DIVISION OF MEDICAL GENETICS

Mission

The mission of the Division of Medical Genetics is:

- To provide state-of-the-art diagnostic evaluations, testing, and genetic counseling for children and families with genetic, teratogenic, metabolic, and dysmorphic conditions at Children's Hospital of Pittsburgh of UPMC and throughout the entire UPMC health system
- To provide or recommend therapeutic interventions to maximize clinical outcomes for each child
- To provide excellence in teaching
- To advance knowledge in pediatric genetics and metabolism through ongoing research and collaborations

FACULTY

Jerry Vockley, MD, PhD
Cleveland Family Endowed Professor of Pediatric Research
Professor of Human Genetics
Division Chief, Medical Genetics
Director, Center for Rare Disease Therapy

Georgianne L. Arnold, MD
Adjunct Professor of Pediatrics

Jane Breck, MD
Clinical Professor of Pediatrics
Director, Phenylketonuria (PKU) Clinic

Areeg El-Gharbawy, MD
Research Assistant Professor of Pediatrics

Maria Escolar, MD, MS
Associate Professor of Pediatrics
Director, Program for the Study of Neurodevelopment in Rare Disorders (NDRD)

Lina Ghaloul-Gonzalez, MD
Research Assistant Professor of Pediatrics

Eric Goetzman, PhD
Associate Professor of Pediatrics

Uta Lichter-Konecki, MD, PhD
Professor of Pediatrics
Director, Inborn Errors of Metabolism Clinic

Suneeta Madan-Khetarpal, MD
Associate Professor of Pediatrics
Clinical Director, Medical Genetics

Al-Walid A. Mohsen, PhD
Research Associate Professor of Pediatrics

Robert D. Nicholls, DPhil
Professor of Pediatrics
Director, Birth Defects Laboratories

Damara Ortiz, MD
Clinical Assistant Professor of Pediatrics
Director, Lysosomal Disorders Clinic

Michele D. Poe, PhD
Research Associate Professor of Pediatrics
Research Manager, Program for the Study of NDRD

Yudong Wang, PhD
Research Assistant Professor of Pediatrics

Audrey Woerner, MD
Clinical Assistant Professor of Pediatrics
Director, Telemedicine Program

OVERVIEW OF THE DIVISION

In 2017, the Division of Medical Genetics clinical team consisted of 10 MDs, nine clinical genetic counselors, two metabolic dieticians, three clinical nurses, two research nurses, and three genetic counselors dedicated to special projects. Three additional tenure-track and four non-tenure-track research faculty provide a strong basic science foundation. The division's goal is to provide state-of-the-art medical genetics services, as well as to generate new information and rapidly incorporate that information into care for children. Basic and clinical research is an intrinsic goal of the division. Faculty members are internationally recognized and play highly visible roles in national and international academic societies and government advisory panels. They participate in graduate-level education within the University of Pittsburgh's School of Medicine and Graduate School of Public Health. The division integrates genetic counseling duties with counselors based in the Division of Laboratory Medicine and the Center for Rare Disease Therapy.

In addition to basic and clinical research, the Medical Genetics team is devoted to the provision of medical genetic diagnostic and counseling services. Members of the division serve as consultants, manage inpatients with inborn errors of metabolism, and provide diagnostic and counseling services to additional Children's Hospital genetic disease clinics, including neurofibromatosis, cleft lip and palate, cystic fibrosis, and fragile X clinics, as well as to providers throughout Western Pennsylvania, eastern Ohio, and northern West Virginia. The clinics for inborn errors of metabolism, lysosomal storage disease, mitochondrial disease, and PKU provide care for patients with chronic, rare metabolic disorders and function as the follow-up center for Pennsylvania's state-mandated newborn screening. The division's physicians provide genetic services for the Hereditary Telangiectasia Center of Excellence at UPMC and are active in the newly constituted Center for Rare Disease Therapy at Children's Hospital. In 2017, the Neurodevelopmental Research Program joined the division, bringing an expanded focus on neurodegenerative disorders.

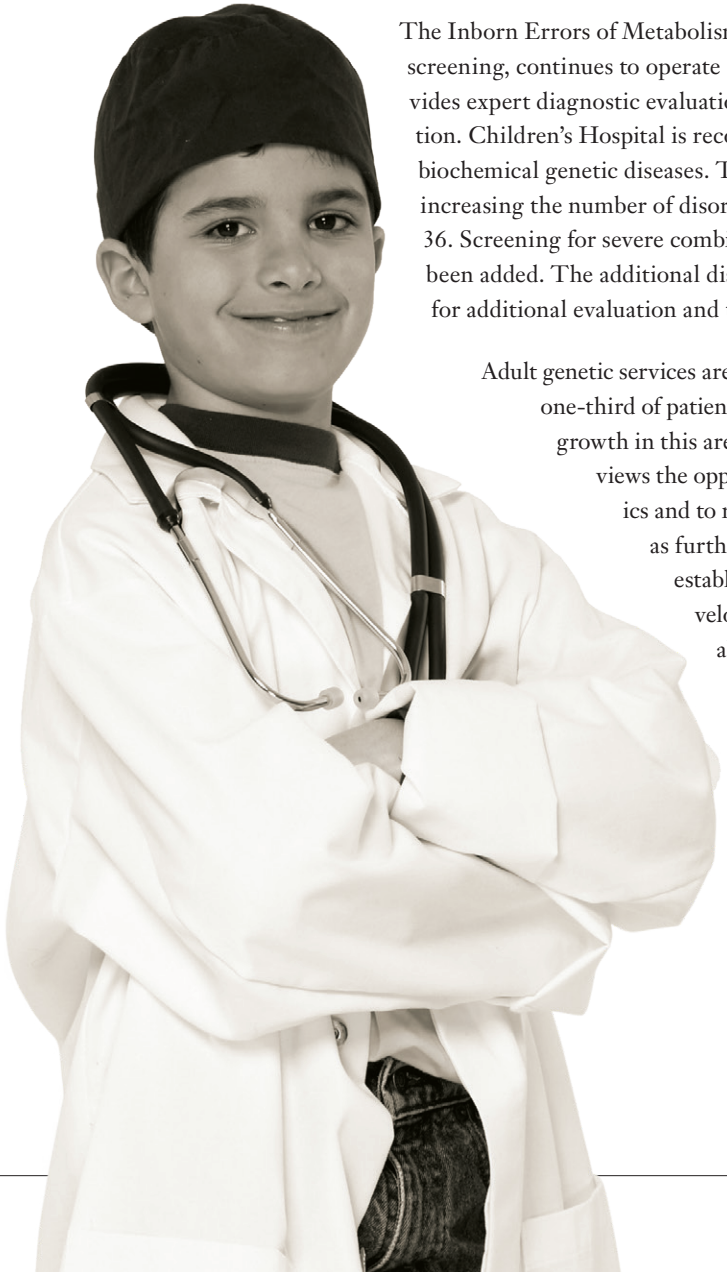
The physicians utilize a team approach to evaluate children thought to have metabolic disorders as well as congenital anomalies, teratogenic disorders, and/or genetic disorders, and they strive to engage patients and families with necessary

support and specialists to optimize clinical and emotional outcomes. Families are provided with state-of-the-art laboratory diagnostic testing. Genetic counseling is provided to optimize the outcomes of children, to provide information to help parents make individualized decisions for family planning, and to initiate support from the community. The division strives to provide realistic hope to families and to provide services in a compassionate and empathetic manner.

CLINICAL ACTIVITIES

An eight-year history of faculty growth in the division has kept pace with increasing patient volume. There were 1,941 visits (981 new and 960 returns) in 2017. Additional visits to the PKU and Program for the Study of NDRD subspecialty clinics totaled 178 and 32, respectively. 1,003 inpatient consultations were performed. The division remains committed to seeing critical inpatients within 24 hours and provides 24/7 on-call coverage for genetic emergencies. Noncritical consultations may be referred to the outpatient clinic upon patient discharge.

The division's specialty clinics offer treatment for lysosomal storage disease, PKU, mitochondrial disorders, and connective tissue disorders. The Neurogenetics Clinic, staffed in conjunction with the Division of Child Neurology, provides comprehensive team care for patients with a known diagnosis of neurogenetic disease, including mitochondrial myopathies. A Connective Tissue Disorders Clinic serves as a regional referral center for patients with such disorders, and the division participates in a nationally recognized Cutis Laxa Clinic. A Plain Communities Translational Medicine Program focuses on the extensive Amish and Mennonite population in Western Pennsylvania and eastern Ohio.



The Inborn Errors of Metabolism Clinic, including its follow-up center for state newborn screening, continues to operate at capacity and is among the largest in the country. It provides expert diagnostic evaluations and ongoing metabolic management to a national population. Children's Hospital is recognized as a national center for the study and treatment of biochemical genetic diseases. The state of Pennsylvania recently passed new legislation increasing the number of disorders in the standard newborn screening panel from seven to 36. Screening for severe combined immune deficiencies and congenital heart disease has been added. The additional disorders are inborn errors warranting referral to the division for additional evaluation and treatment.

Adult genetic services are an integral part of the division's clinical mission, and nearly one-third of patients are adults. The division's leadership anticipates continued growth in this area, with two internal medicine faculty members. The division views the opportunity to demonstrate growing capabilities in adult genetics and to represent Children's Hospital and the University of Pittsburgh as further evidence of its leadership role across UPMC. A proposal to establish a formal adult genetics clinic in internal medicine is in development. In addition, several outside institutions have inquired about possible outreach or telemedicine clinics. The division also looks to explore outreach activities as staffing increases.

DIVISION HIGHLIGHTS

Research and teaching constitute major activities within the division. All division faculty members participate in research and receive at least some external funding (see individual faculty member entries). Division faculty members were awarded more than $7.78 million in research funding in 2017: $5.03 million in faculty grants and $2.75 million in clinical trials funding.

The entire faculty and many genetic counselors participate in and have salary support from externally

funded projects. The division anticipates continued and expanding support. The division has more than 50 protocols approved by the Institutional Review Board. Two PhD students from the Department of Human Genetics are currently performing their thesis research under the direction of Medical Genetics faculty. Multiple genetic counseling students are pursuing thesis projects. The division's faculty and counselors are much in demand for a wide range of continuing medical education, as well as for lectures for fellows and residents. Members of the division have published 60 articles in peer-reviewed journals in the past three calendar years.

Jerry Vockley's service at the state, national, and international levels raises the prominence of the division. He is chair of Pennsylvania's Newborn Screening and Follow-Up Technical Advisory Board, and he serves on the Department of Health's Committee on Lead Exposure and its Birth Defects Registry. He served on the Therapeutics Committee of the American College of Medical Genetics and Genomics (ACMG) and served as co-chair for the PKU clinical guideline work group. Vockley chairs the research career development ("K") award Metabolomics Study Section for the National Institutes of Health (NIH). Vockley is founder and chair of the International Network for Fatty Acid Oxidation Research and Management (INFORM). He is a distinguished editor for the NIH Director's New Innovative Editorial Board. Vockley is past president of the Society for Inherited Metabolic Disorders and is founder and director of its national training program for medical genetics residents, the North American Metabolic Academy. This important program reaches half of the medical genetics residents in the country annually, as well as many from Canada and Mexico. He serves on the European Registry and Network for Intoxication Type Metabolic Diseases, for which he co-chairs the working group on isovaleric acidemia guidelines.

Georgianne L. Arnold is the chair of the Maintenance of Certification Committee for the American Board of Medical Genetics and Genomics. Robert Nicholls and Eric Goetzman have both received major new research grants in the past year.

The division runs an Accreditation Council for Graduate Medical Education (ACGME) training program for the newly established Medical Biochemical Genetics Fellowship, one of only seven in the country.

RESEARCH AND OTHER SCHOLARLY ACTIVITIES

Vockley, MD, PhD

RESEARCH

Jerry Vockley's research focuses on mitochondrial energy metabolism, branched chain amino acid metabolism, inborn errors of metabolism, and development of novel therapies for inborn errors of metabolism. He also has a strong interest in the genetics of the Plain Communities (Amish and Mennonites) and in identification of novel genetic disorders in the general population.

Characterization of a Multifunctional Fatty Acid Oxidation Complex. Fatty acid β-oxidation (FAO) and oxidative phosphorylation (OXPHOS) are key pathways involved in cellular energetics. Genetic disorders of FAO and OXPHOS are among the most frequent inborn errors of metabolism. Patients with deficiencies of either FAO or OXPHOS often have clinical or biochemical findings indicative of a disorder of the other pathway. This study examined the physical and functional interactions between these pathways. It provided evidence of a multifunctional FAO complex within mitochondria that is physically associated with OXPHOS supercomplexes and promotes metabolic channeling.

Jerry Vockley, MD, PhD
Division Chief, Medical Genetics

Very-Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency. More than 100 cases of VLCAD deficiency have been documented in the literature, with three different disease phenotypes. A severe infant-onset form is characterized by acute metabolic decompensation with hypoketotic hypoglycemia, dicarboxylic aciduria, liver dysfunction, and cardiomyopathy. A second form of the disease presents later in infancy or childhood but has a milder phenotype without cardiac involvement. The third form is of adolescent or adult onset and is dominated by muscle dysfunction often induced by exercise. Not surprisingly, a study found that children with the severe phenotype tended to have null mutations (71% of identified alleles in these patients), whereas patients with the

two milder forms of the disease were more likely to have missense mutations (82% and 93% of identified alleles for the milder childhood form and the adult form, respectively). Nevertheless, a few missense mutations were clearly associated with the severe phenotype. Although the data suggest that missense mutations in VLCAD might obviate clinical symptoms due to some degree of residual activity, no correlation was seen between the mutations identified and residual VLCAD activity in fibroblasts. Moreover, the function effects of few of the known VLCAD missense mutations have been directly characterized.

Team researchers have previously used prokaryotic expression systems to express, purify, and characterize the biochemical properties of several ACAD enzymes. Several have been crystallized and studied by X-ray diffraction, yielding informative three-dimensional models. The team has used its prokaryotic expression system to study six previously missense mutations described in VLCAD-deficient patients (T220M, V243A, R429W, A450P, L462P, and R573W). T220M and V243A are the most frequently reported missense mutations in VLCAD-deficient patients. R429W and R573W are among the few missense mutations believed to result in the severe clinical phenotype. A450P and L462P are located in the C-terminal domain unique to VLCAD and ACAD9. Characterization of purified wild-type, A450P, and L462P VLCAD proteins confirmed the long-held assumption that the C-terminus plays a key role in mitochondrial membrane association. The prokaryotic system developed will greatly facilitate investigation of VLCAD structure and function. Funding for this project is included in the above-referenced grant.

Based on this progress, the laboratory is developing therapeutic agents for treatment of long-chain fatty acid oxidation disorders. Several potential drugs have already been patented and are moving toward clinical trials.

ACAD9. Mitochondrial β-oxidation of long-chain fatty acyl-CoAs is a primary metabolic pathway for maintenance of energy homeostasis and body temperature. It also recycles carbons from many long-chain fatty acids for lipid synthesis. Little is known about the mechanistic role of the latter in the pathogenesis of symptoms in genetic defects of β-oxidation, and its derangement may, in part, explain features of these disorders, such as neurological dysfunction and acute respiratory distress syndrome, which respond poorly to treatment with alternative energy sources. VLCAD is considered the dominant long-chain acyl-CoA dehydrogenase (LCAD) in energy generation in human muscle and heart cells. In contrast, this study provides evidence that acyl-CoA dehydrogenase 9 (ACAD9) and LCAD more likely function in lipid recycling and synthesis in human brain and lung, respectively, given their unique substrate utilization and tissue distribution pattern. Furthermore, the team has identified a new genetic deficiency of LCAD presenting with congenital surfactant deficiency. This disorder represents the first in an α, β-oxidation enzyme primarily involved in lipid recycling or synthesis, revealing a new mechanism of pathogenesis in human disease. Funding for this project by the NIH has been renewed, and a supplement through the economic stimulus grant program has been received.

Human ACAD10. In the last half of the 20th century, the incidence of type 2 diabetes mellitus (T2DM), previously unrecognized in the Pima Indians, began to rise. Multiple factors were postulated to be responsible, including environmental factors, such as diet and resultant obesity, along with a number of genetic determinants. ACAD10 was one of 30 genes examined after demonstrating a significant signal for diabetes in a genome-wide association study. To characterize the physiologic role of *ACAD10* in intermediary metabolism and its possible link to T2DM, the researchers have characterized an *ACAD10* gene trap mouse model. Aging animals become obese on a normal diet and develop insulin-resistant hyperglycemia in response to an intraperitoneal glucose challenge. Tissue and blood acylcarnitine profiles are similar to those previously described for adult humans with T2DM. The findings identify *ACAD10* deficiency as a new monogenic cause of T2DM in mice and provide valuable insight into its potential role in the development of T2DM in Pima Indians.

A New Disorder in Sterol Metabolism. Defects in cholesterol synthesis result in a wide variety of symptoms, from neonatal lethality to the relatively mild dysmorphic features and developmental delay found in Smith-Lemli-Opitz syndrome (SLOS). The team identified mutations in *SC4MOL* as the cause of a newly recognized autosomal recessive syndrome that includes psoriasiform dermatitis, arthralgias, congenital cataracts, microcephaly, and developmental delay. This gene encodes a sterol-C4-methyl-oxidase, catalyzing demethylation of C4-methylsterols in the cholesterol synthesis pathway. C4-methylsterols are members of the meiosis-activating sterols (MAS) family of molecules. MAS are ligands of the liver X receptors α and β, which are important in regulating not only lipid transport in epider-

mis but also the innate and adaptive immunity. They were first found in high concentration in testis and ovary cells and play roles in meiosis activation. The team found that MAS affect cell proliferation in both skin and blood. They also found that inhibition of sterol-C4-methyl-oxidase significantly altered immune regulation in immunocytes. Deficiency of *SC4MOL* represents a new biochemical defect in the cholesterol synthesis pathway, the clinical spectrum of which remains to be defined.

Sterol Rare Disease Consortium. Vockley is the site principal investigator for a new, unique clinical research consortium (the Sterol and Isoprenoid Diseases Research Consortium, or STAIR) to study a group of diseases bound by common biochemistry, impact on health, and rarity: cerebrotendinous xanthomatosis (CTX), hyperimmunoglobulinemia D with periodic fever syndrome (HIDS), Niemann-Pick disease type C (NPC), sitosterolemia, Sjögren-Larsson syndrome (SLS), and SLOS. STAIR activities will be performed by a team of investigators chosen for their clinical research strengths and resources, diverse geographic access to potential research subjects, and the commitment of their institutions to support the consortium. In five years, STAIR will conduct two major clinical studies (a longitudinal natural history study of NPC and a therapeutic trial to evaluate the efficacy of antioxidant therapy in SLOS) and six pilot research studies involving patients with SLS, SLOS, CTX, HIDS, or sitosterolemia. Together with the intramural NIH program, the consortium will support a full-scale training program in the field of sterol and isoprenoid diseases and share its resources and data with the NIH Rare Diseases Clinical Research Network. Participating institutions include Oregon Health and Science University (OHSU), Eunice Kennedy Shriver National Institute of Child Health and Human Development, Children's Hospital of Pittsburgh of UPMC, Cincinnati Children's Hospital Medical Center, University of Nebraska Medical Center, and University of Manitoba (Canada). OHSU will be the administrative home of the consortium. Patient-support organizations (Smith-Lemli-Opitz/RSH Foundation, Hide and Seek Foundation, Ara Parseghian Medical Research Foundation, Dana's Angels Research Trust, Foundation for Ichthyosis and Related Skin Types, and United Leukodystrophy Foundation) will participate in consortium activities. STAIR will foster multidisciplinary clinical research, promote training and education, and support projects to explore promising leads in the mechanisms, diagnostics, and treatments of sterol and isoprenoid diseases. This grant is in its third year of funding from the NIH.

A Pig Model of PKU. Phenylalanine hydroxylase (PAH) deficiency, traditionally known as PKU, results in accumulation of phenylalanine (PHE) in the blood of affected individuals and was the original motivation for population-based newborn screening. This project is developing a miniature pig model for greater genetic homology and more clinical relevance. The new model system will elucidate biomedical bases, facilitating development of therapeutic approaches, especially for mental retardation and neurological and neuropsychological features. Using bioinformatics and phylogenetic comparison to humans, the researchers initially assembled the entire pig *Pah* gene encoding a 452 amino acid enzyme and confirmed high expression of PAH in pig liver and kidney. Furthermore, they successfully targeted deletions and inversions of the *Pah* gene using a CRISPR/Cas9 RNA-guided nuclease approach. Studies over the first eight months of the National PKU Alliance funding period have utilized that *in vitro* model system and successfully optimized the genome editing reagents and mutation-detection assays for the pig *Pah* locus. Working with Missouri collaborators, the researchers have shown that the CRISPR gRNAs function *in vivo* in pig pre-implantation embryos, and a pregnancy has been obtained from embryo transfers of genome-edited embryos (~ 35% modified alleles). Affected animals have now been identified, and clinical characterization is proceeding.

Development of a Home PHE Meter. Early identification of PKU and dietary treatment prevent neurological devastation, but neurodevelopmental and psychological problems are regularly diagnosed even in patients who are identified early and treated continuously. The ACMG recently published a clinical treatment guideline that recognizes the difficulty of lifelong compliance to therapeutic regimens. The guideline reports that nearly all adolescents and adults have blood PHE levels that are out of the recommended therapeutic range, leading to diminished executive function and other neurologic and neuropsychiatric problems. To improve PKU patient outcomes, the ACMG guideline says: "Better tools and strategies are required to optimize care for the individual and improve long-term outcomes." Vockley has recently been awarded two NIH grants to develop and test a home PHE meter for use in treatment of this disease.

Characterizing the Burden of Genetic Disease in Old Order Amish. The Old Order Amish communities (Plain People) of North America have altered health risks that stem from unbalanced population sampling of European founders followed by genetic drift in derivative generations. The population effects have resulted in a high prevalence

of specific genetic disorders that vary from the general population and from each other. Several characteristics of those communities facilitate genetic analysis. Most isolates keep excellent historical and genealogical records. Due to their sociologic and/or geographic isolation, there is usually little or no migration into the group, and the members of the group exhibit relatively homogeneous lifestyles. Large nuclear families are frequent, which provides adequate numbers of affected and unaffected siblings within a sibship for blood samples. The primary genetic advantage, however, results from the interaction of two overlapping phenomena: the founder effect and inbreeding. In collaboration with Ghaloul-Gonzalez, Vockley has developed a new program to characterize the genetic variability between the Amish population in Mercer County and Amish populations in other counties by doing whole-exome and mitochondrial DNA sequencing. This will be crucial to determining the phenotype and frequency of other known and unknown genetic disorders in the populations. This project will allow the researchers to characterize the genetic disease load in Old Order Amish of Mercer County and identify disorders that can benefit from early treatment.

Metabolic Imbalance in Treatment-Resistant Depression. Treatment-refractory depression, defined as depression that has no response to three or more maximum-dose treatment trials of adequate duration, is a devastating clinical problem with significant morbidity and mortality that affects at least 15% of adolescents and adults with depression. Its etiology remains unclear. Several metabolic disorders affect neurotransmitter pathways and are associated with psychiatric symptoms, including depression. The team recently published a report of a sentinel patient with severe and unremitting depression and multiple suicide attempts who was unresponsive to pharmacotherapy or electroconvulsive therapy. A neurometabolic evaluation identified a severe deficiency of all metabolites of biopterin. Treatment with sapropterin, a BH4 analog, led to a dramatic remission of his depression and suicidal ideation that has lasted four years and is still maintained. This finding triggered an exploratory case-control trial in which researchers found 24 of 40 additional patients with treatment-refractory depression to have central nervous system neurometabolic abnormalities. Additional therapeutic options were identified for 23 of the 24 patients based on their metabolic findings. Fourteen patients were identified as having cerebral folate deficiency, and subsequent treatment with folinic acid resulted in a sustained improvement of depressive symptoms in 11 of the individuals. The experience has allowed streamlining of the experimental testing protocol in this population. None of the current tools aimed at developing personalized strategies for the treatment of depression (e.g., functional neuroimaging, pharmacogenetics) would have identified the defects or led to effective therapy. The research continues, funded by a generous donor to the Children's Hospital of Pittsburgh of UPMC Foundation.

Clinical Research. Vockley continues to coordinate a vigorous program in clinical research for the treatment of inborn errors of metabolism. Expanded detection of inborn errors of mitochondrial fatty acid oxidation via tandem mass spectrometry has placed them among the most frequently identified errors. Vockley formed and leads INFORM, which provides a collaborative framework for clinicians and investigators to exchange information on the disorders and their global effect on metabolism. Two medications for fatty acid oxidation disorders that were developed in the Vockley laboratory have reached phase II and III U.S. Food and Drug Administration trials, including triheptanoin, the first drug in development to treat long-chain fatty acid oxidation disorders. Additional diseases under study include lysosomal storage diseases, disorders of sterol metabolism, disorders of the urea cycle, and abnormalities of bone mineralization.

STUDY SECTIONS

- Review Panel, NIH Pioneer Award
- Review Panel, NIH Young Innovators Award
- Ad hoc panels to review Big Data project, Human Mutant Cell Repository Application, NIH
- Chair, NIH K Award Metabolomics Study Section
- Basic to Clinical Collaborative Research Program, University of Pittsburgh

ADVISORY COMMITTEE MEMBERSHIPS

- Collaborating partner, European Registry and Network for Intoxication Type Metabolic Diseases
- Chair, Therapeutics Committee, ACMG Work Group on Evidence-Based Clinical Practice Guidelines, ACMG
- Founder and chair, International Network for Fatty Acid Oxidation Disorders Research and Management
- Chair, INFORM annual meeting, 2017
- Scientific Advisory Board, United Mitochondrial Disease Foundation
- Chair, Pennsylvania State Newborn Screening Advisory Committee
- Member, Pennsylvania State Birth Defects Registry Committee
- Member, Pennsylvania State Lead Screening Committee

- Medical advisor, Organic Acidemia Family Foundation
- Medical advisor, Fatty Acid Oxidation Family Support Group
- Medical advisor, Saving Lives Through Screening Foundation
- Director's Young Investigator Award Second Tier Review Group, NIH ad hoc review committee, Director's Award, NIH, 2017

EDITORSHIPS

- Assistant editor, *Molecular Genetics and Metabolism*
- Founder and managing editor, *North American Metabolic Academy*
- Communicating editor, *Journal of Inherited Metabolic Disease*

MAJOR LECTURESHIPS, SEMINARS, AND TEACHING

University of Pittsburgh:

- School of Medicine Biochemistry and Molecular Medicine course lecturer
- Graduate School of Public Health Biochemical and Molecular Genetics course lecturer
- Medical genetics and pediatric resident lectures

National:

- Course creator and director, North American Metabolic Academy, a weeklong course on inborn errors of metabolism given to medical genetics residents from across the United States and Canada. The course has trained more than half of the medical genetics residents nationally in the past four years.
- "Positive Response to Infliximab in a Patient with VLCAD Deficiency," ACMG annual meeting, Phoenix, Ariz., 2017
- "Newborn Screening for Heavy Metals," Newborn Screening Translational Research Network annual meeting, Baltimore, Md., 2017

International:

- Course faculty, academy course on fatty acid oxidation defects, Society for the Study of Inborn Errors of Metabolism, Lyon, France
- "Triheptanoin in the Treatment of Long-Chain Fatty Acid Oxidation Disorders: Report of Two FDA Phase II Trial Results," Portuguese Society of Metabolic Disorders annual meeting, Lisbon, Portugal, 2017
- "Fatty Acid Oxidation Update," plenary lecture, International Congress on Inherited Metabolic Disorders, Rio De Janeiro, Brazil, 2017
- "Results from a 78-Week Single-Arm, Open-Label Phase II Study to Evaluate UX007 in Pediatric and Adult Patients With Moderate to Severe Long-Chain Fatty Acid Oxidation Disorders," International Congress on Inherited Metabolic Disorders, Rio De Janeiro, Brazil, 2017
- "Phase II Long-Term Pegvaliase Treatment for Adults with PKU: Updated Year 5 Safety and Efficacy Data From the PAL-003 Extension," International Congress on Inherited Metabolic Disorders, Rio De Janeiro, Brazil, 2017
- "Endoplasmic Reticulum-Mitochondria Crosstalk and Redox Homeostasis Disruption in VLCAD-Deficient Fibroblasts," International Congress on Inherited Metabolic Disorders, Rio De Janeiro, Brazil, 2017
- "Antioxidant Therapy as an Adjunct for Treatment of Long-Chain Fatty Acid Oxidation Disorders," International Congress on Inherited Metabolic Disorders, Rio De Janeiro, Brazil, 2017
- "Novel Mechanisms of Pathogenesis in Mitochondrial Trifunctional Protein Deficiency: Implications for Clinical Outcome and Treatment," International Congress on Inherited Metabolic Disorders, Rio De Janeiro, Brazil, 2017
- "Elucidating the Mitochondrial Architecture of Branched-Chain Amino Acid Metabolism Enzymes," International Congress on Inherited Metabolic Disorders, Rio De Janeiro, Brazil, 2017
- "PKU Research Update," Asia-Pacific PKU Summit, Osaka, Japan, 2017

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- ACMG
- American Society of Human Genetics
- American Academy of Pediatrics
- American College of Pediatrics
- American Association for the Advancement of Science
- Society for the Study of Inborn Errors of Metabolism
- Society for Inherited Metabolic Disorders
- American Society for Clinical Investigation

HONORS/AWARDS

- Haworth Visiting Professor, University of Manitoba and Children's Hospital of Manitoba, April 2017
- Boston Children's Hospital Grand Rounds Manton Lecture, Boston, Mass., October 2017
- Past president, Society for Inherited Metabolic Disorders
- Champion for Babies Award, March of Dimes, 2015
- Distinguished editor, NIH Director's New Innovator Award Editorial Board, 2016
- Past chairman, International Congress on Metabolic Disorders
- Postdoctoral trainee Emir Tas, 2016 Fellow Basic Research Award, Society for Pediatric Research, 2016
- Faculty Honors, University of Pittsburgh, 2014

Georgianne L. Arnold, MD

RESEARCH

Clinical Outcomes in FAO Disorders. Georgianne Arnold is part of a collaborative, funded by the NIH and Health Resources and Services Administration, that collects information on clinical management protocols and outcomes studies for common disorders of FAO, including VLCAD, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), medium-chain acyl-CoA dehydrogenase, and short-chain acyl-CoA dehydrogenase deficiencies. In aggregate, the disorders are fairly common, and expanded newborn screening has profoundly changed the landscape regarding patient outcomes and recommended management. LCHAD and VLCAD deficiencies were initially believed to be life-threatening disorders in infancy, yet many patients diagnosed by newborn screening remain asymptomatic. Furthermore, the severe fat restriction formerly recommended for older patients may be harmful to the developing brain. Some studies suggest that the use of carnitine, a staple in the management of FAO disorders, might actually be harmful in long-chain FAO disorders. At present, Arnold's team is seeking information regarding which patients require more rigorous management versus those who might actually be harmed by over-management. Arnold has published Delphi-based clinical practice protocols for patient management (for which the VLCAD deficiency protocol was awarded the Emmanuel Shapira Award for best paper in *Molecular Genetics and Metabolism* by a member of the Society for Inherited Metabolic Disorders). Her outcomes study on MCAD deficiency was presented to the International Congress of Inborn Errors of Metabolism and published in *Molecular Genetics and Medicine*. She is research funded for participation in gathering outcomes data through the Inborn Errors of Metabolism Information System and is actively seeking funding to conduct outcomes studies on the data.

3-Methylcrotonyl-CoA Carboxylase (3-MCC) Deficiency. This is a disorder in the catabolism of the amino acid leucine. Before the advent of expanded newborn screening, 3-MCC deficiency was believed to be a rare and life-threatening disorder, causing acidosis, failure to thrive, and mental retardation. It is now apparent that most infants who have the disorder detected by newborn screening appear healthy, and some countries have removed the disorder from the newborn screen. However, data collected by Arnold suggest that a subset of affected individuals may indeed be at higher risk of poor outcomes. The study database is being expanded, and a multicenter outcomes study is also under way. Arnold published a Delphi-based management protocol for this disorder and is seeking funding for additional long-term studies for the development of evidence-based guidelines. If some infants are at risk from this disorder, it is important to identify the at-risk infants and offer them appropriate evidence-based treatment.

A Clinical Trial of Sapropterin Dihydrochloride for Cognitive Dysfunction in PKU. Well-managed patients with PKU have long been known to have neuropsychological difficulties and depression even though intelligence quotient is preserved by diet therapy. The drug sapropterin dihydrochloride is a commercial preparation of biopterin, the cofactor for PAH. It appears that a larger than expected number of patients achieves better control of PHE levels while taking supplemental biopterin as sapropterin dihydrochloride. However, the biochemistry of biopterin as a cofactor for tyrosine hydroxylase (important in dopamine metabolism) and tryptophan hydroxylase (important in serotonin metabolism) suggests a biological basis for improved well-being and neurocognitive function reported by patients taking sapropterin dihydrochloride, even if PHE levels do not improve. Arnold is currently funded as a part of a national study to determine the effects of sapropterin dihydrochloride on cognitive and psychological functioning in patients with PKU.

Additional Clinical Investigation Studies. Arnold is an active participant in other clinical studies in the division, including a phase II clinical trial on the use of an investigational medication (triheptanoin) for treatment of FAO defects. Arnold is now leading the UPMC site for phase III trials investigating the safety and efficacy of new enzyme-replacement therapies in the treatment of PKU.

ADVISORY COMMITTEE MEMBERSHIPS

- Database Advisory Board, PKU Demographics, Outcomes, and Safety registry
- Chair, Maintenance of Certification Committee, ACMG
- Program Committee, Evidence-Based Review Group, ACMG
- Board of Directors and program chair, Society for Inherited Metabolic Disorders
- Pennsylvania Newborn Screening Lysosomal Disorders Advisory Board
- Board of Directors, program chair, and president-elect, Society for Inherited Metabolic Disorders

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- Society for Inherited Metabolic Disorders
- Society for the Study of Inborn Errors of Metabolism
- ACMG
- American Society of Human Genetics
- International Society for Neonatal Screening

MAJOR LECTURESHIPS, SEMINARS, AND TEACHING

- Core biochemical genetics curriculum, University of Pittsburgh, Pittsburgh, Pa., 2016

HONORS/AWARDS

- Best Doctors, *Pittsburgh Magazine*, 2012–2015
- *Best Doctors in America*, Woodward/White, Inc., 2007–2017
- *Top Doctors*, Castle Connolly, 2009–2017
- Visiting professorship, Children's National Medical Center, Washington, D.C., July 2013
- Visiting professorship, University of Colorado, September 2013
- Visiting professorship, Greenwood Genetic Center, Greenwood, S.C., February 2017

Jane Breck, MD

RESEARCH

Jane Breck is involved in the recruitment and preparation of PKU patients for several research grants. They include the use of hepatocyte transplant for the treatment of metabolic diseases; the use of enzyme-replacement therapy (Peg-Pal) to treat PKU with alternative nondietary treatment; and the neuropsychological effects in addition to the biochemical effects of a PKU medication, sapropterin (Kuvan®).

As a research co-investigator, Breck works with Steve Dobrowolski as he studies the DNA gene mutations of the many patients who attend the PKU Clinic and develops a gene database tracking the effects of gene interaction on various responses to PKU treatment.

Breck's teaching activities include precepting medical students, lecturing graduate students, and interacting with pediatric residents who rotate through an elective in medical genetics. Breck is also active in welcoming genetic counseling students and postdoctoral fellows to observe and participate in the PKU Clinic.

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- American Academy of Pediatrics
- American Medical Association
- Physicians for Social Responsibility

ADVISORY COMMITTEE MEMBERSHIPS

- Consultant, Head Start Programs of Fayette and Green Counties
- Professional Advisory Committee, Epilepsy Foundation of Western Pennsylvania
- Board of Trustees, Easter Seals Society of Allegheny County
- Advisory Board, Parental Stress Center
- Advisory Board, Caring Foundation, Center for Grieving Children and Adolescents
- Consultant in family communication, WQED TV
- Medical consultant, Shuman Center Juvenile Justice Center

Areeg El-Gharbawy, MD

RESEARCH

Currently, Areeg El-Gharbawy participates as a co-investigator on industry-sponsored clinical trials being conducted in the division on novel pharmaceuticals for inborn errors of metabolism. They include trials that address new therapies for patients with PKU; fatty acid oxidation and glycogenosis disorders; hypophosphatasia; urea cycle disorders; and lysosomal storage disorders, including Pompe, Fabry, and Gaucher disease, and mucopolysaccharidoses. In Vockley's laboratory, she has begun a series of experiments examining cell lines from patients with LCHAD/trifunctional protein (TFP) deficiency and Barth syndrome who share overlapping features with patients with complex 1 respiratory chain defects, including cardiomyopathy, fatigue, exercise intolerance, hypoglycemia, and lactic acidosis, to study the relationships between cellular bio-energetic pathways. Preliminary results on the mechanisms involved and availability of new treatments that target the mitochondria and stabilize cardiolipin are encouraging. El-Gharbawy has submitted an investigator-initiated clinical trial proposal to study the use of the novel anaplerotic agent triheptanoin in patients with glycogen storage disease type 1.

MAJOR LECTURESHIPS AND SEMINARS

- "Fatty Acid Oxidation Disorders," Endocrine Seminar, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., 2016
- "Clinical and Translational Insights in Pompe Disease: Disease Pathology, Patient Identification, and Treatment," Pompe Disease Continuing Medical Education Symposium, American Society of Human Genetics meeting, Orlando, Fla., 2017
- "Energy Defects: More to Learn, More To Do," molecular medicine grand rounds, Oregon Health and Science University, Portland, Ore., 2017
- "Understanding the Underlying Mechanisms Involved in Energy Defects Associated With Overlapping Features," Molecular Medicine Research Symposium, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., 2017
- "Glycogen Storage Disorders: Overview and Updates," endocrine grand rounds, University of Pittsburgh, Pittsburgh, Pa., 2017

- "Study of the Relationship Between Fatty Acid Oxidation, the Electron Transfer Chain, and Cardiolipin in Patients' Cells with LCHAD/TFP Deficiency and Barth Syndrome: Implications for New Patho-Mechanisms and Therapeutic Targets," abstract, United Mitochondrial Foundation meeting, Alexandria, Va., 2017
- "The Biochemical Basis for Overlap of Clinical Features of LCHAD/TFP Deficiency With Mitochondrial Respiratory Chain Defects: Implications for New Therapeutic Approaches," poster presentation, International Congress of Inborn Errors of Metabolism, Rio de Janeiro, Brazil, 2017

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- Society for Inherited Metabolic Disorders
- American Medical Association

HONORS/AWARDS

- Research grant award, Promoting Academic Talent in the Health Sciences, 2014
- Nominee, Climb Metabolic Hero Award, 2017

Maria Escolar, MD, MS

RESEARCH

Maria Escolar recently transitioned from the Division of Neurology to the Division of Medical Genetics. Her research takes a multidisciplinary approach focused on the interactions of genes, brain, and behavior and their influences on aberrant development in rare neurodegenerative diseases. Escolar is an expert in leukodystrophies, such as Krabbe disease, metachromatic leukodystrophy (MLD), and adrenoleukodystrophy, as well as other metabolic conditions that can affect the brain, such as Sanfilippo syndrome, Hurler's syndrome, and Hunter's syndrome, among others.

Natural History of Krabbe Disease. Krabbe disease, also known as globoid cell leukodystrophy, is a rare autosomal recessive metabolic disorder characterized by the deficiency of galactocerebrosidase, a lysosomal enzyme responsible for the degradation of psychosine to galactose and sphingosine. The subsequent accumulation of psychosine destroys oligodendrocytes and Schwann cells, causing the formation of multi-nucleated globoid cells, severe demyelination, axonopathy, and neuronal death. The degradation of the central and peripheral nervous systems clinically manifests as progressive neurodegeneration, spasticity, irritability, blindness, deafness, seizures, and premature death. The incidence of Krabbe disease has been estimated as 1 in 100,000 live births. The disease is divided into four subgroups based on age at symptom onset: early infantile (birth to 5 months), late infantile (6–47 months), juvenile (4–17 years), and adult (> 18 years).

As a leading center in the study and treatment of Krabbe disease, the NDRD team has evaluated more than 180 patients, providing the largest single-center database on Krabbe disease in the world. Because of the large and comprehensive database, Escolar has been able to advance research on the different phenotypes. With 97 early-infantile patients and 39 late-infantile patients, Escolar has designed natural history studies to evaluate variability in progression. In Escolar's natural history design, children are evaluated prospectively following a protocol of standardized multidisciplinary testing. Evaluations are completed by a multidisciplinary team of specialists, including neurodevelopmental pediatricians, neuroradiologists, ophthalmologists, speech pathologists, audiologists, physical therapists, genetic counselors, and psychometricians.

Overall, the data collected help establish the initial symptoms and characteristics of disease progression, which can be beneficial in staging of the disease. Resolution of early symptoms can be used for monitoring disease progression and assessing the efficacy of therapeutic interventions. Further work is necessary to understand the correlations among symptoms, function, and genetic mutations. A better understanding of the presenting symptoms of Krabbe disease will increase awareness among pediatricians and result in earlier diagnostic referrals and recruitment for future clinical trials. Such knowledge will become increasingly important as methodological and legislative advances in newborn screening practices continue. Ultimately, natural history data will enable researchers to establish rate and severity of disease progression, allowing clinicians to make better decisions regarding the management and treatment of patients diagnosed via newborn screening.

Psychosine, a Marker of Krabbe Phenotype and Treatment Effect. Although the phenotypic spectrum associated with this condition is broad, the most common form, known as early-infantile Krabbe disease, results in rapid neurodegeneration and death within the first few years of life. Because the only treatment for this condition, hematopoietic stem cell transplantation (HSCT), is most effective if performed prior to the onset of neurological deterioration, it is essential that affected patients be diagnosed during the presymptomatic or minimally symptomatic period. Biomarkers are urgently needed to aid in the prediction of phenotype and assessment of clinical course in patients who are diagnosed with or determined to be at risk for Krabbe disease. Two small prior studies have found evidence that the concentration of psychosine, a substrate of the galactocerebrosidase enzyme, is elevated in patients with early-infantile Krabbe disease. However, given that the prior studies were limited to cross-sectional measurements in a small number of patients,

additional data are needed to assess the value of dried blood spot (DBS) psychosine as a potential biomarker for Krabbe disease.

In July 2017, Escobar reported the findings of the largest study of DBS psychosine concentrations in patients with Krabbe disease to date. The team was the first to longitudinally assess DBS psychosine concentrations in a phenotypically diverse cohort of patients with early-infantile, late-infantile, and juvenile-onset Krabbe disease, along with carriers and at-risk patients who screened positive for Krabbe disease at birth but remain asymptomatic. Substantially elevated DBS psychosine during the newborn period has 100% specificity as a biomarker for infantile-onset Krabbe disease. The findings suggest that measuring psychosine as a second-tier newborn screening test could aid in phenotypic prediction and help clinicians to determine which patients require urgent treatment with HSCT. Future work is aimed toward examining the relationship between psychosine increase and disease progression in later-onset patients and the implications of psychosine concentration changes over time.

Developmental Outcomes of Cord Blood Transplantation for Krabbe Disease: A 15-Year Study. Currently, Krabbe disease is without cure, but umbilical cord blood transplantation (UCBT) has been shown to significantly improve neurological outcomes in asymptomatic neonates. However, when transplantation is performed in symptomatic patients with early-infantile disease, the neurologic insult remains severe. The purpose of this prospective study, which was accepted for publication in *Neurology* in August 2017, was to summarize long-term neurodevelopmental outcomes of 18 children with early-infantile Krabbe disease who were transplanted in the first 7 weeks of life. Long-term outcomes of transplanted patients were assessed with a standardized protocol. Despite failing to cure Krabbe disease, HSCT performed before the onset of severe symptoms delayed disease progression and improved length and quality of life. Children who survived the peritransplant period functioned at a much higher level than untreated patients. Gross motor function responded less well to treatment. Fine motor skills were generally preserved. Cognition was normal or developed at a slightly slower rate than that of typical children. The clinically and statistically significant associations between age at transplantation and expressive language and gross motor function highlight the importance of transplantation as soon as possible for children with early-infantile disease, ideally before 2 weeks of age.

Improvements in Brain Development Following HSCT in Krabbe Disease. Krabbe disease causes severe demyelination of the brain, with rapidly progressing atrophy of certain regions. HSCT is the only treatment available that can halt disease progression. In this study, the NDRD team investigated the development of cerebral myelination by magnetic resonance imaging (MRI) and propose a more sensitive and objective tool to assess the effects of this treatment. The team also compared MRI data from patients who underwent HSCT against natural history. Diffusion tensor imaging (DTI), which utilizes fractional anisotropy to measure the water diffusion property of the white matter and reflects the direction of the axonal microstructure, was used to assess the white matter integrity of the brain. Combined with Escolar's neuroimaging protocol and algorithm, the methods allow for precise quantification of myelin content. A total of 55 patients with early-infantile Krabbe were analyzed, 14 of whom underwent transplantation and 31 who had natural disease progression. Patients treated with HSCT mostly followed the normal developmental trajectory of the corticospinal tract, albeit in the lower part of the normal range. Patients who were not treated with HSCT started with lower-than-normal fractional anisotropy, and the measure decreased significantly within two years after an initial increase. The fractional anisotropy values are consistent with the motor function as measured in behavioral testing. Diffusion-based brain MRI quantitates abnormalities in white matter integrity in patients with early-infantile Krabbe disease. Patients who are treated with HSCT early in life retain corticospinal tract integrity and follow a normal trajectory over time. More broadly, the findings support using diffusion tensor imaging as a tool to measure white matter integrity and effects of treatment in persons with neurodegenerative diseases.

Treatment of Krabbe Disease With Intravenous Adeno-Associated Virus Gene Therapy. Treatment with UCBT can extend life and preserve cognitive function in presymptomatic patients with early-infantile Krabbe disease and in presymptomatic/minimally symptomatic patients with the late-infantile form of the disease. However, all treated children experience some degree of motor disability post-UCBT due to a combination of peripheral nerve disease and early, irreversible damage of the corticospinal tracts. Intravenous gene transfer has been shown to correct myelination of both central and peripheral nervous systems in mice, addressing the critical problem that HSCT is not able to correct—progressive deterioration of the peripheral nerves. Furthermore, UCBT offers no significant benefit once a patient is already symptomatic

because of the extensive early damage to the motor tracts. Therefore, no effective treatments are available once a child manifests signs or symptoms of Krabbe disease. In mice, as explained above, intravenous gene therapy administered shortly after HSCT rapidly improves myelination in both brain and peripheral nerves while the immune system reconstitutes after myeloablative conditioning. In this way, adding gene therapy may shorten the interval between diagnosis and delivery of normal galactocerebrosidase enzyme to oligodendrocytes and Schwann cells, potentially extending the benefits of treatment to patients who have begun to show symptoms.

There is renewed interest in gene therapy, as the development of new viral vectors has reduced the risk of immunogenicity and insertional mutagenesis. Results of recent clinical trials evaluating gene therapy for genetic diseases such as adrenoleukodystrophy and MLD are highly encouraging. Recent advances in gene delivery technologies and the team's newly patented treatment combining gene therapy with reduced-conditioning UCBT may hold the key to effective treatment for more infants and children affected by Krabbe disease. If successful, the proposed clinical trial may transform the standard of care for patients with Krabbe disease. Currently, the project is in the preclinical stages, the toxicology studies. Once those studies are completed, the team intends to move into a phase I/II clinical trial, which will test for safety and explore efficacy in humans.

Krabbe Translational Research Network. Escolar began holding the annual Krabbe Translation Research Network (KTRN) meeting in 2010 while at the University of North Carolina. The KTRN is a consortium of scientists and clinicians who are dedicated to helping children with Krabbe disease live longer and healthier lives. The KTRN brings together the complementary knowledge and skills of investigators who are working in different disciplines at different institutions; it aims to accelerate the development of research findings into new treatments. KTRN members share data and resources to identify promising therapeutic approaches for further development. Specific goals of this year's meeting will include addressing the challenges of gene therapy and effective designs for future trials, discussing the use of gene therapy in patients who were previously transplanted, and considering the treatment of peripheral nerve disease.

Natural History of MLD. MLD is an inherited lysosomal storage disease caused by deficient activity of arylsulfatase A, an enzyme involved in the degradation of 3'-O-sulphogalactosylceramide, otherwise known as sulfatide. Sulfatide exists as a membrane-bound sphingolipid abundant in the myelin sheath and predominantly found in oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system. In MLD, the gradual accumulation of undegraded sulfatide in these myelin-producing cells results in progressive demyelination and neurodegeneration in both the central nervous system and peripheral nervous system. The disease is fatal, with a variable clinical course, and it is typically classified into subtypes based on age of onset. The limitations of previous cohort studies inspired the team to carry out a larger, more comprehensive (prospective and retrospective) study of the onset, prevalence, and severity of clinical manifestations of MLD, enabling physicians to recognize early symptom onset and to select patients likely to benefit from current and future therapies. The data will be used to design clinical trials and to assess treatment outcomes. Because all evaluations were conducted at a single site with

a standardized protocol, the data are the most reliable to date. They also favor patients with early onset, the time of greatest therapeutic opportunity. The substantially larger cohort—totalling 134 patients—enabled arraying the population on a continuous spectrum as opposed to discrete subtypes. The approach allows physicians to conceive of the disease as a diverse set of symptoms and varying forms of clinical presentation, instead of distinct, nonoverlapping phenotypes. In sum, the prospective, longitudinal study provides an improved understanding regarding the clinical course of the insidious disease. The findings will lead to improved clinical outcomes by facilitating earlier diagnoses and assisting in the treatment and management of MLD. Additionally, they will provide a baseline for investigators designing clinical trials for novel therapies.

NDRD Brain and Tissue Bank. This biorepository is housed in Rangos Research Center, and post-mortem specimens are housed at the Alzheimer's Brain Bank at the University of Pittsburgh. It currently houses more than 1,000 specimens collected since 2010. The project has been funded by grants awarded by the Legacy of Angels Foundation and a donation from the Believing for Bryleigh Foundation and Partners for Krabbe Research. The tissue bank provides a plethora of research opportunities for multiple collaborations, as most specimens are connected to clinical data in the NDRD database. Escolar works closely with Julia Kofler to draw connections among histological, pathological, and clinical findings.

Clinical Trials. In addition to coordinating internal research at the NDRD, Escolar continues to be involved as principal investigator in several industry-sponsored projects. Current projects include a safety, pharmacokinetics, and pharmacodynamics/efficacy phase I trial of SBC-103, a new treatment for mucopolysaccharide disease (Sanfilippo) type B (MPS IIIB); a phase I/II trial investigating a treatment for pantothenate kinase–associated neurodegeneration; and a retrospective cross-sectional study to evaluate the neurodevelopmental status of patients with severe MPS type II.

MAJOR LECTURESHIPS, SEMINARS, AND TEACHING

- "Neurodevelopment in MPS Syndromes, Natural History, and Treatment Outcomes," International Symposium on MPS and Related Diseases, Bonn, Germany, July 2016
- "Gene Therapy for Rare Diseases," New York Academy of Sciences and the Biochemical Pharmacology Discussion Group, New York, N.Y., April 2017
- MLD Family Conference, Suffolk, Va., July 2017
- 20th Annual Family and Medical Symposium, Hunter's Hope, Ellicottville, N.Y., July 2017
- "Outcomes of First GM3 Synthase Deficiency Unrelated Matched Umbilical Cord Transplant Following Reduced Conditioning Regimen," Translational Medicine in the Plain Populations Conference, Pittsburgh, Pa., August 2017
- "Psychosine, a Marker of Krabbe Phenotype and Treatment," 13th International Congress of Inborn Errors of Metabolism, Rio de Janeiro, Brazil, September 2017
- Keynote speaker, Paul M. Fernhoff Memorial Lecture, Centers for Disease Control and Prevention and Emory University, Atlanta, Ga., September 2017
- "MPS II Early Diagnosis," Shire Human Genetics Advisory Board Meeting, September 2017
- "MPS II," Regenxbio Advisory Board Meeting, Washington, D.C., September 2017
- "Krabbe Disease Natural History Outcomes," 2017 Global Leukodystrophy Initiative Conference, Philadelphia, Pa., November 2017

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- Adrenoleukodystrophy Advisory Board, MPS II Advisory Board, Regenxbio
- Zellweger Spectrum Disorders Advisory Board, Retrophin
- Lysosomal Storage Disease Advisory Board, Regenxbio
- Advisory Board, Abeona
- Shire Human Genetics
- Global Leukodystrophy Association
- Global Leukodystrophy Initiative
- Newborn Screening Translational Network Workgroup, ACMG, supported by the National Institute of Child Health and Development
- Medical Advisory Board, Jacob's Cure
- Advisory Committee, Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center (U54)
- New York State Krabbe Newborn Screening Consortium
- Medical and Scientific Advisory Board, MLD Foundation
- KTRN

HONORS/AWARDS

- RARE Tribute to Champions of Hope, Medical Care and Treatment Award Recipient, Global Genes Summit (chosen among 300 nominees)

Lina Ghaloul-Gonzalez, MD

RESEARCH

Identification of Novel Genetic Disorders by Exome and Genome Sequencing. Lina Ghaloul-Gonzalez recently transitioned from her position as a fellow in medical genetics to the faculty of the division. Her primary focus is genome and personalized medicine. Current projects include exome and genome sequencing in newborns and genome sequencing in the Western Pennsylvania Plain Communities (Amish and Mennonite).

Characterizing the Burden of Genetic Disease in Old Order Amish. The Old Order Amish communities (Plain People) of North America have altered health risks that stem from unbalanced population sampling of European founders followed by genetic drift in derivative generations. The population effects have resulted in a high prevalence of specific genetic disorders that vary from the general population and from each other. Several characteristics of the communities facilitate genetic analysis. Most isolates keep excellent historical and genealogical records. There is usually little or no migration into the group, and the members of the group exhibit relatively homogeneous lifestyles. Large nuclear families are frequent, which provides adequate numbers of affected and unaffected siblings within a sibship for blood samples. The primary genetic advantage, however, results from the interaction of two overlapping phenomena: the founder effect and inbreeding.

Amish populations are unique in that they represent genetic bottlenecks dating back to the 18th century, distinguishing them from the European population as well genetic drift, which has given rise to variable distributions of pathogenic alleles among North American settlements. The division's mitochondrial studies and other clinical encounters led to the hypothesis that many unrecognized genetic disorders are present in the Mercer County Amish.

The Mercer County Amish are among the least genetically characterized Amish communities in the United States, with no catalog of either genetic disorders or variants seen in the community. The division's researchers have developed a new program to characterize the genetic variability between Amish Mercer County population and other Amish counties by doing whole-exome and mitochondrial DNA sequencing. The project will allow the team to characterize the load of genetic disease in Old Order Amish of Mercer County and identify disorders that can benefit from early treatment.

Mitochondrial DNA mutations have not previously been reported in any Old Order Amish community. The team recently described an Amish family with the MTTL1 mitochondrial gene mutation m.3243A>G. A second patient with an m.13513G>A (D393N) mutation has also been diagnosed. The mutations classically cause mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (otherwise known as MELAS) syndrome. A third patient in that Amish community has been diagnosed with an autosomal recessive respiratory chain disorder due to a homozygous deletion in the NDUFAF2 gene, which was in one of the nine areas of homozygosity detected on single nucleotide polymorphism microarray.

Identification of Reticular Dysgenesis Due to AK2 Mutation: A Novel Genetic Disorder in the Amish Population. Homozygous *AK2* gene mutation [c.622T>C; p.S208P] was identified in an Amish boy for the first time, with immunodeficiency by whole-exome sequencing. *AK2* mutation causes reticular dysgenesis, which is characterized by severe combined immunodeficiency and leukopenia. No Amish patients with AK2 deficiency have been reported in the literature. This highlights the importance of whole-exome sequencing as a diagnostic tool and will add this gene to the already-available Plain People's database of genetic disorders. Functional studies are ongoing to confirm pathogenicity of this mutation.

Human ITCH E3 Ubiquitin Ligase Deficiency in a Non-Amish Girl. Syndromic multisystem autoimmune disease due to human ITCH E3 ubiquitin ligase deficiency was first reported in 10 Old Order Amish children. The children had failure to thrive, with weight and height below the third percentile; relative macrocephaly; developmental delay; delays in gross motor and cognitive skills; dysmorphic features; organomegaly; and autoimmune inflammatory cell infiltration of the lungs, liver, and gut. The team identified a 13-year-old, non-Amish female with a medical history significant for failure to thrive, with height below the third percentile, relative macrocephaly, and mild dysmorphic features with *ITCH* deficiency. Whole-exome sequencing identified a novel, maternally inherited variant in exon 8, c.599 dupC (p.S201fs) that causes frameshift. Deletion studies revealed a *de novo* deletion involving exons 25 and 26. *ITCH* gene mutations in a non-Amish patient provide additional evidence connecting *ITCH* deficiency to human disease. The case also highlights the cost-effectiveness of whole-exome sequencing as a first-tier genetic test in complex patients, which would have reduced the time to diagnosis and saved numerous other tests and procedures that were either non-specific or unrevealing. Functional studies are ongoing to prove pathogeneticy of the mutations.

Characterization of Genetic Factors Contributing to Sepsis in Subjects With Concurrent High Ferritin Levels by Whole-Exome Sequencing. Ghaloul-Gonzalez is co-investigator on this research project with Joseph Carcillo, MD. Organ shutdown in multiple organ dysfunction syndrome (MODS) results when persistent macrophage activation induces inflammation-driven endothelial, epithelial, mitochondrial, and immune cell dysfunction. Ferritin is released into the circulation by activated macrophages. Hyperferritinemic MODS (ferritin > 500 ng/mL) is characterized by reticuloendothelial system activation–induced hepatobiliary dysfunction and disseminated intravascular coagulation. It is variably described by clinicians as sepsis

MODS, macrophage activation syndrome (MAS), and reactive hemophagocytic lymphohistiocytosis. The Histiocytosis Society recommends etoposide and chemotherapy for the condition. In contrast, the researchers studied children with five to six organ failure hyperferritinemic MODS and showed 100% survival with daily plasma exchange, methylprednisone, and intravenous gamma globulin compared to only 50% survival in those treated with the Histiocytosis Society etoposide-based protocol. They also showed that adults with sepsis and features of MAS treated with interleukin 1 receptor antagonist protein had a reduction in mortality to 30%, compared to 60% with placebo. To address this therapeutic controversy, the researchers will test the hypothesis that hyperferritinemic MODS is a common end pathway of inflammation in children, caused by a group of inflammatory conditions that are best treated with precision medicine rather than an etoposide-for-all approach. The researchers are addressing several knowledge gaps in that regard. First, they have determined the ferritin threshold and isotypes related to mortality, which can be used as therapeutic triggers. Second, they have identified the unique "inflammasome" cytokine pattern, which can be targeted with anti-cytokine therapies in patients with ferritin levels above the threshold. Third, they have identified the proportion of patients with gene variants related to (a) inflammasome-driven cryopyrin-associated periodic syndrome and macrophage activation syndrome (IRAP is approved by the U.S. Food and Drug Administration), (b) hypercomplementemia-driven atypical hemolytic uremic syndrome/*aHUS* (C5a antibody is approved by the U.S. Food and Drug Administration), and (c) failed granzyme/perforin or Fas/FasL-mediated activated immune cell death syndromes in hemophagocytic lymphohistiocytosis (etoposide is recommended by the Histiocytosis Society). Fourth, they will explore the feasibility of targeting ferritin heavy-chain potentiation of MODS inflammation with inhibitors of ferritin heavy-chain production and inhibitors of ferritin heavy-chain–induced monocyte/macrophage activation.

STUDY SECTIONS

- Research grant reviewer, Clinical and Translational Science Institute, 2017

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- American Society of Human GeneticsSociety for Inherited Metabolic Disorders

MAJOR LECTURESHIPS, SEMINARS, AND TEACHING

- "Genetic Variants Associated With Hyperinflammation in Septic Shock, poster/oral presentation, Society of Critical Care Medicine meeting, Hawaii, 2016
- "Translational Medicine in the Plain Communities," grand rounds, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., February 2017
- "Mitochondriopathy in AK2 Deficiency, a Novel Genetic Disorder in the Amish Population," Fifth Annual Plain Populations Translational Medicine Meeting, Pittsburgh, Pa., 2017
- "Diagnostic Mysteries Cases," Fifth Annual Plain Populations Translational Medicine Meeting, Pittsburgh, Pa., 2017
- "Metabolic Diseases in the Plain People: The Path From Genomic Discovery to Therapy," co-chair, International Congress of Inborn Errors of Metabolism, Rio de Janeiro, Brazil, 2017
- "Reticular Dysgenesis and Mitochondriopathy Induced by Adenylate Kinase 2 Deficiency Identified in the Amish Population," International Congress of Inborn Errors of Metabolism, Rio de Janeiro, Brazil, 2017
- "Reticular Dysgenesis and Mitochondriopathy Induced by Adenylate Kinase 2 Deficiency Identified in the Amish Population," poster/oral presentation, International Congress of Inborn Errors of Metabolism, Rio de Janeiro, Brazil, 2017

Eric Goetzman, PhD

RESEARCH

Regulation of Mitochondrial Metabolism by Reversible Lysine Acylation. Eric Goetzman's laboratory studies mitochondrial FAO, the pathway by which fatty acids are broken down for energy. Mutations in the FAO genes are among the most prevalent inborn errors of metabolism. FAO enzymes are heavily modified by post-translational modifications. There are three mitochondrial sirtuin deacylases (SIRT3, SIRT4, and SIRT5), which are believed to reverse some of those modifications. The laboratory's current research focuses on the functional effects of lysine acetylation and succinylation on the FAO pathway and the role the sirtuins play in regulating metabolism. Preliminary data show that SIRT5 also may regulate peroxisomal FAO, important in the kidney and liver. SIRT5 "knockout" mice have reduced mitochondrial and peroxisomal function in the kidney but paradoxically are protected from acute kidney injury. Experiments are under way to investigate the phenomenon.

Lung FAO. Mice "knocked out" for the FAO enzyme LCAD demonstrate reduced lung function. Goetzman's team hypothesizes that LCAD and the FAO pathway are involved in synthesizing and secreting pulmonary surfactant in a specialized lung cell known as the type II pneumocyte. Surfactant is a mixture of phospholipids and proteins that

reduces surface tension in the lung; the effect is necessary to prevent the collapse of the alveoli and promote gas exchange. LCAD knockout mice have reduced amounts of surfactant lipids and an altered phospholipid composition. Preliminary studies have shown an increased susceptibility to infection by influenza. Efforts are under way to determine the molecular mechanisms behind the changes.

Cancer Metabolism. Cancer cells have an unusual reliance on glycolysis for energy. Research has not revealed how and why cancer cells alter their metabolism or what role changes in mitochondrial energy metabolism play in the etiology of cancer or in the ability of cancer cells to escape apoptosis. Answering those questions may reveal cancer's Achilles heel and lead to a cure. Goetzman's team is collaborating with Ed Prochownik to study how the oncogenic transcription factor c-Myc drives cells toward an anabolic metabolic phenotype. It may involve changes in mitochondrial enzyme lysine acetylation, as well as changes in partitioning among glucose, glutamine, and fatty acid metabolism.

MAJOR LECTURESHIPS, SEMINARS, AND TEACHING

- "Regulation of Fatty Acid Oxidation by Reversible Lysine Acylation," Sanford Burnham Prebys Medical Discovery Institute, Lake Nona, Fla., 2016
- "Novel Protein Modifications as Regulators of Fatty Acid Oxidation," INFORM, Boston, Mass., 2016
- "Sirtuin Regulation of Peroxisomes in Cancer," Stimulating Pittsburgh Research in Geroscience Work in Progress Seminar Series, Pittsburgh, Pa., November 2016
- "Fatty Acid Oxidation: Relevance and Regulation," endocrine grand rounds, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., November 2016
- "Mitochondrial Fission/Fusion" and "Mitochondria in Health and Disease," MSCBMP2880: Cellular Biology of Normal and Disease States, University of Pittsburgh, Pittsburgh, Pa., April 2017
- "Gm3 Synthase Deficiency in Mice," Gm3 Synthase Family Day, Clinic for Special Children, Strasburg, Pa., May 2017

STUDY SECTIONS

- Research grant reviewer, Discovery Award, U.S. Department of Defense, August 2016
- Research grant reviewer, Prinses Beatrix Spierfonds, Netherlands, March 2017
- Research grant reviewer, Fondiazone Telathon, Italy, April 2017
- Research grant reviewer, Young Investigator Award Program, Children's Hospital of Pittsburgh Foundation, April 2017
- Research grant reviewer, , Peer-Reviewed Medical Research Program, U.S. Department of Defense, June 2017
- Research grant reviewer/ad hoc member, DDK-B Study Section, NIH, June 2017

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- Society for Inherited Metabolic Disorders
- Mitochondria, Aging, and Metabolism Working Group
- Scientific Organizing Committee, INFORM

HONORS/AWARDS

- Team lead, Basic Science, Gm3 Research Summit, Strasburg, Pa., October 2016
- Scientific advisor, International Network for Fatty Acid Oxidation Disorders Research and Management, July 2015 to the present

Uta Lichter-Konecki, MD

RESEARCH

Uta Lichter-Konecki joined the division in August 2016 and has a longtime clinical and research interest in inborn errors of metabolism, beginning with her early clinical and laboratory training. She is an internationally recognized expert in the molecular genetics of PKU. She has published groundbreaking work in the molecular characterization of PKU, including the first description of a mutation in the *PAH* gene causing PKU, and she helped establish the molecular basis for the phenotypic heterogeneity of PKU, a novel genetic property that ultimately became known as genotype-phenotype correlation. In addition to her seminal research in the laboratory, Lichter-Konecki was a member of the multicenter German Collaborative Study on PKU, as well as a member of the international Maternal PKU Study.

Lichter-Konecki's strongest research interest remains the pathophysiology of the brain injury caused by inborn errors of metabolism, whether PKU or urea cycle disorder (UCD). Focusing on an animal model of ornithine transcarbamylase deficiency, a UCD, as well as the patients enrolled in the longitudinal study of UCD, she has examined the role of ammonia and the amino acid glutamine as the toxic agents in UCD. In the culmination of her animal experiments, she was able to show that the primary pathophysiology in acute hyperammonemic encephalopathy was likely a disturbance of astrocyte-mediated water and potassium homeostasis in brain, a major shift in a field previously focused on glutamine-induced hyperosmolality. The findings hold the potential key to developing neuroprotective therapies for acute hyperammonemia in patients with inborn errors of metabolism and hepatic encephalopathy of other causes. Lichter-Konecki has conducted a multicenter pilot study that demonstrated feasi-

bility and safety of hypothermia treatment in acute hyperammonemia, and she has obtained an R34 planning grant from the National Institute of Child Health and Human Development to plan for a large multicenter clinical trial and build consensus regarding treatment during the trial across four different pediatric subspecialties at the 30 sites involved. The planning phase was completed successfully, but the trial was not funded by the NIH. She is now focusing her efforts regarding neuroprotection in hyperammonemia on drugs that can affect water and potassium homeostasis in brain and is collaborating with a researcher that performs drug screens in hyperammonemic zebra fish to take the best candidates and test them in a new mouse model for acute hyperammonemic encephalopathy (from the same collaborator) due to a UCD. On the clinical research side, she is completing analysis of data collected during the longitudinal study for UCD to show the effect of ammonia and glutamine on outcomes in UCD.

She is a co-investigator on the R01 grant for the PHE meter and is working on that clinical research project, too, as well as on the division's industry-sponsored clinical trials regarding inborn errors of metabolism.

Lichter-Konecki studies lysosomal storage diseases. She participated in the hunt for the gene responsible for cystinosis and mapped the locus for an autosomal dominant form of renal Fanconi syndrome (ADRFS) in the human genome. She has an ongoing collaboration with colleagues in the United States and Europe regarding the pathophysiology of the gene defect in ADRFS, and the group is in the process of publishing their work.

MAJOR LECTURESHIPS, SEMINARS, AND TEACHING

- Grand rounds speaker, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., October 2016
- Fellow lecturer, Pediatric Intensive Care Unit (ICU), Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., October 2016
- Fellow lecturer, Neonatal ICU, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., October 2016

STUDY SECTIONS

- Research grant reviewer, Scientific Advisory Board, National PKU Alliance, 2011 to the present
- Research grant reviewer, U.S.–Israel Binational Science Foundation, 2011 to the present
- Research grant reviewer, Raine Medical Research Foundation at the University of Western Australia, 2011 to the present

ADVISORY COMMITTEE MEMBERSHIPS

- Metabolism Work Group, Clinical Genome (ClinGen) Resource Program
- Ad Hoc Review Committee, reviewing staff clinicians of the Medical Genetics Branch of the National Human Genome Research Institute, NIH
- Scientific Advisory Board, National PKU Alliance Therapeutics Committee, ACMG
- Consultant regarding new product development for PKU and UCD, Sanofi

Suneeta Madan-Khetarpal, MD

RESEARCH

Suneeta Madan-Khetarpal is a co-investigator on Vockley's clinical trial projects. She also is a co-investigator on an R01 grant with Zsolt Urban of the Department of Human Genetics in the Graduate School of Public Health, examining genetic disorders of the extracellular matrix. She is a co-investigator on a grant with Judith Yanowitz of the Magee-Womens Research Institute, looking at the effects of the CHD7 genetic mutation. Madan-Khetarpal is collaborating with Cecilia Lo and Ashok Panigraphy on researching the genetic causes of congenital heart defects and brain–cilia defects. She also collaborates with Beth Roman on research regarding hereditary hemorrhagic telangiectasia (HHT).

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- American Society of Human Genetics
- American Medical Association
- ACMG
- American Cleft Palate–Craniofacial Association
- National Marfan Foundation
- Society for Inherited Metabolic Disorders
- Society for the Study of Inborn Errors of Metabolism
- German Society for Pediatric and Adolescent Medicine
- German Society for Human Genetics
- Society for Neuroscience
- Society for Pediatric Research

MAJOR LECTURESHIPS AND SEMINARS

- "Dysmorphology Assessment for Ear, Nose, and Throat," Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., 2016
- "Introduction to Dysmorphology," Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., October 2016
- "A Day in Clinical Genetics," immunology grand rounds, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., November 2016
- HHT rounds speaker, UPMC Presbyterian Hospital, Pittsburgh, Pa., 2016
- HHT rounds speaker, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., 2016

Al-Walid A. Mohsen, PhD

RESEARCH

Al-Walid A. Mohsen has a dual role. His primary role has long been to provide Vockley's research personnel with experimental design support and research direction to pursue the specific aims of his NIH grants and his new biotech-funded projects. Mohsen has for years been a driver of discovery and innovation. Last year, he introduced a concept with breakthrough potential in drug discovery for biochemical genetic disorders. He demonstrated evidence of its viability in three different pathways in patient cells. One patent application was filed for trimetazidine (TMZ) to treat fatty acid oxidation disorders, and clinical trials are under way. Mohsen is currently focused on optimizing drug efficacy and confirming drug mechanism interaction. Confirming the mechanisms and the pharmacodynamics and characterization of the proposed drug therapy for five fatty acid mitochondrial metabolic disorders, on the molecular level *in vitro* and *in vivo*, will help win a "Breakthrough Therapy" designation by the U.S. Food and Drug Administration.

Development of Chemical Chaperone for Inherited Metabolic Enzyme Deficiencies. Genetic disorders that result from missense mutations can often render the mutated proteins structurally defective, leading to their misfolding or instability. Mutant enzymes that reach the native tertiary or quaternary assembled state may have partial activity, but they are usually thermolabile and vulnerable to proteolysis, making fever, strenuous exercise, or other stress factors life-threatening decompensation triggers. Often protein thermostability and vulnerability to proteolysis improve significantly by ligand binding. Ligands that improve protein stability include the protein/enzyme's own substrate, a substrate analog, or its reaction product(s). Other stabilizing ligands also include ones that bind to allosteric sites or small chaperone molecules that provide stability through mostly undefined mechanisms. Although screening for small chaperone molecules that bind enzymes at sites away from their catalytic sites to stabilize structurally compromised mutants has been a major rationale for drug development, stabilizing molecule(s) such as the enzyme's own reaction product or pathway intermediates of the distal pathway steps may provide such stabilizing effect. Inhibitors of downstream pathway reactions may increase the presence of a defective enzyme's product or other pathway intermediates *in situ* to levels high enough to bind to the defective enzyme/protein. This is the basis for the concept that Mohsen introduced, which has the potential to be a breakthrough in drug discovery for genetic disorders. The validity of his concept, now named inhibitor-induced *in situ* chaperone therapy (I3CT), was tested by investigation of the effect in patient cells with missense mutations of three known drugs that are inhibitors of distal reactions in three different pathways: fatty acid β-oxidation, leucine metabolism, and PHE metabolism pathways.

Development of an I3CT for Fatty Acid β-Oxidation Cycle Enzyme Deficiencies. Mitochondrial fatty acid β-oxidation cycle is a spiral pathway that includes four enzymatic reaction steps. Inherited defects in the *ACADVL* or *HADHA/HADHB* genes coding for the VLCAD and TFP proteins, respectively, are the cause of some of the most serious life-threatening metabolic disorders. Although VLCAD deficiency is the most common among the defects, TFP deficiency shows more life-threatening symptoms. VLCAD deficiency results in a decrease in energy output from long-chain fatty acid β-oxidation, causing the heart, which draws ~ 80% of its energy requirement from long-chain fatty acids, to be at risk of cardiomyopathy. More than 65 of the mutations identified in patients with defects in the ACADVL gene are missense mutations, which are hypothesized to cause instabilities. TMZ is an inhibitor of long-chain ketoacylthiolase (LCKAT) recognized to slow long-chain fatty acid β-oxidation enough, shifting cardiac energy fulfillment from fatty acid oxidation to glucose oxidation, and it is used to treat angina pectoris induced by ischemia of the heart. Compared to conventional therapy, TMZ is reported to have shown significant improvements in non-ischemic and ischemic cardiomyopathy. Because it is an inhibitor of LKCAT, Mohsen examined the effect of TMZ on the presence of β-oxidation enzymes in patients with β-oxidation disorders. Experimental results supported the concept, showing a positive effect of TMZ FAOD cells. In addition, other TMZ analogs have been introduced and have a similar effect on slowing β-oxidation by inhibiting LCKAT. The advantages of the TMZ derivatives are in their added reactive oxygen species (ROS) scavenging activity, a needed feature, as experimental evidence suggests that increased ROS in VLCAD patients may contribute to the pathophysiology of the disease.

Development of Chemical Chaperone for MCAD Deficiency. Deficiency of MCAD rivals PKU as the most common biochemical genetic disorder. Patients with MCAD deficiency are asymptomatic at birth but are at risk for episodes of acute, life-threatening metabolic decompensation. They usually first occur between three and 24 months of age but can occur at any age in association with physiologic stress, such as fasting or infection. The mortality rate during an acute crisis in previously undiagnosed patients pushes 20%. Newborn screening via tandem mass spectrometry now

identifies MCAD deficiency pre-symptomatically, nearly eliminating mortality from the disease. However, treatment requires lifelong dietary monitoring, and significant morbidity still occurs due to hospitalizations for intravenous glucose therapy in the face of reduced oral intake. A single mutation in the *MCAD* gene (a G985A point mutation) has been identified in 90% of the alleles in the *MCAD* gene in deficient patients. The K304E destabilizes the quaternary structure of the enzyme, and the resultant mutant protein is rapidly degraded. *In vivo*, the mutant protein is catalytically active when stabilized, and restoration of only a few percent of normal MCAD activity will restore near-normal metabolic balance in patients. The objective of this current research is to establish the drugability of the MCAD K304E mutant by identifying lead compounds that can stabilize the mutant protein using *in vitro* and *in silico* approaches. Mohsen's current research has led to three different drug-development approaches.

1. Targeting the substrate binding site by using substrate analogs as stabilizing agents. An example that has seen success is the use of phenylbutyrate to stabilize the protein *in vivo* and provide thermal stability. Mohsen's studies led to a clinical trial led by Horizon Pharma to evaluate the effects of the drugs Buphenyl (sodium phenylbutyrate) and Ravicti (glycerol phenylbutyrate) on patients with MCAD K304E and their biochemical acylcarnitine profiles. Mohsen will continue with detailed characterization of Buphenyl's effects in other MCAD-deficient cell lines harboring other missense mutations and use a mouse model with the MCAD K304E mutation to better understand the pharmacokinetics.

2. Targeting remote pharmacophore sites to identify ligands that can bind to known sites on the MCAD tetramer and that have stabilizing pharmacophore characteristics. Using molecular modeling, Mohsen has identified the electron transfer flavoprotein docking site as a drug-development target for MCAD and other ACADs. A mutant 12-mer peptide designed to bind to the docking site increased thermal stability by 2–2.5°C. The proof-of-concept finding was critical in pursuing this site for drug design. Future experiments will focus on this peptide, and its structure will be used to scaffold fragment-based drug design and *in silico* screening.

3. Development of an I3CT to treat MCAD deficiency. Patients' fibroblasts with MCAD K304E mutation respond positively to TMZ treatment. The increase in enzyme activity and protein presence is hypothesized to be due to inhibition of the medium-chain 3-ketoacyl-CoA thiolase in a mechanism similar to the case of the long-chain acyl-CoA mentioned above.

4. Use of chaperone generating agents, namely triphenylbutyrylglycerol or trimetazidine in combination with PPARd agonist, which was shown to increase VLCAD mutant presence. Mohsen found that the combination of trimetazidine and a PPARd agonist tripled the effect of either alone.

Development of Chaperone for Leucine Metabolism Pathway Disorders. Using the I3CT concept, Mohsen identified a potential drug therapy for patients afflicted with Leucine metabolism pathway disorders. Treating patient cells with various Leucine metabolism pathway disorders with epigallocatechin gallate (EGCG), a naturally occurring compound found in green tea, is promising. The intent is to use EGCG, the enzyme that catalyzes the end-product step of the leucine catabolism pathway, to slow pathway intermediates' generation and accumulate ones that can bind back to enzymes and catalyze reactions in the pathway. Several diseases can be targeted with this treatment. Follow-up experiments will be carried out to prepare for clinical trials.

De-Risking the Use of Nitisinone (NTBC) for the Treatment of PKU. Using the same I3CT concept, Mohsen has used NTBC on PKU patients' cells. NTBC is an inhibitor of 4-hydroxyphenylpyruvate dioxygenase and is expected to cause an accumulation of 4-hydroxyphenylpyruvate and tyrosine and bind to tyrosine aminotransferase and PAH, respectively, and increase their stability in case of their deficiencies. Mohsen's studies on PKU patient cells provide a possible mechanistic explanation of the efficacy of NTBC in the PKU mice. The new patient cell data are expected to enable funded clinical trials and further de-risking experiments.

Elucidating the Function of New ACADs and Detailing the Roles of ACAD9 and VLCAD in Physiology.

1. Identification of roles for ACAD10 and mouse *Acad12* in physiology. *ACAD10* has been implicated in diabetes in humans. *Acad10* knockout mice experiments have confirmed a relationship. Although ACAD10 protein has an ACAD domain that is very similar to the ACAD family of flavoenzymes, it also has an extra-large domain that Mohsen hypothesizes is an electron transfer domain that likely binds NAD. Moreover, its active site according to the crystal structure of ACAD11 and modeling seem to contain basic residues, implying possibly more than just an α,β-dehydrogenation biochemical function, but perhaps another function comparable to glutaryl-CoA dehydrogenase, which has an additional decarboxylation function. Another exciting result from the investigations of ACAD10 in mice is the confirmation of the presence of another ACAD protein, ACAD12. This one is surprisingly very similar to a short peptide at the N-terminus, ~ 160 amino acids, plus the ACAD domain of ACAD10 to almost 97% homology. Mohsen is currently pursuing the identification of the function of this version of an ACAD.
2. Differentiation of roles for ACAD9 and VLCAD variant 3 in physiology. A mitochondrial β-oxidation spiral is mostly known to start with VLCAD for long-chain substrates. Whereas ACAD9 seems to utilize mostly unsaturated fatty acids and has been implicated to have a role as an assembly factor interacting with ECSIT, an apparent VLCAD variant, named variant 3, has never been studied for function and role in physiology; only its isoenzyme VLCAD short has been studied. The latter is more specific to very long (> 16 carbon chain length), saturated acyl-CoAs, respectively. Recombinant ACAD9 has activity toward saturated and unsaturated long-chain acyl-CoA substrates, but it is not upregulated in the case of VLCAD deficiency. Mohsen is studying this mechanism.

Characterization and Stability Studies of Isovaleryl-CoA Dehydrogenase (IVD) Naturally Occurring, Disease-Causing Missense Mutations. As many as six naturally occurring missense mutations found in IVA patients have been introduced into recombinant IVD cloned in a prokaryotic expression vector. Four were stable enough to produce, and two failed to produce protein in the cell-free extract. Three of the four had activity. Mohsen intends to characterize the mutants and their thermal stability, then assess them as potential targets for therapy.

Optimization of Anaplerotic Agents for Treating β-Oxidation Disorders. Triheptanoin (UX007) is a synthetic C7 fatty acid triglyceride that is being tested by Ultragenix to treat long-chain fatty acid oxidation disorders and glucose transporter 1 deficiency. Although clinical trials using UX007 have shown positive indicators and met some end points in clinical trials (unpublished), they have missed end points in phase II for the latter indication. Mohsen has proposed to compare the use of other branched chain organic acids to compare their efficacy in alleviating the biochemical phenotypes of many of the energy pathway deficiencies. Mohsen will continue to refine some of the anaplerotic agents and look for metabolic phenotype differences.

MAJOR LECTURESHIPS, SEMINARS, AND TEACHING

- "Mitochondrial Energy Metabolism and Reactive Oxygen Species Level Disruption in ACAD9-Deficient Fibroblasts," abstract, INFORM, Boston, Mass., 2016
- "Assessment of Mitochondrial Bioenergetics in Medium-Chain and Very-Long-Chain Fatty Acid Oxidation–Deficient Fibroblasts," abstract, INFORM, Boston, Mass., 2016
- "Mitochondrial Bioenergetics Disturbance and Increased Superoxide Production in Very-Long-Chain Acyl-CoA Dehydrogenase–Deficient Fibroblasts," abstract, annual

symposium of the Society for the Study of Inborn Errors of Metabolism, Rome, Italy, September 2016
- "Characterization of the Impairment of Mitochondrial Bioenergetics and Dynamics in Fibroblasts From Patients With Complex I Deficiency," abstract, annual symposium of the Society for the Study of Inborn Errors of Metabolism, Rome, Italy, September 2016
- "Newborn Screening for Time-Critical Metabolic Disorders: A New Paradigm to Test at Point of Care," oral presentation, Pediatric Academic Societies meeting, San Francisco, Calif., May 2017
- "Inhibitor-Induced *In Situ* Chaperone Therapy: A Novel Strategy for Treating MCAD and VLCAD Deficiencies," abstract, Flavins and Flavoproteins 19th International Symposium, Groningen, Netherlands, July 2017
- "Inhibiting Long-Chain 3-Ketoacyl-CoA Thiolase: A Novel Strategy for Treating Fatty Acid Oxidation Disorders," abstract, INFORM, Rio de Janeiro, Brazil, September 2017
- "Endoplasmic Reticulum-Mitochondria Crosstalk and Redox Homeostasis Disruption in Very-Long-Chain Acyl-CoA Dehydrogenase–Deficient Fibroblasts," abstract, INFORM, Rio de Janeiro, Brazil, September 2017
- "A Mitochondrial Targeted Antioxidant and a Cardiolipin Binding Peptide Decrease Superoxide Generation and Improve Mitochondrial Respiration in ACAD9-Deficient Fibroblasts," abstract, INFORM, Rio de Janeiro, Brazil, September 2017
- "A Novel Small-Molecule PPARδ Modulator for the Treatment of Fatty Acid Oxidation Disorders," abstract, INFORM, Rio de Janeiro, Brazil, September 2017
- "Elevated Superoxide Levels, Mitochondrial Dysfunction, and Endoplasmic Reticulum-Mitochondria Crosstalk Disruption in ETHE1- and Sulfite Oxidase-Deficient Fibroblasts," abstract, International Congress of Inborn Errors of Metabolism, Rio de Janeiro, Brazil, September 2017
- "Mitochondrial-Targeted Compounds Improve Mitochondrial Bioenergetics Disturbance in Very-Long-Chain Acyl-CoA Dehydrogenase-Deficient Fibroblasts," abstract, International Congress of Inborn Errors of Metabolism, Rio de Janeiro, Brazil, September 2017
- "The Biochemical Basis for Overlap of Clinical Features of LCHAD/TFP Deficiency with Mitochondrial Respiratory Chain Defects: Implications for New Therapeutic Approaches," abstract, International Congress of Inborn Errors of Metabolism, Rio de Janeiro, Brazil, September 2017
- "Developing a Tissue-Specific ACAD9-Deficient Mouse Model Using Cre-lox Recombination," abstract, International Congress of Inborn Errors of Metabolism, Rio de Janeiro, Brazil, September 2017
- "Reticular Dysgenesis and Mitochondriopathy Induced by Adenylate Kinase 2 Deficiency Identified in the Amish Population," abstract, International Congress of Inborn Errors of Metabolism, Rio de Janeiro, Brazil, September 2017
- "Inhibitor-Induced *In Situ* Chaperone Therapy: A Novel Drug Targeting Strategy for Treating Metabolic Disorders," abstract, International Congress of Inborn Errors of Metabolism, Rio de Janeiro, Brazil, September 2017
- "A Novel Drug Therapy Strategy for Treating Fatty Acid β-Oxidation Disorders," abstract, National Organization of Rare Disorders Summit, Washington D.C., October 2017

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- Society of Inborn Errors of Metabolism
- Society for the Study of Inborn Errors of Metabolism, European Union

Robert D. Nicholls, DPhil

Robert D. Nicholls is a professor of pediatrics and director of the Birth Defects Laboratories.

RESEARCH

A Pig Model of Prader-Willi Syndrome (PWS). The overarching goals of this work have been to establish a preclinical model for therapeutic testing and to determine the pathophysiological basis of PWS. PWS results from loss of function of a cluster of paternally expressed, imprinted genes and features neonatal failure to thrive, abnormal body composition, childhood-onset hyperphagia, and obesity. In contrast to mouse models, the team hypothesizes that pig models of PWS will display hyperphagia, obesity, and other clinical features of PWS. Using CRISPR/Cas9 genome editing in pig zygotes to generate mutations of the 2.05-kb imprinting control (PWS-IC) region, the team established the first pig models of PWS. Each non-rearranged allele has site-specific mutations ("scarring") at the gRNA target sites, indicating a 100% efficiency of genome editing *in vivo*. Manuscripts describing this work are in preparation. Next, the team will breed gene-edited pigs with PWS-IC mutations to generate cohorts of ~ 4 minipigs each for a PWS group and a control group. Affected animals have the mutation on the paternal allele, and unaffected carriers (mutation on the maternal allele) will allow natural breeding to maintain each stock (via maternal transmission) and continuous production of PWS piglets (via paternal transmission). The team will perform preliminary phenotype analyses for hypoglycemia; hormone deficiencies; body weight; height and length; hyperphagia; and obesity.

A Pig Model of PKU. Nicholls, in collaboration with UPMC pathologist Steven Dobrowolski, PhD, and Randall S. Prather, PhD, and colleagues at the University of Missouri, has generated the first PKU pig and a heterozygous carrier by CRISPR/Cas9 genome editing of the *Pah* gene. The PKU pig presents classic PKU with growth retardation and hypopigmentation; neurological features are currently under study. The *PAH* locus is heterozygous for a deleted allele and has an intact allele having mutations at each gRNA target site, whereas the PKU pig shows compound heterozygosity for deletions of exon 6 and of exons 6-7. The porcine model of PKU is expected to provide a suitable preclinical model for understanding PKU neuropathophysiology and for exploring new therapeutics.

Understanding Multiple Hormone Secretion Deficits in PWS. This project includes collaboration with Peter F. Drain, Department of Cell Biology at the University of Pittsburgh, for his expertise in mechanisms of secretory granule maturation and exocytosis, especially for insulin from β cells. PWS is a multisystem disorder with neonatal failure to thrive; childhood-onset hyperphagia; obesity; and deficits in growth hormone, gonadotropin-releasing hormone, oxytocin, insulin, and glucagon. In a PWS mouse model with failure to thrive, the team previously found severe pancreatic endocrine abnormalities, including early developmental defects and deficient basal and glucose-stimulated insulin secretion. To overcome genetic and physiological complexities in mouse models or humans, the team is using endocrine cell models that express PWS genes to determine the molecular and cellular mechanisms by which PWS genes control hormone secretion, focusing initially on insulin and glucagon (and on growth hormone in a collaboration with Leticia Guida's laboratory in Rio de Janeiro, Brazil). The team demonstrated a deficiency in insulin secretion specifically for the PWS cells, establishing an *in vitro* model. The work is now being written up for publication. Further work is ongoing to: (a) generate sublines with specific deletion of the top PWS candidate gene, (b) assess a small-molecule inhibitor of an enzyme considered to be a therapeutic target for PWS, and (c) generate PWS deletions in the αTC1-6::mCherry model of glucagon secretion.

Activation of Silenced Genes in PWS. The major goal is to develop CRISPR-dCas9 reactivation of imprinted genes from the silenced maternal chromosome for PWS genes. Using standard approaches for epigenetic editing, researchers can activate further the paternal PWS-IC allele encoding the bicistronic *SNURF-SNRPN* locus but not the maternal allele. Therefore, the team is currently assessing a novel approach using the DNA binding domain of a chromatin protein that binds only to the silent, maternal allele. In addition, a novel approach is being tested to increase the frequency of DNA repair by homologous recombination during CRISPR/Cas9 genome editing, because HR-based methods would improve the applications of genome editing for generation of novel cellular and animal models of disease as well as gene therapy approaches.

Transcriptional and miRNA Regulation in the Spastic Paraplegias (SPGs). The major goals of this project are to characterize the transcriptional and miRNA regulatory mechanisms for the 24 cloned SPG loci and to use the regulatory signatures to predict top candidate genes for the ~ 25 uncloned SPG loci. Following their identification of *NIPA1* mutations in SPG type 6 (SPG6), the researchers characterized transcriptional and miRNA regulation in the SPGs, beginning with work published on *SPAST*, the gene most frequently mutated in hereditary SPG, and continuing with identification of regulation of many additional SPG genes by a single miRNA operon (manuscript in preparation).

Molecular Basis for Overexpression of the BMI1 Oncogene in Cancer. The major goal of this project is to determine the molecular basis for overexpression of BMI1 in most cancer types that have been examined, based on epigenetic (DNA hypermethylation) or rare mutation of transcription factor binding sites in a novel "goldilocks enhancer" that normally acts to keep levels of BMI1 mRNA at moderate levels. Funding is being sought to move this exciting project forward.

Other Ongoing PWS-Related Research Projects. The Nicholls laboratory has characterized the PWS imprinted gene domain and the phenotypic characteristics of a brain-derived cell line in ferrets, representative of an epithelial-mesenchymal transition stage. They have also demonstrated efficient genome editing, as a prelude to attempting to generate ferret models of neurobehavioral disease as an alternative mammalian model with a complex, gyrencephalic brain (similar to humans and pigs but unlike rodents, which are lissencephalic). The group has characterized the cat PWS-imprinted domain as a potential mammalian model that is gyrencephalic and useful for reproductive technologies; next steps include collaboration with Leslie Lyons in Missouri to apply genome editing in this species to generate unique animal models. The latter two projects are aimed at ensuring the successful development of a clinically appropriate model of PWS for study of hyperphagia, obesity, and neurobehavioral features of this complex disorder in a species, with lower costs and space requirements for housing, care, and feeding than the current pig models of PWS.

Another ongoing project is assessing the role and translational mechanisms in expression of the SNURF-SmN operon in PWS, and, in collaboration with Vockley, the evolution and function of SNURF, putatively as a ubiquitin-like molecule. New collaborative studies include: (a) a project examining genetic susceptibility to schizophrenia, led by Vishwajit L. Nimgaonkar (Department of Psychiatry, University of Pittsburgh); and (b) collaboration on "A Postmortem Study of von Economo Neurons From Frontal Cortex of Brains of Persons With PWS" with Patrick R. Hof (Mt. Sinai, New York, N.Y.) and Jan Forster (Pittsburgh), funded by a research grant from the Foundation for Prader-Willi Research (FPWR).

STUDY SECTIONS

- Research grant review, FPWR

MAJOR LECTURESHIPS, SEMINARS, AND TEACHING

- "Research Into the Cause (and Cure) of Human Genetic Disease: The Roles of Genetically Modified Animal Models," middle school eighth-grade science, Winchester Thurston School, Pittsburgh, Pa., March 2017
- "Clinical Implications of Genome Editing," Summer Undergraduate Breakfast with Mentors Program, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., July 2017
- "Pancreatic β Cells with CRISPR/Cas9-Engineered 3.16 Mb Deletions Recapitulate the Insulin Secretory Deficits in Prader-Willi Syndrome," FPWR Scientific Day Conference, Indianapolis, Ind., August 2017
- "PWS Hormone-Secreting Cell Lines Generated by CRISPR/Cas9 Genome Editing," FPWR Workshop on Cell-Based Assays for PWS, Indianapolis, Ind., August 2017
- "Porcine Models of Neurobehavioral Genetic Disorders: PKU and PWS," sixth Swine in Biomedical Research Conference, Baltimore, Md., September 2017

ADVISORY COMMITTEE MEMBERSHIPS

- Member, Scientific Advisory Board, PWS Association (United States), includes scientific and medical statements on PWS and grant review, 1992 to the present

Damara Ortiz, MD

RESEARCH

Damara Ortiz is a co-investigator in several studies investigating the natural history of and potential therapeutics for several inborn errors of metabolism, including PKU, FAO defects, and urea cycle disorders. She is the primary investigator for several lysosomal storage disorders, including Fabry disease, Gaucher disease, and select mucopolysaccharidosis. She is a co-investigator for experimental therapies for Hunter disease and Fabry disease.

ADVISORY COMMITTEE MEMBERSHIPS

- Faculty member, Diversity and Inclusion Committee, Children's Hospital of Pittsburgh
- Regional advisor, LAL-D Regional Advisory Board, Alexion Pharmaceuticals

MAJOR LECTURESHIPS AND SEMINARS

- "Introduction to the Dysmorphology Exam," Department of Pediatrics, Division of Neonatology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., 2016
- "General Principles of Emergency Management of Genetic Disorders," Department of Pediatrics, Division of Emergency Medicine, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., 2016
- "Introduction to the Dysmorphology Exam," Department of Pediatrics Noon Conference, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., 2017
- "The Pennsylvania Newborn Screening Experience for Pompe Disease," abstract, WORLD Symposium of the Lysosomal Disease Network, San Diego, Calif., 2017
- "Newborn Screening for Pompe Disease: The Pennsylvania Experience," abstract, ACMG annual meeting, Charlotte, N.C., April 2017
- "A Novel Derivative Chromosome 5 in a Patient With Multiple Congenital Anomalies: Two-Step Mechanism for Segmental Duplication Mediated Chromosomal Rearrangement," abstract, ACMG annual meeting, Charlotte, N.C., April 2017

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- American Academy of Pediatrics
- American Society of Human Genetics
- ACMG

HONORS/AWARDS

- UPMC's Award for Commitment and Excellence in Services (ACES), 2017
- Assistant program director, Medical Genetics, 2016 to the present
- Director, Lysosomal Storage Disorders Program, 2015 to the present

Michele D. Poe, PhD

RESEARCH

Michele D. Poe is the lead statistician and research manager for the Program for the Study of NDRD. Her research interests include finite population statistics and the analysis of longitudinal neurodevelopmental data and neuroimaging. She has been the primary statistician for the NDRD since 2003.

ADVISORY COMMITTEE MEMBERSHIPS

- Early Diagnosis/HGT-HIT-090 MPS II Advisory Board, Shire
- Consensus Conference on Cognitive Endpoints in MPS, National MPS Society, MPS Society of the UK

MAJOR LECTURESHIPS, SEMINARS, AND TEACHING

- "Natural History of Metachromatic Leukodystrophy," WORLD Symposium of the Lysosomal Disease Network, San Diego, Calif., 2016
- "Natural History of Hurler Syndrome," WORLD Symposium of the Lysosomal Disease Network, San Diego, Calif., 2016
- "Psychosine as a Biomarker for Krabbe Disease," WORLD Symposium of the Lysosomal Disease Network, San Diego, Calif., 2016

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- International Society for Pharmacoepidemiology
- Newborn Screening Translational Research Network Workgroup

Yudong Wang, PhD

RESEARCH

Yudong Wang's research is focused on the functional and physical interactions among FAO, electron transfer chain, and tricarboxylic acid cycle. Mitochondria are the site of three of the most important energy-generating pathways in humans: OXPHOS, FAO, and the tricarboxylic acid cycle. The general perception is that the three energy metabolism systems are working independently. Wang's research explores the physical basis of these interactions, hypothesizing that the enzymes together form a functional complex within the mitochondrial matrix. Defining the functional linkages is important to the theoretical understanding of energy metabolism and has potential direct benefit for the clinical diagnosis and treatment of patients with genetic defects in these enzymes.

MAJOR LECTURESHIPS, SEMINARS, AND TEACHING

- "Elucidating the Architecture of Branched Chain Amino Acid Metabolism Enzymes," Seventh Annual Rangos Research Symposium, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., June 2017
- "Elucidating the Architecture of Branched Chain Amino Acid Metabolism Enzymes," Dean's Day, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pa., April 2017

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- Consular, Association of Chinese Scholars and Students of West Virginia University

Audrey Woerner, MD

RESEARCH

Audrey Woerner's primary research interests overlap her clinical efforts to develop telemedicine for medical genetics consultation. Prior to moving to Pittsburgh, she was funded through the Innovation Acceleration Program at Boston Children's Hospital for a pilot project to provide inpatient genetics consultations to Beverly Hospital and South Shore Hospital utilizing telemedicine. The project ultimately moved into clinical practice. Woerner has continued those efforts in Pittsburgh and is launching both an outpatient telemedicine clinic at the Erie Specialty Care center and an inpatient telegenetics consultation service for the UPMC Hamot neonatal ICU in Erie.

ADVISORY COMMITTEE MEMBERSHIPS

- New England Genetics Collaborative, Quality Improvement Workgroup, University System of New Hampshire, 2016

PROFESSIONAL AFFILIATIONS/SOCIETY MEMBERSHIPS

- ACMG
- American Telemedicine Association
- American Medical Association
- New England Regional Genetics Group

MAJOR LECTURESHIPS, SEMINARS, AND TEACHING

- "A Novel Derivative Chromosome 5 in a Patient With Multiple Congenital Anomalies: Two-Step Mechanism for Segmental Duplication Mediated Chromosomal Rearrangement," abstract, ACMG annual clinical genetics meeting, Phoenix, Ariz., March 2017

TEACHING ACTIVITIES

The division's physicians are actively involved in the training of fellows, medical residents, medical students, genetic counseling students, and nursing students at the University of Pittsburgh. Faculty members lecture in the School of Medicine, School of Nursing, and Graduate School of Public Health. In addition, faculty members give presentations for local support and community groups. They actively teach pediatric residents and medical students in one- to four-week genetics electives or rotations, usually for one month at a time, as well as on routine inpatient rounds. Approximately five to six medical students and residents per year take the genetics elective. Additionally, the division, with extensive involvement of genetic counselors, trains master's-level genetic counseling students. This commitment recently increased from eight to 10 students, each for a one-month rotation. Madan-Khetarpal coordinates the division's teaching activities. The division is one of a handful nationally that have a Medical Biochemical Genetics Fellowship Program.

The division actively participates in the Medical Genetics Residency Training Program recognized by the American Board of Medical Genetics. Ortiz is the program's codirector. Medical genetics residents (as many as four per year) rotate on the clinical genetics service for two months at a time and collaborate on clinical research projects, as time and interest allow. The division has been approved for an ACGME fellowship training program in medical biochemical genetics, with Lichter-Konecki as the program director. Vockley is the founder and director of a national training course given each year by the Society for Inherited Metabolic Disorders for all first-year genetics residents nationally.

Genetic counselors and physicians play an active role in the curriculum of the master's degree program in genetic counseling in the Graduate School of Public Health. This includes lecturing in didactic courses and serving as supervisors for counseling students' rotations through the division. In addition, division counselors provide educational content to a number of patient support groups, including the National Niemann-Pick Disease Foundation, the Fatty Oxidation Disorders Family Support Group, the Organic Acidemia Association, the United Mitochondrial Disease Foundation, and the Pennsylvania chapter of the PKU Family Support Group.

THREE-YEAR BIBLIOGRAPHY

2015

Mohsen AW, **Vockley J**. Kinetic and spectral properties of isovaleryl-CoA dehydrogenase and interaction with ligands. *Biochimie*. 2015;108:108-19.

Bodian DL, Klein E, Iyer RK, Wong WS, Kothiyal P, Stauffer D, Huddleston KC, Gaither AD, Remsburg I, Khromykh A, Baker RL, Maxwell GL, **Vockley J**, Niederhuber JE, Solomon BD. Utility of whole-genome sequencing for detection of newborn screening disorders in a population cohort of 1,696 neonates. *Genet Med.* 2015.

Longo N, **Arnold GL**, Pridjian G, Enns GM, Ficicioglu C, Parker S, Cohen-Pfeffer JL; Phenylketonuria Demographics, Outcomes, and Safety Registry. Long-term safety and efficacy of sapropterin: The PKUDOS registry experience. *Mol Genet Metab*. 2015 Apr;114(4):557-63.

Schiff M, Haberberger B, Xia C, **Mohsen AW**, **Goetzman ES**, **Wang Y**, Uppala R, Zhang Y, Karunanidhi A, Prabhu D, Alharbi H, Prochownik EV, Haack T, Häberle J, Munnich A, Rötig A, Taylor RW, **Nicholls RD**, Kim J-J, Prokisch H, **Vockley J**. Complex I assembly function and fatty acid oxidation enzyme activity of ACAD9 both contribute to disease severity in ACAD9 deficiency. *Hum Mol Genet*. 2015;24:3238-47.

Chauhan BK, Hoover JM, Scanga H, Medsinge A, **Arnold GL**, Nischal KK. Isolated sagittal synostosis in a boy with craniofrontonasal dysplasia and a novel EFNB1 mutation. *Plast Reconstr Surg Glob Open*. 2015 Jul 8;3(6):e427.

Beck M, Peterson JF, McConnell J, McGuire M, Asato M, Losee JE, Surti U, **Madan-Khetarpal S**, Rajkovic A, Yatsenko SA. Craniofacial abnormalities and developmental delay in two families with overlapping 22q12.1 microdeletions involving the MN1 gene. *Am J Med Genet, 2014.* 2015 May;167A(5):1047-53.

Dobrowolski SF, Lyons-Weiler J, Spridik K, Biery A, **Breck J**, **Vockley J**, Yatsenko S, Sultana T. Altered DNA methylation in PAH deficient phenylketonuria. *Mol Genet Metab*. 2015 Jun-Jul;115(2-3):72-7.

Edmunds LR, Sharma L, Kang A, Lu J, **Vockley J**, Basu S, Uppala R, **Goetzman ES**, Beck ME, Scott D, Prochownik EV. c-Myc programs fatty acid metabolism and dictates acetyl-CoA abundance and fate. *J Biol Chem.* 2015;290:20100.

Haack TB, Staufner C, Kopke MG, Straub BK, Kolker S, Thiel C, Freisinger P, Baric I, McKiernan PJ, Dikow N, Harting I, Beisse F, Burgard P, Kotzaeridou U, Kuhr J, Himbert U, Taylor RW, Distelmaier F, **Vockley J**, **Ghaloul-Gonzalez L**, Zschocke J, Kremer LS, Graf E, Schwarzmayr T, Bader DM, Gagneur J, Wieland T, Terrile C, Strom TM, Meitinger T, Hoffmann GF, Prokisch H. Biallelic mutations in NBAS cause recurrent acute liver failure with onset in infancy. *Am J Hum Genet.* 2015;97:163-9.

Lee B, Diaz GA, Rhead W, **Lichter-Konecki U**, Feigenbaum A, Berry SA, Le Mons C, Bartley JA, Longo N, Nagamani SC, Berquist W, Gallagher R, Bartholomew D, Harding CO, Korson MS, McCandless SE, Smith W, Cederbaum S, Wong D, Merritt JL, 2nd, Schulze A, **Vockley J**, Kronn D, Zori R, Summar

M, Milikien DA, Marino M, Coakley DF, Mokhtarani M, Scharschmidt BF. Blood ammonia and glutamine as predictors of hyperammonemic crises in patients with urea cycle disorder. *Genet Med.* 2015;17:561-8.

Nagamani SC, Diaz GA, Rhead W, Berry SA, Le Mons C, **Lichter-Konecki U**, Bartley J, Feigenbaum A, Schulze A, Longo N, Berquist W, Gallagher R, Bartholomew D, Harding CO, Korson MS, McCandless SE, Smith W, **Vockley J**, Kronn D, Zori R, Cederbaum S, Lawrence Merritt J II, Wong D, Coakley DF, Scharschmidt BF, Dickinson K, Marino

M, Lee BH, Mokhtarani M. Self-reported treatment-associated symptoms among patients with urea cycle disorders participating in glycerol phenylbutyrate clinical trials. *Mol Genet Metab.* 2015;116:29-34.

Nahabet EH, Gatherwright J, **Vockley J**, Henderson N, Tomei KL, Grigorian AP, Kaminski B, Bass N, Selman WR, Lakin GE. Postnatal pancraniosynostosis in a patient with infantile hypophosphatasia. *Cleft Palate Craniofac J.* 2015.

Prabhu D, Goldstein AC, El-Khoury R, Rak M, Edmunds L, Rustin P, **Vockley J**, Schiff M. ANT2-defective fibroblasts exhibit normal mitochondrial bioenergetics. *Mol Genet Metab Rep.* 2015;3:43-6.

Vockley J, Marsden D, McCracken E, DeWard S, Barone A, Hsu K, Kakkis E. Long-term major clinical outcomes in patients with long chain fatty acid oxidation disorders before and after transition to triheptanoin treatment–A retrospective chart review. *Mol Genet Metab.* 2015;116:53-60.

Zhang Y, Bharathi SS, Rardin MJ, Uppala R, Verdin E, Gibson BW, **Goetzman ES**. SIRT3 and SIRT5 regulate the enzyme activity and cardiolipin binding of very long-chain acyl-CoA dehydrogenase. *PLoS One.* 2015;10(3):e0122297.

Uppala R, McKinney RW, Brant KA, Fabisiak JP, **Goetzman ES**. Nickel inhibits mitochondrial fatty acid oxidation. *Biochem Biophys Res Commun.* 2015; 463(4):806-10.

Otsubo C, Bharathi S, Uppala R, Ilkayeva OR, Wang D, McHugh K, Zou Y, Wang J, Alcorn JF, Zuo YY, Hirschey MD, **Goetzman ES**. Long-chain acylcarnitines reduce lung function by inhibiting pulmonary surfactant. *J Biol Chem.* 2015;290(39):23897-904.

Goetzman ES. The regulation of liver metabolism by sirtuins: Emerging roles. In: Han D, Kaplowitz N (Eds.), *Mitochondria and Liver Disease*. CRC Press; 2015.

Strauss KA, Ferreira C, Bottiglieri T, Zhao X, Arning E, Zhang S, Zeisel SH, **Escolar ML,** et al. Liver transplantation for treatment of severe S-adenosylhomocysteine hydrolase deficiency. *Mol Genet Metab.* 2015;116(1-2):44-52.

Zuccoli G, Narayanan S, Panigrahy A, **Poe MD**, **Escolar ML**. Midbrain morphology reflects extent of brain damage in Krabbe disease. *Neuroradiology.* 2015;57(7):739-45. PMID: 25859833.

Turgeon CT, Orsini JJ, Sanders KA, Magera MJ, Langan TJ, **Escolar ML**, Duffner P, Oglesbee D, Gavrilov D, Tortorelli S, Rinaldo P, Raymond K, Matern D. Measurement of psychosine in dried blood spots-–A possible improvement to newborn screening programs for Krabbe disease. *J Inherit Metab Dis.* 2015;38(5):923-9.

Helman G, Van Haren K, **Escolar ML**, Vanderver A. Emerging treatments for pediatric leukodystrophies. *Pediatric clinics of North America.* 2015;62(3):649-66.

Helman G, Van Haren K, Bonkowsky JL, Bernard G, Pizzino A, Braverman N, Suhr D, Patterson MC, Ali Fatemi S, Leonard J, van der Knaap MS, Back SA, Damiani S, Goldman SA, Takanohashi A, Petryniak M, Rowitch D, Messing A, Wrabetz L, Schiffmann R, Eichler F, **Escolar ML**, Vanderver A; GLIA Consortium. Disease-specific therapies in leukodystrophies and leukoencephalopathies. *Mol Genet Metab.* 2015;114(4):527-36.

Coletti HY, Aldenhoven M, Yelin K, **Poe MD**, Kurtzberg J, **Escolar ML**. Long-term functional outcomes of children with Hurler syndrome treated with unrelated umbilical cord blood transplantation. *JIMD Rep.* 2015;20:77-86.

Helman G, Van Haren K, **Escolar ML,** Vanderver A. Emerging treatments for pediatric leukodystrophies. *Pediatr Clin North Am*. 2015;62(3):649-66.

Gupta A, **Poe MD**, Styner MA, Panigrahy A, **Escolar ML**. Regional differences in fiber tractography predict neurodevelopmental outcomes in neonates with infantile Krabbe disease. *Neuroimage Clin.* 2015; 7:792-8.

El-Gharbawy A, Koeberl D. Glycolysis: Inborn errors of metabolism: From neonatal screening to metabolic pathways. In: Lee B and Scaglia F (Eds.), *Oxford Monographs Medical Genetics*, 2015.

Arnold GL, **Vockley J**. Amino acids and related disorders. In: (), *Genetic Disorders and the Fetus* (7th ed.). Wiley-Blackwell; 2015.

Wooderchak-Donahue W, VanSant-Webb C, Tvrdik T, Plant P, Lewis T, Stocks J, Raney JA, Meyers L, Berg A, Rope AF, Yetman AT, Bleyl SB, Mesley R, Bull DA, Collins RT, Ojeda MM, Roberts A, Lacro R, **Woerner A**, et al. Clinical utility of a next generation sequencing panel assay for Marfan and Marfan-like syndromes featuring aortopathy. *Am J Med Genet.* Part A 9999A:1-11.

Smpokou P, Samanta M, Berry GT, Hecht L, Engle EC, **Lichter-Konecki U**. Menkes disease in affected females: The clinical disease spectrum. *Am J Med Genet.* ; Part A 167A:417-20.

De Castro M, Zand DJ, **Lichter-Konecki U**, Kirmse B. Severe neonatal holocarboxylase synthetase deficiency in West African siblings. *JIMD Rep.* 2015;20:1-4.

Burrage LC, Sun Q, Elsea SH, Jiang MM, Nagamani SC, Frankel AE, Stone E, Alters SE, Johnson DE, Rowlinson SW, Georgiou G; **Urea Cycle Disorders Consortium**, Lee BH. Human recombinant arginase enzyme reduces plasma arginine in mouse models of arginase deficiency. *Hum Mol Genet*. ;15;24:6417-27.

Brown CS, **Lichter-Konecki U**. Phenylketonuria (PKU): A problem solved? *Mol Genet Metab Rep*. ;6:8-12.

Lichter-Konecki U. Neurotransmission and neurotoxicity (phenylketonuria and dopamine) In: Lee B, Scaglia F (Eds.): *Inborn Errors of Metabolism from Neonatal Screening to Metabolic Pathways* (1st ed.). 2015.

Hu J, Sathanoori M, Kochmar S, Azage M, Mann S, **Madan-Khetarpal S**, Goldstein A, Surti U. A novel maternally inherited 8q24.3 and a rare paternally inherited 14q23.3 CNVs in a family with neurodevelopmental disorders. *Am J Med Genet A.* 2015;167A(8):1921-6.

Su CT, Huang JW, Chiang CK, Lawrence EC, Levine KL, Dabovic B, Jung C, Davis EC, **Madan-Khetarpal S**, Urban Z. Latent transforming growth factor binding protein 4 regulates transforming growth factor beta receptor stability. *Hum Mol Genet.* 2015;24(14):4024-36.

2016

Celik N, Squires RH, **Vockley J**, Sindhi R, Mazariegos G. Liver transplantation for maple syrup urine disease: A global domino effect. *Pediatr Transplant.* 2016;20:350-1.

Dobrowolski SF, Lyons-Weiler J, Spridik K, **Vockley J**, Skvorak K, Biery A. DNA methylation in the pathophysiology of hyperphenylalaninemia in the PAH mouse model of phenylketonuria. *Mol Genet Metab.* 2016;119:1-7.

El-Gharbawy A, **Vockley J**. Chapter 14: Non-mitochondrial metabolic diseases. In: Jefferies J, Blaxall B, Towbin J, Robbins J, eds., *Cardioskeletal Myopathies in Children and Young Adults* (1st ed.). Academic Press; 2016.

Forsyth R, Vockley CW, Edick MJ, Cameron CA, Hiner SJ, Berry SA, **Vockley J**, **Arnold GL**, Inborn Errors of Metabolism Collaborative. Outcomes of cases with 3-methylcrotonyl-CoA carboxylase (3-MCC) deficiency—Report from the Inborn Errors of Metabolism Information System. *Mol Genet Metab.* 2016;118:15-20.

Ghaloul-Gonzalez L, Goldstein A, Walsh Vockley C, Dobrowolski SF, Biery A, Irani A, Ibarra J, Morton DH, **Mohsen AW**, **Vockley J**. Mitochondrial respiratory chain disorders in the Old Order Amish population. *Mol Genet Metab.* 2016;118:296-303.

Guarani V, Jardel C, Chrétien D, Lombès A, Bénit P, Labasse C, Lacène E, Bourillon A, Imbard A, Benoist JF, Dorboz I, Gilleron M, **Goetzman ES**, Gaignard P, Slama A, Elmaleh-Bergès M, Romero NB, Rustin P, Ogier de Baulny H, Paulo JA, Harper JW, Schiff M. QIL1 mutation causes MICOS disassembly and early onset fatal mitochondrial encephalopathy with liver disease. *Elife*. 2016 Sep 13;5.

Lee B, Diaz GA, Rhead W, **Lichter-Konecki U**, Feigenbaum A, Berry SA, Le Mons C, Bartley J, Longo N, Nagamani SC, Berquist W, Gallagher RC, Harding CO, McCandless SE, Smith W, Schulze A, Marino M, Rowell R, Coakley DF, Mokhtarani M, Scharschmidt BF.

Glutamine and hyperammonemic crises in patients with urea cycle disorders. *Mol Genet Metab*. 2016;117(1):27-32.

McCoin CS, Piccolo BD, Knotts TA, Matern D, **Vockley J**, Gillingham MB, Adams SH. Unique plasma metabolomic signatures of individuals with inherited disorders of long-chain fatty acid oxidation. *J Inherit Metab Dis.* 2016;39:399-408.

Pena LD, van Calcar SC, Hansen J, Edick MJ, Walsh Vockley C, Leslie N, Cameron C, **Mohsen AW**, Berry SA, **Arnold GL**, **Vockley J**. Outcomes and genotype-phenotype correlations in 52 individuals with VLCAD deficiency diagnosed by NBS and enrolled in the IBEM-IS database. *Mol Genet Metab.* 2016;118:272-81.

Rivera-Vega MY, Schneck FX, **Madan-Khetarpal S**, Reyes-Mugica M, Witchel SF. Infant with WT1 mutation, ambiguous genitalia, and congenital diaphragmatic hernia. *Genetics Disorders and Dysmorphic Conditions*. In press.

Shneider BL, Morris A, **Vockley J**. Possible phenylacetate hepatotoxicity during 4-phenylbutyrate therapy of Byler disease. *J Pediatr Gastroenterol Nutr.* 2016;62:424-8.

Sonnet SD, O'Leary NM, Gutierrez AM, Nguyen MS, Mateen S, Hsu Y, Mitchell PK, Lopez JA, **Vockley J**, Kennedy K, Ramanathan A. Metformin inhibits branched chain amino acid (BCAA) derived ketoacidosis and promotes metabolic homeostasis in MSUD. *Scientific Reports.* 2016;6:28775.

Staufner C, Haack TB, Kopke MG, Straub BK, Kolker S, Thiel C, Freisinger P, Baric I, McKiernan PJ, Dikow N, Harting I, Beisse F, Burgard P, Kotzaeridou U, Lenz D, Kuhr J, Himbert U, Taylor RW, Distelmaier F, **Vockley J**, **Ghaloul-Gonzalez L**, Ozolek JA, Zschocke J, Kuster A, Dick A, Das AM, Wieland T, Terrile C, Strom TM, Meitinger T, Prokisch H, Hoffmann GF. Recurrent acute liver failure due to NBAS deficiency: Phenotypic spectrum, disease mechanisms, and therapeutic concepts. *J Inherit Metab Dis.* 2016;39:3-16.

Tokita MJ, Braxton AA, Shao Y, Lewis AM, Vincent M, Kury S, Besnard T, Isidor B, Latypova X, Bezieau S, Liu P, Motter CS, Melver CW, Robin NH, Infante EM, McGuire M, **El-Gharbawy A**, Littlejohn RO, McLean SD, Bi W, Bacino CA, Lalani SR, Scott DA, Eng CM, Yang Y, Schaaf CP, Walkiewicz MA. *De novo* truncating variants in SON cause intellectual disability, congenital malformations, and failure to thrive. *Am J Hum Genet.* 2016;99:720-7.

Vicini P, Fields O, Lai E, Litwack ED, Martin AM, Morgan TM, Pacanowski MA, Papaluca M, Perez OD, Ringel MS, Robson M, Sakul H, **Vockley J**, Zaks T, Dolsten M, Sogaard M. Precision medicine in the age of big data: The present and future role of large-scale unbiased sequencing in drug discovery and development. *Clin Pharmacol Ther.* 2016;99:198-207.

Vockley J, Bennett MJ, Gillingham MB. Mitochondrial fatty acid oxidation disorders. In: Beaudet AL, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A, Gibson KM, Mitchell G, eds., *The Online Metabolic and Molecular Bases of Inherited Disease.* McGraw-Hill; 2016.

Vockley J, Charrow J, Ganesh J, Eswara M, Diaz GA, McCracken E, Conway R, Enns GM, Starr J, Wang R, Abdenur JE, Sanchez-de-Toledo J, Marsden DL. Triheptanoin treatment in patients with pediatric cardiomyopathy associated with long chain-fatty acid oxidation disorders. *Mol Genet Metab.* 2016 Nov;119(3):223-231.

Vockley J, Longo N, Andresen BS, Bennett MJ. Mitochondrial fatty acid oxidation defects. In: Sarafoglou K, Hoffman GF, Roth K, eds. *Pediatric Endocrinology and Inborn Errors of Metabolism*. McGraw-Hill; 2016.

Wang H, Lu J, Edmunds LR, Kulkarni S, Dolezal J, Tao J, Ranganathan S, Jackson L, Fromherz M, Stolz DB, Uppala R, Bharathi S, Monga SP, **Goetzman ES**, Prochownik EV. Coordinated activities of multiple myc-dependent and myc-in-dependent biosynthetic pathways in hepatoblastoma. *J Biol Chem.* 2016;291(51):26241-26251.

Wang Y, **Lichter-Konecki U**, Anyane-Yeboa K, Shaw JE, Lu JT, Östlund C, Shin JY, Clark LN, Gundersen GG, Nagy PL, Worman HJ. A mutation abolishing the ZMPSTE24 cleavage site in prelamin A causes a progeroid disorder. *J Cell Sci*. 2016;129(10):1975-80.

Edmunds LR, Otero PA, Sharma L, D'Souza S, Dolezal JM, David S, Lu J, Lamm L, Basantani M, Zhang P, Sipula IJ, Li L, Zeng X, Ding Y, Ding F, Beck ME, **Vockley J**, Monga SP, Kershaw EE, O'Doherty RM, Kratz LE, Yates NA, **Goetzman ES**, et al. Abnormal lipid processing but normal long-term repopulation potential of myc-/- hepatocytes. *Oncotarget.* 2016;7(21):30379-95.

Wasserstein MP, Andriola M, **Arnold GL**, Aron A, Duffner P, Erbe RW, **Escolar ML**, et al. Clinical outcomes of children with abnormal newborn screening results for Krabbe disease in New York State. *Genet Med.* 2016;18(12):1235-43.

Hwang M, Zuccoli G, Panigrahy A, Rodriguez D, **Poe MD, Escolar ML**. Thickening of the cauda equina roots: A common finding in Krabbe disease. *Eur Radiol.* 2016;26(10):3377-82.

Orsini JJ, Kay DM, Saavedra-Matiz CA, Wenger DA, Duffner PK, Erbe RW, Biski C, Martin M, Krein LM, Nichols M, Kurtzberg J, **Escolar ML**, Adams DJ, **Arnold GL**, et al.; New York State Krabbe Disease Consortium. Newborn screening for Krabbe disease in New York State: The first eight years' experience. *Genet Med.* 2016;18(3):239-48.

Escolar ML, West T, Dallavecchia A, **Poe MD**, LaPoint K. Clinical management of Krabbe disease. *J Neurosci Res.* 2016;94(11):1118-25.Bongarzone ER, **Escolar ML**, Gray SJ, Kafri T, Vite CH, Sands MS. Insights into the pathogenesis and treatment of Krabbe disease. *Pediatr Endocrinol Rev.* 2016;13 Suppl 1:689-96.

Bentler K, Zhai S, Elsbecker SA, **Arnold GL**, Burton BK, **Vockley J**, Cameron CA, Hiner SJ, Edick MJ, Berry SA; Inborn Errors of Metabolism Collective. 221 newborn-screened neonates with medium-chain acyl-coenzyme A dehydrogenase deficiency: Findings from the Inborn Errors of Metabolism Collaborative. *Mol Genet Metab.* 2016;119(1-2):75-82.

Lemke JR, Geider K, Helbig KL, Heyne HO, Schutz H, Hentschel J, Courage C, Depienne C, Nava C Heron D, Moller RS, Hjalgrim H, Lal D, Newbauer BA, Nurnberg P, Thiele H, Hurlemann G, **Arnold GL**, et al. Delineating the GRIN1 phenotypic spectrum: A distinct genetic NMDA receptor encephalopathy. *Neurology.* 2016;86:2171-8.

Madan SK, Arnold GL: Genetic Disorders and Dysmorphic Conditions. *Zitelli and Davis' Atlas of Pediatric Physical Diagnosis*, Zitelli BJ, McIntire SC, Nowalk AJ, eds. Seventh edition, Elsevier Saunders, Philadelphia, PA, 2016

Nagamani SC, **Lichter-Konecki U**. Inborn Errors of Urea Synthesis. In: Swaiman K, Ashwal S, Ferriero D (eds): *Pediatric Neurology: Principles and Practice*, 6th edit.; 2016.

Lichter-Konecki U, Caldovic L, Morizono H, Simpson K (2016). Ornithine Transcarbamylase Deficiency. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mefford HC, Stephens K, Amemiya A, Ledbetter N, editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; updated 2016 Apr 14.

Lichter-Konecki U. Defects of the Urea Cycle. In: Farrell P (ed) *Metabolic Diseases Foundations of Clinical Management*. IOS Press BV Amsterdam; 2016.

Wang, W., Palmfeldt, J., **Mohsen, AW**, Gregersen, N., **Vockley J**.* Fasting induces prominent proteomic changes in liver in very long chain acyl-CoA dehydrogenase deficient mice. *Biochem. Biophys. Reports* 2016; 8:333-39.

Camp KM, Krotoski D, Parisi MA, Gwinn KA, Cohen BH, Cox CS, Enns GM, Falk MJ, Goldstein AC, Gopal-Srivastava R, Gorman GS, Hersh SP, Hirano M, Hoffman FA, Karaa A, MacLeod EL, McFarland R, Mohan C, Mulberg AE, Odenkirchen JC, Parikh S, Rutherford PJ, Suggs-Anderson SK, Tang WH, **Vockley J**, Wolfe LA, Yannicelli S, Yeske PE, Coates PM. Nutritional interventions in primary mitochondrial disorders: Developing an evidence base. *Mol Genet Metab.* 2016; 119: 187-206.

Vicini P, Fields O, Lai E, Litwack ED, Martin AM, Morgan TM, Pacanowski MA, Papaluca M, Perez OD, Ringel MS, Robson M, Sakul H, **Vockley J**, Zaks T, Dolsten M, Sogaard M. Precision medicine in the age of big data: The present and future role of large-scale unbiased sequencing in drug discovery and development. *Clin Pharmacol Ther.* 2016; 99: 198-207.

Vockley J, Gillingham MB, Matern D. Mitochondrial Fatty Acid Oxidation Disorders. *The Online Metabolic and Molecular Basis of Inherited Disease*, (Valle D, ed.). McGraw Hill, NY. 2016

Vockley J. Inborn Error of Metabolism. *Rudolph's Pediatrics*, 23rd edition. Senior Editor Andrew Moyer. In press, 2016.

2017

Pop A, Williams M, Struys EA, Monné M, Jansen EEW, De Grassi A, Kanhai WA, Scarcia P, Ojeda MRF, Porcelli V, van Dooren SJM, Lennertz P, Nota B, Abdenur JE, Coman D, Das AM, **El-Gharbawy A**, et al. An overview of combined D-2- and L-2-hydroxyglutaric aciduria: Functional analysis of CIC variants. *J Inherit Metab Dis*. 2017. doi: 10.1007/s10545-017-0106-7.

Goyal RK, Ibrahimova A, **Escolar ML**, Szabolcs P, Lugt MV, Windreich RM, Weiner DJ. Forced deflation pulmonary function test: A novel method to evaluate lung function in infants and young children. *Pediatr Blood Cancer*. 2017;64(4).

Pan LA, Martin P, Zimmer T, Segreti AM, Kassiff S, McKain BW, Baca CA, Rengasamy M, Hyland K, Walano N, Steinfeld R, Hughes M, Dobrowolski SK, Pasquino M, Diler R, Perel J, Finegold DN, Peters DG, Naviaux RK, Brent DA, **Vockley J**. Neurometabolic disorders: Potentially treatable abnormalities in patients with treatment-refractory depression and suicidal behavior. *Am J Psychiatry*. 2017;174(1):42-50.

Uppala R, Dudiak B, Beck ME, Bharathi SS, Zhang Y, Stolz DB, **Goetzman ES**. Aspirin increases mitochondrial fatty acid oxidation. *Biochem Biophys Res Commun.* 2017; 482(2):346-51.

Zhang Y, Bharathi SS, Rardin MJ, Lu J, Maringer KV, Sims-Lucas S, Prochownik EV, Gibson BW, **Goetzman ES**. Lysine desuccinylase SIRT5 binds to cardiolipin and regulates the electron transport chain. *J Biol Chem.* 2017; 292(24):10239-49.

Jackson LE, Kulkarni S, Wang H, Lu J, Dolezal JM, Bharathi SS, Ranganathan S, Patel MS, Deshpande R, Alencastro F, Wendell SG, **Goetzman ES**, et al. Genetic dissociation of glycolysis and the TCA cycle affects neither normal nor neoplastic proliferation. *Cancer Res.* 2017;77(21):5795-807.

Goetzman ES. Advances in the understanding and treatment of mitochondrial fatty acid oxidation disorders. *Curr Genet Med Rep.* 2017;5(3):132-42.

Shapiro E, Jones S, **Escolar ML**. Developmental and behavioral aspects of mucopolysaccharidoses with brain manifestations: Neurological signs and symptoms. *Molecular Genetics and Metabolism.* 2017;122S:1-7.

Wright MD, **Poe MD**, DeRenzo A, Haldal S, **Escolar ML.** Developmental outcomes of cord blood transplantation for Krabbe disease: A 15-year study. *Neurology.* 2017;10:212.

Escolar ML, Jones S, Shapiro E, Muenzer J, Horovitz D, Lampe C, Amartino H. Practical management of behavioral problems in mucopolysaccharidoses disorders. *Mol Genet Metab*. 2017;122S:35-40.

Muenzer J, Scarpa M, Orchard P, Schulz A, Dicksone P, Haskins M, **Escolar ML**, Giugliani R. Treatment of brain disease in the mucopolysaccharidoses. *Mol Genet Metab.* 2017;122S:25-34.

Adang L, Sherbini O, Ball L, Bloom M, Darbari A, Amartino H, DiVito D, Eichler F, **Escolar ML**, … Vanderver A. Revised consensus statement on the preventive and symptomatic care of patients with leukodystrophies. *Mol Genet Metab.* 2017;122(1-2):18-32.

Escolar ML, Delaney K, Mitchell J. Assessments of neurocognitive and behavioral function in the mucopolysaccharidoses. *Molecular Genetics and Metabolism.* 2017. 121(5 suppl).

van der Lee JH, Morton J, Adams HR, Clarke L, Ebbink BJ, **Escolar ML**, et al. Cognitive endpoints for therapy development for neuronopathic mucopolysaccharidoses: Results of a consensus procedure. *Mol Genet Metab.* 2017;121(2):70-9.

Liao HC, Spacil Z, Ghomashchi F, **Escolar ML**, Kurtzberg J, Orsini JJ, et al. Lymphocyte galactocerebrosidase activity by LC-MS/MS for post–newborn screening evaluation of Krabbe disease. *Clin Chem.* 2017;63(8):1363-9.

Escolar ML, Kiely BT, Shawgo E, Hong X, Gelb MH, Orsini JJ, Matern D, **Poe MD**. Psychosine, a marker of Krabbe phenotype and treatment effect. *Molecular Genetics and Metabolism.* 2017;121(3): 271-8.

Kiely BT, Kohler JL, Coletti HY, **Poe MD**, **Escolar ML**. Early disease progression of Hurler syndrome. *Orphanet J Rare Dis.* 2017;12(1):32.

Bloom K, **Mohsen AW**, Karunanidhi A, El Demellawy D, Reyes-Múgica M, **Wang Y**, **Ghaloul-Gonzalez L**, Otsubo C, Tobita K, Muzumdar R, Gong Z, Tas E, Basu S, Chen J, Bennett M, Hoppel C, **Vockley J**. Investigating the link of ACAD10 deficiency to type 2 diabetes mellitus. *J Inherit Metab Dis.* 2017. doi: 10.1007/s10545-017-0013-y.

Ortiz D, **Lichter-Konecki U**. New in newborn screening. *Curr Genet Med Rep.* 2017;5:143-8.

Joyce E, Ho J, **El-Gharbawy A**, Salgado CM, Ranganathan S, Reyes-Múgica M. The value of renal biopsy in diagnosing infantile nephropathic cystinosis associated with secondary nephrogenic diabetes insipidus. *Pediatr Dev Pathol.* 2017;20(1):72-5.

Liang J, Alfano DN, Squires JE, Riley MM, Parks WT, Kofler J, **El-Gharbawy A, Madan-Kheterpal S**, Acquaro R, Picarsic J. Novel NLRC4 mutation causes a syndrome of perinatal autoinflammation with hemophagocytic lymphohistiocytosis, hepatosplenomegaly, fetal thrombotic vasculopathy, and congenital anemia and ascites. *Pediatr Dev Pathol.* 2017;20(6):498-505.

Infante E, Alkorta-Aranburu G, **El-Gharbawy A**. Rare form of autosomal dominant familial Cornelia de Lange syndrome due to a novel duplication in SMC3. *Clinical Case Reports*, 2017;5(8):1277-83.

Gillingham MB, Heitner SB, Martin J, Rose S, Goldstein A, **El-Gharbawy AH**, Deward S, Lasarev MR, Pollaro J, DeLany JP, Burchill LJ, Goodpaster B, Shoemaker J, Matern D, Harding CO, **Vockley J**. Triheptanoin versus trioctanoin for long-chain fatty acid oxidation disorders: A double blinded, randomized controlled trial. *J Inherit Metab Dis.* 2017;40(6):831-43.

El-Gharbawy A, **Vockley J**. Inborn errors of metabolism with myopathy: Defects of fatty acid oxidation and the carnitine shuttle system. In: *Pediatric Clinics of North America: Inborn Errors of Metabolism*. 2017. doi: 10.1016/j.pcl.2017.11.006.

El-Gharbawy A, Goldstein A. Mitochondrial fatty acid oxidation disorders associated with cardiac disease. *Curr Pathobiol Rep.* 2017;5(3):259-70.

Wang X, Charng WL, Chen CA, Rosenfeld JA, Al Shamsi A, Al-Gazali L, McGuire M, Mew NA, **Arnold GL**, et al. Germline mutations in ABL1 cause an autosomal dominant syndrome characterized by congenital heart defects and skeletal malformations. *Nat Genet.* 2017;49(4):613-7.

Berry SA, Longo N, Diaz GA, McCandless SE, Smith WE, Harding CO, Zori R, Ficicioglu C, **Lichter-Konecki U**, Robinson B, **Vockley J**. Safety and efficacy of glycerol phenylbutyrate for management of urea cycle disorders in patients aged 2 months to 2 years. *Mol Genet Metab.* 2017. pii: S1096-7192(17)30491-2.

Sklirou E, **Lichter-Konecki U**. Inborn errors of metabolism with cognitive impairment: Metabolism defects of phenylalanine, homocysteine and methionine, purine and pyrimidine, and creatine. In: *Pediatric Clinics of North America: Inborn Errors of Metabolism*. 2017.

Thomas J, Nguyen-Driver M, **Bausell Breck J**, Birardi V, et al. Strategies for successful long-term engagement of adults with phenylalanine hydroxylase deficiency returning to clinic. *Journal of Inborn Errors of Metabolism and Screening*. 2017;5:1-9.

Vockley J, Burton B, Berry GT, Longo N, Phillips J, Sanchez-Valle A, Tanpaiboon P, Grunewald S, Murphy E, Humphrey R, Mayhew J, Bowden A, Zhang L, Cataldo J, Marsden DL, Kakkis E. UX007 for the treatment of long chain-fatty acid oxidation disorders: Safety and efficacy in children and adults following 24 weeks of treatment. *Mol Genet Metab.* 2017;120:370-7.

Goldstein A, **Vockley J**. Clinical trials examining treatments for inborn errors of amino acid metabolism. *Expert Opinion on Orphan Drugs.* 2017;5(2):153-64.