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Beyond “one disease at a time” : Genetic therapy platforms for rare monogenic disease

P.J. Brooks, Ph.D.

Deputy Director,

Division of Rare Disease Research Innovation

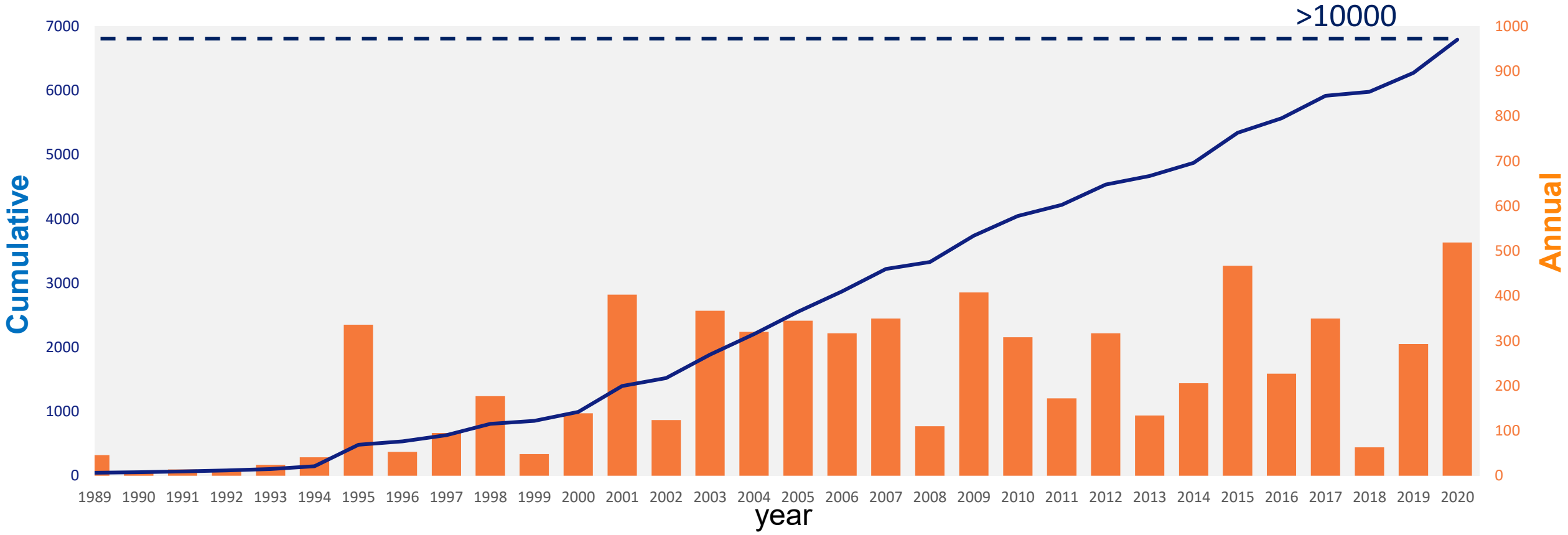
National Center for Advancing Translational Sciences (NCATS), NIH

National Center for Advancing Translational Sciences

Disclosure Statement

- I have no conflicts of interest to disclose
- Any reference to off-label product use or clinical trials are made only in an educational context
- The views expressed are those of the speaker and do not necessarily reflect the policies of the National Institutes of Health or the Department of Health and Human Services

The Number of Disorders with Known Molecular Basis Is Rapidly Rising



But the number of diseases with approved therapies is lagging far behind (≈600)

Adapted from Online Mendelian Inheritance in Man (OMIM),
https://www.omim.org/statistics/geneMap

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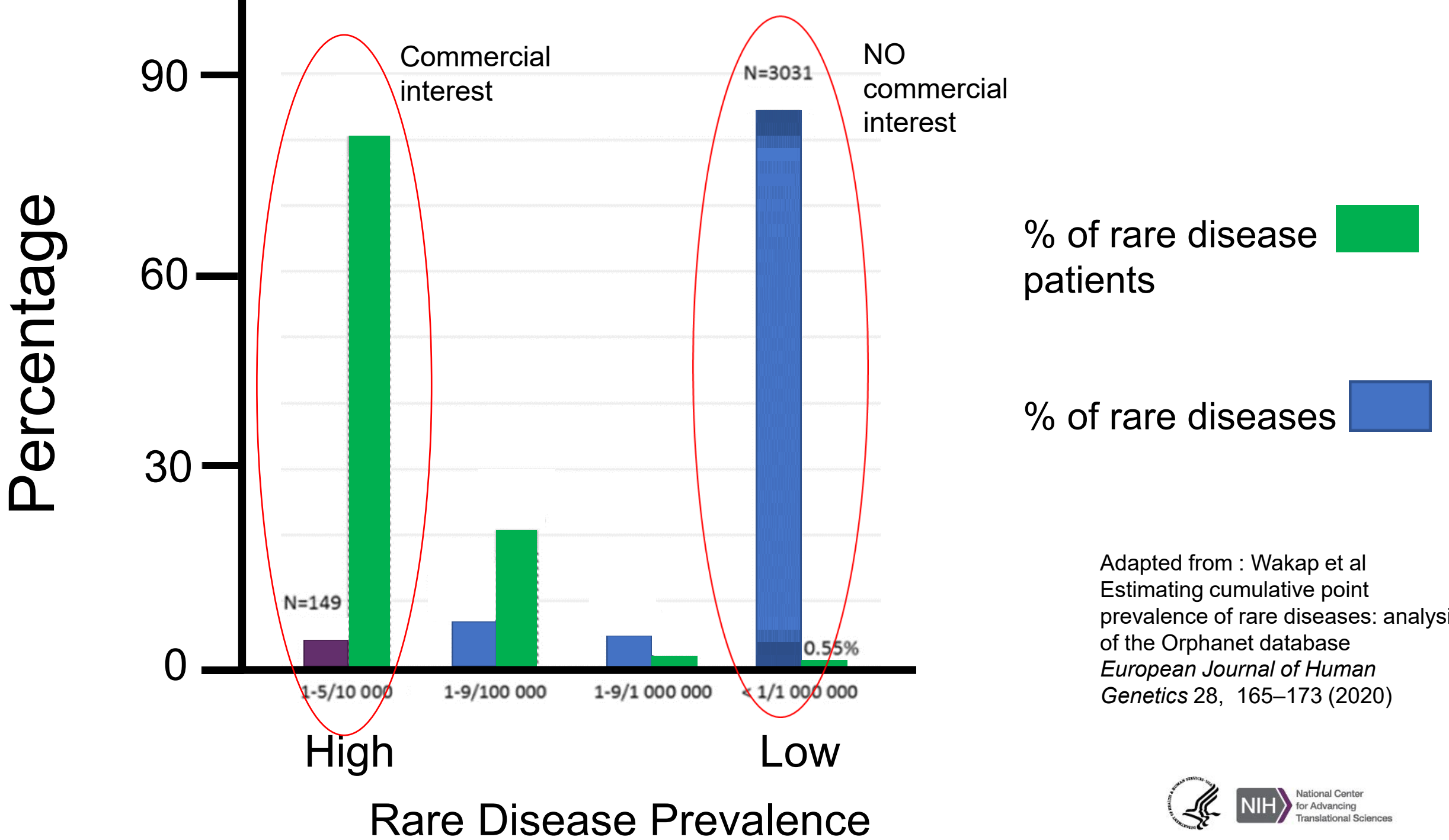

Adapted from : Wakap et al Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database *European Journal of Human Genetics* 28, 165–173 (2020)

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Thousands of Rare Monogenic Diseases, but fewer Etiologies

- Limited number of mutation types
  - Nonsense mutations → premature stop codon
    - Stop codon read-through compounds
  - Missense mutations → abnormal protein folding
    - proteastasis pathway modulators
  - Abnormal RNA splicing
    - Splice-switching oligonucleotides
  - Dominant (gain of function) mutations
    - siRNA
  - Signallopathies

Gene Therapy

Gene Editing

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Platform Vector Gene Therapy (PaVe-GT)

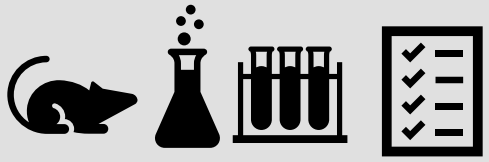
Hypothesis: A Platform Vector Approach Will Increase Efficiency in Preclinical Testing and Clinical Trial Start-up

Platform
Vector

Organic Acidemias

Congenital Myasthenia Syndromes

Same
Manufacturing Processes, Analytical Methods, Study Designs



Proof-of-Concept
Full IND-enabling Studies
INTERACT, Pre-IND, IND Filing

Common
Clinical Protocols when Possible

AAV Lead Candidates	Preclinical Development and Regulatory Pathway	Phase 1/ 2 Clinical Trials

Charles Venditti, M.D., Ph.D.

NIH National Human Genome Research Institute

Carsten Bonnemann, M.D.

NIH National Institute of Neurological Disorders and Stroke

Use Common Processes and Make the Data Publicly Available

NIH National Center for Advancing Translational Sciences

Human Gene Therapy > Vol. 34, No. 5-6 > Clinical Developments

Successfully Navigating Food and Drug Administration Orphan Drug and Rare Pediatric Disease Designations for AAV9-hPCCA Gene Therapy: The National Institutes of Health Platform Vector Gene Therapy Experience

NIH PaVe-GT Team (in alphabetical order): Gilberto V. Averion, Krishna Balakrishnan, Carsten G. Bönnemann, Philip J. Brooks, Steven J. Burden, Eggerton Campbell, Catherine Chen, Eun-Young Choi, Claire Driscoll, Oksana Dukhanina, Susan Ferry, A. Reghan Foley, Janelle Geist Hauserman, Lina Li, Donald C. Lo, Venkata Mangalampalli, Irini Manoli, Christopher Mendoza, Julien Oury, Forbes D. Porter, Deanna Portero, Lili Portilla, Jachinta Rooney, Dimah Saade, Jennifer L. Sloan, Mitali Tambe, Pramod Terse, Joshua Todd, London Toney, Carol Van Ryzin, Rodica Stan, Sury Vepa, Erik Wagner, Amy Wang, Xin Xu, and Yaqun Zou.

https://www.liebertpub.com/doi/10.1089/hum.2022.232

Sign-up for PaVe-GT updates.

Subscribe

PAVE-GT RESOURCES

Rare Pediatric Disease (RPD) Designation Request for AAV9-hPCCA

This pdf file contains the RPD designation request for AAV9-hPCCA (NCATSBL-0746) and associated communications between NCATS and FDA OOPD.

https://pave-gt.ncats.nih.gov/outputs

Human Gene Therapy > Ahead of Print

Research Article | OPEN ACCESS | Published Online: 20 February 2025

Adeno-Associated Virus Gene Therapy Development: Early Planning and Regulatory Considerations to Advance the Platform Vector Gene Therapy Program

Authors: Richa Madan Lomash, Jean Dehdashti, Oleg A. Shchelochkov, Randy J. Chandler, Lina Li, Irini Manoli, Jennifer L. Sloan, ... SHOW ALL ... , and Elizabeth A. Ottinger

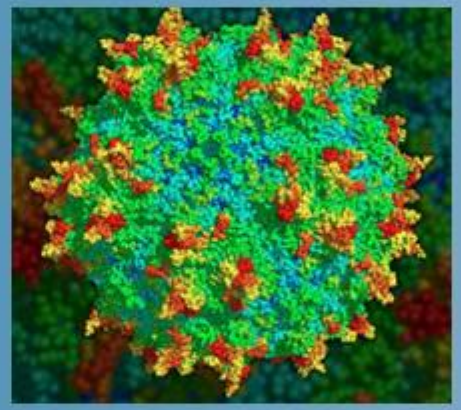
AUTHORS INFO & AFFILIATIONS

Publication: Human Gene Therapy • https://doi.org/10.1089/hum.2024.230

National Center for Advancing Translational Sciences

Accelerating Medicines Partnership®
Bespoke Gene Therapy Consortium (BGTC)






Steering Committee Co-Chairs:

PJ Brooks, NCATS/NIH
Tim Miller, ThermoFisher
FDA (non-voting)

Program Management:

Kira Gillette, FNIH

FNIH
Foundation for the National Institutes of Health

https://fnih.org/our-programs/AMP/BGTC

BGTC combines resources from a broad set of public and private partners

- National Center for Advancing Translational Sciences
- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
- National Eye Institute — Research Today...Vision Tomorrow
- National Heart, Lung, and Blood Institute
- National Human Genome Research Institute
- National Institute of Arthritis and Musculoskeletal and Skin Diseases
- National Institute of Dental and Craniofacial Research
- National Institute of Mental Health
- National Institute of Neurological Disorders and Stroke
- National Institute on Deafness and Other Communication Disorders

BRAIN INITIATIVE

FDA

$39.5M *Public commitments*

$35M *Private donations*

$22.4M+ *Private in-kind contributions*

Biogen

DANAHER

Elpida Therapeutics

janssen

NOVARTIS

Ovid Therapeutics

Pfizer

REGENXBIO

Spark THERAPEUTICS

Takeda

ThermoFisher SCIENTIFIC

ultragenyx pharmaceutical

Alliance for Regenerative Medicine

American Society of Gene + Cell Therapy

CIRM CALIFORNIA'S STEM CELL AGENCY

Cure Duchenne

FOUNDATION FIGHTING BLINDNESS

GENETHON CURE THROUGH INNOVATION

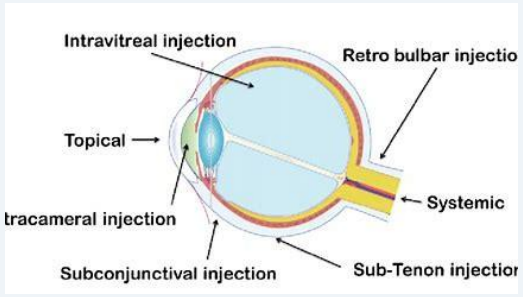
NIMBL The National Institute for Innovation in Manufacturing Biopharmaceuticals

NORD National Organization for Rare Disorders

rett syndrome research trust Making Rett History

RTW Charitable Foundation

BGTC – *Project Portfolio*



Ocular

- **Congenital Hereditary Endothelial Dystrophy (CHED)** CIRM
- **Retinal Degeneration (NPHP5)**
- **Retinitis pigmentosa 45 (CNGB1)**

Neurological

- **Multiple Sulfatase Deficiency (MSD)**
- **Charcot Marie Tooth disease type 4J (CMT4J)** CIRM
- **Spastic Paraplegia type 50 (SPG50)** CIRM

Systemic

- **Propionic Acidemia (PA-PCCB)**
- **Morquio A syndrome (Mucopolysaccharidosis IVA)**

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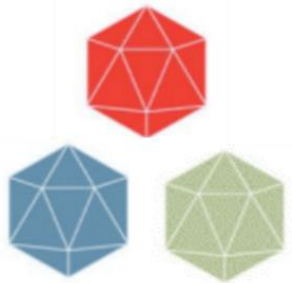
BGTC is comprised of research and clinical workstreams

1 AAV Basic Biology Translational Implications



- Enhancing Vector Generation
- Enhancing therapeutic gene expression

Goal: Increase efficiency by orders of magnitude.

Therapies for patients

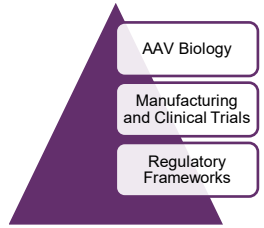
2 Advancing Access to AAV Technologies and Vectors for Bespoke Clinical Applications

Gene therapy target for rare disease

Create & Build Capacity	Harmonize best practices	Streamline Regulatory Paths
Manufacture of therapeutic	Pre-clinical testing	Clinical ability to treat patients

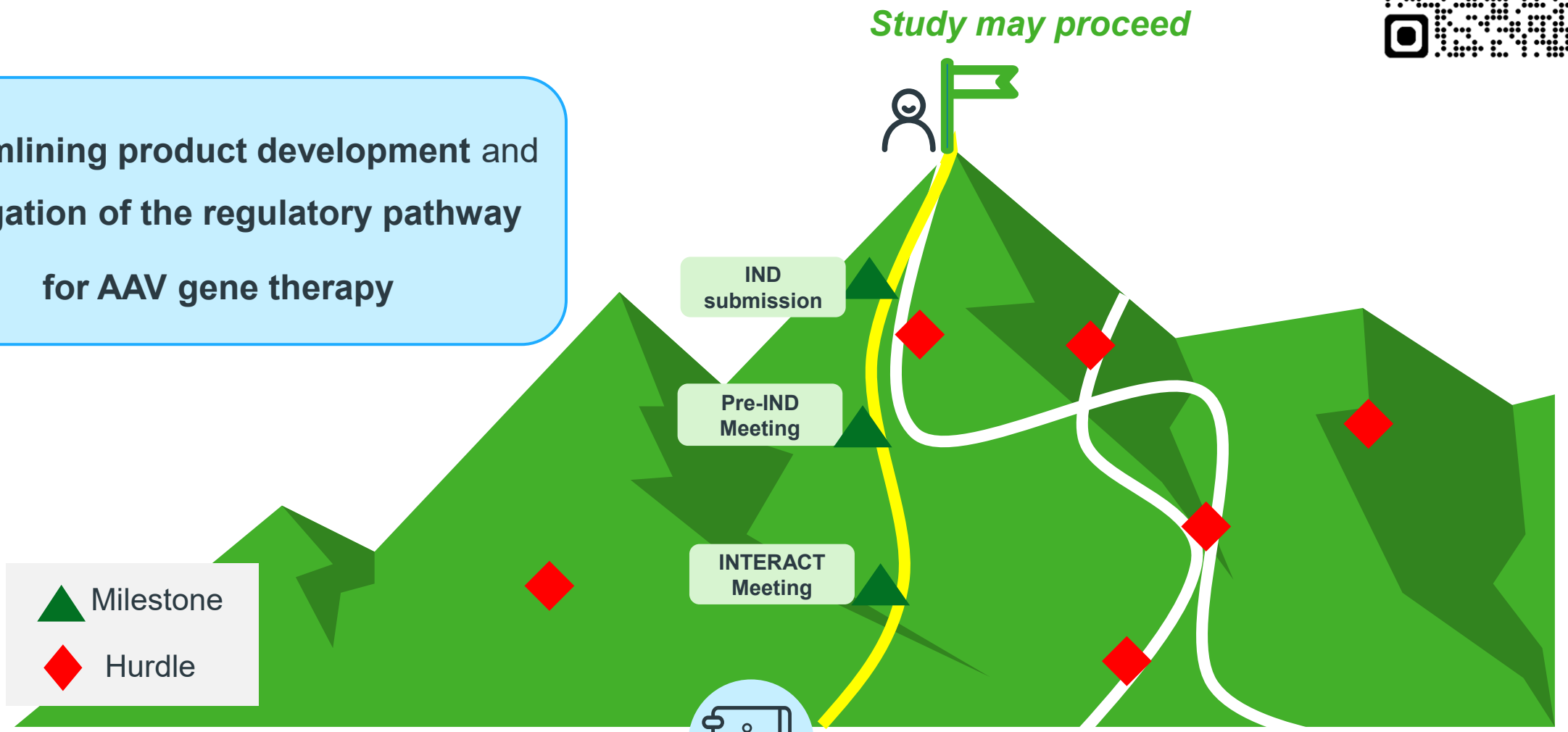
- CQAs
- GLP/Tox

Goal: Standardized, faster, reduced $



Digitized Version of Bespoke Gene Therapy Consortium (BGTC) Playbook Version Released May 2025

Streamlining product development and **navigation of the regulatory pathway for AAV gene therapy**



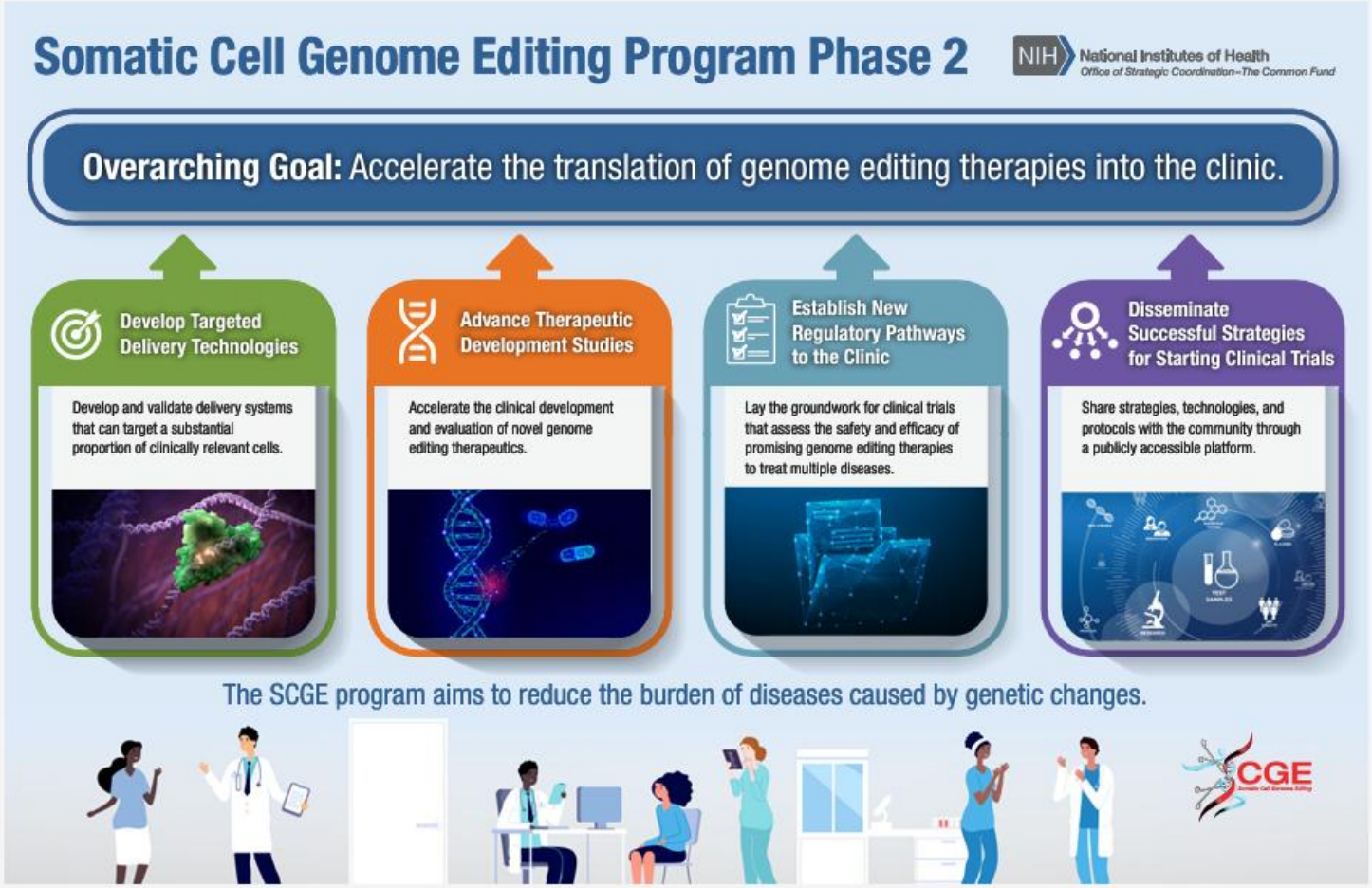
BGTC Regulatory Playbook

https://bgtcplaybook.document360.io/

The NIH Somatic Cell Genome Editing (SCGE) Program Phase 2

SCGE Overview: Phase 2-Therapy Development

The Common Fund



IND-enabling Studies of Somatic Genome Editing Therapeutic Leads (U19, Clinical Trial Not allowed) RFA-RM-22-015		
PI Name	**Institution Name**	**Title**
DOUDNA, JENNIFER A	UNIVERSITY OF CALIFORNIA, BERKELEY	Correction of Neurological Disease via Allele Specific Excision of Pathogenic Repeats
LUTZ, CATHLEEN M (contact) ARBAB, MANDANA GRAY, STEVEN J LIU, DAVID R MOURO PINTO, RICARDO	JACKSON LABORATORY	Preclinical Genome Editing for Rare Neurological Diseases
PERANTEAU, WILLIAM H (contact) MUSUNURU, KIRAN	CHILDREN'S HOSP OF PHILADELPHIA	Postnatal and Prenatal Therapeutic Base Editing for Metabolic Diseases
SAHA, KRISHANU	UNIVERSITY OF WISCONSIN-MADISON	The CRISPR Vision Program: Nonviral Genome Editing Platforms to Treat Inherited Retinal Channelopathies
VALLABH, SONIA MINIKEL	BROAD INSTITUTE, INC.	Therapeutic editing to lower PrP in prion disease

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SCGE
Phase 2

Science

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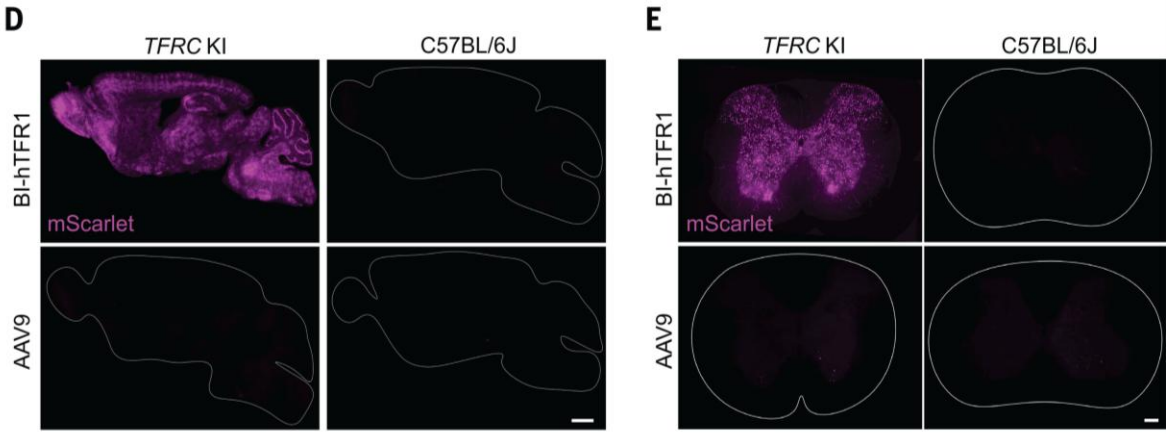
HOME > SCIENCE > VOL. 384, NO. 6701 > AN AAV CAPSID REPROGRAMMED TO BIND HUMAN TRANSFERRIN RECEPTOR MEDIATES BRAIN-WIDE GENE DELIVERY

RESEARCH ARTICLE | GENE THERAPY

An AAV capsid reprogrammed to bind human transferrin receptor mediates brain-wide gene delivery

QIN HUANG, KEN Y. CHAN, JASON WU, NURIA R. BOTTICELLO-ROMERO, QINGXIA ZHENG, SHAN LOU, CASEY KEYES, ALEXANDER SVANBERGSSON, JENCILIN JOHNSTON, ALLAN MILLS, CHIN-YEN LIN, PAMELA P. BRAUER, GABRIELLE CLOUSE, SIMON PACOURET, JOHN W. HARVEY, THOMAS BEDDOW, JENNA K. HURLEY, ISABELLE G. TOBEY, MEGAN POWELL, ALBERT T. CHEN, ANDREW J. BARRY, FATMA-ELZAHRAA EID, YUJIA A. CHAN, AND BENJAMIN E. DEVERMAN fewer Authors Info & Affiliations

SCIENCE • 16 May 2024 • Vol 384, Issue 6701 • pp. 1220-1227 • DOI: 10.1126/science.adm8386



SCGE Phase 1

Science

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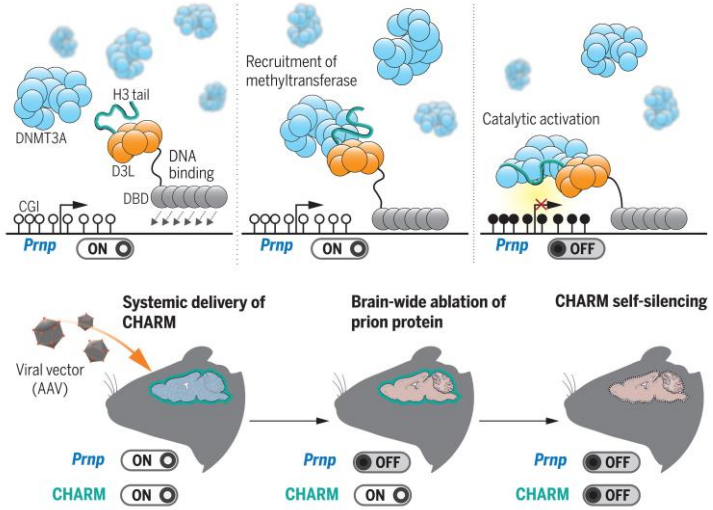
RESEARCH ARTICLE | EPIGENETIC MEDICINE

Brainwide silencing of prion protein by AAV-mediated delivery of an engineered compact epigenetic editor

EDWIN N. NEUMANN, TESSA M. BERTOZZI, ELAINE WU, FIONA SERACK, JOHN W. HARVEY, PAMELA P. BRAUER, CATHERINE P. PIRTLE, ALISSA COFFEY, MICHAEL HOWARD, NIKITA KAMATH, KENNEY LENZ, KENIA GUZMAN, MICHAEL H. RAYMOND, AHMAD S. KHALIL, BENJAMIN E. DEVERMAN, ERIC VALLABH MINIKEL, SONIA M. VALLABH, AND JONATHAN S. WEISSMAN fewer Authors Info & Affiliations

CHARM (Coupled Histone tail for Autoinhibition Release of Methyltransferase)



SCGE Phase 2

NIH Director's Blog

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Epigenetic Editor Silences Toxic Proteins in the Mouse Brain, Offering Promising Path to Treat Deadly Prion Diseases

Posted on July 25th, 2024 by Dr. Monica M. Bertagnolli

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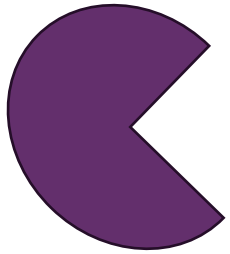
A (over)simplified view of AAV gene therapy

Gene editing as a modular therapeutic



(or mRNA encoding)

delivery system

guide RNA (if necessary)

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Platform Clinical Trials of Genome Editors in Multiple Diseases (UG3/UH3, Clinical Trial Required)

Provide support for applications that propose a novel genome editing clinical trial that includes at least two different diseases, using the same genome editor, route of administration, and delivery system.

PI Name	Institution Name	Title
JIANG, YONG-HUI (contact) BERRY-KRAVIS, ELIZABETH MARA ZHOU, JIANGBING	YALE UNIVERSITY	A non-viral CRISPR-mediated genome editing delivery platform as a potential therapy for neurogenetic diseases

IND-enabling Studies for Platform Clinical Trials of Genome Editors in Multiple Diseases (U01 Clinical Trial Not Allowed) RFA-RM-24-001

PI Name	Institution Name	Title
AHRENS-NICKLAS, REBECCA CLARE (contact) MUSUNURU, KIRAN	CHILDREN'S HOSP OF PHILADELPHIA	Personalized prime editing as a platform for hepatic inborn errors of metabolism
CHEN, ZHENG-YI	MASSACHUSETTS EYE AND EAR INFIRMARY	AAV-mediated editing to treat human autosomal dominant hearing loss DFNA41 and DFNA2

https://www.nejm.org/doi/full/10.1056/NEJMoa2504747

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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 Info & Affiliations

Published May 15, 2025 | DOI: 10.1056/NEJMoa2504747 | Copyright © 2025

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EDITORIAL | MAY 15, 2025

Progress in the Development of N-of-1 Therapy

P. Marks

"Although not all rare diseases may be eligible for a gene-editing approach with available technology, there could be hundreds to thousands of diseases that could be treated through an approach similar to the one described," wrote Dr. Peter Marks, former FDA CBER director .

https://www.npr.org/sections/shots-health-news/2025/05/15/nx-s1-5389620/gene-editing-treatment-crispr-inherited

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Target Area 1: Programmable Delivery System for Gene Editing

Winning Solutions $250,000 USD Prize

- **Exosome Engineers (University of Nebraska-Lincoln)** from Lincoln, NE and Durham, NC: *Editing the Genome in Any Tissue of Choice Through Programmable Milk Exosomes*
- **Perelman School of Medicine at the University of Pennsylvania** from Philadelphia, PA: *Targeted Delivery of Genome Editing Machinery to Lungs, Systemic Endothelium, and Muscles*
- **David R. Liu Group, Broad Institute of MIT and Harvard** from Cambridge, MA: *Tissue Specific Targeted eVLPs Through Barcoded Lentiviral Screening and Rational Engineering*
- **Beth Israel Deaconess Medical Center and University of Washington** from Boston, MA and Seattle, WA: *ENTER: Elastin-based Nanoparticles for Therapeutic delivERy, Self-Assembled Protein Nanoparticles for Targeted Gene Editor Delivery*
- **Ben Deverman Vector Engineering Laboratory, Broad Institute of MIT & Harvard** from Cambridge, MA: *Engineering Receptor-Targeted AAVs with Predictable Cellular and Species Tropism*

Target Area 2: Crossing the Blood-Brain Barrier

Winning Solutions $250,000 USD Prize

- **Crisaptics Trans-BBB Genome Editing Team (University of Maryland School of Medicine)** from Baltimore, MD: *Crisaptics Trans-BBB*
- **PERCEPT (Innovative Genomics Institute at UC Berkeley)** from California and Ohio, USA : *Chemically engineered CRISPR enzymes for accessible whole-brain genome editing*
- **Icahn School of Medicine at Mount Sinai** from New York, NY: *Blood-brain barrier-crossing lipid nanoparticles for genome editing*
- **STEP Team (Yale University)** from New Haven, CT: *BRAIN TARGETED-STEP RNPs for Delivery of Genome Editing to the Brain*

https://www.freelancer.com/nih/targeted-challenge

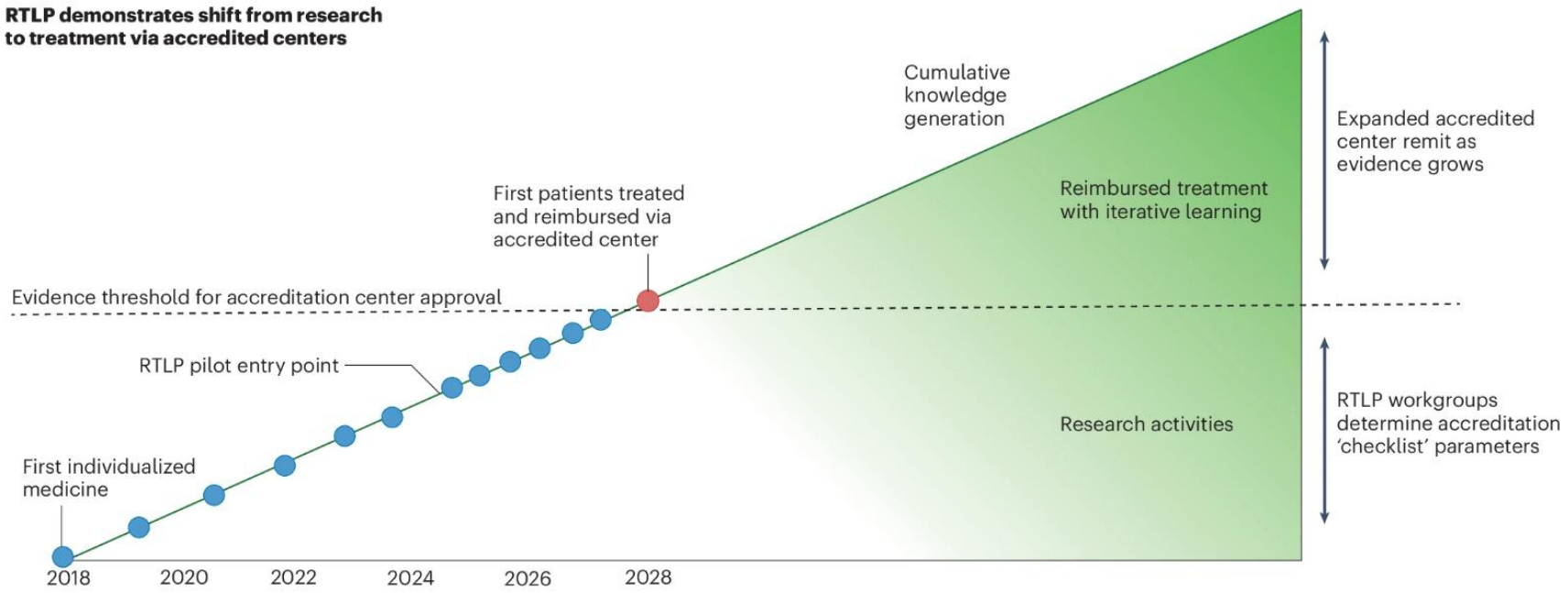
Correspondence | Published: 10 March 2025

The Rare Therapies Launchpad: a pilot program for individualized medicines in the UK

Daniel J. O'Connor, Parker Moss, Matthew Wood, Martin Murphy, Michael Parker, Nicola Blackwood, Matthew A. Brown, Deb Lancaster, Vanessa Newman, Jenny Taylor, Tim Yu & Julia Vitarello

Nature Medicine (2025) | Cite this article

From: The Rare Therapies Launchpad: a pilot program for individualized medicines in the UK

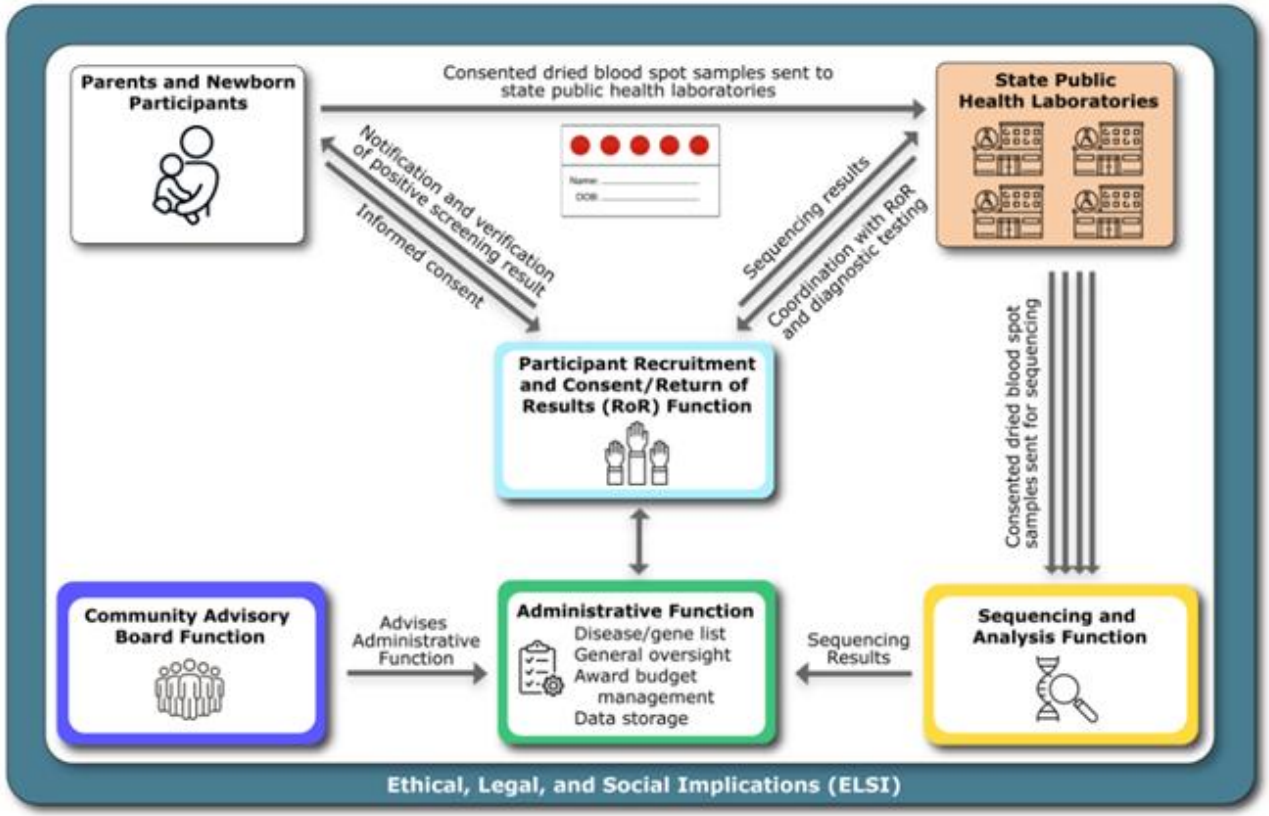


Newborn Screening by Whole-Genome sequencing

NBSXWGS

The Common Fund

This initiative will assess the feasibility of developing a collaborative model to allow incorporation of genomic sequencing as a screening tool for select monogenic diseases that are actionable in early childhood into the existing state-based U.S. public health newborn screening program .



https://commonfund.nih.gov/venture/nbsxwgs/funding-opportunities/OTA-25-004#overviewinformation

Many

~~One~~ diseases at a time

Therapeutic platforms
for monogenic disease