Disparities in Myeloma and Its Precursors in African Americans

Timothy R. Rebbeck, PhD
Disclosures

- None
Disparities Framework

- Self-Identified Race or Ethnicity
  - Culture
  - Environment
  - Behavior
- Phenotype
  - Ancestry
  - Genomic Variation
- Disease-Causative Genetic Variation
  - Tissue-specific Changes

Disease/Outcome

Prevention, Treatment

Adapted from: Rebbeck and Sankar *CEBP* 2005, Rebbeck et al. *JCO* 2006
### Number of New Cases per 100,000 Persons

<table>
<thead>
<tr>
<th>Race/Group</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Races</strong></td>
<td>8.3</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>7.8</td>
<td>4.6</td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td>15.9</td>
<td>11.4</td>
</tr>
<tr>
<td><strong>Asian / Pacific Islander</strong></td>
<td>4.7</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>American Indian / Alaska Native</strong></td>
<td>5.0</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Hispanic</strong></td>
<td>7.7</td>
<td>5.3</td>
</tr>
<tr>
<td><strong>Non-Hispanic</strong></td>
<td>8.4</td>
<td>5.3</td>
</tr>
</tbody>
</table>

SEER 18 2010-2014, Age-Adjusted
### Number of Deaths per 100,000 Persons

<table>
<thead>
<tr>
<th>Race</th>
<th>Male Death Rate</th>
<th>Female Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Races</td>
<td>4.2</td>
<td>2.7</td>
</tr>
<tr>
<td>White</td>
<td>4.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Black</td>
<td>7.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Asian / Pacific Islander</td>
<td>2.1</td>
<td>1.3</td>
</tr>
<tr>
<td>American Indian / Alaska</td>
<td>3.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>4.3</td>
<td>2.7</td>
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</tbody>
</table>

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)

Landgren 2017 (N=12,372)
Landgren 2014 (N=12,482)
Earlier Age at MM Diagnosis in Blacks

SEER, 2011-2015
Disparities Framework

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Culture

Environment

Behavior

Phenotype

Ancestry

Genomic Variation

Disease-Causative Genetic Variation

Tissue-specific Changes

Disease/Outcome

Prevention, Treatment

Adapted from: Rebbeck and Sankar CEBP 2005, Rebbeck et al. JCO 2006
<table>
<thead>
<tr>
<th>Trait</th>
<th>Citations</th>
</tr>
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<tbody>
<tr>
<td>Familial Relative Risk of MM</td>
<td>2.5-fold excess risk</td>
</tr>
<tr>
<td>Proportion of MM that is familial</td>
<td>2.4%</td>
</tr>
<tr>
<td>Reported clustering of MM with other tumors</td>
<td>Tumor sites: colorectal*, breast and prostate cancers, non-thyroid endocrine tumors, leukemia (*a syndrome?)</td>
</tr>
</tbody>
</table>

Altieri et al., 2006  
Landgren et al. 2006  
Hemminki et al. 2004  
Frank et al. 2015  
Frank et al. 2016
## Association of MM Family History with MM Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>European American</th>
<th>African American</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Valkenburg et al. 2016</td>
<td>2.0 (0.83-5.04)</td>
<td>20.9 (2.59-168)</td>
</tr>
<tr>
<td>Brown et al. 1999</td>
<td>1.5 (0.3-6.4)</td>
<td>17.4 (2.4-348)</td>
</tr>
</tbody>
</table>
Disparities Framework

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

Hazard Ratio (Normal:Obese) = 1.98, P<0.001

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

Chang et al. JNCI 2017
### Selected MGUS Risk Factor Exposures

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

*Limitation: Associations largely unreported in African Americans*
## Selected Myeloma Risk Factor Exposures

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

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- Disease-Causative Genetic Variation
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Adapted from: Rebbeck and Sankar *CEBP* 2005, Rebbeck et al. *JCO* 2006
• 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

<table>
<thead>
<tr>
<th>SNP</th>
<th>BP</th>
<th>Risk/Ref</th>
<th>Freq</th>
<th>OR</th>
<th>P</th>
<th>Power</th>
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<tbody>
<tr>
<td>2p23.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs6746082a</td>
<td>25659244</td>
<td>A/C</td>
<td>0.76</td>
<td>1.29</td>
<td>1.22 × 10⁻⁷</td>
<td>0.96</td>
</tr>
<tr>
<td>rs6761076b</td>
<td>25607758</td>
<td>T/C</td>
<td>0.81</td>
<td>1.23</td>
<td>7.23 × 10⁻³</td>
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<tr>
<td>2q12.3</td>
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<tr>
<td>rs12614534a</td>
<td>107642482</td>
<td>A/G</td>
<td>0.33</td>
<td>1.39</td>
<td>1.70 × 10⁻⁵</td>
<td>0.99</td>
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<tr>
<td>rs1341665b</td>
<td>107621925</td>
<td>G/T</td>
<td>0.50</td>
<td>1.01</td>
<td>8.03 × 10⁻¹</td>
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<tr>
<td>3p22.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>rs1052501a</td>
<td>41925398</td>
<td>G/A</td>
<td>0.22</td>
<td>1.23</td>
<td>4.42 × 10⁻³</td>
<td>0.99</td>
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<tr>
<td>rs14353165b</td>
<td>4816589</td>
<td>G/C</td>
<td>0.10</td>
<td>1.06</td>
<td>2.21 × 10⁻¹</td>
<td>0.99</td>
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<tr>
<td>3q26.2</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>rs10936599a</td>
<td>169429101</td>
<td>G/A</td>
<td>0.79</td>
<td>1.12</td>
<td>8.41 × 10⁻²</td>
<td>0.92</td>
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<tr>
<td>rs981121b</td>
<td>176777501</td>
<td>T/C</td>
<td>0.74</td>
<td>1.10</td>
<td>1.33 × 10⁻³</td>
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<tr>
<td>6p21.33b</td>
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<td></td>
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<td></td>
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<tr>
<td>rs2285803b</td>
<td>31107258</td>
<td>A/G</td>
<td>0.29</td>
<td>1.11</td>
<td>1.27 × 10⁻¹</td>
<td>0.84</td>
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<tr>
<td>7p15.3</td>
<td></td>
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<tr>
<td>rs4487645a</td>
<td>21938240</td>
<td>C/A</td>
<td>0.65</td>
<td>1.38</td>
<td>3.33 × 10⁻¹⁵</td>
<td>0.99</td>
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<tr>
<td>rs1254002b</td>
<td>21945563</td>
<td>G/A</td>
<td>0.70</td>
<td>1.23</td>
<td>7.47 × 10⁻⁴</td>
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<tr>
<td>17p12</td>
<td></td>
<td></td>
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<tr>
<td>rs4273077a</td>
<td>16849139</td>
<td>G/A</td>
<td>0.11</td>
<td>1.26</td>
<td>1.41 × 10⁻⁷</td>
<td>0.83</td>
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<tr>
<td>rs3456225a</td>
<td>16842991</td>
<td>A/G</td>
<td>0.12</td>
<td>1.37</td>
<td>2.46 × 10⁻⁴</td>
<td>0.97</td>
</tr>
<tr>
<td>22q13.1</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>rs877529a</td>
<td>39542292</td>
<td>A/G</td>
<td>0.45</td>
<td>1.21</td>
<td>4.31 × 10⁻⁴</td>
<td>0.97</td>
</tr>
<tr>
<td>rs139425b</td>
<td>39559742</td>
<td>C/G</td>
<td>0.46</td>
<td>1.21</td>
<td>4.43 × 10⁻⁴</td>
<td>0.99</td>
</tr>
</tbody>
</table>
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 directionally consistent
  - 9 replicated at $P < .05$
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         | *     | 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         | **    | 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         | ***   | 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
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Prevention, Treatment

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

Hazard ratio for progression, 0.18
P<0.001

Hazard ratio for death, 0.31
P=0.03

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

No. at Risk
Treatment group 57 57 55 48 26 17 0
Observation group 62 60 57 46 27 17 0

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

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

Screening and Interception of Precursor Myeloma

Probability of Survival

Years

P < 10^-50

Dana-Farber Cancer Institute
BROAD Institute
MIT
Johns Hopkins Medicine
Mayo Clinic
Harvard School of Public Health
• 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.
Acknowledgements

Getz, Gad
Adalsteinsson, Viktor

Ghobrial, Irene M
Hamilton, Courtney
Warren, Michael
Watson, Donald
Higgins, Allison
Hadfield, Andrea
Perilla-Glen, Adriana
Ebert, Benjamin
Park, Jihye
Soiffer, Jennifer
Marinac, Catherine
Detappe, Alexandre

Birmann, Brenda
Mucci, Lorelei
Borello, Ivan
Fronseca, Rafael
Johnson, Jeramiah

Ahlstrom, Jenny
Boyce, Cheryl