Incidence Rates by Race and Ethnicity
US, 1999-2014

Death Rates by Race and Ethnicity
US, 1999-2014

https://www.cdc.gov/
Prostate cancer (PC) health disparities among racial groups

Number of New Cases per 100,000 Persons

- All Races: 147.8
- White (W or CA): 139.9
- Black (AA): 223.9
- Asian / Pacific Islander: 79.3
- American Indian / Alaska Native: 71.5
- Hispanic: 122.6
- Non-Hispanic: 151.5

Number of Deaths per 100,000 Persons

- All Races: 23.0
- White: 21.2
- Black: 50.9
- Asian / Pacific Islander: 10.1
- American Indian / Alaska Native: 20.7
- Hispanic: 19.2
- Non-Hispanic: 23.2

Oncology Health Disparities Model

Polite et al., J Clin Oncol, 2006, 24(14), p.2179-87
Individual Risk Factors
Age, SES, Education, Obesity, Tobacco Use, Acculturation, Diet, Race, Environment,

Biologic/Genetic Pathways
Allostatic Load, Metabolic Processes, Physiological Pathways, Genomics/epigenomics, BIOMARKERS, Pharmacogenomics/Metabolomics

Social Conditions and Policies
Culture, Norms, Racism, Sexism, Discrimination, Public Policies, Poverty

Institutions
Health Care System, Families, Churches, Communities, Health Economics, Legal & Political Systems, Media, Workforce

Social/Physical Context

Social Relationships
Social Networks, Social Support, Social Influences, Social Engagement

Upstream Factors
Fundamental Causes
HealthCare Delivery
Health Outcomes
Social and Physical Context
HealthCare Delivery

Individual Demographic and Risk Factors

Biologic Responses and Pathways

Adapted from Warnecke 2009
The Healthcare System Maze Needs a GPS for everyone, but especially vulnerable populations

- Employment/Loss Wages
- Perceptions and Beliefs
- Language/interpreter
- Fear
- Transportation
- Comorbidities
- Location of Facility
- Problems with Scheduling
- Communication with Medical Personnel
- Uninsured, Underinsured
- Disability
- Literacy
- Child/Adult Care
Barriers presenting a logistical challenge to engaging in care and have a potential logistical action or resource available.

Barriers that arise as a result of patients’ ethnic, social and cultural beliefs and may not be easily overcome by logistical actions.

<table>
<thead>
<tr>
<th>Logistic/Structural</th>
<th>Socio-Cultural</th>
<th>Financial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transportation</td>
<td>-Fear</td>
<td>-Child care</td>
</tr>
<tr>
<td>Location of facility</td>
<td>-Perceptions about tests</td>
<td>-Adult care</td>
</tr>
<tr>
<td>System scheduling problems</td>
<td>-Literacy</td>
<td>-Housing</td>
</tr>
<tr>
<td>Out of town/country</td>
<td>-Social/practical support</td>
<td>-Financial problems</td>
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<tr>
<td>-Disability</td>
<td>-Communication concerns with</td>
<td>-Employment issues</td>
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<tr>
<td>Mental/Medical co-morbidities</td>
<td>medical personnel</td>
<td></td>
</tr>
<tr>
<td>-Language</td>
<td>-Attitudes towards providers</td>
<td></td>
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<tr>
<td>-Insurance</td>
<td></td>
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</tr>
</tbody>
</table>

How do such barriers “play out” in the real world?

Barriers related to socioeconomic status that can not be easily explained by patients’ cultural background and may not be overcome by simple logistical actions.
Individual Determinants of Health Can Influence Health Care Outcomes

**Distal: Societal Factors**
- Lives in a City/Suburb
  - Healthy Insurance
  - College Education
  - Gleasons 6
- Lives in a Rural Town or Inner City
  - No Health Insurance
  - High School Education
  - Gleasons 9

**Intermediate: Environmental Factors**
- Neighborhood Factors (availability and utilization of providers)
- Health Insurance
- College Education
- Gleasons 6

**Proximal: Biological Factors**

Cancer detected early: good prognosis

Cancer detected late: poor prognosis
NCI/ACS funded 9 sites as a Cooperative Agreement (U01) across the USA to empirically evaluate effectiveness of patient navigation.
PNRP Main Questions, over 11,000 enrolled

Will navigated patients...

Receive **timelier, definitive resolution** following an abnormal finding?

Receive **timelier treatments** following a positive diagnosis?

Improve their **satisfaction** with the health care system experience?


Longitudinal Patient Navigation Matrix:
A “To and Through” Model for Overcoming Barriers Across a Health System Continuum and the Cancer Care Continuum

Community Navigation
- Outreach
- Education
- Screening
- Coordinate w CHWs

Treatment Navigation
- Lay Navigators
- RN Navigators
- New Patient-Coordinators
- Social Workers
- Financial Counselors
- Therapists
- Volunteers
- Supportive-Care Leaders
- Transportation
- Language
- Care- Coordination
- Scheduling
- Social Work
- Insurance
- Psycho-oncology
- Therapy Services
- Palliative Care
- End of Life Care

Survivorship Navigation
- Survivorship Clinic
- Onc-Rehab
- Primary Care

Distress Tool Triage

Abnormal results/ Diagnosis → Treatment and Supportive Care → Survivorship

Eliminating critical delivery gaps for people & populations experiencing disparities
PC health disparities remain after adjustment for social determinants of health

Duke Cancer Institute Cancer Disparities
Translational Research Paradigm

- SNPs, gene expression, alternative RNA splicing, epigenetics
- siRNAs, expression vectors, small molecules, SSOs
- AA and white cell lines, xenografts, PDXs, blood
- AA and white tissue and blood
RACE IS NOT A BIOLOGICAL CONSTRUCT

RACE/ETHNICITY ARE SOCIO-CULTURAL CONSTRUCTS

But, RACIAL ANCESTRY, AS A FUNCTION OF THE HUMAN DIASPORA, AFFECTS GENETIC, PHENOTYPIC & CULTURAL DIVERSITY AND THEREFORE DISEASE RISK AND OUTCOMES
RACE IS NOT A BIOLOGICAL CONSTRUCT

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But, RACIAL ANCESTRY, AS A FUNCTION OF THE HUMAN DIASPORA, AFFECTS GENETIC, PHENOTYPIC & CULTURAL DIVERSITY AND THEREFORE DISEASE RISK AND OUTCOMES
FACTORS CONTRIBUTING TO CLINICAL AGgressiveness OF AA PROSTATE CANCER

- epigenetic alterations
- differential somatic gene expression
- germ-line SNPs

DNA & RNA

AA AND CA PROSTATE TUMOR SPECIMENS

preclinical prostate tumor models to assess biologic significance of factors

AA AND CA BLOOD SPECIMENS

prostate cancer patient-derived explants
derivative cell lines

GENomics of CAncer DisparitiEs (GENCADE)

- Duke Cancer Institute
- George Washington University Cancer Center
Translational Prostate Cancer Disparities Research

- Interrogate molecular mechanisms underlying race-related tumor aggressiveness
- Develop novel biomarkers and therapeutic agents based on such mechanisms
- Elucidate importance of such mechanisms for response to current therapeutic strategies
• **Proactive Assessment of Study Design:** Provide recommendations during the study design phase to increase minority accrual.
• **Patient-Community Advocates in Research:** Involve a diverse group of community and patient advocates trained to provide feedback and input on research protocols.
• **Communications Consultation** - Ensure patient demographics, perceptions, and perspectives are appropriately captured in study materials.
• **Informed Consent Supplemental Tools** – Compliment study documents with culturally appropriate tools to effectively facilitate communication between patient and research teams.
• **Clinical Trial Awareness Campaign** – Increase awareness about clinical trials and participation through a variety of campaigns, including faith based conferences and educational dinners on prostate cancer and clinical trials. (In one year reaching over ~2000 people)

• **Communication and Dissemination of Research Findings** – Provides resources and mechanisms to communicate study findings to our patients and the broader community.

• **Diversity, Culture and Bias Training** – Incorporates key training strategies around valuing diversity using a self reflective and power analysis framework to raise awareness of one’s implicit bias and who it impacts our interactions when discussing research.
Central Dogma of Molecular Biology

DNA

Exon 1  intron 1  Exon 2  intron 2  Exon 3  intron 3  Exon 4

Transcription

pre-mRNA

Exon 1  intron 1  Exon 2  intron 2  Exon 3  intron 3  Exon 4

Alternative RNA splicing

mRNAs

Exon 1  Exon 2  Exon 3

Exon 1  Exon 3  Exon 4

Exon 1  Exon 2  Exon 4

Exon 2  Exon 3  Exon 4

Translation

Protein A with Function A

Protein B with Function B

Protein C with Function C

Protein D with Function D
Differential Gene vs Exome Level Analysis Between AA and CA Prostate Cancer Biopsy Specimens

A  exon-level analysis

B  gene-level analysis

934 differentially expressed exons

861 corresponding genes

1.5  0  0  3 (fold)
Alternative RNA splicing (ARS) events in AA versus white PC

2,520 Race-related ARS in PC

Prostate Cancer Driver Mutations vs Alternatively Spliced RNA Burden

~11 : >2500
Genomic Differences Between AA and W PCa


- 1,188 differentially expressed genes between AA and W PCa
- 2,520 differentially expressed RNA splice variants between AA and W PCa
- 644 RNA splice variants also present in the patient’s adjacent normal prostate tissue
What drives race-related Alternative RNA Splicing?
What if it pre-exists in the germ line and carries into PC?
Does it affect PC biology?
Does it contribute to clinical aggressiveness of PC in different races? AND HOW?
Does it predict risk or survival?
Is it targetable?

differential somatic gene expression
alternative splicing of somatic genes
epigenetic alterations
germ-line SNPs
cis-acting splicing elements
trans-acting splicing factors
qRT-PCR Validation of Differential Splicing

(a) Exon diagrams showing splicing variations for different genes:
- **PIK3CD**: Exon 17-21 with 19 and 20 excluded in AA.
- **FGFR3**: Exon 13-16 with 14 excluded in AA.
- **TSC2**: Exon 18-21 with 20 excluded in AA.
- **ITGA4**: Exon 17-20 with 18 and 19 excluded in AA.
- **MET**: Exon 12-16 with 14-15 excluded in AA.
- **NF1**: Exon 7-9 with 8 excluded in AA.
- **BAK1**: Exon 4-11 with 3 and 12 excluded in AA.
- **RASGRP2**: Exon 13-11 with 12 excluded in AA.

(b) Gel images showing splicing patterns for AA and EA:
- **PIK3CD**: LS bands in AA and EA.
- **FGFR3**: LS bands in AA and EA.
- **TSC2**: LS bands in AA and EA.
- **ITGA4**: LS bands in AA and EA.
- **MET**: LS bands in AA and EA.
- **NF1**: LS bands in AA and EA.
- **BAK1**: LS bands in AA and EA.
- **RASGRP2**: LS bands in AA and EA.

(c) Statistical analysis showing PIK3CD expression levels:
- **PPA1**: Lower expression in EA compared to AA.
- **EIF1AX**: Higher expression in EA compared to AA.
qRT-PCR Validation of Differential Splicing

Supplementary Fig. 4. Quantification of QRT-PCR results of race-specific/-enriched oncogene and tumor suppressor gene variants in AA and EA PCa specimens. Quantitative real time RT-PCR was performed on samples depicted in Fig. 3b. RNA from n= 22-25 AA PCa and n= 21-24 EA PCa specimens were analysed. Shown are the plots for the AA-specific/-enriched variants FGFR3-S, TSC2-S, ITGA4-L, MET-L, NF1-L, BAK1-L and RASGRP2-b; and plots for the EA-specific/-enriched variants FGFR3-L, TSC2-L, ITGA4-S, MET-S, NF1-S, BAK1-S and RASGRP2-a. EIF1AX and PPA1 transcripts served as internal normalization controls. * P < 0.05 using Student t-test.

**FGFR3 (S/L)**

**TSC2 (S/L)**

**ITGA4 (L/S)**

**MET (L/S)**

**NF1 (L/S)**

**BAK1 (L/S)**

**RASGRP2 (b/a)**
Biological significance of race-related alternative RNA splicing: PIK3D Isoform Knockdown
Biological significance of race-related alternative RNA splicing: Clinical Significance: Survival Plots as function of S/L ratio

Supplementary Fig. 9. Survival plots for breast, colon and prostate cancer patients with high and low PIK3CD-S/PIK3CD-L expression ratios. RNA-Seq and disease free survival data for breast (n = 1,068 patients), colon (n = 277 patients) and prostate cancers (n = 494 patients) were obtained from The Cancer Genome Atlas (TCGA) (https://tcga-data.nci.nih.gov/tcga/). P-values for survival curves were determined by the log-rank test.
Function of Alternatively Spliced Genes with race-related SNPs that Associate with PC Aggressiveness and/or Survival

BPTF, CD44, COL6A3, FGFR3, FN1, INSR, MET, NCOR2, NF1, PIK3CD, RHOU, SPAG5, THRB, WDR4

ACACA, ADH1C, EHBP1, FASN, HPGD, INSR, LAT2, SREBF2, STEAP4

BAK1, BPTF, CD44, COL6A3, FGFR3, INSR, MET, NF1, PIK3CD, RHOU, SPAG5, THRB, ZNF385B

RECQL4

COL6A3, FGFR3, MET, SEMA3C, WARS

ABLIM3, CD44, EHBP1, EPB41L2, EXOC1, FGFR3, FN1, FXR1, ITGA4/6, LMO7, MET, MYBPC1, RELN, RHOU, SEMA3C, NCOR2, PIK3CD, RELN, SPAG5, THRB
Related Trials: Abi & Abi/App Race

- Metastatic, CRPC
- No history of chemotherapy
- Karnofsky performance status ≥ 70
- Adenocarcinoma of the prostate
- No evidence of neuroendocrine cancer

Baseline, during, end of treatment (whole blood, plasma, serum)
- Clinical
  - PSA response, duration of response, objective response, radiographic disease progression
- Genetic
  - Race- and splicing-related SNPs, angiome, AMPK targets, steroid levels

Registration

Self-reported AA
Abiraterone + Prednisone

Disease progression or Adverse event
Results thus far…..

• Alternative RNA Splicing is a dominant source of genomic and phenotypic heterogeneity in cancer
• SNPs in both coding and non-coding splice regulatory regions of DNA may serve as biomarkers of risk for aggressive disease
• ARS produces a broad array of targetable proteins
• ARS itself is a target for therapeutic intervention
• In addition to sequencing patient tumors for DNA mutations we should be performing deep RNA sequencing for ARS profile. It will be a richer source of “actionable” molecular targets.
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