MEETING LOCATIONS		
DATE/TIME	**FUNCTION**	**LOCATION**
Wednesday, July 10, 2024		
7:00 p -	SERGG Board of Directors Dinner Meeting	Paparazzi Room (12th Floor)
Thursday, July 11, 2024		
8:30 a – 5:00 p	Registration Open	Salon A Foyer
10:00 a – 10:15 a	Welcome/Announcements	Salon C
10:15 a – 10:30 a	Update on Federal Grant Status	Salon C
10:30 a – 12:20 p	Platform Session 1	Salon C
12:30 p – 1:30 p	Sanofi Symposium (with box lunch)	Windsor Ballroom
12:30 p – 2:00 p	Lunch on your own (if not attending symposium)	
2:00 p – 4:45 p	Platform Session 2	Salon C
3:15 p – 3:45 p	Break	Salon A Foyer
5:00 p – 7:00 p	Reception and Poster Session	Salon A-B
Friday, July 12, 2024		
8:00 a – 9:00 a	Alexion Symposium (with breakfast)	Swannanoa Room (2nd Floor)
8:00 a – 9:00 a	Ultragenyx Symposium (with breakfast)	Victoria Room (2nd Floor)
8:00 a – 9:00 a	Continental Breakfast (for those not attending a symposium)	Salon A-B
8:00 a – 2:00 p	Exhibits and Posters Open	Salon A-B
9:00 a – 3:00 p	Registration Open	Salon A Foyer
9:00 a – 9:15 a	Welcome/Announcements	Salon C
9:15 a – 10:45 a	Platform Session 3	Salon C
10:45 a – 11:15 a	Break	Salon A-B
11:15 a – 12:15 p	Platform Session 4	Salon C
12:30 p – 2:00 p	Lunch	Salon A-B & Windsor Ballroom
2:00 p – 3:00 p	Invitae Symposium	Swannanoa Room (2nd Floor)
2:00 p – 3:00 p	UCB Symposium	Victoria Room (2nd Floor)
3:15 p – 4:45 p	Platform Session 5	Salon C
6:00 p – 8:00 p	A Taste of eGNA: Palynziq and Maternal PKU Case Presentations **(by invitation only)**	Top of the Plaza (12th Floor)
Friday, July 12, 2024 - CONCURRENT SESSION – FAMILY ALLIANCE		
3:00 p – 4:00 p	Family Alliance Plenary Session	Alexander Room (2nd Floor)
4:00 p – 4:15 p	Family Alliance Break	Alexander Room (2nd Floor)
4:15 p – 5:30 p	Family Alliance Plenary Session	Alexander Room (2nd Floor)
Saturday, July 13, 2024		
8:00 a – 9:00 a	Ambry Genetics Symposium (with breakfast)	Victoria Room (2nd Floor)
8:00 a – 9:00 a	Variantyx Symposium (with breakfast)	Swannanoa Room (2nd Floor)
8:00 a – 9:00 a	Continental Breakfast (for those not attending a symposium)	Salon A-B
9:00 a – 10:45 a	Registration Open	Salon A Foyer
8:00 a – 11:15 a	Exhibits and Posters Open	Salon A-B
9:00 a – 10:45 a	Platform Session 6	Salon C
10:45 a – 11:15 a	Break	Salon A-B
11:15 a – 12:30 p	Platform Session 7	Salon C
12:30 p – 1:00 p	SERGG Business Meeting	Salon C

41st ANNUAL MEETING of the SOUTHEASTERN REGIONAL GENETICS GROUP (SERGG)
July 10-13, 2024
Asheville, North Carolina

Wednesday, July 10, 2024

7:00 pm -	**SERGG Board of Directors Dinner Meeting – Paparazzi Room (12th Floor)**

All Sessions and Workgroup Meetings are open to everyone!

Thursday, July 11, 2024

8:30 am – 5:00 pm	**Registration Open – Salon A Foyer**
10:00 am – 10:15 am	**Welcome/Announcements – Salon C** – Barbara DuPont, PhD, SERGG President
10:15 am – 10:30 am	**Update on Federal Grant Status – Salon C** – Rani Singh, PhD, RD, Emory University
10:30 am – 12:20 pm	**Platform Session 1 – Salon C *(CME and CEU Approved)*** Moderator: Anna Hurst, MD, University of Alabama at Birmingham **"Workflow Innovations for an Overtaxed System"**
10:30 am – 10:50 am	**"Using PAs in the Genetics Clinic"** Wesley Patterson, PA-C, PhD, Greenwood Genetic Center
10:50 am – 11:10 am	**"The Use of Genetic Counselors to Increase Patient Access to Care"** Meg Keating, MS, CGC, Greenwood Genetic Center
11:10 am – 11:30 am	**"Activities at the Smith Family Clinic in Huntsville, Alabama"** Anna Hurst, MD, University of Alabama at Birmingham
11:30 am – 11:50 am	**"Strategies for Creating Efficiencies in General Genetics Clinics"** Christine Spaeth, MS, CGC, Childrens Hospital of New Orleans
11:50 am – 12:20 pm	**Panel Discussion with Invited Speakers**
12:30 pm – 1:30 pm	**Industry Supported Symposium – Windsor Ballroom - ""Over Yonder" - The Blood Brain Barrier as the New Frontier in LSDs" –** Sanofi (Box Lunch provided for attendees) *(CME and CEU Not Provided)*
12:30 pm – 2:00 pm	**Lunch On Your Own**
2:00 pm – 4:45 pm	**Platform Session 2 – Salon C *(CME and CEU Approved)*** Moderator: Rani Singh, PhD, RD – Emory University
2:00 pm – 2:45 pm	**Keynote Speaker: "Treatment of Fatty Acid Oxidation Disorders: The Next Generation"** **Jerry Vockley, MD, PhD – University of Pittsburgh Medical Center**
2:45 pm – 3:00 pm	**"Endogenous Non-reducing End Glycosaminoglycan Analysis Provides Disease-specific Biomarkers for Diagnosis and Monitoring of Mucolysaccharidoses"** Francyne Kubaski, PhD, Greenwood Genetic Center
3:00 pm – 3:15 pm	**"False Positive Newborn Screening for Galactosemia in G6PD Patients in Florida"** Jeimy Alfonso Rodrigues, BS, University of Miami Miller School of Medicine
3:15 pm – 3:45 pm	**BREAK – Salon A Foyer**
3:45 pm – 4:00 pm	**"Genotype-phenotype Correlations in Very-long-chain ACYL-CoA Dehydrogenase Deficiency: Insights from a Florida Cohort"** Elizabeth Fletcher, MD, University of South Florida Morsani College of Medicine

	4:00 pm – 4:15 pm	**"Genetic Needs Assessment of Children with Intellectual Disability, Developmental Delay, Hearing Loss, and/or Autism Spectrum Disorder in the Southeastern United States"** Gwen Gunn, PhD, MS, Emory University School of Medicine
	4:15 pm – 4:30 pm	**"CNS Involvement in Pompe: Unveiling Risks Through Neuroradiological Surveillance"** Neha Regmi, MBBS, MD, Duke University Medical Center
	4:30pm – 4:45 pm	**"Effect Size Analysis of Cipaglucosidase Alfa Plus Miglustat Versus Alglucosidase Alfa in ERT-Experienced Adults with Late-onset Pompe Disease in PROPEL"** Priya Kishnani, MD, Duke University Medical Center
5:00 pm – 7:00 pm		**Welcome Reception and Poster Session (Cash Bar) – Salon A-B** *(CME and CEU Not Provided)*

Please place all phones on vibrate when in the meeting rooms.

Conference Room Internet Access:

Network: Renaissance_Conference

Password : avlbr2

Wi-fi is also available in the lobby areas and guest rooms.

Be sure to visit each exhibit during the reception, breaks and sessions you are not attending to get your card punched for the gift card drawing!

CEUs are being offered for Genetic Counselors for this meeting. In order to receive CEUs, you must select the CEU add on as part of the online conference registration (your registration is able to be edited) and will cost $35.00. You must provide your NSGC ID during the online registration as well as the payment in order to receive CEUs. The CEU surveys are online this year at SERGG.org under the genetic counseling button. Please complete surveys no later than 8/31/24 for CEUs, or you may not be able to receive CEUs for the conference. **Platform Codes will be printed and displayed on the backs of the doors to the lecture room entrance. These codes MUST be included to prove attendance.** For any questions, or if you could not locate a platform attendance code, please find Amy Jonasson during the meeting or ask the front registration desk. Amy's e-mail is argladstione@ufl.edu for additional questions or concerns.

All attendees will receive an email from Mollie Titus from Self Regional following the meeting. If you wish to have a certificate with the CMEs or a Certificate of Attendance, complete the link in the email. Any questions contact her at Mtitus2@selfregional.org.

All Sessions and Workgroup Meetings are open to everyone!

Friday, July 12, 2024

8:00 am – 9:00 am **Two Concurrent Industry Supported Symposiums *(CME and CEU Not Provided)***
(Continental Breakfast included for attendees)
#1 - "Clinical Approach to Hypophosphatasia" – *Alexion* - **Swannanoa Room**

#2 - "Cardiomyopathy and Arrhythmia in LC-FAOD"- *Ultragenyx* - **Victoria Room**

8:00 am – 9:00 am **Continental Breakfast – (for those not attending a Symposium) – Salon A-B**

8:00 am – 2:00 pm **Exhibits and Posters Open – Salon A-B**

9:00 am – 3:00 pm **Registration Open – Salon A Foyer**

9:00 am – 9:15 am **Welcome/Announcements – Salon C -** Barbara DuPont, PhD, SERGG President

9:15 am – 10:45 am **Platform Session 3 – Salon C *(CME and CEU Approved)***
Moderator: Neena Champaigne, MD, Medical University of South Carolina

9:15 am – 10:00 am **Invited Speaker: "ScreenPlus: Laboratory Challenges and Implementation Strategies"**
Joseph J Orsini, PhD – New York State Department of Health Newborn Screening

10:00 am – 10:15 am **"DHX16-Associated Neuromuscular Oculoauditory Syndrome: A Novel Case"**
Sloane Clay, BS, Louisiana State University Health Sciences Center, New Orleans

10:15 am – 10:30 am **"The Utility of Referrals from a State Early Intervention System to a Pediatric Genetics Clinic to Increase Access to Genetic Services"**
Mikayla Jennings, BS, University of South Carolina School of Medicine

10:30 am – 10:45 am **"Using Genome Sequencing to Screen Newborns in North Carolina: Successes and Challenges in the First Six Months"**
Elizabeth Jalazo, MD, UNC Chapel Hill

10:45 am – 11:15 am **Break with Exhibits and Posters – Salon A-B**

11:15 am – 12:15 pm **Platform Session 4 – Salon C *(CME and CEU Not Approved)***
Moderator: Amy Jonasson, MS, CGC, University of Florida

11:15 am – 11:30 am **"Tailored Diagnostic Decision Tree Resulting from Machine Learning to Improve Early Diagnosis of ASMD"**
Laura Croal, PhD, Sanofi

11:30 am – 11:45 am **"Long-term Safety and Urea Cycle Function Following a Phase ½ Trial of DTX301 in Adults with Late-onset Ornithine Transcarbamylase Deficiency (OTCD)"**
Julian Mesa, MD, MBA, Ultragenyx Gene Therapy

11:45 am – 12:00 pm **"Stroke in Patients with Fabry Disease: A Fabry Registry Analysis of Natural History Data from Patients Stratified by Disease Phenotype"**
Marta Reviriego-Mendoza, PhD, Sanofi

12:00 pm – 12:15 pm **"Efficacy and Safety of Oral Sepiapterin in Participants with Phenylketonuria on Sapropterin Dihydrochloride at Time of Phase 3 APHENITY Study Entry"**
Jonathan Blaize, PhD, PTC Therapeutics, Inc

12:30 pm – 2:00 pm **Lunch – Salon A-B with overflow seating in Windsor**

CONCURRENT INDUSTRY-SUPPORTED SYMPOSIUM
(CME and CEU Not Approved)

TIME	Swannanoa Room	Victoria Room
2:00 pm – 3:00 pm	**"Evolving with Purpose: Innovations in Variant Interpretation to Reduce Uncertainty"** - Invitae	**"TK2d: Navigating Common Mimickers, Unraveling Clinical Clues and Exploring the Patient Journey"** - UCB

3:15 pm – 4:45 pm **Platform Session 5 – Salon C *(CME and CEU Approved)***
Moderator: Julie Jones, PhD, Greenwood Genetic Center

3:15 pm – 4:00 pm **Invited Speaker: "Rett syndrome: The Emerging Landscape of Treatment Strategies"**
Alan Percy, MD – University of Alabama at Birmingham

4:00 pm – 4:15 pm **"D-Aspartate in *SPTAN1*-related Hereditary Spastic Paraplegia: A Model for the Development of Accessible Treatments in Rare Genetic Disease"**
Aubrey Rose, MS, CGC, Greenwood Genetic Center

4:15 pm – 4:30 pm **"Lightning Strikes Twice: Dual Diagnosis of De Novo X-linked Disorders"**
Christine Spaeth, MS, Children's Hospital of New Orleans

4:30 pm – 4:45 pm **"Expanding the Clinical Phenotype and Variant Spectrum Associated with *RFX7*"**
Talia Sisroe-Dos Santos, AS, BS, Medical College of Georgia

Family Alliance Session – Alexander Room
(This session is open to everyone!)
Co-Chairs: Linda Starnes, Amy Cunningham, and Saran Gurung
(CME and CEU Not Approved)

8:00 am – 9:00 am	***Continental Breakfast** – **Salon A-B**
9:00 am – 3:00 pm	**Join the SERGG sessions of your choice** – **Salon C**
3:00 pm – 3:15 pm	**Welcome and Introductions** - Saran Gurung – **Alexander Room**
3:15 pm – 3:30 pm	**Updates: Grant Opportunities, Family Alliance Engagement** – Rani Singh, PhD, RD, LD
3:30 pm – 4:00 pm	**Care Mapping: A Tool for Shared Decision Making** – Linda Starnes
4:00 pm – 4:15 pm	**Break**
4:15 pm – 5:00 pm	**Facilitated Discussion: The Future of the Family Alliance – Purpose, Aim, Goals** – Linda Starnes and Suran Gurung
5:00 pm – 5:15 pm	**Round Table: State Updates, Open Topics, Networking** – All Attendees
5:15 pm – 5:30 pm	**Wrap-up and Closing Remarks** – Linda Starnes and Amy Cunningham

***All Family Alliance members are invited to connect over breakfast from 8:00 am – 9:00 am in Salon A-B. Meet and network with the other members!**

5:00 pm – 5:30 pm **Adjournment for the Day** – Enjoy your evening in Asheville!

6:00 pm – 8:00 pm **A Taste of eGNA: Palynziq and Maternal PKU Case Presentations Using Emory eGNA Project ECHO Model – Top of the Plaza (12th Floor)**
An Educational Event including Dinner (by invitation)

All Sessions and Workgroup Meetings are open to everyone!

Saturday, July 13, 2024

9:00 am – 10:45 am **Registration Open – Salon A Foyer**

8:00 am – 9:00 am **Two Concurrent Industry Supported Symposiums** ***(CME and CEU Not Approved)***
(Continental Breakfast included for attendees)
#1 - ***"*Bridging the Gap: Diagnostic and Clinical Implications of RNA Analysis for Rare Disease"** – *Ambry Genetics* **– Victoria Room**

#2 - ***"*Dual whole genome sequencing improves results: Clinical Cases"** – *Variantyx* **– Swannanoa Room**

8:00 am – 9:00 am **Continental Breakfast – (for those not attending a Symposium) – Salon A-B**

8:00 am – 11:15 am **Exhibits with Posters – Salon A-B**

9:00 am – 9:15 am **Announcements – Salon C** – Barbara DuPont, PhD, SERGG President

9:15 am – 10:45 am **Platform Session 6 – Salon C** ***(CME and CEU Approved)***
Moderator: Jennifer Gass, PhD, Florida Cancer Specialists

9:15 am – 10:00 am **Invited Speaker: *"*Unlocking Genomic Complexity: The Clinical Impact of Optical Genome Mapping in Oncology Testing*"***
Ravi Kolhe, MD, PhD – Augusta University

10:00 am – 10:15 am **"The Power of International Collaboration in Rare Genetic Diseases: Advancing the Understanding of Muscle Phosphorylase Kinase Deficiency (GSD IXα1)"**
Angie Fares, MD, Duke University Medical Center

10:15 am – 10:30 am **"The Effect of Methotrexate Treatment on Neurocognitive Development and Neuroinflammation Gene Expression in Pediatric Cancer Patients"**
Gabrielle Sheets, BS, Louisiana State University Health Science Center, New Orleans

10:30 am – 10:45 am **"Ehlers Danlos Syndrome Clinic: A Single-site Experience and Clinical Outcomes"**
Morgan Bryars, MS, CGC, The University of Alabama at Birmingham

10:45 am – 11:15 am **Break with Exhibits and Posters – Salon A-B**

11:15 am – 12:30 pm **Platform Session 7 – Salon C** ***(CME and CEU Approved)***
Moderator: Krista Mantay Ringey, MS, RD, LD/N, University of Florida

11:15 am – 12:00 pm **Invited Speaker: "Sources of Cognitive Variability in Phenylketonuria Beyond Phe"**
Meriah Schoen, PhD, RDN, Emory University School of Medicine

12:00 pm – 12:15 pm **"Racing Towards a Diagnosis: Rapid Genomic Sequencing in Hospitalized Pediatric Patients"**
Kristen Lancaster, MD, Medical University of South Carolina

12:15 pm – 12:30 pm **"Results of Molecular Genetic Autopsies in Florida"**
Edwin Naylor, PhD, MPH, NCGM Laboratory

12:30 pm – 1:00 pm **SERGG Business Meeting & Student Award Presentations – Salon C –** Hans Andersson, MD, SERGG Incoming President

1:00 pm **Adjournment** – See you next year!

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Medical Association of Georgia through the joint providership of Self Regional Healthcare and the Southeastern Regional Genetics Group (SERGG). Self Regional Healthcare is accredited by the Medical Association of Georgia to provide continuing medical education for physicians.

Self Regional Healthcare designates this live activity for a maximum of **10.0** ***AMA PRA Category 1 Credits™.*** Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Save the Dates!

Future SERGG Meetings

July 15-19, 2025

July 14-18, 2026

Renaissance Downtown Marriott
Asheville, North Carolina

PLATFORM PRESENTATIONS IN ORDER PRESENTED

ENDOGENOUS NON-REDUCING END GLYCOSAMINOGLYCAN ANALYSIS PROVIDES DISEASE-SPECIFIC BIOMARKERS FOR DIAGNOSIS AND MONITORING OF MUCOLYSACCHARIDOSES

Kubaski F, and Pollard L
Greenwood Genetic Center, Biochemical Genetics Laboratory, Greenwood, SC

Mucopolysaccharidoses are caused by a deficiency of lysosomal enzymes that lead to impaired glycosaminoglycan (GAG) metabolism. One of the newest methods used for the analysis of GAGs by tandem mass spectrometry is endogenous non-reducing end (NRE) analysis, which measures the disease-specific endogenous NRE fragment that accumulates in vivo due to an enzyme deficiency. This method can be used in a variety of specimen types, including dried blood spot for second-tier newborn screening. It also provides a biomarker for treatment monitoring that more directly represents disease pathogenesis. In this study, we have validated the semi-quantification of nine NRE fragments (UA-HNAc(1S) early retention time for MPS I; UA-HNAc(1S) late retention time for MPS II; HN-UA (1S) for MPS IIIA; HNAc-UA-HNAc for MPS IIIB; HNAc-UA (1S) for MPS IVA/VI; $(Hex\text{-}HNac)_2(2S)$ for MPS IVB/GM1; HNAc(2S) for MPS VI; UA-HN-UA(1S) for MPS VII; HNAc(1S) for MPS IVA/VI) by ultra-high performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) in urine. Clinical sensitivity was demonstrated using urine samples from untreated MPS patients (MPS I=33, MPS II= 43, MPS IIIA= 21, MPS IIIB= 9, MPS IVA= 23, MPS IVB/GM1= 8, MPS VI= 14, MPS VII= 12), and 78 age-matched controls. Despite the assay being semi-quantitative, intra-day and inter-day precision was also confirmed. . This study shows that urine endogenous NRE analysis can be used for diagnosis and monitoring of patients with MPS disorders. Further evaluation is needed to determine if the method can define disease severity and/or clearly distinguish affected patients from those with clinically benign hypomorphic (pseudodeficiency) alleles.

FALSE POSITIVE NEWBORN SCREENING FOR GALACTOSEMIA IN G6PD PATIENTS IN FLORIDA

Alfonso Rodriguez J, Gonzalez JM, Hacker S, Mishkin V, Tellez M, Thorson W
Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami Miller School of Medicine, FL

Classic Galactosemia results from a deficiency in the galactose-1-phosphate uridyltransferase (GALT) enzyme, impacting galactose metabolism. Newborn screening (NBS) for galactosemia in Florida follows a two-step process, measuring GALT enzyme and total galactose levels. It is standard for newborns who screen positive for galactosemia to switch to a galactose-free formula, usually soy-based, until confirmatory testing can be obtained. Reported instances where positive galactosemia screenings were later linked to glucose-6-phosphate dehydrogenase (G6PD) deficiency underscores a necessity for comprehensive evaluation to prevent misdiagnosis, as soy-based formula has been reported to trigger hemolysis in G6PD deficient patients. We report on a baby boy born in Florida who had an abnormal NBS suggestive of galactosemia, prompting a switch to soy formula. Six days following the switch, the baby had a hemolytic crisis. Genetic workup returned negative for *GALT,* but positive for a *G6PD* variant of uncertain significance (VUS). This incident prompted a retrospective chart review revealing five additional cases with false-positive NBS for galactosemia that were linked to G6PD deficiency, since G6PD testing started being offered as part of galactosemia workup in our Genetics Center. These infants had also been switched to a soy-based formula, but fortunately had not had hemolytic crises before their G6PD diagnosis. Given the frequency at which G6PD may be diagnosed following abnormal NBS for Galactosemia, we propose consideration of G6PD co-testing during galactosemia confirmatory testing and the use of elemental formula for infants with positive NBS for galactosemia (especially males) before confirmatory testing is complete, aiming to prevent hemolytic crisis.

PLATFORM PRESENTATIONS IN ORDER PRESENTED

GENOTYPE-PHENOTYPE CORRELATIONS IN VERY-LONG-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY: INSIGHTS FROM A FLORIDA COHORT

Fletcher E[1], Sethuraman M[2], Bloom K[2], Vockley J[2], Racobaldo M[1], Sanchez-Valle A[1]
[1]Division of Genetics and Metabolism, Department of Pediatrics, College of Medicine, University of South Florida, [2] Division of Genetic and Genomic Medicine, Department of Pediatrics, School of Medicine, University of Pittsburgh

Background: Very-long chain acyl-CoA dehydrogenase deficiency (VLCADD) is a fatty acid oxidation disorder resulting from biallelic mutations in the *ACADVL* gene. In Florida, screening for this condition involves assessing metabolite C14:1 level. Confirmatory genetic testing is conducted following elevated C14:1 levels, guiding diagnosis and management. This study explores the genetic variant spectrum in 24 VLCADD patients identified on newborn screening (NBS). Methods: We conducted a retrospective chart analysis of 24 individuals aged 0-12 years identified with VLCADD on NBS. To assess pathogenicity of protein-coding variants, we transfected mammalian expression plasmids containing the variant or control *ACADVL* cDNA and transfected into an *ACADVL* null HEK293T cell line. VLCAD protein presence and enzyme activity were quantitated by Western blot and a fluorescence reduction enzyme assay, respectively. Results: Among the 24 patients, 11 harbored biallelic *ACADVL* mutations, with three experiencing rhabdomyolysis episodes (creatine phosphokinase level >1000U/L). Notably, all three individuals had at least one pathogenic severe variant. Symptomatic patients exhibited a mean newborn screening C14:1 level of 3.43umol/L, significantly higher than asymptomatic individuals (mean:1.60umol/L, p=0.0028). Patients with one or more pathogenic severe mutations had a higher mean newborn screening C14:1 level (1.84umol/L) compared to those with pathogenic mild or benign mutations (1.51 umol/L). Conclusion: This study elucidates genotype-phenotype correlations in VLCADD, particularly the association between genetic variant analysis, clinical creatine phosphokinase (CPK) levels, and newborn screening C14:1 level. We hope that variant analysis will aid in predicting disease phenotype and facilitating tailored management and surveillance strategies for VLCADD patients.

GENETIC NEEDS ASSESSMENT OF CHILDREN WITH INTELLECTUAL DISABILITY, DEVELOPMENTAL DELAY, HEARING LOSS, AND/OR AUTISM SPECTRUM DISORDER IN THE SOUTHEASTERN UNITED STATES

Meier C[1], Gunn G[1], and Kenneson A[1]
[1]Emory University, School of Medicine, Department of Human Genetics, Atlanta, GA

Referral to genetics specialists plays a pivotal role in the diagnostic journey of children with conditions such as autism spectrum disorder (ASD), developmental delay, intellectual disability, and hearing loss. Although there are referral guidelines in place from the American College of Medical Genetics and Genomics (ACMG), not all eligible children receive referrals. Our study delves into barriers hindering pediatric patients' access to genetics services in Florida and South Carolina. We invited parents/carers of young children with one or more of these conditions to participate in an online survey, in English or Spanish. Of the 140 completed responses, 43 of respondents reported that they were not referred to a genetics provider. Of the individuals who reported being referred to genetics, only two-thirds actually met with a geneticist and/or genetic counselor. Knowledge of insurance coverage for genetic testing was found to be a common barrier for both referral to genetics and attendance at a genetics consultation. In addition, child's race was a predictor of whether or not the genetics consultation was attended after a referral was made. Finally, those who were referred and attended a genetics consultation were more likely to have a specific genetic diagnosis/known etiology of their child's diagnosis. This highlights the important role these consultations play in understanding the etiology of conditions and informing recurrence risks for family members. Overall, this research emphasizes the need for genetics education and improved accessibility to genetics services, helping us work towards better outcomes for pediatric patients and their families.

PLATFORM PRESENTATIONS IN ORDER PRESENTED

CNS INVOLVEMENT IN POMPE: UNVEILING RISKS THROUGH NEURORADIOLOGICAL SURVEILLANCE

Regmi N[1], Jung S-H[1], Malinzak M[2], Kenney-Jung D[3,] Jones HN[4], Spiridigliozzi GA[5], and Kishnani PS[1]

[1]Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center, Durham, NC; [2]Division of Radiology, Duke University School of Medicine, Durham, NC; [3]Department of Child Neurology, Duke University Medical Center, Durham, NC; [4]Department of Head and Neck Surgery & Communication Sciences, Duke University School of Medicine, Durham, NC; [5]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center.

Enzyme replacement therapy (ERT) with alglucosidase alfa has transformed the outlook of Pompe disease. As children with Infantile onset Pompe disease (IOPD) are living longer, neurological issues such as sensory neural hearing loss, gait abnormalities, dysarthria and white matter hyperintensities (WMHI) on MRI are being recognized. Patients have also developed seizures and in rare cases, mortality. At Duke University, our monitoring of IOPD patients, has enabled us to assess central nervous system (CNS) involvement. We have developed the 'Modified Fazekas Scoring System' to quantify white matter hyperintensities in 9 brain regions using MRI in the superficial and deep white matter. Baseline MRI starts at age 5 followed by scans every 2-3 years. Each brain region is assigned a score from 1 to 5, culminating in a total score of 45 (range: 0-45), with a score of ≥ 20 indicating severe involvement. We analyzed total of 48 MRI scans and clinical data from 13 patients, divided into two cohorts: those with seizures and/or encephalopathy(n=6), and long-term survivors over age 18 yrs. doing well clinically (n=7). Neither group had additional secondary genetic diagnosis. Patients with severe phenotypes had higher baseline scores (>20), which progressed over time with neurological deterioration and seizure. Among the long-term survivors, all had low baseline scores and maintained similar trend throughout exhibiting favorable neurocognitive outcomes. These findings highlight the crucial role of baseline MRI in assessing risk and neurological monitoring. We recommend initiating baseline MRI assessments at age 5 to mitigate sedation risks that could worsen airway issues.

EFFECT SIZE ANALYSIS OF CIPAGLUCOSIDASE ALFA PLUS MIGLUSTAT VERSUS ALGLUCOSIDASE ALFA IN ERT-EXPERIENCED ADULTS WITH LATE-ONSET POMPE DISEASE IN PROPEL

Dimachkie MM[1], Bratkovic D[2], Byrne BJ[3], Claeys KG[4], Díaz-Manera J[5,6,7], Kishnani PS[8], Kushlaf H[9], Roberts M[10], Toscano A[11], Castelli J[12], Holdbrook F[12], Das SS[12], Schoser B[13], Mozaffar T[14], *on behalf of the PROPEL Study Group*

[1]Department of Neurology, University of Kansas Medical Center, Kansas City, KS; [2]PARC Research Clinic, Royal Adelaide Hospital, Adelaide, SA, Australia; [3]University of Florida, Gainesville, FL; [4]Department of Neurology, University Hospitals Leuven, and Laboratory for Muscle Diseases and Neuropathies, Department of Neurosciences, KU Leuven, Leuven, Belgium; [5]John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, UK; [6]Neuromuscular Disorders Unit, Neurology Department, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain; [7]Centro de Investigación en Red en Enfermedades Raras (CIBERER), Barcelona, Spain [8]Duke University Medical Center, Durham, NC; [9]Department of Neurology & Rehabilitation Medicine, University of Cincinnati College of Medicine, Cincinnati, OH; [10]Salford Royal NHS Foundation Trust, Salford, UK; [11]ERN-NMD Center for Neuromuscular Disorders of Messina, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [12]Amicus Therapeutics, Inc., Princeton, NJ; [13]Friedrich-Baur-Institute at the Department of Neurology, LMU University Hospital, LMU Munich, Munich, Germany; [13]Department of Neurology, University of California, Irvine, CA.

PLATFORM PRESENTATIONS IN ORDER PRESENTED

Background The randomized, double-blind PROPEL study (NCT03729362) compared the efficacy and safety of the two-component therapy cipaglucosidase alfa plus miglustat (cipa+mig) with alglucosidase alfa plus placebo (alg) in adults with late-onset Pompe disease (LOPD); 77% of patients had received enzyme replacement therapy (ERT) with alg before study entry (median 7.4 years). **Objective** To analyze effect sizes of cipa+mig and alg for efficacy outcomes in ERT-experienced patients with LOPD. **Methods** Standardized within-group effect sizes (Cohen's d for correlated measurements, baseline to week 52) were calculated for outcomes including motor and lung function, muscle strength, quality of life and biomarkers in ERT-experienced patients by dividing mean change from baseline by standard deviations of the difference scores. **Results** Patients remaining on alg (n=30) showed worsening ($d \leq -0.2$) or stability ($-0.2 < d < 0.2$) across most outcomes, while those switching to cipa+mig (n=65) showed improvement ($d \geq 0.2$) or stability. Patients remaining on alg demonstrated statistically significant within-group worsening for sitting and supine forced vital capacity; slow vital capacity; maximal expiratory pressure; creatine kinase (CK) and hexose tetrasaccharide (Hex4) levels, and significant improvement only for Patient-Reported Outcomes Measurement Information System (PROMIS)–Dyspnea score. Patients switched to cipa+mig did not demonstrate significant within-group worsening and showed significant improvements for 6-minute walk distance; manual muscle tests; PROMIS–Fatigue score; Physician and Subject Global Impression of Change (five subdomains); and CK and Hex4. **Conclusions** ERT-experienced patients with LOPD switched to cipa+mig achieved improvements in various outcomes, highlighting the potential of cipa+mig as a treatment option for these patients. Supported by Amicus Therapeutics, Inc.

DHX16-ASSOCIATED NEUROMUSCULAR OCULOAUDITORY SYNDROME: A NOVEL CASE

Clay S[1] and Zambrano R[2]

[1]Louisiana State University Health Sciences Center New Orleans, Department of Genetics, New Orleans, LA; [2]Louisiana State University Health Sciences Center and Children's Hospital of New Orleans, Department of Pediatrics, Division of Clinical Genetics, New Orleans, LA

DHX16, a member of the DexD/H-box RNA helicase family, facilitates ATP-dependent unwinding of RNA secondary structures. Pathogenic variants produce spliceosome function defects and intron retention leading to neuromuscular oculoauditory syndrome (MIM #618733). To date, there are eight published cases. We report a ninth case: 7-month-old female with mild developmental delay, very blonde fundus with choroidal vasculature around the optic disc, myopia, esotropia, forehead hemangioma, low set ears, digital abnormalities, and increased infections. Invitae Inherited Retinal Disorder Panel testing identified non-diagnostic variants of uncertain significance (VUS). Whole-exome and mitochondrial sequencing revealed a *de-novo* Likely Pathogenic variant: *DHX16* c.692 G>C p.(R231P) and confirmed paternal inheritance of non-diagnostic VUS. Published cases report developmental delay/intellectual disability, seizures, myopathy, ocular anomalies, and hearing loss. Our case may represent a milder presentation or a distinct *DHX16* phenotype given she is now 2 years old without additional symptoms. Literature review revealed no published variants located upstream of amino acid position 399, representing a demarcation between known functional domains downstream and unknown domains upstream. 2 of 3 programs predict pathogenicity in-silico. Missense3D modeling demonstrates no structural damage to the protein. Drackley et. al. 2023 found 3 of 7 published variants also produce no structural damage using Missense3D, suggesting a mechanism of pathogenicity that is difficult to assess via modelling. This case represents the importance of further testing after detection of non-diagnostic VUS without phenotypic match. This case also illustrates a *DHX16* variant in an unknown domain that may lead to a mild phenotype.

PLATFORM PRESENTATIONS IN ORDER PRESENTED

THE UTILITY OF REFERRALS FROM A STATE EARLY INTERVENTION SYSTEM TO A PEDIATRIC GENETICS CLINIC TO INCREASE ACCESS TO GENETIC SERVICES

Jennings M[1]; Rose A[2]; Drazba K[2]; Lyons M[2]
[1]Genetic Counseling Program, University of South Carolina School of Medicine; [2]Greenwood Genetic Center

Infants or toddlers enrolled in state early intervention programs have developmental delays or are diagnosed with conditions resulting in developmental delays. South Carolina's early intervention program, BabyNet, offers genetic evaluations for enrollees at no cost to the family. Exploring the relationship between early intervention programs and genetic clinics and the impact on this patient population can provide support for the new and continued use of this service delivery model. The purpose of this study was to determine if the collaboration between the Greenwood Genetic Center (GGC) and BabyNet effectively increases access to genetic services. A retrospective review of electronic medical records was completed to compare participants referred by BabyNet to those referred by other providers. Participants referred by BabyNet and evaluated by eVisit were compared to those who had in-person or telemedicine visits to assess eVisits as an alternative service delivery model used for genetic evaluations of patients referred by early intervention. Included in the study were 680 participants under age three at the time of their initial clinical evaluation at GGC. A statistically significant difference in the distribution of race and ethnicity between BabyNet and provider-referred patients was found. BabyNet referrals increased access to genetic services for racial and ethnic minority groups. Genetic testing was indicated for over 50% of the BabyNet-referred participants, providing evidence for early intervention enrollees being an ideal group to receive comprehensive genetic evaluations. BabyNet participants evaluated by eVisit had similar diagnostic rates and fewer days from when their referral was placed to their evaluation.

USING GENOME SEQUENCING TO SCREEN NEWBORNS IN NORTH CAROLINA: SUCCESSES AND CHALLENGES IN THE FIRST SIX MONTHS

Cope HL[1], Jalazo ER[2], Sullivan JA[2], Forsythe AM[1], Kucera KS[1], Powell CM[2], Peay HL[1]
[1]RTI International; [2]UNC Department of Pediatrics, Division of Genetics and Metabolism

Early Check is a voluntary newborn screening research program available to parents in North Carolina. In September 2023, we began offering screening via genome sequencing for two panels of monogenic conditions and risk for type 1 diabetes (T1D) using a genetic risk score (GRS). Panel 1 includes 178 gene-condition pairs with high actionability. Panel 2 offers screening for an additional 29 gene-condition pairs with emerging actionability. In the first six months, 1805 newborns were enrolled. Most parents (~80%) chose Panel 1, Panel 2 and T1D risk. Six months post launch, 1466 newborns were successfully screened and resulted, 254 in progress, 42 excluded due to insufficient residual DBS, and 43 excluded due to insufficient DNA quantity. Of those resulted, 1432 had negative monogenic results and 34 had positive results (2.3%). The most common screen positive result was G6PD deficiency. Challenges in interpreting the clinical implications of screen positive results included genes with variable expressivity and reduced penetrance (*SCN1A*), genes with both autosomal recessive and dominant phenotypes (*ABCC8*) and determining the phase of two heterozygous variants when both biologic parents were not available. Calculated GRS were converted into lifetime risk groups and reported as low (<2% risk), moderate (2-5%), or higher concern (>5%). Follow-up is offered to newborns with positive monogenic results and higher concern T1D risk results including genetic counseling and condition-specific follow-up testing. Early Check successfully implemented voluntary state-wide supplemental screening with genome sequencing. Our study informs feasibility, acceptability, and utility of future offering of newborn screening via genomic sequencing.

PLATFORM PRESENTATIONS IN ORDER PRESENTED

TAILORED DIAGNOSTIC DECISION TREE RESULTING FROM MACHINE LEARNING TO IMPROVE EARLY DIAGNOSIS OF ASMD

Croal L[7], on behalf of Scarpa M[1], Cappellini MD[2], Giugliani R[3], Törnqvist M[4], Clemente C[4], Montmerle M[5†], Chiorean A[4], Reppelin T[4], Sansen S[6], Dumitriu A[7], Shah N[7*], Gasparic M[8]
*[1]Regional Coordination Center for Rare Diseases, Central Friuli University Health Authority, Udine, Italy; [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Department of Clinical Sciences and Community Health, University of Milan, Italy; [3]UFRGS, HCPA, INAGEMP, DASA and CASA DOS AROS, Porto Alegre, Brazil; [4]Quinten Health, Paris, France; [5]Sanofi, Neuilly-sur-Seine, France; [6]Sanofi, Diegem, Belgium; [7]Sanofi, Cambridge, MA, USA; [8]Sanofi, Amsterdam, The Netherlands; *Former employee of Sanofi, Cambridge, MA, USA [†]Former employee of Quinten Health, Paris, France*

Acid sphingomyelinase deficiency (ASMD) is a rare, debilitating, and underdiagnosed lysosomal storage disease. We employed machine learning (ML) on electronic health records (EHRs) to develop a data-driven decision tree (algorithm) for identifying high-risk ASMD patients based on clinical and laboratory traits. EHRs from Optum's de-identified Market Clarity Data (2007-2020) were utilized for algorithm training. To generate the decision tree, the available ASMD cohort (N=51) was enriched with 199 clinical characteristics and 11 laboratory measurements, and a matched-control cohort was extracted at 1:20 ratio (N=1020). The resulting decision tree used a combination of four laboratory measurements (HDL cholesterol, LDL cholesterol, platelet count, and triglycerides) and one clinical feature (hydrocephalus). It distinguished ASMD from the matched-control population with a sensitivity of ~80% and specificity of >99%. We internally validated this decision tree and compared its performance to a published clinical algorithm (McGovern, 2017) from a more recent version of the same database (data up to January 2023). For this, 5 newly diagnosed ASMD patients, and 250,000 randomly sampled controls (non-overlapping with the training cohort) were included. The ML-derived decision tree correctly flagged 2/5 ASMD patients (40% sensitivity) and 1,763/250,000 controls (0.61%; specificity >99%). Sensitivity of the clinical algorithm matched that of the decision tree. Although, the ML-derived decision tree flagged fewer control patients, thus the clinical algorithm exhibited lower specificity (3,733/250,000; specificity 98.5%). Due to fewer ASMD patients available in the validation cohort, further assessment in another independent EHR is advisable. **Funding:** Sanofi.

LONG-TERM SAFETY AND UREA CYCLE FUNCTION FOLLOWING A PHASE 1/2 TRIAL OF DTX301 IN ADULTS WITH LATE-ONSET ORNITHINE TRANSCARBAMYLASE DEFICIENCY (OTCD)

Harding GO[1], Geberhiwot T[2], Couce ML[3], Guffon N[4], Tan W-H[5], Hualde LC[6], Khan A[7], Konczal LL[8], Thomas JA[9], Breilyn MS[10], Patra K[11], Merritt, II JL[11], and Crombez E[11] on behalf of the CAPtivate DTX301 investigators. Presented by Julian Mesa.[11]
[1]Oregon Health & Science University, Portland, OR; [2]University of Birmingham, Birmingham, UK; [3]University of Santiago de Compostela, Santiago de Compostela, Spain; [4]Reference Centre in Inherited Metabolic Diseases, HCL, Lyon, France; [5]Boston Children's Hospital, Harvard Medical School, Boston, MA; [6]Cruces University Hospital, Biocruces Bizkaia Health Research Institute, Barakaldo, Spain; [7]M.A.G.I.C. Clinic Ltd., and University of Calgary, Calgary, Canada; [8]University Hospitals of Cleveland Medical Center, Cleveland, OH; [9]University of CO School of Medicine and the Children's Hospital Colorado, Aurora, CO; [10]Icahn School of Medicine at Mount Sinai, New York, NY; [11]Ultragenyx Gene Therapy, Cambridge, MA.

Background: OTCD is an X-linked urea cycle disorder that can lead to episodic hyperammonemia, coma, irreversible brain damage, and death. DTX301 is an AAV8 vector containing the OTC transgene under investigation for treatment of OTCD. We report LTFU of 11 adults with late-onset OTCD who received DTX301 in the Phase 1/2 trial (NCT02991144). **Methods:** The Phase 1/2 study lasted 52 weeks; all patients

are being followed for up to an additional 8 years. Patients received a single IV infusion of DTX301 on Day 1 ranging from $3.4x10^{12}$ to $1.7x10^{13}$ GC/kg. Cohort 4 patients received a prophylactic oral steroid taper. All received reactive steroids as needed. Data cutoff was 09Dec2023. **Results:** Patients have been followed for 3-6.3 years. No treatment-related serious AEs, dose-limiting toxicities, or infusion-related events have been reported. During the primary study, six patients experienced vector-induced hepatic effects. All resolved following corticosteroid administration. During LTFU, three patients experienced mild ALT elevations and one patient experienced hyperammonemic crises (all considered unrelated to DTX301). Corticosteroids were generally well tolerated. Five patients had non-serious corticosteroid-related AEs. Most corticosteroid-related AEs were mild (grade 1), though one patient had grade 3 AEs. Neither prophylactic nor reactive corticosteroids were associated with increased ammonia, hyperammonemia, or hyperammonemic crisis. Rate of ureagenesis improved over time and was increased 79% relative to baseline at Week 182 (the last time point with >1 patient, n=4). **Conclusions:** DTX301 continues to show manageable safety and durable efficacy. The Phase 3 trial (NCT05345171) is currently enrolling patients >12 years of age.

STROKE IN PATIENTS WITH FABRY DISEASE: A FABRY REGISTRY ANALYSIS OF NATURAL HISTORY DATA FROM PATIENTS STRATIFIED BY DISEASE PHENOTYPE

Burlina AP,[1] Politei JM,[2] Crespo A,[3] Ponce E,[3] Batista JL,[4] Maski M,[3] Ebels JT,[3] Al-Shaar L[4]
(Presented by Reviriego-Mendoza M)
[1]Neurology Unit, St Bassiano Hospital, Bassano del Grappa, Italy; [2]Neurology Department, Fundación SPINE, Buenos Aires, Argentina; [3]Global Medical Affairs, Rare Nephrology, Sanofi, Cambridge, MA; [4]Epidemiology/Biostatistics, Sanofi, Cambridge, MA.

In Fabry disease (FD), absent/deficient α-galactosidase-A activity causes lysosomal glycosphingolipid substrate accumulation triggering detrimental cellular and tissue reactions, resulting in progressive dysfunction of kidneys, heart, and nervous system. We analyzed the prevalence and characteristics of stroke during the natural history (NH) period in patients stratified by predicted FD phenotype. NH data were collected until end of follow-up (never-treated patients) or date of treatment initiation (ever-treated patients) from 7,996 patients enrolled in the Fabry Registry (NCT00196742) as of August 4, 2023. Patients with a report of a stroke finding but no available date of occurrence (n=24) were excluded. Overall, 5.4% (190/3499) male and 4.7% (211/4473) female patients had reported stroke(s) occurrence during the NH period. Among classic males (n=102) and females (n=145), first stroke occurred at median age 37.9 vs 45.4 years, and before FD diagnosis in 64.7% vs 42.1%. Among later-onset males (n=25) and females (n=12), first stroke occurred at median age 47.3 vs 44.8 years, and before FD diagnosis in 68.0% vs 91.7%. The majority of first strokes were ischemic. Recurrent NH strokes were most prevalent among classic males (23.5%) and later-onset females (25.0%). Other severe clinical events occurring at/before stroke (≥10% patients) included cardiac (classic: males, 17.6%; females, 17.9%; later-onset: males, 16.0%) and renal events (classic males, 11.8%). This large, real-world FD study demonstrates that patients with classic or later-onset phenotypes are at risk of developing stroke, often occurring at a young adult age, as the first severe clinical event leading to a diagnosis of FD.

EFFICACY AND SAFETY OF ORAL SEPIAPTERIN IN PARTICIPANTS WITH PHENYLKETONURIA ON SAPROPTERIN DIHYDROCHLORIDE AT TIME OF PHASE 3 APHENITY STUDY ENTRY

Zori R[1], Lah M[2], Offord S[3], Lund A[4], Opladen T[5], Peters H[6], Guilder L[7], Ezgü F[8], Breilyn MS[9], Manti F[10], Guerra IdCC[11], Ingalls K[2], Zhao Z[12], Larkin A[12], Hughes C[12], Somera-Molina K[12], Blaize J[12], Dong E[12], Smith N[12] and Longo N[13]
[1]Department of Pediatrics, University of Florida College of Medicine, Gainsville, FL; [2]Department of Medical and Molecular Genetics, Indiana University School of Medicine Indianapolis, IN; [3]Department of Pediatrics, Medical College of Wisconsin, Milwaukee, WI; [4]Department of Pediatrics and Clinical Genetics, Copenhagen University Hospital, Rigshospitalet, Copenhagen,

Denmark; [5]Heidelberg University, Medical Faculty Heidelberg, Center for Pediatric and Adolescent Medicine, Division of Pediatric Neurology and Metabolic Medicine, Heidelberg, Germany; [6]Department of Metabolic Medicine, Royal Children's Hospital, Melbourne, VIC, Australia; [7]The Hospital for Sick Children, Toronto, ON, Canada; [8]Faculty of Medicine, Gazi University, Ankara, Turkey; [9]Department of Genetics and Genomics, Icahn School of Medicine at Mount Sinai, New York, NY; [10]Department of Human Neuroscience, Unit of Child Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy; [11]PanAmerican Clinical Research, Guadalajara, Jalisco, Mexico; [12]PTC Therapeutics Inc., South Plainfield, NJ;[13]Division of Medical Genetics, University of Utah, Salt Lake City, UT.

Objectives: The Phase 3 APHENITY trial (NCT05099640) was a global, two-part, registration-directed study evaluating the efficacy and safety of sepiapterin in a broad PKU population. APHENITY met its primary endpoint demonstrating significant reductions in blood Phe with sepiapterin. We assessed the efficacy and safety of sepiapterin versus placebo in a subset of participants receiving sapropterin dihydrochloride at study entry. **Methods**: Participants receiving sapropterin dihydrochloride at study entry completed a 7-day washout period prior to sepiapterin dosing. Part 1 was a 14-day sepiapterin-responsiveness test. Participants ≥2 years with ≥15% reduction in blood Phe progressed to Part 2 (6-week, randomized, placebo-controlled, double-blind). Safety was also evaluated. **Results**: Of the 157 participants in APHENITY, 27 (17.2%) (median age 14.0 years; [min, max; 2, 42]) were receiving sapropterin dihydrochloride at study entry (mean blood Phe of 581.8µmol/L). Following a 7-day washout, mean blood Phe increased to 680.9µmol/L. After 14 days of sepiapterin treatment (60 mg/kg), mean blood Phe was reduced by 48% from 581.8µmol/L to 304.6µmol/L. Most participants (23/27, 85.2%) responded to sepiapterin with a blood Phe reduction of ≥30% from baseline (Part 1). At Weeks 5 and 6 of Part 2, a significant reduction in mean blood Phe from baseline was observed with sepiapterin (n=14; least-square mean change [SE], −467.5 [44.5]µmol/L) compared to an increase with placebo (n=7; 123.6 [62.3]µmol/L; p<0.0001). Overall, sepiapterin was well tolerated. **Conclusions**: Treatment with sepiapterin resulted in a clinically meaningful and significant reduction in blood Phe in children and adults with PKU receiving sapropterin dihydrochloride at study entry.

D-ASPARTATE IN *SPTAN1*-RELATED HEREDITARY SPASTIC PARAPLEGIA: A MODEL FOR THE DEVELOPMENT OF ACCESSIBLE TREATMENTS IN RARE GENETIC DISEASE

Rose A[1], Lu P-N[1], Dupont BR[1], Jones JR[1], Lyons MJ[1], and Flanagan-Steet HF[1]
[1]*Greenwood Genetic Center, Greenwood, SC*

Heterozygous pathogenic variants in the *SPTAN1* gene are associated with a range of neurologic manifestations including developmental delay, intellectual disability, seizures, and motor neuropathy. More recently, homozygous pathogenic variants in *SPTAN1* have been reported in association with hereditary spastic paraplegia (HSP) and intellectual disability. Here, we will describe the case of a now 18 year-old female patient who was diagnosed through the Greenwood Genetic Center (GGC) Laboratory with autosomal recessive *SPTAN1*-related HSP, caused by a *de novo* pathogenic variant in *SPTAN1* in combination with uniparental disomy of chromosome 9. This diagnosis was made prior to published reports of autosomal recessive *SPTAN1*-related HSP through collaboration between GGC's clinical, laboratory, and research divisions. With the use of zebrafish models, D-Aspartate was identified as a potential over-the-counter treatment for our patient's symptoms of paraparesis, weakness, and unsteady gait. This supplement was administered to the patient and her progress was closely followed over the course of 2 years. During this time, improvements were observed in the patient's overall functioning and quality of life. This case exemplifies one of the primary goals of GGC's developing treatment program, which aims to identify other novel treatments for rare genetic conditions. As exemplified in this case, GGC's treatment program will rely on collaboration between laboratory, research, and clinic staff to drive translational research. We will highlight important insights from this case that will allow us to expand and grow a model for developing treatments for other patients with rare genetic disorders across the state of South Carolina.

PLATFORM PRESENTATIONS IN ORDER PRESENTED

LIGHTNING STRIKES TWICE: DUAL DIAGNOSIS OF DE NOVO X-LINKED DISORDERS

Spaeth C and Zambrano R
Children's Hospital of New Orleans and LSU Health Sciences Center

De novo genetic variants are a known contributor to genetic disease. We present a case of a female found to have de novo variants in two different X-linked genes which explain her clinical presentation. Our patient (CB) was a 10-month-old female referred for developmental delays and bilateral cataracts. CB was born to a 35-year-old G5 P2 SAb female. Pregnancy was complicated by oligohydramnios at 35 weeks, prompting c-section. Birthweight was 6 pounds 1 ounce with no perinatal complications reported. At 8 months bilateral cataracts were detected and one was resected. At 10 months of age CB was sitting independently for brief periods of time and not yet babbling. Trio whole exome sequencing detected de novo variants in the HUWE1 (c.2479 G>A, p.V827I) and NSH (c.4450 C>T, p.R1484*) genes. Variants in HUWE1 have been reported in females with variable degrees of developmental delay/intellectual disability, hypotonia, speech issues and short stature. Females with NSH variants have been reported to have ocular issues, including cataracts, but typically do not have developmental delays as reported in males. This case illustrates the utility of whole exome sequencing in providing a complete diagnostic evaluation, since a targeted panel for ocular anomalies would not have detected the HUWE1 variant. While this case may be an example of lightning striking twice, it raises the possibility that other factors may be contributing to the dual diagnoses in our patient.

EXPANDING THE CLINICAL PHENOTYPE AND VARIANT SPECTRUM ASSOCIATED WITH *RFX7*.

Santos TS[1], Santos AD[1], Rippert AL[2], Gray C[2], Skraban CM[2], Nelson B[3], Li D[3,4], Bhoj EJ[3,4], Sobering AK[1]
[1]AU/UGA Medical Partnership Campus of the Medical College of Georgia; [2]The Children's Hospital of Philadelphia, Division of Human Genetics, Department of Pediatrics, Philadelphia, PA; [3]St. George's University School of Medicine, Clinical Teaching Unit, Grenada; [4]The Children's Hospital of Philadelphia, Center for Applied Genomics, Philadelphia, PA.

Background: *RFX7* encodes a ubiquitously expressed transcription factor which is important for neural development. Haploinsufficiency of *RFX7* is associated with intellectual disability, developmental delay, and various brain malformations. Only three studies describing 16 individuals with variants in *RFX7* have been published thus far. Currently, there is no recognizable pattern of malformation in individuals with variants in *RFX7*. Case Presentation: Here, we describe two additional individuals with novel *de novo* variants in RFX7. Individual 1 is a 14-year-old Afro-Caribbean female who had ID, language delay, GDD, microcephaly, rocker-bottom feet, and facial dysmorphisms. She was born with an eventually repaired patent ductus arteriosus. Individual 2 is a 30-month-old male who had microcephaly, developmental delay, exotropia, an accessory nipple, cutaneous toe syndactyly and partial biotinidase deficiency. Trio exome sequencing showed a novel *de novo* variant in *RFX7* (NM_001370561.1: c.2905_2908dup; p.(Ala970Aspfs*24)) in individual 1 and a novel *de novo* variant in *RFX7* NM_001370561.1: c.2750dupA, p.(Ser918Valfs*50). Individual 1's variant is predicted to be pathogenic by criteria established by the American College of Medical Genetics and Genomics. Conclusions: Our report expands the knowledge of the allelic heterogeneity associated with *RFX7* variants and the heterogeneous phenotype associated with monoallelic loss of function variants in this gene. Understanding of *RFX7* is limited, with a variety of clinical presentations, which may include ID, GDD, multiple congenital abnormalities, facial dysmorphism, behavioral issues, and ASD. As more is learned about *RFX7* and its associated phenotypes, a recognizable pattern in humans may eventually be uncovered.

PLATFORM PRESENTATIONS IN ORDER PRESENTED

THE POWER OF INTERNATIONAL COLLABORATION IN RARE GENETIC DISEASES: ADVANCING THE UNDERSTANDING OF MUSCLE PHOSPHORYLASE KINASE DEFICIENCY (GSD IXα1)

Fares AH[1], Koch RL[1], Cocanougher BT[1], Lim J[1], Schreuder AB[2], Derks TGJ[2], Grünert SC[3], Sharma R[4], and Kishnani PS[1]

[1]Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center, NC; [2]Division of Metabolic Diseases Beatrix Children's Hospital University of Groningen University Medical Center Groningen, the Netherlands; [3]Department of General Pediatrics Adolescent Medicine and Neonatology Faculty of Medicine Medical Center - University of Freiburg Freiburg, Germany; [4]Mark Holland Metabolic Unit, Adult Inherited Metabolic Diseases Department, Salford Royal NHS Foundation Trust, Salford, UK.

Muscle phosphorylase kinase (PhK) deficiency results from X-linked inherited pathogenic variants in the *PHKA1* gene, leading to glycogen storage disease (GSD) type IXα1, or GSD IXd. With only 19 reported cases (onset age: 0.5 – 72 years), understanding its clinicopathological-genetic spectrum remains challenging. Through international collaboration, we describe 10 previously unreported, molecularly confirmed cases (9 males, 1 female; age range: 1.2 – 68 years). Longitudinal data on patients with pathogenic *PHKA1* variants from the United States and Canada (N=6), the United Kingdom (N=1), Germany (N=1), and the Netherlands (N=2) were collected. Muscle biopsy histology was analyzed when available (N=4). Findings were compared with 19 previously reported cases and 32 patients with pathogenic *PHKA1* variants from the All of Us dataset (N=245,288). In our cohort, primary manifestations included myopathic symptoms (lower extremity myalgia, exercise intolerance, weakness, and fatigue) during moderate/high-intensity activity, presenting between 0.5 and 49 years. Of the 10 cases, 5 had elevated creatine kinase levels. Management included a high-protein diet (N=3), and physical therapy (N=5) improving myalgia and muscle strength. Histological examination revealed glycogen accumulation and Type I fiber predominance, consistent with previous cases. The All of Us cohort reflected our findings, highlighting chronic pain manifestation. Our cohort underscores trends characterizing GSD IXα1, an underdiagnosed condition with clinical variability and limited functional studies. Combining our data with All of Us and previous cases yields 61 patients, with only 19 clinically identified. Multidisciplinary approaches and comprehensive natural history studies remain necessary to improve disease detection and management guidelines.

THE EFFECT OF METHOTREXATE TREATMENT ON NEUROCOGNITIVE DEVELOPMENT AND NEUROINFLAMMATION GENE EXPRESSION IN PEDIATRIC CANCER PATIENTS

Sheets G[1], Doss J[3], Nieves-Rivera C[3], Moore B[1], Beaton EA[2], Stark M[3], Norman M[4], Prasad P[3], Zabaleta J[4], Li L[4], Hicks C[1], Tsien F[1].

[1]Louisiana State University Health Sciences Center New Orleans, Department of Genetics; [2]University of New Orleans; [3]Children's Hospital, New Orleans, Louisiana; [4]Stanley S. Scott Cancer Center, Louisiana Cancer Research Center, NO, LA

Introduction: One of the greatest scientific achievements of our time is the increased survival rates of pediatric cancer. Therefore, it is important that research now focuses on improving life after cancer. Methotrexate (MTX) treatment in pediatric patients has been associated with the development of long-lasting sequelae following cancer treatment (late effects). Symptoms may include deficits in intelligence and behavioral changes. We hypothesize that MTX treatment causes changes in psychosocial development, and abnormal gene expression in the brain. **Methods:** The hypothesis was tested using two specific aims. Specific Aim 1: a retrospective study of neuropsychological assessments (BASC, WISC and WAIS) of cancer survivors from the Treatment After Cancer and Late Effects Center at Children's Hospital of New Orleans, LA (CHNOLA). Specific Aim 2: RNA microarray of neuroinflammation genes, followed by bioinformatics (pathway and network analyses) on formalin-fixed paraffin embedded white matter brain specimens from deceased MTX-treated patients and age-matched controls at CHNOLA. **Discussion**:

Specific Aim 1: Patients treated with MTX showed a higher frequency of low-average and impaired performance across all indices, especially for Attention Problems (p = 0.0339). Specific Aim 2: abnormal regulation of genes related to hearing loss, demyelination, and intellectual disability were found when compared to controls. The present study provides information regarding gene-environment interactions and thus reveals candidate risk genes and pathways contributing to neuropsychiatric late effects. Our study suggests the need for longitudinal screening of pediatric cancer survivors as problems identified during adolescence are associated with reduced educational achievements in adulthood.

EHLERS DANLOS SYNDROME CLINIC: A SINGLE-SITE EXPERIENCE AND CLINICAL OUTCOMES

Bryars M, Denton J, Hurst A, Al-Beshri A, Callaway K
The University of Alabama at Birmingham, Birmingham, AL

Hypermobile Ehlers Danlos syndrome (hEDS) is a multisystemic connective tissue disorder with symptoms that overlap with other hypermobility spectrum disorders, complicating both the patient referral and diagnostic process. Currently, there are no hEDS practice guidelines or hEDS specialty provider training. This study aimed to describe the University of Alabama at Birmingham (UAB) EDS Clinic by using a retrospective review of 158 patient charts to characterize referral patterns and diagnostic outcomes. The review found that patients were more likely to be referred to the UAB EDS Clinic by family physicians (n=44, 28%) than other providers. Patients were also more likely to be diagnosed with hypermobility syndrome (n=52, 32%) than hEDS (n=21, 14%). After receiving their diagnosis, patients were referred to other providers and/or offered genetic testing when appropriate. Genetic testing for connective tissue disorders was ordered for 33 patients (20%), 75% of which returned negative results. Genetic testing changed the diagnostic outcome for three patients that tested positive, two for other EDS subtypes and one for Loeys-Dietz syndrome. Patients diagnosed with hEDS had eight comorbid diagnoses on average. These included rheumatoid arthritis (n=11, 52%), pain in various joints (n=8, 38%), and postural orthostatic tachycardia syndrome (n=8, 38%). This study was able to provide information about the UAB EDS Clinic framework which may assist in establishing hEDS diagnostic expectations for patients and providers. Additionally, this data could be used to revise the patient referral process to increase the proportion of appropriate referrals and as well as the hEDS diagnostic rate.

RACING TOWARDS A DIAGNOSIS: RAPID GENOMIC SEQUENCING IN HOSPITALIZED PEDIATRIC PATIENTS

Lancaster K, Ohlin M, BS, Thompson O, Pai GS, Champaigne NL
Medical University of South Carolina, Department of Pediatrics, Division of Pediatric Genetics, Charleston, SC

Background & Study Design: Rapid genomic sequencing in the hospital setting can aid in timely diagnosis and medical management decisions, especially in infants and children with critical illnesses. Recent studies show rapid whole exome sequencing (WES) or genome is often superior to gene panels in detecting a diagnosis, however time to return of results remains an issue. This study is a retrospective chart review that examines diagnostic yield, time to completion, and changes in management among patients who underwent rapid sequencing at MUSC Shawn Jenkins Children's Hospital from January 2021 through January 2024. **Results:** A total of 53 patients underwent rapid genomic sequencing during the 3-year period with 46 WES and 7 targeted panels. Mean age at time of sequencing was 19 months old (Range: 0 days to 18 years). Mean turn-around-time for results was 17 days (WES: 17 days; Panel: 22 days). Positive diagnostic yield was 36% (WES: 28%; Panel: 86%) with almost all leading to changes in medical management. **Conclusions:** This study demonstrates the clinical utility of rapid genomic sequencing for pediatric patients hospitalized with critical illnesses. The diagnostic yield of exome sequencing at our center is similar to previously published data on WES. Ultimate diagnosis in cases with variants of uncertain significance relied on interpretation from a Clinical Geneticist. Additionally, the high diagnostic yield with targeted diagnosis-

specific gene panels emphasizes the importance of consultation with a Clinical Geneticist. Long turn-around-times continue to remain an area of concern and should be further explored.

RESULTS OF MOLECULAR GENETIC AUTOPSIES IN FLORIDA

Naylor EW and Parth N
NCGM, Inc., Apex, NC

Sudden deaths often occur with normal autopsy and toxicology screen. Half of sudden unexplained deaths have a normal autopsy. Not all cardiovascular abnormalities are identified including channelopathies, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome. Mutation analysis on post-mortem DNA is a molecular autopsy and identifies pathogenic mutations. Results from Florida medical examiners are presented. Dried blood spot specimens were used to simplify collection and lower costs. Whole Exome Sequencing was used to identify mutations in genomic DNA. Samples were enriched for coding regions, splice site junctions, and a custom bait-capture system utilizing paired end sequencing on an Ilumina platform. Reads were assembled, aligned to reference sequences with data filtering, and analyzed with variant calling by bioinformatic programs. Re-analysis is performed if initial results are negative. Data interpretation is a challenge due to high incidence of variants of unknown significance. Specimens were screened from 125 autopsies. Analysis showed 95/125 (76%) had pathological or likely pathological mutations. Some conditions identified include: Paragangliomas, Loeys-Dietz, Long QT, and Vici Syndromes; Dilated/Hypertrophic Cardiomyopathies; Immunodeficiences; Arrhythmogenic Right Ventricular Dysplasia; Thoracic Aortic Aneurism; Developmental Epileptic Encephalopathy; Mitochondrial Complex III2; and Polycystic Kidneys. Molecular autopsy screening demonstrates a high yield of diagnostic results. A total of 76% of cases submitted were found to have a clinically significant mutation directly linked to the sudden unexplained death. Molecular autopsy should be a part of clinical autopsy protocols when there is no cause of death. Most conditions are autosomal dominant, so family studies are important.

POSTER PRESENTATIONS
(Alphabetical by Presenting Authors)

COMPLEX INTERPLAY OF GENETIC TESTING AND FAMILY DYNAMICS IN PROPIONIC ACIDEMIA: A CASE STUDY OF COMPOUND HETEROZYGOUS VARIANTS WITH DISCREPANT PARENTAL TESTING RESULTS

Almanza D, Wilson K, and Sanchez-Valle A
Department of Pediatrics, Division of Genetics and Metabolism, University of South Florida, Tampa, FL

Propionic acidemia (PA) is a rare autosomal recessive inborn error of metabolism caused by biallelic pathogenic variants in either the *PCCA* or *PCCB* genes. Early identification through newborn screening allows for prompt intervention. We present a case study of a neonate identified with PA through newborn screening and confirmed via genetic and biochemical testing. During the initial family visit, information regarding the inheritance pattern was provided including the most common scenario of parents being obligate carriers. Subsequent genetic analysis revealed biallelic compound heterozygous pathogenic variants in *PCCB*, with maternal inheritance of one variant, while the origin of the other variant remained undetermined with negative paternal testing.
Pre-disclosure discussions among the clinical team included consideration of various scenarios including de novo mutation, paternal germline mosaicism, or non-paternity, though these possibilities are more theoretical and are not well established in the literature. The revelation of genetic results triggered familial distress due to discordance with online resources leading to independent paternity testing which confirmed biological fatherhood. This case highlights the complex interplay between genetic testing outcomes and familial dynamics, emphasizing the necessity of integrating genetic counseling with social and emotional support. Our case also underscores the importance of considering genetic mechanisms in clinical practice when explaining inheritance to parents, and the profound impact of genetic testing results on affected families.

ARIMOCLOMOL IN ADULTS WITH NPC IN A REAL-WORLD SETTING: LONG-TERM DATA FROM AN EXPANDED ACCESS PROGRAM IN THE USA

Al-Hertani W[1], Berry-Kravis E[2], Wang R[3], Ficicioglu C[4], Ortiz D[5], Hastings C[6], Julich K[7], Pena L[8], Schleifer P[9], Ellis A[10], O'Reilly R[11], Hart M[11], Gallo D[11], Patterson M[12] (To be presented by Elana Buglo)
[1]Boston Children's Hospital, Harvard Medical School; [2]Rush University Medical Center; [3]Children's Hospital of Orange County; [4]Children's Hospital of Philadelphia; [5]UPMC Children's Hospital; [6]UCSF Benioff Children's Hospitals; [7]The University of Texas at Austin, Dell Medical School; [8]Cincinnati Children's Hospital; [9]Nicklaus Children's Hospital; [10]Stratevi LLC; [11]Zevra Therapeutics; [12]Mayo Clinic Children's Hospital

Niemann-Pick Disease Type C (NPC) is a rare, progressive neurodegenerative disease with no approved treatments. In the double-blind, placebo-controlled, Phase 2/3 study (NCT02612129), arimoclomol showed a significant and clinically meaningful slowing of NPC progression. Here we present data from the adult cohort within the Expanded Access Program (NCT04316637) which provides access to arimoclomol to patients with NPC. Routine clinical care was maintained; clinical assessments were scheduled at baseline, 4, 7 and 12 months with routine visits thereafter. Physician-reported 5-domain NPC Clinical Severity Scale (5DNPCCSS) scores were analyzed 1- and 2-years post-treatment initiation. As of July 2023, 26 adults completed ≥ 1 year follow up, with mean age (standard deviation, SD) at NPC diagnosis and arimoclomol initiation, 23.7 (9.0) and 28.5 (6.5) years, respectively; mean treatment duration of 21 months (range: 12-32) and concomitant miglustat use in 18 patients. Mean 5DNPCCSS change (SD) at 1 and 2 years of treatment was -0.3 (2.2 and 2.5) points from 11.7 (5.6) and 10.6 (4.4) points at baseline, respectively. Mean 5DNPCCSS change in the 18 adults on Miglustat and 8 adults without Miglustat was -0.6 (2.1) and 0.4 (2.3) at 1 year and -0.7 (2.7) and 0.8 (1.5) at 2 years, respectively. This contrasts with natural history NPC disease mean progression of 1.2-1.7 in cohorts on routine clinical care. 26 adults reported a total of 60 adverse events, including 10 severe events (determined to be unrelated to treatment). In conclusion, these data support the effectiveness and safety of arimoclomol in adults with NPC.

POSTER PRESENTATIONS
(Alphabetical by Presenting Authors)

TRRAP-ASSOCIATED NEURODEVELPMENTAL DISORDER: A CASE REPORT

Clay S[1] and Zambrano R[2]
[1]Louisiana State University Health Sciences Center New Orleans, Department of Genetics, New Orleans, LA; [2]Louisiana State University Health Sciences Center and Children's Hospital of New Orleans, Department of Pediatrics, Division of Clinical Genetics, New Orleans, LA

TRRAP encodes the transformation and transcription domain associated protein, an essential component of histone acetyltransferase complexes modifying chromatin. The physiologic role of *TRRAP* is not well understood, however, Pathogenic variants cause a rare neurodevelopmental disorder with a highly variable clinical presentation. Cogné et. al. report a strong genotype/phenotype relationship between variants within the 1031-1159 codon cluster and severe, "syndromic" abnormalities such as renal, cardiac, and genital malformations. Variants outside this region tend to produce more neurological/behavioral abnormalities, notably autism spectrum disorder and seizures. We present the case of a 9-year-old African American male with a *de-novo*, Pathogenic *TRRAP* variant located within the 1031-1159 codon region (OMIM #618454). His past medical history includes left cleft lip and palate, omphalocele, poor feeding requiring g-tube supplemental feeds, resolved hypothyroidism, short stature, undescended testes bilaterally, left kidney malrotation, and learning delay. He had a normal microarray as an infant. A *de-novo*, pathogenic variant, c.3475 G>C p.(G1159R), was detected on whole-exome sequencing. We compared his presentation to a previously published case (Cogné et. al.): *TRRAP* c.3475 G>A (p.G1159R), which only differs from ours at the nucleotide level. They share key features of intellectual disability, developmental delay, and facial dysmorphisms; however, they do not share many other phenotypic features, supporting the disorder's previously documented variable presentation. Missense3D modelling detected structural damage via replacing a buried Glycine with Arginine, a charged amino acid. Our case supports the correlation previously described by Cogné et. al. and contributes to the body of knowledge regarding this rare disease.

PRELIMINARY RESULTS FROM THE ONGOING APHENITY EXTENSION STUDY: SEPIAPTERIN REDUCES BLOOD PHE WITH IMPROVED DIETARY PHE TOLERANCE IN PARTICIPANTS WITH PHENYLKETONURIA

Sacharow S,[1] Bratkovic D,[2] Muntau AC,[3] Margvelashvili L,[4] Agladze D,[4] Guilder L,[5] Schwartz IVD,[6] Minami MAY,[7] Kiykim E,[8] Guerra IdCC,[9] Zori R,[9] Campistol J,[11] Oliveira A,[12] Janeiro P,[12] Rutsch F,[13] Lund A,[14] Mungan H,[15] Vijay S,[16] MacDonald A,[17] Chakrapani A,[18] Opladen T,[19] Tchan M,[20] Ingalls K,[21] Hughes C,[21] Zhao Z,[21] Larkin A,[21] Dong E,[21] Blaize J,[21] Smith N,[21] and Lah M[22]
[1]Division of Genetics and Genomics, Boston Children's Hospital and Department of Pediatrics, Harvard Medical School, Boston, MA; [2]PARC Clinical Research, Adelaide, SA, Australia; [3]University Children's Hospital, University Medical Center Hamburg Eppendorf, Germany; [4]Pediatric Surgery Center, Tbilisi, Georgia; [5]The Hospital for Sick Children, Toronto, ON, Canada; [6]Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil; [7]Hospital Das Clinicas Da Faculdade De Medicina De Ribeirao Preto, Ribeiraro Preto, Brazil; [8]Istanbul University-Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul, Turkiye; [9]PanAmerican Clinical Research, Guadalajara, Jalisco, Mexico; [10]Department of Pediatrics, University of Florida College of Medicine, Gainsville, FL; [11]Neuropaediatrics Department, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain; [12]Centro Hospitalar Universitario Lisboa Norte, Lisbon, Portugal; [13]Department of General Pediatrics, Muenster University Children's Hospital, Muenster, Germany; [14]Centre for Inherited Metabolic Diseases, Departments of Pediatrics and Clinical Genetics, Copenhagen University Hospital, Denmark; [15]Cukurova Universitesi Tıp Fakultesi Balcalı Hastanesi, Adana, Turkiye; [16]Paediatric Inherited Metabolic Disease, Birmingham Women's and Children's, Birmingham, UK; [17]Department of Dietetics, Birmingham Children's Hospital NHS Foundation Trust, Birmingham, UK; [18]Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; [19]Heidelberg University, Medical Faculty Heidelberg, Center for Pediatric and Adolescent Medicine, Division of Pediatric Neurology and Metabolic Medicine, Heidelberg, Germany; [20]Department of Genetic Medicine, Westmead Hospital, Sydney, NSW, Australia; [21]PTC Therapeutics Inc, South Plainfield, NJ; [22]Department of Medical and Molecular Genetics, Indiana University School of Medicine Indianapolis, IN.

Objectives: The Phase 3 APHENITY trial (NCT05099640) was a global, two-part, registration-directed study evaluating the efficacy and safety of sepiapterin in a broad phenylketonuria (PKU) population. Upon completion, participants could enroll into the APHENITY open-label extension study (NCT05166161). Here, we describe preliminary results from the ongoing extension study, which assesses the safety of sepiapterin

and its effect on dietary Phe tolerance. **Methods**: Participants receive sepiapterin once daily for ≥12 months. Those with mean blood Phe <360µmol/L from Month 1 undergo a concurrent assessment of dietary Phe tolerance. For a 26-week period, mean blood Phe is assessed along with dietary Phe consumption; changes in prescribed Phe are allowed. Participants with mean blood Phe ≥360µmol/L continue treatment but without Phe tolerance assessment. **Results**: As of September 22, 2023, 104 participants (median age, 14.0 years [min,max: 2,54]) received sepiapterin treatment. Dietary Phe tolerance assessments were performed in 73 participants. The least-square mean change (95% CI) in daily dietary Phe consumption (baseline to Week 26) was 54.6 mg/kg/day (44.2,64.9). An ~3.3-fold increase from baseline (24.4 mg/kg/day) in mean daily Phe consumption was achieved at Week 26 (79.3 mg/kg/day). Overall, sepiapterin showed a favorable safety profile and was well tolerated in the study. **Conclusions**: Preliminary data from the ongoing APHENITY extension study demonstrate continued clinical benefit and a consistent safety profile with sepiapterin. The gradual increase in dietary Phe consumption while maintaining blood Phe within target levels suggests sepiapterin may allow a more liberalized diet in patients with PKU.

HIGH-DOSE ENZYME REPLACEMENT THERAPY AND IMMUNOMODULATION: TRANSFORMING THE CLINICAL OUTCOME OF TWINS WITH CRIM-NEGATIVE INFANTILE-ONSET POMPE DISEASE

Fares AH[1], Koch RL[1], Case LE[1], Kirby A[2], Lisi MT[2], and Kishnani PS[1]
[1]Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center, North Carolina; [2]Department of Pediatrics, Wake Forest School of Medicine, Winston-Salem, North Carolina.

Infantile-onset Pompe disease (IOPD), the infantile form of Pompe disease, results from pathogenic variants in the *GAA* gene, causing acid α-glucosidase (GAA) deficiency. It manifests in the first year of life with cardiomyopathy, muscle weakness, failure to thrive, and respiratory insufficiency. Enzyme replacement therapy (ERT) using recombinant alpha glucosidase enzyme (rhGAA) has been lifesaving. Yet, the age at ERT initiation, dose, baseline muscle damage, anti-rhGAA IgG antibodies, and cross-reactive immunologic material (CRIM) status influence outcomes. We present CRIM-negative dizygotic twins treated with 40mg/kg/week alglucosidase-alfa and a 5-week course of rituximab, methotrexate with monthly IVIG, started at 28 and 44 days, respectively. Initially, they exhibited elevated LVMI, urine Glc4, creatine kinase (CK), and Aspartate aminotransferase (AST) levels. Urine Glc4 normalized by 1.7 and 2.5 months and AST by 3 and 4.5 months, respectively. Twin B's CK levels normalized by 4.5 months, whereas mild CK elevations were reported between 8-14 months in Twin A, in the setting of persisting clinical improvement. They received age-specific immunizations without complications, achieving complete B-cell count recovery at 4 months. Transition to avalglucosidase-alfa 40 mg/kg every other week at 2 years and 4 months ensured continued improvement. Currently 3 years old, they exhibit normal cardiac function, and biomarkers. Their gross motor skills align with the average range compared to peers. While making great linear motor progress, they display postural deviations, indicating decreased core and proximal strength. Their case comparison with CRIM-negative patients on standard dose alglucosidase-alfa highlights the efficacy of tailored approaches in Pompe disease management.

ENHANCING PSYCHOSOCIAL SUPPORT THROUGH STORYTELLING: UNDERSTANDING THE CHALLENGES OF WOMEN WITH PHENYLKETONURIA AND MAPLE SYRUP URINE DISEASE

Albano M[1], Gurung SR[2], Blair RB[2], Schoen MS[2], Singh RH[2]
[1]Department of Epidemiology, Emory University, Rollins School of Public Health, Atlanta, GA;
[2]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA.

Background: Treatment adherence is critical for women of reproductive age with Phenylketonuria (PKU) and Maple Syrup Urine Disease (MSUD). Holistic treatment with psychosocial support, and dietary control of phenylalanine (Phe) and branched-chain amino acids (BCAAs), may improve adherence. The study aimed to summarize the central themes emerging from experiences living with PKU or MSUD through storytelling activity, providing psychosocial support. **Methods:** Participants from Emory Metabolic Camp were divided into small groups based on age for storytelling activity. A list of topics based on World Health Organization Quality of Life (WHOQOL) framework was customized for relevance to individuals with PKU and MSUD. Each participant chose one topic to serve as the thematic foundation for their narratives. The

activity was recorded, transcribed, and analyzed with MAXQDA2022. A post-activity survey assessed participants' experience. **Results:** The sample consisted of 3 MSUD and 25 PKU females, mean age of 20.5 years. The central themes were anxiety, psychosocial support, and cognitive and emotional challenges. Increased anxiety resulted from constantly having to adhere to strict dietary regiments, fluctuating blood Phe/BCAAs levels and changes in individual dietary prescriptions. Supportive networks, effective communication and practical support were identified as crucial aspects of psychosocial support. Concentration difficulties, mood swings, and depression were common cognitive and emotional challenges. Survey results indicated a positive impact of the activity, with high agreement on usefulness and group support. **Conclusions:** The narratives emphasized the importance of a holistic approach to managing PKU and MSUD, including comprehensive support systems and interventions for women facing multifaceted challenges.

PROJECT SEARCHLIGHT STUDY METHODOLOGY: REAL-WORLD EVALUATION AND VALIDATION OF AN ALGORITHM TO IDENTIFY PERSONS AT RISK OF GAUCHER DISEASE

King LS[1], Chiorean A[2], Dumitriu A[3], Hull J[1], Mistry P[4], Modave F[5], Montmerle M[2], Pavlick P[1], Weinreb N[6], Wilson A[7]

[1]US Rare Medical, Sanofi, Cambridge, MA; [2]Quinten Health, Paris, France; [3]Digital Data, Data Science, Sanofi, Cambridge, MA; [4]Department of Internal Medicine, Yale University School of Medicine, New Haven, CT; [5]Health Outcomes and Biomedical Informatics, University of Florida, Gainesville, FL; [6]University of Miami Miller School of Medicine, Miami, FL; [7]Health Economics and Value Assessment, Sanofi, Cambridge, MA.

Introduction: Long diagnostic delays are common in patients with Gaucher disease (GD) and acid sphingomyelinase deficiency (ASMD). Machine-learning methods based on characteristics indicative of GD, curated from the literature and diagnoses in known GD patients within a deidentified US Electronic Health record database of >100M individuals, were used to develop two models to detect undiagnosed GD, one based on age of occurrence, the other based on prevalence of the characteristics. We are conducting a prospective study to evaluate these models in real-world settings. **Methods:** Step 1) Optimize the models in the clinical data infrastructures of participating US health systems. Patients will be ranked based on their likelihood of having GD. Step 2) Review charts of the 50 highest ranked patients at each site who have had an interaction with the health system in the preceding 12 months. Step 3) Refer patients for informed consent and confirmatory testing. Diagnostic and biomarker testing will be performed in parallel for GD and ASMD. Exclusion criteria for Step 3 include a documented diagnosis of GD or ASMD. **Results:** The diagnostic yield of the models among the highly ranked patients will be estimated. Characteristics of highly ranked individuals will be described. The relationship between the ranking score and diagnostic yield, and assessing the time and resources needed within the bioinformatics and clinical departments for algorithm implementation, will also be described. **Conclusions:** The study demonstrates a new paradigm for identifying patients with GD and will test the ability to identify undiagnosed patients with GD or ASMD.

SWITCHING TREATMENT TO CIPAGLUCOSIDASE ALFA PLUS MIGLUSTAT POSITIVELY AFFECTS MOTOR FUNCTION AND QUALITY OF LIFE IN PATIENTS WITH LATE-ONSET POMPE DISEASE

Kishnani PS,[1] Byrne BJ,[2] Claeys KG,[3] Clemens PR,[4] Díaz-Manera J,[5,6,7] Dimachkie MM,[8] Kushlaf H,[9] Mozaffar T,[10] Roberts M,[11] Toscano A,[12] Hummel N,[13] Goldman M,[14] Holdbrook F,[14] Shohet S,[15] Schoser B,[16] *on behalf of the ATB200-07 Study Group.*

[1]Duke University Medical Center, Durham, NC; [2]University of Florida, Gainesville, FL; [3]Department of Neurology, University Hospitals Leuven, and Laboratory for Muscle Diseases and Neuropathies, Department of Neurosciences, KU Leuven, Leuven, Belgium; [4]Department of Neurology, University of Pittsburgh School of Medicine and VA Pittsburgh Healthcare System, Pittsburgh, PA; [5]John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, UK; [6]Neuromuscular Disorders Unit, Neurology Department, Hospital de la Santa Creu I Sant Pau, Barcelona, Spain; [7]Centro de Investigación en Red en Enfermedades Raras (CIBERER), Barcelona, Spain; [8]Department of Neurology, University of Kansas Medical Center, Kansas City, KS; [9]University of Cincinnati, Cincinnati, OH; [10]Department of Neurology, University of California, Irvine, CA; [11]Salford Royal NHS Foundation Trust, Salford, UK; [12]ERN-NMD Center for Neuromuscular Disorders of Messina, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [13]Certara GmbH, Lörrach, Germany; [14]Amicus Therapeutics, Inc., Princeton, NJ; [15]Amicus Therapeutics Ltd, Marlow, UK;[16]Friedrich-Baur-Institute at the Department of Neurology, LMU University Hospital, LMU Munich, Munich, Germany

Late-onset Pompe disease (LOPD) substantially impacts motor function and health-related quality of life (HRQoL). The Phase III PROPEL trial (NCT03729362) assessed efficacy and safety of the two-component therapy cipaglucosidase alfa plus miglustat (cipa+mig) versus alglucosidase alfa plus placebo (alg+pbo) in adults with LOPD. Here we evaluate the impact of switching to cipa+mig on motor function and HRQoL in enzyme replacement therapy (ERT)-experienced patients (prespecified population). PROPEL included assessments of motor function (6 minute walk test; Gait, Stairs, Gowers' maneuver, and Chair) and patient-reported outcomes (PROs: EQ-5D-5L; Rasch-built Pompe-specific Activity; Subject Global Impression of Change [SGIC]; Patient-Reported Outcomes Measurement Information System). Group-level analyses estimated between-group differences (least squares mean) for motor function and PRO change from baseline to week 52 using analysis of covariance adjusted for baseline age, gender, height, weight, and ERT status. Patient-level responder analyses of PROs compared the proportion of patients satisfying literature-based responder thresholds using chi-square or Fisher's exact tests. Group-level analyses favored cipa+mig versus alg+pbo in most motor function and PRO measures, with nominal significance for walking tests and SGIC's "ability to move around" and "energy level". Patient-level responder analyses showed that a greater proportion of patients improved with cipa+mig versus alg+pbo for most PRO measures. Differences in proportions of responders between cipa+mig versus alg+pbo were nominally significant for SGIC's "overall wellbeing", "ability to move around", "muscle function", and "energy level". These analyses highlight the patient perspective and provide evidence that switching from alg+pbo to cipa+mig benefits patients' motor function and HRQoL. Support: Amicus Therapeutics, Inc.

DEVELOPMENT OF AN INTERNATIONAL REGISTRY FOR INDIVIDUALS WITH DISEASE-ASSOCIATED *PRDM16* VARIANTS

Kishnani S[1,2], and Landstrom A[1]
[1]Department of Pediatrics, Division of Pediatric Cardiology, Duke University School of Medicine, Durham, NC; [2]Albany Medical College, Albany, NY.

1p36 deletion syndrome is the most common terminal deletion syndrome, occurring in 1/5000 births. Loss of the *PRDM16* locus has been implicated in the development of left ventricular noncompaction and dilated cardiomyopathy in 1p36 deletion syndrome, although pathogenic variants in *PRDM16* itself are exceedingly rare and not systematically described. In this IRB-approved, multicenter cohort study, our goal is to develop the first international rare disease registry for *PRDM16*-associated variants to determine the natural history of *PRDM16*-associated disease and full spectrum of cardiovascular manifestations. We have built a secure database to collect genetic history, cardiac and noncardiac manifestations, and family history using REDCap. Inclusion criteria for subjects to be added to the registry are 1) a pathogenic variant found in *PRDM16*, 2) at least one clinical encounter, and 3) from a transmitting center with local IRB approval to join the registry. To date, we have reached out to 18 institutions through GeneMatcher and 3 institutions through literature review to establish a volunteer-based registry of cases worldwide. We have received requests for more information from 16 of these institutions, of which 9 have confirmed participation and completed all regulatory approvals. We anticipate continuing to enroll sites with a projected number of 30 cases. We will use standard descriptive statistics to describe clinical and demographic characteristics of the cohort. Our goal is to identify *PRDM16* as an independent gene implicated in cardiomyopathy and guide future clinical surveillance.

IMPROVING OUR UNDERSTANDING OF AUTOSOMAL RECESSIVE CONDITION FREQUENCIES: LESSONS LEARNED FROM THE RARE GENOMES PROJECT'S PREVALENCE STUDY OF *GBE1*-RELATED DISEASE

Koch RL[1], Morgan M[2], Akman HO[3], Orthmann-Murphy JL[4], Lu Q[5], Baxter S[6], Pires N[2]
[1]Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center, Durham, NC; [2]Adult Polyglucosan Body Disease Research Foundation, Brooklyn, NY; [3]Department of Neurology, Columbia University Irving Medical Center, New York City, NY; [4]Department of Neurology, University of Pennsylvania, Philadelphia, PA; [5]Department of Biostatistics, University of Florida, Gainesville, FL; [6]Program in Medical and Population Genetics Translational Genomics Group, Broad Institute of MIT and Harvard, Cambridge, MA

Glycogen storage disease type IV (GSD IV) is an autosomal recessive disorder caused by pathogenic variants in *GBE1*, resulting in deficient glycogen branching enzyme (GBE) activity and formation of abnormal glycogen ("polyglucosan"). GSD IV exhibits phenotypic heterogeneity, manifesting across a spectrum of clinical dimensions – including hepatic, neurologic, muscular, and cardiac involvement – and

varying in severity. The pediatric-onset forms of GSD IV present at different stages ranging from in utero to adolescence. The adult-onset form, referred to as adult polyglucosan body disease (APBD), is a neurodegenerative disease with typical presentations in middle to late adulthood. A variety of pathogenic variants and large gene deletions in *GBE1* are known to cause GBE deficiency and underscore the disease heterogeneity. To date, an epidemiological study of all GSD IV phenotypes has not been performed. With the ongoing research of potential treatments, it is critical to understand the global prevalence of GSD IV which will support therapeutic development. In collaboration with the Rare Genomes Project at the Broad Institute of MIT and Harvard and the APBD Research Foundation, a study was conducted to estimate the global prevalence of all known *GBE1* variants at the gene level. The estimated genetic prevalence reports are publicly available through the Genetic Prevalence Estimator (GeniE) tool which enables users to estimate carrier frequency and genetic prevalence for recessive conditions. This model of collaboration between researchers, patient advocacy organizations, and genetic data sharing programs provides a framework for estimating prevalence of other rare diseases in the global population.

SENSITIVITY AND SPECIFICITY OF SERUM OLIGOSACCHARIDE ANALYSIS FOR THE DIAGNOSIS AND TREATMENT MONITORING OF PATIENTS WITH ALPHA-MANNOSIDOSIS

Kubaski F; Cason A; and Pollard L
Biochemical Genetics Laboratory, Greenwood Genetic Center, Greenwood, SC

Alpha-mannosidosis is a lysosomal disease caused by deficiency of alpha-mannosidase leading to the accumulation of mannose-rich oligosaccharides. Historically, the only treatment option was a stem cell transplant; however, enzyme replacement therapy has also recently been approved by regulatory agencies. Therefore, a reliable biomarker is needed both to aid in the diagnosis of affected patients, and for treatment monitoring. In this study, we have evaluated the sensitivity and specificity of 5 different mannose-rich free oligosaccharides [GlcNAc$(Man)_{2-6}$] in serum by ultra-high performance liquid chromatography tandem mass spectrometry. GlcNAc$(Man)_{2-6}$ oligosaccharides were analyzed in 60 plasma/serum samples from healthy controls and 16 plasma samples from alpha-mannosidosis patients. The average concentration of GlcNAc$(Man)_2$ measured by true quantification in alpha-mannosidosis patients was 7.08 µM (range: 4.95-13.15 µM) (normal range ≤0.07 µM). Semi-quantitative analysis was also performed for GlcNAc$(Man)_3$ (affected range: 1,157-9,643 apparent nM; normal range ≤ 137 apparent nM), GlcNAc$(Man)_4$ (affected range: 343-1,939 apparent nM; normal range ≤ 39 apparent nM), GlcNAc$(Man)_5$ (affected range: 223-1,256 apparent nM; normal range: ≤11 apparent nM), and GlcNAc$(Man)_6$ (affected range: 59-369 apparent nM; normal range ≤ 3.5 apparent nM). Each of the five serum oligosaccharides exhibited 100% sensitivity for the detection of patients with α-mannosidosis. In addition, plasma samples from patients treated by HSCT were analyzed revealing reductions in the levels of all 5 species of oligosaccharides post-treatment. These results demonstrate that the quantification or semi-quantification of GlcNAc$(Man)_{2-6}$ oligosaccharides in serum can serve as a useful and reliable biomarker for the diagnosis and treatment monitoring of patients with alpha-mannosidosis.

CARDIAC BIOMARKERS IN FABRY DISEASE

Veleva-Rotse BO[1], Nandi P[2], Hiros J[1], Howard P[1], Ellis R[3] (Presented by Lawson, LA)
[1]Amicus Therapeutics, Inc., Princeton, NJ; [2]Product Management, Koneksa Health, New York, NY; [3]Biomarker Exploration, Koneksa Health, New York, NY.

Fabry Disease (FD) is an X-linked, multisystemic lysosomal disorder caused by GLA variants resulting in α-galactosidase A deficiency. Although cardiovascular disease is the leading cause of death in FD, progression of cardiac degeneration remains poorly understood, mainly due to a lack of clinical measurements able to predict progression on relevant timescales. Therefore, new, accessible cardiac measures, capable of measuring functional change and predicting event risk, are needed. Such measures must demonstrate concurrent validity with established cardiac measures. Digital tools that patients can use at home can provide high-frequency data collection that may detect elevated cardiac risk, inform management decisions, and support novel therapy development. Novel digital measures are developed and validated using recognized frameworks, like the Evidentiary Framework and the Digital Health Technology guidance. We conducted a targeted literature search, patient advisory board, and clinical advisory board to identify important FD signs/symptoms related to cardiac function, and to identify the most suitable cardiac patient-reported outcomes and digital tools for remote collection of subjective and objective data. The resulting composite measurement concept includes the signs/symptoms most important for patients with FD, as well as impacts on heart rate variability, electrocardiograms, blood pressure and other

measures of interest that can be staged in a progression model. The clinical association and concept development work completed to date aligns with industry standards, and the composite biomarker outlined here could be used as the foundation for future analytical validation, usability, and clinical validation seeking to capture the progression of cardiac dysfunction in patients with FD.

COMPARISON OF DATA METRICS OF PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

Marlowe K and Jahagirdar P
Cohesion Phenomics

Hypertrophic Cardiomyopathy (HCM) is an autosomal dominant disease that affects the contractility of the sarcomeres found in cardiac muscle (Basit, Brio, Sharma, 2023). HCM affects the left ventricle of the heart. Symptoms include arrythmia, syncope, or even sudden cardiac arrest. Data metrics have been collected on behalf of Cohesion Phenomic's ongoing diagnostics testing in order to analyze the pathogenic mutation rate and genetic breakup of pathogenic mutations. Clinical data shows that out of 449 patients, 215 (47.88%) present a pathogenic mutation, 38 (8.46%) with a VUS mutation, and 196 (43.65%) as benign. Clinical testing has found
that the genetic breakup that make up most pathogenic mutations for HCM found that out of 180 patients, 144 (63.33%) of pathogenic mutations were found in MYBPC3, followed by MYH7 with 43 (23.89%). What was found by Cohesion Phenomics is that out of 238 patients, 100 (42.02%) present as pathogenic, 19 (7.98%) present as VUS, and 119 (50%) as benign. Cohesion Phenomic's genetic breakup out of 96 patients was found to be as follows: 114 (63.33%) MYBPC3, 23 (23.96%) MYH7. Sometimes HCM symptoms are due to mutations found in phenocopies, which include; PRKAG2, LAMP2, and GLA. Clinical studies found that out of 180 patients, GLA makes up 6 (3.33%) of all mutations. One patient had a mutation in PRKAG2 (0.56%), as well as 1 (0.56%) in LAMP2. This is in line with Cohesion Phenomic's findings of out of 96 patients tested, 4 (4.17%) were GLA, 1 (1.04%) PRKAG2, and 1 (1.04%) was LAMP2.

PRIMARY CARE PROVIDERS' KNOWLEDGE AND ATTITUDES OF STATE-ISSUED NEWBORN SCREENING FACT SHEETS

Morgan K, Connors L, Owen N, and Phillips JA
Vanderbilt University School of Nursing/ Vanderbilt University Medical Center

The project aims to improve fact sheets given to PCPs in Tennessee for positive NBS results to enhance the PCPs' understanding and facilitate initial counseling for parents. In addition, the fact sheets will be updated to improve the patient experience of care related to NBS result disclosure.
TN NBS sheets were updated with modified ACMG (American College of Medical Genetics) ACT sheets, where each condition has an ACT sheet. Primary Care Providers in Tennessee were surveyed anonymously through the Redcap platform from Jan 1st to Feb 19th, 2024, for pre-and post-survey analysis. Utilizing updated presumed positive NBS sheets increased the likelihood of correctly answering questions related to metabolic disorders for 60% (3/5) of the surveyed conditions. 100% of the participants (N=9) in the study preferred the updated Presumed Positive Fact Sheets compared to the current documents that the state utilizes. TN currently screens for about 67 conditions. Bellcross et al. (2015) found that primary care providers lack knowledge of metabolic disorders identified in NBS and face difficulty informing parents of abnormal results. They recommended additional resources for PCPs, NBS staff, and families to address this. All nine participants have approved utilizing the modified ACMG ACT sheets as the presumed positive fact sheet. However, due to the small sample size, larger studies will be needed in the future. Using the ACMG ACT sheets increased the likelihood of correct answers for specific metabolic disorders, improving understanding for PCPs regarding disorders screened for on NBS.

LONG-CHAIN FATTY ACID OXIDATION DISORDERS (LC-FAOD): REPORTING GENETIC DIVERSITY, CLINICAL SIGNS, AND NEWBORN SCREENING INSIGHTS FROM A SPONSORED GENETIC TESTING PROGRAM

Palmieri N[1], Miller VR[1]; Gutierrez H[1]; Japalaghi OK[1]; Konczal L[2]; Marsden D[1]; McNutt II, M[3]; Morales A[4]; Vela-Amieva M[5]; Miller N[1]
[1]Ultragenyx Pharmaceutical Inc., Novato, CA; [2]University Hospitals Cleveland Medical Center, Cleveland, OH; [3]UT Southwestern Medical Center, Dallas, TX; [4]Invitae Corporation, San Francisco, CA; [5]National Institute of Pediatrics, Mexico City, Mexico

Background: LC-FAOD are rare, life-threatening, treatable autosomal-recessive conditions impairing energy production. LC-FAOD present clinically with hypoglycemia, cardiomyopathy, cardiac arrhythmias, retinopathy, and rhabdomyolysis. LC-FAOD can be detected at birth through NBS and/or later via molecular diagnosis (MDx) and/or acylcarnitine testing. **Methods**: Patients with clinical diagnosis/suspicion of LC-FAOD and an acylcarnitine test ordered are eligible for the sponsored program. The panel includes the 6 LC-FAOD genes (*ACADVL, CPT1A, CPT2, HADHA, HADHB, SLC25A20*) plus 19 genes/disorders associated with abnormal acylcarnitines. **Results**: January 2024: 111/1,314 patients tested had an LC-FAOD MDx (positive/potential-positive), 78 positive (≥2 P/LP) and 33 potential-positive (LP/VUS, P/VUS, VUS/VUS): 67% *ACADVL*, 16% *CPT2*, 10% *HADHA*, 3% *HADHB*, 3% *SLC25A20*, 1% *CPT1A*. LC-FAOD MDx varied by age: 10.6% <1y, 2.5% 1y-12y, 7.2% 13y-20y, 13.5% 21y-40y, and 11.3% ≥40y. Of MDx-lacking patients: seventeen were heterozygous for variants in ≥2 LC-FAOD genes and 123 had one LC-FAOD variant; eighty-seven had a positive/potential positive MDx in non-LC-FAOD genes. Eighty-four LC-FAOD MDx patients (n=111) reported an abnormal NBS and 64 reported abnormal/inconclusive acylcarnitines. Abnormal NBS for LC-FAOD was reported for 112/134 patients with single or digenic LC-FAOD variant(s) and 67/134 reported abnormal/inconclusive acylcarnitines. The 5 most frequently reported clinical signs/symptoms in patients with a LC-FAOD MDx were elevated CK (63%), rhabdomyolysis (44%), myopathy (32%), cardiomyopathy (15%), and hypoglycemia (15%). **Conclusion**: LC-FAOD may be identified at birth but must be considered later in life also. Higher LC-FAOD MDx rates in adolescents/adults suggest patients missed NBS, consistent with the timing of LC-FAOD addition to US NBS in 2008.

ASSESSMENT OF PLASMA ISOPROSTANOIDS AS BRAIN-SPECIFIC BIOMARKERS OF OXIDATIVE STRESS IN PHENYLKETONURIA

Schoen MS[1], Milne GL[2], Singh RH[1]
[1]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA; [2]Division of Clinical Pharmacology, Vanderbilt University Medical Center, Nashville, TN.

Oxidative stress contributes to the neurological sequelae in PKU. F2-Isoprostanes (F2-IsoPs, peroxidation product of arachidonic acid) are widely considered the reference marker for assessing oxidative stress. However, F4-neuroprostanes (F4-NeuroPs, peroxidation product of docosahexaenoic acid) and F2-dihomo-isoprostanes (F2-dihomo-IsoPs, peroxidation product of adrenic acid) could serve as more sensitive and specific biomarkers for neurological damage. This study evaluated blood isoprostanoid concentrations (5- and 15-series F2-IsoPs; 4, 10, and 14-series F4-NeuroPs; 7 and 17-series F2-dihomo-IsoPs) in 70 individuals with PKU (43 adults, 27 children) and 41 healthy, non-PKU adults matched based on age group and sex. Eighty-three percent of the PKU sample was female, and median (IQR) age was 26 years (22.5, 33.5) for adults and 15 years (13, 15.5) for children. Compared to non-PKU participants, adults with PKU had higher total concentrations of 15-F2t-IsoP, 14-F4t-NeuroP, 4-F4t-NeuroP, and 17-F2t-dihomo-IsoP (q<0.05 for all), and lower concentrations for 10-F4-NeuroP and 7-F2t-dihomo-IsoP. No significant concentration differences were found for the 5-F2c- and 5-F2t-IsoP isomers. Isoprostanoid concentrations were not linearly correlated with plasma Phe and did not differ across PKU samples when stratified based on clinically relevant ranges of metabolic control (Phe ≤360µmol/L, Phe >360µmol/L and ≤600 µmol/L, Phe >600 µmol/L; q>0.05 for all). Higher concentrations of F2-IsoPs, F4-NeuroPs, and F2-dihomo-IsoPs in adults with PKU may reflect enhanced oxidative damage in the grey and white matter regions of the brain. Future studies should evaluate how other factors beyond metabolic control contribute to these observations and if isoprostanoid concentrations correlate with cognitive performance in participants with PKU.

CAREGIVERS' PERSPECTIVES ON TRANSITIONING YOUTH WITH PAH DEFICIENCY FROM PEDIATRIC TO ADULT HEALTH CARE MANAGEMENT

Lowe TB and Shu L
Clemson University School of Nursing – Ph.D. Healthcare Genetics and Genomics Program, Clemson, SC

Phenylalanine hydroxylase (PAH) deficiency, commonly known as phenylketonuria (PKU), is an autosomal recessive disorder affecting the metabolism of phenylalanine (PHE). Treatment involves lifelong PHE-restricted diets, yet challenges persist, particularly during the transition from pediatric to adult healthcare management. This study aims to explore caregivers' perspectives on transitioning their children affected by PAH deficiency to adult care. Key study objectives include gaining an understanding of caregivers' perceptions of patient needs during the transition period, such as their perceptions of needed medical,

educational, and psychosocial support. Using the pediatric self-management framework as a guide, interviews will be conducted with caregivers of individuals aged 10 to 24 affected by PAH deficiency in the United States. A purposive sampling method will be used to recruit participants from the National PKU Alliance patient registry. A recruitment email will be sent to families. Additionally, a social media announcement will be made. Both will include a web link to the study description, a prescreening form, and the informed consent. All individuals who meet the inclusion criteria will be contacted to complete a telephone interview. Following the interview, the transcripts will be analyzed using content analysis to identify essential themes and concepts associated with transitioning a child from pediatric to adult healthcare management. Gaining knowledge of the vital insights into caregivers' perceptions of transition care is crucial. By identifying perceived knowledge gaps in transition care, this study seeks to develop ways to optimize transition care practices and enhance the quality of life for individuals with PAH deficiency.

CASE STUDY OF PHENOCOPIES OF HYPERTROPHIC CARDIOMYOPATHY

Thomas R and Joseph S
Cohesion Phenomics, Spindale, NC

Hypertrophic Cardiomyopathy (HCM) is an autosomal dominant condition that has a prevalence of 1 in 500 worldwide. It is caused by mutations in sarcomeric genes, and is distinguished by an abnormally thick (≥15mm) left ventricular wall. HCM is characterized by variable expression; symptoms range from mild to severe. HCM phenocopies are conditions that can mimic the clinical presentation of HCM, but have a different genetic etiology. This is an important distinction to identify because it can inform treatment plans. The phenocopies discussed will be Fabry Disease (FD), Danon Disease (DD), and Wolff-Parkinson Syndrome (WPS). FD is an X linked lysosomal disorder caused by a mutation in the GLA gene. This leads to an accumulation of waste products and most severely affects the heart and kidneys. DD is also an X linked lysosomal disorder, but it's caused by a mutation in the LAMP2 gene. Early identification of DD is critical as males need a heart transplant by age 19 and females by 34. WPS can be sporadic and have no genetic basis, but in cases where it mimics HCM it is caused by a mutation in the PRKAG2 gene. The mutation leads to issues with electrical pathway of the heart and causes arrythmias. This poster will review three HCM phenocopies that had previously been misdiagnosed as HCM. The objective of this poster is to compare the following between HCM and the phenocopies: Genetic mutations and testing, Clinical Presentation and Treatment.

DISCOVERY OF A NOVEL DYRK1A MUTATION (c.524del) IN INTELLECTUAL DEVELOPMENT DISORDER AUTOSOMAL DOMINANT 7 (MRD7): A COMPREHENSIVE CASE ANALYSIS.

Whitaker F and Serrano A
East Tennessee State University

Dual-specificity tyrosine kinase 1A (DYRK1A) is a member of the CMGC family that is linked to a multitude of neuronal development pathways. Both, overexpression and insufficiency of this gene are associated with many recognizable disorders, including Down Syndrome and DYRK1A-related intellectual disability syndrome which is characterized by distinct physical features with microcephaly and global developmental delay. We report a case of DYRK1A-related intellectual disability syndrome caused by a novel mutation. The patient presented to the genetics clinic with global developmental delay. On exam, he had microcephaly with a broad and tall forehead, low set, posteriorly rotated ears with a thin upper lip and pointed chin. Patient also presented with foot abnormalities. Patient had scoliosis found on x-ray and a normal renal ultrasound. Karyotype, CMA, Fragile X and exome sequencing were requested. CMA and Fragile X were non-diagnostic. Proband-only exome sequencing showed a heterozygous pathogenic variant in DYRK1A denominated c.524del (p.K175Rfs*15), a novel DYRK1A mutation. The identification of a new mutation causing MRD7 adds evidence that haploinsufficiency of DYRK1A results in a recognizable syndrome.

DIAMOND EXHIBITORS

Amgen
One Amgen Center Drive
Thousand Oaks, CA 91320
253.880.9394
https://www.amgen.com/
Representative Onsite: Matt German

Amgen is committed to unlocking the potential of biology for patients suffering from serious illnesses by discovering, developing, manufacturing and delivering innovative human therapeutics. A biotechnology pioneer since 1980, Amgen has reached millions of patients around the world and is developing a pipeline of medicines with breakaway potential.

BioMarin Pharmaceutical, Inc
105 Digital Drive
Novato, CA 94949
(707) 799-9549, (603) 856-4642
www.biomarin.com
Representative Onsite: Kimberly Harrison

BioMarin is a world leader in developing and commercializing innovative therapies for rare diseases driven by genetic causes. Products include medicine for MPS4a/MPS6/Achondroplasia. Brineura (cerliponase alfa) is the only enzyme replacement therapy that helps treat CLN2 Batten disease, a neurodegenerative genetic condition. Brineura is approved to slow loss of ability to walk or crawl (ambulation) in symptomatic pediatric patients 3 years of age and older with CLN2 disease.

DIAMOND EXHIBITORS

Eton Pharmaceuticals
21925 W. Field Parkway, Suite 235
Deer Park, IL 60010
(708) 752-0044
www.Etonpharma.com
Representative Onsite: Jeff Zuffrano

At Eton, we search the world over for meaningful therapies that we can bring to patients living with rare diseases.

Sanofi Rare Diseases
450 Water Street
Cambridge, MA 02141
(704) 421-1699, (704) 200-3597, (678) 591-0965
www.sanofi.com
Representatives Onsite: Antwaun Cook, Gayle Durham, Kathryn Williams, Tee Woody

We chase the miracles of science to develop rare new medicines and transform lives. We provide potentially life-changing treatment options and life-saving vaccine protection to millions of people globally, while putting sustainability and social responsibility at the center of our ambitions. With a foundation in Lysosomal storage disorders caused by enzyme deficiencies, our products include treatments for diseases: Fabry, Gaucher, Pompe, MPS1, and ASMD.

PLATINUM EXHIBITORS

Ultragenyx Pharmaceutical
60 Leveroni Court
Navato, CA 94949
(919) 656-9660
Ultragenyx.com
Representative Onsite: Geoffrey Simken

Dojolvi for treatment of LC-FAOD

GOLD EXHIBITORS

Amicus Therapeutics
3675 Market Street
Philadelphia, PA 19104
(609) 662-3897
www.amicus.com
Representative Onsite: Lisa Imel

Amicus Therapeutics is a global, patient-dedicated biotechnology company focused on discovering, developing and delivering novel high-quality medicines for people living with rare metabolic diseases.

Baylor Genetics
2450 Holcombe Road
Houston, TX 77021
(281) 849-7149
www.baylorgenetics.com
Representative Onsite: Tim Neuman and Daniel Taylor

For 45 years, Baylor Genetics has been the leading pioneer in genetic testing. Our primary goal is to empower patients, healthcare providers, and partners with trusted insights, translating scientific innovations into accessible clinical solutions.

GOLD EXHIBITORS

Chiesi Global Rare Diseases
One Boston Place, Suite 4000
Boston, MA 02108
(239) 273-1722
Chiesirarediseases.com
Representive Onsite: Esther Flannery

Elfabrio (pegunigalsidase alfa-iwx) is an enzyme replacement therapy (ERT) for the treatment of adults with confirmed Fabry disease.

Lamzede (velmanase alfa-tycv) The first and only enzyme replacement therapy (ERT) for the treatment of non-central nervous system manifestations of alpha-Mannosidosis in adult and pediatric patients.

Cycle Pharmaceuticals
The Broers Buioding
21 JJ Thomson Avenue
Cambridge, United Kingdom CV3 0FA
(205) 602-0945
www.cyclepharma.com
Representative Onsite: Jamie Murfee, Jennifer Mimkha

Helping to empower rare disease patients with treatments for over a decade. We have two metabolic products: NITYR (Nitisinone) Tablets and Javygtor (sapropterine dihydrochloride) Tablets for oral use and powder for oral solution.

GOLD EXHIBITORS

Mirum Pharmaceuticals
950 Tower Lane, Suite 1050
Foster City, CA 94404
(443) 570-0344
www.mirumpharma.com
Representative Onsite: Paul Auffarth, Alexis Isalgue

Mirum is dedicated to transforming scientific discoveries into therapies poised to change the trajectory of rare Inborn Errrors of Metabolism. Cholbam is indicated for: Treatment of bile acid synthesis disorders due to single liver enzyme defects ; and Adjunctive treatment of peroxisomal disorders including Zellwegers Spectrum Disorders, in patients who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat-soluble vitamin absorption.

Prevention Genetics
3800 S Business Park Ave
Marshfield, WI 54449
(304) 615-3569
www.preventivegenetics.com
Representative Onsite: Trevor Wyatt

We provide genetic test for nearly all clinically relevant genets including our PGMax Panels with Exome wide CNV analysis, our powerful and comprehensive whole-genome sequencing test, PGnome®, and whole-exome sequencing test, PGxome®.

GOLD EXHIBITORS

Takeda Pharmaceuticals
95 Hayden Avenue
Lexington, MA 02421
(404) 274-3220
www.takeda.com
Representative Onsite: Christian Meighan

Takeda is committed to activating meaningful change for the rare disease communities we serve. We work tirelessly to support patients on their journey by improving the standard of care, accelerating time to diagnosis and breaking down barriers with values-driven partners to increase equitable access, because rare disease patients and their caregivers deserve answers and a path forward to live a full life.

Thermo Fisher Scientific
5823 Newton Drive
Carlsbad, CA 92008
(661) 388-1306
www.thermofisher.com
Representatives Onsite: Pablo Sagaribay and Clint Valkenburgh

Thermo Fisher Scientific is proud of our Mission: To enable our customers to make the world healthier, cleaner and safer. Through our Applied Biosystems brand and clinical microarray solutions, we help customers accelerate innovation and enhance productivity.

GOLD EXHIBITORS

Variantyx, Inc
1671 Worcester Rd Ste 300
Framingham, MA 01701
(508) 479-5481
https://variantyx.com/
Representative Onsite: Dave Keane

Variantyx is a technology-driven precision medicine company providing state-of-the-art diagnostic solutions for the rare genetic disorders and reproductive genetics markets, and treatment optimization in oncology with our proprietary whole genome analysis platform.

Zevra Therapeutics
1180 Celebration Blvd, Suite 103
Celebration, FL 34747
(410) 916-0078
www.zevra.com
Representative Onsite: Kelli Powell

Zevra Therapeutics is a rare disease company combining data and patient needs to create transformational therapies for people living with rare diseases.

SILVER EXHIBITORS

Ambry Genetics
One Enterprise
Aliso Viejo, CA 92656
(919) 437-5627
www.ambrygen.com
Representative Onsite: Melissa Holman, MS, CGC

Ambry Genetics, a part of REALM IDx, excels at translating scientific research into clinically actionable test results based upon a deep understanding of the human genome and the biology behind the genetic disease.

Biogen
225 Binney St,
Cambridge, MA 02142
917-991-2365
www.biogen.com
Representative Onsite: Trevor Papkov

We have products for ALS and SMA (spinal muscular atrophy) and sponsor genetic testing through InVitae.

Ipsen
One Main St
Cambridge, MA 02142
724 709 9007
www.ipsenus.com.
Representative Onsite: Christopher Ashley

Ipsen is a global biopharmaceutical company focused on innovation and specialty care. We develop and commercialize medicines in three key therapeutic areas – Oncology, Rare Disease and Neuroscience. For more information, visit www.ipsenus.com.

EXHIBITS

ALEXION PHARMACEUTICALS
121 Seaport Blvd
Boston, MA 02210
(843) 200-4204
www.alexion.com
Rep Onsite: Lisa Quirk
Lisa.quirk@alexion.com

Alexion is a global pharmaceutical company focused on developing life-changing therapies for people living with rare disorders. Alexion's mission is to transform the lives of people affected by rare diseases and devasting conditions by continuously innovating and creating meaningful value in all that we do.

DENALI THERAPEUTICS
161 Oyster Point Blvd
South San Francisco, CA 94080
(832) 948-5176
www.denalitherapeutics.com
Rep Onsite: Kwangchae (KC) Yoon
yoon@dnli.com

Denali Therapeutics is committed to developing treatments for people living with MPS II and other LSDs. DNL310, our investigational IV ERT designed to cross the blood-brain barrier, alims to treat the behavioral somatic, and cognitive aspects of MPS II.

EMORY UNIVERSITY
DEPARTMENT OF HUMAN GENETICS
101 Woodruff Circle, Suite 7130
Atlanta, GA 03022
(404) 778-8521
www.emory.edu
Rep Onsite: Rosalynn Borlaza Blair
rbolaz@emory.edu

Emory's Genetic Metabolic Nutrition Research and MNT4P Program provides nutrition support to inherited metabolic disorders patients by: Addressing gaps in medical foods access and related services, providing educational and research opportunities to advance treatment strategies, and enabling active patient engagement.

GENEDX
333 Ludlow St
North Tower, 6th Floor
Samford, CT 06902
(540) 892-8553
www.genedx.com
Rep Onsite: Ryan Hartman
rhartman@genedx.com

Genetic testing company focusing on Exome and Genome based testing.

GREENWOOD GENETIC GROUP
511 Lodge Drive
Greenwood, SC 29646
(864) 992-1391
www.ggc.org
Rep Onsite : Alex Finley
afinley@ggc.org

The Greenwood Genetic Center is a nonprofit institute organized to provide clinical genetic services, diagnostic laboratory testing, educational programs and resources and research in the field of medical genetics.

INVITAE
1400 16TH Street
San Francisco, CA 94103
(205) 368-9930
www.invitae.com
Rep Onsite: Heather Thomas
Heather.thomas@invitae.com

Invitae's misión is to bring comprehensive genetic information into mainstream medical practice to improve the quality of healthcare for billions of people. Our goal is to aggregate the world's genetic tests into a single service with higher quality, faster turnaround time, and lower prices.

METASYSTEMS, INC
200 Rivers Edge Drive
Medford, MA 02155
(617) 865-3198
www.metasystems.org
Rep Onsite: Peter Hartmayer
phartmayer@metasystems.org

The cornerstone of our business mission is the automation of microscopy for healthcare and biotechnology – a commitment since 1986. With a global presence, our customers can be found in institutes, hospitals, and universities across more than 100 countries.

PTC THERAPEUTICS
100 Corporate Court
South Plainfield, NJ 07080
(484) 557-7977
www.ptcbio.com
Rep Onsite: Jennifer Coyle
jcoyle@ptcbio.com

PTC is an established global biopharmaceutical company that dlivers transformative therapies for people living with rare diseases. For 25 years, we have been harnessing our scientific platforms to create new therapies that address the underlying cause of the disease and deliver on our promise to create more moments for those who count on us.

RECORDATI RARE DISEASES, INC
440 Route 22, Suite 205
Bridgewater, NJ 08807
(404) 820-5902
www.recordatirarediseases.com
Rep Onsite: Sylvia Poulos
Poulos.s@recordati.com

Recordati Rare Diseases' Medical Affairs group shares clinical information and knowledge with medical and healthcare providers and patients. Our areas of focus include: Acute intermittent Porphyria, Cystinosis, Homocystinuria, N-Acetylglutamate Synthase (NAGS) Deficiency, Propionic and Methylmalonic Acidemias.

UCB, Inc
1950 Lake Park Drive
Smyrna, GA 30080
(949) 606-5322
www.ucb.com
Rep Onsite: Matthew Redmann
Matthew.redmann@ucb.com

UCB, Brussels, Belgium is a global biopharmaceutical company focused on the discovery and development of innovative medicines and solutions to transform the lives of people living with several diseases of the immune system or of the central nervous system. UCB is listed on Euronext Brussels (symbol: UCB).