Towards a Quantified Science of Engagement and Recruitment

GSA/LINC-AD Webinar Series

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Review	**Review** existing outcome measures and care tools and identify gaps
Promote	**Promote** the development of new person-centered outcome measures and care tools to fill identified gaps
Facilitate	**Facilitate** the dissemination, adoption, implementation and sustained use of existing and new outcome measures and care tools

Towards a Quantified Science of Engagement and Recruitment

CARE
at Massachusetts General Hospital

Jonathan Jackson, PhD
March 8, 2023

Disclosures

- Employed by Massachusetts General Hospital (Physician’s org)
  - Academic appointment through Harvard Medical School

- CARE’s research is currently supported by grants from
  - National Institute on Aging
  - The Michael J. Fox Foundation

- CARE’s community activities are currently supported by
  - National Institute on Aging (grant)
  - UsAgainstAlzheimer’s (prize)

- CARE’s research was previously supported by grants from
  - NIH (All of Us Research Program)
  - National Institute of Neurological Diseases and Stroke
  - Massachusetts General Hospital
  - Patient-Centered Outcomes Research Institute (PCORI)
  - Massachusetts General Hospital

- CARE’s community activities were previously supported by
  - Amgen Foundation (grant)
  - Otsuka Pharmaceutical (gift)
  - Massachusetts General Hospital (grant)

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Of all forms of *inequality*, injustice in *healthcare* is the most *shocking* and *inhuman*.

—Martin Luther King, Jr.

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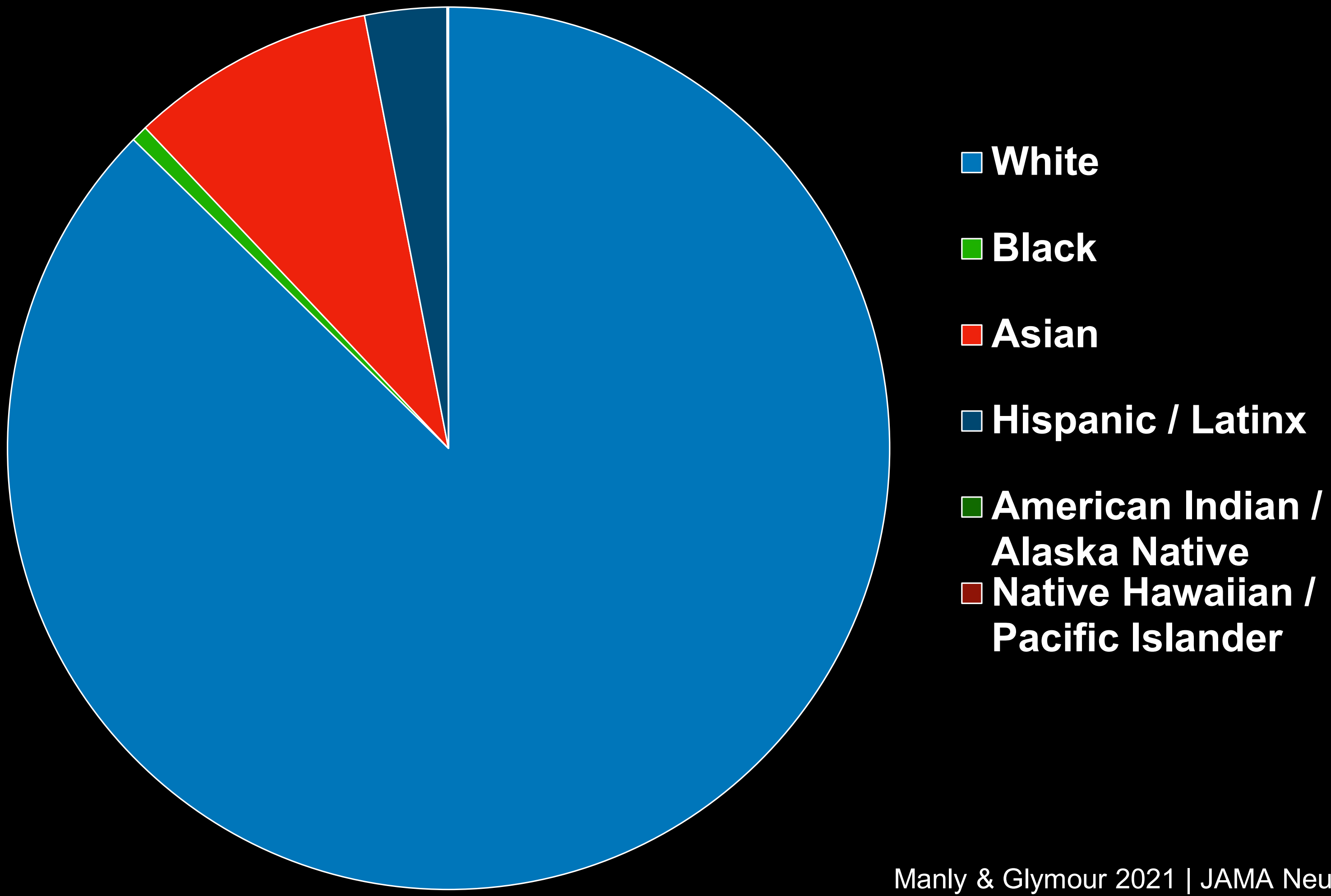
Current efforts in diverse recruitment



Manly & Glymour 2021 | JAMA Neur

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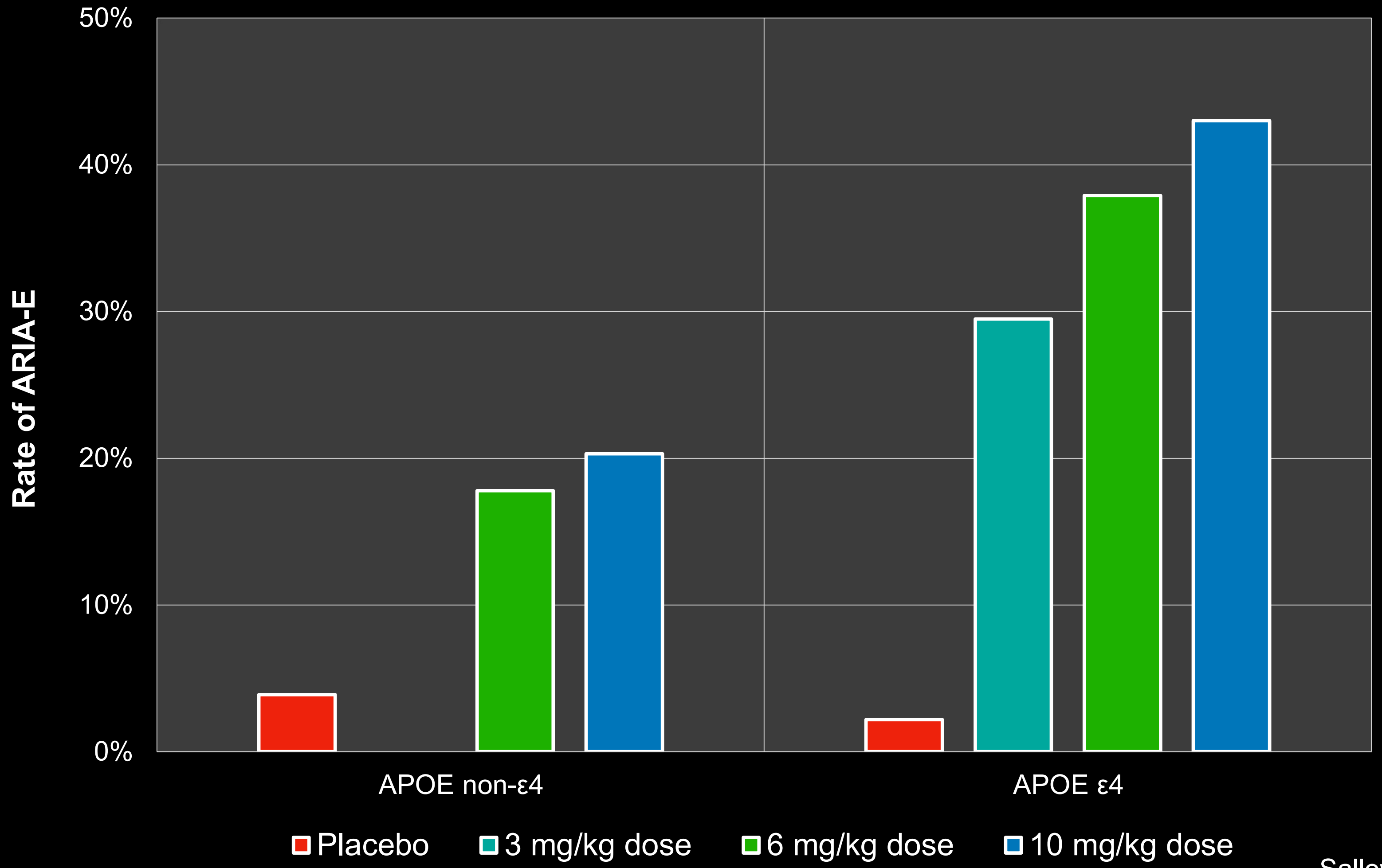
Current efforts in diverse recruitment



Salloway 2021 | JAMA Neur

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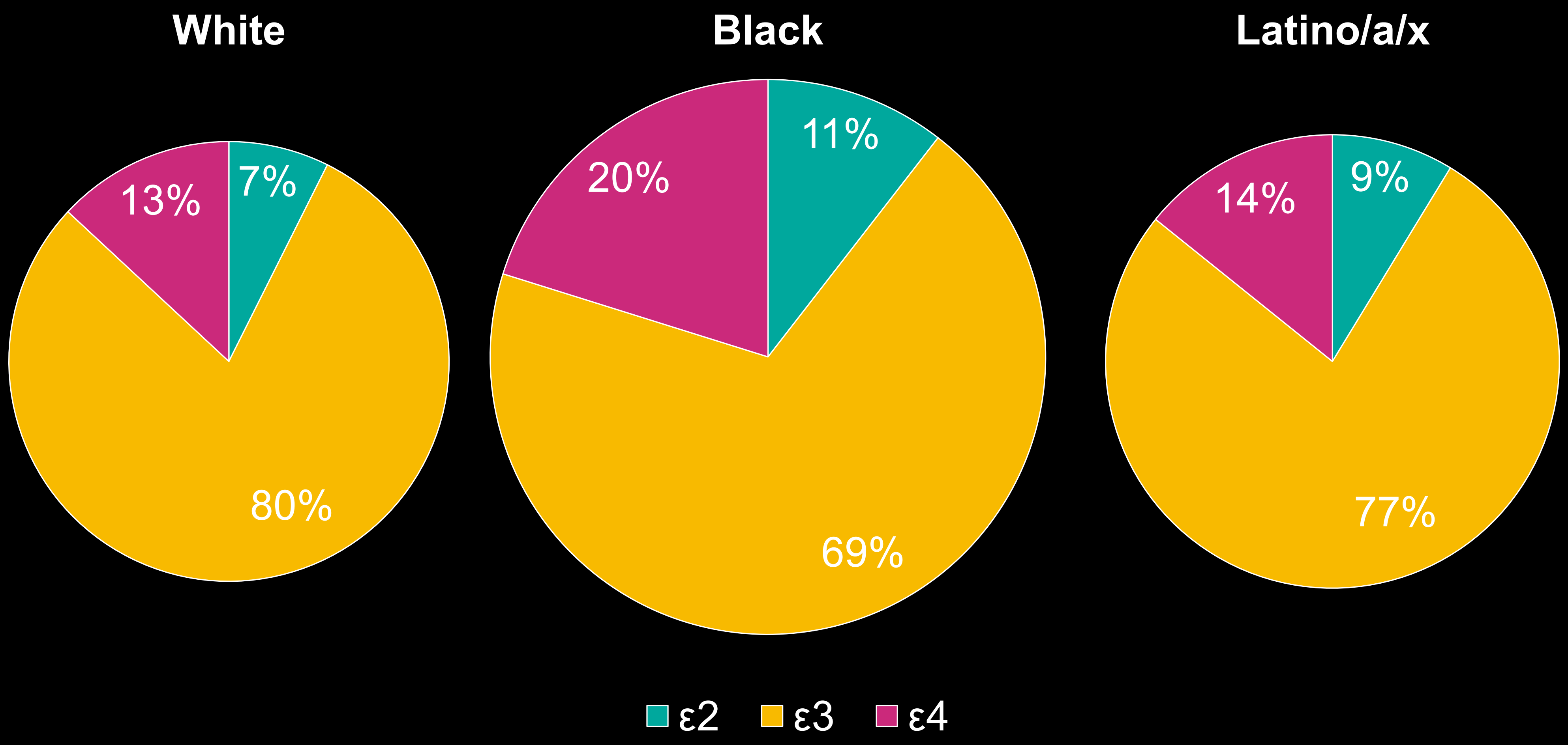
Current efforts in diverse recruitment



Tang 1998 | JAMA

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The Belmont Report (1979)

- **Respect for Persons**
  - Must provide informed consent
- **Beneficence**
  - Do no harm
  - All parties must understand and accept risks/benefits
- **Justice**
  - Fair distribution of costs and benefits

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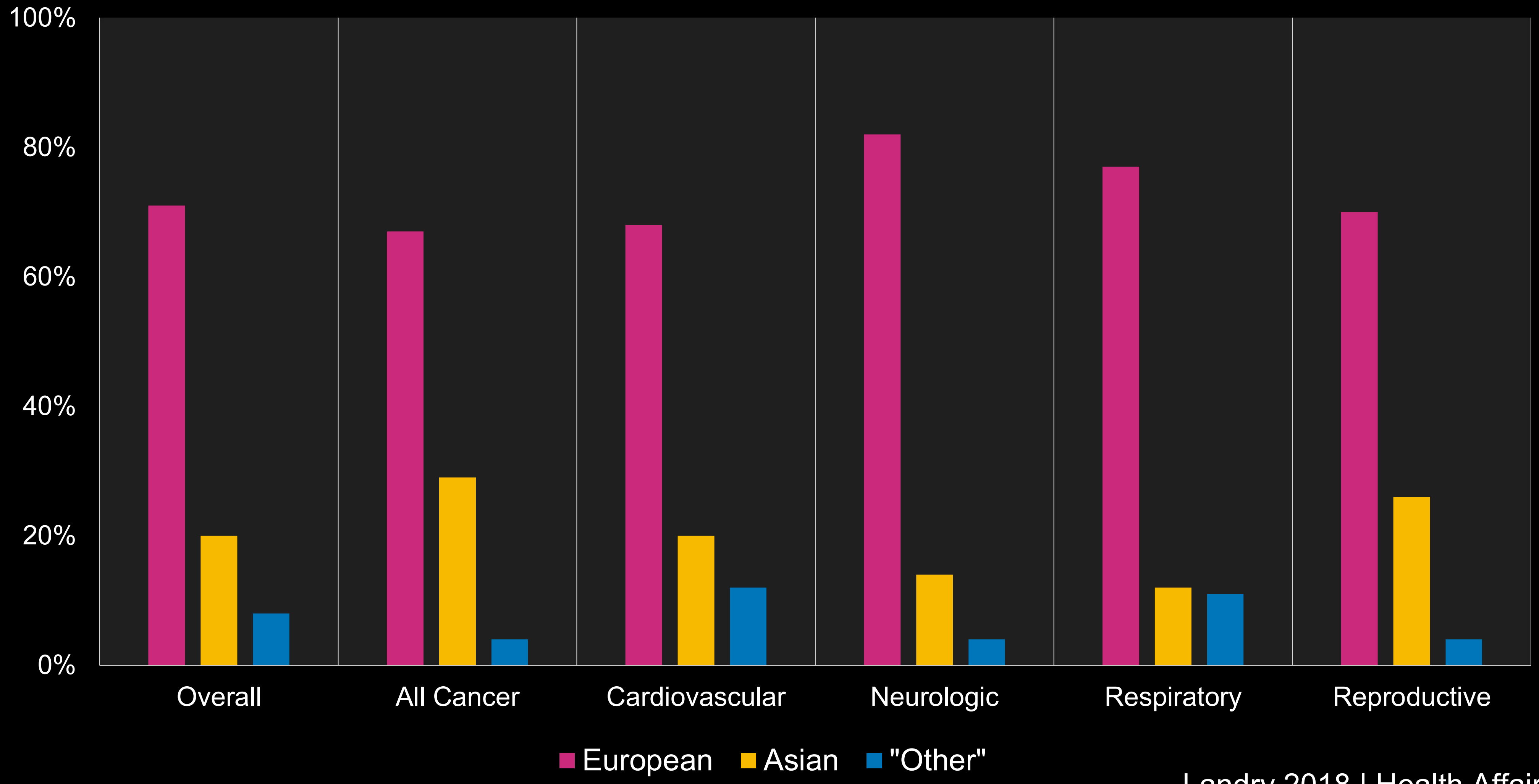
How do federal research guidelines encourage diverse inclusion?

- Over 30 aspirational policies since 1977
  - Civil Rights Act of 1965
  - FDA Labeling Rule (1979)
  - Belmont Report (1979)
  - NIH Revitalization Act of 1993
  - CDC Inclusion of Women and Racial and Ethnic Minorities (1995/1996)
  - NIH Policy - Inclusion of Women and Minorities (2001)
  - FDA guidance on Racial Inclusion (2016)
  - NIH Inclusion Across the Lifespan (2019)
  - AHRQ Policy on the Inclusion of Priority Populations in Research (2021)
- We didn't address the convenience factor
  - Marginalized groups became convenient to exclude
  - But at what cost?

Diversity in GWAS Databases

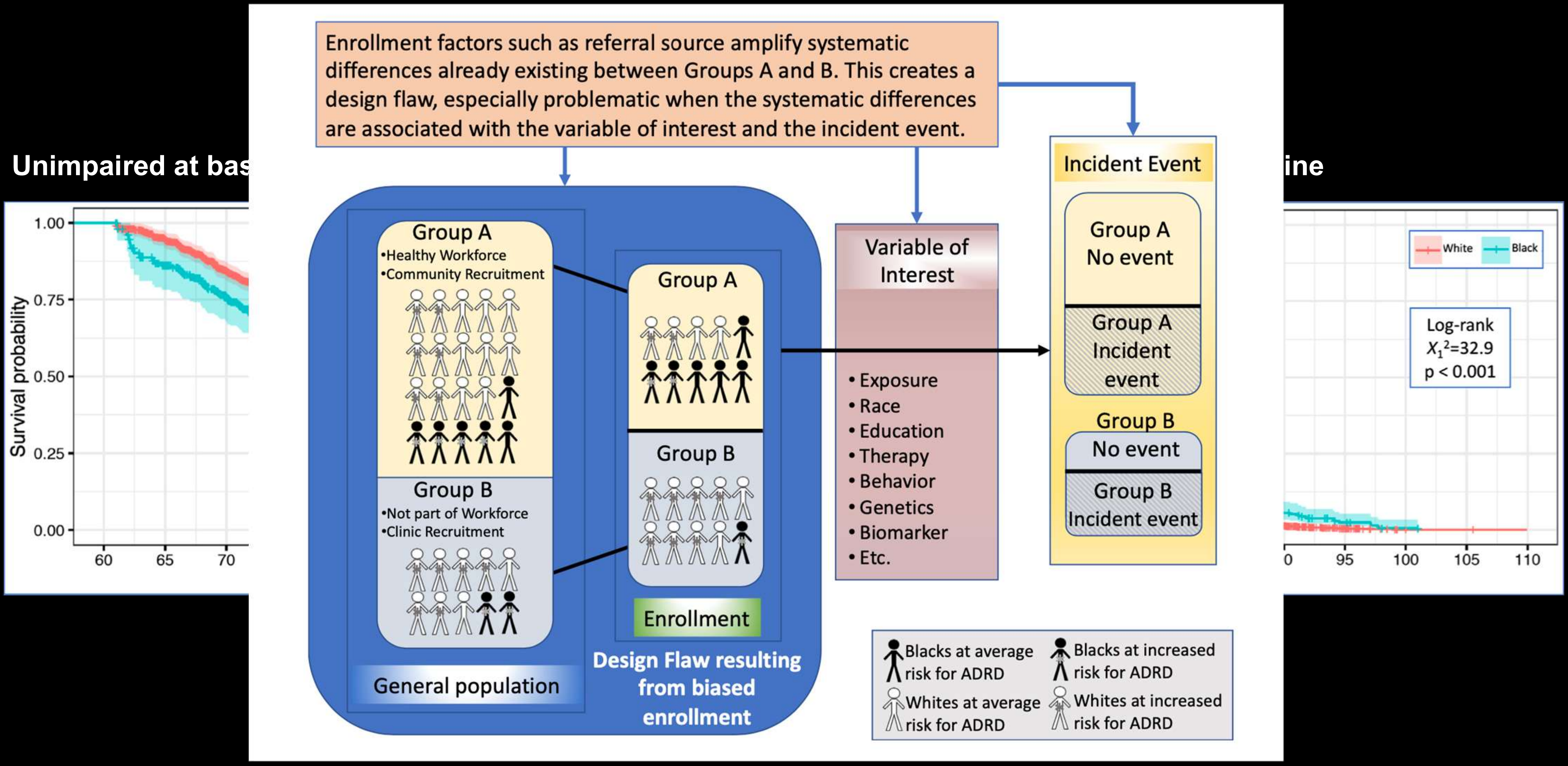


Landry 2018 | Health Affairs

Lack of representation destabilizes science

- Biased sampling threatens **external** validity (Ramamoorthy et al., 2015, Manly & Glymour, 2021)
- Undermines construct validity (Crane et al., 2004; Ortiz et al., 2007; Ramirez et al., 2006)
- Additionally limits internal validity (Deters et al., 2021; Gleason et al., 2019; Indorewalla et al., 2021; Manly & Glymour, 2021)
- And endangers statistical conclusion validity and causal estimation (Mayeda 2018; Weuve 2015)
- What happens if we don't recruit **representatively**?

Current efforts in diverse recruitment



Enrollment factors such as referral source amplify systematic differences already existing between Groups A and B. This creates a design flaw, especially problematic when the systematic differences are associated with the variable of interest and the incident event.

General population

Group A
- Healthy Workforce
- Community Recruitment

Group B
- Not part of Workforce
- Clinic Recruitment

Enrollment

Group A

Group B

Design Flaw resulting from biased enrollment

Variable of Interest
- Exposure
- Race
- Education
- Therapy
- Behavior
- Genetics
- Biomarker
- Etc.

Incident Event

Group A No event

Group A Incident event

Group B No event

Group B Incident event

Blacks at average risk for ADRD	Blacks at increased risk for ADRD
Whites at average risk for ADRD	Whites at increased risk for ADRD

Gleason 2019 | Alz & Dementia

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The state of representation science

- Field is fragmented
  - No
  - Mo nrollment
  - Co cate, measure
- Conf
  - (Wh
  - Co
  - Is aid CRCs?
- Infra
  - Few
  - Stu
  - Eng rotocols
  - Systemic failures are left to individual study teams, research participants

Indorewalla 2021 | J Alz Dis

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So how (and when, and why) should we reconcile *health justice* with *research rigor*?

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> The incidence of patient availability *sharply decreases* when a clinical trial begins and *returns to its original level* as soon as the trial is completed.
>
> —Lasagna's Law

Why can’t we recruit diverse populations?

1. Lack of awareness of research opportunities
2. Deep mistrust of healthcare system and research studies
3. Confusion and concern over what research is
4. Limited transportation options / times
5. Inclusion / exclusion criteria (e.g., lumbar puncture, study partner)
6. Lack of plain language use in documents
7. Fear of placebo / fear of intervention
8. Health insurance coverage
9. Limited diversity on study staff
10. Poor targeting within catchment area
11. Insufficient return of value

Selected references:

Bonevski 2014 | BMC Med Res Method
Dunbar 2019 | Ped Neur
Ejiogu 2011 | The Gerontologist
George 2014 | Am J Public Health
Gilmore-Bykovskyi 2019 | Alz & Dem: TRCI
Gul & Ali 2010 | J Clin Nursing
Howell 2020 | Alz & Dem
Indorewalla 2021 | J Alz Dis
Oh 2015 | PLoS Medicine
Otado 2015 | Clin Trans Sci
Probstfield & Frye 2011 | JAMA
Robinson & Trochim 2007 | Ethn Health

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Diversity as a *selection* problem

Sampling frame
Awareness
Trust/Engagement
Literacy/Motivation
Equity/Return of Value
Screening
Setting
Implementation
Retention

Lack of awareness of research opportunities
Deep mistrust of healthcare system and research
Confusion and concern over what research is
Limited transportation options / times
Inclusion / exclusion criteria
Lack of plain language use in documents
Fear of placebo / fear of intervention
Health insurance coverage
Limited diversity on study staff
Poor targeting of catchment area
Insufficient return of value

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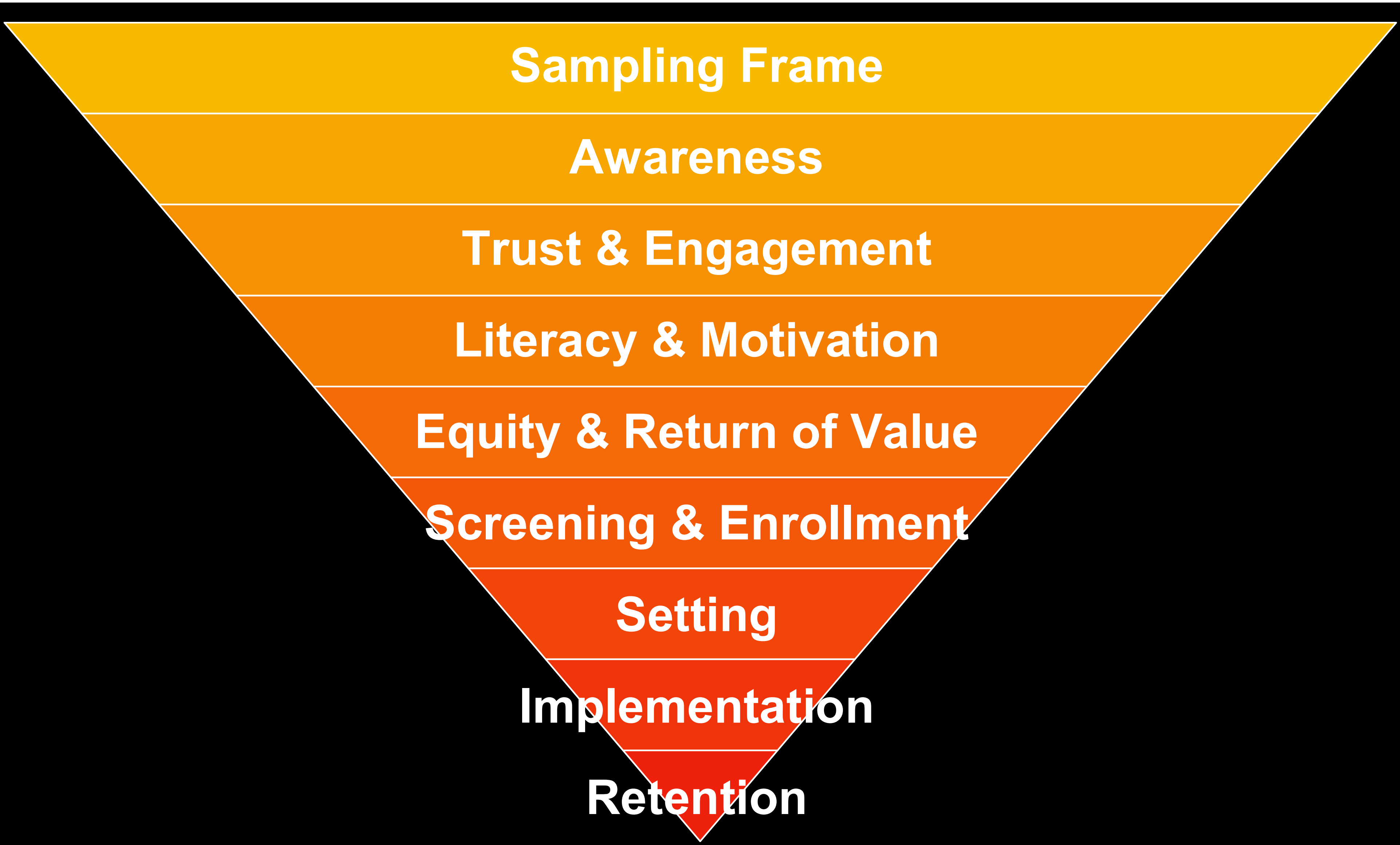

Sampling Frame

Awareness

Trust & Engagement

Literacy & Motivation

Equity & Return of Value

Screening & Enrollment

Setting

Implementation

Retention

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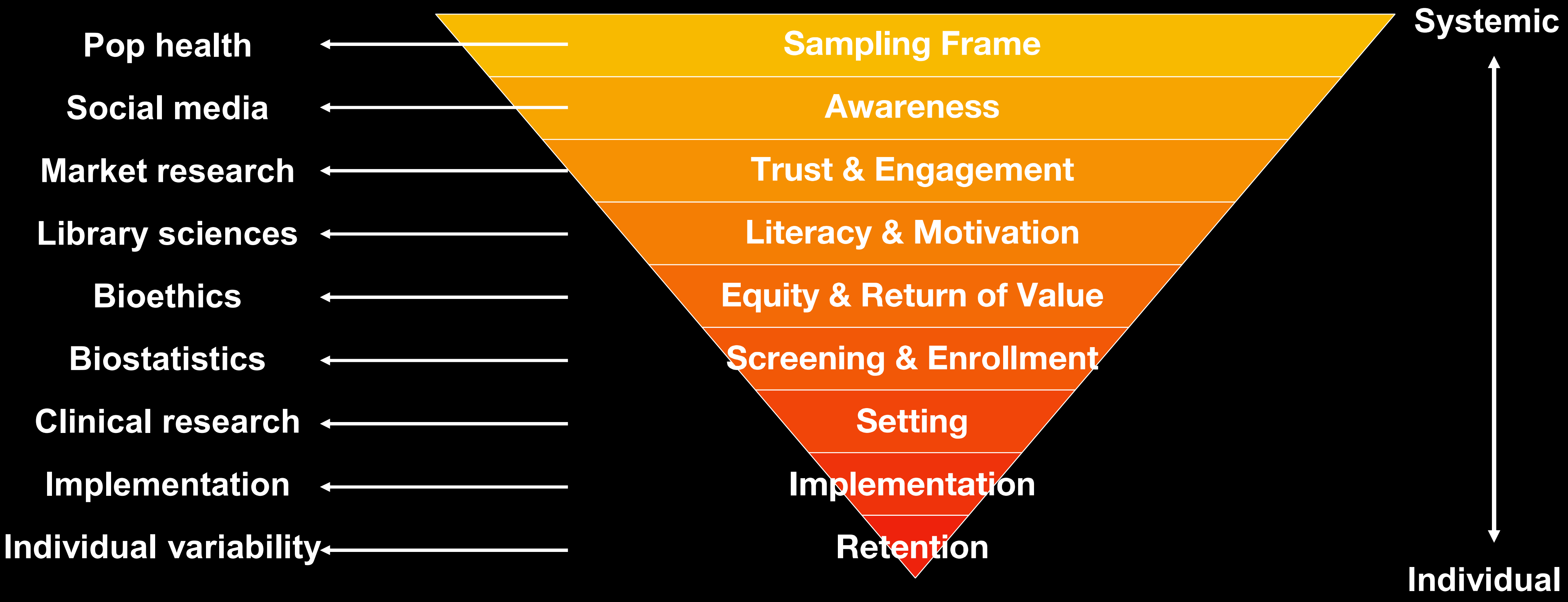
What’s next for a science of representation



Pop health	Sampling Frame
Social media	Awareness
Market research	Trust & Engagement
Library sciences	Literacy & Motivation
Bioethics	Equity & Return of Value
Biostatistics	Screening & Enrollment
Clinical research	Setting
Implementation	Implementation
Individual variability	Retention

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Diversity as a coal-mine canary

Essentialized / Biological Disparities

Selection Biases

- **Science of RER**
- **Inferential Table 1**
- **Simulation research**
- **Sociospatial mapping**
- **Transport tools**
- **Diversity feasibility**
- **Inclusive team structure**

Measurement Error

- **Differential item functioning**
- **Meta-analysis**
- **Interrater reliability**
- **Sensitivity analysis**
- **Move beyond central tendency & NHST**
- **Patient-centered outcomes**

Implementation & Design Biases

- **Flexible design**
- **Implicit bias analysis**
- **Implementation science**
- **SMART & N-of-1 designs**
- **Social science of research**
- **Learning healthcare system**

Social Inequities

- **Local engagement**
- **Translation & interpretation**
- **Transportation support**
- **Equitable payment**
- **Trust-building**
- **Structural discrimination measures**

Biological Disparities

- **Epigenomic analysis**
- **Precision medicine**
- **Immunotherapy**
- **Subpopulation studies**

Social Inequities

Biological Disparities

- Biased treatment
- Biased access
- Environmental factors
- Structural discrimination

- Intraindividual variance
- Individual variance
- (Epi)genomic variance

Jackson | under review

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What should we do with race?

- Race / ethnicity as risk factor for disease
  - E.g., African-Americans 2-4x more likely than Whites to develop dementia
  - Latinx 1.5x more likely than Whites
  - Commonly attributed to comorbid factors in vasculature
- Race is often used for the following reasons in research and care settings:
  - As a construct: e.g., dimension reduction
  - As a variable: e.g., proxy for genetic variation or ancestry
  - As a marker for racism: e.g., selection effects in research or healthcare access
- Unfortunately, none of these are appropriate or valid conditions
  - No justifiable basis for using race as anything other than as one (poor) marker of identity
  - Conflation of all five proposed levels of bias

Selection Biases
Measurement Error
Implementation Biases
Social Inequities
Biological Disparities

Pham & Jackson | in revision

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What should we do with race?

- On race as a construct

  - Race is typically a poor and undercorrelated proxy of socioeconomic factors
  - Likely because race itself lacks any empirical definition
  - Reliance on race as construct tends to reduce external, internal, stats validity
- On race as a variable

  - Race is an insufficient marker of genetic variation and ancestry
  - In the US, race is often tied to US Census, which changes its definition every decade
  - Inadvertent baselining and norming of privileged identities, sacrificing validity
- On race as an indicator of racism

  - Erases bias, and therefore responsibility, from researchers and clinicians
  - Similar shift in focus from barriers to individuals
  - Creates misleading monoliths, for both racial minorities and majorities

Pham & Jackson | in revision

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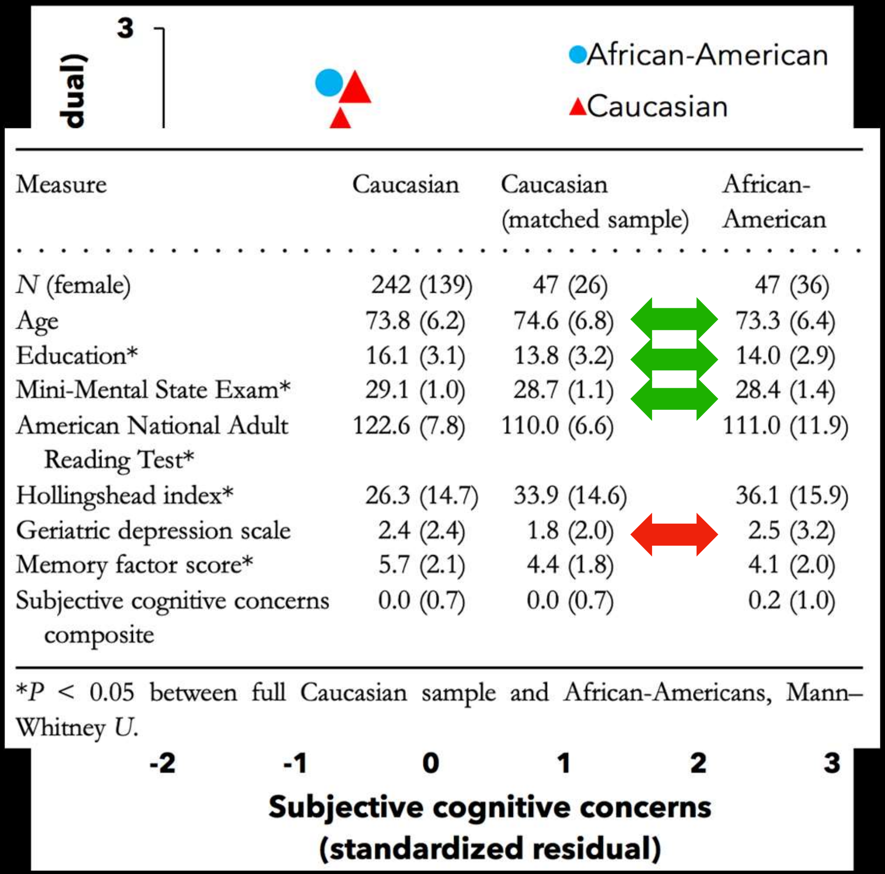
THIS BROKE ME
Global

Walk me through this, Jackson

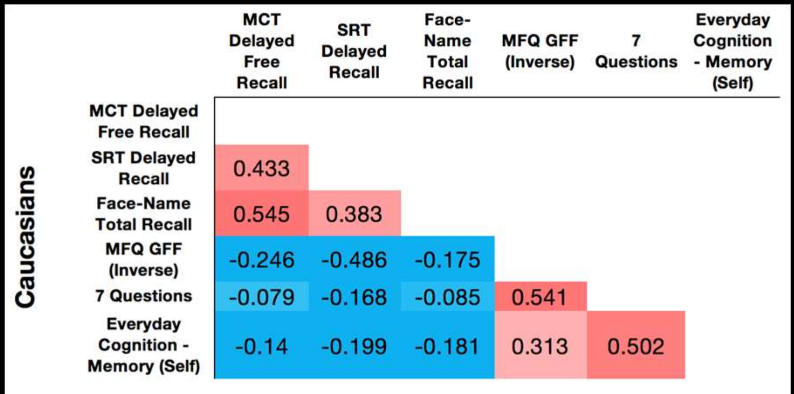
- Think about your mechanism of action
  - Apart from pulse oximeters, it's not going to be melanin
  - Do your best to measure that mechanism, environment, or exposure instead
- Leverage more useful group differentiators
  - Access to care, rurality, nutrition, health literacy, housing, pollution
  - But still be careful about your referent groups – what are you normalizing?
- Consider standardized set of socioevironmental factors (e.g., CDEs)
  - Moving from social determinants to a quantified social exposome
  - Can spot intersectional diversity and resilience factors
  - Centers exposures and systems, rather than essentialization
  - May help reconcile domestic health equity and global health equity research
- Race isn't the third rail
  - Can help you see potential issues in recruitment and selection, for example
  - But racial identity can only ever be a marker of racial identity

Lest you think I'm immune…



Measure	Caucasian	Caucasian (matched sample)	African-American
N (female)	242 (139)	47 (26)	47 (36)
Age	73.8 (6.2)	74.6 (6.8)	73.3 (6.4)
Education*	16.1 (3.1)	13.8 (3.2)	14.0 (2.9)
Mini-Mental State Exam*	29.1 (1.0)	28.7 (1.1)	28.4 (1.4)
American National Adult Reading Test*	122.6 (7.8)	110.0 (6.6)	111.0 (11.9)
Hollingshead index*	26.3 (14.7)	33.9 (14.6)	36.1 (15.9)
Geriatric depression scale	2.4 (2.4)	1.8 (2.0)	2.5 (3.2)
Memory factor score*	5.7 (2.1)	4.4 (1.8)	4.1 (2.0)
Subjective cognitive concerns composite	0.0 (0.7)	0.0 (0.7)	0.2 (1.0)

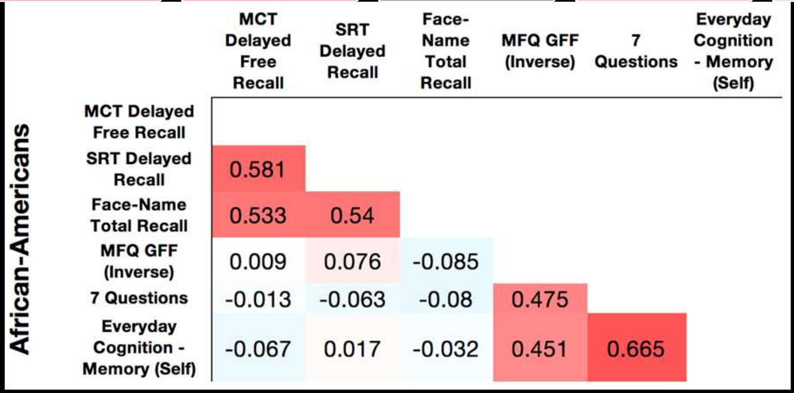
*$P < 0.05$ between full Caucasian sample and African-Americans, Mann–Whitney *U*.



Caucasians

	MCT Delayed Free Recall	SRT Delayed Recall	Face-Name Total Recall	MFQ GFF (Inverse)	7 Questions	Everyday Cognition - Memory (Self)
MCT Delayed Free Recall						
SRT Delayed Recall	0.433					
Face-Name Total Recall	0.545	0.383				
MFQ GFF (Inverse)	-0.246	-0.486	-0.175			
7 Questions	-0.079	-0.168	-0.085	0.541		
Everyday Cognition - Memory (Self)	-0.14	-0.199	-0.181	0.313	0.502	

Selection Biases → Measurement Error → Implementation Biases → Social Inequities → Biological Disparities



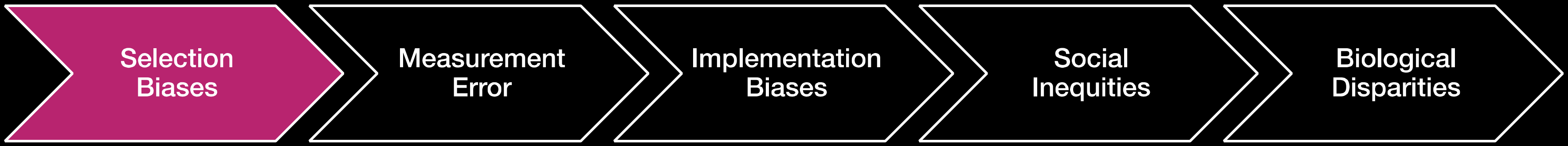
African-Americans

	MCT Delayed Free Recall	SRT Delayed Recall	Face-Name Total Recall	MFQ GFF (Inverse)	7 Questions	Everyday Cognition - Memory (Self)
MCT Delayed Free Recall						
SRT Delayed Recall	0.581					
Face-Name Total Recall	0.533	0.54				
MFQ GFF (Inverse)	0.009	0.076	-0.085			
7 Questions	-0.013	-0.063	-0.08	0.475		
Everyday Cognition - Memory (Self)	-0.067	0.017	-0.032	0.451	0.665	

Jackson 2017 | Age & Ageing

Using race as a marker of group differences

Using specific exposures and mechanisms as a marker of group differences



Selection Biases

Measurement Error

Implementation Biases

Social Inequities

Biological Disparities

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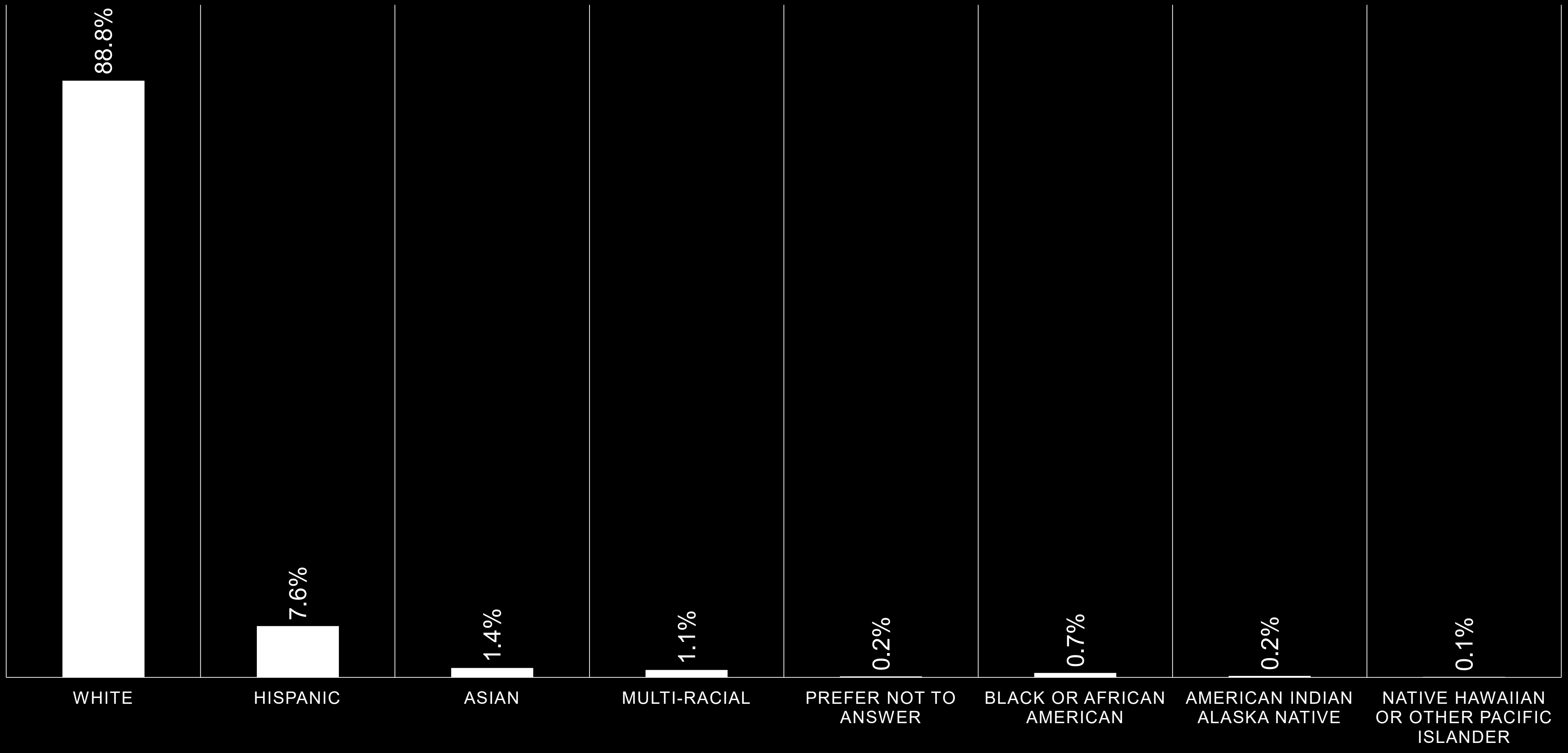
Selection Biases › Measurement Error › Implementation Biases › Social Inequities › Biological Disparities

2018 ACCRUAL TO DIGITAL STUDY



Courtesy Michael J Fox Foundation

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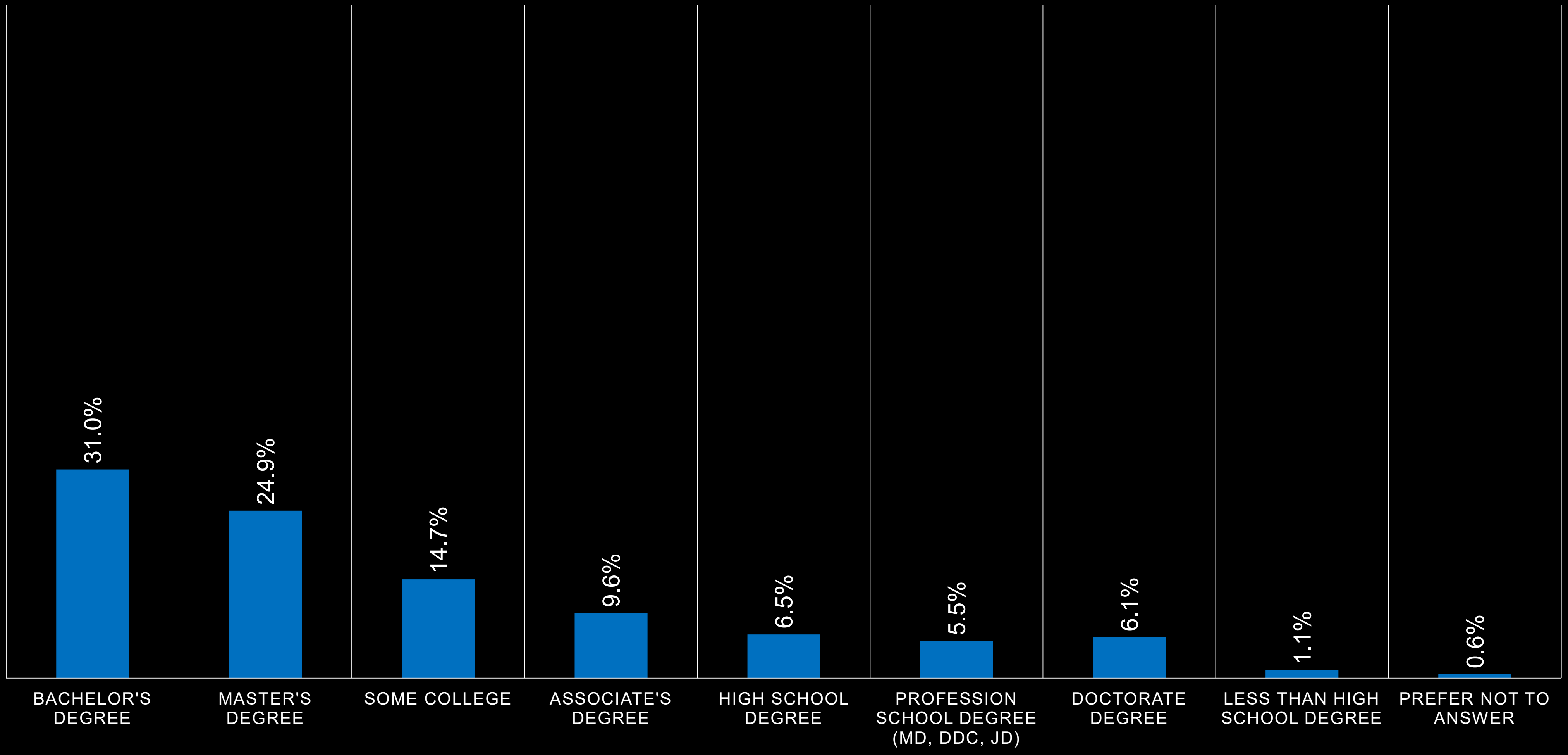
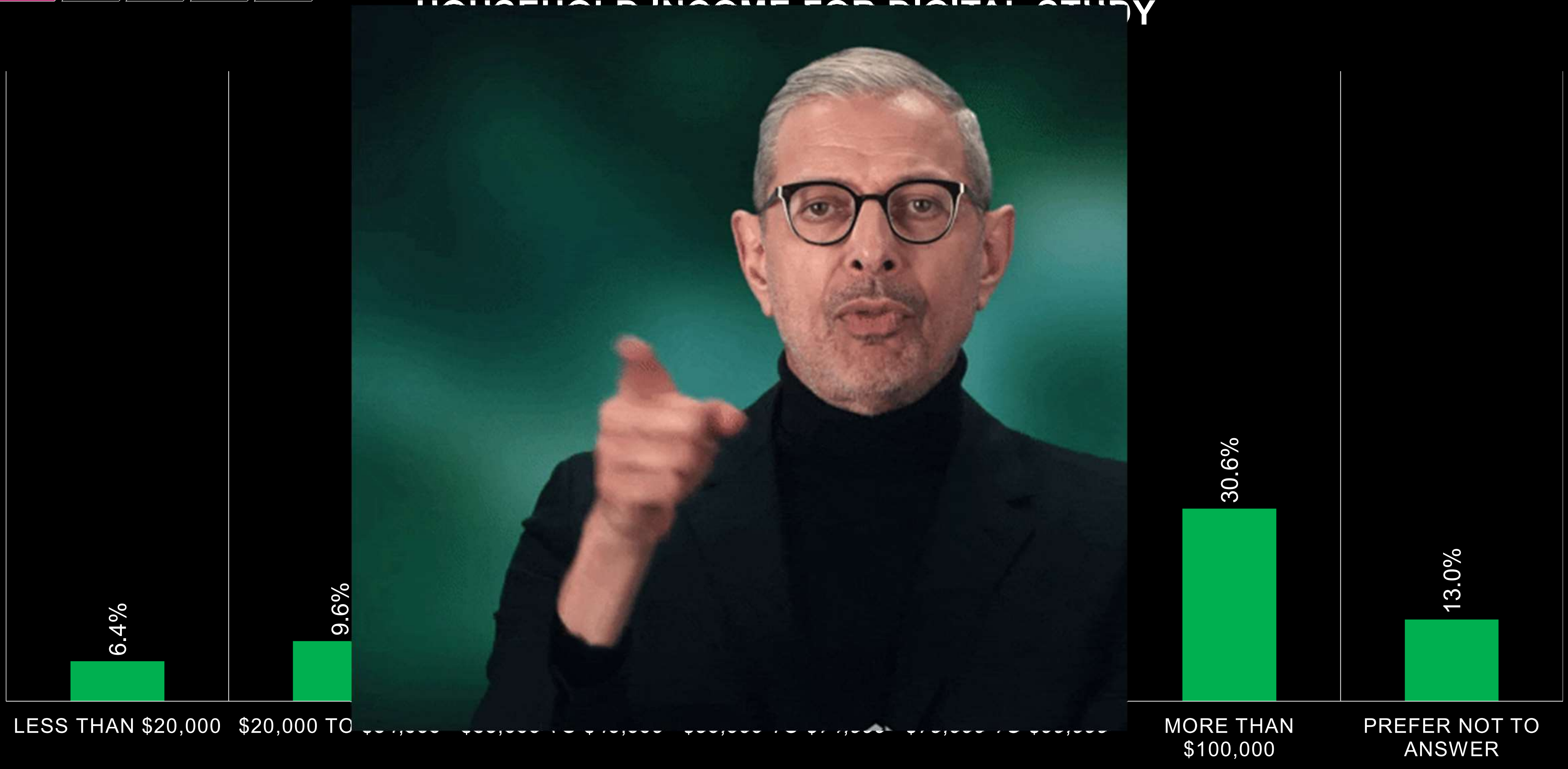
EDUCATION LEVEL FOR DIGITAL STUDY



Courtesy Michael J Fox Foundation

Selection Biases › Measurement Error › Implementation Biases › Social Inequities › Biological Disparities

HOUSEHOLD INCOME FOR DIGITAL STUDY



Courtesy Michael J Fox Foundation

The FIRE-UP PD Study

Sampling selection

Awareness

Trust/Engagement

Literacy/Motivation

Return of Value

Screening

Setting

Implementation

Retention

- Study designed to focus on multiple barriers
    - Powered primarily for engagement metrics, cost
    - Can assess dependent nature of framework
    - Preliminary assessment of comparative effectiveness
- Broad definition of “minority”
    - Race, ethnicity, gender, education, income, rurality
- Strong focus on sampling frame, protocol
    - Which minorities can or want to access Fox Insight?
    - Detailed engagement protocols help clarify “we’ve done that” or “charismatic individual” effects

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The FIRE-UP PD Study

Sampling selection

Awareness

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Literacy/Motivation

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Screening

Setting

Implementation

Retention

- Eight sites (four control)
  - All sites pre-identified barrier, population, intervention
  - Randomized to intervention / control within pairs
  - Five month intervention
  - $45,000 to intervention / $10,000 to control
- Interventions focus on community, physicians
  - Multi-pronged approach to address barriers

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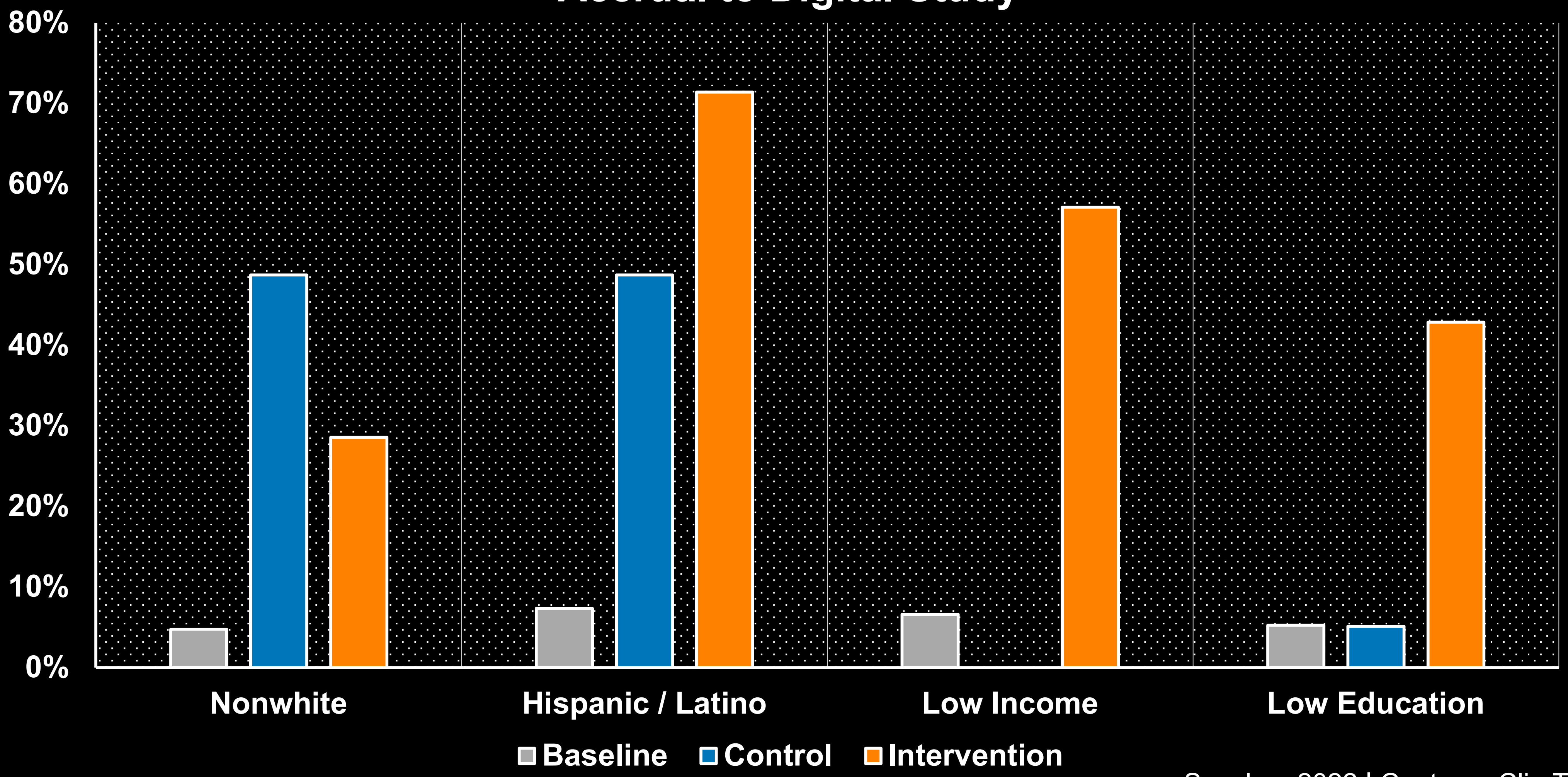
Selection Biases
Measurement Error
Implementation Biases
Social Inequities
Biological Disparities

Accrual to Digital Study



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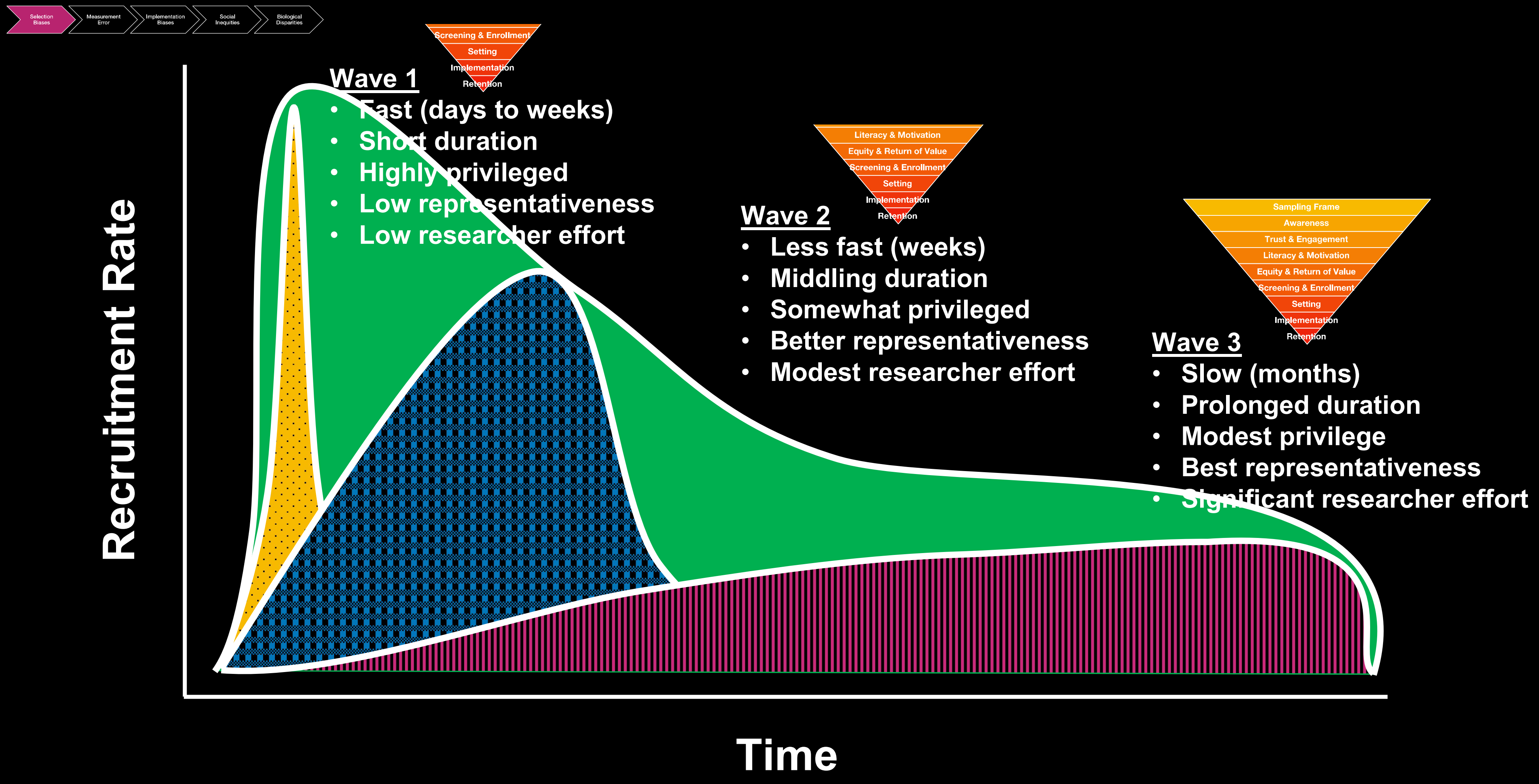

Selection Biases | Measurement Error | Implementation Biases | Social Inequities | Biological Disparities

Screening & Enrollment
Setting
Implementation
Retention

Wave 1

- Fast (days to weeks)
- Short duration
- Highly privileged
- Low representativeness
- Low researcher effort

Literacy & Motivation
Equity & Return of Value
Screening & Enrollment
Setting
Implementation
Retention

Wave 2

- Less fast (weeks)
- Middling duration
- Somewhat privileged
- Better representativeness
- Modest researcher effort

Sampling Frame
Awareness
Trust & Engagement
Literacy & Motivation
Equity & Return of Value
Screening & Enrollment
Setting
Implementation
Retention

Wave 3

- Slow (months)
- Prolonged duration
- Modest privilege
- Best representativeness
- Significant researcher effort

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Selection Biases
Measurement Error
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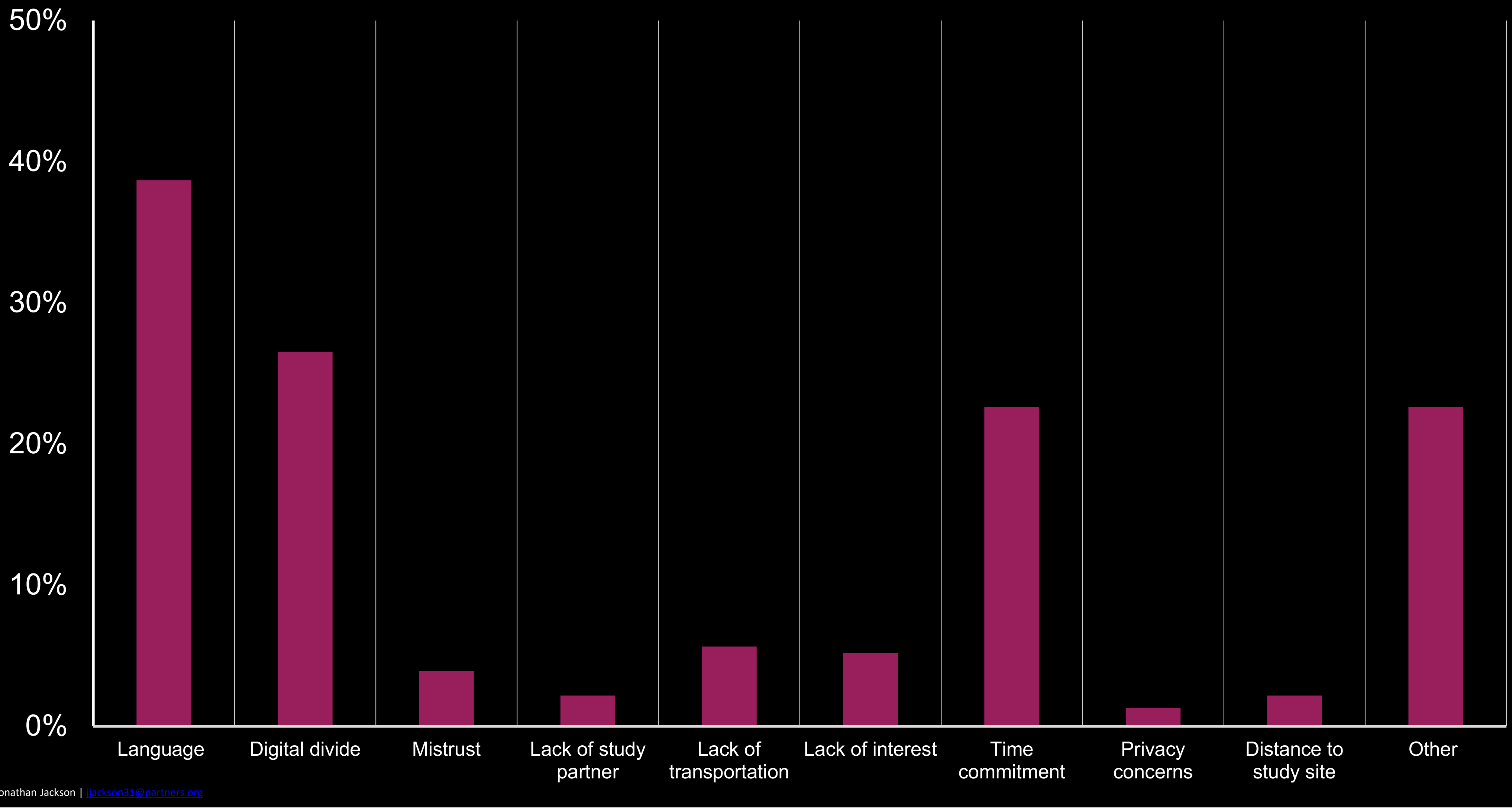
Participant Barriers to Participation (*n* = 230)



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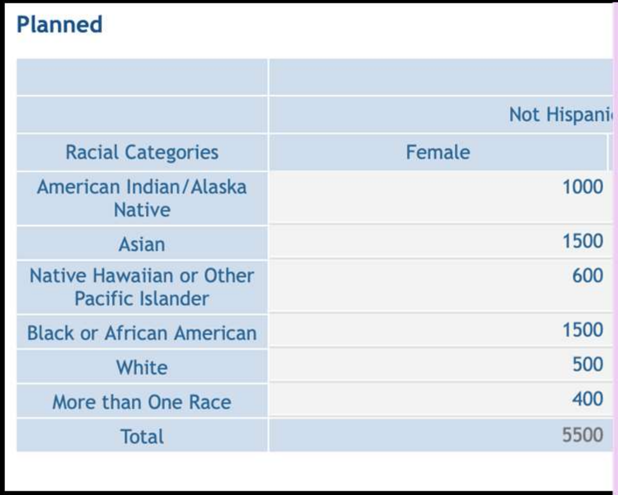
A different kind of deep phenotyping

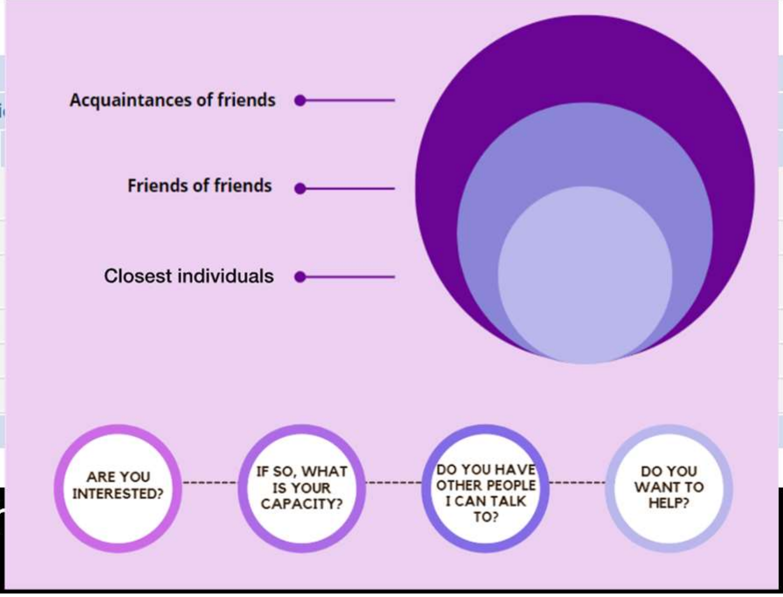
FOREVER
dementia study

- Ongoing DP1 award
- Phase I – Assess lay communities (*n* = 15,680)
  - Intersectional focus on ethnoracial minorities, queer communities, low SES, rural, Native
  - Novel recruitment method: relational organizing
  - Develop mapping tools and norms based on this data for national use



Planned

	Not Hispani		Total
Racial Categories	Female	Male	
American Indian/Alaska Native	1000	90	2180
Asian	1500	0	3000
Native Hawaiian or Other Pacific Islander	600	0	1200
Black or African American	1500	500	4000
White	500	1500	4000
More than One Race	400	250	1300
Total	5500	2340	15680



  - Restructure NIA outreach

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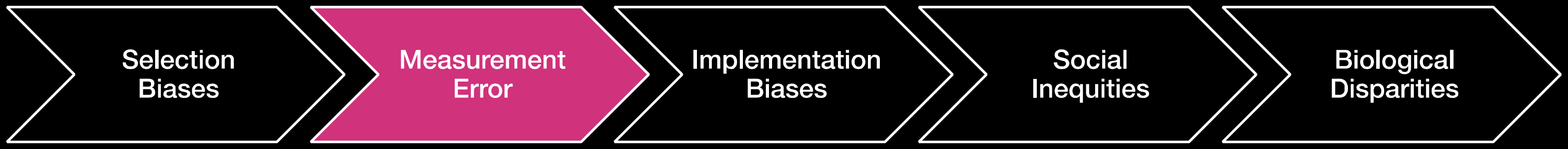

Selection Biases

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Implementation Biases

Social Inequities

Biological Disparities

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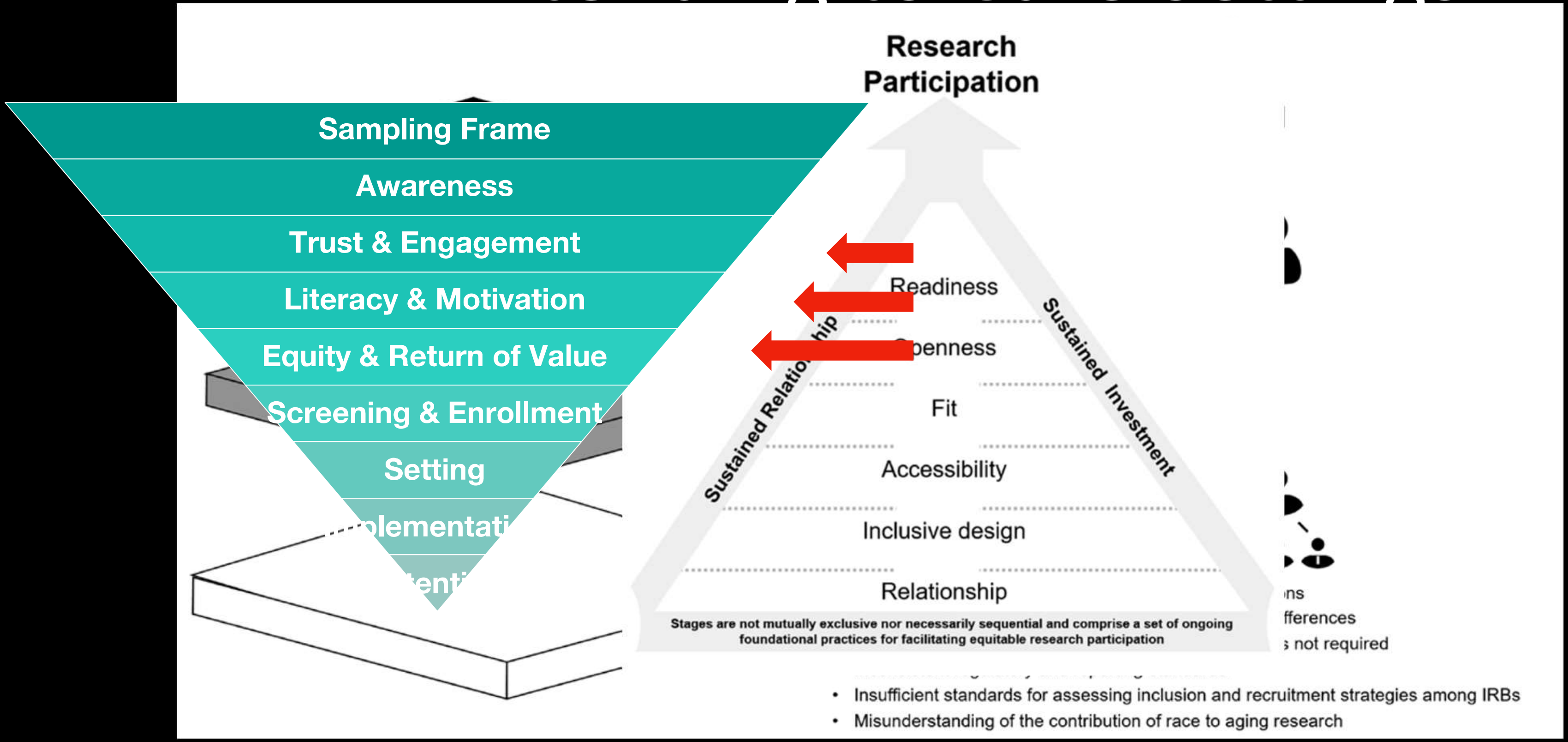
Selection Biases › **Measurement Error** › Implementation Biases › Social Inequities › Biological Disparities

Justice & Rigor: Extending to Care Settings

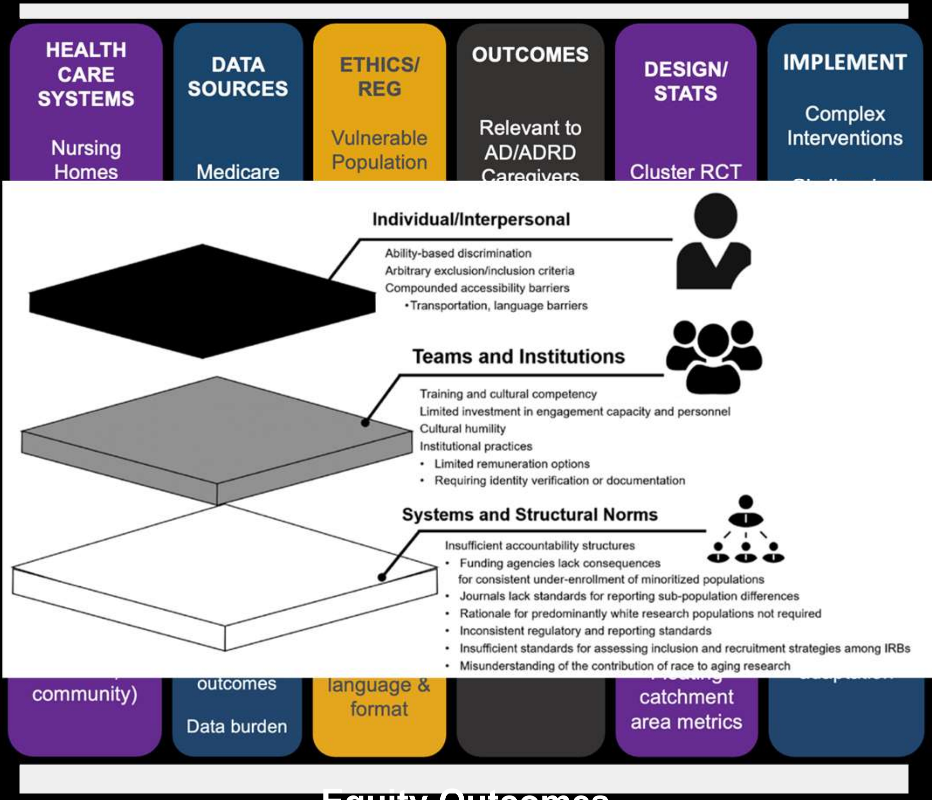


- Insufficient standards for assessing inclusion and recruitment strategies among IRBs
- Misunderstanding of the contribution of race to aging research

Gilmore-Bykovskyi 2021 | The Geron

Justice & Rigor: ePCTs

Traditional Outcomes



Individual/Interpersonal

Ability-based discrimination
Arbitrary exclusion/inclusion criteria
Compounded accessibility barriers
- Transportation, language barriers

Teams and Institutions

Training and cultural competency
Limited investment in engagement capacity and personnel
Cultural humility
Institutional practices
- Limited remuneration options
- Requiring identity verification or documentation

Systems and Structural Norms

Insufficient accountability structures
- Funding agencies lack consequences for consistent under-enrollment of minoritized populations
- Journals lack standards for reporting sub-population differences
- Rationale for predominantly white research populations not required
- Inconsistent regulatory and reporting standards
- Insufficient standards for assessing inclusion and recruitment strategies among IRBs
- Misunderstanding of the contribution of race to aging research

Equity Outcomes

- The PRECIS-2 framework for pragmatic trials
  - Nine domains to assess how pragmatic a trial is
  - Often considered strong real-world evidence (but stats are unfavorable)
  - Randomizes health care systems rather than individuals
- However, need to integrate equity
  - Selection biases *still* occur at level of individual
  - In addition to selection effects at *any* level of randomization
- Proposed changes promoting equity & representation
  - Equity considerations at each domain
  - Additional domain of Value, to focus on Wilkins' Return of Value
  - Added dimension of stakeholder groups for each domain
    - Organizational level: Health care system
    - Team level: Clinician / Research team
    - Individual: Patient and care partner(s)
  - New metrics for each Core Working Group of IMPACT Collaboratory

Quiñones 2020 | J Am Ger Soc
Gilmore-Bykovskyi 2021| The Gerontologist

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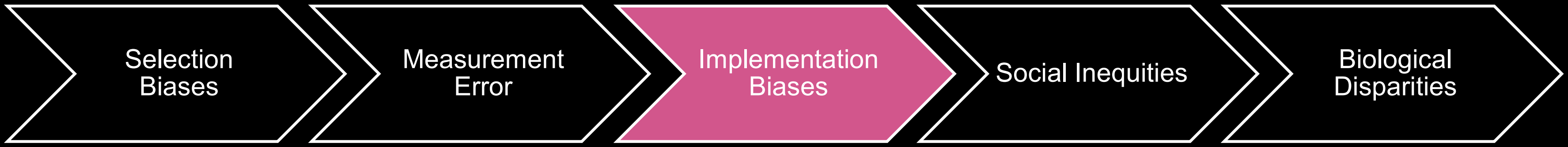

Selection Biases

Measurement Error

Implementation Biases

Social Inequities

Biological Disparities

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Justice & Rigor: Trial Outcomes

- What should we do when clinical trials stop early?
  - Lots of concerns emerge, with respect to safety, communications, even emotions
  - Trial participants often hear about these stoppages when we do—from the news
- What is our duty as trialists, sponsors, advocates?
  - Convened stakeholder group to discuss pretrial, midtrial, posttrial stopping
  - How do we communicate and support participants and their families?
- Our recommendations
  - Fiendishly complicated legal and fiduciary requirements, esp for public companies
  - But there should be a detailed plan and resources for all trials in case of early stopping
    - This includes dyads, families, and study partners
    - Let people know during consent, and remind them often
    - Stay in touch, in the event of related coverage
    - Set up private meetings to discuss study details, including treatment condition assignment
    - Working closely with advocacy organizations may help all stakeholders
  - News releases should provide some direction for participants and their families
  - Study sites must get in touch with participants as soon as possible
  - Leverage social and digital media platforms to let folks know *when they'll know*

Largent 2022 | Alz & Dem

Selection Biases › Measurement Error › Implementation Biases › Social Inequities › Biological Disparities

Justice & Rigor: Neuroimaging

- How should we handle emergent technologies?
  - MRI is now highly portable, and can be used in remote and resource-limited settings
  - Exciting and concerning consequences to democratizing access to brain imaging tools
  - RF1 grant to examine ethical, legal, and social issues in this space
- Broader access is good, but…
  - Practical concerns such as safety, training, research design
  - Differential access to fixed vs portable MRI for marginalized populations
  - Elided distinction between clinical research and care
  - Legal consequences when technology is widely available
- Developing recommendations on ELSI
  - Focus on including marginalized and minoritized populations at all levels
  - Ensure data are not identifiable
  - Use of algorithmic analysis should be transparent and interrogable
  - Robust communication to minimize / mitigate misinformation tactics
  - How to handle participant access (and <u>ownership</u>) of results

Shen 2021 | NeuroImage
Jackson et al | under review
Jackson, Shen, Iles | in prep

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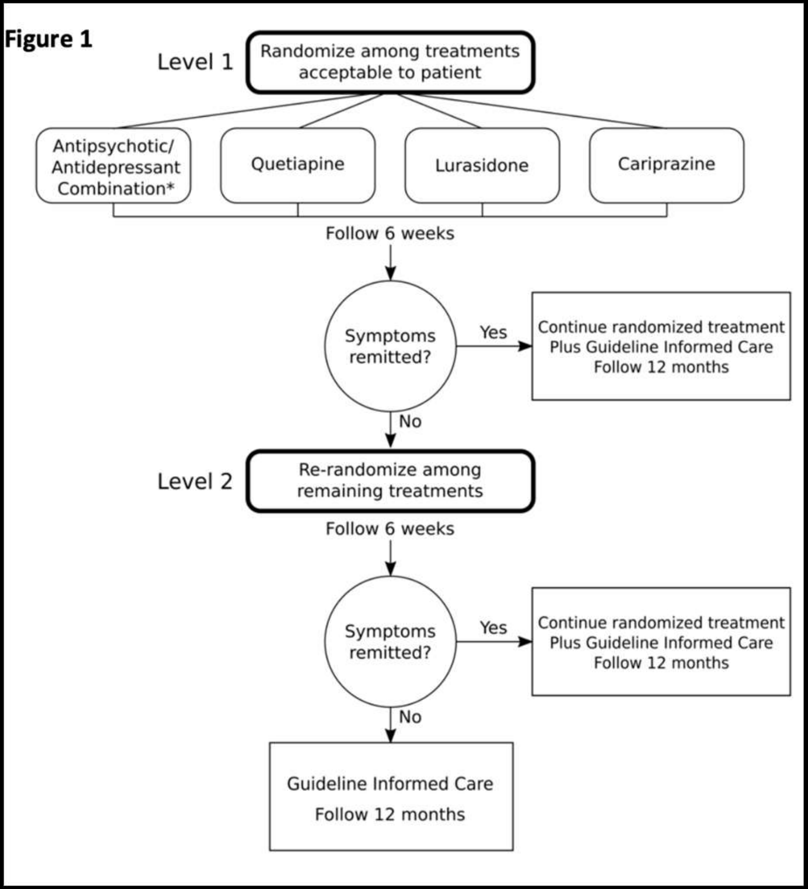
Justice & Rigor: Rethinking Trial Designs

Figure 1



Level 1

Randomize among treatments acceptable to patient

Antipsychotic/ Antidepressant Combination*

Quetiapine

Lurasidone

Cariprazine

Follow 6 weeks

Symptoms remitted?

Yes

Continue randomized treatment
Plus Guideline Informed Care
Follow 12 months

No

Level 2

Re-randomize among remaining treatments

Follow 6 weeks

Symptoms remitted?

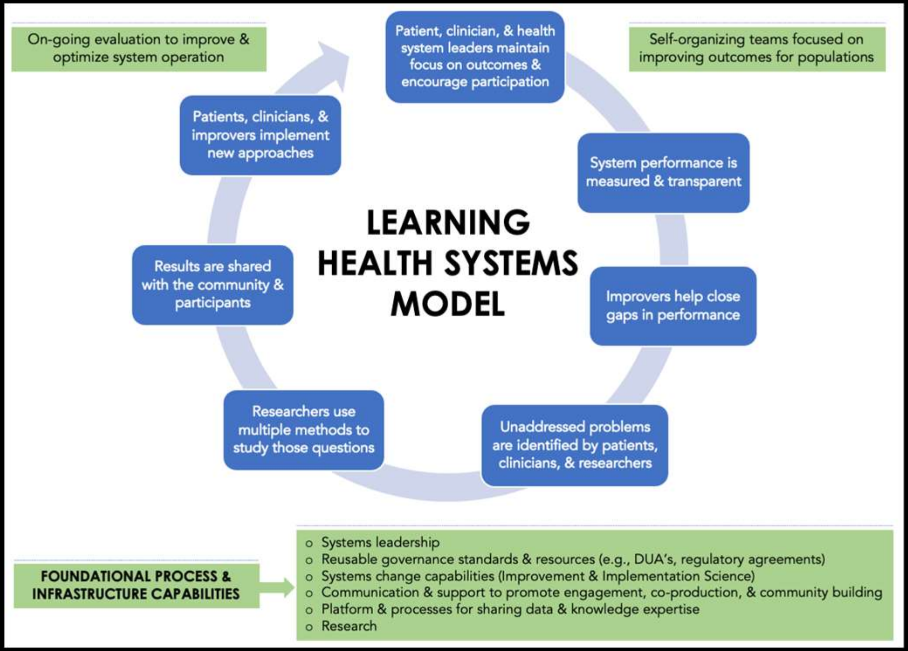
Yes

Continue randomized treatment
Plus Guideline Informed Care
Follow 12 months

No

Guideline Informed Care

Follow 12 months



LEARNING HEALTH SYSTEMS MODEL

On-going evaluation to improve & optimize system operation

Patient, clinician, & health system leaders maintain focus on outcomes & encourage participation

Self-organizing teams focused on improving outcomes for populations

System performance is measured & transparent

Improvers help close gaps in performance

Unaddressed problems are identified by patients, clinicians, & researchers

Researchers use multiple methods to study those questions

Results are shared with the community & participants

Patients, clinicians, & improvers implement new approaches

FOUNDATIONAL PROCESS & INFRASTRUCTURE CAPABILITIES

- Systems leadership
- Reusable governance standards & resources (e.g., DUA's, regulatory agreements)
- Systems change capabilities (Improvement & Implementation Science)
- Communication & support to promote engagement, co-production, & community building
- Platform & processes for sharing data & knowledge expertise
- Research

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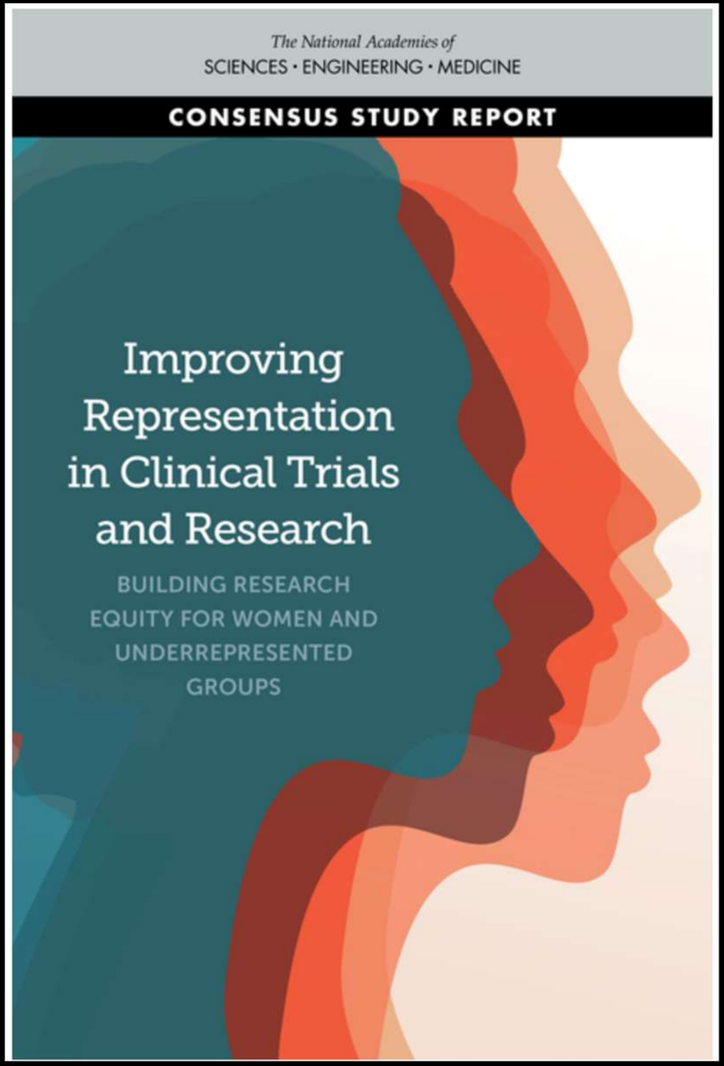

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CONSENSUS STUDY REPORT

Improving Representation in Clinical Trials and Research

BUILDING RESEARCH EQUITY FOR WOMEN AND UNDERREPRESENTED GROUPS

- NASEM Report issued in May 2022
  - Note: I served on this committee through June 2021
- Lack of representation has wide-ranging effects
  - Using Future Elderly Model, savings in the hundreds of billions
  - Stunning limits to generalizability
  - But also limits overall scientific innovation
- An apparent contradiction in policy
  - Agencies hope to improve diverse participation and inclusion
  - Same agencies tried to improve protections for “exploited” and “vulnerable”
  - Clear policies for one but not the other – effort over efficacy
- Missingness is pervasive in data reporting
  - SGM populations in research is barely reported
  - FDA is particularly excoriated for lack of action
- Other barriers to representative trials abound
  - Individual and community factors are often misrepresented
  - Most barriers stem from research teams, funders, policymakers
  - Trust is indeed an issue – but not willingness to participate

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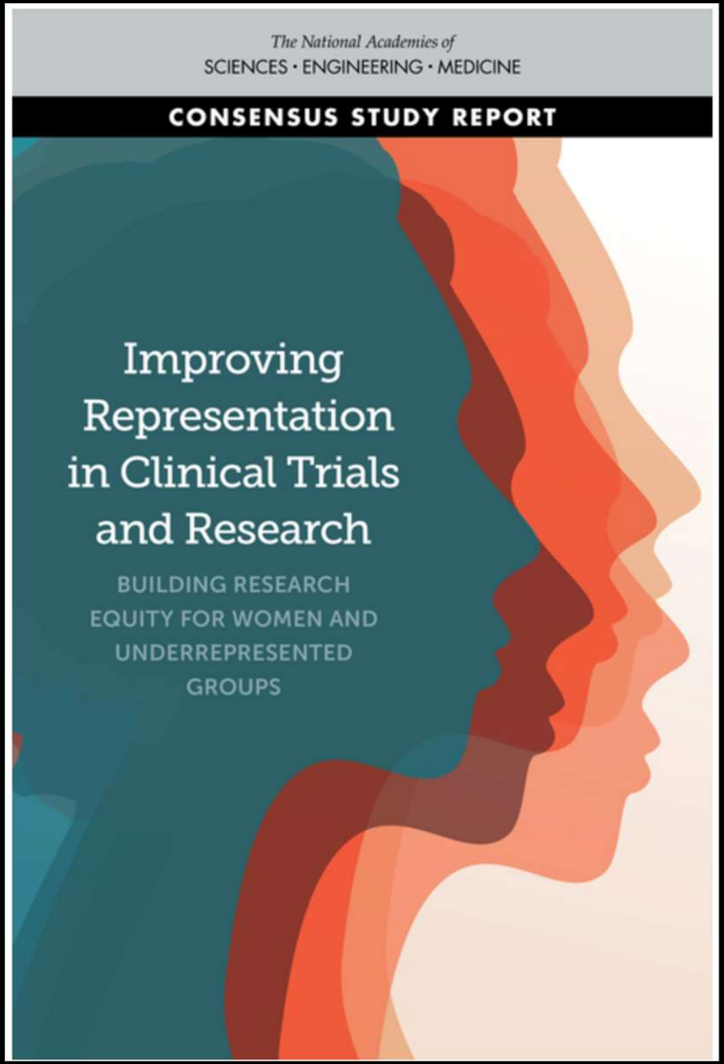

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CONSENSUS STUDY REPORT

Improving Representation in Clinical Trials and Research

BUILDING RESEARCH EQUITY FOR WOMEN AND UNDERREPRESENTED GROUPS

- Recommendations attuned to systemic needs
- HHS and agencies need to improve fidelity
  - Can’t fix what we aren’t observing
  - Need to better plan, monitor, report, evaluate representativeness
  - Improve incentives like tax credits, fast-track, exclusivity
  - Journals need to help out too
- Better approaches to remuneration
  - Largent and Lynch (2017) heavily invoked
  - Allow for differential compensation based on hardship/burden
- Improve infrastructure and workforce
  - Particularly for leaders
  - Provide training, promotion incentives
  - Build infrastructure across systems to make diversity easier
- These are solid recommendations
  - Implementing these recommendations may create new challenges
  - Risk of substandard quantification of representation
  - But what if we could go further?

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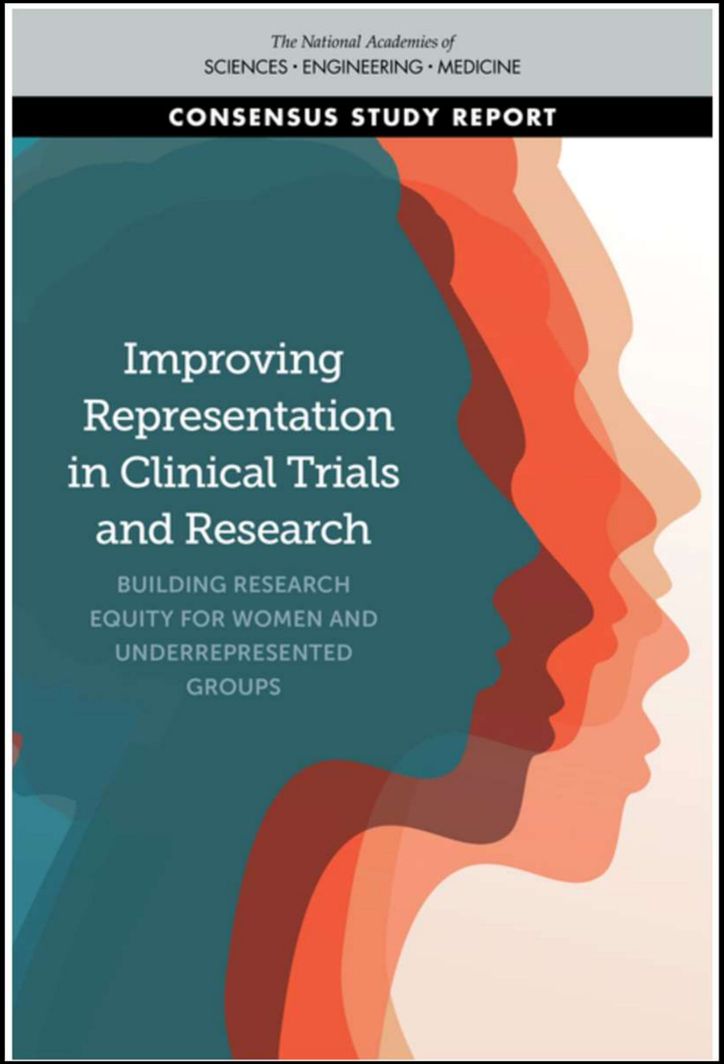

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CONSENSUS STUDY REPORT

Improving
Representation
in Clinical Trials
and Research

BUILDING RESEARCH
EQUITY FOR WOMEN AND
UNDERREPRESENTED
GROUPS

- What does going further look like?
- There are tools available at the researcher level
    - The best ones need time, money, and/or expertise
    - Better integration of marginalized voices
    - More robust efforts at recruitment, engagement, retention
    - Alternatives to RCT: modifications, PCTs, n-of-1, SMART, equipoise
    - Statistical supports: inverse probability weighting, g-estimation
    - Moving beyond NHST and central tendency
- What about balancing risks of *exclusion*?
    - May consider new models of data ownership, access, licensing
    - Community IRBs or External Review Boards
    - Broadened definitions of participation and expertise in research
    - Bioethics was largely missing from report (policy’s there!)
        - May more elegantly approach nuance with this approach
        - But systems / intersectional approaches are paramount
- What if lack of diversity isn’t the whole problem?
    - There may be fundamental limits to the way we typically conduct research
    - Diversity will likely come at the cost of inclusion in the short term
    - Perhaps diversity problems are symptomatic of larger shortcomings
    - Science may need operationalized approach to Justice for elegant solutions

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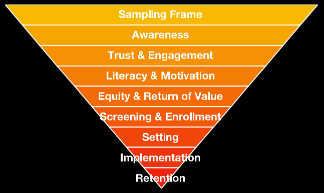
So what does all this mean?

- <u>Diversity</u> is a stopgap for <u>inclusion</u> on the way to <u>representation</u>
  - The terms have never been interchangeable
  - Strong scientific justification for representative sampling
  - “Diversity” is a floor, not a ceiling
  - We have work to do within science before we blame larger societal failures
- JEDI needs quantification to fit in our world of health
  - Dire need for creation of CDEs, workflows, and protocols
  - Precision measurement and intervention is within reach
  - Convergent compatibility with thoughtful statistical theory
- This is just the tip of the iceberg
  - Resources from market research, epidemiology, LIS, bioethics, social theory
  - Possible new field of research, between pop health and clinical research
  - Glimmers from pragmatic trials, imp sci, learning networks
- Equity will soon be the primary driver of health innovation
  - The emergence of personalized and precision approaches requires it
  - All rigorous science and policy must *necessarily be equitable*



Sampling Frame
Awareness
Trust & Engagement
Literacy & Motivation
Equity & Return of Value
Screening & Enrollment
Setting
Implementation
Retention

HCS	DATA SOURCES	ETHICS/ REG	OUTCOMES	DESIGN/ STATS	IMPLEMENT
Demography (within / among HCS) Representa-tiveness (census, disease burden, community)	Missing-ness & gaps in data sources Stakeholder outcomes Data burden	Engage-ment metrics for vulnerable populations Consent language & format	Triangulation and alignment of outcomes across all stakeholder groups	DAGs Quantitative bias analyses (modified E-value) Floating catchment area metrics	GOI Score CFIR analyses Positive / negative adaptation

Selection Biases
Measurement Error
Implementation Biases
Social Inequities
Biological Disparities

Many, many thanks to:

CARE
at Massachusetts General Hospital

Michelle Anderson*
Erin Bennet
Abby Bergey
Shana Birly
Chastity Bowick
Diana Cardona
Rebekah Caruthers
Whitney Dodson
Fran Eddings
Luis Fernandez-Castro*

Jose Luis Gonzalez
Helen Hemley
Chien-Chi Huang*
Juliana Ison
Mike Kincade*
Allison Lane
Rosie Munoz-Lopez*
Tiffany Pham
Maria Mercedes Pica

Jason Resendez
Marissa Reynolds
Ashley Richards
Angie Sanchez
Ashley Soriano
Pata Suyemoto*
Nicole Taikeff Gabela
Doreen Ward*
Ana Zambrano*

Grant Support

NIH DP1 AG069873
PCORI EAIN 19521

MJFF 18881
MJFF 19527

MJFF 19576
NIH R61 AG081880

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Thanks!

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Bonus slides

(oh dear)

Here’s some broad advice

- Separate catchment area from sampling frame
  - Who can *really* participate in that protocol, given its design?
  - Helps avoid fallacy of overestimating participant willingness (Lasagna’s Law)
- Be thoughtful before implementing quick fixes from other sites
  - Don’t recruit in Black churches unless you have time to spend in Black churches
  - There are no cultural monoliths, so it’s always better to trust local input
- You probably have an awareness problem that needs fixing
  - Failing to solve for this barrier tends to negate other efforts
- If you want to get new folks in your study, you have to do new things
  - Diverse participation in research is a workflow problem, not a scaling problem
- Trust the experts - your CRCs and RAs
  - They can clearly see the barriers and effective solutions
  - When in doubt, be <u>scientific</u> - *go out and measure some stuff*

Here’s a little concrete advice

- Use plain language for everything, including your ICF
  - Language equity shouldn’t be the problem it is, but let’s at least get English right
  - Aim for 5th grade reading level, but no higher than 8th
- Use clinician champions and research ambassadors
  - This becomes easier if you have a solid clinic / community presence
  - Think about what you can offer clinicians to support research (hint: your expertise)
- Design for a strong return of value
  - Beyond return of results - make it easy / free / fun to participate
  - If you can’t return any results or decent compensation, do participant celebrations
- Sustained community entrenchment works but takes time
  - Can’t float in and out, magic number seems to be around 7 years
  - Talk to communities and families, not just prospective participants

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Here’s some more concrete advice

- Schedule visits with the patient in mind
  - Low-traffic times of day, maintain familiar faces for study visits
  - Thank them often, build in extra time to explain study and novel findings
- Make sure there are participation options for screen-fails
  - Other studies should be offered, even outside your study team
  - At least build a database or registry for recontact
  - Retain them as ambassadors because they’re already engaged
- Do some social, digital, and traditional media
  - Your CRCs and RAs are better at this than you
  - Media presence gives you solid set of engagement metrics
- Diversify your team. At all levels
  - Look for local voices, not just faces that reflect the group you want

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Selection Biases › Measurement Error › Implementation Biases › Social Inequities › Biological Disparities

Justice & Rigor:
A Targeted Theory of Change

TIERS OF ENGAGEMENT

“Research… n't fr… Bost… and d… 't know th… hist… y of t… own… tituti… and th… com… engage. *They don’t understand why they’re not welcome.”*

Engage Stakeholders

- 12 stakehol… from divers… backgroun…
- $ = acknowledg… of expertise
- Transparen… about IRB process

Community Ownership

- Develop guidelines for researcher interaction with deliverables
- Model for community ownership of ToC & Outcome Map
- Sustainability: Dissemination of research findings model

What a… peo… with the data? *We have to be at the table asking the questions*, not just being … as guinea … *that has been the reality*.”

organization who we are trying to reach in our programming.

Hemley et al | under review

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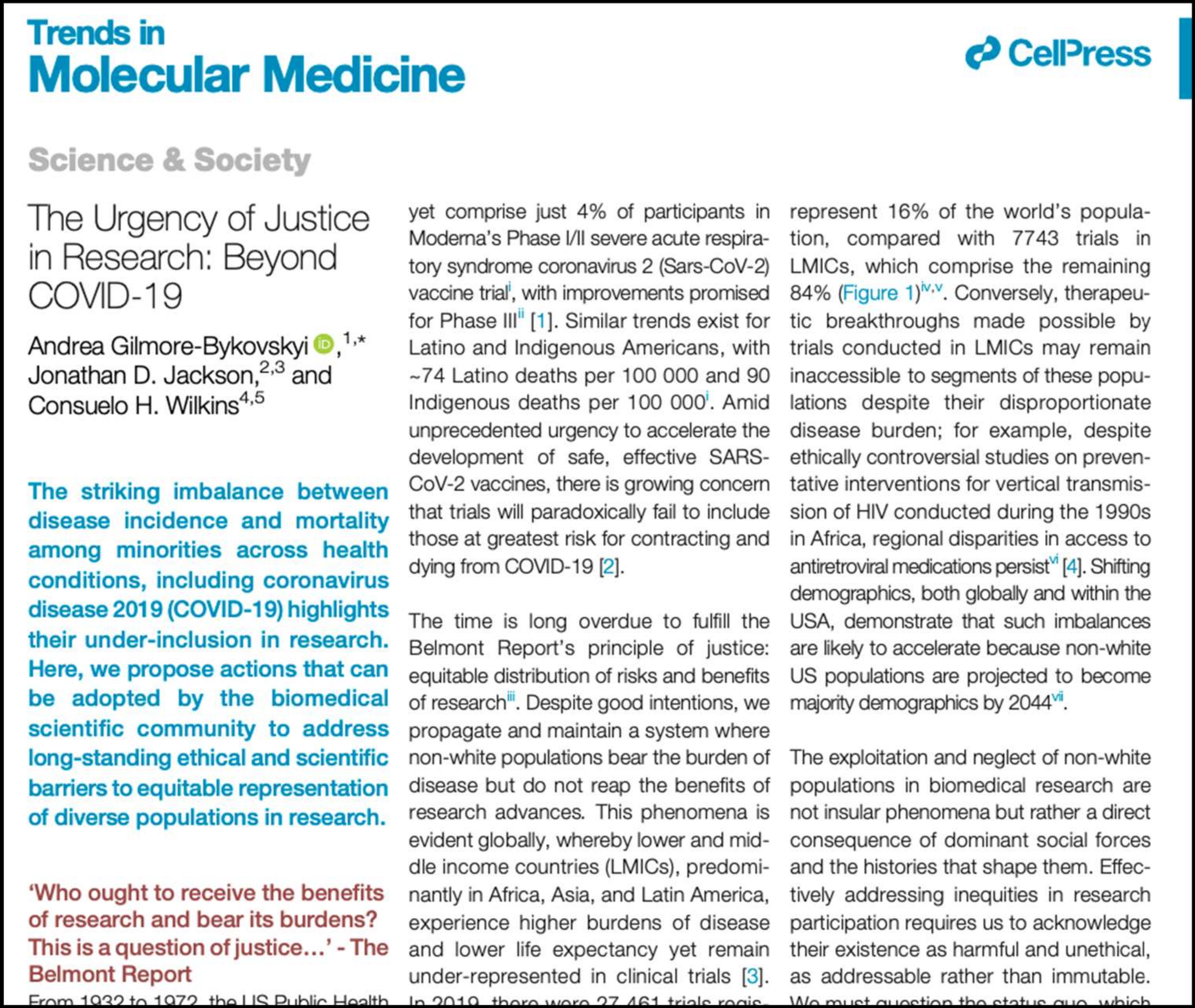

Trends in
Molecular Medicine

CellPress

Science & Society

The Urgency of Justice in Research: Beyond COVID-19

Andrea Gilmore-Bykovskyi,[1,*]
Jonathan D. Jackson,[2,3] and
Consuelo H. Wilkins[4,5]

The striking imbalance between disease incidence and mortality among minorities across health conditions, including coronavirus disease 2019 (COVID-19) highlights their under-inclusion in research. Here, we propose actions that can be adopted by the biomedical scientific community to address long-standing ethical and scientific barriers to equitable representation of diverse populations in research.

> ‘Who ought to receive the benefits of research and bear its burdens? This is a question of justice…’ - The Belmont Report

From 1932 to 1972, the US Public Health

yet comprise just 4% of participants in Moderna's Phase I/II severe acute respiratory syndrome coronavirus 2 (Sars-CoV-2) vaccine trial[i], with improvements promised for Phase III[ii] [1]. Similar trends exist for Latino and Indigenous Americans, with ~74 Latino deaths per 100 000 and 90 Indigenous deaths per 100 000[i]. Amid unprecedented urgency to accelerate the development of safe, effective SARS-CoV-2 vaccines, there is growing concern that trials will paradoxically fail to include those at greatest risk for contracting and dying from COVID-19 [2].

The time is long overdue to fulfill the Belmont Report's principle of justice: equitable distribution of risks and benefits of research[iii]. Despite good intentions, we propagate and maintain a system where non-white populations bear the burden of disease but do not reap the benefits of research advances. This phenomena is evident globally, whereby lower and middle income countries (LMICs), predominantly in Africa, Asia, and Latin America, experience higher burdens of disease and lower life expectancy yet remain under-represented in clinical trials [3]. In 2019, there were 27 461 trials regis-

represent 16% of the world's population, compared with 7743 trials in LMICs, which comprise the remaining 84% (Figure 1)[iv,v]. Conversely, therapeutic breakthroughs made possible by trials conducted in LMICs may remain inaccessible to segments of these populations despite their disproportionate disease burden; for example, despite ethically controversial studies on preventative interventions for vertical transmission of HIV conducted during the 1990s in Africa, regional disparities in access to antiretroviral medications persist[vi] [4]. Shifting demographics, both globally and within the USA, demonstrate that such imbalances are likely to accelerate because non-white US populations are projected to become majority demographics by 2044[vii].

The exploitation and neglect of non-white populations in biomedical research are not insular phenomena but rather a direct consequence of dominant social forces and the histories that shape them. Effectively addressing inequities in research participation requires us to acknowledge their existence as harmful and unethical, as addressable rather than immutable. We must question the status quo, which

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Justice: the Third Pillar

- Strengthen compliance, reporting, transparency
  - Demographic / subgroup data often unreported, missing, despite requirements
  - Develop detailed, transparent reporting as well as accountability (enforcement)
  - End ongoing research abuses
- Identify, measure, systemically address exclusionary research
  - Assess and address data burden
  - Model overlapping, currently unmeasured selection biases
  - Promote language equity, even for English speakers
  - End practices that exclude on the basis of researcher convenience
- Move beyond proportional representation
  - No scientific basis for representation at the level of census tracts
  - Focus on disease risk or burden
  - No basis for Whites as referent group

Gilmore-Bykovskyi 2020 | Trends Mol Med

Justice: the Third Pillar

- Build sustained, reciprocal relationships with marginalized communities
  - Stop centering research goals on researcher / institution
  - Develop participant experience metrics
  - Broaden definition of “participation” in research
  - Don’t lament mistrust – become trust*worthy*
- Develop sciences of research participation and inclusion
  - Build evidence-based, mechanistic guidance for study design, recruitment, retention
  - Systemically identify and address research barriers
  - Remember that the plural of anecdote is not data, even for diverse recruitment
- Recognize connection between research and health inequities
  - Without justice in research, we cannot solve health inequities
  - Build an infrastructure to support measurement and intervention on justice pillar
  - If successful, will create daylight between *inequities* and *disparities*

Gilmore-Bykovskyi 2020 | Trends Mol Med

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PBS (1993)

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The FIRE-UP PD II Study

- What was the mechanism of action in Phase I?
  - Control sites saw a bump in representation, too
  - Is merely orienting to “diversity” sufficient?
  - Do bespoke interventions contribute over & above best practices?
  - Are there separable influences on diversified recruitment?
- Design
  - Harmonize community engagement activities prior to study recruitment
  - 3 activities (1/month) with CBO and CHC partner ($10k stipend)
  - 4 intervention-control pairs ($50k - $20k)

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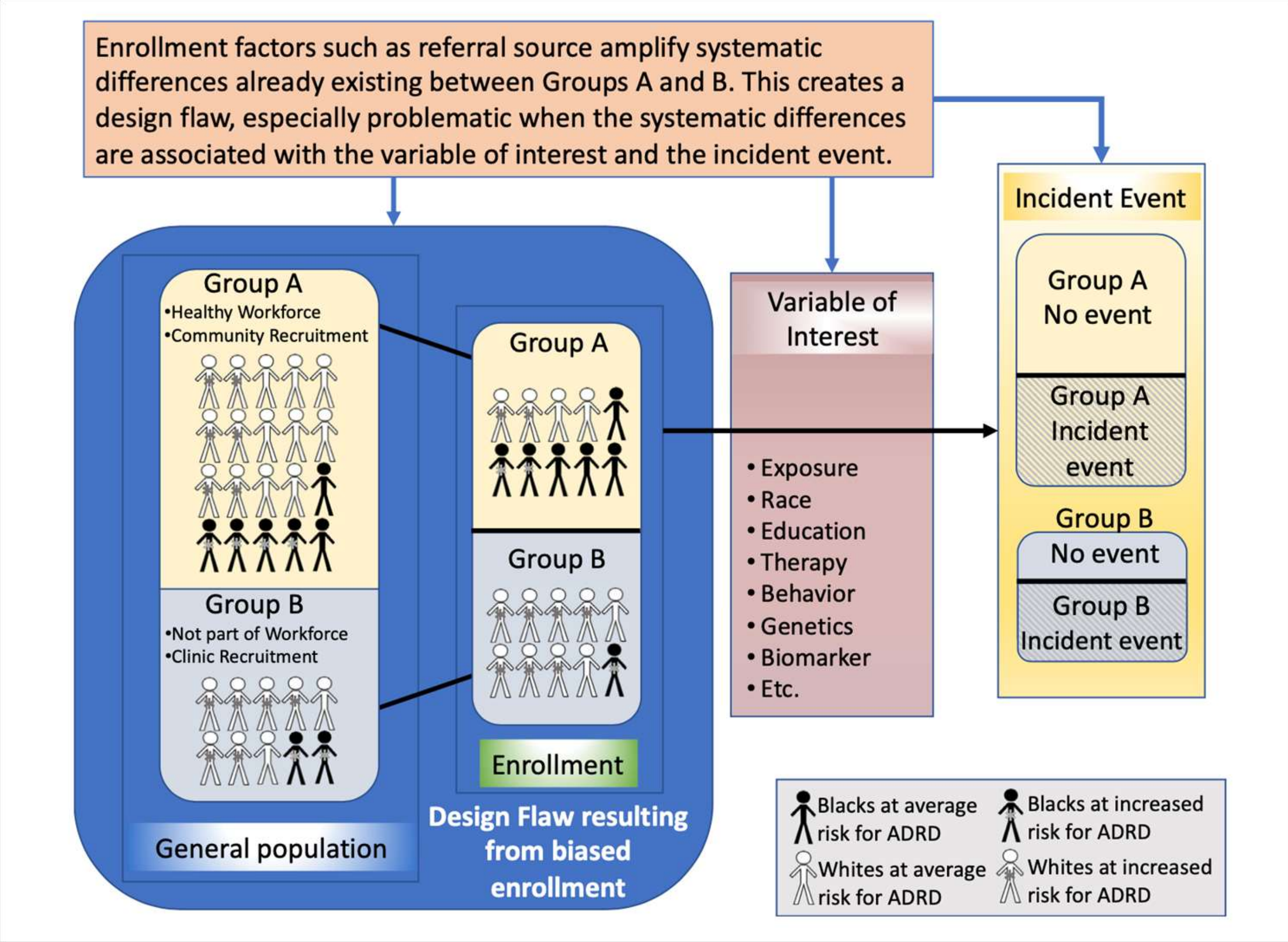
But, uh, how do we operationalize Justice?

it seems so. hard.

Current efforts in diverse recruitment



Enrollment factors such as referral source amplify systematic differences already existing between Groups A and B. This creates a design flaw, especially problematic when the systematic differences are associated with the variable of interest and the incident event.

Group A
- Healthy Workforce
- Community Recruitment

Group B
- Not part of Workforce
- Clinic Recruitment

General population

Group A

Group B

Enrollment

Design Flaw resulting from biased enrollment

Variable of Interest
- Exposure
- Race
- Education
- Therapy
- Behavior
- Genetics
- Biomarker
- Etc.

Incident Event

Group A No event

Group A Incident event

Group B No event

Group B Incident event

Blacks at average risk for ADRD

Blacks at increased risk for ADRD

Whites at average risk for ADRD

Whites at increased risk for ADRD

Gleason 2019 | Alz & Dementia

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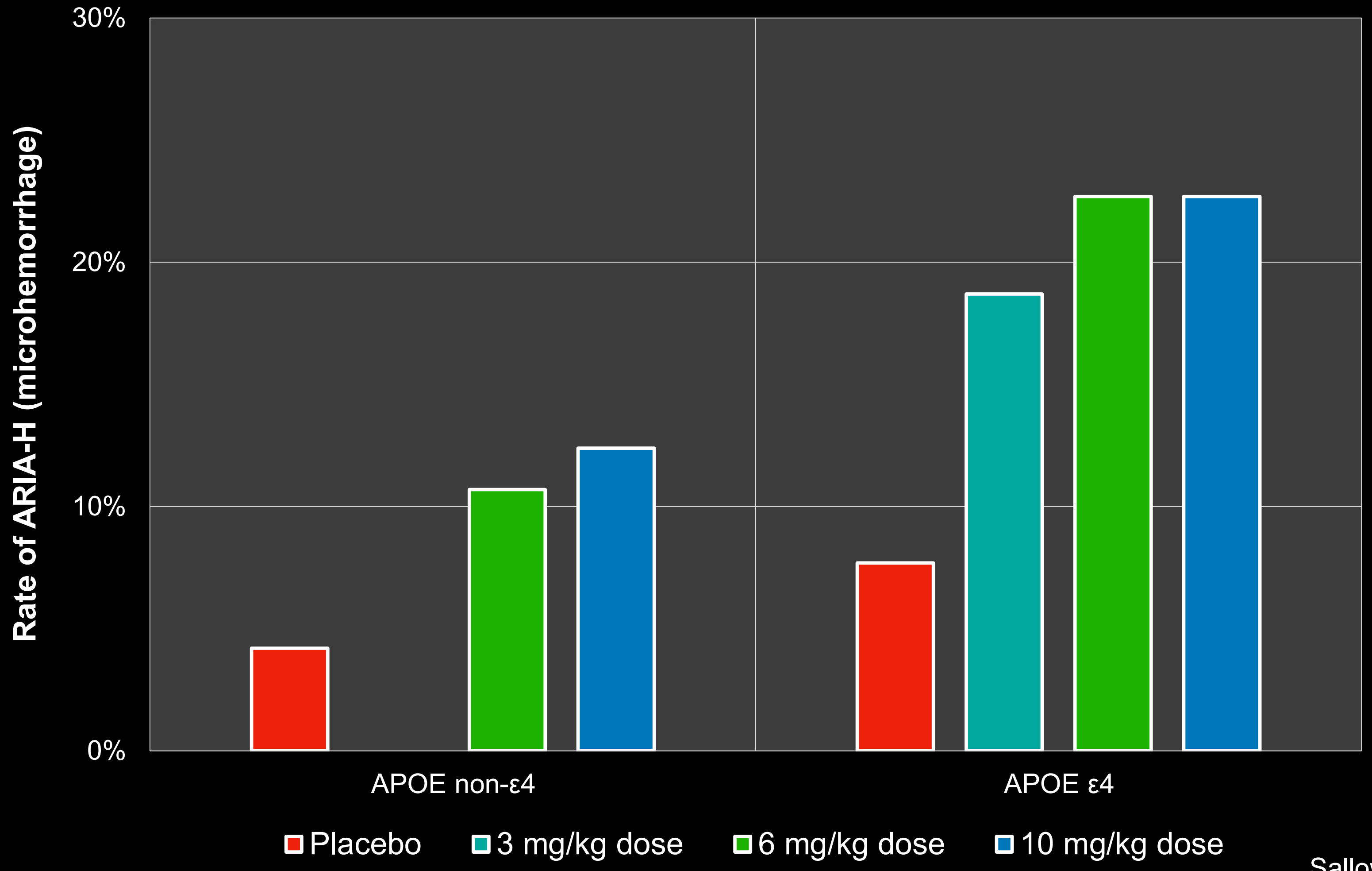
Current efforts in diverse recruitment



Salloway 2021 | JAMA Neur

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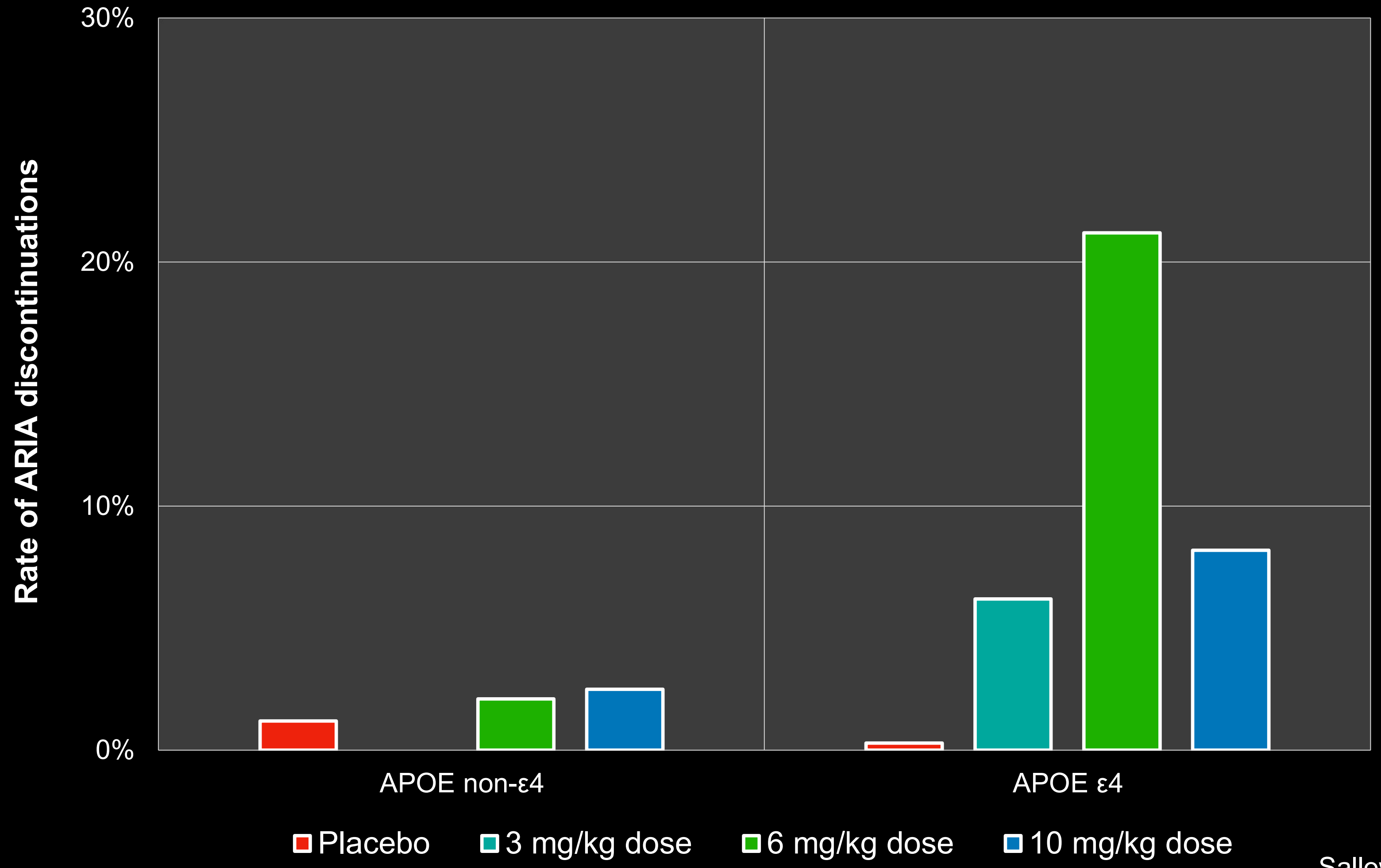
Current efforts in diverse recruitment



Salloway 2021 | JAMA Neur

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That Third Pillar

- A fundamental need to restore and empower
  - Historically, policy has been slow, ineffective, piecemeal
  - Major policy shifts have been reactive, introducing downstream headaches
  - Revisiting the goals of justice to balance risks of inclusion and exclusion is our best bet
- Justice means elegant solutions to hard questions
  - Broadened, omni-stakeholder benefits from science - on self-determined timelines
  - Individual, institutional, community and societal risks of exclusion integrated into models
  - Risks of inclusion need to be clarified and addressed with systems approach too
  - Introducing flexibility and context leads way for future of research
- Better us, better science, together
  - Reifying what we mean by Justice, and for whom, is an excellent first step
  - Integrated approach to bias reduction presents us with many available tools and frameworks
  - There is no tension between rigorous science and just science
    - Diversity and representation may be regarded as a symptom of scientific quality

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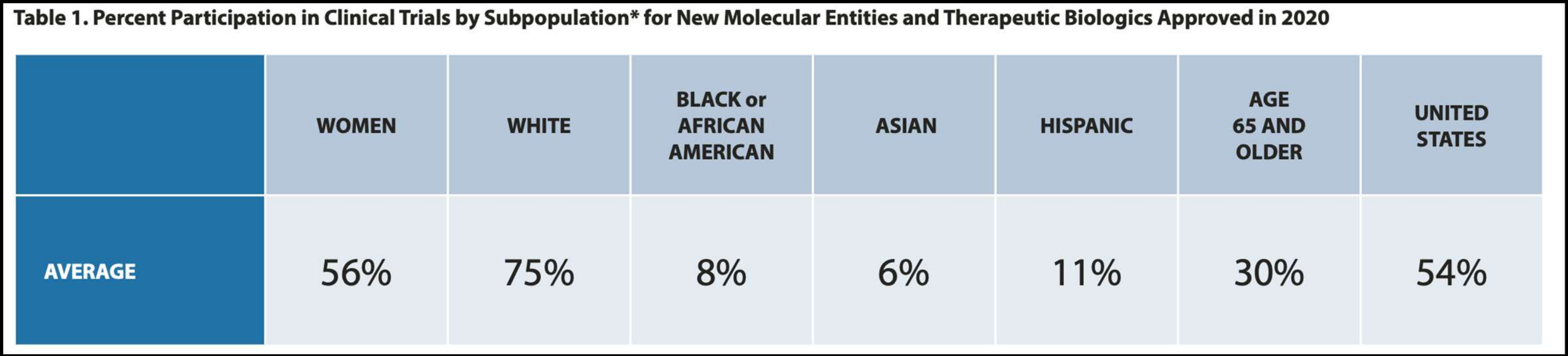
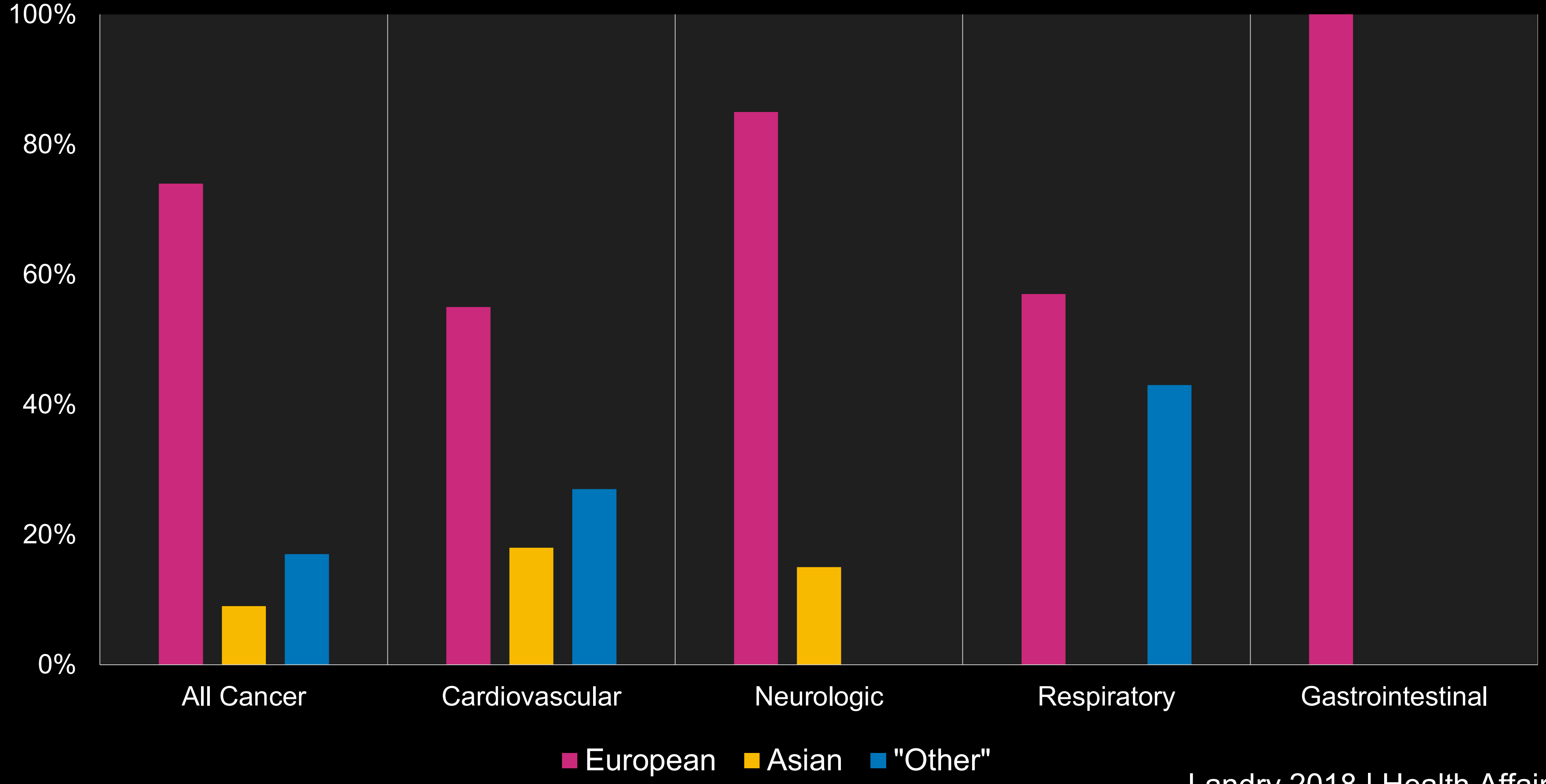


Table 1. Percent Participation in Clinical Trials by Subpopulation* for New Molecular Entities and Therapeutic Biologics Approved in 2020

	WOMEN	WHITE	BLACK or AFRICAN AMERICAN	ASIAN	HISPANIC	AGE 65 AND OLDER	UNITED STATES
AVERAGE	56%	75%	8%	6%	11%	30%	54%

Est US pop	**50.8%**	**76.5%**	**13.4%**	**5.9%**	**18.3%**	**16.0%**	
Median DTS	**55%**	**78%**	**3%**	**5%**	**8%**	**11.5%**	**36%**
CoV DTS (SD / mean)	**0.47**	**0.35**	**1.64**	**1.44**	**0.85**	**1.10**	**0.80**

Diversity in Genotypic/Phenotypic Databases



Landry 2018 | Health Affairs

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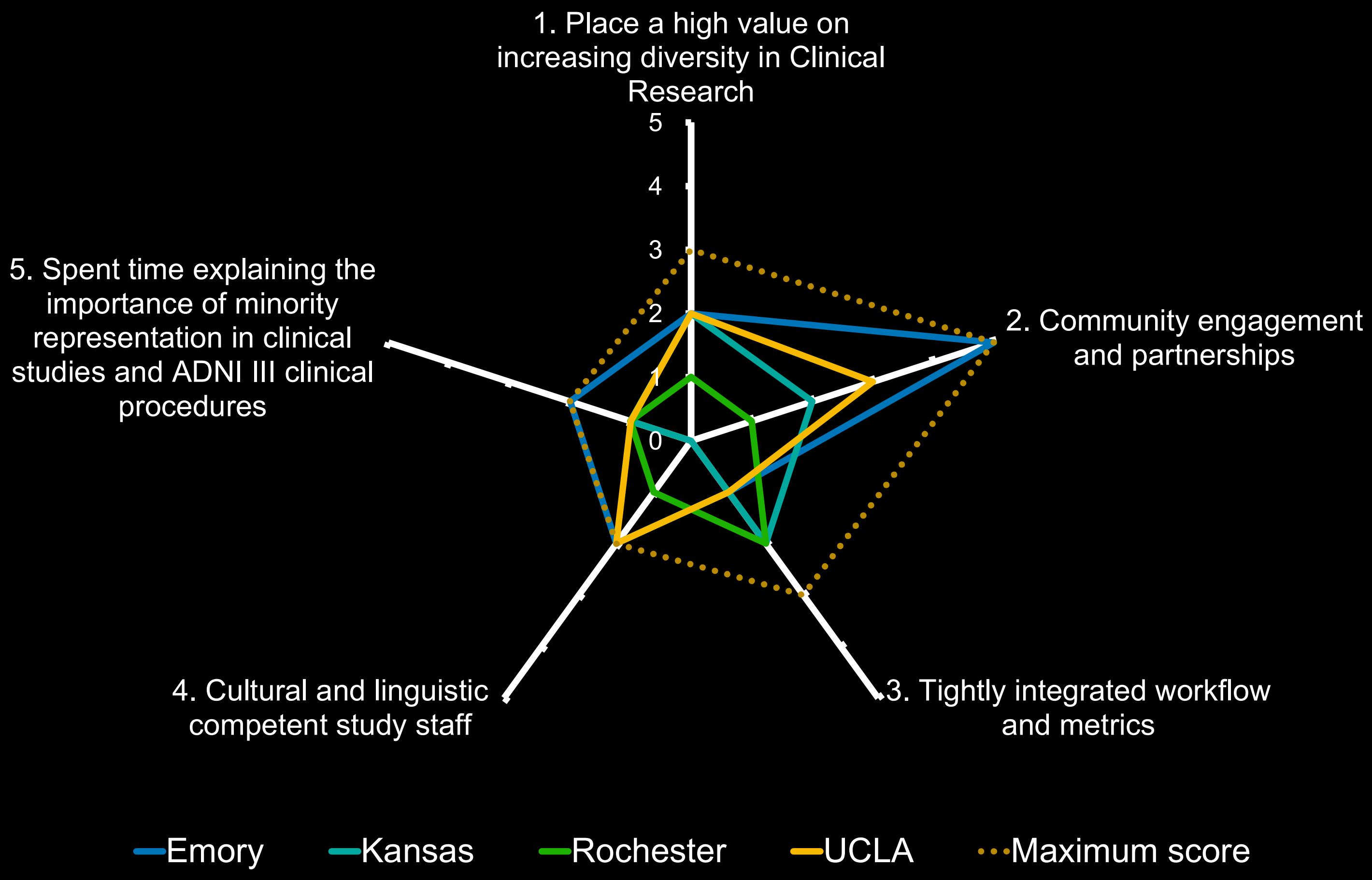
Selection Biases | Measurement Error | Implementation Biases | Social Inequities | Biological Disparities

Recruitment for ADNI3



Ison et al | in revision

Selection Biases › **Measurement Error** › Implementation Biases › Social Inequities › Biological Disparities

Recruitment for ADNI3

Rochester

Recruitment phase	Target populations (number of participants)			
	African-American women	African-American males	Other males	Total
1. Reach out (communicated information about ADNI III)	11	6	136	153
2. Engaged (showed interest and met the enrollment criteria)	2	1	43	46
3. Recruited (were screened)	0	0	9	10
4. Enrolled (filled out the forms)	0	0	8	8

Minorities reached out

Engaged
18%

Recruited
0%

Enrolled
0%

Emory

Recruitment phase	Target populations (number of participants)		
	African-American	All seniors	Total
1. Reached out	25	72	97
2. Engaged	15	58	73
3. Recruited	8	22	30
4. Enrolled	6	17	23

Minorities reached out

Engaged
60%

Recruited
53%

Enrolled
75%

Ison et al | in revision

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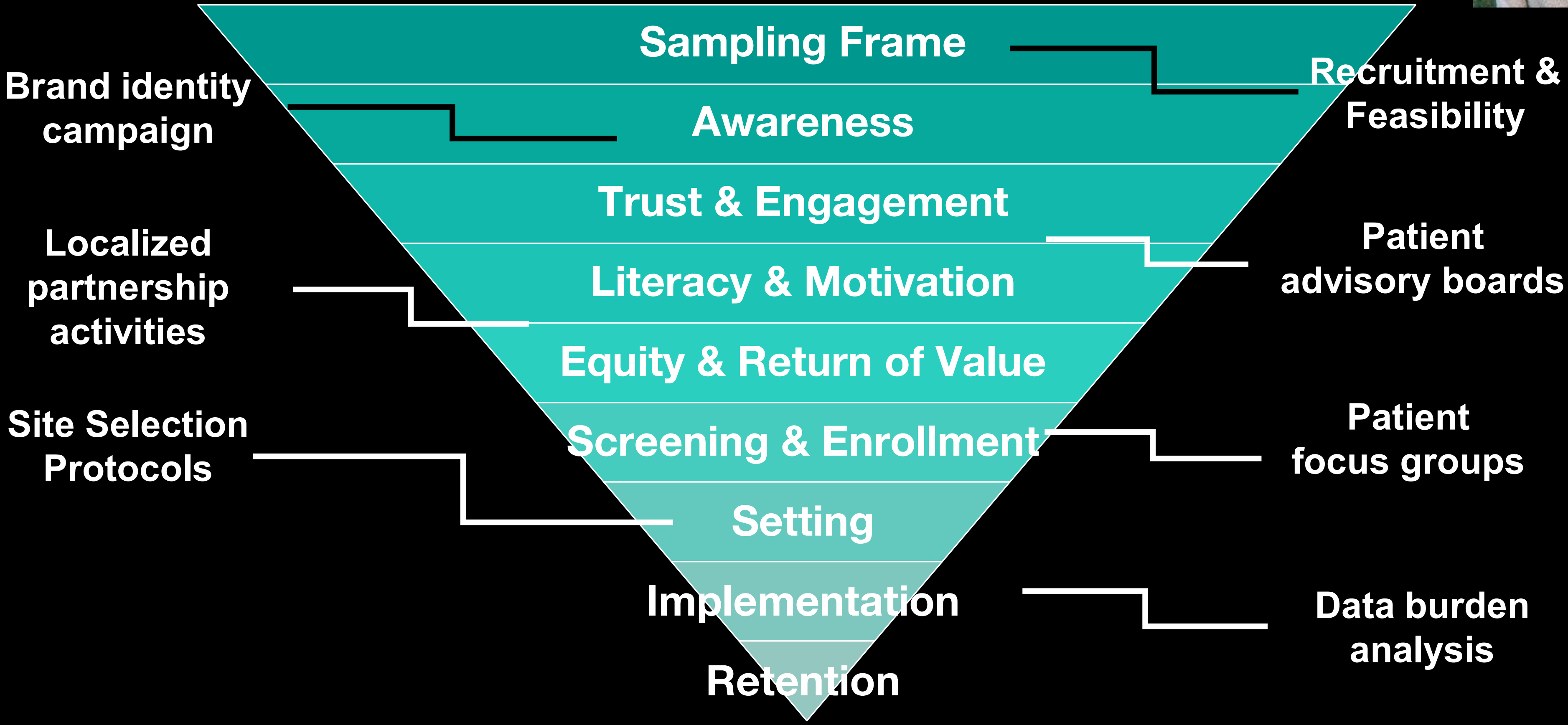
EPPIC-Net Clinical Trial Network



Sampling Frame

Awareness

Trust & Engagement

Literacy & Motivation

Equity & Return of Value

Screening & Enrollment

Setting

Implementation

Retention

Brand identity campaign

Localized partnership activities

Site Selection Protocols

Recruitment & Feasibility

Patient advisory boards

Patient focus groups

Data burden analysis

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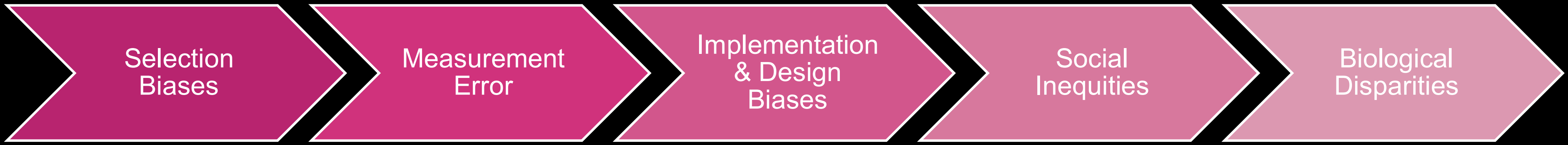


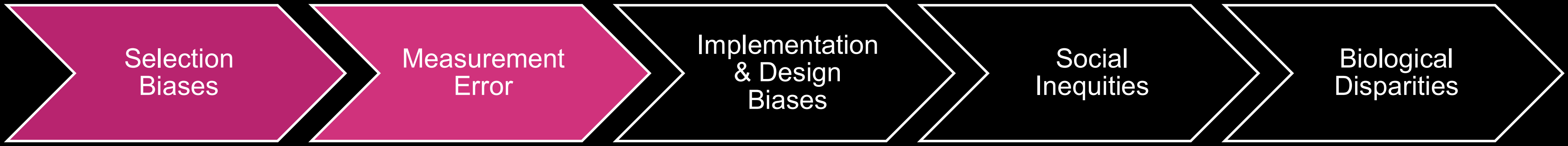
Selection Biases

Measurement Error

Implementation & Design Biases

Social Inequities

Biological Disparities



Selection Biases

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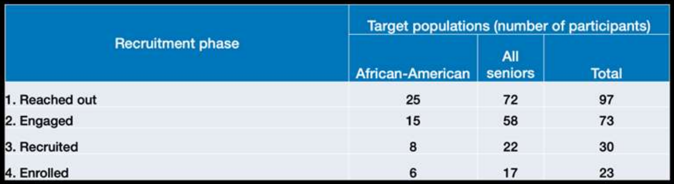
Social Inequities

Biological Disparities

What's next for a science of inclusion



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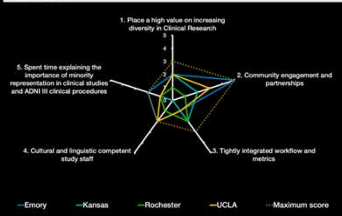
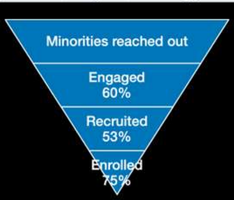
3. Recruited	8	22	30
4. Enrolled	6	17	23





Minorities reached out

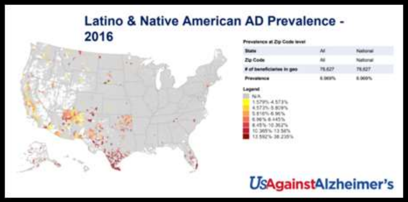
Engaged
60%

Recruited
53%

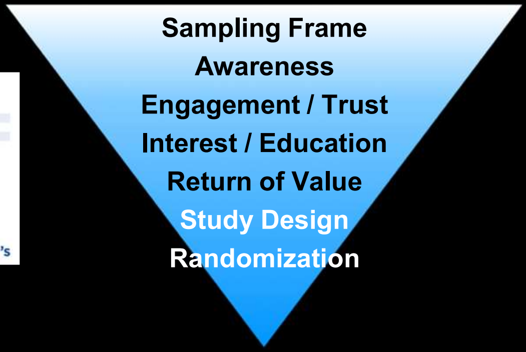
Enrolled
75%

Ison, Gonzalez & Jackson | in prep

Ison et al | under review



Jackson et al | in prep



Sampling Frame

Awareness

Engagement / Trust

Interest / Education

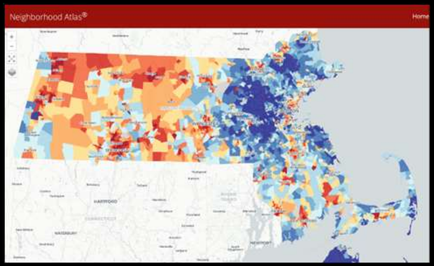
Return of Value

Study Design

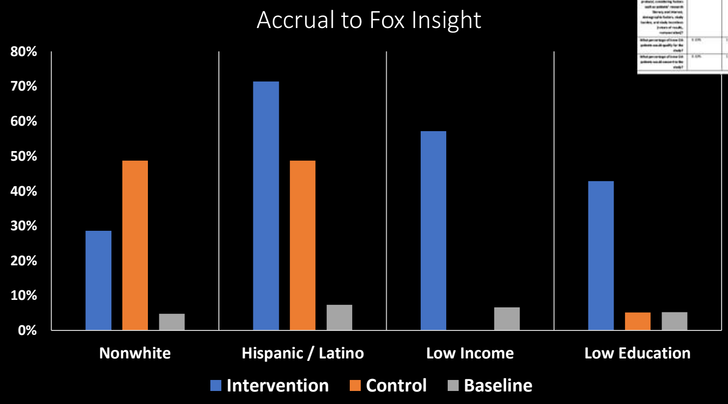
Randomization

Jackson | in prep
Jackson | under review
Indorewalla et al | in revision

Macht et al | in prep



Kind et al | forthcoming



Sanchez et al | under review

Do you have Parkinson's disease?
Does someone you know?
Do you want to learn more about Parkinson's disease?

JOIN US FOR A FREE WORKSHOP ABOUT PARKINSON'S FROM

THE CHICAGO MOVEMENT COALITION

MAKING MOVES FOR PARKINSON'S

Where: Edgewater Satellite Senior Center
5917 N. Broadway Street, Chicago, IL 60660

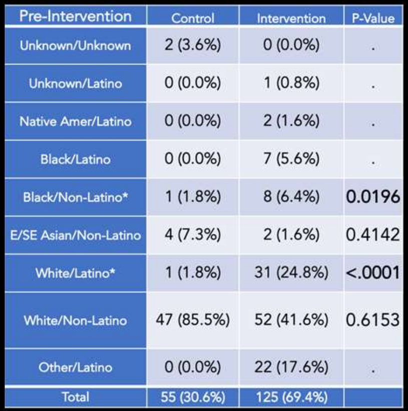
When: January 15, 2020, 12:30 - 2:30 PM

- Hear from people in your community who have Parkinson's
- Find out what the symptoms are.
- Discover resources in your Chicago community

Food will be served.
Free tote bag with Parkinson's info.
A Spanish interpreter will be there.

To join the workshop or ask questions, contact Karen at (312) 503-0755 or ChicagoMovementCoalition@northwestern.edu

Indorewalla et al | in revision

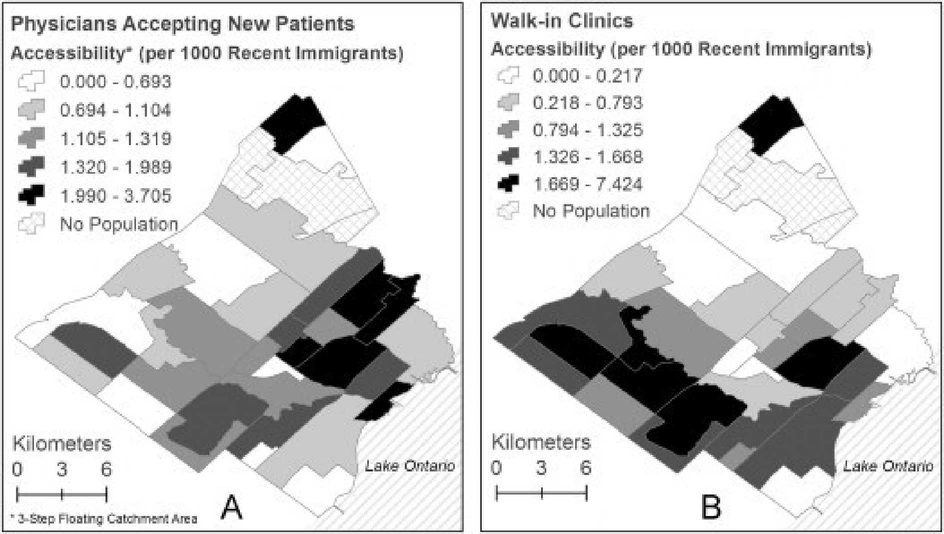


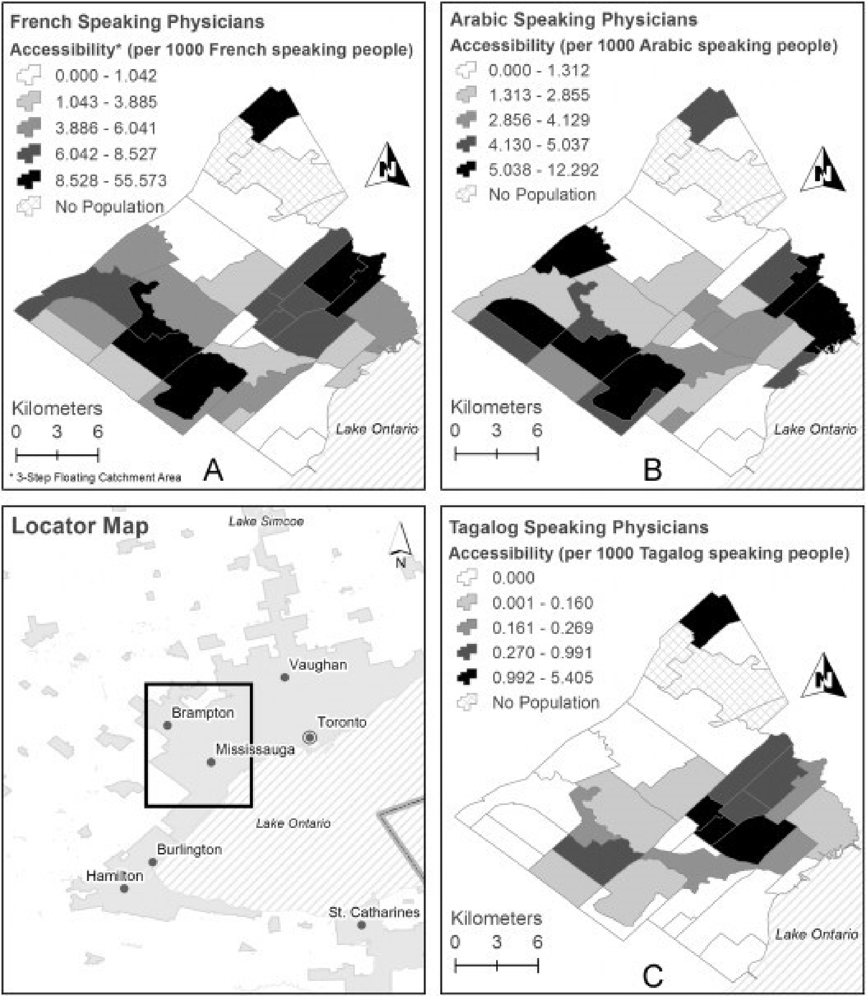
Pre-Intervention	Control	Intervention	P-Value
Unknown/Unknown	2 (3.6%)	0 (0.0%)	.
Unknown/Latino	0 (0.0%)	1 (0.8%)	.
Native Amer/Latino	0 (0.0%)	2 (1.6%)	.
Black/Latino	0 (0.0%)	7 (5.6%)	.
Black/Non-Latino*	1 (1.8%)	8 (6.4%)	0.0196
E/SE Asian/Non-Latino	4 (7.3%)	2 (1.6%)	0.4142
White/Latino*	1 (1.8%)	31 (24.8%)	<.0001
White/Non-Latino	47 (85.5%)	52 (41.6%)	0.6153
Other/Latino	0 (0.0%)	22 (17.6%)	.
Total	55 (30.6%)	125 (69.4%)	

Sanchez et al | under review

Jonathan Jackson | jjackson31@partners.org

What’s next for a science of inclusion





Bissonnette 2012 | Health & Place

The FIRE-UP PD II Study

Pre-intervention harmonized activities (**3 months**)

- ALL SITES
- 2 PARTNERS:
  - Community-Based Organization
  - Community Health Center
- 3 MONTHLY COMMUNITY ACTIVITIES (starting in March)
- CLINIC WORKFLOW: written materials for consideration, including all patients

Surveys (35 participants / site)

Intervention (6 months)

- CONTROL : Regular recruitment workflow
- INTERVENTION:
- *Clinical awareness
- * Trust
- *Referrals

Surveys (35 participants / site)

Jonathan Jackson | jjackson31@partners.org

Towards a Quantified Science of Engagement and Recruitment

GSA/LINC-AD Webinar Series

THE GERONTOLOGICAL SOCIETY OF AMERICA®