

Cancer Control in the 21st Century Observations on Disparities in Health and Clinical Trials

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JOHNS HOPKINS
M E D I C I N E

Disclosures

- Employment:
 - Johns Hopkins University
- Consulting
 - National Institutes of Health
 - Centers for Disease Control
 - Department of Defense
 - Lyell Immunopharma
 - PDS Biotech
 - Agilent
 - Incyte
 - Grail
- Book Royalties - MacMillan

An Emotional Conflict of Interest (a philosophy)

- The “Scientific Method” is a legitimate search for truth and reality
- It is asking a question in a rigorous thought-out process
- It is also realizing that your assumption of truth or reality may change as additional information is elicited
- Science evolves overtime!!!

An Emotional Conflict of Interest (a philosophy)

I was taught from an early age that one be reflective, one:

- Should label things:
 - What you know
 - What you do not know
 - What you believe
- Question all things, but question what you know more so than anything else.

These are good rules in the assessment of healthcare.

Disparities in Health

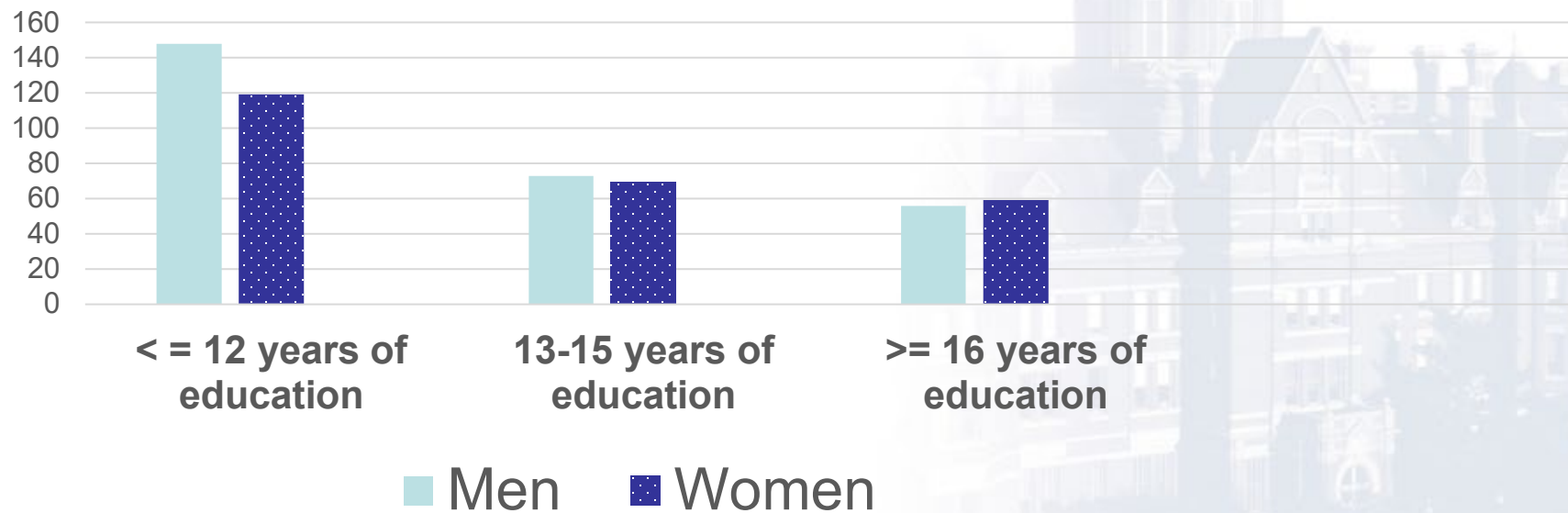
- The concept that some populations (however defined) do worse than others.
- Populations can be defined or categorized by:
 - Race
 - Ethnicity and Culture
 - Area of geographic origin
 - Socioeconomic Status

Disparities in Health

- The concept that some populations (however defined) do worse than others.
- The measure can be:
 - Incidence
 - Mortality
 - Survival
 - Quality of life

Rate per 100,000 population

Cancer Death Rate by Educational Attainment



National Center for Health Statistics, 2017

Disparities in Health

- We need to approach this issue in a scientific fashion (logically and rationally).
- We must focus on what we can change and not on what we cannot change.
- We must carefully define social and logistical issues versus biologic issues.

Health Disparities

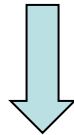
Cancer disparities are often due to differences in:

- Access to quality care.
- Utilization of available care.

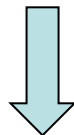
Health Disparities

Care Includes:

Prevention / Risk Reduction



Screening / Diagnosis



Treatment

Breast Cancer Quality of Care

- Receipt of “minimum expect care” in SEER-Medicare data 1992-1999
- Blacks less likely 0.67 95% CI (.59-.76)
- Hispanics less likely 0.77 95% CI (.66-.90)
 - Haggstrom, Cancer 2005

Disparities in Treatment

Studies suggest that disparities in treatment may be due to:

- Cultural differences in acceptance of therapy.
- Disparities in comorbid diseases making aggressive therapy inappropriate.
- Lack of convenient access to therapy.
- Racism and SES discrimination.

Health Disparities

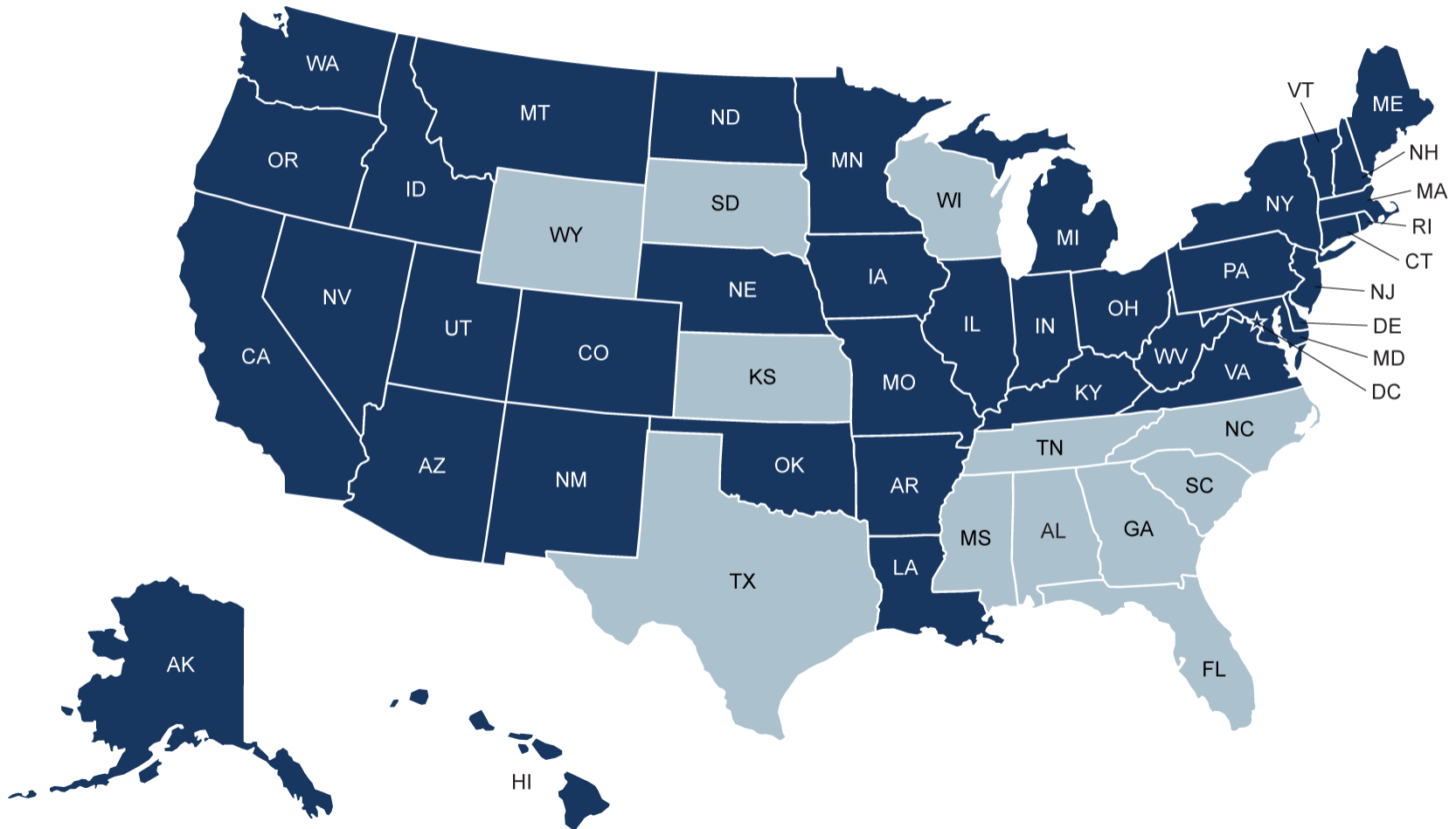
- The Medicaid Expansion Provision adopted in some states has allowed residents aged 18 to 65 to obtain Medicaid Coverage
- For adults, the ACA (Obamacare) is associated with a reduction in disparities in:
 - stage at diagnosis and
 - in outcomes.

Diessner, Weigel, Murugan et al JAMA Netewroik Open, 2020

Malik, Alexander, Khan, Scharschmidt. Clin Orthop Relat Res. 2021

State Medicaid Expansion Decisions, March 2022

Not expanding (12 states) Expanding (38 states and DC)



The Affordable Care Act

- There are decreases in disparities in those states.
- There are increases in state by state disparities

Malik, Alexander, Khan, Scharschmidt. Clin Orthop Relat Res. 2021

Medicaid

- Does it encourage worse outcomes?
 - Patients are treated in a system with lower reimbursement.
 - Patients do not get the supports needed to receive the care.
 - Patients are often treated in a segregated system (FQHC's, county and safety net hospitals).

Key Point

The Most Important Question in Cancer Control

How can we provide adequate high-quality care (to include preventive services) to populations that so often do not receive it?

- Unnecessary care consumes limited resources and interferes with abilities to provide necessary care.
- The provision of unnecessary care consumes resources and thus is a cause of health disparities.

PRINCIPLES OF CLINICAL TRIALS

March 27, 2023

18

Efficacy Trials

Does the intervention work?

It is tested in relatively ideal circumstances:

- Highly resourced clinical setting
- Well trained healthcare providers
- Motivated patients/often healthier
- Adherence to protocol is audited

Most NIH funded clinical trials are efficacy studies!

Effectiveness Trials

How well does the intervention work in the real world!

- Patients more likely to have comorbid diseases
 - Hospitals and clinics of varying resources
 - Physicians and staff may be less familiar with the intervention
 - Administration of therapy is not audited
-
- Effectiveness studies are rare!

Outcomes of a Clinical Intervention

- **Generalizability** to a population requires the study mirror the population.
 - Clinical setting
 - Socioeconomics
 - Genetics
- **Applicability** is specific to an individual or to people with specific genetics/targets

Clinical Trials

- Much discussion of diversity in clinical trials
- Much (not all) of this discussion is political and not scientific
 - NIH Revitalization of 1993 calls for valid subset analysis among the races and ethnicities in phase 3 trials
 - The authors of the law seem to not realize that subset analysis are not statistically significant by nature.

Kaluzny, Warnecke et al. Cancer Invest. 1995

Clinical Trial Concepts

- Subset analysis should be avoided as they can be very wrong!
- Subset analysis often require over-sampling. An ethical issue, putting the minorities at greater risk.

FACT

NIH interpretation:

When congress said “valid subset analysis” they did not mean statistically significant analysis.

Key Point

Clinical trials participation (especially treatment trials) should be encouraged as especially participation in NCI sponsored clinical trials provides greater assurance of high-quality care.

Kaluzny, Warnecke et al. Cancer Invest. 1995

Cancer Disparities

- Are we asking the right scientific questions?
- Are we allow race to be used as a “biological categorization”
- Are we allowing certain questions to allow us to ignore other legitimate issues and questions?

Population Categorization

- Racism: the belief that different races possess distinct characteristics, abilities, or qualities, especially so as to distinguish them as inferior or superior to one another.
- Racialism: a belief that race determines human traits and capacities.

Population Categorization

Race is defined by US Office of Management and Budget (OMB) every ten years.

- Sociopolitical and not biologic by OMB definition
- Race as defining biology has been rejected by the Anthropological community as non-scientific
- Recent AMA statements condemn the biologic use of race

Population Categorization

- Race is broad
- Area of geographic origin is more specific and scientific, although still broad
- Ancestry is also more specific and scientific

Admixture complicates all

A Note on Clinical Variation

There is genetic variation among populations, but race is not the appropriate way to categorize populations, e.g.:


- Forms of G6PD deficiency is more common amongst people originating in the Mediterranean, certain areas of Africa, India and the middle east.
- The HLA-B*1502 allele is common among people living within 150 kilometers of the Thai-Burmese border. They have a Stevens-Johnson reaction to Carbamazepine (Tegretol).
- The sickle cell mutation has a prevalence among people originating in southern Greece, Southern Italy, the middle east and has a higher prevalence in Sub Saharan Africa.

My Concern

The propagation of medical misinformation

and


The resulting harm to the population



Effects of Zidovudine Therapy in Minority and Other Subpopulations With Early HIV Infection

Stephen Lagakos, PhD; Margaret A. Fischl, MD; Daniel S. Stein, MD; Lynette Lim, PhD; Paul Volberding, MD

JAMA. 1991 Nov 20;266(19):2709-12.



Racial and Ethnic Differences in Outcome in Zidovudine-Treated Patients With Advanced HIV Disease

Philippa J. Easterbrook, MD, MRCP, MPH; Jeanne C. Keruly, RN; Terri Creagh-Kirk, MS; Douglas D. Richman, MD; Richard E. Chaisson, MD; Richard D. Moore, MD, MHS; the Zidovudine Epidemiology Study Group

JAMA, November 20, 1991-Vol 266, No. 19, 2713-18

My Concern

To this day in many of America's inner city the folklore is that anti-aids drugs have been proven not to work in Blacks.

VIEWPOINT

Reconsidering the Consequences of Using Race to Estimate Kidney Function

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Clinicians estimate kidney function to guide important medical decisions across a wide range of settings, including assessing the safety of radiology studies, choosing chemotherapy, and reviewing the use of common nonprescription medications such as nonsteroidal anti-inflammatory drugs. Because direct measurement of kidney function is infeasible at the bedside, the usual approach involves using estimating equations that rely on serum creatinine. These equations assign a higher estimated glomerular filtration rate (eGFR) to patients who are identified as black. Yet in some medical and social science disciplines, a consensus has emerged that race is a social construct rather than a biological one.¹ In this Viewpoint, we argue that the use of kidney function estimating equations that include race as a variable cause problems for transparency and unduly restrict access to care in some cases, yet offer only modest benefits to precision.

Estimated GFR equations fulfill an important need for clinicians to conveniently assess kidney function and, secondarily, for public health authorities to assess the prevalence of kidney disease. These equations, such as the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) and its predecessor, the

mutations like sickle cell trait or cystic fibrosis. However, eGFR equations are distinct because they instead assert that existing organ function is different between individuals who are otherwise identical except for race. Population studies reveal only small differences in gene distributions between racial groups while showing greater variation between individuals of the same race. Meanwhile, the history of medicine offers abundant evidence that racial categories were often generated arbitrarily and at times implemented to reinforce social inequality.⁵

Racial categorization is often used in a nonstandardized way. Consider a hypothetical 50-year-old woman with a creatinine level of 2.0 mg/dL and no proteinuria. Her father self-identified as black race and her mother self-identified as white race. If this patient is admitted to the hospital, an administrator or clinician may assess the patient's skin tone or hair and label her as black in the medical record. Alternatively, the patient may be asked to identify her race. Yet she would have no way to know that her answer would affect assessments of her organ function or treatment. Furthermore, 3% of individuals in the United States identified as multiracial in the 2010 Census, whereas in Brazil and some other countries, the multiracial category exceeds one-third of the population. Decision support provides little guidance about how to calculate the patient's eGFR if she is biracial, refuses to answer the question about race, or self-identifies with a race that is different than that recorded in the medical record.

Estimated GFR equations are distinct because they assert that existing organ function is different between individuals who are identical except for race.

My Concern

The Federal mandate puts undo pressure on NIH funded researchers and especially data managers to give white patients the option of entering a clinical trial and give Blacks and other minorities the hard sell.

The National Cancer Institute Clinical Cooperative Groups

- Part of NCI Clinical trials program which enrolled over 20,000 cancer patients per year to treatment trials and cancer prevention trials.

Clinical Trials

Studies do show that in general participants in NCI sponsored clinical trials do get a better quality of care than those getting standard care in the community.

Cancer physicians who participate in clinical trials give better care to all their patients.

– Kaluzny et al JCO 1994

The Emphasis on Increasing Minority Accrual

Studies of the dynamics of clinical trial accrual show that minorities and the underserved enroll in equal proportions compared to majority patients in institutions with a history of service to minority communities.

Key is the reputation of the institution.

Tejeda et al. JNCI 1996

Cancer Distribution 1991 to 1994

| | Proportion with Cancer | Proportion in Trials |
|-----------|------------------------|----------------------|
| NHBlacks | 9.4% | 2.6% |
| Hispanics | 3.4% | 4.2% |
| NH Whites | 87.2% | 2.4% |
| Total | 100% | 2.5% |

Tejeda et al, JNCI 88, 1996

Cancer Distribution 1991 to 1994

Pediatric Patients

| | Proportion with Cancer | Proportion in Trials |
|-----------|------------------------|----------------------|
| NHBlacks | 12.4% | 63.0% |
| Hispanics | 11.9% | 71.4% |
| NH Whites | 75.7% | 72.2% |
| Total | 100% | 71.0% |

Tejeda et al, JNCI 88, 1996

Breast Cancer Adults

| | NH Blacks | Hispanics | NH Whites |
|-----------------|-----------|-----------|-----------|
| Cases in Trials | 8.6% | 2.5% | 88.9% |
| Cases in US | 7.4% | 2.7% | 89.9% |

Tejeda et al, JNCI 88, 1996

Prostate Cancer Adults

| | NH Blacks | Hispanics | NH Whites |
|-----------------|-----------|-----------|-----------|
| Cases in Trials | 14.7% | 2.5% | 82.8% |
| Cases in US | 10.3 | 2.6% | 87.1% |

Tejeda et al, JNCI 88, 1996

Leukemia Adults

| | NH Blacks | Hispanics | NH Whites |
|-----------------|-----------|-----------|-----------|
| Cases in Trials | 8.2% | 3.3% | 88.9% |
| Cases in US | 7.3% | 2.7% | 90.0% |

Tejeda et al, JNCI 88, 1996

Race/Ethnicity: NCI Clinical Trials

| Race/Ethnicity | Proportion of Cancer Population | Proportion of the Clinical Trials Population |
|------------------------|---------------------------------|--|
| White | 83.3% | 71.0% |
| African American/Black | 11.0% | 11.0% |
| API | 3.3% | 4.0% |
| NA/AN | 0.6% | 0.5% |
| Hispanic | 8.0% | 10.1% |

Of 79,832 cancer treatment patients accrued 2017 to 2019

NCI Datafile assessed August 2021

Clinical Trials Lessons

- When offered Blacks, Hispanics and Whites go onto trial in similar proportions.
- Less than 5% of cancer patients go onto clinical trial.
- Less than 10% of cancer patients are offered clinical trials.

Key Factors in Trial Participation

- The nature of the the study (Treatment vs Prevention Trials)
- The study population (pediatric versus adult)
- The reputation of the enrolling center in the community .



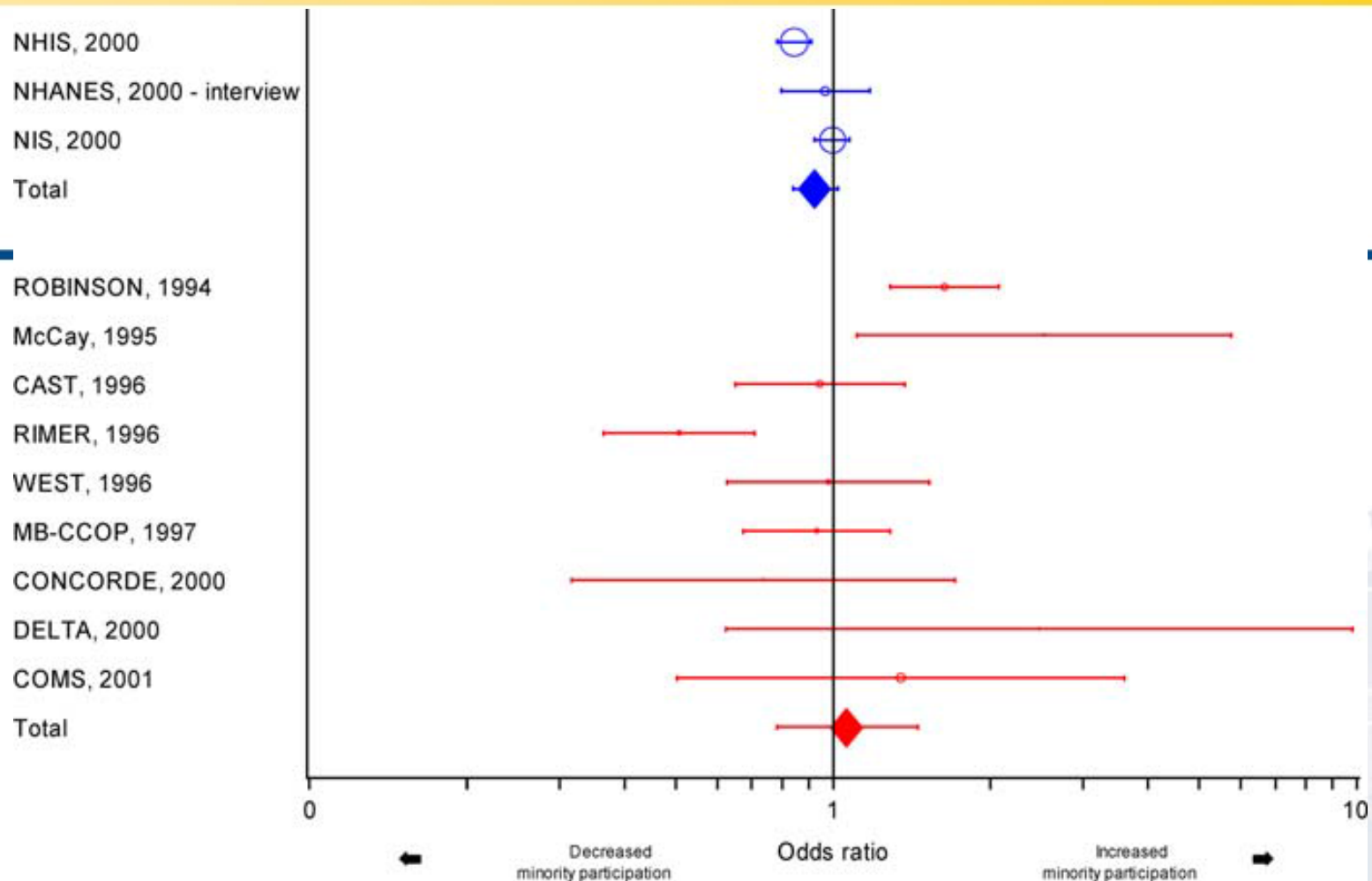
Are Racial and Ethnic Minorities Less Willing to Participate in Health Research?

David Wendler^{1*}, Raynard Kington², Jennifer Madans³, Gretchen Van Wye⁴, Heidi Christ-Schmidt⁵, Laura A. Pratt³, Otis W. Brawley⁶, Cary P. Gross⁷, Ezekiel Emanuel¹

1 Department of Clinical Bioethics, National Institutes of Health Clinical Center, National Institutes of Health, Bethesda, Maryland, United States of America, **2** Office of Behavioral and Social Sciences Research, National Institutes of Health, Bethesda, Maryland, United States of America, **3** National Center for Health Statistics, Centers for Disease Control and Prevention, Hyattsville, Maryland, United States of America, **4** Department of Epidemiology, Yale University School of Medicine, New Haven, Connecticut, United States of America, **5** Statistics Collaborative, Washington, D. C., United States of America, **6** Winship Cancer Institute, Emory University, Atlanta, Georgia, United States of America, **7** Section of General Internal Medicine, Yale University School of Medicine, New Haven, Connecticut, United States of America

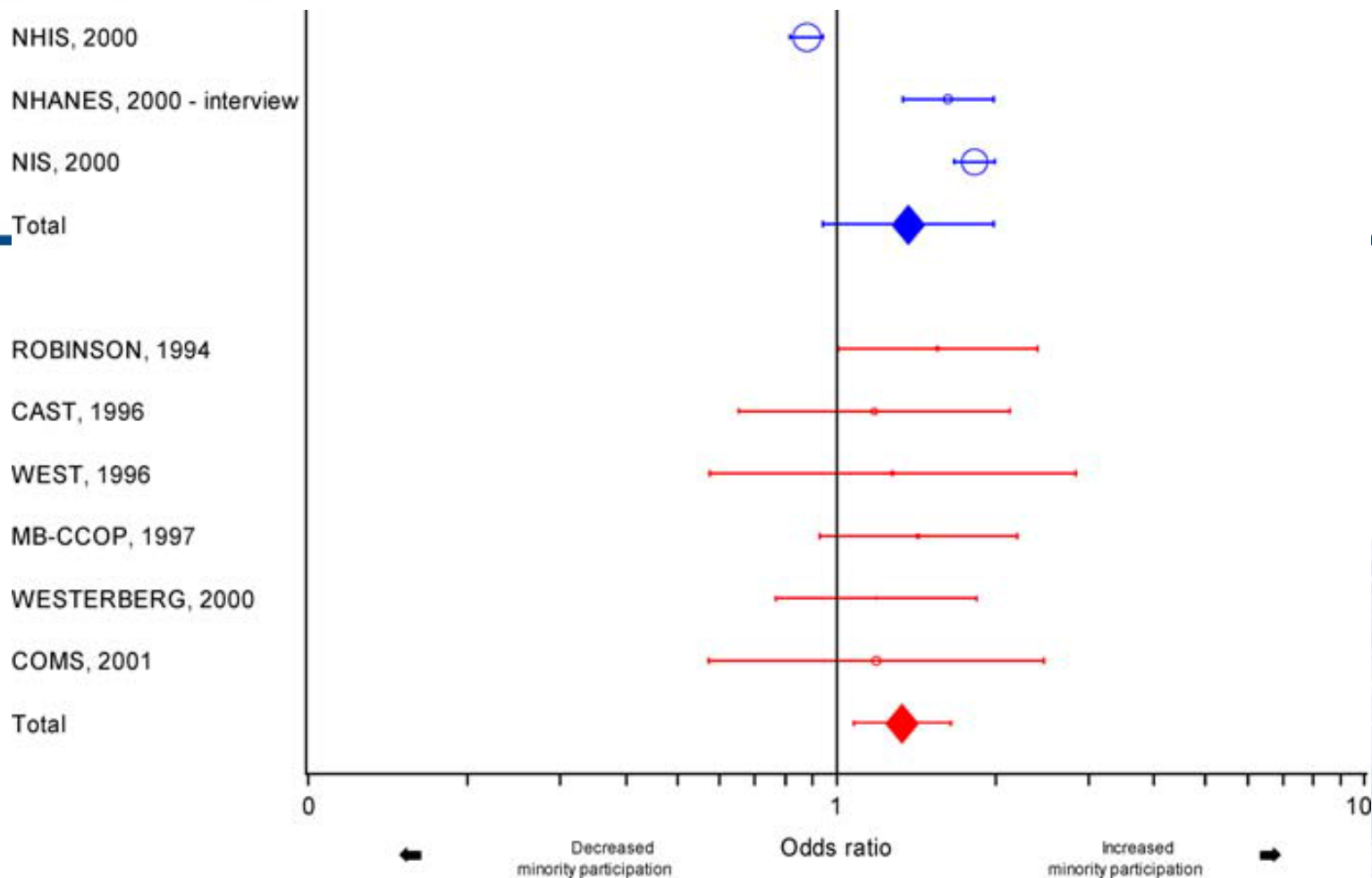
Clinical Intervention Trials

- Robinson 1994 Drug maintenance (schizophrenia)
- McKay 1995 Day hospital vs. inpatient (substance abuse)
- CAST 1996 Drug trial (cardiac arrhythmia)
- Rimer 1996 Risk counseling (breast cancer)
- WEST 1996 Estrogen treatment (cardiovascular disease)
- MBCOOP 1997 Drug trial (cancer)
- Concorde 2000 Drug trial (HIV infection)
- Delta 2000 Drug trial (HIV infection)
- Westerberg 2000 Treatment trial (alcohol abuse)
- COMS 2001 Radiation Therapy (ocular melanoma)



Comparison of African-American versus non-Hispanic White Consent Rates

Circle diameter is proportional to the sample size of the individual studies. The diamond represents the overall OR. The vertical line indicates the 95% confidence interval on the OR. Blue indicates interview and non-intervention studies; red indicates clinical intervention studies.



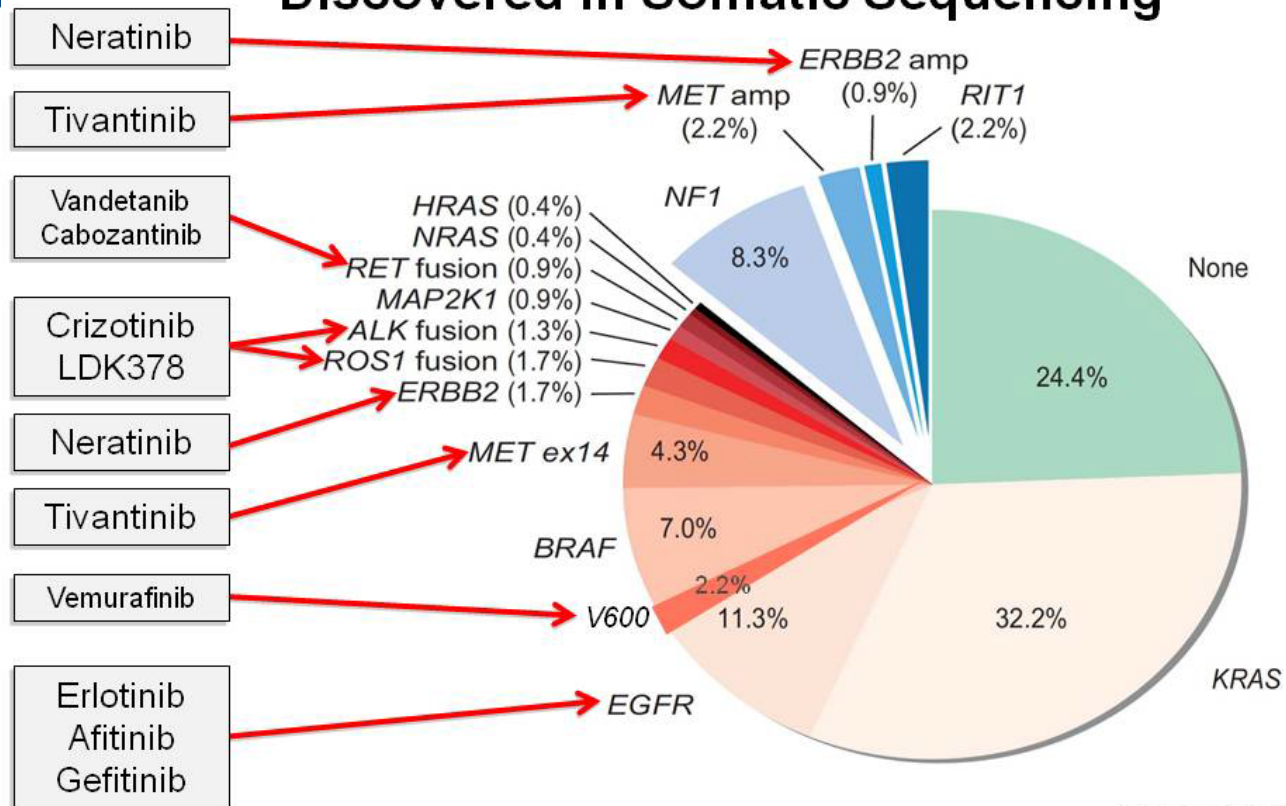
Comparison of Hispanic versus non-Hispanic White Consent Rates

Circle diameter is proportional to the sample size of the individual studies. The diamond represents the overall OR. The vertical line indicates the 95% confidence interval on the OR. Blue indicates interview and non-intervention studies; red indicates clinical intervention studies.

Cancer Control in the 21st Century

- In oncology, the era of precision medicine and targeted drug therapy has arrived.
- The large-scale clinical trial is far from obsolete.
- Indeed, large descriptive studies may be more important.

'Driver Genes' in Adult Lung Adenocarcinoma Discovered in Somatic Sequencing



TCGA Nature 2014

Cancer Control in the 21st Century

The development and use of tailored drugs will have to rely on response rate in 30-to-50-person phase II studies as a surrogate for improvement in survival.

From the scientific standpoint there will be less emphasis on racial differences and more emphasis on genomic markers.

Key Factors in Outcome

Precision Medicine

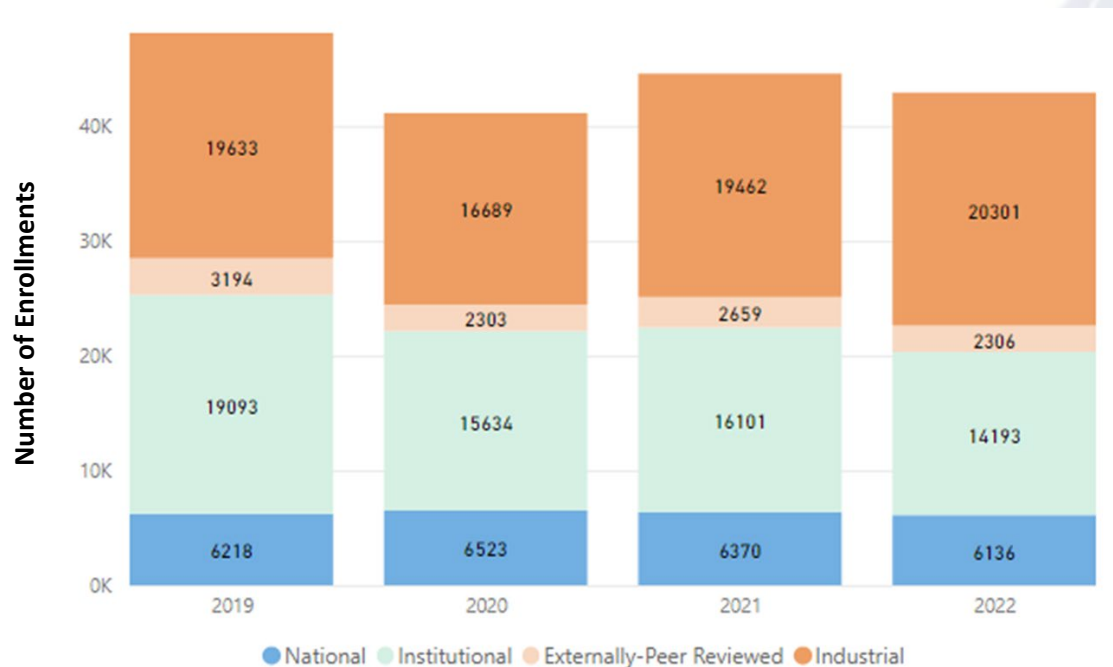
- Finding drugs and druggable genetic markers/targets
- Tailoring treatment to the patient (not the race!!!!).
- Studying the distribution of genetic markers/targets among well defined populations will be critical.

Minority Health and Health Disparities Research

A part should focus on:

- The study of the distribution of these markers amongst populations.
- Clearly defining those populations.
- Engaging with lay communities and explaining what we scientists do and assuring it is of value to the community.

Annual Enrollment to Treatment Trials by Study Source* NCI-Designated Cancers: 1/1/19-12/31/22

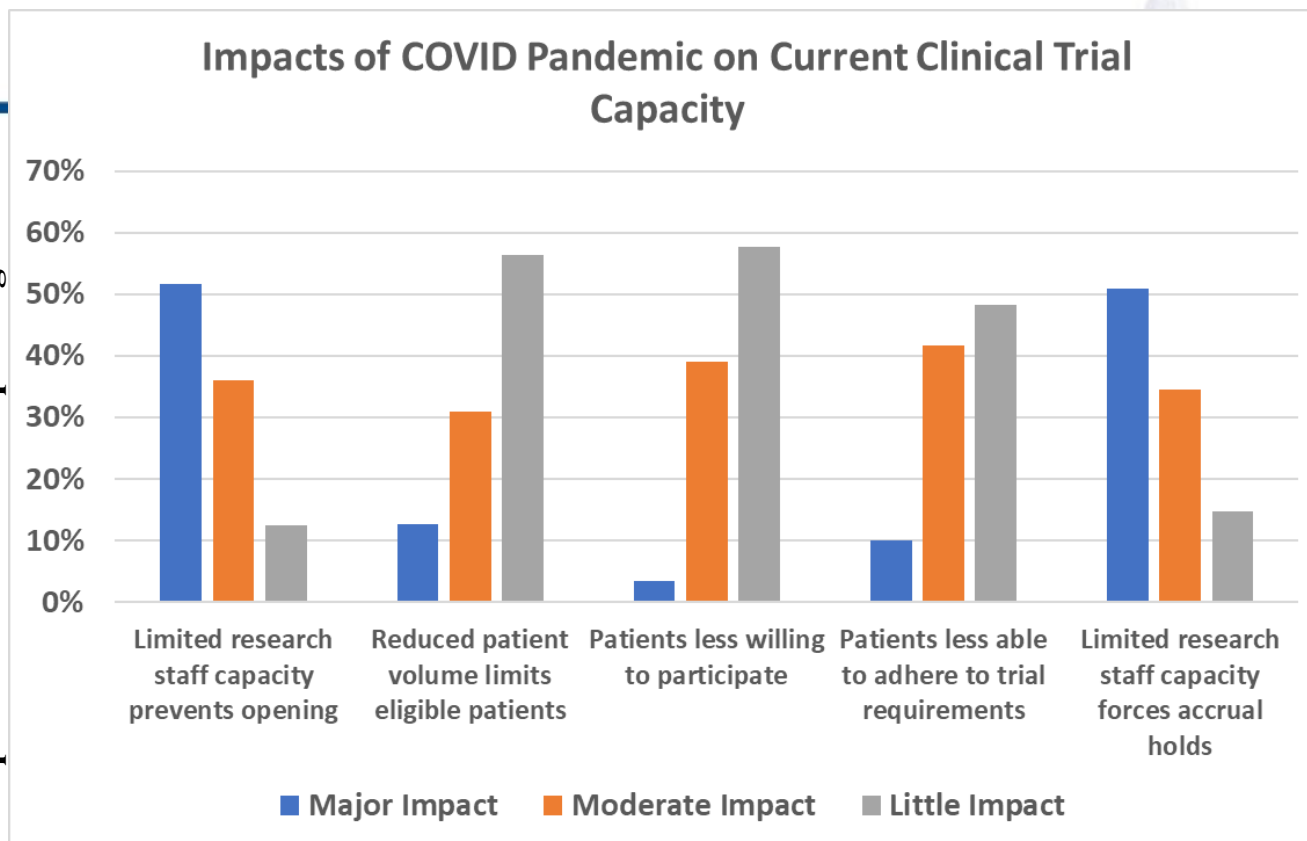


Data source: NCI's Clinical Trials Reporting Program (CTRP)

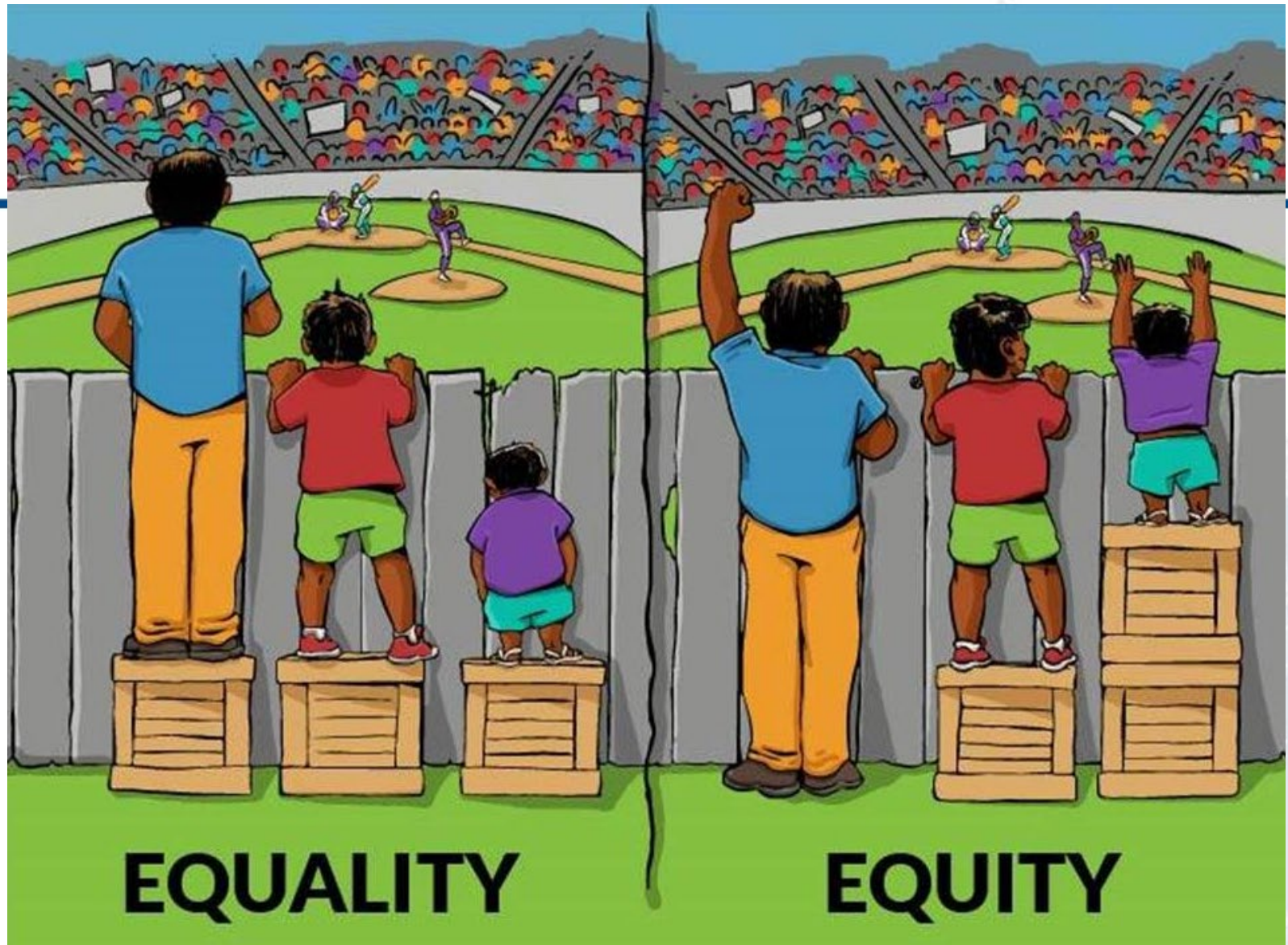
*NCI P30 Cancer Center Support Grant Data Table Guide v3.1.1

<https://cancercenters.cancer.gov/GrantsFunding/DataGuide>

Proportion of Centers Reporting Each View



Respondent group for this question: all 64 clinical Cancer Centers



The Johns Hopkins Medical Institutions



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