Ensuring Diverse Populations in Clinical Research

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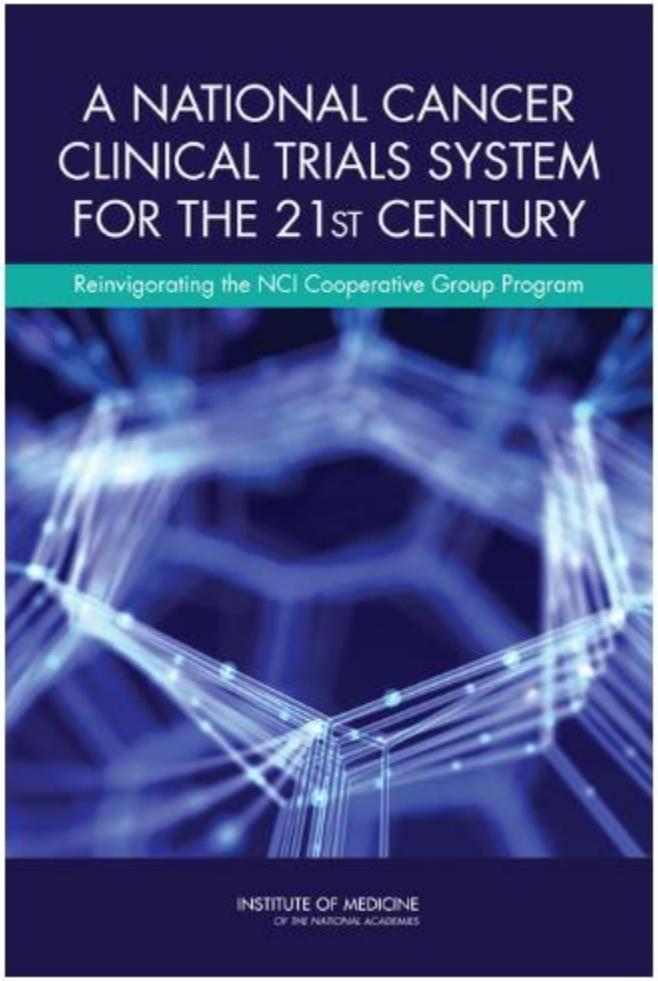
Clinical Trials as a *Research Process*



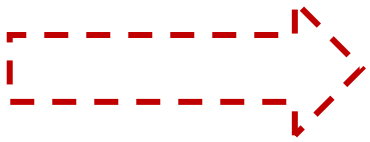
2010 IOM Report on the 50 year history of the NCI clinical trial network

- The NCTN "has played a critical role in testing new cancer therapies"
- "More than 25,000 patients and thousands of clinical investigators participate in these clinical trials annually"
- "Cooperative Group trials have diminished the impact of cancer on many fronts..."
- "Establishing the therapies that are now routinely used to treat patients with cancer"

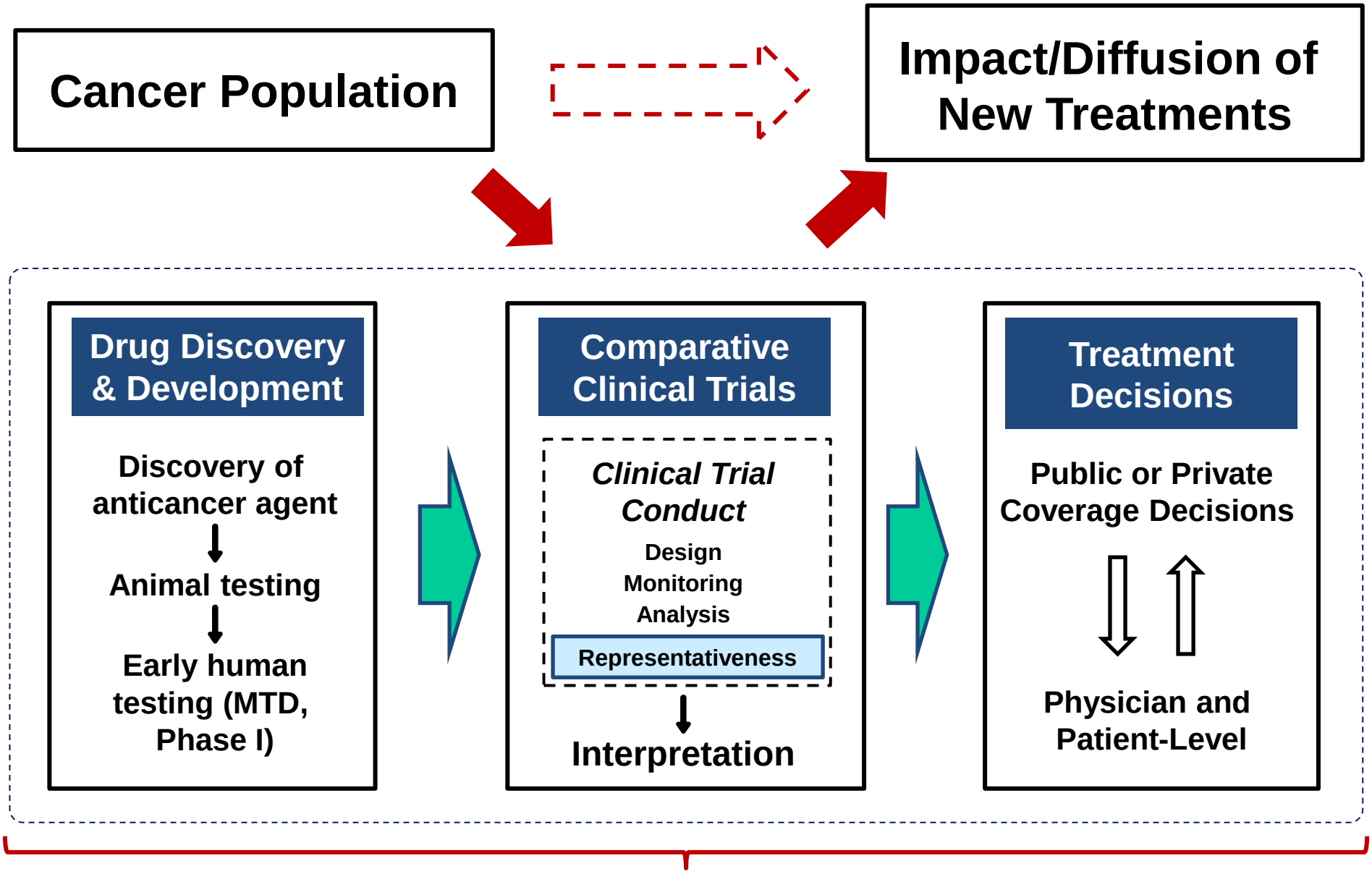
Cancer Moonshot

"The Blue Ribbon Panel also recognized that accelerating progress against a disease as complicated as cancer requires … a more efficient *research process*."

Cancer Population



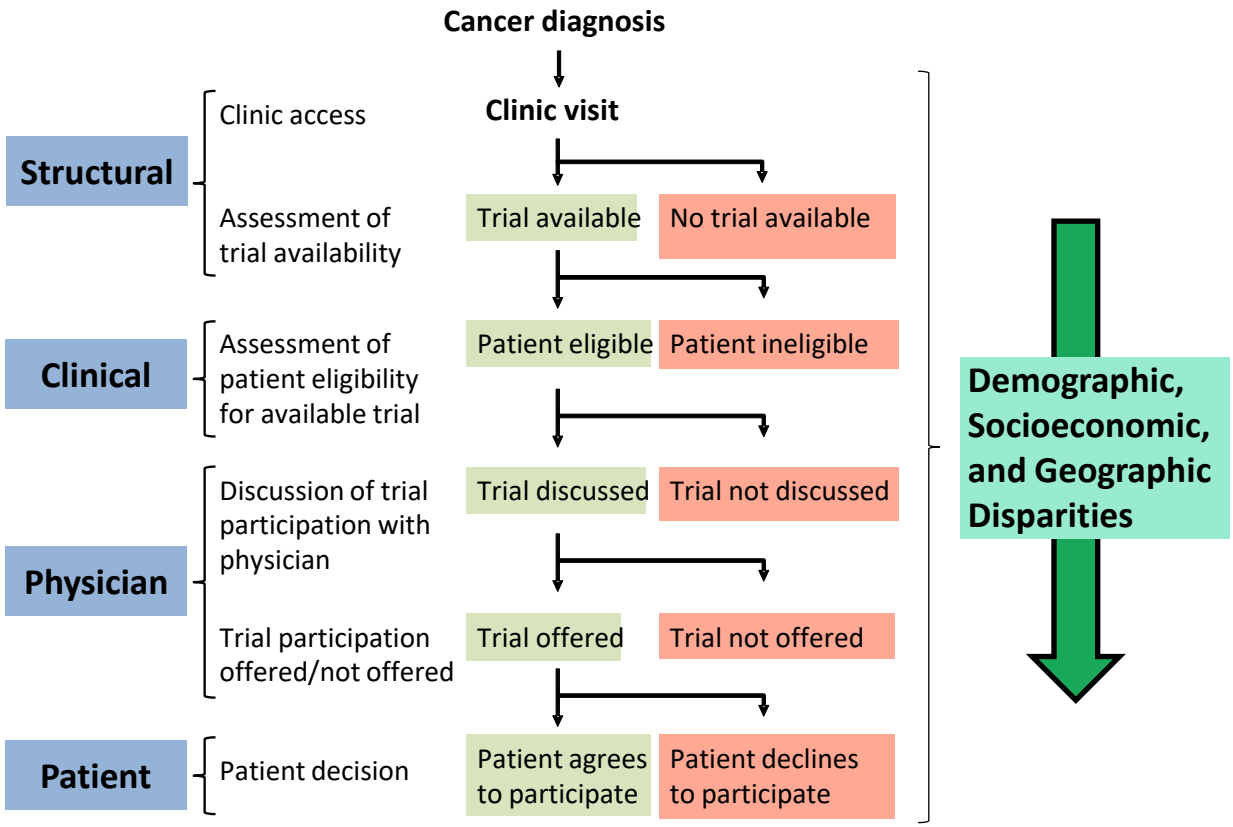
Impact/Diffusion of New Treatments


Cancer Population
Impact/Diffusion of New Treatments
Drug Discovery & Development
Discovery of anticancer agent
Animal testing
Early human testing (MTD, Phase I)
Comparative Clinical Trials
Clinical Trial Conduct
Design
Monitoring
Analysis
Representativeness
Interpretation
Treatment Decisions
Public or Private Coverage Decisions
Physician and Patient-Level
Mediating (Research) Process

Barriers to Trial Participation

- Few adult cancer patients participate in clinical trials
  - Majority express willingness to participate in trials
- Therefore large gap between willingness to participate and actual participation
- Reflecting the many barriers that patients face
- Understanding the magnitude and types of barriers patients experience is critical because entire clinical trial system hinges on patient willingness to participate
- To understand trial barriers/disparities in access as a system, useful to establish a framework

Model Framework for Trial Participation*



- Framework to understand clinical trial barriers
  - Structural
  - Clinical
  - Physician
  - Patient
- Demographic, socioeconomic, and geographic disparities

** Unger et al., JNCI, 2019*

Structural Barriers

- Clinical trial conduct requires substantial institutional commitment*
- Administrative, financial, and organizational challenges**
  - Lack of understanding/appreciation of value and conduct of trial participation
  - Cost of supporting the program and meeting program requirements
  - Managing clinic workflow changes wrt patient recruitment, physician involvement
  - Sustaining hospital leadership support
- Access to a locally available clinical trial
  - Influenced by transportation, travel costs, access to childcare

**** Minasian & Unger, JCO Oncol Pract, 2020***

***** McAlearney et al, J Healthc Manag, 2013***

Clinical Barriers

- Even if trial is available, patients may not be eligible
- Trial eligibility attempt to satisfy opposing factors*:
  - Sufficiently narrow so that treatment effect is ~constant
  - Sufficiently broad so trial results apply to a meaningful population of patients

*** Green et al, Clinical Trials in Oncology, 2012***

Clinical Barriers (cont'd)

- Trials often criticized for having narrow eligibility criteria, sacrificing generalizability
  - Reduces access for patients
- Dominant reason for ineligibility exclusions is presence of comorbid conditions
  - Average number of eligibility criteria: 16 (60% related to comorbidity)*
- ASCO, FoCR, FDA effort to "modernize" clinical trial eligibility**

** Unger et al, JNCI, 2014*
*** Kim et al, JCO, 2017*

Physician Barriers

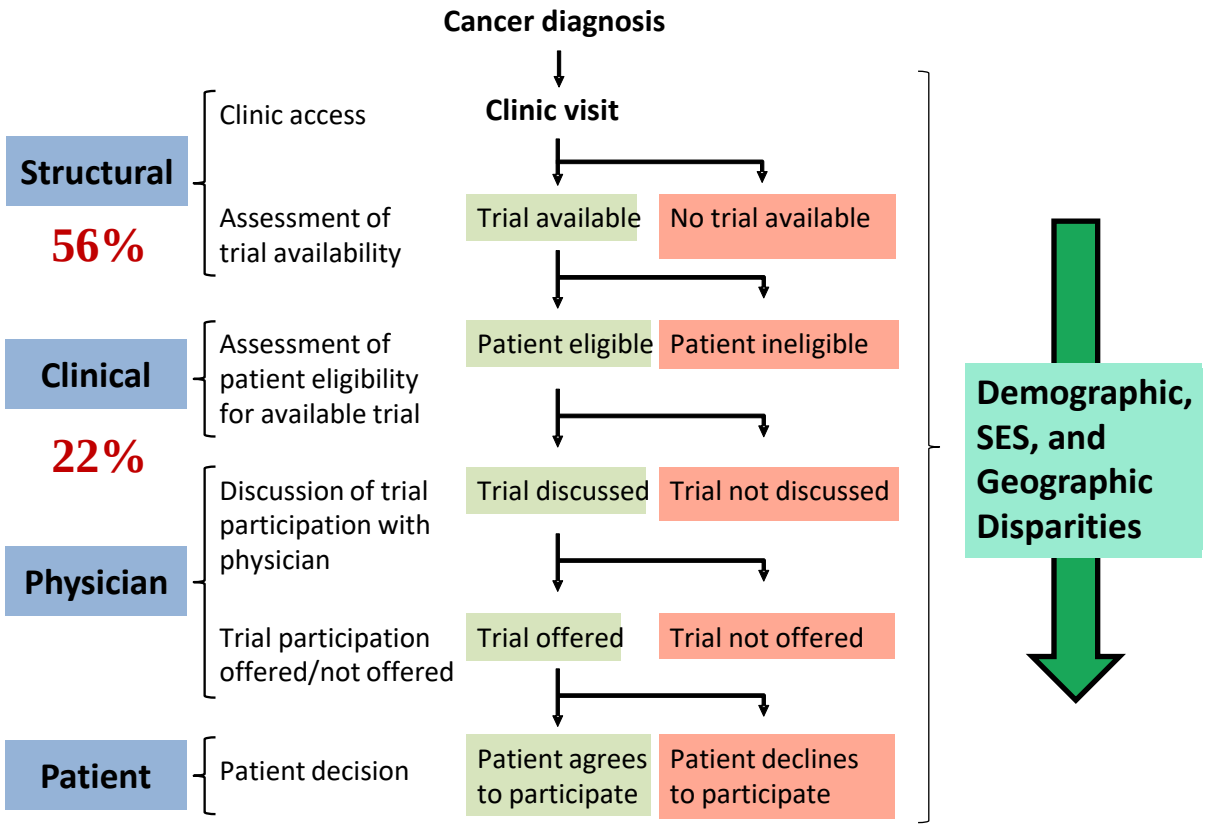
- In their role guiding patients care, physicians may prefer a specific treatment
- Trial participation can interfere with physician-patient relationship
- Practical considerations:
  - Time and effort can be burdensome
  - Reimbursement

Patient Barriers

- Ultimate decision rests with the patient
- Altruism is one motivation
- A primary concern is finding the best treatment for their disease*
- Patients report being uneasy/fearful about trial participation/experimentation
  - Residual mistrust of medical science due to past abuses

**** Unger et al, JCO, 2013***

Model Framework for Trial Participation*



- Most patients have limited opportunity to even consider trial participation as a treatment option
- **Key question**: What is the rate of trial participation among patients who are actually offered an opportunity to participate?

** Unger et al., JNCI, 2019*

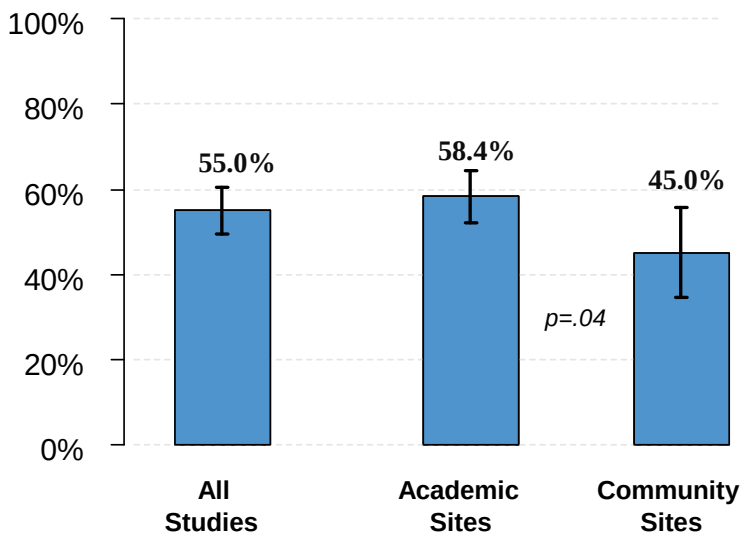
Systematic Review and Meta Analysis

- Studies from 1/1/2000-1/1/2020 (20 years in total) examining clinical trial participation in the U.S.
- Studies specified number of patients offered a trial and number enrolled
- PubMed, Web of Science, and Ovid Medline databases

Search Terms		
"cancer"	and	"clinical trial accrual", or "clinical trial enrollment", or "enrollment in clinical trials", or "clinical trial enrollment barriers", or "patient participation in clinical trials", or "patient decision making", or "participation factors"

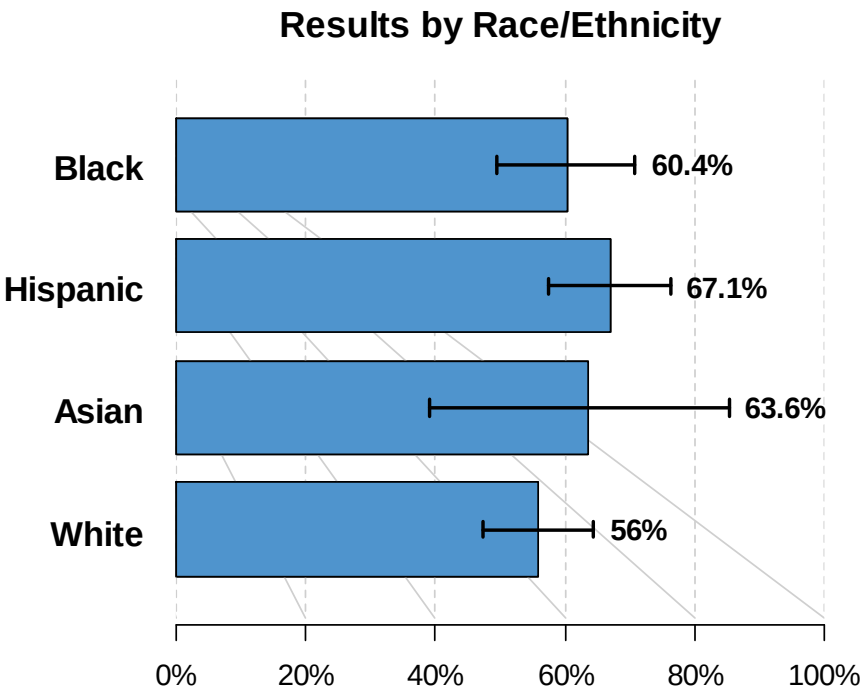
** Unger et al., JNCI, 2020*

Results



- Overall rate of agreement to participate if offered a trial was **55.0%**
- Participation rates were significantly higher at academic centers (58.4%) versus community centers (45.0%, p=.04)

Results



- No evidence that rates of agreement to participate differed by race/ethnicity
- Rates trended highest for Hispanic patients (67.1%) and lowest for White patients (56.0%)

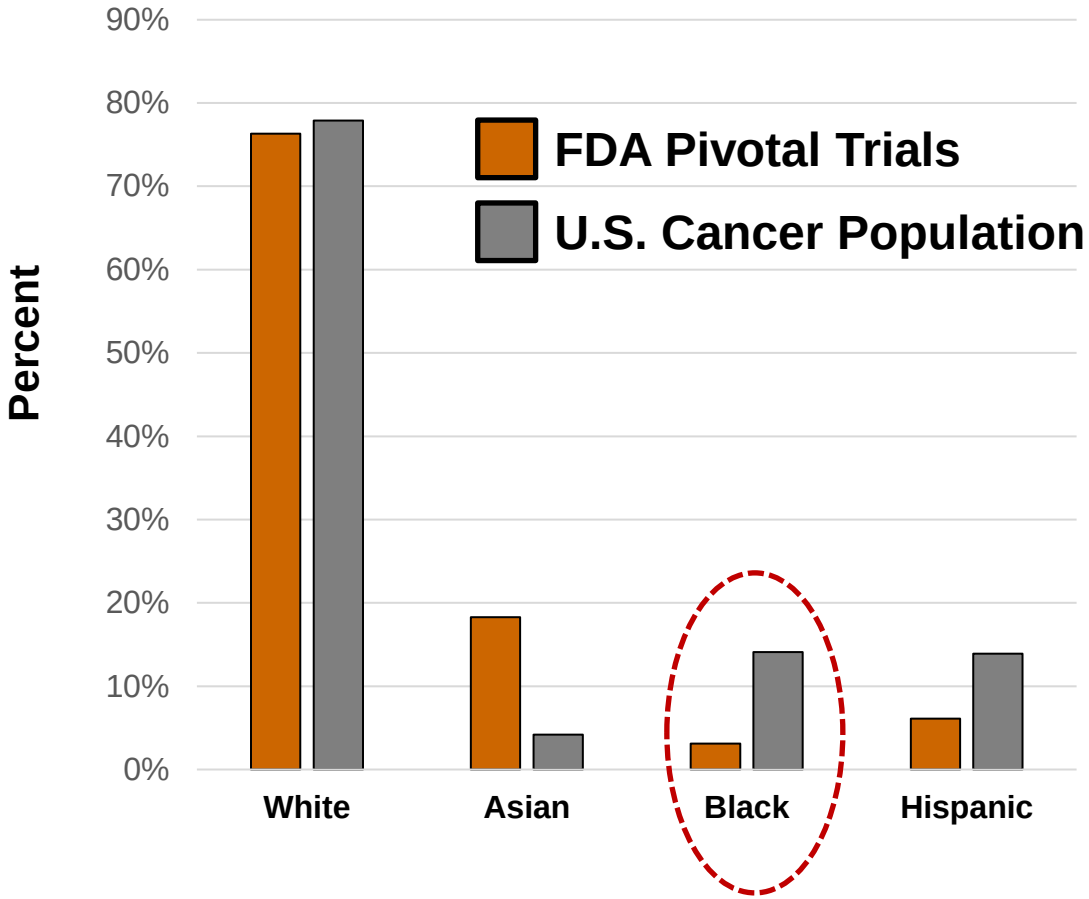
Discussion

- Results dramatically underscore the willingness of cancer patients to participate in a trial ***if one is offered***
- Findings stand in stark contrast to commonly cited statistic that only 5% of adult cancer patients participate in trials…
- … a statistic that fails to reflect the many structural and clinical hurdles that stand in the way of trial participation for patients

Discussion

- Black, Hispanic, and Asian patients enrolled at rates at least as high as White patients
- Suggests that observed racial/ethnic disparities in trial participation manifest earlier in treatment decision-making
- Finding indicates that a good way to improve enrollment of minority patients is to ensure they are invited to participate

Percent of patients in FDA pivotal cancer clinical treatment trials



*Disparity of Race Reporting and Representation in Clinical Trials Leading to Cancer Drug Approvals From 2008 to 2018**

- Examined proportional race representation in trials supporting FDA oncology drug approvals
- 2008-2018
- 230 trials with 112,293 patients
- Black patients comprised only **3.1%** of all enrollments compared to 14.1% in the U.S. cancer population for the represented cancers

** Loree et al, JAMA Oncology, 2019*

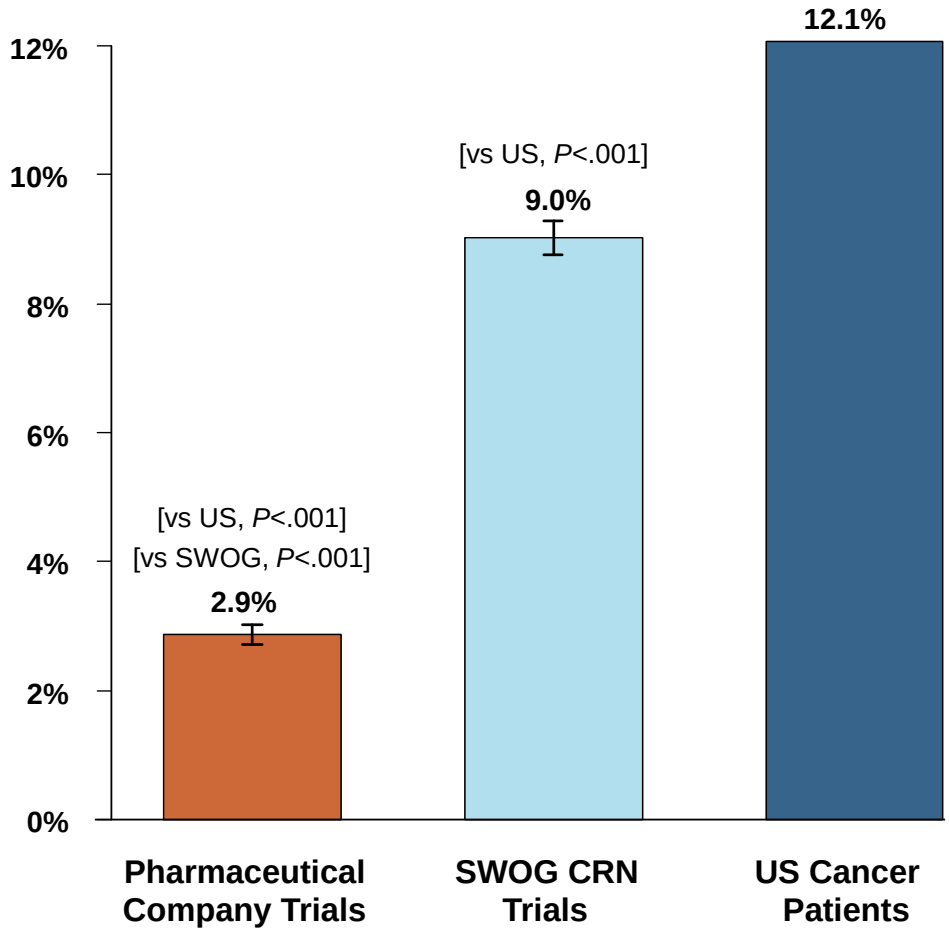
Discussion

- The FDA, in partnership with the American Association for Cancer Research, has examined ways to improve representation of Black patients in FDA registration trials*
- Focus was on trials for myeloma, given the high prevalence of myeloma in the Black population
- But models for improving minority participation could be extended to other cancer settings

**** Gormley et al, Blood Ca Discovery, 2021***

Race/Ethnicity Disparities in Enrollment

Proportion of Black patients by research setting and for the US cancer population



Representativeness of Black Patients in Cancer Clinical Trials Sponsored by the National Cancer Institute Compared With Pharmaceutical Companies

- Data from:
  - 85 pharmaceutical company-sponsored trials (n= 46,313)
  - 273 SWOG trials (n-47,512)
- 15 separate cancers
- Average proportional enrollment of Black patients in pharma was much less (2.9%) than SWOG (9.0%) and U.S. cancer patients (12.1%)

- … Why the vast difference between FDA pivotal trials and NCTN trials of SWOG?

**** Unger et al., JNCI CS, 2020***

Pharma vs. NCI

- Trials supporting new drug applications to the FDA are primarily sponsored by pharmaceutical companies
  - Trial contributions by sponsor in Loree et al:
    - Academia and/or academia and industry, 3.0%
    - Industry, 97.0%
- In contrast, the NCI's NCTN groups examine more expansive research questions to serve the diverse needs of cancer patients*
  - Comparisons of different treatment combinations
  - Treatment modalities
  - Combinations of multiple approved drugs in other cancers

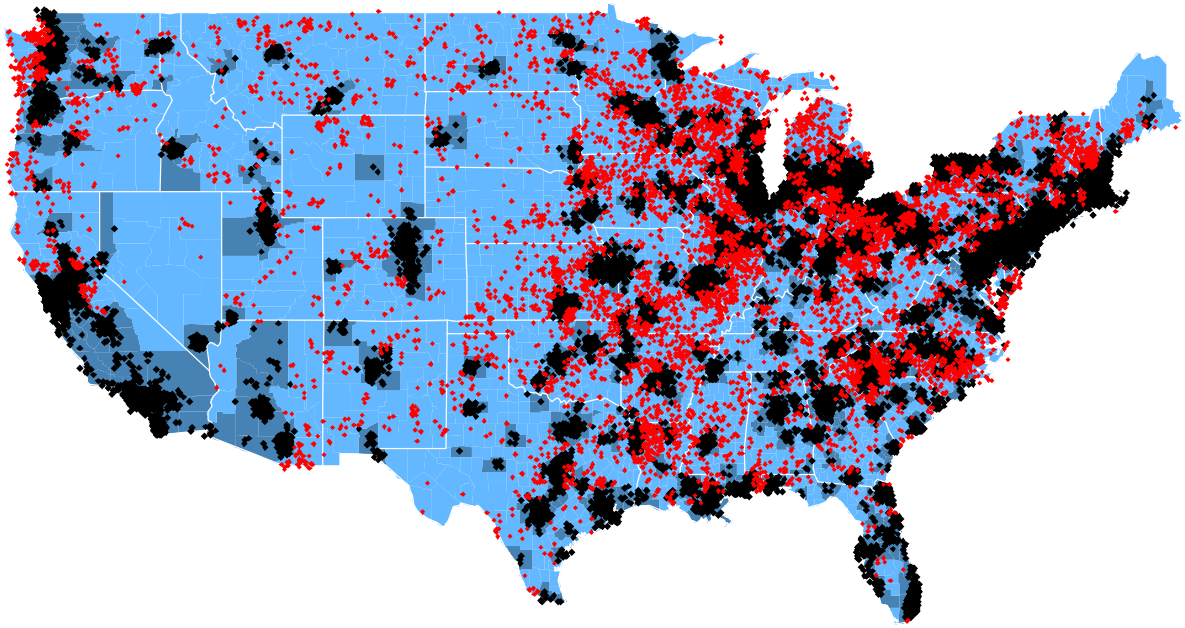
**** Institute of Medicine, 2010***

Role of the NCI's Community Oncology Research Program (NCORP)

- The NCORP brings clinical trials into community hospitals and clinics including in rural areas
- This represents the community-level outreach that can provide the kind of quality cancer care that is needed
- Represents a model for improving enrollment of diverse populations

Geographic Disparities in Enrollment

RESULTS: SWOG Enrollments from 1986-2012 by Rural vs Urban County of Origin (n=36,995)



	% of Total		% Rural	
	SWOG	US	SWOG	US
West	23%	23%	13%	11%
Midwest	39%	21%	23%	22%
South	24%	37%	23%	24%
Northeast	14%	18%	14%	16%

*Geographic Distribution and Survival Outcomes for Rural Patients With Cancer Treated in Clinical Trials**

- N=36,995 examined from 1986-2012
- 44 SWOG trials, 17 cohorts
- 19.4% of patients were rural (**same as** U.S. cancer population)
- Patient enrollments represented from all 50 states
- Good rural representation within each geographic region

** Unger et al., JAMA Netw Open, 2018*

Discussion

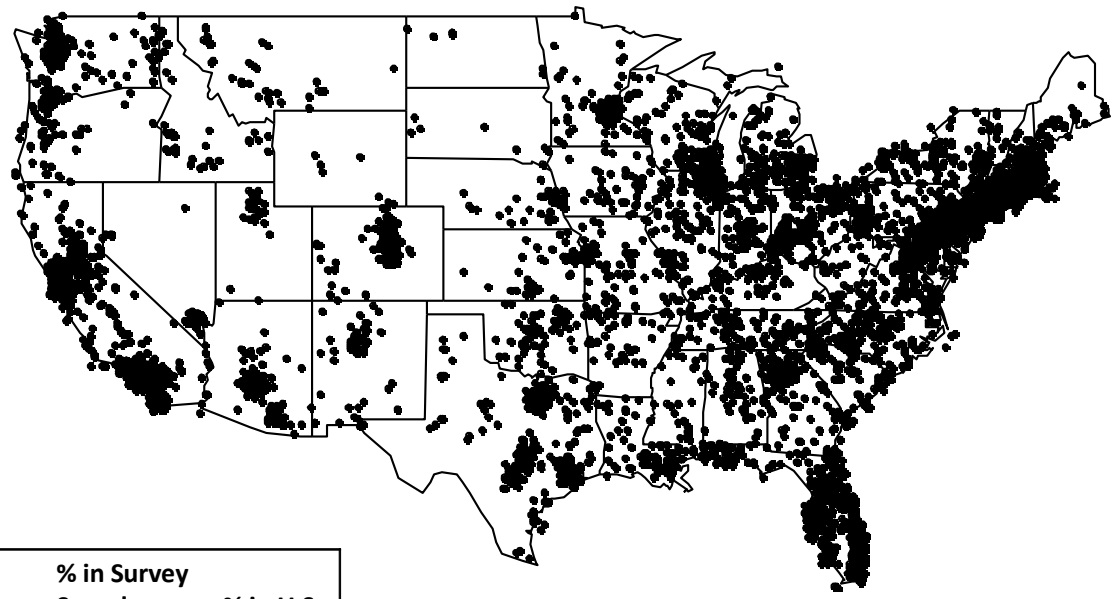
- FDA Guidance: “Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials” (April 2022)
  - Sponsors must “submit plans that help ensure the adequate participation of relevant and underrepresented populations and analyses of data collected from clinically relevant subpopulations”
- The FDA also advises sponsors extend considerations of diversity in trial enrollment to include:
  - Other demographic factors (age, sex)
  - Socioeconomic status
  - Clinical factors (e.g., comorbidity status)

**** Gormley et al, Blood Ca Discovery, 2021***

Income 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

Geographic Distribution of Survey Respondents

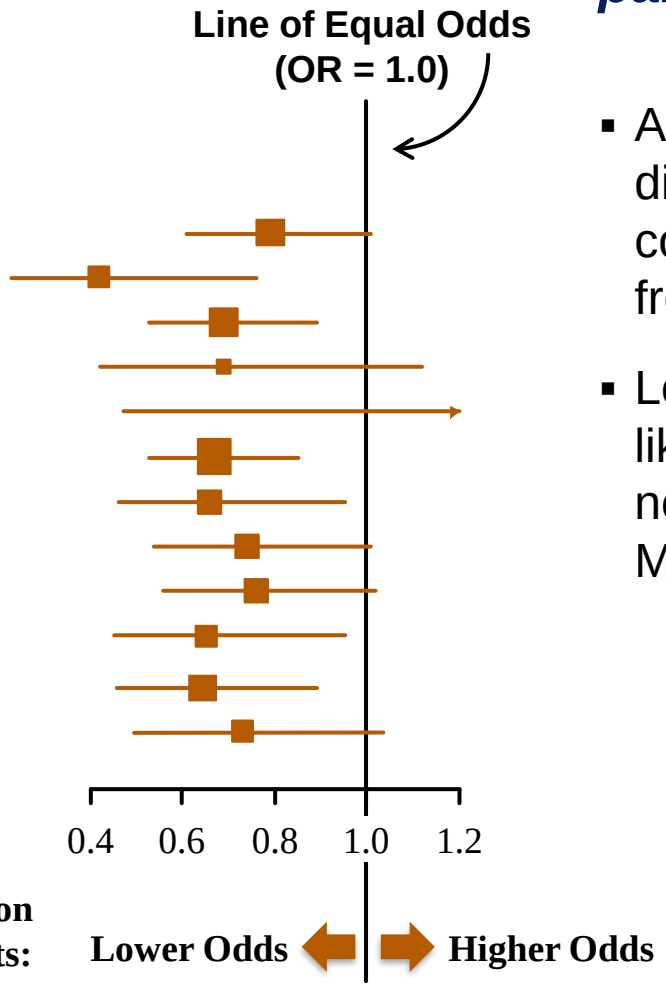


Region	% in Survey Sample	% in U.S.
West	25%	23%
Midwest	21%	22%
Northeast	19%	18%
South	35%	37%

- Web-based survey study using an online treatment decision tool
  - Linked to major cancer oriented websites (i.e. American Cancer Society)
- Patient level income, education, demographic variables, travel distance, and comorbidity status
- 5,499 patients surveyed

Forest plot of the association of income and clinical trial participation

Factor	Category	OR	p-value
Age	≥65 years	0.79	.06
	<65 years	0.42	.005
Sex	Female	0.69	.005
	Male	0.69	.13
Race	Black	1.51	.49
	White	0.67	<.001
Education	<College	0.66	.02
	≥College	0.74	.06
Comorbidities	0 or 1	0.76	.07
	≥2	0.65	.03
Distance to clinic	<13 miles	0.64	.005
	≥13 miles	0.73	.08



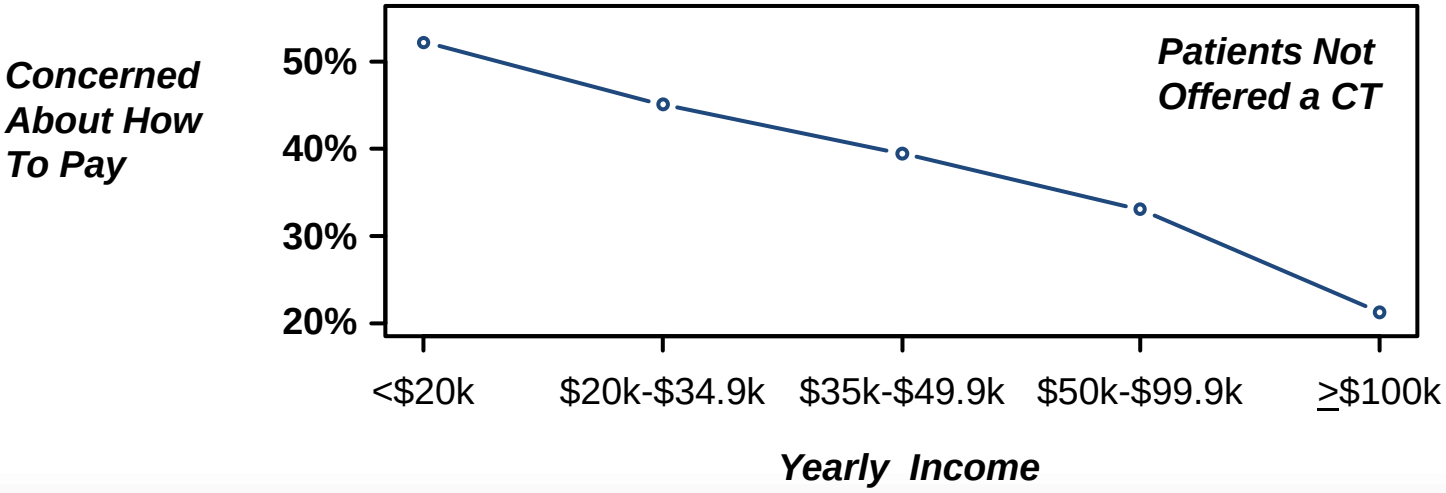
*Patient income level and cancer clinical trial participation**

- Adult patients with new diagnosis of breast, lung, colorectal, or prostate cancer from 2007-2011
- Lower income patients less likely to participate across nearly all subgroups, even in Medicare covered population

** Unger et al., JCO, 2013*

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



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

Financial Hardship Among Cancer Patients

OXFORD

JNCI J Natl Cancer Inst (2022) 00(0): djab210

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Article

S1417CD: A Prospective Multicenter Cooperative Group-Led Study of Financial Hardship in Metastatic Colorectal Cancer Patients

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Abstract

Background: Financial toxicity is a growing problem in oncology, but no prior studies have prospectively measured the financial impact of cancer treatment in a diverse national cohort of newly diagnosed cancer patients. S1417CD was the first cooperative group-led multicenter prospective cohort study to evaluate financial hardship in metastatic colorectal cancer (mCRC) patients. **Methods:** Patients aged 18 years or older within 120 days of mCRC diagnosis completed quarterly

Ned Sharpless, MD Retweeted

NCI Prevention & Early Detection
@NCIprevention

An important study from #NCORP

Ned Sharpless, MD
@NCIDirector

SWOG Cancer Research Network @SWOG · Jan 4

.@SWOG study of 380 patients w metastatic CRC: nearly 3/4 had major financial hardship in 1st year after diagnosis. Almost all had #HealthInsurance. Hardship associated w drop in social functioning and QoL. In @JNCI_Now w editorial. #FinancialToxicity doi.org/10.1093/jnci/d...

Veena Shankaran, MD
SWOG S1417CD Study Chair

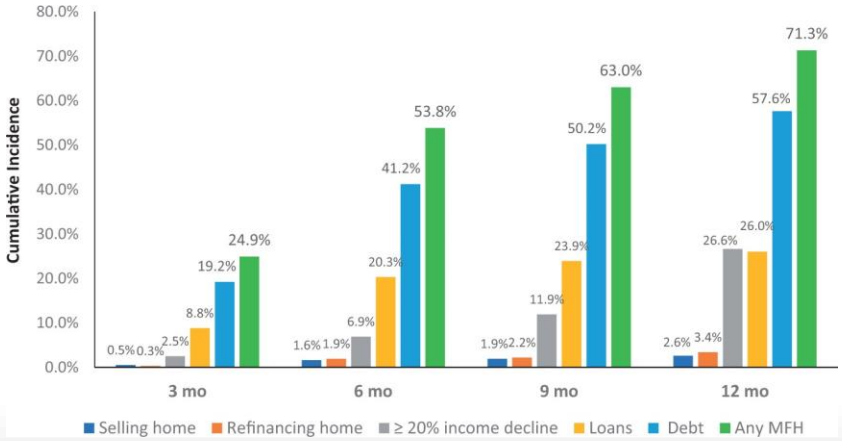
SWOG CANCER RESEARCH NETWORK

Results of S1417CD

Despite having health insurance, almost three-fourths of patients with metastatic colorectal cancer experienced financial hardship within the first year after diagnosis

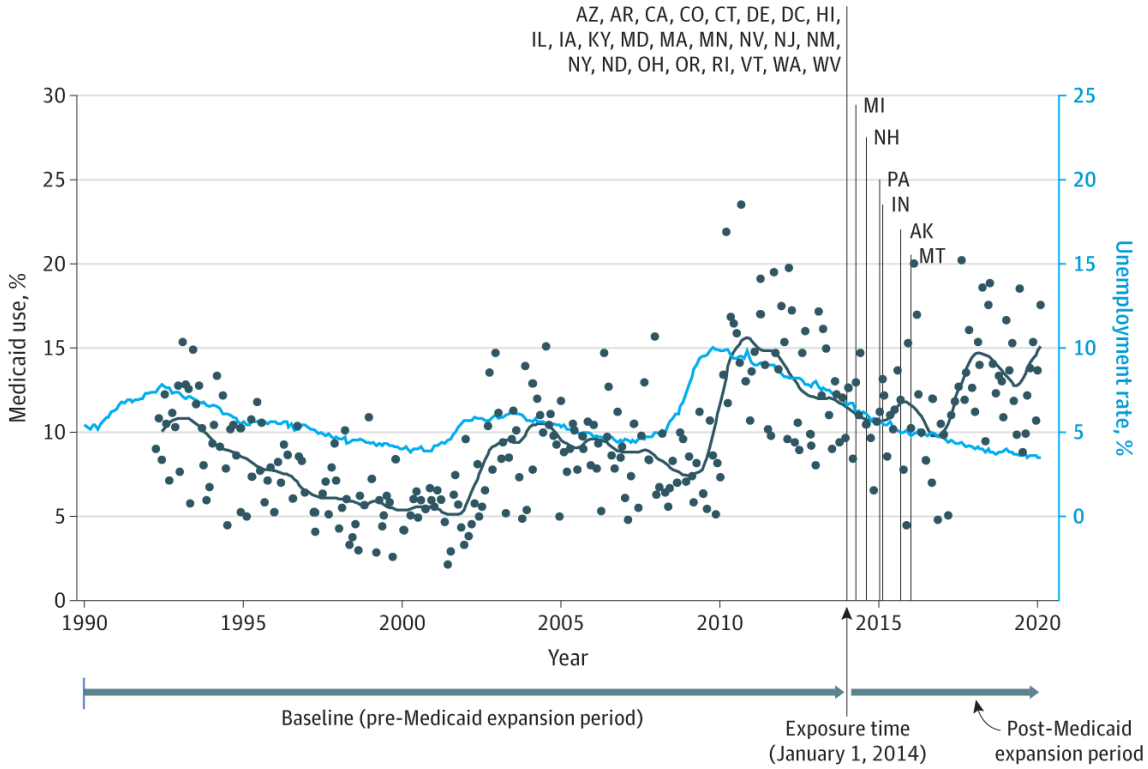
Key Findings

- Among 380 patients with mCRC almost all (98%) insured
- Cumulative incidence of Major Financial Hardship at 1 year was **71.3%** (95% CI, 65.7%-76.1%)
- No differences by age, race, or marital status



Income Disparities in Trial Participation

Figure: Proportion of Patients Using Medicaid Insurance and US Unemployment Rate Before and After Implementation of Patient Protection and Affordable Care Act (ACA) Medicaid Expansion



Dark blue = proportion of patients using Medicaid
Light blue = monthly national unemployment rate

*Medicaid Expansion of the Patient Protection and Affordable Care Act and Participation of Patients With Medicaid in Cancer Clinical Trials**

- What is the association between the ACA Medicaid expansion and access to cancer clinical trials?
- Among 51,751 patients <65 yrs (1992-2020), ACA Medicaid expansion associated with 19% annual increase in odds of using Medicaid insurance for trial participation
- Association greatest in states implementing the expansion

** Unger et al., JAMA Onc, 2023*

Implications

- Sociodemographic composition of clinical trial cohorts can be highly variable over time and should be recognized to be, in part, organic manifestations of extant socioeconomic conditions
- Targeted policies can act to counterbalance the potential adverse consequences of societal influences on trial composition

Fred Hutch trials: How diverse are they?

- Study proposal: “Diverse representation and barriers to participation in cancer clinical trials at the Fred Hutchinson Cancer Research Center” (PI: Unger)*
- Design:
  - Prospectively follow patients with breast, prostate, and lymphoma through their clinical trial decision making process
  - Identify barriers to participation for key demographic, socioeconomic, and geographic groups of patients
- *Co-Investigators: Riha Vaidya, PhD; Hanna Linden, MD; Evan Yu, MD; Ajay Gopal, MD; Wendy Law, PhD*

* Support from the **Andy Hill Care Fund**

Conclusions

- Participation in clinical trials often represents an opportunity to receive the newest treatments
- For patients, such a system should be free of the structural and patient barriers that have been routinely identified
- Such a system would also build greater confidence that trial findings are widely applicable, encouraging more rapid uptake of new treatments in practice

How to ensure diverse populations in clinical research?

- Ensure that trials are accessible to patients where they receive their care
- Offer them the opportunity to participate in a trial
- Provide the resources and support to do so