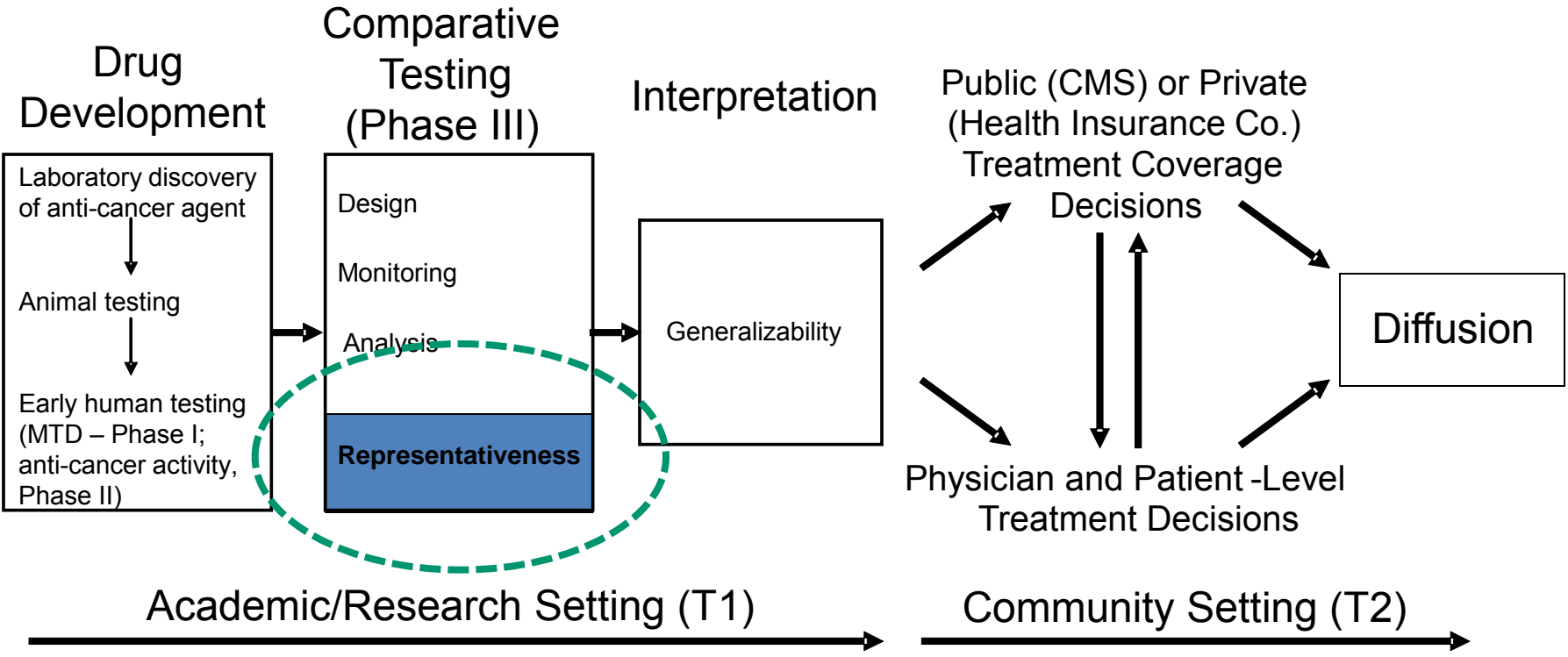# Models to Identify and Support Clinical Trial Participants

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

Joseph Unger, Ph.D.

SWOG Statistical Center
Fred Hutchinson Cancer Research Center
Seattle, WA

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

Representativeness

Interpretation

Generalizability

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

Physician and Patient -Level Treatment Decisions

Diffusion

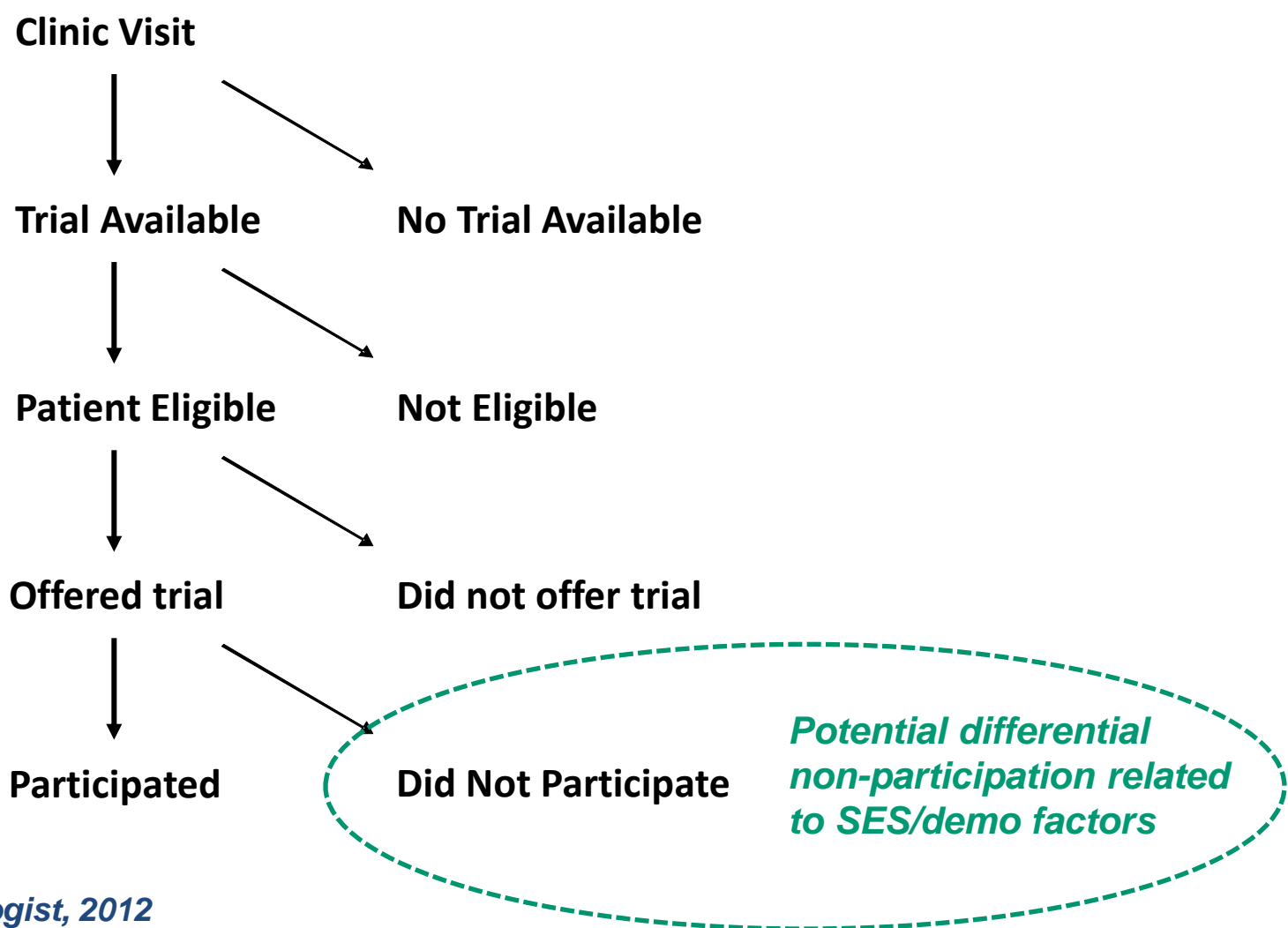Academic/Research Setting (T1)

Community Setting (T2)

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

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)
  - Link & Phelan, *Social Conditions as Fundamental Causes of Disease*, 1995

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
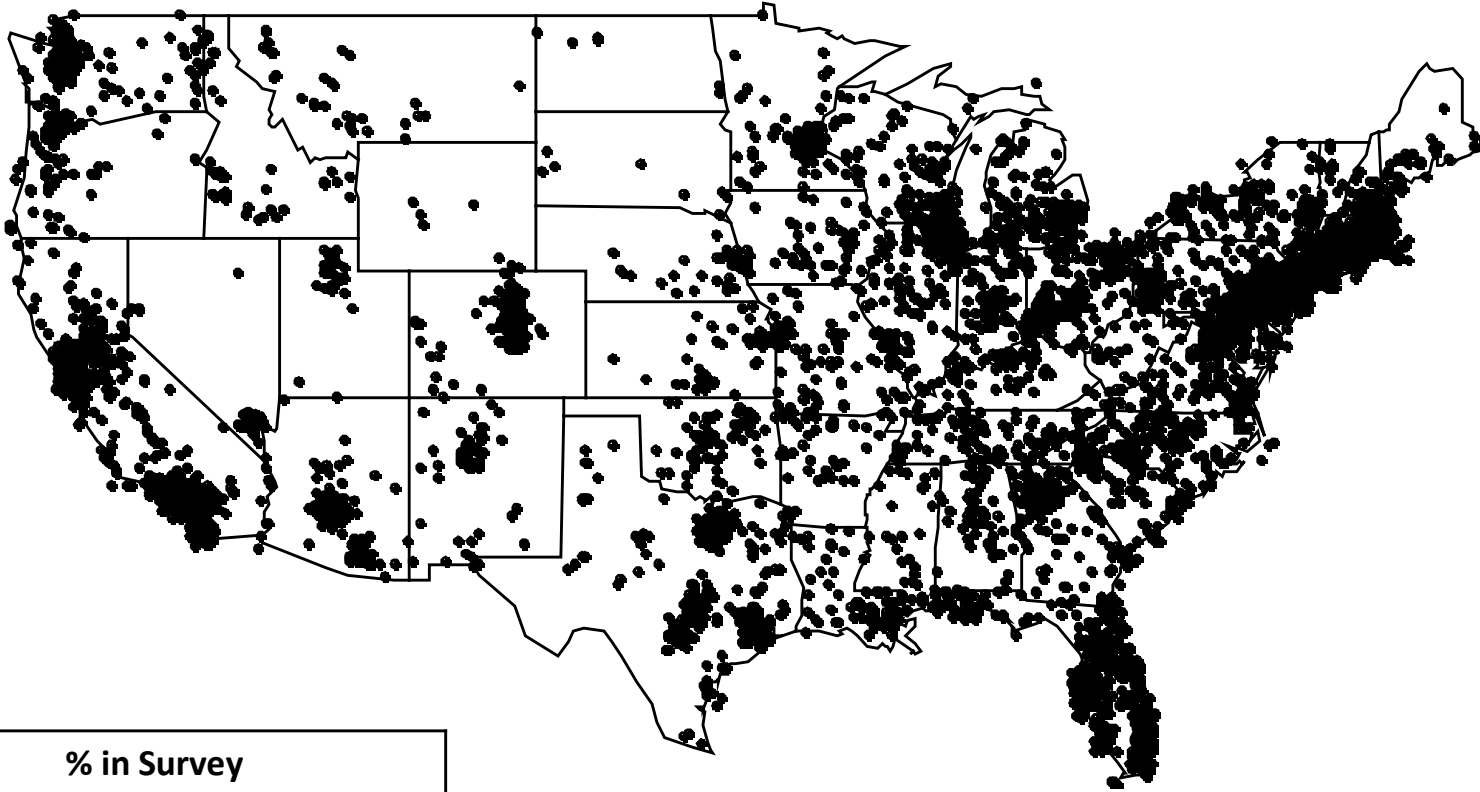
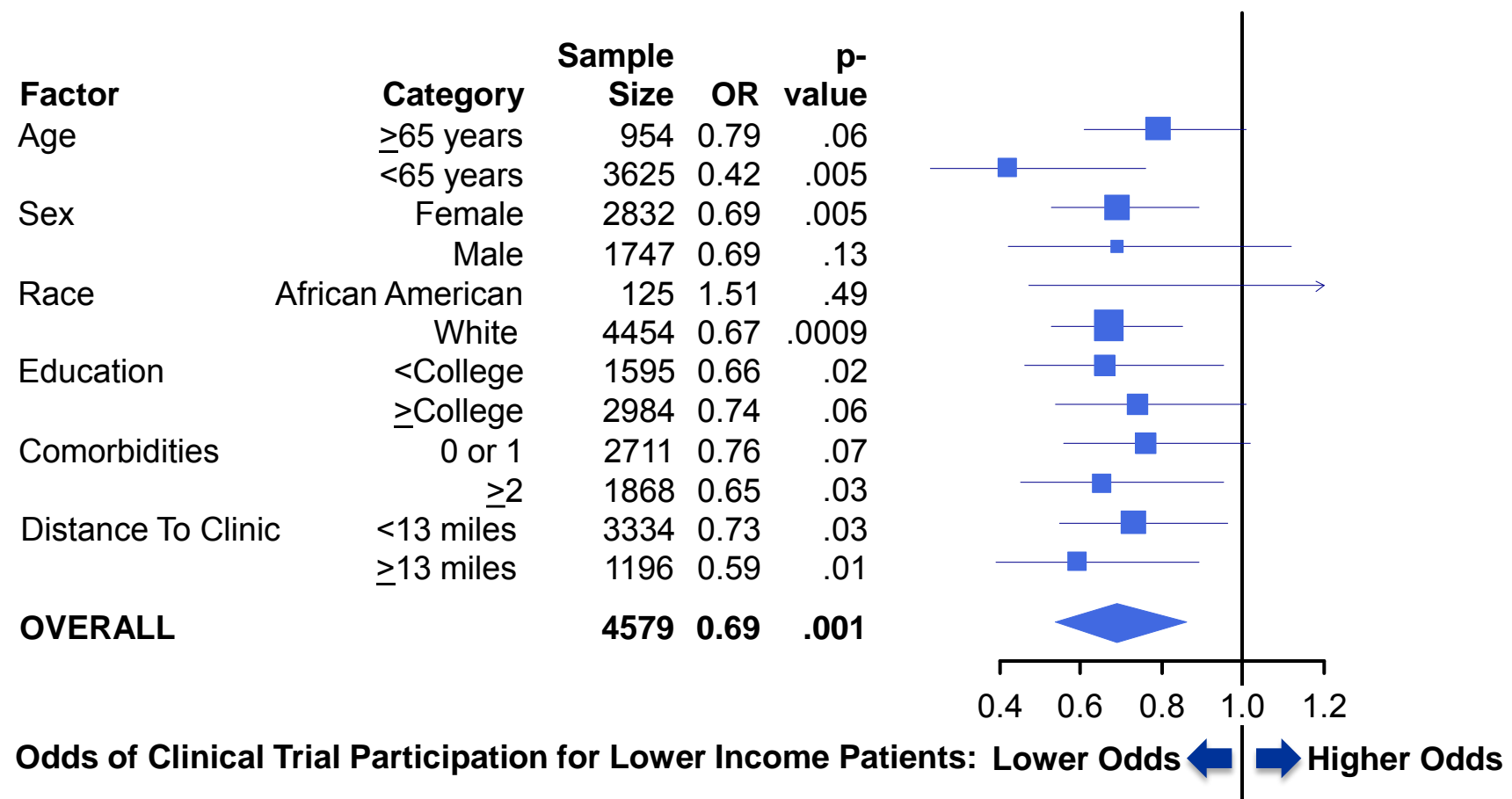| Region	% in Survey Sample	% in U.S.
West	25%	23%
Midwest	21%	22%
Northeast	19%	18%
South	35%	37%

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

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)

| Cutpoint	% Less Likely	P-value
$20,000	44%	.02
$35,000	27%	.04
$50,000	27%	.01
$100,000	21%	.04

Forest Plot

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

Factor	Category	Sample Size	OR	p-value	
Age	>65 years	954	0.79	.06	
	<65 years	3625	0.42	.005	
Sex	Female	2832	0.69	.005	
	Male	1747	0.69	.13	
Race	African American	125	1.51	.49	
	White	4454	0.67	.0009	
Education	<College	1595	0.66	.02	
	>College	2984	0.74	.06	
Comorbidities	0 or 1	2711	0.76	.07	
	>2	1868	0.65	.03	
Distance To Clinic	<13 miles	3334	0.73	.03	
	>13 miles	1196	0.59	.01	
OVERALL		**4579**	**0.69**	**.001**	

0.4 0.6 0.8 1.0 1.2

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
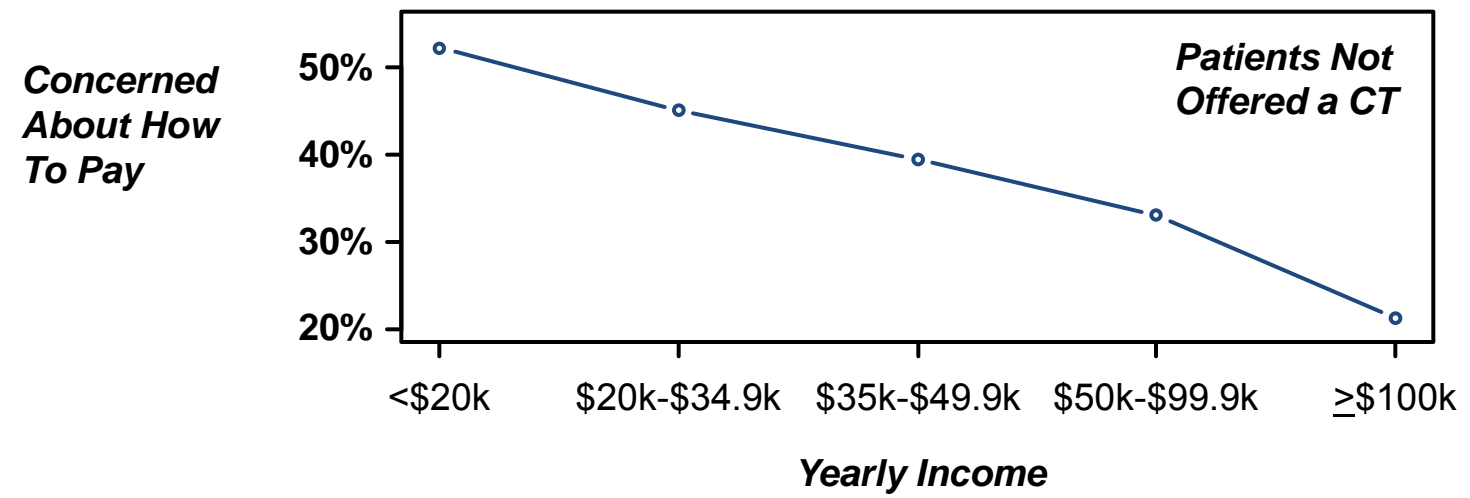
Main Findings

- 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 <u>all</u> patients

- Even in an insured population, co-pays and co-insurance deters clinical trial participation*

2000: Year of Medicare Policy Change
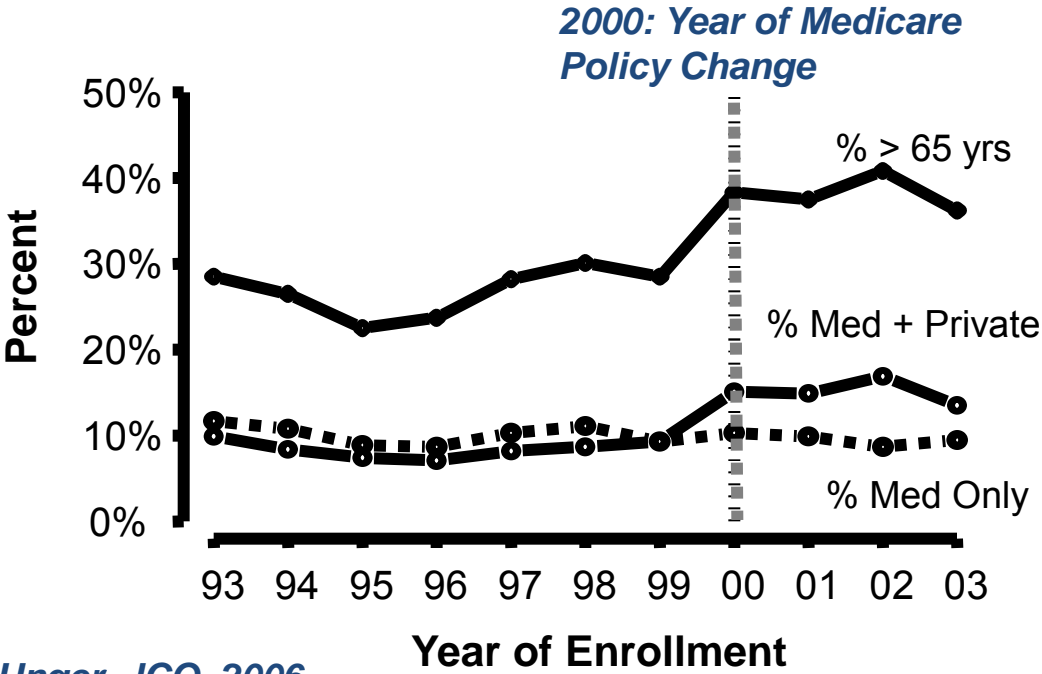
	'93-'99	'00-'03	P-value
% ≥ 65 yrs	26.5%	38.1%	<.0001
% Med+Private	8.3%	15.2%	<.0001
% Med Only	9.9%	9.7%	.50

% > 65 yrs

% Med + Private

% Med Only

Year of Enrollment

* 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)

Policy Prescriptions (cont'd)

- 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 tradeoffs and an ethical debate: What are tradeoffs 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)

- **<u>Reimbursement model:</u>** 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

Direct to Consumer Advertising

- Direct-to-consumer-advertising (DTCA) targeted in particular to lower income patients

- DTCA has increased in recent years*

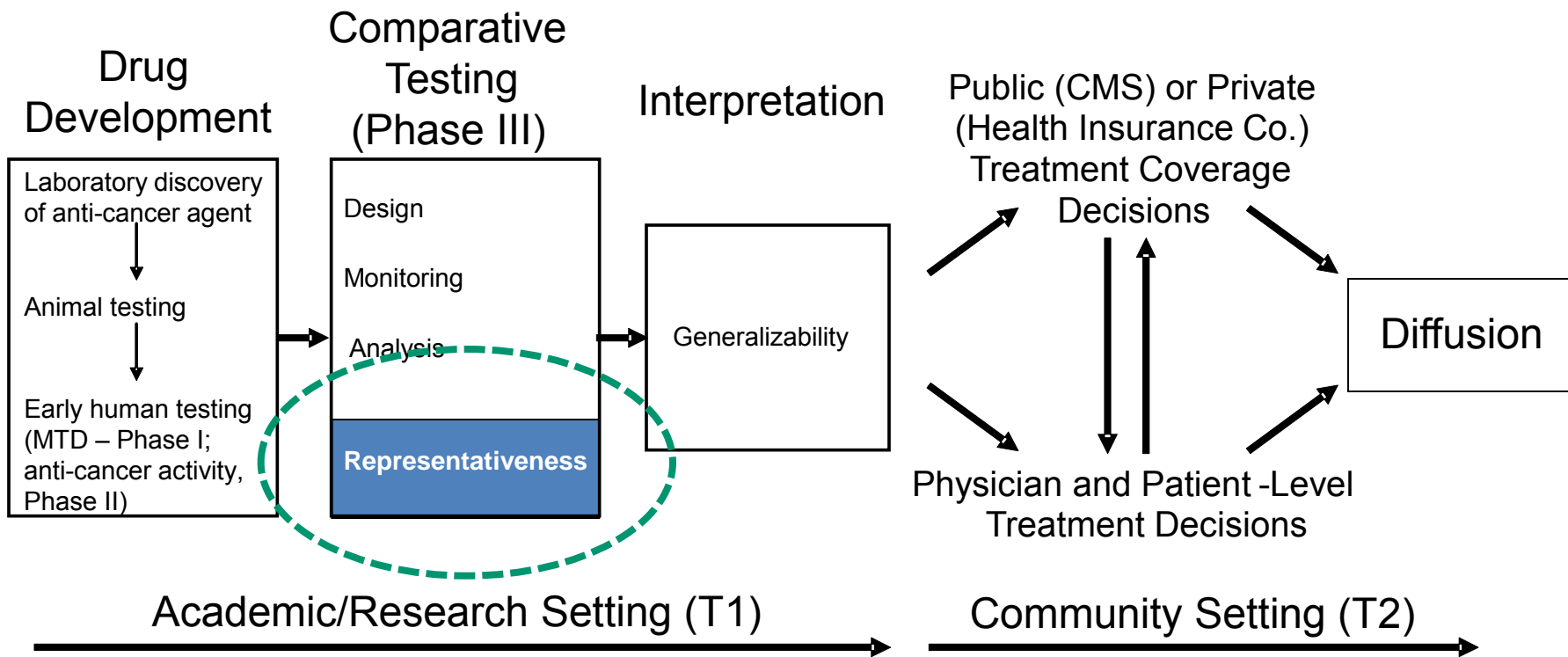- Awareness of oncology-related DTCA is high among cancer patients**

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

Conclusion

Why is income representativeness important?

Conceptual Model: Study to Diffusion of New Cancer Therapy

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 <u>equal access</u> to trials

Thank You