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Ethics & Social Justice in Health Research Involving Vulnerable Adolescents

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The Adolescent Research Ethics Dilemma

- Respect youth's developing autonomy and protect them from research harms arising from age vulnerabilities
- Avoid over-protective policies that deprive them of participation in research essential to improving age appropriate health services
- Critically evaluate whether implicit systemic biases are placing an undue research burden on socially marginalized youth

Vulnerability: The Definitional Problem

- CFR 46.111a(3) and 46.111b: Vulnerable populations (i.e. children) require additional safeguards to ensure “selection of subjects is equitable” and not subject to “coercion”
- What safeguards are required above those stipulated in Subpart D?
- To what extent do these “vulnerabilities” persist into adolescence

Adolescence \neq Research Vulnerability



Failure to distinguish between vulnerabilities in adolescents' lives & research vulnerabilities can lead to under-or over estimation of research risks

Goodness-of-Fit Ethics (GFE)

(Fisher 1999, 2002, 2004, 2014; Fisher & Goodman, 2009; Mastly & Fisher, 2008)

- The burden of identifying research vulnerability does not simply lie in the fact that a Ss is an adolescent
- Failure to recognize youth strengths can be as harmful as failure to recognize youth frailties
- Research vulnerability occurs when human subjects protections are not fitted to youth developmental strengths as well as needs
- *Empirical data is critical to identifying research ethics relevant youth research assets and susceptibility to harm*

Importance of Participant “Expertise”

Science Establishment

- Ethical principles
- Regulations
- IRB & PI experience
- Traditional ethical protections

Participants

- Moral values
- Trust in the scientific enterprise
- Implementation in real world contexts
- How ethical decisions will affect their rights and welfare

Today's Examples of GFE Research

- HIV/PrEP adherence trials involving LGBTY: *Waiver of guardian permission*
- Pediatric cancer trials: *Waiver of adolescent assent*
- Genomic research on violent behaviors involving ethnic minority youth: *Avoiding bias and social harms*

Waiver of Guardian Permission for HIV Prevention Research Involving LGBTY



The Ethical Challenge

- CDC recommends pre-exposure prophylaxis (PrEP) for high-risk populations to prevent HIV infection
- YMSM, bisexual women and transgender youth 13 - 24 comprise majority of new HIV diagnoses
- There are currently no evidenced-based HIV prevention programs for LGBTY
- Perceived youth vulnerability ➔ guardian permission ➔ low recruitment

Justice: Fair Access

- **Without youth involvement in research, PrEP will continue to be unavailable to LGBTY and prescribed off-label**

Goodness of fit questions

- When is guardian waiver ethically justified?
- Is adolescent self-consent an adequate protection?

Guardian Permission: Are LGBTY “Children” under Federal Regulations?

- OHRP classifies minors as “adults” if they have attained their state defined legal age for consent to treatment or procedures involved in a research study §45CFR 46.402a
- Most state mature minor laws permit youth independent access to HIV testing and treatment (Culp & Cauci, 2013)



Waiver of Guardian Consent Under §46.408 Subpart D

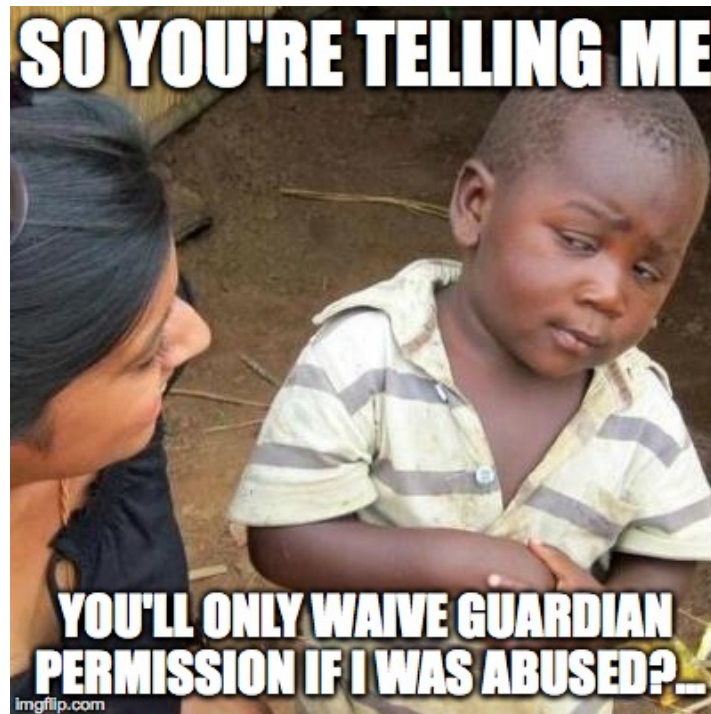
Minimal Risk Research (§46.404)

“Research could not be practicably carried out”

Greater than Minimal Risk §46.405c, §46.405c, §46.406d, §46.407iii

“When guardian permission is not a reasonable requirement to protect the subjects (e.g. neglected or abused children)”

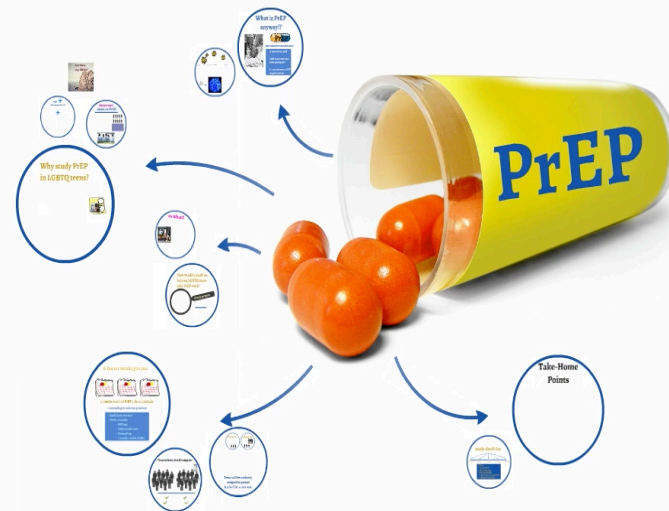
The Definitional Problem



Guardian Waiver & Youth Self-Consent

Participants: 74 sexually active 14 – 17 yr old LGBTY

Method: viewed animated descriptions of a PrEP HIV prevention study and responded to web-based survey questions and asynchronous focus group discussions



Funding: NIMHD R01MD009561-01 PI's: Celia B. Fisher & Brian Mustanski

Reference: Fisher, C. B. , Arbeit, M., Dumont, M., Macapagal, K., & Mustanski, B. (2016). Self-consent for HIV prevention research involving sexual and gender minority youth: Reducing barriers through evidence-based ethics. *Journal of Empirical Research on Human Research Ethics*, 11, first published online 3.7.16 DOI: 10.1177/1556264616633963

PrEP Adherence Study Description

HIV Basics

- What is HIV
- How is it transmitted
- What is it like to get an HIV test

PrEP Basics

- How PrEP works to prevent HIV
- Does not protect against STIs
- Side effects: nausea, diarrhea, rare bone weakness
- Pill must be taken daily

Purpose of Study

- To test whether text messaging improves PrEP adherence for LGBTY

Random assignment: “like a coin toss”

- One group would get daily text message reminder to take pill

Inclusion Requirements

- Must be HIV negative
- At-risk sexual behavior
- Return to study appointment every 3 months for HIV testing and counseling

Would you Participate in a PrEP Study if Guardian Permission is Required?



Who would refuse?

61% of youth not “out” to parents;

21% of youth “out” to parents

Reasons for and against GP

Reasons for GP

- *My parents are supportive of my sexual orientation*
- *Help with taking care of my health*
- *Help with informed and voluntary consent*
- *I can explain and get support*

Reasons against GP

- *GP would out me to parents*
- *I'm out, but parents unsupportive*
- *They would punish me or kick me out of house*
- *Parents would ask questions about sex*

If you tested HIV+ would you want the researcher to help you tell your parents?

NO 34%

"I would come out of it... homeless"

My mom would call me a "stupid whore"

"I would want advice on how to show them that I need new medications"

YES 46%

"Having another adult there would soften the blow"

I'd be scared...to tell my parents...I would definitely want a professional's help"

"Explain it better than I could"

Is Guardian Permission “Practicable” or a “Reasonable Protection”?

- LGBTY at high HIV risk who lack parental support would not participate in a PrEP study if guardian permission was required
- Many fear punishment or family rejection if their LGBT status was revealed through GP requirements
- For these youth GP is neither “practicable” nor a “reasonable protection”

GFE for Guardian Waiver

- IRBs should first consider whether adolescents recruited for HIV prevention research are “children” under Subpart D
- If “children” is there evidence indicating the GP is not practicable or a reasonable protection
- When GP is waived youth should be given the option of including parents in participation decision
- A participant advocate can help provide appropriate substitute protections “*an unbiased opinion*”
- Investigators should develop procedures for youth who test HIV+ that are: Sensitive to risk of “outing” and provide support for sharing diagnosis with parents or referring youth to age and LGBT appropriate HIV services.

CAN LGBTQY MAKE A “REASONED” PARTICIPATION DECISION



Random Assignment

- *“I feel like being randomly put into groups is the fairest way to decide who gets the reminders and who doesn’t”*
- *“Allowing us to choose our own group could in some way make the information irrelevant”*
- *“Feel a bit like a dog following orders”*
- *“They should do what’s best for me”*

Research Benefits

- *“Good to know my HIV status” (60% of youth more likely to get tested in research than with their regular physician)*
- *“Having protection against HIV on a daily basis”*
- *“Help me focus more on the possibility of getting HIV and in turn make me practice better sex”*
- *“Because it would not only benefit myself, but possibly thousands of LGBTQ teens across the country in getting the help they need to prevent HIV”*

Side Effects

- “It’s important to take into account risks when starting any medication”
- Whether I could “tolerate side effects”
- “My only concern would be the pill affecting my bones, but in the video they said there would be check-ups every couple of months so I would always make sure to ask how my bones were doing”
- Risks are “nothing compared to living with HIV”

Privacy Risks



I'd "fear being outed [if] someone saw the text or pills"

"No one goes through my phone aside from my friends, and those that do know that I am not straight"

"I usually delete my texts"

"If I was that worried about privacy, I wouldn't be a part of that kind of study"

Appreciation of Personal HIV Risk

- *“I would think about where it would fit in my lifestyle and if I needed it”*
- *“How sexually active I’ve been recently and the likelihood of me becoming active”*
- *“I’d weigh risks and benefits “both personal and for others”*

Adherence Challenges

- *“I take birth control and Zoloft in the mornings so adding PrEP [is] easy to remember*
- *“I feel the commitment of having to take a pill everyday would be hard for me because I am kinda forgetful”*

GFE: Enhancing Youth Self-Consent

- LGBTY can make a reasoned consent decision when investigators take an age appropriate educative approach
- Investigators should ensure that consent is fitted to informational, health and social needs of participants
- IC can be enhanced through fact sheets, respectful and caring delivery, welcoming questions, giving time to decide, and involving a youth advocate “I would like to see past results and proof”
- Given insurance and financial limitations, studies should carefully consider approaches to post-experimental access to PrEP “*Make it clear at the beginning that it does not continue*”

Should Assent be Required in Pediatric Cancer Trials involving Adolescents?

Regulations

§46.408 Child assent is NOT required when:

- Capability ... so limited that child cannot reasonably be consulted or
- Intervention or procedure involved in the research holds out a prospect of direct benefit ...available only in the context of the research



Background

Research Benefits: In the last 30 years pediatric cancer survival has improved from 20% - 75%; 70% -90% of patients are enrolled in clinical trials

Timing: Consent is often required when the family first learns the teen's diagnosis, that the patient has been unresponsive to current treatments or the adolescent is in pain or cognitively impaired by the disease or current medications

Adolescent Assent Dilemmas

Patient involvement in consent decision may increase self-worth, sense of autonomy, and ability to cope with illness anxieties

- Serious health problems and current treatment side effects may impair teen's cognitive and emotional consent abilities
- IC may negatively affect youth's health outlook and confidence in confidence in practitioners
- P-C disagreement over participation may cause family conflict

Parent-Teen Perspectives: Assent for Pediatric Cancer Trials

- **Participants:** 23 adolescent cancer patients (11 – 23 years) 15 parents of patients who had participated in cancer trials and were in continued treatment at the medical setting where the trials had been conducted.
- **Method:** Responded to the Family Decision-Making Questionnaire followed by group discussion
- **Reference.** Mast, J., & Fisher, C. B. (2008). A goodness of fit approach to parent permission and child assent pediatric intervention research. *Ethics & Behavior*, 13, 139–160.

What Factors Should Determine Patient's IC Involvement?

Majority of patients and parents (73% -100%) agreed:

- Patient's age/consent maturity
- Current health (weakness, pain)
- Prior research experience
- Knowledge of current diagnosis
- How patient will react learning experimental treatment may not work
- How patient usually feels about making treatment decisions

What Should Patient be Told?

Majority of patients and parents (79% - 100%):

- Recruited because they had cancer
- Mild risks e.g. nausea, severe pain or damage to healthy organs, interference with school work
- Medical procedures they will undergo
- Other treatment options

Parents (53% - 60%) were more wary than patients (70% - 78%)

- Recruited because other treatments not effective
- Dr. does not know whether treatment will work
- Random assignment

Adolescent Autonomy & Parental Responsibility

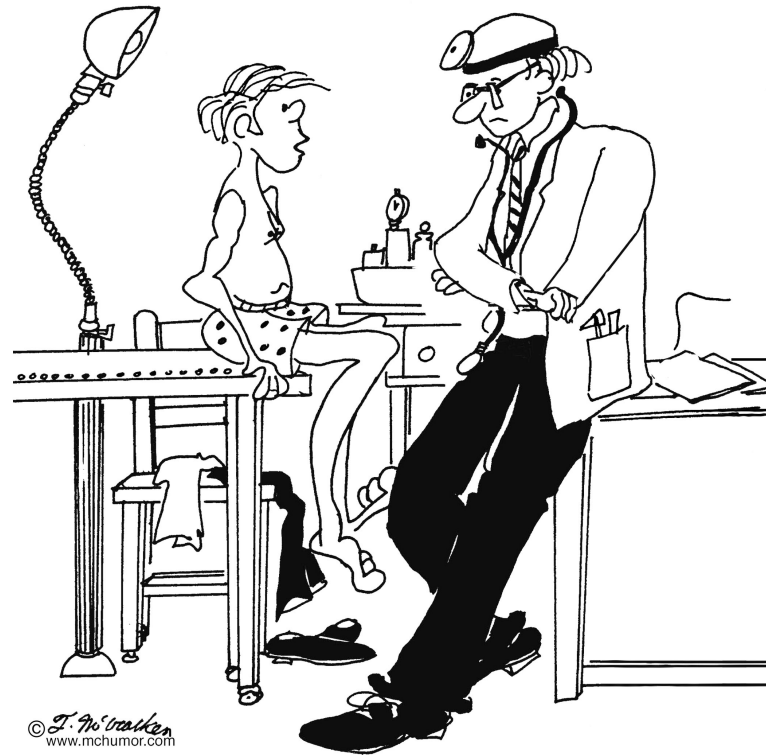
Majority of both parents and patients(83% - 100%) believed:

- Involvement in IC can give patients a sense of control over their lives
- Parents had responsibility to shield children from feelings of self-blame or guilt if participation did not produce results

Parents (87% -100%) more than patients (52% - 65%) believed

- Parents should shield children from research information that might cause emotional distress
- It is the parents' responsibility to make serious health decisions for children

Should Patient Assent Always Be Sought?



"GEE, I HAD HOPED TO MAKE IT TO THE ADULT
TABLE AT THANKSGIVING BEFORE YOU
RECOMMENDED I HAVE MY FIRST COLONOSCOPY."

GFE: When should assent be sought or waived?

- **Child characteristics:** Maturity, current health, emotional readiness to understand disease and unknown effectiveness of experimental treatment
- **Preserving family cohesion:** History of medical decision-making, child and parent preferences, consequences of potential decisional conflict
- **Severity of disease and potential research benefits.** Responsivity to available treatments, benefits not available outside research

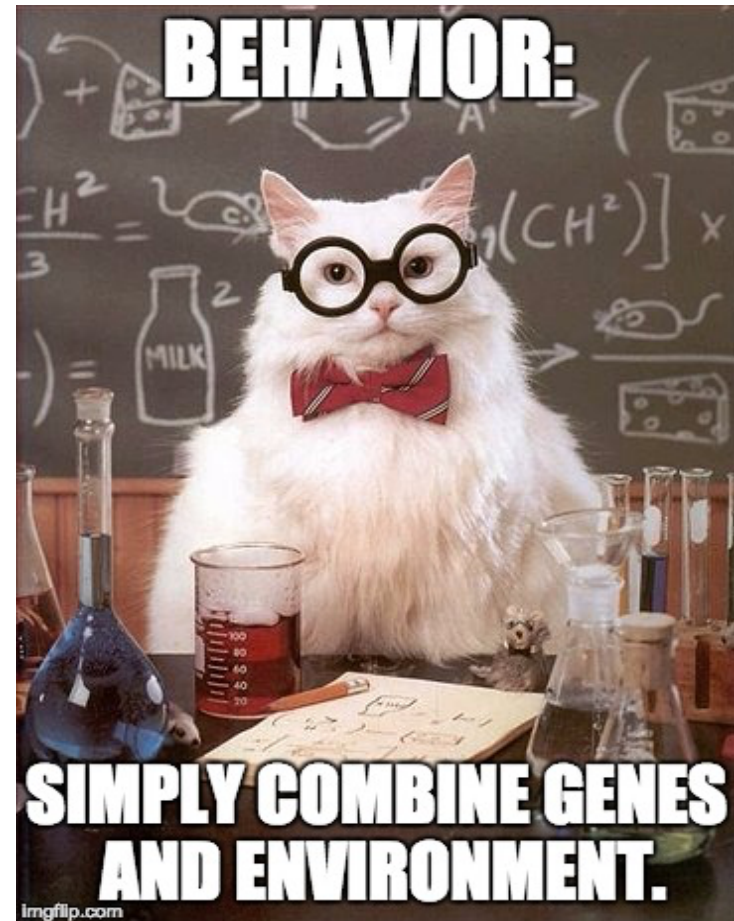
Never ask a teen for assent if their dissent will not be determinative

Rather....Provide teens with age and health appropriate information, obtain feedback to best fit procedures to patient's informational, emotional and treatment needs

Genomic Research on Risk Behaviors Involving Ethnic Minority Youth

Genetic Testing and Research on Violence Prevention

Genetic testing is increasingly used to study correlates of behavioral problems and responsivity to intervention programs



“Gene-Intervention” Studies: Majority involve African American Youth

The NIMH Violence Initiative

- Inner city youth with a genetic predisposition to violence (an older sibling with a criminal record) would receive biomedical psychiatric intervention to prevent future delinquency (Goodwin, 1992)

The “Family School Partnership”

- Youth (80% African American) with a genetic predisposition to aggressive behavior (BDN SNPT cluster) received an early childhood school based intervention to reduce aggressive behavior in early adolescence (Musci et al., 2013)

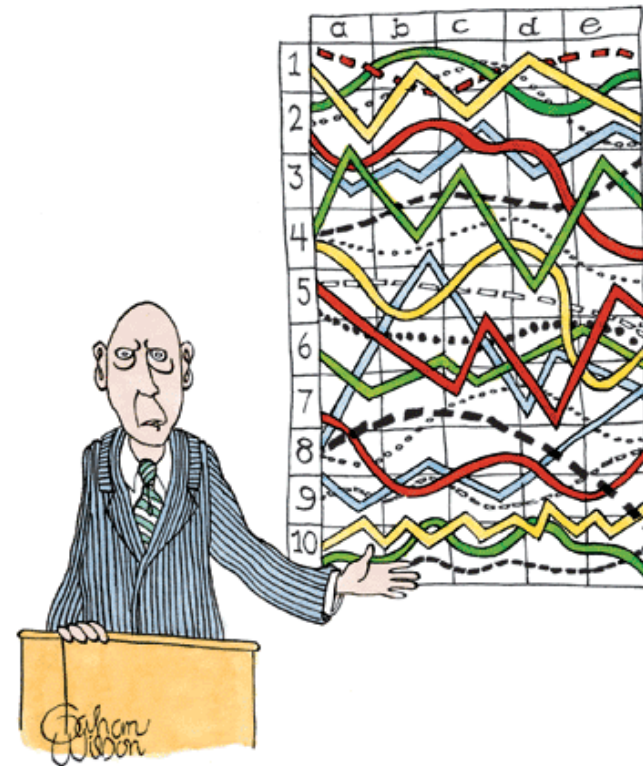
- To be of benefit, an “experiment should be such as to yield fruitful results for the good of society”

Nuremberg Code, 1946, Principle 2

What are “fruitful results for the good of society”?

Genetic factors associated with Impulsivity, aggression and violence

- Multiple genes acting in combination
- 100s of different genes may independently influence the same behaviors
- Genetic effects account for only a small proportion of individual differences (heritability)
- Gene-intervention effects are probabilistic—lack individual utility



“I’ll pause for a moment so you can let this information sink in.”

Genomic Adolescent Violence Research Whose Benefit? Who Decides?

Method: 100 racially and economically diverse teens and parents were shown video clips of adolescent risk research and participated in focus group discussions research risks and benefits.

Funding: National Science Foundation #SBR 9710310; PI. C. B. Fisher

Reference: Fisher, C. B., & Wallace, S. A. (2000). Through the community looking glass: re-evaluating the ethical and policy implications of research on adolescent risk and psychopathology. *Ethics & Behavior*, 10, 99–118. PMID: 11841105.

Socio-Political Bias

- *They do “research in the school about [white] students who do good and about crimes they only talk about black people”*
- *“ “They know the reason why [there is violence]...ghettos... racism...and prejudices may still exist, but they don’t want to say that. They want to say it’s in their genes...to make a cover story.”*
- *“We’re sick and tired of researchers studying our kids drug use, nothing will help until you start studying why the government keeps letting the drugs into our community”*

Scientific Validity: Implicit Race-Based Inferences

- *I think it might be possible for it to be biological, but its not one race... look at white Hitler... and South Africa apartheid...Why don't they study white suburban serial killers or the KKK?"*
- *My Moms and Pops spoil me...and...I'll still be a bitch...I will still fight. Why? Because it's already in me. I guess it probably is genetic. Hey, I'm Puerto Rican, Black Dominican, Italian, and Cuban. You pick a race where it came from."*
- *Scientists are "always trying to make generalizations...They want to make a statement like X percent of this and Y percent of that [but] the next week they'll...get completely different results."*

Social Value vs. Social Harms

- Such research “promotes supremacy of the races...that one race is better than the other.”
- “So they take...an honor student...the kid’s been doing great and then you’ve got that violent gene and we’re going to start treating you for this gene problem when the problem is not there”
- “I think we’ve been duped to think that any of the results will be used to improve the African community...because too much has been used against us”

Will Research Contribute to Morally Sound Social Policies?

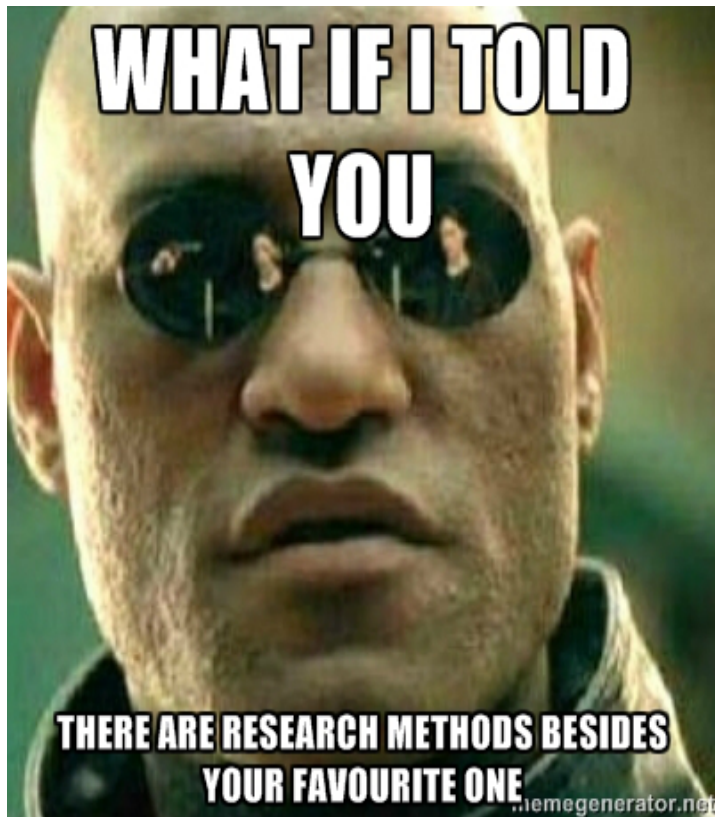
- Funding for genomic research is often driven by economic and political concerns of the majority
- These may have little to do with or are antithetical to the concerns and social circumstances of participant groups
- New “genetized” diseases may be created for behaviors resulting from social inequities
- Potential for genetic stereotyping ➔ racially segregated interventions

Goodness-of-Fit Ethics

Assessing Scientific & Social Value

- Are there a scientifically valid reasons for research explicitly or implicitly targeting racial/ethnic minority youth behaviors?
- Are there implicit socio-political biases influencing recruitment and inclusion criteria?
- Is the design sufficient to adequately assess genetic vs systemic inequities?
- Do human subjects protections reflect the values and merit the trust of participants?
- **Ethical decision-making cannot be isolated from knowledge of how participant's view the informational goods and harms of genomic research**

If it can be studied, should it?



"The key is Dr. Fisher, that when you...talk to your counterparts...ask yourselves what will others do with this research?"

No matter what role that you have played to make this happen, you could have the purist intention, but if it gets into the wrong hands then it becomes a weapon"



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