



## **Advocate Partnership Program**

**American College of Medical Genetics**

**2006 Annual Clinical Genetics Meeting**

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**San Diego, California**

## **Sandy Gordon** **Trimethylaminuria (TMAU) Foundation**

**Title: *Analysis of Inquiries* to a Federal Public Education and Health Care Professional Resource *on Genetic and Rare Diseases*.**

### **Authors:**

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*For more than four years, the Genetic and Rare Diseases Information Center (GARD) has provided a bridge between seekers of information and reliable resources on genetic and rare diseases. A rare disease is considered to have a prevalence of fewer than 200,000 affected individuals in the United States. Together, the more than 6,000 rare diseases affect approximately 25 million Americans. Information about many of these conditions can take hours to locate and may be hard to understand; this difficulty can, in turn, add to the stress of a genetic or rare disease diagnosis for a patient, a patient's family, and the health care provider.*

*To help ease the frustration of this process, the National Human Genome Research Institute (NHGRI) and the Office of Rare Diseases (ORD), National Institutes of Health, launched GARD to provide free and timely access to accurate, reliable information about genetic and rare diseases in English and Spanish. GARD is a multi-channel resource, with Information Specialists responding to inquiries received through toll-free telephone, TTY, email, fax and letter. People requesting information receive an individualized response from GARD within four to seven business days, on average. Depending on the nature of the request, however, inquirers may receive a response even sooner.*

*Inquiries to GARD have been collected and analyzed during four years of operation. Personal identifiable information obtained in developing responses to inquiries is not retained in any form. The data analyzed are in the aggregate. Data analysis of inquiries includes the following:*

- *Audience segments and characteristics.*
- *Inquiry topics by audience, channel, region, and language in which the inquiry was received (English or Spanish).*
- *Resources requested and provided.*
- *Trends in volume, by channel and time of year.*
- *The impact of outreach efforts on volume.*

*Data have been collected for the 12,000+ inquiries on more than 3,500 diseases handled by GARD to date. Of the people who provided information about themselves (86%), inquiries came from patients (28%), their families (42%), health professionals (10%), and the general public (20%). Approximately 92% of GARD users requested information about a specific disease. The diseases for which GARD has received the most information requests are **trimethylaminuria** and cystic fibrosis. Ten percent of inquirers requested information about genetic services, testing, and research.*

*Being aware of the types of information people search for and obtain when they contact GARD will help genetics professionals stay abreast of trends in their clients' information-seeking behaviors, help them understand their clients' underlying questions and information needs, and enable them to more effectively structure patient sessions and communicate with allied health professionals. Other stakeholders in genetics (researchers, allied health professionals, and others) might also find it helpful to know how they can use GARD to assist them in connecting people to information and resources about genetics and rare diseases.*

This poster outlined the existence and function of the NIH-funded **Genetic and Rare Diseases Information Center (GARD)**—an invaluable source of information for both people living with

rare diseases and health care providers who need to learn about these diseases. When at a loss for information and assistance, many turn to the government for assistance and are referred to the National Institutes of Health (NIH). The Office of Rare Diseases (ORD) within NIH has been providing a lifeline to this desperate population for many years. The National Human Genome Research Institute (NHGRI) has also done a good job of sharing genetic information with the public. Together, their combined resources behind GARD, along with utilizing genetics professionals through Genetic Alliance to manage this resource, ensures a quality product that satisfies a substantial, national public need.

### ***Highlight***

I am pleased to highlight that **Trimethylaminuria (TMAU)** is one of the rare diseases for which GARD received the most requests for information. TMAU is ultra-rare as there are less than 2,000 known cases in the U.S. It has a devastating effect on the lives of affected people and that is what drives the high volume of information searches. The reported statistics will make a difference to the mission and strategy of the Trimethylaminuria (TMAU) Foundation. Every day our support network—which includes support groups, investigators and researchers—receives a minimum of five requests for help from distressed individuals searching for direction and medical assistance for this condition. We will use the information to re-emphasize to our public health departments and stakeholders the urgent need to step up all of our efforts to deliver more support, increased awareness, and resources to better serve this vulnerable community. We will continue to pursue new initiatives to stimulate studies, investigations, and scientific research opportunities.

*Trimethylaminuria is a big word with life changing consequences for those who are born with or later acquire it. Hard to diagnose, hard to treat, hard to endure.... and currently there are few treatment options and no cure. TMAU presents with a crushing aura of body odors, which results from the accumulation of excessive amounts of unoxidized trimethyl amine that is excreted in body secretions. This disease may be inherited as an autosomal recessive trait or may be secondary to impaired hepatic metabolism of trimethyl amine in the face of substrate overload. Researchers demonstrated in 1997-1998 that mutations of the human flavin containing monooxygenase isoform 3 (FMO3) gene impair N-oxygenation of xenobiotics and are responsible for the severe Trimethylaminuria phenotype.*

Lack of public knowledge surrounding rare disease conditions often leads to misjudgments and condemnation of those afflicted as well as some of those affected people being perceived as different and offensive. It leaves those suffering with symptoms feeling hopeless and helpless until they discover that there is a name for this condition and that they are not alone. Bullying, in the form of mental and verbal harassment, is a common occurrence in the workplace and schools, and our children are desperately in need of solutions. This information resource is so critical to solving these problems. At the very least, GARD is a good source of information for those who have been searching for a long time for answers.

It is important that the information maintained in the GARD database is updated regularly to ensure accuracy and meaningful support. It is even more important that we find a way to get more health professionals to take the extra five minutes to go to this database when they have a patient with unfamiliar symptoms to try and learn more instead of dismissing the patient or

misdiagnosing the illness. In this age of technological innovations, it is still unusual for a doctor to follow up and find the answers with regard to rare diseases. For TMAU-affected people, the usual experience has been for the patient to find the information and bring the evidence to the doctor's office and ask the doctor to rule out TMAU in order to get a diagnosis.

### *The next steps*

I found this presentation to be an insightful and great reference tool. However, the important message cannot be lost. The number of inquiries coming in also tells us that we need to take this database to the next level. It would be helpful to explore ways to directly promote the database to health care professionals, especially genetics professionals. I think more outreach work needs to be done to connect the care seekers with the health care providers.

How do we meet the challenge of getting a GARD reference link in every genetics clinic and office? How do we get the genetics professionals to use it? I recommend the formation of a short-term committee composed of representatives from GARD, ACMG, and advocacy organizations to explore ways to expand and realize the full potential of the GARD database. The collaborative efforts of the ACMG and Genetic Alliance are always powerful and significant opportunities for advancement. It is time to ensure that we prioritize the commitment to increased awareness and reduced hopelessness and helplessness caused by a lack of information and felt by all with unknown and little known diseases. The extra steps those affected by rare diseases must take to get health care will someday be one too many. We have the tools we need to bring this project to the next level of excellence.

## **Sandy Gordon** **Trimethylaminuria (TMAU) Foundation**

**Presidential Symposium: The *Changing Face of Medical Genetics***

**Type:** Platform presentation

### **Presenters:**

*Moderator and Speaker: Marilyn C. Jones, MD; FACMG, Children's Hospital/University of California, San Diego, CA. **A Reasonable Answer to the Cheshire Cat***

*Speakers: Allan T. Bombard, MD; FACMG, Sharp Mary Birch Hospital for Women, San Diego, CA;*

### **Health Insurance and the Provision of Genetic Services**

*Bruce R. Korf, MD, Ph.D., FACMG, University of Alabama at Birmingham, Birmingham, AL;*

### **Training of Medical Geneticists in the Genomics Era**

*Aubrey Milunsky, MD, FACMG, Boston University School of Medicine, Boston, MA;*

### **“Survival” in Clinical Genetics: Perceptions of Reality and Truth**

### **Goals and Objectives of the session**

*The specialty of Medical Genetics faces many challenges as genetic concepts, genetic testing, and genomics move into the mainstream on the translational edge where research becomes clinical practice, they must understand the forces that are driving the change and carve out specific areas of expertise while at the same time adapting to an increasing market driven health care system. This symposium will address some of these challenges as well as strategies that might be considered to secure a place for clinical and laboratory genetics at the health care table.*

### **“Survival” in Clinical Genetics: Perceptions of Reality and Truth**

*A. Milunsky Pediatrics, Boston University School of Medicine, Boston, MA, United States*

*It's a paradox! We are indisputably in the golden era of human genetics and discussing “survival” of clinical genetics. Enormous advances have captured the interest and involvement of almost every medical specialty. Indeed, clinical genetics occupies the center of the universe of medicine. Medical schools at last have human genetics in the curriculum. Clinical genetics is a Board-certified specialty and much can now be offered to a broad range of patients. So much, then, for reality. Why then are there issues of “survival”, and why is clinical genetics in such a perilous state? The most important reasons are self-evident, as is the truth:*

- 1. We have failed to establish required standards of care for **other physicians** who without training or certification profess to practice clinical genetics, thereby allowing the usurpation of clinical genetics by other specialties.*
- 2. Commercialization of genetic laboratory testing and the associated predatory practices has resulted in the closing of many laboratories, loss of clinical and laboratory training sites, loss of cost centers, diminished research opportunities, and loss of salary support for clinical geneticists.*
- 3. We have failed to maintain or establish laboratory cost centers to support clinical operations in our own institutions.*
- 4. We have failed to support each other's laboratories and thereby further empowered commercial laboratories.*
- 5. We have failed to educate Deans and Department Chairs in **other specialties** about the vital nature and importance of the work we do.*

6. *We have failed to establish a salary structure and work environment that would attract new medical graduates to a career in clinical genetics.*
7. *We have made institutional application and maintenance requirements into clinical residency programs arduous and difficult rather than aim to facilitate entry to nascent careers in clinical genetics.*

*There is much we can do to remedy and reverse the deteriorating state of affairs. We need to publish technical type bulletins that clearly enunciate what is required of **other physicians** who “provide genetic counseling”; to halt the predatory practices of commercial laboratories; establish laboratory cost centers in our own institutions; reclaim the importance (and salary requirements) of clinical genetics within medical centers and schools; provide working and salary structures that encourage new medical graduates to emulate their mentors; and ease residency programmatic requirements without impairing standards.*

*Vigorous and imaginative leadership by the College is now vital. The College must aspire to be the voice of authority in clinical genetics whenever this subject emerges in the public arena – which is almost daily. We should not be reticent in espousing the fact that clinical genetics occupies a central role in the universe of medicine.*

Most of the presentations focused on administrative and governance essentials. The speakers espoused the importance of practitioners being prepared to meet the challenges facing the medical genetics community; developing specialist networks to serve as proficient practices; setting important training and certification standards and requirements for specialists; presenting structure models for the medical genetics office to ensure proper insurance reimbursement for patient services; and much more. The commitment of the ACMG to ensuring the best educational experience and support for their members was authenticated by their efforts to ensure that everyone has a place at the table and every voice is heard.

Dr. Milunsky presented a slightly different tempo when he shared some impassioned views on issues that are of the utmost importance to medical geneticists, other genetics professionals and those considering a career in medical genetics. There is a growing trend toward the closing of financially under-performing university labs, the corresponding growth of new commercial labs, and the escalating cost to the consumer for testing. One way to slow the trend is for academic and hospital-based labs to support each other instead of commercial labs. This showing of support can ensure that consumer patients will not be priced out of the testing market, and that there will be clinical and university lab training sites to attract new technicians and scientists. With fewer academic and hospital-based labs available, it also means less research opportunities especially for lesser-known and unknown diseases. Medical geneticists are the clinicians who translate the research innovations into the specialty care we urgently need. They should not be spending their efforts trying to survive but rather on expanding their services to reach those who need genetic care and education.

It is important that geneticists assume the central, leadership role in health care and set high, organized standards so that consumers, in turn, will begin to receive the better care options they deserve. The future is now and Dr. Milunsky suggested that the ACMG should seize the opportunity to position the organization at the center and get that message out at every opportunity.

This presentation inspired many in the audience to applaud Dr. Milunsky for his courage to speak out about this controversial subject while many were chagrined. The important point is that, as a respected leader in genetics, he got the opportunity to tell his opinion with regard to

many important issues, especially concerning the extent to which professionals are compromising their own integrity by accepting the status quo and buckling under the pressure of perks flowing from the medical supply vendors. Dr. Milunsky's talk urged the ACMG body to ponder these issues to see what changes must be made in the future to strengthen the organization.

These issues hit close to home for us. I often contemplate the issue of the economics of living with a rare disease and all the associated consequences. For many rare disorder organizations and certainly for the Trimethylaminuria community, the academic and hospital-based non-profit labs have been the resources without which we would not exist. They have provided testing, descriptive literature and definitions, as well as studies and investigations that laid the groundwork for our organization's work and our limited progress. Dr. Milunsky's talk will motivate us to continue to support those institutions. While we recognize that there is a need for commercial labs (and the consumer market will ultimately determine their market shares), we cannot risk the elimination of more university labs and the lower testing costs they offer. For most people with rare genetic disorders, the difference in price for testing at a commercial lab versus a university lab is \$2,000 in the U.S. and it goes from free testing to £300 to £1,200 in Europe. Genetic care is not a luxury for sufferers like us but rather an essential need. Commercial labs have the right to profits but not to profiteering from our vulnerable populations.

One of the reasons for my interest in the Consumer Advocacy Training Partnership Program and scholarship opportunity was to gain a better understanding of the essential roles of medical geneticists and genetic counselors, and this session and the overall opportunity exceed my expectations in every way. It takes an average of five to seven years and bouncing between 12 and 16 medical doctors to get a **TMAU** diagnosis. However, since we started advising patients to seek consults through their local genetics departments, and because it is now easier for those with a computer to get good information on the web, in many cases the average time to secure a diagnosis has been significantly reduced to as short as two to three years. Additionally, due to the time allocation limitations in the doctor's office, the patient is not always satisfied with their after-diagnosis care. Therefore, as Dr. Milunsky pointed out, it is important that qualified genetic counselors be available to provide the important counseling services that are needed and that they are paid appropriately for their services. At first glance, specialty care might seem like an expensive proposition; however, when we consider the reality of our journey to diagnosis that is not the case. The Trimethylaminuria Foundation has found that our adults with TMAU or TMAU-like disease spent between \$25,000 and \$42,000 (unreimbursed by insurance) in search of a diagnosis – on unreimbursed doctor visits and consultations, unnecessary exploratory surgeries, surgeries based on misdiagnoses, alternative medicine and treatments, etc. In many cases, there was still no diagnosis at the end of the spending frenzy. In conclusion, genetics professionals must get the word out regarding WHO, WHAT, WHY, AND WHERE - WHO to contact when dealing with an unknown or little known disorder, WHAT to expect, WHY going to the source is critical, and WHERE to find a medical geneticist. Most people who have found themselves in this predicament would have gladly spent a few hundred dollars to go out of their insurance network to a genetic clinic if it meant getting good genetic health care and a diagnosis. Investigators and scientific researchers are available to work with the genetic clinicians, and together they can make a real difference and positively affect lives.

I am most impressed with the ACMG. The organization is seemingly attuned with the need to provide a forum where all stakeholders can voice their varied opinions. This egalitarian attitude breathes growth, innovation, and satisfaction and ensures a fast paced environment that is keeping up with genetic trends and the leadership needs of its members. Human genetics must retain the human side of medical care and satisfied practitioners will lead to more satisfied patients. We cannot be motivated, controlled and driven only by financial considerations. Perhaps one of the most impressive qualities of the ACMG organization is its egalitarian posture. The rallying cry – *We recognize our differences, we support our differences; let's find our common ground.*

## Colleen Yinger Marinesco-Sjogren Syndrome Support Group

**Title:** “*New Quality Assurance Standards for Rare Disorder Testing*” (Invited Session on Clinical and Laboratory Issues in Rare Disease Testing)

**Presenter:** W.W. Grody, MD, PhD, UCLA School of Medicine, Los Angeles, CA

*Genetic tests for ultra-rare, or orphan, disorders present special challenges to the laboratories that choose to offer them. Because of their rarity, the volume of test requests for any one disease will be very low and prior experience with clinical testing often meager. Access to patients or specimens carrying the mutant analytes of interest for use as positive controls is extremely limited. And the boutique nature of the testing market places it outside the scope of organized national programs for quality assurance and proficiency testing. Indeed, the QA guidelines established by those programs (CLIA, CAP, ACMG) for validation and performance of more routine, common genetic tests are often not applicable to orphan disease tests. Falling in a translational area at the border of research and clinical service, the latter have unique constraints for clinical and analytic validation, quality control, interpretation of sequence variants, informed consent, and genetic counseling. This presentation will review each of these aspects and the progress made by ACMG to establish guidelines to address them, striving to maintain high standards while also enhancing access to these tests for the patients and families who need them.*

### Summary

W.W. Grody, MD, PhD addressed the challenges facing rare-disease testing and the new ACMG (American College of Medical Geneticists) standards created to help address them. New standards are needed since existing quality assurance guidelines, such as those established by CLIA (Clinical Laboratory Improvement Amendments) and CAP (College of American Pathologists), are not adequate for ultra-rare genetic testing. For example, if one tries to apply the CAP checklist to ultra-rare disorders, many of the items will not be applicable.

Ultra-rare disease genes are generally discovered in research laboratories. Initially there is high-interest in the disease, specimens are collected, the gene is mapped, and mutations are identified. The research laboratory typically “gets bored” with the disease, but continues to do mutation testing as a favor to families, and testing quality may become degraded. There are several options available to the research laboratory: continue testing outside of CLIA (illegal to provide research results), cease testing (which may eliminate availability of the test), become CLIA certified (expensive and time-consuming), partner with a CLIA-certified lab, or refer to a dedicated orphan disease lab (e.g., UCLA orphan disease testing center).

A task force was established to determine how to provide quality genetic testing, while ensuring availability of testing to families and physicians. The new standards focus on translation of tests from the research to the clinical laboratory, informed consent, the rarity of positive mutation controls, and proficiency testing. The determination of whether a research test is ready for the clinical laboratory is based on validity, utility, and benefits versus risks.

There are special considerations for ultra-rare genetic testing. For example, complete gene sequencing, rather than targeted mutation analysis, is generally required. It is the duty of the lab to address interpretation of results, including clinical interpretation of novel sequence variants. Custom mutation analysis requires that a new sample be provided to the clinical laboratory and

use the proband as the positive mutation control. Alternate approaches are needed for proficiency testing because of the small number of available samples for a very rare disorder.

### Impact and Impressions

There is a challenging balance between quality and availability of ultra-rare genetic testing, but ACMG standards have been developed to help address this problem. Research and clinical laboratories have several options (described in this presentation and others in the same Invited Session) for participating and potentially collaborating in rare disease testing.

Families dealing with a rare disorder may find the issues of genetic testing confusing. Advocacy groups can serve a useful role in clarifying the difference between research and clinical testing, defining available testing options, and participating in research/clinical translation programs like Collaboration, Education, Test Translation (CETT). As in all genetic testing, good counseling is essential to help families understand the implications of positive and the more challenging “negative” results. This invited session was a great opportunity to learn about rare disease testing issues so that I can more effectively participate in genetic testing discussions and advocate for families affected by rare diseases.

### Definitions

- CETT (Collaboration, Education, Test Translation) – a NORD/NIH program to increase clinical availability of diagnostic tests for rare genetic diseases.
- Custom mutation analysis – clinical laboratory confirmation (repeat analysis) of a mutation previously identified in a research lab
- Orphan (ultra-rare) disorder – a disorder with less than 1 in 200,000 prevalence in the United States
- Positive mutation control – a DNA sample with a known, detrimental sequence change
- Proband – person from whom the genealogy is traced
- Sequence variant – a change from the normal sequence of a gene (may or may not cause disease)

## Colleen Yinger Marinesco-Sjogren Syndrome Support Group

*Title: “Clinical Trial Design and Achieving Clinical Significance in Small Trials”,  
NICHD/ORD Sponsored Workshop – Opportunities and Impediments in National Collaborative  
Studies for Rare Genetic Diseases*

*Presenter: Edward Kaye, MD, Genzyme Corporation, Cambridge, MA*

*The ACMG has received a five-year grant from the National Institute of Child Health and Human Development and the Office of Rare Diseases of the National Institutes of Health to run a series of workshops at the Annual Clinical Genetics meeting, and to convene an oversight group that will synthesize the information from the workshops and other sources to identify opportunities for collaborative research. Models for such study groups include the national cancer cooperative groups and the CF Consortium that facilitate long-term studies related to epidemiology, etiology and biology, treatment/intervention trials and natural history. Many issues arise when considering collaborative study group models for genetic diseases. These include IRB issues for multicenter trials, the wide breadth of diseases and specialists involved with those patients, and the significant genetic variation among those affected that requires a national collaborative approach. This third workshop focuses on some of the issues that have to be addressed in order for national collaborative studies to occur.*

### Summary

Ed Kaye, MD, discussed the challenges of **orphan drug development**. In recent years, investigational new drug filings and approvals have been declining. Terminations are due to failure of the drug to work (38%), economics (34%), and safety (20%). The duration of the drug development process (clinical trials and approval) has also increased from an average of five years (20 years ago) to eight years (currently). The phases of clinical trials are preclinical (animal tests, proof of concept), phase 1 (safety), phase 2 (dosing), phase 3 (efficacy and statistical significance), and phase 4 (surveillance and follow-up). Drug approval occurs after phase 3.

The United States provides orphan drug incentives through a 50% tax credit. Orphan drugs are defined as those developed for diseases with less than 200,000 cases in the country, or where research and development costs would not be recovered in seven years. Orphan diseases need international trials because of their small numbers. For example, Fabry, MPS, and Hunter diseases have only 50-100 cases in their international studies.

There are many challenges to orphan drug development: economic, disease understanding, clinical trial development, regulations, reimbursement, sample size, patient enrollment, and the heterogeneous nature of the patient population, maintenance of the patient population in the trial for the required duration, definition of “success” as disease reversal or stopping progression), and ethics of placebo use. Surrogate markers can reduce the clinical trial duration if the clinical measurement correlates well with outcome. End-point selection for statistical significance can also be problematic. For example, a drug may “work”, but the trial may fail because the treatment effect was not significant enough given the number of patients. Early treatment is critical in many diseases because pathologic substrate accumulation usually increases linearly with age, and clinical progression can occur rapidly at some point in this process.

## Impact and Impressions

Dr. Kaye's presentation provided a clear, dynamic overview of the numerous challenges facing drug development for very rare disorders. Although the presentation did not specifically address the role of advocacy groups, there appears to be many ways in which groups can contribute, e.g., developing and maintaining databases of affected individuals, encouraging family participation and continuation in suitable research studies, helping families understand complex processes and paperwork, and advocating for increased research funding and improved health care policies.

The other presentations in this workshop addressed development of collaborative research groups and a national IRB (Institutional Review Board) process for multi-center studies. Although these initiatives are positive for the long-term, there is frustration on the part of many advocacy groups about the length of time it takes to move collaborative activities forward, the need for international (not just national) research for orphan diseases, and no well-defined role for advocacy groups in the process. This was particularly interesting given two common topics of discussion at the ACMG meeting - the need for medical geneticists to be perceived by the public and other physicians as being more than diagnosticians, and the rapidly expanding role of industry in genetic testing and training. I believe that formal collaborative groups and processes will need to proceed more rapidly and aggressively on an international scale if they are to play an effective, competitive role in orphan disease research.

## Definitions

- Efficacy – the ability of a drug or treatment to provide a result
- Pathologic substrate accumulation – accumulation of a disease-causing substance, as in a lysosomal storage disorder
- Surrogate marker – a clinical measurement that correlates with outcome (predicts clinical benefit); e.g., glucose (sugar) measurement for diabetes

**Terri L. Klein**  
**ISMRD (International Advocate for Glycoprotein Storage Diseases)**

*Session Title: **Clinical and Laboratory Issues in Rare Disease Testing***

*Presenters/Authors: Roberta A. Pagan, MD, FACMG, Pediatrics University of Washington, Seattle WA, United States, “Children’s Hospital and Regional Medical Center, Seattle, WA, United States*

*The CETT Program ([www.cettprogram.org](http://www.cettprogram.org)) was developed by the Office of Rare Diseases (ORD)-NIH following three meetings in 2004 and 2005 on quality testing for rare genetic diseases sponsored by CDC, NIH-ORD and Emory University in collaboration with HRSA, ASHG, SIMD and the Genetic Alliance. The purpose of the CETT Program is to provide funding to increase clinical availability of diagnostic tests for rare genetic diseases. The CETT Program guiding principles are that all parties benefit maximally when: (1) the quality of testing for rare disorders meets or exceeds existing standards; (2) clinical laboratories, researchers, clinicians and patient advocacy groups collaborate; and (3) high quality educational materials inform about test ordering, test sensitivity and test uses in patient care. The CETT Program was initiated in January 2006 with a “facilitated application process” that uses short forms and provides constructive feedback to applicants. Applications are accepted continuously and are evaluated monthly by five members of a 15-member Review Board for the quality of the scientific evidence, the laboratory qualifications, data collection methods, and educational materials. Funding does not include equipment or institutional costs and is based on the complexity of the test process (for example, a molecular test development proposal might receive ~\$1000 per amplicon of proposed test and ~\$1000 for educational materials).*

The concurrent session on Clinical and Laboratory Issues in Rare Disease Testing defined the importance of my attendance as an advocate at the Spring 2006 ACMG meeting. This session focused on issues surrounding clinical availability of testing for rare disorders and how the demand is greater than available working resources. Four topics were presented, one of which I have chosen to highlight. The **Collaboration, Education, Test Translation (CETT) Program** illustrates a model in which one of the key stakeholders is the patient advocacy group in collaboration with clinical laboratories and researchers to develop testing and educational materials for specific rare disorders.

Information reported from the NIH states there are over 6,000 rare diseases and more than 25 million Americans are affected. The presentation stated that as of January 2006 testing for over 1,200 inherited disorders is currently offered & approximately less than 500 are available on a research basis or through international laboratories. At the request of the United States Congress, the NIH’s Office of Rare Diseases (ORD) began a collaboration to initiate new genetic testing that will raise developmental issues in understanding and awareness for both laboratory and clinical geneticists.

Roberta Pagan, MD, FACMG discussed in the CETT program the importance of paradigm shifts that are recognized as a result of this program’s implementation. One of these shifts involves the level of equal collaboration by the three stakeholders: clinical labs, researchers, and advocacy groups. All parties will exemplify maximum benefits when the quality of testing for rare disorders meets or exceeds the existing standards, the three stakeholders’ groups collaborate equally and a high level of quality educational materials as outlined by criteria set forth by the CETT program are generated.

Another paradigm shift that was presented involves collection of the data, how it will be presented and whom it will benefit. The scope of all three of these elements within the collection of data and test results will create new opportunities for genotype and phenotype correlations. Once new genetic testing developments have occurred by CLIA (Clinical Laboratory Improvement Amendments) approved facilities, the researchers involved with the program have a responsibility to collect and maintain both clinical and individual/family test information in a publicly accessible database.

The CETT program focuses on the elements of streamlining qualitative testing for rare disorders and R. Pagan, MD. FACMG, presented the format for any of the stakeholders to initiate their eligibility or opportunity. The application process will be ongoing and there is a Review Board that has set guidelines to determine the quality of submitted applications. The program has determined types of testing and gene review is required. With all of these elements fulfilled, the final paradigm shift will result in a clearer understanding of genetic test results by clinicians and therefore by affected families.

As an advocate for an international non-profit organization supporting ultra orphan diseases, this presentation of the CETT program made me excited for these emerging opportunities. The inclusion of advocacy patient groups as a stakeholder in the CETT process as outlined by the NIH-ORD clearly illustrates that rare diseases can be better understood by those patients and families that are living day to day with the effects and secondary medical implications. Additionally, by streamlining the processes in an effort to gain future models that can promote a better understanding of diagnostic testing by clinical geneticists and therefore to affected families, the path becomes less subjective. By providing more accurate and clearly understood data in a correlated database, the general public will have access to this information, which subsequently will hopefully increase its awareness.

I am excited about the potential this holds for all rare disease groups and hope that a campaign for awareness of the CETT program establishes itself in all known networking groups. This presentation was selected because currently our disorders are in the process of crossing over into clinical analysis of natural history studies from a diagnostic testing process for the first time in the United States. I find myself wondering at this time how our international support group of nine orphan diseases can become involved in an all inclusive CETT program where no disease group is left behind and how these elements can be achieved with families outside of the United States. Can or will there be testing labs on an international level that will collaborate with those in the United States that are CETT approved for those families that are affected and interested?

The possibility of genetic diagnostic testing appears very hopeful. Models created from the CETT program that can help increase the collaboration on tests between researchers and clinical geneticists, create educational materials that will promote a better understanding of rare disorders by the public and the potential for an increase in research related to rare disorders that may not have existed prior to the implementation of CETT, as well as present a new opportunity for advocacy organizations that seem to never have a voice. I think that providing a place at the table for advocacy patient support groups and allowing them representation as a stakeholder is an excellent decision.

CETT, Collaboration Education and Test Translation Program, <http://www.cettprogram.org>  
geneTESTS,  
<http://www.genetests.org/servlet/access?id=8888891&key=kqGfOBVjKNx9E&fcn=y&fw=n7nR&filename=/about/content/reviews.html>

## Mary Fete National Foundation for Ectodermal Dysplasias

**Title:** *Practical **Insights in the Development of a Rare Disorder Testing Program***

**Presenter:** *Sherri Bale, PhD, FACMG, GeneDx, Inc.*

*GeneDx is a 6-year old molecular diagnostic company that provides DNA-based diagnosis, prenatal testing, carrier testing, and other services to patients and families with “ultra-rare” mendelian disorders. The company was formed to translate the findings in rare diseases from the research laboratory into a CLIA-approved laboratory setting. Determination of when a test is ready to be translated to the clinical lab involves evaluation of the clinical utility and sensitivity of the test, applicability and adaptation of the testing methods available in the laboratory to the specific test requirements, cost to develop the test, cost per sample to perform the test, and expected number of patient samples that will be tested. Other issues to be addressed beside development of the test menu include impact of gene patents, professional liability insurance, billing and reimbursement, proficiency testing, and recruitment of essential personnel. GeneDx is one company that provides genetic testing for rare diseases and was established out of a desire to provide testing for such conditions. The founders were frustrated by the inability to provide diagnostic carrier and prenatal testing due to regulatory issues, a lack of resources and the inability to provide the diagnostic services that patient and physicians needed. The doors opened as a for profit company after a futile effort to establish a not for profit company and after finances and appropriate licensing and credentialing were in place.*

*Laboratory licensing, accreditation, and operating standards need to be closely monitored by credentialing agencies such as CLIA and CAP to protect the public’s interest and safety. The goals of these regulatory boards are to improve the accuracy of testing and to insure that these laboratories adhere to uniform operational standards.*

GeneDx offers the following comprehensive services:

- Diagnostic and carrier testing
- Presymptomatic testing
- Custom mutation confirmation
- Prenatal testing
- Genetic counseling
- Legal support
- Research support
- Training of molecular geneticists and laboratory based genetic counselors

GeneDx does not offer direct to customer testing: this is a decision point for many laboratories. A physician must order the test and the results are sent directly to the physician. There is concern among some patient advocacy groups that families are reluctant to have their physicians order genetic testing. They are afraid that this information will be placed in their medical records and that this information can be used in a discriminatory manner by their employers or insurers. This is a concern for individuals as the cost of health insurance continues to rise and more and more companies are using self-insured insurance plans.

The ordering physician has the responsibility to provide correct sample type and to order the correct test. Physicians also need to provide the appropriate clinical information. In prenatal tests, they need to provide a clean fetal sample and provide parental samples when requested. Preliminary or verbal results are not provided to make sure the most accurate results are given. Physicians need to understand that the turnaround times are approximate and may take a week or

two longer than anticipated. When ordering genetic tests through any laboratory, the clinician must be knowledgeable that the genetic test has received appropriate peer review to ensure clinical validity and utility. They must be aware of the clinical guidelines and accreditation standards for genetic laboratories in order to be able to determine what type of services the lab can provide and know whether the services and personnel are appropriate for the gene in question. Physicians also need to be aware of the criteria for the specific test being ordered and the associated risk of false-positive and false-negative results as well as to make sure to discuss informed consent with the patient. They should also be aware of the laboratory's procedure for processing the test and reporting the results. A tracking system should be developed to ensure that test results are received and communicated appropriately to the patient.

In the clinical setting, someone must be able to appropriately interpret and communicate the results to the patient. Referrals for genetic counseling are a core activity in the testing process. Patients must be referred for timely, comprehensive genetic counseling. The role of the genetic counselor in genetic testing may also include making sure the test ordered is appropriate, coordinating the test, communicating with the research and clinical labs, acting as a liaison between labs, providing support and accurate clinical information and coordinating the obtainment of the samples from the appropriate persons.

Physicians should expect that the laboratory directors and staff are appropriately trained and have accurate information about the sensitivity, specificity and reliability of the methods. They should expect to receive documentation of the methods used, the results obtained and its interpretation in a timely manner. They should have access to knowledgeable individuals as a resource.

In a presentation of a clinical study that was presented by Dr. Howard Levy when they studied the ordering of a genetic test in a physician's office, it was frightening to see the percentage of genetic testing requisitions that were filled out by receptionists or secretaries and even more startling to hear the percentage of offices (60%) where results were given to patients by secretaries. Physicians have a responsibility to their patients to order the right test and make sure a qualified professional discusses the results with the patient and provides appropriate counseling services.

Billing and reimbursement are an important consideration. If laboratories do not bill and do not collect the necessary fee, they will not survive. GeneDx does not contract with third party payers. Because they are always considered "out of network", they advocate for patients with the insurance company to pay at a higher rate. They get letters of medical necessity and CPT codes from physicians and written pre-authorization letters from the insurance carriers. They advocate for higher payment from the insurer as there are no in-network laboratories that can provide this service for rare diseases and their efforts are often successful. The patient is informed that there will most likely be some out of pocket expenses.

Careful consideration goes into developing new genetic tests. In the case of GeneDX, they first look at the genes that are being considered to see if there is strong evidence of clinical utilization of ACGM guidelines. The test must have a high sensitivity and an expert clinician must be available to serve as an advisor. The test has to be doable by their methods and they need to

anticipate a minimum number of 10 cases per year. Cost, including what it is going to cost to develop the test, cost per sample to perform, personnel time and administrative cost, must be considered. They also must consider the number of tests anticipated. The cost of the test may go down with higher volumes but this is not always the case. Tests are often administratively prohibited if there is a patent on the gene. One of the concerns associated with gene patents is that they may have an adverse impact on the availability of genetic testing services and may add an inappropriate financial burden, making the testing cost prohibitive.

GeneDx currently offers 115 tests. They have 34 employees and have done 7,000 tests on 4,000 patient samples in 2005. What started as a small company offering just 16 genetic tests has grown into a lab that now provides a service for many rare diseases. One issue facing GeneDx and all clinical laboratories that provide genetic testing for rare diseases is the sky rocketing cost of insurance. Insurance costs went from \$1500 in 2000 to \$50,000 in 2006. A false-negative could result in wrongful birth and tort claims. It is a growing concern for laboratories with the highly sensitive nature of this testing that litigation could put genetic testing laboratories out of business.

This information has meaning for all patients and patient advocacy groups who provide support and education to individuals affected by rare genetic syndromes. Patients must be educated and have a good understanding in regards to what is involved in genetic testing, what to expect from their physicians, the genetic testing laboratories and genetic counseling services.

## Mary Fete National Foundation for Ectodermal Dysplasias

**Title:** *Qualitative Genetic Risk Assessment in a Primary Care Practice*

**Presenters:** H. P. Levy, S. Ashley, H. Maibach, L. Doucette, N. Khanna Internal Medicine, Johns Hopkins University, Baltimore, MD, United States, Family Medicine, University of Maryland, Baltimore, MD, United States, Independent, Potomac, MD, United States

*We are investigating the clinical utility of integrating a genetic counselor in a family medicine clinic to assess familial risks and help promote appropriate prevention, screening and detection of common disease in the primary care setting.*

*Participating adult patients scheduled for routine history and physical examination are divided randomly into intervention and control groups. Control subjects receive standard care from the family physician. Intervention subjects meet with a genetic counselor prior to their physician visit. A three generation pedigree is recorded and later reviewed with the medical geneticist on the team to develop a qualitative estimate of risk. This is standardized by assigning points for specific “red flags” in the family history. Point totals are converted to qualitative assessments of average, moderate or high risk for each disease identified in the family history. Standard recommendations include routine care for average risk, increased clinical awareness and closer monitoring for moderate risk and closer monitoring plus consideration of risk factor modification and/or specialty consultation for high risk conditions. A summary of the risk assessment with recommendations and a copy of the pedigree are forwarded to the family physician. All patients complete a satisfaction survey after their visit. Physicians complete a pre and post study assessment of their perception of the family history intervention and their knowledge of genetics and available genetic resources.*

*Among the first 26 intervention subjects, 77% were found to be at moderate risk for at least one condition, 65% were at high risk for at least one condition, excluding diagnoses already made in the proband. Additional conditions were identified in the pedigree but estimated at average risk for 38% of the subjects. There were 0-5 moderate risk conditions, 0-4 high risk conditions and 0-6 average risk conditions identified for each participant. Measured on a 5-point Likert scale, intervention subjects were more satisfied than controls with time spent discussing family history during their visit.*

*Inclusion of a genetic counselor in the Family Medicine clinic appears to be practical and well accepted, and can potentially enhance risk assessment for common disease, improve knowledge of genetics among patients and providers, and encourage appropriate referral and disease prevention strategies. These results suggest additional opportunities for incorporation of genetic counselors into primary care practices and for cross-specialty education of trainees in genetic counseling and various primary care medical fields.*

This project is investigating the clinical utility of integrating a genetic counselor in a family medicine clinic to assess familial risks, and help promote appropriate prevention, screening and detection of common disease in a primary care setting. They concluded that including a genetic counselor in the family medicine setting can be practical, well received and can enhance the risk assessment for common disease. It also can help educate the general population about genetics and promote appropriate referrals. Integrating family histories and risk assessment in these practices can be critical in initiating preventive health strategies.

The main point of these presentations was to **emphasize the importance of integrating genetics into general practice**. Both of these sessions are included in this report as both have direct implications for primary care practitioners. General practitioners, nurses and other health care

professionals need to be current in this rapidly changing health care market to make sure their patients get the resources and care that they need and deserve.

Genetic and genomic science is redefining our understanding of the continuum of human wellness, health and illness. Recognition of genomics as a central science for health professional knowledge is essential. Options of care will increase to include genetic and genomic information for the purposes of prevention, screening, diagnosis, prognostics, selection of treatment and monitoring the effectiveness of treatment. Registered nurses will also need to use genetic and genomic information and technology when providing care for clients. The clinical application of this new knowledge will have major implications for the health care profession.

One of the areas discussed is the importance of a family health or family medical health care history. An accurate family history needs to become a part of the primary care physician's evaluation of the patient. The family history is becoming a critical piece in making a diagnosis, assessing risk and providing preventive medicine. Family histories can give the practitioner answers to important questions such as whether the disorder is genetic, the pattern of inheritance, what laboratory testing is needed to confirm a diagnosis and possible environmental issues that can impact the patient and the risk of occurrence and reoccurrence among other family members.

The primary care physician is the overseer of the health care plan and should initiate the collection of a good family history. Health care professionals who provide genetic testing and counseling need to be able to construct an accurate family pedigree. A family pedigree is a graphic representation of the family history that spans at least three generations. The family history may contain vital information related to the patient's risk that will only be recognized by taking a three generational family history.

Family medical histories can have a direct bearing on the clients we serve, especially for those who are affected by rare, familial genetic diseases or syndromes. For example, the average age for diagnosis for individuals affected by **hypohydrotic ectodermal dysplasia (HED)** is 18 months. Oftentimes, individuals are not diagnosed until grade school, high school or even adulthood. If a detailed three generational family history were taken, the diagnosis would be much clearer very shortly after birth. Female carriers would be identified early on and support services would be available much earlier. Identification of individuals who are at risk can have significant implications for their unborn children. Genetic services, including counseling, could be implemented early so that couples had the information available to make informed family decisions.

This information has a direct impact on the individuals who are affected by hypohydrotic ectodermal dysplasia (HED). There is a potential cure for the symptoms of HED on the horizon that is still in the very early investigational phase. In the event that treatment modalities that need to be administered shortly after birth are identified, it will be critical to identify these at risk infants very early. If the diagnosis is missed and there was treatment available and not offered, there would be serious implications for the patient, his or her family and the health care provider. Providers could be held accountable for missing the opportunity to offer a cure to the symptoms of this syndrome.

Nurses will also need to adapt to this ever-changing health care environment. Nurses are often the health care professional who does the initial assessment. Education and nursing assessment will need to change to include assessing, nursing diagnosis, planning, intervention and evaluation through a genetic lens. To provide quality care for clients, nurses will need to understand the genetic and genomic basis for disease, treatment selection, variables that impact treatment response to facilitate client education and the delivery of competent nursing care.

A three generational family history will enable physicians to assess patients more accurately and to classify syndromes as well as to make appropriate interventions and to give necessary guidance and support services. Detailed family medical histories are the best initial strategy for identification of potential genetic disorders and should be implemented in all initial primary care visits.

Another area that is rapidly exploding is the use of pharmacogenetics when treating patients with medications. This will also have significant implication for primary care providers. They will have to be knowledgeable in these areas and make the appropriate referrals. It is the primary care providers who will be ordering medications and treating diseases that might already, or in the near future, have the potential for personalized treatment. Population and recommended base dosages may be altered to meet an individual patient's sensitivity, response and potential for side effects. The human genome project along with personalized medicine will develop into huge public expectations for quality, individual care. Drug toxicity, a very common and costly health care issue, may be eliminated in some cases with proactive and knowledgeable providers.

There are many implications of genetic and genomic information for healthcare. The use of personalized medicine in the care of clients will soon become a standard of care. Biotechnology and bioinformatics are opening the door for risk prediction, pharmacogenetics, and new therapies. For this era of medical technologies and care to move forward in a positive, productive way, there must be continued advances in medical research, protection against genetic discrimination, and improved access to care and competency in genomic medicine.

**Janalee Heinemann**  
**Executive Director of PWSA (USA)**

***Title of Presentation/Poster: Study of 56 patients with Prader-Willi syndrome: higher incidence of seizures in deletion group***

***Presenters/Authors: Z. Fan, A. Fisher, C. M. Powell – Chapel Hill, NC***

*Prader-Willi syndrome (PWS), unlike its “sister genetic imprinting syndrome” Angelman syndrome (AS), usually is not thought to have a strong association with epilepsy. A retrospective study of 56 patients with PWS {45 with 15q deletions, 10 with uniparental disomy (UPD) and 1 with imprinting defect} revealed recurrent seizures in 10 patients (17.9%) and possible seizures in 6 patients (10.7%). Of the 10 with recurrent seizures, 9 were treated with antiepileptic drugs. Age of seizure onset ranged from one month to six years in the recurrent seizure group, and all have had seizures without fever. All 10 patients with recurrent seizures have a 15q deletion and 9 were treated with antiepileptic drug(s). Fifteen of the 56 patients (28.6%) were born prematurely; the incidence of recurrent seizures in this subgroup is 20% (3 of 15). With a seizure incidence of approximately 18% in our patient population, it is important for physicians caring for patients with PWS to be aware of this risk and for parents to be informed of signs of seizure activity to look for in their children. Seizure evaluation and management should be included in the multidisciplinary care of PWS patients.*

In this retrospective study of 56 patients, there was a much higher incident of seizures in the deletion group. It was a retrospective study of 45 with the deletion, 10 with UPD, and one with imprinting defect. Of the 10 with recurring seizures, all 10 had the deletion. Six other children had possible seizures, putting the seizure group at a possible 18%--much higher than reported in the literature.

In our large medical database, we have reported more individuals with PWS who have seizures than in the literature, but not as high as the NC study. We have a report of 6% in the 0-5 age group having seizures, 9% in the 6-18 age group, and 13% in the 18 and above age group.

We have never compared the type of **Prader-Willi Syndrome (PWS)** (deletion, UPD, translocation, and imprinting) to see which had more **seizures**. After returning to the office, we immediately reviewed our data base to compare the type of PWS with those that had reported seizures. We have 150 who reported seizures out of 1,450 individuals entered. It was very interesting to compare. Although not to the degree of their study, our findings did support the Chapel Hill results in that out of those who had seizures, the majority were those who displayed the deletion. Of those who had the deletion, 11 ½ % reported seizures (70 out of 609) as compared to the UPD with 5 ½ % reporting seizures (16 out of 292). But also, those with a translocation exhibited a rate of 28% (7 out of 25) whereas those with imprinting had only a 3% occurrence rate(1 out of 30). We did not include those who did not know the type of PWS their child had (460) or those who are PWS like (31).

Due to the fact that I handle medical crises on a national level, I have been convinced for some time that there are more children and adults with PWS who have seizures than previously reported, and so it will be helpful to have the support of this study and that of our new medical data base entries. It also made me realize we need to do more follow up on the issue of vulnerability of seizures by type of PWS. In our next survey, we also need to define further what

the reporting party considers a seizure, since many of our children have what I would call “atypical” seizures. We also need to encourage further research to re-test if those with the most common type of PWS (deletion) are more at risk for seizures.

**Janalee Heinemann**  
**Executive Director PWSA (USA)**

***Title of Presentation/Poster: “Opportunities and Impediments in National Collaborative Studies for Rare Genetic Diseases.”***

***Presenters/Authors: Michael Watson, PhD, Executive Director of ACMG, assisted by Dr. Edward McCabe from Mattel Children’s Hospital UCLA***

*The ACMG has received a five-year grant from the National Institute of Child Health and Human Development and the Office of Rare Diseases of the National Institutes of Health to run a series of workshops at the Annual Clinical Genetics meeting, and to convene an oversight group that will synthesize the information from the workshops and other sources to identify opportunities for collaborative research. Models for such study groups include the national cancer cooperative groups and the CF Consortium that facilitate long-term studies related to epidemiology, etiology and biology, treatment/intervention trials and natural history. Many issues arise when considering collaborative study group models for genetic diseases. These include IRB issues for multicenter trials, the wide breadth of diseases and specialists involved with those patients, and the significant genetic variation among those affected that requires a national collaborative approach. This third workshop focuses on some of the issues that have to be addressed in order for national collaborative studies to occur.*

There are several national and international collaborative children’s oncology groups that serve as a positive example of what can be done with collaborative studies. In the **Children’s Oncology Group (COG)** alone, there are 5,000 pediatric oncologist participating from 240 medical centers with 85-95% of the children with cancer (40,000) enrolled in clinical trials. Due to this type of collaboration, some of the survival rates for various childhood cancers have dramatically improved. An example is the Wilm’s tumor studies that started in 1964, which has gone from a 20% to a 90% survival rate.

Lessons learned from the oncology groups include:

- Competition between researchers and/or institutions can be a major impediment. They need to be willing to give up their autonomy. This is difficult in the university arena of “publish or perish.” It becomes even more difficult when you have a company involved and there are patent issues.
- There is a tendency to base research questions on finance (what is more likely to be funded) than on the real need.
- There is a tendency for the ‘old guard’ to dominate, making it difficult for new researchers to work their way into the main arenas or to be heard.
- It can be a major challenge to get through each institution’s IRB.

In spite of this, there is great potential in collaboration with rare disorders.

- Collaboration between disciplines or within disciplines in different academic settings enriches ideas. There is power in collective intelligence.
- The pooling of patients improves the statistical power of data.
- It allows for establishing a tissue repository for current and future studies.

- It helps establish a standardization of data.
- It allows for intense collaborative meetings.
- It necessitates closer communication between NIH and the research groups.
- It becomes a venue for advocacy and public awareness.

Although with rare disorders, there is a much wider range of patients than in oncology, we should not let this diversity be the ultimate barrier to our attempts to collaborate.

As we pave the way through new territory, it helps me to appreciate the painstakingly slow process of the **Rare Disease Clinical Network** collaborative study in which we are participating involving **Rhett's syndrome, Angelman syndrome, and Prader-Willi syndrome**. It also makes me appreciate our yearly scientific meeting at our conference where we bring together specialists from different disciplines and different medical settings., our Study of Death project, which includes researchers and physicians from different medical settings, and the ongoing collaboration we have among our two medical boards. It has also motivated me to renew our efforts to work out a centralized repository for PWS brain tissue with the most renowned world-wide expert on PWS brain research, Dr. Dick Swaab, at the Netherlands Institute for Brain Research.

This presentation was of particular interest to me because Dr Watson and I go back many years when we both worked at St Louis Children's Hospital, which is part of the Washington University Medical complex in St Louis. We both worked with the children's oncology groups, POG, COG, and CCG. In the past, I have thought about the question he was pondering in his presentation which was "*Why can't there be the same type of collaboration with rare disorder groups and the geneticists studying these disorders?*" Dr. Watson and the other presenters did an excellent job of clarifying for me the "whys?"

**Durhane Wong-Rieger**  
**Canadian Organization for Rare Disorders**

**Title of Presentation/Poster:** *Ethical Considerations in the Use of Enzyme Replacement Therapy for Lysosomal Storage Disorders* (Platform Presentation: Educational/Public Health/Legal/Ethical)

**Presenters/Authors:** M.A. Fox<sup>1</sup>, E.A. Crombez<sup>1</sup> & S.D. Cederbaum<sup>1,2,1</sup> Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States, <sup>2</sup>Human Genetics, UCLA, Los Angeles, CA

*With the increasing availability of enzyme replacement therapy (ERT) for lysosomal storage disorders (LSD), geneticists and genetic counselors face complex and diverse ethical issues surrounding the appropriateness of treatment. We present three cases in which the efficacy of children with significant CNS involvement at the time of diagnosis in which there were ethical concerns surrounding the use of ERT. Patient 1 is a six-year-old with severe MPS I, who was awaiting the start of FDA-approved ERT at a time when he was starting to exhibit mild developmental delay. ERT was started at the age of 4 in hopes of helping his systemic manifestations which have seriously deteriorated over the last two years. He now has a permanent tracheotomy, is G-tube dependent and has increasing vision and hearing loss. With the patient's family, we have struggled with the question of when and even if to stop ERT. Patient 2 is a 2-year-old who has both MPS I and III. Treatment was offered in hopes of ameliorating some of the systemic manifestations of MPS I, knowing that ERT will not help his increasing difficult behavior due in large part to his MPS III. Did we do the "right thing" by offering treatment? Patient 3 is a 15-month-old newly diagnosed with Gaucher type II with hepatosplenomegaly, hypotonia, and developmental delay. While ERT will not help with her developmental delay, her parents are very interested in start ERT. Will instituting ERT "buy" a little time for her and her family knowing that her prognosis is poor? We present these cases to open a much needed dialogue at a time of expanding treatment options and decreasing financial resources.*

Three case studies of children diagnosed with **lysosomal storage disorders (LSD)** were presented to illustrate the need for deliberate discussion around the ethics of starting and/or stopping expensive therapies when the benefits may be mitigated by other circumstances. A common feature of the family of LSDs is the lack of an essential enzyme, which may lead to serious clinical outcomes, including developmental delays or organ failure. While **ERT** may halt progression of clinical outcomes, the therapy is still relatively new and data are limited as to long-term benefits and the ability to reverse symptoms. In case one, the child, who had been on therapy for two years, had already exhibited some symptoms by the time treatment was started. Now, the child was having serious problems with breathing, feeding, vision, and hearing. In the second case, the child had two types of **MPS disorder** (I and III). ERT could address I but not III, and physicians had started treatment with that knowledge. Now the child was exhibiting increasing behavior problems associated with type III. The final case was a 15-month-old, not yet on therapy, who was already manifesting serious liver, muscular, and development problems. Even though ERT would not change the prognosis, it might slow down the rate of deterioration.

Although the specifics of the cases varied, there were a number of common dilemmas. First, what are the ethics of providing expensive treatment to patients whose overall prognosis was poor? Second, what is the ethical responsibility of the physician in advising the parents? Third, what are the ethics of discontinuing therapy? These issues will become increasingly important to address directly.

This presentation made a tremendous impact on me, both because I am directly involved with groups that support patients with lysosomal storage disorders but also because of the ethical issues raised. At one level, we are still struggling to justify the costs of ERT to health care plans, especially in environments where cost-benefits assessments would conclude that these treatment exceed the typical “cost-per-quality-adjusted-life-year” threshold to warrant giving patients access. Interestingly, this was not the problem for the hospital in these cases, which apparently had a policy to start therapy without reference to cost-benefits. Nevertheless, the author(s) indicated that this was, in fact, likely to be a consideration in starting or maintaining patients on therapy as more of these types of therapies, with their concomitant high costs, become available. As advocates for the patient and family, especially in individual situations, we strive to make the case for access. As patient partners in healthcare policy, we want to make sure that the impact of access decisions on patient well being, including quality of life as well as clinical outcomes, are adequately represented.

In terms of the ethics of continuing treatment when the patient’s condition has deteriorated significantly, the issue becomes akin to the question of when, or if, to discontinue life support. Should there be something like a “living will” or “pre-treatment agreement” that patients or parents sign prior to starting therapy? Should the conditions for discontinuance of therapy be specified, like a living will, at the outset, especially when it is known beforehand that the therapy will not halt or reverse serious clinical outcomes? Should patients be expected, allowed, or provided with support to decide to discontinue therapy based on specific criteria, such as the patient’s clinical status, or some other standard? Is there an obligation to continue treatment, once started, regardless of the patient’s condition?

The question of whether to start expensive therapy when there are other extenuating circumstances that may compromise the patient’s mental and physical prognosis is also important to address beforehand, as two of the presented cases suggest. The presenter did not propose any solutions to these dilemmas but called for dialogue, especially since, as she said, more of these therapies are become available at a time when healthcare systems are facing increasing costs in all sectors and financial resources become more strained.

The presenter is obviously a very patient-centered clinician who recognizes that she has the benefit of being able to support many of her patients with difficult-to-access treatments. I felt it took courage to raise this issues as directly as she did. Also, by presenting three very real cases, she took the question beyond the theoretical to the personal, applied realm. She did not minimize the difficulties that these cases present to the treating physician, as well as to the patients and families.

It was a pleasure to have had the opportunity to meet the lead author in one of the patient advocate sessions. I think we all recognize the value of discussing these questions in the context of health policy where patients can have a role. However, even in an open debate situation, it is unlikely that we will arrive at solutions that will satisfy all stakeholders equally.

**Durhane Wong-Rieger**  
**Canadian Organization for Rare Disorders**

**Title of Presentation/Poster:** *Genetic Testing and the Family: Ethical Issues*

**Presenters/Authors:** *M.L. van Riper<sup>1</sup> School of Nursing/Carolina Center for Genome Science, University of North Carolina at Chapel Hill, NC, United States*

*Despite growing awareness that genetic testing is inherently a family experience, relatively few researchers have used a family perspective to study the genetic testing experience. The overall purpose of this research, which was guided by the family management style framework developed by Knafi and Deatrck, was to examine how families define and manage the ethical issues that emerge during six types of genetic testing: maternal serum screening for Down syndrome, newborn screening for sickle cell diseases, carrier testing for cystic fibrosis, BRCA1/2 testing for breast and ovarian cancer susceptibility, Factor V Leiden testing, and mutation analysis for Huntington disease. In-depth interviews were conducted with one or more individuals from 95 families. Findings from these interviews suggest that most of the family members viewed the genetic testing experience as a family experience. That is, they recognized that their family influenced, and was influenced by, how individual family members made sense of, responded to, and used the genetic information they received. Most participants reported that the genetic testing experience had profound and enduring implications for individual family members and the family as a whole. While the right of each family member to make their own decisions about whether or not to be tested was generally respected, some participants indicated that they felt pressured to change their testing decision, and others noted that they had tried to get relatives to change their testing decision for “the good of the family.” Ethical issues for family members included concerns about privacy, informed consent, freedom of choice in reproductive decisions, insurability, discrimination, and stigmatization; many of these concerns related to when, how, or whether, to disclose the genetic information they received to other family members, friends, co-workers, and employers. Factors that influenced how family members defined and managed the ethical issues they encountered included: the timing and setting of genetic testing; past experience with the condition being tested for; their decision about whether or not to undergo testing; and test results for those who chose to be tested. Findings from this study will facilitate the development and testing of tailored, family-centered interventions for families being tested for and living with genetic conditions.*

Genetic testing, even when it is made as an individual decision, affects the entire family. This research focused on the ethical issues that families face when deciding who should get tested, when testing should be done, and how results should be shared. More importantly, the research also considered the whole family experience and how they influenced each other in the decision-making process. The researchers conducted in-depth interviews with individuals and families representing six types of genetic diseases or disorders, where individual results of testing could have different implications for other family members. The results from the interviews showed that genetic testing, while an individual decision, did involve other family members in most cases. In some cases, individuals felt pressured by other family members to either undergo testing or to reveal the results of tests. Similarly, some of those interviewed revealed that they had to negotiate with other family members to persuade them to participate in testing. Some families worked out their own solutions to respect individual choice. For example, a member of a family might undergo testing for the sake of the family but would choose not to learn the results. The results suggests that creating interventions and guidelines for helping families make decisions about testing that respect individual privacy and choice while also serving the needs of the family in terms of their decisions to have children, the potential impact on their insurance, and the resulting stigma and discrimination on the rest of the family would be beneficial.

This presentation brings into perspective the importance of engaging the family in decisions about genetic testing. It is also very clear that we do not have good guides on how to help families make decisions that respect individual preferences as well as the need for families to know. As we have more types of genetic testing available, the need for models and ethical guidelines will become more important. Should the rules differ depending on whether we're dealing with children or adults? Should the right to refuse testing differ depending on the seriousness of the disorder, or the availability of treatment?

As a voluntary organization, we are often asked to provide guidance or support to parents or individuals about genetic testing. We often encounter families where members have very different opinions about testing and we are often called upon to side with one member or another. Clearly, no decision is "right or wrong." We all have personal opinions about the value and need of testing which serve as a guide on how to deal with personal preferences when talking with the family.

The presenter provided interesting anecdotes to help illustrate the key findings from the interviews. The presenter did not try to over-generalize from this limited number of interviews but the conclusions and recommendations were compelling. It is obvious that the researcher also had very good insights into the varied experiences of the different families and empathized with them. There were no clear recommendations but the depth of understanding would clearly help to develop appropriate counseling and educational guidelines.

**Cathy Sherman**  
**Executive Director, Birt Hogg Dube Family Alliance**

**Title of Presentation/Poster: *DNA Banking: Saving for the Future***

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*In some families diagnosis of a known hereditary cancer syndrome may not be currently possible, yet future molecular genetic testing may be available to help explain the etiology of these cancers. However, if action is not taken in the present, it may preclude ability for critical information in the future. Individuals and families are frequently not referred for genetic evaluation until an affected family member is deceased or terminally ill. For these reasons, DNA banking is essential to ensure future availability of DNA, from an individual with cancer, so that if additional genetic testing becomes available it can be done. We investigated use, offering and policies of DNA banking by cancer genetic counselors within the NSGC Cancer SIG (response rate 24.7% [98/396]), and separately awareness and utilization of DNA banking by oncologists listed with the Medical Society of the State of New York (response rate 22.7% [105/462]). Responses by members of the Cancer SIG and the Medical Society of the State of New York indicated that in 92/95 (96.8%) and 64/70 (91.4%) respondents respectively, their institution or group does not have a policy and/or routine approach to offering DNA banking. Further, while 87/93 (93.6%) Cancer SIG respondents have discussed DNA banking with a patient at some point in their career, 50/82 (61.0%) indicated that they discuss DNA banking with less than 20% of candidate patients. Cancer SIG responses showed that the mean percentage of time patients/families are seen where all affected relatives are deceased was 23.0% (n=85). The mean percentage of time that patients/families are seen where the only remaining affected family member is terminally ill was 10.7% (n=83). Questionnaires returned by New York state oncologists indicated that 72/101 (71.3%) were vaguely aware or unaware of DNA banking for clinical purposes, and of this group 38/71 (53.5%) respondents indicated that they refer (most of the time or always) patients for genetic counseling/evaluation when the family history is suggestive of inherited cancer risk. In completing the questionnaire 64/104 (61.5%) of oncologists indicated that they would like to receive additional information on DNA banking. Awareness and utilization of DNA banking is critical as the impact of genetics and family history on individual risk, assessment of such, and healthcare decisions increases and evolves. Approaches to increase awareness and use of DNA banking in clinical practice include the development of educational materials (as done in conjunction with this study) and policies or criteria for when and to whom DNA banking should be offered. Additionally, the lack of awareness and utilization of DNA banking by oncologists supports the need for new approaches to educating and providing resources to other health care practitioners.*

DNA banking may be a valuable tool for many families faced with hereditary cancers. This is particularly true for those families whose specific syndrome or genetic mutation has not yet been identified. In the past, afflicted family members may have become ill and passed away while specifics about their cancer and its genetic links were unknown. If they had they left a DNA sample, it would be possible for future researchers to use this information to help other family members. However, for this to take place, awareness of banking as an option has to be more widespread. To examine current practices regarding the use of DNA banking, a study was undertaken by the Roswell Park Cancer institute of Buffalo, NY. A survey of New York State oncologists and of cancer genetic counselors was conducted, with respective response rates of 22.7% and 24.7%. Questions were asked regarding the participants' own awareness of DNA banking, as well as the frequency with which DNA banking was discussed with patients.

Genetic counselors were more familiar with the concept of banking than oncologists, who only discussed the possibility with a minority of their patients. It was concluded that oncologists were

interested in learning more about DNA banking as it applies to their patients but the majority of them have not been aware of this option to date. While genetic counselors have discussed DNA banking with more families, neither they nor oncologists have any organized policy for discussing the topic. This is particularly relevant as nearly one fourth of affected family members are deceased when the family consults with genetic counselors.

New methods of spreading awareness are clearly needed. A brochure will be published on the National Society of Genetic Counselors' website at [www.nsgc.org](http://www.nsgc.org).

DNA banking has implications on many levels for those who are affected by genetic conditions. In her presentation, Mollie Hutton described research that helps to illustrate the current status of DNA banking in families with hereditary cancers. There are several ways in which this information has relevance for those who are affected by **Birt Hogg Dube syndrome**.

Nickersen et al. described the Birt Hogg Dube gene in 2002. Genetic testing is available to families who suspect they have the syndrome. Although Birt Hogg Dube can lead to conditions that pose serious health risks, such as bilateral multi-focal renal cell carcinoma, we often see a reluctance in family members in regards to testing – even if there is already a case of RCC in the family or if the family mutation has already been identified. One of the suggested uses for DNA banking mentioned during this presentation was for those who are currently reluctant to have the actual genetic test. This is certainly relevant in cases where hesitance for any number of reasons, including denial, prevents family members from being tested. It would be a novel approach should the Birt Hogg Dube Family Alliance promote this alternative, but it does fill a need for many of our families.

If it were possible to convince a family member who does not want to be tested for BHD to have DNA stored for the future, we might convince more people to at least have a DNA sample taken. However, it would be necessary to overcome some of the same pre-conceived ideas that exist regarding genetic testing in general. In addition, dealing with aversions to having a genetic test labeled with one's name in a repository would play a role. We are finding that many of our family members have fears about potential genetic discrimination in insurance and job related issues that go beyond finding out whether or not they have a genetic condition. Our Alliance chose to promote genetic testing for BHD while respecting individual choices. Although individuals with Birt Hogg Dube may not be in the same situation as those in the Roswell survey, DNA banking may offer acceptable options – we just have to make people aware of the possibility.

A quick search of the Internet will provide anyone with a variety of sites on DNA banking. Given the findings outlined by Sharon Terry of the Genetic Alliance in her speech on "Consumer Interests in the Delivery of Genetic Services" at the 2006 ACMG meeting, lay persons do seem to use the Internet as their primary source for research. Twice as many consumers went online for information as to their provider or support group. However, people looking for disease or treatment specific information are unlikely in my opinion to search for something like DNA banking as it relates to their situation – so they are likely to be unaware of this option. If their physician, oncologist or other medical professional is also unaware, their likelihood of finding out about DNA banking is greatly reduced.

Many of our families do not see genetic counselors or geneticists. There seem to be several reasons for this: they are diagnosed by a dermatologist who is unaware of the option; there is no counseling available in their area; there are misperceptions about cost, or a fear of discrimination in various areas. I see a need to bridge this gap, to use the information from the survey discussed in this presentation and to find out how to get this information out. The most well-informed population of the survey, namely the genetic counselors, will soon have a tool that will give them more information in the form of a brochure on their website. The question is how other professionals will be able to share it with their patients. There are families with genetic cancers and other conditions who see multiple doctors in several fields and it seems that they would be less likely to present the DNA banking information to their patients than the oncologists in the survey would.

This presentation was very thought provoking for me. It has opened my eyes to new pathways for dissemination of information about BHD. Mollie Hutton was very helpful, both in answering questions after the presentation and in providing me with a copy of the Power Point slide show that inspired additional research on my part. I believe that DNA banking has been an overlooked tool for families affected by several of the hereditary kidney cancer syndromes, including Birt Hogg Dube. I think it will be particularly important for families who apparently have hereditary renal cell carcinoma, which does not fit into any currently known syndromes. We will be including information about my findings on our website. I will be recommending DNA banking for many of the families with whom I am in contact, particularly for those who do not have a definitive diagnosis of a familial kidney cancer.