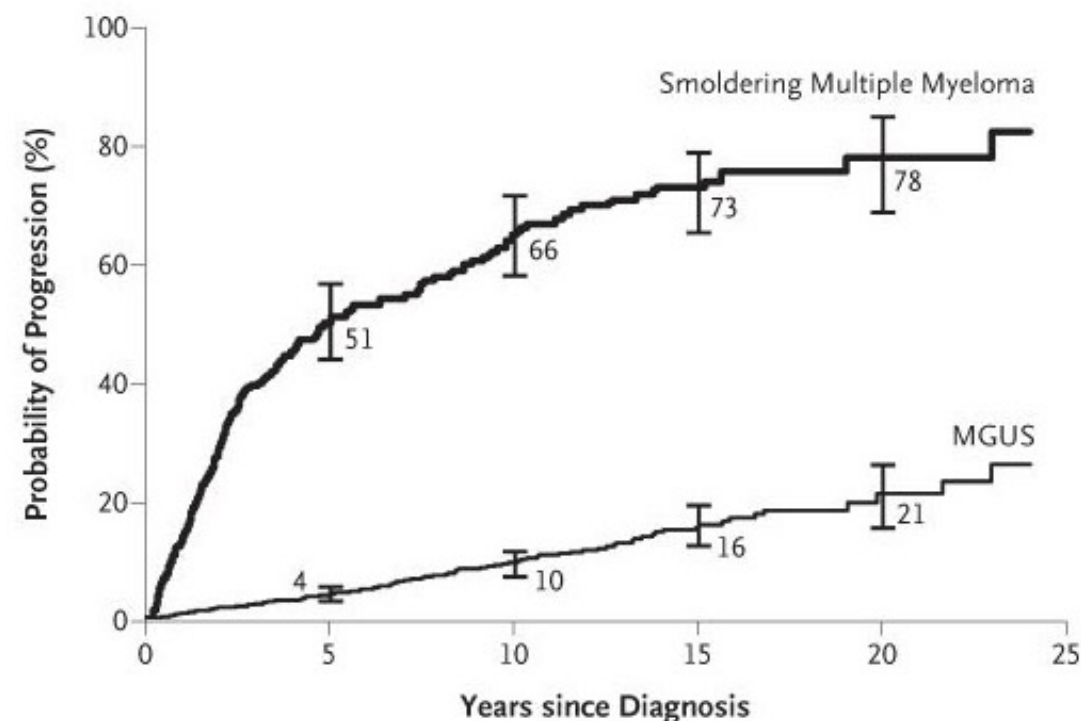
**Increasing levels of monoclonal protein**



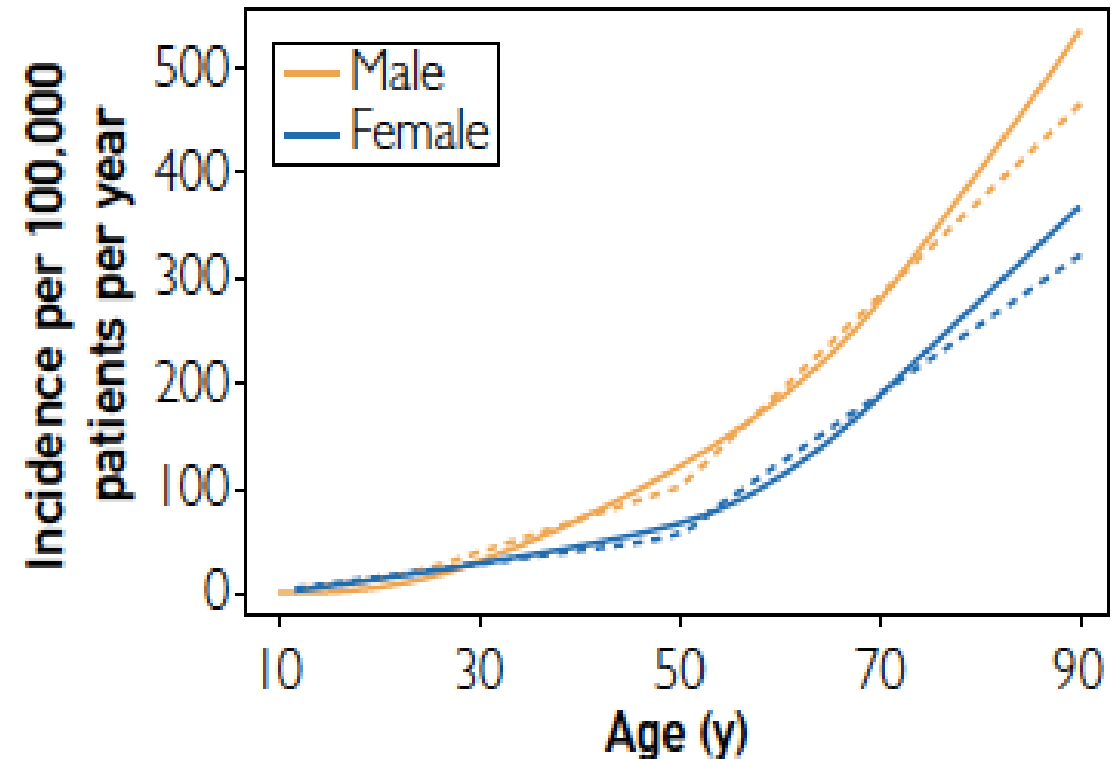
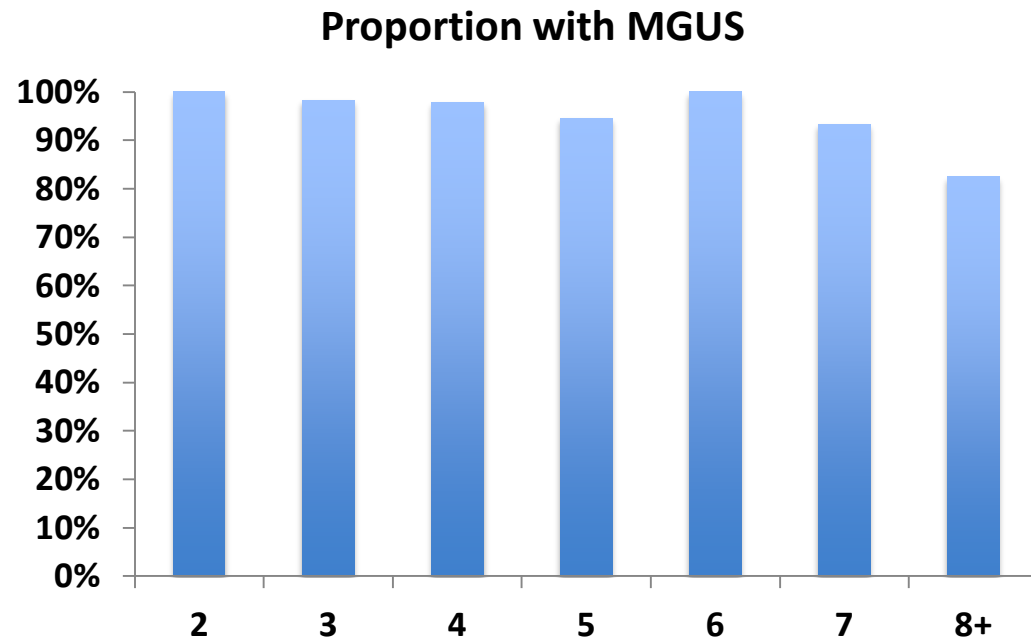
**Increasing marrow plasma cell percentage**



**Development of End Organ Damage**

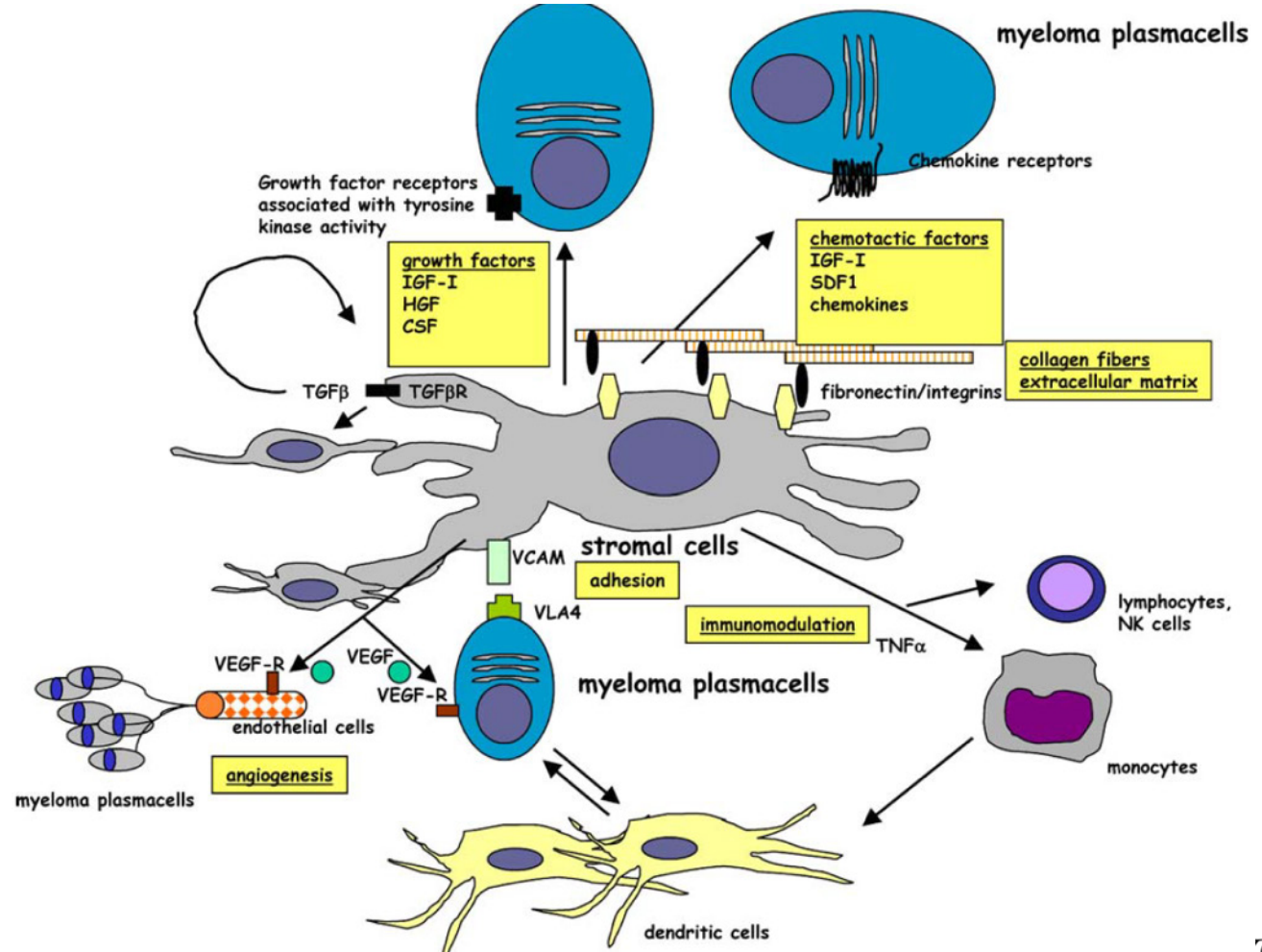
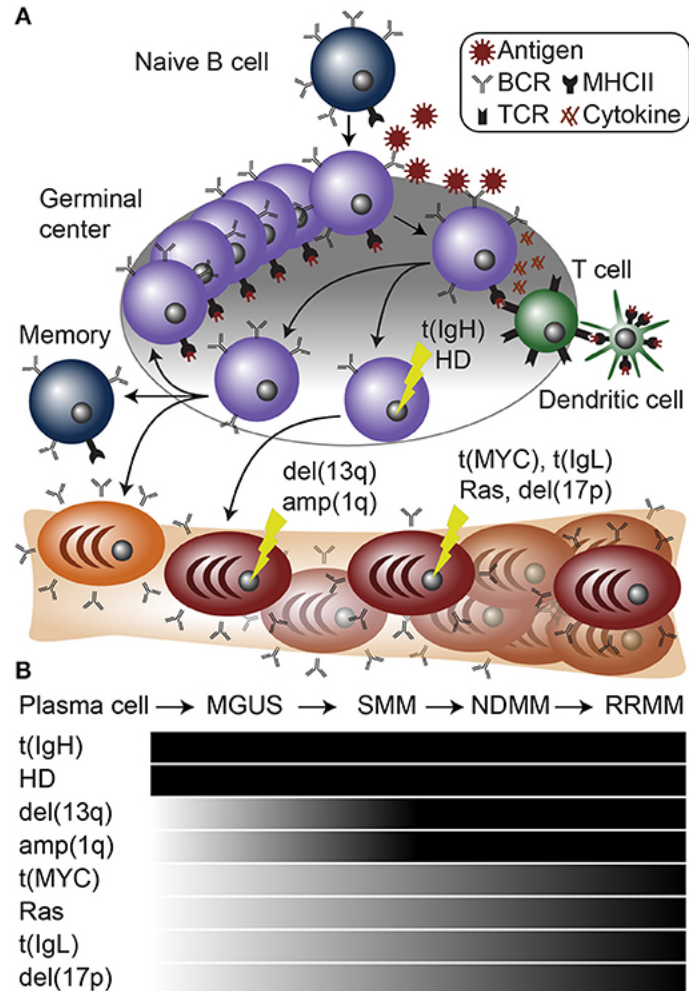


# MGUS always precede MM, evolves over a long time



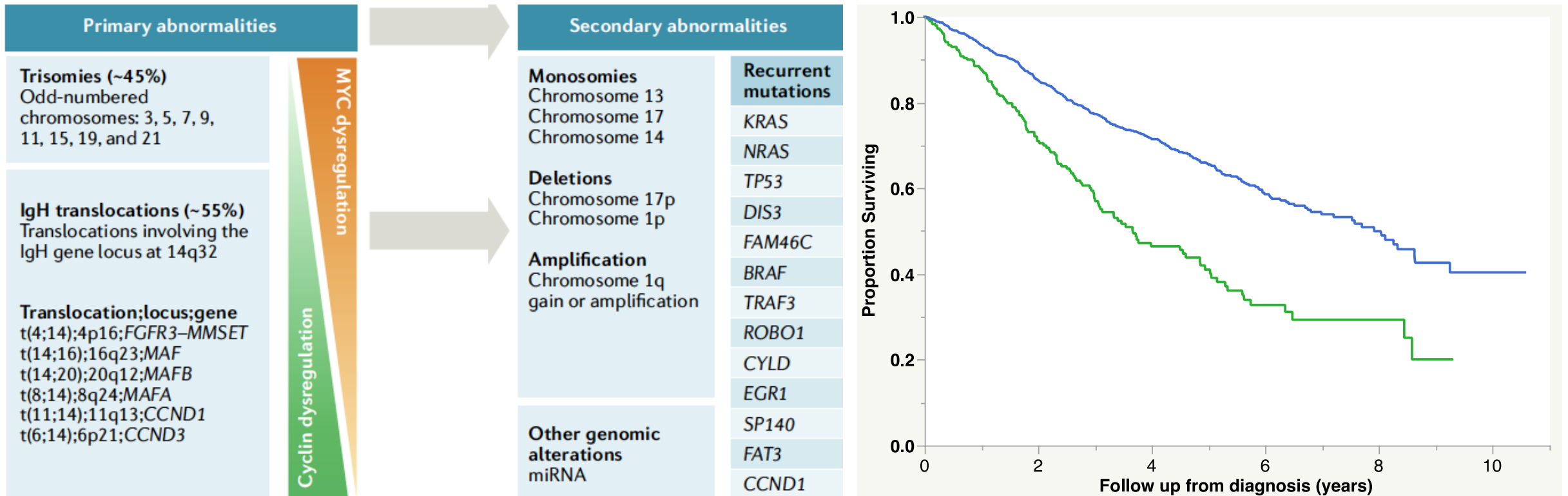


# Progression events and mechanisms





# Multiple Myelomas



# **WHAT IS DIFFERENT IN AFRICAN AMERICANS?**

# MGUS is 2-3 times more common in AA

Age-adjusted prevalence rate for MGUS was 3.0-fold (2.7-3.3 95% CI) higher in African Americans than in whites

Compared with white men, the age-adjusted prevalence of MGUS was 1.97-fold (95% CI, 1.94-2.00) higher in Ghanaian men

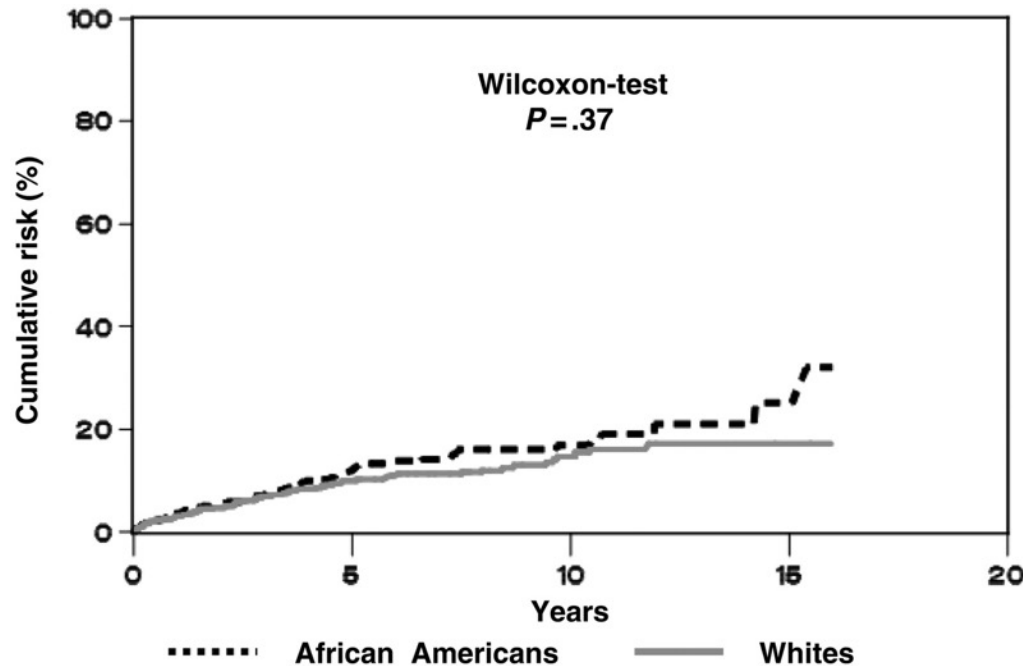
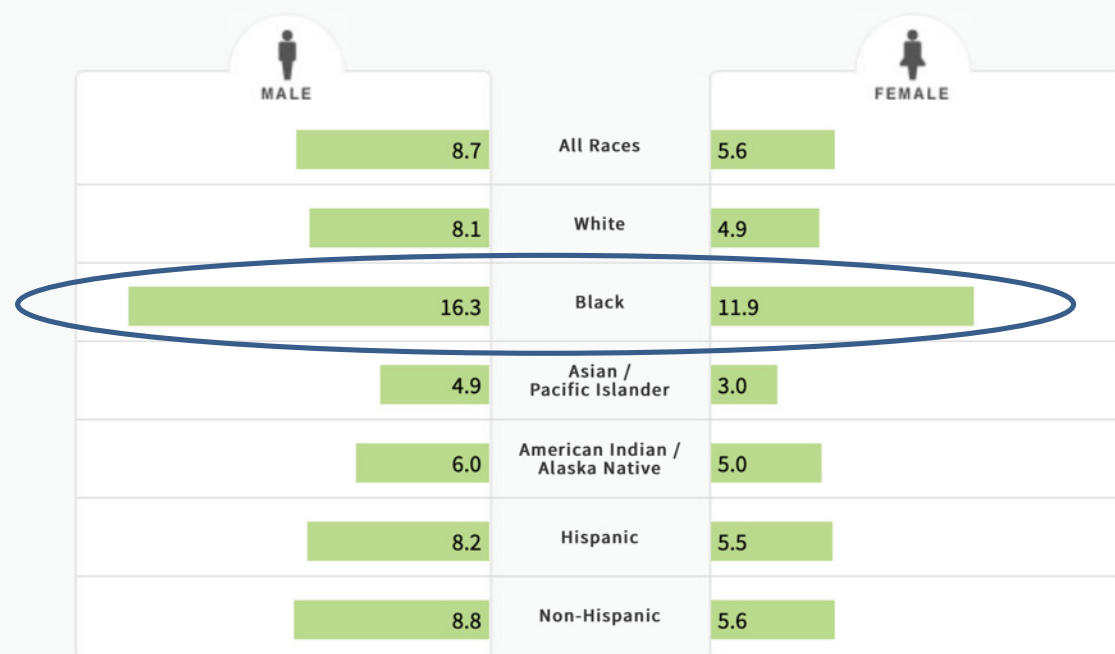


TABLE 2. Prevalence of MGUS in 917 Men in Accra, Ghana, and in 7996 Men in Olmsted County, MN\*

| Variable                     | Ghana     |                   |                                  | Olmsted County <sup>6</sup> |                   |                                  |
|------------------------------|-----------|-------------------|----------------------------------|-----------------------------|-------------------|----------------------------------|
|                              | Total No. | No. (%) with MGUS | Prevalence (95% CI) <sup>†</sup> | Total No.                   | No. (%) with MGUS | Prevalence (95% CI) <sup>†</sup> |
| Age (y)                      |           |                   |                                  |                             |                   |                                  |
| 50-54                        | 244       | 13 (5)            | 5.33 (2.51-8.15)                 | 2181                        | 40 (2)            | 1.83 (1.27-2.40)                 |
| 55-59                        | 209       | 12 (6)            | 5.74 (2.59-8.90)                 | 1857                        | 42 (3)            | 2.26 (1.59-2.94)                 |
| 60-64                        | 166       | 9 (5)             | 5.42 (1.98-8.87)                 | 1520                        | 52 (3)            | 3.42 (2.51-4.33)                 |
| 65-69                        | 168       | 13 (8)            | 7.74 (3.70-11.8)                 | 1344                        | 53 (4)            | 3.94 (2.90-4.98)                 |
| 70-74                        | 130       | 7 (5)             | 5.38 (1.50-9.26)                 | 1094                        | 56 (5)            | 5.12 (3.18-6.42)                 |
| Total, unadjusted            | 917       | 54 (6)            | 5.89 (4.36-7.42)                 | 7996                        | 243 (3)           | 3.04 (2.66-3.42)                 |
| Total, adjusted <sup>‡</sup> |           |                   | 5.84 (4.27-7.40)                 |                             |                   | 2.97 (2.59-3.34)                 |

# Myeloma is 2-3 times more common as well

Number of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Myeloma



SEER 21 2012-2016, Age-Adjusted

AGE-ADJUSTED AND STANDARDISED INCIDENCE MYELOMA RATES\*  
IN SOUTH AFRICAN AND U.S. BLACKS

| Age                                | Black males  |            | Black females |            |
|------------------------------------|--------------|------------|---------------|------------|
|                                    | South Africa | U.S.       | South Africa  | U.S.       |
| 30-34                              | 2.92 (1)     | 0.91 (2)   | .. (0)        | .. (0)     |
| 35-44                              | 3.17 (2)     | 2.97 (10)  | 1.81 (1)      | 1.98 (8)   |
| 45-54                              | 12.29 (6)    | 9.71 (34)  | 5.77 (2)      | 6.67 (26)  |
| 55-64                              | 27.17 (6)    | 27.97 (66) | 33.79 (5)     | 18.17 (49) |
| 65-74                              | 45.09 (3)    | 44.02 (60) | 16.45 (1)     | 36.11 (60) |
| 75+                                | 56.50 (1)    | 79.87 (44) | 36.81 (1)     | 47.18 (41) |
| Age adjusted rate (world standard) | 7.47         | 7.52       | 5.11          | 5.17       |

\*Per 100 000 (no. of cases in italic type).

# Earlier onset of MGUS in African Americans

- The disparity in prevalence of MGUS between blacks and whites was most striking in the 40–49 age-group; 3.26% (95% CI 2.04–5.18) versus 0.53% (95% CI 0.20–1.37),  $P = 0.0013$ .
- There was a trend to earlier age of onset of MGUS in blacks compared with whites.

**Table 1.** Prevalence of monoclonal gammopathy of undetermined significance (MGUS) (%), by race, age and gender

| <i>Variable (# with MGUS)</i> | <i>Number of persons with MGUS</i> | <i>Blacks (34)<sup>a</sup><br/>% (95% CI)</i> | <i>Whites (9)<sup>a</sup><br/>% (95% CI)</i> | <i>Mexican-American (17)<br/>% (95% CI)</i> |
|-------------------------------|------------------------------------|-----------------------------------------------|----------------------------------------------|---------------------------------------------|
| <i>Age group, years</i>       |                                    |                                               |                                              |                                             |
| 10–19                         | 2                                  | 0.00 (NA)                                     | 0.00 (NA)                                    | 0.11 (0.02–0.84)                            |
| 20–29                         | 3                                  | 0.26 (0.08–0.84)                              | 0.00 (NA)                                    | 0.00 (NA)                                   |
| 30–39                         | 17                                 | 0.81 (0.43–1.53)                              | 0.32 (0.11–0.99)                             | 0.23 (0.06–0.79)                            |
| 40–49                         | 41                                 | 3.26 (2.04–5.18)                              | 0.53 (0.20–1.37)                             | 2.20 (1.22–3.95)                            |
| <i>Sex</i>                    |                                    |                                               |                                              |                                             |
| Male                          | 32                                 | 0.84 (0.54–1.29)                              | 0.26 (0.10–0.68)                             | 0.47 (0.25–0.87)                            |
| Female                        | 31                                 | 0.92 (0.58–1.48)                              | 0.18 (0.06–0.53)                             | 0.36 (0.16–0.78)                            |
| Total                         | 63                                 | 0.88 (0.62–1.26)                              | 0.22 (0.11–0.45)                             | 0.41 (0.23–0.73)                            |

# MGUS: Clinical differences

**Table 4.** Characteristics of the subjects with monoclonal gammopathy of undetermined significance (MGUS), by race/ethnicity

| <i>Total, n</i>                           | <i>Black (N = 34)</i> | <i>White (N = 9)</i> | <i>Mexican-American (N = 17)</i> |
|-------------------------------------------|-----------------------|----------------------|----------------------------------|
| Male sex % (95% CI)                       | 44 (30.6–58.2)        | 59.6 (25.8–86.2)     | 58.9 (39.6–75.7)                 |
| <i>Age, categories, % (95% CI)</i>        |                       |                      |                                  |
| 10–19                                     | 0                     | 0                    | 8.2 (1.2–38.9)                   |
| 20–29                                     | 7.7 (2.4–22.4)        | 0                    | 0                                |
| 30–39                                     | 24.3 (12.8–41.5)      | 42.6 (4) (14.8–76.0) | 12.7 (3.5–36.8)                  |
| 40–49                                     | 67.9 (50.3–81.6)      | 57.4 (24.0–85.2)     | 79.2 (54.2–92.4)                 |
| <i>Immunoglobulin isotype, % (95% CI)</i> |                       |                      |                                  |
| IgG                                       | 74.0 (53.0–87.8)      | 72.9 (33.9–93.4)     | 60.9 (28.4–85.9)                 |
| IgA                                       | 10.0 (2.7–30.7)       | 27.1 (6.6–66.1)      | 18.1 (3.8–55.2)                  |
| IgM                                       | 0                     | 0                    | 5.3 (0.7–31.5)                   |
| Biclonal                                  | 16.0 (7.0–32.7)       | 0                    | 15.7 (3.7–47.8)                  |
| <i>Light chain type, % (95% CI)</i>       |                       |                      |                                  |
| Kappa                                     | 45.9 (30.3–62.4)      | 68.3 (27.8–92.4)     | 68.6 (47.4–84.2)                 |
| Lambda                                    | 54.1 (37.6–69.7)      | 11.1 (1.4–52.3)      | 31.4 (15.8–52.6)                 |
| Biclonal                                  | 0                     | 20.5 (2.9–69.2)      | 0                                |
| <i>Monoclonal protein, g/dl</i>           |                       |                      |                                  |
| Median <sup>a</sup>                       | 0.1                   | 0.1                  | 0.1                              |
| Range                                     | 0.1–1.5               | 0.1–2.4              | 0.1–1.8                          |

# Myeloma: Different presentation?

| Covariate         | No. of Patients (%)  |                       |                    |                    | Adjusted $P^a$ |
|-------------------|----------------------|-----------------------|--------------------|--------------------|----------------|
|                   | White,<br>N = 25,823 | Hispanic,<br>N = 2624 | Black,<br>N = 5789 | Asian,<br>N = 1486 |                |
| At diagnosis      |                      |                       |                    |                    |                |
| Hypercalcemia     | 2494 (9.7)           | 244 (9.3)             | 629 (10.9)         | 126 (8.5)          | .586           |
| Renal dysfunction | 2910 (11.3)          | 347 (13.2)            | 830 (14.3)         | 190 (12.8)         | <.001          |
| Anemia            | 4370 (16.9)          | 475 (18.1)            | 1269 (21.9)        | 274 (18.4)         | <.001          |
| Bone fracture     | 4349 (16.8)          | 371 (14.1)            | 661 (11.4)         | 222 (14.9)         | <.001          |
| Dialysis          | 155 (0.6)            | 25 (1.0)              | 60 (1.0)           | 14 (0.9)           | .118           |
| After diagnosis   |                      |                       |                    |                    |                |
| Hypercalcemia     | 2789 (11.8)          | 303 (12.6)            | 822 (15.3)         | 148 (10.7)         | .063           |
| Renal dysfunction | 4883 (20.7)          | 554 (23.0)            | 1461 (27.2)        | 316 (22.9)         | <.001          |
| Anemia            | 5788 (24.6)          | 597 (24.8)            | 1684 (31.4)        | 333 (24.1)         | <.001          |
| Bone fracture     | 5528 (23.5)          | 529 (21.9)            | 898 (16.7)         | 275 (19.9)         | <.001          |
| Dialysis          | 557 (2.4)            | 87 (3.6)              | 225 (4.2)          | 50 (3.6)           | <.001          |

# Spectrum of genetic abnormalities is different

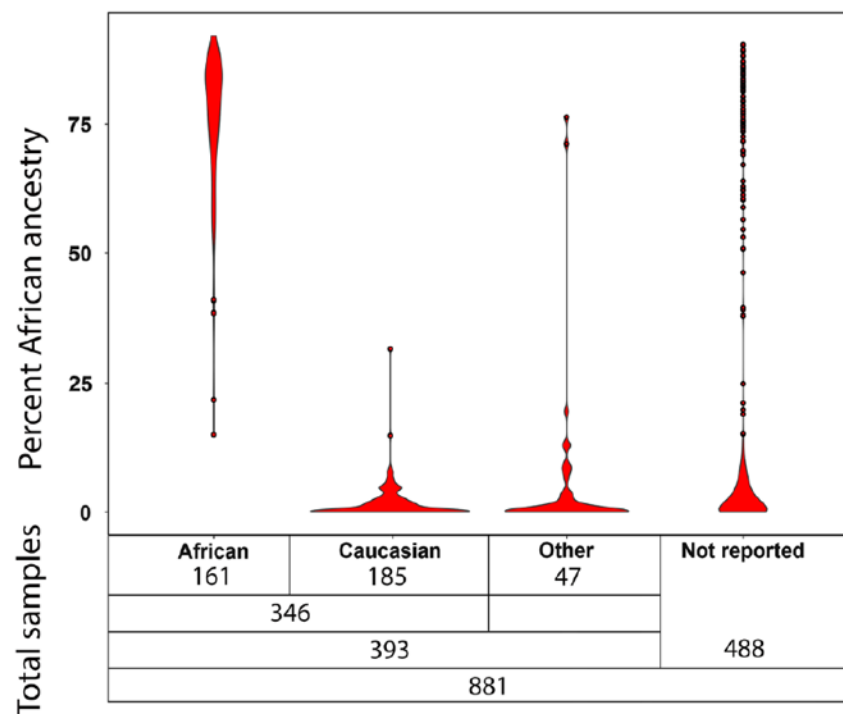


**Fig. 1 Percent African ancestry by self-reported race in cohort of 881 individuals.** Distribution of the percent of African ancestry based on the sum of all 10 African regional ancestries within the 881 samples in this study by self-report race in 393 samples or non-reported race information in 488 samples

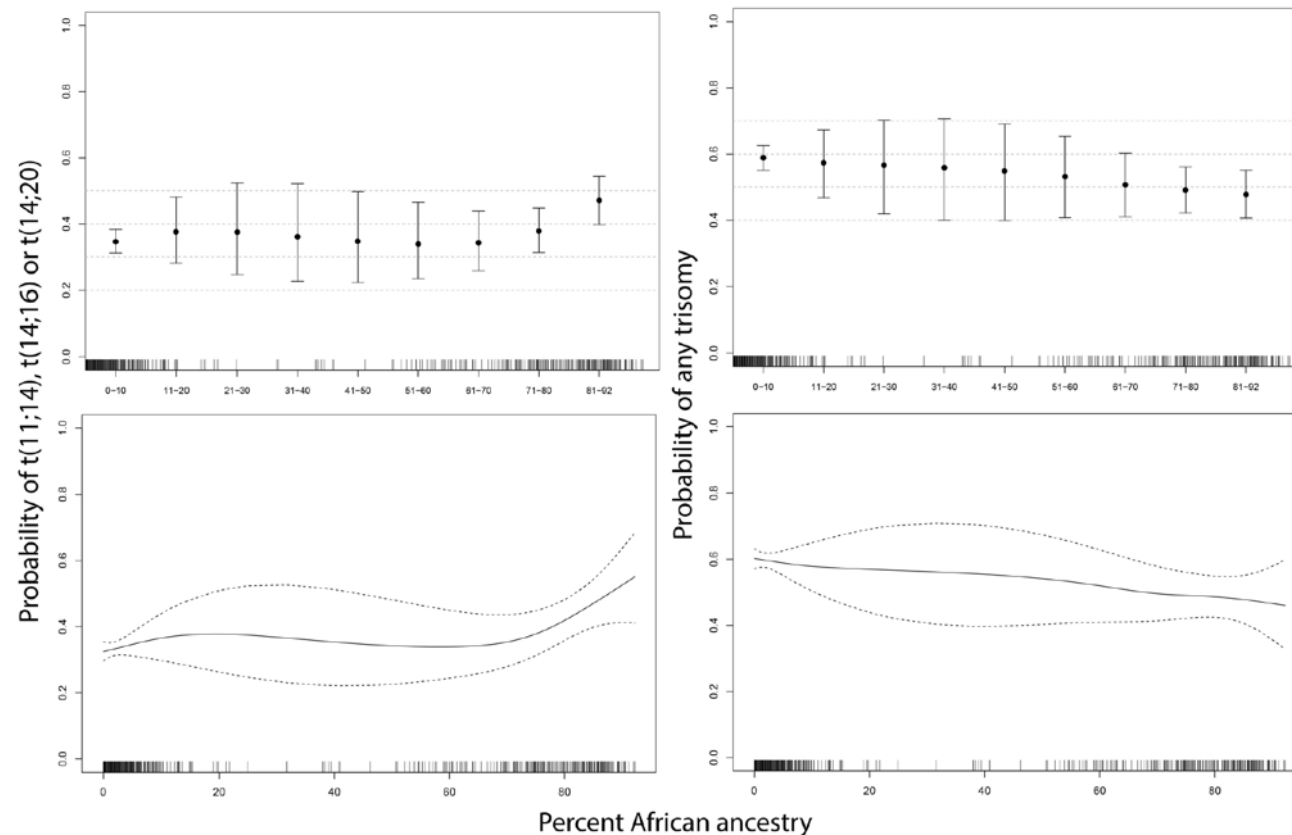


**Fig. 2 Probability of either t(11;14),t(14;16) or t(14;20) or any trisomy in relation to percent African ancestry.** Smoothing spline was used to visualize the relationship between percentage of African genetics and probability of t(11;14), t(14;16) or t(14;20) or of any trisomy



# Spectrum of genetic abnormalities

**Table 2 Frequency of IgH translocations, hyperdiploidy, and copy number variations and comparison between race**

| Gene          | Type             | ALL, n (N = 68) | CA, n (N = 47) | % (n/N) | AA, n (N = 21) | % (n/N) | P-value* |
|---------------|------------------|-----------------|----------------|---------|----------------|---------|----------|
| 4;14          | Translocation    | 2               | 2              | 4.3     | 0              | 0       | 1        |
| 8;14          | Translocation    | 2               | 2              | 4.3     | 0              | 0       | 1        |
| 11;14         | Translocation    | 6               | 0              | 0       | 6              | 28.6    | 0.0005   |
| 14;16         | Translocation    | 1               | 0              | 0       | 1              | 4.8     | 0.309    |
| Hyperdiploidy | Chromosomal gain | 34              | 24             | 51.1    | 10             | 47.6    | 1        |
| amp(1q)       | Amplification    | 13              | 6              | 12.8    | 7              | 33.3    | 0.091    |
| del(1p)       | Amplification    | 3               | 0              | 0       | 3              | 14.3    | 0.027    |
| del(13q)      | Amplification    | 21              | 15             | 31.9    | 6              | 28.6    | 1        |
| del(17p)      | Amplification    | 13              | 10             | 21.3    | 3              | 14.3    | 0.74     |

No difference observed in the common mutations

# Genetic polymorphisms and MM risk

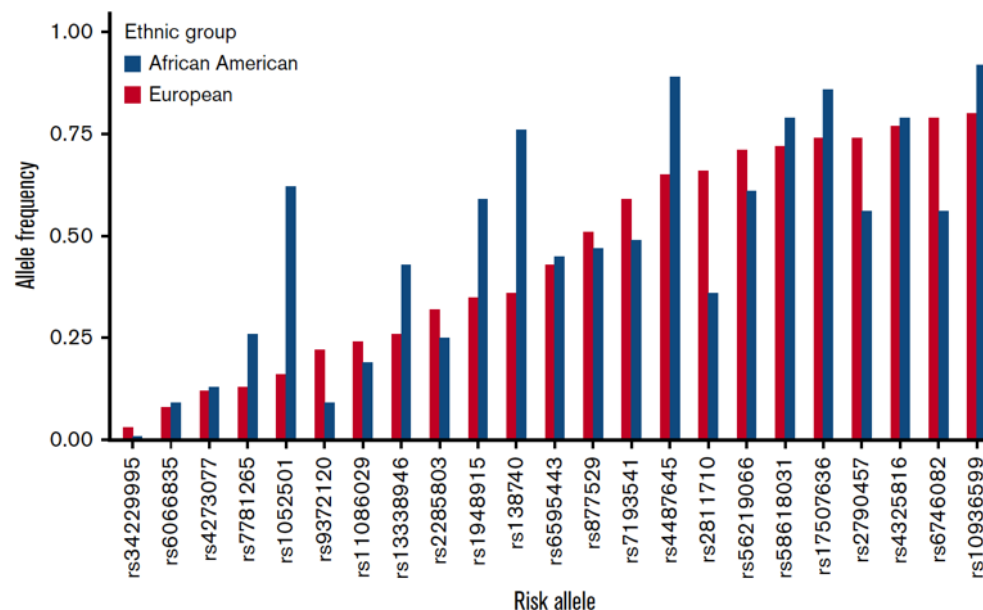


**Table 2. Associations between categorical PRSs and MM risk in 1813 patients and 8871 controls of AA**

| PRS category        | European-weighted PRS* |                       |                  | AA-weighted PRS <sub>1</sub> † |                        |                  | AA-weighted PRS <sub>2</sub> ‡ |                        |                  |
|---------------------|------------------------|-----------------------|------------------|--------------------------------|------------------------|------------------|--------------------------------|------------------------|------------------|
|                     | OR (95% CI)            | P                     | P <sub>Het</sub> | OR (95% CI)                    | P                      | P <sub>Het</sub> | OR (95% CI)                    | P                      | P <sub>Het</sub> |
| 0%-10%              | 0.70 (0.57-0.86)       | $6.52 \times 10^{-4}$ | .94              | 0.52 (0.41-0.65)               | $1.49 \times 10^{-8}$  | .90              | 0.48 (0.37-0.60)               | $9.68 \times 10^{-10}$ | .56              |
| 10%-25%             | 0.78 (0.66-0.92)       | $3.10 \times 10^{-3}$ | .30              | 0.70 (0.59-0.84)               | $7.16 \times 10^{-5}$  | .01              | 0.72 (0.60-0.85)               | $1.34 \times 10^{-4}$  | .83              |
| 25%-75% (reference) | 1                      | NA                    | NA               | 1                              | NA                     | NA               | 1                              | NA                     | NA               |
| 75%-90%             | 1.24 (1.07-1.43)       | $3.71 \times 10^{-3}$ | .78              | 1.36 (1.18-1.56)               | $1.54 \times 10^{-5}$  | .99              | 1.39 (1.21-1.60)               | $2.76 \times 10^{-6}$  | .80              |
| 90%-100%            | 1.61 (1.38-1.88)       | $1.41 \times 10^{-9}$ | .31              | 1.66 (1.43-1.94)               | $7.54 \times 10^{-11}$ | .37              | 1.82 (1.56-2.11)               | $9.43 \times 10^{-15}$ | .65              |

ORs were adjusted for age, sex, and PCs 1-10, *P* values are Wald *P* values, and *P*<sub>Het</sub> are *P* values of heterogeneity in fixed-effect meta analyses.

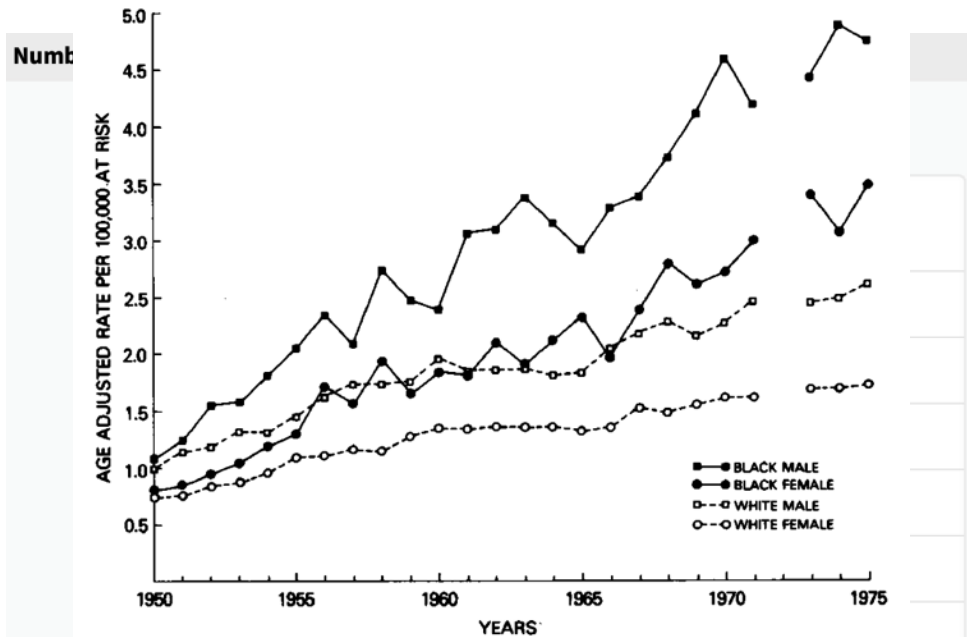
NA, not applicable.

\*European-weighted PRSs were constructed using the known 22 index SNPs reported in EUR GWASs, and weights were from original EUR GWASs.

†AA-weighted PRS<sub>1</sub> were constructed using the known 22 index SNPs reported in EUR GWASs, and weights were from AA MM.

‡AA-weighted PRS<sub>2</sub> were constructed using 14 index SNPs (weights from AA MM) and 8 better AA markers (weights from AA MM and adjusted for their "winner's curse" using a Bayesian approach).

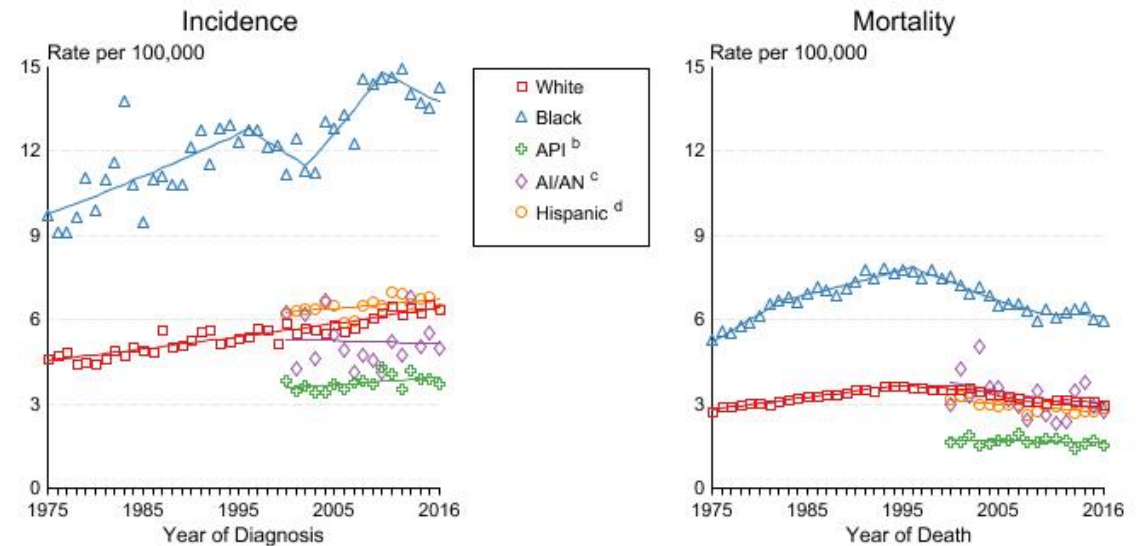
# Survival outcomes



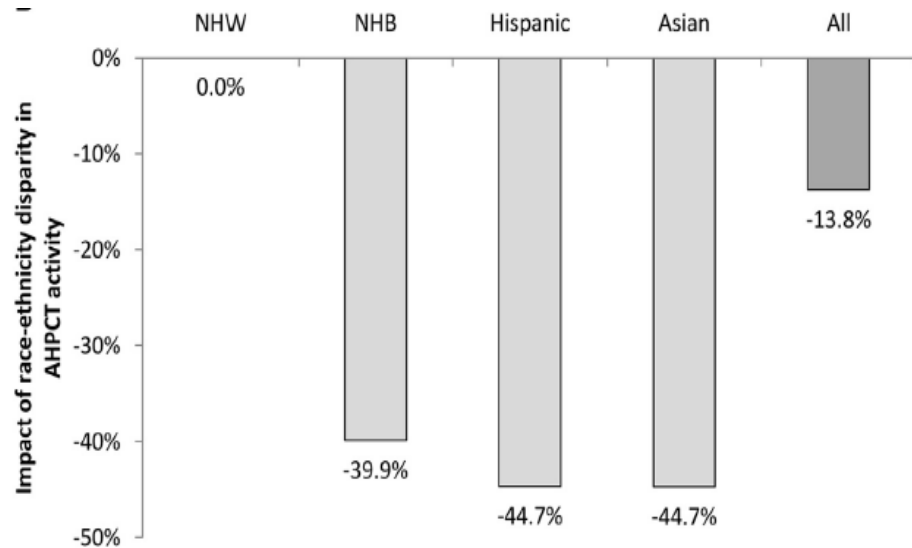
U.S. 20

Figure 1. Age-Adjusted Mortality Rates from Multiple Myeloma per Hundred Thousand Population in the United States, 1950-1975.

SEER Incidence and US Death Rates<sup>a</sup>  
Myeloma, Both Sexes  
Joinpoint Analyses for Whites and Blacks from 1975-2016  
and for Asian/Pacific Islanders, American Indians/Alaska Natives and Hispanics from 2000-2016



# Difference in access to therapy?



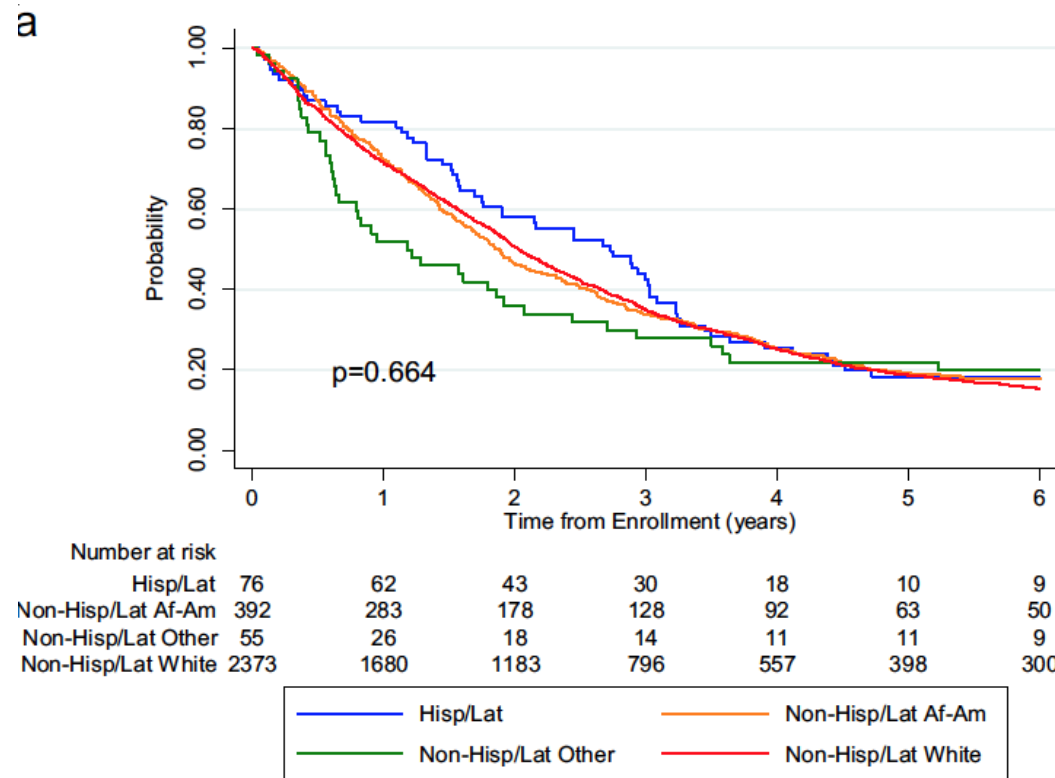
Use of ASCT

| Characteristic                                   | White<br>n = 3574 | Hispanic<br>n = 531 | African-American<br>n = 945 | Asian<br>n = 288 | Adjusted<br>P value <sup>1</sup> |
|--------------------------------------------------|-------------------|---------------------|-----------------------------|------------------|----------------------------------|
| <b>Lenalidomide</b>                              |                   |                     |                             |                  |                                  |
| Any use, No. (%)                                 | 814 (22.8)        | 126 (23.7)          | 183 (19.4)                  | 61 (21.2)        | <0.01                            |
| Median days of use (Q1, Q3) <sup>2</sup>         | 98 (49, 192)      | 84 (42, 172)        | 98 (42, 178)                | 112 (56, 189)    | 0.72                             |
| Median days to first dose (Q1, Q3)               | 79 (31, 186)      | 74 (29, 191)        | 67 (30, 165)                | 139 (35, 216)    | 0.14                             |
| <b>Thalidomide</b>                               |                   |                     |                             |                  |                                  |
| Any use, No. (%)                                 | 654 (18.3)        | 148 (27.9)          | 177 (18.7)                  | 82 (28.5)        | <0.01                            |
| Median days of use (Q1, Q3)                      | 140 (56, 224)     | 140 (56, 252)       | 140 (84, 252)               | 112 (56, 224)    | 0.56                             |
| Median days to first dose (Q1, Q3)               | 38 (20, 100)      | 43 (23, 84)         | 35 (18, 84)                 | 38 (20, 61)      | 0.64                             |
| <b>Bortezomib</b>                                |                   |                     |                             |                  |                                  |
| Any use, No. (%)                                 | 456 (12.8)        | 44 (8.3)            | 112 (11.9)                  | 22 (7.6)         | <0.01                            |
| Median days to first dose (Q1, Q3)               | 51 (23, 116)      | 117 (40, 212)       | 46 (22, 127)                | 50 (26, 140)     | 0.02                             |
| <b>Stem cell transplant</b>                      |                   |                     |                             |                  |                                  |
| Any use, No. (%)                                 | 206 (5.8)         | 10 (1.9)            | 35 (3.7)                    | 6 (2.1)          | <0.01                            |
| <b>Combination therapy</b>                       |                   |                     |                             |                  |                                  |
| Bortezomib only, No. (%)                         | 301 (8.4)         | 22 (4.1)            | 80 (8.5)                    | 11 (3.8)         | <0.01                            |
| Lenalidomide/thalidomide only, No. (%)           | 1191 (33.3)       | 225 (42.4)          | 300 (31.7)                  | 116 (40.3)       |                                  |
| Lenalidomide/thalidomide and bortezomib, No. (%) | 155 (4.3)         | 22 (4.1)            | 32 (3.4)                    | 11 (3.8)         |                                  |

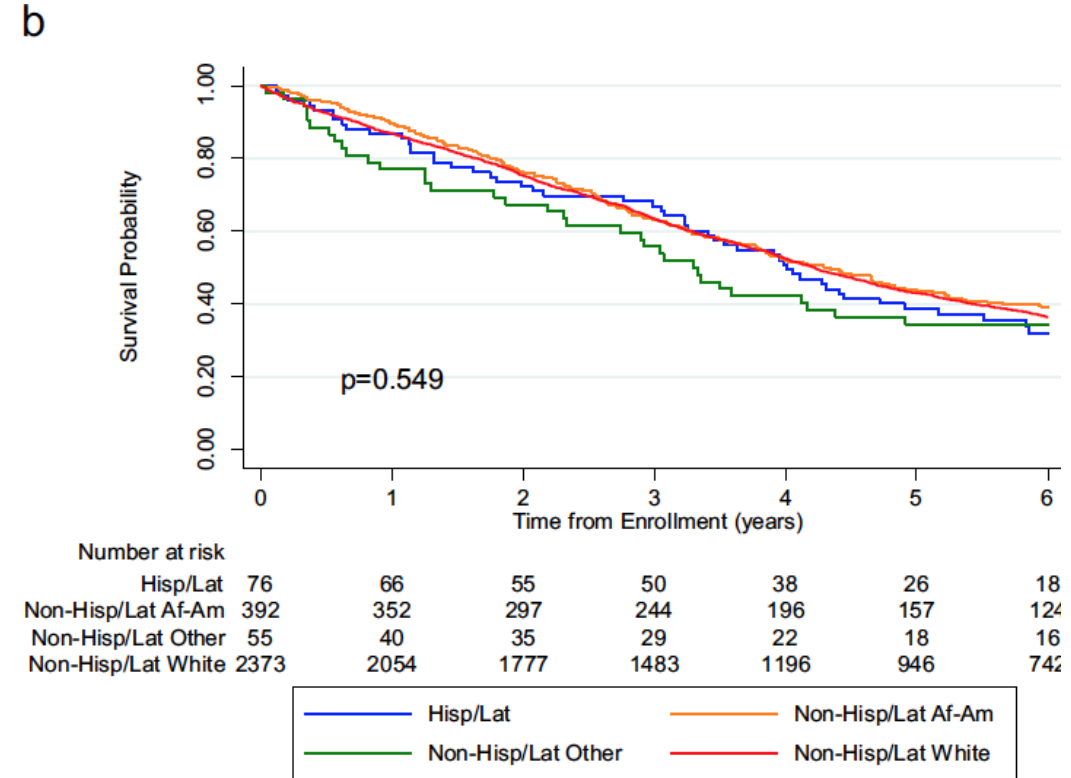
# Are treatment approaches different?

| Covariate              | No. of Patients (%)  |                       |                    |                    | Adjusted $P^b$ |
|------------------------|----------------------|-----------------------|--------------------|--------------------|----------------|
|                        | White,<br>N = 25,823 | Hispanic,<br>N = 2624 | Black,<br>N = 5789 | Asian,<br>N = 1486 |                |
| Any treatment          | 8281 (32.1)          | 958 (36.5)            | 1830 (31.6)        | 513 (34.5)         | <.001          |
| Proteasome inhibitor   | 2422 (9.4)           | 204 (7.8)             | 489 (8.4)          | 116 (7.8)          | <.001          |
| IMiD                   |                      |                       |                    |                    |                |
| Any                    | 2856 (11.1)          | 468 (17.8)            | 714 (12.3)         | 245 (16.5)         | <.001          |
| Lenalidomide           | 2055 (8.0)           | 306 (11.7)            | 467 (8.1)          | 148 (10.0)         | .010           |
| Thalidomide            | 1342 (5.2)           | 257 (9.8)             | 369 (6.4)          | 155 (10.4)         | <.001          |
| Cytotoxic chemotherapy |                      |                       |                    |                    |                |
| Any                    | 1172 (4.5)           | 113 (4.3)             | 199 (3.4)          | 69 (4.6)           | <.001          |
| Melphalan              | 346 (1.3)            | 47 (1.8)              | 59 (1.0)           | 41 (2.8)           | <.001          |
| Cyclophosphamide       | 918 (3.6)            | 67 (2.6)              | 147 (2.5)          | 30 (2.0)           | <.001          |
| SCT                    | 1561 (6.0)           | 96 (3.7)              | 289 (5.0)          | 61 (4.1)           | <.001          |
| Steroids               | 6161 (23.9)          | 792 (30.2)            | 1357 (23.4)        | 417 (28.1)         | <.001          |

# Treatment outcomes



Hisp/Lat: Hispanic/Latino, Af-Am: African American



Hisp/Lat: Hispanic/Latino, Af-Am: African American

**Fig. 3 Survival outcomes for patients included in the study by race-ethnicity. a** Progression-free survival (PFS) by patient race-ethnicity. **b** Overall survival (OS) by patient race-ethnicity

# Outcomes with autologous SCT

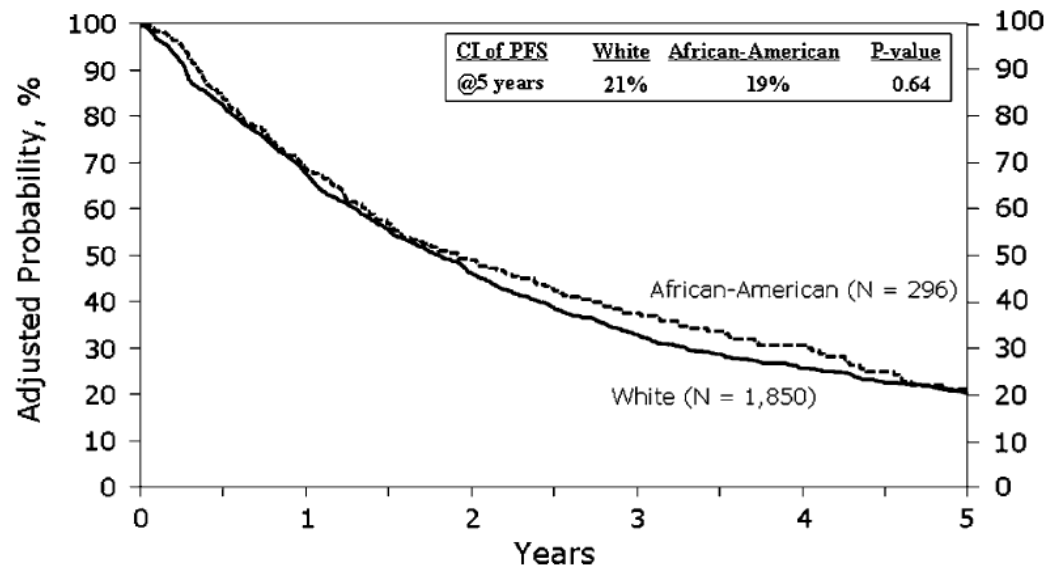


**Figure 3.** Probability of progression-free survival.

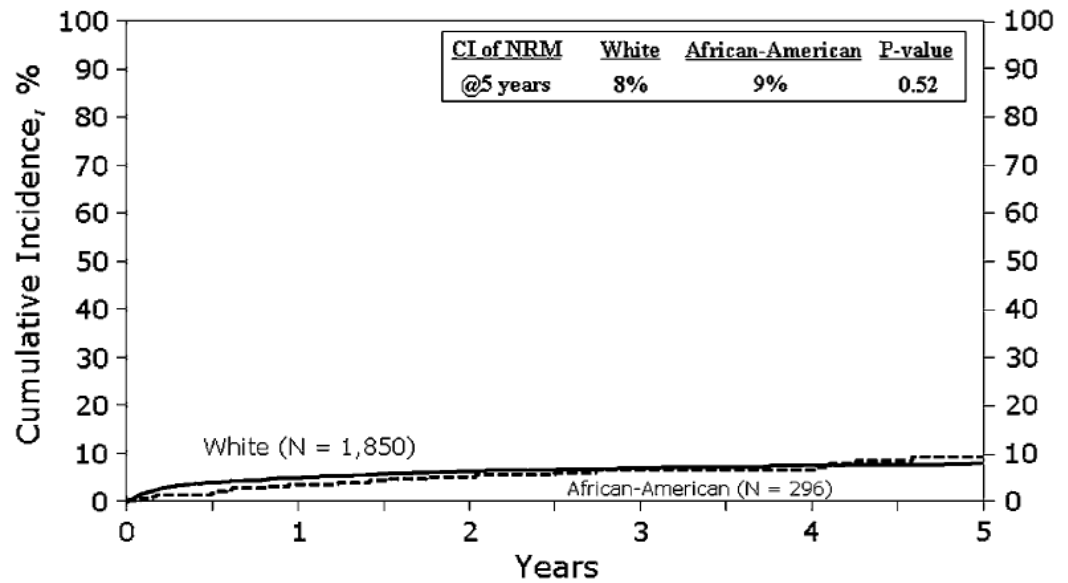
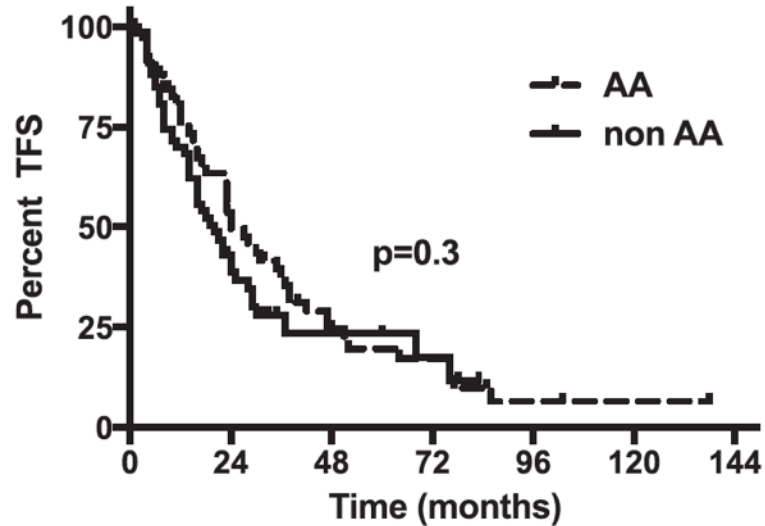
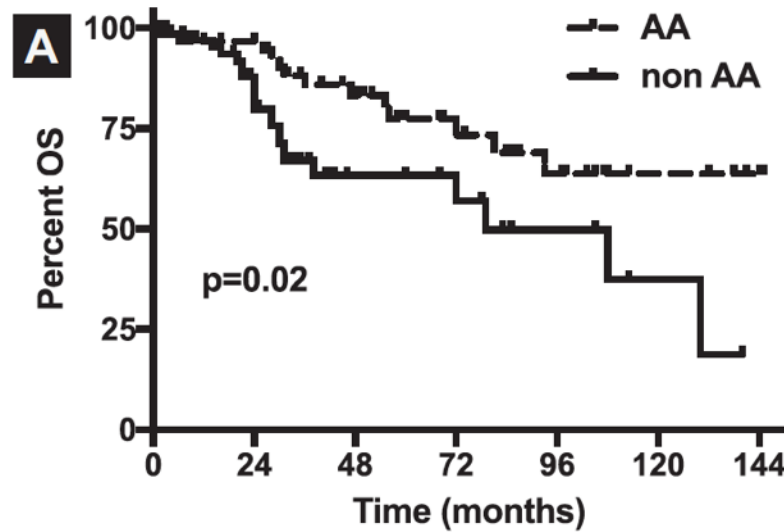


**Figure 1.** Cumulative incidence of nonrelapse mortality.

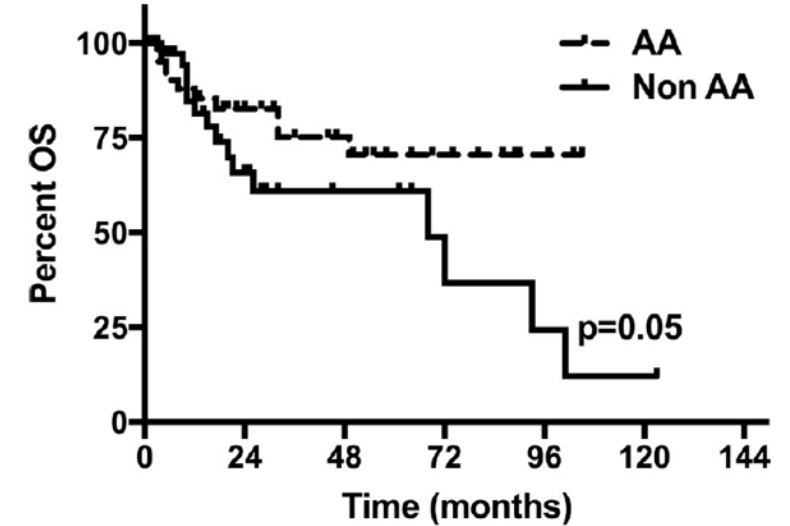
# Outcomes with transplant



PFS



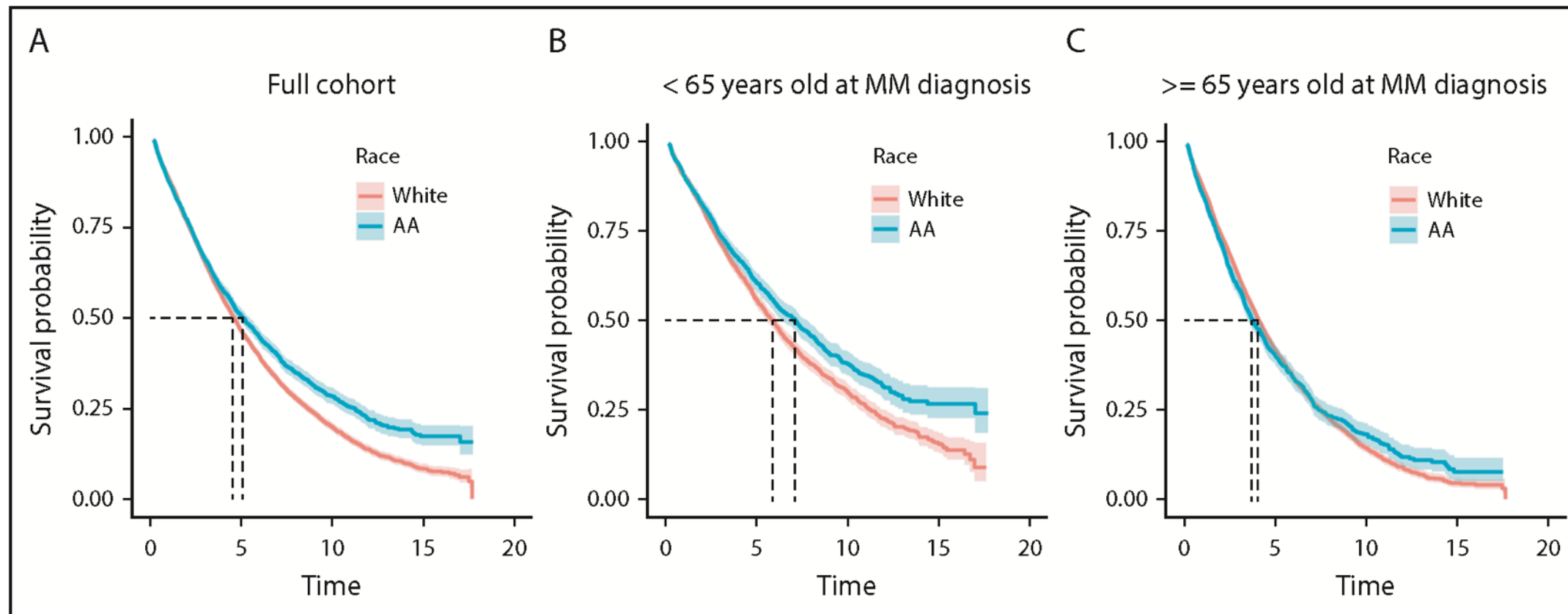
OS



OS from Relapse

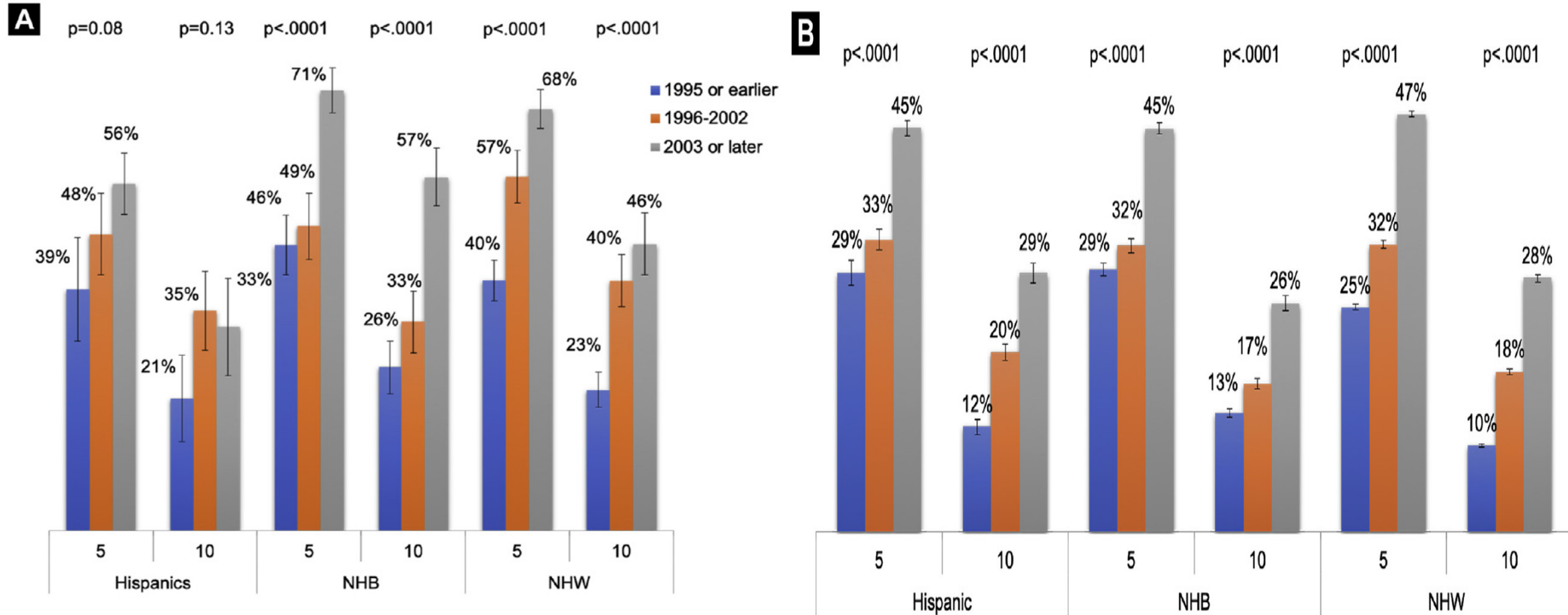


# Equal survival with comparable access



Center (HHC) black myeloma patients and 46 white and 46 black controls at Columbia-Presbyterian Medical Center (CPMC), analyzed by the Gehan test ( $P < 0.0001$ ).

# Are we making equal progress?



**HOW CAN WE USE THIS INFORMATION?**

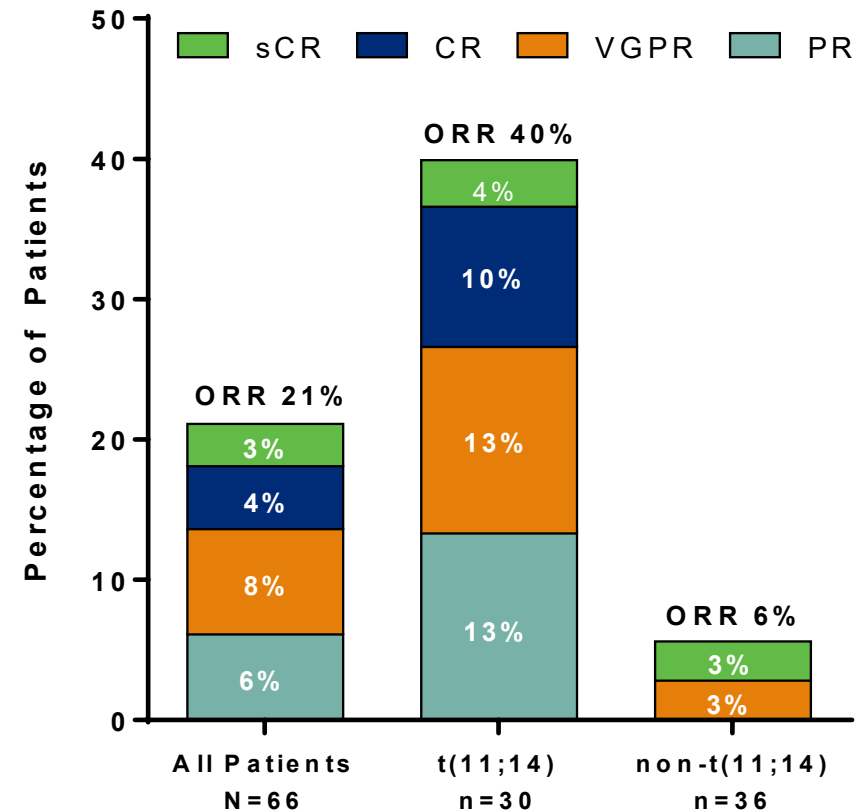
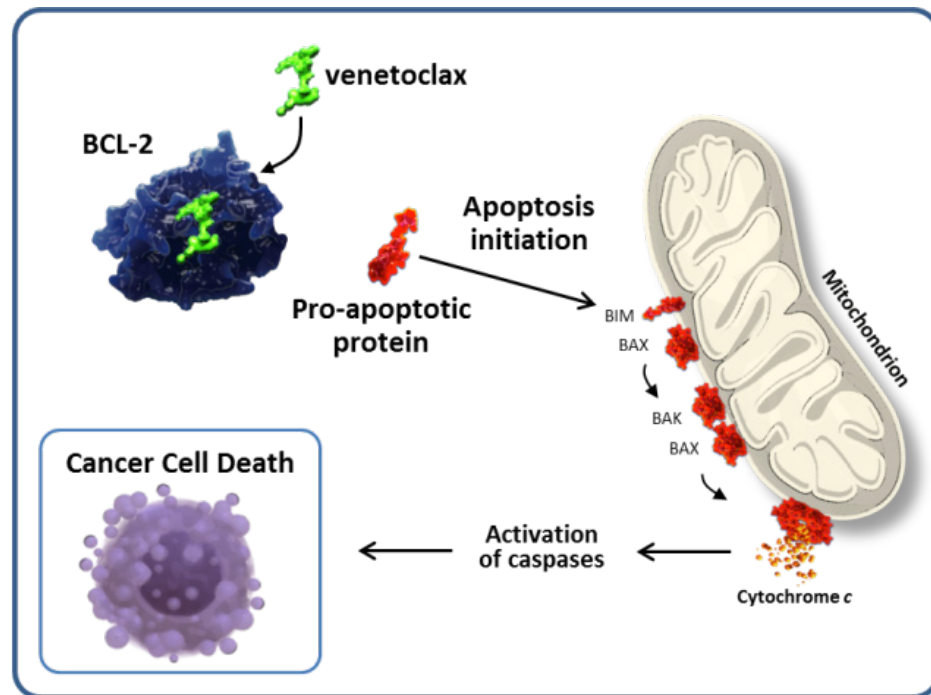
# Screening

- Recent data support early intervention in high risk SMM
- If we do intervene early in HRSMM, we need to screen and identify them
- Screening those at high risk:
  - AA, family members etc
- Given earlier disease onset → earlier diagnosis?

# Access to therapy

- Access to SCT still remains an issue
- Particularly relevant to AA as they appear to do well with this therapy
- Important role for organizations like ASTCT

# Targeted Therapy: Venetoclax





Kumar.shaji@mayo.edu

**THANK YOU**



# **Increasing Minority Accrual in Myeloma Clinical Trials: Emory Experience and Lessons Learned**

Ajay K. Nooka, MD, MPH, FACP

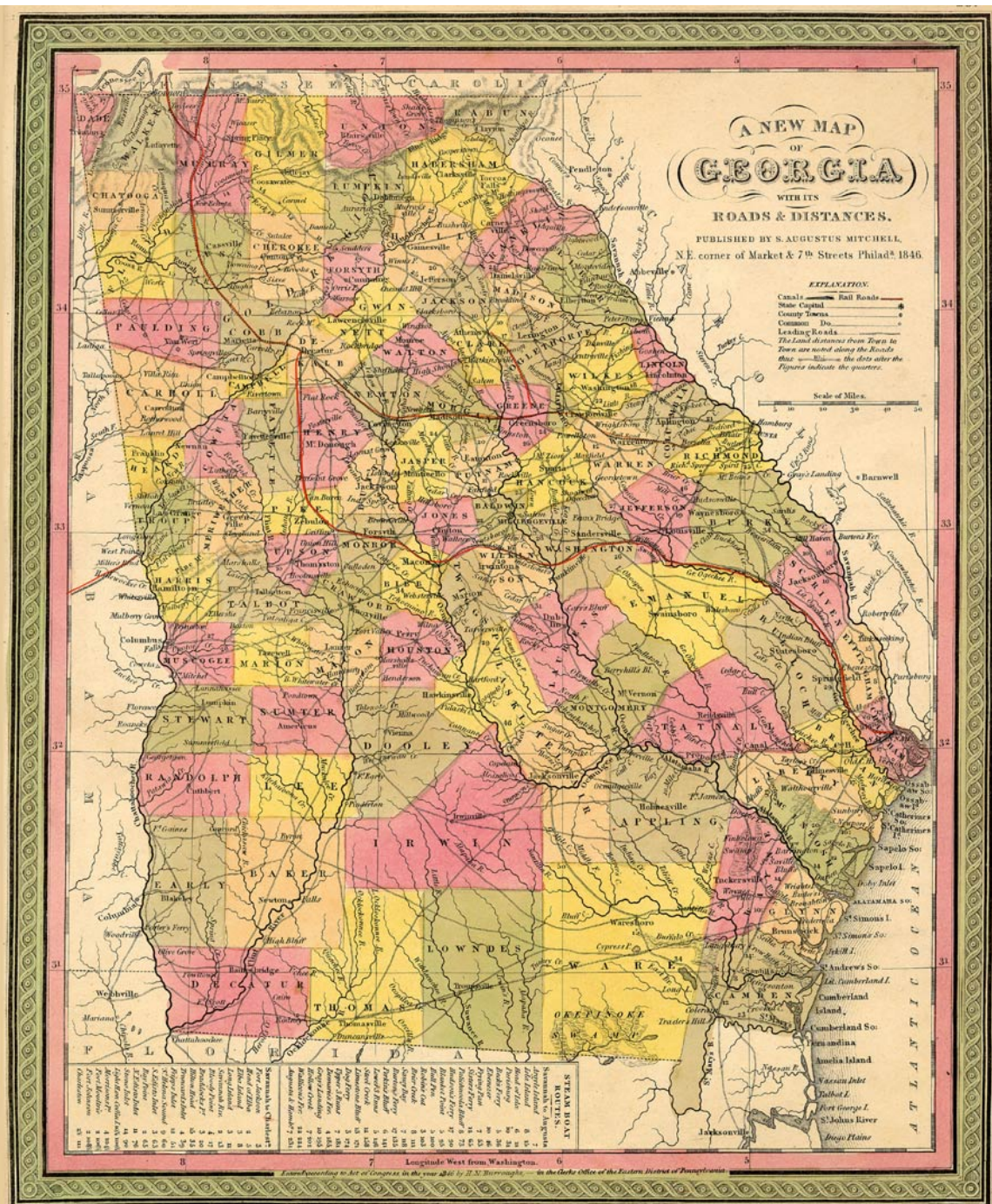
Associate Professor

Department of Hematology and Oncology

Winship Cancer Institute of Emory University

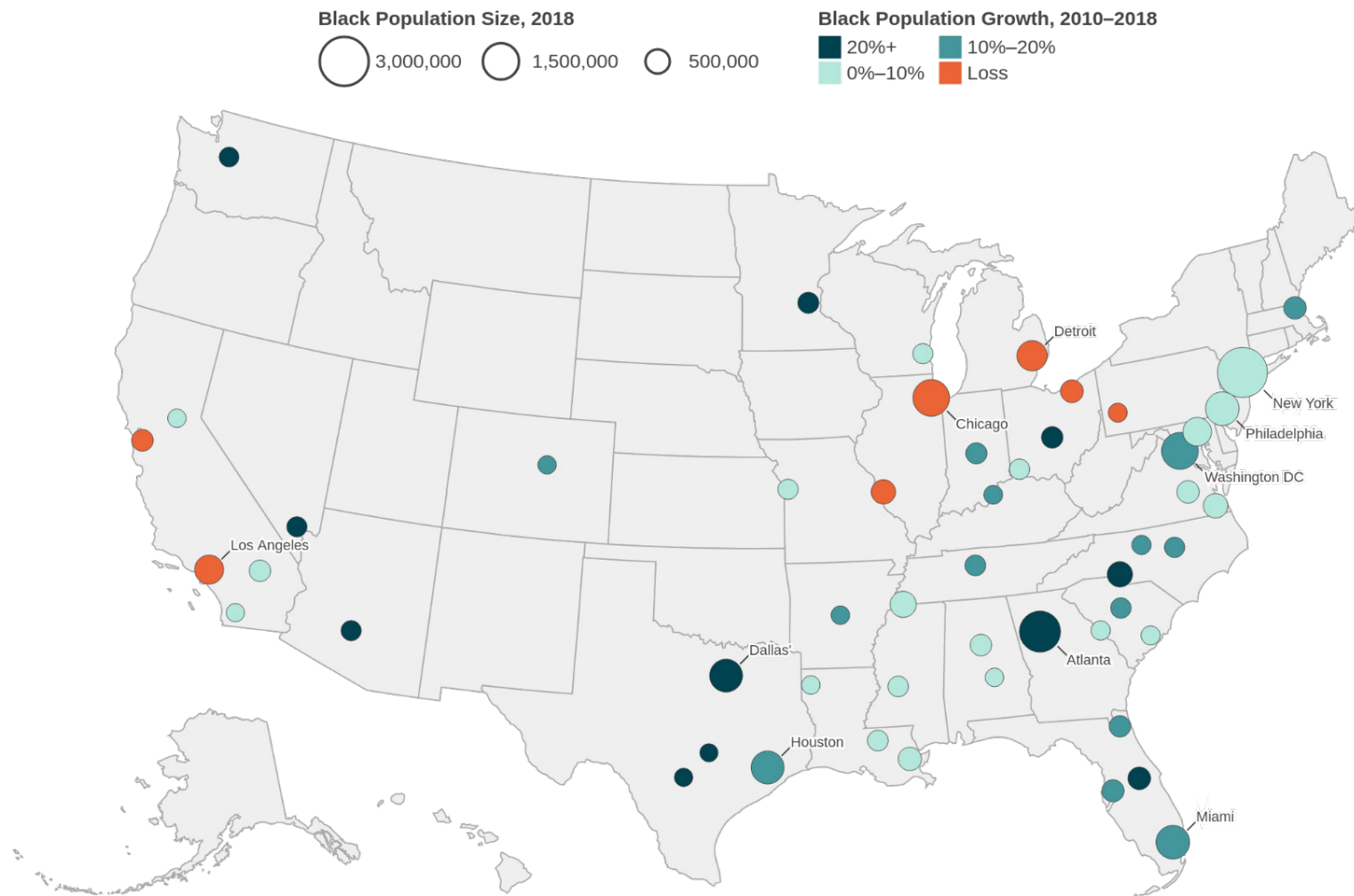
Emory University School of Medicine





- In 2020, of the 1,806,590 new cases of cancer in the US
  - 32,270 cases of myeloma
  - 12830 deaths from myeloma
- In 2020, 1100 Georgians will be diagnosed with myeloma.
  - 420 deaths from myeloma

Siegel, et al. Cancer Statistics, 2020. CA Cancer J Clin. 2020;70:7–30



Source: William H. Frey analysis of US Census population estimates, 2018

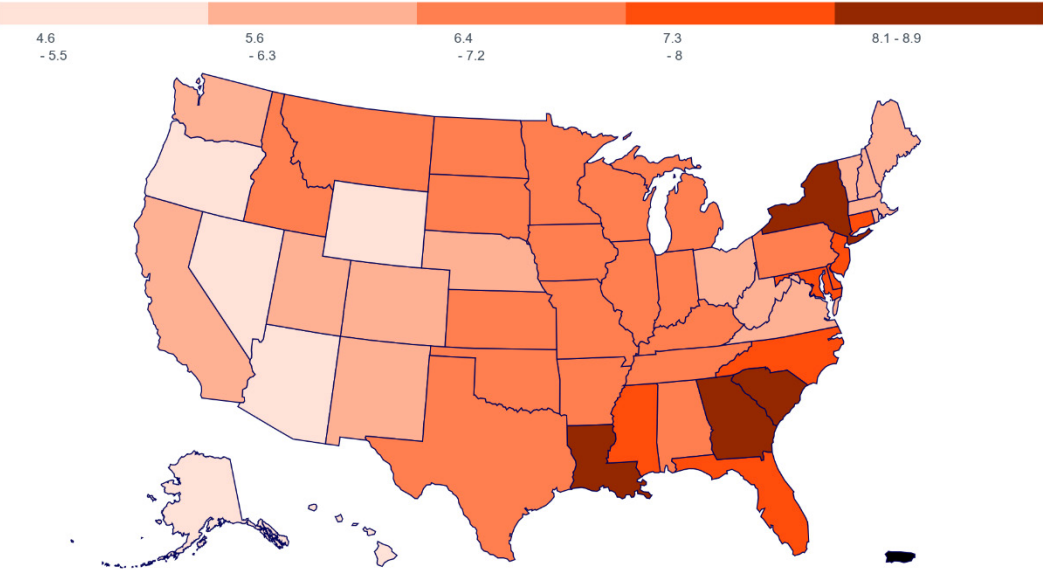
A group is highly represented if its share of the area population is larger than its share of the national population for Hispanics (18.3%), blacks (12.5%), and Asians, Native Hawaiians and Other Pacific Islanders (5.9%) and at least 4% for American Indians/Alaska Natives, or persons identifying as multiracial

\*Non Hispanic members of group

\*\*Two or more minority groups are highly represented or persons identified as multiracial are highly represented



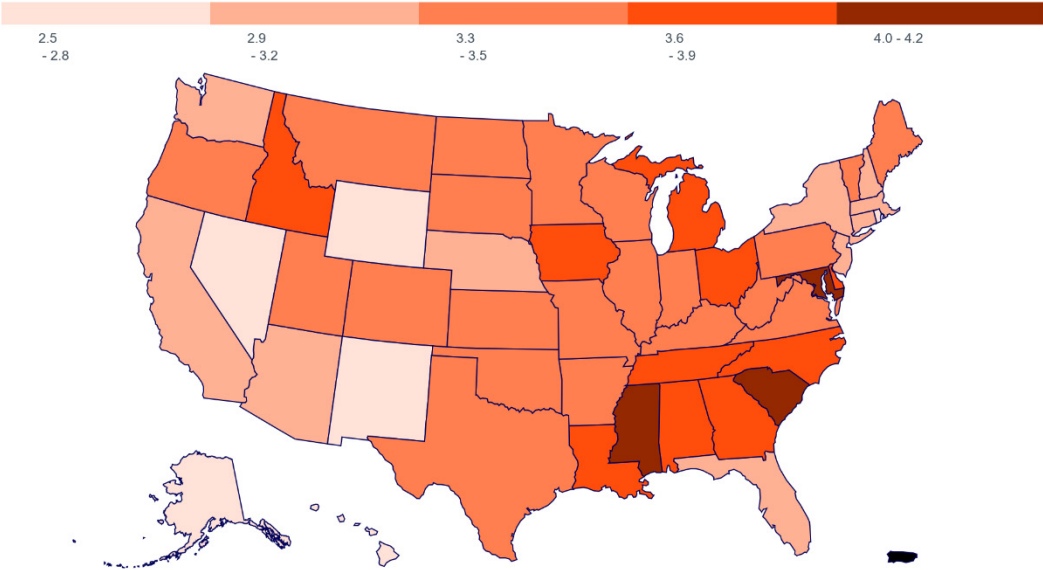
Incidence rates, 2012-2016  
by state, for myeloma  
Average annual rate per 100,000, age adjusted to the 2000 US standard population.



Data Sources: North American Association of Central Cancer Registries (NAACCR), 2019  
© 2020 American Cancer Society

CancerStatisticsCenter.cancer.org

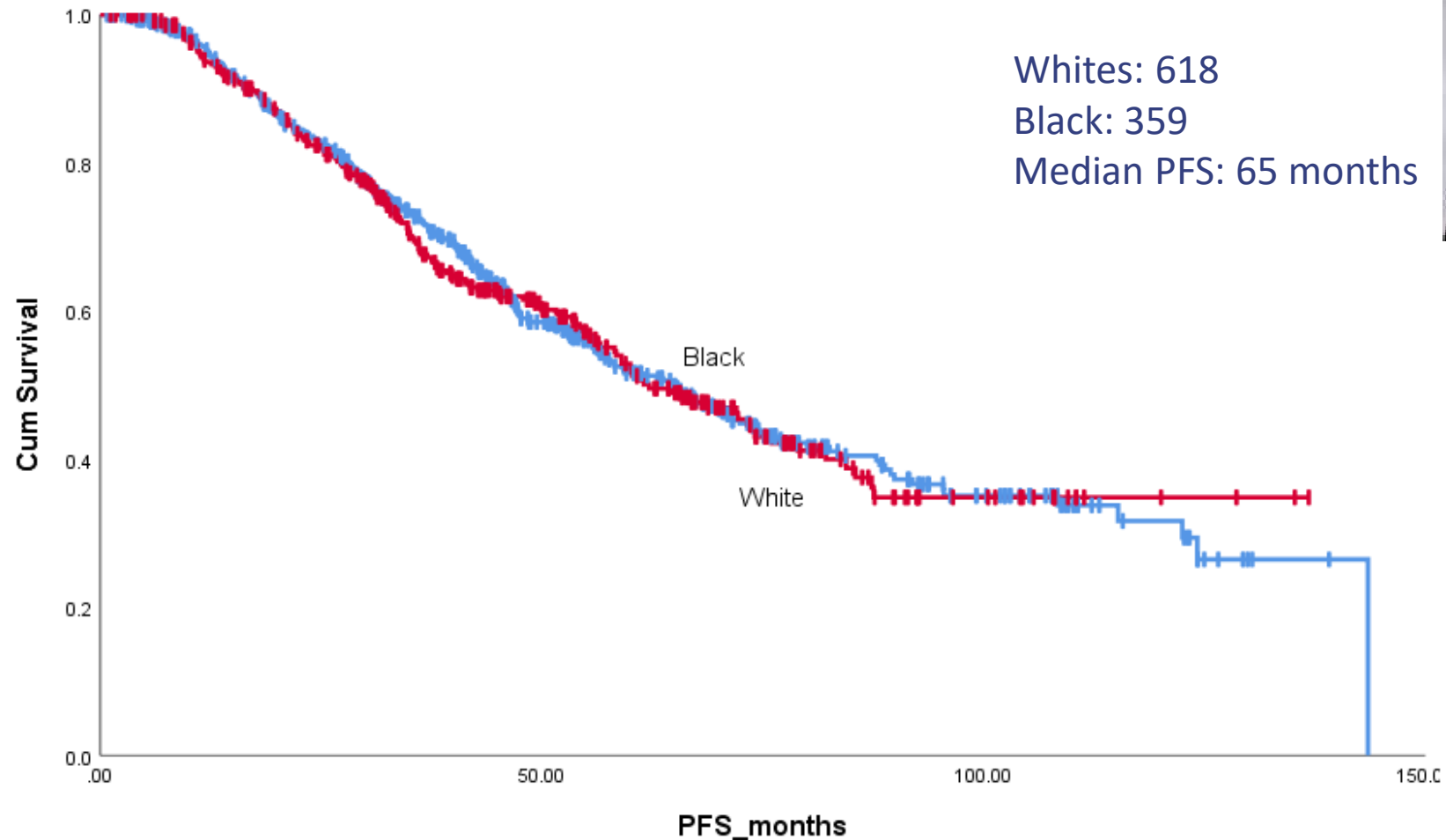
Death rates, 2013-2017  
by state, for myeloma  
Average annual rate per 100,000, age adjusted to the 2000 US standard population. Rates for PR are for 2011-2015.



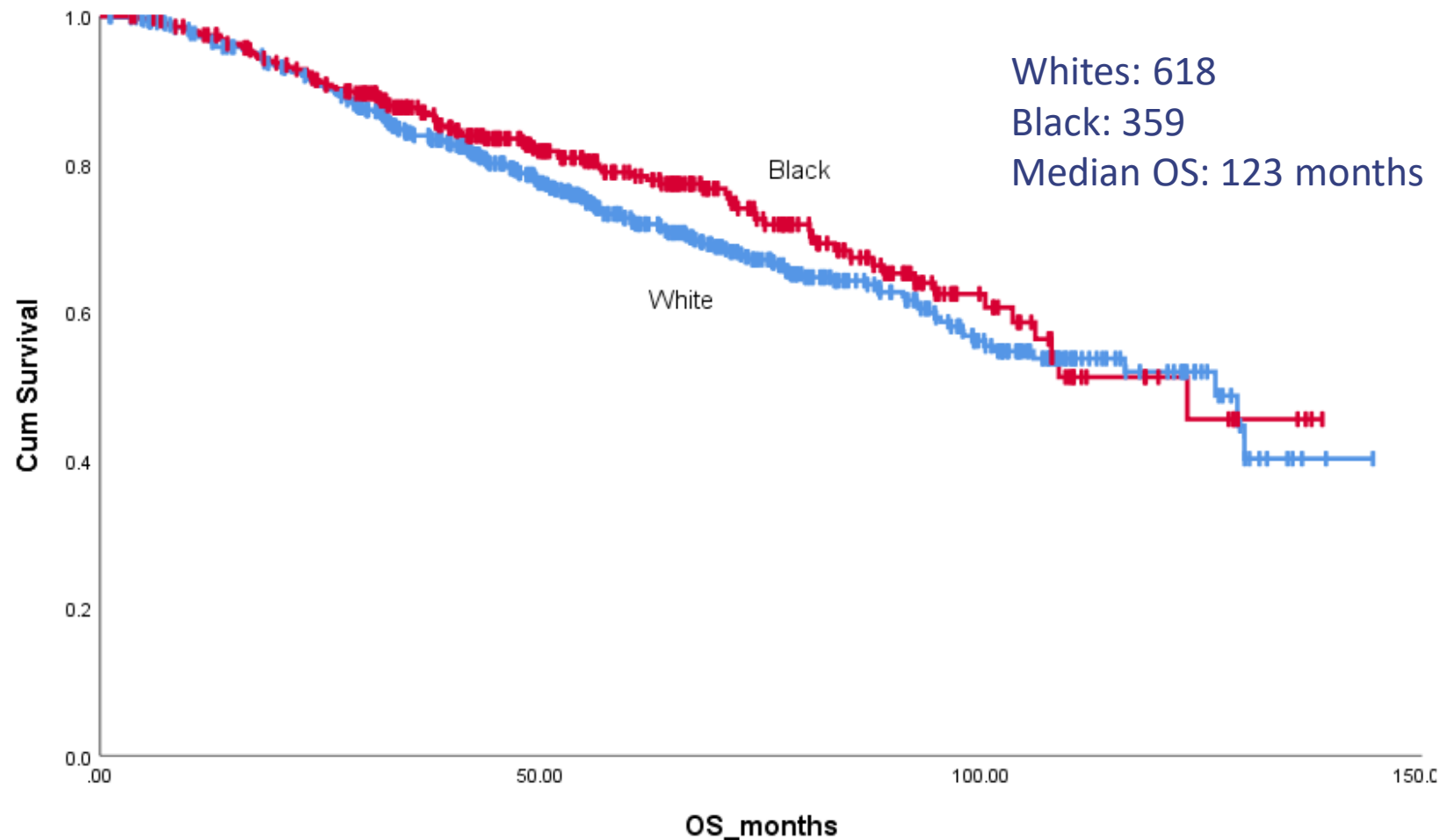
Data Sources: National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2019  
© 2020 American Cancer Society

CancerStatisticsCenter.cancer.org

# RVD induction with risk stratified maintenance: progression free survival, by race



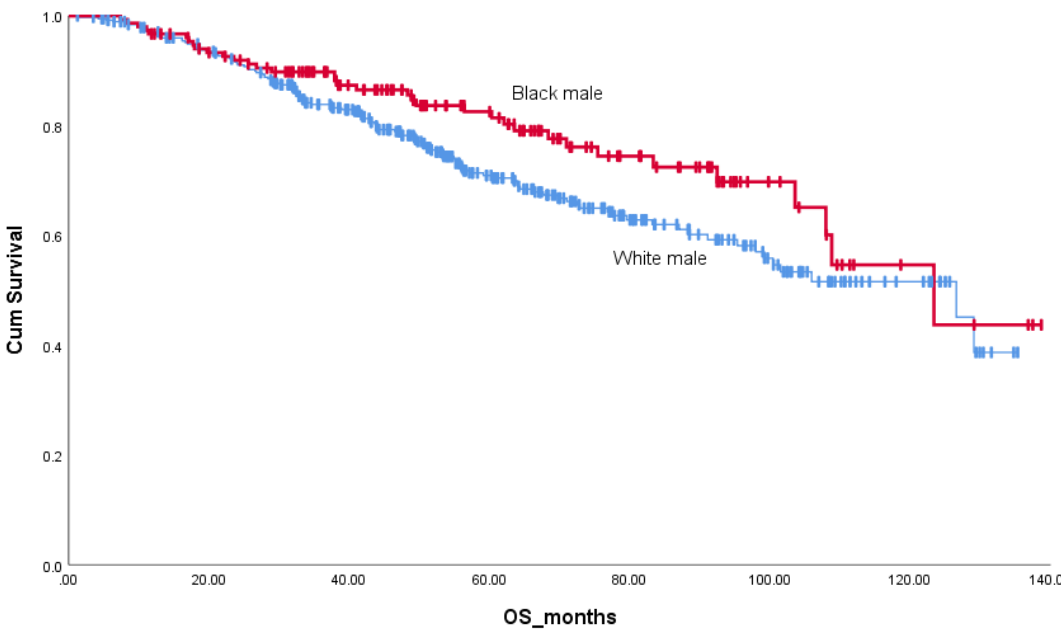
# RVD induction with risk stratified maintenance: Overall survival, by race



# RVD induction with risk stratified maintenance: Overall survival, by race and gender

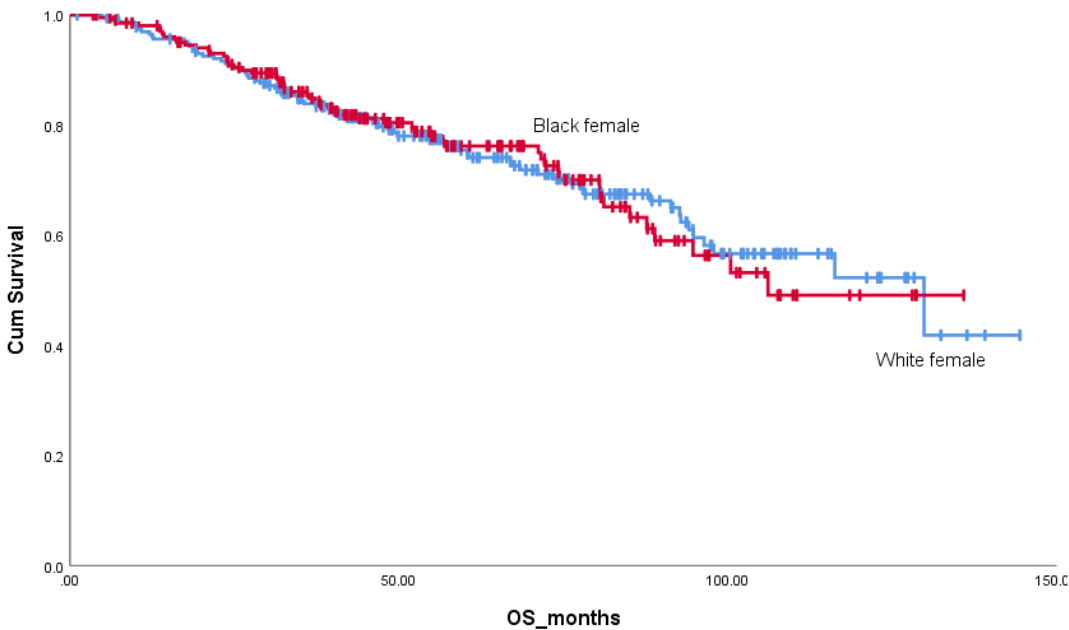
## Males

White male: 383  
Black male: 152



## Females

White female: 235  
Black female: 207



# Winship Myeloma Treatment Trials Enrollment (Main Sites)

## Black Patients

**32%**  
of Georgia residents

**35%**  
of Winship patients

**34%**  
of clinical trial enrollment

---

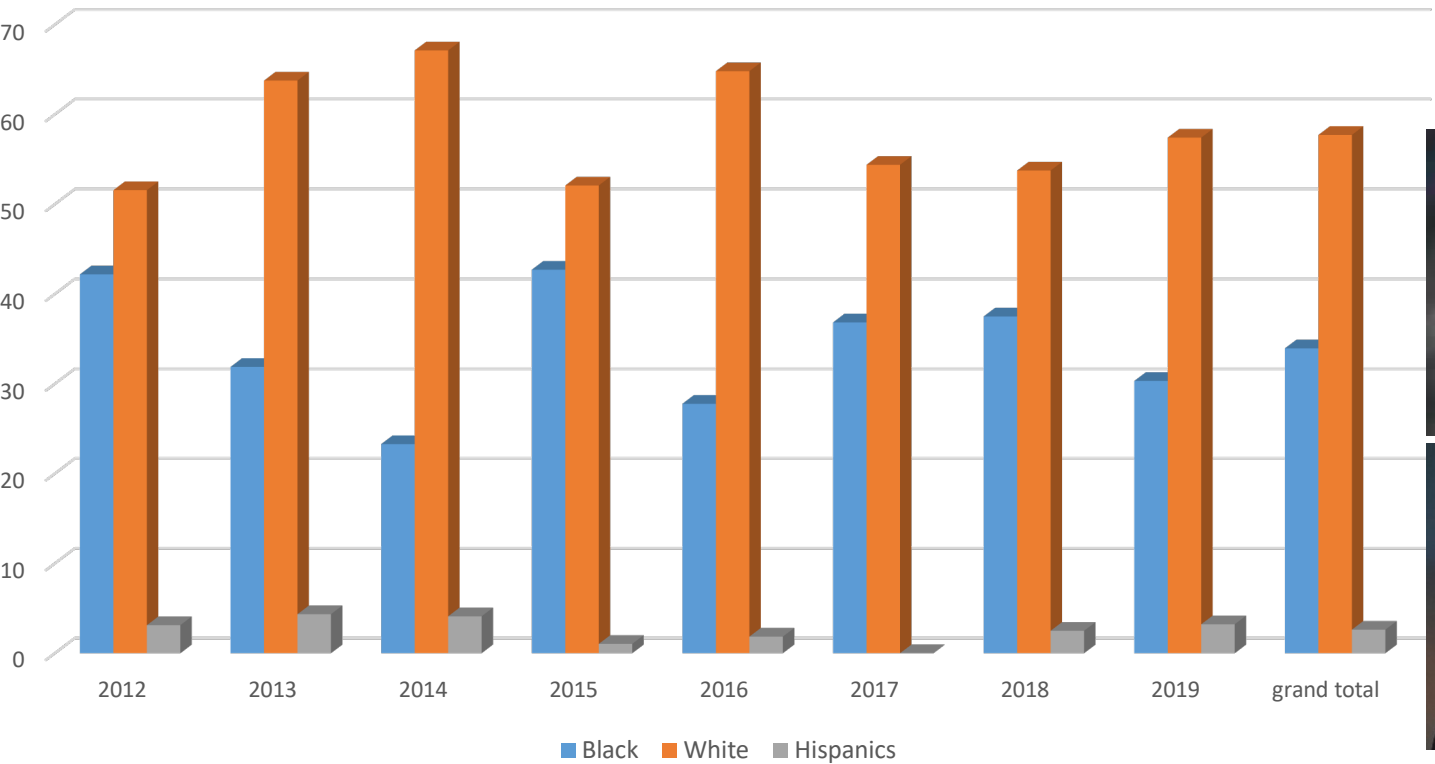
## Hispanic Patients

**9%**  
of Georgia residents

**4%**  
of Winship patients

**2.6%**  
of clinical trial enrollment

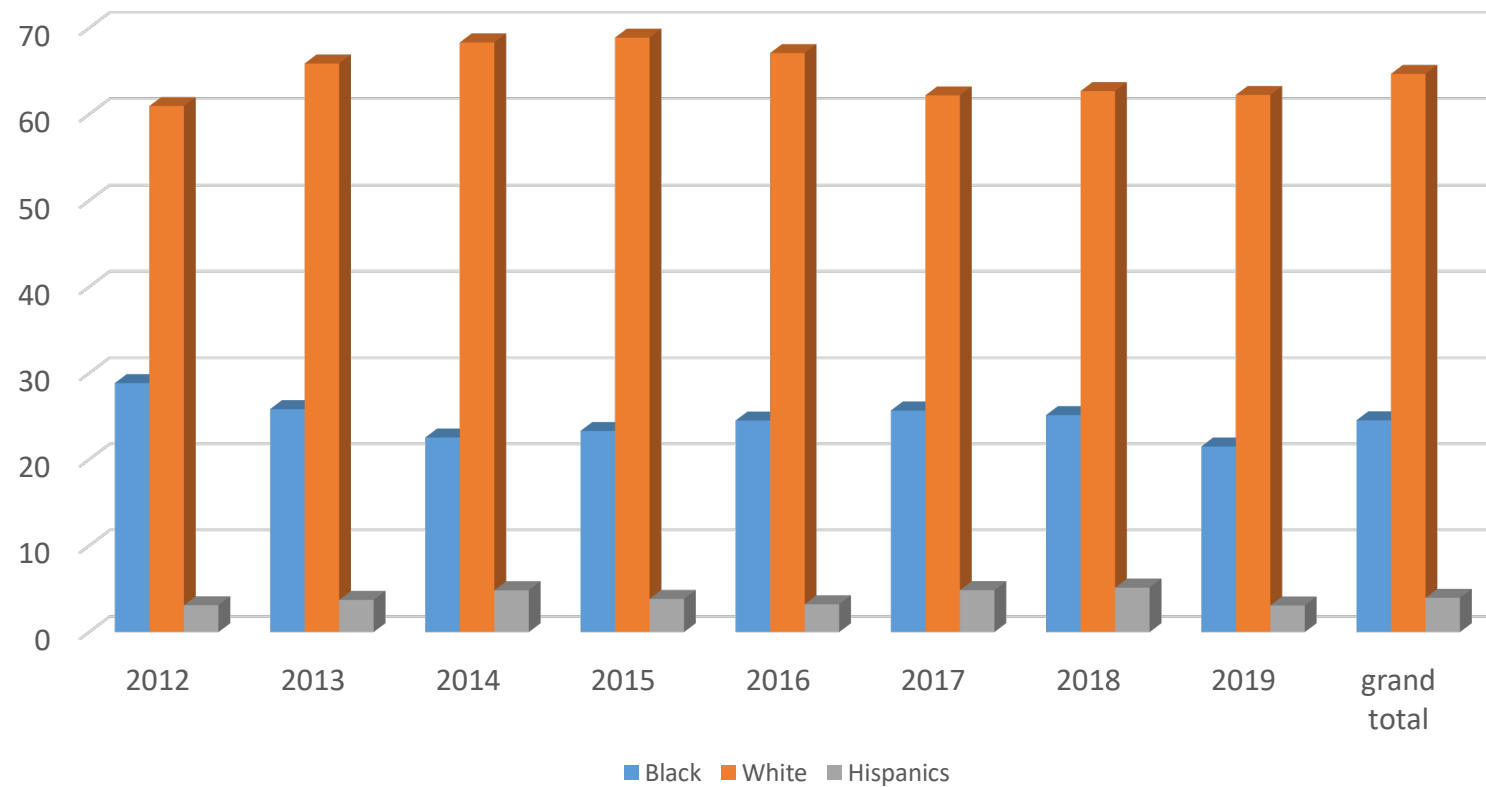
Myeloma clinical trial enrollment, by race  
2012-2019



| Race        | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | Total |
|-------------|------|------|------|------|------|------|------|------|-------|
| Black       | 27   | 22   | 17   | 41   | 15   | 21   | 30   | 47   | 220   |
| White       | 33   | 44   | 49   | 50   | 35   | 31   | 43   | 89   | 374   |
| Hispanics   | 2    | 3    | 3    | 1    | 1    | 0    | 2    | 5    | 17    |
| Grand total | 64   | 69   | 73   | 96   | 54   | 57   | 80   | 155  | 648   |



Winship Clinical trials enrollment, by race  
2012-2019



| Race        | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | Total |
|-------------|------|------|------|------|------|------|------|------|-------|
| Black       | 204  | 187  | 163  | 182  | 190  | 201  | 215  | 209  | 1551  |
| White       | 431  | 477  | 494  | 538  | 520  | 487  | 536  | 605  | 4088  |
| Hispanics   | 22   | 27   | 35   | 30   | 25   | 38   | 44   | 30   | 251   |
| Grand total | 707  | 724  | 723  | 781  | 775  | 783  | 855  | 972  | 6320  |

# Winship Treatment Trials Enrollment (Main Sites)

## Black Patients

**32%**

of Georgia residents

**27%**

of Winship patients

**25%**

of clinical trial enrollment

## Hispanic Patients

**9%**

of Georgia residents

**2%**

of Winship patients

**4%**

of clinical trial enrollment

## Women

**52%**

of Georgia residents

**49%**

of Winship patients

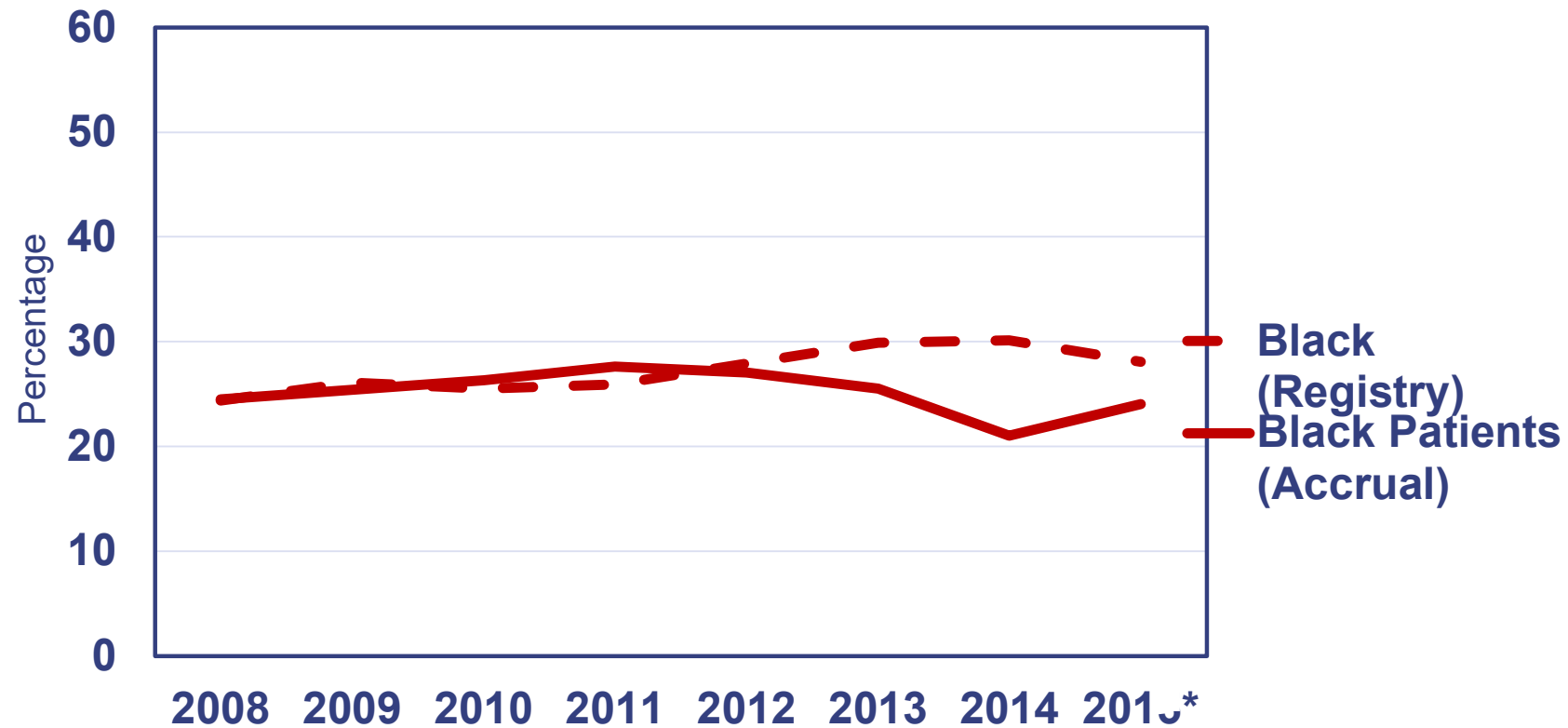
**42%**

of clinical trial enrollment

**Access to Children's Oncology Group and Pediatric Brain Tumor Consortium phase 1 clinical trials:  
Racial/ethnic dissimilarities in participation. Nooka A, Pentz R et al. Cancer 2016**

Although sex and racial/ethnic groups are mostly proportionally represented in phase 1 trials, some specific subgroups such as Hispanic children are underrepresented and may benefit from focused accrual.

## Percent of Enrolled Subjects on Winship Treatment Trials Who Are Black Mirrors Percent of New Winship Patients Who Are Black



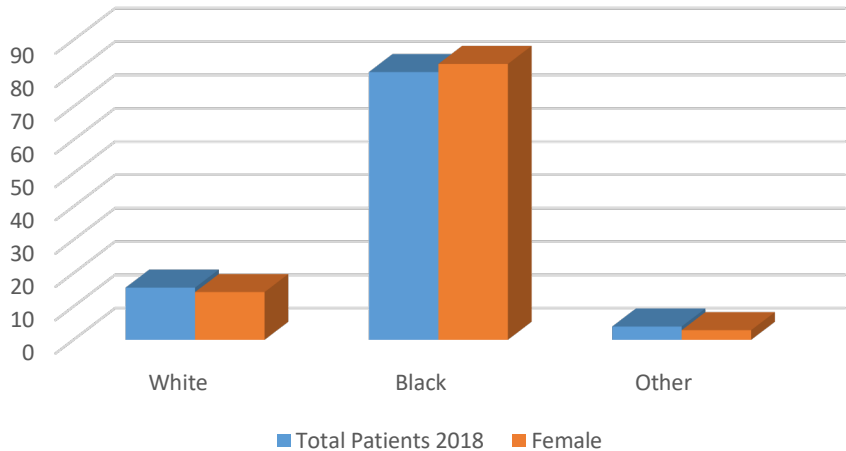
# Barriers for clinical trial enrollment

- System level barriers
  - Lack of clinical trial infrastructure
  - Insurance
- Individual level
  - Mistrust
  - Fear related to research participation
  - Inadequate information about research
  - Access/Convenience of participation

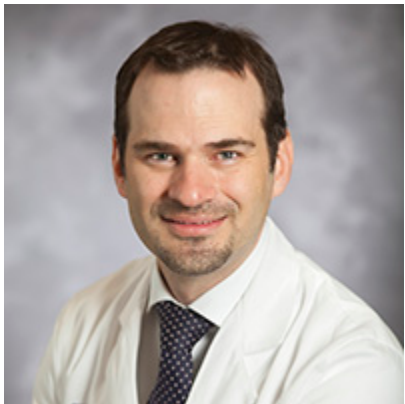
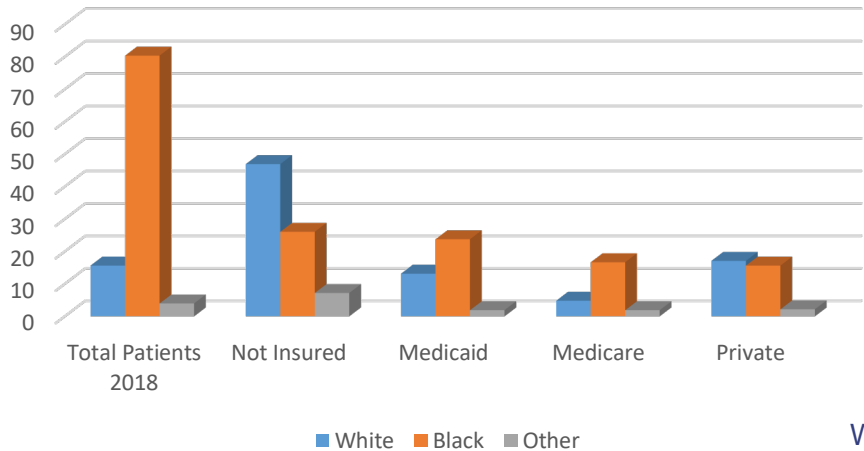
# System level barriers



Total patients in 2018



Insurance status



Courtesy: Leon Bernal

# Mistrust



- Research on Stored Biological Samples: Views of African American and White American Cancer Patients
- To assess whether the views of African American patients and patients with lower income and education, differ from the views of non-Hispanic white research participants.
- 315/452 (70%) patients completed the survey
  - 206/244 (84%) from Winship(W)
  - 109/208 (52%) from Grady (G)

TABLE I. Demographic Characteristics

|                               | Winship<br>(n = 206) | Grady<br>(n = 109) | Total<br>(n = 315) |
|-------------------------------|----------------------|--------------------|--------------------|
|                               | n (%)                | n (%)              | n (%)              |
| Sex                           |                      |                    |                    |
| Male                          | 96 (50)              | 38 (37)            | 134 (45)           |
| Female                        | 96 (50)              | 65 (63)            | 161 (55)           |
| Missing                       | 14                   | 6                  | 20                 |
| Age                           |                      |                    |                    |
| Mean                          | 54.7                 | 52.2               | 53.8               |
| Missing                       | 16                   | 8                  | 24                 |
| Race                          |                      |                    |                    |
| Indian or Pacific<br>Islander | 3 (2)                | 0                  | 3 (1)              |
| Black or African<br>American  | 22 (12)              | 87 (86)            | 109 (38)           |

TABLE II. Willingness to Donate

|                                                                    | Winship<br>(n = 206) | Grady<br>(n = 109) | Total<br>(n = 315) |
|--------------------------------------------------------------------|----------------------|--------------------|--------------------|
|                                                                    | n (%)                | n (%)              | n (%)              |
| Research on cancer                                                 |                      |                    |                    |
| Yes                                                                | 194 (95)             | 99 (95)            | 293 (95)           |
| No                                                                 | 11 (5)               | 5 (5)              | 16 (5)             |
| Missing                                                            | 1                    | 5                  | 6                  |
| Research on diabetes                                               |                      |                    |                    |
| Yes                                                                | 193 (95)             | 97 (92)            | 290 (94)           |
| No                                                                 | 11 (5)               | 8 (8)              | 19 (6)             |
| Missing                                                            | 2                    | 4                  | 6                  |
| How willing for research<br>on Alzheimer's<br>compared to diabetes |                      |                    |                    |
| Less willing                                                       | 5 (3)                | 5 (5)              | 10 (3)             |
| Equally willing                                                    | 168 (85)             | 79 (76)            | 247 (82)           |
| More willing                                                       | 25 (13)              | 20 (19)            | 45 (15)            |
| Missing                                                            | 8                    | 5                  | 13                 |

- Almost all participants (95% W, 95% G) authorized future research on biological samples for cancer. The majority (92%–97%) was as willing to have their tissue used for research on diabetes and Alzheimer's Disease as on cancer



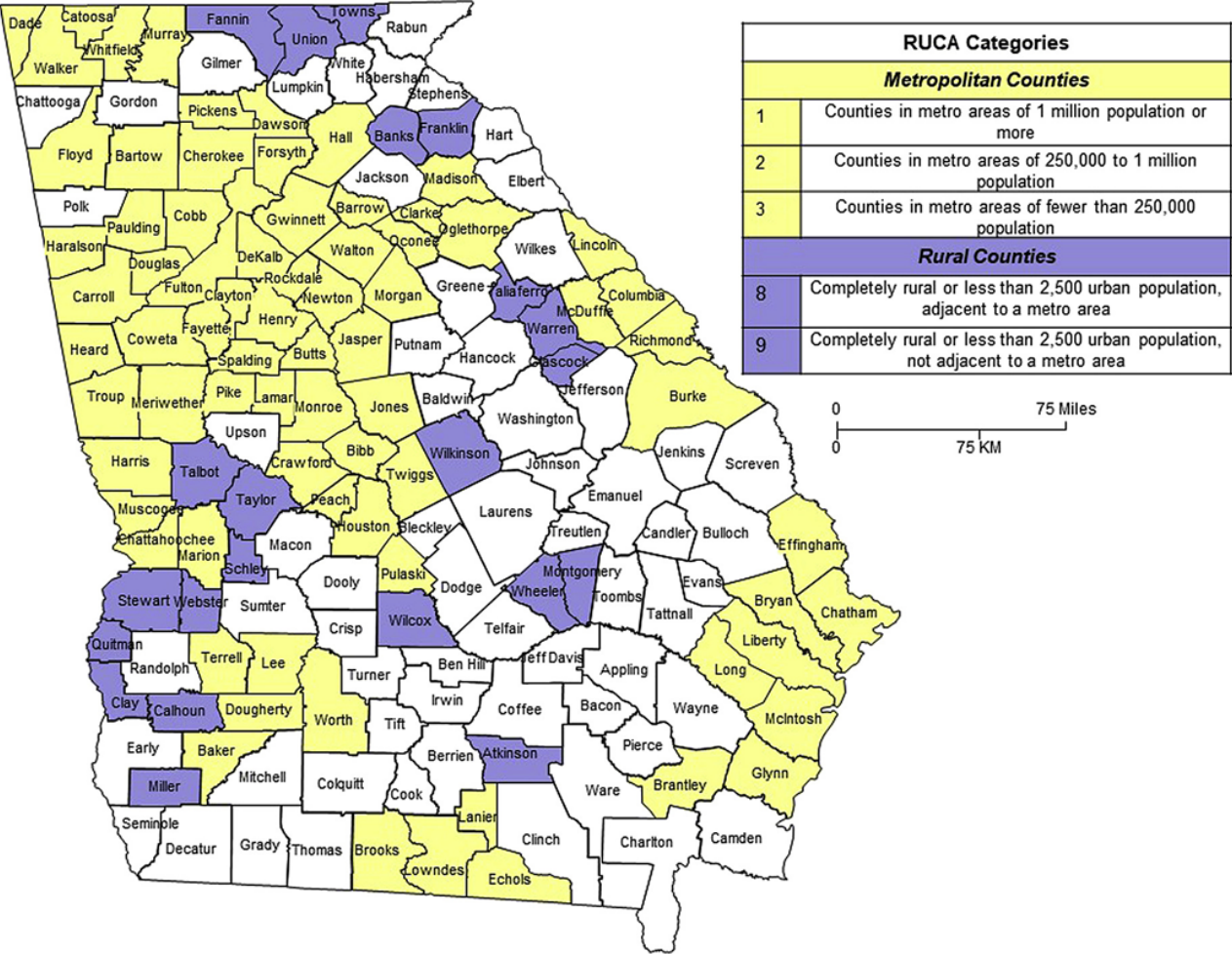
# Tissue procurement protocols in Black patients



- P30 CA138292-10S3 (Curran)
- Winship Cancer Institute Cancer Center Support Grant
- The goal of the CCSG is to support addressing the racial disparities for African American patients.
- Bio banking African American precursor samples
- 95% acceptance rate
- R01CA134786 (Cozen W)
- *A Genome Wide Scan of Multiple Myeloma in African Americans*
- The major goal of this project is to conduct a Genome Wide Admixture Scan of Multiple Myeloma in African Americans.
- 90% acceptance rate



# Priorities for Rural Lymphoma Survivors: A Qualitative Study



And um, you know, I'd be facing a trip to Atlanta which will be three hours, you know, and it could be worse traffic wise and getting people out, you know, was, was the problems that I didn't want to do and stuff like that."

"No, the only thing is I get might be that I have to go back to Atlanta for appointments and so that a six hour drive sometimes..."

"Yes, every time I had to drive there. It was 6 hours of my day just driving."

"It was, I am lucky enough to be in driving distance of Emory, but that was kind of a pain, arranging transportation to and from when you can't drive."

"I had to travel. Milledgeville is about the center of Georgia and we had to travel up to Atlanta."

"...there was very little inconvenience other than the fact that I had to be away from home for seventeen straight days."

"Well the only thing that we tried to look to see how to deal with get help with my traveling, you know expense for traveling in places to stay or not had to go to Atlanta, and back and forth but it seemed like I just walked in the rock. All I get is so superior. And it just seemed like if you didn't get Medicaid or something like that, you didn't qualify for expense travel or anything so other than that. No. Medicare and my supplement post took care of everything."

# Phase I program proposed plan



- Frequency of visits
  - Distance/reimbursement model
- Duration of visits
  - Role of caregiver to children/parents
  - Accompaniment
- Strategies:
  - Philanthropy
    - Uber rides
    - Child care/eldercare
    - Policy approaches - leave
- Prospective payment vs reimbursement
  - Lodging
  - Travel
  - Food
  - Parking

Courtesy: Donald Harvey

# Educating community

- LLS, MMRF
- Referral news letters
- Post ASH updates
- Support groups





# Support groups

Dear Dr. Nooka,

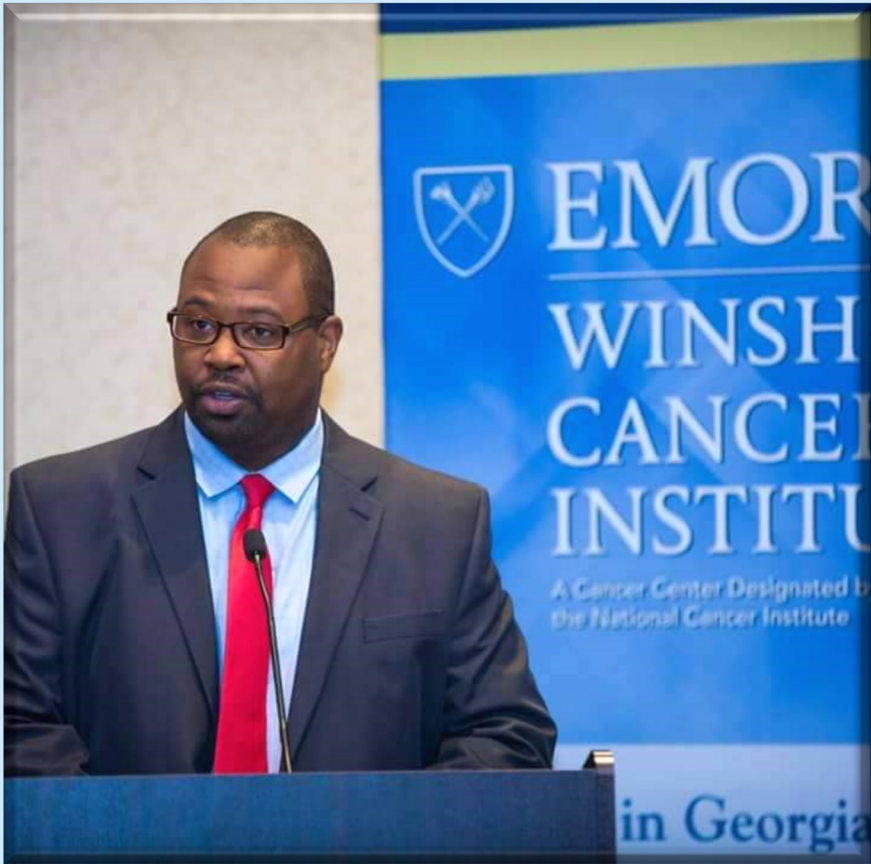
I hope this email finds you well. It is always an exciting, informative time when you bring your current research interests to us at the annual ASH update. I have heard from many of your patients and fellow providers that you are the consummate teacher for your patients. They speak about the flip chart or chart board to help make your points.

We hope you are able to come and present your research, especially as it applies to African Americans to our Support Group. Are you able to come in March (Myeloma Awareness Month) or April? That would be Saturday, March 28 or Saturday, April 25. The time would be 10:30 AM.

We are open to any other topics or information you feel we should be aware of. Our Group meets from 10 AM - 12 noon at Macy's Greenbriar, 2nd floor Community Room.

Please let me know what is better for you. Have a wonderful rest of the week.

# Winship Cancer Institute Health Disparities, Health Literacy and Minority Accrual Committee



- Chair, Bradley Carthon, MD, PhD.
- Associate Professor, Medical Director Inpatient Oncology
- Key Members: Drs. Torres, Pence, and Gullatte.
- Established 4/2018 to Address Winship Initiatives
- Develop action plans for outreach, literacy efforts and clinical trial maintenance and increase among pertinent groups
- Participate in partnership formation with rural healthcare entities

# Community Outreach in Clinical Trials



- Mary Gullatte, PhD, RN, FAAN (CPC), Former ONS President
  - Emory Corporate Director of Nursing Innovation & Research
  - Leads Winship efforts to raise awareness among underrepresented minorities regarding clinical trials as an option for cancer diagnosis, prevention, and therapy

## Selected Research and Partnerships

- Factors that result in delay in seeking cancer care by black patients
- Role of religiosity and spirituality as determinants of the extent of delay in seeking care, resulting in more advanced stage at diagnosis
- New R01 with Utah (PI Mooney) Evaluation of SymptomCare@Home
  - Longitudinal, multi-site study evaluating telehealth system in 750 chemotherapy participants over 6 months
- Partnership with Concerned Black Clergy of Metro Atlanta

# Strategies for Inclusion of Women, Minorities, and Children

- Dr. Rebecca Pentz: Working groups and patient navigators focused on reducing barriers to clinical trial enrollment for minorities, women, and children

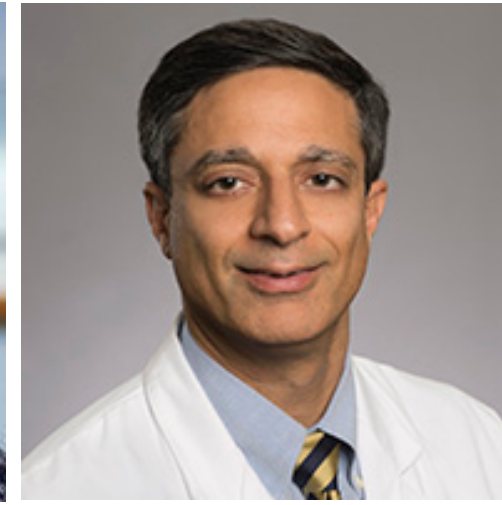
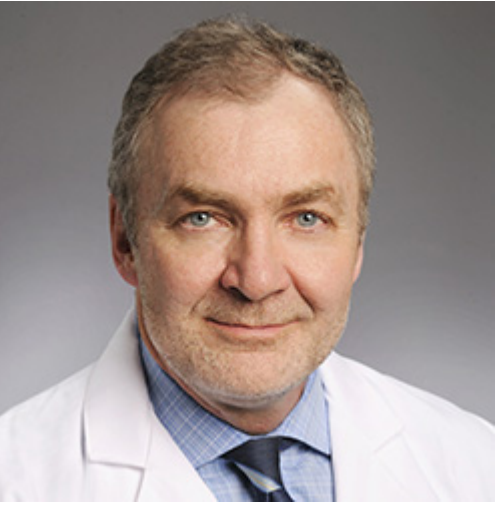


- Prioritizing trials for patients with breast and gynecologic cancers
  - Health literacy research and interventions [*Supported by Winship Invest\$ pilot funding*]
- 
- Translators in clinical areas
  - Translation of consent forms and IRB library of short consents
  - Accessibility for non-English speaking minorities





# Leadership buy-in





# Some solutions

- creating community advisory boards
- delivering culturally targeted education programs
- partnering with community-based organizations serving the Black community
- improving access to clinical care and support services
- myeloma awareness events
- faculty diversity
- leadership buy-in
- addressing the problem

# Thank you

anooka@emory.edu  
@AjayNookaMD



Sagar Lonial  
Jonathan L. Kaufman  
Lawrence H. Boise  
Madhav Dhodapkar  
Nisha Joseph  
Craig Hofmeister  
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Vikas Gupta  
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# **Working Group 1**

## **Approaches to Improve Data on Outcomes in Racial and Ethnic Minorities Prior to Drug Approval**

Craig E. Cole, MD  
Michigan State University Breslin Cancer Center

## ■ Excellent Resources on Diversifying Your Clinical Trials

- Regnante JM, Richie NA, Fashoyin-Aje L, et al. **US Cancer Centers of Excellence Strategies for Increased Inclusion of Racial and Ethnic Minorities in Clinical Trials.** J Oncol Pract. 2019;15(4):e289–e299.
- **White Paper on the Dialogues on Diversifying Clinical-Trials; Successful Strategies for Engaging Women and Minorities in Clinical Trials.** The Society for Women's Health Research United States Food and Drug Administration Office of Women's Health. September 2011; [www.fda.gov/files/science%20&%20research/published/White-Paper-on-the-Dialogues-on-Diversifying-Clinical-Trials-Conference.pdf](http://www.fda.gov/files/science%20&%20research/published/White-Paper-on-the-Dialogues-on-Diversifying-Clinical-Trials-Conference.pdf)
- George S, Duran N, Norris K. **A systematic review of barriers and facilitators to minority research participation among African Americans, Latinos, Asian Americans, and Pacific Islanders.** Am J Public Health. 2014;104(2):e16–e31.
- Wallington SF, Dash C, Sheppard VB, et al. **Enrolling Minority and Underserved Populations in Cancer Clinical Research.** Am J Prev Med. 2016;50(1):111–117.
- Otado J, Kwagyan J, Edwards D, Ukaegbu A, Rockcliffe F, Osafo N. **Culturally Competent Strategies for Recruitment and Retention of African American Populations into Clinical Trials.** Clin Transl Sci. 2015;8(5):460–466.
- Michaelis, Laura. **The Sickle Cell Clinical Trials Network: One Year In.** The Hematologist. July-August 2019, Volume 16, Issue 4. <https://www.hematology.org/Thehematologist/Features/9705.aspx>.

# INTRODUCTION



# WORKING GROUP 1 ROSTER

- Vishal Bhatnagar, MD, U.S. Food and Drug Administration
- Ruemu E. Birhiray, MD, Hematology Oncology of Indiana
- Yelak Biru, Patient Advocate
- Kathleen Bond, Patient Advocate
- Craig E. Cole, MD, Michigan State University Breslin Cancer Center
- Madhav V. Dhodapkar, MBBS, Emory University School of Medicine
- Sagar Lonial, MD, FACP, Winship Cancer Institute of Emory University
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- Elisa Weiss, PhD, Leukemia and Lymphoma Society

- Develop principles for promoting diversity and promote adherence to those principles through trial “registration.”
  - Set concrete targets for trial enrollment based on disease epidemiology/incidence and current evidence that addresses biological and cultural barriers.
  - Consider review or publication incentives for adhering to principles.
  - Share examples of strategies that help to meet target enrollment.



- Study plans should include proposals for how appropriate populations will be included in trials and how targets will be met.
  - The goal should be for trial populations to be representative of disease incidence from an early stage.
  
- Prespecify what subgroup analyses should be performed and the endpoints which will be assessed.
  - Potentially ask for modeling on the effects of having more or fewer patients than expected for a given subgroup.
  - Explore potential alternative endpoints, including minimal residual disease.



- Design trials around the type and stage of disease, and subtypes most commonly seen in African Americans.
  - Study the genetics of multiple myeloma patients, exploring potential variables that affect differences in outcome.
  - Pursue safety signals detected in African American patients, or other subpopulations, as thoroughly as possible.
  - Collect and analyze PK/PD data, pursue signals in subpopulations to the extent that is reasonable.

- Trials should reflect U.S. clinical practice (standard-of-care).
- Recommend that randomized phase II and phase III clinical trials involve a diversity officer to help design the trial and recruitment strategies, including predetermined goals for representativeness/inclusion.
  - Define this role and offer training for sponsors and investigators on characteristics of a “good” diversity officer.

# RECOMMENDATIONS

- Provide grant funding dedicated to studying subpopulation signals.
  - NCI could potentially play a role.
- Consider prioritizing the inclusion of African American patients over global patients with African ancestry.
- Educate investigators and referring physicians on cultural competence and stress the importance of community engagement.



# **Working Group 2**

## **Approaches to Using Postapproval Clinical Trial Data to Better Understand Effectiveness and Safety of Therapies in Racial and Ethnic Minorities**

Richard F. Little, MD  
National Cancer Institute

# WORKING GROUP 2 ROSTER

- Sikander Ailawadhi, MD, Mayo Clinic Cancer Center Jacksonville
- CAPT Richardae Araojo, U.S. Food and Drug Administration
- Jim Bond, Patient Advocate
- John D. Carpten, PhD, USC Keck School of Medicine
- Joya Harris, American Cancer Society
- Bindu Kanapuru, MD, U.S. Food and Drug Administration
- Shaji K. Kumar, MD, Mayo Clinic
- Gary Lambert, Patient Advocate
- C. Ola Landgren, MD, Memorial Sloan Kettering Cancer Center
- Christine Lee, PharmD, PhD, U.S. Food and Drug Administration
- Richard F. Little, MD, National Cancer Institute
- Joseph Mikhael, MD, MEd, FRCPC, FACP, International Myeloma Foundation | TGen
- Anuradha Ramamoorthy, PhD, U.S. Food and Drug Administration
- Jeffrey Zonder, MD, Wayne State University

- The basic problem we considered is the potential lack of minority representation on pivotal clinical trials for drug approvals
- Guiding principles of generalizability
  - Efficacy
    - Only large differences are likely to be seen
    - Underpowered
  - Toxicity
    - Signals are likely to be seen with enough representation

- Liberalize eligibility criteria for clinical trials whenever possible and appropriate.
  - When eligibility criteria for registrational trials are more conservative, postmarketing studies of those agents should have liberalized eligibility criteria so populations who use the agents in the real world are better represented.
  - Additionally, sponsors should consider approaches that utilize expansion cohorts with liberalized eligibility criteria within registrational trials to assess feasibility/tolerability and to collect more data in racial and ethnic subpopulations.

- Prospective plans to collect data on racial outcomes should be incorporated early and throughout development, when feasible, to inform investigations later.
  - Collect genomic data with aims to establish basis for differences in outcomes.
    - Model after updated ICH guidelines
  - Emphasize the importance of prospectively collecting this data to investigators.
    - Ex-U.S. trial sites may have confidentiality laws that do not allow reporting on or collecting of race/ethnicity data.



- Conduct prespecified, exploratory analyses to identify differences among subpopulations defined by race and ethnicity when there is a safety signal or question about efficacy.
  - These exploratory analyses should be described in the trial protocol.
  - If safety signals are detected or insufficient data are generated in registrational trials, it may be necessary to carry out a pilot study or expansion cohort of a phase I trial in African Americans to generate data necessary to test the hypothesis that there are PK/PD differences among races/ethnicities.

# RECOMMENDATIONS

- Pool or merge data across studies of older drugs (e.g., lenalidomide) by the pharmaceutical industry and cooperative groups to aggregate sufficient numbers for racial and ethnic subpopulations to analyze safety and efficacy.
- Stakeholders should prospectively devise strategies to address clinical, social, and socioeconomic impediments to trial access.
  - Forge partnerships through outreach to include pharmaceutical companies, social groups not traditionally approached for trial enrollment (e.g., barbershops, churches, sororities/fraternities), and medical societies.

- Develop precompetitive programs that make resources available to support clinical trial infrastructure in treatment locations that are race/ethnicity rich but have not traditionally been part of the clinical trial ecosystem.
- Recommend that industry sponsors submit specific, prospective plans with detailed strategies for enrolling African Americans into studies in numbers reflective of disease prevalence and for tracking accrual.
  - Recommend that FDA review divisions assure plans are in place and ask sponsors to monitor accrual targets.

# RECOMMENDATIONS

- Design postapproval studies to retrospectively collect data from patients who received standard-of-care therapy vs. experimental therapy to better account for selection bias.
- Engage with patient advocacy groups to build trust and encourage participation in trials and registry studies.
  - Having patients share their trial experiences with others considering clinical trials can help alleviate fears or concerns about joining a trial.

- Stakeholder groups (nongovernment employee-based groups) should discuss approaches with Congress to provide incentives to sponsors that encourage conduct of clinical trials that prioritize inclusion of relevant subpopulations such as is done for orphan drug or pediatric indications.
  - (This recommendation was put forward by non-government working group members)



# **Working Group 3**

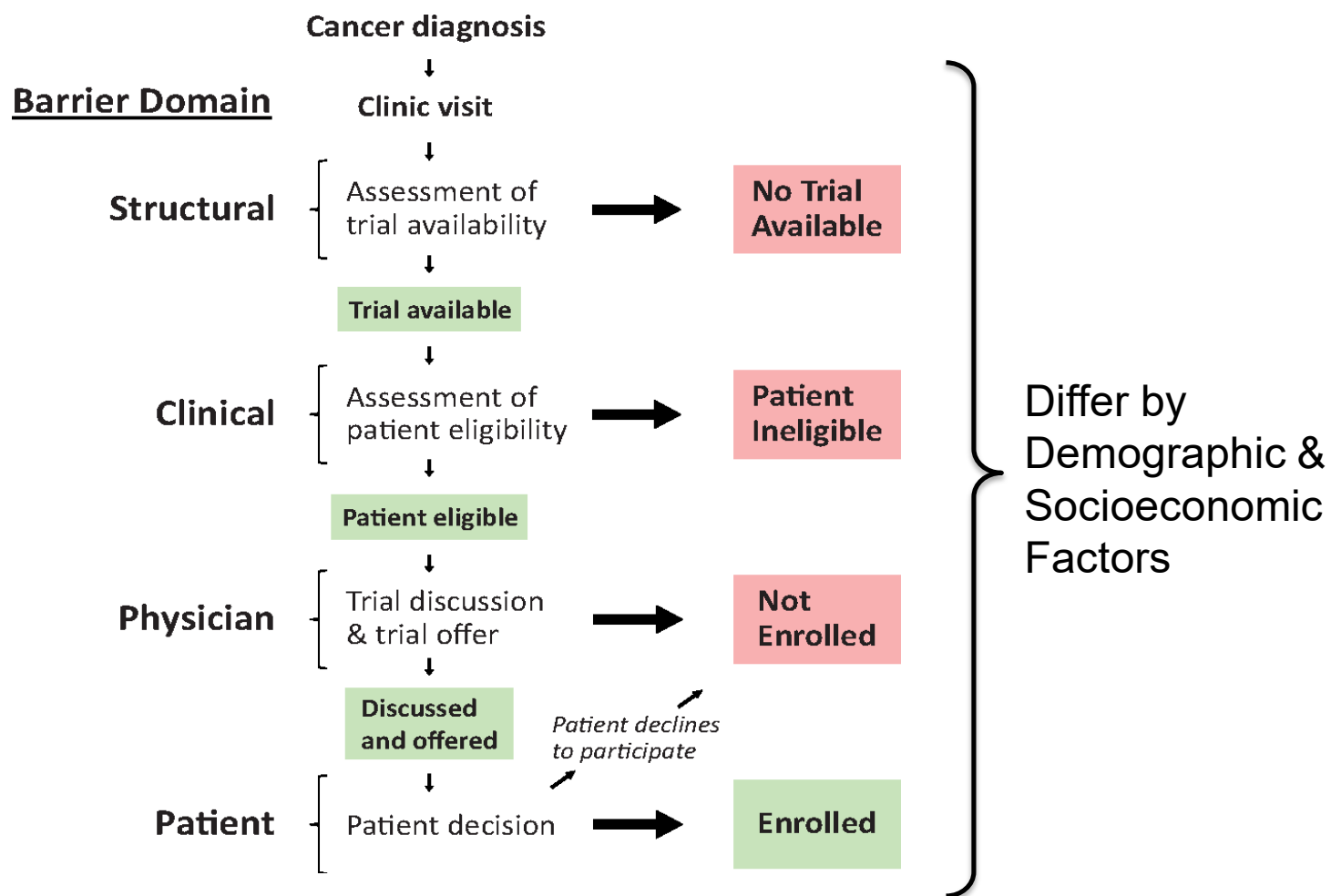
## **Approaches to Utilize Real-world Data to Understand Outcomes with Specific Therapies in Racial and Ethnic Minorities**

Joseph Unger, PhD, MS  
Fred Hutchison Cancer Research Center

- African Americans are severely under-represented in registrational clinical trials
- This limits confidence that care givers have in the outcomes (efficacy) and side-effect profiles (safety) for African Americans when novel agents are used in real world

# INTRODUCTION

## CANCER CLINICAL TRIAL DECISION-MAKING FRAMEWORK



## Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation\*

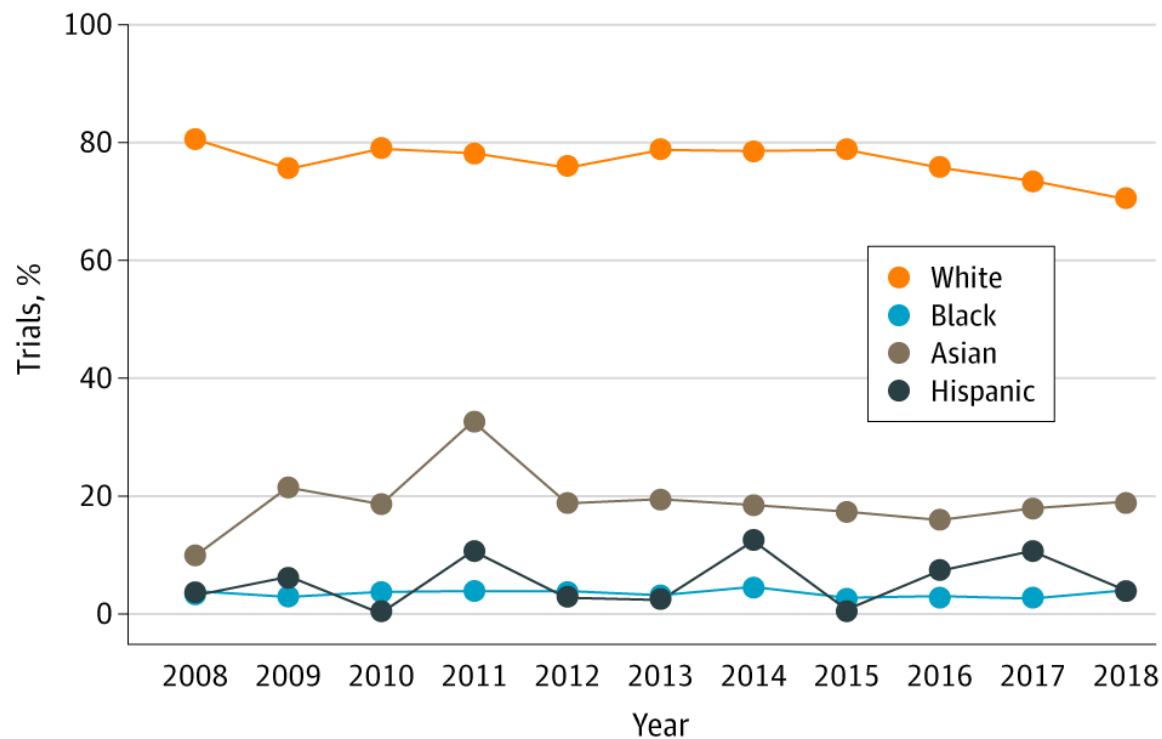
- 13 studies with 8883 patients
- 56% had no trial available at their institution
- 21% were ineligible for an available trial
- 15% did not enroll
- 8% participated in a trial
- **Structural and clinical barriers** make trial participation unachievable for 3 out of 4 cancer patients



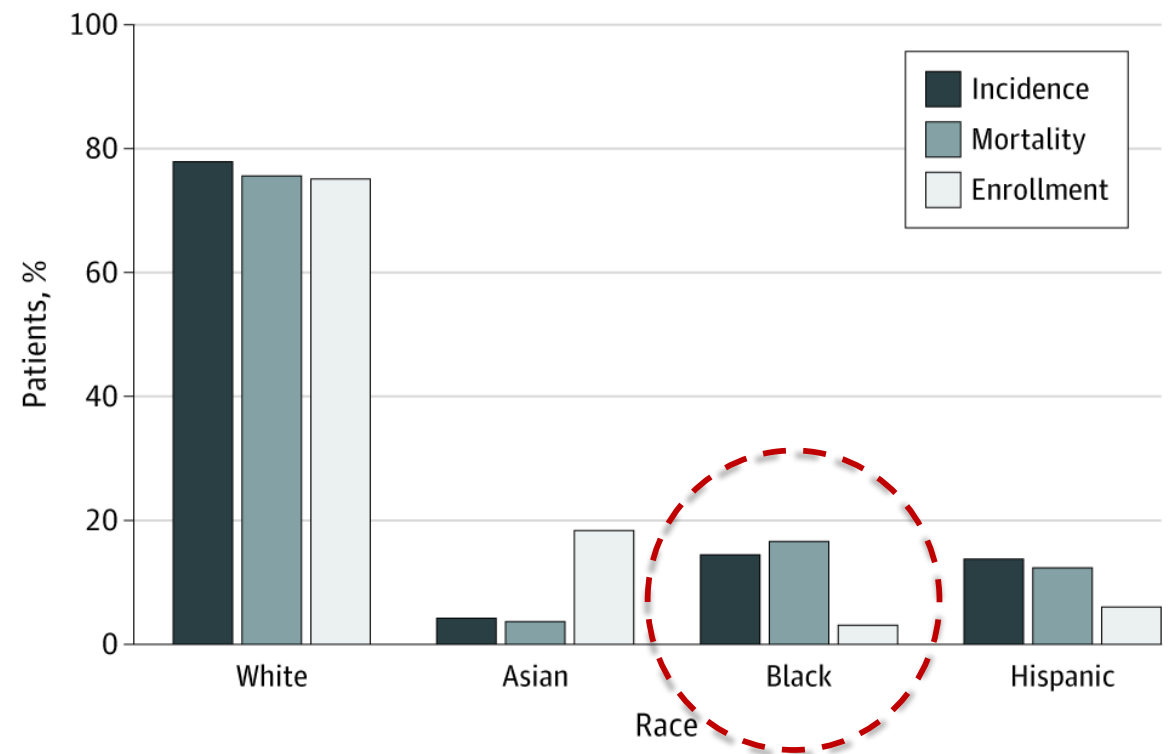
# INTRODUCTION

## ■ Disparity of Race Reporting and Representation in Clinical Trials Leading to Cancer Drug Approvals From 2008 to 2018\*

**A** Percentage of patients enrolled in FDA drug approval trials by race



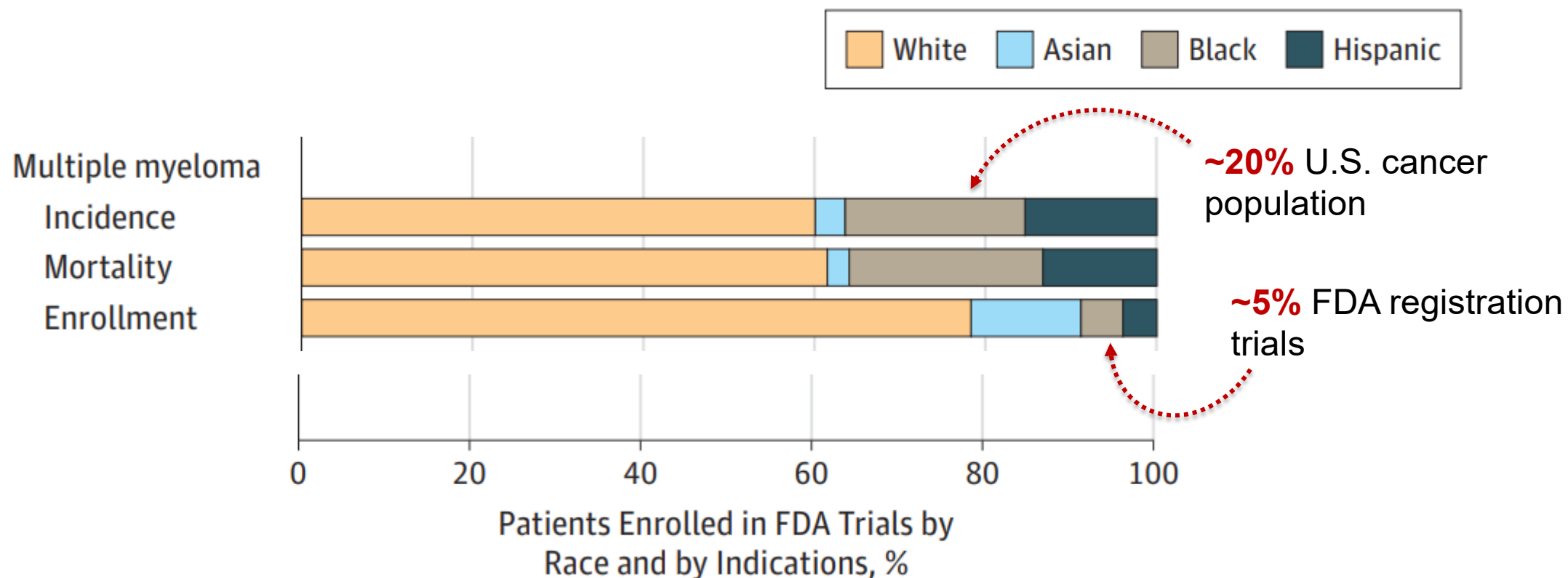
**B** Comparison of incidence and mortality of patients with cancer vs trial enrollment



\* Loree et al., JAMA Oncology, 2019

# INTRODUCTION

- Relative Differences in Incidence, Mortality, and Enrollment in **Multiple Myeloma** Clinical Trials Leading to FDA Drug Approval for Specific Indications\*



- In this context, there's a significant gap in our understanding of how promising new therapies for multiple myeloma perform in African American patients
- An important question is whether the increased use of real-world data can help bridge this potential gap in knowledge for this key demographic group at increased risk

- Real-world data include data derived from:
  - Electronic health records
  - Product or disease registries
  - Claims and billing data
  - Patient generated data
  - Others

- What kinds of questions can we ask/answer with RWD?
- What limitations exist?
- What are the operational challenges of systematically leveraging RWD to address the information gap?
- What are the policy challenges?
- How do we address issues of representativeness?

- Does the availability of RWD represent a **paradigm shift** in understanding cause and effect in an experimental setting (especially for patient subgroups)?

- The challenges of how to draw an appropriate causal inference is not new
  - Investigations into subgroups are fraught with false positive and negative findings
  - Even with best of intentions in mind, these incorrect inferences can end up hurting the very patients we wish to help by potentially denying or delaying the administration of potentially efficacious new therapies

- Best approach in experimentation is to randomize
- But randomization is not always appropriate, feasible or ethical
- How do we derive a convincing answer to an important research question, especially in the absence of a randomized study?



- However, the use of RWD does provide powerful new tools to:
  - Flag potential differences in outcomes/side effects for patient subgroups
  - Generate critical hypotheses for further evaluation
  - Even potentially fill in missing data, though with appropriate caveats
- Can be especially powerful when aligned with strong theory/insights into biological, health, or socioeconomic systems

- The primary aim of this working group is to consider how real-world data may be used to inform our understanding of the effectiveness and safety of approved drugs in racial/ethnic minorities

# WORKING GROUP 3 ROSTER

- Rafat Abonour, MD, Indiana University
- Daniel Auclair, PhD, Multiple Myeloma Research Foundation
- Doris Browne, MD, MPH, National Medical Association
- Kunthel By, PhD, U.S. Food and Drug Administration
- Keri Portis Daniel, American Cancer Society
- Irene M. Ghobrial, MD, Dana-Farber Cancer Institute
- Candace Henley, Blue Hat Foundation
- Meghan O'Conner, International Myeloma Foundation
- Yuan-Li Shen, PhD, U.S. Food and Drug Administration
- William A. Wood, MD, UNC Lineberger Comprehensive Cancer Center

- Categories of recommendations:
  - General recommendations regarding refining research questions and generating hypotheses
  - Pre-market trial recommendations
  - Post-marketing study recommendations

- Perform a brief inventory of efficacy and tolerability data in African Americans in existing multiple myeloma registries with the goal of describing an ideal registry and minimal data elements necessary to ask and answer pertinent questions.

- Require sponsors to set targets for representativeness and inclusion (e.g., for recruitment, accrual, and retention) during clinical study, including by planning for enhanced outreach to African Americans and other patient groups.
  - Encourage sponsors to hit set targets in premarket trials.
  - Require sponsors to set prospective plans for how to meet targets in the postmarket setting if goals are not met in premarket trials.
  - If plans include the use of supplemental real-world data, sponsors should prespecify what analyses will incorporate those data and recognize the lack of randomization to control for unknown confounders.

# RECOMMENDATIONS

- Meta-analyses combining data from multiple trials could be performed to evaluate patient subpopulations studied in a clinical trial environment.

- Use real-world evidence from studies such as INSIGHT MM, CONNECT MM, and others to refine research questions and to generate hypotheses concerning efficacy and tolerability in African American multiple myeloma patients in the real world.
  - When using real-world evidence to interrogate safety and efficacy, be very specific about the questions being asked and the sufficiency of the underlying data.
  - Define real-world endpoints for multiple myeloma.
  - Capture safety lab data in a different way to better understand tolerability from real-world data.



# RECOMMENDATIONS

- Discuss, determine, and disseminate a common reporting framework for multiple myeloma real-world data with minimal data elements that all stakeholders accept as the minimal amount of data that was collected and should be abstracted.

- If evidence from meta-analyses or real-world data indicates the need to investigate a critical hypothesis about how a cancer drug may work differently in a patient subpopulation, further evaluation should be undertaken, preferably by means of a randomized trial.
  - If the conduct of a randomized trial is not feasible, practical, or timely, prospective studies should be conducted, or the use of existing real-world data should be used for further assessment that can contribute to the understanding of the causal inference in convincing fashion.

# RECOMMENDATIONS

- Use real-world data to study specific subpopulations, such as African Americans, which could in turn generate hypotheses for clinical trials enriched for African American participation.