PHEN Twelfth Annual Summit – African American Prostate Cancer Disparities

INCREASING AFRICAN AMERICAN PARTICIPATION IN CLINICAL TRIALS

September, 2016

Duke Cancer Institute
Prostate cancer (PC) health disparities among racial groups

Number of New Cases per 100,000 Persons

- All Races: 147.8
- White: 139.9
- Black: 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

(W or CA) (AA)

The Healthcare System Maze Needs a GPS for everyone, but especially vulnerable populations

- Comorbidities
- Transportation
- Fear
- Uninsured, Underinsured
- Disability
- Literacy
- Child/Adult Care
- Employment/Loss Wages
- Perceptions and Beliefs
- Language/interpreter
- Location of Facility
- Problems with Scheduling
- Communication with Medical Personnel
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>
</tr>
<tr>
<td>-Disability</td>
<td>-Communication concerns with medical personnel</td>
<td>-Employment issues</td>
</tr>
<tr>
<td>Mental/Medical co-morbidities</td>
<td>-Attitudes towards providers</td>
<td></td>
</tr>
<tr>
<td>-Language</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Insurance</td>
<td></td>
<td></td>
</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

Intermediate: Environmental Factors

Proximal: Biological Factors

Lives in a City/Suburb
- Neighborhood Factors (availability and utilization of providers)
- Health Insurance
- College Education
- Gleasons 6

Lives in a Rural Town or Inner City
- Neighborhood Factors (distance to providers, lack of transportation)
- No Health Insurance
- High School Education
- Gleasons 9

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

Outreach
Education
Screening
Coordinate w CHWs

Distress Tool Triage

Community Navigation
Treatment Navigation
Survivorship 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 Clinic
Onc-Rehab
Primary Care

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

Adopted from Robbins et al., Am J Epidemiol, 2000, 151(4), p.409-16
Duke Cancer Institute Cancer Disparities Translational Research Paradigm
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

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
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

Social and Physical Context

Health Outcomes

Fundamental Causes

HealthCare Delivery

Social and Physical Context

HealthCare Delivery

Individual Demographic and Risk Factors

Biologic Responses and Pathways

Adapted from Warnecke 2009
FACTORS CONTRIBUTING TO CLINICAL AGGRESSIVENESS OF AA PROSTATE CANCER

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

PRECLINICAL PROSTATE TUMOR MODELS TO ASSESS BIOLOGIC SIGNIFICANCE OF FACTORS

DNA & RNA

prostate cancer patient-derived explants
derivative cell lines

AA AND CA BLOOD SPECIMENS

AA AND CA PROSTATE TUMOR SPECIMENS

▪ 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
Reduce Disparities & Promote Health Equity

Integrated Focus Areas
- Community Engagement and Longitudinal Patient Navigation
- Diversity in Research, Clinical Trials, and the workplace
- Health Disparities Education, Training, PI consults, and Research

Ongoing Data Collection
- Bench Mark/Baseline Data
- Minority Accrual Program Activities
- Community and Patient Assessments

Vision

• **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

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
Alternative RNA splicing (ARS) events in AA versus white PC

2,236 Race-related ARS in PC

Prostate Cancer Driver Mutations vs Alternatively Spliced RNA Burden

\[ \sim 11 : >2000 \]
Why is “JUST ASK” so important?

We need to understand Alternative RNA Splicing in AA PC. How does it contribute to aggressiveness of AA PC? Does it predict increased AA risk or worse survival? Is it targetable?
Results thus far…..

- Alternative RNA Splicing is the dominant source of genomic and phenotypic heterogeneity in cancer.
- SNPs in 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.
Acknowledgements

Clinical Team
- Dan George, MD
- Andy Armstrong, MD
- Mike Harrison, MD
- Tian Zhang, MD
- Michael Ferrandina MD
- Brant Inman, MD
- Judd Moul, MD
- Cary Robertson, MD
- Tom Polascik, MD
- Wen-Chi Fu, MD
- John Madden, MD

Laboratory Team
- April Deveaux, MD/PhD
- Dong Yang, MD PhD
- Tim Robinson, MD PhD
- Bonnie LaCroix, BS
- Brendon Patierno, BS

Collaborator Lab Teams
- Hongliang Liu, MD PhD
- Yanru Wang, MD PhD
- Wayne Glover, BS
- Jason Somarelli, PhD
- Katie Ware, PhD
- Gabor Kemeny, MS

Clinical Regulatory Team
- Kelly Mundy, MSCR
- Monika Anand, PhD
- Carol Winters, RN OCN
- Angela Clayton, RT
- Kellie Shobe, BSN RN
- Julie Kephart, PhD

Outside Collaborators
- Rick Kittles, PhD
- Norman Lee, PhD
- Zefeng Wang, PhD

Duke Collaborators
- Wen-Chi Foo, MD
- Amanda Hargrove, PhD
- Terry Hyslop, PhD
- David Hsu, PhD
- Jiaoti Huang, MD PhD
- Brant Inman, MD
- Jason Locasale, PhD
- John Madden, MD PhD
- Donald McDonnell, PhD
- Trish Moorman, PhD MSPH
- Susan Murphy, PhD
- Smita Nair, PhD
- Andy Nixon, PhD
- Neil Spector, MD
- Bruce Sullenger, PhD
- Tuan Vo-Dinh, PhD
- Qingyi Wei, MD PhD
- Doug Wixted, PhD
- Kristin Newby, MD
Acknowledgements

- Duke Laboratory Cores
- BRPC
- CCRL
- PDX
- Integrative Cancer Genomics
- Flow Cytometry
- Biostatistics and Bioinformatics
- DNA Analysis
- Office of Health Equity and Disparities