NCATS

COLLABORATE. INNOVATE. ACCELERATE.

The National Center for Advancing Translational Sciences (NCATS)

MOVING THE NEEDLE ON RARE DISEASE RESEARCH

Joni L. Rutter, PhD
Acting Director, NCATS

National Press Foundation
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NIH National Center for Advancing Translational Sciences

Why we need to “move the needle” on rare diseases

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for Advancing
Translational Sciences

The Public Health Challenge

10,000

Diseases

and only

500 Treatments or Cures

Time from early development to the medicine cabinet takes 10-15 years.

9 out of **10**

promising therapeutic candidates that enter clinical trials fail to be safe and effective.

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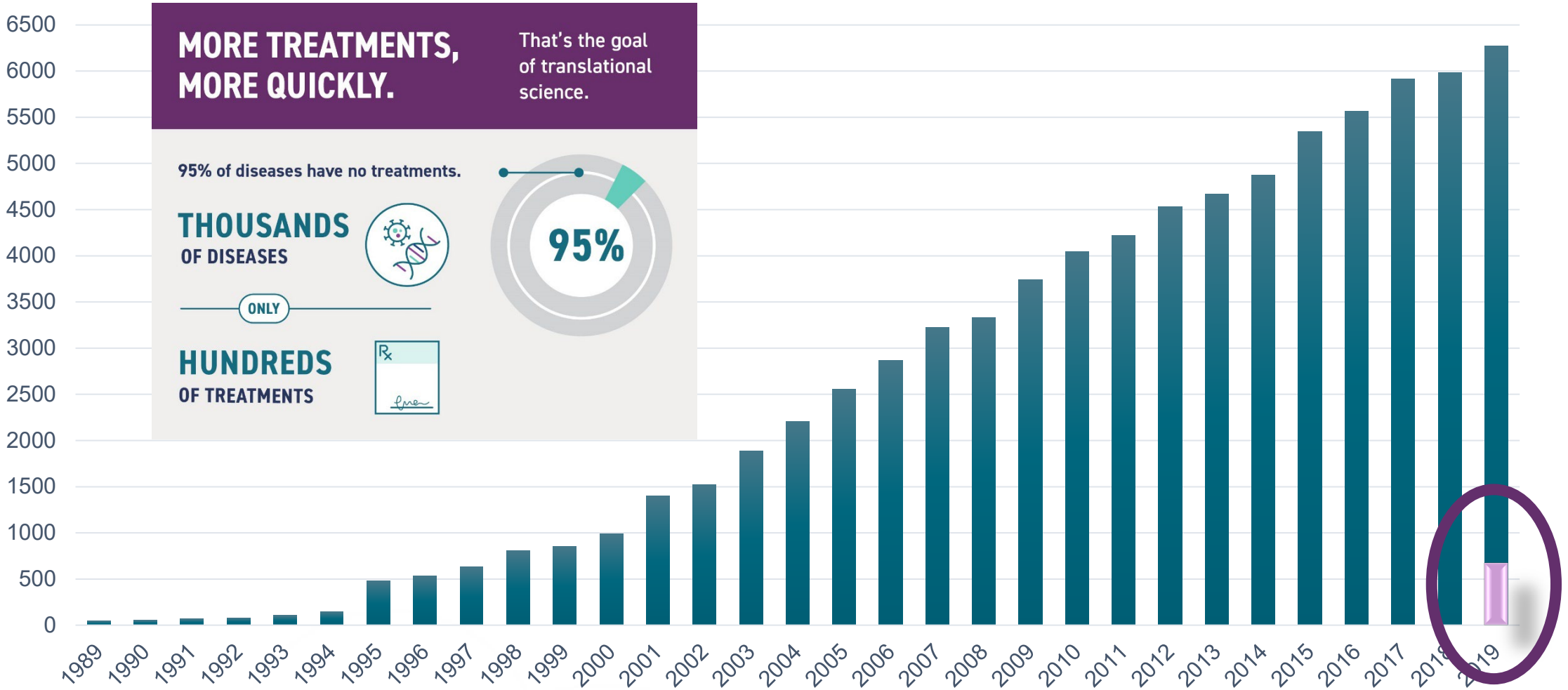
Diseases of Known Molecular Basis with Treatments



Source: Online *Mendelian Inheritance in Man*, Morbid Anatomy of the Human Genome

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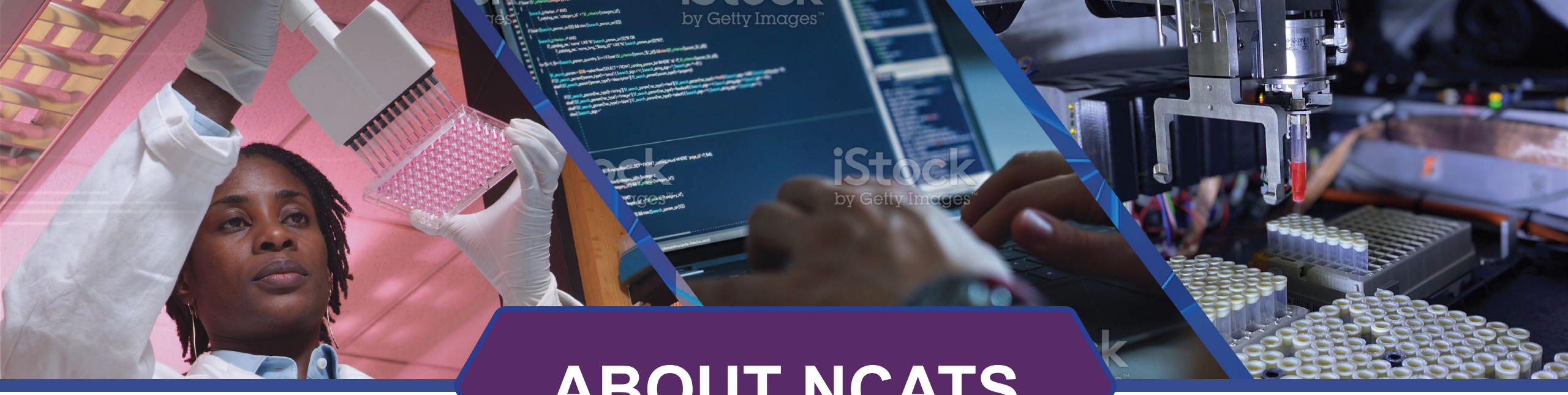
NCATS MISSION

Turn research observations into health solutions through translational science



ABOUT NCATS

We tackle ongoing challenges in research so that new treatments reach people faster.

We focus on what's common across diseases, especially rare diseases, and develop solutions that overcome bottlenecks in the translational process.

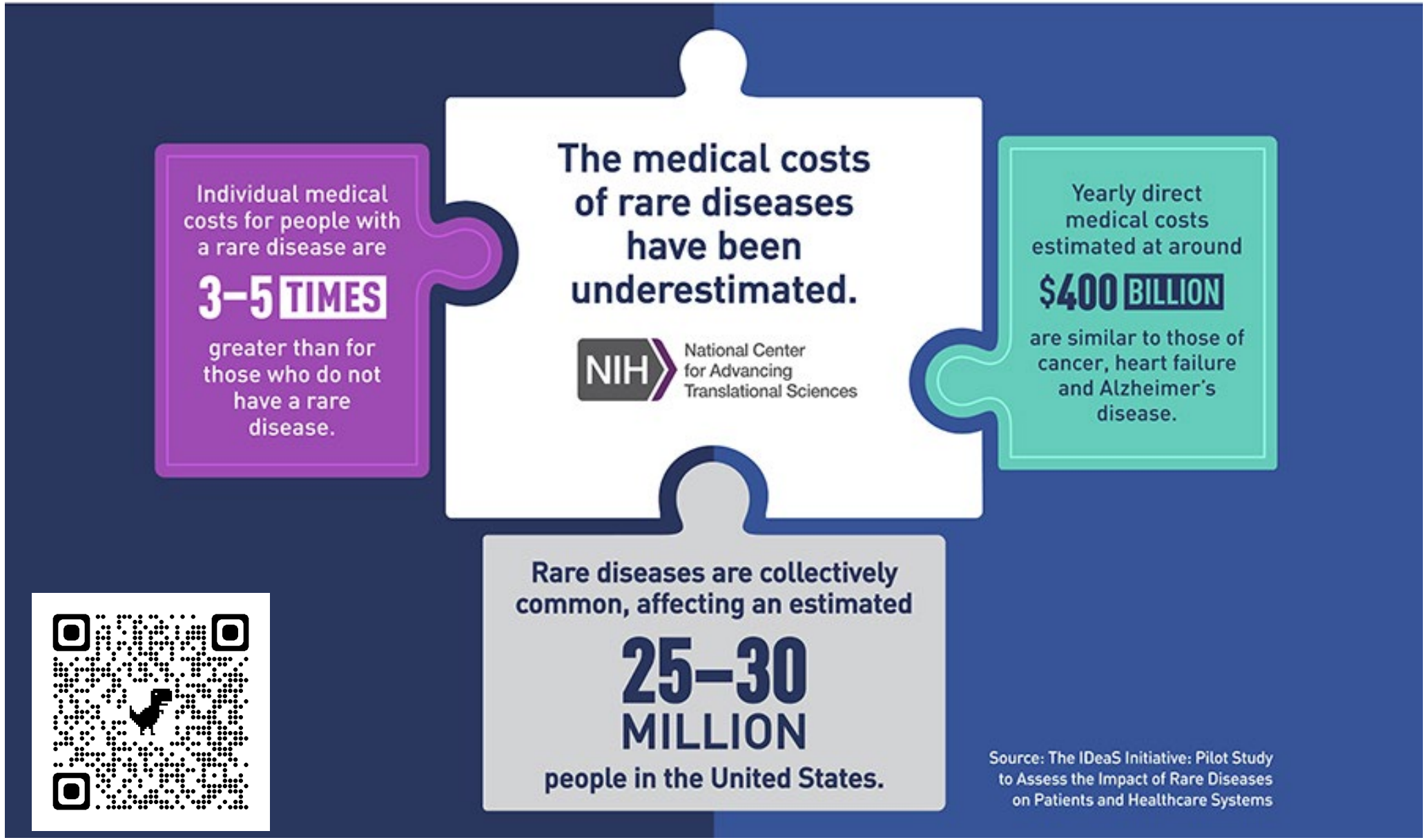
Our vision is a future of more treatments for all people more quickly.

Rare diseases affect around 30 million people, roughly 10% of the U.S. population

Rare Diseases are Not Rare

An estimated 350 million people suffer from rare diseases worldwide

NIH Study Suggests People with Rare Diseases Face Significantly Higher Health Care Costs



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Shortening the rare disease diagnostic odyssey

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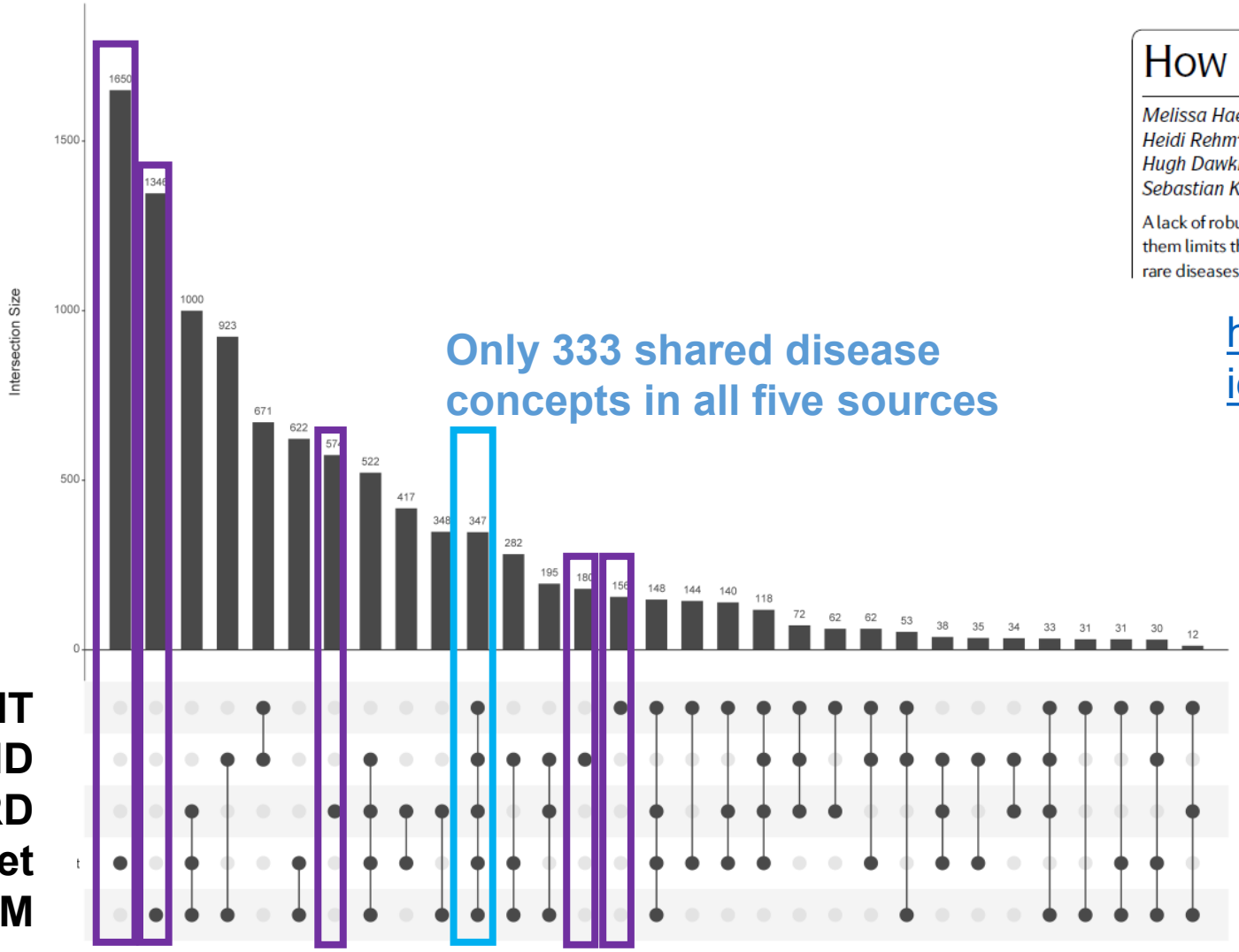
Five sources comprise 10,577 unique rare disease concepts

NCIT
DOID
GARD
Orphanet
OMIM



Only 333 shared disease concepts in all five sources

Many diseases are in only one source

How many rare diseases are there?

Melissa Haendel[1], Nicole Vasilevsky[1], Deepak Unni[2], Cristian Bologa[3], Nomi Harris[2], Heidi Rehm[4], Ada Hamosh[5], Gareth Baynam[6], Tudor Groza[7], Julie McMurry[8], Hugh Dawkins[9], Ana Rath[10], Courtney Thaxon[11], Giovanni Bocci[3], Marcin P. Joachimiak[2], Sebastian Köhler[12], Peter N. Robinson[13], Chris Mungall[2] and Tudor I. Oprea[3]**

A lack of robust knowledge of the number of rare diseases and the number of people affected by them limits the development of approaches to ameliorate the substantial cumulative burden of rare diseases. Here, we call for coordinated efforts to more precisely define rare diseases.

https://www.nature.com/articles/d41573-019-00180-y

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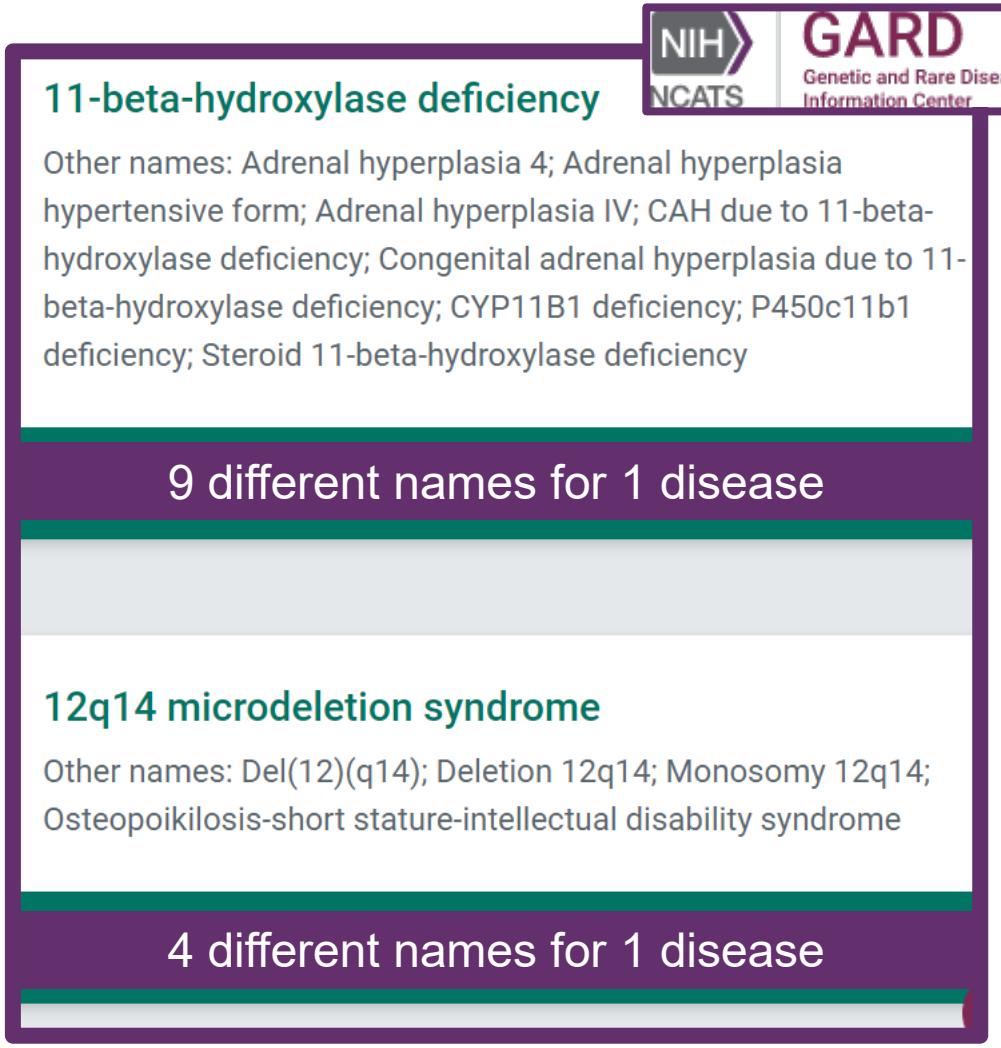
The exact number of rare diseases is hard to determine

- **Different countries define "rare" differently** (keionline.org)

Absolute prevalence			Percentage prevalence	
US <200,000	Japan <50,000	S. Korea <20,000	EU <1 in 2,000	Australia <1 in 20,000

  - Several countries do not have a definition in legislation
  - *Prevelance and costs of RDs are ballpark estimates*
- **Estimated >200 new diseases are added each year**
  - New rare diseases are discovered every week by organizations such as the Undiagnosed Disease Network
- **Rare diseases are not defined in the same way, making them difficult to "see" in our health systsms**
  - Dozens of disease registries exist, each with their own system
  - Rare diseases are often not included in standard clinical terminologies (such as ICD codes)
  - Definitions of a rare disease are not interoperable



Rare Disease Patients Experience Diagnostic Odyssey

- Despite ~10% of the population having a rare disease, inability to count = an inability to identify rare disease patients
- Lack of clear definitions makes it hard to diagnose people and develop therapies
- High-quality evidence to guide treatments is scarce
- Very few expert centers are available for diagnosis, management, and research
- Patients often see many clinicians over a years-long time before receiving an accurate diagnosis.

Opportunity: “Zebra Triggers”? Think Rare Diseases

Old medical school adage

“When you hear hoofbeats, think of horses not zebras”

New adage → think zebra when…

Medical records show potential zebra triggers

- ✓ Young age
- ✓ High utilization
- ✓ Multiple consults, “geography”
- ✓ Imprecise diagnostic codes, e.g.,
  - Failure to thrive/delay in growth
  - Developmental/motor delay
  - Refractory seizures
  - Recurrent serious infections

More tools are needed!

“Diagnostic Odyssey:” 3-pronged approaches to accelerated rare disease diagnosis

Machine-assistance + genetics + clinical team

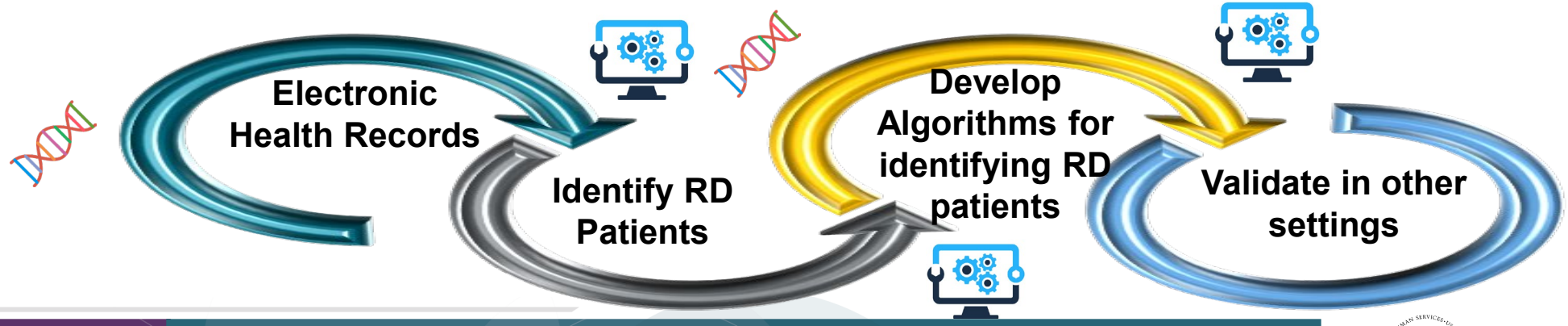
Shortening the Diagnostic Odyssey

For more information, contact Alice Chen Grady, M.D.

Multidisciplinary Machine-Assisted, Genomic Analysis and Clinical Approaches to Shortening the Rare Diseases Diagnostic Odyssey (UG3/UH3 Clinical Trial Optional)

Principal Investigator(s)	Year Awarded	Institution	Title
Gelb, Bruce D.; Chen, Rong; Balwani, Manisha	2022	Icahn School of Medicine at Mount Sinai	Using Electronic Medical Record Data to Shorten Diagnostic Odysseys for Rare Genetic Disorders in Children and Adults in Two New York City Health Care Settings
Gropman, Andrea Lynne; Berger, Seth I.; Vilain, Eric J.	2022	Children's Research Institute	Machine-Assisted Interdisciplinary Approach for Early Clinical Evaluation of Neurodevelopmental Disorders
Lalani, Seema R.; Lee, Brendan	2022	Baylor College of Medicine	Virtual Platforms for Genetics Evaluation in the Medically Underserved

https://ncats.nih.gov/programs/diagnostic-odyssey



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Increasing the number of treatments for rare diseases

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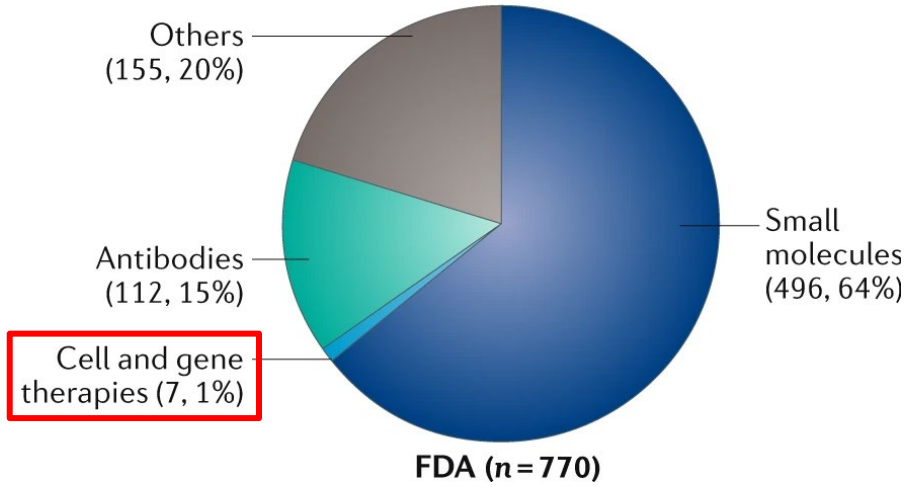
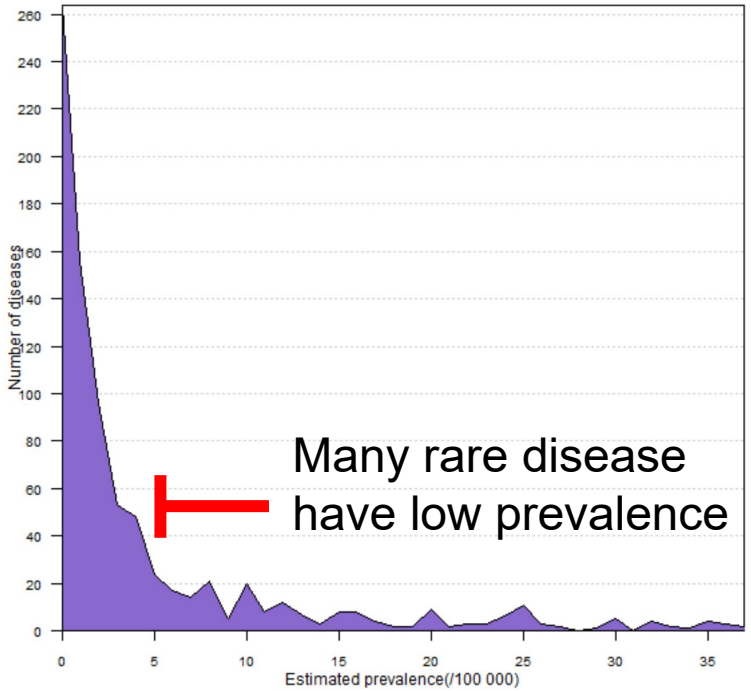
Translational Science is not based in any one organ or disease or discipline

The Promise of Translational Science for Rare Diseases

- Over 7,000 Rare Diseases with known molecular cause
  - ~85% are single gene disorders
  - ~50% onset in early childhood
- There is **little to no commercial interest or market incentives** in the rare disease space
- There are many different causes of rare diseases
  - The majority are thought to be genetic, **directly caused by changes in genes** or chromosomes.
  - Other rare diseases are caused by infections
  - Some are sporadic—not inherited: Rare cancers, and some autoimmune diseases

Development of Gene Therapies for Rare Diseases





Prevalence and incidence of rare diseases: Bibliographic data
***Orphanet*, January 2022**

Challenges:

- Access to expertise and resources
- Cost of development and manufacturing of gene therapy ($5M+)
- Lack of experience in FDA regulatory processes
- Intellectual property issues – both patents and proprietary methods/know-how

Opportunities:

- ~ 85% of rare and ultra-rare diseases are due to pathogenic variants in single genes that alter gene product function
- Development process can be improved, including manufacturing to increase accessibility for patients

Tambuyzer, E. et al. Nat Rev Drug Discov. 2020 Feb;19(2):93-111.

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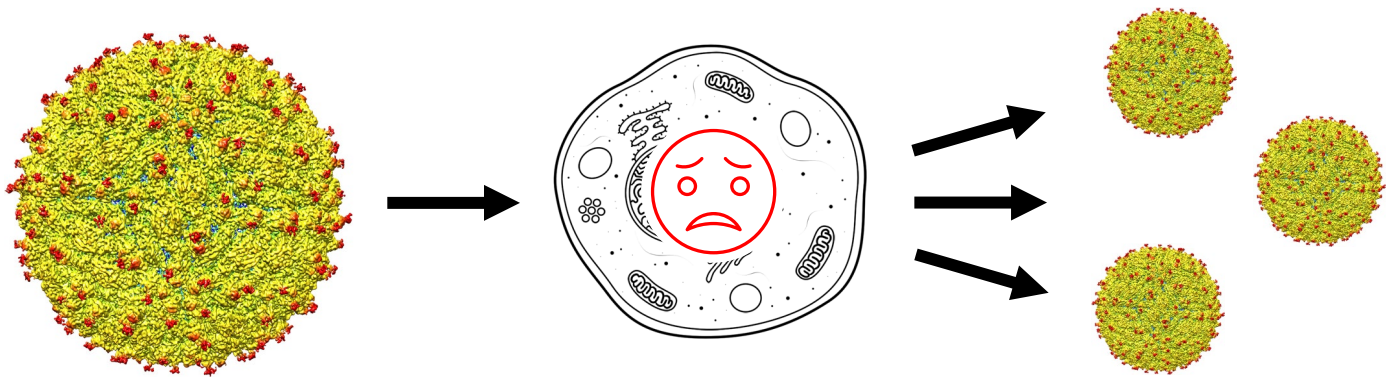
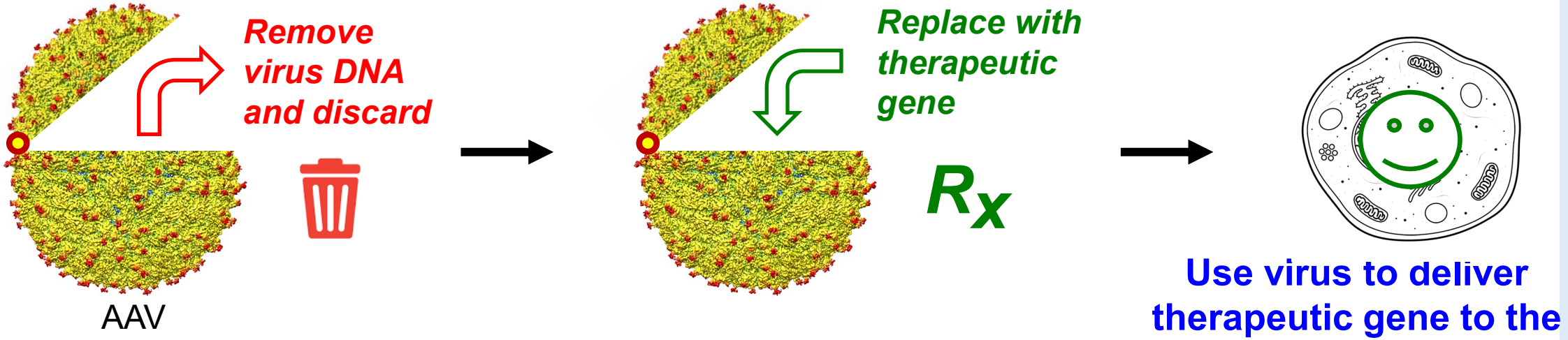
Normally, an adeno-associated virus injects its DNA (= genes) into a human cell to make more virus:



AAV

human cell

In **gene therapy**, we replace the viral DNA with a human therapeutic gene:



AAV

Use virus to deliver therapeutic gene to the patient's cells!

- **11 AAV serotypes identified**
- **AAVs differ in cell types they infect/target**
- **Can use specific AAV to infect specific cells**

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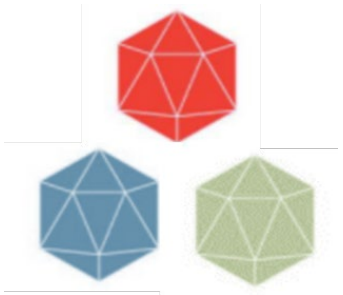
NIH Accelerating Medicines Partnership (AMP) Bespoke Gene Therapy Consortium (BGTC)

$89.4M PROGRAM

1 AAV Basic Biology Translational Implications



- Enhancing Vector Generation
- Enhancing therapeutic gene expression

Goal: Increase efficiency by orders of magnitude.

Crosstalk & Learnings

Therapies for patients

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

Gene therapy target for rare disease

Create & Build > Capacity	Harmonize best practices	Streamline Regulatory Paths
Vector generation	Manufacture of therapeutic	Clinical ability to treat patients

Goal: Standardized, faster, reduced $

Standard vector menu:

- Instructions for use
- Tropism
- Ease of use for gene type
- Non-proprietary tools

Standard process menu:

- Known safety database
- Facilitate preclinical testing
- Leverage existing and novel expertise in manufacturing processes and protocols

Standard delivery menu:

- Standard clinical and delivery protocols
- Establish Master File(s) for std vectors & facilitate out-licensing if appropriate

- Why we need to join hands across the globe to maximize trials for rare disease treatments and cures

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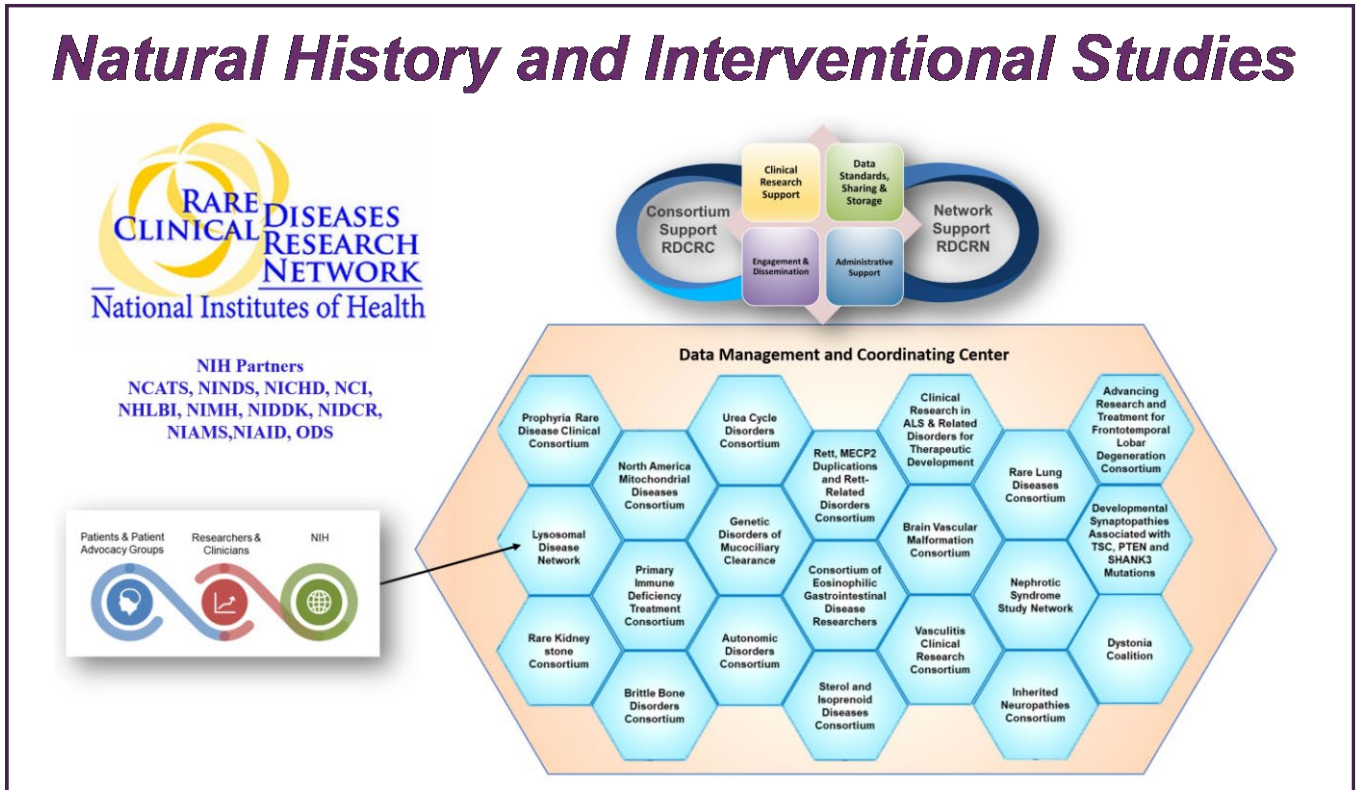
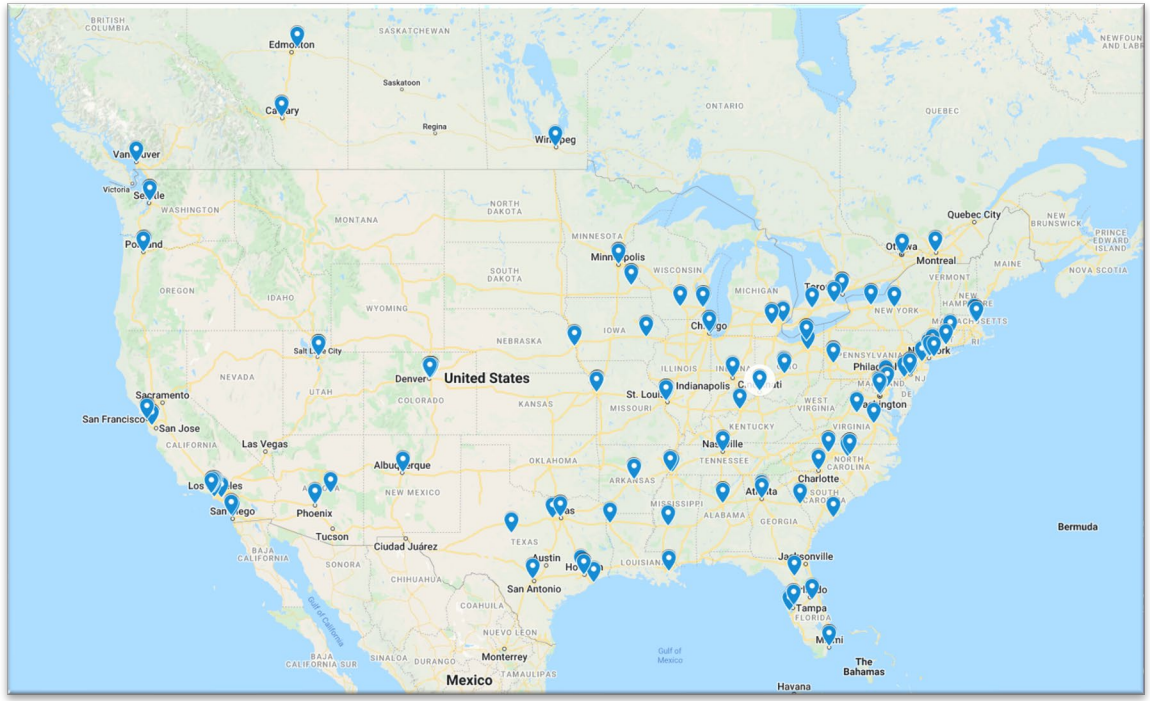
NCATS "Many Diseases at a Time" Research Programs: The Rare Disease Clinical Research Network (RDCRN)

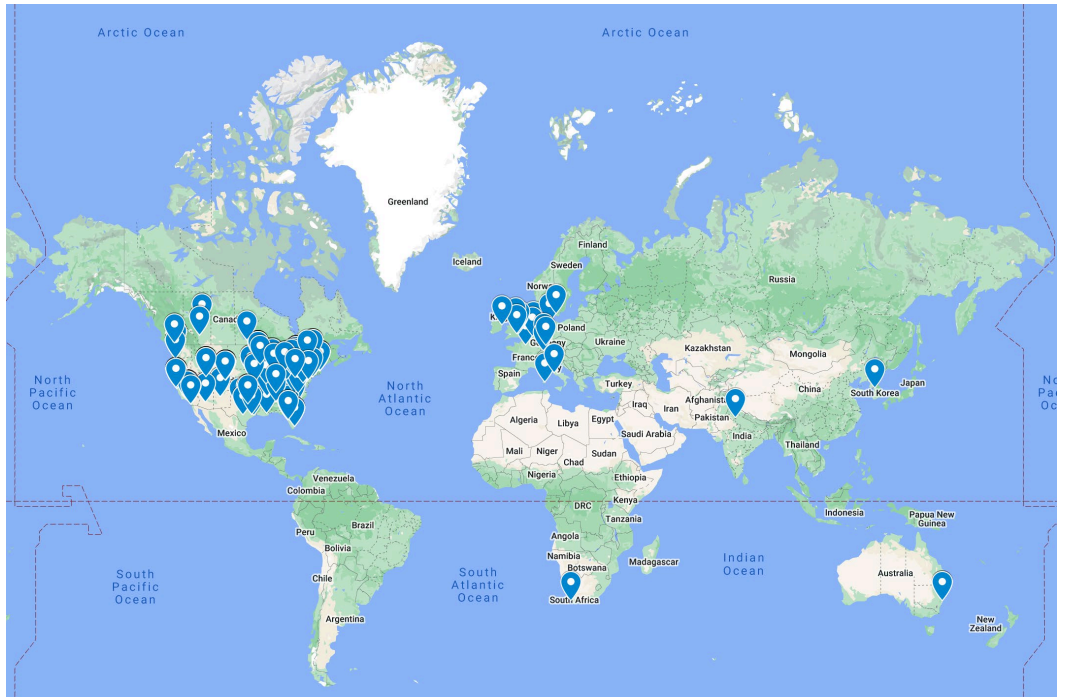
- **Facilitate clinical research by:**
  - 20 rare diseases research groups focusing on ≥3 related diseases
  - Sharing the costs of our research infrastructures across the network
  - Establishing uniform studies for data collection
  - Making meaningful large-scale natural hx studies possible
- **Directly engage with patients and their advocates**
- **Train new investigators in rare diseases research**



273 Clinical Sites

in the United States and internationally with affiliated patient advocacy groups





RARE DISEASES
CLINICAL RESEARCH NETWORK

Informational NCATS Resources for Patients & Patient Advocates

GARD
Genetic and Rare Diseases Information Center

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

Contact Center
- Individualized Support

Health Information Website
- General Information on Rare Diseases, finding support; ICD codes

New Beta Website to launch in 2021
-Focuses on Health Literacy and providing equitable access to information for patient communities

RareDiseases.info.nih.gov

Toolkit
For Patient-Focused Therapy Development

Who: Patient Groups
What: Therapeutic R&D

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 2.0

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Towards Improving Lives of Rare Disease Patients

- **A better understanding of disease burden on rare disease patients will inform research priorities in diagnostic and treatments for rare diseases**

  - Improve rare disease burden through coordinated research and disease understanding
  - Develop better methods to accelerate diagnosis and improve diagnostic accuracy
  - Accelerate treatment development with more precise data and platform-based approaches

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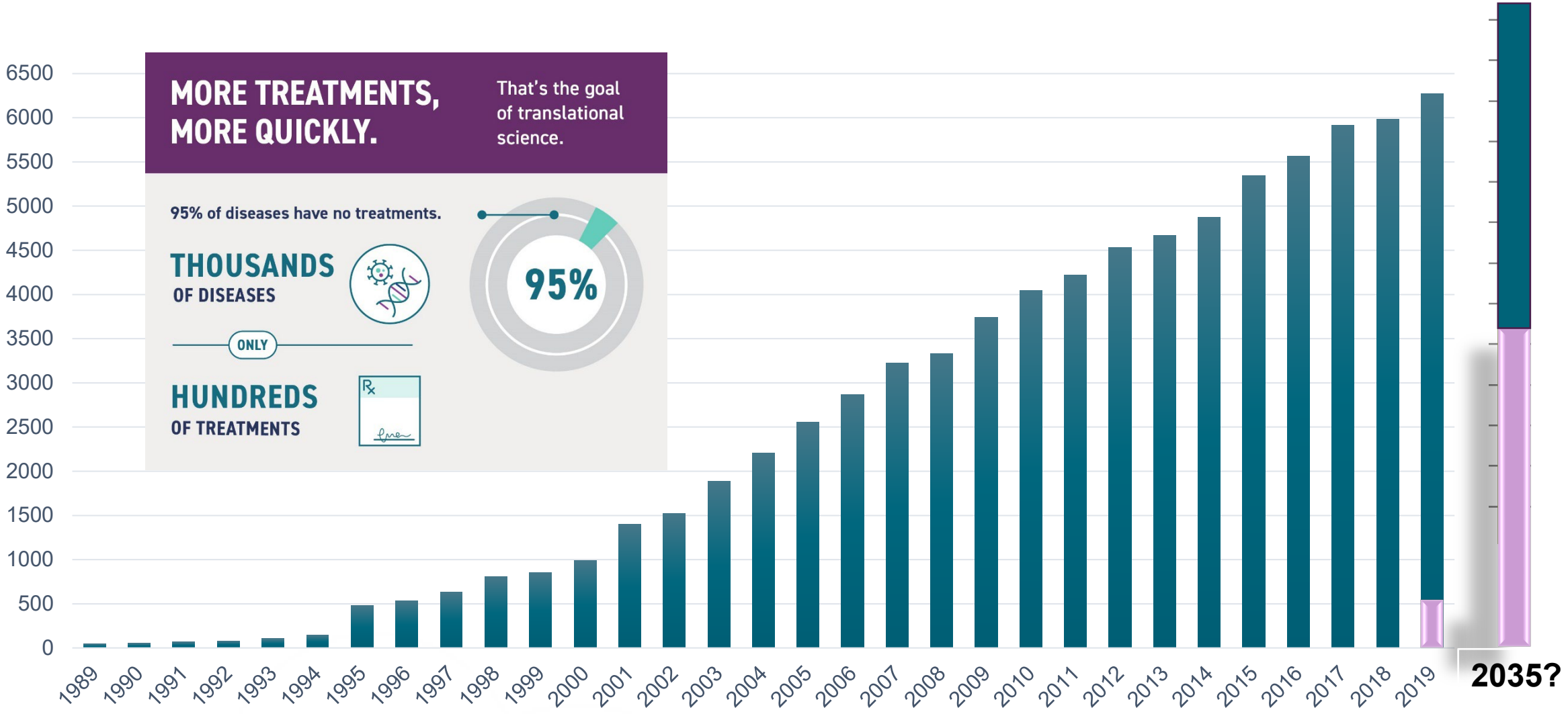
Diseases with Treatments in the Decade Ahead



Source: Online *Mendelian Inheritance in Man*, Morbid Anatomy of the Human Genome

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Rare Disease Day at NIH
February 28, 2023

This is a future VideoCast event

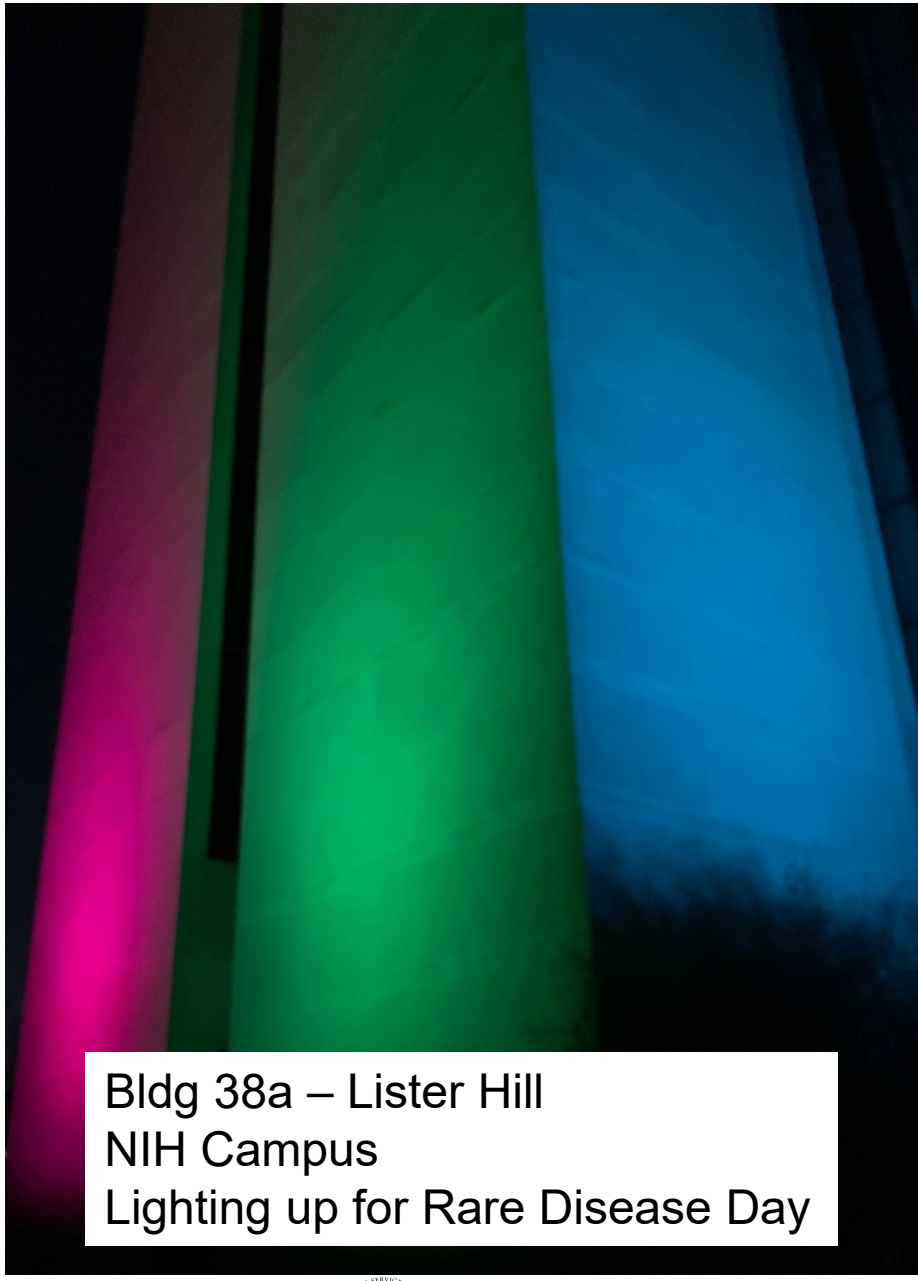
You will be able to view this event at
https://videocast.nih.gov/ on the day of the event.

Rare Disease Day at NIH 2023

Air date: Tuesday, February 28, 2023, 9:00:00 AM
Time displayed is Eastern Time, Washington DC Local

iCalendar: ICAL 2.0 *Add an upcoming event to your calendar.*

Description: Rare diseases affect an estimated 30 million people in the United States. On February 28, 2023, NIH will host its annual Rare Disease Day event to raise awareness about these disorders, the people they affect, and NIH collaborations that advance research for new treatments. Sponsored by the National Center for Advancing Translational Sciences (NCATS) and the NIH Clinical Center, the event will feature panel discussions, rare diseases stories, and more. Participants can share their thoughts, photos, and experiences via social media using the hashtag #RDDNIH. Explore virtual exhibits, view scientific posters, and network with attendees and speakers in this year's event app (details TBD).



Bldg 38a – Lister Hill
NIH Campus
Lighting up for Rare Disease Day

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Annie Kennedy

Chief of Policy, Advocacy, and Patient Engagement