Encouraging Research Into Rare Diseases – The Rare Diseases Clinical Research Network

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Office of Rare Diseases
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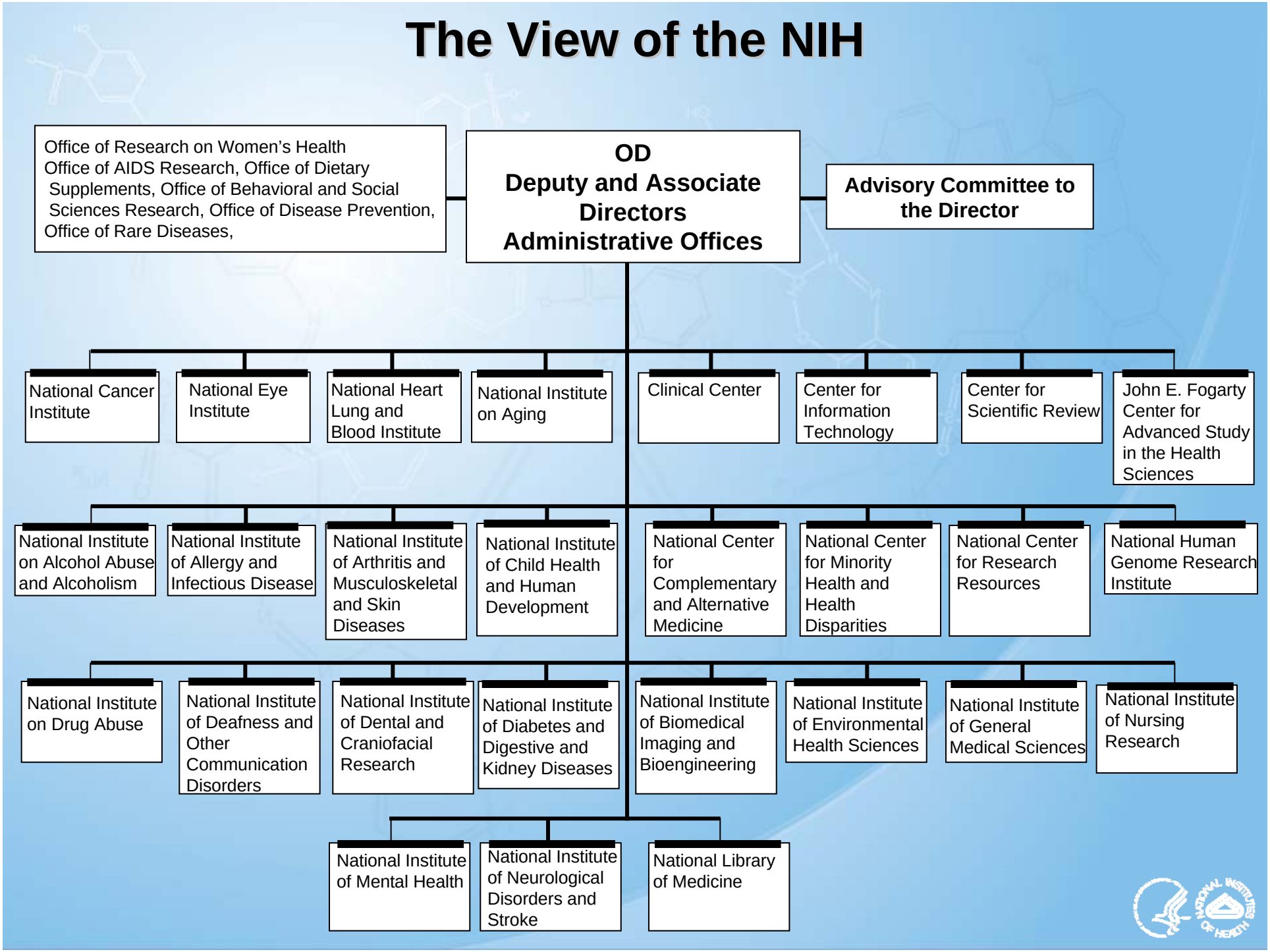
The View of the NIH



Office of Rare Diseases
Public Law 107-280, Rare Diseases Act of 2002

- Collaborative Clinical Research Programs With Institutes and Centers of NIH
- Intramural Research Program
- Extramural Research Program
- Rare Diseases Clinical Research Network
- Information Development and Dissemination Activities
- Trans-NIH Working Group on Rare Diseases Research
  - Genetic Testing
  - Bio-Specimen Collection, Storage, and Distribution

ORD Extramural Research Program

- **Scientific Conferences ~ 112 in FY 2005; > 640 since 1995**
- **10 Rare Diseases Clinical Research Consortia and a Data and Technology Coordinating Center (NIAMS, NICHD, NIDDK, NHLBI, NINDS, NCRR)**
- **Regional Workshops with Leaders of Patient Support Groups**
- **Request for Applications – Join Research Teams Before Grant Applications to NIH**
  - **NHLBI – Demonstration/Pilot Projects (R21)**
  - **NINDS – Improving Treatment Outcomes of Lysosomal Storage Disorders (R01/R21 and PAS)**
  - **NHGRI - Mentored Patient-Oriented Research Career Development Award (K23) Approaches of Genomics and Proteomics to the Study of Rare Diseases**
  - **NIH - Clinical Trial Planning Grant (R34)**

Coordinated Efforts for Successful Orphan Product Development/Rare Diseases Research

- Industry (Domestic and International, Large and Small)
- Academic and Research Community- Multidisciplinary Research Efforts
- Medical Specialty Societies
- Patient Advocacy Groups
- Federal Government
  - Regulatory
  - Reimbursement
  - Research
    - Intramural Research Program
    - Extramural Research Program

ClinicalTrials.gov – Rare Diseases

- Rare Diseases
- Total Studies (Including Those No Longer Recruiting – Significant to Include)
  - 9,851 Studies (26,802 Total)
  - 980 Rare Diseases
- Active Recruiting Studies
  - 4,588 Studies (11,619 Total)
  - 820 Rare Diseases

Trans-NIH Working Group on Rare Diseases Research

- NIH Institutes and Centers
- Selected Government Agencies
- Coordination of Research and Public Education Components
- Identify Research Opportunities and Advances
- Develop Cooperative Research Agreements – PAs, RFAs and RFPs
- Promote Collaborative Intramural and Extramural Research Programs
- Development of Diagnostic Genetic Tests
- Collection, Storage, and Distribution of Biomaterials for Research

Purposes of The Cooperative Rare Diseases Clinical Research Network

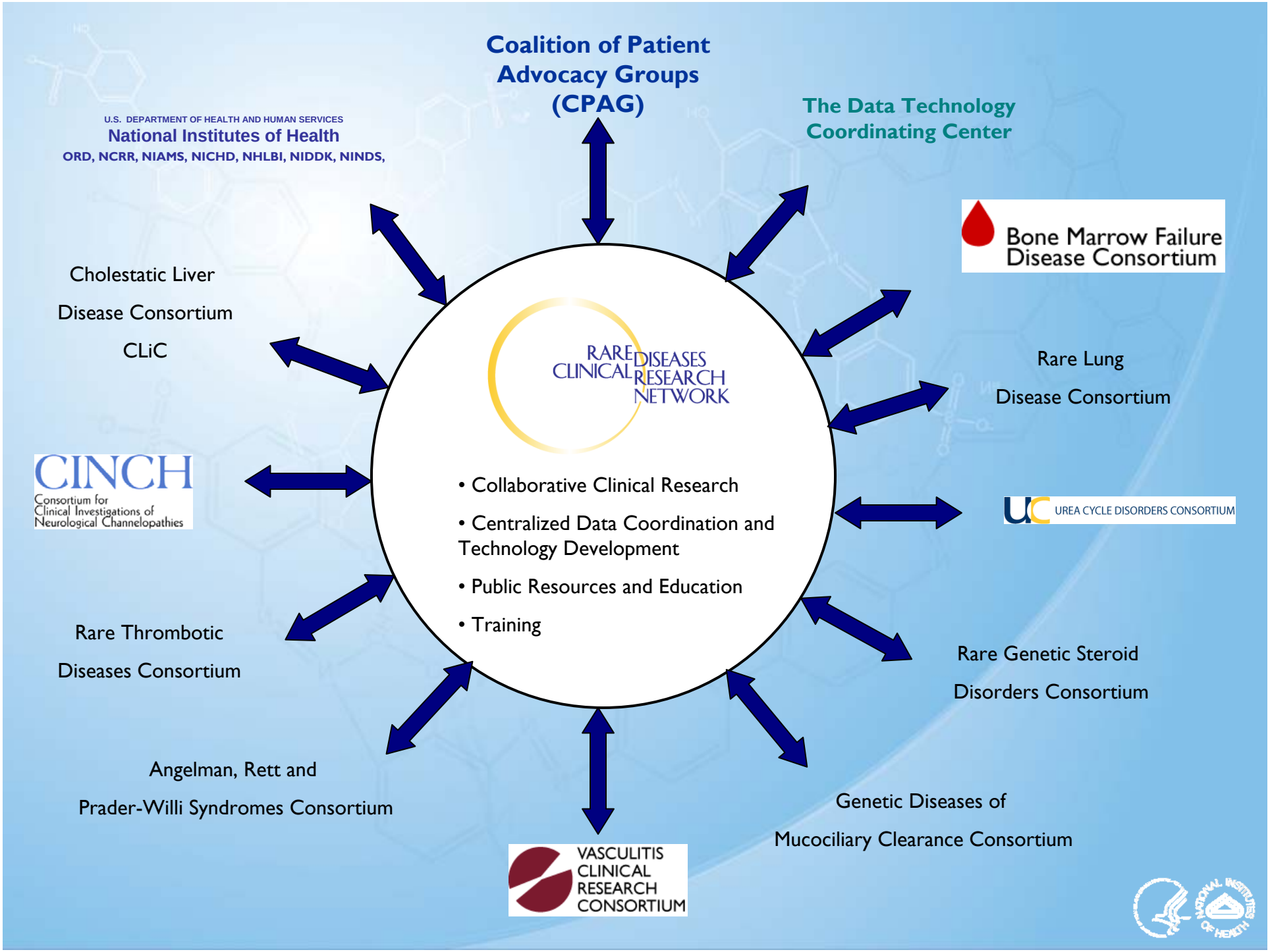
http://www.rarediseasesnetwork.org/

Facilitate clinical research in rare diseases to support :

- **collaborative clinical research in rare diseases, including longitudinal studies of individuals with rare diseases, clinical studies, phase one and two trials, and/or pilot and demonstration projects.**
- **a test bed for distributed clinical data management that incorporates novel approaches and technologies for data management, data mining, and data sharing across rare diseases, data types, and platforms.**
- **promote training of new clinical investigators in rare diseases**

Rare Diseases Clinical Research Network Consortia (2004) http://www.rarediseasesnetwork.org/

- Angelman, Rett, Prader-Willi Syndromes – A. Beaudet
- Bone Marrow Failure – J. Maciejewski
- Genetic Diseases of Mucociliary Clearance – M. Knowles
- Genetic Steroid Disorders – M. New
- Nervous System Channelopathies – R. Griggs
- Rare Liver Disorders – R. Sokol
- Rare Lung Diseases – B. Trapnell
- Rare Thrombotic Disorders – T. Ortel
- Urea Cycle Disorders – M. Batshaw
- Vasculitis Clinical Research – P. Merkel
- Data and Technology Coordinating Center (DTCC) – J. Krischer


Coalition of Patient Advocacy Groups (CPAG)
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
ORD, NCRR, NIAMS, NICHD, NHLBI, NIDDK, NINDS,
The Data Technology Coordinating Center
Bone Marrow Failure Disease Consortium
Cholestatic Liver Disease Consortium CLiC
RARE DISEASES CLINICAL RESEARCH NETWORK
Rare Lung Disease Consortium
CINCH Consortium for Clinical Investigations of Neurological Channelopathies
UREA CYCLE DISORDERS CONSORTIUM
• Collaborative Clinical Research
• Centralized Data Coordination and Technology Development
• Public Resources and Education
• Training
Rare Thrombotic Diseases Consortium
Rare Genetic Steroid Disorders Consortium
Angelman, Rett and Prader-Willi Syndromes Consortium
Genetic Diseases of Mucociliary Clearance Consortium
VASCULITIS CLINICAL RESEARCH CONSORTIUM

Angelman, Rett, and Prader-Willi Syndromes Consortium

Dr. Art Beaudet

Bone Marrow Failure Diseases

Dr. Jarek Maciejewski

- Aplastic Anemia
- Myelodysplastic Syndrome (MDS)
- Paroxysmal Nocturnal Hemoglobinuria (PNH)
- Large Granular Lymphocyte (LGL) Leukemia
- Single Lineage Cytopenias:
  - Pure Red Cell Aplasia
  - Amegakaryocytic Thrombocytopenic Purpura
  - Autoimmune Neutropenia

Genetic Diseases of Mucociliary Clearance Consortium

Dr. Michael Knowles

- Primary Ciliary Dyskinesia (PCD)
- Cystic Fibrosis
- Pseudohypoaldosteronism (PHA)

Rare Genetic Steroid Disorders Consortium

Dr. Maria New

- Congenital Adrenal Hyperplasia
- Androgen Receptor Defects
- Apparent Mineralocorticoid Excess (Low Renin Hypertension)

Neurological Channelopathies
- Dr. Robert Griggs

- Andersen-Tawil Syndrome (Periodic paralysis)
- Episodic Ataxias
- Non-dystrophic Myotonic Disorders

Cholestatic Liver Diseases
Dr. Ron Sokol

- PFIC (Progressive Familial Intrahepatic Cholestasis)
- Bile Acid Synthesis Defects
- Alagille Syndrome
- Alpha One Antitrypsin Deficiency
- Mitochondrial Hepatopathies

Rare Lung Disease Consortium
Dr. Bruce Trapnell

- Hereditary Interstitial Lung Disease (hILD)
- Lymphangioleiomyomatosis (LAM)
- Pulmonary Alveolar Proteinosis (PAP)
- Alpha-1 Antitrypsin Deficiency (Alpha-1)

Rare Thrombotic Diseases Consortium
Dr. Tom Ortel

- Antiphospholipid Antibody Syndromes (APS)
- Heparin-induced Thrombocytopenia (HIT)
- Paroxysmal Nocturnal Hemoglobinuria (PNH)
- Catastrophic Antiphospholipid Antibody Syndrome (Thrombotic Storm)
- Thrombotic Thrombocytopenic Purpura (TTP)

Urea Cycle Disorders
Dr. Mark Batshaw

- N-Acetylglutamate Synthase (NAGS) Deficiency
- Carbamyl Phosphate Synthetase (CPS) Deficiency
- Ornithine Transcarbamylase (OTC) Deficiency
- Argininosuccinate Synthetase Deficiency (Citrullinemia I)
- Citrin Deficiency (Citrullinemia II)
- Argininosuccinate Lyase Deficiency (Argininosuccinic Aciduria)
- Arginase Deficiency (Hyperargininemia)
- Ornithine Translocase Deficiency (HHH) Syndrome

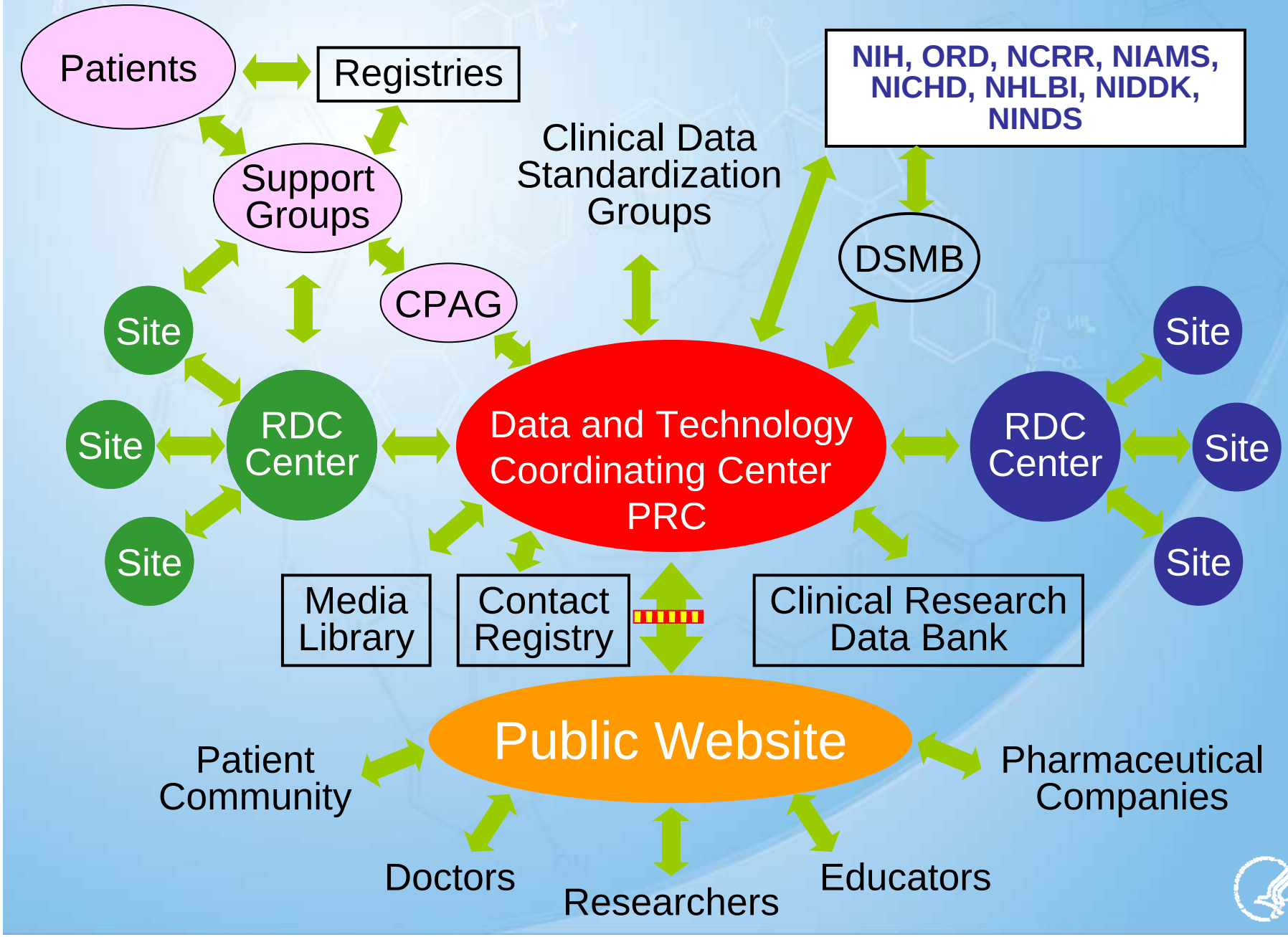
Vasculitis Clinical Research Consortium
Dr. Peter Merkel

- Wegener's Granulomatosis (WG)
- Microscopic Polyangiitis (MPA)
- Churg-Strauss Syndrome (CSS)
- Polyarteritis Nodosa (PAN)
- Takayasu's Arteritis (TAK)
- Giant Cell (Temporal) Arteritis (GCA)

Data and Technology Coordinating Center
Dr. Jeffrey Krischer

- Collaboration in design of clinical protocols, data management and analysis
- Develop a coordinated clinical data management system for the collection, storage and analysis of data from multiple diseases and multiple clinical sites
- Develop tools for web based recruitment and referral, cross disease data mining
- Construct a portal for access and integration of public data resources
- Promote communication and coordination of Network (including internet video conferencing, centralized secure website)

Organization of the RDCRN



Promoting Quality Genetic Testing

- Gaining acceptance of global testing services (NIH,ORD, CDC, HRSA, ASHG, ACMG, SIMD, FDA, GA)
- Develop Quality Assurance Procedures
- CLIA Certification Standards
- Interpretation of results with appropriate patient counseling
- **Formed - National Laboratory Network for Rare Disease Genetic Testing (NLN) http://www.rarediseasetesting.org**
- **NIH Sponsored Organization – (CETT)**
- Partnerships and networks to improve research translation and data sharing
    - Between and among research and clinical laboratories
    - Among research investigators, clinical laboratories, patient groups, clinicians, payers

ORD “CETT” Program

- ***Collaboration***
- ***Education***
- ***Test***
- ***Translation***
- **Program for Rare Genetic Diseases**
- **Dr. Roberta Pagon, Andrew Faucett, Dr. Giovanna Spinella, and Dr. Suzanne Hart**

Key Features of CETT

- Model of Cooperation between researcher, diagnostic laboratory and patient advocate group to translate diagnostic tests from research to a clinical laboratory
- Flexibility of process to allow for development of different types of genetic tests, collaborations and sources of test development
- Development of clinical materials and data collection to improve understanding of the genetic test and understanding of the rare disease.

Process

- **Application must be submitted by team**
  - **Clinical (CLIA-certified) laboratory**
  - **Patient advocate group**
  - **Researcher (laboratory and/or clinician)**
- **Preliminary review by Program Coordinator & Program Scientific Advisor**

Process

- Application forwarded to Review Board Coordinator
- Reviewed by 4 members of Review Board (clinician, molecular/biochemical geneticist, patient advocate, clinical geneticist)
- Accepted for translation or
- Returned to submission team with questions and suggestions – “facilitated process”

Requirements

- Information about the correlation between the disease and the test
- Information about the potential impact of the test on healthcare management
- Evidence that the clinical lab is experienced in diagnostic testing (e.g., number of tests, experience of staff, genetic counselors, CLIA certification)
- Proposed method(s) of testing is the most appropriate methods for the disorder
- Projections for cost of tests set-up and charge for individual test

Requirements

- Statement of collaborative commitments between researcher, clinical lab and advocacy group
- Educational materials in a standardized format for clinical care providers and for patients to address correlation between the disease and the test, potential impact of the test on healthcare management, test ordering, test interpretation, and the benefits and risks of testing

Requirements

- Phenotype / genotype data collection plan to improve understanding of the disease and test interpretation including the method of storage for the phenotype and genotype data
- Annual report form on volume of testing, detection rate, mutations found to be used to update “Gene Reviews”

Projected Timeline

- September 2005 – January 2006
  - **Development of web site**
    - **Submission criteria and forms**
    - **Examples of educational / information materials**
  - **Appointment of Review Board**
    - **Laboratory experts**
    - **Clinical genetic experts**
    - **Patent advocate**
  - **Development of review process**
  - **Broad publicity for program**
- January/February 2006
  - **Acceptance of first proposals**
    - **Goal of 4-6 week turn-around**
    - **Facilitated process**
- June / July 2006
  - **Evaluation of program**

Contacts

- Hosted through ORD website
  - http://rarediseases.info.nih.gov/
- Questions
  - **Giovanna Spinella – spinellg@od.nih.gov**
  - **Andy Faucett – afaucett@genetics.emory.edu**

The Genetic and Rare Diseases Information Center (NHGRI/ORD)

- **>12,500 Inquiries (2002 – 2005)**
- **> 3,900 Rare Diseases or Conditions**
- **> 6,700 Rare Diseases Terms**
- **Provide Links From Rare Diseases Terms to Information Responses – Future Goal**
- **Toll-free 1-888-205-3223 (USA)**
- **International Access Number: 301-519-3194**
- **Fax: 240-632-9164**
- E-mail: GARDinfo@nih.gov

ORD Website

http://rarediseases.info.nih.gov/

- Rare Diseases Information – Pub Med
- Research and Clinical Trials - CRISP, ClinicalTrials.gov
- Patient Support Groups - CHID Database > 1200 Patient Advocacy Groups, NORD, Genetic Alliance
- Patient Travel & Lodging
- Genetics Information – Gene Tests, OMIM, NCHPEG
- Research Resources
- Scientific Workshops, Archived Reports
- Annual Report On NIH-Supported Research Activities
- Website Trends
  - ~ 75,000 Users per Month
  - Average Visit ~ 17.24 Minutes

Office of Rare Diseases - Staff

- **Ms. Mary Demory**
- **Dr. John Ferguson (Consultant)**
- **Dr. Rashmi Gopal-Srivastava**
- **Mr. Christopher Griffin**
- **Ms. Henrietta Hyatt-Knorr**
- **Ms. Sharon Macauley**
- **Ms. Geraldine Pollen (Consultant)**
- **Dr. Giovanna Spinella**
- **Dr. William Gahl (Clinical Director**, NHGRI)

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