RARE CLINICAL DISEASES RESEARCH NETWORK

National Institutes of Health

A Model Structure for Advancing Rare Diseases Research

April 16, 2013

Jeffrey Krischer, PhD

Office of Rare Diseases Research
National Center for Advancing Translational Sciences – NIH

Rare Clinical Diseases Research Network
National Institutes of Health

RDCRN Overview

- Established by the Office of Rare Diseases Research
- 2003--10 Consortia supported by ORDR, NCRR, NINDS, NIAMS, NICHD, NHLBI, NIDDK
- 2009--17 Consortia supported by ORDR, NINDS, NIAMS, NICHD, NHLBI, NIDDK, NIAID, NIDCR, NCI
- 192 institutions around the world
- 2,290 consortium members
- 90+ patient advocacy groups
- 174 trainees
- 87 accruing studies

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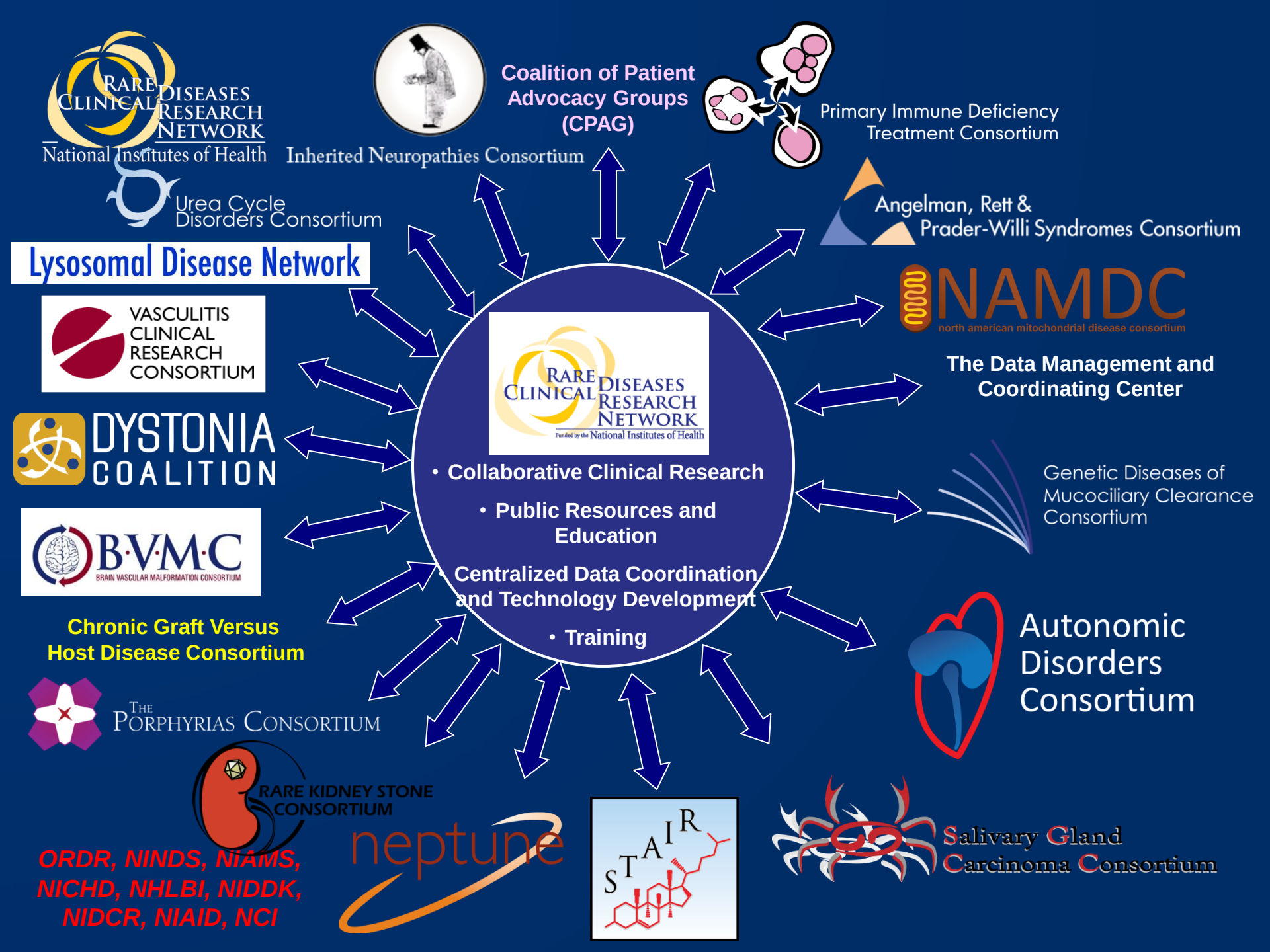
Goals of the RDCRN

- Facilitate clinical research by:
  - Creation of Consortia focused on related diseases
  - Cost-sharing research infrastructures
  - Establishing uniform protocols for data collection
  - Making meaningful large-scale studies possible
    - Longitudinal cohorts, pilot projects, and randomized trials
- Directly engage patients and their advocates
- Train new investigators in rare diseases research


Rare Clinical Diseases Research Network
National Institutes of Health
Coalition of Patient Advocacy Groups (CPAG)
Primary Immune Deficiency Treatment Consortium
Inherited Neuropathies Consortium
Urea Cycle Disorders Consortium
Angelman, Rett & Prader-Willi Syndromes Consortium
Lysosomal Disease Network
NAMDC
north american mitochondrial disease consortium
VASCULITIS CLINICAL RESEARCH CONSORTIUM
The Data Management and Coordinating Center
Rare Clinical Diseases Research Network
Funded by the National Institutes of Health
DYSTONIA COALITION
• Collaborative Clinical Research
• Public Resources and Education
• Centralized Data Coordination and Technology Development
• Training
Genetic Diseases of Mucociliary Clearance Consortium
B·V·M·C
BRAIN VASCULAR MALFORMATION CONSORTIUM
Chronic Graft Versus Host Disease Consortium
Autonomic Disorders Consortium
The Porphyrias Consortium
RARE KIDNEY STONE CONSORTIUM
neptune
STAIR
Salivary Gland Carcinoma Consortium
ORDR, NINDS, NIAMS, NICHD, NHLBI, NIDDK, NIDCR, NIAID, NCI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Coalition of Patient Advocacy Groups (CPAG)
Dystonia Coalition
Chronic Graft Versus Host Disease Consortium
North America Mitochondrial Diseases Consortium
Genetic Disorders of Mucociliary Clearance Consortium
Primary Immune Deficiency Treatment Consortium
Porphyria Rare Disease Clinical Research Consortium
The Data Management and Coordinating Center
Vasculitis Clinical Research Consortium
Rare Clinical Diseases Research Network
Funded by the National Institutes of Health
Lysosomal Disease Network
Rare Kidney Stone Consortium
• Collaborative Clinical Research
• Centralized Data Coordination and Technology Development
• Public Resources and Education
• Training
Inherited Neuropathies Consortium
Nephrotic Syndrome Rare Disease Clinical Research Network
Urea Cycle Disorders Consortium
Angelman, Rett and Prader-Willi Syndromes Consortium
Molecular and Epidemiologic Characterization of Salivary Gland Carcinomas Consortium
Brain Vascular Malformation Consortium
ORDR, NINDS, NIAMS, NICHD, NHLBI, NIDDK, NIDCR, NIAID, NCI
Sterol and Isoprenoid Diseases Consortium
Autonomic Rare Diseases Clinical Research Consortium

Basic Units of the RDCRN: DMCC & Rare Disease Consortia

(Only 2 of 17 Consortia shown for clarity)

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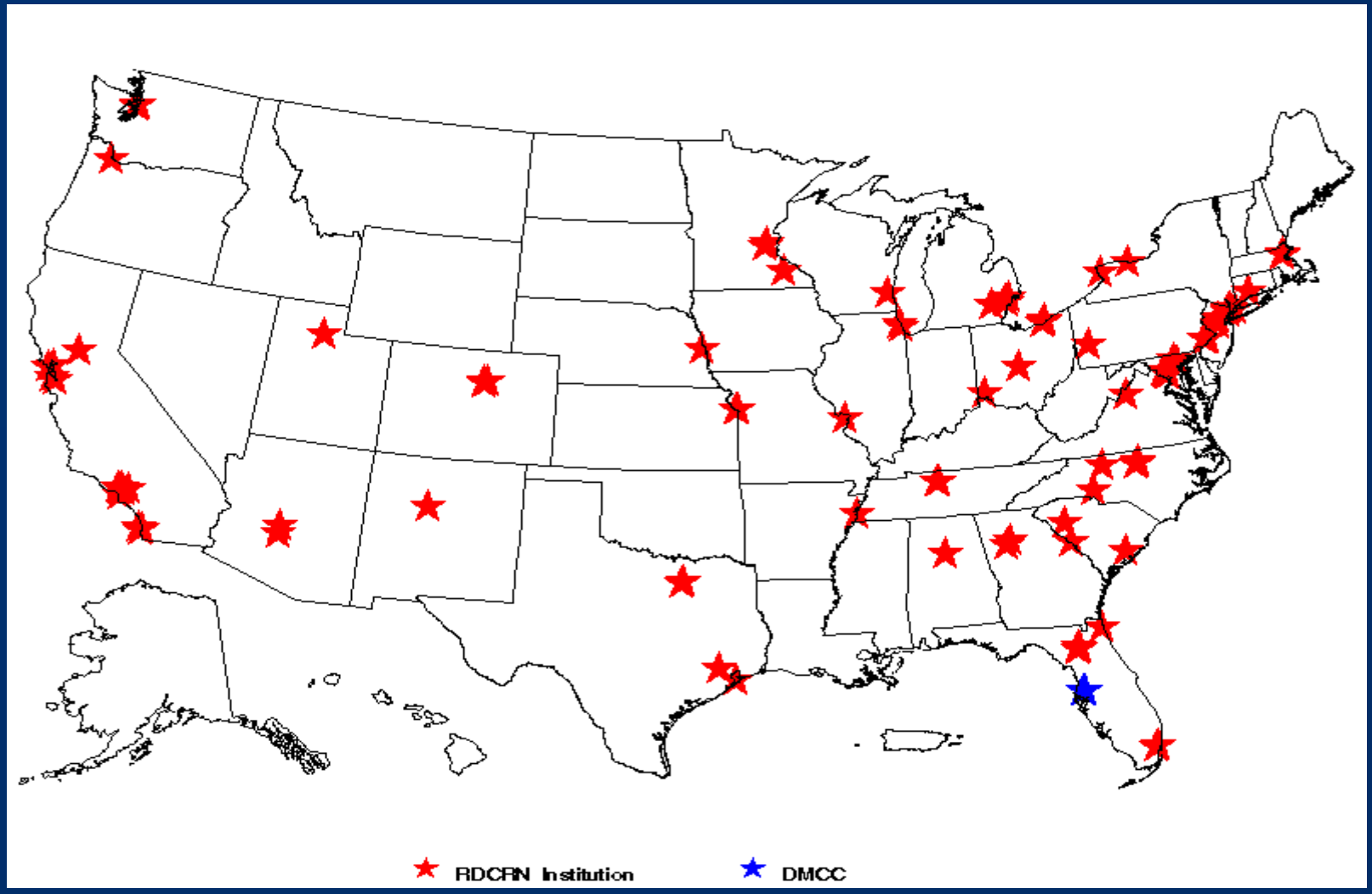
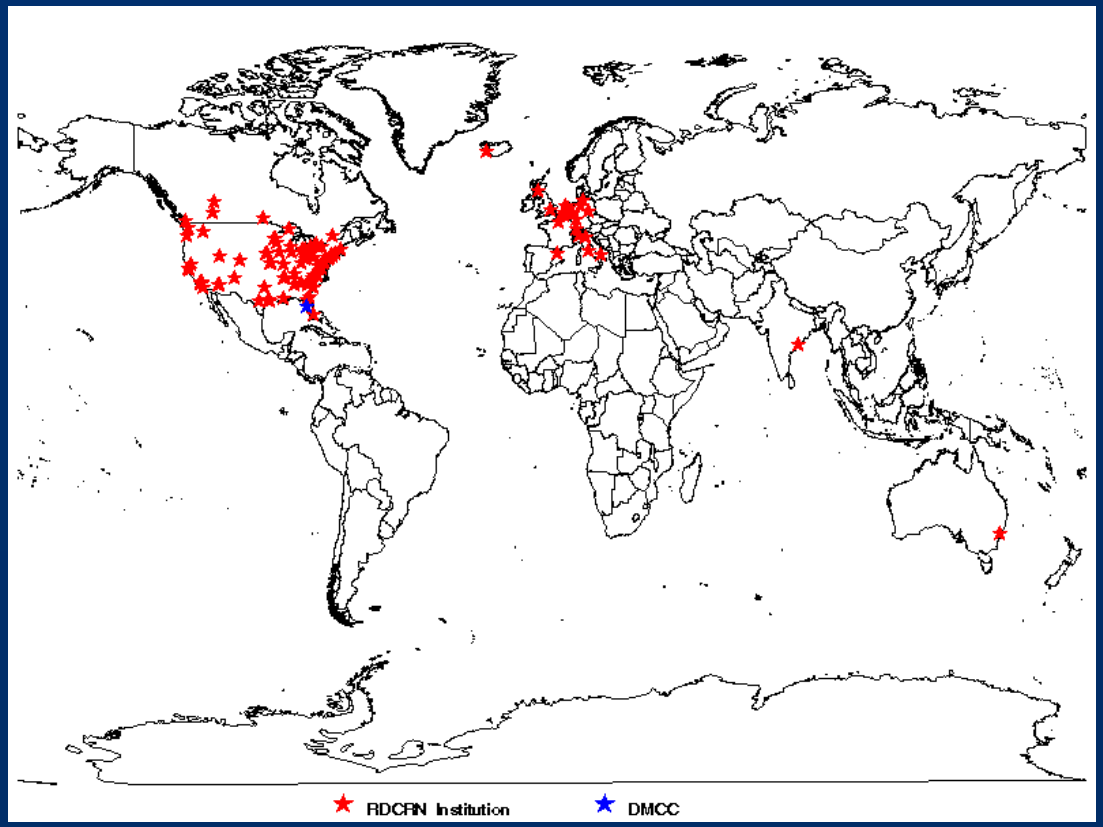
RDCRN U.S. Sites



RDCRN International Sites

- Australia (INC)
- Belgium (DC)
- Canada (BVMC, DC, LDN, MCC, NAMDC, NEPTUNE, PIDTC, RKSC, STAIR, UCDC, VCRC)
- England (DC, INC)
- France (DC, RKSC)
- Germany (DC, INC, RKSC, UCDC)
- Iceland (RKSC)
- India (DC)
- Italy (DC, INC, RKSC)
- Netherlands (DC, RKSC)
- Scotland (DC)
- Spain (RKSC)
- Switzerland (UCDC)



Vasculitis Clinical Research Consortium

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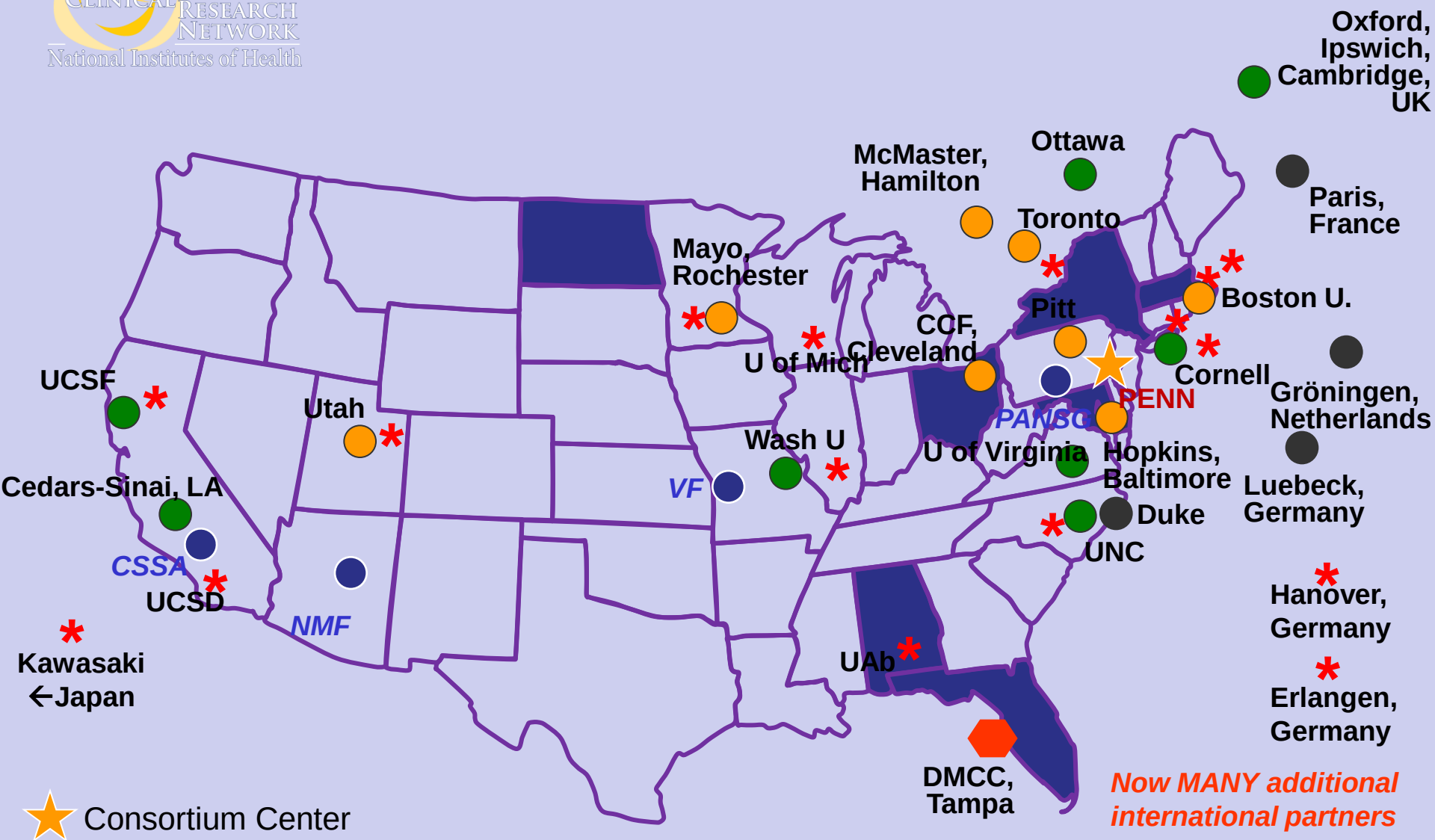


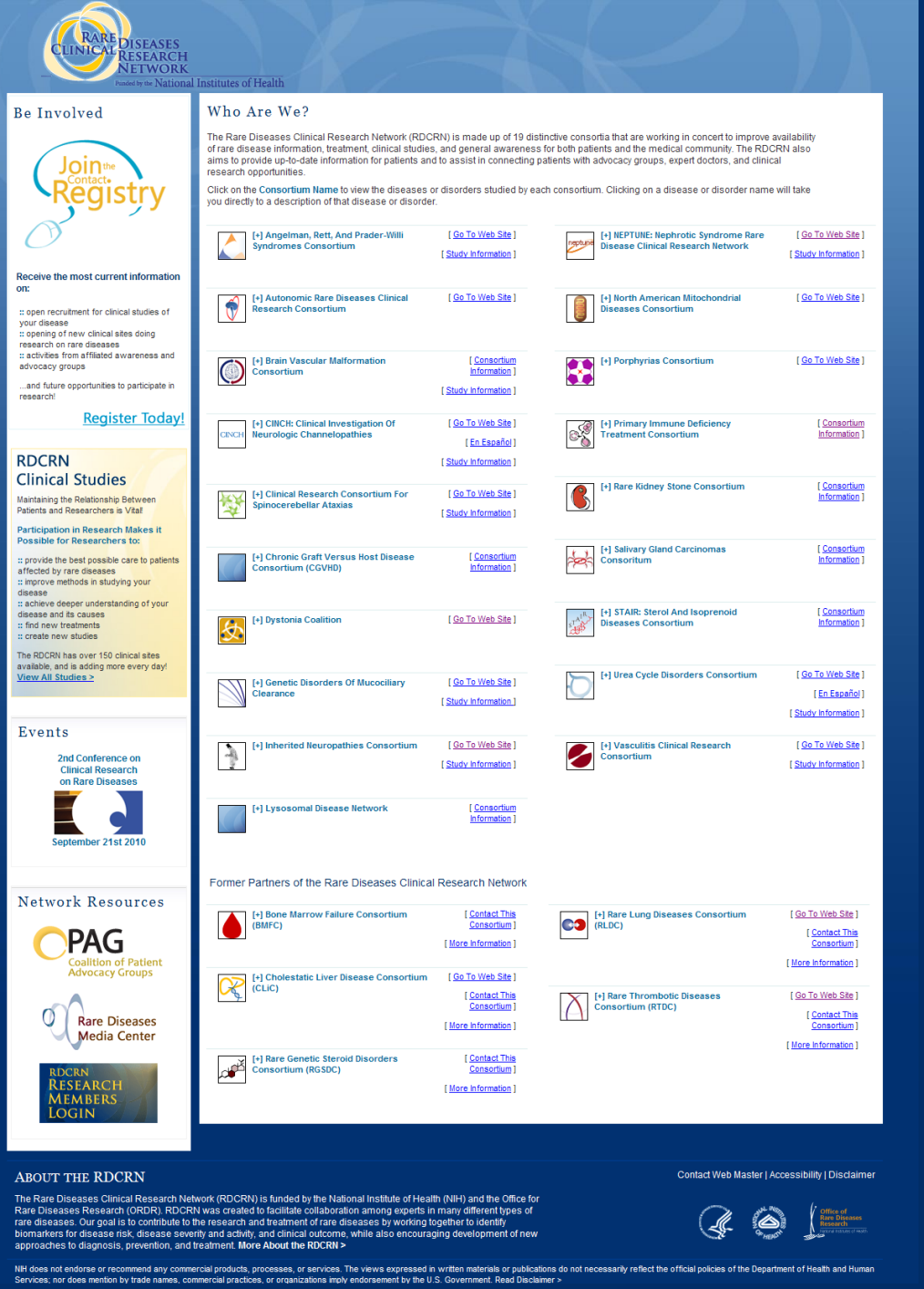
VASCULITIS CLINICAL RESEARCH CONSORTIUM

Basic Units of the RDCRN: DMCC & Rare Disease Consortia

(Only 2 of 17 Consortia shown for clarity)

Data Management and Coordinating Center (DMCC)

- Supports RDCRN by providing technologies, tools, and support of study design and data analysis
- On-line protocol management system
  - Patient enrollment/randomization
  - Data entry and collection with data standards
  - Adverse event reporting
- Protocol training for research staff
- Members' website: documentation, databases
- Hosts RDCRN public website (>3 million hits/year)
- Oversees the RDCRN Patient Contact Registry



RDCRN Website

http://rarediseasesnetwork.org

- Portal to websites for each Consortium
- Portal to members' website
- Portal for patient advocacy groups
- RDCRN Contact Registry
- 3+ million hits/yr

DMCC Technologies/Tools

- Web-based data management system
  - Public Website
  - Consortium Portal
  - Full Study Support
- Adverse event reporting and review
- Specimen Tracking
  - Collection, Shipment, Receipt
- Pharmacy System
  - Treatment assignment, inventory, dose management
- Patient Contact Registry

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Study Design and implementation

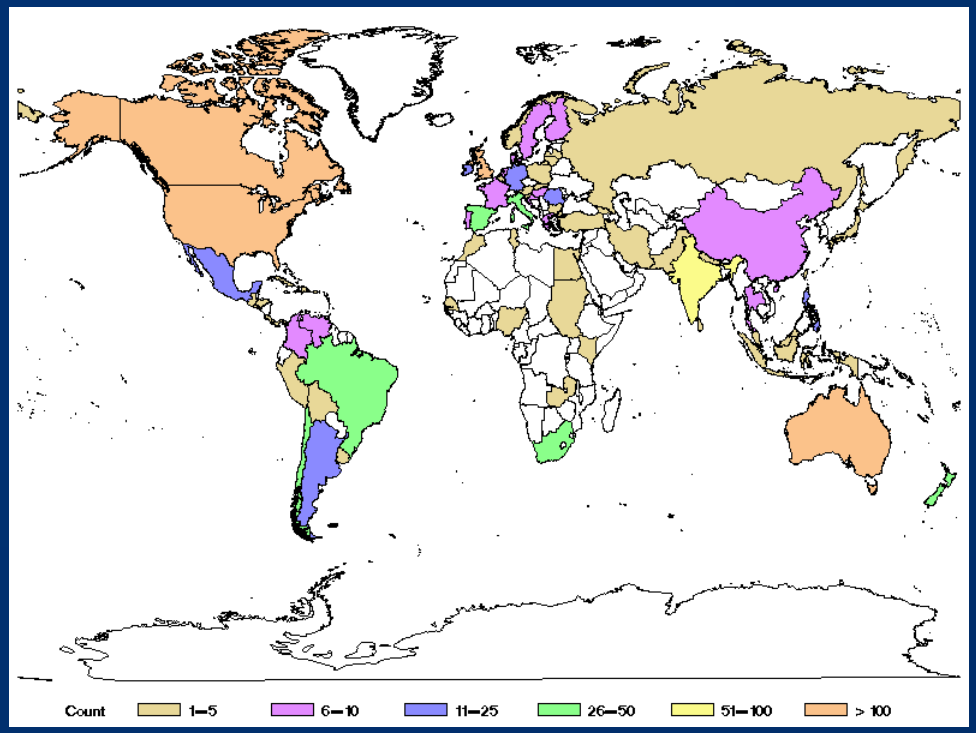
- Identifying population to draw from.
- Estimating event rates.
- Genotype-phenotype correlations.
- Hypothesis testing.

Members' Website Resources

- Automated Slide Sets
- RDCRN Power Point Template Slides
- RDCRN, NIH and Consortium Logos
- Reports (Network, Consortium, Protocol level)
- Visiting Professorship Application Form
- Lecture Log
- Training (ClinicalTrials.gov, Audit, GCP, Ethics, etc.)
- Regulatory Templates (protocol, ICF, MOO, eCRFs)

RDCRN Contact Registry

Data as of April 3, 2013



- Over 120 diseases*
- 95 countries
- 11,279 total registrations*
- 42% from PAGs
- 40% from internet
- 7% from medical profess.

Goals:

To inform registrants about RDCRN studies available;

To disseminate information about RDCRN activities

*Excluding former consortia diseases/registrations (BMF, CINCH, CLiC, CRC-SCA, GSD, RLD, RTD)

Charcot Marie Tooth International Database (CMT-ID) Overview

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Sites that have been activated for CMT-ID:
· South Korea
· Brazil
· Australia
· Lebanon

Sites that are pursuing activation:
· Italy
· Germany
· United Kingdom
· Hungary
· Morocco
· New Zealand
· Canada

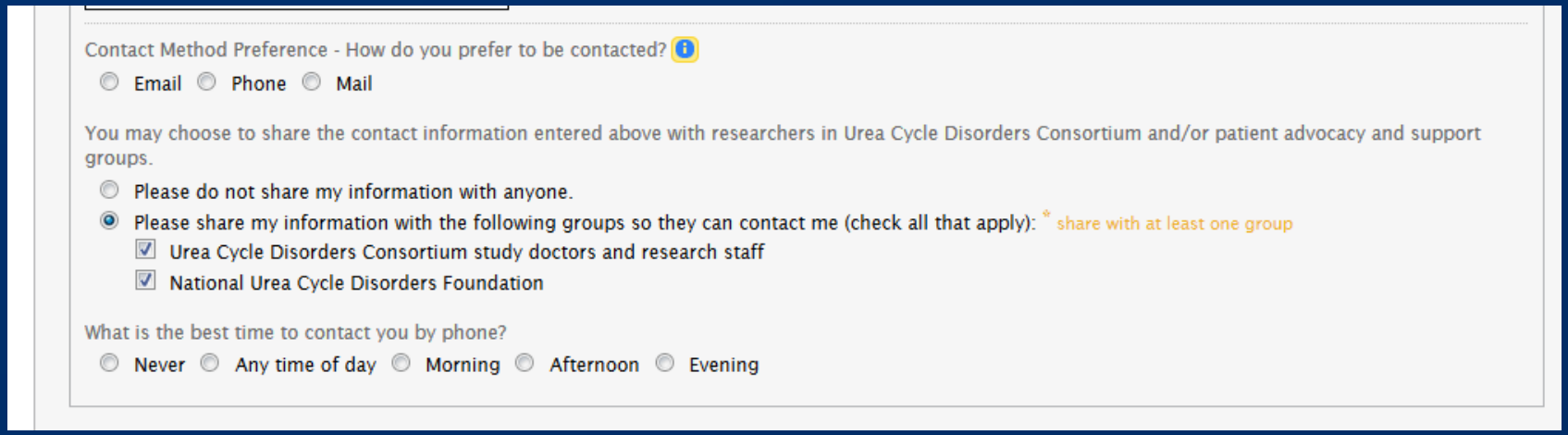
- International registry database for patients with inherited neuropathies
- Will allow investigators to acquire standardized clinical data on patients throughout the world
- Will greatly facilitate the ability to develop common approaches and definitions to characterize CMT genotypes and phenotypes
- Will facilitate development of new clinical trials and, eventually, treatments

TREAT-NMD Neuromuscular Network

Contact Registry
Option to Share Information

Data as of April 9, 2013

- 12 consortia are participating in the CR data sharing feature (ARD, BVMC, cGVHD, INC, LDN, NAMDC, NEPTUNE, PC, PIDTC, RKSC, STAIR, UCDC)
- 2,744 registrants have opted to share their information (168 with Consortia and others)
- Share with consortia and others went live 06/27/12



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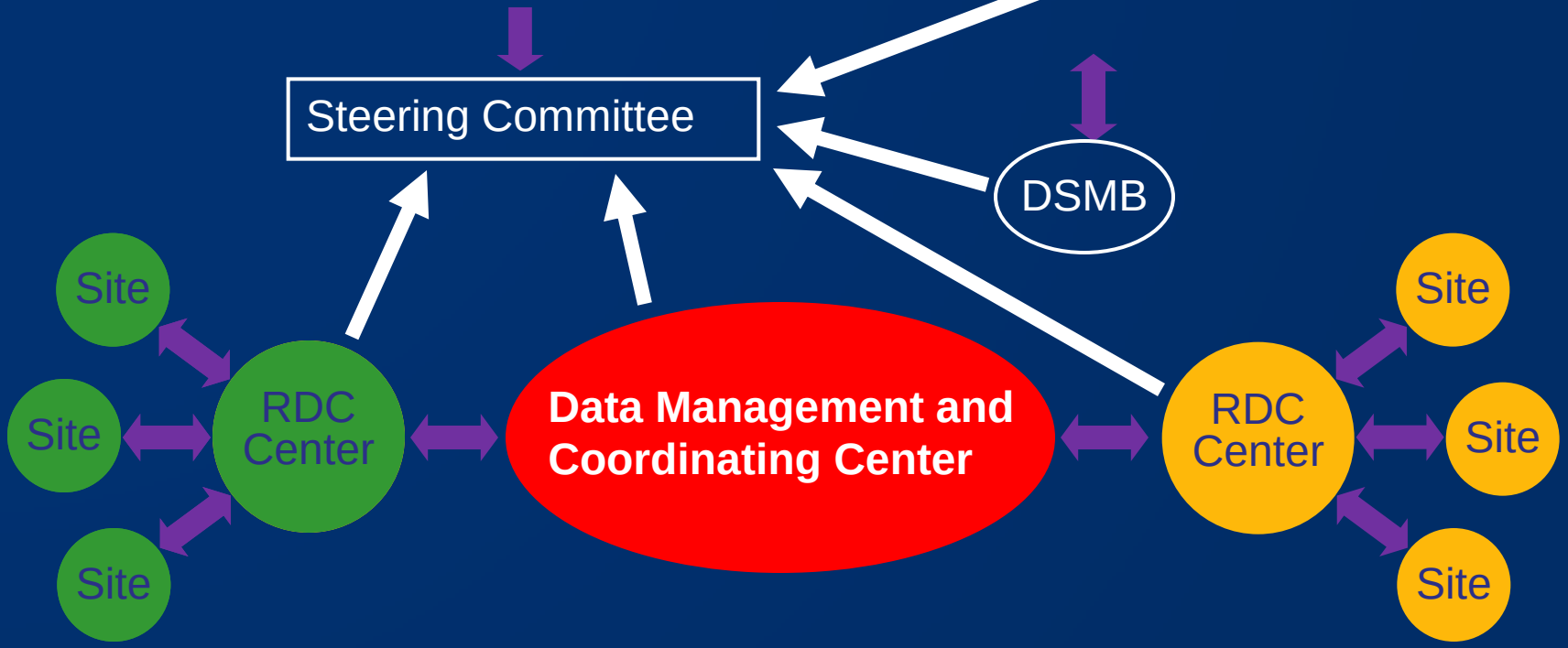
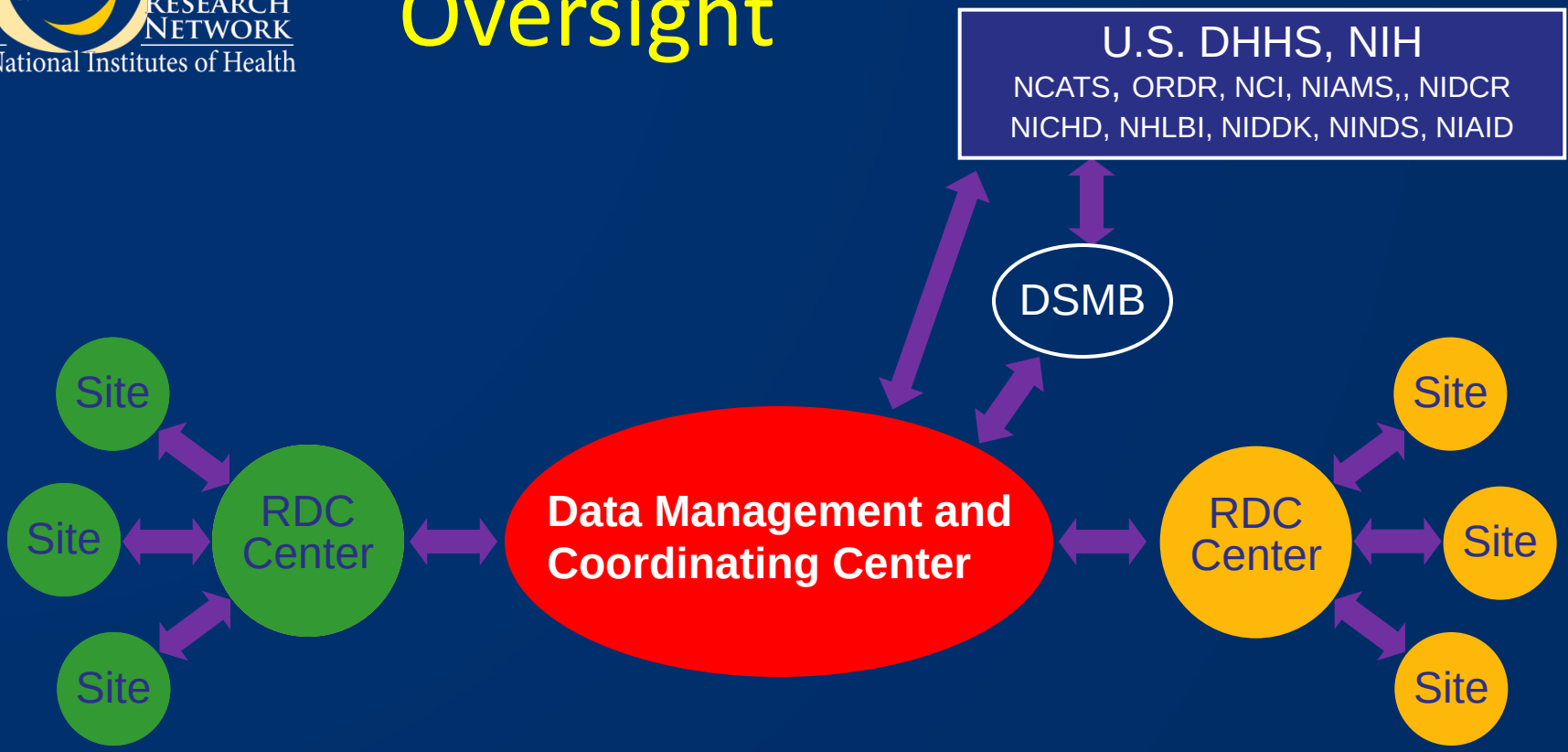
Guidance



Oversight


U.S. DHHS, NIH
NCATS, ORDR, NCI, NIAMS,, NIDCR
NICHD, NHLBI, NIDDK, NINDS, NIAID
DSMB
Site
Site
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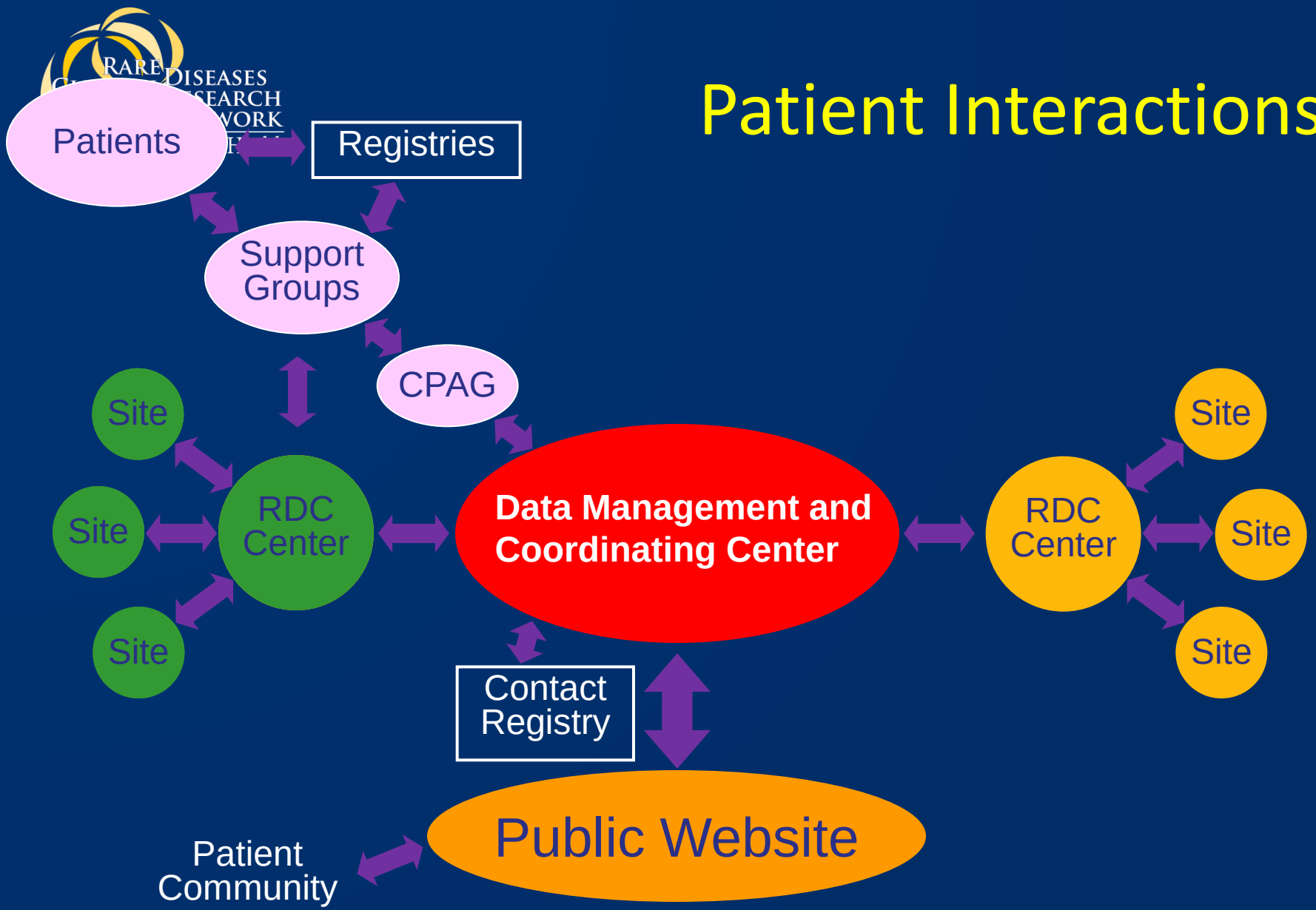
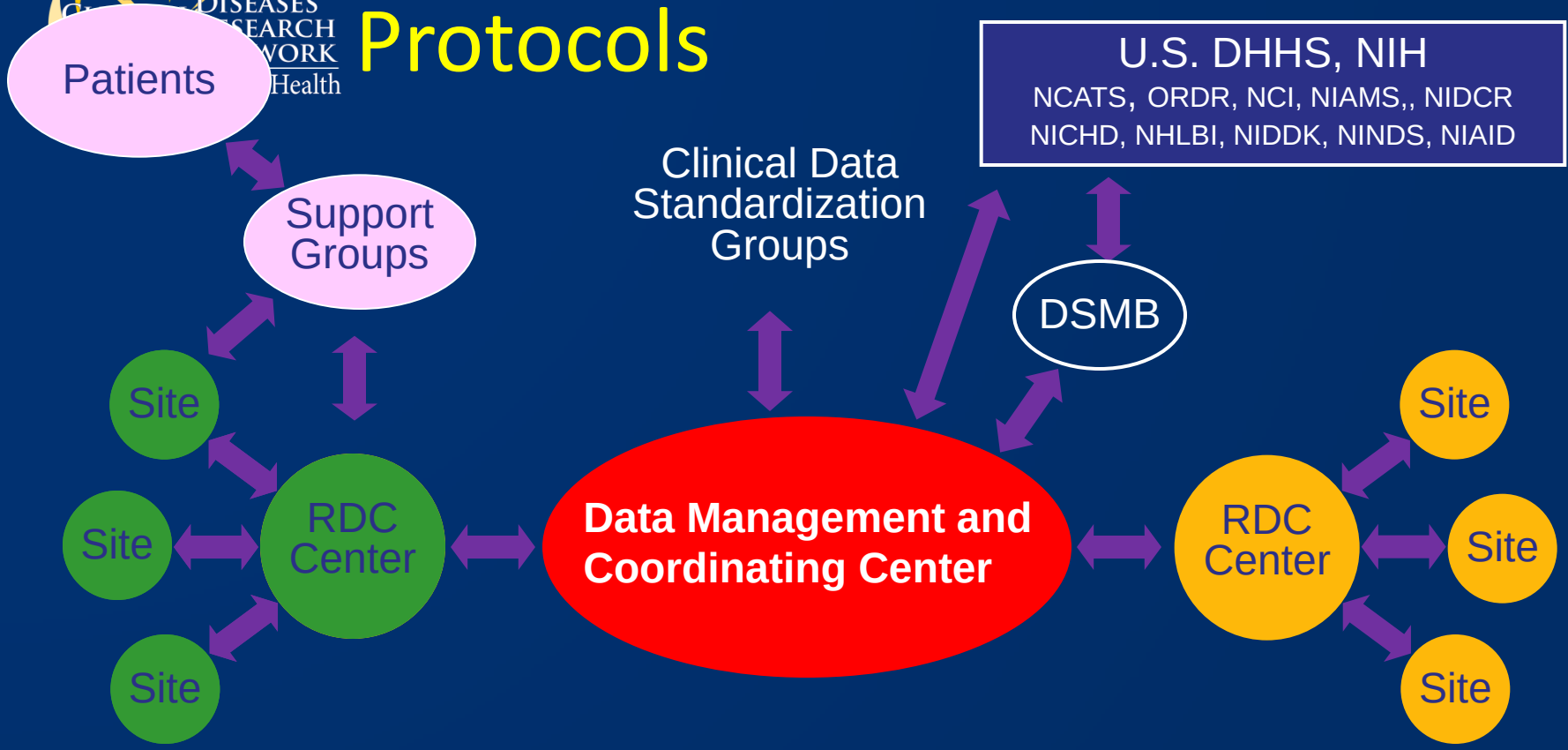
RDC Center
Data Management and Coordinating Center
RDC Center
Site
Site
Site

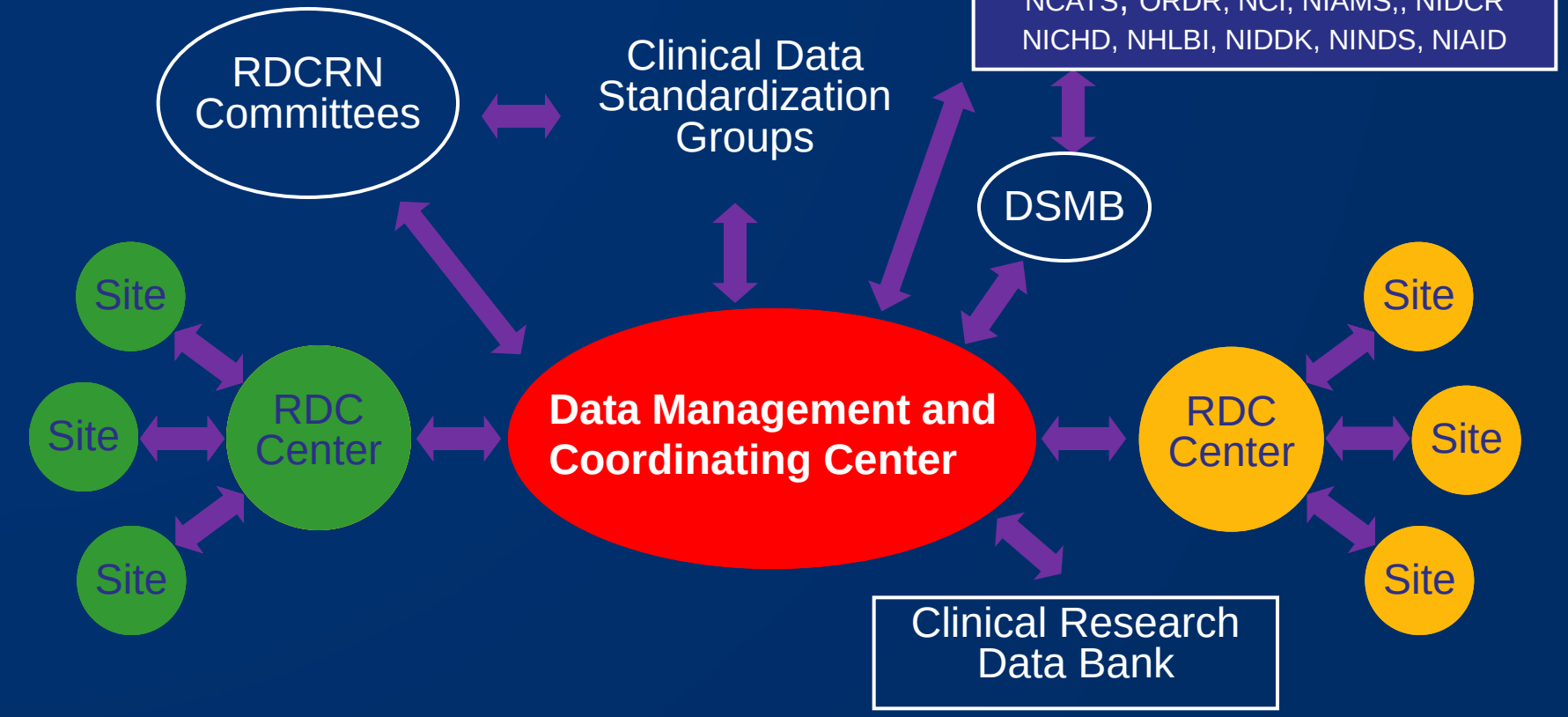
Patient Interactions



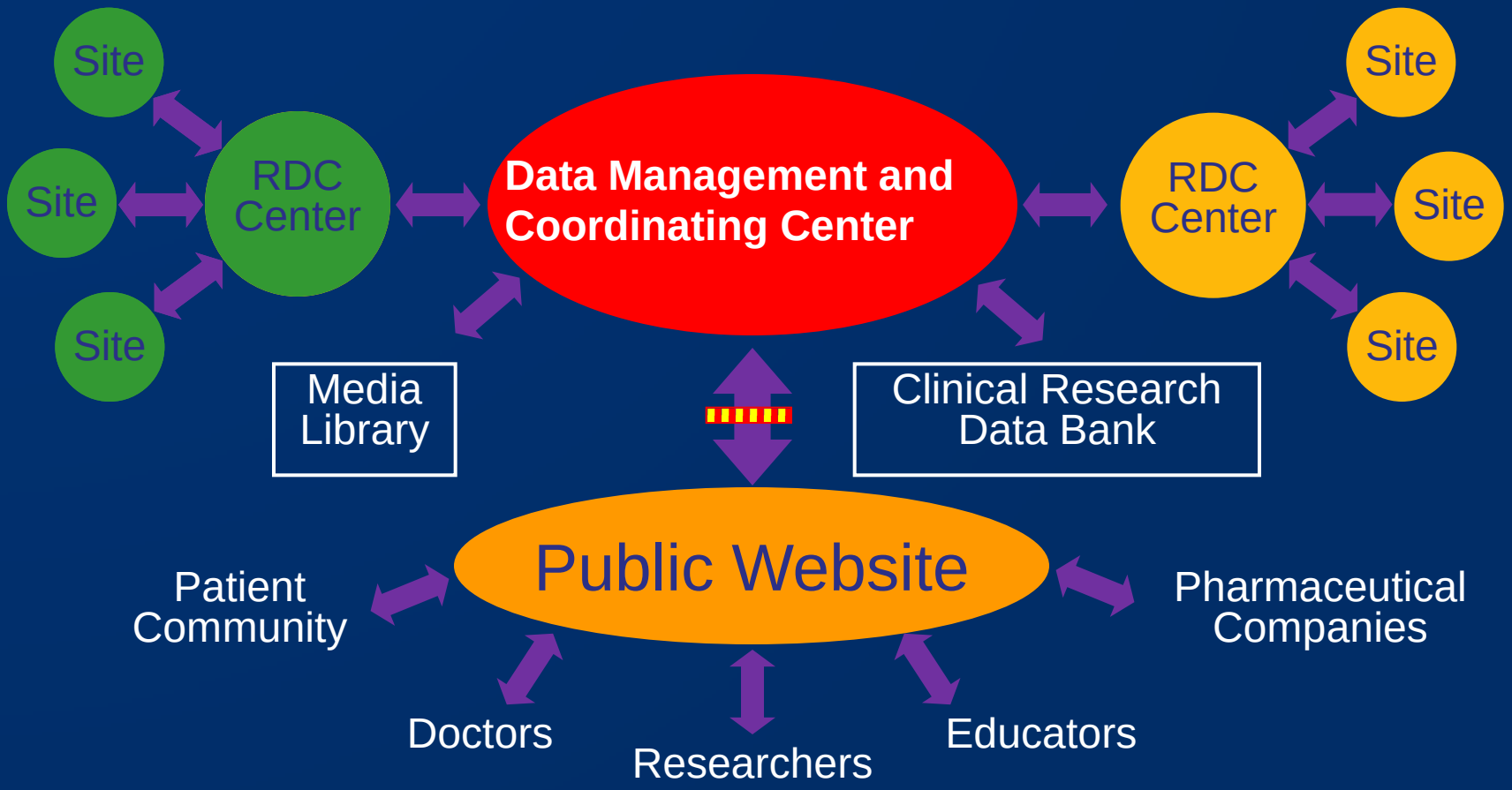
Development of Clinical Study Protocols



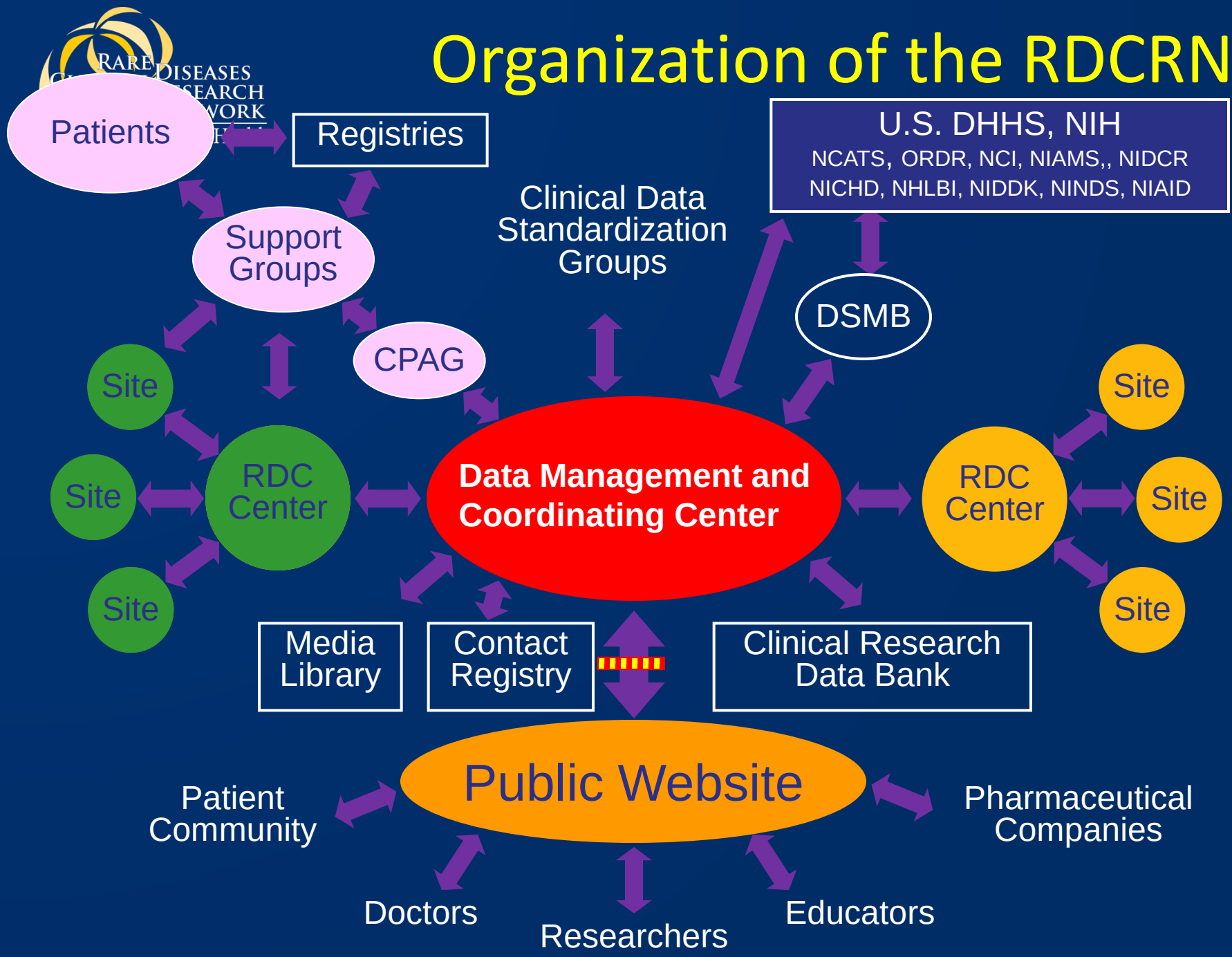
Standardization of Clinical Research Data



Public Access to Rare Disease Information



Organization of the RDCRN



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How well does it work?

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RDCRN2 Accomplishments

2nd grant cycle August 1, 2009 – April 9, 2013

- 73 activated studies
- 11,624 participants enrolled on studies
- 11,279 participants enrolled on Contact Registry
- 130 trainees
- 293 journal articles
- 61 conference presentations
- 50 books and book chapters
- 19 posters

Collaboration with Industry

Protocol	Pharmaceutical Company	Type of support	Protocol Status
UCDC5102	Ucyclyd Pharma, Inc.	Drug	Closed to Accrual
UCDC5105	Orphan Europe	Drug	Pending implementation
UCDC5111	Orphan Europe	Full funding	Active
VCRC5522	Bristol-Myers Squibb	Supplemental funding and drug	Closed to accrual
VCRC5523	Bristol-Myers Squibb	Supplemental funding and drug	Active
VCRC5524	Office of Orphan Products Development	Full funding and drug	Pending implementation
VCRC5525	Roche, Genentech	Supplemental funding and drug	Pending implementation
VCRC5527	Bristol-Myers Squibb	Full funding and drug	Pending implementation
ARD6105	Baxter	Drug (IVIG)	Active
cGVHD6502	Novartis Corporation, Genentech	Drug	Active
cGVHD6503	GlaxoSmithKline Merck & Co., Inc.	Drug	Active
LDN6703	Genzyme Corporation, Shire HGT	Supplemental funding	Active
LDN6707	Shire HGT	Supplemental funding	Active
LDN6708	Genzyme Corporation	Supplemental funding	Active
LDN6709	Genzyme Corporation	Funding for processing of whole blood sample, skin fibroblasts and mutation analysis	Active
LDN6711	Amicus Therapeutics, Shire HGT, Genzyme Corporation	Supplemental funding	Pending implementation
LDN6714	BioMarin Pharmaceutical, Inc.	Supplemental funding (vials of Aldurazyme from commercial source)	Active
NEPTUNE6803	Genentech	Drug	Pending implementation
NEPTUNE6804	Genentech	Full Funding & drug	Active

Contact Registry Protocols

RDCRN #	Title	Status
VCRC 5531	Reproductive Health of Men and Women with Vasculitis*	Closed to Accrual (N = 467) Accrual goal met in 2 mos.
VCRC 5533	Illness Perceptions, Fatigue, and Function in Systemic Vasculitis† (The VCRC Vasculitis Perception (VIP) Study)	Closed to Accrual (N = 707) Accrual goal met in 2 mos.
INC 6604	Development and Validation of a Disability Severity Index for Charcot-Marie-Tooth Disease (CMT)	Closed to Accrual (N = 249) Accrual goal met in 4 mos.
VCRC 5534	Educational Needs of Patients with Systemic Vasculitis - An International Study	Closed to Accrual (N = 386) Accrual goal met in 2 mos.
INC 6606	An Analysis of the Symptomatic Domains Most Relevant to Charcot Marie Tooth Neuropathy (CMT) Patients	Recruiting (opened 07/17/12) N = 357 as of 04/03/13
NEPTUNE 6802	Assessment of Educational Experience for Patients with Newly Diagnosed Nephrotic Syndrome	Recruiting (opened 01/03/13) N = 186 as of 04/03/13

Abstracts:

* Clowse M, Richesson R, Pieper C, Merkel PA, Consortium VCRC. Pregnancy in Men and Women with Vasculitis. Paper presented at: American College of Rheumatology Annual Scientific Meeting; November 5-9, 2011; Chicago, IL. http://www.rheumatology.org/education/annual/2011_abstract.pdf.
* Clowse M, Richesson R, Pieper C, Merkel PA, Consortium VCRC. Infertility Among Patients with Vasculitis. Paper presented at: American College of Rheumatology Annual Meeting; November 5-9, 2011; Chicago, IL. http://www.rheumatology.org/education/annual/2011_abstract.pdf.
† Grayson PC, Amudala NA, McAlear C, Leduc, RL, Shereff D, Richesson, R, Fraenkel L, Merkel PA, Consortium VCRC. Illness Perceptions Among Patients with Different Forms of Vasculitis. Paper presented at: American College of Rheumatology Annual Meeting; November 10-14, 2012; Washington, D.C.
† Grayson PC, Amudala NA, McAlear C, Leduc, RL, Shereff D, Richesson, R, Fraenkel L, Merkel PA, Consortium VCRC. Assessing Fatigue in Systemic Vasculitis from the Patient's Perspective. Paper presented at: American College of Rheumatology Annual Meeting; November 10-14, 2012; Washington, D.C.
† Grayson PC, Amudala NA, McAlear C, Leduc, RL, Shereff D, Richesson, R, Fraenkel L, Merkel PA, Consortium VCRC. Causal Beliefs of Disease Among Patients with Systemic Vasculitis. Paper presented at: American College of Rheumatology Annual Meeting; November 10-14, 2012; Washington, D.C.

Why RDCRN is successful

- Funding for Rare Disease Research
- Collaboration with Patient Advocacy Groups
- Common Infrastructure
- Rare Diseases Researcher Expertise and Support
- Mentoring of Next Generation of Researchers
- Coordinating Center Web Tools and Expertise
  - Contact Registry
  - eCRFs, Randomization, Treatment Assignment, etc.
  - Statistical Analysis expertise
  - IND submission expertise
  - Facilitating DSMB review
  - Audit program

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New Treatments

Lung
DOI 10.1007/s00408-012-9410-z

Treatment of Idiopathic Pulmonary Fibrosis with Losartan: A Pilot Project

Marisa Couluris · Brent W. Kinder · Ping Xu · Margaret Gross-King · Jeffrey Krischer · Ralph J. Panos

Received: 9 January 2012 / Accepted: 2 July 2012

Abstract
Background Idiopathic pulmonary fibrosis is a progressive interstitial lung disease with no current effective therapies. Treatment has focused on antifibrotic agents to stop proliferation of fibroblasts and collagen deposition in the lung. We present the first clinical trial data on the use of losartan, an antifibrotic agent, to treat idiopathic pulmonary fibrosis. The primary objective was to evaluate the effect of losartan on progression of idiopathic pulmonary fibrosis measured by the change in percentage of predicted forced vital capacity (%FVC) after 12 months. Secondary outcomes included the change in forced expiratory volume at 1 second, diffusing capacity of carbon monoxide, 6-minute walk test distance, and baseline/transition dyspnea index.
Methods Patients with idiopathic pulmonary fibrosis and a baseline %FVC of ≥50 % were treated with losartan 50 mg by mouth daily for 12 months. Pulmonary function testing, 6-minute walk, and breathlessness indices were measured every 3 months.
Results Twenty participants with idiopathic pulmonary fibrosis were enrolled and 17 patients were evaluable for response. Twelve patients had a stable or improved %FVC at study month 12. Similar findings were observed in secondary end-point measures, including 58, 71, and 65 % of patients with stable or improved forced expiratory volume at 1 second, diffusing capacity for carbon monoxide, and 6-minute walk test distance, respectively. No treatment-related adverse events that resulted in early study discontinuation were reported.
Conclusion Losartan stabilized lung function in patients with idiopathic pulmonary fibrosis over 12 months. Losartan is a promising agent for the treatment of idiopathic pulmonary fibrosis and has a low toxicity profile.

Keywords Pulmonary fibrosis · Angiotensin receptor blocker · Forced vital capacity · Dyspnea · Six-minute walk test

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Published online: 19 July 2012

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disorder with no identifiable cause or proven effective treatment [1]. Even though IPF is considered rare, it is the most common idiopathic interstitial lung disease and has both high morbidity and mortality. The median survival of patients with IPF is 2–4 years, which has not changed over the past decade [2, 3]. There is considerable evidence that angiotensin II (AII) is involved in multiple models of fibrosis. Angiotensin II is known to activate the angiotensin II type 1 receptor, inducing transforming growth factor expression [4, 5], which stimulates lung fibroblast proliferation and lung procollagen production. Losartan's ability to alleviate fibrosis by reducing the expression of

DMCC and the Rare Lung Disease Consortium

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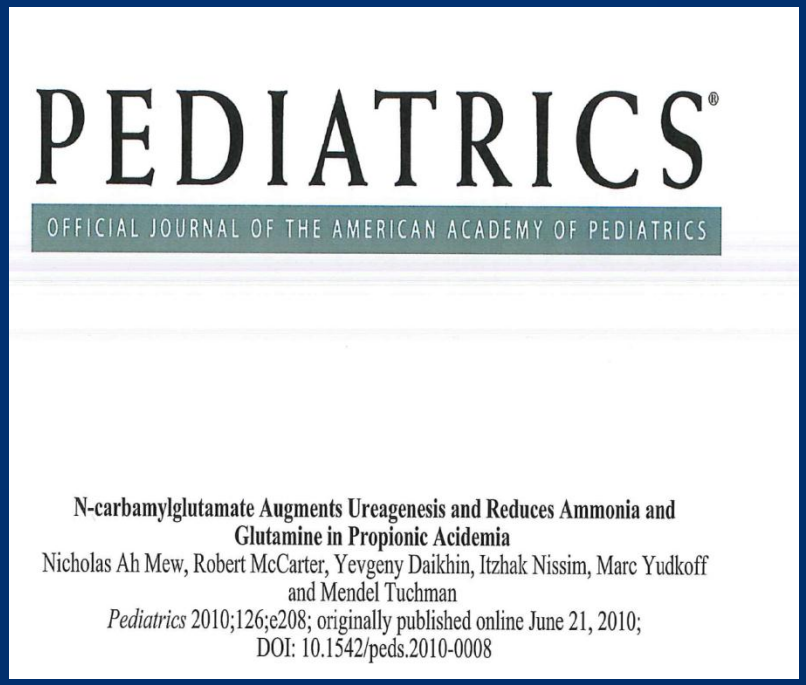
New Treatments



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N-carbamylglutamate Augments Ureagenesis and Reduces Ammonia and Glutamine in Propionic Acidemia

Nicholas Ah Mew, Robert McCarter, Yevgeny Daikhin, Itzhak Nissim, Marc Yudkoff and Mendel Tuchman

Pediatrics 2010;126;e208; originally published online June 21, 2010;
DOI: 10.1542/peds.2010-0008

Urea Cycle Disorders Consortium

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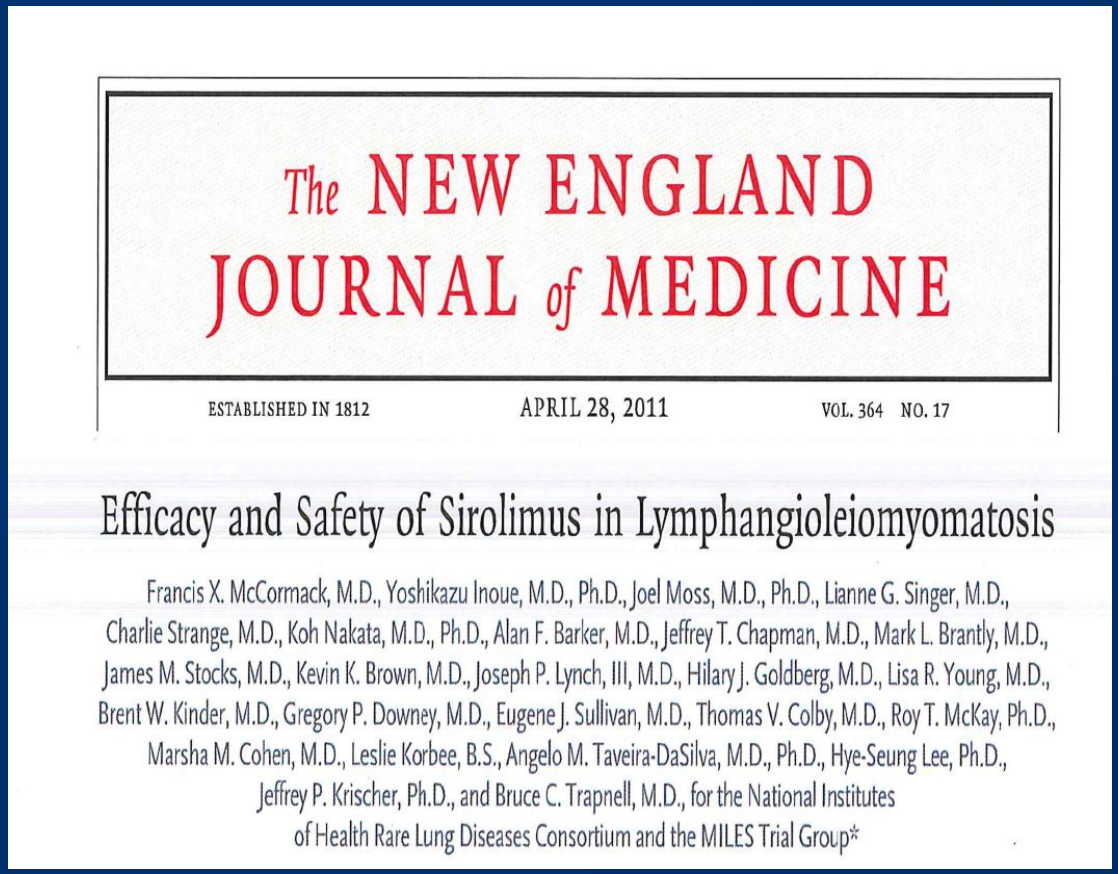
National Institutes of Health

New Treatments



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 28, 2011 VOL. 364 NO. 17

Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis

Francis X. McCormack, M.D., Yoshikazu Inoue, M.D., Ph.D., Joel Moss, M.D., Ph.D., Lianne G. Singer, M.D., Charlie Strange, M.D., Koh Nakata, M.D., Ph.D., Alan F. Barker, M.D., Jeffrey T. Chapman, M.D., Mark L. Brantly, M.D., James M. Stocks, M.D., Kevin K. Brown, M.D., Joseph P. Lynch, III, M.D., Hilary J. Goldberg, M.D., Lisa R. Young, M.D., Brent W. Kinder, M.D., Gregory P. Downey, M.D., Eugene J. Sullivan, M.D., Thomas V. Colby, M.D., Roy T. McKay, Ph.D., Marsha M. Cohen, M.D., Leslie Korbee, B.S., Angelo M. Taveira-DaSilva, M.D., Ph.D., Hye-Seung Lee, Ph.D., Jeffrey P. Krischer, Ph.D., and Bruce C. Trapnell, M.D., for the National Institutes of Health Rare Lung Diseases Consortium and the MILES Trial Group*

Rare Lung Diseases Consortium

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New Treatments

Mexiletine for Symptoms and Signs of Myotonia in Nondystrophic Myotonia

A Randomized Controlled Trial

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Yunxia Wang, MD
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Jaya R. Trivedi, MD
Valeria A. Sansone, MD
Mohammad K. Salajegheh, MD
Shannon L. Venance, MD
Emma Ciafaloni, MD
Emma Matthews, MRCP
Giovanni Meola, MD
Laura Herbelin, BS
Robert C. Griggs, MD
Richard J. Barohn, MD
Michael G. Hanna, FRCP
for the Consortium for Clinical Investigation of Neurologic Channelopathies

Context Nondystrophic myotonias (NDMs) are rare diseases caused by mutations in skeletal muscle ion channels. Patients experience delayed muscle relaxation causing functionally limiting stiffness and pain. Mexiletine-induced sodium channel blockade reduced myotonia in small studies; however, as is common in rare diseases, larger studies of safety and efficacy have not previously been considered feasible.

Objective To determine the effects of mexiletine for symptoms and signs of myotonia in patients with NDMs.

Design, Setting, and Participants A randomized, double-blind, placebo-controlled 2-period crossover study at 7 neuromuscular referral centers in 4 countries of 59 patients with NDMs conducted between December 23, 2008, and March 30, 2011, as part of the National Institutes of Health–funded Rare Disease Clinical Research Network.

Intervention Oral 200-mg mexiletine or placebo capsules 3 times daily for 4 weeks, followed by the opposite intervention for 4 weeks, with 1-week washout in between.

Main Outcome Measures Patient-reported severity score of stiffness recorded on an interactive voice response (IVR) diary (scale of 1=minimal to 9=worst ever experienced). Secondary end points included IVR-reported changes in pain, weakness, and tiredness; clinical myotonia assessment; quantitative measure of handgrip myotonia; and Individualized Neuromuscular Quality of Life summary quality of life score (INQOL-QOL, percentage of maximal detrimental impact).

Results Mexiletine significantly improved patient-reported severity score stiffness on the IVR diary. Because of a statistically significant interaction between treatment and

Consortium for Clinical Investigation of Neurologic Channelopathies

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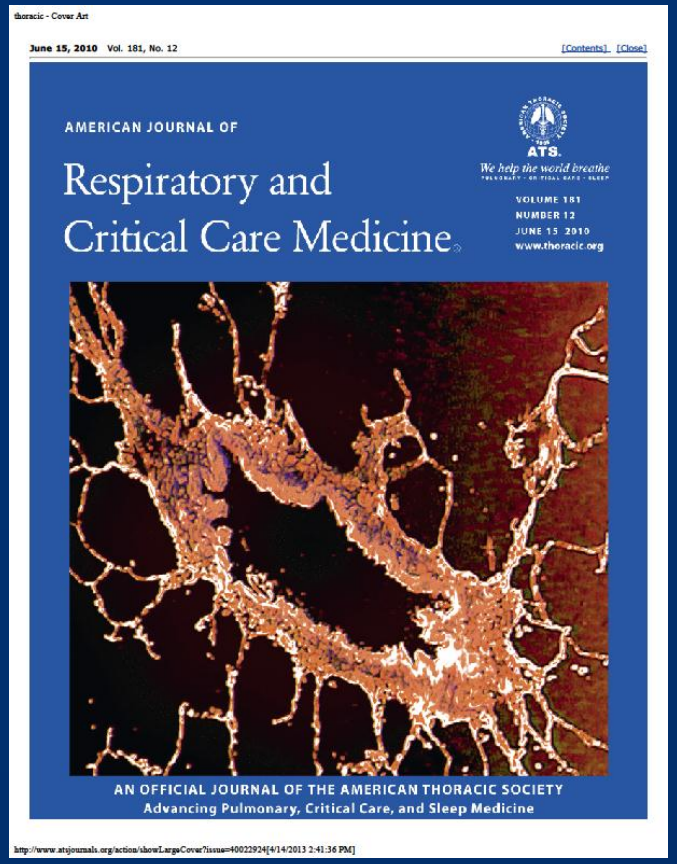
National Institutes of Health

New Treatments



Inhaled Granulocyte/Macrophage–Colony Stimulating Factor as Therapy for Pulmonary Alveolar Proteinosis

Rare Lung Disease Consortia

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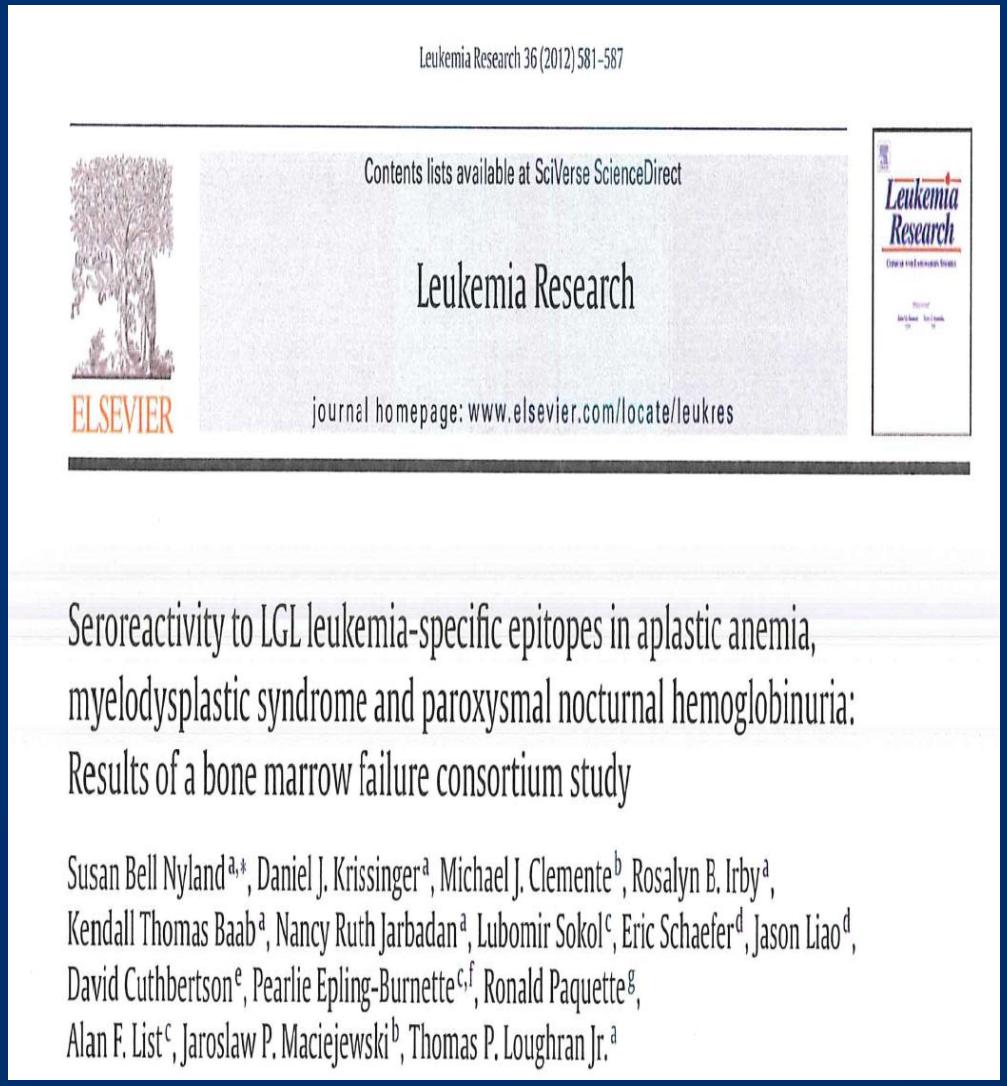
New Pathways



Leukemia Research 36 (2012) 581–587

Contents lists available at SciVerse ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

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Seroreactivity to LGL leukemia-specific epitopes in aplastic anemia, myelodysplastic syndrome and paroxysmal nocturnal hemoglobinuria: Results of a bone marrow failure consortium study

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Thank you!

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