

Collaborative research efforts and related activities of the Office of Rare Diseases Research at the USA National Institutes of Health

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Abstract

Introduction: Rare diseases present unique challenges to meet the numerous and varied needs of the rare diseases community and it is required to identify and address these needs. Significant financial and personnel resources are required to address these needs identified. The Office of Rare Diseases Research (ORDR) at the USA National Institutes of Health (NIH) has attempted to meet many of these needs in collaborative efforts with the research Institutes and Centers of NIH and other partners in the private and public sectors in the USA and around the world. Several of the activities of the NIH and the ORDR are presented as possible collaborative efforts available to research investigators and include the Rare Diseases Clinical Research Network, the Bench-to-Bedside research program at NIH, the Genetic and Rare Diseases Information center, the genetic test development program, and the information on clinical research studies made available through Clinical trials.gov. The value of an appropriate family medical history is discussed as are the provisions of the Genetic Information Non-Discrimination Act of 2008 (GINA). Definitions of rare or orphan diseases vary from country to country and may cause some confusion to the rare diseases community.

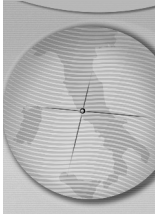
Conclusions: Rare diseases are not limited by geographical or historical boundaries and global partnerships of the rare diseases community are experiencing rapid expansion to assist in the development of orphan products for the prevention, diagnosis and treatment of rare diseases and conditions. The unmet needs of the rare diseases community require additional innovative research and educational programs to reach the extensive global populations affected by the thousands of different rare diseases including activities with the National Organization for Rare Disorders and the Genetic Alliance.

Key words: rare diseases, orphan diseases, research collaboration, orphan drugs, orphan products, Office of Rare Diseases Research

Collaborative research efforts and related activities of the Office of Rare Diseases Research at the USA National Institutes of Health

Rare diseases present unique challenges to meet the numerous and varied needs of the rare diseases community including patients and their families, research investigators, health care providers, the pharmaceutical, biotechnology, and medical device industries, and patient advocacy organizations. Significant financial and personnel resources are required to address the needs identified by the rare diseases community. Since 1989, the Office of Rare Diseases Research (ORDR) at the USA National Institutes of Health (NIH) has attempted to meet many of these needs. All of the current activities require collaborative efforts with the research Institutes and Centers of NIH and other partners in the private and public

sectors. Several of the activities of the NIH and the ORDR are presented as possible collaborative efforts available to research investigators. The definition of a rare or orphan disease varies in different countries and on different continents. A rare disease is defined as a disease or condition affecting fewer than 200,000 persons in the United States of America. Approximately 6,500 such disorders have been identified, affecting an estimated 25-30 million people in the USA. The legal definition of a rare disease is one that affects fewer than 50,000 patients in Japan. The European Union defined rare diseases as life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them. Low prevalence is defined as occurring in less than 1 in 2,000 people. Australia utilizes a definition of a rare



disease as one with a prevalence of less than 2000 individuals. In Taiwan the official definition of rare disorders is a disease with a prevalence less than 1:10,000 people. Even with this variability in the definition of a rare disease, there is a general acceptance of the need for collaborative rare diseases research and orphan products development efforts.

Rare Diseases Clinical Research Network

The NIH and ORDR announced support for 19 consortia in the Rare Diseases Clinical Research Network (RDCRN) which conduct studies of the natural history, epidemiology, diagnosis, and treatment of more than 95 rare diseases.[1] Funds and scientific oversight for the RDCRN are provided by ORDR and seven NIH Institutes, which will also contribute considerable administrative support to the network. These include the following: the National Institute of Neurological Disorders and Stroke (NINDS), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Heart, Lung and Blood Institute (NHLBI). Several consortia will also receive financial support from their associated patient advocacy groups.

Initially created in 2003, the RDCRN is unique in its approach to addressing rare diseases as a group. Most research focuses on individual rare diseases in their respective disease-type or organ domains. The RDCRN aims to create a specialized infrastructure to support rare diseases research utilizing multidisciplinary research teams from multiple institutions at different geographical locations. Since its creation, the RDCRN has enrolled over 5,000 patients in 37 clinical studies in rare diseases. Patient recruitment for clinical studies is a fundamental challenge in rare diseases research because there are typically so few affected patients in any one geographical area. Network consortia have also established training programs for clinical investigators who are interested in rare diseases research. One interesting outcome after several years of activity is the expansion of the research consortia with the addition of previous trainees at new research sites. This has been a goal to gain the interest and provide support for the next generation of rare diseases researchers.

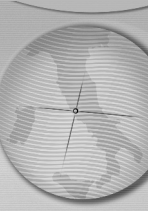
A major feature of the RDCRN is the direct involvement of over 55 patient advocacy groups in network and consortia operations, activities, and strategy. Each consortium in the network includes relevant patient advocacy groups in the consortium membership and activities. These patient advocacy group representatives serve as research partners within their own consortia. Collectively, the Coalition of Patient Advocacy Groups (CPAG) represents the perspective and interests of all patient advocacy organizations associated with the RDCRN. The CPAG participants meet frequently throughout the year by teleconference and face-to-face meetings. They participate in network-level discussions and meetings. The CPAG chairperson is a voting member of the RDCRN Steering Committee.

During the first phase of the Network, the Data and Technology Coordinating Center (DTCC) developed a management system for the collection, storage, and analysis of data, and additional systems to address needs of individual studies, such as a laboratory data collection system, a specimen tracking system, and a pharmacy management system (to support blinded distribution of study agents and placebos). The DTCC also created RDCRN's central public Web site, developed as a portal for the rare diseases community, including patients and their families and health care professionals, to provide information on rare disease research, consortium activities, study protocols, disease information, and practice guidelines. The DTCC also developed a unique voluntary patient contact registry that provides ongoing contact with approximately 5,000 individuals from over 60 countries representing 42 diseases in the RDCRN, alerting them when new studies are opened in the network or when ongoing studies expand to new sites.

In this second phase of the RDCRN, the University of South Florida will continue these data management efforts and with a slightly different charge, as the Data Management Coordinating Center (DMCC). The DMCC will develop uniform clinical research protocols for data collection, monitor protocol adherence, data collection and data submission, and work with each consortium's Data and Safety Monitoring Boards to establish protocols for adverse events notification and reporting.

The rare diseases and conditions included in the RDCRN are provided in Table 1. Individual Consortia in the RDCRN include the following:

- Angelman, Rett, and Prader-Willi Syndromes Consortium - University of Alabama at



- Birmingham - Alan K. Percy, M.D.
- Autonomic Rare Diseases Clinical Research Consortium - Vanderbilt University - David Robertson, M.D.
 - Brain Vascular Malformation Consortium - University of California, San Francisco - William L. Young, M.D.
 - Clinical Investigation of Neurologic Channelopathies (CINCH) - University of Rochester - Robert C. Griggs, M.D.
 - Dystonia Coalition - Emory University - Hyder A. Jinnah, M.D.
 - Genetic Disorders of Mucociliary Clearance - University of North Carolina at Chapel Hill - Michael R. Knowles, M.D.
 - Hereditary Causes of Nephrolithiasis and Kidney Failure - Mayo Clinic College of Medicine, Rochester - Dawn S. Milliner, M.D.
 - Immune Mediated Disorders After Allogeneic Hematopoietic Stem Cell Transfer - Fred Hutchinson Cancer Research Center - Stephanie J. Lee, M.D., M.P.H
 - Inherited Neuropathies Consortium - Wayne State University - Michael E. Shy, M.D.
 - Lysosomal Disease Network -University of Minnesota Twin Cities - Chester B. Whitley, M.D
 - Molecular and Epidemiologic Characterization of Salivary Gland Carcinomas - University of Texas M.D. Anderson Cancer Center - Adel K. El-Naggar, M.D., Ph.D.
 - Nephrotic Syndrome Rare Disease Clinical Research Network - University of Michigan, Ann Arbor - Matthias Kretzler, M.D.
 - North American Mitochondrial Diseases Consortium - Columbia University Medical Center - Salvatore DiMauro, M.D.
 - Porphyria Rare Disease Clinical Research Consortium - Mount Sinai School of Medicine of New York University - Robert J. Desnick, M.D., Ph.D
 - Primary Immune Deficiency Treatment Consortium - University of California, San Francisco - Morton Cowan, M.D.
 - Spinocerebellar Ataxia Clinical Research Consortium - University of Florida, Gainesville - Tetsuo Ashizawa, M.D.
 - Sterol and Isoprenoid Diseases Consortium - Oregon Health and Science University - Robert David Steiner, M.D.
 - Urea Cycle Disorders Consortium - Children's National Medical Center Research Institute, Washington - Mark L. Batshaw, M.D.
 - Vasculitis Clinical Research Consortium - Boston University Medical Campus - Peter A. Merkel, M.D.
 - Data Management and Coordinating Center

(DMCC) - University of South Florida - Jeffrey C. Krischer, Ph.D.

Genetic and Rare Diseases Information Center

Patients and their families, health care providers, industry, researchers, students and the public are in need of information about rare diseases and conditions, approved treatments, products in research status, availability of patient advocacy groups, genetic tests and genetic services and resources for the research community. The Genetic and Rare Diseases (GARD) Information Center was established in 2002 with support from ORDR and the National Human Genome Research Institute. Since that time nearly 25,600 individual responses have been provided to the rare diseases community for more than 6,500 rare and genetic diseases. Information from GARD supplements the information provided to the rare diseases community from the ORDR and other sources in the public and private sectors. During the past four years, more than 521,600 visitors per year have visited the ORDR website and these visitors sought information from ORDR with an average of 1,261,000 visits per year throughout the same time period. In addition to the ORDR website, the GARD website currently receives an average 62,000 visits per month or nearly 744,000 visits per year from nearly 38,000 visitors per month. An encouraging and positive trend is emerging. It appears from this data that visitors are returning to the website to seek additional information, an activity encouraged to obtain more recent information. Information is developed and presented by genetic counselors and physicians in response to the inquiries.

To simplify the search for information, GARD presents information as archived documents prepared from previously received inquiries. The activity resulted initially in a decrease of individual phone calls and email requests with a significant increase in visitors to the website. More recently the individual queries have increased and continued to exceed the 2008 levels. Updated information is provided in response to the individual requests and included on the archived documents when additional queries are received on specific disorders. Periodic assessments of user satisfaction are conducted and guide the revisions of the web site and the information made available.

There are two major reasons for contacting GARD. Some believe they have received insufficient information and others believe they need to validate information provided to them. Approximately 71 per cent of inquiries to GARD

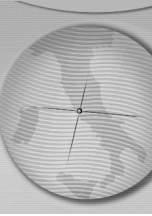


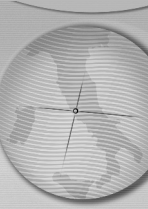
Table 1. Diseases under investigation in the USA National Institutes of Health's Rare Diseases Clinical Research Network.

Consortium Title	Diseases to be studied
Angelman, Rett, and Prader-Willi Syndromes Consortium	Angelman syndrome, Rett syndrome, Prader-Willi syndrome
Autonomic Rare Diseases Clinical Research Consortium	Multiple system atrophy (MSA), baroreflex failure, autoimmune autonomic neuropathy, pure autonomic failure (PAF), hypovolemic postural tachycardia syndrome (hPOTS), dopamine beta hydroxylase deficiency (DBHD)
Brain Vascular Malformation Consortium	Vascular malformations: cerebral cavernous malformation progression, Sturge-Weber syndrome, hereditary hemorrhagic telangiectasia
Clinical Investigation of Neurologic Channelopathies	Nervous system channelopathies: Andersen-Tawil syndrome, episodic ataxias, non-dystrophic myotonic disorders
Dystonia Coalition	Focal dystonias, cervical dystonia, blepharospasm, spasmodic dysphonia, craniofacial dystonia, limb dystonia
Genetic Disorders of Mucociliary Clearance	Primary ciliary dyskinesia (PCD), cystic fibrosis (CF), pseudohypoaldosteronism (PHA)
Hereditary Causes of Nephrolithiasis and Kidney Failure	Rare hereditary stone diseases: primary hyperoxaluria, cystinuria, dihydroxyadeninuria, Dent's disease
Immune Mediated Disorders After Allogeneic Hematopoietic Stem Cell Transfer	Cutaneous sclerosis, bronchiolitis obliterans, late acute graft versus host disease (GVHD)
Inherited Neuropathies Consortium	Inherited peripheral neuropathies: Charcot-Marie-Tooth diseases (CMT) including 1) CMT1, the dominantly inherited demyelinating neuropathies, 2) CMT2, the dominantly inherited axonal neuropathies, 3) CMT4, the recessively inherited neuropathies
Lysosomal Disease Network	Lysosomal diseases: mucopolysaccharidosis (MPS), MPS bone disease, Pompe disease, Niemann-Pick disease type C, glycoproteinosis, Wolman disease, late infantile ceroid lipofuscinosis, (LINCL), mucopolipidosis type IV, hexosaminidase deficiency, Fabry disease nephropathy, Batten-Turner muscular dystrophy

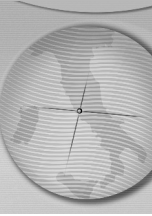
are received from patients, their parents and relatives. Nearly 9 per cent of requests for information are received from health care providers. Approximately 8 per cent of inquiries are from the general public and students seeking information for school assignments. Surprisingly, only 1% of inquiries are received from patient advocacy groups. One of the goals is to encourage access to patient advocacy groups by highlighting their presence, information available and

activities. Inquiries are received from around the globe. Domestic inquiries from the USA account for 79% of the use and the other 21% are from international inquiries or are unknown. Patterns for web trend traffic to the web site are very similar with 73% of information seekers from the USA and 27% of visitors from international countries.

GARD also responds to questions about more common, complex conditions including autism,



Molecular and Epidemiologic Characterization of Salivary Gland Carcinomas	Salivary gland carcinomas: mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (ACC), adenocarcinoma (ACC)
Nephrotic Syndrome Rare Disease Clinical Research Network	Focal and segmental glomerulosclerosis (FSGS), minimal change disease (MCD) and membranous nephropathy (MN)
North American Mitochondrial Diseases Consortium	Mitochondrial encephalopathy lactic acidosis with stroke-like episodes (MELAS); mitochondrial neurogastrointestinal encephalomyopathy (MNGIE); Leber's hereditary optic neuropathy (LHON), LHON and dystonia, Leigh syndrome; encephalomyopathy; ALS-like syndrome of encephalomyopathy; neuropathy, ataxia and retinitis pigmentosa syndrome (NARP); maternally inherited Leigh syndrome (MILS); familial bilateral striatal necrosis (FBSN); leukodystrophy; CoQ deficiency; encephalopathy; cardioencephalomyopathy; leukodystrophy/tubulopathy; fatal infantile encephalomyopathy
Porphyria Rare Disease Clinical Research Consortium	Porphyrias: Acute Intermittent Porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), aminolevulinic acid dehydratase deficiency porphyria (ADP), porphyria cutanea tarda (PCT), erythropoietic protoporphyria (EPP), congenital porphyria (CP)
Primary Immune Deficiency Treatment Consortium	Primary immune deficiencies: severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome (WAS) and chronic granulomatous disease (CGD)
Spinocerebellar Ataxia - Clinical Research Consortium	Spinocerebellar ataxia: SCA 1, 2, 3, and 6
Sterol and Isoprenoid Diseases Consortium	Niemann-Pick disease type C, Smith-Lemli-Opitz syndrome, Sjögren-Larsson syndrome, mevalonate kinase deficiency, hyper-IgD syndrome, cerebrotendinous xanthomatosis (CTX), sitosterolemia
Urea Cycle Disorders Consortium	Urea cycle disorders: N-acetylglutamate synthetase (NAGS) deficiency, carbamoyl phosphate synthase 1 (CPS) deficiency, ornithine transcarbamylase (OTC) deficiency, argininosuccinate synthetase deficiency (classic citrullinemia), citrin deficiency (citrullinemia type 2), argininosuccinate lyase deficiency (argininosuccinic aciduria), arginase deficiency (hyperargininemia), ornithine translocase deficiency syndrome (HHH)
Vasculitis Clinical Research Consortium	Vasculitides: Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), polyarteritis nodosa (PAN), Takayasu's arteritis (TAK), giant cell (temporal) arteritis (GCA)
Data Management and Coordinating Center (DMCC)	



Alzheimer disease, bipolar disorder, Crohn disease and multiple sclerosis. The services are provided with no charge to the public. The GARD constantly seeks better methods to gather, store and distribute useful and accurate information. Most responses are provided within two to six working days unless an urgent request is made.

Gaining access to clinical research studies

One of the major needs of the rare diseases community is to have ready access to ongoing and planned research studies. ClinicalTrials.gov is a service provided and maintained by the National Library of Medicine, the National Institutes of Health and the Food and Drug Administration. ClinicalTrials.gov provides up-to-date information for locating Federal and private sector clinical trials. Three types of studies can be found in the searchable database including the following: Clinical trials and clinical research studies, intervention trials, and observational studies. (URL: <http://clinicaltrials.gov>) More than 80,000 trials are included in ClinicalTrials.gov. The studies are conducted and reported from 170 countries. Over 3,000 studies have been reported from the research community and industries in Italy and 1,140 studies are currently open and recruiting patients. The rare diseases community is urged to review the database on a regular schedule for recent updates and additions. The presence of closed or completed studies is a significant issue. For many rare diseases, gaining access to investigators is a significant step even though a study may be closed. Another study could be in development and patients or volunteers may be needed when a new study opens for recruiting. Research investigators of other closed rare diseases studies may be the best source of information about a disease. All research investigators of rare diseases are encouraged to submit their studies to the database, along with regular updates. There are nearly 50,000 visitors to the web site every day.

Reporting requirements: results of clinical trials

The USA Food and Drug Administration Amendments Act of 2007 expanded the reporting requirements for clinical trials to include study results to the study profile [2]. Summary informational results are required for Phase 2-4 intervention studies initiated or ongoing as of September 27, 2007 and studies having at least one site in the USA or are conducted under an Investigational New Drug application (IND) or Investigational Device Exemption (IDE) [3]. Phase

1 drug trials are excluded from the reporting requirements as are small feasibility or pilot studies of medical devices and observational studies. Study results are now required within one year of completing data collection for the primary outcome.

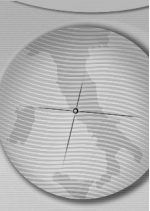
Submission of results can be delayed [1] if the clinical trial of the drug or device has not been approved for marketing, [2] if the trial of a drug or device for which the sponsor (manufacturer) has filed or will file an application seeking approval of the new use studied in the trial or [3] if trials for which a request that "demonstrates good cause" has been granted by the NIH Director.

Reporting requirements: adverse events

Starting on September 27, 2009, summary adverse event information is to be submitted when providing study results to ClinicalTrials.gov. The adverse event module includes two tables. One table is for serious adverse events and the other table is for adverse events that exceed a frequency threshold of 5% within any arm of the clinical trial. Sponsors of trials may voluntarily use a reporting threshold of less than 5% if they choose to do so.

Collaboration, Education, Genetic Test Translation (CETT) Program

Rapid progress is being made in discovering the genetic basis of many rare diseases, but access to genetic tests and genetic test development is lagging behind as the need increases. The CETT Program facilitates the translation of genetic tests from the research laboratories and clinics to Clinical Laboratory Improvement Amendments (CLIA) certified laboratories through collaborations among clinicians, laboratories, researchers, and rare disease-specific patient advocacy groups [4]. Numerous goals have been established for the CETT Program. The first goal is to promote the development of new genetic tests for rare diseases. The second goal is to facilitate the translation of genetic tests from research laboratories to clinical practices. The next goal is to establish collaborations and provide educational materials about each rare genetic disease, related genetic research, and the clinical impact of testing. The final goal is to support the collection and storage of genetic test results information in a publicly accessible database to leverage the information into new research programs leading to new treatment possibilities. The CETT Program has approved the translation of new or improved tests for 110 genes involving



67 rare diseases.

Addressing the genetic testing issues

In 2003, the NIH's ORDR became aware of the limited translation of research discoveries and genetic tests development to clinical laboratories. There also was a concern with research laboratories providing test results to individuals, families, and clinicians who were requesting clinical testing. This was a problem because most research laboratories do not provide clinical services, do not have CLIA certification, do not have clinically trained staff to give test results to patients and their families, and do not have the resources within their research grants to absorb the costs of providing clinical testing to meet the CLIA certification requirements. Between 2003 and 2005, ORDR and the Centers for Disease Control and Prevention (CDC), along with the Health Resources and Service Administration (HRSA), Emory University, American Society of Human Genetics (ASHG), American College of Medical Genetics (ACMG), Society for Inherited Metabolic Disorders (SIMD), Genetic Alliance (GA), and others, coordinated a series of conferences to address the issue of facilitating rare disease genetic test translation from the research setting into clinical laboratories and services. These discussions led to the development of the CETT Program.

From the numerous conferences and discussions held over the same time period, a number of key issues became apparent with regard to access to quality genetic test development and translation. These included a lack of understanding and appropriate interpretation that a genetic test result was clinical information and can only be given to individuals through a CLIA-certified laboratory. There was a need for expert support in test result interpretation, coordinating referrals of individuals with atypical results back to research laboratories for further research studies, and providing educational materials for clinicians and individuals and families with a rare disease to understand genetic tests and what expertise and resources were available to them after receiving the diagnosis. There was also a need to provide the same level of quality assurance and quality control for low-volume rare disease testing.

Developing a model program

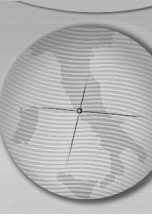
From these considerations, the CETT Program was developed as a demonstration or pilot project for genetic test translation that could become a model process for rare disease test translation.

After early experiences developing genetic tests in the NIH Intramural Research Program, several activities required additional support if the program was to become an appropriate model for future expansion. Many shortcomings were identified. Most clinical laboratories performing rare genetic disease testing have limited funds and limited personnel to develop new tests. Most clinical laboratories do not have the resources needed for data collection and educational materials development. Many researchers are not aware of clinical laboratories that can translate the test developed in their research.

The CETT Program model now requires applicants seeking support for genetic test translation to form a CETT Collaborative Group comprised of a clinical laboratory, a researcher, an expert clinician investigating the disease, and a patient advocacy group representative for the rare condition. Once established, the Collaborative Group can register in CETTrack and apply to the CETT Program for support to develop new clinical tests for rare genetic diseases. CETTrack is an online portal designed to allow applicants to communicate and share draft documents as they build their Collaborative Group and CETT Program Application. The portal tracks the application through the review process, funding and submission of annual reports. All new Applications must be submitted via CETTrack. (URL:

http://rarediseases.info.nih.gov/cettprogram/getting_started.aspx)

Support is now provided for three areas identified from earlier experiences. The first of these, Collaborative Group Development, has been mentioned previously. Secondly, since researchers play a critical role in the test translation process, support is also provided for the translation and clinical consultation activities of the research member(s) of each CETT Program application. Lastly, guidance and support is available for developing effective educational materials that are critical to the appropriate use of newly available clinical tests. These educational materials are made available to the clinician requesting the test and to the individual patients or their families. Genetic counseling is encouraged before and after the genetic test results are reported. Educational materials are needed to help clinicians and individuals or families have a better understanding of the test ordering process, the benefits and limitations of the requested genetic test, and how to interpret the test results. Supplementary funds are made available for these activities in addition to the



funds allocated for genetic test translation.

Genetic Information Nondiscrimination Act (GINA) of 2008

On May 21, 2008, the Genetic Information Nondiscrimination Act (GINA) was enacted in response to a very strong concern by the public that genetic information about individuals would be used in the workplace to prevent people from obtaining a position of employment or advancement. There was also a major concern that genetic information would be used to discriminate in determining eligibility for health insurance. GINA also restricts acquiring and disclosure of this information [5].

Recently, concern has been expressed about participation in clinical trials that include investigation of genetic data from individuals who could be identified with the published results. Without the continued participation of individuals with rare diseases, research advances will be delayed and possible products will be even slower to reach the marketplace than current experiences indicate. It is thought that by identifying the genetic factors associated with a disease, researchers and the pharmaceutical and biotechnology industry may be able to take advantage of the advances in the understanding of genetics and genomics. If they are able to identify and translate the genetic factors associated with a rare disease, patients will receive the benefits from the development of more effective drugs.

GINA has two major provisions. Title I applies to health coverage and group health plans sponsored by private employers, unions and state and local government employers, issuers in the group and individual health insurance markets, and issues of Medicare supplemental insurance (Medigap). Title I prohibits discrimination in group premiums based on genetic information and the use of genetic information as a basis for establishing eligibility or costs of premiums in these markets. Several departments of the Federal government – the Departments of Labor, Treasury and Health and Human Services are responsible for administering and enforcing the Title I nondiscrimination provisions.

Title II of GINA prohibits the use of genetic information in the employment contexts, restricts acquisition of genetic information by employers and strictly limits organizations from disclosing genetic information. Genetic information will be considered confidential. The Equal Employment Opportunity Commission is responsible for the administration and enforcement of the Title II nondiscrimination provisions.

Family medical history

The majority of rare diseases have a genetic component. Many are single gene diseases, some are chromosomal conditions and epigenetic rare disorders, and others are due to interactions between genes and the environment. A number of rare disorders are considered genetic in origin based on pedigree analysis revealing familial clustering and separation in definite proportions. A careful medical history including the family history of disease and wellness may provide clues to both rare and common diseases and diseases that patients may be at risk of developing. By tracing the family history, patients may discover illnesses that can be predicted to occur during their lifespan. The family health history is a useful screening tool. Unfortunately, many people remain unaware of their family medical history.

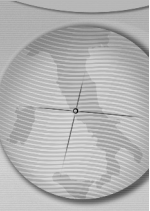
The Surgeon General of the United States Public Health Service, Department of Health and Human Services, initiated a national public health campaign in 2004 urging all families to learn more about their family health history [6]. A computerized web-based tool is now available to assist in creating their family medical history. (URL: <http://www.hhs.gov/familyhistory/>)

The “My Family Health Portrait” tool is used to gather information and assist in organizing the family history in a way that can be presented to physicians. One of the more popular holidays for family gatherings in the USA is Thanksgiving Day. All families are encouraged to develop and maintain their family health history on this day.

The conclusion of the recent NIH State-of-the-Science Conference on Family History and Improving Health, recognized that family history has an important role in the practice of medicine and may lead to positive changes in lifestyle, enhance the empowerment of patients on the decision-making process and influence clinical intervention [7]. More information is needed on the effect of family histories on morbidity and mortality. The benefits and potential harm that could occur due to misinterpretation or misapplication of information developed in the family history are also major concerns that need to be evaluated. In the not too distant future, sequencing an individual patient's genome will become more readily available and will occur more frequently. Appropriate interpretation of information gathered from these results will be a major challenge to health care providers.

Bench-to-bedside research program at the NIH Clinical Center

Another activity to foster research collaboration



of rare diseases between institutions is the NIH Bench-to-Bedside Research Program. The program was established in 1999 to integrate the work of basic and clinical intramural scientists from different Institutes or Centers at NIH. Since 2006, collaborative partnerships have been encouraged between intramural (within the NIH) and extramural (outside of NIH) programs. More than 500 principal and associate investigators have collaborated on 152 projects.

Extramural principal investigators (PIs) with an existing NIH grant may initiate proposals by seeking an intramural partner at NIH who would function as the project leader and serve as the point of contact. Intramural collaborators can be located at NIH's database of all current intramural research. (URL: <http://intramural.nih.gov/search/index.html>) Most research protocols require patients to travel to the Intramural Research Program at the NIH Clinical Research Center Hospital. Collaboration between individuals with

basic science and clinical skills has been stimulated and has led to new research protocols.

Collaboration between intramural and extramural investigators stimulated enthusiastic expectations of accomplishments.

Conclusions

Global partnerships and a research infrastructure are being established and are considered necessary if significant progress is to be achieved in the development of products for the prevention, diagnosis, and treatment of rare diseases and conditions. Rare diseases know no geographical or historical boundaries. Despite increased emphasis in activities by both public and private sector organizations in many countries around the world, including organizations such as the National Organization for Rare Disorders and the Genetic Alliance, the unmet needs of the rare diseases community require additional innovative research and educational programs to reach the extensive global populations affected by the thousands of different rare diseases.

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