The Challenge of Health Equity in Clinical Research

Towards a Quantifiable Science of Inclusion

Jonathan Jackson, PhD
May 7, 2020

Goals for today

1. Reframe the history of recruitment science and connection to diversity
2. Discuss early data on quantifying engagement and recruitment to research
3. Provide a few suggestions to bolster recruitment

Disclosures

- Community engagement work (Boston) supported by
  - Otsuka Foundation
- Research supported by
  - NIH (various ICs)
  - Michael J Fox Foundation
  - Massachusetts General Hospital
- Intellectual disclosures (h/t @MariaGlymour)
  - US-centric view
  - Belief that expanding access to clinical research is good
  - Motivation to develop nascent subfield
  - Desire to receive research funding for this work
  - Secret desire to be an epidemiologist

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

—Martin Luther King, Jr.

Tuskegee – the origin of diverse recruitment

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The New York Times

NEW YORK, WEDNESDAY, JULY 26, 1972

Syphilis Victims in U.S. Study Went Untreated for 40 Years

By JEAN HELLER

The Associated Press

WASHINGTON, July 25—For 40 years the United States Pub-

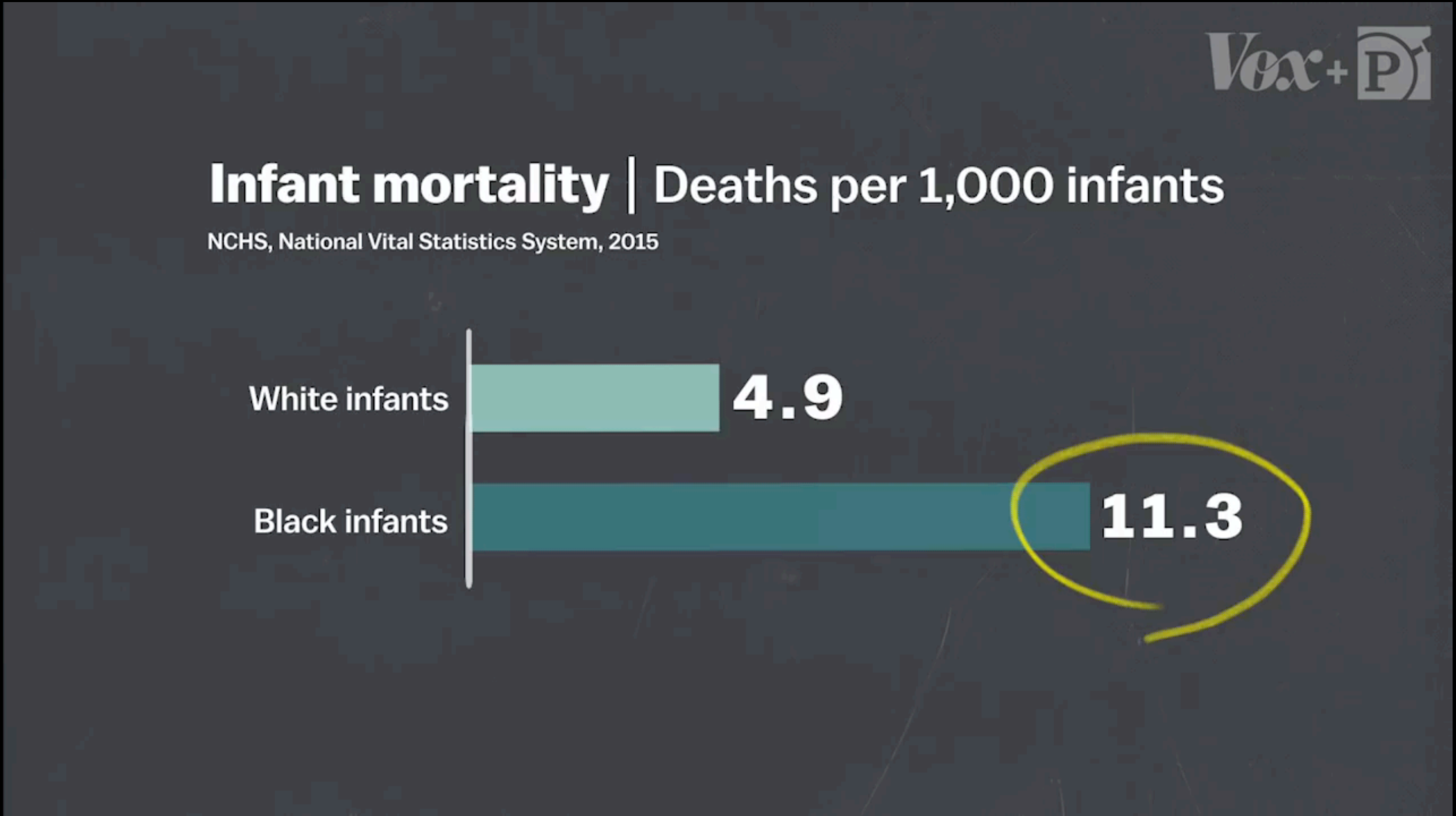
have serious doubts about the morality of the study, also say

Source: Nova, PBS, 1993

Other medical abuses against Blacks

- **Samuel Cartwright (1840s) -** *coined drapetomania and dysthaesthesia aethiopica to justify slavery*
- **Marion Sims (1850s) -** *learned to repair prolapsed uteri on Black slaves without anesthesia*
- **Joseph Goldberger (1912) -** *induced pellagra in prisoners*
- **American South (1920s) -** *medical use of “idiot,” “imbecile,” & “moron” to force sterilization of Blacks*
- **George Gey (1951) -** *took Henrietta Lacks’ cells without consent, created HeLa immortal cell line*
- **Chester Southam (1952, 1963) -** *injected cancer cells in prisoners*
- **Vertus Hardiman (1925) -** *skull dissolved after being irradiated as 5 year old, parents deceived*
- **Ebb Cade (1941) -** *injected with plutonium, denied medical care after severe car accident*
- **Eugene Saenger (1960-1971) -** *forged consent documents, irradiated patients*
- **Johns Hopkins (1970) -** *misled participants, looking for genetic predisposition to crime*
- **Centers for Disease Control (1990) -** *experimental measles vaccines for babies without consent*
- **Columbia University (1997) -** *broke sealed juvenile records, specifically excluded Whites*

Abuses give way to disparities



The Belmont Report (1979)

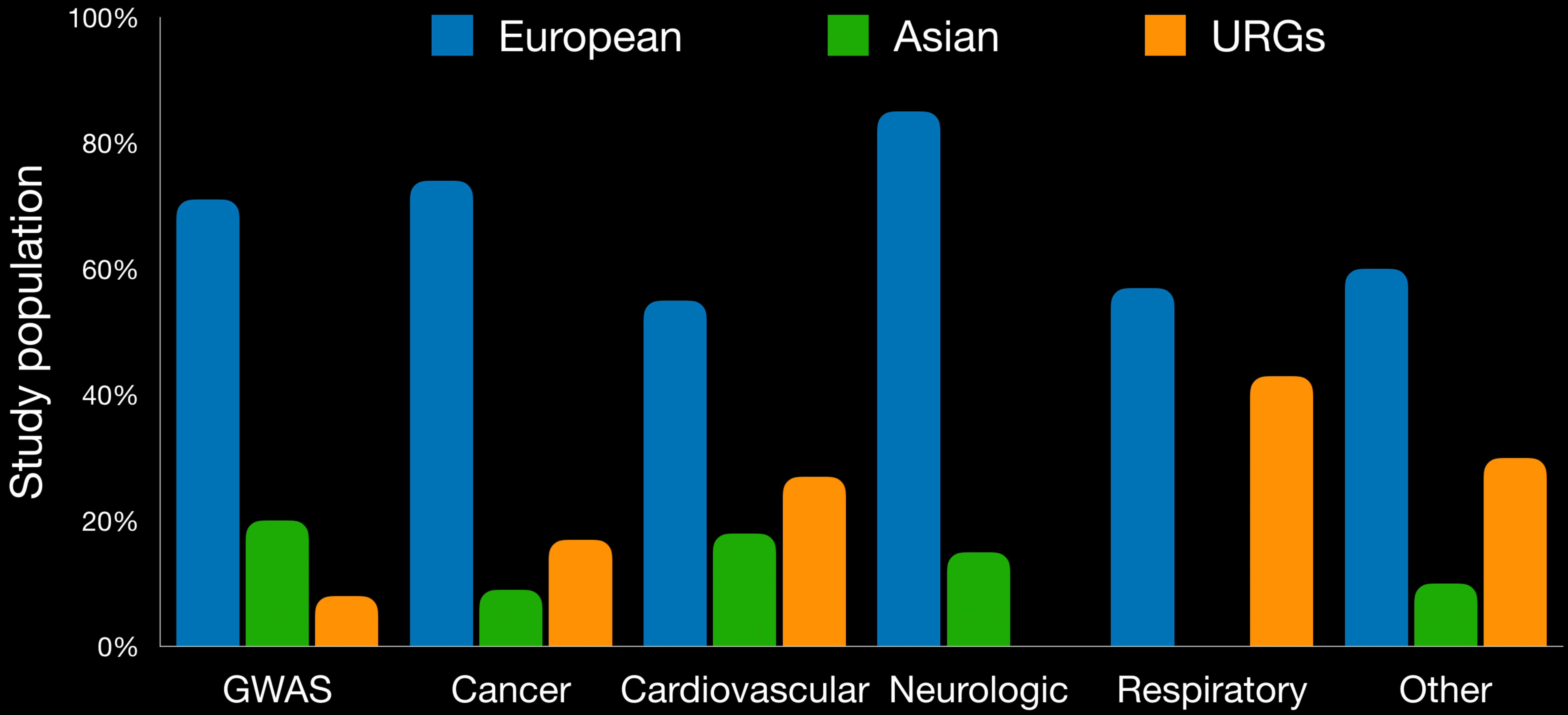
- **Respect for Persons**
  - Must provide informed consent
- **Beneficence**
  - Do no harm
  - All parties must understand and accept risks/benefits
- **Justice**
  - Fair distribution of costs and benefits

How do federal research guidelines encourage inclusion?

- Numerous aspirational policies; all fell short
  - NIH Revitalization Act of 1993
  - NIH Policy - Inclusion of Women and Minorities 2001
  - Establishment of Special Populations offices within ICs at NIH
  - NIH Inclusion Across the Lifespan 2019
  - Many, many, <u>many</u> FDA strategies, guidances, declarations
    - Including new draft guidance from late June 2019
- But <u>why</u> is diversity important for research?
  - Is it a social justice thing?

Why is diversity crucial for clinical research?

- 1 in 5 FDA approvals differed in exposure / response as a function of racial / ethnic group (Ramamoorthy et al., 2015)
- Representation issues particularly acute in precision / personalized medicine (Jackson et al., 2016; Landry et al., 2018)
- Selection and survival biases skew estimates of causal factors (Mayeda 2018; Weuve 2015)
- What happens if we don’t recruit diversely?



Landry 2018 | Health Affairs

Table 1. Demographic Subgroups in 2019

DEMOGRAPHIC SUBGROUPS	WOMEN	WHITE	BLACK or AFRICAN AMERICAN	ASIAN	HISPANIC	AGE 65 AND OLDER	UNITED STATES
AVERAGE	72%	72%	9%	9%	18%	36%	40%

*Data presented in this report are from 49 snapshots as one drug was approved for two indications.

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

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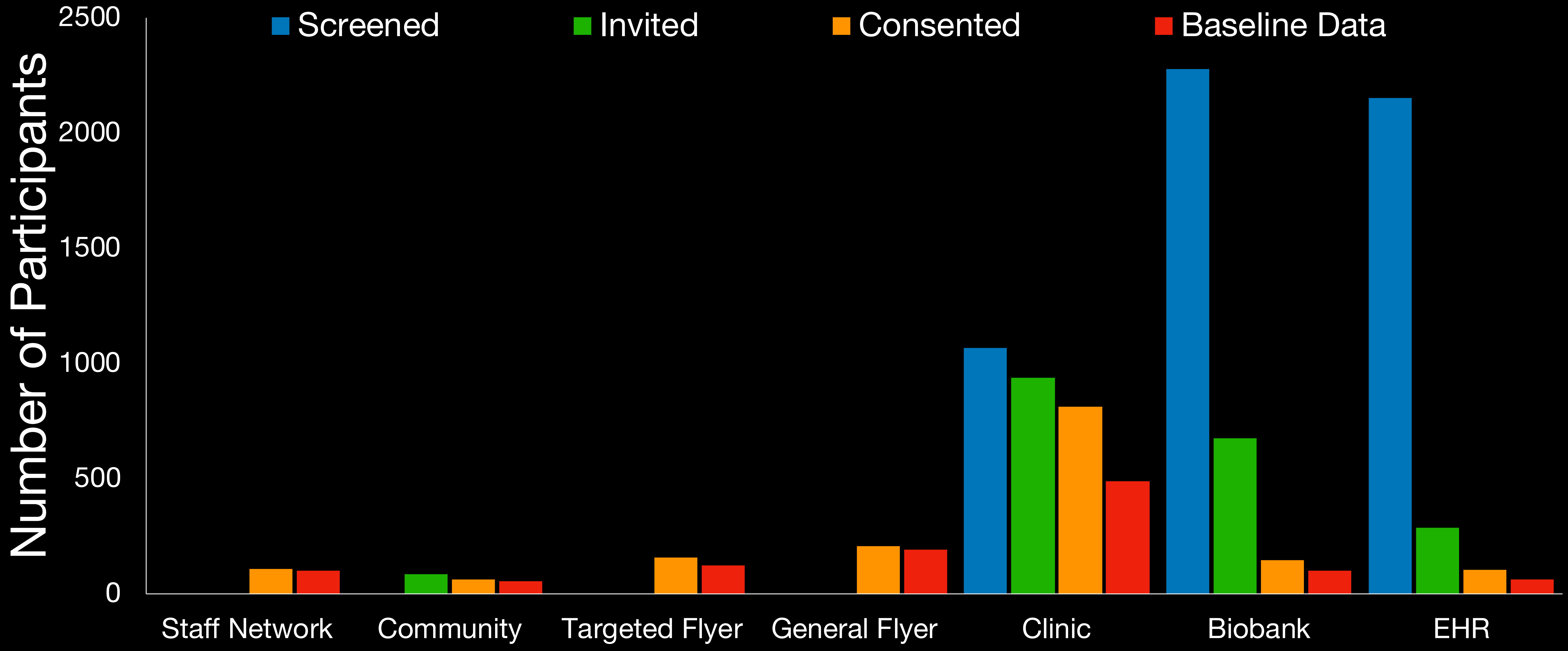
Which method recruits the most people?



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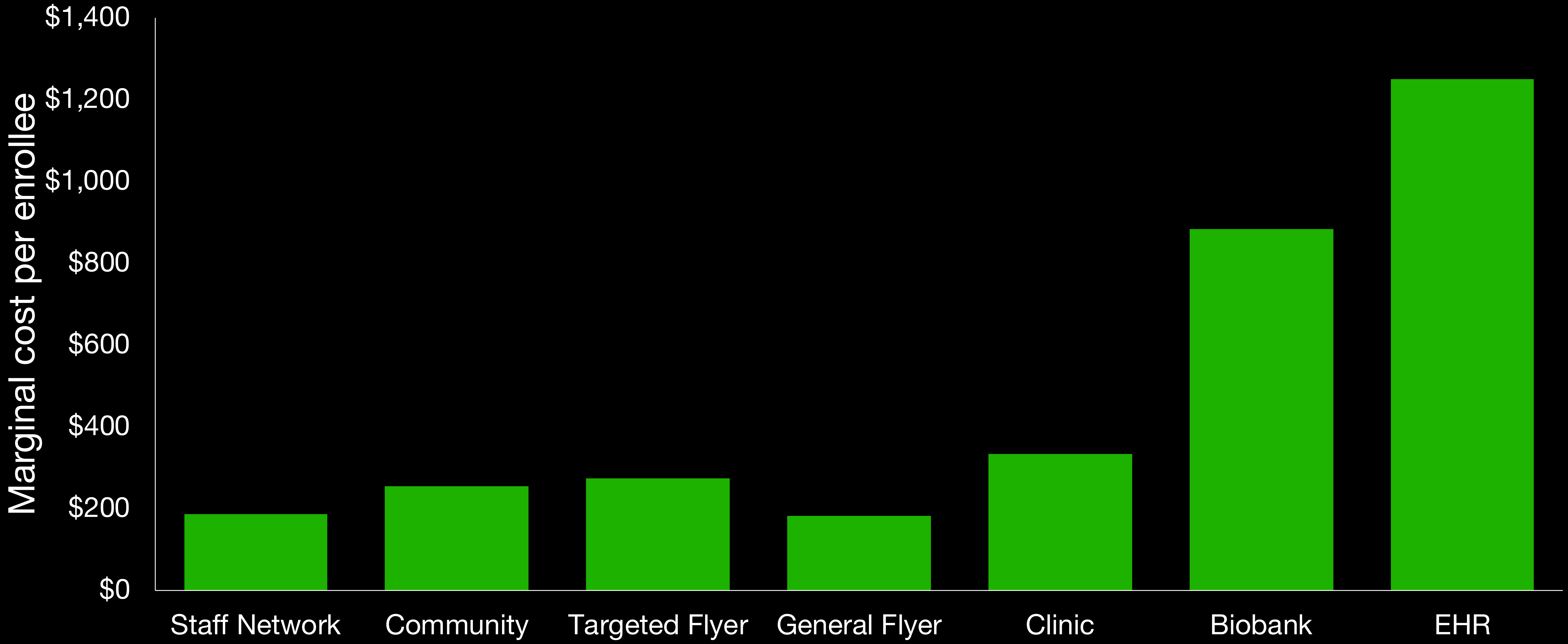
Which method is cheapest?



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Which method yields a diverse sample?

Table 3 CBQ sample: recruitment effectiveness, participants' characteristics, and cost per CBQ participant for all methods combined

			Full CBQ Sample	EHR	Flyer-Targeted	Community Events	Clinic	Biobank	Staff Network	Flyer-General
Invitation	**Type**			Active	Passive	Active invitation of a group	Active	Active	Active invitation of network	Passive
Recruitment effectiveness	**N**		**1118**	63	124	54	487	100	99	191
		Consent Rate	**56%**	36%	na	73%	88%	22%	na	na
		CBQ Rate	**70%**	60%	79%	89%	60%	68%	90%	92%
Participants characteristics	**Age**	**< 45 y old**	**47%**	-	+	+	-	-	+	+
		> 65 y old	**21%**	+	-	-	+	+	-	-
	Gender	**male**	**36%**	-	-	+	+	-	-	-
	Race and Ethnicity	**Latino/a**	**35%**	-	+	-	-	+	-	-
		not White non-Latino/a	**46%**	-	+	-	-	-	+	+
	Education	**High school or less**	**18%**	-	-	-	+	+	-	-
	Employment	**not employed**	**40%**	+	-	+	+	+	-	-
	Geo-Income	**< $33,948**	**16%**	-	+	+	+	+	-	-
Cost (marginal and start-up)			**$787**	$1,669	$676	$656	$733	$1,295	$582	$578

CBQ consented, provided blood, and completed the questionnaire, *EHR* electronic health records, *NA* not available.
Dark grey (+): higher consent or CBQ rate, more diverse cohort, and lower cost per CBQ participant for the recruitment method compared with the full CBQ sample.
White (-): lower consent or CBQ rate, less diverse cohort, and higher cost per CBQ participant for the recruitment method compared with the full CBQ sample.

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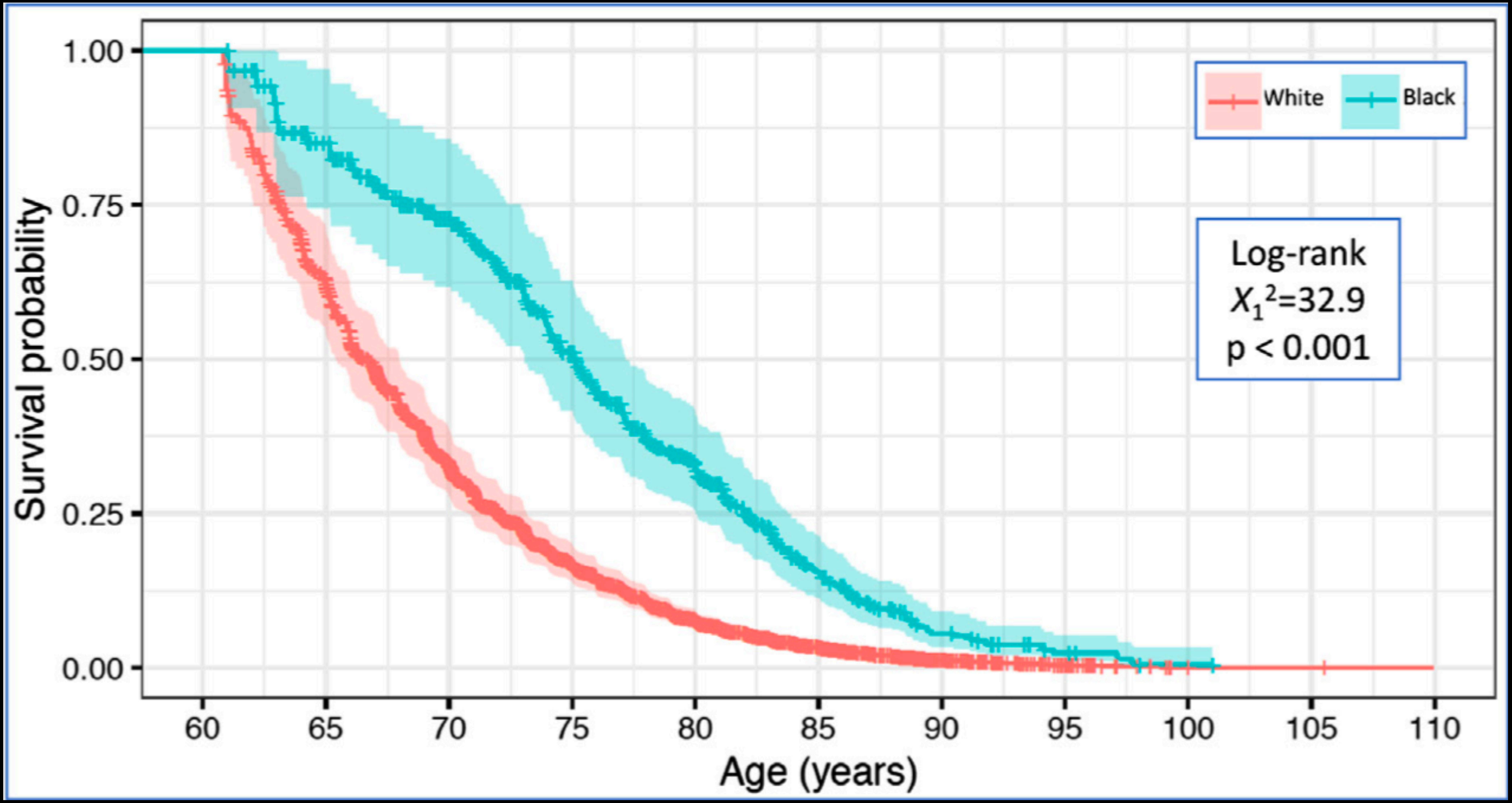
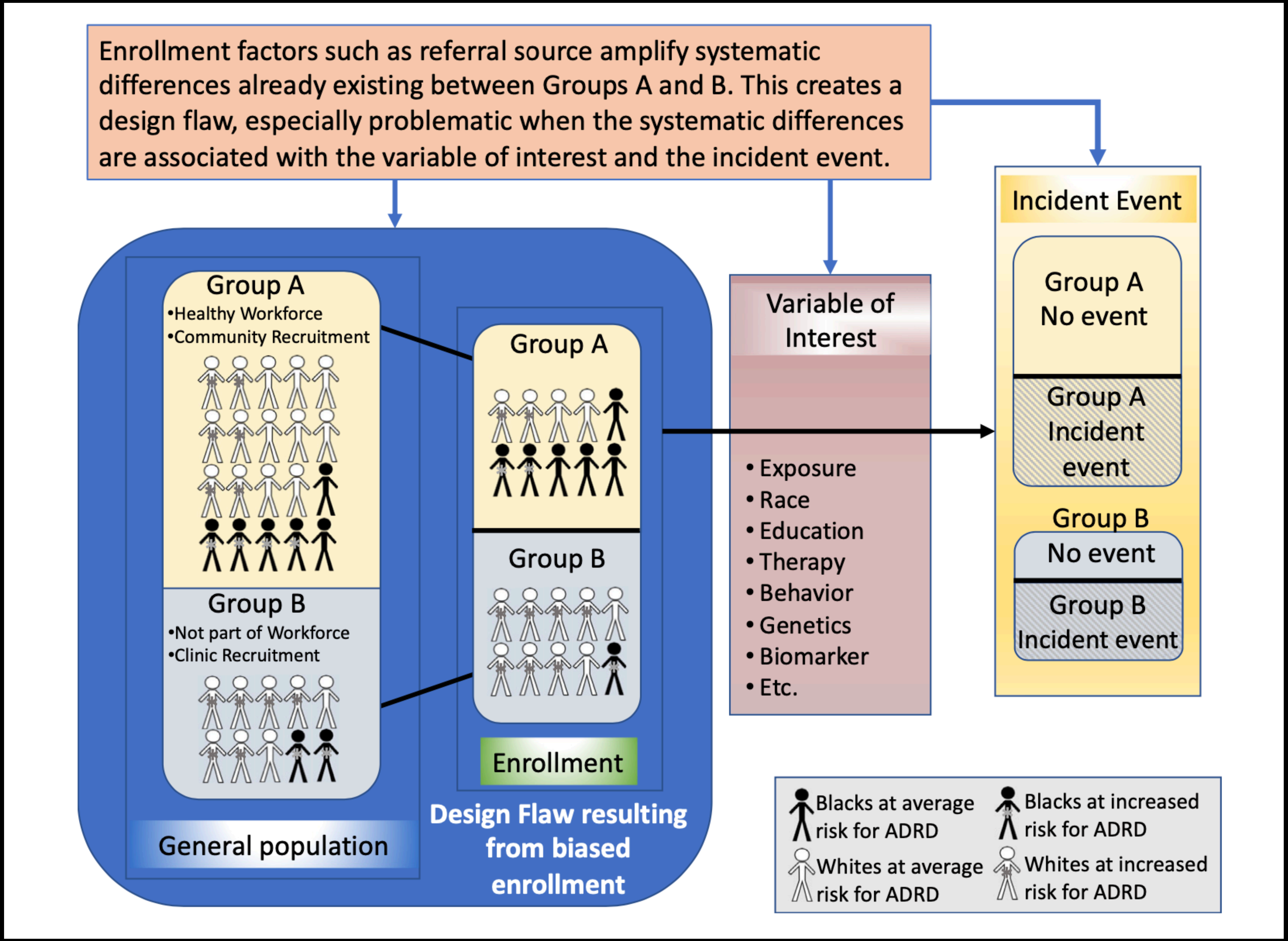
Current efforts in diverse recruitment



Gleason 2019 | Alz & Dementia

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.

Gleason 2019 | Alz & Dementia

The state of inclusion science

- Numerous peer-reviewed manuscripts across every discipline
  - Field is fragmented: no clear definitions, data ontology, comparative effectiveness
  - Most articles focus on single-site case studies, metrics focus only on enrollment
  - Conclusions tend towards advice that is difficult to operationalize, replicate, measure
- Confounds abound
  - Is most of diverse recruitment just the byproduct of charismatic, underpaid CRCs?
  - (What is a "minority," even?)
  - We fail to de-confound "available" from "accessible"
  - Conflation of outreach, recruitment, retention, engagement activities
- Infrastructure is largely absent
  - Few experts, tools, resources available in generalizable, scalable form
  - Study staff is rarely dedicated to recruitment
  - Engagement and recruitment are entirely separated from most study protocols

Jackson | under review

Why can’t we recruit diversely?

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. Insufficient return of value

Selected references:
Bonevski 2014 | BMC Med Res Method
Ejiogu 2011 | The Gerontologist
George 2004 | Am J Public Health
Gul & Ali 2009 | J Clin Nursing
Jackson Moy Evans 2016 | The Oncologist
Oh 2015 | PLoS Medicine
Otado 2015 | Clin Trans Sci
Probstfield & Frye 2011 | *JAMA*
Robinson & Trochim 2007 | Ethn Health

Diversity as a workflow problem

Sampling frame

Awareness

Engagement/Trust

Interest/Education

Screening

Randomization

Retention

- Bottlenecks may occur at multiple stages
- Earlier bottlenecks may manifest at later stages, however
- Effective solutions must address earliest source of flow constriction, not later ones
- Differentiation of outreach, engagement, recruitment, retention activities
- Appropriate characterization of participant availability is primary barrier (Lasagna's Law)

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Workflow as a diversity problem

Sampling frame

Awareness

Engagement/Trust

Interest/Education

Screening

Randomization

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- Bottlenecks may occur at multiple stages
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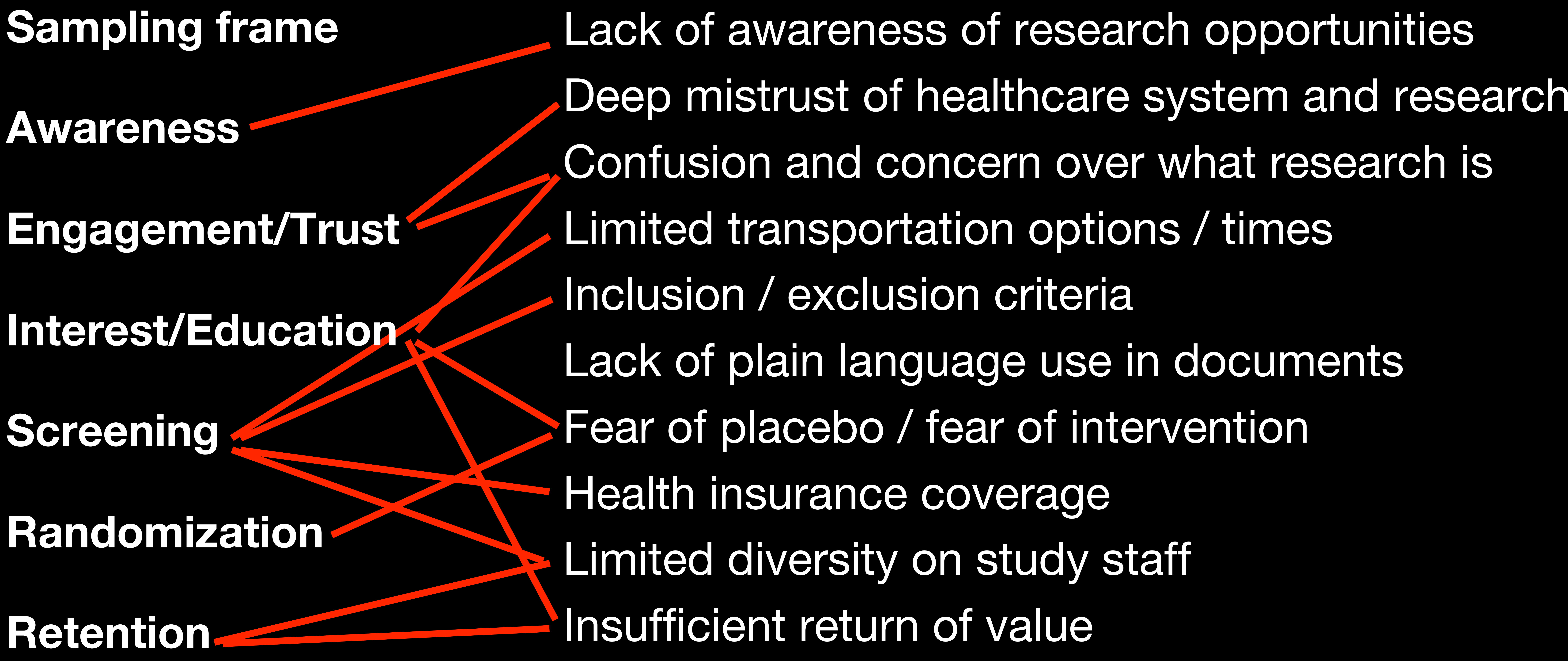
Diversity as a workflow problem



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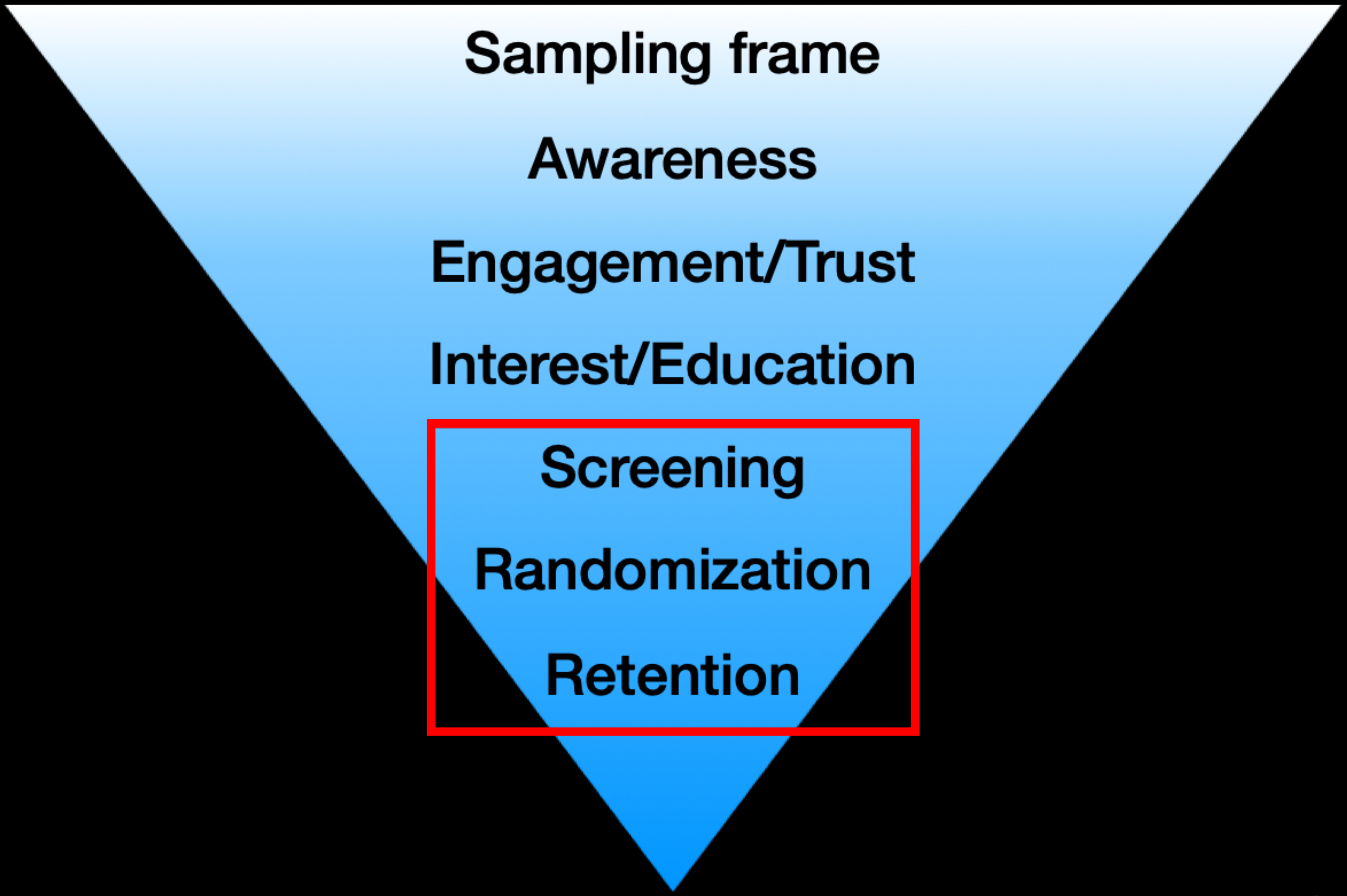

Sampling frame

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Leveraging the framework

- Multisite, multiyear observational study of cognitive impairment
  - Embedded as minor protocol at 59 sites
  - Nine visits over 48 months for CN, MCI, AD participants (including MRI and LP)
  - No return of results / information to participants
  - Very low “minority” recruitment - approx 10%
  - “Minority” = Racial / ethnic groups other than Western European White
- Solicited proposals for ~5 month intervention
  - Four sites selected across US (West, Great Plains, Northeast, South)
  - Sites identified specific barrier and intervention plan
  - Approximately $40,000 budget
  - Monthly dashboard reports, phone conferences

Gonzalez & Jackson | in prep

Leveraging the framework

Sampling frame

Awareness

Engagement/Trust

Interest/Education

Screening

Randomization

Retention

- Identified barriers occurred outside typical research workflow
  - Challenges in awareness of study, trust, interest
- Interventions focused on engaging communities
  - One site engaged with minority-serving physicians
- Monitored sites until Dec. 2018
  - Checked in again this past summer
  - 3 of 4 sites had returned to pre-intervention engagement activities
  - Remaining site had created strong relationship with Spanish-speaking clinic for referrals

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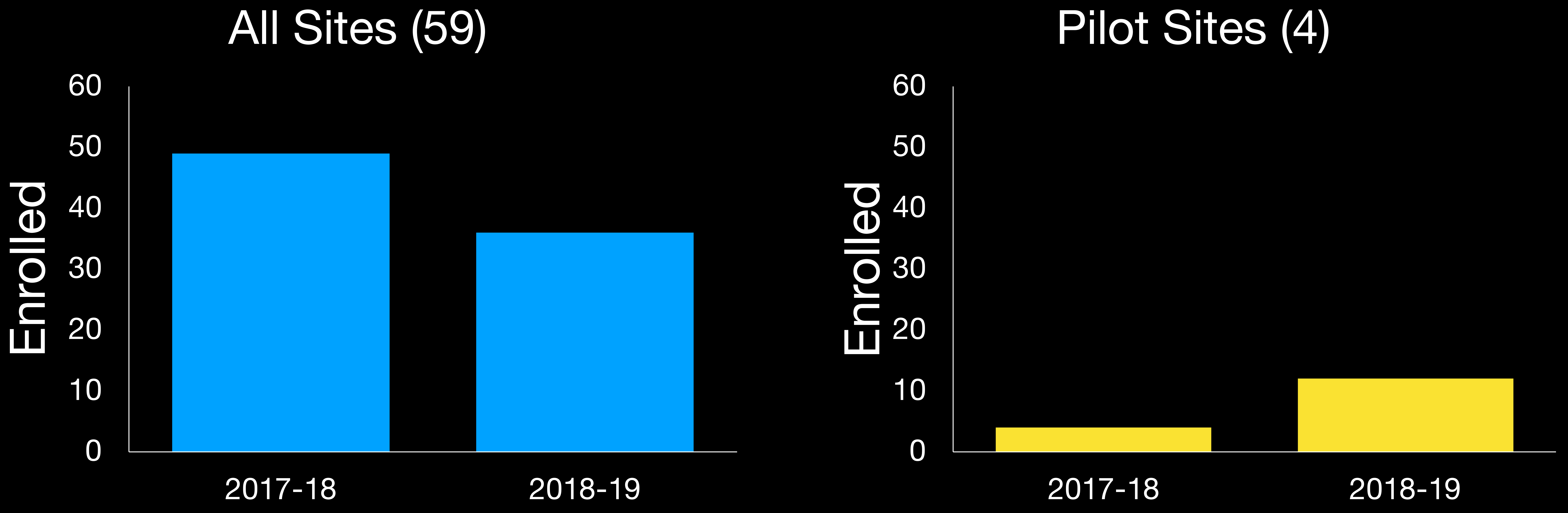
“Minority” recruitment



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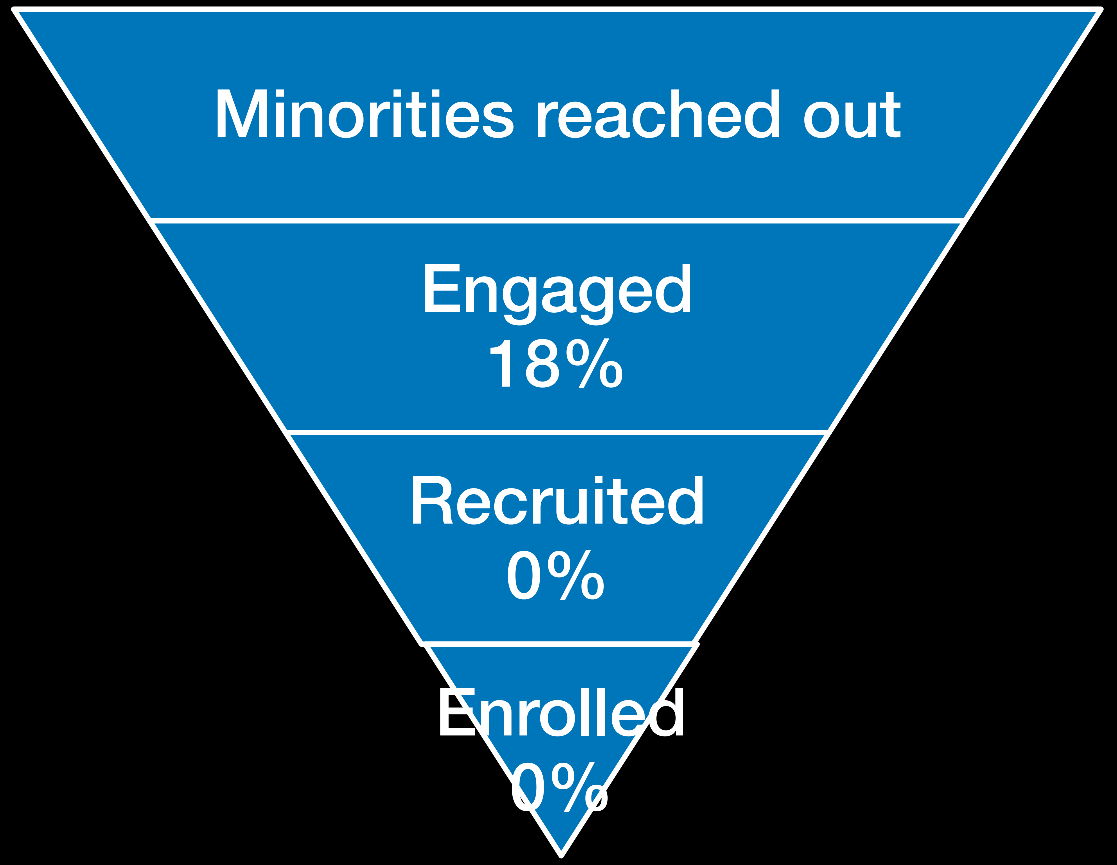
Typical vs Deep Engagement

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

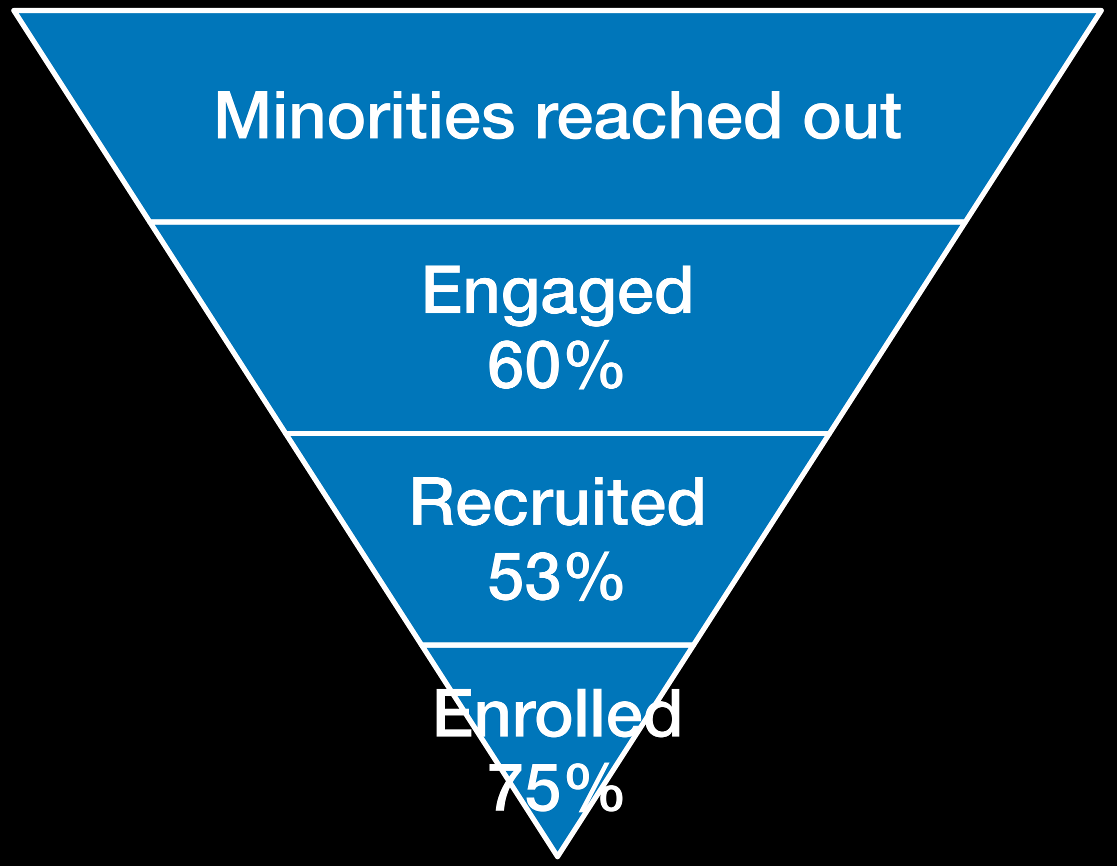

Minorities reached out

Engaged
18%

Recruited
0%

Enrolled
0%

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

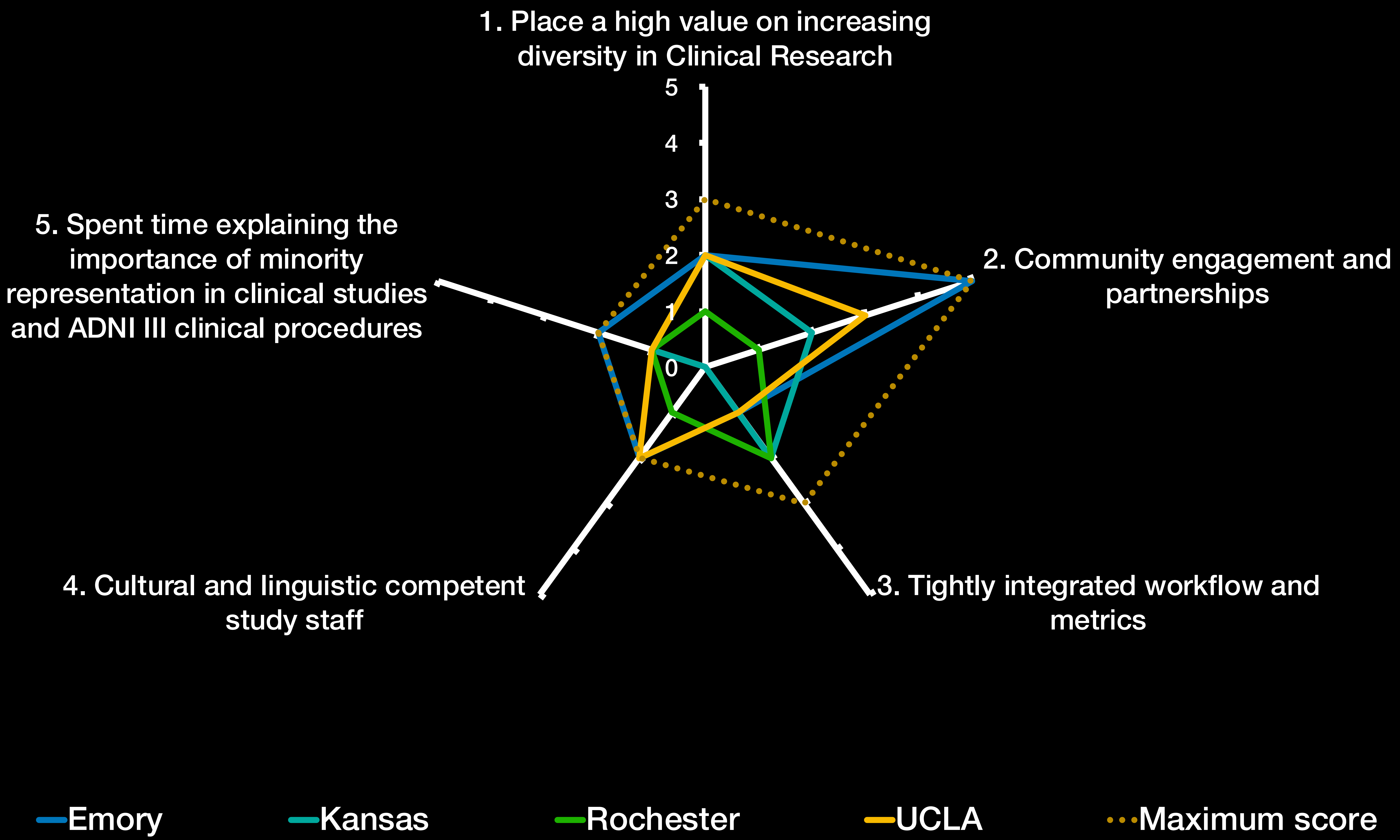
Engaged
60%

Recruited
53%

Enrolled
75%

Ison, Gonzalez, & Jackson | in prep

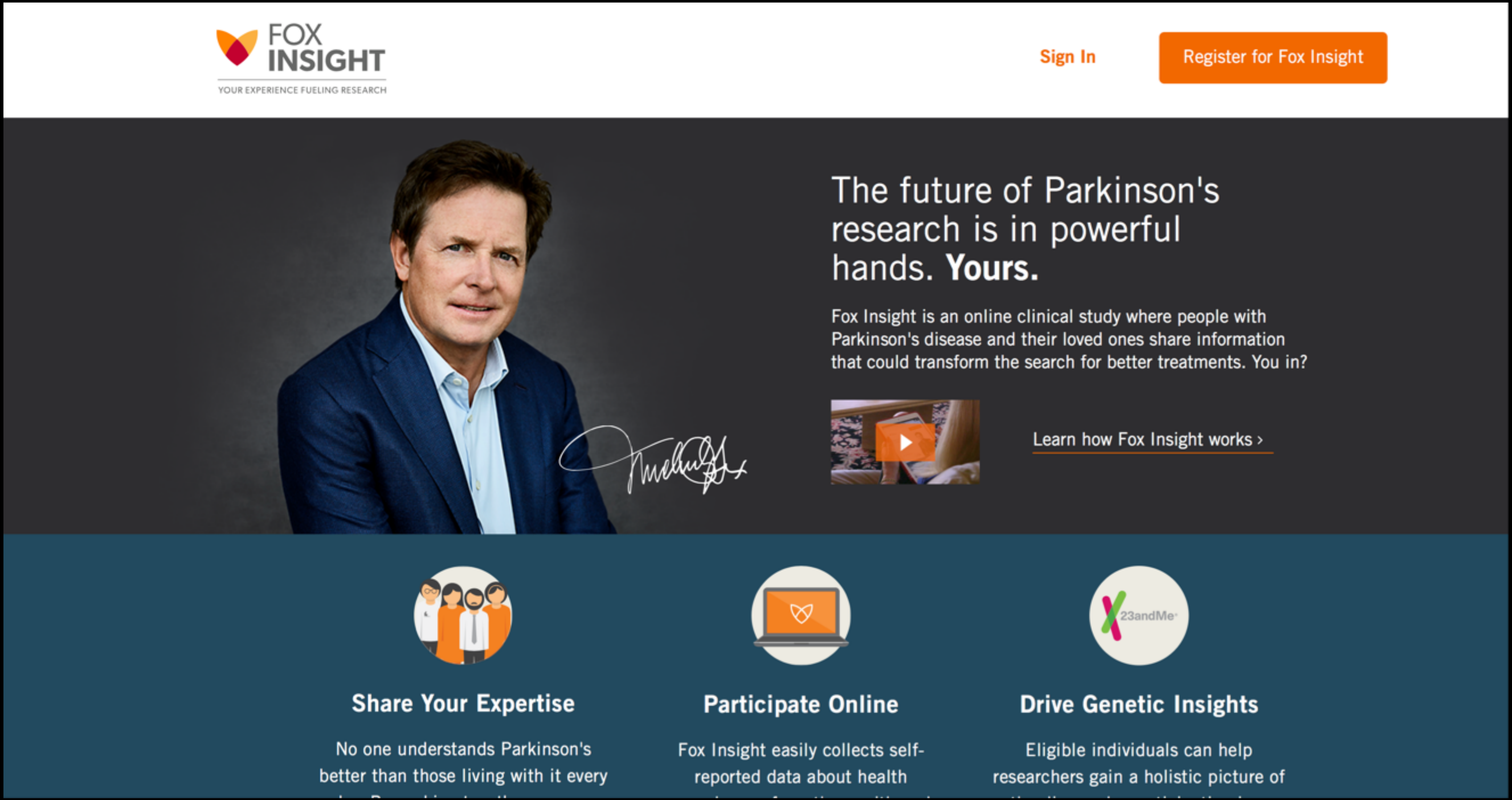
Typical vs Deep Engagement



Ison, Gonzalez, & Jackson | in prep

Conclusions

- Early data suggests institutional support, sustained entrenchment as key
  - Boosted study-wide minority recruitment from 10% to 12% in 12 months
  - The four pilot sites recruited 1/3 of all minorities in 2018-19
- The most successful pilot sites shifted recruitment burden from URMs
  - The return of value is largely in the established relationships
  - Trust was less of an issue than expected
- Establishment of engagement metrics separate from enrollment also helps
  - What gets measured, gets maintained
- Still, some challenges remain
  - Recruited minorities differed from non-minority sample; e.g., Gleason et al. (2019)
  - Large gaps in metrics, implementation difficulties
  - Ongoing challenge of defining “minority”
  - Can we *systematically* address these barriers in a comparative design?



The future of Parkinson's research is in powerful hands. **Yours.**

Fox Insight is an online clinical study where people with Parkinson's disease and their loved ones share information that could transform the search for better treatments. You in?

Share Your Expertise

No one understands Parkinson's better than those living with it every

Participate Online

Fox Insight easily collects self-reported data about health

Drive Genetic Insights

Eligible individuals can help researchers gain a holistic picture of

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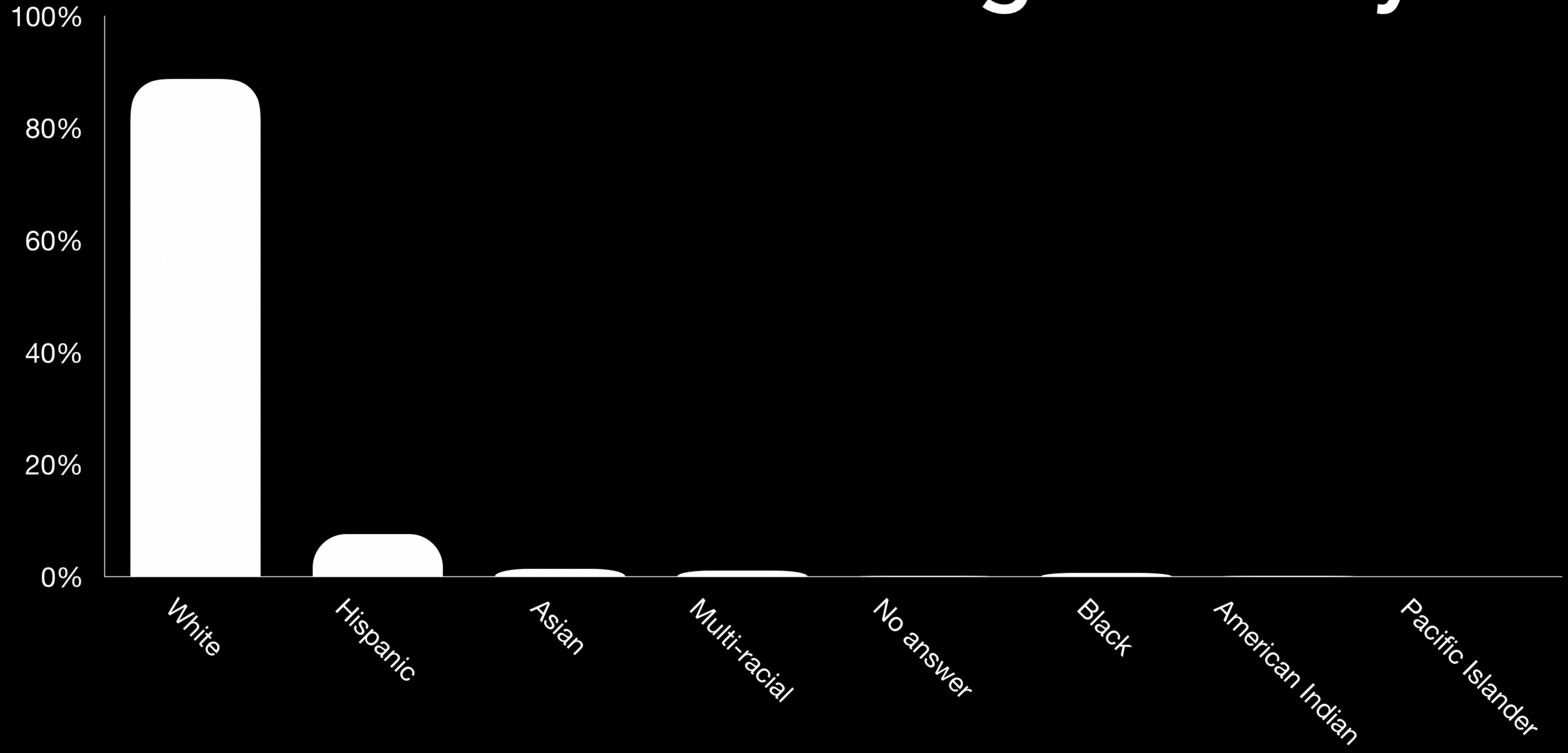
Courtesy Michael J Fox Foundation

Recruitment to digital study



Courtesy Michael J Fox Foundation

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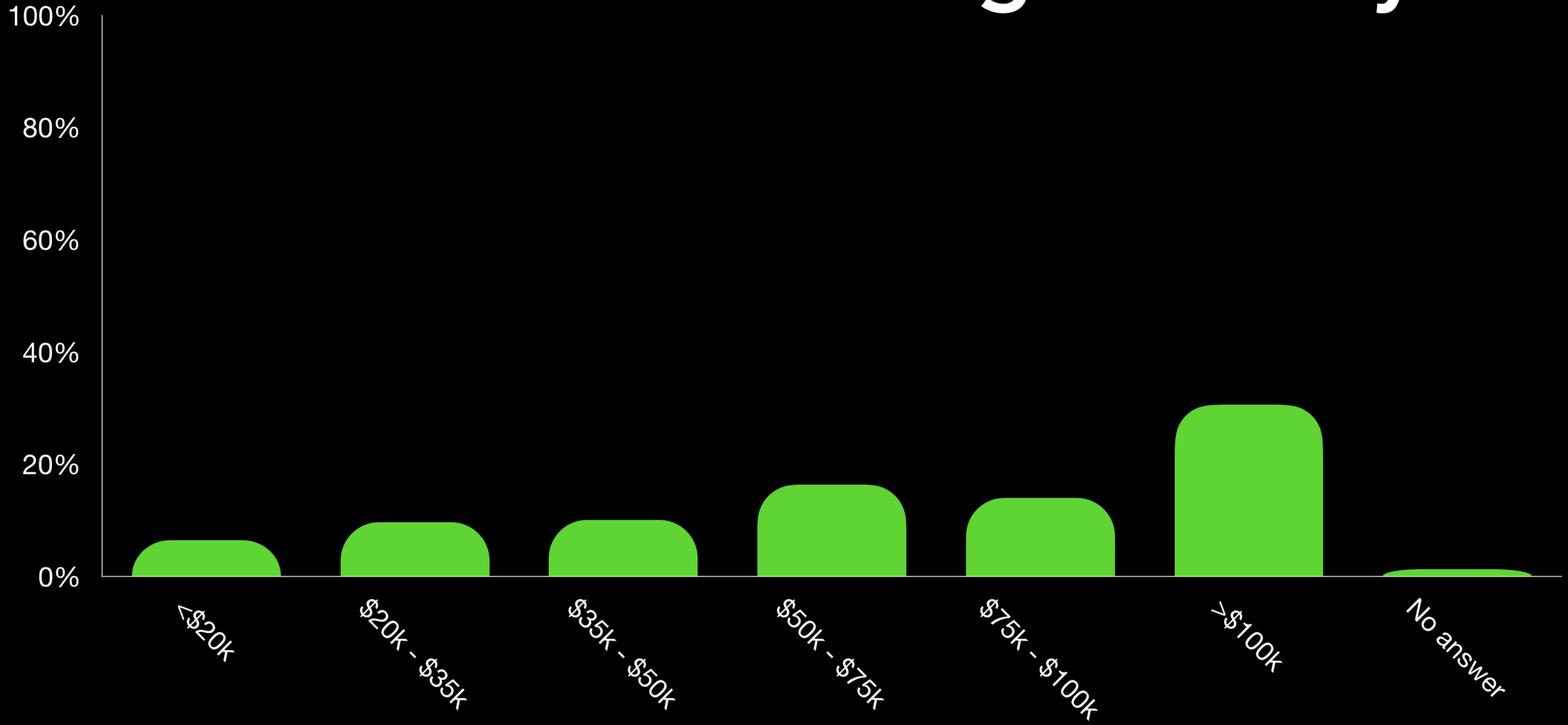
Recruitment to digital study



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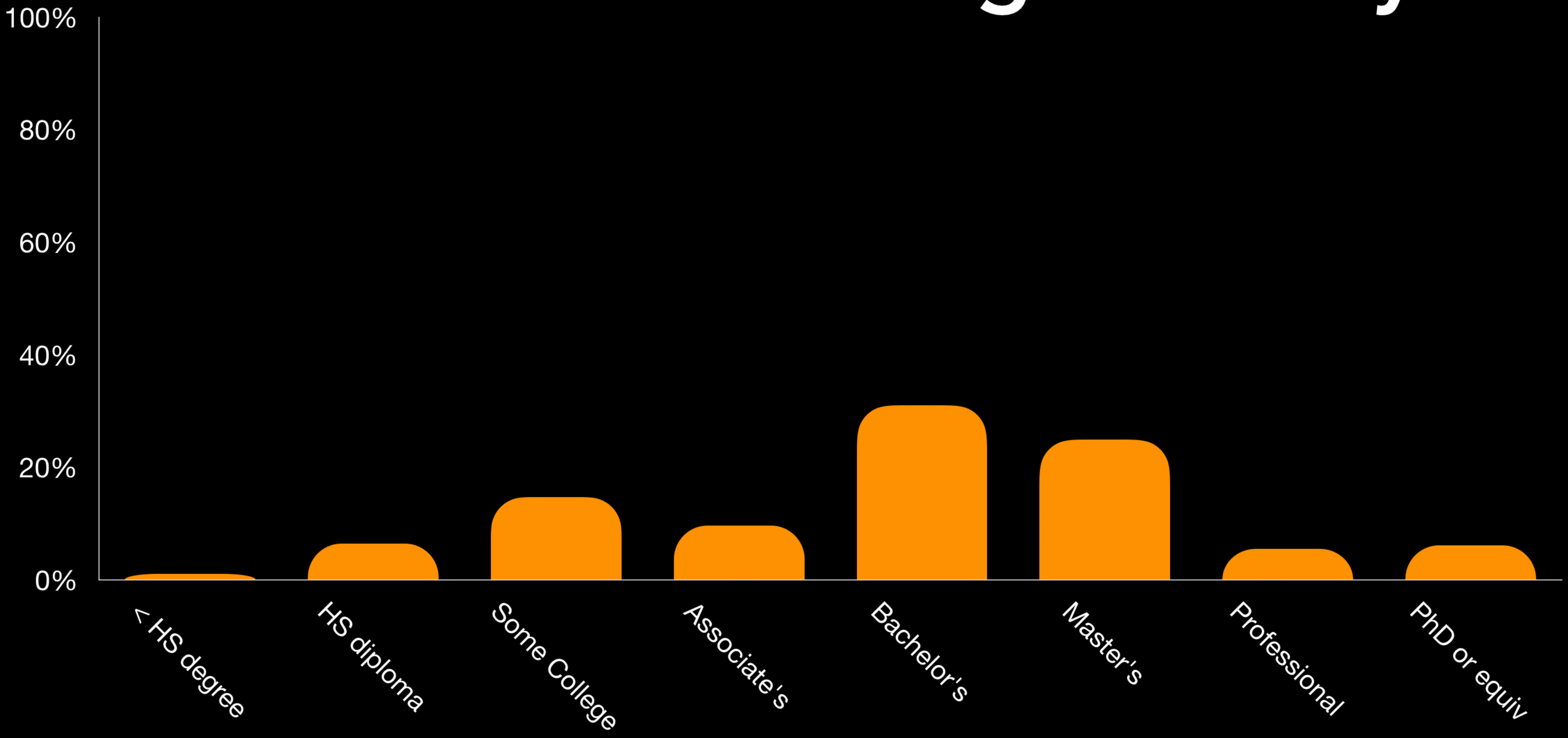

Courtesy Michael J Fox Foundation

Improving URM representation

Sampling frame

Awareness

Engagement/Trust

Interest/Education

Screening

Randomization

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

Sanchez & Jackson | submitted

Improving URM representation

Sampling frame

Awareness

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Screening

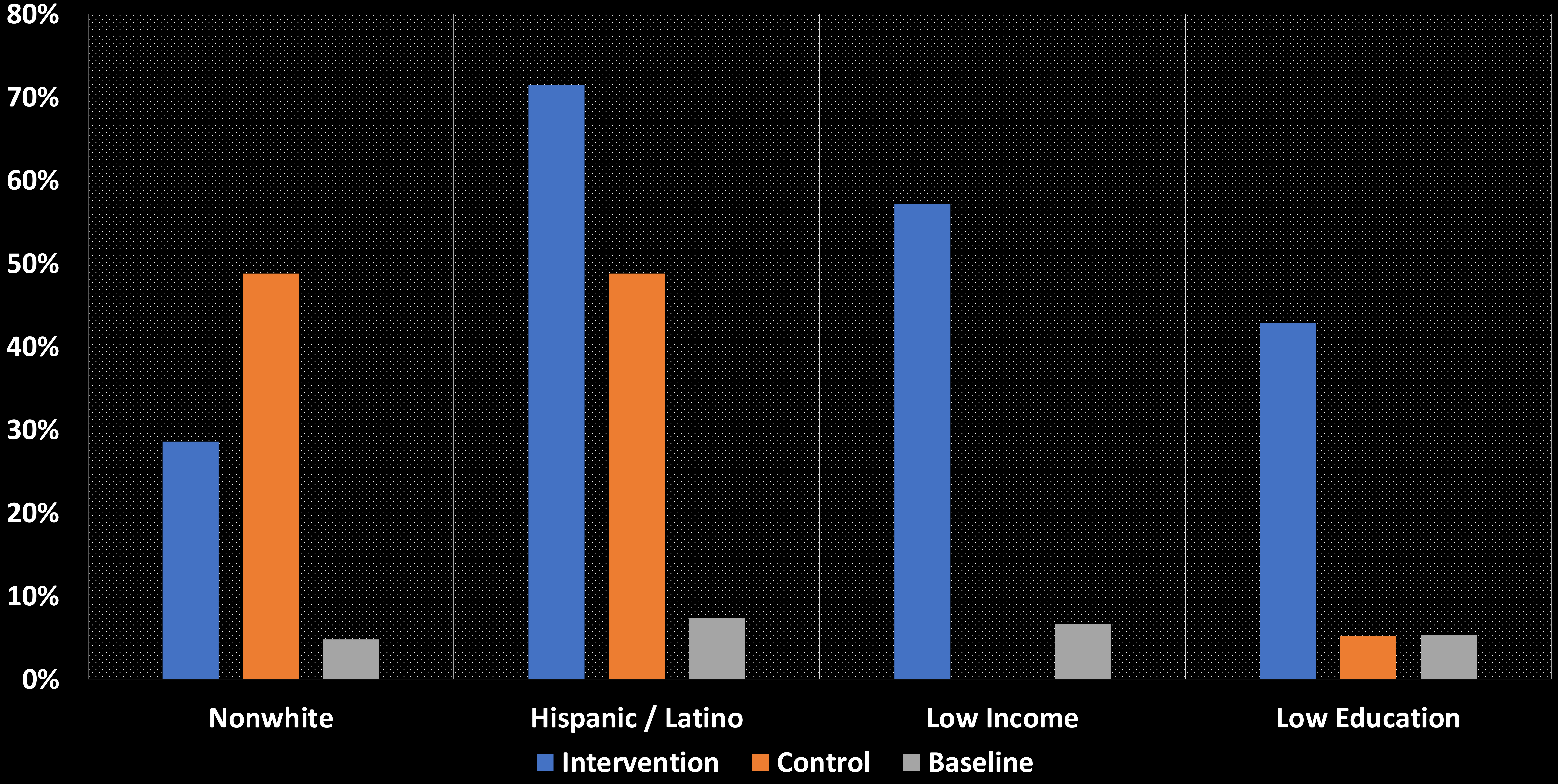
Randomization

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
- Pre-intervention launched September 2019
  - So far: 20% loss due to digital / language barriers
  - Trust again a non-factor
  - Sites with clear sampling frame are outperforming

Sanchez & Jackson | submitted

Accrual to Fox Insight



What does this tell us about diversity?

- One place's solutions won't necessarily work for another
  - Recruitment solutions must be matched to specific barriers for specific communities
  - Trust and transportation barriers are complex – must address upstream barriers first
- We must stop blaming the underserved for not taking part in research
  - Solutions and barriers need to be solved by researchers and institutions
  - We have to give them tools, support, and metrics for success, however
- Working with communities is always a good idea
  - Solutions to these problems feel too complex for scientists, but experts are in the community
  - Be local, be diverse, but if you have to pick one…be local

What’s next for a science of inclusion

- Validating metrics for each workflow stage
  - Borrowing heavily from epidemiology selection models, social media, and market research
  - Repurposing bias / confound(er) estimates
    - Like DAGs, E-value, floating catchment areas, multidimensional network analyses
  - Professionalization and integration of expertise for these stages
- Comparative effectiveness (starting with non-inferiority) research
  - Most recruitment data is qualitative and difficult to implement / compare
  - Devising best practices given specific constraints
  - Network-level implementation (likely learning networks)
- Further examining workflow model in other environments
  - “Democratizing” research out of universities and academic medical centers
  - Meta-research: De-siloing information across health research disciplines to confront sources of bias

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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

The promise of tomorrow’s medicines

Thanks!

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