Innovative Approaches to Social and Behavioral Research in Rare Diseases
March 15, 2007
Meeting Summary

Meeting Aim: To foster discussion of ideas for the application of new social science research methods or study design to understand better the impact of living with rare genetic conditions on individuals, families and the larger community.

What is the Need? Studying the impact of rare genetic conditions on individuals' and families informs the design of intervention studies to improve adaptation, psychological well-being and/or quality of life.

What is the Problem?
Quality social science research into the impact of living with rare diseases is lacking. This is the result of limitations imposed by measurement constraints, small sample size, selection biases and a preponderance of descriptive, rather than outcomes-based, research. There is often a lack of normative data or informative control groups. Rare genetic conditions occur within a complex backdrop of socio-cultural, ethnic/racial, familial, and individual characteristics. Determining challenges that are attributable to living with a condition means that we have to understand them within but also beyond the context in which they occur.

What is a rare disease?
A disease or condition affecting fewer than 200,000 persons in the United States; An estimated 25 million people in the United States have a rare disease.

Types of studies that have been done:
Health-related well-being:
- Trust/use of medical care system/compliance
- Communication with health care providers
- Participation in research/uptake of genetic testing

Psychological well-being:
- Adaptation to a condition
- Family communication of genetic risk or diagnosis
- Social integration/functioning
- Quality of life
- Feelings of stigmatization or isolation

Questions about the scope of the problem:
Do the limitations stem from our limited ability to characterize the conditions or the limited numbers of individuals who are affected? There is great heterogeneity among rare disorders, including congenital to adult onset, so one cannot generalize. Is it that we do not have the measures? Do we need open-ended studies to narrow understanding? Is it how you use the instruments? What is the difference in rare disease? How are they characterized? Is the variation within and among them any different from that in common disease? Can we learn about common disease by studying the uncommon?

Characterization:
There are smaller numbers of rare genetic conditions by definition but also the issue of passing on the condition within families, thereby a concentrated number of those at risk (although there is variation in mode of transmission). There is a decentralization and dispersal of affected individuals, and this poses challenges for selection bias, as researchers often rely on support groups for recruitment. Thought needs to be given to the similarities and differences among rare genetic disorders and general chronic disease. There needs to be a different definition of the "denominator," in order to facilitate more "generalizable" data.

It is well known that stigma is an aspect of rare genetic conditions; do we need to further document this or is there sufficient evidence to study interventions? Do we need to document further or understand the burden? Clinically, it has not been characterized, only observed. How is it different from other sources of stigmatization? Is there heterogeneity in the stigma associated with rare disease? Is there such thing as institutional stigmatization, like institutional racism? What does it look like?

Stigmatization is a key issue, and an area where further research is needed, both related to "visible" and "non-visible" conditions. Stigma in rare diseases could be used as a model for studying differences in general, and may help to define possible interventions for improving self-concept and quality of life. What ways exist to take advantage of technology and the Internet for learning about stigmatization and the potential for interventions? Experiences of stigmatization, as well as perceived stigmatization, need to be assessed.

Is it that the social and behavioral aspects become more important because there is less we are able to do medically for those who are affected with rare diseases?

Potential Projects:

- Evaluating the social benefits of advocacy groups
- Funding research into amalgamated groups of rare conditions that share attributes
- Stigma interventions--model projects that could be useful beyond rare diseases
- E-health resources--little research on how effective these resources are (technologies out there)

Methods and Measurements

The focus ought to be on how we can do research and make improvements on the fundamental problem, which is low numbers. We need to evaluate what we have and what we can do with what already exists, as well as define what we need, such as a consortium for collection of data. Small sample size and statistical power need to be thought of as more than just the "N." With a captive audience, there can be strength in multiple measures (measure fewer subjects multiple times). It is also important to think about multi-dimensional or hierarchical data (i.e.: family level, individual level). There may also be value in taking a sample from a subset of multiple conditions to study a concept like stigma.

While numbers will never be statistically significant to the degree of generalizability, we can think of the power associated with being able to capture a large percentage of affected individuals. Large population representation means something completely different.

We need to consider which is more important: internal validity or external validity. Can we get both? The LAM Foundation can provide examples of methods for success in capturing all affected individuals with a particular rare condition.

Burden of disease (QOL) across many conditions generically may be useful to collecting broader health care data on the impact of rare diseases.

Practical research questions that can be asked:

- What is the best control group??
- What is the value of support groups? What about support groups is helpful?
- How to randomize (ex: support group vs. support group PLUS intervention)
- On-line sporadic information vs. brochure (beyond support group?)
- When to use a RCT (characterize groups prospectively, etc).
- Comparison among groups to avoid selection bias in small number constraints.
- Clinical equipoise between support groups and other sources of support can be tested.
- Role of minorities/cultural differences in living with rare genetic conditions
- Diagnosis, access to the system, general disparities
- How to target those at highest risk?

Priorities:

There is a need for strategic planning to create a system that binds rare diseases. We can start with registries to which we already have access, improve methodologies to find what interventions may be needed and those that work. Registries also provide us with potential control groups (sibs, family members). Efforts need to be spent intensifying cross-cutting aspects of living with rare diseases that can lend themselves to meta-analysis. We need to develop tools to accomplish this outcome. Methods challenges are the top priority.

Meeting Follow-Up:

- To function as an ongoing informal working group through e-mail (and perhaps conference calls)
- To write and publish a manuscript on methodological considerations in social science research into the impact of living with rare genetic conditions
- To consider holding an annual meeting (piggy-backing onto another?)
- To consider hosting a meeting of the players--SIMD, ORD, Gen Alliance, etc…
- To consider addressing this topic in a special issue of a journals
- To work toward the development of web-based resources

Meeting Participants:

Barbara Bowles Biesecker, M.S., Social and Behavioral Research Branch, National Human Genome Research Institute, NIH
Ms. Biesecker conducts social and behavioral rare disease research at NHGRI and is initiating efforts to foster innovative new approaches to address limitations in this type of research.

Thomas Eng, V.M.D., M.P.H., EvaluMetrix LLC.
Dr. Eng's areas of expertise include the application of emerging technologies, especially the Internet, to health communication, health care, public health, evaluation, and research.

Bill Gahl, M.D., Ph.D., Office of the Clinical Director, National Human Genome Research Institute, NIH
Dr. Gahl studies rare inborn errors of metabolism through the observation and treatment of patients in the clinic and through biochemical, molecular biological, and cell biological investigations in the laboratory.

Steve Groft, Pharm.D., Office of Rare Diseases, NIH
Dr. Groft is the Director of the Office of Rare Diseases at NIH, and is dedicated to improving research on rare diseases.

Scott D. Halpern, M.D., Ph.D., Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine.
Dr. Halpern has written extensively on the topic of ethical issues in underpowered clinical trials.

Janine E. Janosky, Ph.D., Department of Family Medicine and Clinical Epidemiology, University of Pittsburgh
Dr. Janosky is an expert in biomedical research designs, biostatistics and the use of statistical power.

Johanna Loewenstein, MPH, Social and Behavioral Research Branch, National Human Genome Research Institute, NIH
Ms. Loewenstein is a research fellow interested in the application of genomics to public health, and in the clinical application of genetic tests.

Colleen McBride, Ph.D., Social and Behavioral Research Branch, National Human Genome Research Institute, NIH
As the Chief of the Social and Behavioral Research Branch at NHGRI, Dr. McBride provides leadership to the branch in developing quality, innovative research to address a variety of populations.

Gurvaneet Randhawa, M.D., M.P.H., Center for Outcomes and Evidence, Agency for Healthcare Research & Quality

Dr. Randhawa is an expert on the principles and process of evidence-based decision-making and the need for outcomes data.

Bryce Reeve, Ph.D., National Cancer Institute, NIH
Dr. Reeve directs an active program to enhance the use of patient-reported outcomes (including health-related quality of life (HRQOL) and patient satisfaction with healthcare) in clinical research and practice to improve quality of care.

Sharon Terry, Genetic Alliance
Mrs. Terry is at the forefront of consumer participation in genetics research, services and policy and serves as a member of many of the major governmental advisory committees on medical research.