**SOUTHEAST REGIONAL GENETICS NETWORK (SERN)**
**38th ANNUAL MEETING of the SOUTHEASTERN REGIONAL GENETICS GROUP (SERGG)**
July 16, 2021
Virtual Meeting

This meeting is supported in part by a grant from the Maternal and Child Health Bureau (MCHB) (Title V, Social Security Act), Grant #UH7MC30772 Health Resources and Services Administration (HRSA), Department of Health and Human Services.

***All Sessions are open to everyone!***

## ***Friday, July 16, 2021***

4:00 pm – 4:05 pm Welcome and Introduction of Speaker – Neena Champaign, MD, President, SERGG

4:05 pm – 5:00 pm Keynote Speaker —
***"Gene Therapy"***
*Dwight D. Koeberl, MD, PhD*
*Professor of Pediatrics*
*Duke University School of Medicine*

5:00 pm – 5:15 pm SERN Update – Rani Singh, PhD, RD – Project Director

5:15 pm – 6:00 pm Concurrent Breakout Sessions

Clinical Genetics – Neena Champaign, MD & Roberto Zori, MD
Consumers – Alisa Bentley, BSW
Genetic Counseling – Amy R Jonasson, MS, CGC
Genetic Laboratories – Barbara DuPont, PhD & Dan Sharer, PhD
Nutritional Genetics – Krista Mantay, MS, RD, LD/N
Public Health Genetics – Dusty Edwards, BSN, RN

6:00 pm – 6:55 pm Poster Presentations (2 minutes each)

### ARGINASE DEFICIENCY PRESENTING SECONDARY TO COVID-19 INFECTION

Abdala Villa C[1], Eversull J[3], Burton W[2], Hurst A[1,2], Dean SJ[1,2]
*[1]Department of Genetics, University of Alabama at Birmingham; [2]Department of Pediatrics, University of Alabama at Birmingham, [3]Department of Emergency Medicine, University of Alabama at Birmingham*

Arginase deficiency is a rare urea cycle disorder (UCD) that can cause episodic hyperammonemia. This UCD usually has milder symptoms compared to other UCDs, as well as a later onset of symptoms starting at around 1-3 years of age and some patients not having symptoms until much later in life. We present a case of a 6-month old male patient with normal prenatal course and development until he developed upper respiratory tract infection symptoms that quickly progressed into lethargy requiring intubation. Subsequently he was confirmed to be COVID-19 positive, and on laboratory work-up noted to have hyperammonemia (2403 umol/L) requiring emergent dialysis. CT of the brain showed cerebral edema secondary to the increased

level of ammonia, and plasma amino acids done were significant for increased arginine (601 umoles/L). Patient's neurological status remained poor despite rapid correction of hyperammonemia and was subsequently declared brain dead. Post-mortem whole exome sequencing revealed a homozygous pathogenic variant in ARG1 (c.722 dup) consistent with the diagnosis of autosomal recessive arginase deficiency. We describe this case as it is an unusually severe presentation of arginase deficiency that presented secondary to COVID-19.

## INCREASING INCIDENCE OF NEUROLOGIC CRISIS IN ADULTS WITH HEREDITARY TYROSINEMIA TYPE 1 (HT1)

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Neurologic crisis due to metabolic disorders is a medical emergency requiring swift diagnosis and immediate management to prevent poor outcomes. Hereditary tyrosinemia type 1 (HT1) with porphyria-like neurologic crisis is a life threatening medical condition with a diverse clinical picture that requires early diagnosis, supportive care, rapid intervention, and appropriate pharmacotherapy in order to reduce the morbidity and mortality associated with the disease. Children with HT1 are surviving into adulthood. Lack of strict compliance with the treatment of the disease can cause severe neurologic crisis. Young adults with HT1 are now presenting for emergency care with porphyria-like neurologic crisis after discontinuing Nitisinone and/or dietary treatment. Delays in diagnosis are common leading to respiratory muscle paralysis requiring prolonged ventilator support. The crisis also causes severe pain, recurrent seizures, ascending motor neuropathy, unusual psychological behaviors, loss of consciousness and neuropathy. The neuropathies may be autonomic or peripheral. Many clinicians think of HT1 as a liver disease, and do not consider HT1 in the differential diagnosis when assessing a client with neurologic crisis. Two other disorders can present in a similar way, they are lead poisoning and ALAD Porphyria. Although lead poisoning is common, ALAD Porphyria is rare. This review of the pathophysiology and treatment of HT1 will help healthcare providers keep this diagnosis on the list of potential causes of neurologic crisis.

## DIAGNOSTIC YIELD AND UNEXPECTED FINDINGS FROM A COMBINED CARDIOMYOPATHY AND ARRHYTHMIA GENETIC TESTING

Dellefave-Castillo LM[1], Cirino AL[2], Callis TE[3], Esplin E[3], Hatchell KE[3], Johnson B[3], Morales A[3], Regalado E[3], Rojahn S[3], Vatta M[3], Nussbaum R[3], McNally EM[1]
*[1]Center for Genomic Medicine, Feinberg Cardiovascular Research Institute, Feinberg School of Medicine, Northwestern University, Chicago, IL; [2]Cardiovascular Division, Brigham and Women's Hospital, Boston, MA; [3]Invitae, San Francisco, CA*

**Background:** To reduce barriers to genetic testing and facilitate implementation of existing guidelines, we initiated a program of counseling-supported, sponsored genetic testing at no cost to patients suspected of having a genetic arrhythmia or cardiomyopathy. Here, we describe the diagnostic yield and clinical utility of the findings. **Methods:** De-identified genetic and clinical data were reviewed from individuals referred for genetic testing through the Detect Arrhythmia and Cardiomyopathy program. Testing consisted of a comprehensive cardiomyopathy and arrhythmia panel of up to 150 genes. **Results:** Among a final cohort of 4,782 probands, 961 (20%) received a molecular diagnosis (regardless of testing indication). When stratified by referral indication, the yield of molecular diagnoses ranged from 4% (catecholaminergic polymorphic ventricular tachycardia; CPVT) to 26% (long QT syndrome; LQTS) depending on the clinical indication. Positive results for 11% (75/691) of evaluable probands would have been missed by condition-specific panels based on clinician-provided referral indications. Following identification of a positive proband, 47% (449/961) of families pursued cascade testing. An average of 2.7 family

members per proband (1,218/449) underwent cascade testing and 33.8% (412/1,218) of family members received positive results. **Conclusion:** Combined cardiomyopathy and arrhythmia genetic testing identified clinically-relevant variants for 1 in 5 patients suspected of a cardiomyopathy or arrhythmia. Combined disease testing captures >10% of patients who would be missed with condition-specific panels and this greater clinical utility may outweigh the burden of uncertain results.

## HEALTH CARE PRACTITIONERS' EXPERIENCE-BASED OPINIONS ON PROVIDING CARE AFTER A POSITIVE NEWBORN SCREEN FOR POMPE DISEASE

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*[1]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA; [2]Department of Biostatistics & Bioinformatics, Rollins School of Public Health and Biostatistics Collaboration Core, Emory University School of Medicine, Atlanta, GA; [3]Clinical Center on TB, Beijing Chest Hospital, Capital Medical University, Beijing, China; [4]Graduate School of Arts and Sciences, Biomedical Sciences Division, Wake Forest University, Winston-Salem, NC*

The addition of Pompe disease (PD) to newborn screening (NBS) in the United States (US) has been controversial. NBS technology cannot discern infantile-onset PD (IOPD) from later-onset PD (LOPD) without clinical follow-up. This study explores genetic health care practitioners' (HCPs) experiences providing NBS patient care in the US and their resultant opinions on NBS for PD. An online survey was distributed to genetic counselors, geneticists, NBS follow-up care coordinators, and nurse practitioners caring for patients with positive NBS results for PD. Analysis of 78 surveys revealed the majority of HCPs support inclusion of PD on NBS. Most HCPs (93.3%) feel their state has sufficient resources to provide follow-up medical care for IOPD; however, only three-fourths (74.6%) believed this for LOPD. Common barriers experienced included time lag between NBS and confirmatory results, insurance difficulties for laboratory testing, and family difficulties in seeking medical care. HCPs more frequently encountered barriers providing care for LOPD than IOPD (53.9% LOPD identified ≥ 3 barriers, 31.1% IOPD). HCPs also believe creation of a population of presymptomatic individuals with LOPD creates a psychological burden on the family (87.3% agree/strongly agree), unnecessary medicalization of the child (63.5% agree/strongly agree), and parental hypervigilance (68.3% agree/strongly agree). Opinions were markedly divided on the use of reproductive benefit as a justification for NBS. Participants believe additional education for pediatricians would be beneficial in providing care for patients with both IOPD and LOPD, in addition to the creation of evidence-based official guidelines for care and supportive resources for families with LOPD.

## SURVEY ASSESSING EDUCATIONAL AND TRAINING NEEDS OF DIETITIANS IN THE FIELD OF INHERITED METABOLIC DISORDERS (IMD) SHOWS UNMET NEED FOR MORE PROFESSIONAL DEVELOPMENT OPPORTUNITIES

Douglas TD, Ryan L, Williamson J, and Singh RH
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**Background**: There are limited training opportunities for registered dietitians (RDs) treating patients with inherited metabolic disorders (IMD). Evidence is lacking that identifies barriers that affect access to fundamental training and resources. We conducted a survey assessing educational needs, resource availability, and barriers related to RD pursuit for professional development and knowledge acquisition. **Methods**: An online assessment survey was distributed via RedCap to RDs globally who treat patients with IMD. Questions focused on professional experience, types and availability of professional resources and growth opportunities, barriers, and interest in educational opportunities. **Results**: Fifty-one RDs completed the survey from April-May 2020. Of respondents, 55% (n=28) had ≥4 years professional experience, 29% >10 years;

47% (n=24) had no training in IMD prior to clinical appointment; for 82% most training occurred on-the-job, with 90% primarily self-taught. Four leading barriers affecting professional education and training: time limitations (84%, n=42), lack of IMD specific education pre- or post- acquiring RD license (54%), few evidence-based IMD nutritional guidelines (52%), and limited institutional support (48%). >90% reported interest in expanding educational and training opportunities. **Conclusion**: IMD specific educational resources prior to and during metabolic RD clinical appointment are insufficient to meet the profession's demands, and RDs recognize this gap. RDs desire more occasions to advance knowledge specific to metabolic patient care, while overcoming recognized barriers. Case-based learning sessions developed by Emory University Department of Human Genetics, in partnership with University of New Mexico's Project ECHO (Extension for Community Healthcare Outcomes) is one initiative tackling the described limitations.

## PLASMA FATTY ACIDS (PFA) IN PATIENTS WITH PHENYLKETONURIA (PKU) DURING ONE YEAR OF SAPROPTERIN RESPONSIVE DIET LIBERALIZATION

Douglas TD, and Singh RH
*Emory University Department of Human Genetics, School of Medicine, Atlanta GA*

**Background**: Sapropterin, a pharmacologic cofactor for phenylalanine hydroxylase, lowers plasma phe, permitting diet liberalization in a subset of patients with PKU. Since fatty acids (FA) have many health and biological roles, FA status in PKU patients liberalizing diet should solicit attention. To determine diet liberalization's impact on FA status in PKU, we analyzed food records and FA markers across one year in sapropterin responders and nonresponders. **Methods**: At baseline and one year, we analyzed three-day diet records (Metabolic Pro) and 57 PFA markers [Kennedy Krieger Institute (Baltimore, MD)]. Sapropterin responders (>15% plasma phe decline with observed dietary phe tolerance increases) remained on sapropterin throughout the study year while nonresponders maintained standard diet therapy. Between-group across-time comparisons completed with multivariate ANOVA in SPSS-26. **Results**: 58 subjects (ages 4-50 years) enrolled; 34% sapropterin responders. PFA analysis revealed significant one year declines in plasma ω-6 PUFAs, MUFAs, and trans-fats among both sapropterin response groups ($P \leq 0.007$ overall) with no between-group differences. Only phytanic acid, a long branch-chain FA, was significantly lower in non-responders vs responders ($P=0.011$), though without change across time points. Trans-fat intake decreased significantly for both response groups during the study ($P=0.025$); declining trends in dietary total fats, MUFA and PUFA intakes were observed without reaching significance. **Conclusion**: Reductions in both dietary and plasma FA across time with minimal between-group differences confirms plasma FA in PKU patients are impacted by reduced MF and fat intake. Specific factors in diet liberalization, and long-term health implications, necessitate further study.

## MOVING BEYOND THE FAMILY ENGAGEMENT CHECK BOX: A FRAMEWORK AND TOOLS TO PROMOTE AUTHENTIC FAMILY ENGAGEMENT IN SYSTEMS CHANGE

Dworetzky B
*Family Voices*

There is increased recognition that family engagement in health care initiatives leads to better health outcomes, improved access to health care, improved health care policies, and important efforts to reduce health inequities. However, families report they frequently feel more like a "check box" than a partner in policy making; that the invitation to participate on decision-making groups is merely to fulfill a requirement to have a family member present, than to authentically incorporate family's lived experience to reassess priorities. Regional Genetics Networks and other health entities may struggle to engage youth and families who represent the populations served, or fail

to provide family members with needed information and support to partner and contribute to decision-making groups. So, what does it take to move beyond the family engagement check box? How can organizations address health equity by identifying, supporting, and genuinely partnering with diverse families in creating new policies or amending existing ones? Based on extensive research, key informant interviews, and cognitive and pilot testing, Family Voices developed four domains of family engagement and a Family Engagement in Systems Assessment Tool and Toolkit that child- and family-serving entities can use to plan,, assess, and improve meaningful family engagement in systems-level initiatives. This poster will provide an overview of the four family engagement domains and an overview of the Family Engagement in Systems Tools.

## CHARACTERIZATION OF LIVER GSD IX γ2 PATHOPHYSIOLOGY IN A NOVEL *Phkg2*$^{-/-}$ MOUSE MODEL

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Liver GSD IX is caused by a deficiency in phosphorylase kinase (PhK), a key enzyme in the glycogenolysis pathway which breaks down glycogen to glucose. Deficiency of liver PhK leads to hepatomegaly, elevated liver enzymes and hypoglycemia. Until the recent availability of gene panels and exome sequencing, the diagnosis of liver GSD IX did not allow for differentiation of liver GSD IX subtypes. There is growing evidence that p atients with the second most common subtype, *PHKG2* GSD IX (GSD IX γ2), develop severe, progressive liver disease, yet research regarding the disease has been minimal to date. Here we characterize the first mouse model of liver GSD IX γ2. Knockout (*Phkg2*$^{-/-}$, KO) and wild type (*Phkg2*$^{+/+}$, WT) mice were compared for morphology, PhK enzyme activity, glycogen content, histology, serum liver markers, and urinary glucose tetrasaccharide ($Glc_4$). KO mice demonstrated significantly decreased liver PhK enzyme activity, increased liver: body weight ratio, and increased glycogen in the liver, with no glycogen accumulation observed in the brain, quadricep, kidney, and heart. KO mice demonstrated elevated serum ALT, AST, and urine $Glc_4$. Histology slides revealed characteristic GSD hepatocyte architectural changes and early liver fibrosis in KO mice, as have been reported in liver GSD patients. This study provides the first evidence of a mouse model that recapitulates the liver-specific pathology of patients with GSD IX γ2. The model will provide the first platform for understanding disease progression as well as the evaluation of novel therapeutics.

## MEDICAL NUTRITION THERAPY FOR PREVENTION (MNT4P) PROGRAM: ASSESSING GAPS IN MEDICAL FOOD COVERAGE FOR THE INHERITED METABOLIC DISORDER (IMD) COMMUNITY IN THE STATE OF GEORGIA

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**PURPOSE:** In the state of Georgia, there is no legislative mandate for coverage of medical food by private medical insurances. Medical food coverage is limited to state funded program such as Women, Infants and Children (WIC) program and Medicaid under the age of 21. MNT4P, a state grant funded, integrated MNT program, aims to understand the coverage of medical food (specialized formula) by both private and public medical insurances and mitigate the burden by bridging the gaps in services for MNT. **METHOD:** Patients and families in need of access to medical food, low protein modified foods (LPMF), amino acid supplements, insurance navigation

for medical food coverage and/or nutrition education, were either self-referred or referred by a provider, assessed for eligibility and enrolled in the MNT4P program. **RESULTS:** During the first three years of its existence, MNT4P program has enrolled 363 patients with service gaps to MNT (67% under the age of 18). Despite being medically insured (50.4% private insurance, 35.8% Medicaid, 4.4% Tricare, and 2.2% Medicare), 34% of IMD patients requested bridge supply of medical foods, including 13% WIC patients not covered outside the WIC maximum allowance. The other needs identified were insurance navigation for medical food coverage after initial insurance denial (24%), LPMF (14.3%), and nutrition education and counseling (7.16%). **CONCLUSION:** The IMD community in the state of Georgia continues to experience inadequate access to medical food despite having private and public insurance.

## SIMPLE, LOW-COST AT-HOME MONITORING FOR RARE METABOLIC DISORDERS: PHENYLKETONURIA AND UREA-CYCLE DISORDERS

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We have been working on the development of simple, low-cost, quick test methods for at-home monitoring of two separate genetic disorders: phenylketonuria (PKU) and urea cycle disorders (UCD) to assist individuals with these conditions in the control of their physiological status on a daily basis. For PKU, we have developed a patented colorimetric urine test that provides a method of monitoring blood phenylalanine (Phe). Over the past two years, we have conducted an IRB-approved clinical trial with a set of 10 volunteers with PKU, with estimated blood Phe levels from this urine test averaging within 1.5 mg/dL of lab-reported blood-Phe values. For UCD, we have developed an exhaled-breath test for ammonia for monitoring blood ammonia concentration. To evaluate this test method we have conducted IRB-approved clinical trials for patients with chronic kidney disease (CKD) as an alternative assessment method due to the low availability of patients with UCD. The breath test for ammonia has shown high correlation with blood urea nitrogen (BUN) levels, which are associated with blood ammonia levels for patients with CKD and which should also be associated with blood ammonia levels for patients with UCD. In the coming year, we will be working with a medical product company for the commercialization of the urine test for PKU. We will also be seeking patent protection for the ammonia breath test technology as well as medical product companies who may be interested in developing this test method into a commercial product for both CKD and UCD applications.

## CLINICAL OUTCOMES OF MAJOR CLINICAL EVENTS AND EMERGENCY TRIHEPTANOIN USE IN CRITICALLY ILL PATIENTS WITH LONG-CHAIN FATTY ACID OXIDATION DISORDERS (LC-FAOD): A RETROSPECTIVE CHART REVIEW

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LC-FAOD patients experience acute metabolic crises often requiring emergency care. Objective: describe clinical course of patients accessing emergency triheptanoin, a recently approved source of calories and fatty acids for patients with molecularly confirmed LC-FAOD. This retrospective chart review included patients with confirmed LC-FAOD receiving emergency triheptanoin (NCT03768817). Primary objective: clinical outcomes of major clinical events (MCEs) leading to triheptanoin initiation. Study period: ≤48 weeks pre- and post-triheptanoin initiation. Serious adverse events (SAEs) reported in sponsor safety database ≤48 weeks post-initiation are

described. Twenty of twenty-two patients consented and were included. Median (IQR) age was 0.9 (2.1) years at triheptanoin initiation. MCEs leading to triheptanoin initiation were cardiomyopathy (18 patients), rhabdomyolysis (10 patients), and hypoglycemia (6 patients); 14 patients had multiple concurrent MCEs. Eighteen patients were on medium-chain triglycerides (MCT) pre-triheptanoin initiation. Among 11 patients with nutrition data pre- and post-triheptanoin initiation, weight-based caloric intake was unchanged. Median MCT was 25.8% daily caloric intake pre-triheptanoin and 25.4% for triheptanoin post-initiation. Median (IQR) left ventricular ejection fraction (LVEF) improved from 32.7% (34.3) before (n=15) to 39.1% (23.5) during triheptanoin treatment (n=16). 14 patients (13 pediatric, 1 adult) were discharged alive. Thirteen patients had ≥1 SAE, including two with triheptanoin-related SAEs as assessed by investigators. One experienced acute kidney injury, dehydration, hypochloremia, and hyponatremia; one experienced increased blood creatine phosphokinase, dehydration, rhabdomyolysis, and diarrhea. Seven SAEs had fatal outcomes, none considered related to triheptanoin. Triheptanoin was well tolerated and associated with improved cardiac function in LC-FAOD patients in critical condition failing MCT therapy.

## URINARY GLUCOSE TETRASACCHARIDE CORRELATES WITH PHENOTYPE IN POMPE DISEASE IN THE NEWBORN PERIOD

Mendez R[1], Bali D[1,2], Stiles A[1,2], Zhang H[1], Li C[2], Blount J[2], Rehder C[3], Kishnani PS[2], Young S[1,2]
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**Background:** Pompe disease is a lysosomal storage disorder caused by a deficiency in acid alpha-glucosidase activity. Disease onset is associated with an increased urinary concentration of the glucose tetrasaccharide, Glcα1-6Glcα1-4Glcα1-4Glc (Glc4). Infantile-onset Pompe disease (IOPD) is a severe phenotype and presents with cardiomyopathy; early intervention is critical for these patients. Late-onset Pompe disease (LOPD) is an attenuated phenotype without cardiomyopathy. Newborn screening (NBS) for Pompe disease is unable to discern between IOPD and LOPD phenotypes. It is also prone to false positives due to carrier status and presence of pseudodeficiency alleles. **Objective:** Evaluate the ability of urinary Glc4 measurement to as a biomarker to differentiate IOPD from LOPD in young infants with a positive NBS for Pompe disease.
**Methods:** A retrospective review of anonymized laboratory data was performed on samples referred for follow-up testing after a positive Pompe NBS. Urinary Glc4 was measured by tandem mass spectrometry. **Results:** Clinical data, enzyme activity level, and genetic sequence of the *GAA* gene were used to assign each sample to one of four cohorts: IOPD, LOPD, carrier/pseudodeficiency, or unaffected. Urinary Glc4 levels were significantly elevated in the IOPD cohort compared with other groups. Glc4 levels in the IOPD, carrier/pseudodeficiency, and unaffected cohorts were not significantly different.
**Conclusions:** Because urinary Glc4 levels are elevated in patients with IOPD compared with those with LOPD, Glc4 analysis is an effective method for differentiating between the two phenotypes. Early diagnosis of the phenotype in patients with Pompe disease leads to earlier treatment and better outcomes.

## EFFICACY OF TELEGENETICS: A DIAGNOSTIC YIELD COMPARISON BETWEEN IN-PERSON AND TELEMEDICINE PEDIATRIC GENETIC EVALUATIONS

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The purpose of this study was to investigate the efficacy of telegenetic services for pediatric genetic evaluations conducted by telemedicine by comparing it to in-person pediatric genetic evaluations. Research into the utility of telegenetics would greatly serve to identify if this is a preferred alternative service delivery model to bridge the gap in accessibility and reach a greater catchment area of the population, especially to those living in underserved and rural locations. This study was a retrospective review of electronic medical records of pediatric patients seen at Greenwood Genetic Center (GGC) for initial in-person genetic visits prior to the COVID-19 pandemic and initial telemedicine genetic visits during the COVID-19 pandemic. Primary indications were reviewed in conjunction with the final clinical assessment made by the geneticist at the time of visit. Diagnostic information from the clinical assessment was used to determine if a clinical diagnosis could be made, which was categorized into clinical genetic diagnosis (met clinical criteria with/without the need for molecular confirmation), environmental etiology, isolated anomaly, multifactorial etiology, within normal variation, and testing not indicated. If testing was indicated, results were categorized into diagnosed, undiagnosed, uncertain, or not completed. Both clinical assessment and genetic testing outcomes were used in the diagnostic yield comparison. We found that visit type did not have a significant effect on the likelihood of diagnosis. Identifying the similarities in diagnostic outcomes for patients seen by telemedicine may strengthen the support for telegenetic services, improve accessibility to genetic services, and benefit both providers and patients.

## MIRO1 IS A MOLECULAR MARKER FOR PARKINSON'S RISK

Nguyen D[1,2], Bharat V[1], Conradson DM[1], Nandakishore P[3], and Wang X[1]
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**Background:** There is a lack of reliable molecular markers for Parkinson's disease (PD) patients and at-risk individuals. The detection of the pre-symptomatic population of PD will empower more effective clinical intervention to delay or prevent disease onset. We have previously found that the mitochondrial protein Miro1 is resistant to mitochondrial depolarization-induced degradation in fibroblasts from a large number of PD patients and several at-risk individuals. Therefore, Miro1 has the potential to molecularly mark PD populations. **Objective:** We aim to determine whether Miro1 is useful for labeling individuals at risk for PD. **Methods:** We examine the Miro1 response to mitochondrial depolarization by biochemical approaches in induced pluripotent stem cells from a cohort of at-risk individuals. **Result:** The Miro1 phenotype is significantly associated with PD risk. **Conclusion:** Miro1 is a promising molecular marker for detecting both PD and at-risk populations. Tracking this Miro1 marker could aid in diagnosis and Miro1-based drug discoveries.

## OPHTHALMIC TELEGENETICS – LESSONS LEARNED DURING THE PANDEMIC

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VisionAmerica is a multispecialty medical/surgical eyecare referral center with satellites throughout Alabama. The ophthalmic genetics service converted to telegenetics in July 2020. The Microsoft Teams HIPAA-compliant platform was used. Initial consults included a comprehensive history, pedigree construction, basic testing and review of records and images from referring doctors. Genetic tests were ordered online, sample kits were shipped to patients

and a post-test telegenetics visit scheduled for counseling. Patient ages ranged from 1-79 years. Average roundtrip distance from home address was ~160 miles (MapQuest).

- Misunderstanding telehealth resulted in two patients confirming a telehealth visit yet coming to the office.
- Some patients took advantage of not being physically present by simultaneously caring for multiple children, sitting in a drive-through lane, driving to work, or having their oil changed.
- Unlike the office, you won't necessarily know everyone present unless they speak or move into camera view.
- Screen sharing was highly effective for explaining test results and demonstrating clinical trial searching. The display is enlargeable for sighted but visually impaired patients.
- 100% of samples submitted were testable.
- Two patients had not submitted a sample after 3 months.
- Four referrals were made to clinical trials, one received gene therapy for choroideremia.
- One patient and father had a medically actionable, potentially fatal, incidental finding.
- Advantages included reduced exposure as well as eliminating unnecessary travel: total miles not traveled for care was ~5,767.

There was no indication that appropriate care or testing could not be provided via telegenetics. Telegenetics will continue to be an effective option post-pandemic.

## GENETIC COUNSELING ASSISTANT-LED IMPLEMENTATION OF A TUMOR SCREENING PROTOCOL

Olive H, Dean SJ, Robin NH, Hurst ACE
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ACMG practice guidelines advise that children with hemihyperplasia and/or signs of Beckwith-Wiedemann syndrome have regular screening for embryonal tumors (Clericuzio, 2009). Phenotypic findings such as macroglossia and organomegaly may indicate overgrowth syndromes, which have varying tumor risks related to specific molecular genetic defects. Affected individuals are often followed in a genetics clinic for evaluation and ongoing screening and management, which includes a renal ultrasound and alpha-fetoprotein level every 3 months until age 4 with continued renal or abdominal ultrasound screening until age 8. However, ensuring adherence to this protocol is a significant challenge for clinicians. To address this, we implemented a protocol using Genetic Counseling Assistants (GCAs). Our GCAs created a list of patients needing routine screening, then contacted and scheduled lab and ultrasound appointments for patients on a rotating basis in the month their screenings are due. We collected data on 17 patients receiving embryonal tumor surveillance. In the year before the protocol, 33% (5/15) patients had completed all scheduled ultrasounds and 14% (2/14) completed all scheduled AFPs. After the first 6 months of the protocol, 41% (7/17) completed all ultrasounds, with all 17 obtaining at least one, and 29% (4/14) completed all AFPs, with all obtaining at least one. This suggests a higher rate of consistency in monitoring patients. Our success thus far highlights the positive impact other organizations can gain from maximizing the role of GCAs in clinic. This illustrates that integrating GCAs into the clinic workflow assists clinicians and staff, enhances care, and provides educational opportunities.

## TITLE: PHENYLBUTYRATE METABOLITE TESTING IN UREA CYCLE DISORDERS: RESULTS OF A CLINICIAN SURVEY

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BACKGROUND/AIMS: Nitrogen scavengers approved for chronic treatment of urea cycle disorders (UCDs), sodium and glycerol phenylbutyrate (PB), undergo hepatic conversion to phenylacetate (PAA), which conjugates glutamine to form phenylacetylglutamine for urinary nitrogen excretion. Elevated PAA has been associated with reversible neurologic toxicity with symptoms similar to hyperammonemia. Plasma PB metabolite analysis can assess for toxicity and therapeutic drug levels. A survey examined test use and perceptions. METHODS: A 21-item clinician survey was distributed online in 2020. US prescribers managing ≥1 UCD patient were eligible. RESULTS: Responses from 52 clinicians were analyzed, including 58% who reported using plasma PB metabolite testing. Test users reported managing more UCD patients than nonusers. Users rated the test as "often helpful" for ruling out PAA toxicity (44%), informing PB dosing decisions (42%), and assessing treatment adherence (28%). Regarding interpretation, findings are often unremarkable (61%) or suggestive of poor adherence (13%); 46% of users have never encountered results indicative of PAA toxicity. Eighty-two percent do not adjust UCD treatment based solely on metabolite results. Forty-six percent of users were unsure of metabolite targets; those conducting only ad hoc (vs regular) testing were significantly more likely to be unsure of targets. One-fifth of users identified uncertainties (eg, validation, timing, interpretation). CONCLUSIONS: Clinicians rated plasma PB metabolite testing as most helpful for assessing PAA toxicity and informing PB dosing. However, uncertainties persist about metabolite targets and appropriate clinical actions depending on results. Increased awareness of published metabolite data and education about test interpretation may help optimize UCD care.

## A LONG-TERM, PROSPECTIVE, MULTICENTER, IN-CLINIC AND ONLINE DISEASE MONITORING PROGRAM (DMP) FOR PATIENTS WITH LONG-CHAIN FATTY ACID OXIDATION DISORDERS (LC-FAOD)

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Long-chain fatty acid oxidation disorders (LC-FAOD) are rare autosomal recessive defects in genes encoding mitochondrial enzymes that convert long-chain fatty acids into energy. LC-FAOD can cause unpredictable, life-threatening episodes of rhabdomyolysis, hypoglycemia, and cardiomyopathy. Triheptanoin is a medium-chain triglyceride indicated as a source of calories and fatty acids for the treatment of patients with molecularly confirmed LC-FAOD. The LC-FAOD DMP is an alternative to traditional registries that will consistently monitor disease manifestations and effects of treatments over a 10-year timeframe. The LC-FAOD DMP consists of two distinct, long-term (10-year), prospective observational studies planned to provide data on the natural history of the disease, as well as effectiveness and safety of treatments from different perspectives: clinical visits in study CL401 and at-home data collection in study CL402. No treatments or interventions will be provided by the Sponsor for either study. The in-clinic study (N=300) will collect data during clinic or telephone visits by site staff. Patients will have in-clinic visits at Enrollment Baseline, Month 6, Year 1, and Year 2, with alternating annual telephone and in-clinic visits starting at Year 3. The online study (unlimited number of participants with LC-FAOD) will collect self-reported, real-time data using a mobile/web-based application accessed by patients or caregivers. The LC-FAOD DMP will provide comprehensive clinical and online data for 10-

years. A unique, core tenet of the CL402 DMP is the planned sharing of data with the participants that will include both personalized data and de-identified/aggregated data from all participants.

## TYROSINEMIA SOCIETY, NON-PROFIT ORGANIZATION, CREATED TO ADVOCATE AROUND THE GLOBE

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Tyrosinemia type I is a rare metabolic disease characterized by the development of liver disease with neurologic events in early infancy and may lead to death due to liver failure in early childhood if left untreated. Typically detected in infancy through newborn screening tests, tyrosinemia occurs in one out of every 100,000-120,000 births worldwide. Rare metabolic disease patients and families all over the world face challenges understanding the disease process, procuring necessary treatments, navigating the complex healthcare system, and connecting with related rare advocacy groups and organizations. In 2019 a group of volunteers with diverse backgrounds, including university professors, healthcare clinicians, and scientists, with a shared interest and vision in advocating for children and families affected by tyrosinemia united to begin the extensive process of forming a nonprofit organization. With the assistance of the National Organization of Rare Disorders and spearheaded by nurses, the group agreed upon a name and centralized mission. Multiple resources were consulted to assist in forming the new nonprofit organizations, the Tyrosinemia Society. The Tyrosinemia Society is a community of advocates, caregivers, and health professionals dedicated to educating and inspiring individuals to improve health outcomes and advocate for adults and children with Tyrosinemia and related metabolic disorders. To date, the Tyrosinemia Society has made contact and advocated for patients and families effected by rare metabolic diseases all around the globe.

## NEW DIRECTIONS IN THE INNOVATIVE MODEL OF ONLINE TRAINING FOR NUTRITIONAL MANAGEMENT OF INHERITED METABOLIC DISORDERS

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Objectives: There is limited formal training available for Registered Dietitians (RDs) in the field of Inherited Metabolic Disorders (IMDs). The Electronic Genetic Nutrition Academy (eGNA) was the first online program developed to meet this need. Methods: Phase I of eGNA includes interactive web-based case conference and journal club, online forum discussions facilitated by national experts, and medical commentary videos from experienced providers. Participants complete pre- and post-tests for each session, receiving certificates of completion for up to 4 continuing education units (CEUs). Data were collected and analyzed from 11 sessions across 4 years covering a variety of topics. Results: Worldwide registration has increased from 266 in year 1 to 1155 by year 4. To date, 538 people have participated in eGNA during live sessions with 46% participating in the case conference, 25% in the journal club and 28% in both. Certificates of completion for 388 CEUs were awarded to participants who completed both pre and post-test including 207 (53%) attendees for case conference and 181 (47%) attendees for journal club. Discussion: Given that more participants chose to complete case conferences rather than journal clubs, we conclude that there is a great worldwide interest in learning about IMDs through a case-based approach. Conclusion: Based on these observations, we have expanded eGNA by utilizing Project ECHO (Extension for Community Healthcare Outcomes) to create eGNA's Genetic Nutrition ECHO, a cohort-based, case-learning platform to provide better care at their home institutions. Further expansion of eGNA will include courses that incorporate didactic modules and case-based learning.

## PLASMA METABOLOMIC PROFILE CHANGES IN FEMALES WITH PHENYLKETONURIA FOLLOWING AN INTEGRATIVE HEALTH INTERVENTION

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There remains a limited understanding of the metabolic perturbations, beyond phenylalanine (Phe) metabolism, that contribute to phenotypic variability in phenylketonuria (PKU). This study aimed to characterize changes in the PKU plasma metabolome following a five-day Metabolic Camp intervention and compare PKU profiles with those of matched controls. Fasting plasma samples were collected from 28 females (12-57 years) on the first and final days of camp to evaluate metabolic control and complete untargeted metabolomic profiling. Three-day dietary records were collected to assess changes in dietary adherence and composition. Univariate (paired and two-sample t-tests) and multivariate (partial least squares discriminant analysis, hierarchical clustering) analyses were performed to identify clinical and metabolic features associated with the intervention and disease state. At baseline, PKU participants had amino acid and lipid perturbations associated with bioenergetic impairment and oxidative stress, as reflected by a higher abundance of Phe catabolites, ketones, and carnitine- and glycine-conjugated fatty acids, and a lower abundance of fatty acylcholines relative to controls. After the intervention, Phe concentrations decreased by an average of 191.2 µmol/L (95% CI: -283.5, -98.9) and 70% of participants demonstrated improved dietary adherence. Metabolomics identified a shift in abundance for 193 metabolites ($q<0.05$), which predominantly included metabolic derivatives of Phe, fatty acids, ketone bodies, tryptophan, histidine, choline, and steroids. Baseline discriminatory analytes were improved or fully normalized by day five of camp, demonstrating the effectiveness of the short-term, holistic intervention. The identified choline-conjugated lipids may modulate pathways associated with oxidative stress, and have not been previously evaluated in PKU.

## THE EPIDEMIOLOGY OF LYMPHEDEMA IN PHELAN-MCDERMID SYNDROME

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Lymphedema occurs as a result of impaired lymphatic drainage resulting in an accumulation of lymphatic fluid in the interstitial tissue, decreased physical functioning, and a significant impact on the overall quality of life. Previously identified mutations in more than 20 genes including *BRAF, CCBE1, FOXC2, GATA2, MAP2K1,* and *SOX18* have been associated with lymphedema development and progression. Phelan-McDermid syndrome (PMS) is caused by a deletion mutation in 22q13 or pathogenic mutations within *SHANK3*. This syndrome is associated with autism spectrum disorder, intellectual disability, neurological deficits, and issues in the endocrine, renal, and gastrointestinal systems. The prevalence of lymphedema in the PMS patient population has been estimated around 22-29%, often increasing in severity with patient age. However, despite being reported as a substantial health concern, little research has been conducted on lymphedema in PMS. The goal of this study is to understand the epidemiology of lymphedema in a PMS cohort of 600 individuals and identify 22q13 genes most associated with this disorder. Identifying a genetic cause for lymphedema in PMS may allow for appropriate diagnosis and management that may limit progression and complications.

**ISOTOPE DILUTION UPLC-MS/MS QUANTIFICATION OF AMINO ACIDS IN DRIED BLOOD SPOTS AND PLASMA USING KAIROS AMINO ACID KIT**

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**Objective:** To develop a rapid and reliable method for amino acid analysis in dried blood spots (DBS). **Background:** Regular monitoring of plasma amino acids is standard of care in patients with inborn errors of metabolism (IEM) treated with protein-restricted diets and amino acid supplementation. Home collection of dried blood spots facilitates this process. We modified the Kairos amino acid kit method (Waters Corporation) to analyse 31 amino acids in DBS by UPLC-MS/MS. **Method:** A 6 mm diameter DBS punch was extracted with methanol containing $^{13}C$, $^{15}N$ universal labeled internal standards and derivatized using 6-aminoquinolyl-N–hydroxysuccinimidyl carbamate (AQC) reagent. Amino acids were separated on a CORTECS™ C18, 2.1 x 150mm, 1.6 µm column and detected by selected reaction monitoring on a Waters Acquity UPLC-Xevo TQ-S Micro system. **Results:** The lower limits of quantification were 2.5 µmol/L with an inaccuracy ≤ 15% for 24 analytes. Overall accuracy of 17 amino acids was 94-111%. Interday imprecision of the DBS assay was ≤18% and recovery ranged from 72 to 125 %. In matched DBS and plasma samples, amino acid concentrations were generally lower in DBS. Phenylalanine, tyrosine, leucine, isoleucine, and valine concentrations were linearly correlated with those in plasma ($R^2 \geq 0.89$). Certain challenges were evident with DBS AA analysis: arginine and ornithine had notably lower concentrations in DBS compared with plasma, and aspartic acid and arginine had co-eluting interference. **Conclusion:** Amino acid analysis in DBS using a modified AQC method is reliable for most amino acids used to monitor patients with IEM.

6:55 pm – 7:00 pm Wrap up – Neena Champaign, MD
President, SERGG