U.S. FOOD & DRUG ADMINISTRATION

Annual Patient Engagement & Regenerative Medicine Meeting: An FDA CBER Workshop for Patient Advocates

Tuesday, May 24, 2022, 11:00 a.m. – 3:00 p.m. ET

Office of Tissues and Advanced Therapies (OTAT)
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

Moderated by:

Anne Rowzee, PhD
Associate Director for Policy, OTAT, CBER, FDA

Workshop Agenda

11:00 a.m.	Welcome Session
11:05 a.m.	Natural History Study Overview
11:45 a.m.	Panel Discussion – Perspectives from Patients and Advocates
1:00 p.m.	Lunch
1:30 p.m.	Panel Discussion – How FDA & Other Organizations are Supporting Natural History Studies
2:30 p.m.	Closing Remarks

Virtual Meeting Considerations

- The webinar will be recorded and available online after the event.
- Closed captioning is available in Zoom.
- Use the Q&A box to submit questions throughout the event.
- Use the chat box to share general comments and report technical difficulties.

RegenMedEd Series

- OTAT's event series about regenerative medicine
- Goals of the RegenMedEd Series:

Discuss foundational information about regenerative medicine therapies, including gene therapy and cell therapy

Explore opportunities to engage with FDA and advance regenerative medicine research and drug development

Hear from FDA, patients, advocates, researchers, and other important stakeholders about their experiences

Session 1:
Natural History Study Overview

Speaker:
Wilson W. Bryan, MD
Director
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

Our 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.

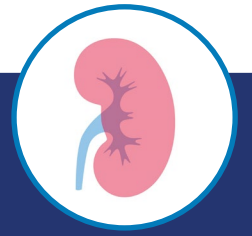
Regenerative Medicine Therapies

- Regenerative medicine involves using stem cells, engineered biomaterials, gene editing, and other technologies to repair or replace damaged cells, tissues, or organs.
- Types of regenerative medicine therapies (RMTs):

Gene therapies (including gene editing)

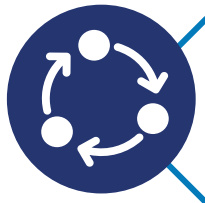
Cell therapies

Tissues and tissue engineering products



Xenogeneic cell products

FDA's Role in Regulating RMTs



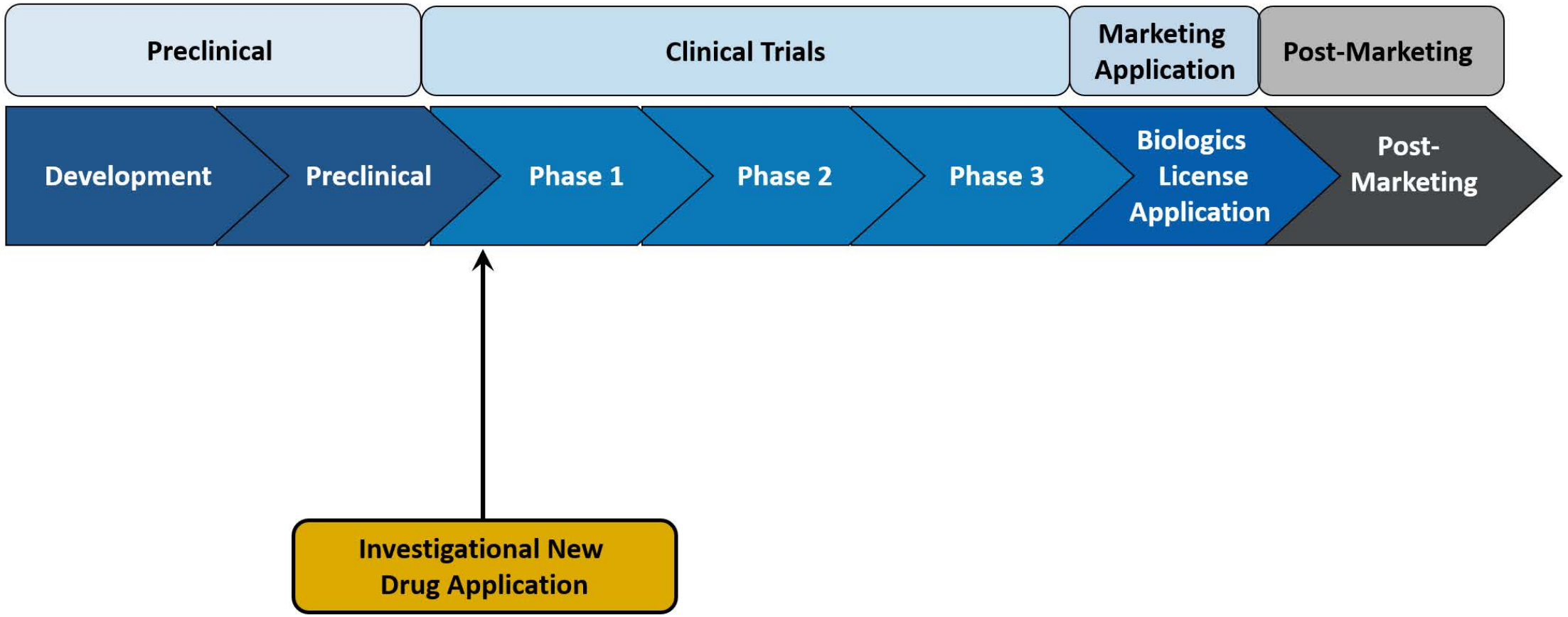
Regulate products over their entire lifecycle—during development and after approval

Provide oversight of clinical trials to protect patient safety and rights

Advance development by providing advice and education to product developers, including academicians and industry

Engage stakeholders to facilitate development of innovative products that meet patient needs

Drug Development Overview



Rare Diseases and Gene Therapy

80% of rare diseases are caused by a single-gene defect.

FDA has approved two gene therapies for single-gene disorders.

1271 investigational new drug applications for ongoing gene therapy clinical trials.

Patient participation in clinical research is critical.

How Patients Can Advance Research & Development

Natural History Studies: *Defined*

- A study that follows a group of people over time who have, or are at risk of developing, a specific disorder.

- A natural history study collects data in order to understand the disorder. Information may include:
  - Age
  - Diagnosis
  - Symptoms
  - Effect on quality of life
  - Test results
  - And more

Natural History Studies: *Purpose*

- Identify demographic, genetic, environmental, and other variables that correlate with disease development and outcomes.
- Better characterize the disease and the patient population.
- Clarify the impact on the lives of patients and their families.
- Collect patient-reported outcomes and other clinical outcomes that are specific to the disease.
- Inform the clinical drug development process.

Natural History Studies: *Types*

Retrospective versus prospective natural history studies: Both rely on data collected from patient visits.

Retrospective: **Past**	• Often a first step in describing progression • Data are collected from existing medical records
Prospective: **Ongoing**	• Establish definitions and data to be collected ahead of time • Data are collected from ongoing patient visits

Natural History Studies: *Types, continued*

Cross-sectional versus longitudinal natural history studies: Both rely on data collected from a cohort.*

Cross-sectional	• Data collected over a specified, limited time period
Longitudinal	• Data collected at various time points over a long period

**Can be either retrospective or prospective*

Natural History Studies: *Protocols*

FDA recommends that natural history study protocols specify, in detail:

- Who should be included in the study (inclusion and exclusion criteria)
- What information is to be collected
- When the data will be collected (if prospective)
- How data are to be collected and analyzed

Natural History Studies: *Drug Development*

- The FDA does not require that natural history studies be conducted for drug development programs.

- To be applied in a drug development program:
  - The FDA recommends an early evaluation of the depth and quality of existing natural history knowledge.
  - Most useful if conducted and data are available prior to drug development program.

- Data should be collected for a sufficient duration to capture clinically meaningful outcomes and determine variability in the course of the disease.

Natural History Studies: *Benefits to Disease Research in Clinical Development*

These studies can inform important aspects of drug development:

1. Refines the target patient population
2. Identifies and develops clinical outcomes
3. Identifies and develops biomarkers
4. Informs design of future clinical trials
5. Serves as external control (in limited circumstances)

Natural History Studies: *Purpose in Rare Disease Research*

- The progression of rare diseases is often poorly described.
- Natural history data can be critical for drug development.
- When knowledge about the disease is insufficient to guide clinical development, a natural history study may help in designing an efficient drug development program.

Enhancing Collaboration

There are many ways stakeholders can work together to advance regenerative medicine; FDA encourages:

Drug developers to invite patients / advocates to their meetings with OTAT

Patient groups to take on natural history studies and patient registries

Patient groups to work together

Groups to begin collaboration early

Contact Information

Wilson W. Bryan, MD

Director

Office of Tissues and Advanced Therapies

Center for Biologics Evaluation and Research

U.S. Food and Drug Administration

wilson.bryan@fda.hhs.gov

Contact Information, continued

- **Regulatory Questions:**
  - OTAT Main Line – 240 402 8190
  - Email: OTATRPMS@fda.hhs.gov and Lori.Tull@fda.hhs.gov
- **OTAT Learn Webinar Series**
- **CBER website**
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.hhs.gov
- **Follow us on Twitter**

FDA Headquarters

Break

11:40 a.m. to 11:45 a.m. ET

Stay tuned! Our next session will begin at 11:45 a.m. ET.

Session 2:
Perspectives From Patients and Advocates

Moderator:

Karen Jackler, MPH
Patient Engagement Program Manager
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

Meet Our Panelists

Leah Schust Myers
Founder, Executive Director
FamilieSCN2A Foundation

Amanda and Bailey Regalado
Type 2/3 New Family Representatives, Gaucher Community Alliance

Bradley Williams, PhD
Director of Research & Diagnostic Innovation, Jain Foundation

Bruce Marshall, MD
Executive Vice President and Chief Medical Officer, Cystic Fibrosis Foundation

SCN2A RELATED AUTISM & EPILEPSY

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FDA CBER Patient Engagement Workshop

May 24, 2022

Conflict of Interest Disclosure

I have nothing to disclose.

Who We Are

WE ARE AN ORGANIZATION CREATED BY PARENTS OF CHILDREN DIAGNOSED WITH RARE FORMS OF EPILEPSY AND AUTISM AS A RESULT OF A CHANGE IN THE SCN2A GENE.

Vision

TO FIND EFFECTIVE TREATMENTS AND A CURE FOR SCN2A-RELATED DISORDERS.

Mission

TO IMPROVE THE LIVES OF THOSE AFFECTED BY SCN2A-RELATED DISORDERS THROUGH RESEARCH, PUBLIC AWARENESS, FAMILY SUPPORT AND PATIENT ADVOCACY.

Values

URGENCY
INTEGRITY
COLLABORATION
INCLUSION

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Meet the Team

Executive Committee

Leah Myers,
Executive Director

Carla Forbes,
Admin Manager

Jennifer Burke,
President

Mery Oman,
Vice President

Board of Directors

Michelle Lewis

Will Hutson

Shawn Egan

Roger Premo

Michael Vasey

Catalina Betancur

Emily Park

Maura Bragg

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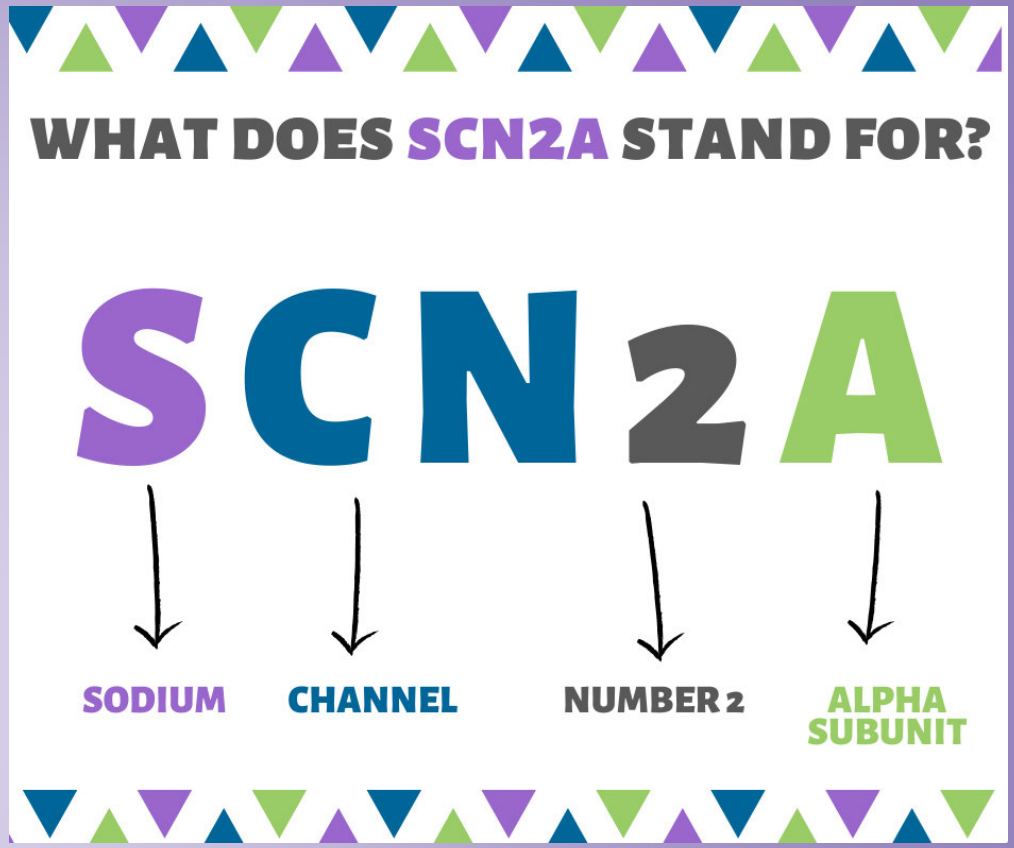
SCN2A-related disorders

- Leading single-gene cause of neonatal-onset seizures and autism spectrum disorder
- Diagnosed exclusively through genetic testing
- Average time to diagnosis is 5 years, much longer in underserved communities
- Precision treatments mean nothing without precision diagnostics



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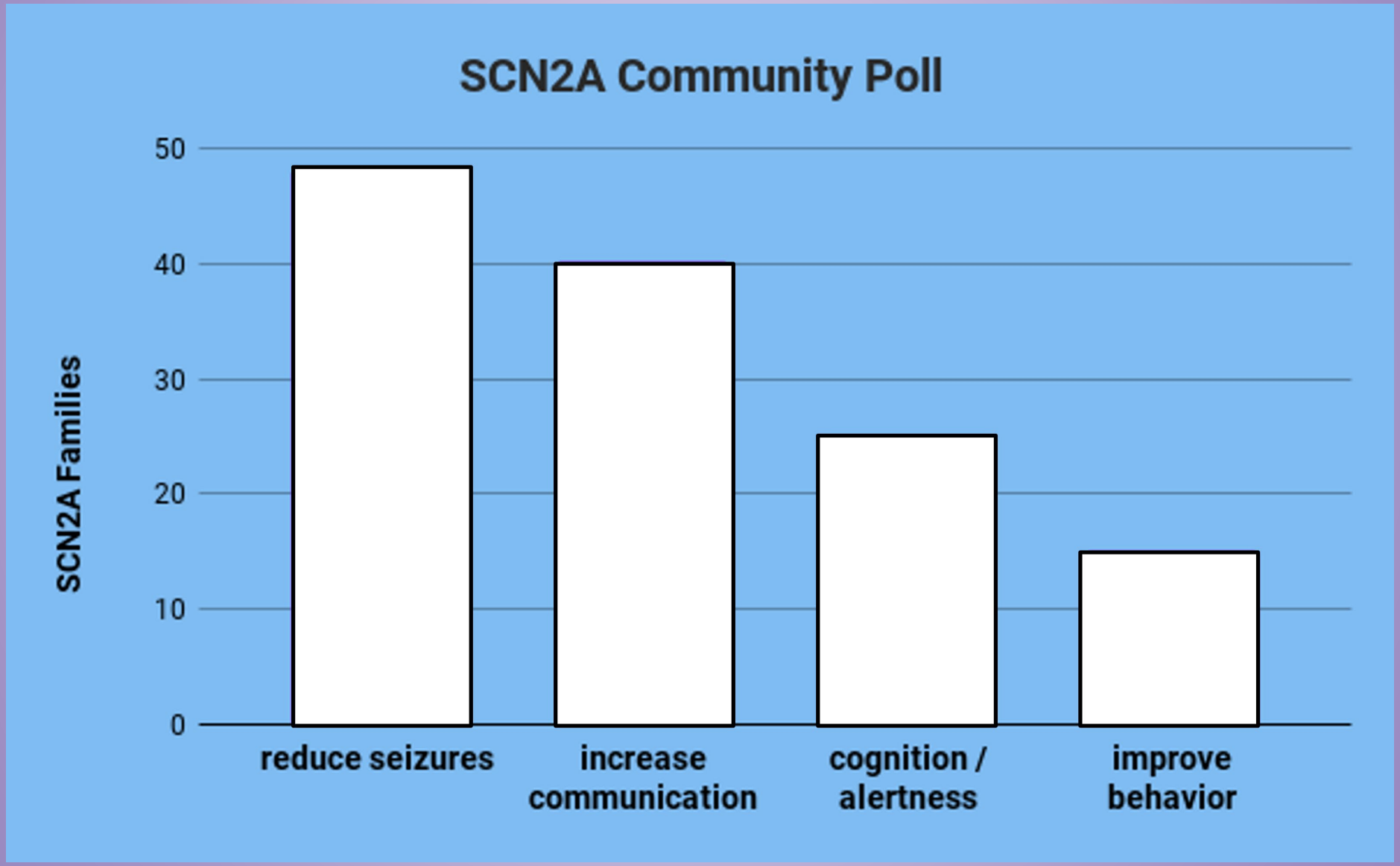
SCN2A VOICES Annual Campaign

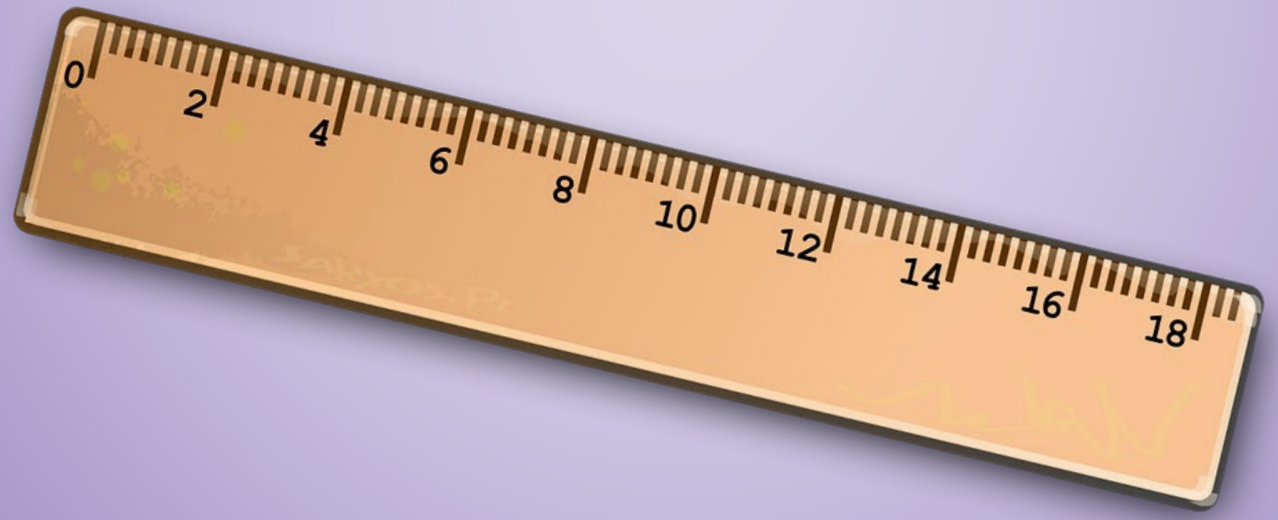



What is important to US (the patients and caregivers)



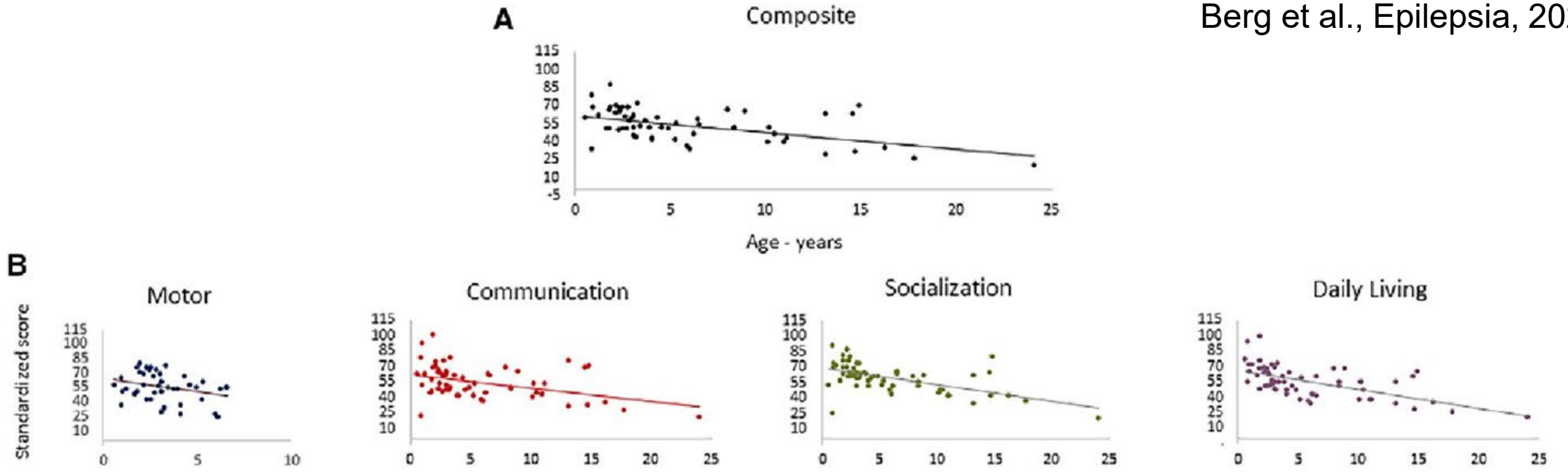
How do you measure improvement in a clinical trial?

- What exactly needs to be measured?
- What does the instrument actually measure?
- Is it appropriate for our severely affected group?



What is already out there

- Standardized scores decrease with age—cannot distinguish why
  - Regression?
  - Plateauing?
  - Slow acquisition of skills?



Berg et al., Epilepsia, 2020

New or adapted?

Create new measurement tools?

- Work
- Time
- Money

OR—

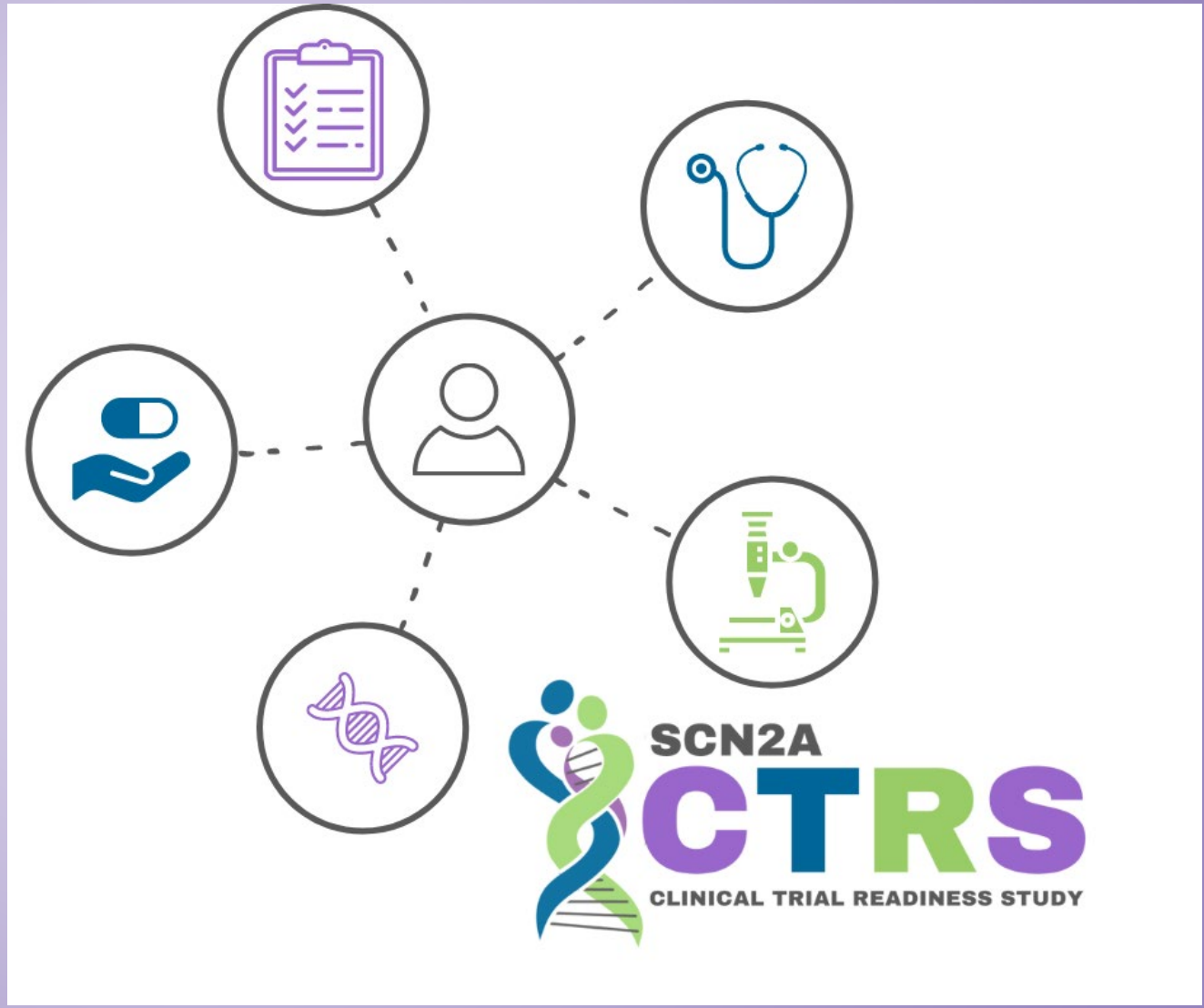
- Understand the population
- Adapt already validated measurement tools

SCN2A: Clinical Trial Readiness Study (CTRS)

This study will provide information on the reliability of specific measurements over a short period of time and the rate at which they change over time in an individual child.

Early data is showing Vineland III is potentially useful, as it has separate expressive and receptive scales.

Also, the CSBS captures social behavior and communication together, with very little floor/ceiling effect.



SCN2A-related disorders defined

- **1,000+** self-identified patients in 2021
- Estimated incidence: 1/9,000–1/10,000
- Diagnosis can be made only through genetic testing
- Treatment with sodium channel blockers for GoF variants has shown to be most useful
- No treatment for LoF
- Severe, life-limiting comorbidities, including:
  - Refractory Epilepsy
  - Autonomic Dysfunction
  - Cortical Visual Impairment
  - Gastrointestinal Dysfunction (reflux & constipation)
  - Movement Disorders (chorea, ataxia, dystonia)
  - Neuropathic Pain
  - Sleep Disorders
  - Urology Problems

SELF-CARE


5% dress themselves


21% use spoon and fork


5% brush own teeth


9% wash and dry their hands


12% drink from a cup


22% use a touchscreen device


14% scribble or write with crayon


5% are completely ***independent*** for toilet use

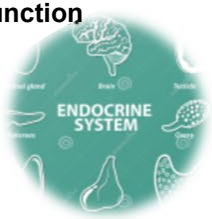
COMMON MEDICAL CONDITIONS

20% reported conditions affecting the lungs
These were related to low muscle tone, aspiration and tracheostomies

Dental

13% Teeth grinding
11% Late baby teeth

18% reported endocrine dysfunction
9% precocious puberty



Musculoskeletal

20% Dystonia
38% Hypotonia
17% Spasticity
23% Scoliosis

Vision

71% had vision/eye concerns
- **41% Cortical-visual impairment**
- **13% Difficulty judging distance, depth, visual-motor impairment**

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Learning more

EATING

44% are completely dependent on a caregiver for feeding

Feeding tube

20% Exclusively G-tube fed

9% Partially G-tube-fed

Can drink or eat these foods with no difficulty*

60% water

66% solids (apple sauce)

57% Bite-sized soft food like piece of bread or banana

46% Bite-sized crunch food like crackers

23% Bite-sized piece of chewy food like meat

20% Bite into a crispy food like an apple

*Non G-tube dependent only

LABOR – DELIVERY – FIRST MONTH

23% - pre-term

35% - complications during labor & delivery

22% - emergency c-section

53% - evaluated & treated for serious condition in neonatal period

32% problems feeding

9% failure to thrive

20% jaundice

12% breathing problems/apnea

16% encephalopathy

34% neonatal epilepsy

40% admitted to NICU

25% NICU admission>=1 month

MOTOR

75% Moderate to severe gross motor delay

21% walk outside independently for distances

39% 2y and older depend on a mobility device for any distance

- Cannot control head
- Cannot sit independently
- Have to be lifted or hoisted

18% cannot grasp objects with their hands

12% pick up raisin with thumb and forefinger

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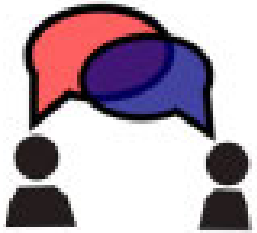
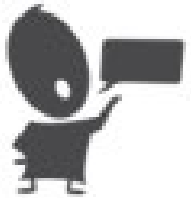
COMMUNICATION

89% Moderate to severe language delay



72% inconsistently or rarely communicate even with people they know (e.g. family)



29% speak a few or more words
16% speak as their primary form of communication
15% communicate by sign or device only
56% have no symbolic language

15% use >100 words/signs/symbols
8% combine 3+ words into sentences
23% understand >100 words/signs/symbols

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Our impact is evolving

- We are most proud of OUR COMMUNITY!
  - Education, financial, and emotional support
- 2021 was the year of the VOICE
  - FDA listening session
  - Launched Clinical Trial Readiness Study
- 2022 is the year for Building Towards a Cure
  - Clinical trials beginning
  - Scheduling a patient-focused drug development (PFDD)

2021 VISION MISSION VOICE

In summary

- Non-seizure outcomes are critical to clinical trial readiness for rare neurodevelopmental disorders, such as SCN2A
- Rare diseases—rare outcomes
    - Not meaningfully assessed with instruments standardized for the typical population
- Alternative approaches are promising
    - Growth scores
    - Adapted
    - Out of range
- Full understanding of the disease and the drivers of outcomes is critical


Thank You!

Meet Our Panelists

Leah Schust Myers
Founder, Executive Director
FamilieSCN2A Foundation

Amanda and Bailey Regalado
Type 2/3 New Family Representatives, Gaucher Community Alliance

Bradley Williams, PhD
Director of Research & Diagnostic Innovation, Jain Foundation

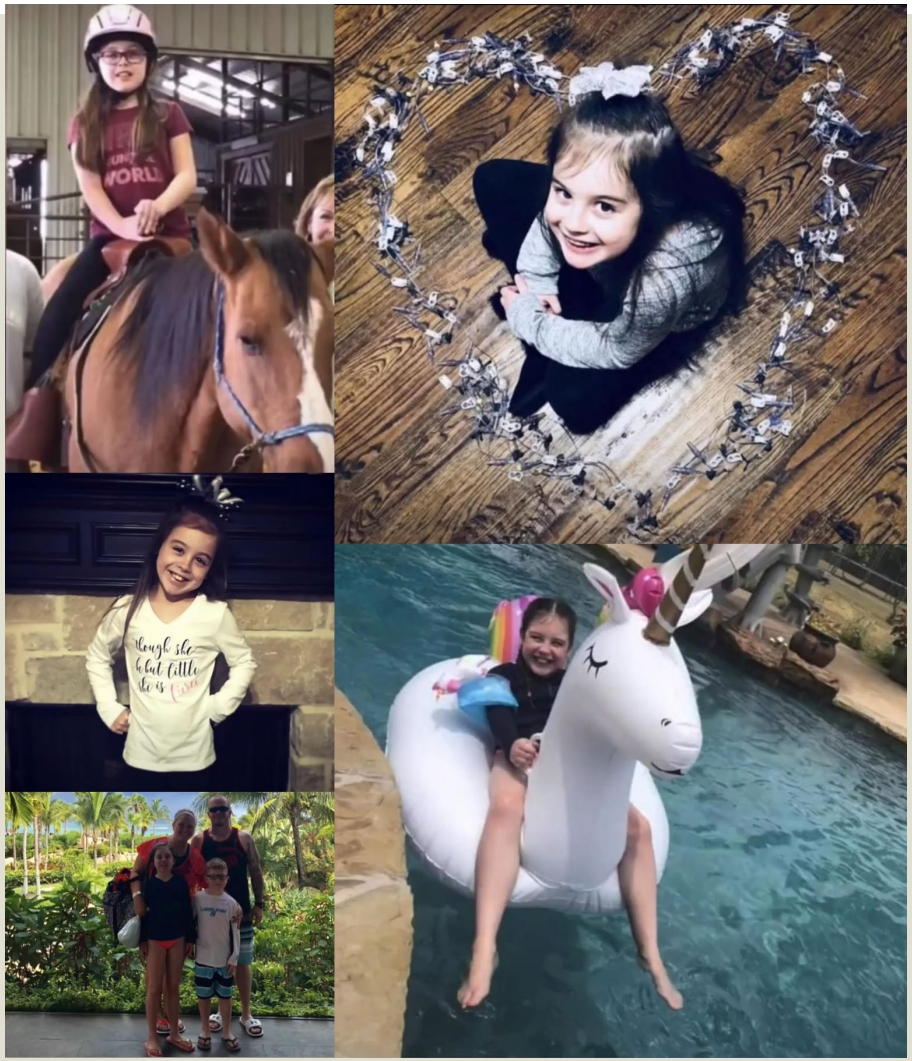
Bruce Marshall, MD
Executive Vice President and Chief Medical Officer, Cystic Fibrosis Foundation

Amanda and Bailey Regalado

I have nothing to disclose.

GAUCHER COMMUNITY ALLIANCE

Bailey Regalado (Age 13)



Hometown: Midlothian, Texas

Hobbies/Interests: Horse riding, dogs

Dreams for the Future: Hopes for a cure, easier access in the U.S. to necessary medications, and trade in port/weekly infusions for a pill

GAUCHER COMMUNITY ALLIANCE

Bailey Regalado (Age 13)

Diagnosis: Neuronopathic Gaucher disease

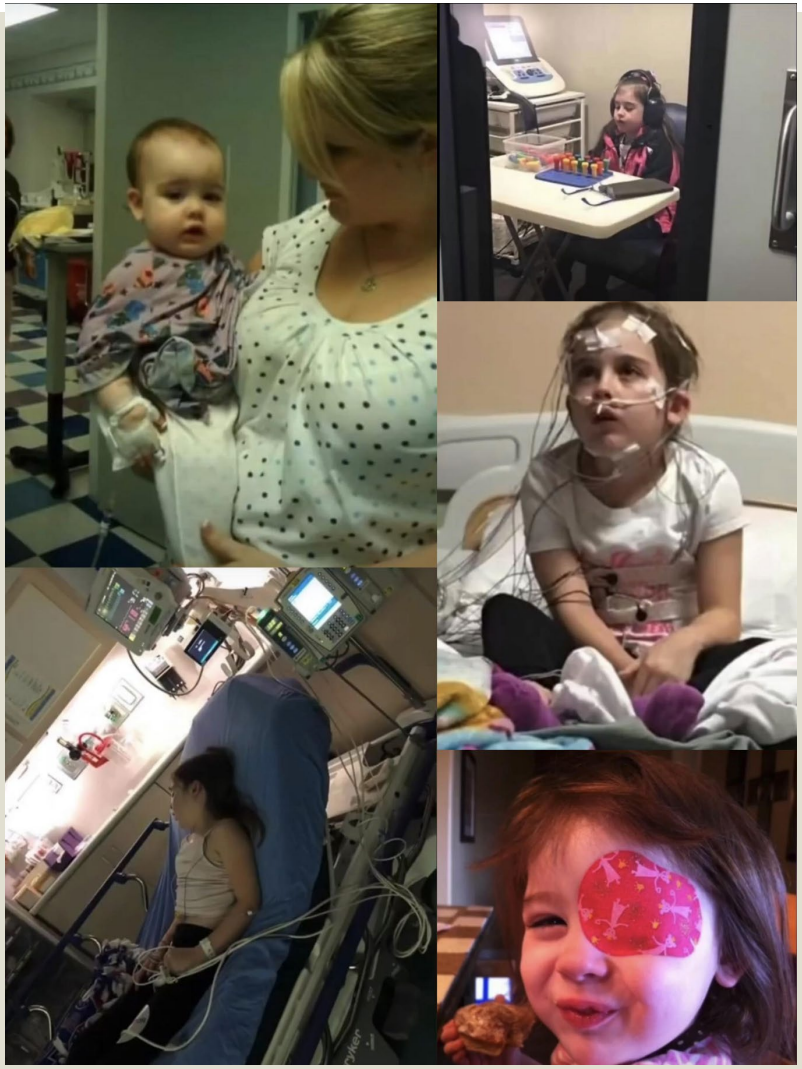
Age of Diagnosis: 10.5 months

Medical History:

- 3 ports placed for infusions
- Plate/screw implants on right side of hip
- 2 strabismus repair surgeries
- Tonsil and adenoid removal
- Cochlear implant surgery

GAUCHER COMMUNITY ALLIANCE

Bailey Regalado (Age 13)



Symptoms:

- Enlarged spleen and liver
- Moderate to profound hearing loss in both ears
- Cognitive impairment
- Epilepsy
- Bone fragility
- Frequent hospitalization due to respiratory illness
- Exhaustion
- Avascular necrosis in right hip

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Executive Vice President and Chief Medical Officer,
Cystic Fibrosis Foundation

Brad Williams, PhD

Director of Research, Jain Foundation

Living with Dysferlinopathy, aka limb-girdle muscular dystrophy type 2B/R2

Disclosures:

- Employee of the Jain Foundation
- The Jain Foundation, and I personally, are entitled to receive contingent payments from Sarepta Therapeutics based on drug commercialization milestones.

What is dysferlinopathy?

- Autosomal recessive type of muscular dystrophy
- Typical onset 15-30 years age
- Estimated 2,000-3,000 patients in the United States

Clinical Outcome Study in Dysferlinopathy (COS)

- 190+ participants, all genetically diagnosed with LGMD2B/R2
- 15 clinical centers in 8 countries
- 2013-2018—each participant followed longitudinally 3-5 years (6-8 visits)
- Several outcome measures evaluated for use in clinical trials
- 11 papers published (so far) on COS findings

Clinical centers located in California, Missouri, North Carolina, Ohio, and Maryland in the United States and in Australia, France, Germany, Italy, Japan, Spain, and the UK.

Findings and Benefits of COS

- Identified best outcome measure (“NSAD” adapted from DMD, now used in clinical trials in other LGMD subtypes)
- Identified:
  - Which patients will be most sensitive to detecting a treatment effect
  - Number of participants needed for a trial
- “Dress rehearsal” for an interventional trial
  - Familiarized clinicians with the disease, evaluation methods, and working together
- Learnings about the disease are informing the development of a standard of care

Start your natural history study *before* there's a treatment to test in a clinical trial—otherwise you'll have to play catchup later.

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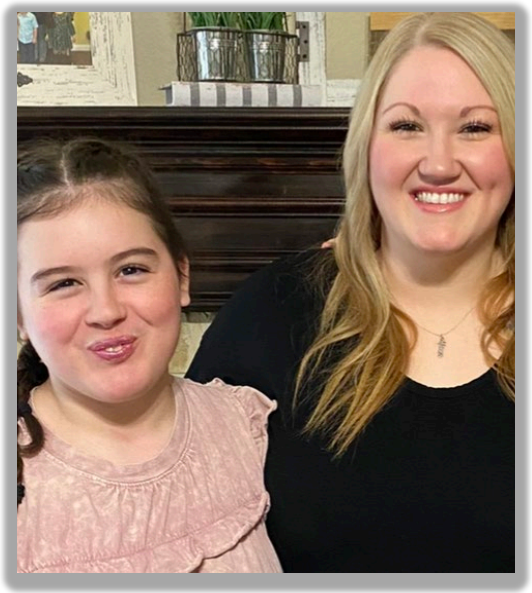
Leah Schust Myers
Founder, Executive Director
FamilieSCN2A Foundation



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Bruce Marshall, MD
Executive Vice President and Chief Medical Officer, Cystic Fibrosis Foundation

The Cystic Fibrosis Foundation Patient Registry

Bruce Marshall, MD
Executive Vice President and
Chief Medical Officer

CYSTIC FIBROSIS FOUNDATION®

Disclosures

Bruce Marshall has no personal disclosures to make. However, to advance drug development and a search for a cure, his employer the Cystic Fibrosis Foundation (CFF) has contracts with several companies to help fund the development of potential treatments and/or cures for cystic fibrosis. Pursuant to these contracts, CFF may receive milestone-based payments, equity interests, royalties on the net sales of therapies, and/or other forms of consideration. Resulting revenue received by CFF is used in support of our mission. See “How Drugs Get on the Pipeline” on the CFF website for more information.

Additionally, CFF may license CFF Patient Registry data to some companies to monitor drug safety as part of the U.S. Food and Drug Administration’s required Phase 4 clinical trials process and to encourage research aimed at improving the care of people with CF, while maintaining our obligation and commitment to protect the privacy of Registry participants. In connection with these licenses, and upon request, CFF may also assist company researchers in interpreting CFF Patient Registry data to aid in designing, analyzing, and interpreting real world studies in CF.

Dorothy H. Andersen, MD

Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease: A clinical and pathologic study. *American Journal of Diseases of Children* 1938;**56**(2):344-399

Cystic Fibrosis Foundation - 1955

Mission: *To ensure the development of the means to cure and control Cystic Fibrosis (CF) and to improve the quality of life for those with the disease*

Journal of Pediatrics 1964; **65**:558-575

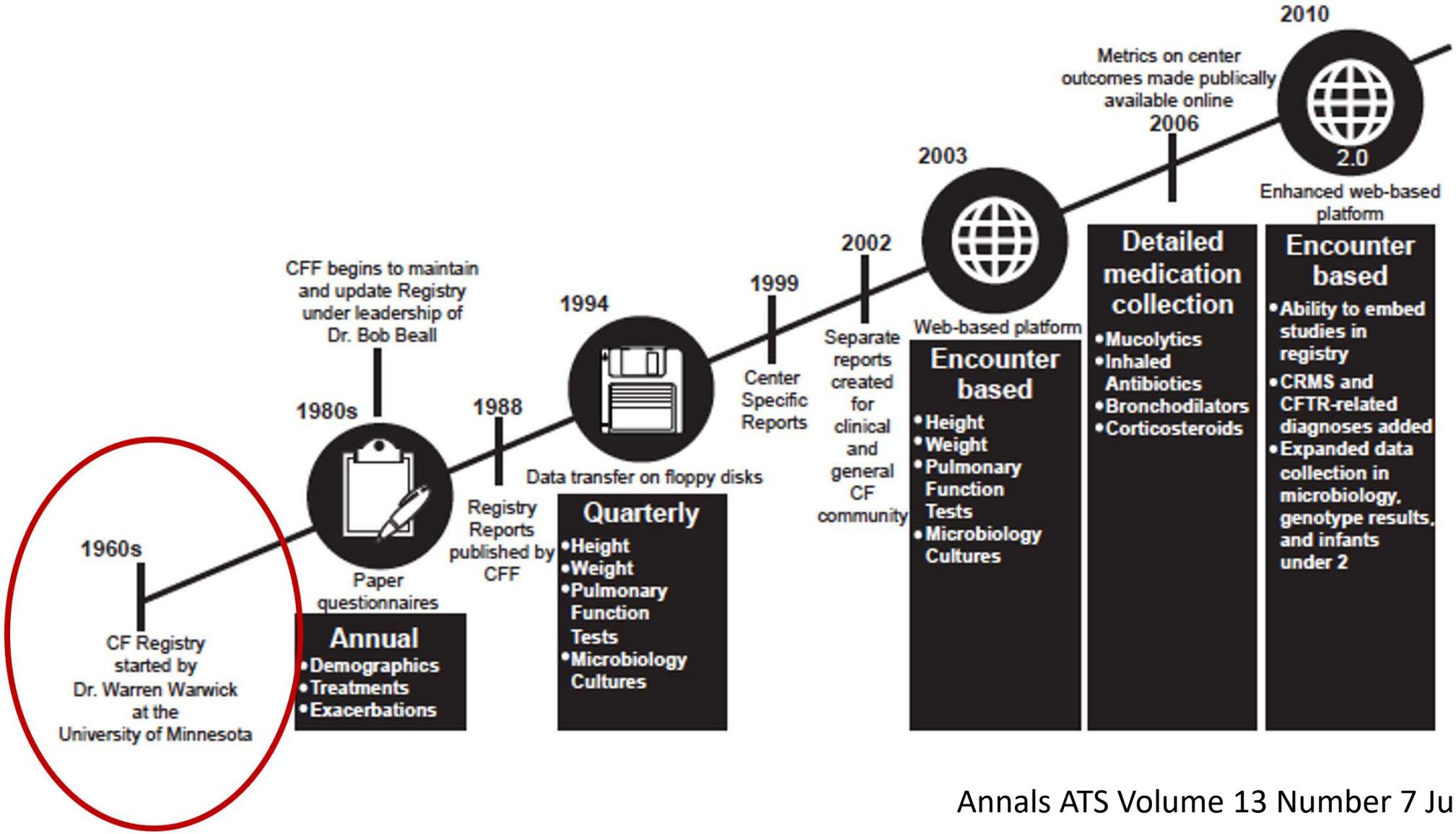
A therapeutic regimen for patients with cystic fibrosis.

LeRoy W. Matthews, M.D.,* Carl F. Doershuk, M.D., Melvin Wise, M.D., George Eddy M.D., Harry Nudelman, M.D., and Samuel Spector, M.D.**

CLEVELAND, OHIO

The Cystic Fibrosis Foundation Patient Registry: Design and Methods of a National Observational Disease Registry

Emily A. Knapp, Aliza K. Fink, Christopher H. Goss, Ase Sewall, Josh Ostrenga, Christopher Dowd, Alexander Elbert, Kristofer M. Petren, Bruce C. Marshall.



Annals ATS Volume 13 Number 7 July 2016

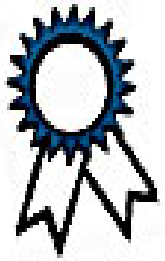
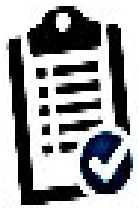
The Cystic Fibrosis Foundation Patient Registry: Design and Methods of a National Observational Disease Registry

Emily A. Knapp, Aliza K. Fink, Christopher H. Goss, Ase Sewall, Josh Ostrenga, Christopher Dowd, Alexander Elbert, Kristofer M. Petren, Bruce C. Marshall.

- Generalizability
  - 81%-84% of individuals with CF in the United States enrolled
- Lost to follow up
  - Retention rate for the 2009 cohort through 2013 was 90.6%
- Completeness
  - 95% of encounters and 90% of hospitalizations in the medical record captured
- Accuracy
  - Registry data matched the medical record 82.6% to 99.9% of the time depending on the data element

Annals ATS Volume 13 Number 7 July 2016

Uses of the Cystic Fibrosis Foundation Patient Registry

DISEASE SURVEILLANCE	FRAMEWORK FOR CLINICAL TRIALS	POST-MARKETING SURVEILLANCE STUDIES	QUALITY IMPROVEMENT	COMPARATIVE EFFECTIVENESS RESEARCH
				
Track progress In curing CF and the Impact of treatments	Test promising new therapies	Ensure safety and effectiveness of approved products	Provide all patients with high-quality care	Promote evidence-based clinical decision making

Identification of the Cystic Fibrosis Gene: Genetic Analysis

BAT-SHEVA KEREM, JOHANNA M. ROMMENS, JANET A. BUCHANAN, DANUTA MARKIEWICZ, TARA K. COX, ARAVINDA CHAKRAVARTI, MANUEL BUCHWALD, LAP-CHEE TSUI

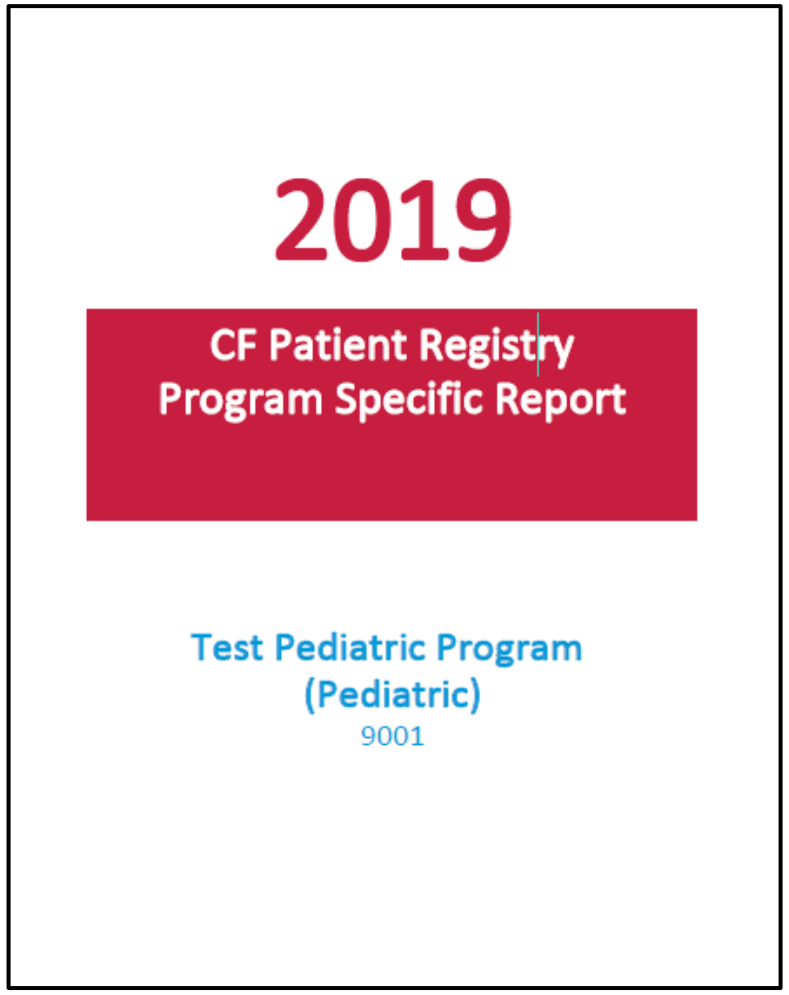
Science; 1989; 245(4922): 1073-1080

Cystic Fibrosis

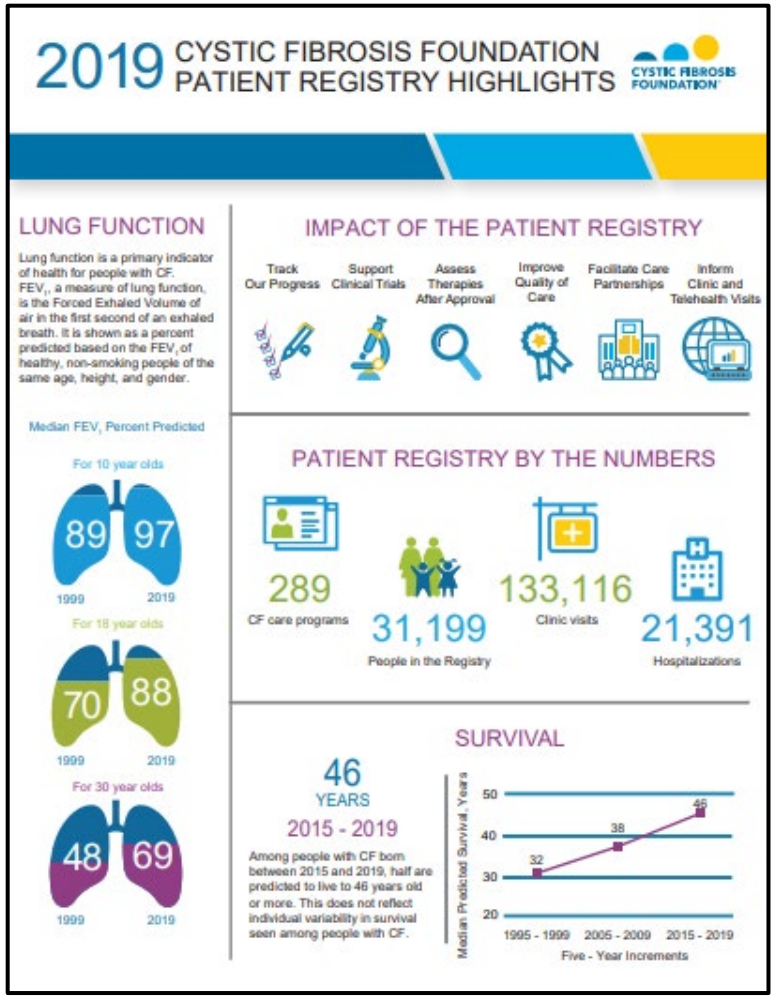
- Complex, multisystem chronic disease
- Nearly 40,000 people with CF in the United States and >100,000 worldwide
- Autosomal recessive, genetic disease
- CFTR gene-major mutation (F508del) and >2,000 variants
- CFTR modulator drugs address basic defect

CF Foundation Patient Registry Annual Reports

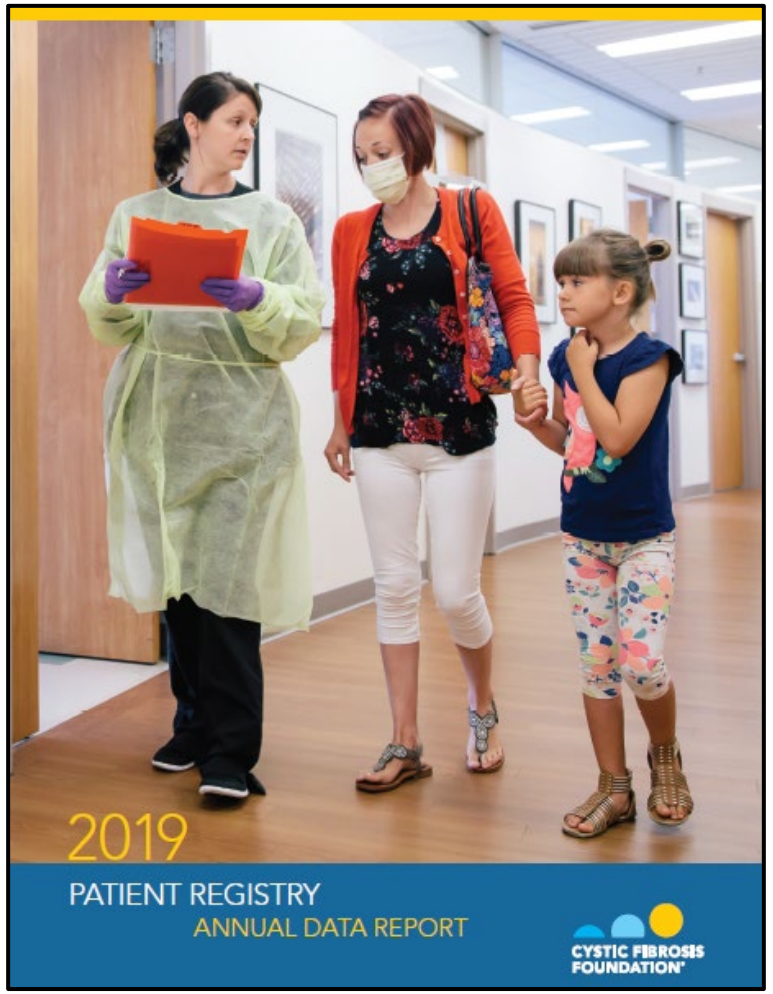
Highlights Report



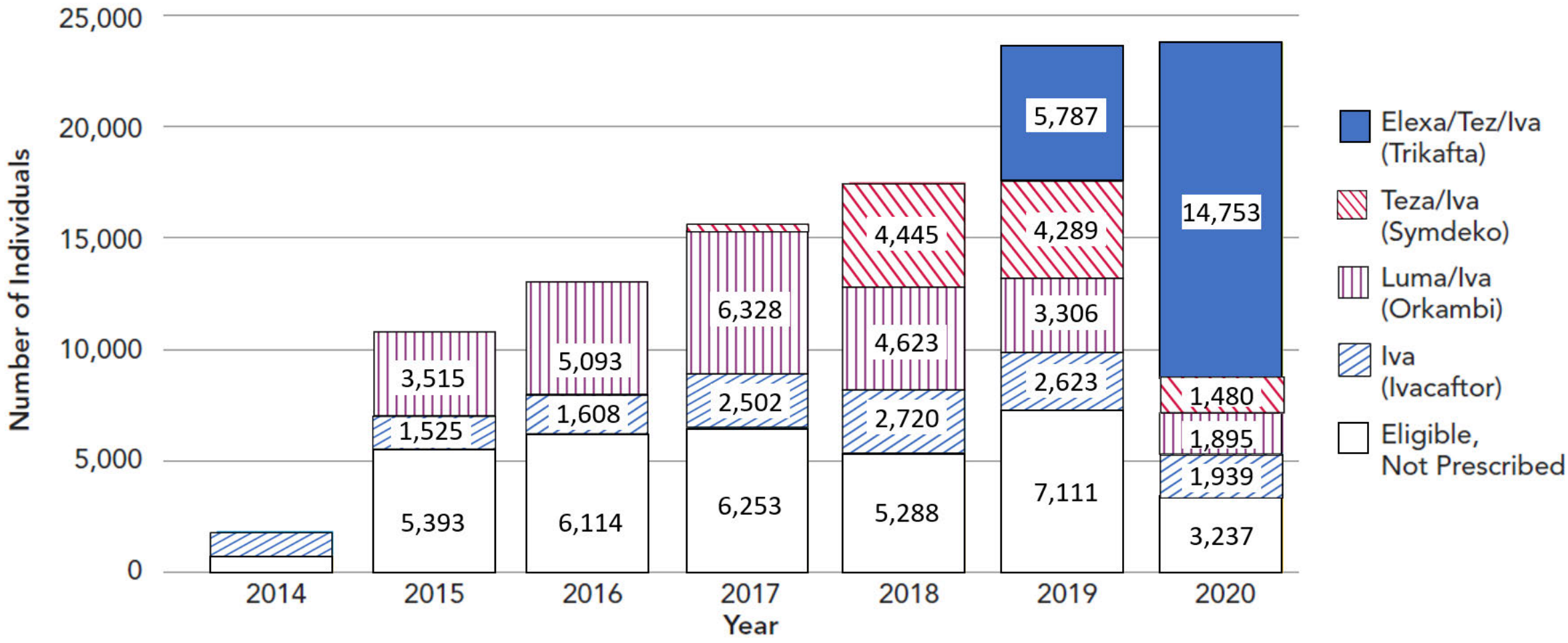
Annual Data Report



Program-Specific Report

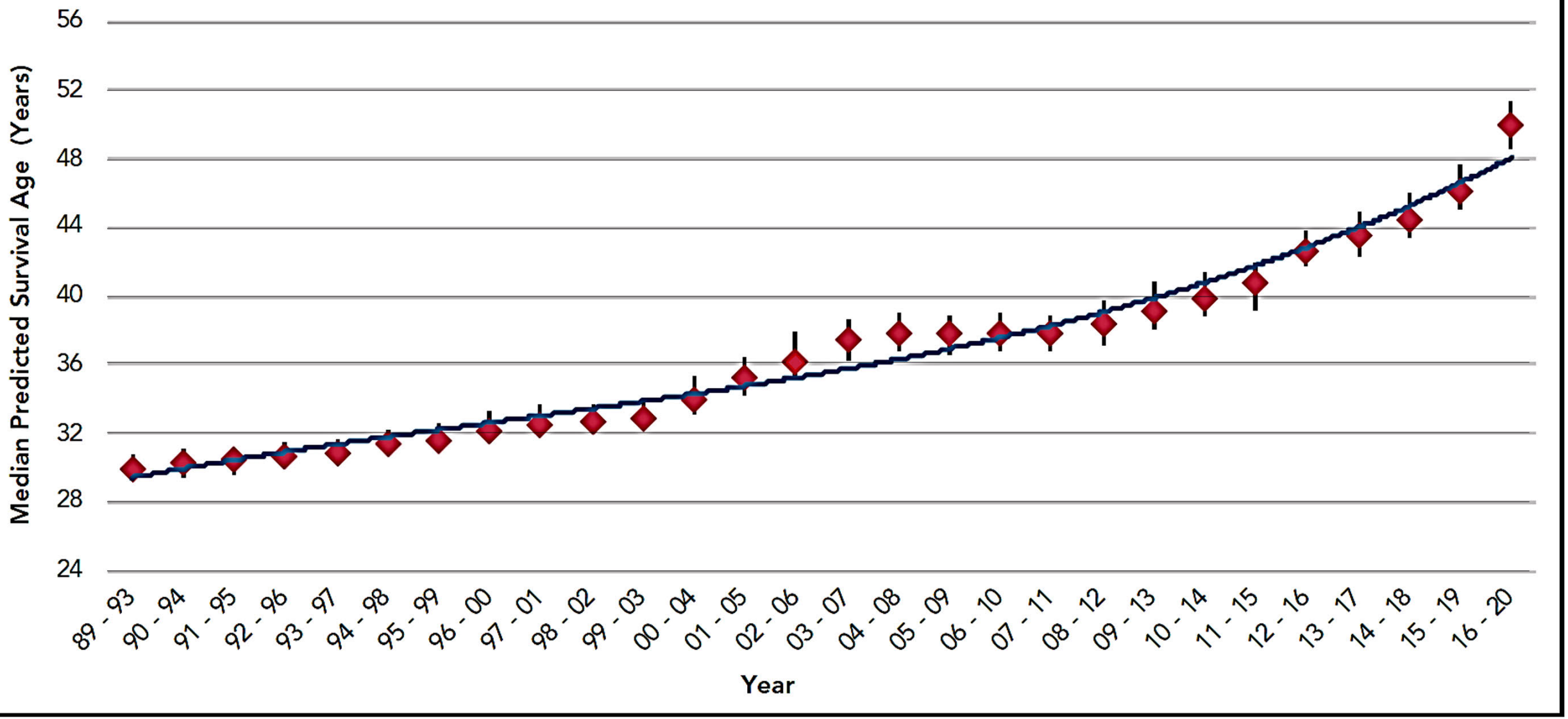


CFTR Modulators by Year, 2014-2020

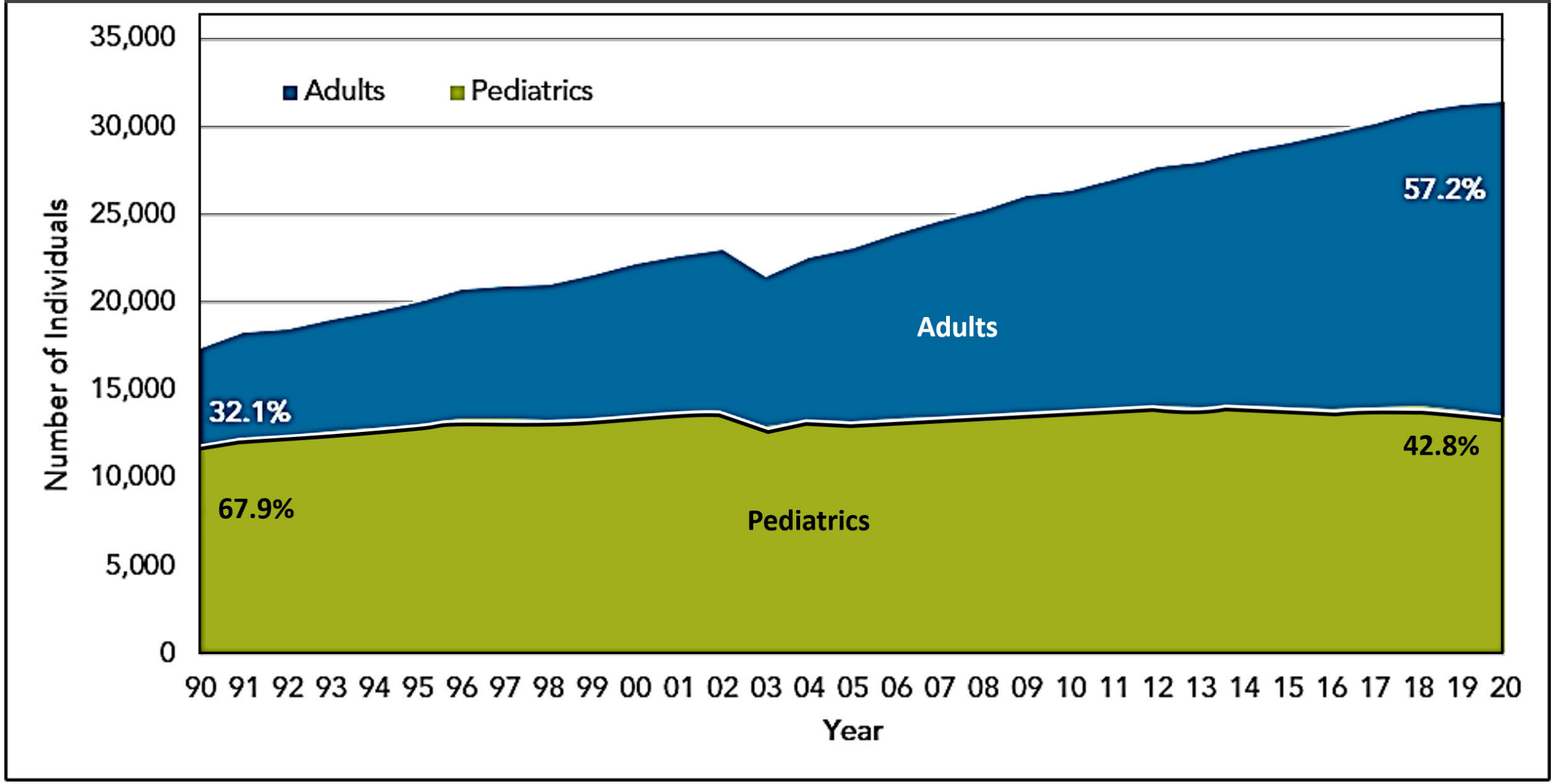


Year	2014	2015	2016	2017	2018	2019	2020
Total Eligible	1,763	10,433	12,815	15,189	17,076	23,116	**23,304**
Pct Eligible on Modulators	60.6%	48.3%	52.3%	58.8%	69.0%	69.2%	**86.1%**
Total on Modulators	**1,069**	**5,040**	**6,701**	**8,936**	**11,788**	**16,005**	**20,067**

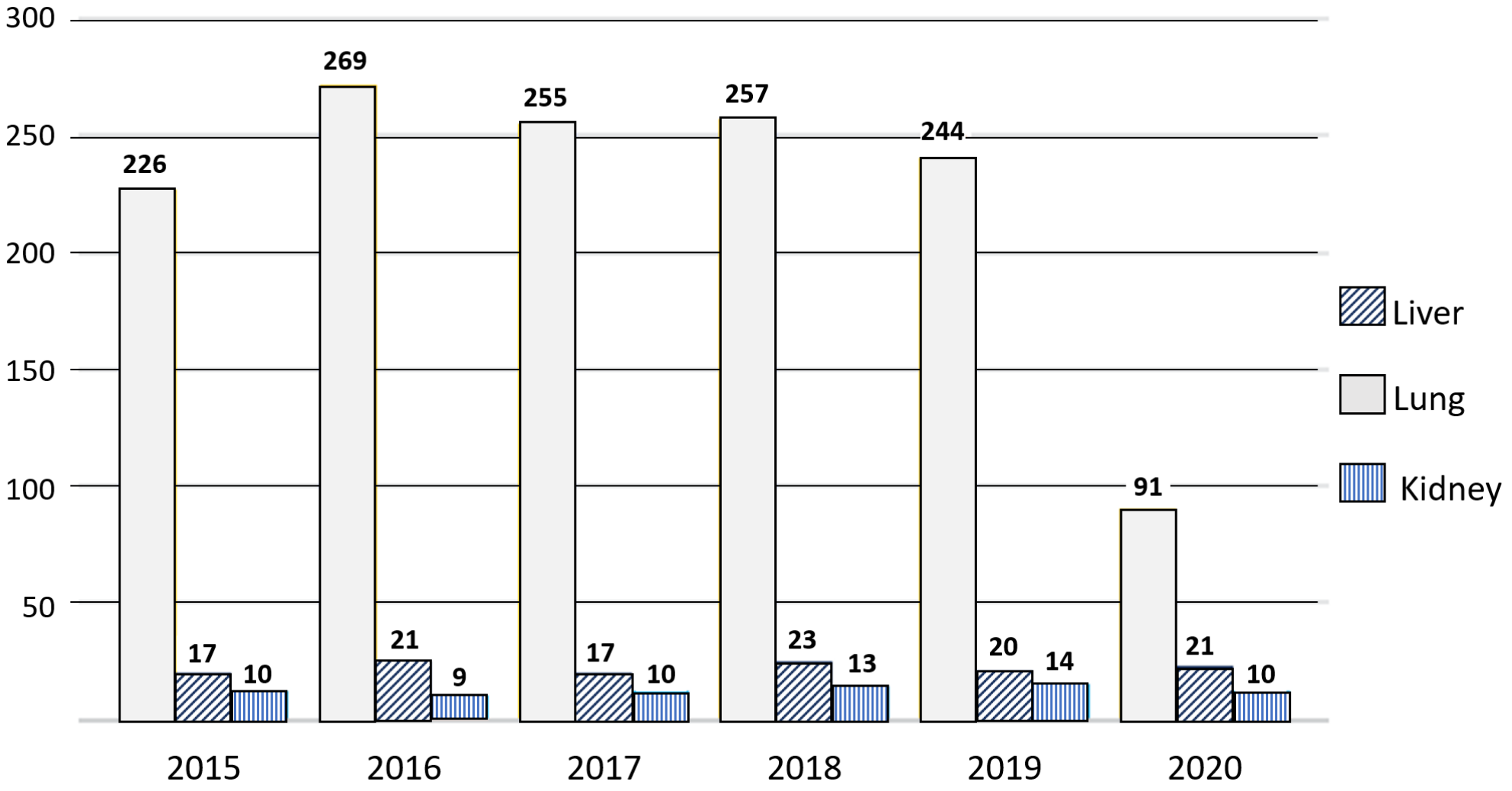
Median Predicted Survival Age, 1989–2020 In Five Year Increments



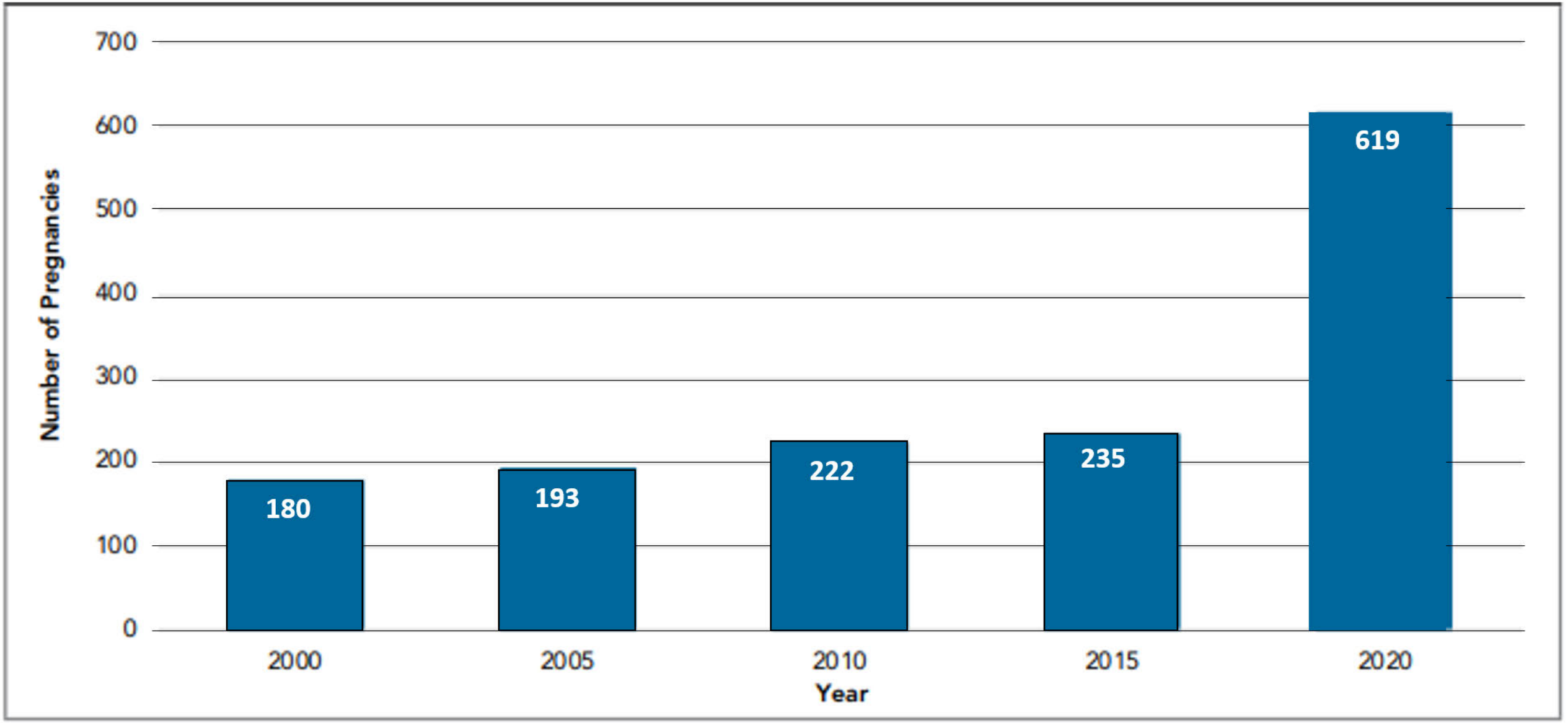
Number of Children and Adults with CF, 1990–2020



Annual Number of Transplant Procedures



Number of Pregnancies in Women 14 to 15 Years with CF, 2000, 2005, 2010, 2015, 2020



Patients Matter: How Rare Disease Patients Can Move Scientific Discovery Forward

Break

1:00 p.m. to 1:30 p.m. ET

Stay tuned! Our next session will begin at 1:30 p.m. ET.

Session 3:
How FDA & Other Organizations Are Supporting Natural History Studies

Moderator:
Devaveena Dey, PhD
Scientific Reviewer
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

Meet Our Panelists

Captain Julienne Vaillancourt, RPh, MPH
Rare Disease Liaison and
Policy Advisor
CBER, FDA
U.S. Public Health Service
Commissioned Corps

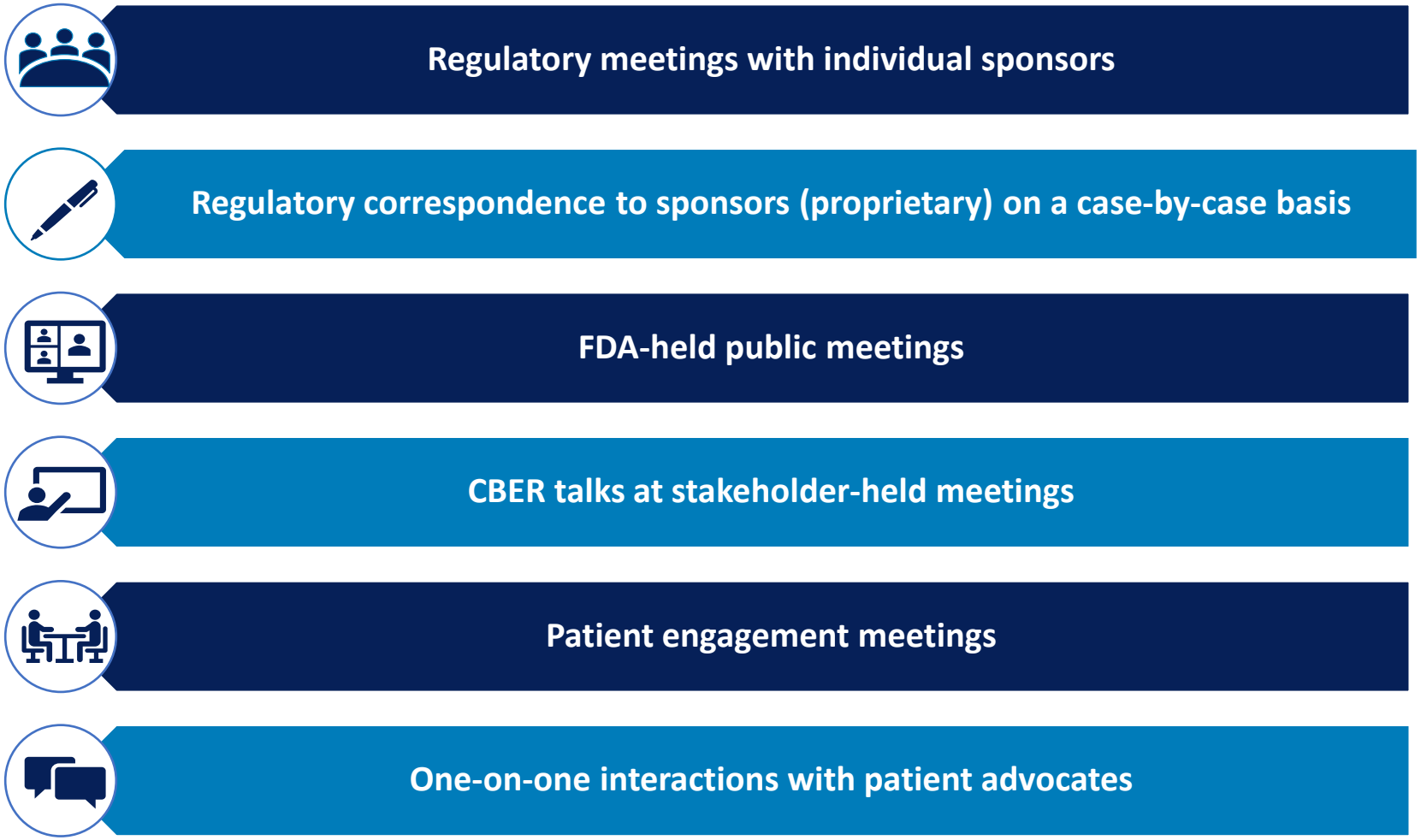
Katherine Needleman, MS, PhD, RAC
Director
Orphan Products Grants Program,
Office of Orphan Products
Development, FDA

Eric Sid, MD, MHA
Program Officer
Division of Rare Diseases Research
Innovation, National Center
for Advancing Translational Sciences,
National Institutes of Health

CBER Support of Natural History Studies for Rare Diseases

CAPT Julienne Vaillancourt, RPh, MPH
CBER Rare Disease Liaison
May 24, 2022

CBER Advises And Encourages Natural History Studies Of Rare Diseases



Regulatory Guidance Addressing Natural History Studies

- *Rare Diseases: Natural History Studies for Drug Development (Draft, 3/2019)*
- *Rare Diseases: Common Issues in Drug Development (Draft, 1/2019)**
- *Human Gene Therapy for Rare Diseases (Final, 1/2020)*
- *Human Gene Therapy for Retinal Disorders (Final, 1/2020)*

"…the need for prospectively designed, protocol-driven natural history studies initiated in the earliest drug development planning stages cannot be overemphasized."

*(lines 115-116)

CBER-Supported, NORD-Sponsored Natural History Study of MLD

The Natural History of Metachromatic Leukodystrophy (MLD)

- Novel framework for building regulatory-grade natural history studies incorporating patient information
- Dynamic data collection via NORD's IAMRARE® registry platform and CBER's SHAPE App

MLD HOME Study

ClinicalTrials.gov Identifier# NCT04628364

Primary Study Aims

- Design & implement a natural history study for MLD to serve as a source of external control data, to augment or replace concurrent controls in clinical trials
- Pilot test & develop guidance on how to design, conduct, & analyze the data from a natural history study to support adaptive trial designs for regulatory use
- Reduce burden of participation in trials & provide a potential solution to patient recruitment challenges, particularly for randomized clinical trials
- Design approaches that support remote participation in studies

MLD HOME Study

Study Update:

- Status: Recruiting
- 26 registered participants as of April 30, 2022

Learn More:

- Visit the website to find out more or to enroll

Thank you to everyone "in the village" who has contributed to this study in one way or another!

SHAPE App: Survey for Health and Patient Experience

SHAPE

CBER-supported mobile app developed by IBM

- Platform for collecting patient experience data via surveys
- Easy to use
- Allows reporting of real-time events
- Compatible with mobile and desktop devices

Use of app not limited to HOME Study (currently open-sourced)

- May be configured for other study types (e.g., clinical trials, registries)
- Available on Apple App Store or Google Play
- To find out more visit: https://patientexperience.app

Other FDA Efforts That Support Natural History Studies

Rare Disease Cures Accelerator Data Analytics Platform

- FDA-supported initiative led by Critical Path Institute (C-PATH) in collaboration with NORD and FDA/CDER
- Provides a centralized and standardized infrastructure to support and accelerate rare disease characterization
- Integrates patient-level data from multiple sources such as natural history studies in a regulatory grade format
- **Goal:** accelerate therapy development across rare diseases
- Learn more on C-PATH's website

Natural History Studies Grant Program

- Administered by FDA's Office of Orphan Products Development
- Launched in 2016
- Supports efficient & innovative natural history studies that advance medical product development in rare diseases and conditions with unmet needs

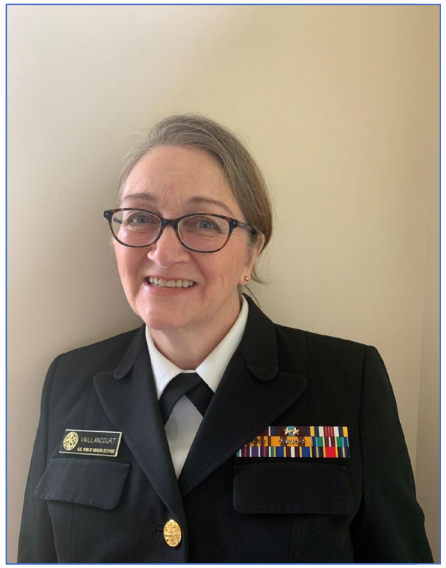
Summary

- Natural history studies can inform regenerative medicine therapy development for rare diseases
- CBER advises and encourages conducting natural history studies for rare diseases
- Several FDA-issued guidances address natural history studies
- The MLD HOME study and the SHAPE App are innovative ways that CBER supports natural history studies
- CBER participates in other FDA efforts that support natural history studies

Thank you!

Julienne.Vaillancourt@fda.hhs.gov

Meet Our Panelists



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National Institutes of Health

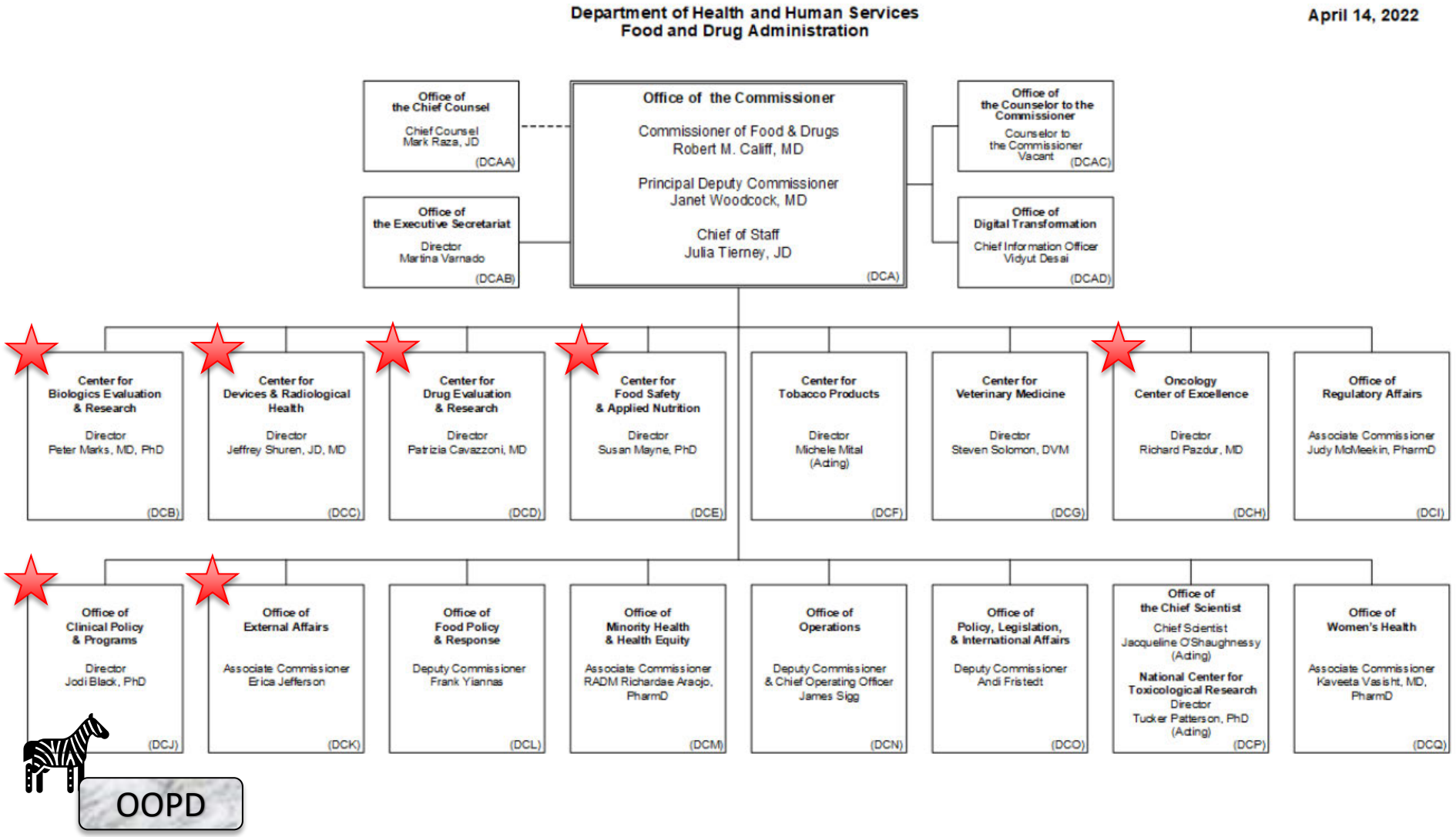
U.S. FOOD & DRUG ADMINISTRATION

Orphan Products Grants Program: Supporting Natural History Studies

Katherine Needleman, MS, PhD, RAC
Director, Orphan Products Grants Program
FDA/OOPD
May 24, 2022

Annual Patient Engagement & Regenerative Medicine Meeting 2022:
FDA CBER Workshop for Patient Advocates

FDA Rare Disease Interactions



OOPD Core Programs

Mission: To promote the development of drugs, devices, biologics, and medical foods for patients with rare diseases and special populations

DESIGNATION PROGRAMS	
1.	Orphan Drug Designation & Exclusivity
2.	Rare Pediatric Disease (RPD) Designation
3.	Humanitarian Use Device Designation (HUD)

GRANT PROGRAMS	
1.	Orphan Products Clinical Trials Grant Program
2.	Orphan Products Natural History Grant Program
3.	Pediatric Device Consortia Grant Program
4.	Rare Neurodegenerative Disease Grant Program

Orphan Products Grants Program

- **Overall Budget**: $17.7M
- **Goal**: To advance the development of orphan products (drugs, biologics, devices, or medical foods) that demonstrate promise for the diagnosis or treatment of rare diseases or conditions

Clinical Trial Grants

- Funding ~75 ongoing studies
- Grants have led to over 80 product approvals, publications, regulatory milestones, impact on field
- Focus on efficiency and innovative trial designs

Natural History (NH) Grants

- Currently funding 8 grants
- Impact in clinical trial development, collaborations with industry and patient groups and publications

OOPD's NH Grants Program: When It Began

- **Launched** the Natural History Grants Program in 2016
- **Goal:** To support drug development for rare diseases through an increased understanding of the impacts and course of rare diseases
- Overwhelming response in terms of interest and applications
- **Funded 6 studies** in FY2017 with $2M budget (2 with support from National Institutes of Health's [NIH] National Center for Advancing Translational Sciences [NCATS])

- Reissued a new funding opportunity in 2018: Focus narrowed, focus on efficiency, innovation, patient input and infrastructure, changes to budget
- **Goal:** To support studies that advance medical product development through the characterization of the natural history of rare diseases and conditions with unmet needs
- **Funded 2 studies** in FY2019

OOPD Natural History Grant Awards

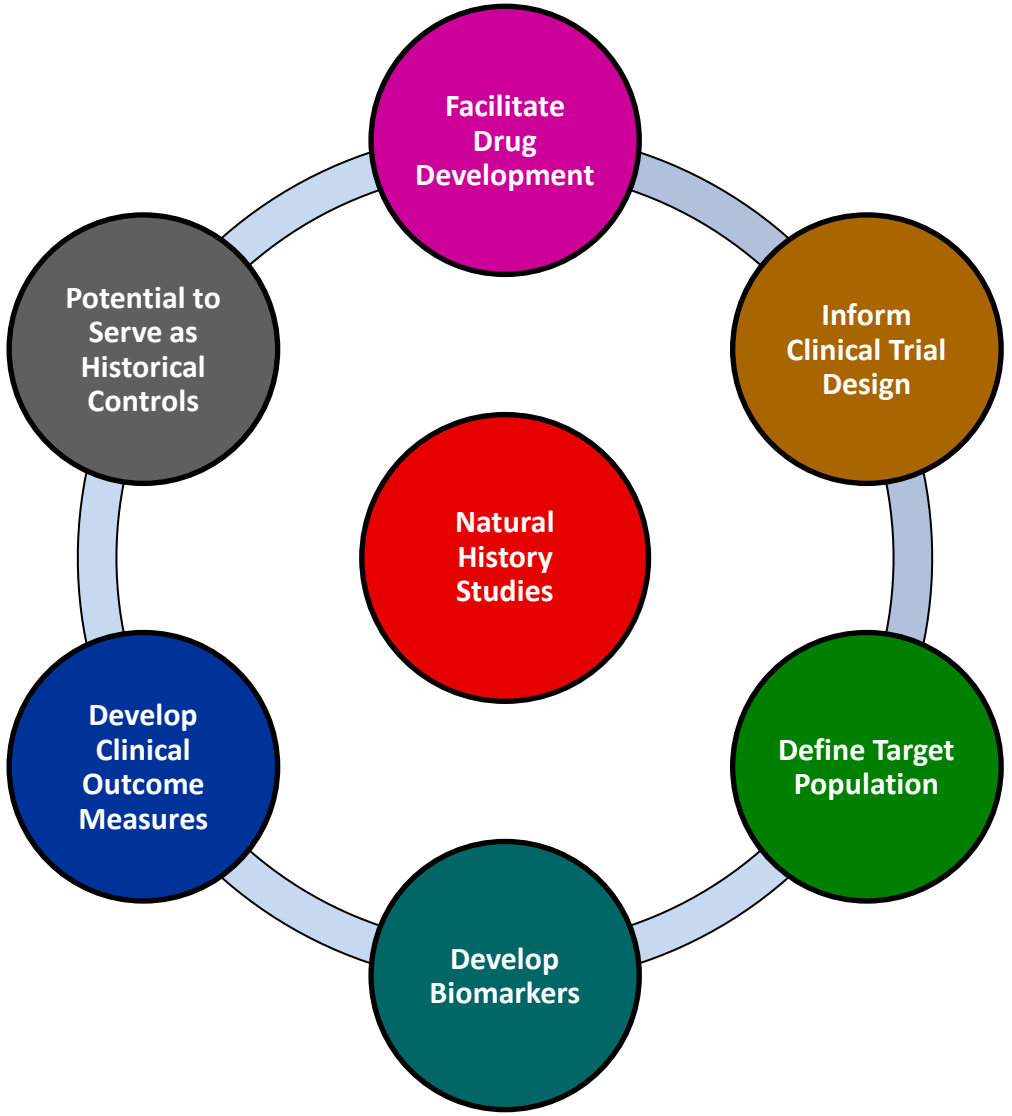
FY2019

1. University of Texas MD Anderson Cancer Center, PI: Elizabeth Grubbs, Prospective Study in **Medullary Thyroid Cancer**
2. Vanderbilt University Medical Center, PI: Jonathan Soslow, Prospective Study in **Cardiac Disease in Duchenne Muscular Dystrophy**

FY2017

1. Children's Hospital Corp, PI: Wen-Hann Tan, Prospective Study in **Angelman Syndrome**
2. Children's Hospital of Philadelphia, PI: David Lynch, Prospective Study in **Friedreich Ataxia**
3. Columbia University Medical Center, PI: Adi Cohen, Prospective Study in **Pregnancy & Lactation Associated Osteoporosis**
4. University of Iowa, PI: Alicia Gerke, Retrospective Study in **Sarcoidosis**
5. University of Tennessee Health Science Center, PI: Kenneth Ataga, Prospective Study in **Sickle Cell Anemia** to Determine Biomarkers of Endothelial Function Changes in Chronic Kidney Disease
6. Virginia Commonwealth University, PI: Nicholas Johnson, Prospective Study in **Myotonic Dystrophy Type 1** to Determine Biomarkers and Clinical Endpoints

Applications of Natural History Studies



Planning for Future Cycles

- **Needs/Wants/Things to Consider**
  - Studies to provide optimal support to rare disease product development
  - Standardized approaches to ensure data quality
  - Well-defined and documented protocols before study initiation
  - Collaborative and efficient approaches
  - Use of patient engagement
  - Ability to exert a broad impact
  - Plans for data dissemination
- **Budget**
- **Focus**

Orphan Products Natural History Grants: New Funding Opportunity

APPLY NOW

- **Efficient and Innovative Natural History Studies Addressing Unmet Needs in Rare Diseases (R01)**
  - **Receipt Date: February 13, 2024**
  - **FOA Number: RFA-FD-22-001**
- **Purpose:** To support efficient and innovative natural history studies that advance medical product development in rare diseases/conditions with unmet needs
- **Focus:** Efficiency, innovation, impact, data quality and interpretability, leveraging patient input, infrastructure and financial resources, future use of data
- **Contact:** Katherine Needleman, Director, Orphan Products Grants Program
  E-mail: katherine.needleman@fda.hhs.gov

Eligibility and Number of Awards

Eligibility:

- Foreign or domestic, public or private, for-profit or nonprofit entities (state and local units of government) are eligible; Federal agencies may not apply
- Orphan Drug Designation not required for grant application
- Must qualify as rare disease, as generally defined in the U.S. Orphan Drug Act: diseases or conditions with a prevalence of fewer than 200,000 persons in the U.S.

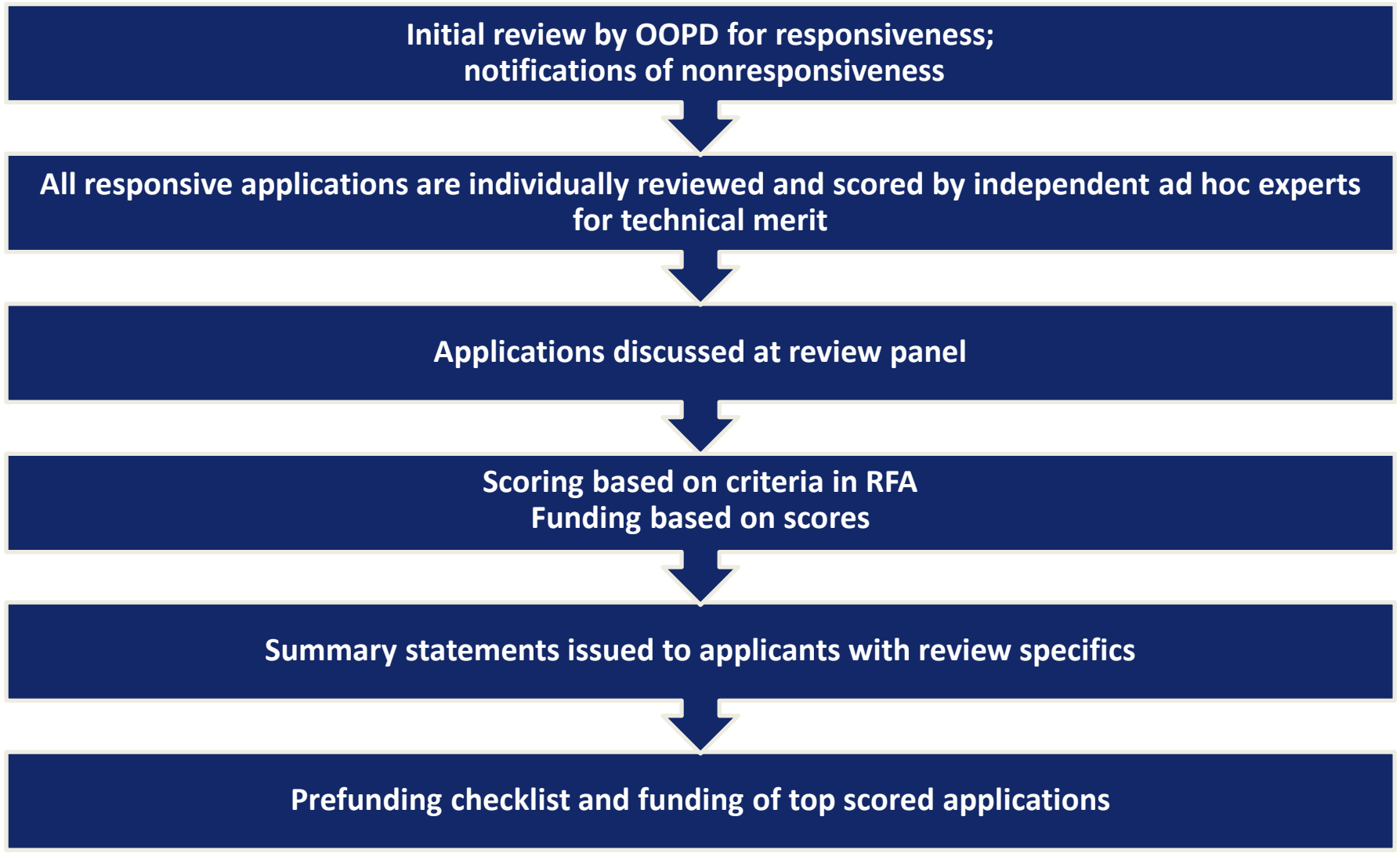
Awards:

- Number of awards is contingent upon FDA appropriations and submission of a sufficient number of meritorious applications
- ~$2 million to fund 2 to 4 applications, depending on the types of studies funded
- Funding dependent on **quality of application** and **availability of Federal funds**

Funding

- Prospective Studies:
  - $400,000/year for up to 4 years
- Retrospective Studies:
  - $150,000/year for up to 2 years

General Review Process



Orphan Grantee/FDA Connect Meetings

- Early interaction with FDA review divisions is beneficial for NH studies
  - To connect and support communication among FDA review staff, funding agencies, and grantees
  - To discuss key challenges faced by the investigator and strategies to address these challenges

Ways to Engage With OOPD and NH Studies

- Importance of community-wide effort
  - Patients Matter Video on OOPD and NH program
- Become a reviewer
- Help with recruitment
- Future proposals

OOPD Contact Information

For more information on OOPD programs go to

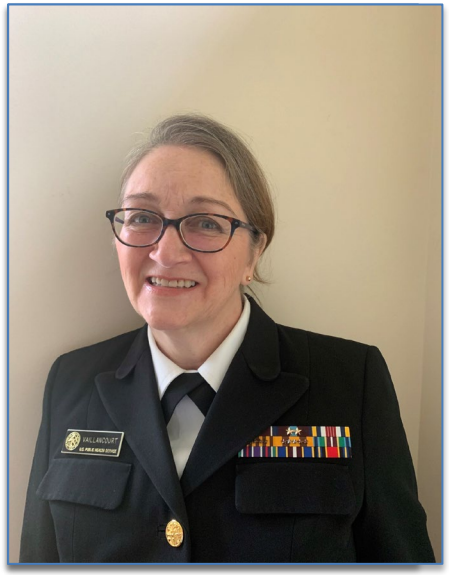
www.fda.gov/orphan

Still have questions?

Email us at orphan@fda.hhs.gov
Or at katherine.needleman@fda.hhs.gov
Call us at 301-796-8660


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Meet Our Panelists



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Program Officer
Division of Rare Diseases Research
Innovation, National Center
for Advancing Translational Sciences,
National Institutes of Health

NCATS

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Session 3: How FDA & Other Organizations Are Supporting Natural History Studies

Eric Sid, M.D., M.H.A.

Division of Rare Diseases Research Innovation,
National Center for Advancing Translational Sciences (NCATS),
National Institutes of Health (NIH)

FDA CBER Annual Patient Engagement & Regenerative Medicine Meeting 2022
May 24, 2022

NIH National Center for Advancing Translational Sciences

Disclosures

- No conflicts of interest

NIH / NCATS /
Division of Rare Diseases Research Innovation

“Advance rare diseases research to benefit patients”

National Center for Advancing Translational Sciences

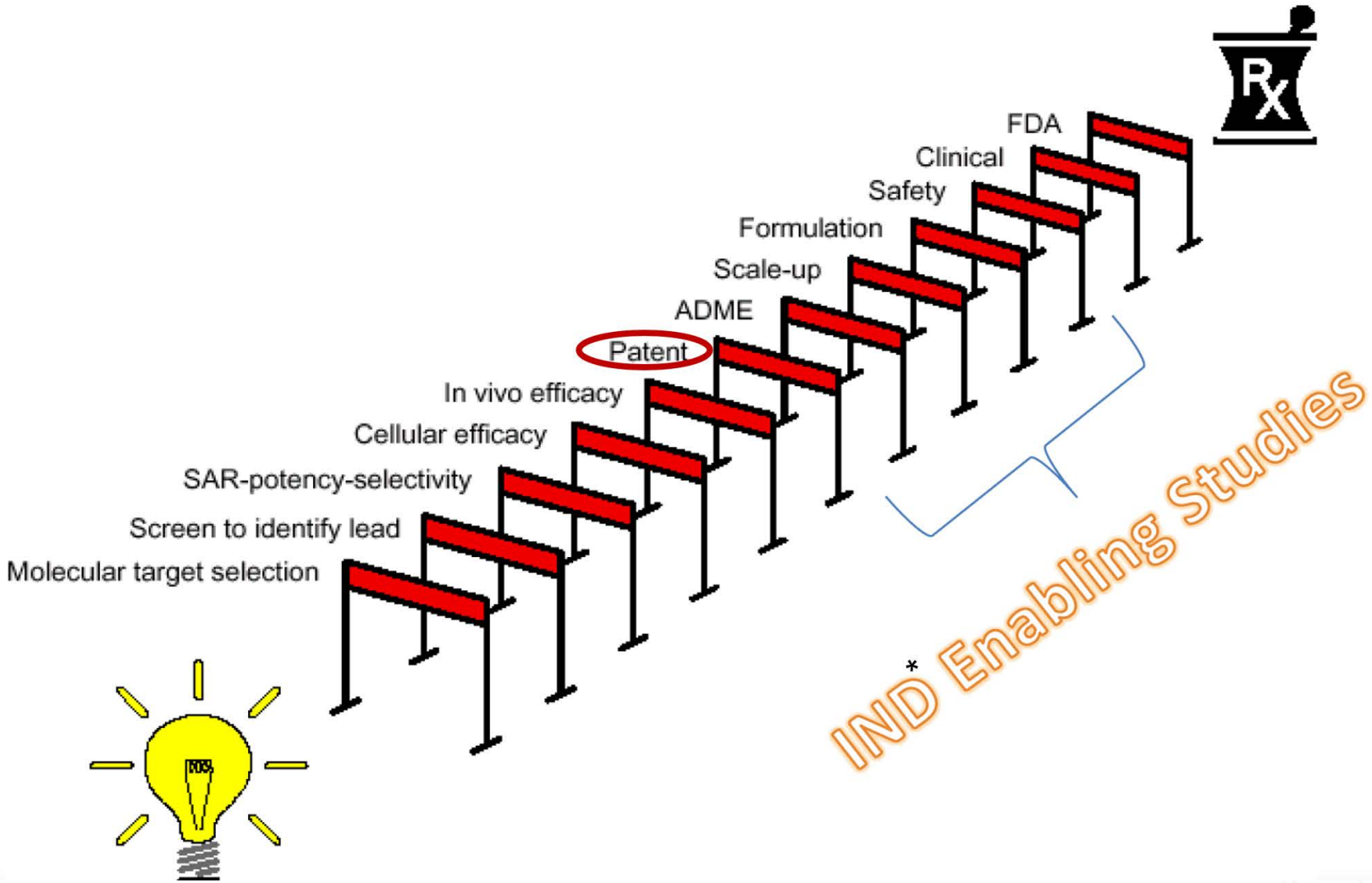
Rare Diseases & Translational Science

Translation is the **process of turning observations** in the laboratory, clinic, and community **into interventions** that improve the health of individuals and the public.

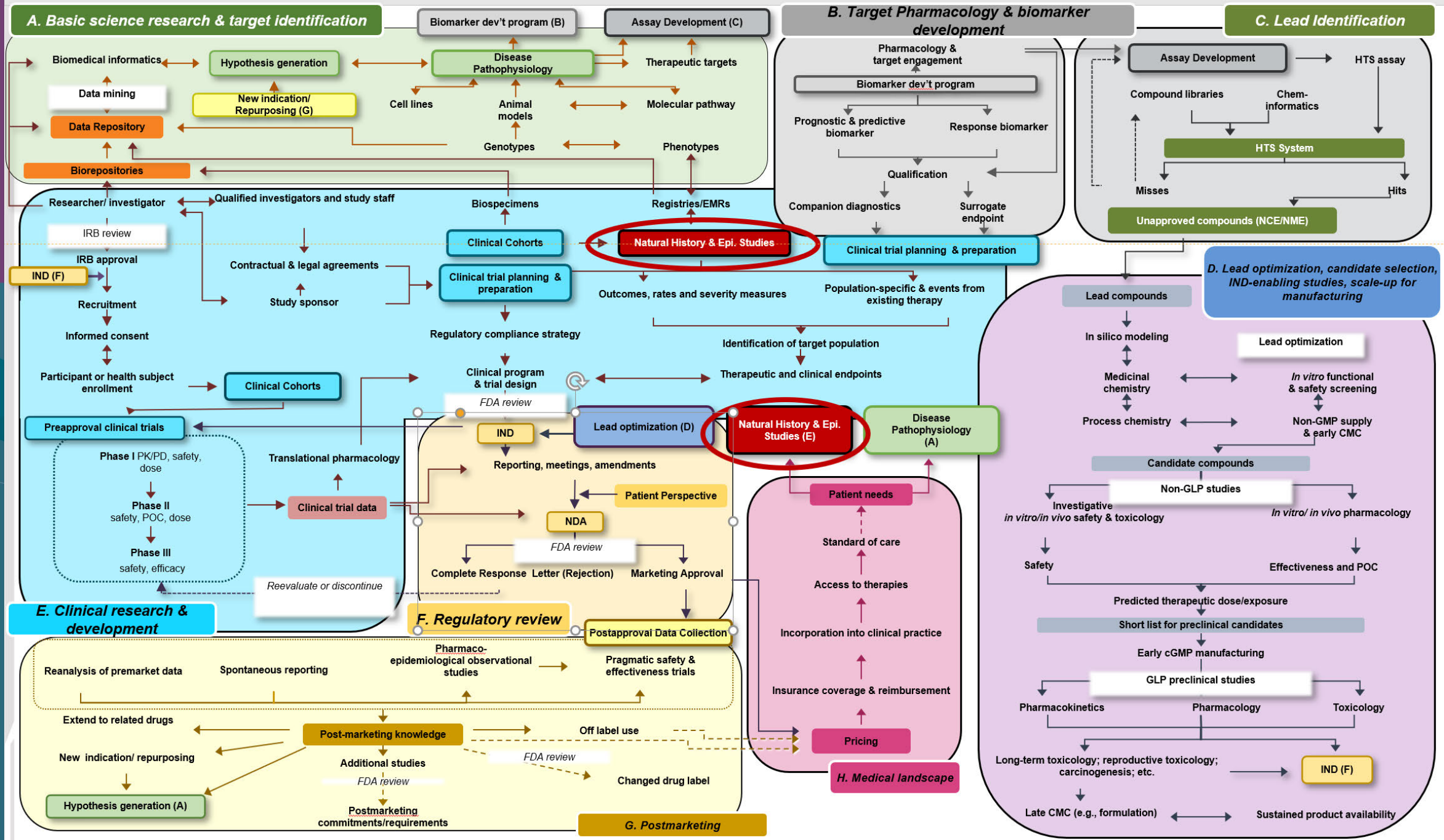
- **Research** on rare diseases has ***collective*** obstacles
  - Small population sizes
  - Limited research studies
- **Patients** with a rare disease face ***common*** challenges
  - Narrow clinical understanding
  - Lack of treatments

National Center for Advancing Translational Sciences

Translation Is a **Team Sport**



*Investigational New Drug



National Center for Advancing Translational Sciences

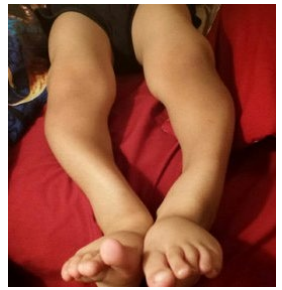
Small Molecule 4D Map

https://ncats.nih.gov/translation/maps

Example: **J**ansen's **M**etaphyseal **C**hondrodysplasia (JMC)

Lead Investigators: **Thomas Gardella, PhD, and Harald Jueppner, MD, Massachusetts General Hospital**

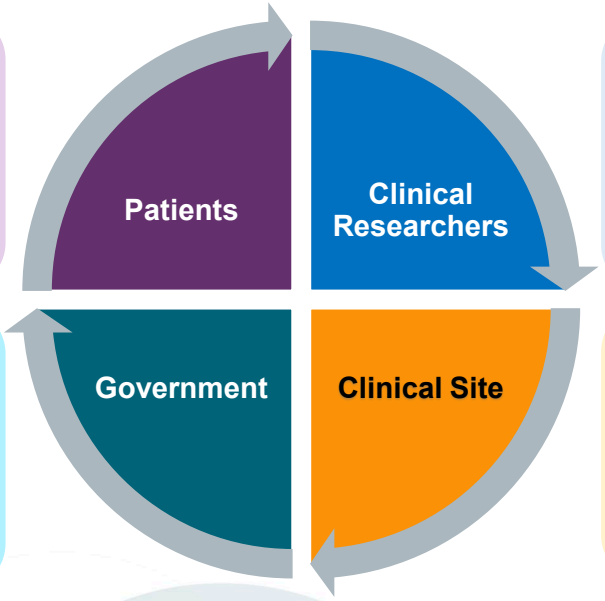
- Extremely rare: ~25 cases known
- Disease of bone development
- Caused by genetic mutations in PTH receptor type 1 (PTHR1)
- No effective treatment options



How do you do drug development for such a small patient population?

Jansen's Disease Foundation
- Connect key partners
- Engage patient community in clinical research

MGH Clinical Researchers
- Provide scientific and disease expertise
- Care for patients



NCATS Preclinical Support
- Provide drug development expertise and coordination
- Enable transition from preclinical to clinical

NIH Clinical Center
- Natural history study
- Execute clinical trials

https://ncats.nih.gov/trnd/projects/active/jansens-metaphyseal-chondrodysplasia

Therapeutic Development Starts and Ends with Patients

Outreach

Patient advocates helped to initiate collaborations
- Clinicians
- Researchers
- Drug developers

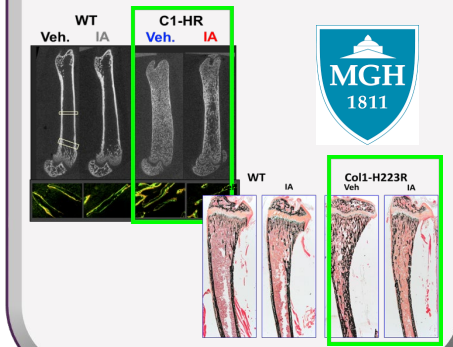
Participation in natural history studies

THE JANSEN'S FOUNDATION

Academic Research

Identification of potential therapeutic candidate

Initial testing in mouse models of disease



MGH 1811

Preclinical Drug Development

Manufacture & formulation of drug candidate

Toxicology studies

Regulatory IND support

Development of clinical assays

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Clinical Planning

Natural history

Phase 1/2 trial

NIH Clinical Center

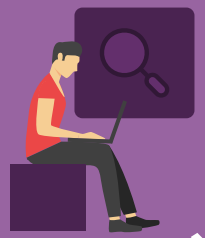
Treatment

Potential benefit to children from drug leading to improved quality of life

Clinical Trial Readiness

WHO

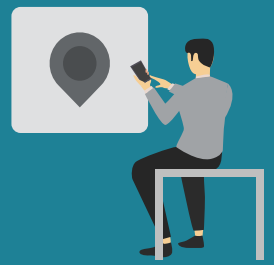
Who do you treat?
Who will conduct the trial?



WHAT

What is the desired treatment outcome?

WHERE



Where are the patients?
Where are the experts?

WHEN

When is the best time to treat a condition?

WHY

Why is this the best proposed treatment?

HOW

How should the trial be conducted?

NCATS Resources for Rare Disease Patients & Patient Advocates

Toolkit
For Patient-Focused Therapy Development

Who: Patient Groups
What: Research & Development

Educational Website
- Educational information, resources, and best practices for collaborating with researchers, industry, and regulators on therapy development

Toolkit.ncats.nih.gov

RaDaR
Rare Diseases Registry Program

Who: Patient Groups & Scientists
What: Patient Registries

Educational Website
- Stepwise educational information, resources, and best practices for starting a registry and best practices around registry data governance and stewardship

Registries.ncats.nih.gov

GARD
Genetic and Rare Diseases Information Center

Who: Patients/Caregivers/Public
What: Public Health Information

Contact Center
- Individualized Support

Health Information Website
- General Information about rare diseases and finding support

New Website in Development!
- Focuses on providing access to information for patients/caregivers and to develop via user experience

RareDiseases.info.nih.gov

NCATS Toolkit for Patient-Focused Therapy Development

Home | Getting Started | Discovery | Prepare For Clinical Trials | Clinical Trials And FDA Review | After FDA Approval | Glossary | About

Understand Translational Research Tools | Determine Patients' Needs | Facilitate Scient

Determine Patients' Needs

- OVERVIEW
- PATIENT REGISTRIES
- CONTACT REGISTRY
- NATURAL HISTORY STUDY
- BUILDING A REGISTRY
- PFDD INITIATIVE
- PLANNING AN EXTERNALLY-LED PFDD
- TIPS FOR SUCCESS
- RESOURCES

Natural History Study

Natural history study databases contain more detailed cli... diagnosis, symptoms, medical images, and test results. Data may be entered by patients, their caregivers, or healthcare professionals.

- **Type of information** stored may include:
  - Patient contact information.
  - Clinical information as it becomes available, such as:
    - Diagnosis
    - Signs and symptoms
    - Medical images
    - Test results.
  - Patient experiences, such as:
    - Effect on quality of life.
    - Positive and negatives of current treatments.
  - Family and caregiver perspectives.
  - Clinicians experience.

Understand The R&D Process

Empower Your Patient Community Voice

Demystify Your Disease R&D Readiness

Build Relationships With Key Partners

User-Friendly Websites

Plain Language Information

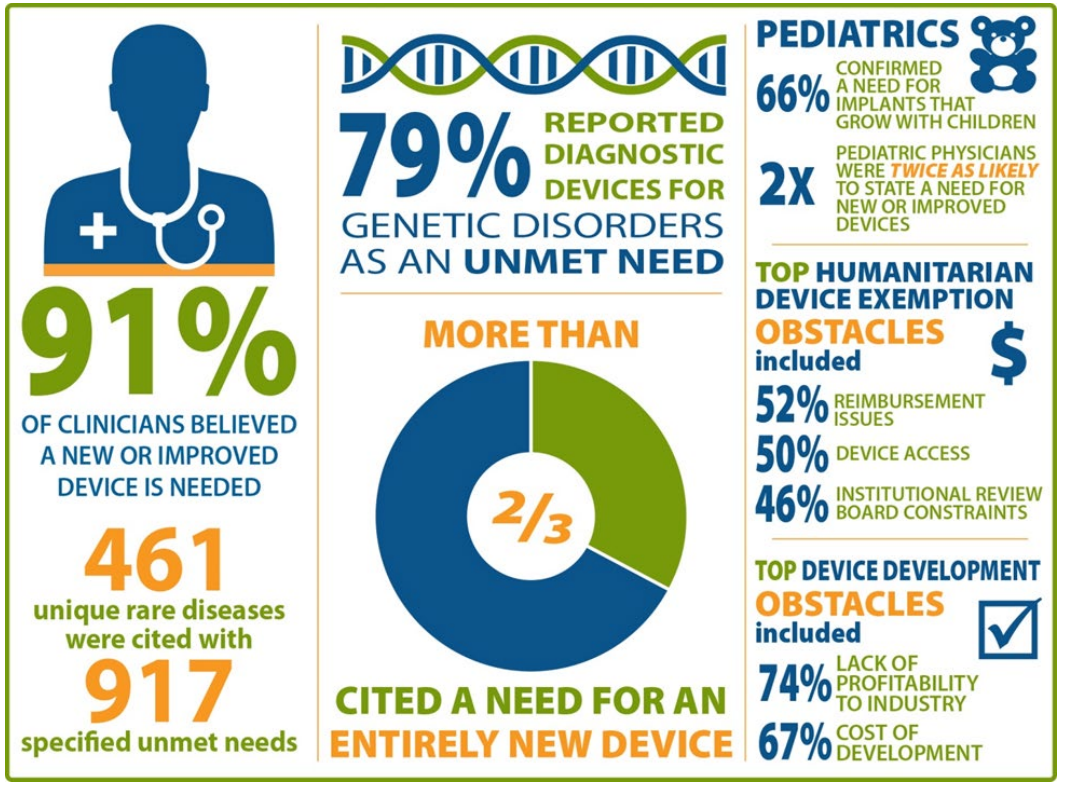
Highlights Reliable Resources

https://toolkit.ncats.nih.gov

National Center for Advancing Translational Sciences

Rare Disease Registry (RaDaR) Website

Data is the currency that research uses to measure success



Registries Translate Stories into Data

GARD

Genetic and Rare Diseases Information Center

A complete reimagining of the GARD website is in development to scale the translation of complex disease ontology data into accessible and actionable information for patients and caregivers

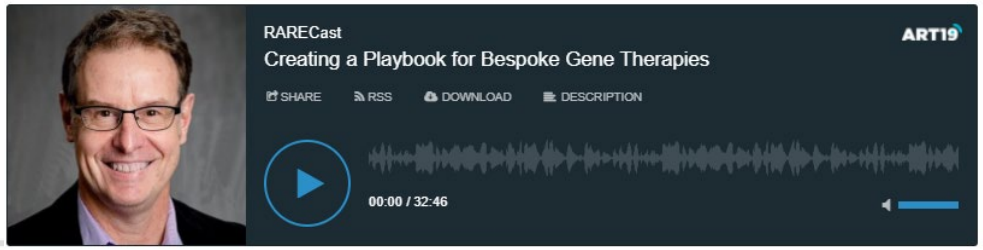
https://rarediseases.info.nih.gov

FNIH
Foundation for the National Institutes of Health

Accelerating Medicines Partnership®
Bespoke Gene Therapy Consortium (AMP® BGTC)

Problem: With the current commercial drug development model, companies cannot recover the costs required to develop gene therapies to treat rare and ultra-rare genetic diseases, because these diseases affect relatively few patients.

Solution: Create tools to streamline the gene therapy development process, aiming to reduce associated costs and encourage companies to pursue gene therapies for rare genetic diseases.



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

https://ncats.nih.gov

NIH National Center for Advancing Translational Sciences

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RareDiseases.info.nih.gov

Toolkit For Patient-Focused Therapy Development
Toolkit.ncats.nih.gov

RaDaR Rare Diseases Registry Program
Registries.ncats.nih.gov

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Closing Remarks - Top Takeaways

Natural history studies can advance the development of regenerative medicine therapies.

Patients and families are the experts in their diseases, and their voice is critical.

There are many opportunities for patients, advocates, and experts to join or support clinical research.

The FDA is committed to engaging with and supporting patients and patient advocacy groups.

Stay Connected!

Helpful Resources:

- Visit CBER's website
- Sign up for our newsletter, "What's New @ CBER"
- Follow us on Twitter: @FDACBER
- Learn more about natural history studies:
  - Rare Diseases: Natural History Studies for Drug Development
  - Patients Matter: How Rare Disease Patients Can Move Scientific Discovery Forward

Thank you!

Workshop materials will be available in the coming weeks on FDA.gov.

Stay tuned for future RegenMedEd events in 2022!

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