Enhancing Rare Diseases Research Efforts:
Fostering Development of Collaborative Research Teams

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Giovanna Spinella, MD., CDR, PHS
Extramural Program Director, ORD, NIH

The Promise of Rare Diseases Research

Rare diseases research can provide novel discovery and medical breakthroughs in development of new treatments for people afflicted by these conditions and has the potential applicability to more common medical conditions in our society

Rare diseases research may hold the keys for understanding the complexities of both normal abnormal disease physiology

Relevant Issues for Rare Diseases Research:

- Small populations dispersed over wide geographic areas
  - Heterogeneous expression of disease
  - Variable diagnostic criteria and assessment measures
- Limited Laboratory Scientists and Clinician Expertise and Experience
- Limited Access to Research Resources
  - Pockets of genetic, clinical, laboratory, pathological materials
  - Restrictions to animal and other disease models, reagents.
- Limited Foreseeable Profits/Financial Incentives
  - Drug/therapeutic agent development costs compared to market
  - Industry greater dependency on clinical and laboratory scientist collaboration-requires negotiations of IP issues, etc.

Facilitating Rare Diseases Research

- **Systematic collection of clinical information**
  - Standard Protocols-agreement across clinical sites on minimum elements to be collected on all patients; identified research questions to be answered; focus on developing measures/markers of disease/ assessment/disease course/outcomes
- **Partnerships and Collaborations**
  - Developing an international research community. Commitment to working across varying policies and regulations to facilitate collaborative research.
  - International coordination of patient disease organizations/ foundations-help bridge the patient populations and cultures; address mutual needs.
  - Industry/other organizations-the coordination of the scientists and patient support organizations within a rare disease population –an asset for partnerships and bringing new treatments to the clinic and interfacing government/regulatory agencies.

- **Exploit Technology to Enhance Communication Systems/Data Accrual and Management/Access Across Nations**
  - Coordinated data management systems for communication and sharing, collection, storage and analysis of data from multiple clinical sites
  - Provide an internationally accessible resource pliable for public information and education as well as a research resource

- **Exploit Opportunities to Nurture New Investigators Trained in Rare Diseases Research, Identify Areas Where Specialized Training is Needed and Provide Access**
  - Developing collaborative research teams generates a research environment for training of new investigators and exposes rare disease scientists to new technologies, methodologies that can be applied to rare diseases research investigations.

Current ORD Activities Towards Building Collaborative Research Teams

- **Rare Disease Clinical Research Network**
  - 10 clinical research consortia comprising 55 medical institutions (over 300 investigators) within the United States and 7 countries;
  - 34 patient advocacy groups representing over 40 rare diseases (Coalition for Patient Advocacy Groups)
  - Data and Technology Coordinating Center
  - Broad NIH sponsorship and participation: 5 NIH Institutes; 1 NIH Center (NCRR) and ORD, NIH.

Rare Diseases Clinical Research Network Consortia

- Angelman, Rett, Prader-Willi Syndromes – A. Beaudet
- Bone Marrow Failure Disease – J. Maciejewski
- Genetic Diseases of Mucociliary Clearance – M. Knowles
- Genetic Steroid Disorders – M. New
- Nervous System Channelopathies – R. Griggs
- Cholestatic Liver Disease – R. Sokol
- Rare Lung Disease – 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

Rare Diseases Clinical Research Network – Goals

http://www.rarediseasesnetwork.org/

- Facilitate Clinical Research in Rare Diseases
- Training of Clinical Investigators in Rare Diseases Research
- Centralized Data and Technology Coordinating Center to assist in design of clinical protocols, data collection, storage and analysis from multiple diseases and multiple clinical sites
- Develop tools for web based recruitment and referral, cross disease data mining
- Support Collaborative Clinical Research
  - Longitudinal Studies of Patients with Rare Diseases (Including Natural History Studies)
  - Clinical Proof of Concept or Demonstration Projects

Rare Diseases Clinical Research Network

- **Rare Diseases Clinical Research Center (Consortium) Key Features:**
  - **Concept:**
    - Consortium of Investigators, Institutions, and Organizations, including Partnership with Patient Advocacy Organizations; encourage partnership with industry
  - **Sub-Grouping of Rare Diseases**
  - **Clinical Research Studies with Longitudinal Component**
    - Includes Human Laboratory Work; Pilot Studies/Phase I/II Trials
    - Utilizes Institutional GCRCs across the Center Consortium (coordination of GCRCs across the rare diseases consortium).
  - **Training of New Rare Diseases Investigators**
  - **Public Resource and Education**
  - **Commitment of Each Rare Disease Clinical Center to Collaboration with other Clinical Centers and the DTCC within the Network**

Current ORD Activities Towards Building Collaborative Research Teams

- Rare Disease Clinical Research Network
- **Networking Meetings: Special workshops focused to fostering coordination and collaboration, bringing potential partners together towards addressing key next steps in moving research in a rare disease forward.**

- Networking Meetings always include patient advocacy group(s) and potential funding sources for activities generated by the discussion.
- Possible Content of Meeting include:
  - Develop clinical research consensus on key questions and measures for developing clinical research protocols; form new collaborations
  - Assess various models of disease, assays, etc., tools for uncovering drug or other discoveries for rare disease therapeutics-develop strategy for moving forward.

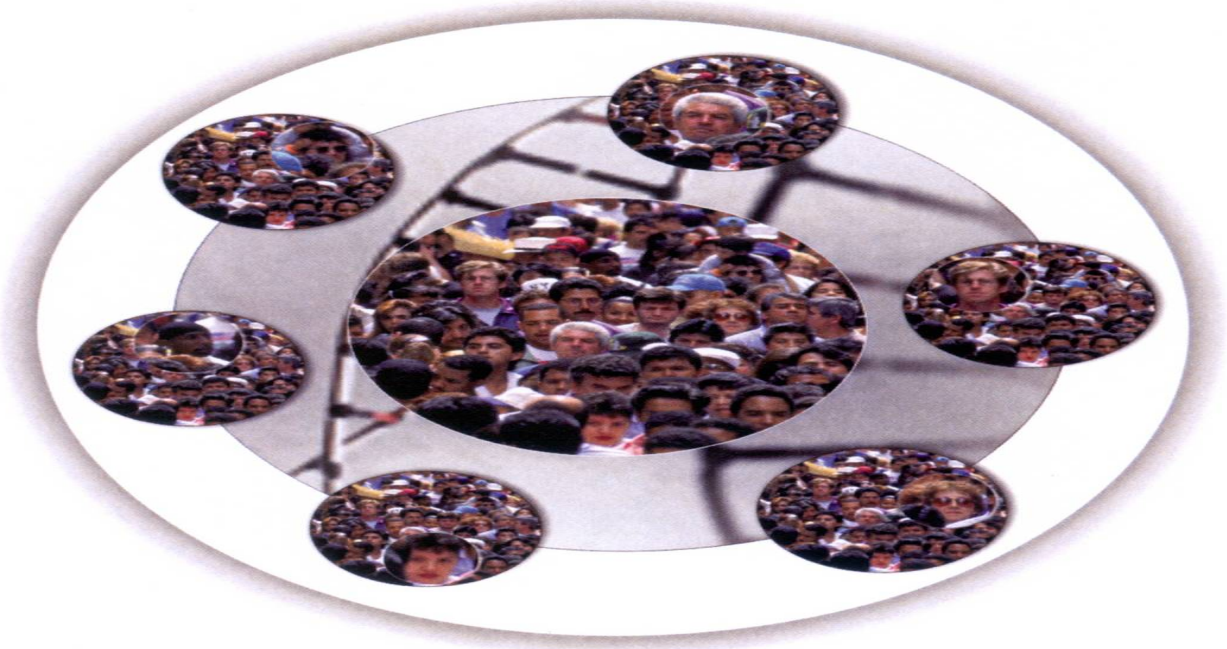
Current ORD Activities Towards Building Collaborative Research Teams

- Rare Disease Clinical Research Network
- Networking Meetings:
- Quality genetic testing: Working across government agencies within the United States towards quality diagnostic testing (genetic and biochemical testing) for rare diseases with goal of integrating efforts internationally

Promoting Quality

Laboratory Testing for Rare Diseases:

Keys to Ensuring Quality Genetic Testing



May 19–21, 2004

Atlanta, GA

EMORY UNIVERSITY SCHOOL OF MEDICINE

DEPARTMENT OF HEALTH AND HUMAN SERVICES • USA

CDC CENTERS FOR DISEASE CONTROL AND PREVENTION

Office of Rare Diseases

Promoting Quality Laboratory Testing for Rare Diseases: Keys to Ensuring Quality Genetic Testing" Conference, Atlanta, May 2004

- Participants include more than 50 experts from government, academic institutions, professional organizations, laboratories, industry, healthcare payers, and patient advocacy groups.
- Goals:
  - Assure access to quality laboratory testing
    - Research laboratories providing patient testing
  - Expedite translation of gene findings into clinical and public health practice
  - Identify data and education needs
  - Promote collaboration, cooperation, partnership, and community involvement

- **Recommendations:**
  - **Education-** to promote quality translation of research findings into clinical testing and to advance understanding of quality standards for patient testing research community(institutional review boards (IRBs), providers and users of laboratory services, healthcare payers, patients, research participants, and advocacy groups, to minimize adverse impact on access to testing
  - **Guidance, strategies, and criteria-** how rare disease tests should be validated, and how analytic validity, clinical validity, and clinical utility should be established for rare disease tests
  - **Quality assurance strategies-** for clinical genetic testing for rare diseases.
  - **Quality data collection-** Mechanisms and strategies during each step of test development through clinical application
  - **Partnership and networks-** to improve and facilitate research translation, data sharing, clinical availability, and quality assurance.
  - **Infrastructure-** to provide momentum and enable development of activities needed, including facilitating the translation process, assuring the quality of testing services, and improving access to testing.

Issues Identified with Regards to Test Referral to Non-US laboratories

- US dependency for rare diseases diagnostic testing-roughly 22% genetic tests are available only from non-US laboratories.
- standards are needed both for specimen shipping and tracking documentation and for the validity and quality of the testing.
- CLIA requirements, US and international privacy regulations, and other requirements may impose restrictions both on cross-border test referrals and on obtaining information necessary for test selection, result interpretation and reporting.
- "Borderless" laboratories may be able to facilitate sending specimens and test results across borders and may provide a model for addressing trans-border testing; however, the use of these laboratories can be problematic when contact information for the testing laboratory is not provided and test results are transcribed or edited on the report issued to the referring institution.

National Laboratory Network for Rare Disease Genetic Testing

A family of laboratories for orphan disease diagnostics.

Six laboratories formed the NLN in May 2004 and agreed to share a commitment to ensure that quality, affordable genetic testing services are accessible to all. Visit the Rare Disease Conference website for additional information: http://www.phppo.cdc.gov/dls/genetics/Rare Disease Conf.aspx

Visit the NLN website soon at:
www.rarediseasetesting.org

The six charter laboratories:

- Medical Genetics Laboratories at Baylor College of Medicine, Houston, TX
- Genetics Laboratory at Emory University School of Medicine, Atlanta, GA
- GeneDx, Inc., Gaithersburg, MD
- Molecular Genetics Laboratory at Hospital for Sick Children, Toronto, Canada
- Orphan Disease Testing Center at University of California at Los Angeles, CA
- University of Chicago Genetics Services Laboratories, Chicago, IL

Current ORD Activities Towards Building Collaborative Research Teams

- Rare Disease Clinical Research Network
- Networking Meetings
- Quality Genetic Testing
- Education and Information Resources for Patient Advocacy Organizations and Research Investigators

ORD Seminar Series:
Gaining Access to Research Resources

Regional Training Workshop for National Patient Support Organizations

- NIH Extramural Research Funding Structure
- NIH Rare Diseases Intramural Research Program and Patient Recruitment and Referral
- The FDA: Orphan Designation and Drug Evaluation for Rare Diseases
- Patenting/Cross Licensing of Genetic Materials
- Ensuring Ethical Research
- What Information You Need and Where To Find It!
- Implications in Genetic Testing: Genetic Counseling
- IRB/Human Subjects Protection /Vulnerable Populations

Trans-NIH Working Group on Rare Diseases Research Issues

- Development of Diagnostic Genetic Tests
- Collection, Storage, and Distribution of Biomaterials for Research
- Research Models for Rare Diseases
- Sources of Rare Diseases Information
- Training – Intramural and Extramural

Web-based inventory of bio-specimen repositories?

- Maintained and updated site with information to include:
  - extent of collection,
  - specimen types collected,
  - donation policies and requirements,
  - preparation and collection procedures,
  - location of repositories,
  - contact information,
  - sources of support, and
  - limitations to access.
- In addition, consideration for:
  - an educational component to guide researchers in areas such as collecting samples, and human subject privacy and informed consent;
  - methods that repositories can use to assess their success in fulfilling requests and ways for them to identify and solve problems that arise;
  - methods ORD/NIH can use, independent of the repositories, to query investigators on their success in obtaining needed samples; and
  - a way to identify a repository's responsiveness to investigator requests for new tissue types.

Broadening Efforts

- How Can We Work More Effectively Together to Meet the Challenges of Rare Diseases Research?
- Can We Develop an International Collaboration and Coordination of Rare Diseases Research to Benefit the People With Rare Diseases?
  - What Form Would It Take?
  - International Teams to Work on specific Areas and Issues to bring suggestions, recommendations and solutions? to interact with the various government agencies and programs?