Disparities in Myeloma and Its Precursors in African Americans

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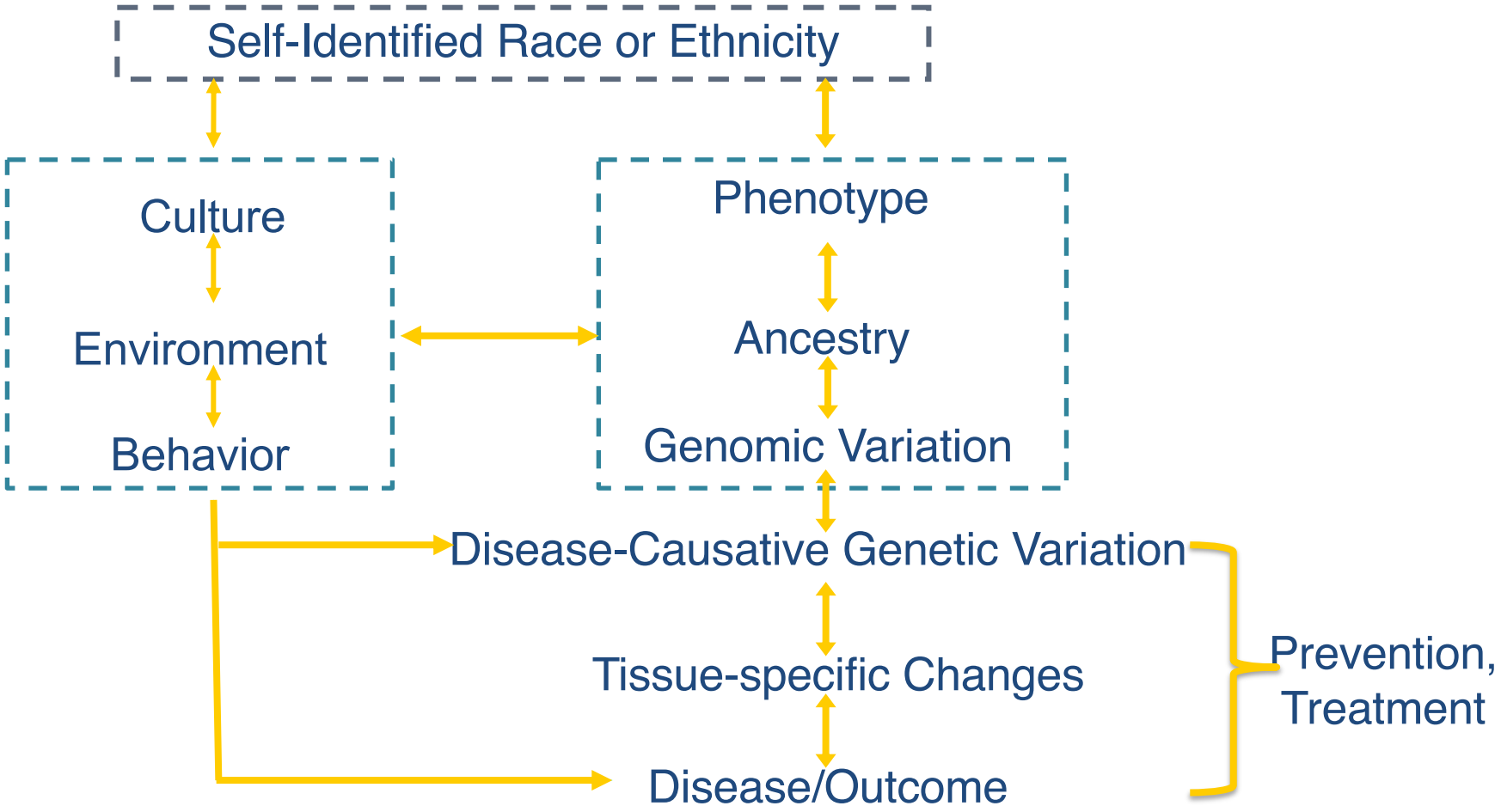
Disclosures

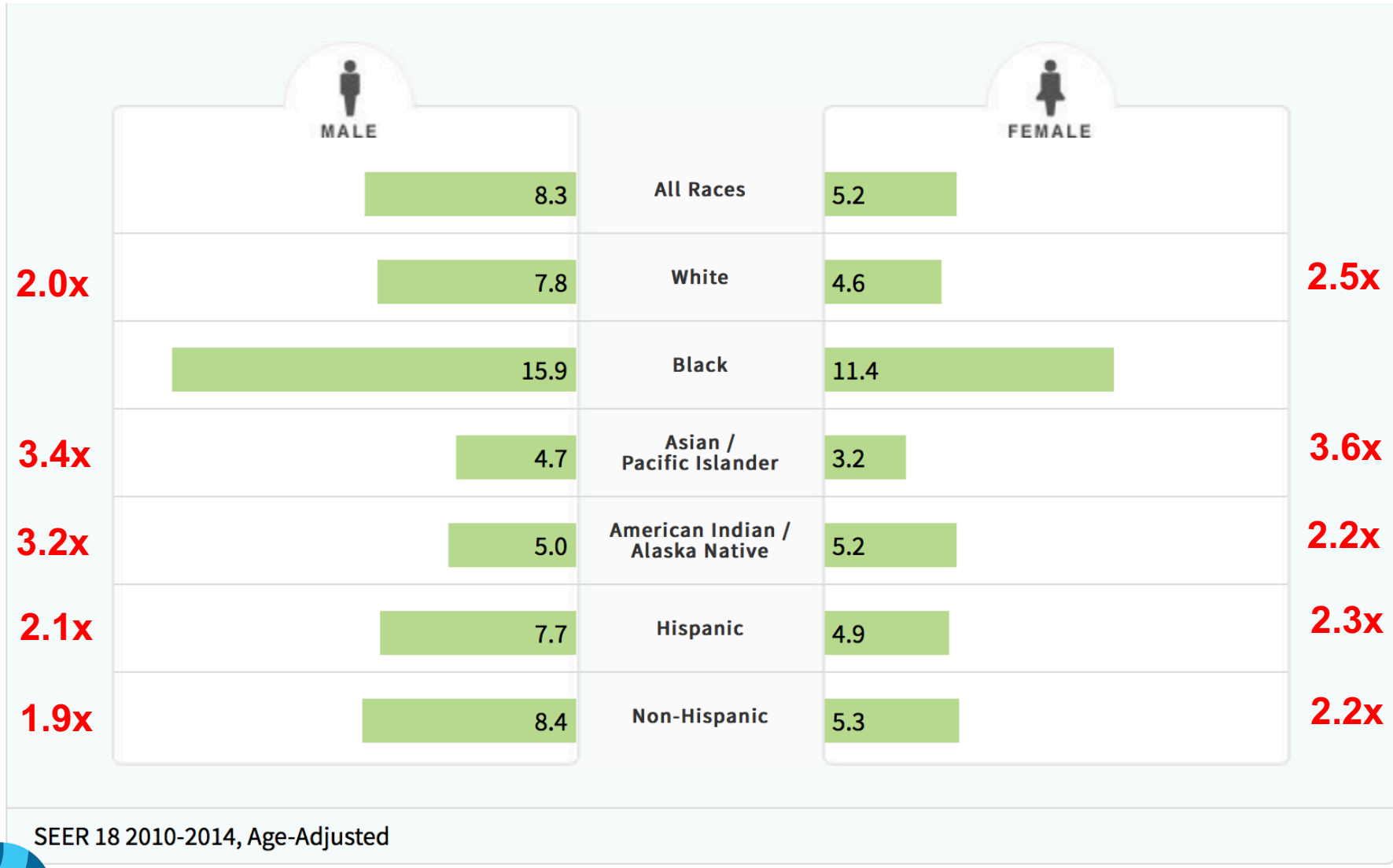
- None

Disparities Framework



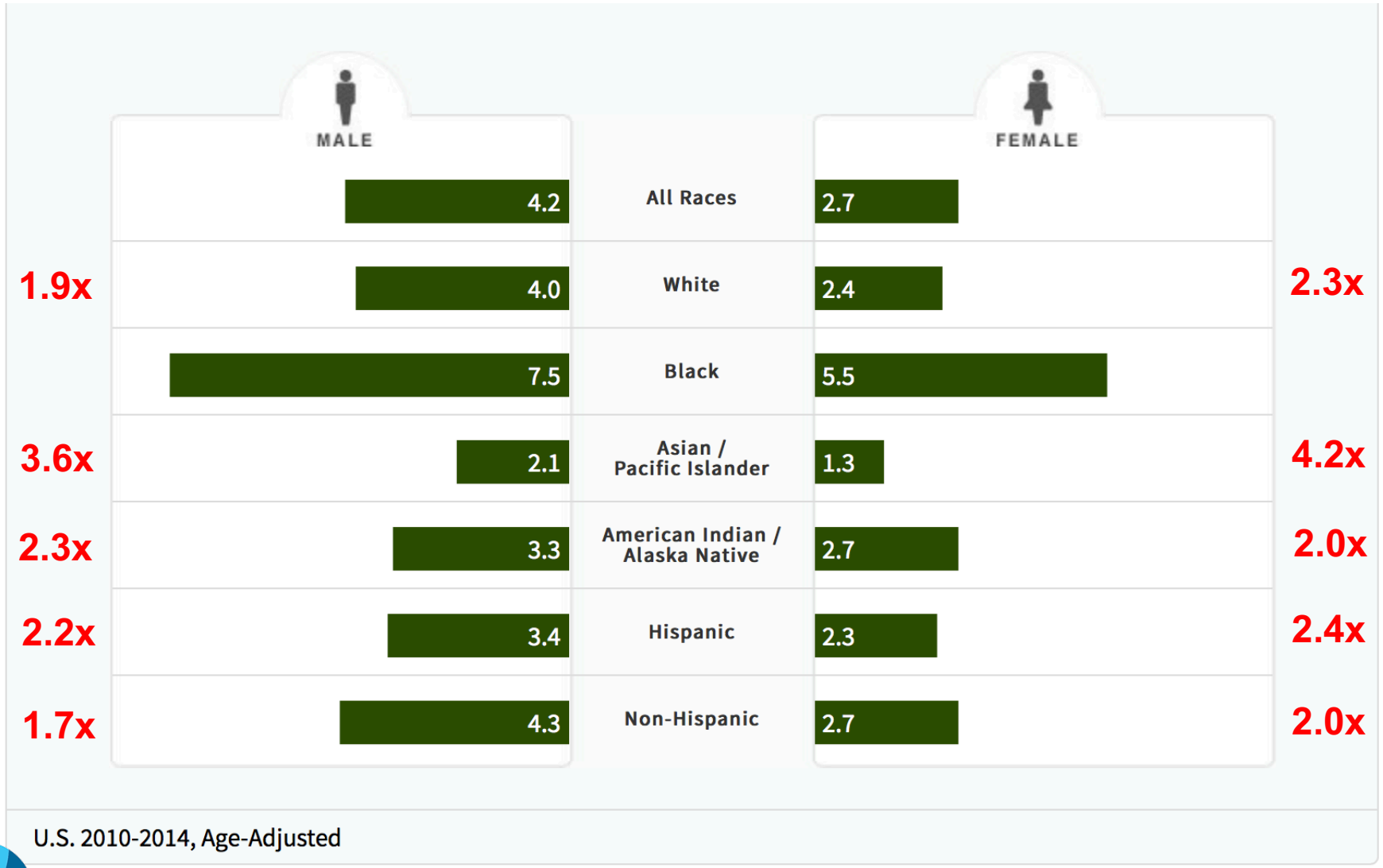
Adapted from: Rebbeck and Sankar *CEBP* 2005, Rebbeck et al. *JCO* 2006

Number of New Cases per 100,000 Persons



SEER 18 2010-2014, Age-Adjusted

Number of Deaths per 100,000 Persons

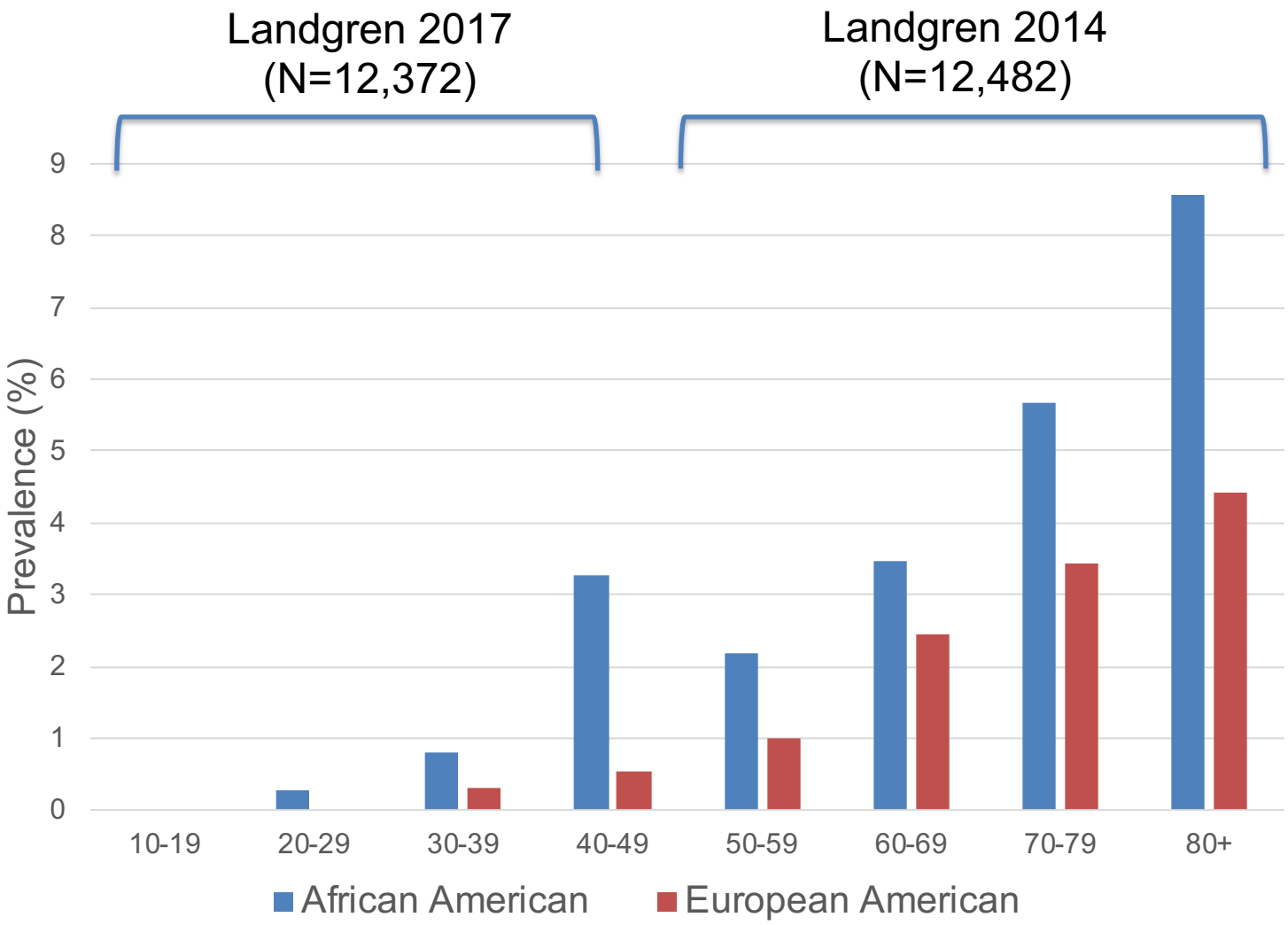


U.S. 2010-2014, Age-Adjusted

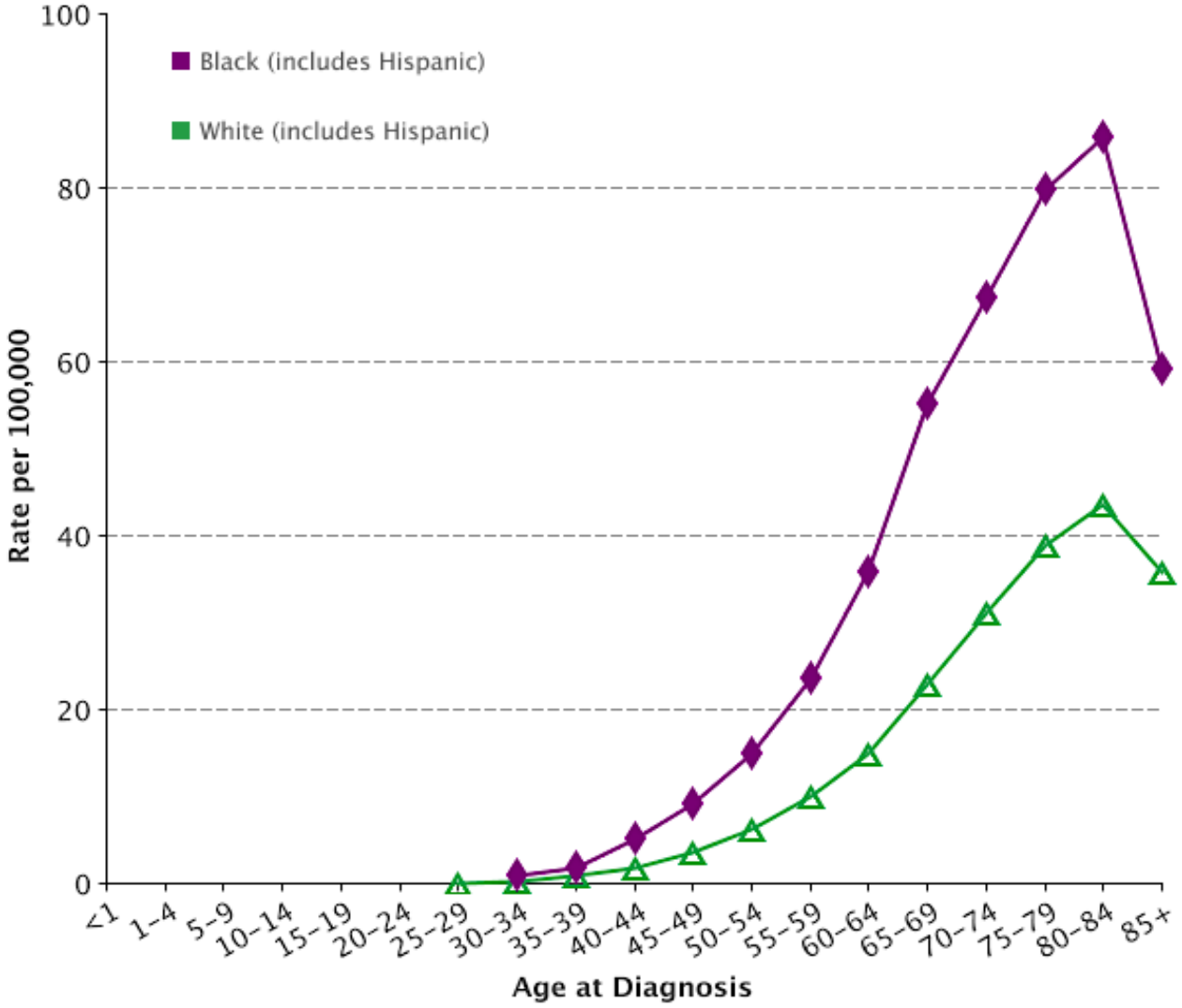
Disparities in MGUS Prevalence

All Myeloma Patients have prior MGUS

(Landgren et al., *Blood*, 2009; Weiss et al; *Blood* 2009)

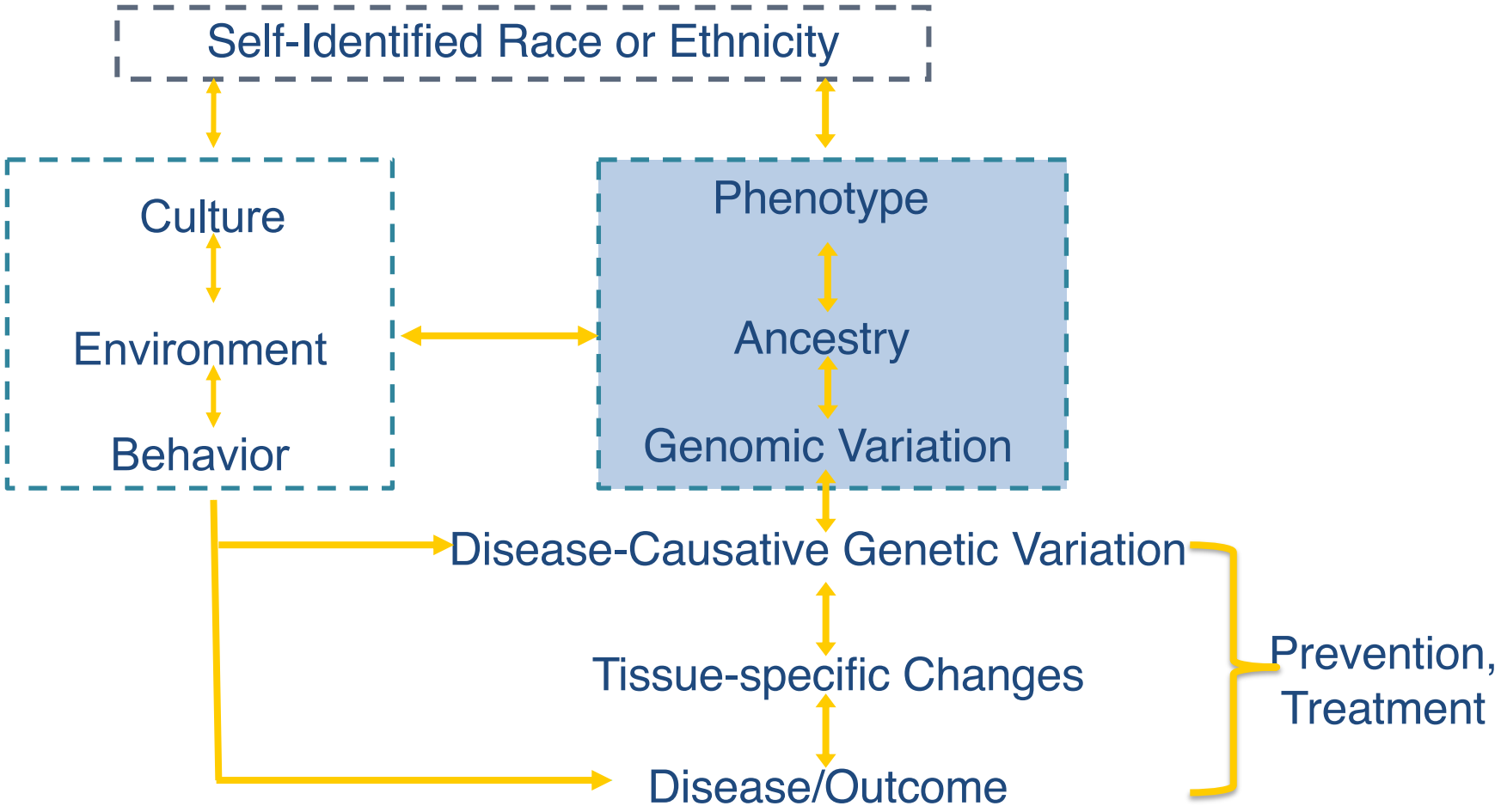


Earlier Age at MM Diagnosis in Blacks



SEER, 2011-2015

Disparities Framework



Adapted from: Rebbeck and Sankar *CEBP* 2005, Rebbeck et al. *JCO* 2006

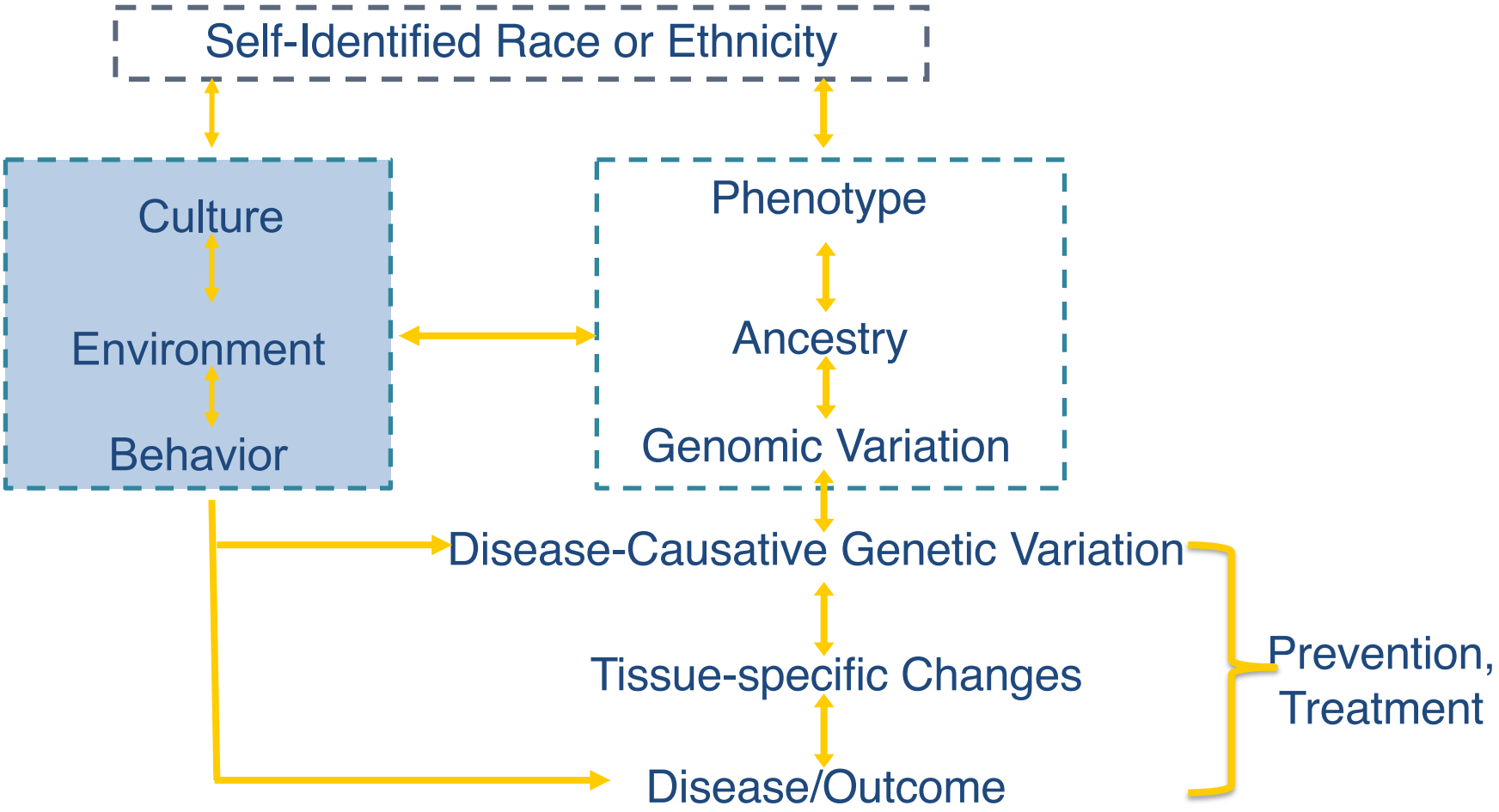
Familial Myeloma

Trait		Citations
Familial Relative Risk of MM	2.5-fold excess risk	Altieri et al., 2006 Landgren et al. 2006 Hemminki et al. 2004 Frank et al. 2015
Proportion of MM that is familial	2.4%	Frank et al. 2016
Reported clustering of MM with other tumors	Tumor sites: **colorectal***, breast and prostate cancers, non-thyroid endocrine tumors, leukemia (*a syndrome?)	Frank et al. 2016

Association of MM Family History with MM Risk

	European American	African American
Van Valkenburg et al. 2016	2.0 (0.83-5.04)	20.9 (2.59-168)
Brown et al. 1999	1.5 (0.3-6.4)	17.4 (2.4-348)

Disparities Framework



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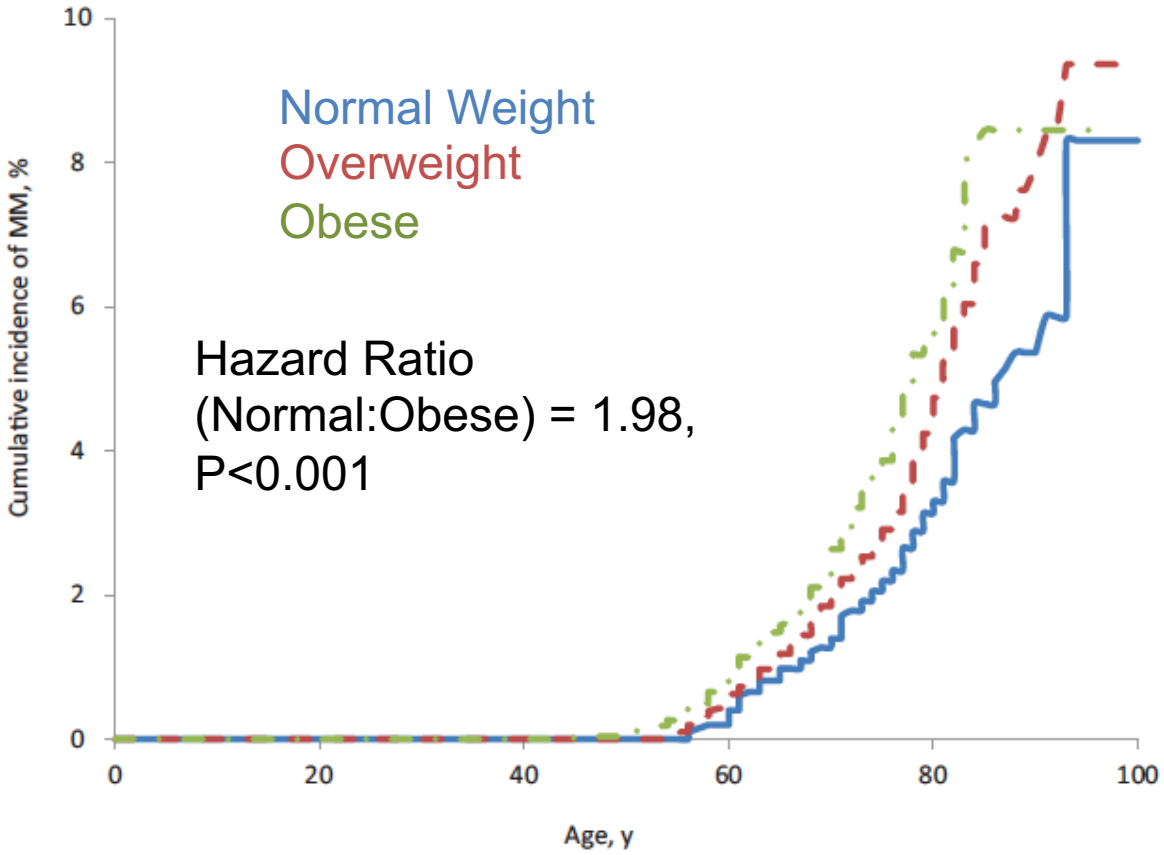
Obesity as a MM Risk Factor:

Cumulative Incidence of MM in 7,878 US Veterans with MGUS, 1999-2009



Adjusted for age, race, gender, marital status, income, creatinine, diabetes, and comorbidities

Chang et al. *JNCI* 2017

Selected MGUS Risk Factor Exposures

Exposure	Association	References
World Trade Center 9/11 Exposed vs. Olmstead County, MN	1.8-fold higher	Landgren et al. *JAMA Oncology* 2018
Pesticide exposed vs. Olmstead County, MN	1.9-fold higher	Landgren et al., *Blood* 2009
Agent Orange Exposed vs. Unexposed	7.1% vs. 3.1% (OR=2.4, 95%CI 1.3-4.4)	Landgren et al. *JAMA Oncology* 2015

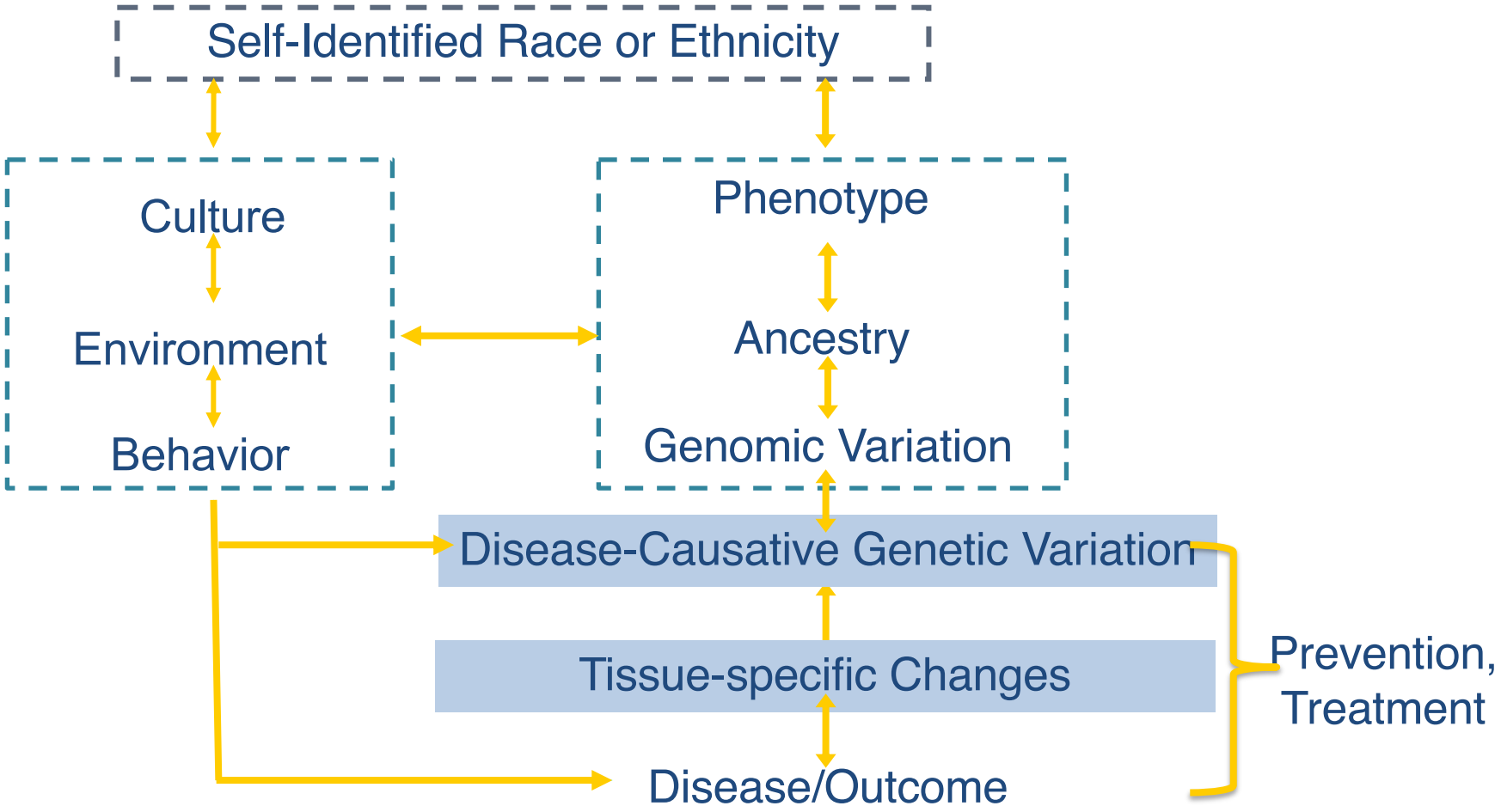
Limitation: Associations largely unreported in African Americans

Selected Myeloma Risk Factor Exposures

Exposure	Association	References
World Trade Center 9/11 Exposed vs. General Population	7.63% in 9/11 Firefighters vs. 1.8% in Olmstead County	Landgren et al. *JAMA Oncology* 2018
Female Agricultural Workers	HR=2.25 (95%CI 1.16-4.37)	Kachuri et al. *BMC Cancer* 2017
Chernobyl Accident Clean-Up Workers	SIR=1.6 (96%CI: 1.01-2.2)	Bazyka et al. *Prob Rad Med Radiob* 2013
Hiroshima & Nagasaki Atomic Bomb Blast Survivors	No excess risk	Hsu et al., *Radiation Research*, 2013

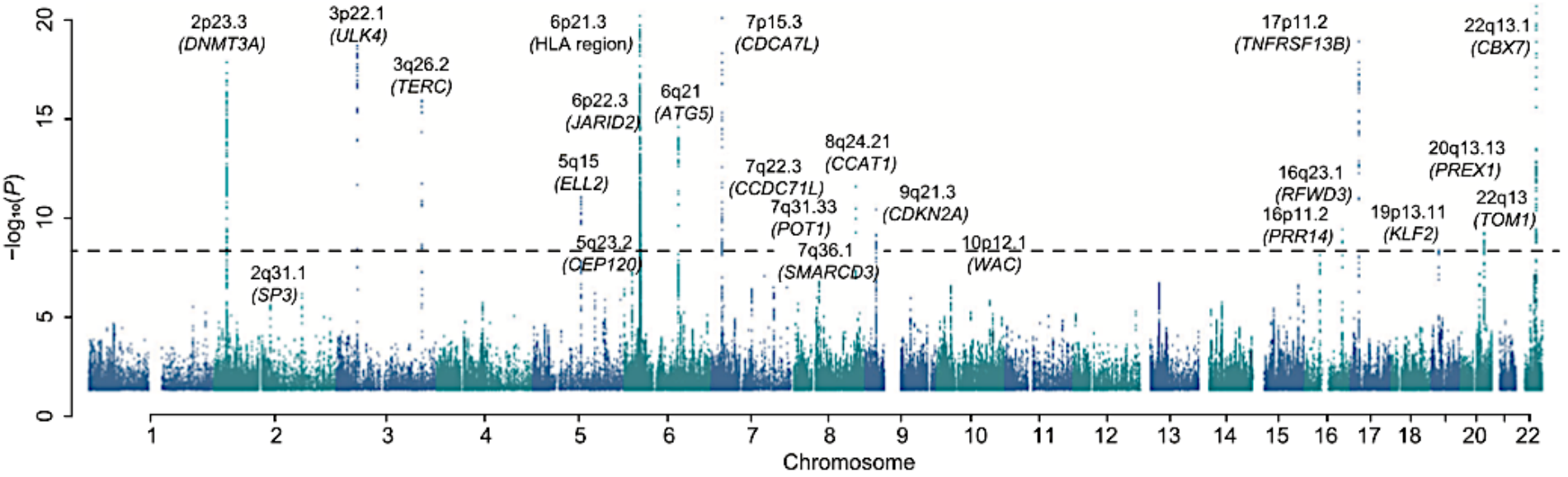
Limitation: Associations largely unreported in African Americans

Disparities Framework



Adapted from: Rebbeck and Sankar *CEBP* 2005, Rebbeck et al. *JCO* 2006

Genetic Associations



- 24 GWAS Loci Include: Telomere Regulation, Tumor Suppressor Genes, Oncogenes, Micro-RNAs, Linc RNAs, Carcinogen Metabolism Genes, *MYC* regulation, and others
- These explain about 16% of heritability.
- Common variants are enriched in familial myeloma
- Few rare loss of function variants have been observed (e.g., *CDKN2A*)

Pertesi et al., *Leukemia*, 2020

Genome-Wide Association by Race

1,318 MM and 1,480 controls of European ancestry
1,305 MM and 7,078 controls of African ancestry

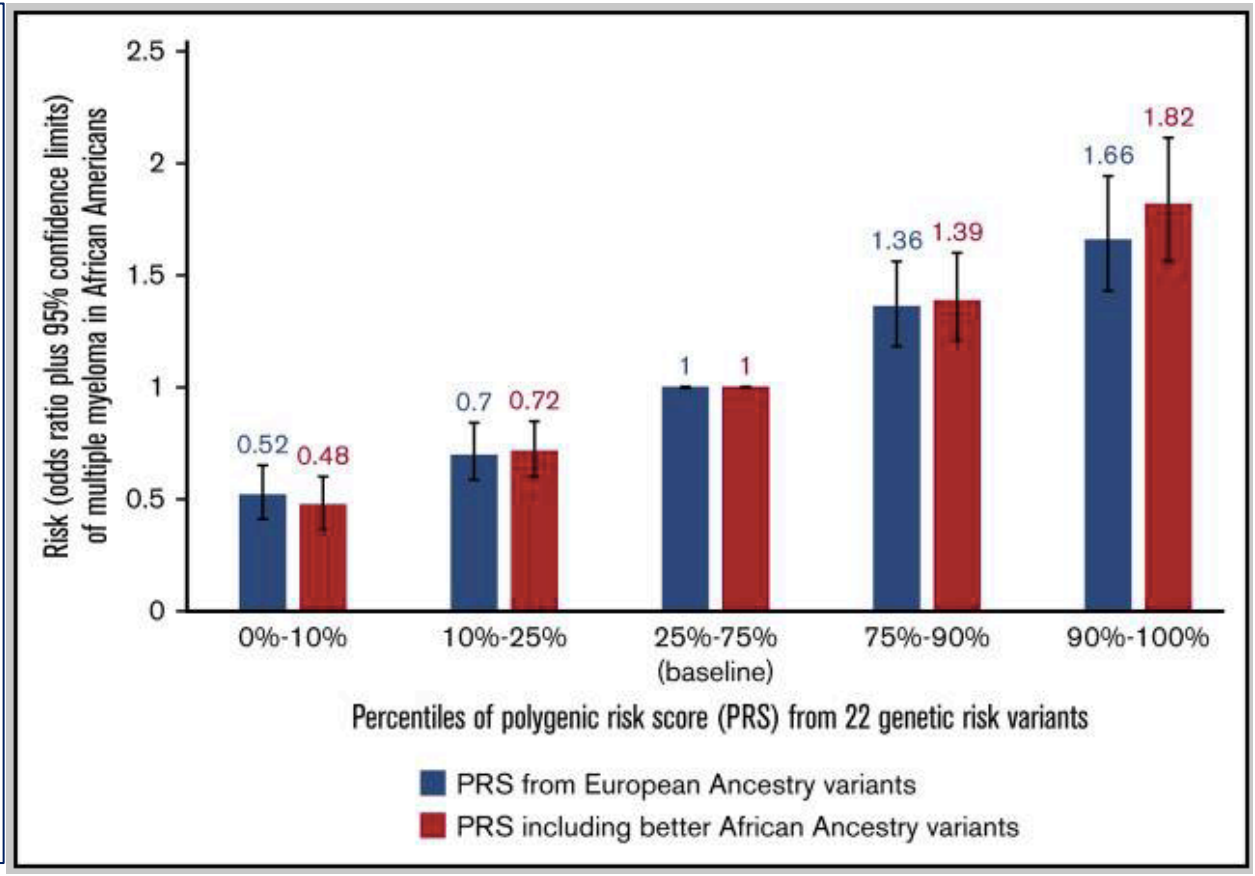
Index SNPs[a]/Most significantly associated SNPs[b]						Association in European ancestry				Association in African ancestry			
SNP	BP	Risk/Ref	Freq	OR	P	Freq	OR	P	Power	Freq	OR	P	Power
2p23.3													
rs6746082[a]	25659244	A/C	0.76	1.29	1.22×10^{-7}	0.79	1.15	5.17×10^{-2}	0.96	0.55	1.04	3.77×10^{-1}	0.80
rs6761076[b]	25607758	T/C				0.81	1.23	7.23×10^{-3}		0.68	1.09	8.33×10^{-2}	
2q12.3													
rs12614346[a]	107642482	A/G	0.33	1.39	1.70×10^{-5}	0.31	1.00	9.45×10^{-1}	0.99	0.16	1.00	9.81×10^{-1}	0.99
rs13416655[b]	107621925	C/T				0.50	1.01	8.03×10^{-1}		0.39	1.10	4.90×10^{-2}	
3p22.1													
rs105250[a]	41925398	G/A	0.20	1.32	7.47×10^{-9}	0.22	1.23	4.42×10^{-3}	0.99	0.63	1.06	2.21×10^{-1}	0.99
rs143531651[b]	41816589	G/C				0.17	1.25	4.91×10^{-3}		0.11	1.27	1.37×10^{-3}	
3q26.2													
rs10936599[a]	169492101	G/A	0.75	1.26	1.74×10^{-13}	0.79	1.12	8.41×10^{-2}	0.92	0.93	1.08	3.84×10^{-1}	0.73
rs9811216[b]	169487501	T/C				0.74	1.11	1.10×10^{-1}		0.70	1.09	8.46×10^{-2}	
6p21.33[d]													
rs2285803[a]	31107258	A/G	0.28	1.19	1.18×10^{-10}	0.29	1.11	1.27×10^{-1}	0.84	0.26	1.06	2.21×10^{-1}	0.95
7p15.3													
rs4487645[a]	21938240	C/A	0.65	1.38	3.33×10^{-15}	0.70	1.23	7.47×10^{-4}	0.99	0.89	1.37	8.30×10^{-5}	0.99
rs12540021[b]	21945563	G/A				0.75	1.24	6.30×10^{-4}		0.89	1.43	2.27×10^{-5}	
17p11.2													
rs4273077[a]	16849139	G/A	0.11	1.26	1.41×10^{-7}	0.12	1.37	2.46×10^{-4}	0.83	0.14	1.17	1.60×10^{-2}	0.97
rs34562254[b]	16842991	A/G				0.11	1.45	2.39×10^{-5}		0.13	1.25	1.33×10^{-3}	
22q13.1													
rs877529[a]	39542292	A/G	0.44	1.23	2.29×10^{-16}	0.45	1.21	4.31×10^{-4}	0.97	0.48	1.11	1.47×10^{-2}	0.99
rs139425[b]	39559742	C/G				0.46	1.21	4.43×10^{-4}		0.71	1.21	5.54×10^{-4}	

Rand et al., *CEBP* 2016

Genome-Wide Association in African Americans

Meta-analysis of 2 GWAS of MM in 1,813 Cases and 8,871 Controls

- No genome-wide significant associations
- Novel locus at 2p24.1-23.1 in AA (from admixture mapping)
- Of 23 known EA risk variants:
  - 20 directionaly consistency
  - 9 replicated at $P < .05$



Du et al. *Blood Advances*, 2020

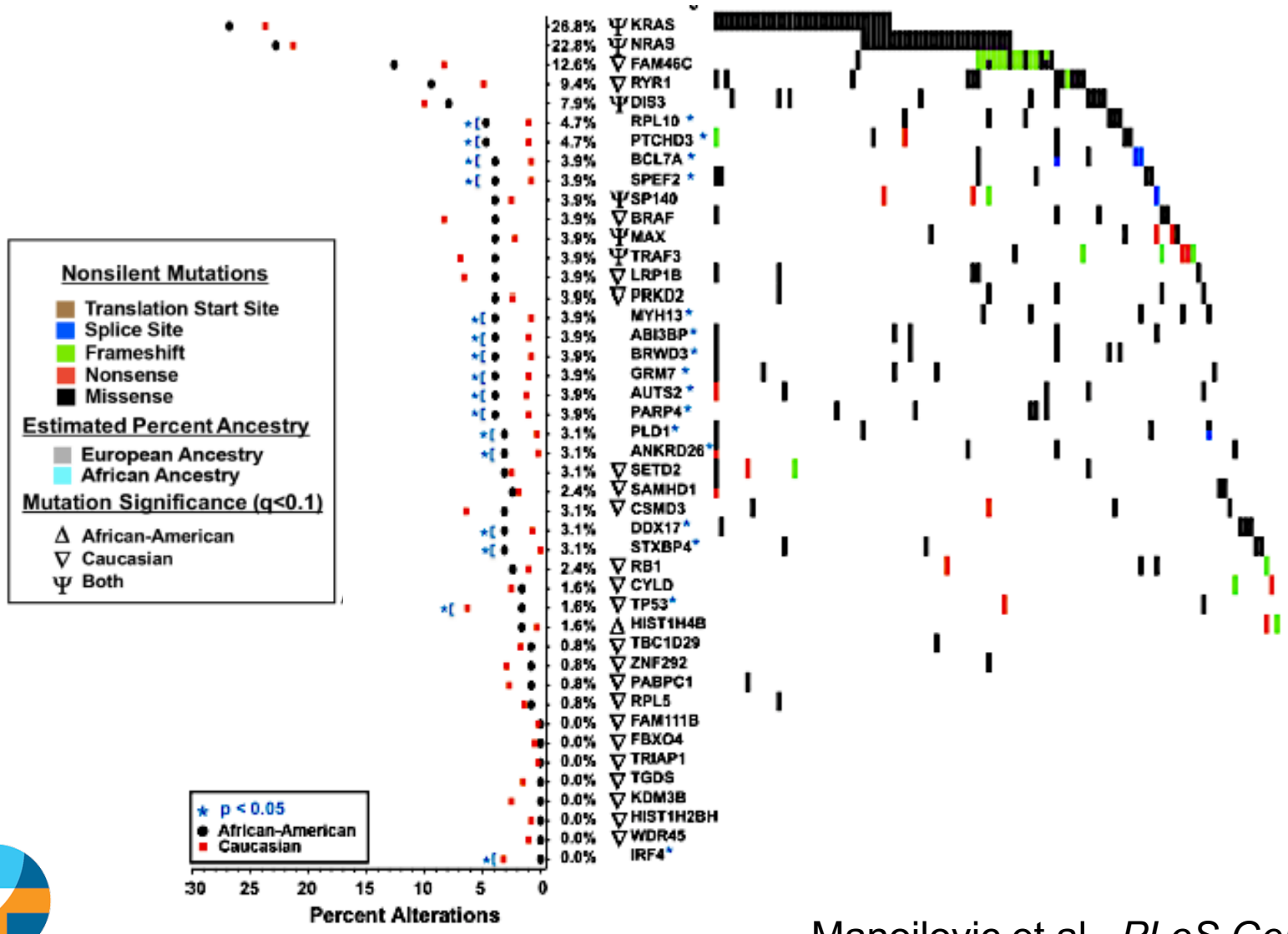
Cytogenetic Abnormalities by Race

Cytogenetic abnormalities		*Black*			*White*			
		Total	*With abnormality*	*%*	*Total*	*With abnormality*	*%*	
t(11;14)								
< 60 years of age		151	8	5.3%	165	31	18.8%	< 0.001
60+ years of age		141	11	7.8%	307	52	16.9%	
t(4;14)								
< 60 years of age	*	151	7	4.6%	165	19	11.5%	0.04
60+ years of age		141	9	6.4%	307	28	9.1%	
Monosomy 13/del 13q								
< 60 years of age	**	151	46	30.5%	165	73	44.2%	< 0.001
60+ years of age		141	39	27.7%	307	150	48.9%	
Monosomy 17/del17p								
< 60 years of age	***	151	15	9.9%	165	23	13.9%	0.027
60+ years of age		141	8	5.7%	307	38	12.4%	
None of the studied abnormalities								
< 60 years of age		151	95	62.9%	165	57	34.5%	< 0.001
60+ years of age		141	90	63.8%	307	106	34.5%	

Associated with *adverse prognosis, **earlier disease onset, ***disease progression

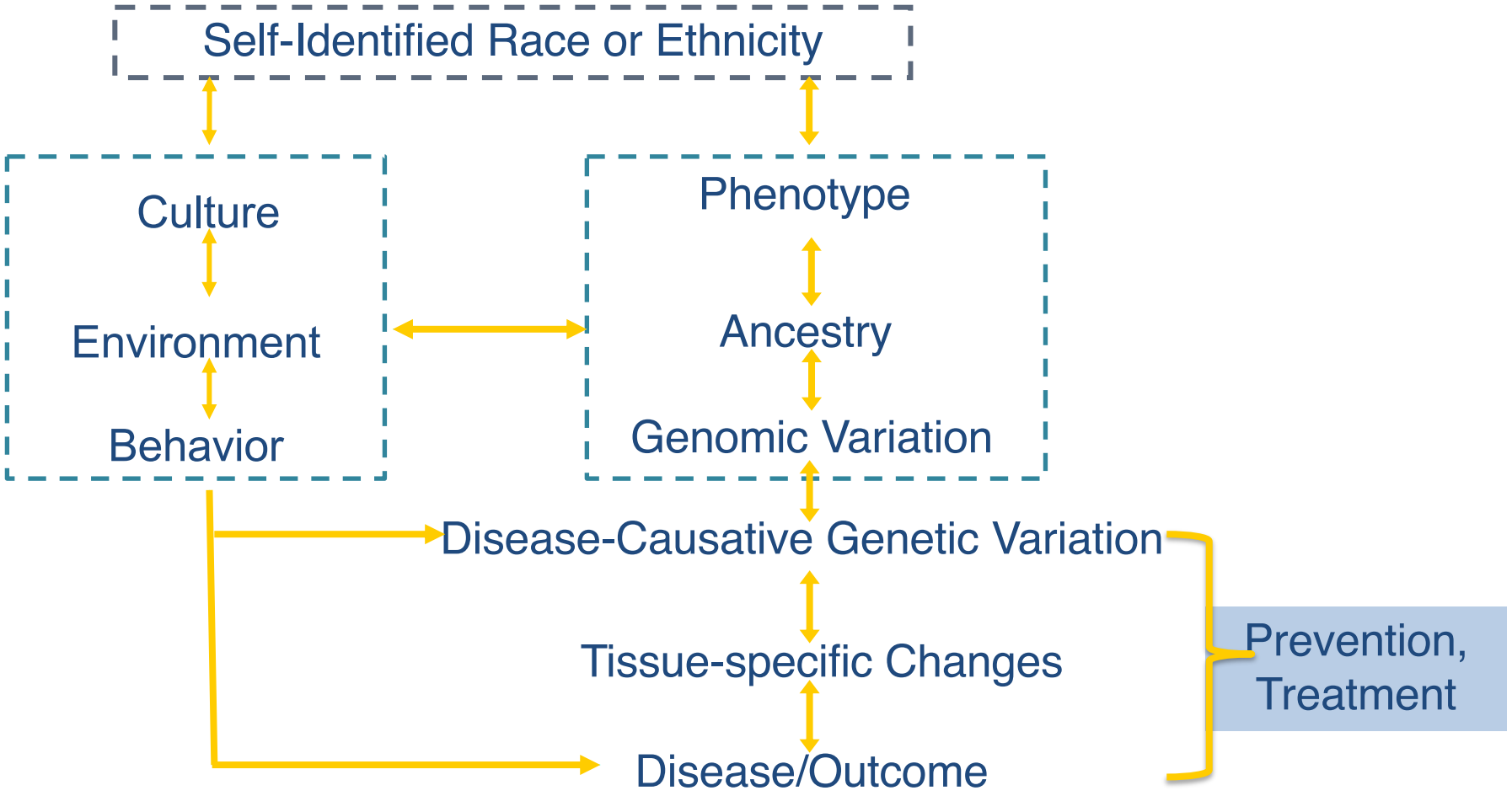
Greenberg et al., *Blood Cancer Journal* 2015

Tumor Mutations by Race



Manojlovic et al., *PLoS Genetics* 2017

Disparities Framework



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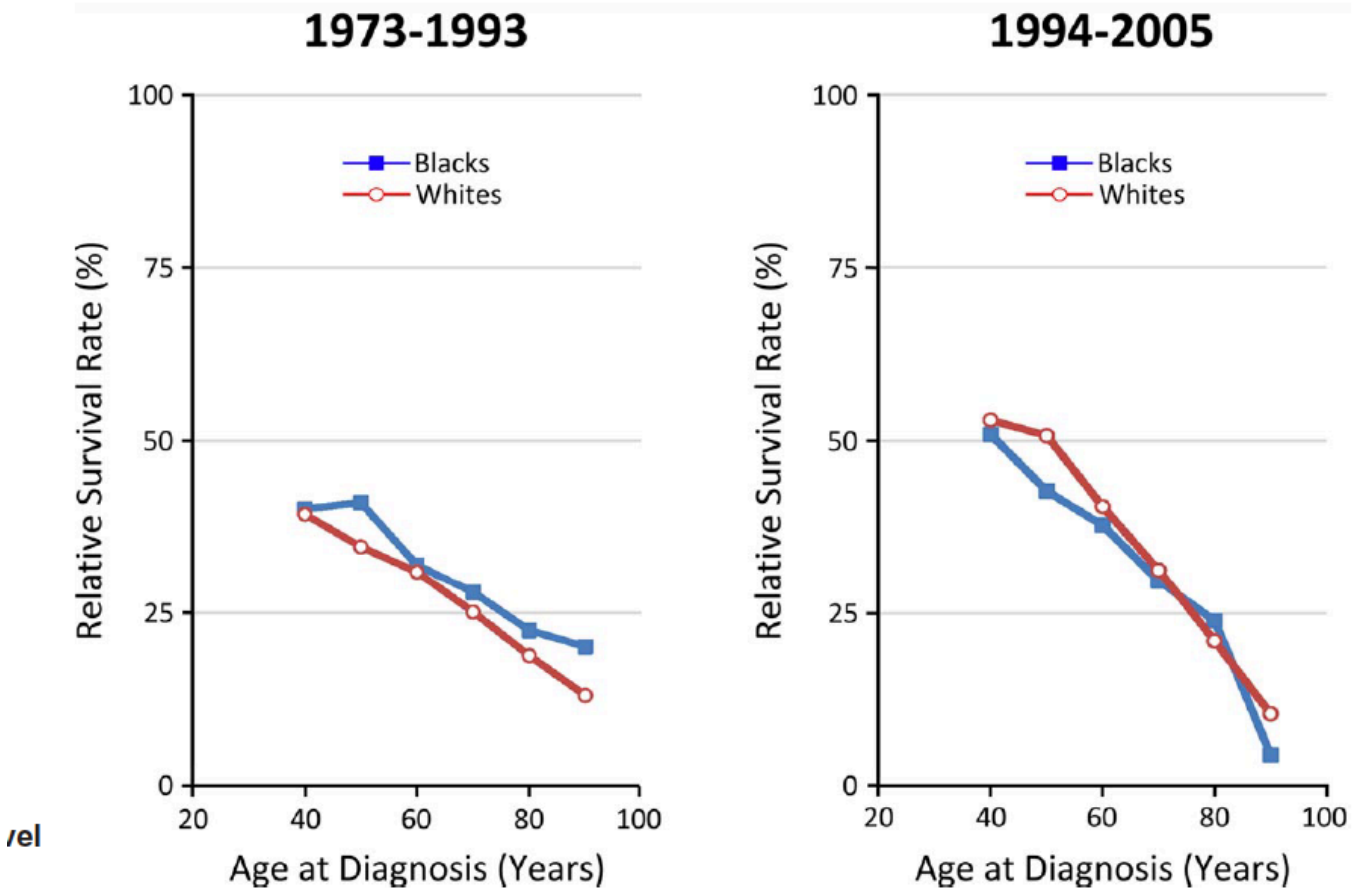
MM-Specific Survival (1973-2005, SEER 9)

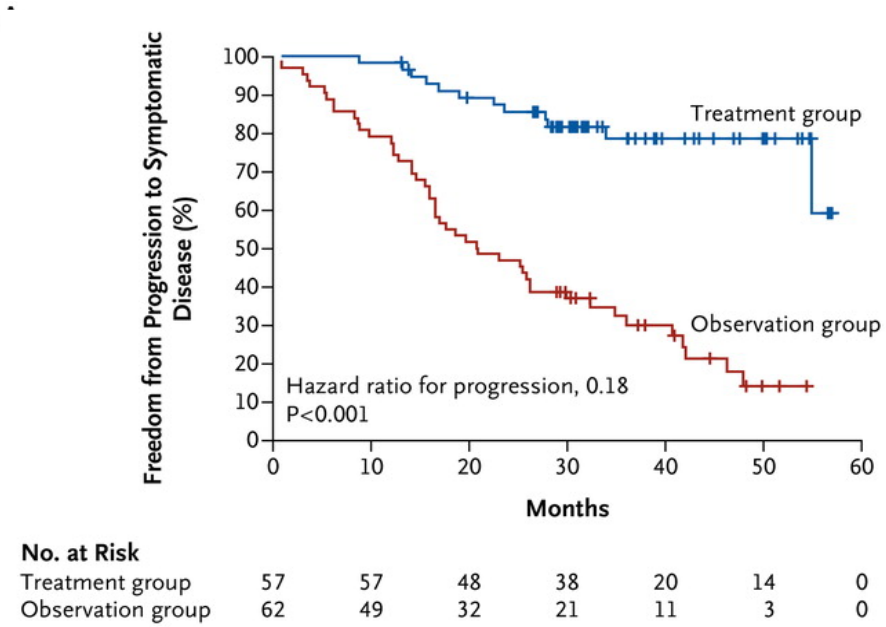


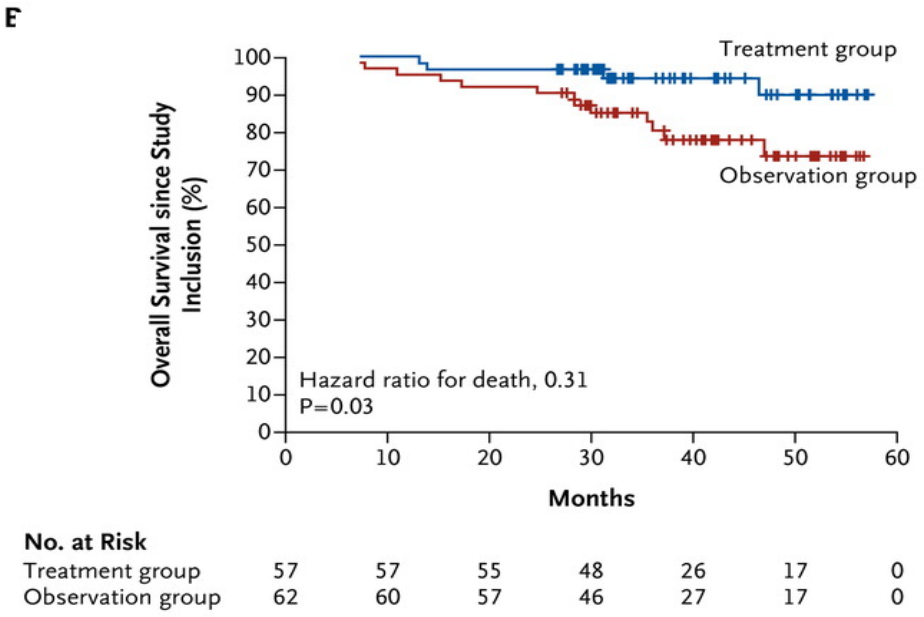
After introduction of ASCT and IMiDs (1990s), magnitude of survival improvement among Blacks was less than 50% of that in Whites

Waxman et al., *Blood* 2010

Early Intervention May Benefit Pre-MM Patients

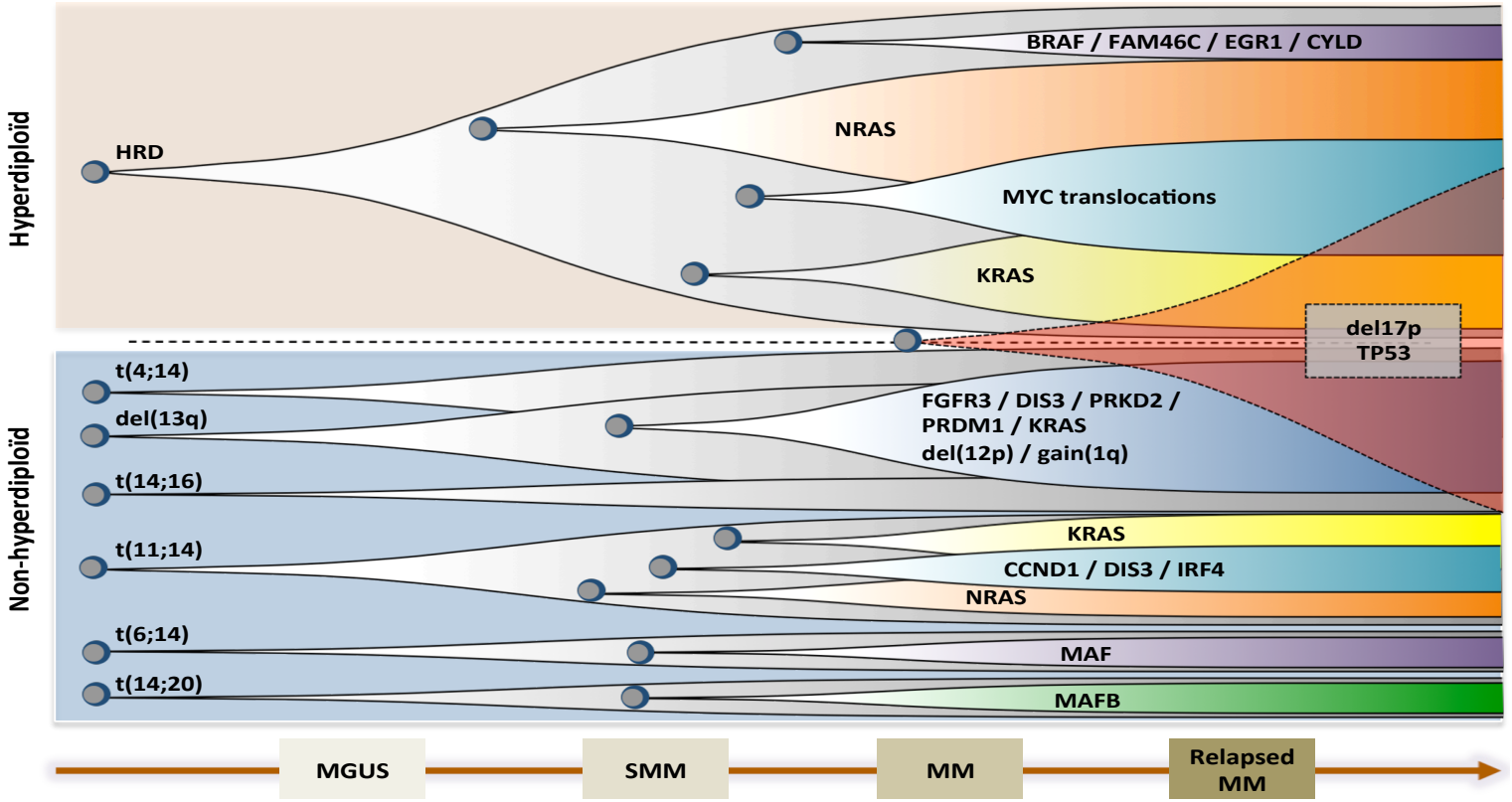
Example: RCT of Lenalidomide + Dexamethasone
for the Treatment of High Risk SMM





Mateos et al., *New England Journal of Medicine*, 2013

Prevent or Delay Myeloma by Early Therapeutic Intervention of High-Risk Precursor Conditions



Manier et al. *Nat Rev Clin Oncol*, 2017

Screening and Interception of Precursor Myeloma

PROMISE

Aim 1. PROMISE Study

Screen N = 50,000 high-risk individuals

Screen –
N = 47,000

Screen +
N = 3,000

Prospective Follow-up

Aim 2. Genomic Characteristics

Viktor Adalsteinsson
Benjamin Ebert
Gaddy Getz
Irene Ghobrial
David Liu
Jihye Park

Aim 3. Race/Obesity

Tim Rebbeck
Catherine Marinac
David Liu
Lorelei Mucci

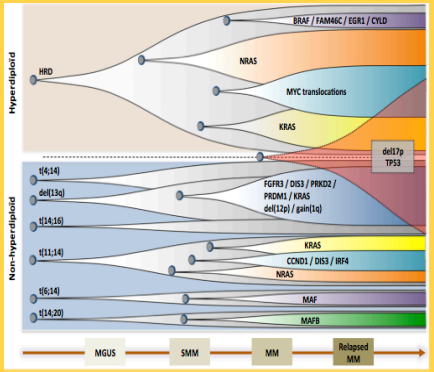
Aim 4. Microenvironment

Ivan Borrello
Irene Ghobrial
Jihye Park

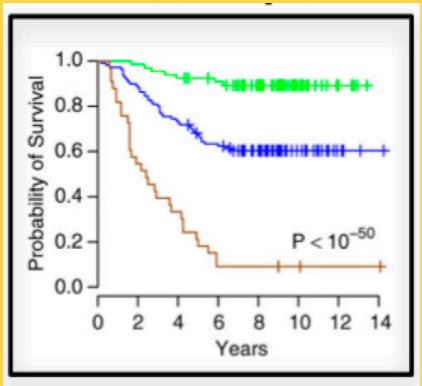
Aim 5. Imaging / Therapeutic

Irene Ghobrial
Alexandre Detappe
Jeremiah Johnson

Develop novel biomarkers & risk stratification tools



Develop new tools to prevent/delay progression



Dana-Farber Cancer Institute
BROAD INSTITUTE
MIT
JOHNS HOPKINS MEDICINE
MAYO CLINIC
HARVARD SCHOOL OF PUBLIC HEALTH

Summary

- The disparity in MM mortality is complex but is in part driven by the increased incidence of MGUS and MM in Blacks as well as disparities in treatment.
- MM survival is equal in Whites and Blacks (or perhaps better in Blacks if treatment is equally applied).
- The genetic, molecular and epidemiological foundation of MGUS and MM risk is not understood, particularly in Blacks.
- Intercepting the progression of MGUS to MM and increasing engagement with Black communities in clinical research may reduce the Black-White disparity.

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Ohio Commission on Minority Health	Boyce, Cheryl

PROMISE

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