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
October 17, 2022
Why we need to “move the needle” on rare diseases
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.
Diseases of Known Molecular Basis with Treatments

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

Individual medical costs for people with a rare disease are 3–5 TIMES greater than for those who do not have a rare disease.

The medical costs of rare diseases have been underestimated.

Yearly direct medical costs estimated at around $400 BILLION are similar to those of cancer, heart failure and Alzheimer’s disease.

Rare diseases are collectively common, affecting an estimated 25–30 MILLION people in the United States.

Source: The IDEaS Initiative; Pilot Study to Assess the Impact of Rare Diseases on Patients and Healthcare Systems
Shortening the rare disease diagnostic odyssey
Five sources comprise 10,577 unique rare disease concepts.

Only 333 shared disease concepts in all five sources:

- NCIT
- DOID
- GARD
- Orphanet
- OMIM

Many diseases are in only one source.

https://www.nature.com/articles/d41573-019-00180-y
Different countries define “rare” differently (keionline.org)

- Several countries do not have a definition in legislation
- Prevalence 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 systems

- 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

The exact number of rare diseases is hard to determine

<table>
<thead>
<tr>
<th>Absolute prevalence</th>
<th>Percentage prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US</strong> &lt;200,000</td>
<td>EU &lt;1 in 2,000</td>
</tr>
<tr>
<td><strong>Japan</strong> &lt;50,000</td>
<td><strong>Australia</strong> &lt;1 in 20,000</td>
</tr>
<tr>
<td><strong>S. Korea</strong> &lt;20,000</td>
<td><strong>EU</strong> &lt;1 in 2,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9 different names for 1 disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-beta-hydroxylase deficiency</td>
</tr>
<tr>
<td>Other names: Adrenal hyperplasia 4; Adrenal hyperplasia hypertensive form; Adrenal hyperplasia IV; CAH due to 11-beta-hydroxylase deficiency; Congenital adrenal hyperplasia due to 11-beta-hydroxylase deficiency; CYP11B1 deficiency; P450c11b1 deficiency; Steroid 11-beta-hydroxylase deficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4 different names for 1 disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>12q14 microdeletion syndrome</td>
</tr>
<tr>
<td>Other names: Del(12)(q14); Deletion 12q14; Monosomy 12q14; Osteopoikilosis-short stature-intellectual disability syndrome</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Principal Investigator(s)</th>
<th>Year Awarded</th>
<th>Institution</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gelb, Bruce D.; Chen, Rong; Balwani, Manisha</td>
<td>2022</td>
<td>Icahn School of Medicine at Mount Sinai</td>
<td>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</td>
</tr>
<tr>
<td>Gropman, Andrea Lynne; Berger, Seth I.; Vilain, Eric J.</td>
<td>2022</td>
<td>Children’s Research Institute</td>
<td>Machine-Assisted Interdisciplinary Approach for Early Clinical Evaluation of Neurodevelopmental Disorders</td>
</tr>
<tr>
<td>Lalani, Seema R.; Lee, Brendan</td>
<td>2022</td>
<td>Baylor College of Medicine</td>
<td>Virtual Platforms for Genetics Evaluation in the Medically Underserved</td>
</tr>
</tbody>
</table>

https://ncats.nih.gov/programs/diagnostic-odyssey
Increasing the number of treatments for rare diseases
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

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

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

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

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

- **Remove virus DNA and discard**
- **Replace with therapeutic gene**

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

**AAV BASIC BIOLOGY TRANSLATIONAL IMPLICATIONS**

1. **Vector generation**
   - Gene therapy target for rare disease

**ENHANCING VECTOR GENERATION**

2. **Hospitalization best practices**
   - Known safety database
   - Facilitate preclinical testing
   - Leverage existing and novel expertise in manufacturing processes and protocols

**ENHANCING THERAPEUTIC GENE EXPRESSION**

3. **Streamline regulatory pathways**
   - Standard clinical and delivery protocols
   - Establish Master File(s) for std vectors & facilitate out-licensing if appropriate

**Crosstalk & Learnings**

- Goal: Increase efficiency by orders of magnitude.
- Therapies for patients
- Goal: Standardized, faster, reduced $89.4M PROGRAM

**ADVANCING ACCESS TO AAV TECHNOLOGIES AND VECTORS FOR BESPOKE CLINICAL APPLICATIONS**

- **Create & Build > Capacity**
  - Standard vector menu:
    - Instructions for use
    - Tropism
    - Ease of use for gene type
    - Non-proprietary tools

- **Manufacture of therapeutic**
  - Standard process menu:
    - Known safety database
    - Facilitate preclinical testing
    - Leverage existing and novel expertise in manufacturing processes and protocols

- **Clinical ability to treat patients**
  - 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
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
Informational NCATS Resources for Patients & Patient Advocates

**GARD**
- **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](https://rarediseases.info.nih.gov)

**Toolkit**
- **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](https://toolkit.ncats.nih.gov)

**RaDaR**
- **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](https://registries.ncats.nih.gov)

GARD 2.0
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
Diseases with Treatments in the Decade Ahead

MORE TREATMENTS, MORE QUICKLY. That’s the goal of translational science.

95% of diseases have no treatments.

THOUSANDS OF DISEASES

HUNDREDS OF TREATMENTS

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

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
Thank You!

Learn More Today

Visit us at ncats.nih.gov

Follow Us:

@ncats.nih.gov
@ncats.nih.gov
@ncats.nih.gov
NIH-NCATS
NCATSMedia
#NCATS
Annie Kennedy
Chief of Policy, Advocacy, and Patient Engagement