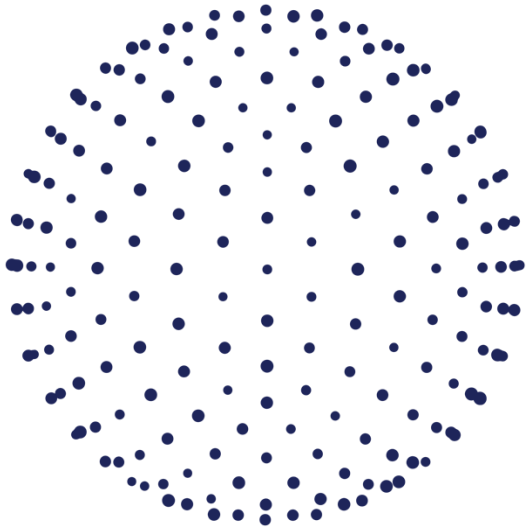
DECIDE-ET

Decentralized Engineering of Cells Informed by Dynamic Evidence Exploration Topic



Resilient Systems Office
Darshak Sanghavi MD, Program Manager

ARPA-H

What if more patients with rare diseases could access clinically effective therapies?

ARPA-H

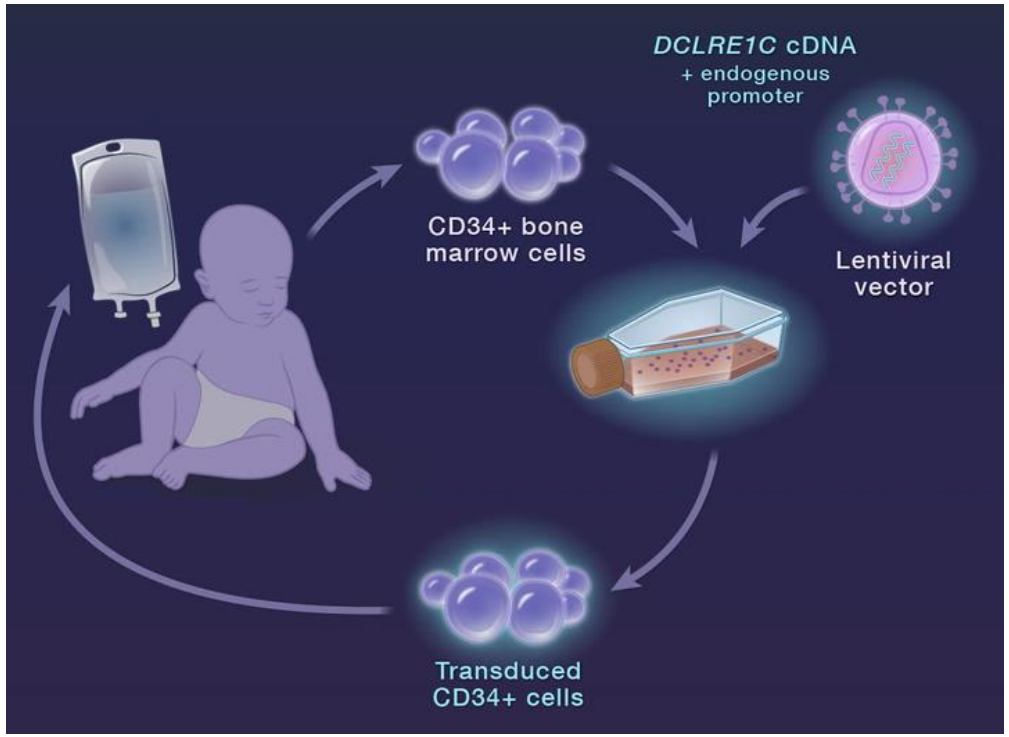
Obstacles to Accessing a Life-saving Treatment

The SCID case study

Artemis-deficient severe combined immunodeficiency (SCID) impacts 1 in 65,000 births in the general population and **1 in 2,000 births** among persons of Navajo or Apache descent.

Autologous cell therapy has proven to be a **durable treatment**.

Academic Medical Centers (AMCs) are **unable** to cost-effectively meet the **current manufacturing requirements** to obtain FDA designation.



Cowan MJ et al. Lentiviral Gene Therapy for Artemis-Deficient SCID. NEJM (2022).

ARPA-H

The Problem

Manufacturing and reimbursement for low-volume therapies is administratively and cost prohibitive.

Manufacturing

AMCs **cannot economically manufacture** small-batch cell therapies partially due to the **significant resources** required to ensure quality and consistency on par with large-scale production.

Regulation

Regulators have a limited number of tools for making risk-adjusted decisions around small-batch manufacturing, which can **increase process validation costs** for cell therapy manufacturing.

Reimbursement

CMS and Payers reimburse for therapies with clinical and manufacturing approval from FDA, which is **not feasible** for many cell therapies produced in small batches.

Patients

~5000 identified rare pediatric diseases impact >100,000 children, yet only **5% of rare diseases have FDA approved treatments**. Without a sustainable ecosystem to manufacture, regulate, and reimburse cell therapies, cures will remain out of reach for patients.

Developers

Companies are **not incentivized** to develop curative therapies for rare diseases that affect small patient populations, unless there are pathways for reimbursement and opportunities to recoup investments.

ARPA-H

The DECIDE ET Solution

Improve small-batch manufacturing and regulatory decision-making confidence, enabling clinically-effective rare-disease therapies to overcome economic barriers and reach patients.

Manufacturing

AMCs use **variability detection and analysis tools** to enhance manufacturing quality and consistency for small-batch autologous cell production.

Regulation

Regulators use **statistical decision-support tools** to make risk-adjusted decisions on number of lots necessary to demonstrate key attributes of small-batch production.

Reimbursement

Within a regulatory environment that enables small-batch manufacturing of cell therapies, institutions can **unlock reimbursement** and **establish sustainable financial models**.

Patients

A **nationwide network** of AMCs capable of manufacturing and administering autologous cell therapies could provide durable treatments for **thousands to millions of Americans** impacted by rare pediatric diseases.

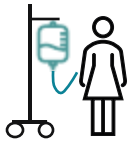
Developers

This approach to dynamically scaling manufacturing targets will help **sick children access cost-effective treatments** and incentivize the development of new therapies for other rare diseases. There are over 1,000 cell therapy clinical trials underway in the US, and this approach could help improve access to a number of treatments.

ARPA-H

How will it work?

Researchers develop therapy



Conduct clinical trials & demonstrate efficacy

Clinically approved therapy

Current State

Commercial GMP certification per FDA policy *(Economics favor therapies with large-scale manufacturing)*

Difficult to qualify for reimbursement

Patients with **rare** diseases **cannot** access affordable treatment

Future state with DECIDE

DECIDE informs FDA guidance on criteria that allows for accelerated approval pathway *(Manufacturing small batch therapies becomes viable)*

Qualification for reimbursement

Patients with **rare** diseases **can** access affordable treatment

Empowered by:
1. Process variation modeling
2. Dynamic decision support tools

ARPA H

Objective 1: Process Variation Modeling

Optimize the consistency of decentralized small-batch autologous cell production by identifying sources of manufacturing variability.

Identify sources of variability

- FDA will **collaborate with ARPA-H** throughout the DECIDE initiative, specifically by providing **technical guidance** to inform the scope, methods, and desired features / capabilities of technologies being created by DECIDE.
- ARPA-H Performers will develop methods that **simulate** the underlying manufacturing processes or components that could allow for a systematic and precise study of **manufacturing variability** and subsequent **attribution to causative sources**. Simulations may include a combination of in silico and in vitro studies.
- ARPA-H Performers will acquire data from samples, using novel technologies or existing tools, that are **representative of the full range of possible conditions and scenarios** for their given system and source material.

Identifying and quantifying source and impact of production variability

Unique signature association

- FDA will **collaborate with ARPA-H** throughout the DECIDE initiative, specifically by providing **technical guidance** to inform the scope, methods, and desired features / capabilities of technologies being created by DECIDE.
- ARPA-H Performers will identify **distinctive markers** (i.e., signatures) in key quality attributes that can be **linked back to specific variations.**
- ARPA-H Performers will develop a **signature library** enabling stakeholders to more efficiently ID causes of variability in their manufacturing.

Example: disease progression impacts cell morphology

ARPA-H

Objective 2: Dynamic Decision Support Tools

Quantitatively inform the minimum number of manufactured lots needed to confidently ensure quality and consistency for rare and/or low-volume therapies.

Statistical methods informing minimum lot quantity

- FDA will **collaborate with ARPA-H** throughout the DECIDE initiative, specifically by providing **technical guidance** to inform the scope, methods, and desired features / capabilities of technologies being created by DECIDE.
- ARPA-H Performers will innovate and demonstrate new **statistical approaches** to support risk-adjusted decision making that **scales** with the intended number of lots to be manufactured.
- ARPA-H Performers will develop approaches that quantitatively inform the **minimum number of lots** to confidently ensure quality consistency for rare and/or low-volume therapies without requiring the same large quantity of test lots as therapies manufactured on the scale of many thousands of doses.
- ARPA-H Performers will **apply and refine statistical methods into a decision support tool** that supports regulators in confidently navigating specific decisions necessary to determine the quality and consistency of small-batch and/or decentralized cell production.
- ARPA-H Performers will ensure that statistical decision support tools and the underlying methods are **transparent and explainable**, such that regulatory bodies can confidently assess their validity.

ARPA-H

Call to Action: Get Engaged

Learn about the ET

Read our press release to find:

- An overview of the ET
- Our Draft Solicitation
- A link to Q&A

Submit a proposal

If you are part of an organization that has innovative solutions for addressing both ET objectives, please **read the solicitation and submit a proposal.**

Spread the word

Share information about the DECIDE ET with your network and reach out to us to answer any further questions!

decide@arpa-h.gov

ARPA H


ARPA H