Custom Genomic Treatments: Lessons Learned and Opportunities

Scott Demarest MD MSCS

Chief Precision Medicine Officer,
Children's Hospital Colorado
Director, International CDKL5 Clinical Research Network
Co-Director, Batten and Neurogenetic Multidisciplinary Clinic
Associate Professor, Departments of Pediatrics and Neurology
University of Colorado School of Medicine

Disclosures

I have consulted for Biomarin, Neurogene, UCB, Marinus, Ultragenyx, Lundbeck, Mahzi, Ovid, and Capsida therapeutics. I also have institutional collaborations with Illumina related to precision medicine implementation.

I have funding from the NIH, the International Foundation for CDKL5 Research, Mila's Miracle Foundation, BDSRA, STXBP1 Disorders and Project 8P.

I also serve on advisory boards for the non-profit foundations SLC6A1 Connect, Project 8P, Ring 14 USA, Familie SCN2A, Rare X (Global Genes) and the N of 1 Collaborative.

The information presented today is based on peer-reviewed evidence and my own flawed opinions.

Objectives

- Our custom ASO experience – historical regulatory framework

- Inductive science vs programmable medicine

- Potential models for safe, sustainable, and scalable interventional genomics programs

Mila

Mila was from Colorado

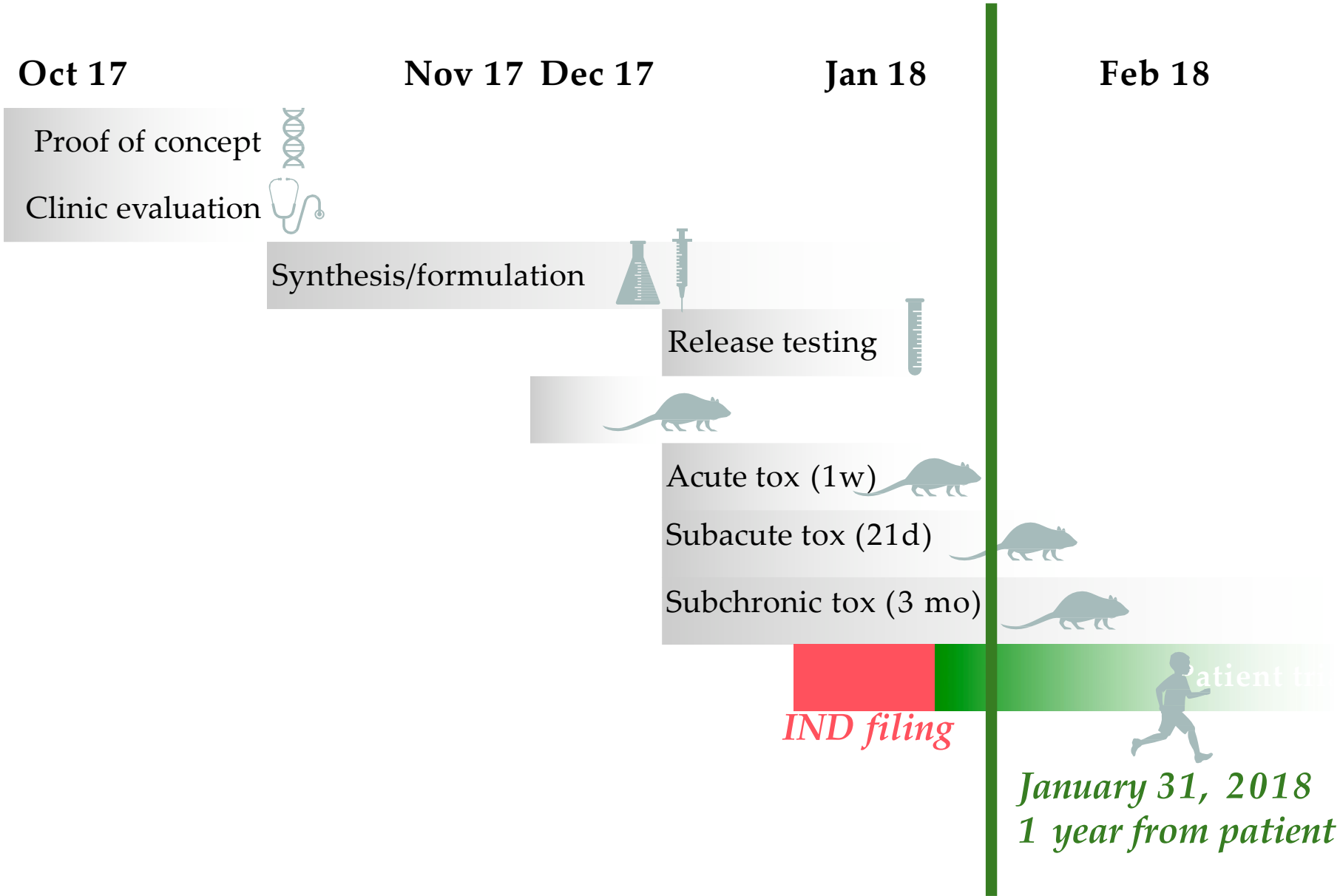
After normal development she began experiencing visual and neurologic declines at 4 years old

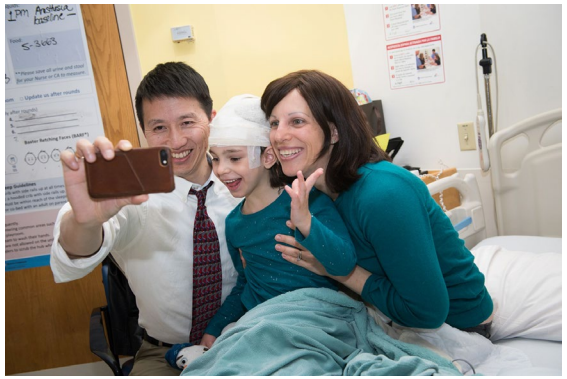
She was seen by Neurology, Genetics, and Ophthalmology

<u>Clinical diagnosis:</u>
<u>CLN7 Batten Disease</u>

Austin Larson, MD
University of Colorado School of Medicine

Trial launched January 31, 2018





CHCO Experience with Custom Therapeutics

Four patients and one starting soon

- Second half of Milasen

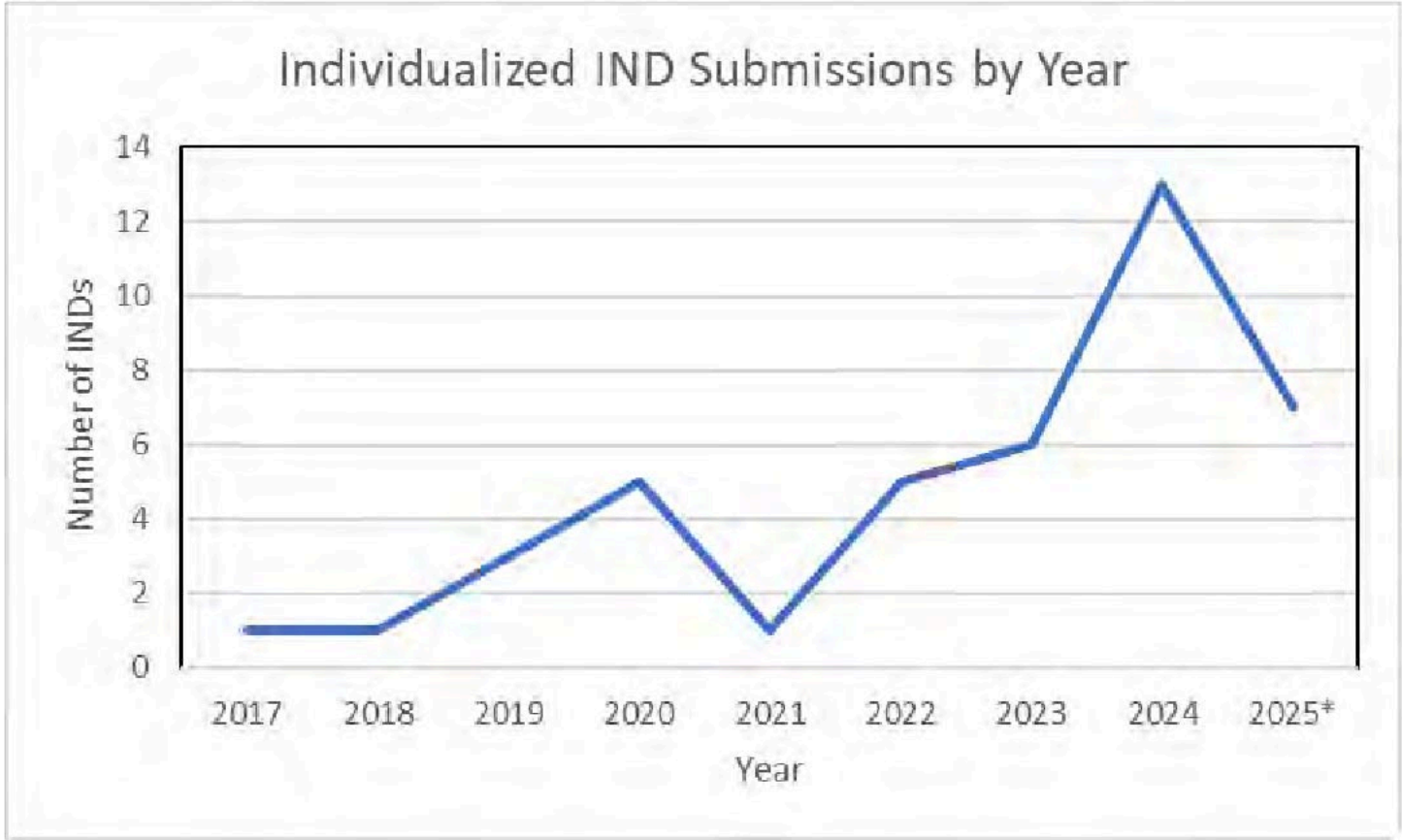
- Ocular ASO for Retinitis Pigmentosa due to FLVCR1 (McCourt, Larson)

- KIF1A ASO - Two patients (third soon) – Made for one patient then found ~ 12 other patients who could use the same ASO

- We have designed some promising ASOs on campus

2018 => 2026

FDA surveyed elements across 49 “n-of-1” IND programs encompassing 35 unique oligonucleotides, treating 82 patients – January 2017- October 2025

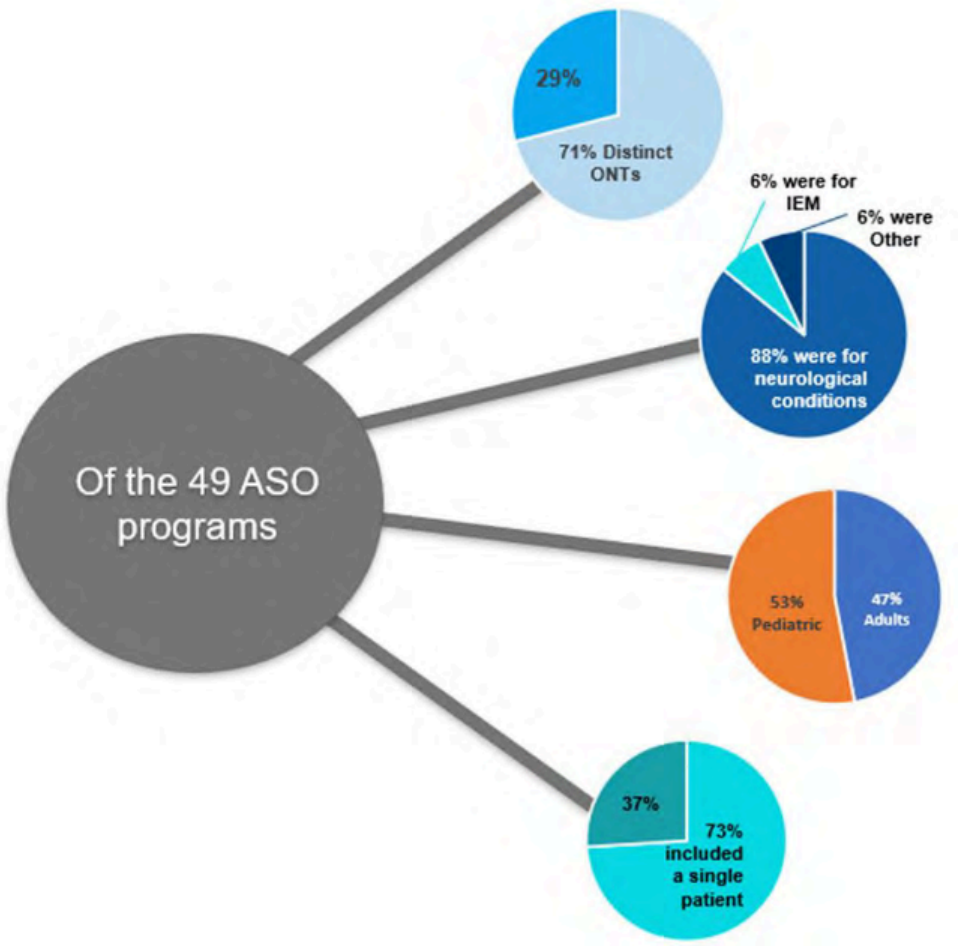


Dr. Bar Rogers - On the Rise Individualized Therapies, conference Nov. 2025 https://healthpolicy.duke.edu/sites/default/files/2025-11/Slides%20Individualized%20Therapies%20on%20the%20RISE.pdf

2018 => 2026

Findings

- 88% (n=39) of the 49 “n-of-1” programs were under development for neurological diseases, 6% were for inborn errors of metabolism, and 6% for other
- 30% of the n-of-1 programs included an adult with ALS
- 53% of the n-of-1 programs were developed for a pediatric patient
- 69% enrolled a single patient



Dr. Bar Rogers - On the Rise Individualized Therapies, conference Nov. 2025

Baby KJ

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE | BRIEF REPORT

Patient-Customized Oligonucleotide Therapy for a Rare Genetic Disease

Authors: Jinkuk Kim, Ph.D., Chunguang Hu, M.D., Ph.D., Christelle Moufawad El Achkar, M.D., Lauren E. Black, Ph.D., Julie Douville, Ph.D., Austin Larson, M.D., Mary K. Pendergast, J.D., +40 , and Timothy W. Yu, M.D., Ph.D. Author

ORIGINAL ARTICLE | BRIEF REPORT

Patient-Specific In Vivo Gene Editing to Treat a Rare Genetic Disease

Authors: Kiran Musunuru, M.D., Ph.D. , Sarah A. Grandinette, B.S., Xiao Wang, Ph.D., Taylor R. Hudson, M.S., Kevin Briseno, B.S., Anne Marie Berry, M.S., Julia L. Hacker, M.S., +37 , and Rebecca C. Ahrens-Nicklas, M.D., Ph.D. Author

Programmable Medicine

VS

Inductive Science

How do we Bridge the Gap?

Bringing Clinical Trial Rigor to Everyday Care

Some thoughts…

- Learn from pediatric oncology and others
- Movement toward every patient is both clinical care and research so we can learn from all rare disease patients
- Use standardized measures in everyday care where feasible
- Establish multi-center infrastructure that supports natural history and clinical trials efforts across rare diseases with less redundancy

Two Models to Safe, Sustainable, Scalable

Regulate the parts of the product - Modular Approach

- Building on precedence don’t have to reprove parts, but you have to prove the new part

Regulate the process for making the parts – Process Approval

- Guardrails, standards, oversight for each step in the process, but if the process is approved then any product that comes out of the pipeline is approved.

FDA Plausible Mechanisms Pathway

Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause

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Draft Guidance for Industry

https://www.fda.gov/media/191247/download

Mandate to convince regulators:

- Severely debilitating or life-threatening disease
- Therapeutic products target the underlying abnormality, its "proximal pathogenic pathway"
- "Adequate and well-controlled clinical investigation in this context will include a small sample size"
- Must Justify why a traditional RCT is not feasible

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Modular Approach

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Modular vs Process Approach

Modular Approval

- Useful if you are reusing components
- Gene Editing / Replacement
  - Same vector
  - Same editor
  - New guide RNA

Process Approval

- Each product is different (but have similar properties)
- When do you lump vs split?
  - Gapmer vs steric blocking
  - Similar diseases or each disease gets it own proof of process
- ASOs

The burden of proof (demonstration of safety) has to be anchored to both the science and the clinical context.

Summary

- It is possible to design and treat ultra-rare populations:
  - Safely (check)
  - Sustainable
  - Scalable
- There are at least two potential models - each have value in certain contexts – Regardless Rigor is Critical

- NIC and ERDERA – have published and have ongoing work related to best practices in this space