commentary

Developing a national collaborative study system for rare genetic diseases

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There are thousands of rare genetic diseases and many genetic and nongenetic contributors to common genetic diseases. The evidence base that is currently available about the great majority of these conditions is limited to case studies and relatively small observational study sets derived from one or several institutions. Hence, the statistical power in any one study is usually quite limited. Further, in the absence of organized registries and data collection on particular patient groups, the information available is weak and the patient resources that are available are limited. It is only through organized and coordinated clinical investigation systems that a sufficient number of patients with these diseases can be accumulated to provide the statistical power needed to inform about clinical history of treated and untreated forms, provide the resources needed for clinical trials of new tests and treatments, provide a sufficiently powered evidence base for public health decision-making and other uses. The meeting in which these issues were raised resulted in a set of proposed principles and associated recommendations as to how best to achieve the vision of creating an extensive and comprehensive collaboration of professional and lay communities to enable translational research to improve clinical care and therapies for persons with rare genetic diseases. ***Genet Med* 2008:10(5):325–329.**

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A meeting was convened in Tyson's Corner, VA, on Monday and Tuesday, February 19–20, 2007 to consider issues and strategies in the development of a national system for collaborative research in rare and heritable genetic diseases.

To this end a total of 35 attendees from academia, clinical medicine, federal institutions, and medical societies were tasked with reviewing some of the existing exemplars of collaborative research groups. After extensive discussions, they produced a set of recommendations to form the basis of a "White Paper" for submission to NICHD and, subsequently, this article. The meeting was sponsored by the National Institutes of Child Health and Human Development (NICHD), the NIH Office of Rare Diseases, and the American College of Medical Genetics (ACMG).

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STATEMENT OF THE PROBLEM

Recent developments in our knowledge of the human genome and the diseases associated with genetic variation have produced a vast amount of information that, at present, is poorly organized and under-utilized.

Of the 4000-plus genetic tests in routine or clinical investigative use, the overwhelming majority are for the diagnosis of rare or orphan diseases with relatively few tests available for common disorder.

Currently, the evidence base for genetic diseases and tests is often badly organized and of poor quality. The observed variability stems from the wide range of testing technologies that have been used over the years and the disparate sources of data that include case reports, observational studies and more recently, the newborn screening (NBS) programs. Recent reviews of a number of conditions under consideration for inclusion in NBS programs point to the need for a much better developed evidence base that includes the greatest possible number of patients. The lack of an organized system within which data are developed and evaluated has significantly contributed to the growing gap.

Experiences from NBS programs that provide a general population perspective have clearly demonstrated that it is difficult to anticipate the full range of genetic disease expression until a general population is assessed. This has led to significant imbalances in the evidence base between the genetic diseases that are part of NBS programs as compared with those identified clinically, often before genetic tests were available, and the

studied phenotypes were more severe. Further, even within NBS, there have been limited efforts to develop data from the long-term follow-up of patients identified in the programs. Recent efforts by NIH-funded Rare Disease Centers have been disappointing, frequently failing to recruit more than 20% of the patients in the United States with a particular condition.

There are significant implications to having a poorly organized evidence base for genetic diseases. The lack of knowledge of the natural history of a disease hinders the development of new chemical entities, as this information must be obtained before treatment outcomes can be set and assessed. This increases the costs of a trial and the time to its completion. Science has clearly outpaced the system of regulatory oversight and has highlighted the need for new approaches to clinical investigation.

Rare genetic diseases are among those most affected by a poorly organized system. Improvement will require that as many patients as possible are entered into systematic studies in which the collection of laboratory and clinical data are driven by disease specific protocols as has occurred in the national cancer cooperative study groups. This may be national or international, as seen with the recent formation of the Duchenne Research Collaborative International.

Expert-driven protocol development and data review will be critical. The limited availability of clinical researchers trained in this area must be addressed. Databases that allow for the collection of data from systematic studies also will be needed. Novel statistical approaches to integrating complex data sets will need to be developed. Prospective studies that consider both health and economic outcomes will be critical to demonstrating utility earlier in this process. Only a systematic approach will improve our understanding of the thousands of heritable diseases with strong genetic determinants.

Context

The ACMG was awarded a grant by the NIH NICHD to run a series of meetings to address issues in the development of a national collaborative study group system in the United States for patients with rare genetic diseases. A series of workshops have been held at the annual meeting of ACMG addressing lessons learned from disease specific study consortia, long-term follow-up of NBS patients, model systems and IRB issues for multicenter clinical investigation, and statistical issues arising from underpowered studies. The meeting discussed herein is of the advisory committee for this grant. Its focus is on the development of a national collaborative study group system for rare genetic diseases including database needs, and group structures that would be amenable to the broadly multidisciplinary nature of genetic diseases.

THE CONSENSUS OPINION

Although not everyone agreed to every point, the following vision, principles, and recommendations were the majority view of the meeting attendees.

The overarching principle is described in the vision. The principles are more specific statements, and are followed by a list of recommendations. The rationale is an attempt to describe the thinking behind each recommendation.

Vision

An extensive and comprehensive collaboration of professional and lay communities will be required to enable translational (basic, clinical, and public health) research to improve clinical care and therapies for persons with rare genetic diseases including conditions in NBS programs or those that might be considered for such screening programs.

Principles

Achieving this vision will require:

- Establishing a clinical research enterprise built on open communication strategies and on trust.
- Employing a multifaceted approach to clinical research, including natural history studies, population studies, epidemiology, genotype-phenotype correlations, and clinical trials.
- Using a wide variety of research approaches to address the distinct issues raised by different disorders.

The development of an organized system for ongoing national collaborative research in rare genetic diseases will be a long-term activity that requires the active and willing involvement of health care professionals, industry, experts in related fields, patients, their families, and communities. As such, it must be predicated on open communication and trust between all participants. There should be tangible results that are of interest and value to participants of all types. Further, a meaningful collaboration should lead to synergistic outcomes for all involved. Regulatory bodies such as the FDA should benefit from an organized system in which surrogate and pathologic endpoints can be validated.

Genetic traits and diseases involve all organ systems and can occur at any time over the lifespan. Hence, primary care professionals, subspecialists, and specialists of all types can be involved in the care of patients and their families. Further, our understanding of genetic disease is strongly informed by our knowledge of the entire population of affected and unaffected individuals, emphasizing the epidemiological aspect of genetic diseases.

RECOMMENDATIONS

Recommendation 1

Partnerships that include communities, patient advocacy groups, local, national and international authorities, industry, and a diverse array of medical and public health professionals, should be established to address long-term translational research needs.

Supporting information

Numerous entities have needs with regard to information, involvement and roles in translational research in rare genetic diseases. Similarly, the outcomes of translational research are broad and can impact a wide range of participants including providers, regulatory bodies, patients, and others. To ensure that the partnerships between providers, investigators and consumers are developed, it will be important to promote the need for team-based science.

Recommendation 2

An open-source tool kit for translational research on genetic disorders should be assembled that will enable the establishment of

a. Accessible repositories of well-curated biological materials.

b. Registries of affected individuals who may be recruited as participants for clinical studies.

c. Systematic phenotypic assessment and analysis of environmental influences using standardized vocabularies and ontologies that underlie electronic health information systems.

d. Flexible and appropriate data collection (historical and prospective), retrieval and communication, among different investigators and studies.

Supporting information

a. Collections of biological materials are needed for academic, government and industry research. In the past such biorepositories have contained materials from patients who may have given ill-informed consent and who were not able to be contacted again to obtain reconsent for further work. The collections may be small and cataloged using nonstandardized language that hinders comparisons with other collections. A standardized system for documenting, indexing, storing, and retrieving items from such collections would facilitate collaboration between the different groups engaged in translational research.

b. The contact details of each individual with a rare disorder should be entered into a registry, allowing research groups to recontact these people in the future for recruitment into research studies. Registries may form around the needs of the various constituencies as well. States maintain registries of genetic disease patients identified through their public health programs. Investigator and groups of investigators maintain registries of the patients of direct research interest to them. Advocacy groups, by establishing a community of affected individuals, are able to draw on the goodwill of these people to participate in registry and data collection activities. All will be needed for success to be realized.

c. Health information systems that use customized, nonstandardized methodologies to categorize their information do not permit the pooling of information from different centers and the advantages that accrue from the accumulation of these data. Open source code systems, such as those employed by ca-BIG permit the interrogation of different databases using a common vocabulary and data format and help to overcome the silo effect seen when nonstandardized systems are used.

d. No current or new system can foresee all the possible future uses of the information stored within it. This places a premium on building in flexibility to cope with future requirements.

Recommendation 3

Develop models that permit the creation of widely dispersed but tightly integrated translational research networks.

Supporting information

The nature of rare genetic diseases is that no one provider will be likely to have enough patients of their own to generate the type of robust data that is needed. Decisions about rare disease services already receive latitude by virtue of the limited statistical power that can be generated from small groups. Further, there are many types of clinical research that might occur within groups with differing expertise. In order for the constituent parts to work together, multidisciplinary groups of experts will need to develop protocols that will be followed to ensure that data are compatible across different widely dispersed provider groups. Federated access to appropriate data and organized quality control and assurance of data are apparent.

Recommendation 4

Professionals and lay communities will require training to enable active participation in translational research and clinical trials.

Supporting information

Many professionals will require training to participate in clinical trials. Existing programs such as the training programs of the Clinical and Translational Science Awards program can be expanded to include training in rare genetic diseases.

The NIH Director's Council of Public Representatives Report on Human Research Protections in Clinical Trials (October 2001) recommended that the NIH should develop model programs that would educate and train the public at large, and in particular trial participants, to better equip them to become empowered and informed partners in the research process.

These programs were also to address the need to instill a sensitivity within the research community that recognizes, respects and invites the collaboration of the public as active partners in this research work.

Recommendation 5

Advocate for modification of the system of ethical review that will facilitate multicenter translational studies and clinical trials.

Supporting information

There is concern and evidence that the current system of approval of clinical trials using institutional review boards is deficient, with individual and institutional conflicts of interest slowing down the times to approval for study protocols. The roles and responsibilities of individual IRB members are often unclear, contributing to the delays in approval of protocols. The introduction of IRBs that are independent of institute affiliations is seen as a way to increase the professionalism of these bodies and to reduce potential conflicts of interest during the review process. A broadly dispersed multi-institution translational research network of the type envisioned will require new approaches to the development and implementation of informed consent and other IRB functions. Examples from the recently funded National Children's Study and the National Cancer Cooperative Groups have offered reasonable examples of alternative strategies. Federated electronic data repositories can address information and data needs of many constituencies while protecting patient privacy and confidentiality.

Recommendation 6

Establish mechanisms to insure that, as part of the research process, participants are informed of relevant outcomes and progress of research studies in which they take part in a timely manner, and before any publication.

Supporting information

There is considerable evidence that those participating in clinical research consider access to information about what has been learned in the studies to be an important feature with regard to their participation. This access to information is typically provided in one of two ways and may include either prepublication or postpublication information. Many of the issues related to public involvement are discussed in reports of the NIH Director's Council of Public Representatives. Consumers have been increasingly interested in ensuring that there is open access to publications about research that have been publicly funded. However, summaries of the implications of the research that is delivered through newsletters and other methods is also valued. Useful examples of such systems can be found in the NHLBI/NHGRI sponsored HEIRS Study of Hemochromatosis and the Framingham Heart Study, both of which include mechanisms of providing information to participants related to ongoing research. The intention here is "*. . . to ensure that clinical research leads not only with the "high tech" of cutting-edge science, but also with the high touch of human interactions that values and empowers patients as active, informed and respected partners.*"[1]

Recommendation 7

Establish models for the handling of intellectual property, to provide incentives for innovation and access to discoveries for clinical application.

Supporting information

Mutual trust between researchers and patients is required for research work to progress in an expeditious manner. The sharing of information may be helped by the creation of a "research enterprise" that maintains a significant amount of research information in the public domain. Central to the creation of such an enterprise is to overcome the barriers to industry partnerships that can arise when there are potential conflicts of interest related to intellectual property.

CONCLUSIONS AND NEXT STEPS

The development of a mechanism through which the aforementioned issues and activities can be coordinated will be essential to moving forward. Significant amounts of money are already being spent on individual components of the system that is envisioned in this report. Much of the work is multidisciplinary and involves clinical service providers, clinical investigators, industry, government, and the public. Further, because many with rare genetic diseases are identified in NBS programs, the involvement of States and public health programs will be necessary. The nature of the work will require the involvement of organized medicine to develop consensus practice guidelines for care and related data collection. Few organizations bridge this wide array of interest groups and expertise as does the ACMG.

1. Assemble and evaluate existing resources.
2. Capture current landscape and assess pros and cons.
3. Identify and engage key partners and stakeholders under a convening authority.
4. A set of demonstration projects should be established that include natural history studies and clinical trials for disorders that reflect various levels of frequency and complexity. NBS should be a major focus of study in this effort.

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