

# Facilitating Development of Gene Therapies for Rare Diseases

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Regulatory Education for Industry  
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# Learning Objectives



- ✓ Describe what is an 'individualized' (bespoke) gene therapy
- ✓ Describe the strategic objectives of the Bespoke Gene Therapy Consortium
- ✓ Describe the role of regulatory streamlining and global collaboration in development of gene therapies for rare diseases

# Definition of 'Rare'

Merriam-Webster dictionary:

- “Seldom occurring or found”,  
“Uncommon”

Definition of a rare disease in the U.S.:

- Affecting fewer than 200,000 people –  
about one in every 1,500 individuals

# Rare Diseases: Current State



- Over 10,000 rare diseases affecting a total of 25-30 million Americans; many more patients globally
- Significant unmet medical need

Having a rare disease is not so rare ...

# Rare Diseases: Significant Unmet Medical Need



- Many disorders are serious and life-threatening
- Many affect children resulting in significant morbidity and early death
- Approximately 60-70% are single-gene diseases that have the potential to be treated with gene therapy

# Bottom Line Up Front

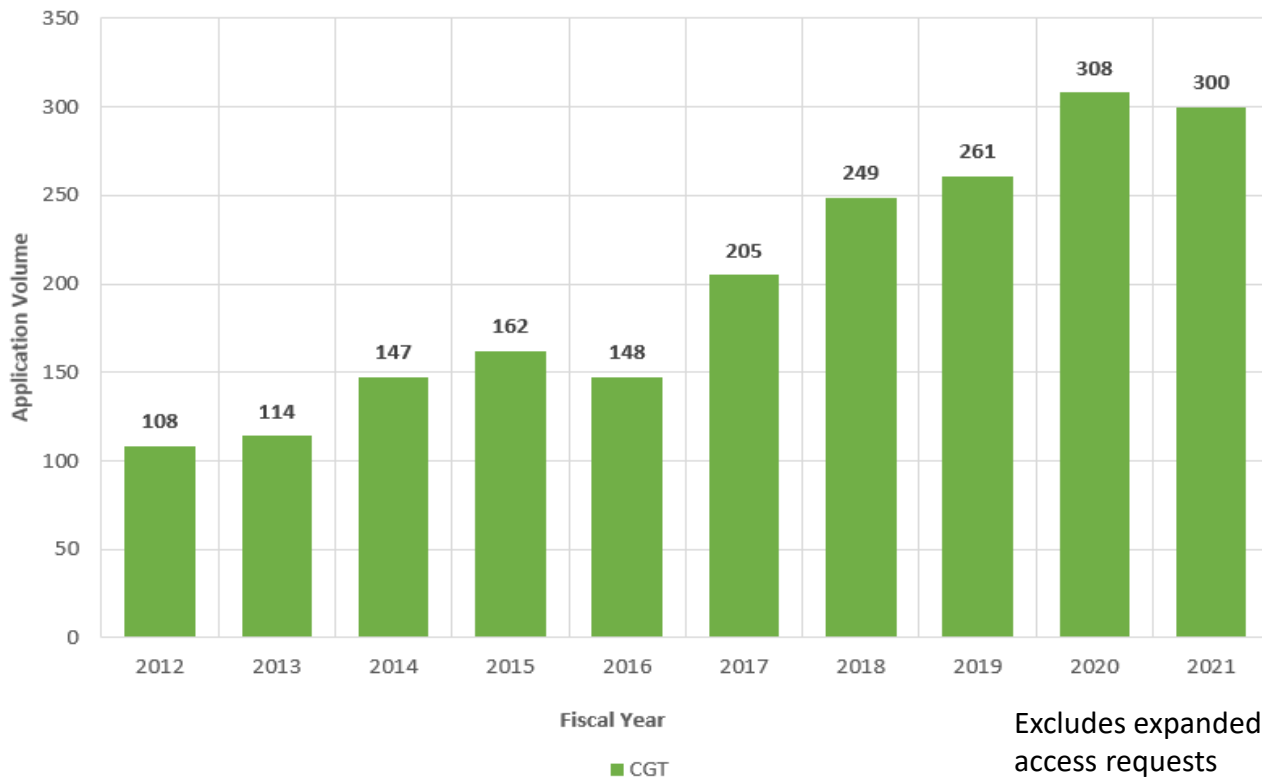


- Delivering safe and effective gene therapies to those in need should be a global priority to alleviate suffering from various serious diseases
- Fast growing area of research with gene therapies for many diseases, both common and rare, under clinical development

# Growth in Cell and Gene Therapy



## Original IND Submissions






Significant  
research  
investment  
in CGTPs

# U.S. Approved Gene Therapies



- Kymriah (2017)
- Yescarta (2017)
- Luxturna (2017)
- Zolgensma (2019)
- Tecartus (2020)
- Breyanzi (2021)
- Abecma (2021)
- Carvykti (2022)
- Zynteglo (2022)
- Skysona (2022)
- Hemgenix (2022)
- Adstiladrin (2022)
- Vyjuvek (2023)
- Elevidys (2023)
- Roctavian (2023)
- Lyfgenia (2023)
- Casgevy (2023, 2024)
- Lenmeldy (2024)
- Beqvez (2024)

-  Stem cell
-  T cell
-  Directly administered

Information on FDA website:

<https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products>



# What are Individualized Therapeutics?



Therapies developed for one or a very small number of patients, based on engineering a product aimed at the specific mechanism underlying a patient's (or small group of patients') illness.

# Examples of Individualized Therapeutics



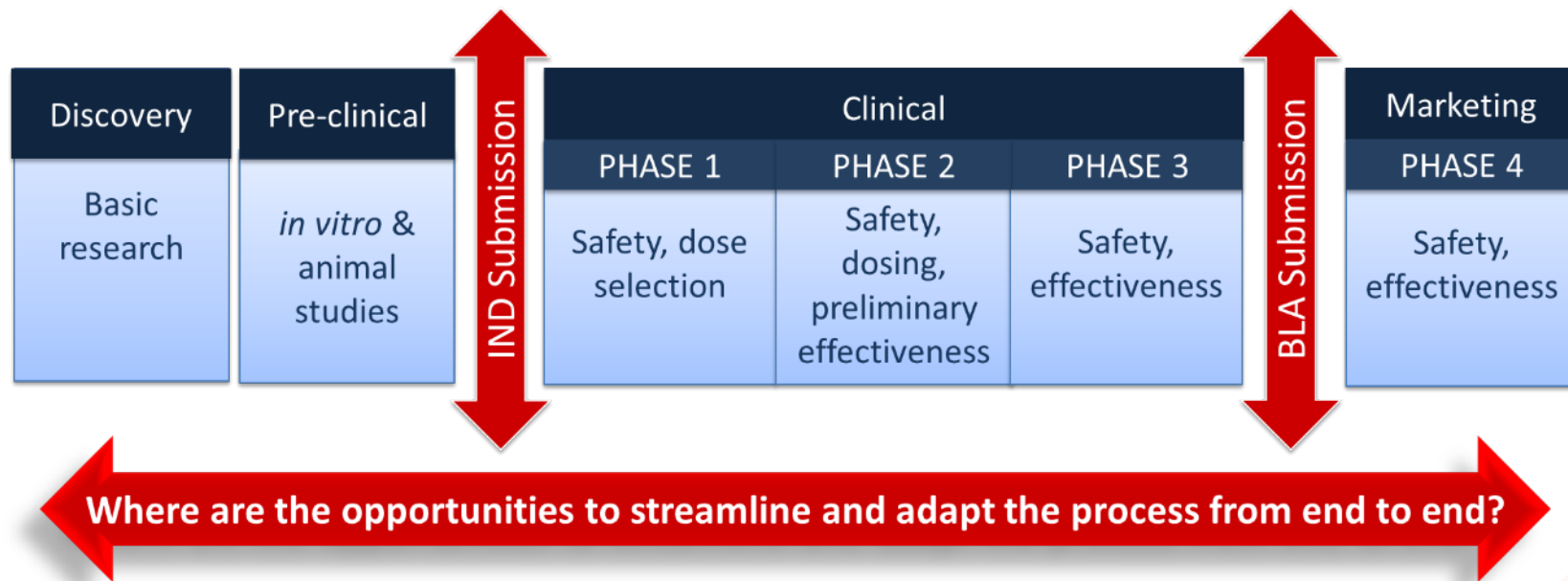
- Antisense oligonucleotides (ASOs)
- Directly administered gene therapy or gene editing for monogenic diseases
- Genetically modified cellular therapies
- Genetically engineered phages for multidrug resistant infection

# Examples of Individualized Therapeutics



- Antisense oligonucleotides (ASOs) (CDER)
- Directly administered gene therapy or gene editing for monogenic diseases (CBER)
- Genetically modified cellular therapies (CBER)
- Genetically engineered phages for multidrug resistant infection (CBER)

# Facilitate Development of Individualized Therapeutics



# Challenges of Individualized Therapies



Current manufacturing constraints present a “Goldilocks” phenomenon -- viable commercial solutions are not available for very small or large populations but do exist for mid-size indications.





# Bespoke Gene Therapy Consortium (BGTC)

# Accelerating Medicines Partnership: Bespoke Gene Therapy Consortium



- AMP-BGTC is a collaboration between
  - FNIH, NIH/NCATS & FDA/CBER (Public)
  - Industry & Non-profit organizations (Private)
- Precompetitive public-private partnership
  - Promote collaboration & information sharing
  - Stimulate innovation; facilitate access

# Accelerating Medicines Partnership: Bespoke Gene Therapy Consortium



Objective: Advance developing gene therapies  
for very small patient populations



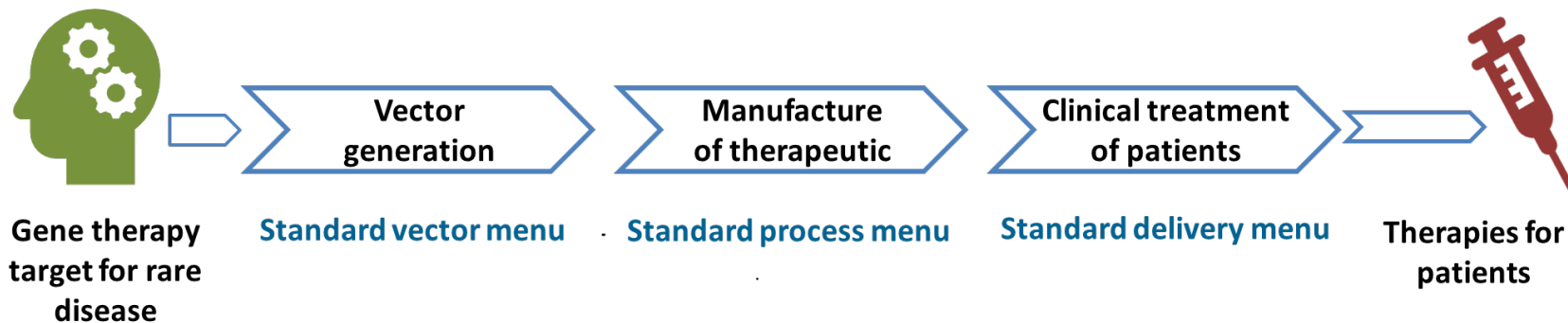


# BGTC “Proof of Principle” Pilot



- Pilot focuses on clinical trials for disorders that have such low prevalence that there is **no current commercial interest**
- **Streamline regulatory requirements** where feasible e.g., Establish Master File(s) for standard vector(s); leverage data, where appropriate
- Anticipate this **program will have broader impact** for common disorders with higher prevalence

# Bespoke Gene Therapy Consortium (Non-profit umbrella organization)



Streamline regulatory requirements to facilitate product development, where feasible  
e.g., Establish Master File(s) for standard vector(s); leverage data, where appropriate

All results from treatments are reported back to the consortium for iterative learning

# BGTC Pilot Program Design



- Leverage existing manufacturing capacity & experience
  - Industry partners or CDMOs will manufacture the gene therapies for the pilot using their standard processes
- Standardize testing where possible (e.g., vector quantity, potency)
- Studies will be conducted sequentially
  - Learnings can be incorporated into later trials

# USG Commitment to Publicly Share Information

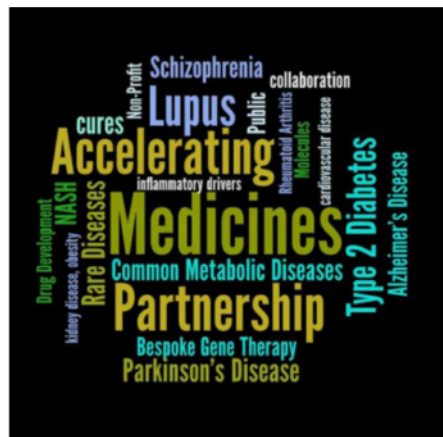


NIH will be the IND holder for the five clinical trials funded by the BGTC and has made the commitment to:

- Publicly share IND submissions and official FDA communications
- Place data from clinical trials in the public domain
- Develop BGTC “Playbook” – a guide for clinical development of AAV gene therapies



# FDA, NIH, and 15 private organizations join forces to increase effective gene therapies for rare diseases



The U.S. Food and Drug Administration, the National Institutes of Health, 10 pharmaceutical companies and five non-profit organizations have partnered to accelerate development of gene therapies for the 30 million Americans who suffer from a rare disease. While there are approximately 7,000 rare diseases, only two heritable diseases

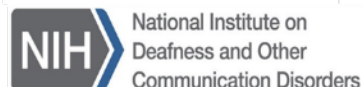
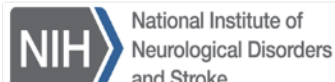
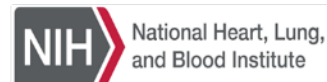
“By leveraging on experience with a platform technology and by standardizing processes, gene therapy product development can be accelerated to allow more timely access to promising new therapies for patients who need them most,” said Peter Marks, M.D., Ph.D., Director of the Food and Drug Administration (FDA)’s Center for Biologics Evaluation and Research. “FDA is committed to developing a regulatory paradigm that can advance gene therapies to meet the needs of patients with rare diseases.”

For Immediate Release: October 27, 2021

<https://www.fda.gov/news-events/press-announcements/fda-nih-and-15-private-organizations-join-forces-increase-effective-gene-therapies-rare-diseases>

The BGTC also will explore methods to streamline regulatory requirements and processes for the FDA approval of safe and effective gene therapies, including developing standardized approaches to preclinical testing (e.g., toxicology studies).

# BGTC: Resources from Public & Private Partners



**\$39.5M**  
Public commitments

**\$35.3M**  
Private donations  
**\$27.9M+**  
Private in-kind contributions



# Progress of BGTC Pilot (October 2021 – Present)

# BGTC Subteams



- Subteams consist of SMEs from BGTC member organizations; provide expert input into all aspects of the projects selected for the pilot
- Current BGTC subteams
  - Clinical
  - Manufacturing
  - Preclinical/Toxicology
  - Regulatory
  - Communications
  - Sustainability



# Disease Selection for the Pilot

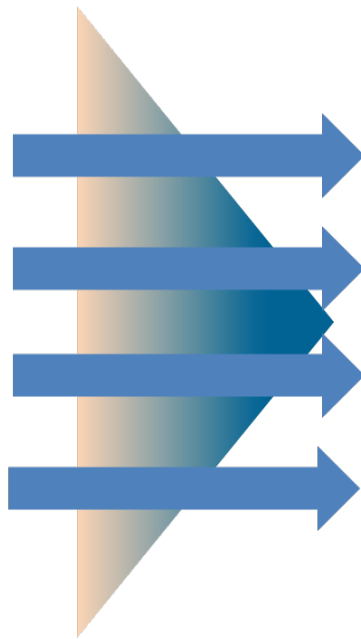


Thousands of  
Rare Diseases



## Submission of potential studies by:

- Academic centers
- Government investigators
- Patient groups
- Others ...

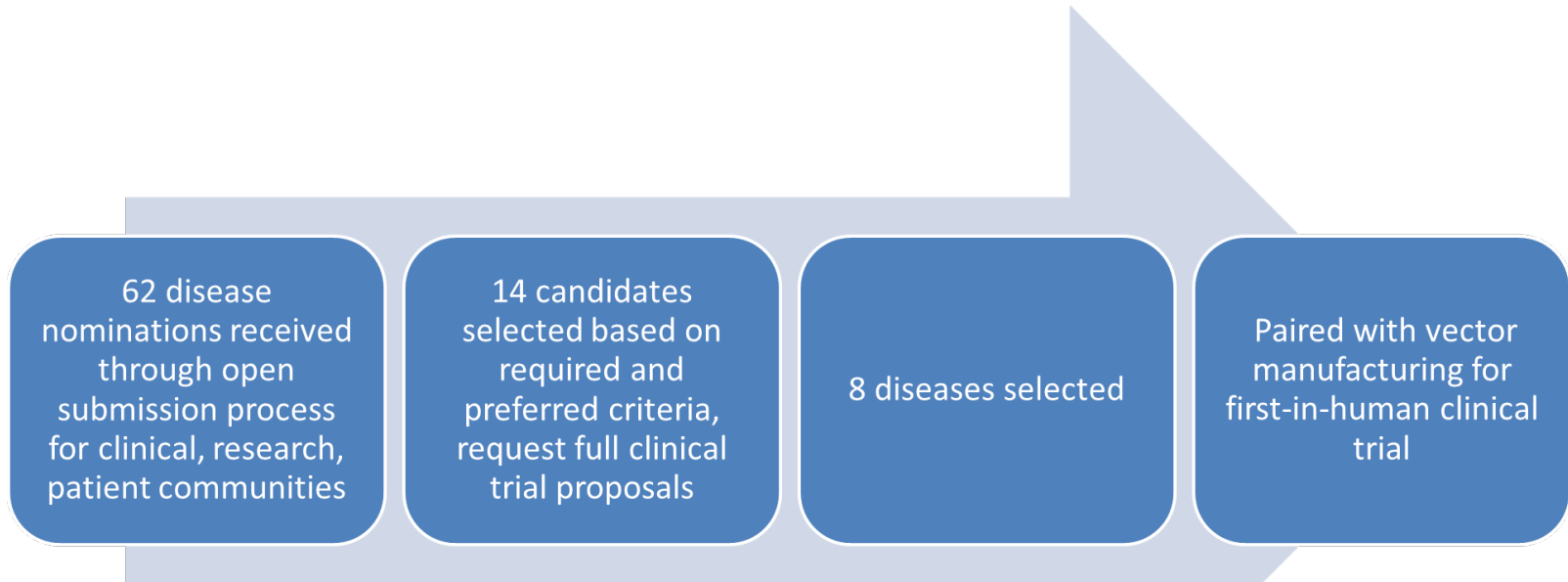


8 Diseases Selected

## Characteristics:

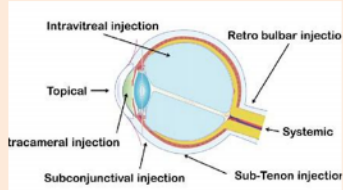
- Clear monogenetic cause that is amenable to AAV therapy
- Animal model available with relevant phenotype
- No commercial business case
- Sufficient information to run a successful clinical trial
- Manageable requirements for testing & follow up (i.e., short trial)
- Currently assembled patient group
- Others ...

# Comprehensive Process for Selecting Rare Diseases for BGTC Pilot Program\*



\* Selection process led by BGTC clinical subteam with input from preclinical/tox subteam

# Clinical Portfolio Approved by Steering Committee



## Ocular

**Congenital Hereditary  
Endothelial Dystrophy (CHED)**

**Retinal Degeneration (NPHP5)**

**Retinitis pigmentosa 45  
(CNGB1)**

## Neurological

**Multiple Sulfatase Deficiency**

**Charcot Marie Tooth disease  
type 4J**

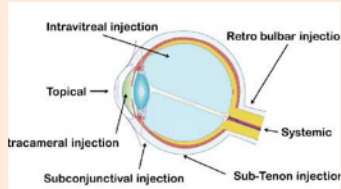
**Spastic Paraplegia type 50**

## Systemic

**Propionic Acidemia**

**Morquio A syndrome  
(Mucopolysaccharidosis IVA)**

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 CIRM  
funding

 NIH  
Clinical  
Center

# Additional BGTC Subteam Activities



## Manufacturing Subteam

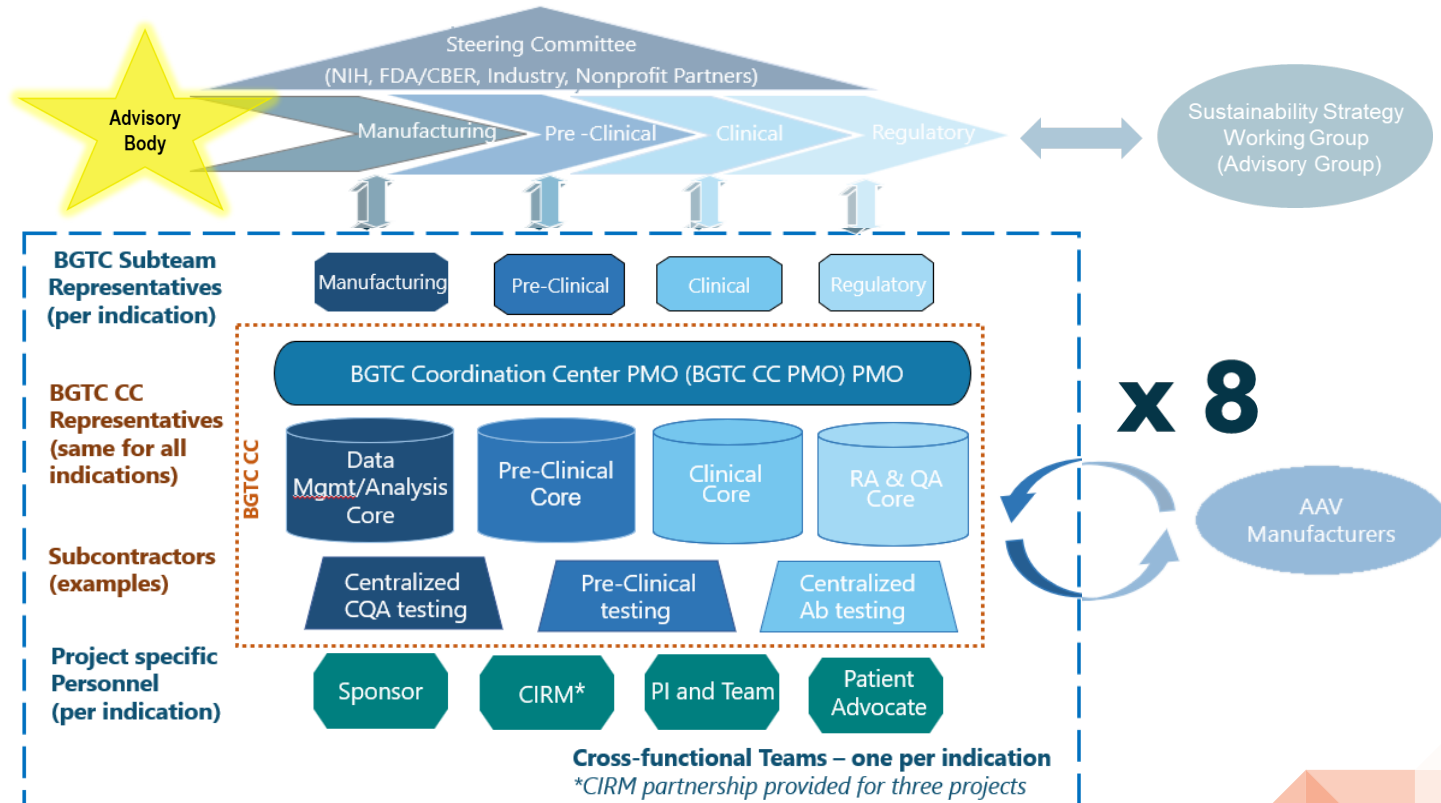
- Developed proposal for minimum set of Critical Quality Attributes (CQAs) for gene therapies for very small patient populations
- Meeting with CBER/OTP SMEs on 9/29/2022 (informal, non-binding)

## Preclinical/Toxicology Subteam

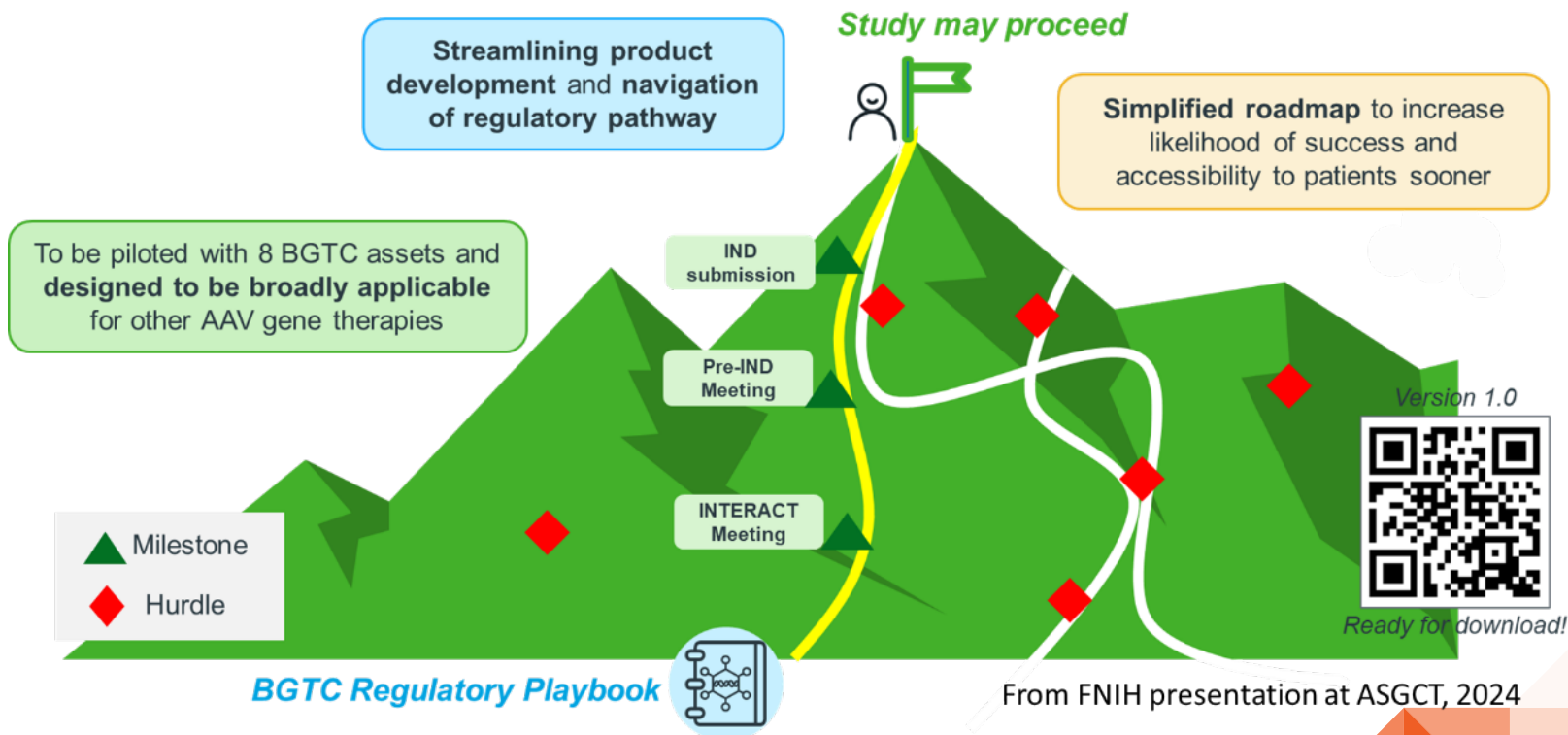
- Developed proposal for minimum toxicology testing for AAV gene therapies for very small patient populations (ocular, neurological, systemic)
- Meeting with CBER/OTP SMEs on 6/27/2023 (informal, non-binding)

Activities focused on streamlining testing & promoting platform approach for AAV gene therapies for rare/very rare diseases

# BGTC Cross-Functional Teams



# BGTC Playbook will Incorporate and Disseminate BGTC Learnings



# Regulatory Framework to Support Development of Bespoke Gene Therapies



# Important Considerations for Individualized Therapies



- Determine **quantity of supportive preclinical evidence** needed prior to patient treatment
- Production of **quality product** that is fit-for-purpose
- Understand **relevant disease-specific clinical information** to capture when patients are treated
- Additionally – need to find a **sustainable way to deliver these products** to individuals if the treatment shows clinical benefit (positive treatment effect)

# Potential for Regulatory Streamlining (Role of FDA)



- Master Files
- Leveraging data (based on past experience with the vector or similar gene therapy product)
- Adaptive clinical trial designs
- Pathway to licensure?



# Treating Diseases with Current Gene Therapy Technology



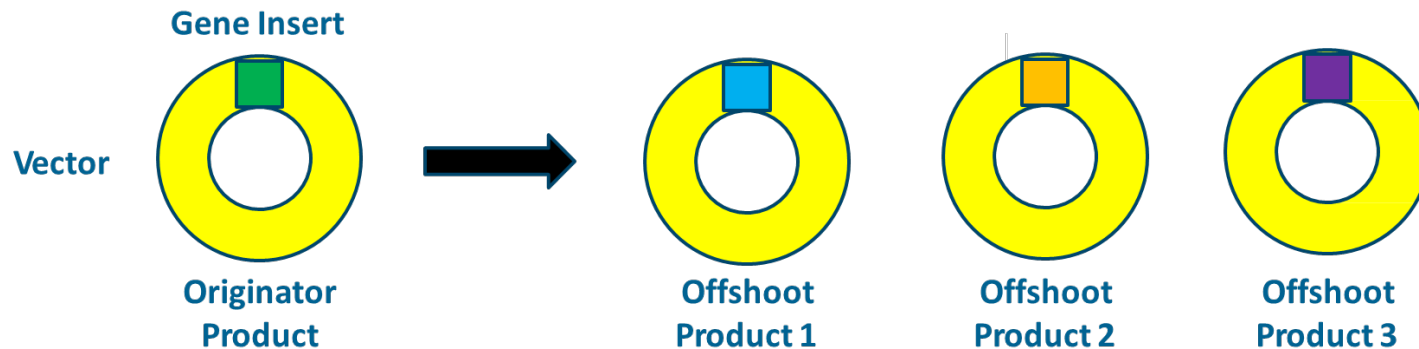
- Many gene therapies for rare disorders are produced as “one-offs” in academic laboratories or small corporate entities
- Current regulatory process does not leverage information to expedite the production of potentially transformative treatments



# Treating Diseases with Current Gene Therapy Technology

- A regulatory program that allows **leveraging non-clinical and manufacturing data** from one application for another can facilitate product development and promote access
  - Concept of **originator product** and **offshoot products**

# Advancing the Development of Bespoke Therapies



Collaborative effort by FDA with relevant stakeholders, including industry partners, to **develop the regulatory framework to leverage existing knowledge** to advance development of bespoke gene therapies

Mission:



**LEAVE  
NO ONE  
BEHIND**



# Global Collaboration and Promoting Regulatory Convergence



# Global Regulatory Convergence: High Income Countries



- Robust commercial viability currently requires ~ 100 to 200 gene therapy treatments per year
- Any one country may not have enough patients to make products for very rare diseases commercially viable
- However, marketing across high-income countries could promote commercial viability

Mission:



LEAVE  
NO ONE  
BEHIND

# Global Regulatory Convergence: Low and Middle Income Countries



- Patients in LMICs may benefit most from gene therapy as they often lack access to supportive care
- Gene therapy that provides long-term benefits or potentially a cure can be transformational
- Regulatory harmonization could facilitate commercial development in HICs; approvals in HICs could be leveraged to provide patient access in LMICs (through reliance)



# Practical Next Steps (1)



- Encourage sponsors with global development programs that include the U.S. to invite other regulators to early-stage meetings (e.g., INTERACT, pre-IND)
  - **Collaboration on Gene Therapies Global (CoGenT Global) Pilot**

# Practical Next Steps (2)



- Actively promote harmonization of regulatory approach in high income countries (US, EU, Japan, Canada, others)
  - Dialogue with regulatory counterparts (EMA, PMDA, HC etc) and collaborations through ICH & other international venues

# Practical Next Steps (3)



- Promote establishment of a ‘fit-for-purpose’ regulatory framework for cell and gene therapies in LMICs
  - World Health Organization (WHO) document on considerations for a regulatory framework for cell, tissue and gene therapies developed and adopted as WHO international standard  
<https://www.who.int/publications/m/item/considerations-in-developing-a-regulatory-framework-for-human-cells-and-tissues-and-for-advanced-therapy-medicinal-products>  
(March, 2023)
  - Continue collaboration with WHO to support LMICs in implementing the WHO ‘considerations’ document and strengthening regulatory capacity in this area

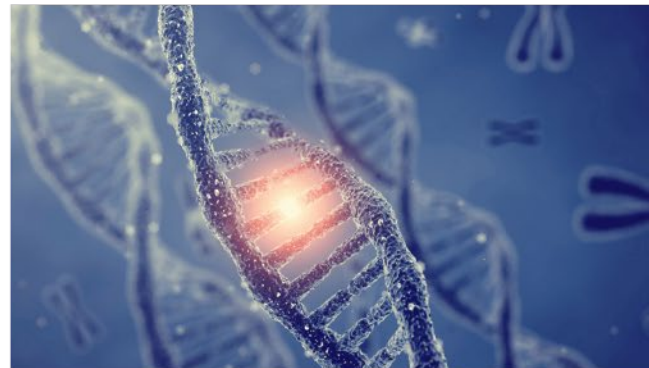
# Summary



- Delivering safe and effective gene therapies to those in need should be a global priority to alleviate suffering from various serious (often rare) diseases
- Global regulatory convergence in high-income countries could promote commercialization and pave the way for the use of gene therapies in low-and-middle-income countries

“CBER aims to make 2024 a breakout year addressing key challenges to the development of cell and gene therapies, especially for rare disorders.”

Dr. Peter Marks, CBER Director



# Challenge Question #1



**An ‘individualized’ therapeutic is a treatment designed for:**

- A. Only one patient
- B. For all patients with the same rare disorder
- C. For one or a few patients with the same rare monogenic disorder
- D. For a class of rare diseases e.g., all monogenic neurological disorders

# Challenge Question #2



**Which of the following actions will facilitate development and access to gene therapies for rare diseases?**

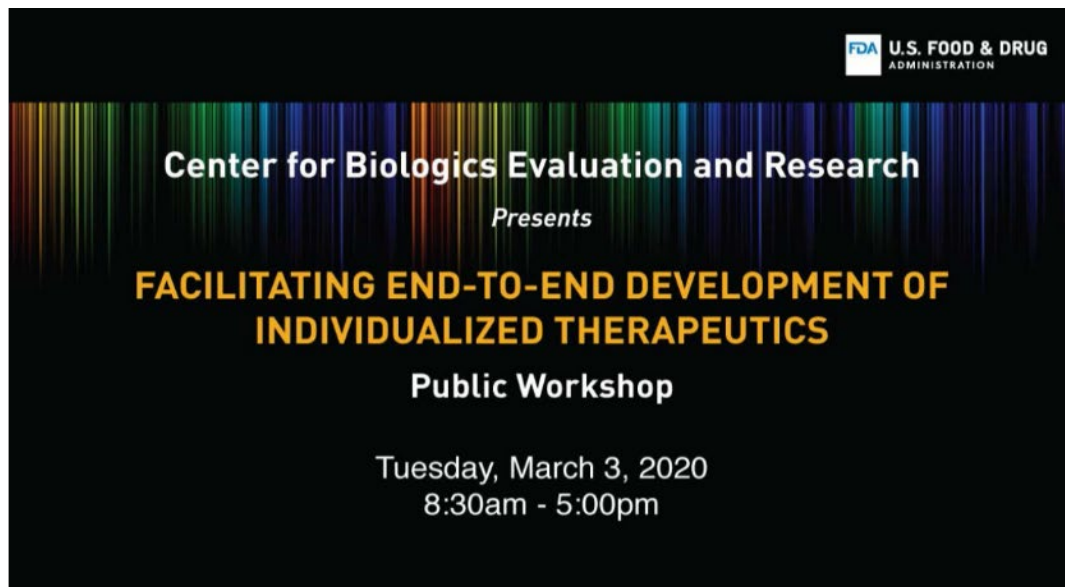
- A. Regulatory streamlining and harmonization of requirements
- B. Collaboration among regulatory authorities including collaborative reviews
- C. Establishment of regulatory framework in LMICs which includes legal authority to practice reliance
- D. All of the above

# Resources

- FNIH website: <https://fnih.org/our-programs/AMP/BGTC>
- NCATS website: <https://ncats.nih.gov/programs/BGTC>
- BGTC Playbook: [BGTC Regulatory Playbook Version 1.0](#)
- Publication in Nature Reviews Drug Discovery (Feb., 2024):  
'The Bespoke Gene Therapy Consortium: Facilitating development of AAV gene therapies for rare diseases'  
<https://www.nature.com/articles/d41573-024-00020-8>



# Additional Resource



Sessions on (1) Manufacturing; (2) Pre-clinical (Tools for Safety Testing and Development); (3) Clinical and; (4) Products to Patients (Access)

Link to workshop: <https://www.fda.gov/vaccines-blood-biologics/workshops-meetings-conferences-biologics/facilitating-end-end-development-individualized-therapeutics-03032020-03032020>

# A Few Closing Thoughts ...



# “It takes a village ...”



Rare diseases are not so rare ...

Significant unmet medical need in U.S. and globally

Collaboration among many stakeholders needed to advance research, manufacturing, clinical development, and patient access

# We all have a role ...



- Academia
- Industry
- Government
- Non-profit groups
- International organizations
- Patient advocacy groups
- Payers

Time to act is now!  
Patients are waiting