Models to Identify and Support Clinical Trial Participants

Income Disparities in Cancer Clinical Trial Enrollment: Evidence and Models for Patient Support

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Conceptual Model: Study to Diffusion of New Cancer Therapy

Drug Development
- Laboratory discovery of anti-cancer agent
- Animal testing
- Early human testing (MTD – Phase I; anti-cancer activity, Phase II)

Comparative Testing (Phase III)
- Design
- Monitoring
- Analysis

Interpretation

Comparative Testing (Phase III)

Representativeness

Academic/Research Setting (T1)

Community Setting (T2)

Diffusion

Generalizability

Physician and Patient-Level Treatment Decisions

Public (CMS) or Private (Health Insurance Co.) Treatment Coverage Decisions
**Representativeness**

- **Representativeness**: How the characteristics of clinical trial cohort compare to treatment population

- Only 2-3% of adult cancer patients participate in NCI-sponsored clinical trials*

* Murthy, JAMA, 2004; Tejeda, JNCI, 2006
Income Disparities in Clinical Trials: BACKGROUND

Conceptual & Study Design Model for Assessing Factors Influencing Clinical Trial Participation

Clinic Visit
  ↓
  Trial Available  No Trial Available
  ↓
Patient Eligible  Not Eligible
  ↓
Offered trial  Did not offer trial
  ↓
Participated  Did Not Participate

Potential differential non-participation related to SES/demo factors

Javid et al, The Oncologist, 2012
Unger et al, JCO, 2013
SES and Clinical Trial Participation

- Clinical trial participation by SES not well studied
- Absence of patient-level SES data in NCI-sponsored trials
- Despite evidence suggesting that SES may be related to both access and outcomes for a range of diseases
  - Whitehall studies (Marmot, Lancet, 1991)
SES and Clinical Trial Participation (cont’d)

- One approach: Use area-level SES estimates from zip code (matched to Census data) as partial surrogate for patient-specific SES

- Useful for statistical adjustment but represents different construct
  - Factors pertaining to neighborhood or regional environment

- Inadequate for examining relationship between SES and trial participation
Web Survey Study Design

- Need to reach beyond the usual consortium-sponsored cooperative group data

- Web-based survey study
  - Collaboration with NexCura®, provider of online treatment decision tools for cancer patients
  - Linked to major cancer oriented websites (i.e. American Cancer Society)
Study Design (cont’d)

- Adult patients with new diagnosis of breast, lung, colorectal, or prostate cancer
- Conducted over 4 year period (2007-2011)
- Collected patient level income and education
  - Also age, sex, race, distance to clinic, comorbidity status
Geographic Distribution of Survey Respondents

5,499 patients surveyed
(overall rate = 9.0%)

<table>
<thead>
<tr>
<th>Region</th>
<th>% in Survey Sample</th>
<th>% in U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>West</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>Midwest</td>
<td>21%</td>
<td>22%</td>
</tr>
<tr>
<td>Northeast</td>
<td>19%</td>
<td>18%</td>
</tr>
<tr>
<td>South</td>
<td>35%</td>
<td>37%</td>
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Regression Results for Income

- Income only SES or demographic factor significantly associated with clinical trial participation in multivariable regression
  - Income <$50,000/year, 27% less likely to participate (p=.01)

<table>
<thead>
<tr>
<th>Cutpoint</th>
<th>% Less Likely</th>
<th>P-value</th>
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<tbody>
<tr>
<td>$20,000</td>
<td>44%</td>
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<td>$50,000</td>
<td>27%</td>
<td>.01</td>
</tr>
<tr>
<td>$100,000</td>
<td>21%</td>
<td>.04</td>
</tr>
</tbody>
</table>
Forest Plot

Association of Income and Clinical Trial Participation by Each Study Factor: Association is Independent of Subgroup Membership

<table>
<thead>
<tr>
<th>Factor</th>
<th>Category</th>
<th>Sample Size</th>
<th>OR</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;65 years</td>
<td>954</td>
<td>0.79</td>
<td>0.06</td>
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<tr>
<td></td>
<td>&lt;65 years</td>
<td>3625</td>
<td>0.42</td>
<td>0.005</td>
</tr>
<tr>
<td>Sex</td>
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<td>0.69</td>
<td>0.005</td>
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<tr>
<td></td>
<td>Male</td>
<td>1747</td>
<td>0.69</td>
<td>0.13</td>
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<tr>
<td>Race</td>
<td>African American</td>
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<td>1.51</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>4454</td>
<td>0.67</td>
<td>0.0009</td>
</tr>
<tr>
<td>Education</td>
<td>&lt;College</td>
<td>1595</td>
<td>0.66</td>
<td>0.02</td>
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<tr>
<td></td>
<td>&gt;College</td>
<td>2984</td>
<td>0.74</td>
<td>0.06</td>
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<td>Comorbidities</td>
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<td>2711</td>
<td>0.76</td>
<td>0.07</td>
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<td></td>
<td>&gt;2</td>
<td>1868</td>
<td>0.65</td>
<td>0.03</td>
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<td>Distance To Clinic</td>
<td>&lt;13 miles</td>
<td>3334</td>
<td>0.73</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>&gt;13 miles</td>
<td>1196</td>
<td>0.59</td>
<td>0.01</td>
</tr>
<tr>
<td>OVERALL</td>
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<td>4579</td>
<td>0.69</td>
<td>0.001</td>
</tr>
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</table>

Odds of Clinical Trial Participation for Lower Income Patients: Lower Odds ← Higher Odds
Concern about How to Pay

- Assessed patient attitudes toward CTs

- Lower income patients much more concerned about how to pay for CT treatment ($p < .0001$)
  - 53% for <$20k/year vs. 24% for >$100k/year
Main Findings

- In multivariate model, lower-income patients much less likely to participate in a clinical trial
- Lower-income patients much more concerned about how to pay for CT participation
Potential Reasons for Income Finding

*Is there an insurance effect?*

- Consistent finding in subset of patients $\geq$65 years covered by Medicare

*Is there an impact of state laws mandating coverage of clinical trials?*

- No evidence that association of income and clinical trial participation differed by type of state (i.e. with vs. without insurance mandate)
Clinical Trial Costs

Are CTs more expensive?

- NCI: Patient care costs for clinical trials are “not appreciably higher” than for non-trial care

- Costs of Cancer Treatment Study (RAND)*
  - Non-significant 6.5% increase for trial patients
  - No increase is prescription out-of-pocket costs**

- But patient cost concerns much higher among lower-income patients

* Goldman, JAMA, 2003
** Kilgore, Contemp Clin Trials, 2008
Clinical Trial Costs (cont’d)

- Concerns about how to pay for treatment in general may interact with anxiety about trial participation to produce a differential impact on lower income patients.

- Lower income patients may be more sensitive to:
  - Direct costs (co-pays and co-insurance)
  - Indirect costs (time off work for extra clinic visits)

- **Policy Implications**: Find ways to help lower-income patients with direct and indirect costs of clinical trial participation.
Cover Co-Pays/Co-Insurance

- Cover excess costs for clinical trials for all patients
- Even in an insured population, co-pays and co-insurance deters clinical trial participation*

* Unger, JCO, 2006
Payments to Participants

- Pay individuals to participate in NCI-sponsored clinical trials

- In 1900, military surgeon Walter Reed paid subjects $100 in gold to participate in his yellow fever experiments*

- In U.S., the practice of paying patients for trial participation is widespread, but also contentious, highly variable, and lacking in general guidance**

* Lederer, 1995
** Grady, 2005
Payments to Participants (cont’d)

- Careful calibration of size of monetary incentive to avoid “undue influence” per US Common Rule for Protection of Human Subjects
- Concern is that a payment inducement might alter a subject’s assessment of potential risks or impair their judgment.
- Little evidence that payment inducements do or do not do this
- See Grady, “Payment of clinical research subjects” (J Clin Invest, 2005)
Some worry that payments to patients would produce a disproportionate burden of research on lower income patients.

In contrast, “offering no money… also has the potential to skew the subject pool and contravene distributive justice” *

Series of trade-offs and an ethical debate: What are trade-offs between benefit to society, benefit to individual, and potential harms to individuals.

* Grady, 2005
Payment Models*

- **Market Model:** Market determines how much to pay in order to recruit the number and type of subjects needed in a given time frame

  Based on traditional libertarian theory (supply and demand)

  Higher payments when:
  - Low intrinsic incentive for participation
  - Need to accrue quickly
  - Small eligible patient pool

  Lower payments when high intrinsic incentive for participation

* Dickert & Grady, NEJM, 1999
Payment Models (cont’d)

- **Wage-payment model:** Payment offered to compensate for time, contribution to study, and effort/discomfort

- Based on egalitarian perspective that participants performing similar functions should be paid similarly

- Amounts to payment based on a standardized hourly wage (i.e. “unskilled” labor rate)

- Completion bonuses to encourage compliance

_Dickert & Grady, NEJM, 1999_
Payment Models (cont’d)

- **Reimbursement model:** Payment offered to reimburse participants for actual expenses

- Based on egalitarian perspective and the idea that research participation should be revenue neutral for participants (i.e. no financial sacrifice or gain)

- One approach: Reimbursement for travel, meals, parking, etc.

- Alternative: Reimbursement as well for time away from work

Dickert & Grady, NEJM, 1999
Payment Model of Choice*

**Wage-payment model**

- Greatly reduces the common worry about undue influence

- Standardization among studies will:
  - Contain the cost of research
  - More egalitarian: Does not favor only well funded studies
  - Easier to determine payment
  - Avoids risk-adjusted payments, so encourages risk minimization

- Adheres to “principle of justice”: Treats people serving similar functions similarly

*Dickert & Grady, NEJM, 1999*
Direct to Consumer Advertising

- Direct-to-consumer-advertising (DTCA) targeted in particular to lower income patients
- DTCA has increased in recent years*
- Awareness of oncology-related DTCA is high among cancer patients**

* Donohue, NEJM, 2007
** Abel, JCO, 2009
Conclusion

Why is income representativeness important?
Conceptual Model: Study to Diffusion of New Cancer Therapy

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Conclusion

Why is income representativeness important?

- **Feasibility**
  - Better participation of lower income patients could speed the conduct of clinical trials

- **Interpretation**
  - Better participation of lower income patients would better assure the applicability of clinical trial results to all income levels

- **Fairness**
  - Clinical trials offer the newest treatments, so crucial that all income groups have **equal access** to trials
Thank You