NORD
National Organization for Rare Disorders

Rare Disease Scientific Symposium

Abandoned, Shelved, and Rescued Therapies for Ultra-Rare Diseases

Edward Neilan, MD, PhD
NORD
(Moderator)

Paul Ayoub, PhD, MBA
Rarity PBC

Terry Pirovolakis
Elpida Therapeutics

Matthew Porteus, MD, PhD
Stanford University,
a NORD Rare Disease
Center of Excellence

Developing Genetic Therapies for Rare Diseases ”Nobody said it would be easy, they just said it would be worth it”

Matthew Porteus MD PhD
Department of Pediatrics
Divisions of Pediatric Hematology/Oncology/Stem Cell Transplantation and Regenerative Medicine
Center for Definitive and Curative Medicine (CDCM)
Institute of Stem Cell Biology and Regenerative Medicine
Maternal Child Health Research Institute
Stanford University
mporteus@stanford.edu
14 April 2026

Potential Conflicts of Interest

Kamau Tx:	Equity, BoD, Founder
Allogene Therapeutics:	SAB
CRISPR Therapeutics:	Equity, Scientific Founder
Biogen:	SAB
Lenz Therapeutics:	Equity

Managed through Stanford in accordance with their conflict of interest's policy.

The list price for commercially approved gene therapies is economically justified based on value to the patient

Not to mention the non-economic value

But they do limit access

Three Drivers of Cost

1. Fixed costs
    - Pre-Clinical Development (may or may not be baked in to cost)
    - Clinical development
    - CMC development
    - Regulatory
    - People
2. Marginal costs
    - Clinical manufacturing costs of drug
    - People
3. Mark-up
    - Pharma/Biotech vs PBC vs Non-Profit

Potential Solutions to Each

1. Fixed costs
   - Regulatory innovation
   - Industrialization
     - ➢ We have supercomputers in our pockets (sometimes more than one) not because we make them locally but because manufacturing has been industrialized
     - ➢ Centralized quality systems will be cheaper than bespoke quality systems
     - ➢ And we are awesome at logistics (aka Amazon)
   - Platforms (“Alone we are rare, together we are strong”)
     - ➢ Unit cost decreases with volume increases
   - Lean entities
   - Speed
2. Marginal costs
   - Industrialization
   - Lean entities
3. Mark-up
   - Can lower but not eliminate by business models that are not ”shareholder value” driven companies

74

MEDICAL DISPATCH

BEFORE

AFTER

NO MISTAKE

The future of medical care: machines that act like doctors, and doctors who act like machines.

BY ATUL GAWANDE

ONE summer day two years ago, Hans Ohlin, the fifty-year-old chief of coronary care at the University of Lund Hospital, in Sweden, sat down in his office with a stack of two thousand two hundred and forty electrocardiograms. Each test result consisted of a series of wavy lines, running from left to right on a letter-size page of graph paper. Ohlin read them alone in his office so that he would not be disturbed. He scanned them swiftly but carefully, one at a time, separating them into two piles according to whether or not he thought that the patient was having a heart attack at the time the electrocardiogram (EKG) was recorded. To avoid fatigue and inattention, he did his work over the course of a week, sorting through the EKGs in shifts no longer than two hours, and taking long breaks. He wanted no careless errors; the stakes were too high. This was the medical world's version of the Deep Blue chess match, and Ohlin was cardiology's Gary Kasparov. He was going head to head with a computer.

The EKG is one of the most common of diagnostic tests, performed more than fifty million times a year in the United States alone. Electrodes are placed on the skin to pick up the low-voltage electrical impulses that, with each beat, travel through the heart muscle, and those impulses are reflected in the waves on an EKG printout. The theory behind an EKG is that in a heart attack a portion of the muscle dies, causing the electrical impulses to change course when they travel around the dead tissue. As a result, the waves on the printout change, too. Sometimes those changes are obvious; more often they are subtle—or, in medical argot, "non-specific."

To medical students, EKGs seem unmanageably complex at first. Typically, an EKG uses twelve leads, and each one produces a different-looking tracing on the printout. Yet students are taught to discern in these tracings a dozen or more features, each of which is given an alphabetical label: for instance, there's the downstroke at the start of a beat (the Q wave), the upstroke at the peak of heart contraction (the R wave), the subsequent downstroke (the S wave), and the rounded wave right after the beat (the T wave). Sometimes small changes here and there add up to a heart attack; sometimes they don't. When I was a medical student, I first learned to decode the EKG as if it were a complex calculation. My classmates and I would carry laminated cards in our white lab-coat pockets with a list of arcane instructions: calculate the heart rate and the axis of electrical flow, check for a

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Allen Edmonds

For All Walks of Life

Atul Gawande, ”No Mistakes” New Yorker 1998

Why is speed and the PRV important? (my use of Anthropic)

Net Present Value (NPV) Analysis: Priority Review Voucher (per $100M Future Value)

Impact of Development Speed and Discount Rate

Time to Market	5% Discount Rate	10% Discount Rate	15% Discount Rate
5 years	$78.4M	$62.1M	$49.7M
10 years	$61.4M	$38.6M	$24.7M
15 years	$48.1M	$23.9M	$12.3M

When we solve cost, the business model for genetic therapies for rare diseases will be even more challenging

For one-time therapies, the business model switches from prevalence to incidence (Different revenue stream than for a disease modifying therapy given for a lifetime)

To paraphrase “Biotechs don’t even get out of bed in the morning if the revenue isn’t at least $200,000,000 a year and Pharma doesn’t for less than $1,000,000,000”

And if the costs are reduced by 90%, the mark-up is reduced by 90%

What is ASGCT doing

1. A key pillar of the Strategic Plan of ASGCT (https://www.asgct.org/about-asgct/leadership-staff/strategic-plan)

   Advocate:

   Represent the entire field of cell and gene therapy, expanding access for patients to therapies that are safe and effective.

   ASGCT will serve as the collective voice of its members and the CGT field with lawmakers, policymakers, and others, promoting its interests and policy positions. The Society will advocate to maximize access, ensure safety, and foster a regulatory environment that supports clinical translation of CGT.

   - Bring together the silos ("Alone we are rare, together we are strong" applies to organizations with shared missions)
2. CGT Exchange: A marketplace of shelved therapies
3. Manufacturing consortium: To provide low-cost manufacturing for rare diseases

It is only through a variety of perspectives and expertise that the most important problems of the world can be solved

And this problem will need collaboration not individual efforts (subsuming of ego)

Abandoned, Shelved, and Rescued Therapies for Ultra-Rare Diseases

NORD®
National Organization for Rare Disorders

Paul Ayoub, PhD MBA
Rare Disease Scientific Symposium
April 14-15, 2026

RARITY PBC

Disclosures

- Co-Founder, equity holder, and President/CEO, Rarity PBC
- Rarity PBC holds an exclusive license to RDP-101, the ADA-SCID gene therapy discussed in this presentation
- No other conflicts to disclose

The Many Faces of ADA-SCID

Before Gene Therapy

Photo by UCLA, supplied by parents
Credit Good News Network

After Gene Therapy

A Global Health Priority

Fatal ultra-rare pediatric disease with inadequate current solutions affecting 100+ infants globally each year

Proven clinical pathway with new regulatory frameworks specifically enabling ultra-rare disease innovation

- ADA-SCID patients **have no functional immune system**
- Common **infections can be fatal,** and patients require isolation from family and friends
- The current treatment of biweekly ADA **injections are lifelong**, only temper the disease, and fail to achieve complete lymphocyte reconstitution*
- A one-time **gene therapy restored complete immune function** and no longer required enzyme replacement for 10+ years and counting

* https://doi.org/10.1182/blood.2022016196

ADA-SCID: The Case for a Cure

- 62+ patients treated in a Phase I/II trial.
- **100% Overall Survival**
- **95% Event Free Survival**

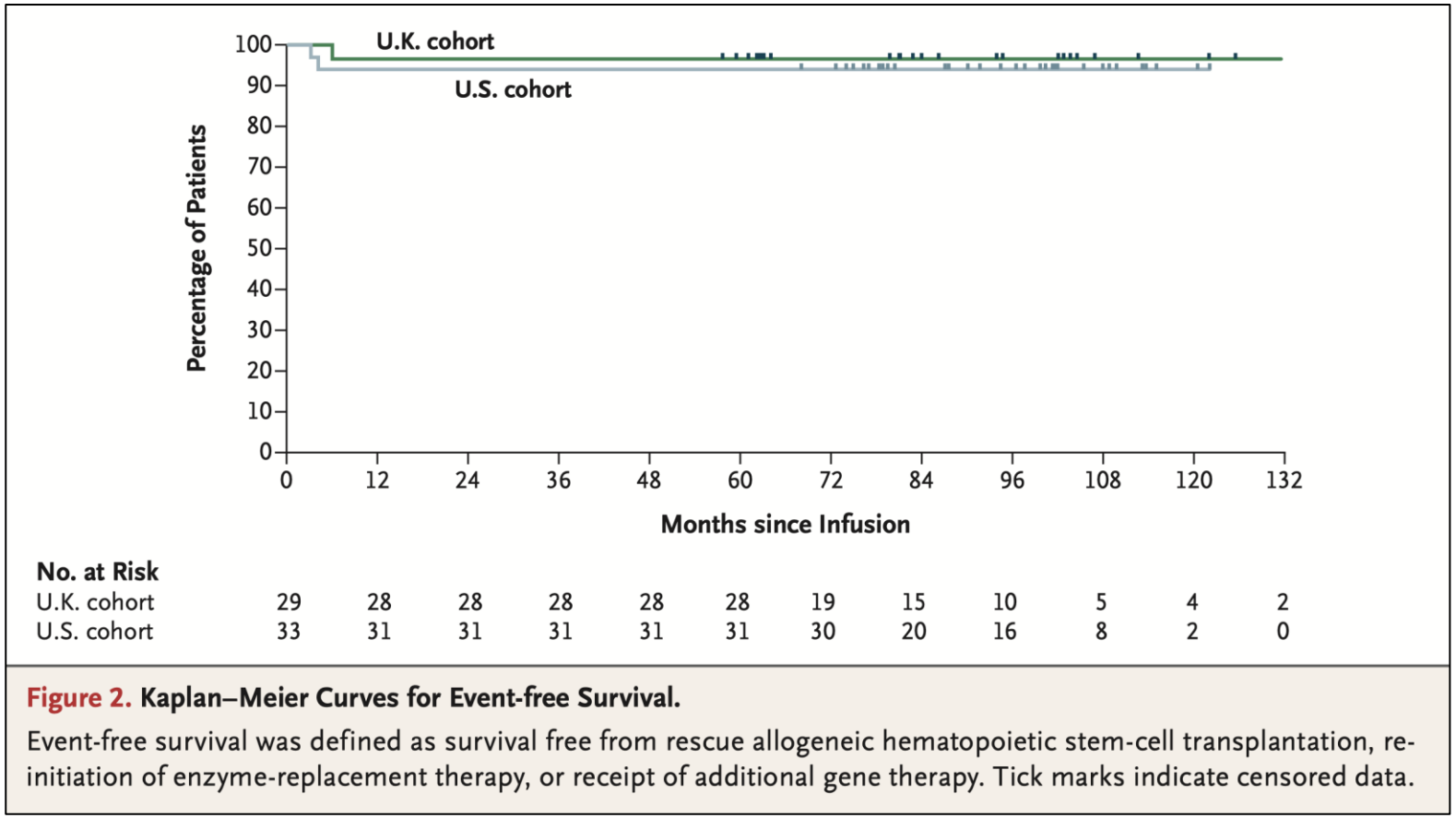


Figure 2. Kaplan–Meier Curves for Event-free Survival.

Event-free survival was defined as survival free from rescue allogeneic hematopoietic stem-cell transplantation, re-initiation of enzyme-replacement therapy, or receipt of additional gene therapy. Tick marks indicate censored data.

For full clinical results and benefits of therapy, see:
Kohn et. al 2021 (DOI: 10.1056/NEJMoa2027675)
Booth and Masiuk et al 2025 (DOI: 10.1056/NEJMoa2502754)

ADA-SCID: The Case for a Cure

- **Stable gene marking** evident throughout entire follow-up period
- **No vector related safety concerns** in any patient across 10+ years of follow-up (data not shown)
    - No leukemia, no abnormal cell growth, no viral reactivation detected

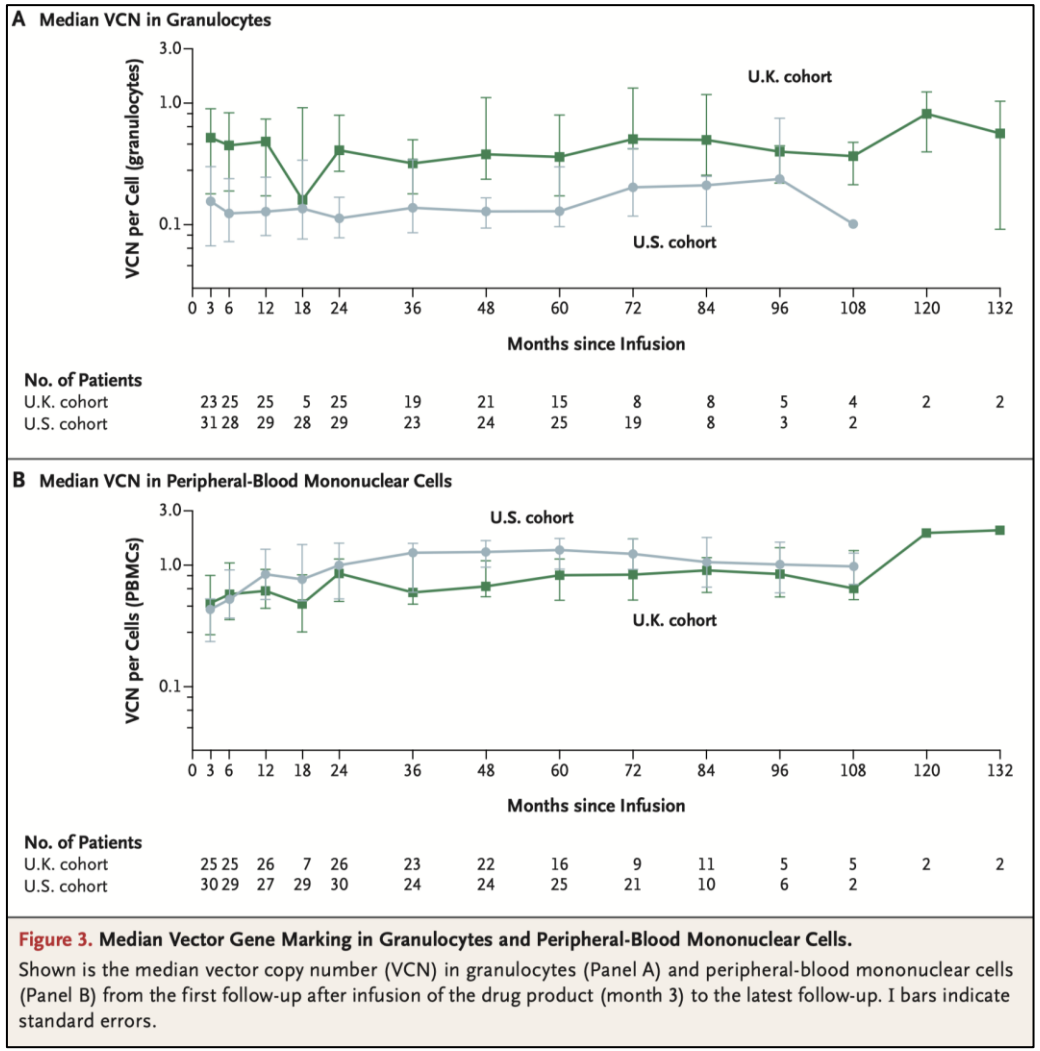


Figure 3. Median Vector Gene Marking in Granulocytes and Peripheral-Blood Mononuclear Cells.
Shown is the median vector copy number (VCN) in granulocytes (Panel A) and peripheral-blood mononuclear cells (Panel B) from the first follow-up after infusion of the drug product (month 3) to the latest follow-up. I bars indicate standard errors.

For full clinical results and benefits of therapy, see:
Kohn et. al 2021 (DOI: 10.1056/NEJMoa2027675)
Booth and Masiuk et al 2025 (DOI: 10.1056/NEJMoa2502754)

ADA-SCID: The Case for a Cure

- **Complete T-cell, B-cell, and NK-cell recovery** maintained through 10+ years
  - 97% achieved immunoglobulin independence with functional antibody production
- **All patients discontinued enzyme replacement therapy** and ADA activity maintained at normal levels (data not shown)

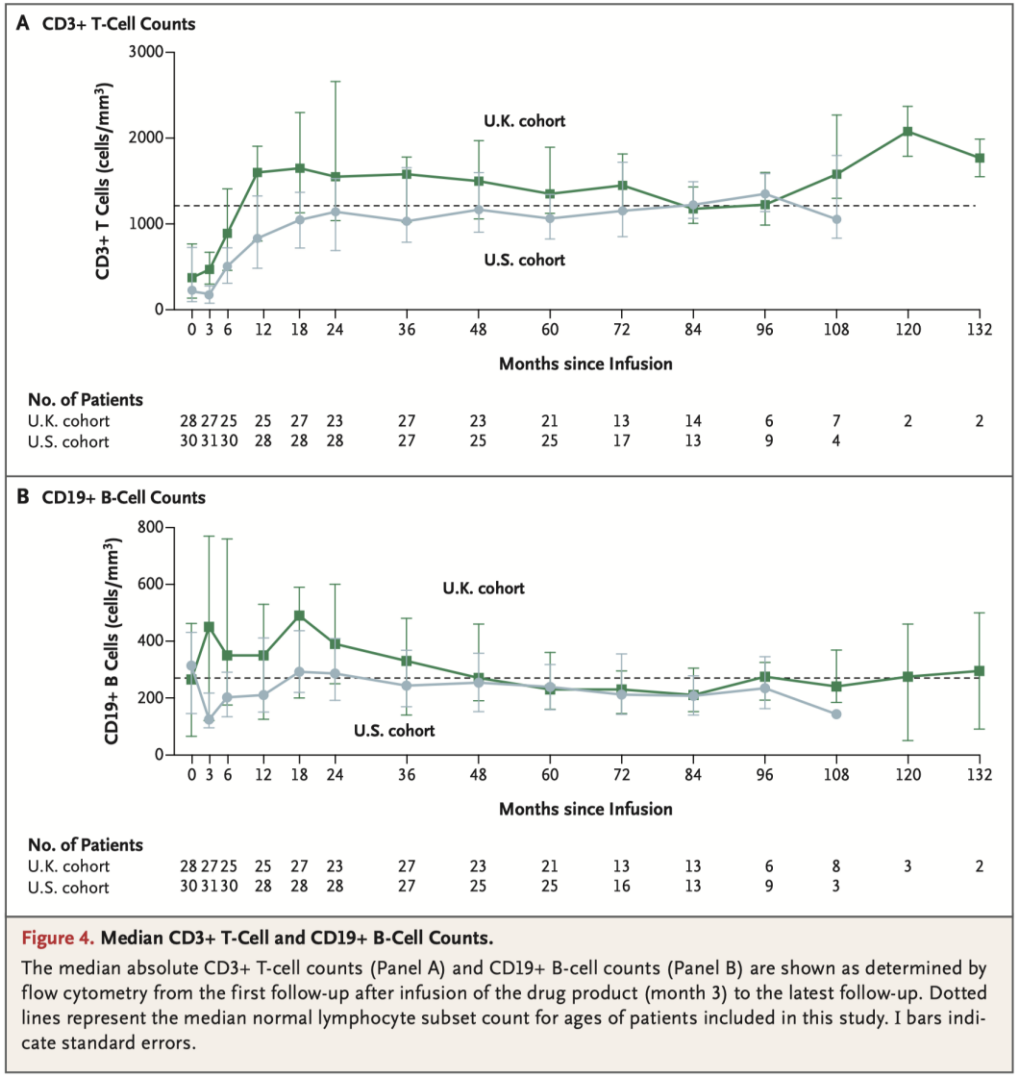
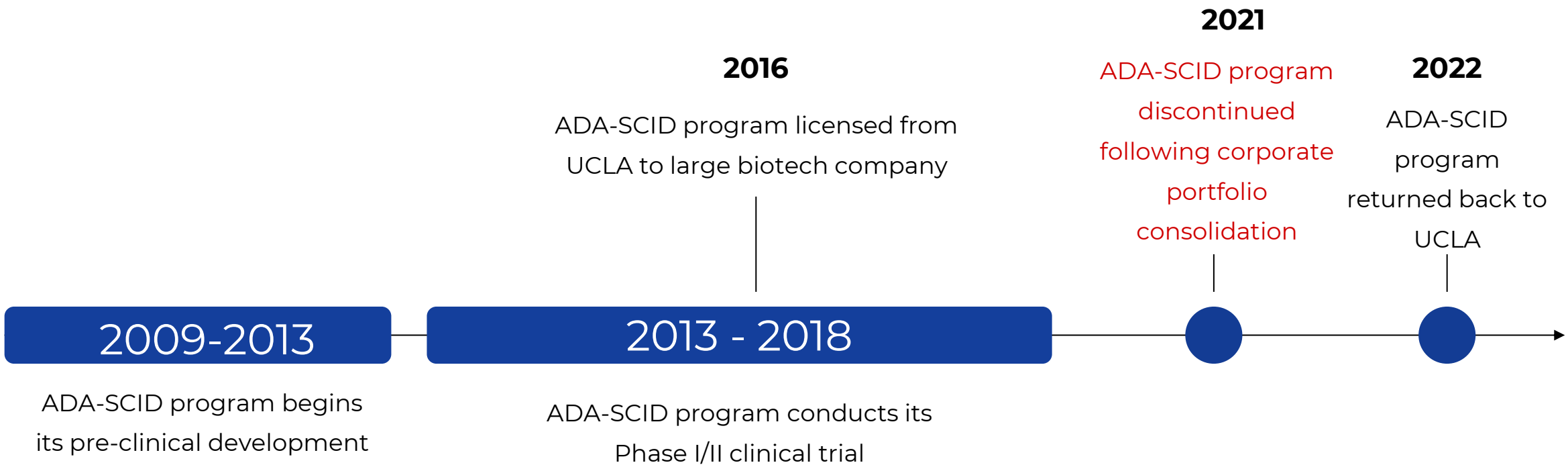


Figure 4. Median CD3+ T-Cell and CD19+ B-Cell Counts.
The median absolute CD3+ T-cell counts (Panel A) and CD19+ B-cell counts (Panel B) are shown as determined by flow cytometry from the first follow-up after infusion of the drug product (month 3) to the latest follow-up. Dotted lines represent the median normal lymphocyte subset count for ages of patients included in this study. I bars indicate standard errors.

For full clinical results and benefits of therapy, see:
Kohn et. al 2021 (DOI: 10.1056/NEJMoa2027675)
Booth and Masiuk et al 2025 (DOI: 10.1056/NEJMoa2502754)

Clinical Success ≠ Commercialization

Despite strong efficacy and safety in the clinic, the ADA-SCID gene therapy was shelved in 2021 before market authorization



abandons promising gene therapy for rare immune disorder

Pharma drops gene therapy program for AAV

drops cell therapy program, braces for layoffs after missing 'commercial viability' goals

winding down in Europe, withdraws another rare disease gene therapy

Drops Development of DMD Gene Therapy Fordadistrogene Movaparvovec

drops lead gene therapy

lays off 25% as unpartnered gene therapies take a back seat

Dropping Batten Disease Gene Therapy;

Drops SCD Gene Therapy Program

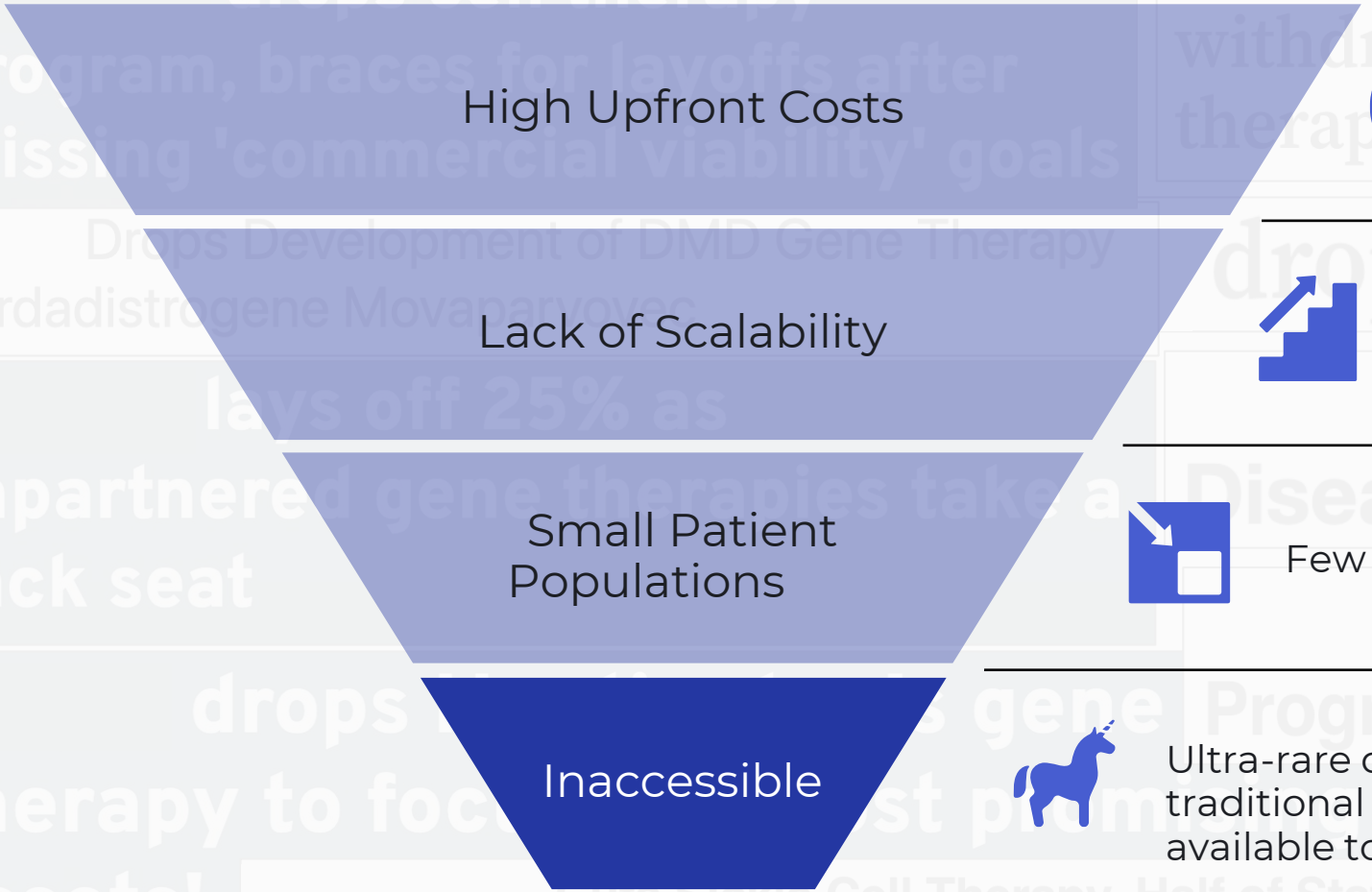
drops Huntington's gene therapy to focus on 'most promising assets'

When a Miracle Cure Is Left on the Shelf

Cuts Sickle Cell Therapy, Half of Staff

Drops Pompe Gene Therapy Program

Why Has Pharma not Solved This?



Expensive initial investment in development.

Extensive manufacturing standards and constrain scalability and distribution

Few patients hinder financial viability.

Ultra-rare disease gene therapies do not fit the traditional biotech model and thus are not made available to patients

Rescuing the ADA-SCID Gene Therapy

NORD® National Organization for Rare Disorders

2026 Rare Disease Scientific Symposium

Program originating from and **supported by leading academic and public-sector institutions,** including UCLA and CIRM, ensuring rigorous clinical, regulatory, and translational oversight.

Rarity PBC Secures Exclusive License from UCLA TDG to Advance a Life-Saving Gene Therapy for ADA-SCID

Donald Kohn awarded $14.7M CIRM grant to advance ADA-SCID gene therapy toward FDA approval

Long-term follow-up of over 10 years for the ex vivo lentiviral vector–mediated CD34+ gene therapy, demonstrating durable clinical benefit and long-term safety (NEJM, 2025).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Safety and Efficacy of Gene Therapy for Adenosine Deaminase Deficiency

Commercial manufacturing partnership with AGC Biologics, a CDMO with multiple FDA and EMA gene therapy approvals, supporting BLA-enabling development and global supply.

businesswire

AGC Biologics Partners with Rarity PBC to Advance Life-Saving Gene Therapy for "Bubble Baby Disease"

Seed financing secured to fund BLA approval activities and enable expansion of patient access in the U.S. and internationally.

businesswire A BERKSHIRE HATHAWAY COMPANY

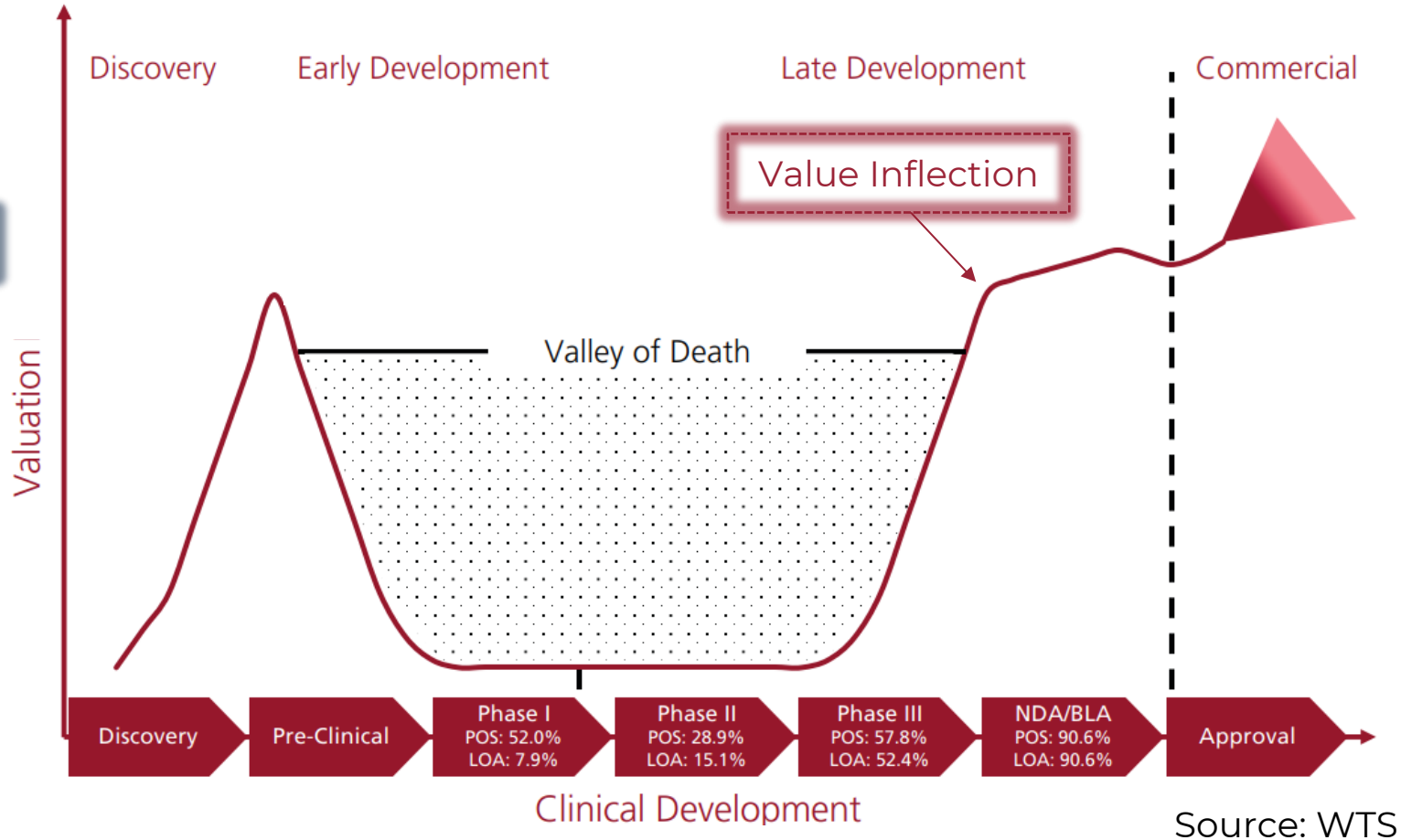
Rarity PBC Raises $4.6 Million Seed Financing to Advance Gene Therapy for ADA-SCID

The Biotech Dilemma – the Valley of Death

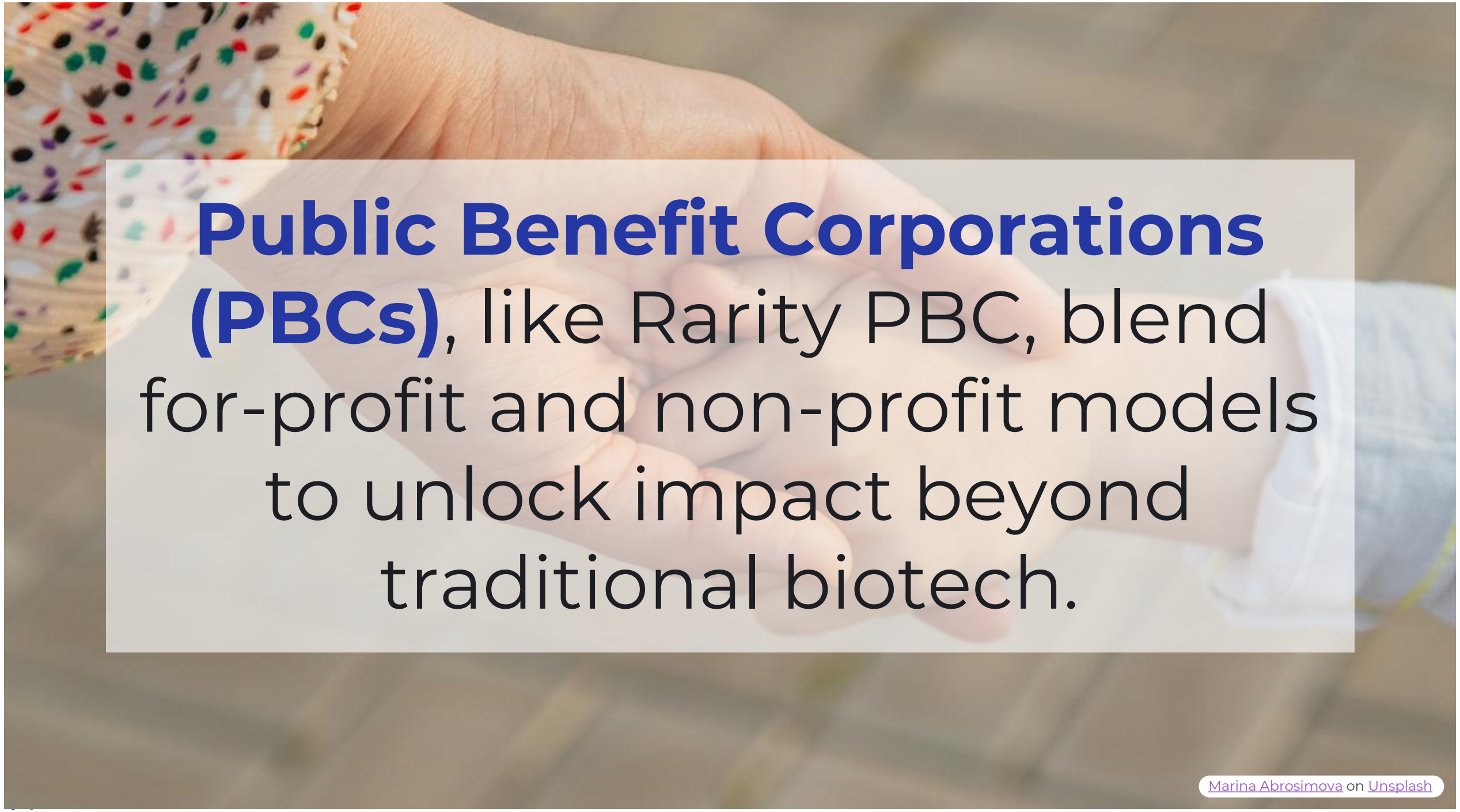
The **valley of death** is the funding and development gap where promising therapies stall between early-stage academic research and commercialization due to lack of investment, high costs, and regulatory hurdles.

Social Valuation

Financial Valuation



Source: WTS Advisory AG



Public Benefit Corporations (PBCs), like Rarity PBC, blend for-profit and non-profit models to unlock impact beyond traditional biotech.

PBCs are Foundational Models for Change

PBCs are a legally recognized business structure in the U.S. that blends the mission-first focus of a nonprofit with the operational flexibility of a for-profit.

Philanthropic and Non-Dilutive Funding

Mission-driven companies attract impact capital and non-dilutive funding.

Long-term Value Creation

Platform thinking and economies of scope make PBCs a natural fit for a portfolio of rare-disease therapies.

Mission Accountability

Mission-aligned decision making and reporting builds trust with partners, payers, and patients.

Reinvesting Regulatory Incentives

Returns and incentives like PRVs can be strategically reinvested into new programs.

Favorable Partnerships and Licensing

Mission alignment supports better terms from institutions, collaborators, and impact-aligned partners.

Realigned Incentive Structure

PBCs shift decision-making toward long-term public benefit, even as some VCs remain cautious about the dual mandate.

Systemic Failure Creates an Opportunity for New Models and Partners

The pharmaceutical system failed these patients, but we don't have to

NORD® National Organization for Rare Disorders

2026 Rare Disease Scientific Symposium

FDA Approves First Gene Therapy Treatment for Wiskott-Aldrich Syndrome

Agency exercises regulatory flexibility to address unmet need for rare, life-threatening disease

For Immediate Release: December 09, 2025

FDA Approves First Gene Therapy for Severe Leukocyte Adhesion Deficiency Type I

For Immediate Release: March 26, 2026

FDA Approves First Topical Gene Therapy for Treatment of Wounds in Patients with Dystrophic Epidermolysis Bullosa

For Immediate Release: May 19, 2023

World's First Patient Treated with Personalized CRISPR Gene Editing Therapy at Children's Hospital of Philadelphia

May 15, 2025

FDA Advances Rare Disease Drug Development with New Evidence Principles

For Immediate Release: September 03, 2025

Secretary Kennedy Adds Duchenne Muscular Dystrophy, Metachromatic Leukodystrophy to Newborn Screenings

WASHINGTON—DECEMBER 16, 2025 -

CMS Expands Access to Lifesaving Gene Therapies Through Innovative State Agreements

FOR IMMEDIATE RELEASE

July 15, 2025

President Trump Signs McCaul's Give Kids A Chance Act Into Law

February 3, 2026 Press Release

FDA's New Plausible Mechanism Pathway

Authors: Vinay Prasad, M.D., M.P.H., and Martin A. Makary, M.D., M.P.H. Author Info & Affiliations

Published November 12, 2025 | N Engl J Med 2025;393:2365-2367 | DOI: 10.1056/NEJMsb2512695

Health and care policy

04 November 2025

MHRA sets out plans to speed up access to rare disease therapies

Rare diseases	Rare Disease Approved Therapies	Genetic Rare Diseases	Gene Therapies in Development
>7,000	**5%**	**80%**	**>2,000**

Thank you!

Contact Us:

on LinkedIn

or visit

raritypbc.com for more info

Scan for LinkedIn

NORD®

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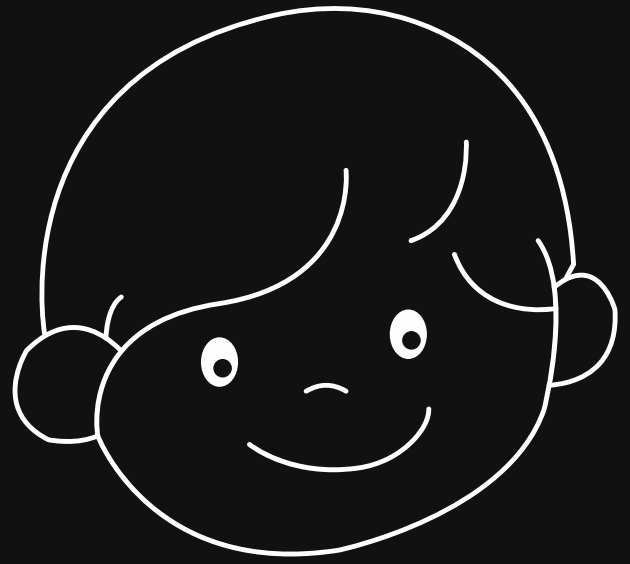
Rare Disease Scientific Symposium
April 14-15, 2026

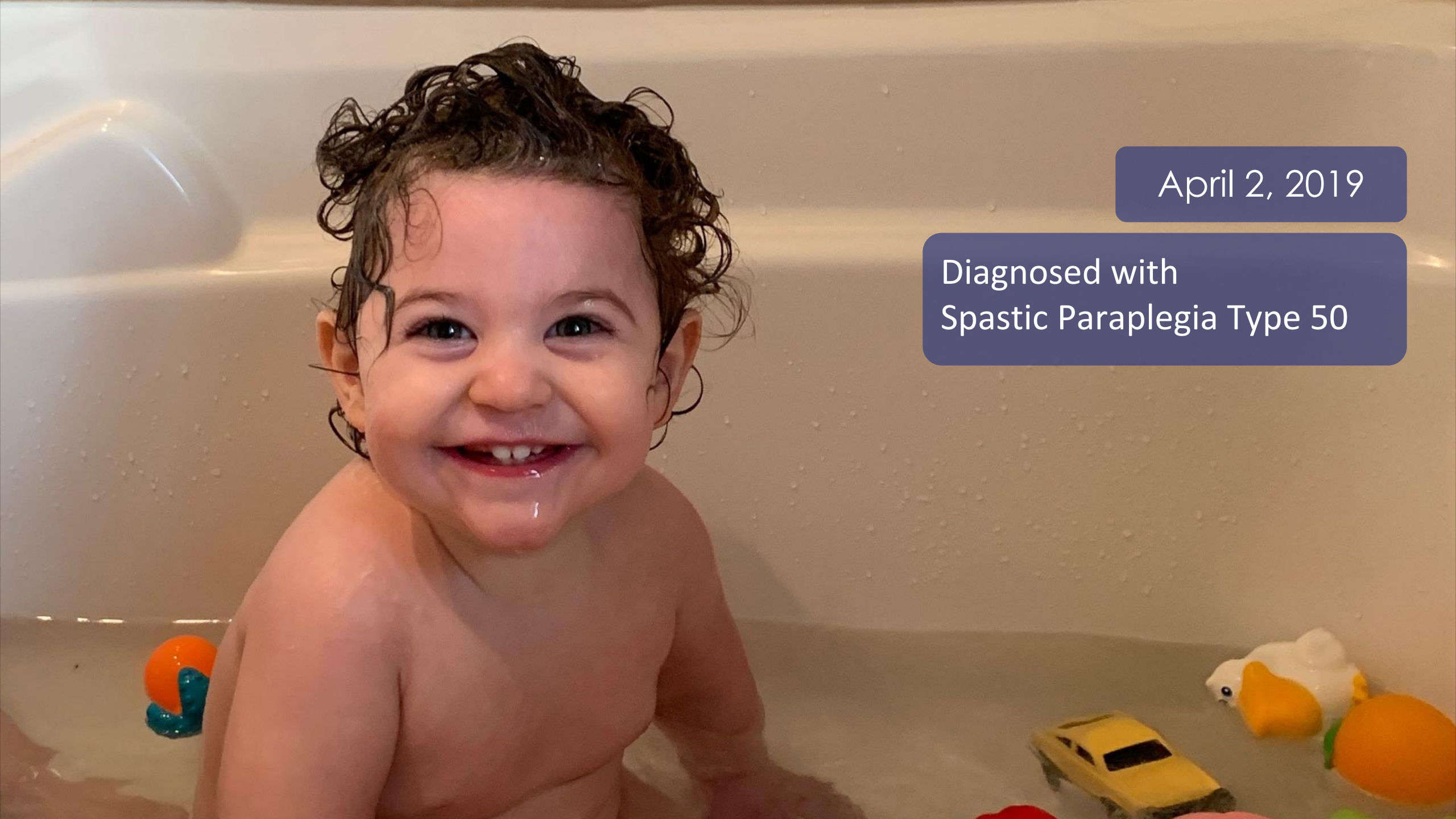
RARITY PBC



#CureSPG50

#JourneyToCureMichael

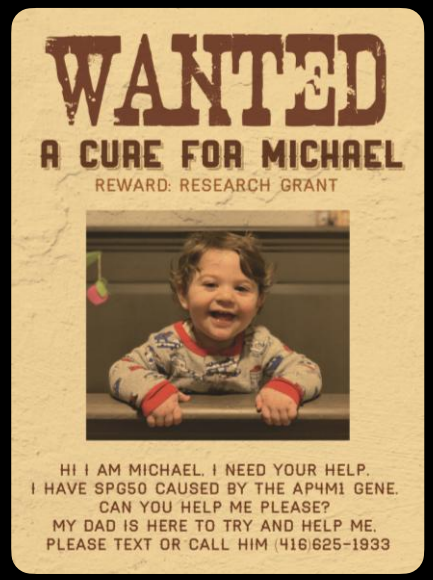

Georgia
Terry
Zoe
Michael
Zach


April 2, 2019
Diagnosed with
Spastic Paraplegia Type 50

Ultragenyx BootCamp

NIH

FDA



ASGCT

Sheffield

Dr. Gray

Dr. Chen

Raise 3 million dollars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CURE MICHAEL
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EVENT
July 28th 3-6pm
Brunswick Bierworks
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Find out more at:
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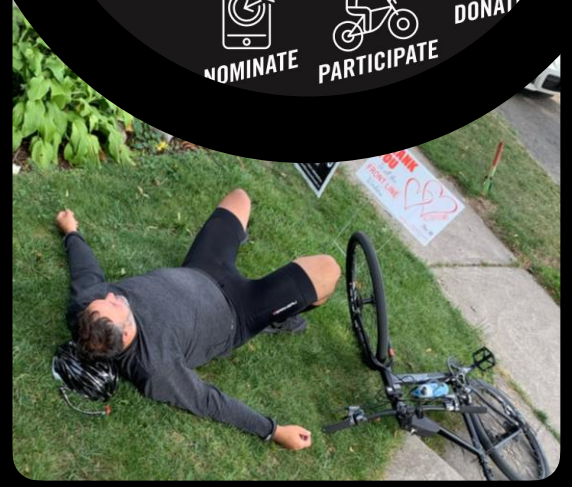
2015
Championships

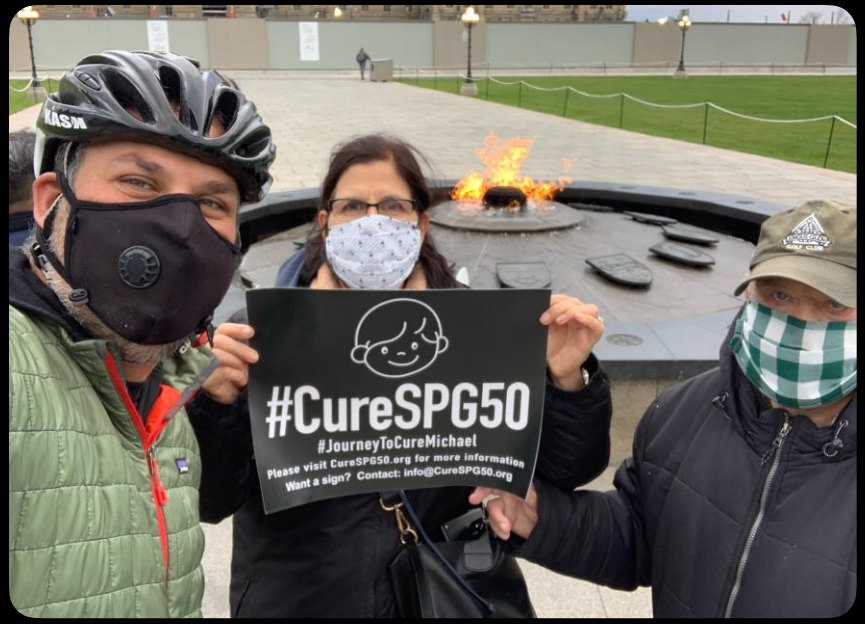

CareFusion
Alaris PC
PHILIPS

Covid Lock Down!

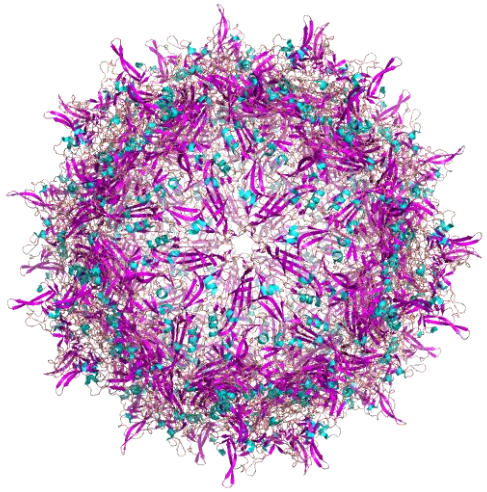
CYCLE FOR MICHAEL

NOMINATE PARTICIPATE DONATE

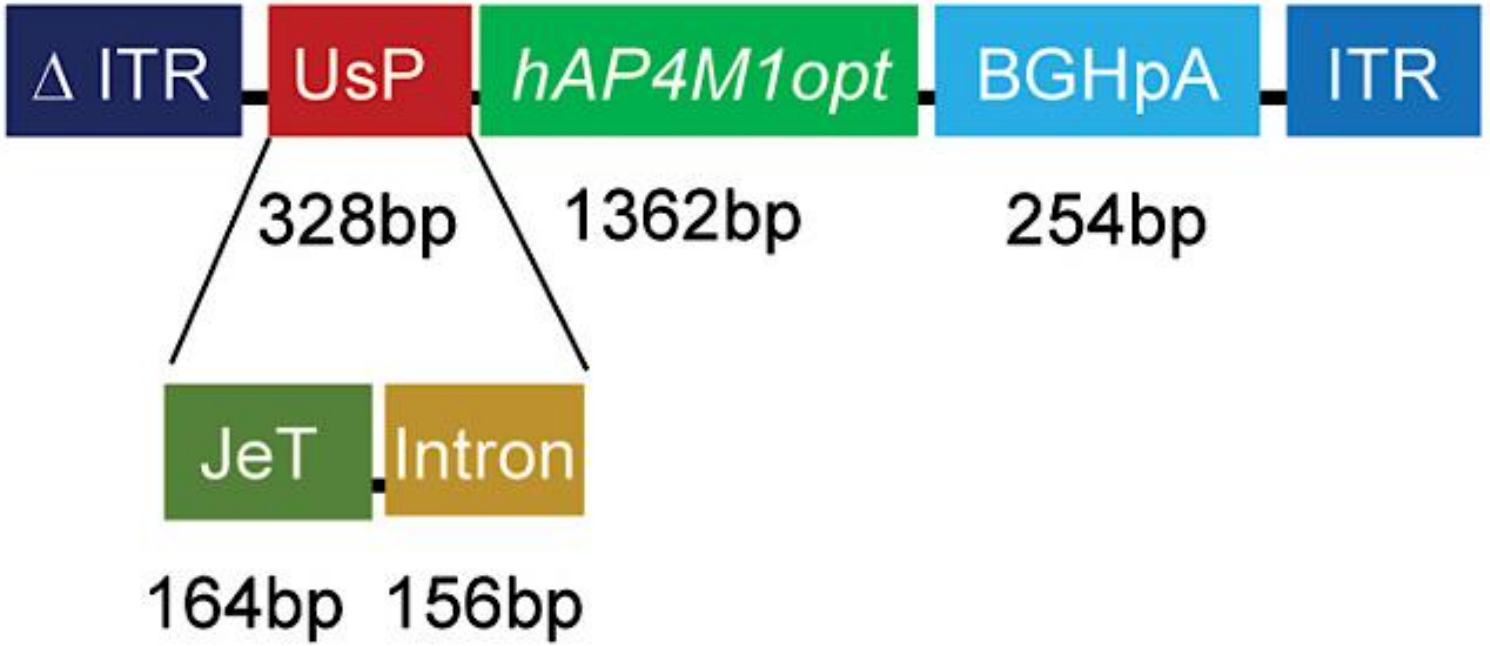




Vector Design



AAV9 Capsid



Mouse Efficacy Mouse Studies

Unaffected

SPG50 Present

Health Canda

No Objection Letter

Dec 30, 2021

Health Canada
Health Products and Food Branch

Santé Canada
Direction générale des produits de santé et des aliments

Biologic and Radiopharmaceutical Drugs Directorate
100 Eglantine Driveway
LCDC Building,
Tunney's Pasture, A.L. 0601C
Ottawa, Ontario
K1A 0K9

December 30, 2021

NO OBJECTION LETTER

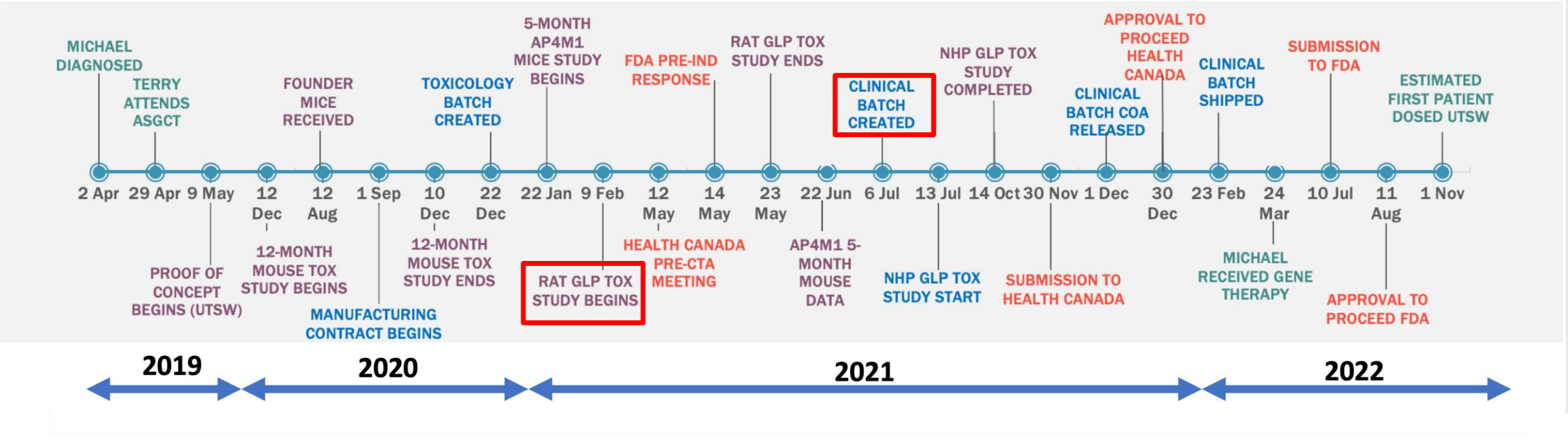
Dear Mr. Kenney:

The Clinical Trial Application for Melpida (AAV9/AP4M1)/ Rapamune (sirolimus)/ Prograf (tacrolimus), Control # 259194, concerning Protocol # MELPIDA FOR SPG50, has been reviewed.

In accordance with Part C, Division 5 of the *Food and Drug Regulations*, there is no objection to initiating this trial.

March 24, 2022

Our Journey


MICHAEL DIAGNOSED
2 Apr
TERRY ATTENDS ASGCT
29 Apr
PROOF OF CONCEPT BEGINS (UTSW)
9 May
12-MONTH MOUSE TOX STUDY BEGINS
12 Dec
FOUNDER MICE RECEIVED
12 Aug
MANUFACTURING CONTRACT BEGINS
1 Sep
12-MONTH MOUSE TOX STUDY ENDS
10 Dec
TOXICOLOGY BATCH CREATED
22 Dec
5-MONTH AP4M1 MICE STUDY BEGINS
22 Jan
RAT GLP TOX STUDY BEGINS
9 Feb
HEALTH CANADA PRE-CTA MEETING
12 May
FDA PRE-IND RESPONSE
14 May
RAT GLP TOX STUDY ENDS
23 May
AP4M1 5-MONTH MOUSE DATA
22 Jun
CLINICAL BATCH CREATED
6 Jul
NHP GLP TOX STUDY START
13 Jul
NHP GLP TOX STUDY COMPLETED
14 Oct
SUBMISSION TO HEALTH CANADA
30 Nov
CLINICAL BATCH COA RELEASED
1 Dec
APPROVAL TO PROCEED HEALTH CANADA
30 Dec
CLINICAL BATCH SHIPPED
23 Feb
MICHAEL RECEIVED GENE THERAPY
24 Mar
SUBMISSION TO FDA
10 Jul
APPROVAL TO PROCEED FDA
11 Aug
ESTIMATED FIRST PATIENT DOSED UTSW
1 Nov
2019
2020
2021
2022

FDA

Study May Proceed

Aug 11, 2022

Diane Balderson

From: [redacted]
Sent: Thursday, August 11, 2022 3:18 PM
To: Diane Balderson
Subject: IND 28202 | Study May Proceed
Signed By: [redacted]

Dear Dr. Balderson,

We have reviewed your IND 28202 and your study may proceed. This email should satisfy your IRB's requirement for written confirmation from FDA. As a reminder, please be sure to submit all documents that have been exchanged via email during the 30-day review period as an amendment to your IND. If there are any additional non-hold comments, you will receive them in a forthcoming e-mail.

Please acknowledge receipt of this email.

Warm Regards,

[redacted]
Regulatory Project Manager (RPM)
Division of Regulatory Project Management
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation Research
U.S. Food and Drug Administration
[redacted]

OTAT LEARN – Video Instructional Webinars for Sponsors
Cellular & Gene Therapy Products | FDA

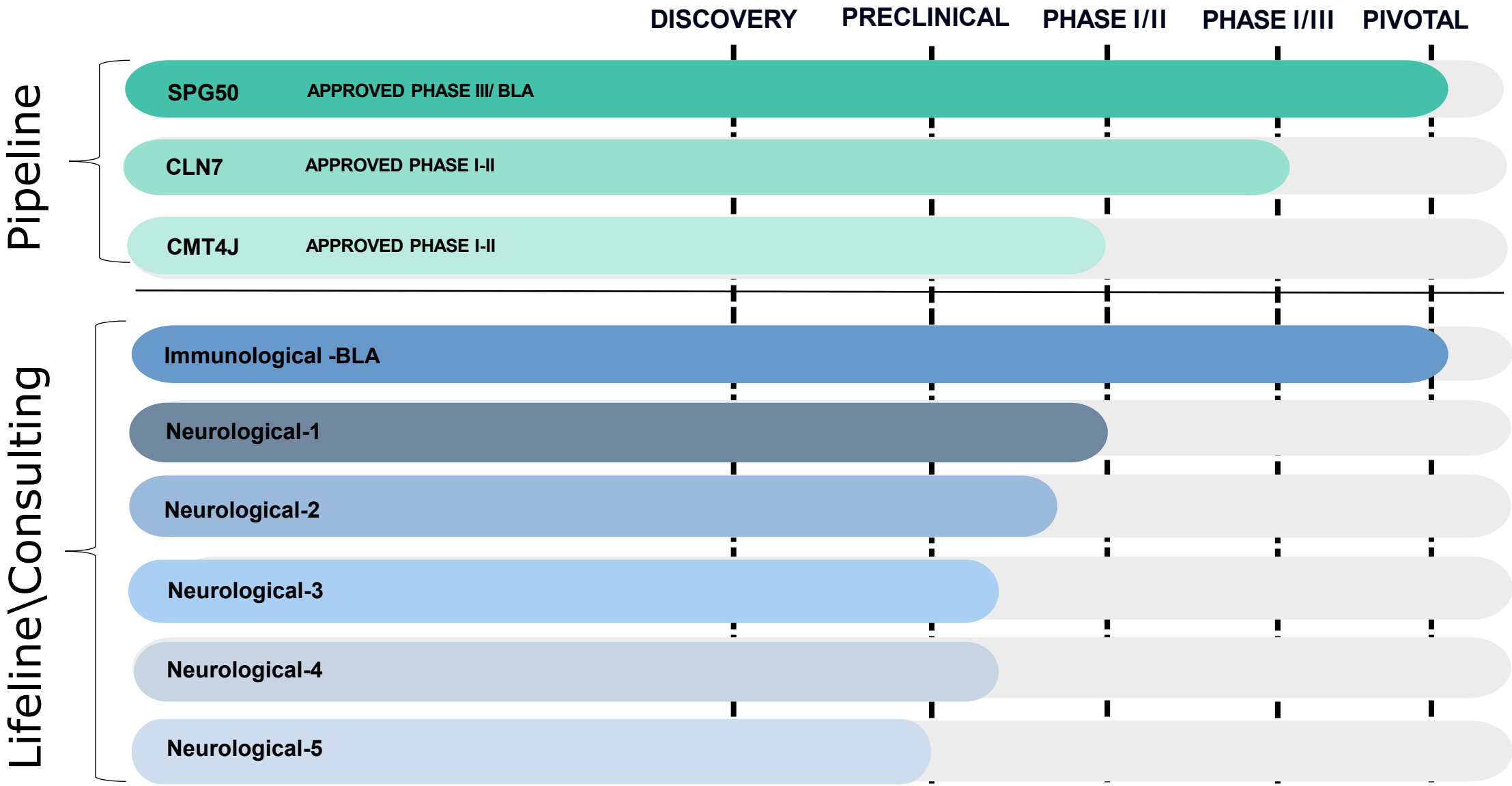
OTAT Mission: The Office of Tissues and Advanced Therapies (OTAT) promotes the public health through collaborative, science-based regulation of medical products. This includes facilitating drug development and ensuring safety of individuals. OTAT's regulatory decisions are data-driven, impartial, and compassionate.

FDA U.S. FOOD & DRUG ADMINISTRATION

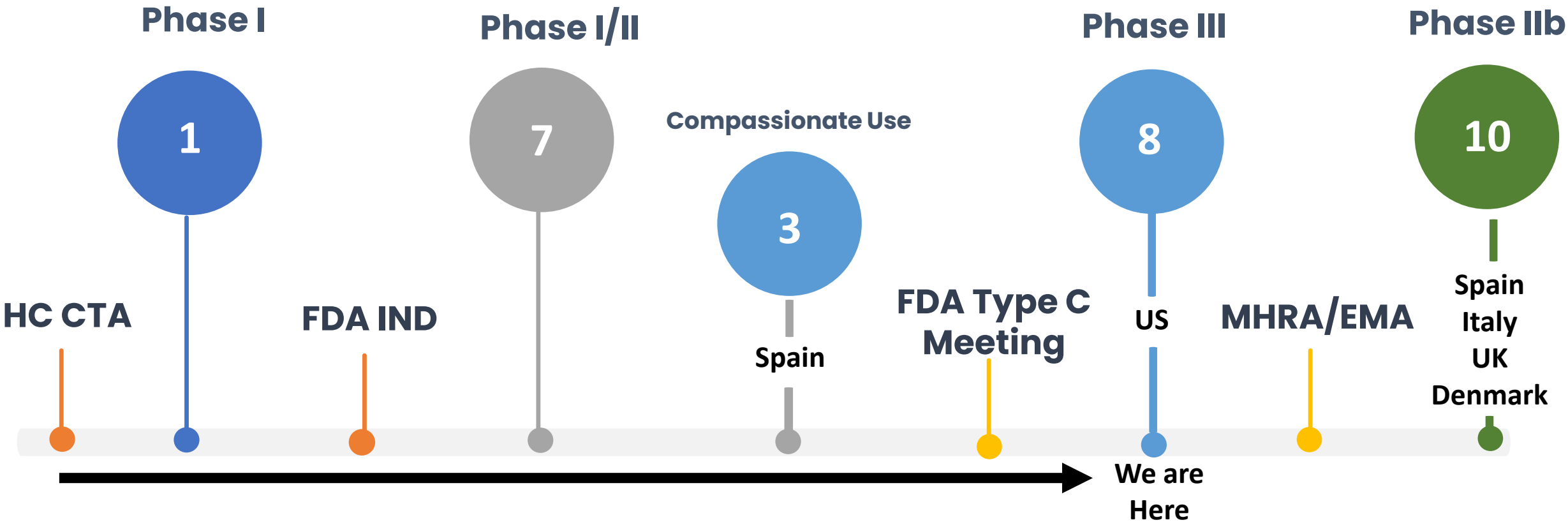

ELPIDA
THERAPEUTICS

The Team

Pipeline


DISCOVERY
PRECLINICAL
PHASE I/II
PHASE I/III
PIVOTAL
Pipeline
SPG50
APPROVED PHASE III/ BLA
CLN7
APPROVED PHASE I-II
CMT4J
APPROVED PHASE I-II
Lifeline\Consulting
Immunological -BLA
Neurological-1
Neurological-2
Neurological-3
Neurological-4
Neurological-5

Clinical Trial Strategy and Execution



Over 25% Of The World Patient Population

Drug Approval

Thank You