Ethical issues in the development, testing and translation of innovative gene therapies

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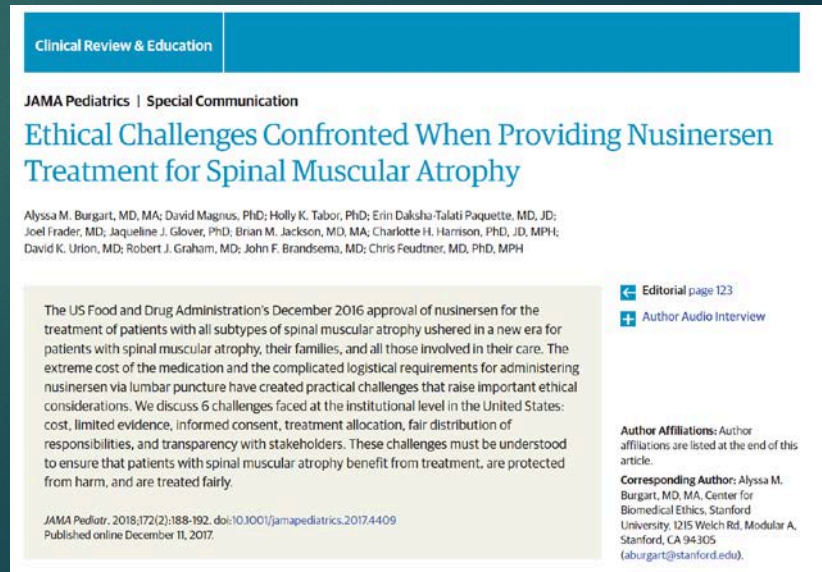
Overview

Four Ethical Challenges…

….but this is in no way an exhaustive list, I only have ten minutes!

And a new framework for approaching ethical challenges!



Clinical Review & Education

JAMA Pediatrics | Special Communication

Ethical Challenges Confronted When Providing Nusinersen Treatment for Spinal Muscular Atrophy

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The US Food and Drug Administration's December 2016 approval of nusinersen for the treatment of patients with all subtypes of spinal muscular atrophy ushered in a new era for patients with spinal muscular atrophy, their families, and all those involved in their care. The extreme cost of the medication and the complicated logistical requirements for administering nusinersen via lumbar puncture have created practical challenges that raise important ethical considerations. We discuss 6 challenges faced at the institutional level in the United States: cost, limited evidence, informed consent, treatment allocation, fair distribution of responsibilities, and transparency with stakeholders. These challenges must be understood to ensure that patients with spinal muscular atrophy benefit from treatment, are protected from harm, and are treated fairly.

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Author Audio Interview

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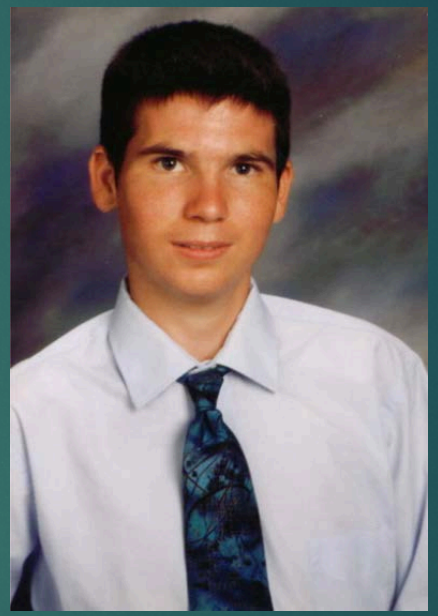
1) Zeal, warning signs, and therapeutic optimism

Jesse Gelsinger Case (1999)

- Had mild form of ornithine transcarbomylase deficiency, an X-inked genetic disease of the liver
- Participated in a Phase 1 trial at Penn, died 4 days after receiving the drug via an AAV vector from a massive immune response
- Three main findings from investigation:
  - Gelsinger's ammonia levels were too high for inclusion
  - Changes to approved protocol, failure to report events/side effects
  - Failure to disclose, in the informed consent documentation, the deaths of monkeys given a similar treatment.
  - Inadequate disclosure of investigator conflicts of interest
  - Fines for Penn and Children's National Medical Center, sanctions against researchers, lawsuit settlements



Gelsinger Lessons/Impacts

- Need to strengthen and improve local and national regulatory structures
- Create systems to prevent even the appearance of a conflict of interest
- Careful consideration of who should be in a Phase 1 trial, how to maximize safety
- "The key to research review is not only consent, but a responsible objective evaluation of the reasonableness of harm in research."

–Julian Savalescu

- "In their zeal to help patients with a life-threatening disease, leading researchers at one of the premier academic medical centers in the United States lost their focus. They overlooked warning signals that experimental intervention was not safe, with tragic, fatal consequences."

–Robert Steinbrook

Next steps

- Build on trends of increased transparency around all stages of clinical trials
- Empirical analysis of informed consent forms for gene therapy trials
- Interviews with participants/researchers
- Development and testing of shareable tools for mitigating therapeutic misconception/optimism

2) Characterizing and understanding the values around treatment decisions.

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Research Report

Perspectives on Spinraza (Nusinersen) Treatment Study: Views of Individuals and Parents of Children Diagnosed with Spinal Muscular Atrophy

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Perspectives on Spinraza Treatment

No to Spinraza Treatment

- “Dr. [Name] was pretty much like even if we put some loading doses in , he is still going to have to go onto a ventilator and really the decision came down to are you willing to have a child that just lays in bed all day on a ventilator and can’t do anything is that right for your child? Like what’s the humane thing to do? What’s the compassionate thing to do? ” (Parent, SMA I)

Yes to Spinraza Treatment

- “I want to feed myself. I want to use my phone independently. I want to drive my chair without have to think about it. It’s all these little things that I kind of didn’t even consider…Before that progressions I was able to have a certain level of independence and interdependence that I was really comfortable with and this new progression has required a different level of help from others that was new and scary and felt pretty invasive and uncomfortable.” (Adult, SMA II)

Trade-offs in values/priorities

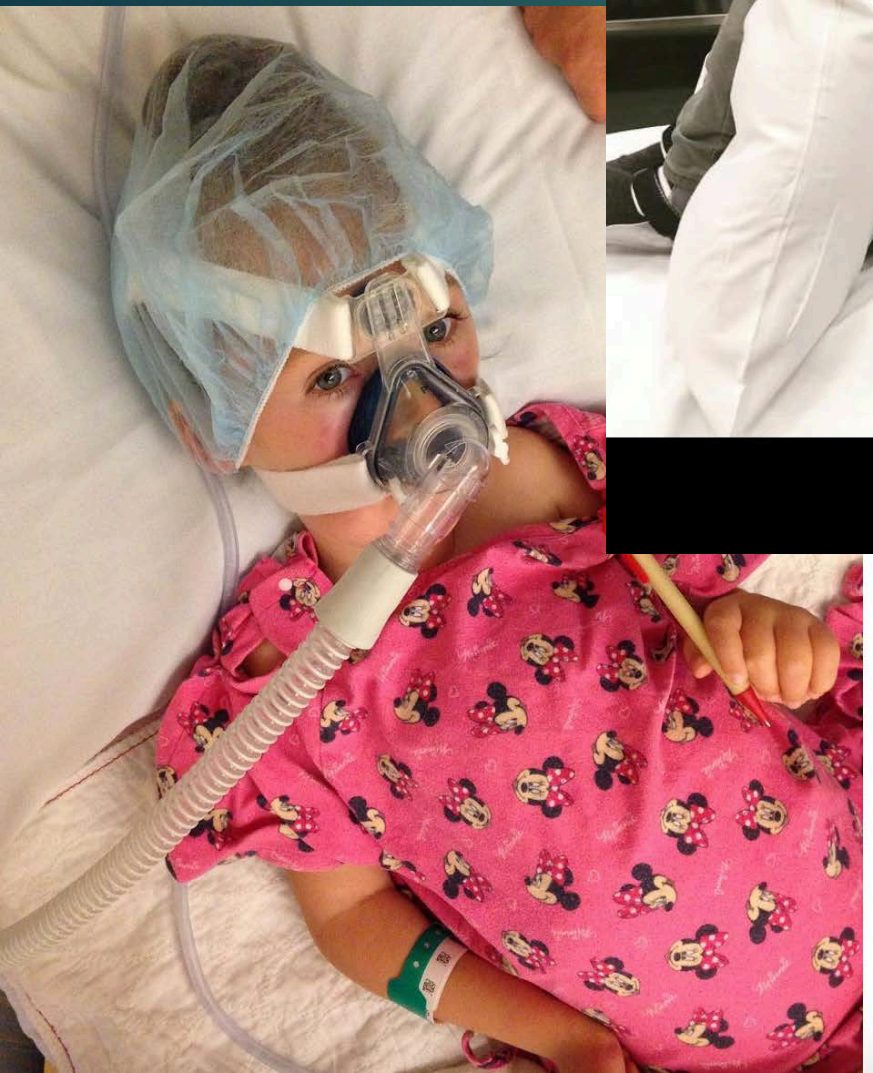
- “How do I reconcile being a disability rights activist and being in the movement, and making out my life’s work while still pursuing Spinraza, they still seem inherently contradictory to me and I don’t have an answer for how to reconcile them. I was kind of just in denial about it for a while…and then I got to neurology and as soon as they got the needle into the hole for the lumbar puncture I started sobbing because I felt like I was betraying my community, my values. I didn’t know who I was anymore.” (Adult, SMA II)

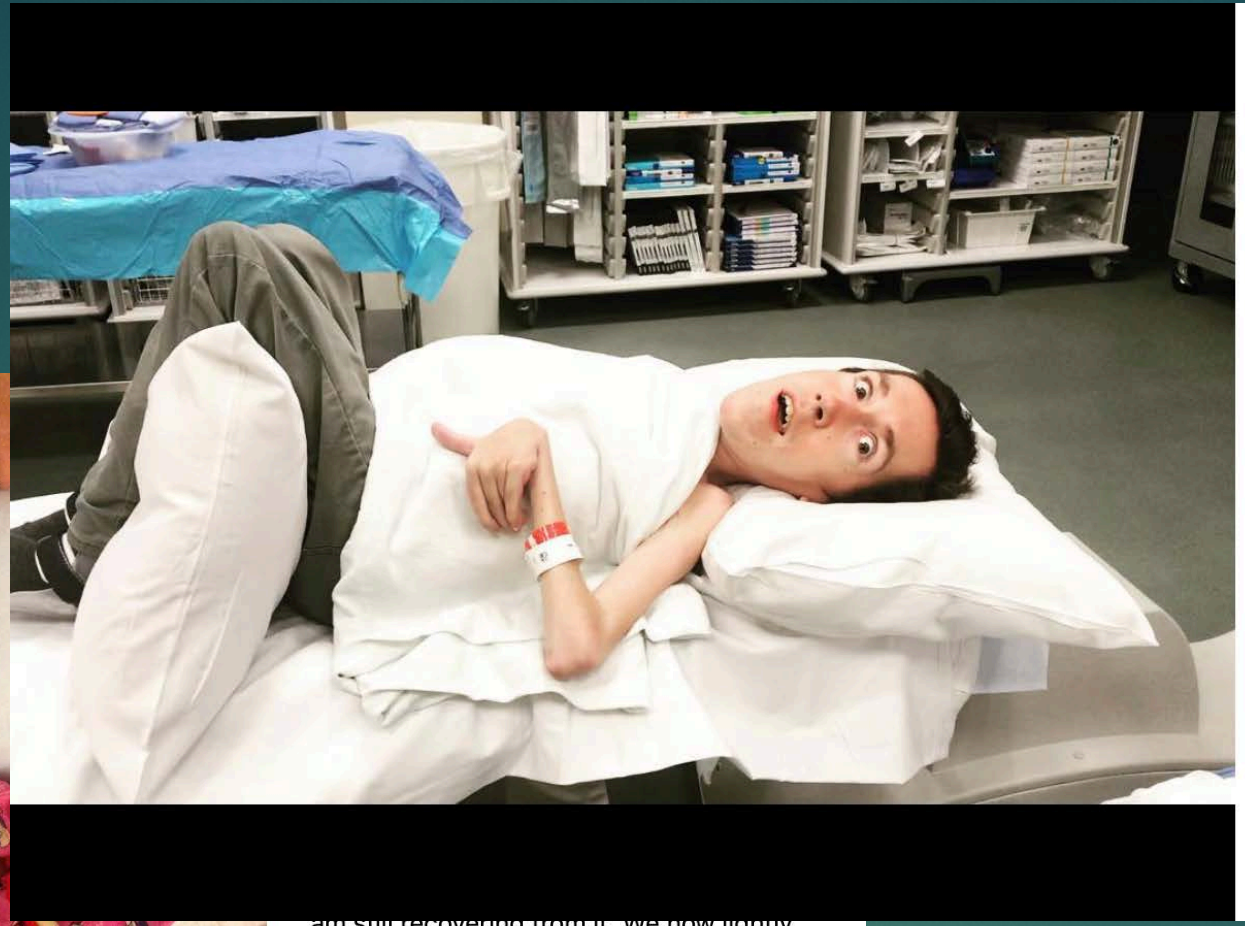
- “It just is not a good fit for our family and our lifestyle because our whole goal with [child] is to not make her feel disabled, to not have her life focused around hospitals…That would take her out of school and out of her social life. I think that would..,destroy her and send her into a depression.” (Parent, SMA II)

Next steps

- Clinicians should engage patients in explicit discussions
  - Elicit patients' awareness and knowledge of the natural history of SMA, including potential functional decline and disease progression
  - Ask questions about patients' values, goals, and knowledge base while improving dissemination of information about Spinraza
  - Discuss patient testimonials on social media
  - Discuss eligibility criteria, research data
  - Discuss ways to navigate insurance, transportation options

3) Challenges surrounding rare disease patients' use of social media and research/clinical use of gene therapies.





am still recovering from it. We now lightly sedate her (the anesthesiologist is in control of her breathing and her medication) and she wakes up when it is all over. She loves that she doesn't have to be awake for the IV. She hates IV's. It is much better for her (and us!). #smaawareness #thisissma

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AUGUST 14, 2018

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shaneburcaw • Follow
Minneapolis, Minnesota

shaneburcaw NEW VIDEO! Yesterday, during my 8th Spinraza injection, the radiologist had a very hard time getting the needle into the correct spot in my spinal cord. It was not fun, but at least it's over, and I'm excited to see the increase in strength that always follows these injections! Tonight's video shares all the behind-the-scenes of my Spinraza injection yesterday!

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Key Findings

1. Patients/families sought out [illegible] and how to get it.
2. They found the informati[illegible]er sources.
3. Members and moderator[illegible] responsiveness, and [illegible]er resources.
4. They [illegible], and viewed, [illegible]tions sites, protocols for patients with spinal fusions, tips to manage side effects, and advice on getting insurance coverage.
5. They found utility in these groups for other SMA-related purposes: finding social support, reducing social isolation, identifying strategies for obtaining and using medical equipment, navigating support services.

> "…people are posting pictures of how the injection is done, what the injection needle looks like, what gauge it is, you know, you eat before or after, or whatever side effects that you face, what are some of the things I can do to avoid those things. Like headache is one common side effect for lumbar puncture, in any case, when you take chemotherapy or pregnancy, you end up with headaches the next day, so one of the key solutions is to keep laying down after you've been given the injection for about an hour, and drink a lot of caffeine. So that seems to be the most common – just knowing about it – and people are scared…"

4) Cost, access and equity

....Stay tuned for Session V!

A new framework for identifying and addressing ethical challenges?

Asilomar Conference on Recombinant DNA

The National Academies of | SCIENCES ENGINEERING MEDICINE

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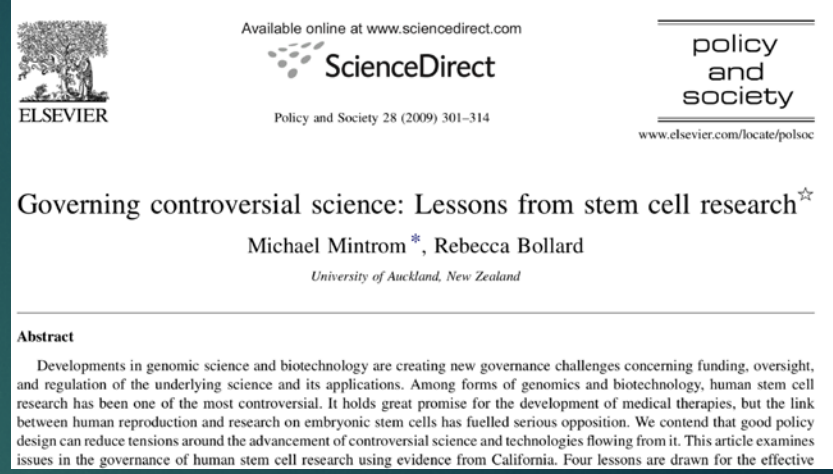
The Forum on Regenerative Medicine provides a convening mechanism for interested parties from academia, industry, government, patient and provider organizations, regulators, foundations, and others to meet and discuss sensitive and difficult issues in a neutral setting in order to engage in dialogue and discussions that address the challenges facing the application of, and the opportunities for, regenerative medicine to improve health through the development of effective new therapies. The Forum:

- Identifies existing and potential barriers to scientific and therapeutic advances;
- Identifies and discusses opportunities to assist in facilitating more effective partnerships among key stakeholders;
- Examines the impact that current policies have on the discovery, development, and translation of regenerative medicine therapies;
- Examines the unique challenges of identifying, validating, and bringing regenerative medicine applications to market; and
- Explores the ethical, legal, and social issues posed by regenerative medicine advances.

A model pathway?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Policy and Society 28 (2009) 301–314
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Governing controversial science: Lessons from stem cell research☆

Michael Mintrom *, Rebecca Bollard
University of Auckland, New Zealand

Abstract

Developments in genomic science and biotechnology are creating new governance challenges concerning funding, oversight, and regulation of the underlying science and its applications. Among forms of genomics and biotechnology, human stem cell research has been one of the most controversial. It holds great promise for the development of medical therapies, but the link between human reproduction and research on embryonic stem cells has fuelled serious opposition. We contend that good policy design can reduce tensions around the advancement of controversial science and technologies flowing from it. This article examines issues in the governance of human stem cell research using evidence from California. Four lessons are drawn for the effective

Lessons from California Stem Cell governance

(1) isolate structural design from controversy

(2) make room for laypeople in the governance structures

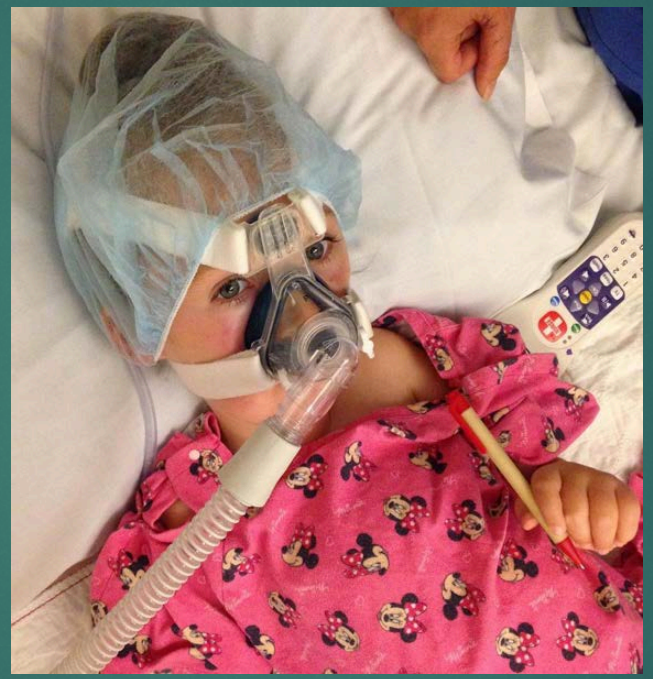
(3) promote transparency, minimize secrecy

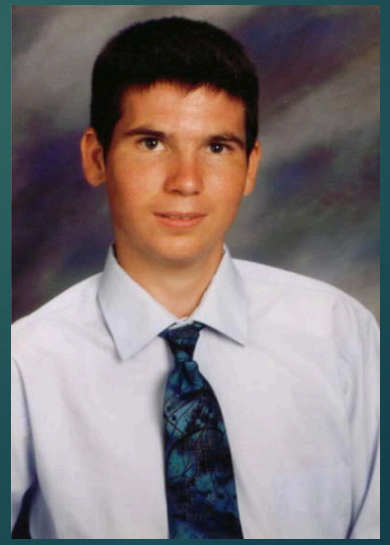
(4) create opportunities for learning and innovation

(5) build alliances and collaboration across stakeholders

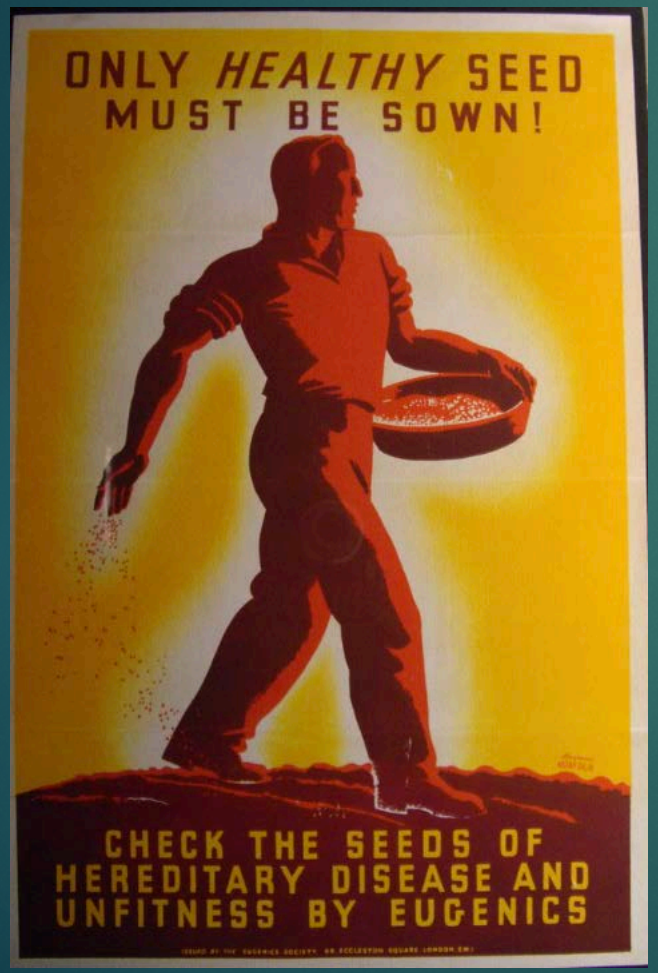
Michael Mintrom & Rebecca Bollard (2009) Governing controversial science: Lessons from stem cell research, Policy and Society, 28:4, 301-314, DOI: 10.1016/j.polsoc.2009.09.004

Meaningful, not just symbolic, patient engagement





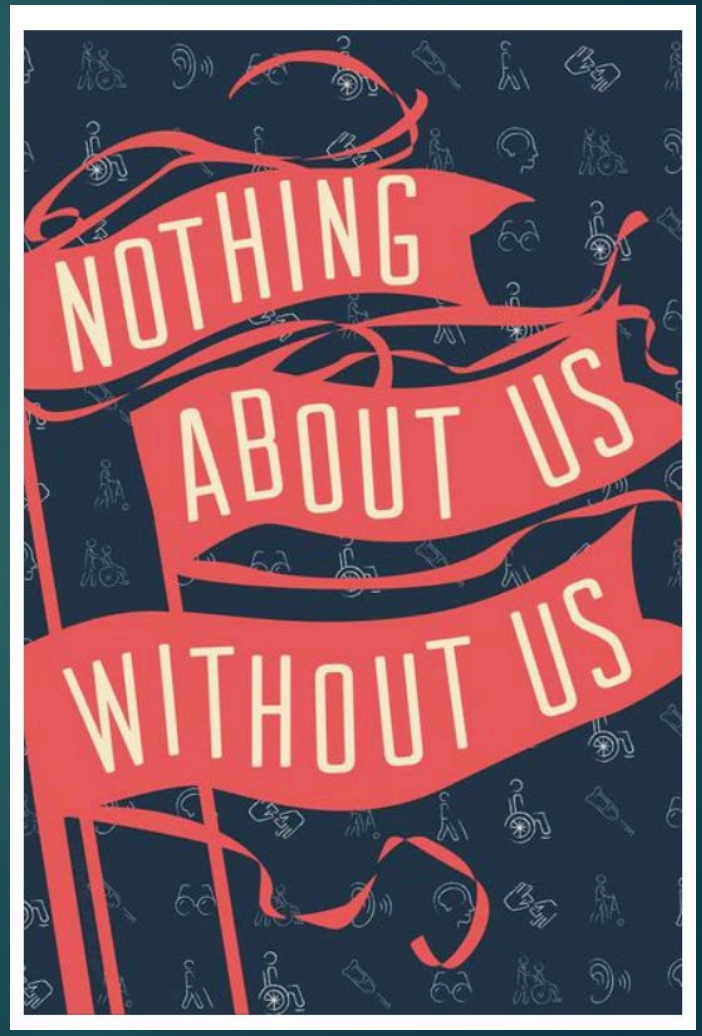
A slippery slope that must be approached with care, caution and respect



"To 'fix' a genetic variation that causes a rare disease may seem an obvious act of beneficence. But such intervention assumes that there is robust consensus about the boundaries between normal variation and disability. Contrary to the prevailing assumption, most people with disabilities report a quality of life that is equivalent to that of non-disabled people."

-Tom Shakespeare

https://www.nature.com/articles/527446a.pdf



Thank you!

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