Rare Diseases Research

-a perspective

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National Center for Advancing Translational Sciences, NIH

National Disabilities Forum

November 7, 2017

NCATS and ORDR

- National Center for Advancing Translational Sciences (NCATS)
  - Established to transform the translational process so that new treatment and cures for disease can be delivered to patients faster
  - Translation = process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals and the public
    - Disease agnostic, not focused on a specific disease or therapeutic area
    - Emphasizes innovation and collaboration

Office of Rare Diseases Research (ORDR)

Mission

"Accelerating rare diseases research to benefit patients"

ORDR facilitates coordination between multiple stakeholders in the rare diseases community, including scientists, clinicians, patients, and patient groups

What is a Rare Disease

- Rare disease (aka Orphan disease) defined in US as:

  "Disease or condition affecting fewer than 200,000 persons in the US"

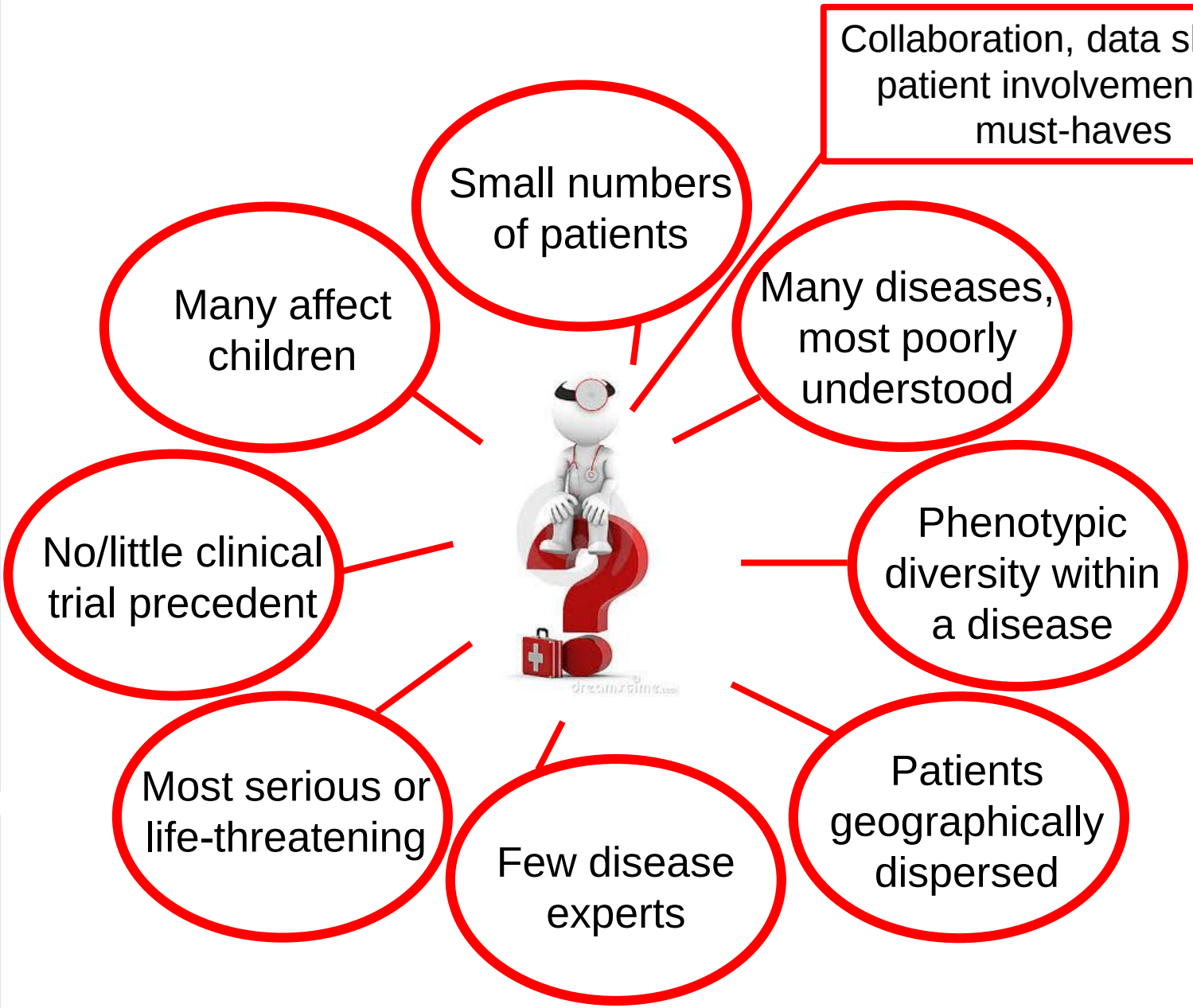
- Most are far less prevalent than this
  - Most a few hundred – a few thousand
- Highly diverse collection of ~6-7,000 diseases and conditions
  - Collectively affect ~8% of US population
  - ~25M Americans
  - ~80% are genetic, ~50% manifest in children
  - 95% have no approved therapies – area of substantial unmet medical needs
- Collectively, a large public health consideration

Orphan Drug Act (ODA) 1983, amended for prevalence 1984
Rare Disease Act (RDA) 2002

Rare diseases, a few milestones in history

- 1983 ODA
  - FDA Office of Orphan Products established
  - Many other countries and regions follow thereafter
- 1989
  - Report from the National Commission
  - Advised to set up Office of Rare Diseases (ORD) at NIH
- 1999
  - Coordination of Rare Diseases Research commission convened by NIH OD
  - 2001 Report issued
- 2002 Rare Diseases Act
  - ORD name changed to ORD Research (ORDR)
  - 2003 Rare Diseases Clinical Research Network established through NIH ORDR
  - GARD information center
- 2008
  - Undiagnosed Diseases Program (UDP) established at NIH Clinical Center
  - RDCRN2
- 2010
  - IOM Rare Diseases Report
  - International Rare Diseases Research Consortium (IRDiRC)
  - FDA Rare Diseases Program established
  - RCDC – quantification through NLM for Orphan drugs development at NIH
- 2013
  - Undiagnosed Diseases Network (UDN) established
  - RCDC categorization of NIH research for all rare diseases
  - RDCRN3
- 2015
  - UDN-I (international)
  - First gene therapy approved in Europe
- 2017
  - First gene therapy approved in US (followed one month later by another)
- 2019 RDCRN4

Rare Diseases Research Challenges



National Center for Advancing Translational Sciences

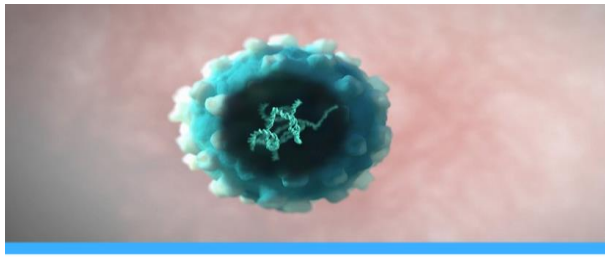
Many Opportunities

Looking Forward: Wearables in Clinical Trials and Post-Approval Programs

Mary James, Patient & Physician Services - December 03, 2015

In my previous blog post, I discussed the definition of mHealth and how current technologies can be used to assist in clinical trials and post-approval programs. I recently returned from this year's mHealth Summit in Washington, D.C., where the focus was not only on mobile applications and expanded communication to patients, but on wearable trackers. Wearable trackers have seen a

U.S. FDA Approves Biogen's SPINRAZA™ (nusinersen), The First Treatment for Spinal Muscular Atrophy



The First Gene Therapy for Children Has Just Been Approved in Europe

This is huge.

DAVID NIELD 3 JUN 2016

msJAMA

February 14, 2001

More

The Internet and Medicine: Building a Community for Patients With Rare Diseases

Mary Patsos

Author Affiliations

JAMA. 2001;285(6):805. doi:10.1001/jama.285.6.805-JMS0214-2-1

The evolution of the Internet has transformed the definition of community for the patient with a rare disease. With the availability of Web pages, bulletin board services, chat rooms, forums, webcams, electronic mailings, video and audio clips, patients with rare diseases finally have a medium to voice their feelings of alienation, bewilderment, and apprehension. They are no longer limited to communicating via traditional face-to-face meetings, telephone, and mail services. With the Internet, members of this neglected and vulnerable population have at their fingertips the tools necessary to relieve fears and answer questions about their specific disease.

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Using big data to understand rare diseases

Date: Wednesday, July 27, 2016, 6:00pm to 7:00pm

See also: For the Public, Bioinformatics

Location: Broad Institute, 415 Main Street, Kendall Square, Cambridge

Midsummer Nights' Science 2016

nature International weekly journal of science

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News & Comment > News > 2017 > April > Article

NATURE | SCIENTIFIC AMERICAN

3-D printed windpipe gives infant breath of life

A flexible, absorbable tube helps a baby boy breathe, and heralds a future of body parts printed on command.

Marissa Fessenden

28 May 2013

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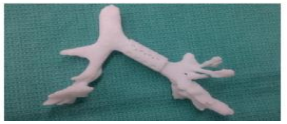
An article by Scientific American.

Kaiba Gionfriddo was six weeks old when he suddenly stopped breathing and turned blue at a restaurant. Kaiba's parents quickly rushed him to the hospital where they learned that his left bronchial tube had collapsed because of a previously undetected birth defect. During the



Two Ways Telemedicine Can Change the Way We Treat Rare Diseases

Have you heard of Brugada syndrome? What about protoporphyria, or Guillain-Barré syndrome? Most people, even health care professionals, haven't heard of them. Afterall, these diseases are uncommon in the general population. Definitions vary, but in the United States, a disease is considered rare if it affects fewer than 200,000 people. Unfortunately, there are thousands of rare diseases. The Rare Disease Foundation estimates that between 1 in 12 and 1 in 13 people will suffer from a rare disease in his

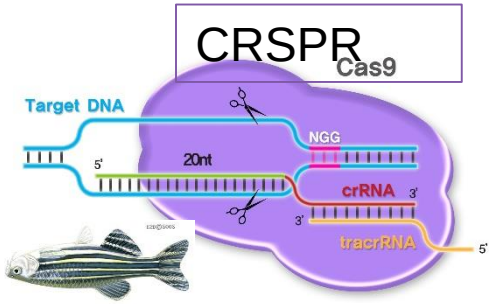
SHORT SHARP SCIENCE 18 October 2016

Dr House goes digital as IBM's Watson diagnoses rare diseases

Penn-led Team Presents Results from Clinical Trial of Personalized Cellular Therapy in Brain Tumor Patients

Investigational "Hunter" T Cells Expand in Blood and Traffic to Glioblastoma Tumors

April 18, 2016



NIH National Center for Advancing Translational Sciences

Rare Diseases Research

- Highly diverse area of research
  - Many stakeholders, multi-disciplinary, many approaches
    - Drugs, biologics (enzyme replacement, gene therapy, gene editing), diagnostics, devices, genetic testing
- Funding and programs from many sources
  - Foundations
  - Non-profits
  - Academia
  - Industry
  - Government
- NIH
  - ~4B in RD research in 2016 (12.5%)
    - Relatively proportional to Institute/Center budget
    - NCI>NIAID>NIDDK, etc
  - ~90% to extramural programs
    - Mainly to research grants
  - Many networks
    - RDCRN, many pediatric, and therapeutic area specific

Rare Diseases Clinical Research Network (RDCRN)

- Network of “Centers of Excellence” grouped around rare disease (RD) therapeutic areas
- RDCRN’s purpose
  - Facilitate RD research through establishment or continuation of RD clinical research consortia
  - Physicians, scientists, and multi-disciplinary teams work together with patient advocacy groups (PAGs) to study rare diseases
- RDA 2002:
  - [NIH shall] “…enter into cooperative agreements with and make grants from regional centers of excellence on rare diseases…”

Rare Disease Act of 2002

RDCRN (2)

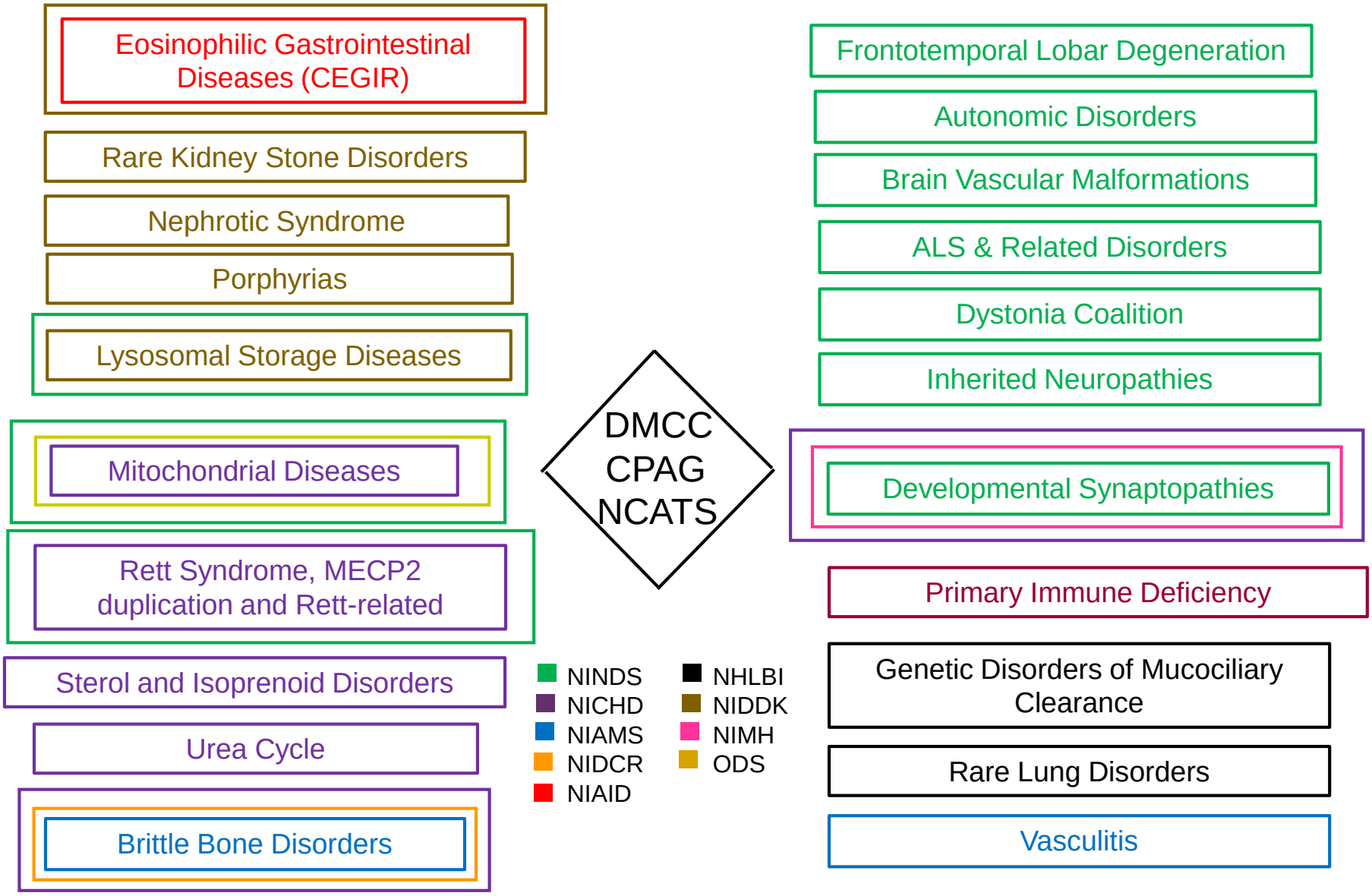
- Established in 2002
  - In 3rd 5-year award cycle
- Current cycle (2014-2019):
  - 21 consortia
  - Data Management and Coordinating Center (DMCC)
    - Data sharing, data coordination
- Criteria
  - Grouped by therapeutic area
    - 3 or more diseases within a consortium
  - Multi-center within a consortium
  - Co-funding NCATS + other NIH Institutes/Centers (ICs)
  - At least one PAG
  - 2 or more studies
    - 1 must be observational, such as a registry or natural history study
    - Pilot studies
  - Training

RDCRN(3)

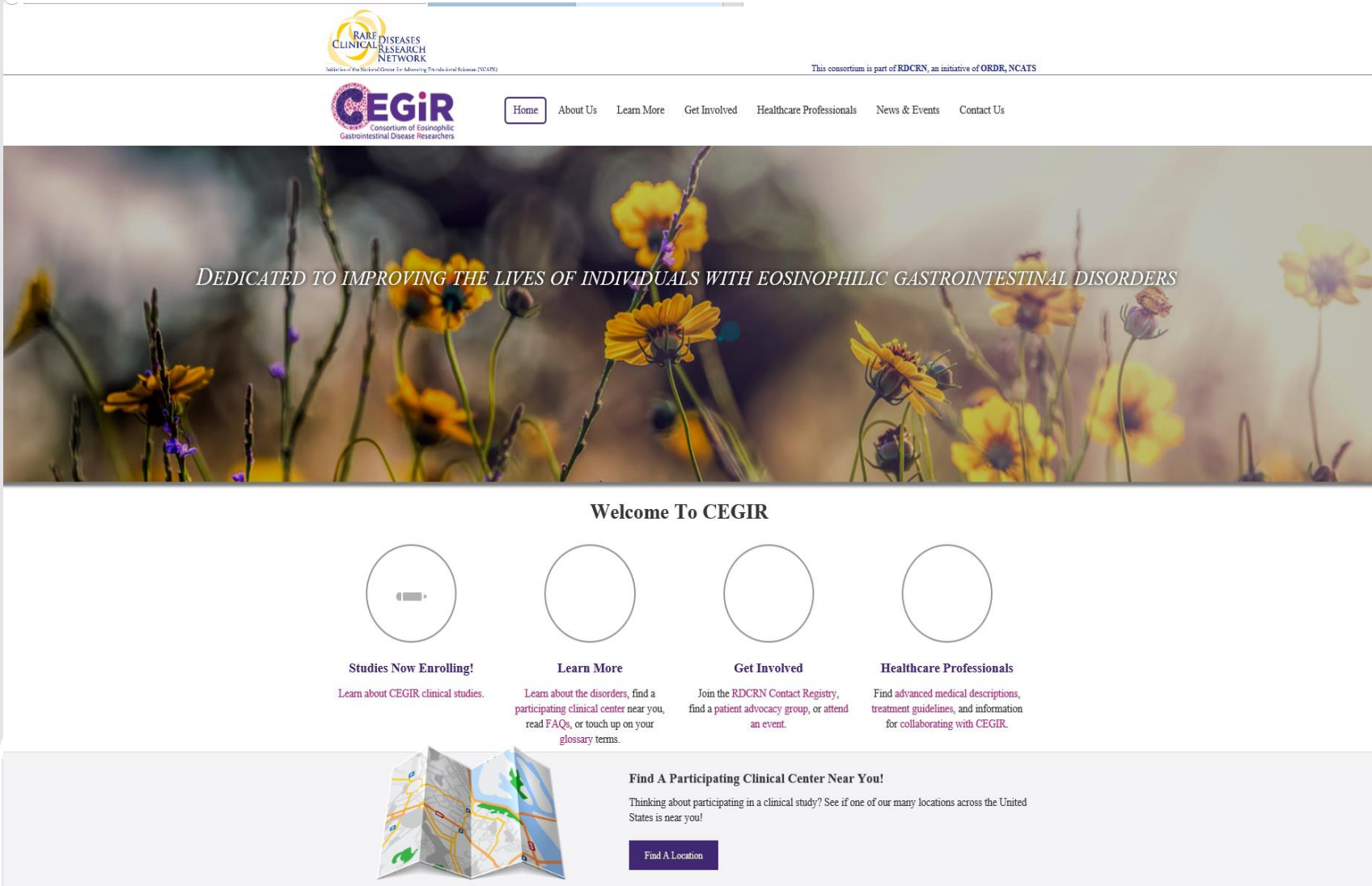
- Very successful program
  - Currently have ~200 rare diseases in the RDCRN
  - ~450 clinical centers worldwide
  - ~100 active protocols
  - >43,000 patients have been enrolled
  - ~350 trainees
  - ~140 PAGs

- Planned 4th cycle (2019-2023)
  - Program announcement: stay tuned https://ncats.nih.gov/connect

RDCRN Consortia



Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGiR)



https://www.rarediseasesnetwork.org/cms/CEGIR

National Center for Advancing Translational Sciences

CEGiR

- Principle Investigator: Marc Rothenberg
- Lead Center: Cincinnati Children's Hospital Medical Center
- Diseases under study: Eosinophilic esophagitis, eosinophilic gastritis, eosinophilic colitis
- Established: 2014
- Aims:
  - Promote collaboration
  - Attract, train and mentor future investigators
  - Collect longitudinal data
  - Develop a better understanding of the diseases' natural history
    - Biomarkers, clinical outcome assessments, etc.
  - Optimize disease therapy
  - Conduct pilot studies
  - Develop a comprehensive website
- Co-funded by: NIAID, NIDDK, NCATS

Chapters 15&16
--The North American Mitochondrial Disease Consortium: a Developing Knowledge Commons
--The Consortium of Eosinophilic Gastrointestinal Disease Researchers: An Emerging Knowledge Commons

"…how efficient the RDCRN approach appears to have been in promoting large-scale collaboration… The RDCRN approach seems to reduce barriers to cooperation primarily by providing institutional infrastructure that leverages physicians' intrinsic motivations to advance science and treat patients..."

Cambridge University Press 2017

https://doi.org/10.1017/9781316544587

Key Points: #1 Patients

- >6-7,000 rare diseases
- ~25 million Americans
- Many undiagnosed
- <500 approved treatments

Key Points #2 & #3

- Rare Diseases – and rare disease research – are highly diverse
  - Many diseases, stakeholders, approaches, and an active area of research innovation
  - However, share some common needs:
    - Infrastructure
    - Centers of excellence
    - Collaborative/collective approaches
  - International collaboration usually necessary
    - E.g., EU has set up rare diseases reference network
- Hard to recognize, diagnose and quantify
  - “Diagnostic odyssey”
  - Need:
    - Granular coding dictionaries
    - Registries
    - Outcome measures, standards and guidelines

Contact Information

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