Fair Access and Equity of Individualized Interventions for Ultrarare Genetic Conditions

September 8, 2023 at 12pm ET/9am PT

Ingrid Holm, MD, MPH
Boston Children's Hospital,
Harvard Medical School

Alison Bateman-House,
MPH, PhD
NYU Langone Health

Moderated by
Meghan Halley, PhD, MPH
Stanford University

ELSI hub CERA

ELSI FRIDAY FORUM

Fair Access and Equity of Individualized Interventions for Ultrarare Genetic Conditions

Center for ELSI Resources and Analysis (CERA)
Friday Forum

09/08/2023

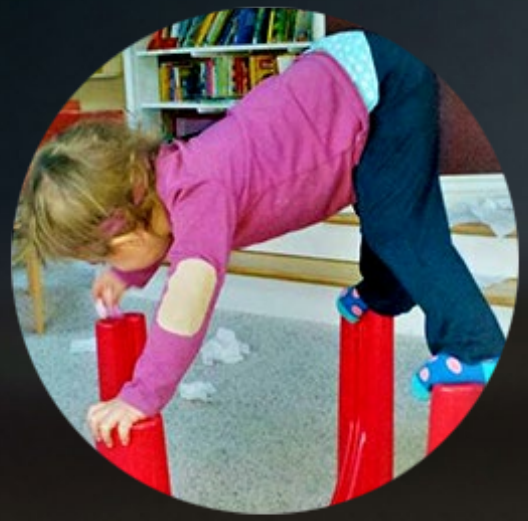
Ingrid A. Holm, MD, MPH

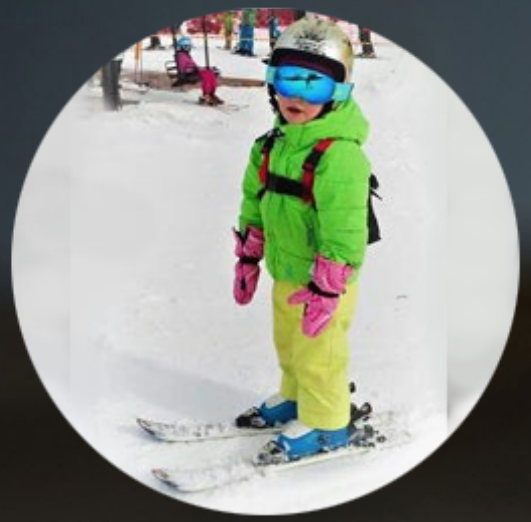
Division of Genetics and Genomics | Boston Children's Hospital

Professor of Pediatrics | Harvard Medical School

Faculty Member | Harvard Medical School Center for Bioethics

6-year-old girl with vision loss, neurologic decline





Mila, age 6

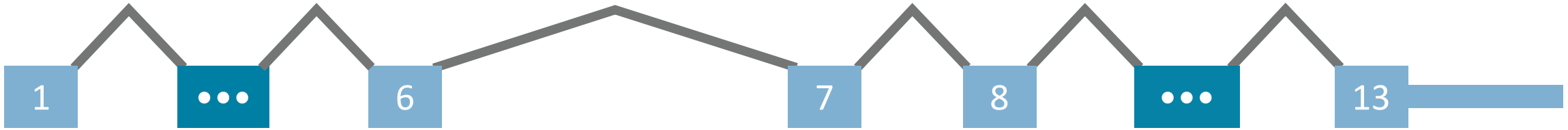
- **Skin biopsy → *Batten Disease***
  - Progressive neuronal cell death
  - Autosomal recessive
  - 14 different forms
  - She had pathogenic variants in both *CLN7/MFSD8* genes

Names & photographs shared with family permission

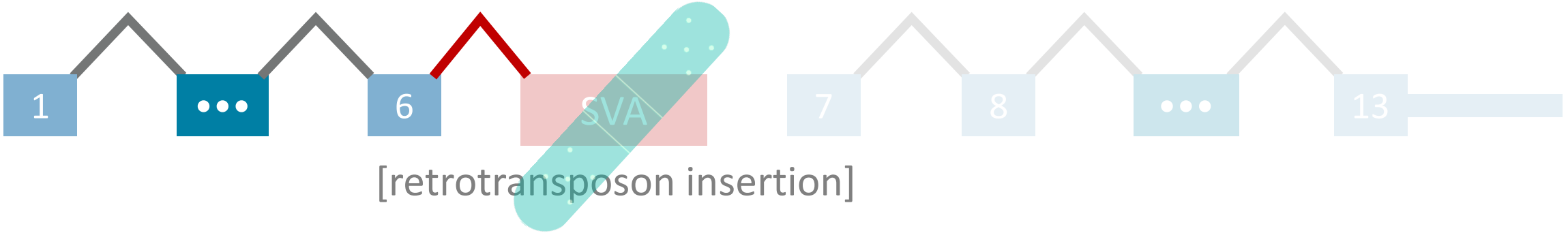
Slide courtesy of Tim Yu, MD, PhD; BCH; https://www.theyulab.org

One of her Pathogenic Variants Disrupted Splicing of the *CLN7/MFSD8* Gene

Normal *CLN7/MFSD8* gene:



Mila's *CLN7/MFSD8* gene:



Slide courtesy of Tim Yu, MD, PhD, BCH, https://www.theyulab.org

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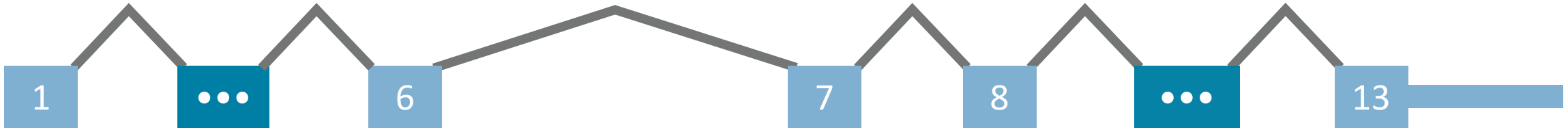
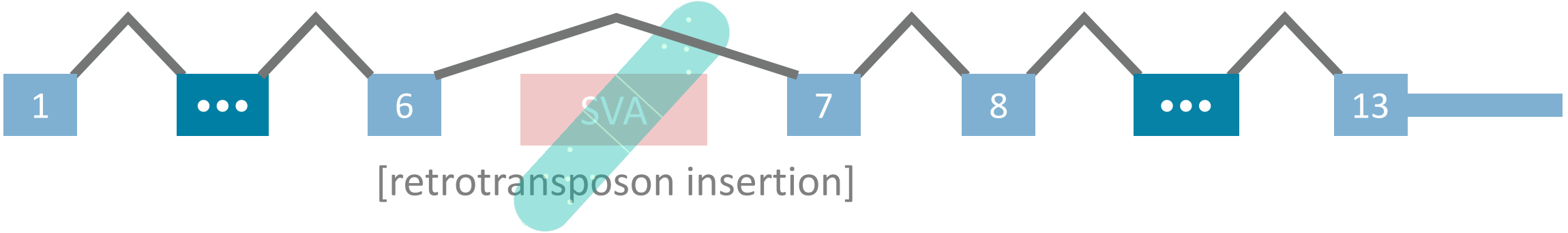


Mila's *CLN7/MFSD8* gene:



Could we develop a customized medicine to silence it and rescue gene function?

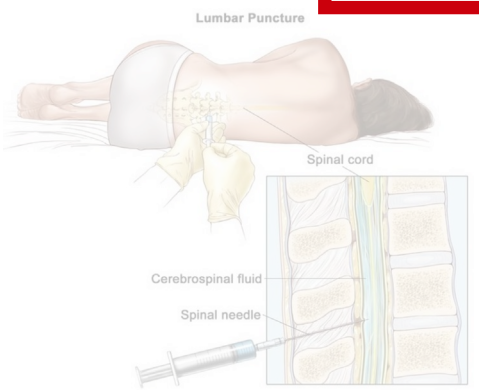
Slide courtesy of Tim Yu, MD, PhD, BCH, https://www.theyulab.org

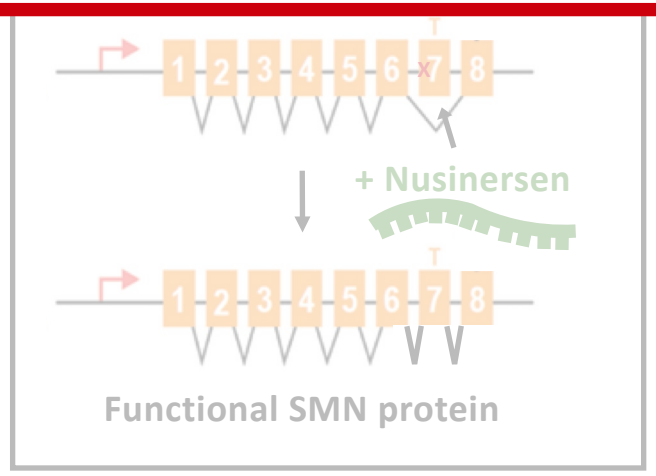
Nusinersen, a splice-modulating antisense oligonucleotide (ASO) for Spinal Muscular Atrophy

TCA CTT TCA TAA TGC TGG

- 18-nucleotide synthetic RNA
- Given by spinal tap 3X/year
- **Binds, restores normal splicing of *SMN2***

Could make “Nusinersen” for the patient?

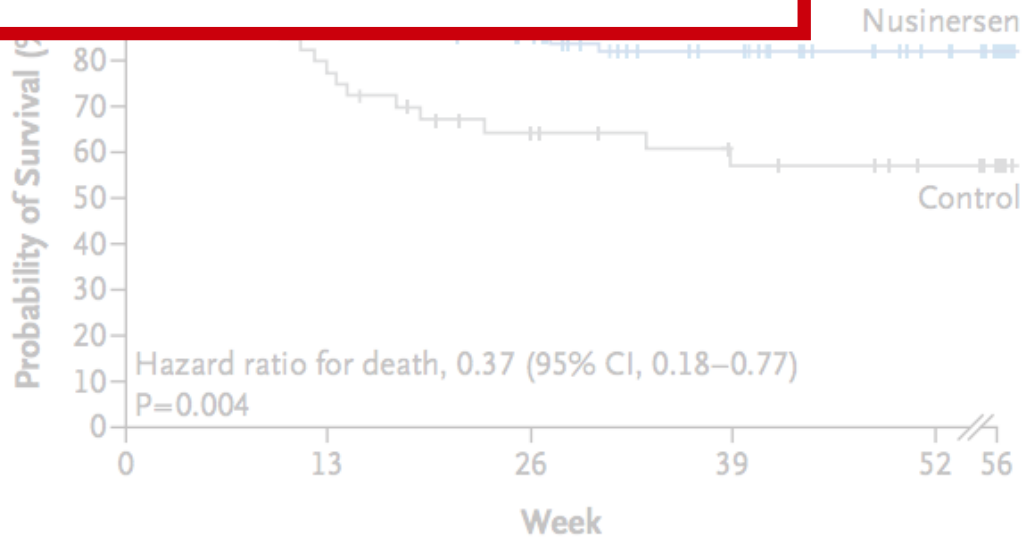




ORIGINAL ARTICLE

Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

R.S. Finkel, E. Mercuri, B.T. Darras, A.M. Connolly, N.L. Kuntz, J. Kirschner, C.A. Chiriboga, K. Saito, L. Servais, E. Tizzano, H. Topaloglu, M. Tulinius, ens, C.F. Bennett, AR Study Group*



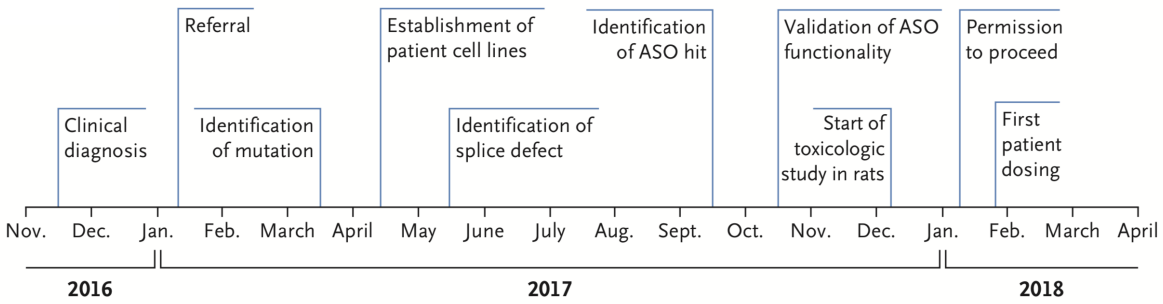
Slide courtesy of Tim Yu, MD, PhD, BCH, https://www.theyulab.org

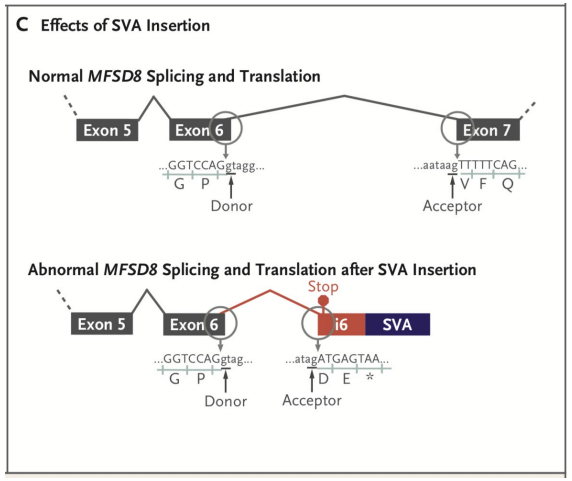
From patient referral to individualized medicine in 1 year
Led by Tim Yu, MD, PhD at Boston Children's Hospital

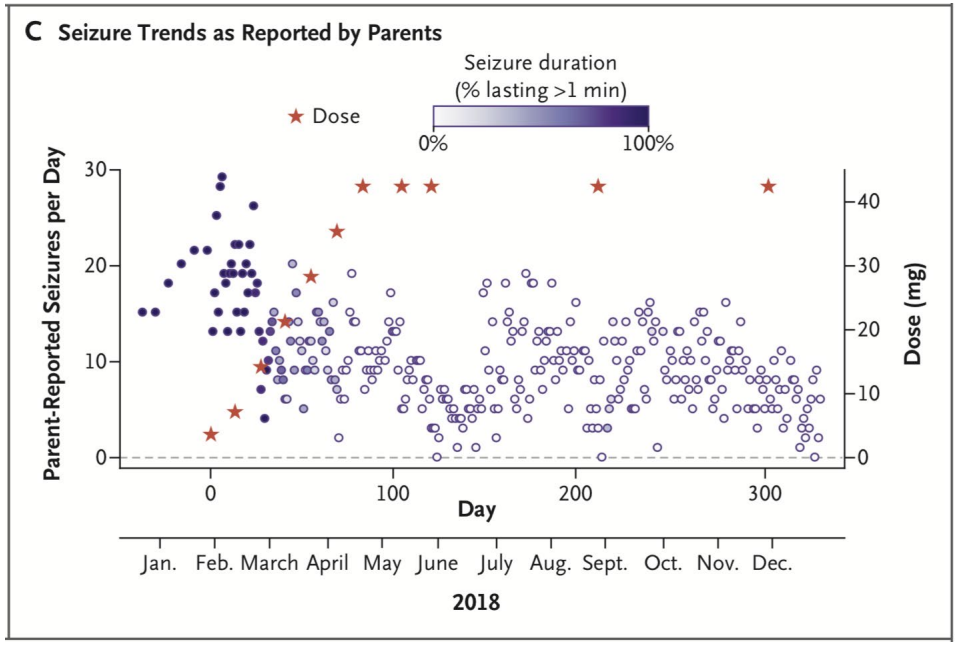
AAT GTT AGT GCT TGT TGA GGG C

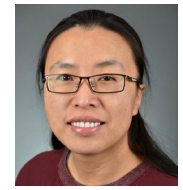
Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease

J. Kim, C. Hu, C. Moufawad El Achkar, L.E. Black, J. Douville, A. Larson, M.K. Pendergast, S.F. Goldkind, E.A. Lee, A. Kuniholm, A. Soucy, J. Vaze, N.R. Belur, K. Fredriksen, I. Stojkovska, A. Tsytsykova, M. Armant, R.L. DiDonato, J. Choi, L. Cornelissen, L.M. Pereira, E.F. Augustine, C.A. Genetti, K. Dies, B. Barton, L. Williams, B.D. Goodlett, B.L. Riley, A. Pasternak, E.R. Berry, K.A. Pflock, S. Chu, C. Reed, K. Tyndall, P.B. Agrawal, A.H. Beggs, P.E. Grant, D.K. Urion, R.O. Snyder, S.E. Waisbren, A. Poduri, P.J. Park, A. Patterson, A. Biffi, J.R. Mazzulli, O. Bodamer, C.B. Berde, and T.W. Yu









April Hu, MD, PhD

Jinkuk Kim, PhD

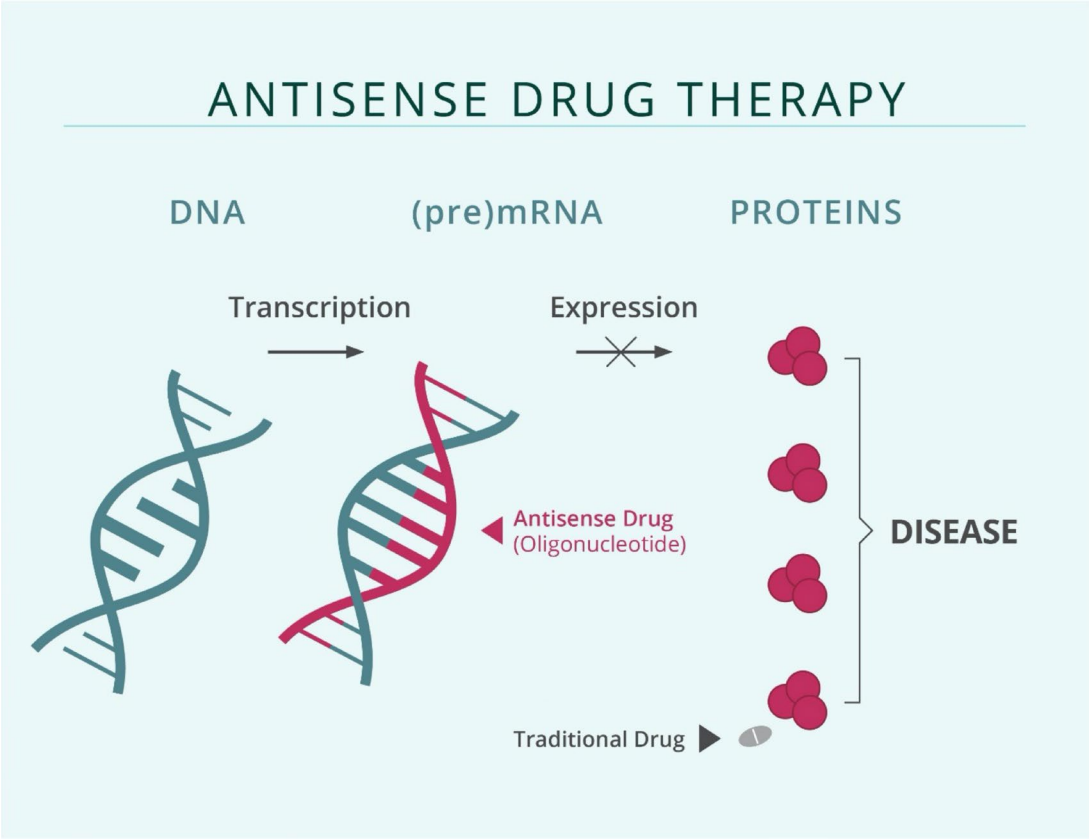
Christelle Achkar, MD

Kim & Hu et al, NEJM 2019

Slide courtesy of Tim Yu, MD, PhD, BCH, https://www.theyulab.org

Disease Candidates for ASO Therapies

- Most are neurologic with severe developmental delays, arrest of development, or death
- Symptoms manifest in infancy and are progressive
- Treating early can lessen/prevent symptoms
- ASOs are variant-specific
  - Genetic variants that lead to disease have to be amenable to ASO therapies



https://www.openaccessgovernment.org/antisense-therapies-tackling-challenging-high-unmet-medical/156151/

A series of individualized ASO trials

Jan 2018

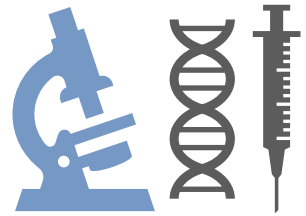
CLN7 Batten Disease

Jan 2020

Ataxia Telangiectasia

Sept 2020

KCNT1 neonatal epilepsy



Working up many more cases

ABCA4, ALDH5A1, ATM, CDKL5, CLN7, EHMT1, FLVCR1, KCNQ2, MECP2, NGLY1, NPC1, SAMD9L, SPTCL2, USH2A

Slide courtesy of Tim Yu, MD, PhD, BCH, https://www.theyulab.org

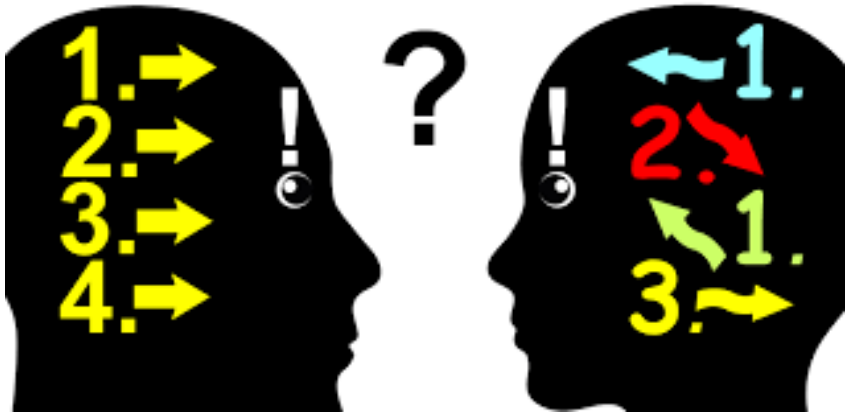
Significantly Abbreviated Proof of Concept / Safety Studies – Rely on Shared Properties of ASOs as a Class

- What is the nature and extent of evidence needed?
- What are the standards for evaluating efficacy?
- What is the minimum assurance of safety needed?
- How persuasive should the mechanistic or functional data be?

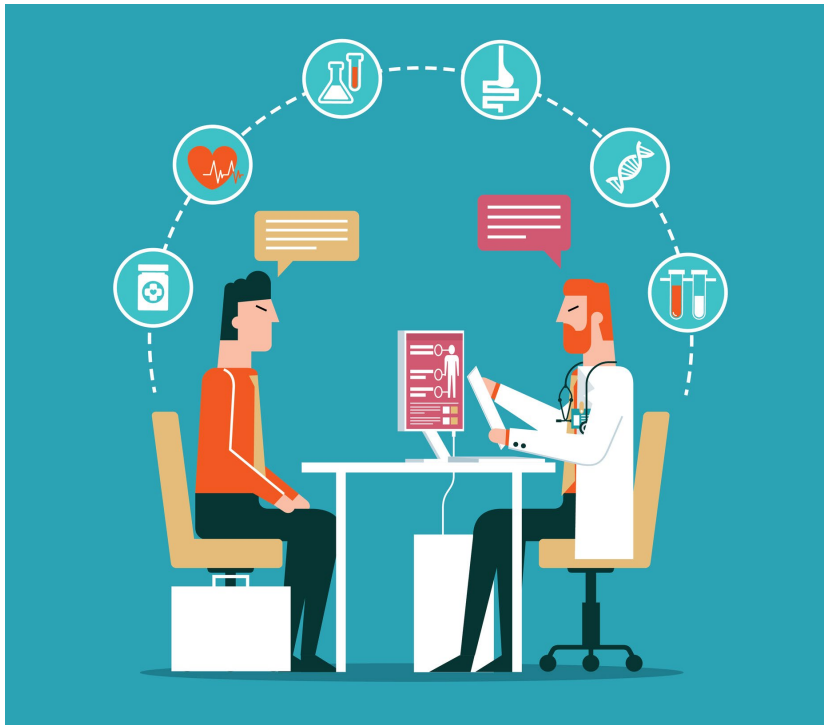
When there is only one patient, is this a Clinical trial? Clinical care?

- **Ethical obligations:**
  - Promote the individual patient's well-being
  - Gain generalizable knowledge
- **Does there need to be a boundary between patient care and research?**
  - Providing best possible care to individual patients should inherently be integrated with gaining generalizable knowledge
  - Integration of patient care with clinical research by collecting and analyzing data alongside clinical care
- **Role of regulatory oversight**
- **The need for a registry and standardized outcome assessments across N-of-1 treatments**

From the patient/participant's perspective

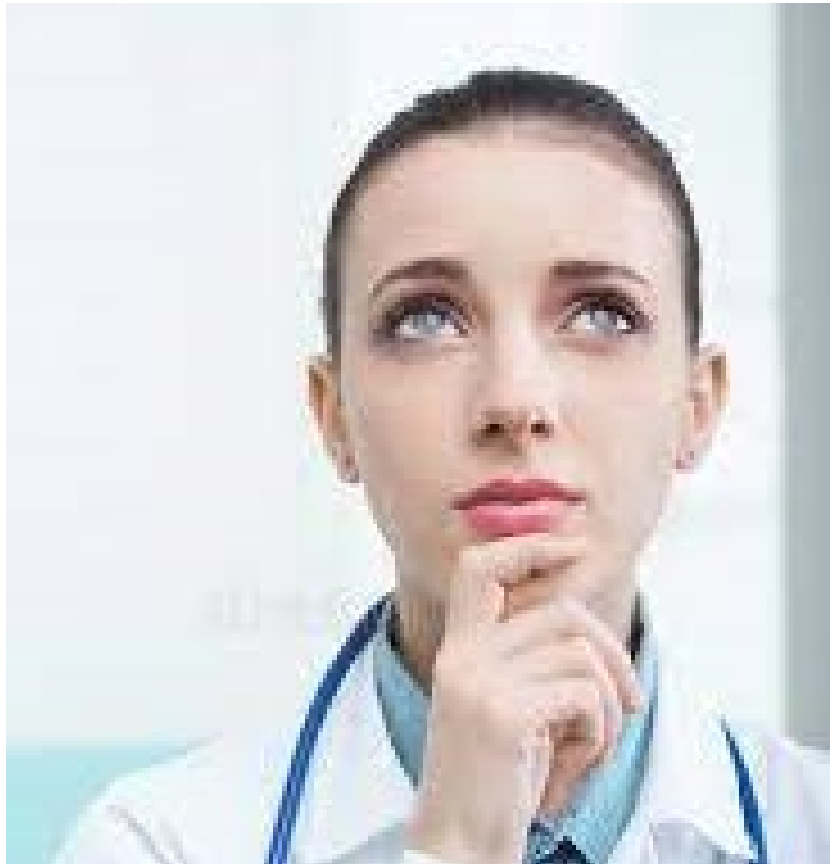


- The continuum between therapeutic hope, therapeutic optimism, and therapeutic misconception
- Informed consent: How can one can best communicate and manage risks in situations with considerable uncertainties and draw particular attention to expectations?



Deciding to Treat

- Urgency of the patient's situation?
- The number of people who could ultimately be treated?
- Who might benefit the most?
- When in the progression of the disease is it most effective to intervene?



Societal issues

- Justice and fairness in access to, and allocation of, resources for these therapies
- Equity of inclusion and exclusion criteria
- Who should pay for the often extremely high cost of developing, administering, and studying these therapeutics?
- Access to N-of-1 therapies in underserved racial, ethnic, and low socio-economic communities exacerbating health disparities
- What is the role and structure for governance and oversight?

Children are an early focus of N-of-1 therapies

- How do we weigh the benefits and harms, especially given high risk and great uncertainty?
- How does the inability of many children undergoing these therapies to assent due to neurocognitive disability impact decision-making?
- In children who can assent, what is the appropriate degree of child engagement in decision-making?
- What role does the child's future autonomy play?

Providing ethical guidance for the development of individualized genomic medicine as rare as n-of-1

aka the “GENIE” study: Guidance and Ethics for N=1 Interventional Efforts

NHGRI R01HG012247

Co-PIs: Timothy Yu, Lynn Bush, Ingrid Holm

The goal: to chart a course in the implementation of N-of-1 therapies that is just, fair, equitable, transparent, and socially responsible by delivering empirically informed, stakeholder-driven guidance

Case-based and stakeholder-based approach

- To examine and catalog the range of ELSI arising in the development of individualized genomic medicine as rare as n-of-1 from the perspective of diverse stakeholders.
- To conduct a modified Delphi process and Roundtables to to develop stakeholder-based ELSI guidance for n-of-1 therapies that will inform the evolving provision of individualized genomic medicine for orphan diseases.

Study Team

Co-PIs at Boston Children's Hospital

Timothy Yu, MD PhD

Ingrid Holm, MD MPH

Lynn Bush, PhD MS Bioethics

Independent Advisor Research Bias

Karen Rothenberg, JD MPA
U Maryland Cary Law. Emeritus
Berman Institute, JHMI

Core Study Team

Jon Marron, MD, MPH
Pediatric Oncologist and Clinical Ethicist, BCH, DFCI HMS

Asha N. Talati, MD MSCR
Maternal Fetal Medicine and Geneticist, "Independent" Researcher, UNC-CH

Hannah Gilbert, PhD
Medical Anthropologist, Global Health and Social Medicine, HMS

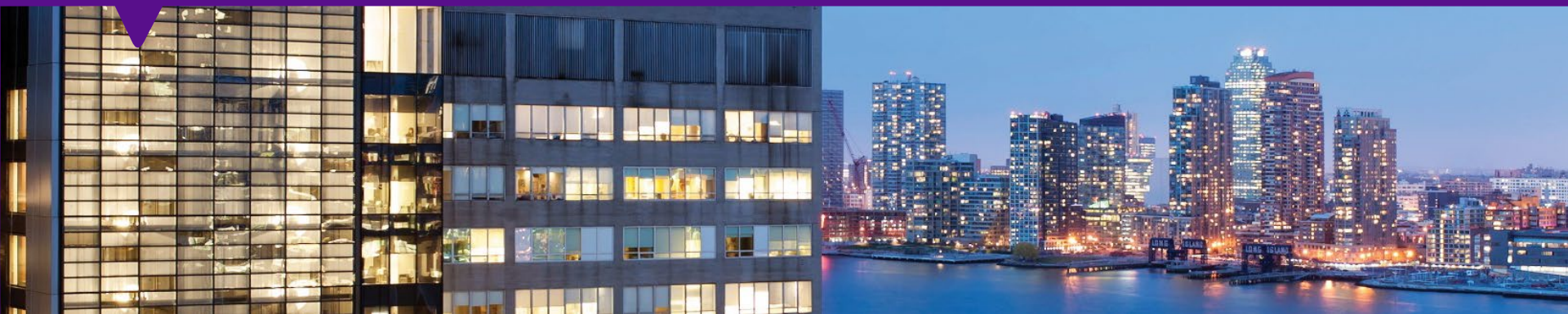
Bizu Gelaye, PhD, MPH
Epidemiologist & Director Mississippi Delta Partnership, HSPH, HMS, CBE

Discussion

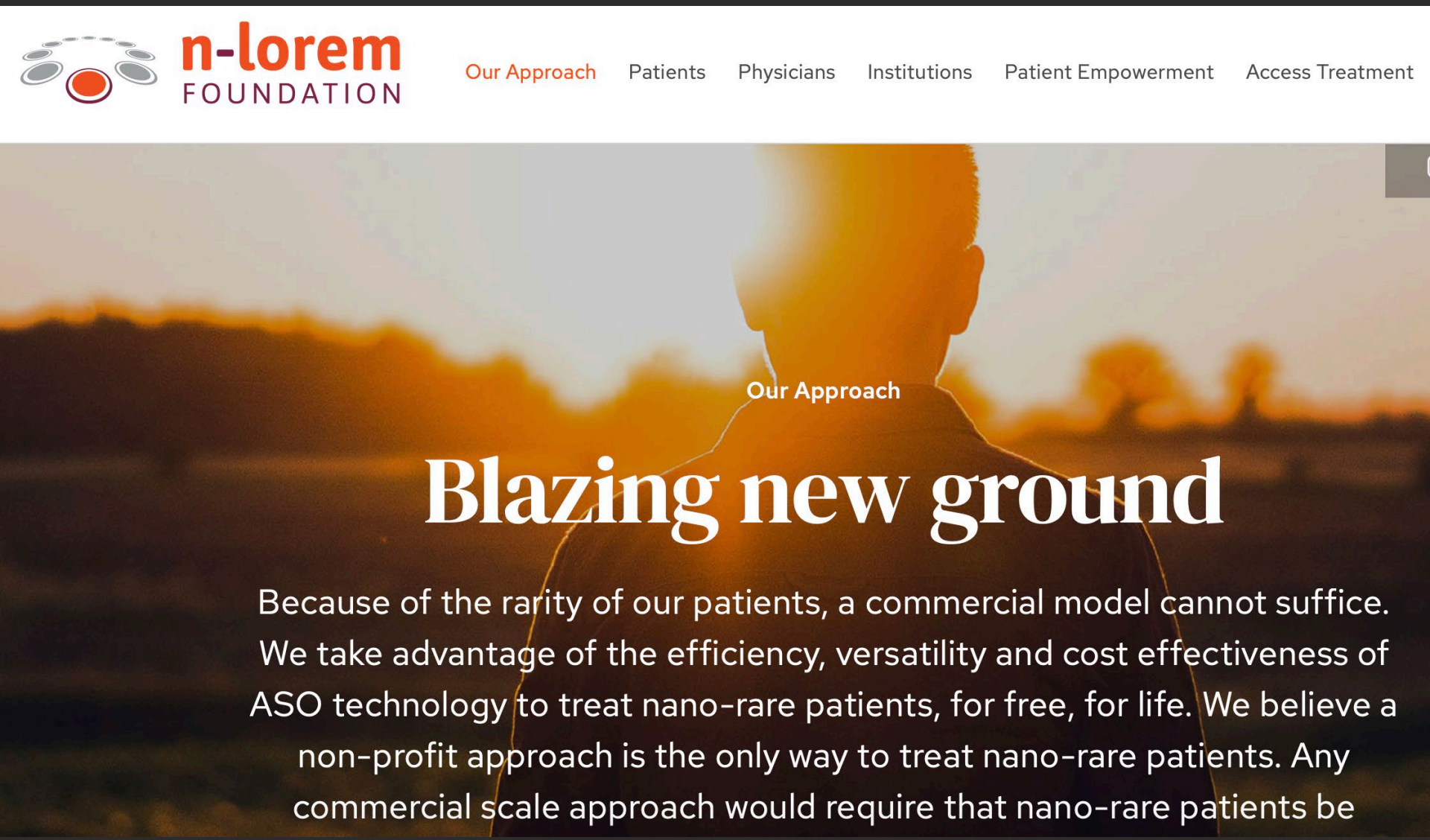
NYU Langone Health

FAIR ACCESS & EQUITY OF INDIVIDUALIZED INTERVENTIONS FOR ULTRARARE GENETIC CONDITIONS

Alison Bateman-House, PhD, MPH
Assistant Professor, Division of Medical Ethics,
NYU Grossman School of Medicine



Disclosures:



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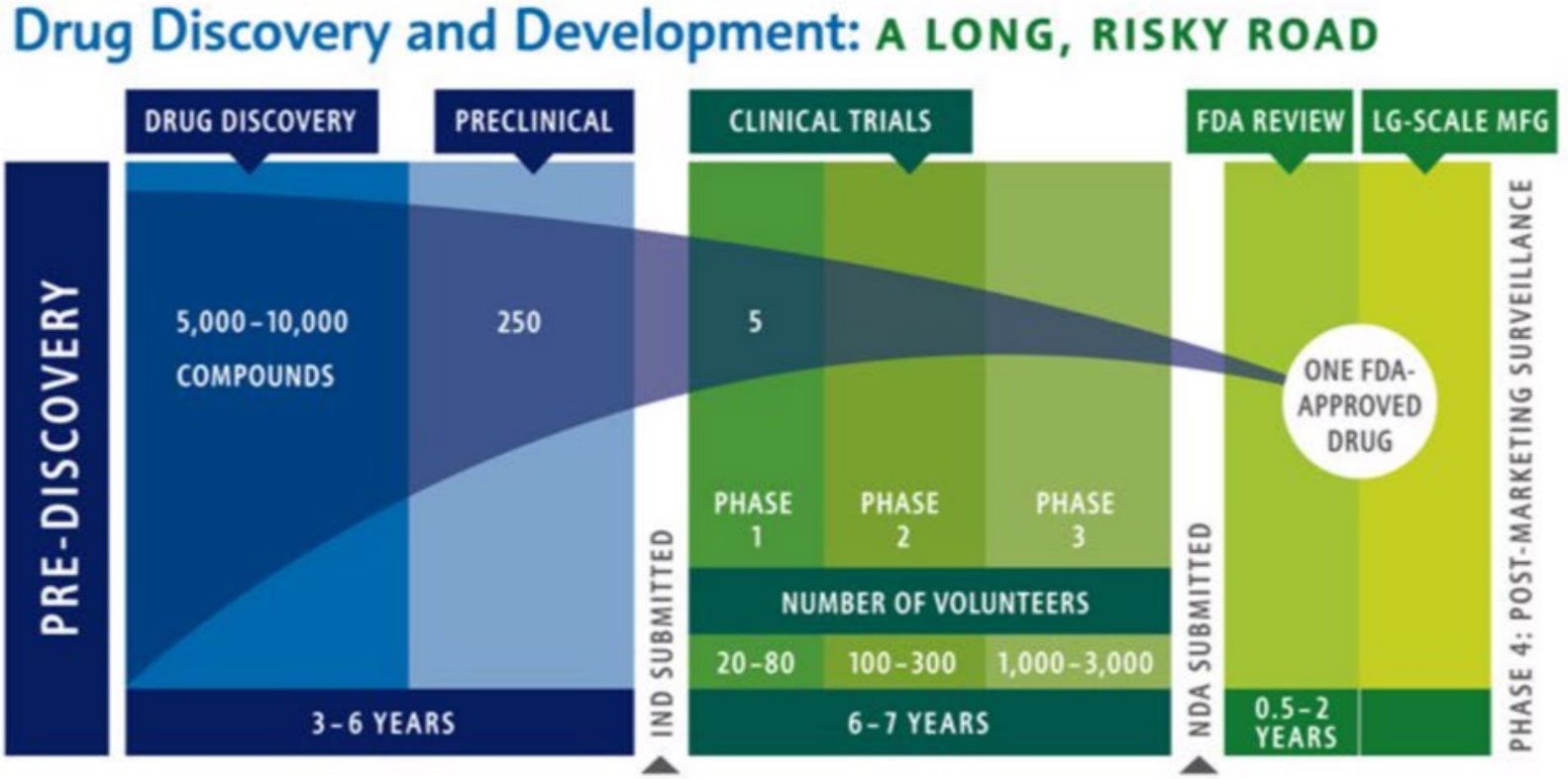
Current situation

Inequitable access to:

- Genetic testing/counselors
- Specialists
- Diagnoses
- Research
- N of few interventions

On what grounds do we justify differentiating our treatment of novel therapeutics for n of few indications from other novel therapeutics?

What exactly are we talking about?



"Individualized ASO drug products are not expected to follow the traditional investigational phases of drug development (i.e., clinical trial phases 1 through 3) as described in 21 CFR 118 312.21." *https://www.fda.gov/media/154664/download*

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Peter Marks and Janet Woodcock editorial re Milasen

- In these “N-of-one” situations, what type of evidence is needed before exposing a human to a new drug? Even in rapidly progressing, fatal illnesses, precipitating severe complications or death is not acceptable, so what is the minimum assurance of safety that is needed? How persuasive should the mechanistic or functional data be? How should the dose and regimen be selected? How much characterization of the product should be undertaken? How should the urgency of the patient’s situation or the number of people who could ultimately be treated affect the decision-making process?
- In addition, how will efficacy be evaluated?

Where do we draw the line & why?

- FDA has released several guidance documents over the years addressing “an individualized antisense oligonucleotide (ASO) drug product for a severely debilitating or life-threatening disease caused by a unique genetic variant here only a small number of individuals are prospectively identified (typically one or two).
- n-Lorem uses the term “nano-rare”; sets cut-off at n of 30.
- Prevalence of any indication will increase once you start looking for it…
- Prevalence of any indication may not be the same globally as it is the US / areas of the world where genetic testing has been done.

Post-Milasen efforts

- So far, no other patient with Mila's mutation has been identified.
- KCNT1-related epilepsy (prevalence, tens of patients globally): development of Valerisan; used in 2 patients, both with SAEs; initial recipient died.
- Rapidly progressive, genetic form of ALS [FUS mutation] (prevalence, 2nd most common gene abnormality to be described in familial ALS): development of Jacifusen; initial recipient died, FDA allowed a small # of other patients to be treated with Jacifusen, stating that any use beyond that point must be done as a clinical trial.
- N-Lorem has publicly announced obtaining 4 INDs.
- N of 1 Gene Therapy

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Where is the dividing line between n of few & ultra-ultrarare?

How justify that one patient (or patient group) with a dire prognosis must go through the traditional clinical trial process when another, with an equally dire diagnosis (but large enough numbers to forecast a profit), can be permitted to try a novel therapeutic after significantly less safety testing, characterization of agent, etc.?

Fairness / Rationality

Race to the bottom re regulatory oversight

Alison.Bateman-House@nyulangone.org
Twitter: @ABatemanHouse

THANK YOU

NYU Langone Health

The Genomics of PTSD Risk: Scientific and Ethical Perspectives

November 10, 2023 at 12pm ET/9am PT

Murray B. Stein, MD, MPH
University of California San Diego,
VA San Diego Healthcare System

Eric Juengst, PhD, MA
University of North Carolina
at Chapel Hill

Moderated by
Josephine Johnston, LLB, MBHL
The Hastings Center,
University of Otago

ELSI hub CERA

ELSI FRIDAY FORUM

TraineeHub

ELSI hub | CERA

Finding and Making Sense of NIH Funding Opportunities

October 3, 2023 - 3:30pm ET

Featuring

Dave Kaufman, PhD
National Human Genome Research Institute

Marsha Michie, PhD
Case Western Reserve University