Congressional Briefing: Gene Editing Technologies

April 4, 2024

American Society of Gene + Cell Therapy

Agenda & Speakers

- Welcome
  Margarita Valdez Martínez, American Society of Gene & Cell Therapy
- ASGCT Overview
  Jeffrey Chamberlain, PhD, University of Washington
- Introduction to Gene Editing
  Fyodor Urnov, PhD, University of California Berkeley
- The Gene Editing Pipeline
  Janice Chen, PhD, Mammoth Biosciences
- Understanding Clinical Trials
  Matthew Porteus, MD, PhD, Stanford University School of Medicine
- Why Gene Editing is an Important Tool for the Rare Disease Community
  Amy Raymond, PhD, Worldwide Clinical Trials
- Q&A

Overview: American Society of Gene & Cell Therapy

Jeffrey Chamberlain, PhD
President, ASGCT
Professor and McCaw Chair in Muscular Dystrophy, University of Washington School of Medicine

American Society of Gene + Cell Therapy

Introduction to ASGCT

Professional membership organization for gene & cell therapy researchers

6200 + Members

Majority: researchers from industry and academia

Majority: gene therapy, including genetically-modified cell therapy

Established in 1996

Mission

To advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease

American Society of Gene + Cell Therapy

Casgevy Approval (December 2023)

Historic FDA gene therapy approvals for sickle cell disease (SCD)

- Casgevy is an *ex vivo,* autologous, CRISPR-Cas9 gene-edited therapy developed by CRISPR Therapeutics and Vertex to treat patients with severe SCD
    - Casgevy is also indicated to treat transfusion-dependent beta-thalassemia.

- Lyfgenia is a lentiviral vector based therapy for the treatment of SCD patients 12 years of age and older with a history of vaso-occlusive events (VOEs), and is marketed by Bluebird Bio

- Both are ex vivo gene therapies using a single infusion of a patient's own modified hematopoietic stem cells.

- SCD affects about 100,000 Americans, **occurring most often** in Black populations
    - This has the potential to be one of the most far-reaching gene therapies to date

We hope that these approvals are the tip of the iceberg in terms of molecular medicine

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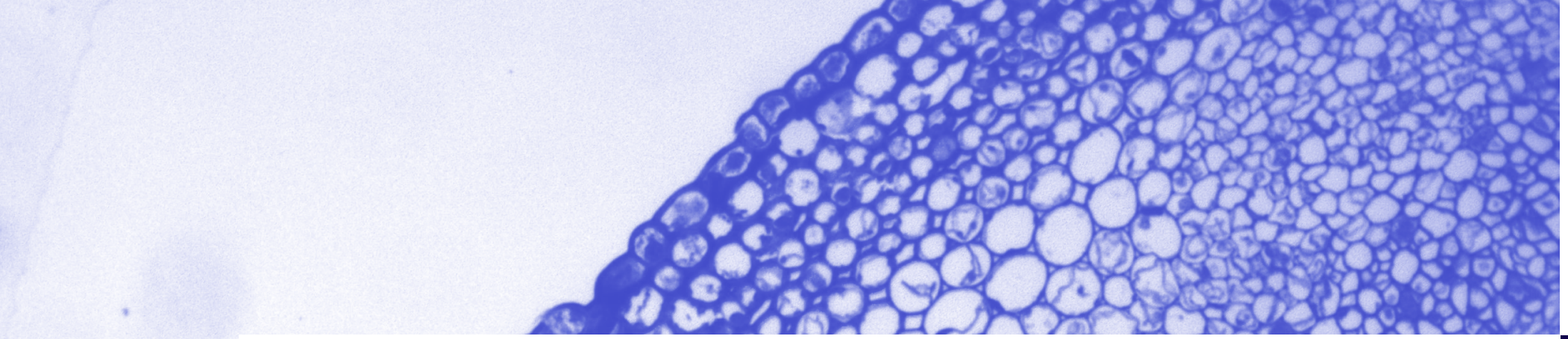
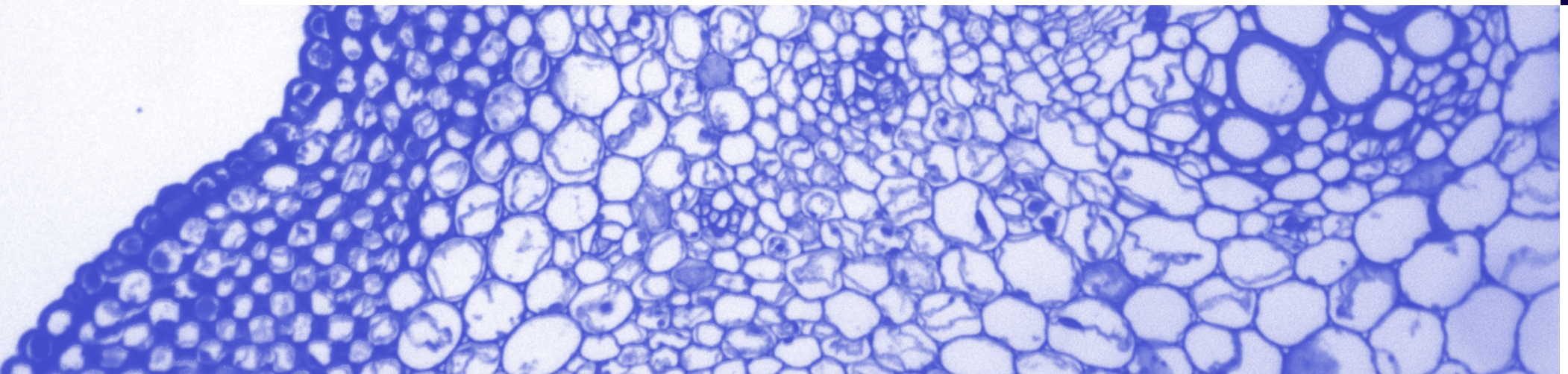


Gene, Cell, & RNA Therapy Landscape

January 2024



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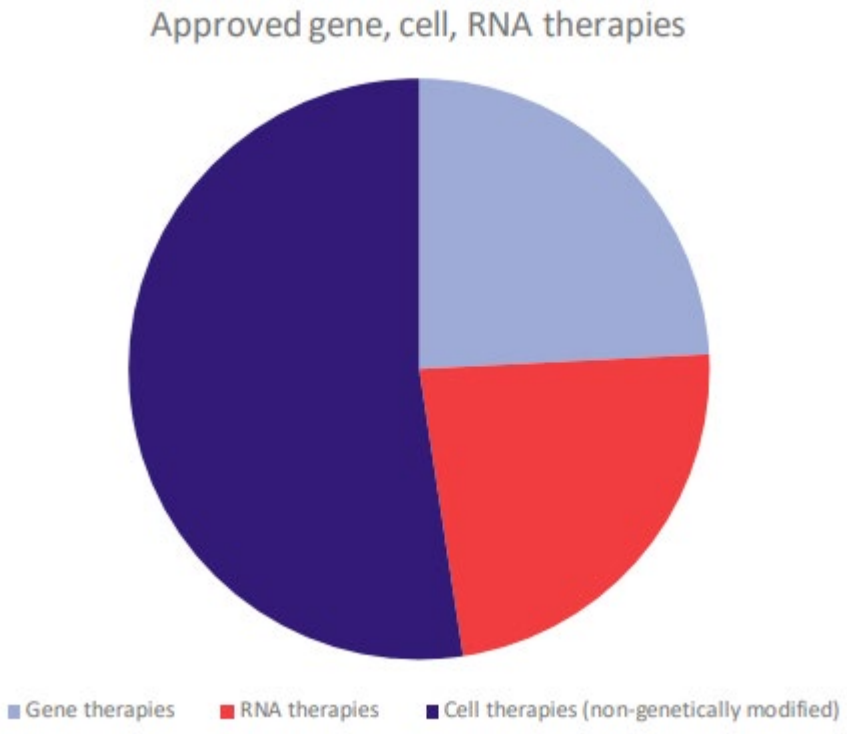
Approved Gene, Cell, and RNA Therapies

Globally, for clinical use:

- 30 gene therapies have been approved (including genetically modified cell therapies)
  - In Q4 2023, Casgevy was approved in the US for sickle cell disease and in the UK for both sickle cell disease and transfusion-dependent β-thalassemia and Lyfgenia was approved in the US for sickle cell disease
  - In February 2024 Amtagvi, a TIL therapy, was approved as the first one-time cell therapy to treat a solid tumor cancer (melanoma). And in March 2024 Lenmeldy was approved for children with pre- or early-symptomatic metachromatic leukodystrophy (MLD)
- 29 RNA therapies have been approved
- 65 non-genetically modified cell therapies are approved



Source: Pharmaprojects | Citeline, January 2024

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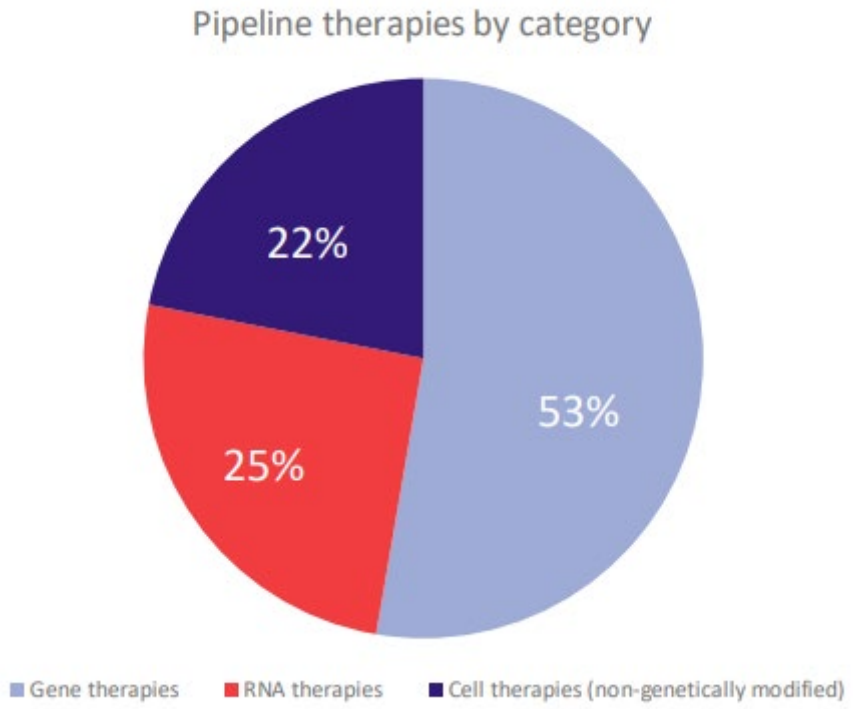
Pipeline of Gene, Cell, and RNA Therapies

3,951 therapies are in development, ranging from preclinical through pre-registration

- 2,111 gene therapies (including genetically modified cell therapies such as CAR T-cell therapies) are in development, accounting for 53% of gene, cell, and RNA therapies
- 878 non-genetically modified cell therapies are in development, accounting for 22% of gene, cell, and RNA therapies



Source: Pharmaprojects | Citeline, January 2024

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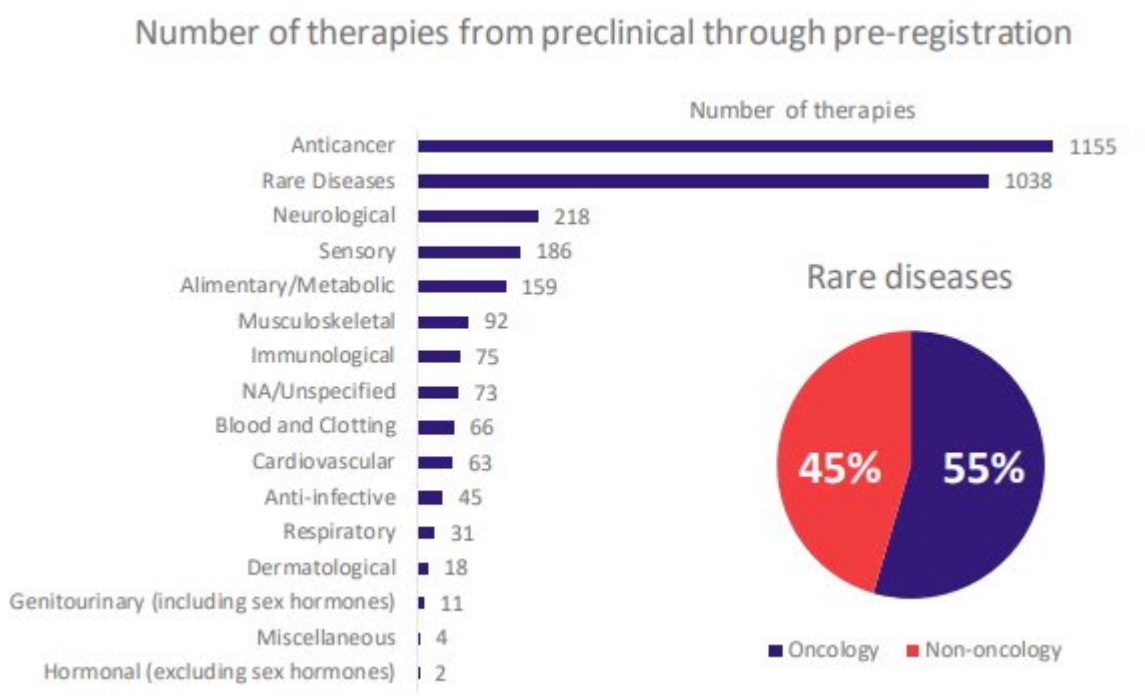
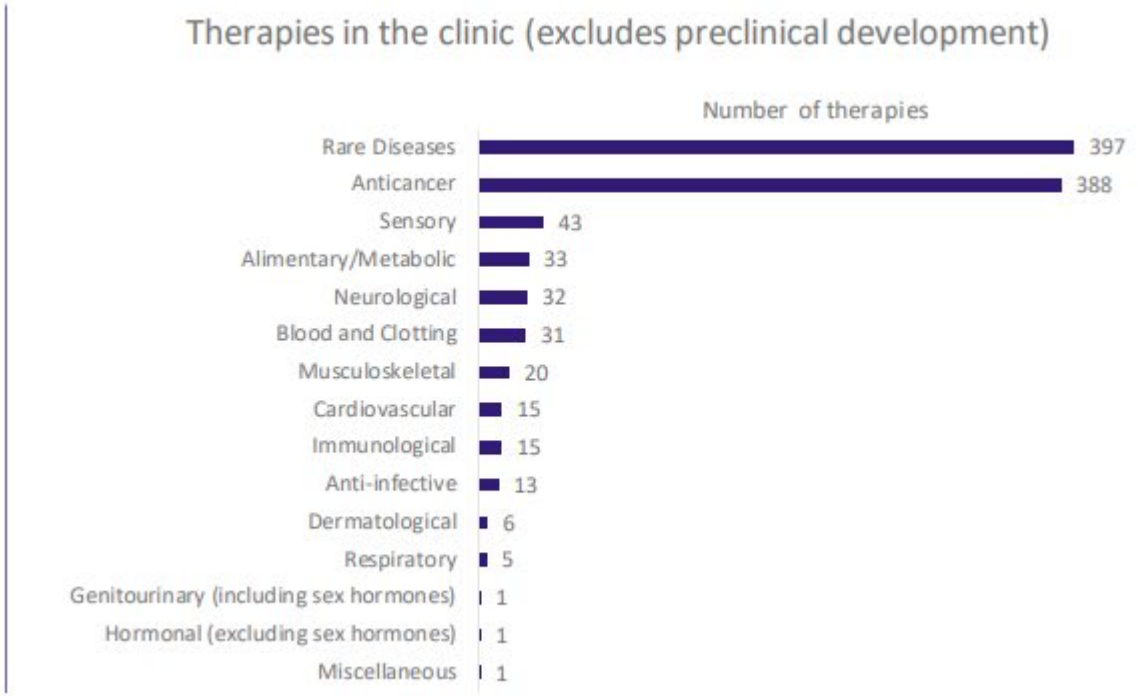
Gene Therapy Pipeline: Most Commonly Targeted Therapeutic Areas

- Oncology and rare diseases remained the top areas of gene therapy development in both the overall pipeline (preclinical to pre-registration) and in the clinic (Phase I to pre-registration)
- Development for rare diseases most commonly occurred in oncology, representing a majority of 55% compared to non-oncology rare disease gene therapy pipeline development





Source: Pharmaprojects | Citeline, January 2024

Note: figures based on indications in pipeline development only for each therapy

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Gene Editing with CRISPR: How it Works

Fyodor Urnov, PhD
Professor of Molecular Therapeutics, University of California, Berkeley
Scientific Director, Innovative Genomics Institute

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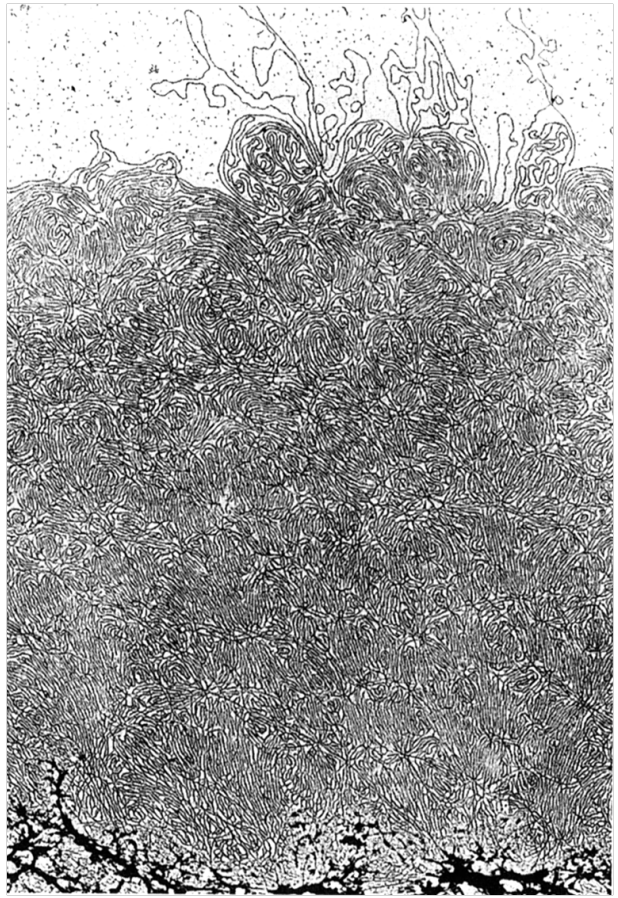
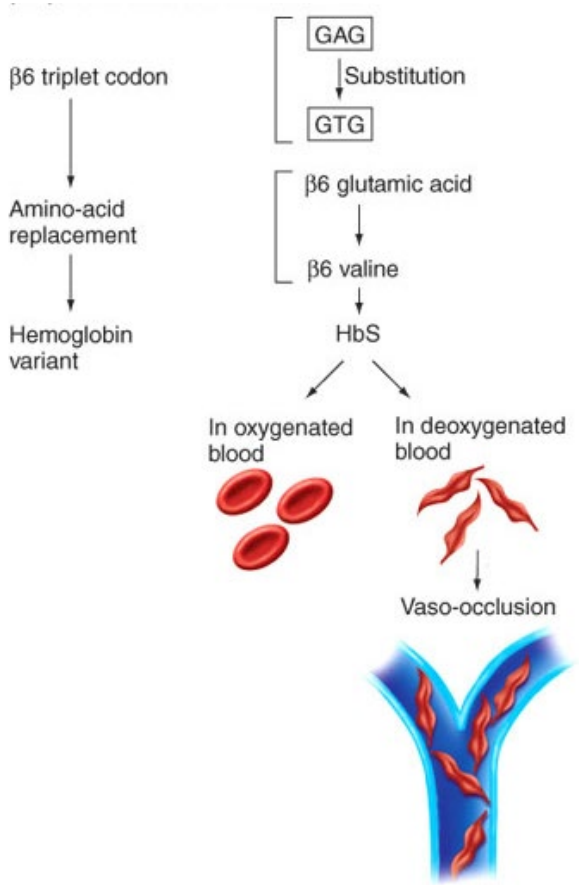
The Human Genome: a Book 6,600,000,000 Letters Long Where One Typo Can Cause Disease

1 meter of DNA – this is 0.3% of it:

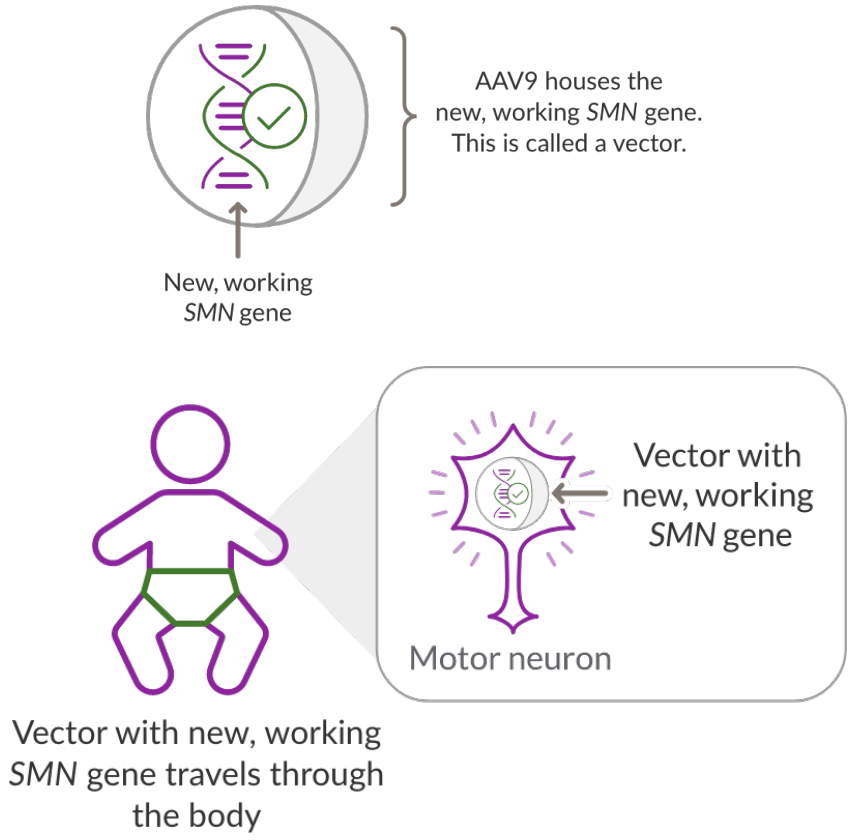


Cause of sickle cell disease – one typo

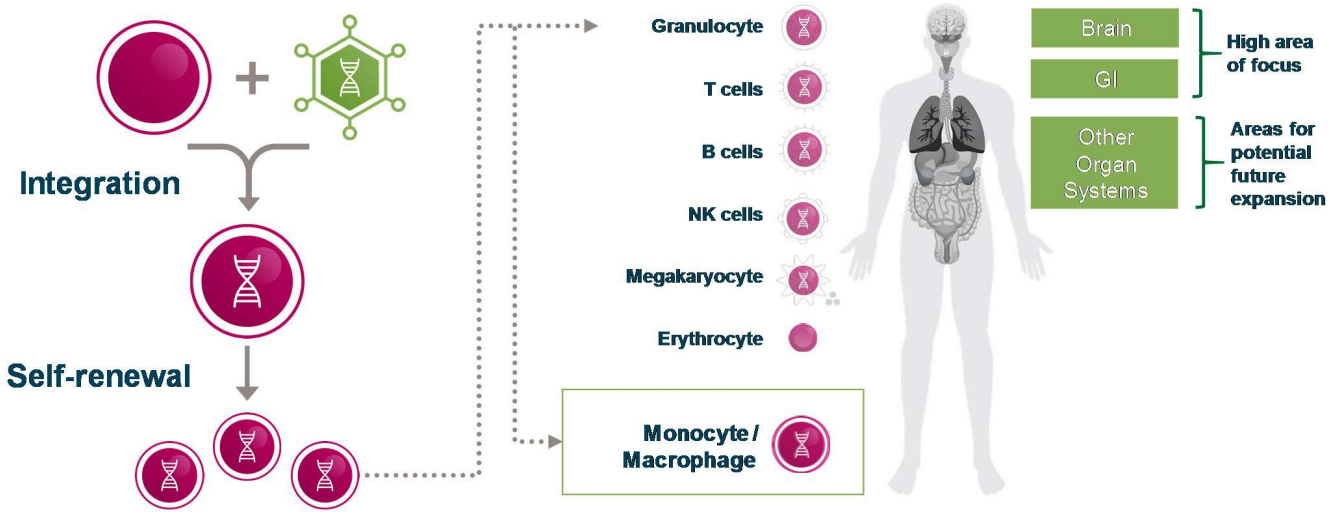


Gene Therapy With Viruses: a Powerful Technology With Limitations

Zolgensma for spinomuscular atrophy



Libmeldy for metachromatic adrenoleukodystrophy



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If you have a car with a flat tire, gene therapy is taking the spare, adding it somewhere onto the car and hoping it runs.

Gene editing is repairing the flat.

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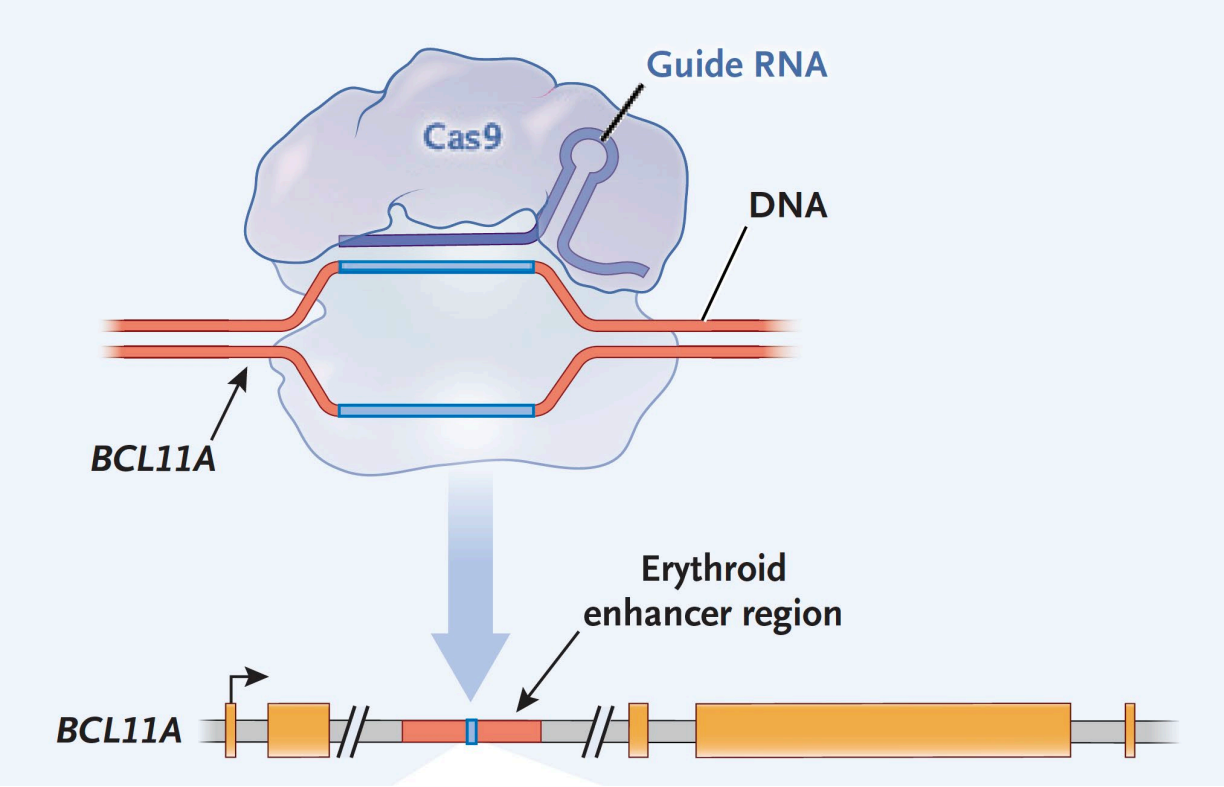
CRISPR Gene Editing: Repairing Faulty Genes or Deleting Toxic Genes “Right Where They Live”



Casgevy for SCD has 2 parts:

a protein part, Cas9 (which does the editing)

a nucleic acid part, “guide RNA,” which “guides” the editor to the right gene

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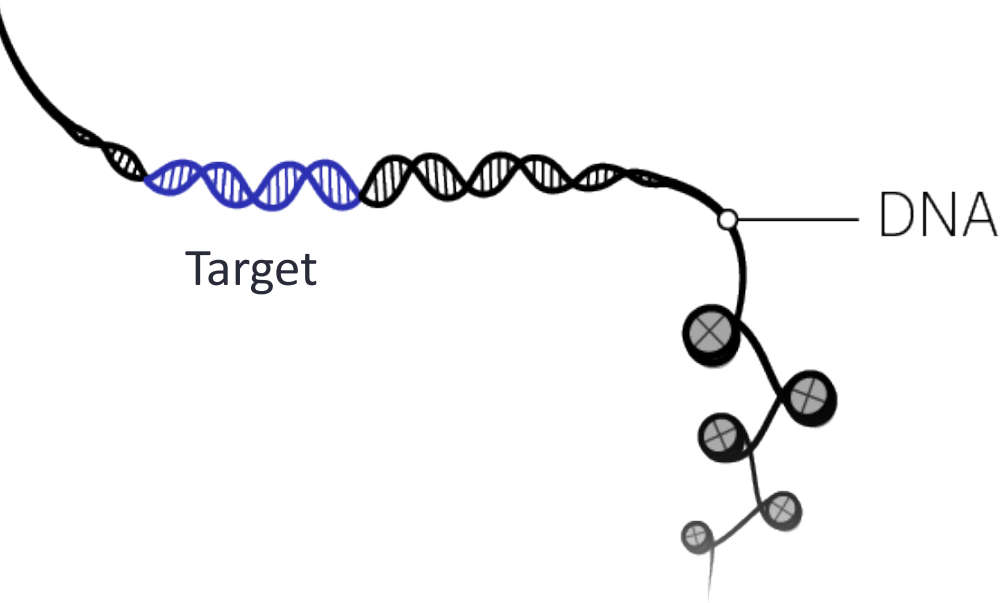
How to Program the CRISPR-Cas9 System

How CRISPR Finds Its Target Gene In a 6,600,000 Letter Genome



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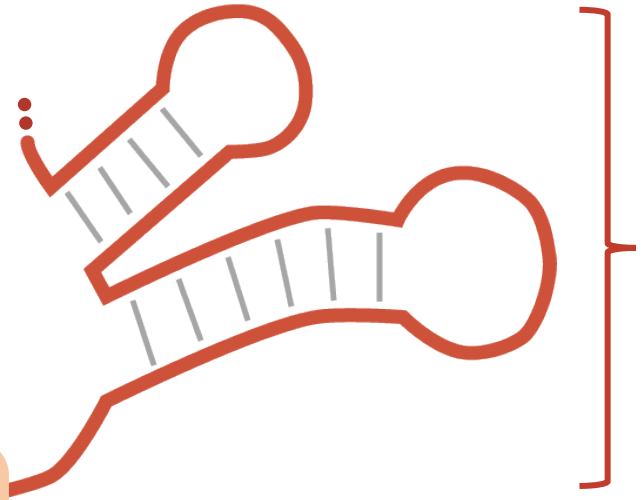
How CRISPR Finds Its Target Gene In a 6,600,000 Letter Genome



constant sequence

sgRNA AUCCCUGUACACCCGCGAAA

programmable

AATAACTATTGACC**TAGGGACATGTGGGCGCTTT**GCCCCCCTTTCAGGTAAACG

TTATTGATAACTGG**ATCCCTGTACACCCGCGAAA**CGGGGGGAAAGTCCATTTGC

SpyCas9 PAM: 5’ NGG 3’

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How CRISPR Finds Its Target Gene In a 6,600,000 Letter Genome

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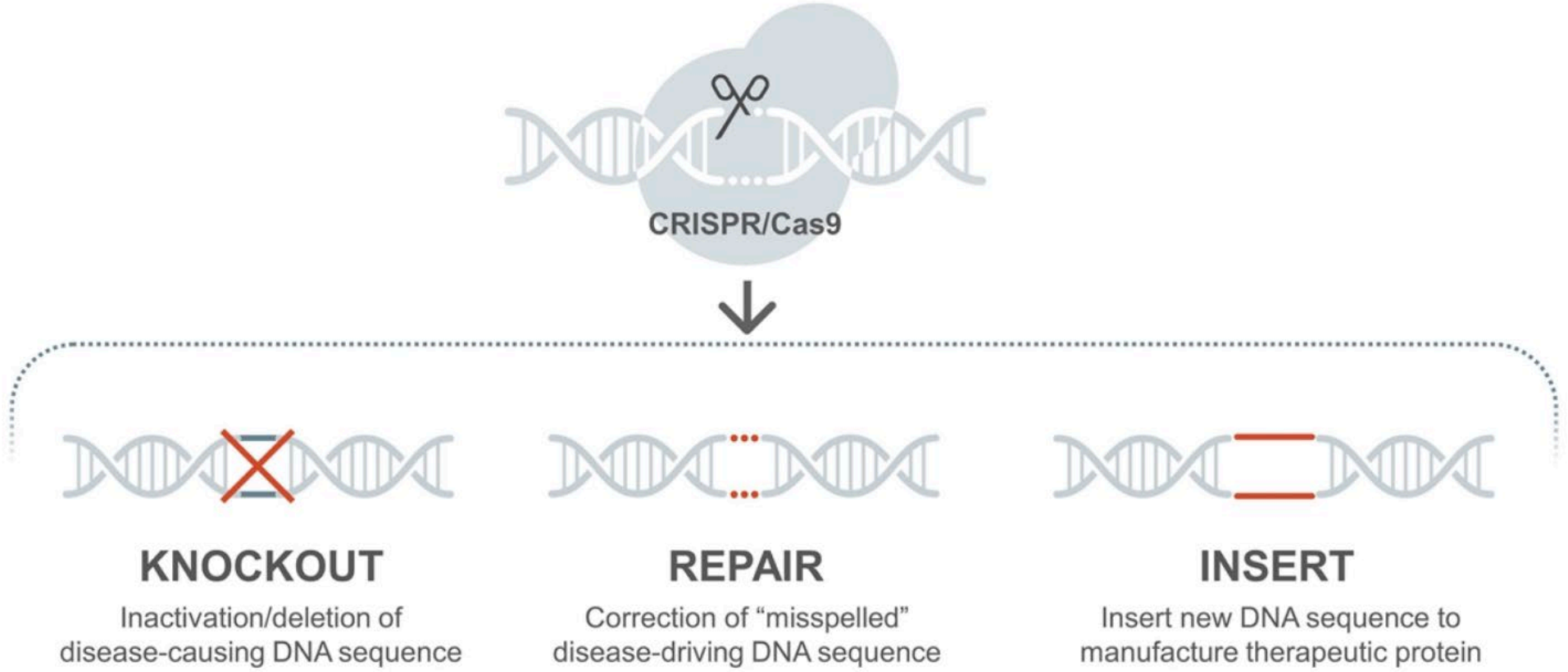
Human Gene Editing With CRISPR



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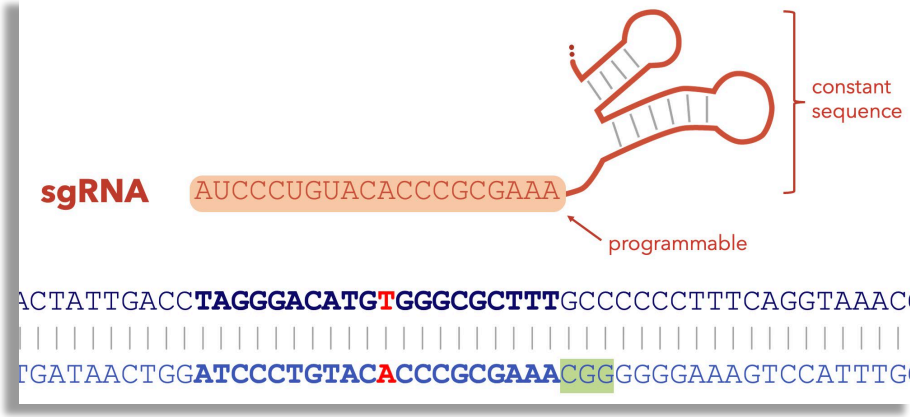
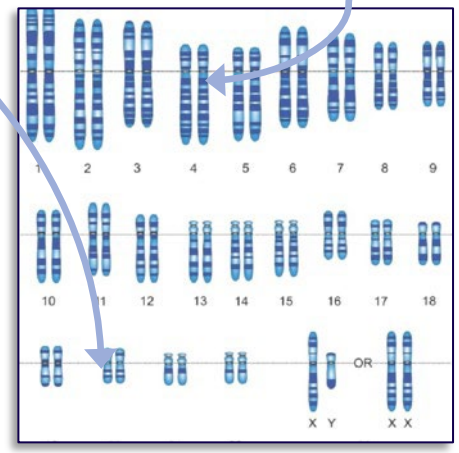
Changing 20 Letters Makes a New CRISPR Medicine



Gene: ATTR on chr 20a

Gene: KLKB1 on chr 4



Disease 1: TTR Amyloidosis

93% target gene knockout in patient liver

Disease 2: Hereditary Angioedema

92% target gene knockdown in patient liver

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The Gene Editing Pipeline

Janice Chen, PhD
Co-Founder & Chief Technology Officer,
Mammoth Biosciences

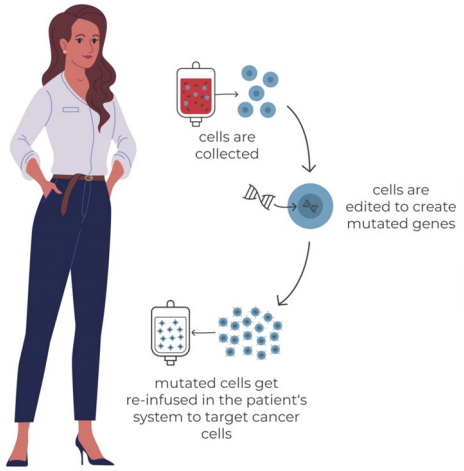
American Society
of Gene + Cell Therapy

The gene editing landscape is evolving to address a broad range of diseases

2012

Where CRISPR Has Been

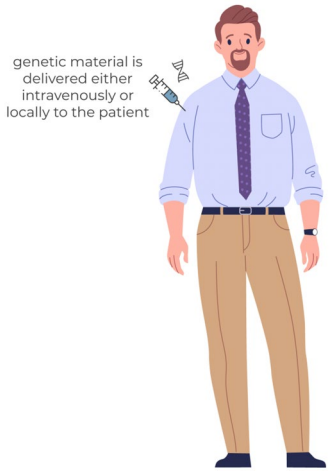
Gene editing takes place **outside** the body (*ex vivo*)



- *Blood disorders*
- *Blood cancers*

Where CRISPR Is Going

Gene editing takes place **inside** the body (*in vivo*)



- *Rare diseases*
- *Muscle diseases*
- *Cardiovascular*
- *Metabolic diseases*
- *CNS diseases*
- *Lung diseases*
- ***...and more***

2024 and beyond

Adapted from Single Use Support

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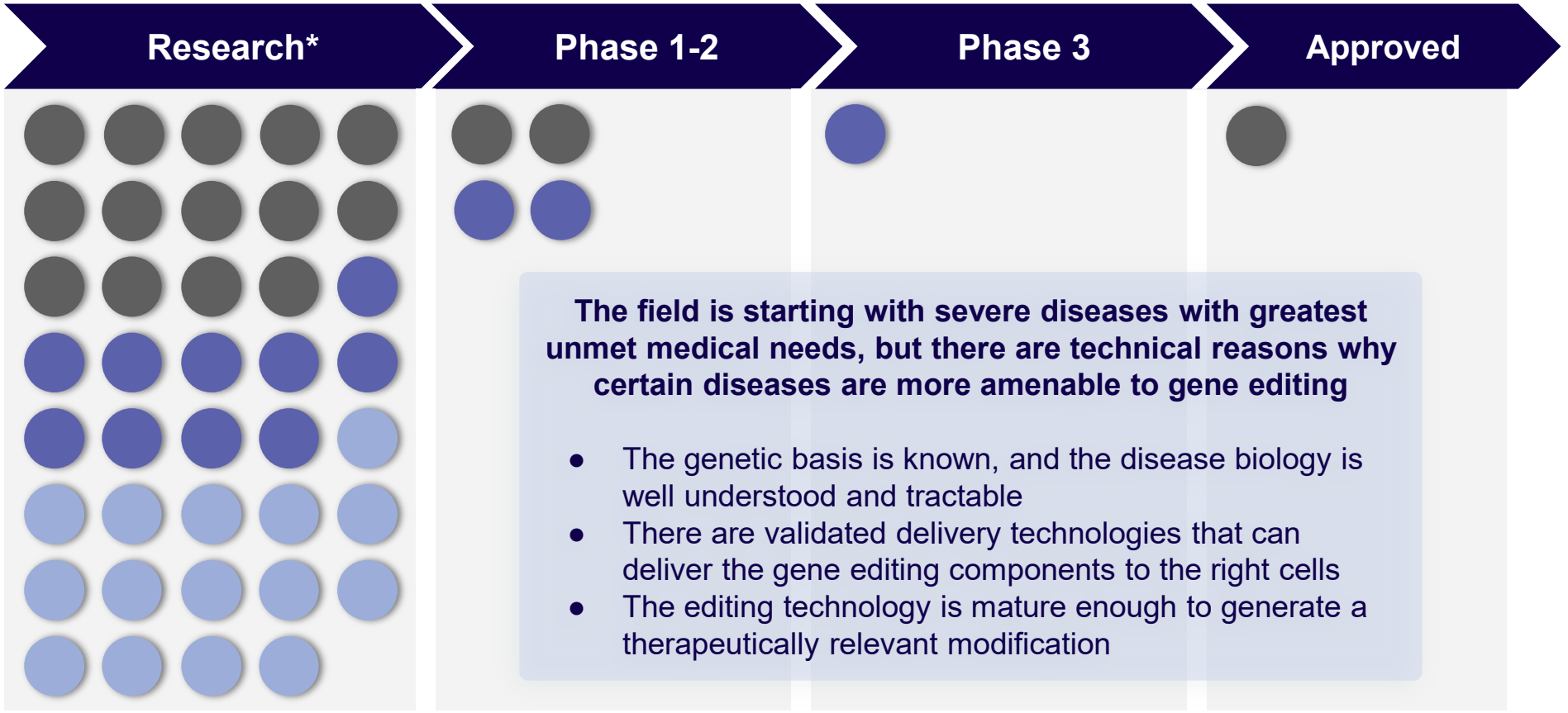
The CRISPR field is progressing rapidly, with several programs advancing to the clinic



The field is starting with severe diseases with greatest unmet medical needs, but there are technical reasons why certain diseases are more amenable to gene editing

- The genetic basis is known, and the disease biology is well understood and tractable
- There are validated delivery technologies that can deliver the gene editing components to the right cells
- The editing technology is mature enough to generate a therapeutically relevant modification

Ex vivo programs

Blood
Sickle cell disease, hemophilia, blood cancers, etc.

In vivo programs

Liver
TTR, HAE, cardiovascular, rare disease, etc.

Beyond Liver
Duchenne Muscular Dystrophy (DMD), Amyotropic Lateral Sclerosis (ALS), Huntington's Disease, Cystic Fibrosis, etc.

Mammoth Biosciences analysis; companies included as of 3/29/24: Arbor Biotechnologies, Beam Therapeutics, Caribou Biosciences, Chroma Medicine, CRISPR Therapeutics, Editas Medicine, Epic Bio, Huidagene Therapeutics, Intellia Therapeutics, Life Edit Therapeutics, Metagenomi, Prime Medicine, Recode Therapeutics, Tessera Therapeutics, Tune Therapeutics, and Verve Therapeutics.
Circles indicate relative number of programs.
*Research only captures programs from companies listed above and does not include work from academic or nonprofit institutions.

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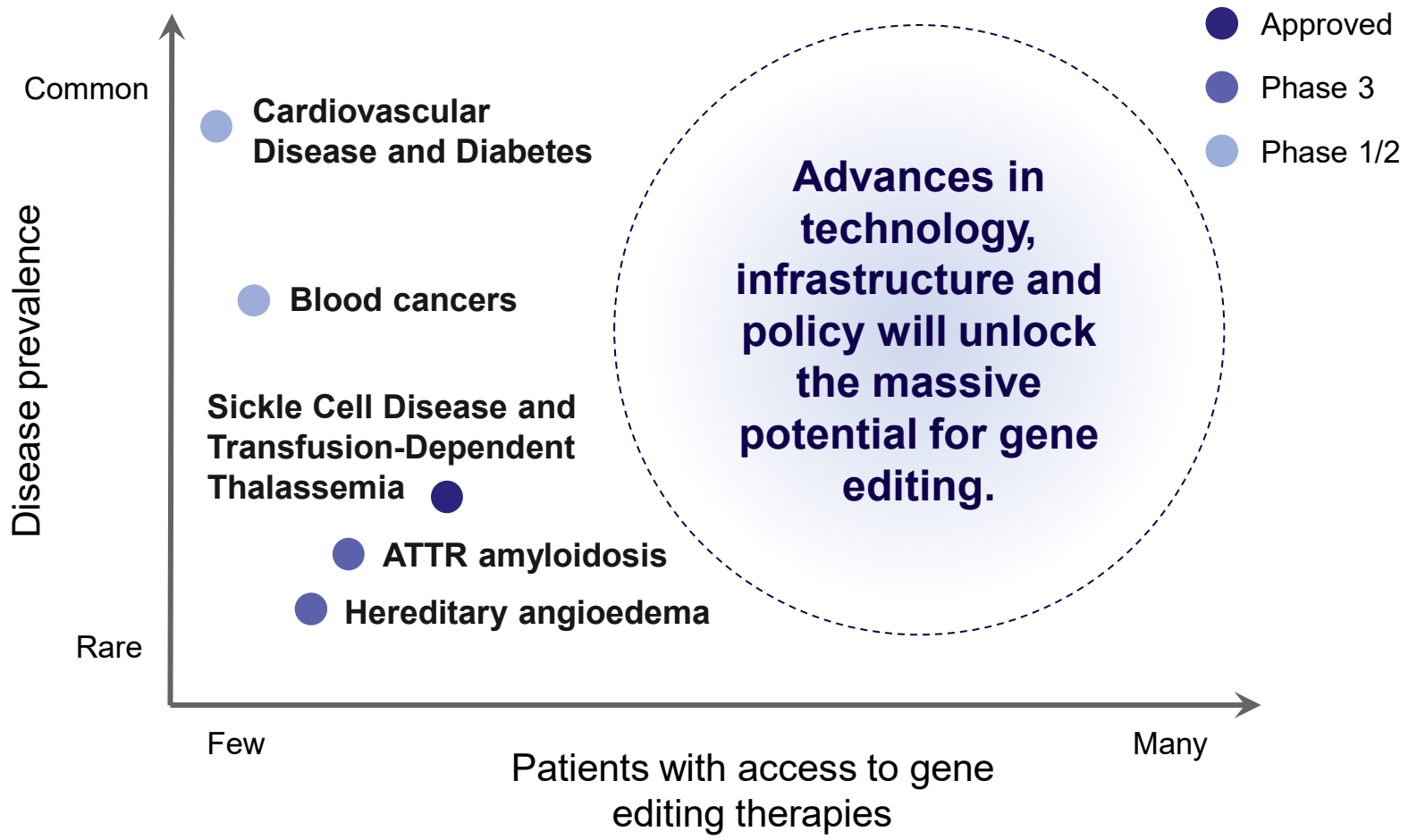
Despite the advances in gene editing, there are still >5,000 genetic diseases with no available cure



The New York Times

New Gene Editing Treatment Cuts Dangerous Cholesterol in Small Study

The trial involved only 10 patients, but it suggests cholesterol can be permanently reduced with a single treatment for patients at risk of heart disease.

THE WALL STREET JOURNAL.

Doctors Can Now Edit the Genes Inside Your Body

It sounds like science fiction, but dozens of people have undergone gene editing for cardiovascular disease and other conditions

Mammoth Biosciences analysis. Figure is not to scale. Additional sources: *New York Times*, *The Wall Street Journal*.

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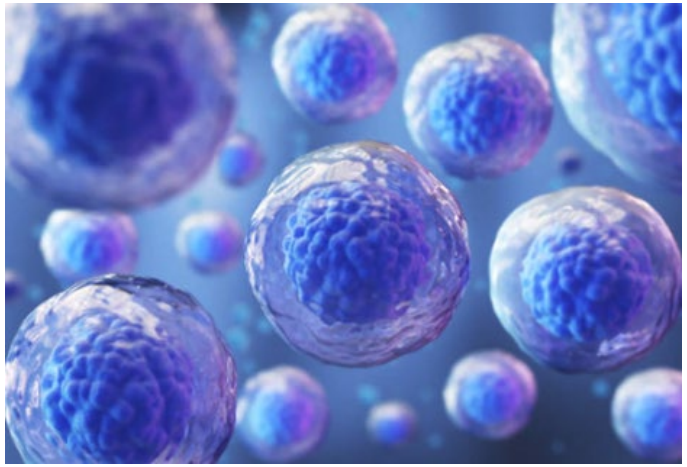
Gene Editing will reshape our future

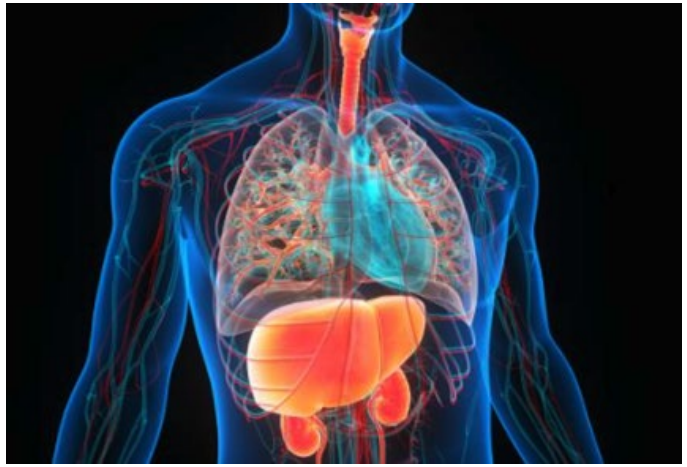
Basic Research

Fundamental understanding of how cells and organisms function



Healthcare

Therapeutics, diagnostics, vaccines, drug targets



Agriculture

Disease resistance, improved crop yields, increased nutritional value

…and beyond

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Understanding Clinical Trials

Matthew Porteus, MD, PhD
Sutardja Chuk Professor of Definitive and Curative Medicine, Stanford Medicine

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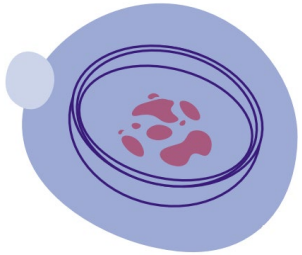
The Traditional Clinical Trial Process

Preclinical Studies

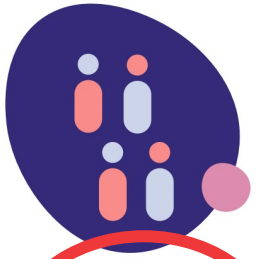


Investigational New Drug (IND) Application

Phase I Trial

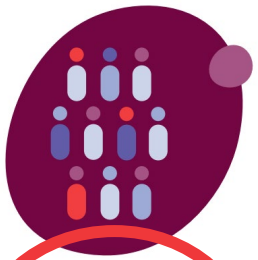
20-100 healthy volunteers

Phase II Trial



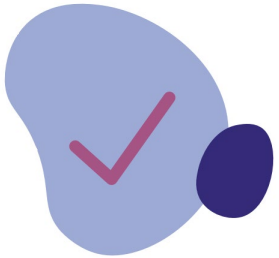
100-300 people with the disease

Phase III Trial



1000-3000 people with the disease

FDA Approval



Phase IV Trial

Studied in the general population

Genetic medicines, including gene editing products, may take a compressed approach to clinical trials given small patient populations and the nature of these therapies.

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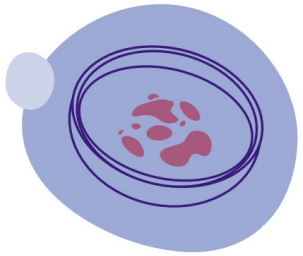
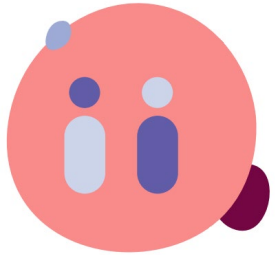
The GE Clinical Trial Process

Preclinical Studies



Investigational New Drug (IND) Application

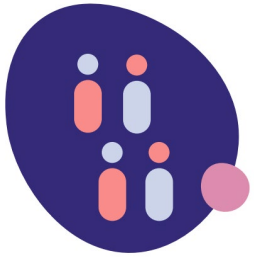
Phase I/II Trial



5-50 people with the disease

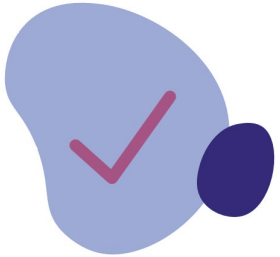
FDA + Sponsor Conversations on Ph III Trial Design

Phase III Trial/ Registration Trial



25-200 people with the disease

FDA Approval



Phase IV Trial

Long-term follow up of treated patients

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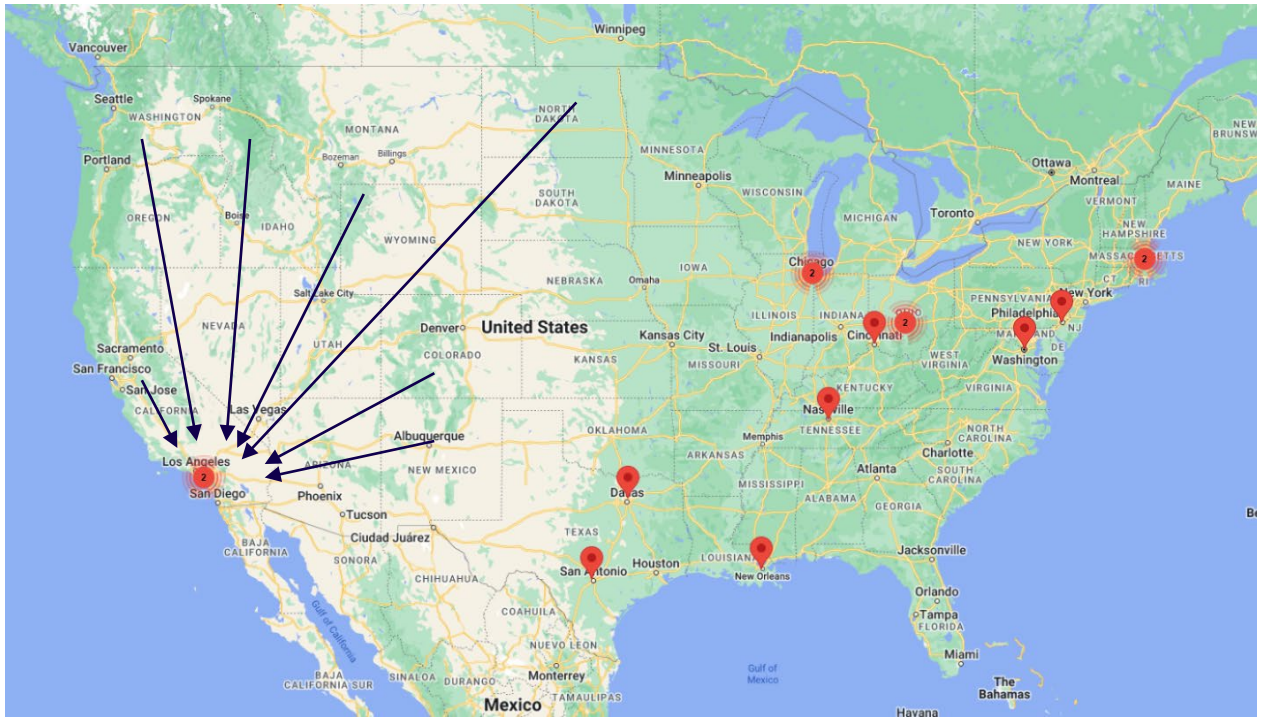
Clinical Trial Considerations for Genetic Medicine Products

- Manufacturing for *in vivo* and *ex vivo* products requires different approaches
- Approved (label) indication may be broader than the clinical trial population
- Where are these products going to be administered once approved?

Casgevy authorized treatment sites (4/2/24)



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Why Gene Editing is an Important Tool for the Rare Disease Community

Amy Raymond, PhD, PMP
Executive Director, Cellular and Genetic Medicines, Worldwide Clinical Trials

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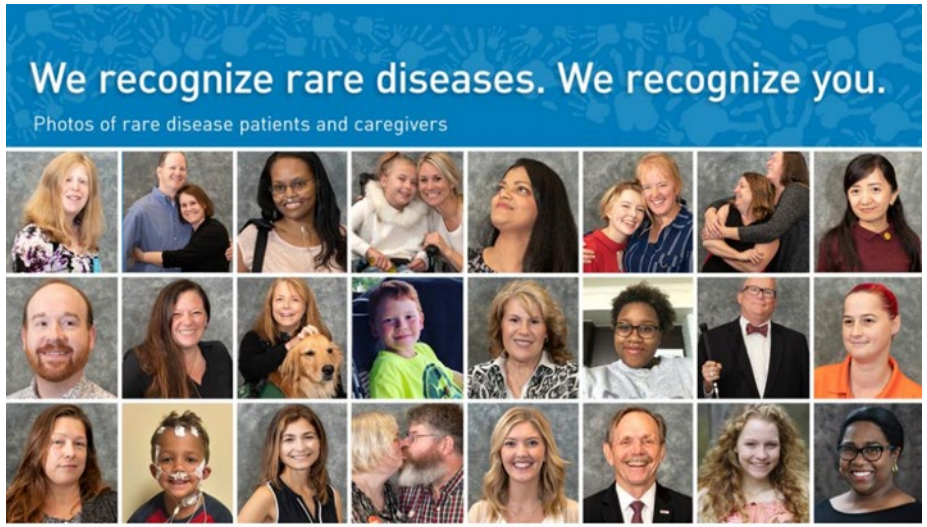
Rare Diseases

- Affecting fewer than 200,000 people in the US
  - Half of rare disease patients are children
  - 3 of every 10 children with a rare disease will not live to see their 5th birthday
  - Roughly 30 Millions Americans
    - one person on any crowded elevator
  - Holding hands, they would circle the globe 1.5X
- There are rare diseases in every therapeutic area (Neurology, Oncology, Cardiology, etc)



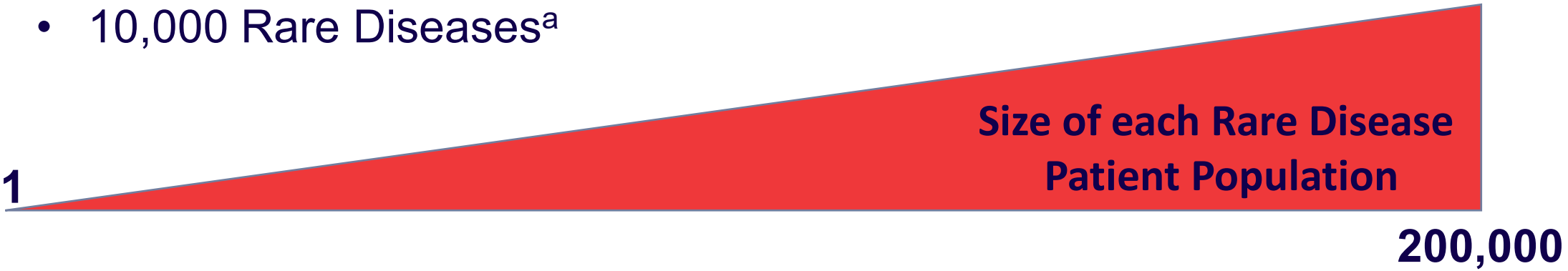
"Rare is many. Rare is Strong. Rare is Proud."

Courtesy of FDA's Rare Diseases Day 2020

American Society of Gene + Cell Therapy

Rare Diseases

- 10,000 Rare Diseases[a]

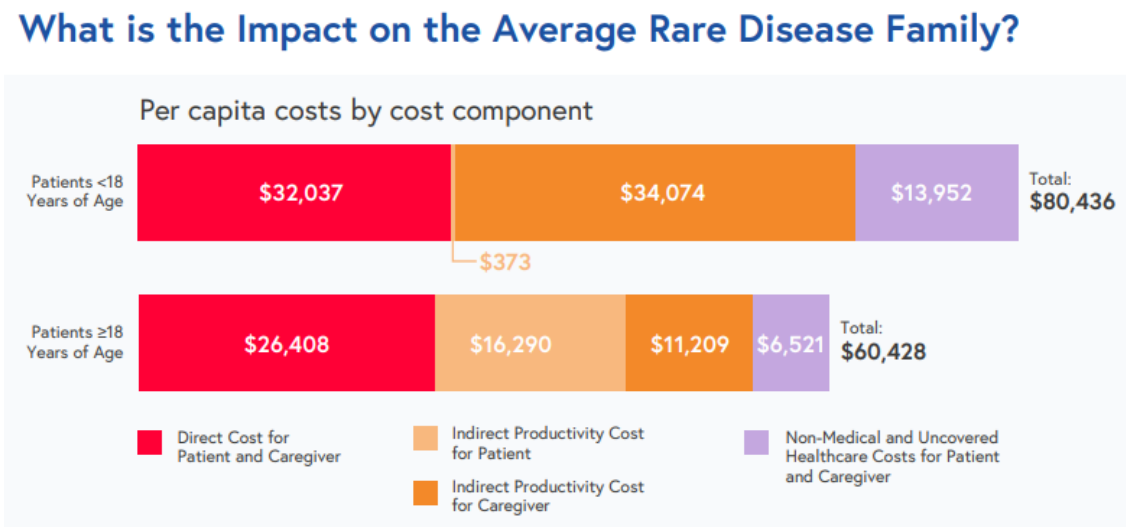


- Orphan Drug Act (1983) - encourage pharmaceutical developers to increase research efforts focused on treatments for rare diseases, specifically those for which a current drug treatment does not exist
  - Tax credits
  - Waiver of some typical approval fees
  - Extended market exclusivity period (7 years)

[a] RareX Power of Being Counted Report, June 2022

Rare Diseases

- In 2019, US costs for rare diseases = $966 billion[b]
  - Direct Medical Costs: $418 Billion[c]
  - Indirect Costs (Productivity Loss): $437 Billion[c]
  - Non-Medical and Uncovered Healthcare costs: $111 Billion[c]



[b] Government Accountability Office, GAO-22-105235, 18OCT2021

[C] Economic Burden of Rare Diseases in America Report, EveryLife Foundation
Yang etal. Orphanet J Rare Dis. 2022 Apr 12;17(1):163. doi: 10.1186/s13023-022-02299-5
https://everylifefoundation.org/wp-content/uploads/2022/04/Orphanet_Journal_of_Rare_Diseases.pdf

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Rare Diseases

- 95% of Rare Diseases communities have no FDA approved treatment
- **Roughly 80% of Rare Diseases are caused by genetic defect [d]**

[d] Fu etal. Rare diseases of epigenetic origin: Challenges and opportunities. Front Genet. 2023 Feb 6;14:1113086. doi: 10.3389/fgene.2023.1113086.

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Impact to Rare Disease Patients and Families

Clinical Trial Participation

- How will my family get to the clinical trials site, and afford to stay there as needed?
- How will I continue to participate when I return home?
- Will I be eligible for future clinical trials?

Receiving Gene Editing Product

- Will my employer find out I received this?
- Will I still be eligible to receive treatment if it didn't work (or work well)?
- How will we know if unintended changes were made to DNA?
- Who will be responsible for my care if there were unintended changes with negative consequences?

Q&A with Presenters