Biodiversity and Health Care Quality: The 21st Century Challenge

Dan Leonard
President
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Key Points

• We are all unique individuals
• These differences matter in health care treatment and access
• We’ve made progress, but we still have many gaps that need to be addressed
Panelists

• Dr. C. Daniel Mullins, Professor, University of Maryland School of Pharmacy
• Dr. Gary Puckrein, Founder & President, National Minority Quality Forum
• Dr. Georgia Dunston, Professor, College of Medicine, Howard University
• Adolph Falcon, Senior Vice President, National Alliance for Hispanic Health
Increased Funding for Comparative Effectiveness Research

- Patient-Centered Outcomes Research Institute (PCORI) has awarded $734.8 million in grants
- National Institutes of Health and Agency for Healthcare Research & Quality have $675 million in available funding
Top Line CER Results Appear Straightforward...

A Better Than B

A $\equiv$ B $\$$
Ignoring Heterogeneity Harms Patients

Slide courtesy of Tomas Philipson and Dana Goldman
The “Average” Patient...

David Kent and Rodney Hayward, “When Averages Hide Individual Differences in Clinical Trials: Analyzing the results of clinical trials to expose individual patients’ risks might help doctors make better treatment decisions,” American Scientist, Volume 95, January–February, 2007, pp 60-68
...is based upon the results of many
There Are Many Causes of Treatment Variability

- Age
- Gender
- Ethnicity
- Disease severity
- Use of concomitant medications
- Care setting
- Comorbidities
- Environment (e.g., diet)

...and then there are genetics...
PCORI Continues to Emphasize Importance of Patient Heterogeneity & Subgroups

- Funded research portfolio on Asthma Treatment Options for African Americans & Hispanics/Latinos
- Encourages the identification and assessment of patient heterogeneity and participant subgroups to inform real-world practice
- Encourages selection and recruitment of study participants representative of the full spectrum of the population
21st Century Cures Seeks to Incorporate All Patients Perspectives

• Build upon Patient Focused Drug Development Program
• Establish a structured framework for the meaningful incorporation of patient experience data into the regulatory decision-making process
Clinical Trial Engagement Network
“Launched with a $215 million investment in the President’s 2016 Budget, the Precision Medicine Initiative will pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients.”
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Patient Differences: Biologic and Non-Biologic Factors

C. Daniel Mullins, PhD
Professor, PHSR Department
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• The views expressed in this presentation are solely those of the speaker and do not necessarily represent the views of the University of Maryland or NPC.

• The findings and conclusions in this presentation have been published as:

Heterogeneity of Treatment-Effect (HTE) for Stage 4 Prostate Cancer (s4PC) Therapies

- HTE factors and patient response to s4PC therapies
  - Biological
  - Non-biological
- Applications & lessons learned for other diseases
- Implications
  - Patients
  - Healthcare Providers
  - Payers
  - Policy Makers
Conceptual Framework for Interactions and Implications of Biologic and Non-Biologic factors in Heterogeneity of Treatment Effect
Systematic Review of HTE in s4PC

• Study Objectives
  – To perform a systematic review of the available published evidence on biologic and non-biologic factors contributing to HTE and s4PC outcomes
  – To discuss the implications of the results on health-care practice and policies
Methodology

- MEDLINE and the PubMed electronic databases were searched for English language, human studies published between January 1946 and March 2012
- Of the final 92 Journal articles selected
  - 87 articles studied the role of biologic factors in HTE
    - genetic factors, age, race, co-morbidities, prior treatment, clinical signs and symptoms, laboratory data and measures of s4PC disease severity
  - 5 articles studied the role of non-biologic factors in HTE
    - social, geographic and dietary factors
Systematic Review of HTE in s4PC

• Characteristics of the 92 studies
  – Conducted in the USA, Canada, or Europe
  – 16 multi-regional studies and half were multi-center studies
  – Included subgroup analyses, cohort studies, and registry data
  – Two studies were pre-specified RCTs that studied the impact of different factors on s4PC treatment-outcomes
  – Post-hoc analyses of RCTs (46%) and comparative observational studies (50%) comprise the majority of the studies
Systematic Review of HTE in s4PC

- AHRQ quality guidelines
  - Quality of the articles was rated as good, fair or poor
    - Majority were of fair quality
    - 15% were of good quality
    - 16% were of poor quality
Systematic Review Findings

• Clinical characteristics of the 92 articles
  – Most common (74%) treatment protocol was hormonal therapy
    • Androgen deprivation therapy, peripheral androgen blockade, orchiectomy and estrogen therapy
  – Main outcome in 53 (58%) was Overall Survival
    • Of these, 25 articles (27%) articles studied OS only
  – Seven percent examined HRQOL
  – Two percent examined adverse events
**Biologic Factors**

- HER2 expression
- AR-CAG repeat length
- Prostatic AR content
- AR binding activity
- Nuclear AR immunostaining intensity
- Tumor growth fraction/Ki67
- AR immunostaining
- CXCR4 expression
- PDGF phosphorylation
- UPAR forms
- TMPRSS2-ERG expression
- Growth fraction/Ki67
- Immunostaining
- Tumor cellular proliferation fraction
- Ploidy of metastases

**Race**

- Age

**Comorbidities**

- Ischemic cerebral disease
- Ischemic heart disease
- Intermittent claudication
- Decompensated heart disease
- Venous thrombosis
- All CV diseases
- Concomitant diseases

**Prior treatment**

- Radiation therapy
- ADT
- Orchiectomy
- Flutamide
- Estrogen therapy
- Chemotherapy

**Clinical signs/symptoms**

- Pain
- Bone pain
- Performance status
- General health status
- Global QOL
- Fatigue
- Urologic symptoms
- Days of motor deficit in MS MCC
- Ambulatory status before RT in MS MCC
- BMI

**Disease severity**

- Grade
- Stage
- Gleason score
- Visceral metastases
- Bone scan (progression, index)
- Extent of disease
- Soloway score
- Months fracture free
- History of skeletal fracture
- Risk group
- Duration of disease, time to CRPC
- Pattern of disease progression
- Malignant pleural effusion
- Tumor growth/regression constant
- Liver scan
- BM biopsy

**Laboratory data**

- PSA (Baseline, 4wk, 2m, 3m, 6m)
- PSA velocity, rate of decrease (4wk, 12wk)
- PSA nadir
- Time to PSA nadir, normalization
- PSADT (pre treatment, post nadir)
- Time to halving time
- PSA Response (decline, progression, % decrease)
- Log PSA, log PSA velocity
- Testosterone level (baseline, 3m, 6m)
- PAP (baseline, 1m, 3m, 6m, flare)
- ALP (baseline, 1m, 3m, 6m, flare)
- LDH
- CTC
- SGOT
- BAP
- PRL
- Albumin
- ESR
- CRP
- BUN
- Creatinine
- LH
- FSH
- SHBG
- CEA
- PINP
- TKL-40
- NSE
- CgA
- TPS
- Plasminogen
- Fibrinogen
- proGRP
- CTX-1
- YKL-40

**Medications**

- ASA
- Warfarin
- Analgesics
- PC-SPES

**Geographic**

- Country of residence
- Social life
- Professional life
- Sexual life
- Partner status
- Partner status

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* Number of good quality articles on overall survival

^ Number of good quality articles on outcomes other than overall survival

Factor explored in 3 or more articles with overall survival as the outcome
# Results for HTE Factors in s4PC Patient, Outcome = OS

<table>
<thead>
<tr>
<th>HTE Factor</th>
<th>No. of times factor studied, N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Significant association + OR – correlation** (Good, Fair, Poor)</td>
</tr>
<tr>
<td>Age (older age at study entry or diagnosis)</td>
<td>-2</td>
</tr>
<tr>
<td>Race (AA vs. non-AA)</td>
<td>-2</td>
</tr>
<tr>
<td>Clinical signs/symptoms</td>
<td>-28</td>
</tr>
<tr>
<td>Disease severity</td>
<td>-58</td>
</tr>
<tr>
<td>Gene/Biomarker expression</td>
<td>+2</td>
</tr>
<tr>
<td>Laboratory data***</td>
<td>-96</td>
</tr>
<tr>
<td>Prior treatment</td>
<td>+3</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>0</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>0</td>
</tr>
<tr>
<td>Social</td>
<td>+2</td>
</tr>
<tr>
<td>Social life****</td>
<td>+1</td>
</tr>
<tr>
<td>Partner status (married vs. single)</td>
<td>+1</td>
</tr>
</tbody>
</table>

*Quality of evidence based on AHRQ guidelines

** + is a positive correlation and – is a negative correlation with OS

***Elevated laboratory values

**** Social life assessed by questionnaire including a score for degree of impairment of family/social life due to the medical condition or the treatment
Lessons Learned and Challenges for HTE in Other Diseases

• Searching for HTE requires casting a wide net
  – HTE not a reliable search term
  – HTE goes by many names (some incorrect)

• Pre-specified HTE factors aid literature searches
  – Adds to the number of articles
  – BUT you don’t know what you don’t know

• HTE challenging to detect retrospectively
  – Analytic rigor of empirical analysis
  – Interpretation of study reports
Lessons Learned and Challenges for HTE in Other Diseases

• HTE likely to be a secondary not primary aim
  – Best case is pre-specified secondary aim
  – Post hoc analyses have methodological challenges

• Many studies provide subgroup analyses
  – Not all address HTE
  – Not always clear how to disentangle principal effect from interaction of {HTE factor x treatment}
Lessons Learned and Challenges for HTE in Other Diseases

• As a proportion of the vast literature in s4PC, focus on HTE is small
  – Most s4PC HTE literature on biologic v. non-biologic
  – Existing evidence leaves significant gaps regarding HTE

• Literature that addresses HTE may be less extensive for other disease states than s4PC
  – Need more studies
  – Need appropriate study designs to address HTE
Policy Implications

• Lessons Learned
  – Patients
    • Promote efficient and targeted treatments
    • Awareness of environmental factors association with cancer and its treatment may modify behavior
    • Aid in treatment decision-making
    • Aid in setting expectations of treatment effectiveness and risk of potential adverse effects
Policy Implications

• Lessons Learned

  – Healthcare Providers

  • Promotes greater awareness of HTE factors
  • Address challenges associated with providing treatment to diverse populations
  • Aid in treatment recommendation
  • Aid in communications with patients regarding treatment benefits and risks
Policy Implications

• Lessons Learned
  – Policy Makers and Payers
    • Because of HTE, FDA may perform (or require the drug sponsor to perform) subgroup analysis
      – Ideally pre-specified
      – Identify subgroups that do not benefit
      – Identify those that suffer severe adverse events
    • Payers may also demand more HTE evidence
      – Target the right patient
      – Develop disease management protocols
Related References


10. NCI. http://www.cancer.gov/cancertopics/types/prostate
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