MEETING LOCATIONS		
DATE/TIME	**FUNCTION**	**LOCATION**
Wednesday, July 16, 2025		
7:00 p -	SERGG Board of Directors Dinner Meeting	Paparazzi Room (12th Floor)
Thursday, July 17, 2025		
9:00 a – 5:00 p	Registration Open	Salon A Foyer
10:00 a – 12:00 p	Platform Session 1	Salon C
12:00 p – 1:30 p	Lunch on your own (if not attending symposium)	
12:15 p – 1:15 p	Sanofi Industry Symposium (with box lunch)	Windsor Ballroom
1:30 p – 1:45 p	Welcome/Announcements	Salon C
1:45 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
7:00 p – 9:00 p	Screening of Film	Salon C
Friday, July 18, 2025		
8:00 a – 9:00 a	Alexion Industry Symposium (with breakfast)	Swannanoa Room (2nd Floor)
8:00 a – 9:00 a	Ultragenyx Industry 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 – 10:30 a	Platform Session 3	Salon C
10:30 a – 11:00 a	Break	Salon A-B
11:00 a – 12:30 p	Platform Session 4	Salon C
12:30 p – 2:00 p	Lunch	Salon A-B & Windsor Ballroom
2:00 p – 3:00 p	Ambry Genetics Industry Symposium	Alexander Room (2nd Floor)
2:00 p – 3:00 p	Chiesi Rare Diseases Industry Symposium	Victoria Room (2nd Floor)
2:00 p – 3:00 p	Denali Therapeutics Industry Symposium	Swannanoa Room (2nd Floor)
3:15 p – 4:45 p	Platform Session 5	Salon C
Saturday, July 19, 2025		
8:00 a – 9:00 a	Acadia Pharma Industry Symposium (with breakfast)	Victoria Room (2nd Floor)
8:00 a – 9:00 a	BioMarin Pharma Industry 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 – 10:30 a	Platform Session 6	Salon C
10:30 a – 11:00 a	Break	Salon A-B
11:00 a – 12:30 p	Platform Session 7	Salon C
12:30 p – 1:00 p	SERGG Business Meeting	Salon C

42nd ANNUAL MEETING of the SOUTHEASTERN REGIONAL GENETICS GROUP (SERGG)
July 17-19, 2025
Asheville, North Carolina

Wednesday, July 16, 2025

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

All Sessions are open to everyone!

Thursday, July 17, 2025

9:00 am – 5:00 pm	**Registration Open – Salon A Foyer**
10:00 am – 12:00 pm	**Platform Session 1 – Salon C** – Hans Andersson, MD, SERGG President
10:00 am – 12:00 pm	**HRSA Co-Propel Meeting** Rani Singh, PhD, LD (Grant PI) and Serei Nath, MPH (Grant Program Manager) **Updates on Southeast Integrative Newborn Screening and Long-Term Follow-Up (SE INBS-LTFU)** **"Breaking Down Barriers: How a Legislative Change is Improving Newborn Screening Follow-up"** Lauren Thompson, DO, Medical University of South Carolina
12:00 pm – 1:30 pm	**Lunch On Your Own**
12:15 pm – 1:15 pm	**Industry Supported Symposium – Windsor Ballroom** **"Beyond Storage: New Insights into Lysosomal Diseases and the Potential for Next Generation SRTs"** Hosted by **Sanofi** (Box Lunch provided for attendees ***(CEU Not Provided)***
1:30 am – 1:45 am	**Welcome/Announcements – Salon C** – Hans Andersson, MD, SERGG President
1:45 pm – 4:45 pm	**Platform Session 2 – Salon C *(CEU Provided)*** Moderator: Hans Andersson, MD, Tulane University
1:45 pm – 2:30 pm	**Keynote Speaker:** **Philip J Brooks, PhD, Deputy Director, Div of Rare Diseases Res Innovation, NIH** *"Therapeutic Platforms Rare Monogenic Disease Clinical Trials"*
2:30 pm – 2:45 pm	"**Beyond Diagnosis: Treating Genetic Disorders with Targeted Therapies"** **Kristen Lancaster, MD, Medical University of South Carolina**
2:45 pm – 3:00 pm	**"From Molecules to Medicine: New Hope Offered by Synthetic Transfer RNA Technology"** **Misty Smith, PhD, RN, University of Alabama in Huntsville:**

3:00 pm – 3:15 pm	**"Substantial Dietary Intake Variation in PKU Highlights Implications for Clinical Trial Design"** **Jessica Strosahl, PhD, RDN, LDN, Emory University**
3:15 pm – 3:45 pm	**BREAK – Salon A Foyer**
3:45 pm – 4:00 pm	**"Outcomes of Liver Transplantation in Glycogen Storage Disease Type IB"** Alicia Khazzeka, MD, Duke University
4:00 pm – 4:15 pm	**"Quantitative Muscle Ultrasound as a Window Into Disease Progression in Infantile-onset Pompe Disease"** Myriam Boueri, MD, Duke University
4 :15 pm – 4:30 pm	**"Dried Blood Spot Arylsulfatase A Enzyme Analysis for Secon-tier Newborn Screening and Diagnosis of Metachromatic Leukodystrophy"** Francyne Kubaski, PhD, Greenwood Genetic Center
4:30 pm – 4:45 pm	**"Perspectives on Pharmacogenomics in the Fragile X Syndrome Community: Insights from a Quantitative Survey"** Erin Whiting, BS, University of Alabama at Birmingham
5:00 pm – 7:00 pm	**Welcome Reception and Poster Session (Cash Bar) – Salon A-B** ***(CEU Not Provided)***
7:00 pm – 9:00 pm	**Screening of the Film *"The Zebra & The Bear"*** Filmed over seven years, The Zebra & The Bear is a documentary film about how a mother's fierce determination to save her daughter from a devastating ultra-rare disease leads her on a journey to raise millions of dollars and drive the development of a pioneering gene-therapy treatment.

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

Conference Room Internet Access:

Network: Renaissance_Conference

Password: dobil

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!

NSGC has authorized SERGG to offer **1 CEU or 10 Category 1 contact hours** for Genetic Counselors for this meeting. In order to receive CEUs, you should have request these when registering for the meeting or by contacting Katy Drazba at the meeting. The cost is $35.00. You must provide your NSGC ID 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 8/31/25 for CEUs, or you may not be able to receive CEUs for the conference. **Platform Codes will be shown at the beginning of each session and 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 Katy Drazba at or following the meeting. Katy's e-mail is kdrazba@ggc.org for additional questions or concerns.

All Sessions are open to everyone!

Friday, July 18, 2025

8:00 am – 9:00 am **Two Concurrent Industry Supported Symposiums *(CEU Not Provided)***
(Continental Breakfast included for attendees)

#1 –"Asofatase Alfa: Enzyme Replacement Therapy for HPP" – Swannanoa Room
Hosted by **Alexion Pharmaceuticals**

#2 – "Bridging the Gap in GSDIa: Addressing unmet needs and standard of care" – Victoria Room
Hosted by **Ultragenyx**

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 – 10:30 am **Platform Session 3 – Salon C *(CEU Provided)***
Moderator: Barbara DuPont, PhD, Greenwood Genetic Center

9:00 am – 9:45 am **Invited Speaker: Gavin Arno, PhD, Associate Director of Research (Innovation), Greenwood Genetic Center**
"Advanced Genomic Analysis of Inherited Eye Disease; Observations and Results from Large-Cohort Studies and Beyond"

9:45 am – 10:00 am **"Early Diagnosis and Genotype Influence Outcomes in CBLC Disorder: A Retrospective Review"**
Julia Eazer, BS, University of South Florica Morsani College of Medicine

10:00 am – 10:15 am **"Spinal Muscular Atrophy Newborn Screening: Parents' Psychosocial Experiences Through Treatment and Onward"**
Lauren Wilson, BS, Emory University

10:15 am – 10:30 am **"Broadening Access to Care: Patient Engagement at a Southeastern Cardiogenetics Program"**
Elizabeth Towles, BA, Medical University of South Carolina

10:30 am – 11:00 am **Break with Exhibits and Posters – Salon A-B**

11:00 am – 12:30 pm **Platform Session 4 – Salon C *(CEU Provided)***
Moderator: Rani H Singh, PhD, RD, LD, Emory University

11:00 am – 11:45 am **Invited Speaker: Yue Guan, ScM, PhD, CGC, Associate Professor, Rollins School of Public Health, Emory University**
"A Multilevel Adaptation Approach to Expand a Statewide Cancer Genetic Risk Screening Program"

11:45 am – 12:00 pm **"Evaluating the Impact of Tailored Cohort Messaging on Patient Participation in Population-wide Genomic Screening"**
Lauren Carroll, MS, Medical University of South Carolina

12:00 pm – 12:15 pm **"How Does Population Genomic Screening Impact Patients? Understanding the Patient Experience and Downstream Implications"**
Sarah English, MS, Medical University of South Carolina

12:15 pm – 12:30 pm **"Genetic Anthropology of the Acadian People"**
John R Doucet, PhD, Nicholls State University

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

CONCURRENT INDUSTRY-SUPPORTED SYMPOSIUM
(CEU Not Provided)

TIME	Alexander Room	Victoria Room	Swannanoa Room
2:00 pm – 3:00 pm	**"Innovations in Genetic Testing: Designing and Curating for Maximized Clinical Utility" - Hosted by Ambry Genetics**	**"Optimizing Therapeutic Proteins through PEGylation" - Hosted by Chiesi Global Rare Diseases**	**"Insights into the Unmet Needs in MPS II" - Hosted by Denali Therapeutics**

3:15 pm – 4:45 pm **Platform Session 5 – Salon C** ***(CEU Provided)***
Moderator: Hans Andersson, Tulane University

3:15 pm – 4:00 pm **Invited Speaker: Ben Solomon, MD, Clinical Director, NHGRI**
"Artificial Intelligence in Medical Genomics"

4:00 pm – 4:15 pm **"Leveraging Machine Learning and Metabolomics for Clinical Applications: Advancing the Diagnosis and Understanding of DEGSI Deficiency"**
Eileen Barr, MS, CGC, Baylor Genetics

4:15 pm – 4:30 pm **"Breaking Records: Updates to Rapid Genomic Sequencing in Hospitalized Pediatric Patients"**
Alyssa Hoelscher, MS, University of South Carolina

4:30 pm – 4:45 pm **"Cone Health Geneconnect: A Collaborative, Community and Value-based, Equitable Population Health Genomic Screening Program"**
Chad R Halderman-Englert, MD, Cone Health

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

All Sessions are open to everyone!

Saturday, July 19, 2025

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

8:00 am – 9:00 am **Two Concurrent Industry Supported Symposiums** ***(CEU Not Provided)***
(Continental Breakfast included for attendees)

#1 – **"Advancements in Rett Syndrome (RTT) Care" – Victoria Room**
Hosted by **Acadia Pharmaceuticals**

#2 – "The Neurotoxicity of PKU" – Shawn Christ, PhD – **Swannanoa Room**
Hosted by **BioMarin Pharmaceuticals**

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 – 10:30 am **Platform Session 6 – Salon C** ***(CEU Provided)***
Moderator: Dawn Laney, MS, CGC, Emory University

9:00 am – 9:45 am **Invited Speaker: Marni Falk, MD, Exec Director, Mitochondrial Medical Frontier Program, Children's Hospital of Philadelphia**
"Developing intelligent mitochondrial medicines: Novel therapeutic insights from preclinical models"

9:45 am – 10:00 am **"Gain-of-Glycosylation Variants in IDUA Represent a Mechanism of Disease Amenable to Treatment with Novel Glycosylation Inhibitors"**
Richard Steet, PhD, Greenwood Genetic Center

10:00 am – 10:15 am **"Prospective Characterization of Early Symptom Onset and Progression in Young Pediatric Patients with Variants in the GLA gene Across Five Years: Longitudinal Data from the Fabry MOPPet Study"**
Dawn Laney, MS, CGC, Emory University

10:15 am – 10:30 am **"Newborn Screening for Pompe Disease in Georgia: Results and Factors Affecting Timely Resolution of a Positive Screen"**
Erin Kistenberg, BS, Emory University

10:30 am – 11:00 am **Break with Exhibits and Posters – Salon A-B**

11:00 am – 12:30 pm **Platform Session 7 – Salon C** ***(CEU Provided)***
Moderator: Katy Drazba, MPH, MS, CGC, Greenwood Genetic Center

11:00 am – 11:45 am **Invited Speaker: Allyn McConkie-Rosell, PhD, Professor of Pediatrics,**
Duke University
"Facing the Unknown: The Ongoing Journey of Genomic Empowerment for Families of Children with Emerging Ultra-Rare Diagnoses"

11:45 am – 12:00 pm **"Breaking New Ground: The Introduction of Inpatient Genetic Counselor Services in South Carolina"**
Olivia Thompson, MS, Medical University of South Carolina

12:00 pm – 12:15 pm **"Prenatal Pitfalls: The Diagnostic Gap Between Prenatal Screening and Postnatal Reality"**
Emily Henderson, MS, Medical University of South Carolina

12:15 pm – 12:30 pm **"The Newborn Screen: An Investigation of Stress and Coping Among Caregivers"**
Emma Sass, BA, University of Miami

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

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

Save the Date!

2026 SERGG Meeting

July 14-18, 2026

Renaissance Downtown Marriott
Asheville, North Carolina

PLATFORM PRESENTATIONS IN ORDER PRESENTED

BREAKING DOWN BARRIERS: HOW A LEGISLATIVE CHANGE IS IMPROVING NEWBORN SCREENING FOLLOW-UP

Read M, Griffin J, **Thompson L,** Champaigne N
Division of Medical Genetics and Genomics, Department of Pediatrics at the Medical University of South Carolina, Charleston, SC

Newborn screening (NBS) programs are critical for the early detection and treatment of many inherited conditions, aiming to reduce long-term health complications. Delays in specialist evaluation and treatment can adversely impact clinical outcomes, particularly for time-critical conditions. In 2023, South Carolina amended the NBS law to allow the NBS program to directly contact qualified specialists with NBS results, aiming to reduce delays in care. This study evaluates the impact of this amendment on referral timeliness and equitable access to services. We conducted a retrospective review of 106 infants with abnormal NBS, 47 pre-amendment and 59 post-amendment, referred to the Medical University of South Carolina between 2020 and 2025. After the NBS amendment, the median time from birth to referral significantly decreased from 28.0 to 21.0 days ($p = 0.0248$). The percentage of infants meeting the 5-day referral target increased from 4.3% to 20.3% ($p = 0.0151$), and evaluations within 7 days of abnormal results rose from 12.8% to 32.2% ($p = 0.0192$). Among time-critical conditions, true positive cases showed marked improvement, although the sample size limited statistical significance. Racial disparities in timeliness were observed. White and Other/Hispanic infants experienced shorter wait times post-amendment, while African American infants had increased delays (64.8 to 83.6 days, $p = 0.0012$). The increased prevalence of pseudodeficiencies in African American populations may have contributed to such delays. Implementation of direct specialist engagement post-amendment has demonstrated an improvement in overall timeliness. This data highlight opportunities to refine existing policies, with particular attention to promoting equitable care for all newborns.

BEYOND DIAGNOSIS: TREATING GENETIC DISORDERS WITH TARGETED THERAPIES

Lancaster K, Thompson L, Champaigne N
Medical University of South Carolina, Department of Pediatrics, Division of Medical Genetics and Genomics

Advancements in precision medicine are reshaping the management of genetic disorders, moving beyond diagnosis toward targeted therapies that address underlying molecular mechanisms. While these treatments were once limited to metabolic conditions, pathway-specific and gene-targeted therapies are now being applied across a broader spectrum of genetic diseases. This single-center experience highlights the integration of targeted therapeutics in the treatment of three distinct genetic disorders. First, we report our experience treating patients with Noonan syndrome and hypertrophic cardiomyopathy by using the MEK inhibitor trametinib. Patients receiving this therapy have demonstrated stabilization in cardiac function and clinical status, reflecting effective modulation of dysregulated RAS/MAPK signaling. Second, we have initiated treatment with alpelisib (Vijoice), a selective PI3Kα inhibitor, in patients with PIK3CA-related overgrowth spectrum. Our early experience with a patient with the megalencephaly-capillary malformation phenotype has shown reduction in progressive overgrowth, improvement in developmental milestones, and notably, a reduction in the frequency and severity of hypoglycemia episodes. Finally, we share outcomes from over six patients with spinal muscular atrophy identified via newborn screening. These infants received onasemnogene abeparvovec-xioi (Zolgensma), a one-time gene therapy, at our infusion center. All treated patients are achieving early motor milestones, demonstrating the importance of early identification and intervention. These cases highlight the expanding role of precision therapeutics in the management of non-metabolic, genetic disorders. They also demonstrate the evolving role of clinical geneticists in not only diagnosing rare conditions, but also in guiding and implementing emerging treatments for genetic diseases.

FROM MOLECULES TO MEDICINE: NEW HOPE OFFERED BY SYNTHETIC TRANSFER RNA TECHNOLOGY

Smith M and Barnby E
University of Alabama in Huntsville, Huntsville, AL

Collaborating with companies offering transfer RNA (tRNA) technology presents a unique opportunity to advance healthcare through tRNA-based therapeutics. Anticodon engineered (ACE) tRNAs can treat diseases by bypassing mutated mRNA codons and delivering the correct amino acids to produce functional proteins. Researchers and disease advocates can drive innovation by using genetic screening to identify treatable protein dysfunctions in genetically defined diseases. As tRNA therapies become more feasible, comprehensive disease genotype characterization is necessary. Morrow et al. (2017) identified around 100 mutations in the *FAH* gene linked to Hereditary Tyrosinemia Type 1 (HT1), but new efforts are needed to refine these molecular profiles. Diseases should be categorized by specific mutations rather than names alone, allowing companies to target treatable sub-populations (O'Leary et al., 2025). With the growing number of treatable genetic diseases, efficient patient recruitment for clinical trials is crucial. Each registry serves a specific population and goal, facilitating the identification of suitable candidates for tRNA-based therapies, such as anticodon engineered tRNA to correct nonsense mutations (Albers et al., 2023). As primary investigators of a registry grant proposal, we recognize the importance of quickly identifying HT1 patients with a R-TGA nonsense mutation. We propose the ClinTrialConnect study to enroll HT1 participants, aiming to connect them to trials that match their mutation. We hope other rare disease communities will adopt similar initiatives to link patients with appropriate trials.

SUBSTANTIAL DIETARY INTAKE VARIATION IN PKU HIGHLIGHTS IMPLICATIONS FOR CLINICAL TRIAL DESIGN

Strosahl J, Schoen MS, Nath SV, Singh RH
Department of Human Genetics, Emory University School of Medicine, Atlanta, GA

Ensuring rigorous dietary control in clinical trials is essential to minimize the confounding effects of dietary intake variation on study outcomes. However, the extent of within- and between-subject variation in dietary intake in individuals with inherited metabolic disorders, including phenylketonuria (PKU), remains underexplored. Our primary aim was to assess within- and between-subject variation in total protein and phenylalanine (Phe) intake among females with PKU (n = 99; median age = 18 years) who attended the Emory Metabolic Camp from 2014–2024. Secondary aims were to (1) evaluate intake variation differences by treatment group (sapropterin, pegvaliase, or diet therapy only), and (2) determine if within-subject variation in protein or Phe intake correlates with blood Phe concentrations. To capture real-world patterns, participants completed three-day diet records prior to camp and blood was collected on the first day to quantify Phe concentrations. Mixed-effects models revealed greater between-subject coefficients of variation (CVb) in total protein (38.4%) and Phe intake (79.8%) compared to within-subject coefficients of variation (CVw; total protein 23.0%, Phe 42.7%). These relationships remained across all treatment groups except pegvaliase, where CVw (total protein 25.11%, Phe 38.73%) exceeded CVb (total protein 16.14%, Phe 15.03%). No significant correlations were identified between within-subject variation in total protein or Phe intake and blood Phe concentrations, even after adjusting for age and energy intake. The substantial variation observed supports the use of robust dietary methods in clinical trials to reduce noise and underscores the need to establish acceptable dietary variation thresholds for future studies.

OUTCOMES OF LIVER TRANSPLANTATION IN GLYCOGEN STORAGE DISEASE TYPE IB

Williams M[1], Koch RL[1], **Khazzeka A**[1], King LY[2], Dalal N[1], Kishnani P[1]
[1]Division of Medical Genetics, Department of Pediatrics, Duke University Medical Center, Durham, NC; [2]Division of Gastroenterology, Duke University Health System, Durham, NC

Glycogen Storage Disease type Ib (GSD Ib) is due to a defect in a glucose-6-phosphate transporter SLC37A4 resulting in hypoglycemia, neutropenia, and neutrophil dysfunction. The disease manifestations include hepatic adenomas (HAs), infections, inflammatory bowel disease (IBD), and chronic kidney disease (CKD). Continuous feeds and/or uncooked cornstarch (UCCS) help maintain metabolic stability. Liver transplantation is recommended for patients with enlarging HAs and/or poor metabolic control, and combined liver-kidney transplantation for those with CKD. We describe two GSD Ib patients who underwent liver and combined liver-kidney transplantation. Patient 1: A 45-year-old male with GSD Ib underwent a liver transplant at age 29 years after experiencing hypoglycemia, HAs, seizures, IBD, and infections. His management included switching from continuous feeds to UCCS, granulocyte colony stimulating factor (G-CSF), allopurinol, and potassium citrate. He underwent a liver transplant after which he discontinued UCCS and expressed improved quality of life. He continued having seizures, CKD stage III, and neutropenia. Patient 2: A 41-year-old female with GSD Ib underwent combined liver-kidney transplantation at age 18 years after experiencing hypoglycemia, cardiac arrest, HAs, renal failure, neutropenia, IBD, and others. She was managed with UCCS, dietary restrictions, allopurinol, and G-CSF. Combined liver-kidney transplantation was done due to HAs, poor metabolic control, and CKD. Afterwards, she did not require dialysis, dietary restrictions, or UCCS, but she developed nephrolithiasis, infections, and chronic pain. Liver transplantation is the only curative treatment for GSD Ib liver disease. It corrects hypoglycemia, but neutropenia persists. Long-term surveillance is needed as transplantation does not correct extrahepatic manifestations.

QUANTITATIVE MUSCLE ULTRASOUND AS A WINDOW INTO DISEASE PROGRESSION IN INFANTILE-ONSET POMPE DISEASE

Makhijani N[1], **Boueri M**[1], Abar B[1], Boggs T[2], Case L[2], Gonzalez NL[3], Hobson-Webb LD[3], Young S[4], Kishnani PS[1]
[1]Division of Medical Genetics, Department of Pediatrics, Duke University School of Medicine, Durham, NC; [2]Department of Rehabilitation Services, Duke University Health System, Durham, NC; [3]Department of Neurology/Neuromuscular Division, Duke University Health System, Durham, NC; [4]Division of Medical Genetics, Duke Hospital Biochemical Genetics Lab, Duke University

*Background***:** Infantile-onset Pompe disease (IOPD) is caused by acid alfa glucosidase deficiency, resulting in glycogen accumulation in muscles. Symptoms include hypertrophic cardiomyopathy, hypotonia, and respiratory distress, resulting in death if untreated. Early enzyme replacement therapy (ERT) initiation, higher dosing, immune tolerance induction, and next generation therapies have improved outcomes. However, better tools are needed to monitor treatment responses and disease progression. Quantitative muscle ultrasound (QMUS) offers a potential non-invasive alternative. *Objective***:** To evaluate the effectiveness and feasibility of QMUS in monitoring muscle involvement in IOPD. *Methods***:** Echo intensity (EI) measurements were retrospectively evaluated in eight IOPD patients on long-term ERT. EI in 7 key muscles (deltoid, biceps brachii, triceps brachii, forearm flexors, quadriceps, medial gastrocnemius, tibialis anterior) was recorded annually. Each patient underwent 2–3 QMUS evaluations. EI values >50 were considered abnormal. The mean EI was compared to Gross Motor Function Measure scores using univariable regression. *Results***:** QMUS assessments were conducted between 2021 and 2024, with a median age of 9.5 years. ERT was initiated at 5 days to 3.5 months of age. All patients showed abnormal EI in at least one muscle group. Lower extremities had significantly higher EI than upper extremities (mean EI: 64.1 vs. 47.3, $p = 0.002$). QMUS findings correlated with clinical outcomes, with two children showing the highest EI having the most severe myopathy. Conversely, IOPD-8 demonstrated mostly normal QMUS results and good motor outcomes at age 3. *Conclusions*: QMUS is a promising non-invasive tool for tracking muscle health in IOPD patients on ERT.

DRIED BLOOD SPOT ARYLSULFATASE A ENZYME ANALYSIS FOR SECOND-TIER NEWBORN SCREENING AND DIAGNOSIS OF METACHROMATIC LEUKODYSTROPHY

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

Metachromatic leukodystrophy (MLD) is caused by a deficiency of the arylsulfatase A (ARSA) enzyme, which degrades sulfatides. Deficiency of this enzyme leads to the accumulation of sulfatides, which causes demyelination and neuronal dysfunction. Gene therapy has been approved for pre-symptomatic or early symptomatic forms of the disease. Thus, an early diagnosis is crucial for treatment eligibility. MLD has been nominated to the Recommended Uniform Screening Panel (RUSP), and is currently under review. Some states plan to screen for MLD regardless of RUSP nomination. The recommended algorithm for MLD newborn screening is sulfatide measurement in dried blood spots (DBS) as the first-tier test, and ARSA enzyme analysis in the same DBS as the second-tier test. Molecular analysis of the *ARSA* gene can be performed as a third-tier test. DBS ARSA analysis is technically difficult and labor-intensive; therefore, newborn screening labs are not likely to perform the assay in-house. Our CAP/CLIA accredited laboratory has validated the analysis of ARSA enzymatic activity by ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) in DBS from 175 controls, 25 MLD patients, and 11 Multiple sulfatase deficiency (MSD) patients. ARSA activity in unaffected controls ranged from 0.18-2.96 μmoL/h/L, while ARSA activity in MLD patients and MSD patients ranged from 0.01-0.05 μmoL/h/L and 0.0025-0.16 μmoL/h/L, respectively. Precision and sample stability was also evaluated as part of assay validation. In addition to the utility of DBS ARSA analysis in newborn screening, this sample type is also useful for routine diagnostic samples that require international shipping.

PERSPECTIVES ON PHARMACOGENOMICS IN THE FRAGILE X SYNDROME COMMUNITY: INSIGHTS FROM A QUANTITATIVE SURVEY

Whiting E[1], Abdul-Rahman O[2], McGwin G[3], Cannon A[1,4]
[1]Department of Clinical and Diagnostic Sciences, University of Alabama at Birmingham, Birmingham, AL; [2]Department of Pediatrics, Weill Cornell Medicine, New York, NY; [3]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL; [4]InformedDNA, St. Petersburg, FL

Background Individuals living with Fragile X syndrome (FXS) often require multiple medications to manage the varied symptoms associated with the condition. Pharmacogenomics (PGx) has demonstrated utility in tailoring medication regimens and reducing adverse side effects in both the general population and in individuals living with rare diseases. Understanding the perspectives of the FXS community on PGx is essential to ensuring that testing meets patient and family needs
while optimizing service delivery. *Methods* This online quantitative study surveyed members of the FXS community including individuals living with FXS, caregivers, individuals living with the FXS premutation, or a combination. The survey aimed to assess community perspectives, prior knowledge, perceived barriers, and interest related to PGx testing. *Results* A total of 18 surveys were evaluable. The majority of participants expressed interest in PGx testing (88.9%). Additionally, participants reported concerns related to the cost and practical application of results. Prior knowledge of PGx was primarily limited to participants working in healthcare and clinical research. *Conclusions* While interest in PGx testing is high within the FXS community, healthcare providers must address concerns related to barriers and clinical utility of PGx testing for successful implementation. Future research with larger sample sizes and broader recruitment strategies is necessary to expand on knowledge related to PGx in the FXS community.

EARLY DIAGNOSIS AND GENOTYPE INFLUENCE OUTCOMES IN CBLC DISORDER: A RETROSPECTIVE REVIEW

Eazer J[1], Shields A[2], Spence K[2], Oberheu F[2], Sanchez-Valle A[2]
[1]USF Health Morsani College of Medicine, Miami, FL; [2]USF Health Department of Pediatrics: Genetics & Metabolism, Miami, FL

Background: Cobalamin C (cblC) disorder is the most common defect in intracellular vitamin B12 metabolism, causing elevated homocysteine and methylmalonic acid (MMA). Clinical features vary and include developmental delays, ophthalmologic abnormalities, and neuropsychiatric symptoms. **Objective:** To assess clinical presentation, genotype, biochemical trends, and treatment response in cblC patients. **Methods:** The retrospective chart review included seven cblC patients with confirmed genetic diagnoses (2010–2024). Data included genotype, biochemical values (homocysteine, MMA), treatment history, diet, and neurodevelopmental findings. **Results:** All patients had biallelic MMACHC variants, most commonly c.271dupA and c.328_331delAACC. Six were diagnosed via newborn screening; one, diagnosed later in childhood, exhibited the most severe neurological symptoms. Most had developmental delays, autism spectrum features, or visual disturbances. IQ ranged from 40–72. No consistent correlation was observed between homocysteine levels and cognition, suggesting genotype and timing of intervention may better predict outcome. One late-onset patient with mildly elevated homocysteine (<80 µmol/L) is doing well developmentally; however, other late-onset cases in literature report extremely high homocysteine. Treatment typically included hydroxocobalamin and betaine; access issues and injection frequency affected adherence. Four were followed by a metabolic dietitian for low-protein diets. One self-restricted, one discontinued diet in the NICU, one received methionine/valine-free formula, and one was on a limited high-protein diet. **Conclusions:** Early diagnosis and treatment may mitigate neurological severity more effectively than homocysteine reduction alone. Genotype and intervention timing appear to predict outcomes. Diet had no effect on prognosis. Improving access to therapies and newborn screening awareness is essential for optimizing care.

SPINAL MUSCULAR ATROPHY NEWBORN SCREENING – PARENTS' PSYCHOSOCIAL EXPERIENCES THROUGH TREATMENT AND ONWARD

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Spinal Muscular Atrophy (SMA) was added to newborn screening (NBS) panels across the United States following approval of the first treatment in 2016. Early identification and treatment initiation for children affected by SMA can be lifesaving and ameliorate severe symptoms. The present study examines the familial psychosocial impact of receiving a child's positive NBS result for SMA. Qualitative interviews were conducted with parents from fourteen families whose child was diagnosed with SMA via NBS, to explore their experiences, how they are coping, and the impact on family life and planning. Participants were predominately female and white (85.7%), across the United States. Interviews were coded using MAXQDA and analyzed for thematic trends. While families are in favor of including SMA on NBS to ensure early treatment, additional support systems would improve coping. Many families emphasized providing anticipatory guidance early in the NBS results discussion, especially regarding the availability and urgency of treatment. Discussion of long-term experiences frequently highlighted that their lives have relatively normalized, and their familial relationships are stronger following the completion of treatment. Perspectives on family planning varied greatly across participants after a positive NBS result. Almost all parents could quote an accurate recurrence risk for the condition, and many of them felt that their viewpoints on family planning changed following the positive SMA NBS result. Recommendations for improvement in delivery of service as well as families' advice for future parents and providers are also discussed.

BROADENING ACCESS TO CARE: PATIENT ENGAGEMENT AT A SOUTHEASTERN CARDIOGENETICS PROGRAM

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Background: MUSC-Charleston offers South Carolina's only comprehensive cardiovascular genetics program, with two pathways to genetic counselor (GC) services: 1) GC-only telehealth available to MUSC cardiology patients and SC residents at known familial risk, and 2) in-person clinic with a cardiologist and GC (MD+GC) for new patients or advanced phenotyping. At the program's 2019 inception, only MD+GC visits were offered; however, we hypothesized GC-only telehealth would reduce wait times and enhance access. Methods: This quality improvement project assessed the geographic distribution of patients and whether testing completion rates differ by rurality or appointment type. Demographic and appointment data from 1/1/24-6/30/24 were retrospectively reviewed, and descriptive and Chi-square analyses performed. Results: GC-only patients (N=267) represented 117 zip codes, age 50.3 ± 17.3, 53.6% male. MD+GC patients (N=38) represented 28 zip codes, age 49.7 ± 17.6, 44.7% male. More GC-only patients lived in rural areas (17.4% vs 7.9%) (p=.14) and were Non-White (34.0% vs. 13.5%) (p=.012). All MD+GC (in-person) testing was completed, which differed from 77.8% among GC-only (p=.003). Among GC-only, testing completion did not differ by rurality or by phone vs. video visit. Nearly all who self-referred (28/29) completed testing, which differed from provider-referred (p=0.008). Similarly, 96.4% of familial testing patients completed testing. Discussion: MUSC's cardiovascular GC-only model effectively expanded access to rural and minority communities; however, test completion rates were lower for telehealth vs. in-person visits, which may be an area of future investigation. Similar workflows may help improve access in other states and specialties.

EVALUATING THE IMPACT OF TAILORED COHORT MESSAGING ON PATIENT PARTICIPATION IN POPULATION-WIDE GENOMIC SCREENING

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In Our DNA SC® (IODNASC) is a community health research project launched by the Medical University of South Carolina (MUSC) in November 2021 with the aim to enroll 100,000 participants in population-wide genomic screening for CDC Tier 1 conditions: Hereditary Breast & Ovarian Cancer (HBOC), Lynch syndrome (LS), and familial hypercholesterolemia (FH). In 2023, the IODNASC team began sending targeted recruitment messages to patients who were scheduled for a mammogram or colonoscopy at a participating MUSC location. This study compares the two cohorts, as well as examines the effects of age, race, ethnicity, and rurality on whether a patient viewed the message, enrolled in the study, and submitted a sample. Consistent with previous studies showing racial differences in participation in research and genetic testing, White participants were found to be more likely to enroll than non-White participants. Age was found to be inversely correlated with message viewing, enrollment, and sample collection. And while rurality does not appear to be a barrier for viewing the message, patients in rural areas were less likely to enroll. Future research could examine patient motivation for participating or declining to participate; compare the individual clinics; or focus on other methods of study recruitment.

HOW DOES POPULATION GENOMIC SCREENING IMPACT PATIENTS? UNDERSTANDING THE PATIENT EXPERIENCE AND DOWNSTREAM IMPLICATIONS

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In Our DNA SC is a population-wide genomic screening (PWGS) program that identifies individuals at-risk for the Centers for Disease Control and Prevention (CDC) Tier 1 conditions: Hereditary Breast and Ovarian Cancer (HBOC) Syndrome, Lynch Syndrome (LS), and Familial Hypercholesterolemia (FH). Participants identified with a pathogenic (P) or likely pathogenic (LP) variant for HBOC, LS, and/or FH through In Our DNA SC are offered post-test genetic counseling as part of the program. This study examined participant-reported experiences and perspectives of those who were identified with a P/LP variant for HBOC or LS and agreed to post-test genetic counseling through In Our DNA SC (n = 283). Surveys were dispatched at three timepoints: prior to genetic counseling, 30-days after, and 6-months after. A total of 260 survey series were initiated to identified participants, of which 52 participants completed the survey series in its entirety. A manual chart review was also conducted to identify potential downstream clinical outcomes. Results demonstrated high participant satisfaction and sustained willingness to recommend participation in the In Our DNA SC PWGS program, indicating trust in the research framework. While emotional responses varied between individuals with HBOC and LS results, no significant differences were observed in adherence to follow-up care or recommended management. These findings highlight the value of integrating genetic counseling into PWGS programs and suggest that untargeted genomic screening can be effectively implemented when paired with appropriate support services. Tailoring emotional and informational support based on the condition identified may further improve participant experiences and engagement.

GENETIC ANTHROPOLOGY OF THE ACADIAN PEOPLE

Doucet JP

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Acadians are known to genetic science by a number of rare disease alleles segregating in the population. Deriving from a small immigrant French group that was settled in the Eastern Canadian Maritimes at the turn of the 17th century, the Acadian population grew to an estimated 15,000 by the time of their Exile by British forces beginning in 1755. Survivors of that political cleansing event struggled to find new settlement across distant locations on the Atlantic seaboard, and a number of survivors reunited in family groups in Louisiana by invitation of the Spanish territorial government. By the early 20th century, their group name was linguistically corrupted to describe the prevalent, agrarian lifestyle of the southern part of the state, and Acadian descendants became identified as part of the indigenous “Cajun” population of Louisiana. A frontier population both in ancestral Canada and in Louisiana, communities of Acadians maintained an extreme social cohesion and interfamilial dependence for over 400 years. This presentation will summarize not only the origin and history of the Acadian people but also the mid-1960s beginnings and subsequent history of genetic discoveries deriving from study of this population. A feature of this work is a curated inventory of genetic studies identifying important differences in the reported cultural descriptions of study populations (Acadian v. Cajun v. French Canadian). Finally, 21st century efforts at education and outreach focused on the population will be discussed.

LEVERAGING MACHINE LEARNING AND METABOLOMICS FOR CLINICAL APPLICATIONS: ADVANCING THE DIAGNOSIS AND UNDERSTANDING OF DEGS1 DEFICIENCY

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DEGS1 encodes sphingolipid delta-4 desaturase, crucial for sphingolipid biosynthesis, maintaining cell membrane structure and function. Pathogenic variants in *DEGS1* are associated with hypomyelinating leukodystrophy 18 (HLD18), characterized by progressive myelin loss, motor dysfunction, and neurodevelopmental delays. This study used untargeted metabolomics and machine learning to investigate metabolic changes associated with DEGS1 deficiency, aiming to enhance clinical diagnostics and identify therapeutic targets. Metabolomic profiling was performed on plasma from five unrelated individuals with suspected HLD18 by prior molecular testing. Semiquantitative analysis involved normalizing spectral intensity values, applying log transformation, and comparing data to a reference population, generating Z-scores. An orthogonal partial least squares discriminant analysis (OPLS-DA) model was developed using the ropls package in R, analyzing 725 compounds from 399 reference samples and five DEGS1-deficient cases. Metabolomic profiling revealed elevated levels of dihydroceramide, the immediate substrate of DEGS1, and its derivatives, while downstream metabolites like ceramide, sphingomyelin, and sphingosine were reduced or absent. These perturbations were consistent across all five patients and distinct from the reference population. The OPLS-DA model successfully distinguished DEGS1-deficient individuals from reference samples, demonstrating high predictive accuracy. In silico predictions enabled reclassification of variants for this DEGS1-deficient cohort. This study demonstrates the power of machine learning and untargeted metabolomics in identifying metabolic signatures of DEGS1 deficiency. Integrating machine learning offers a promising tool for diagnosing and validating metabolic disorders, discovering biomarkers, and identifying therapeutic targets. This approach could extend to metabolomic data analysis in other genetic disorders, with broad implications for machine learning in personalized medicine.

BREAKING RECORDS: UPDATES TO RAPID GENOMIC SEQUENCING IN HOSPITALIZED PEDIATRIC PATIENTS

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Background: Rapid genomic sequencing (rGS) is an invaluable diagnostic tool that has demonstrated clinical utility, particularly for critically ill pediatric patients. It can lead to a timely diagnosis that informs medical management. We previously presented data on the use of rGS at MUSC Shawn Jenkins Children's Hospital (MUSC) from 2021-2024. With rising knowledge about rapid genetic testing and its implications on medical management, inpatient consultations and testing have grown exponentially. This study is an updated retrospective chart review that compares data from August 2024-March 2025 to the previously presented data. Results: Prior data from 2021-2024 identified that 54 inpatients underwent rGS at MUSC, with an average turnaround time of 17 days. The diagnostic yield was 36%, with nearly all results influencing medical management. From August 2024-March 2025, 81 patients received rGS, including 56 rapid whole genome sequencing, 19 rapid whole exome sequencing, and six rapid gene panels. Preliminary data show a reduced turnaround time of nine days, while the diagnostic yield remained consistent, with most diagnoses impacting medical management. Conclusions: Over the last seven months, we have had a 1.5-fold increase in rapid testing compared to the preceding three years. This update demonstrates the demand for inpatient genetic services, particularly due to the clinical utility of rGS. Educational efforts for care teams have played a significant role in provider's understanding and interest in rGS. As the demand for genetic services increases, it is important to acknowledge any barriers that might coincide with an uptake of orders for rGS.

CONE HEALTH GENECONNECT: A COLLABORATIVE, COMMUNITY AND VALUE-BASED, EQUITABLE POPULATION HEALTH GENOMIC SCREENING PROGRAM

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The implementation of an equitable population health genomic screening program within community-based healthcare systems can be challenging given the lack of key components that are typically present in larger academic centers. However, our institution is uniquely positioned to provide this type of program due to existing structures within our community: clinical genetics and genetic counseling services, genetic counseling training, research/academic affiliations, a Center for Health Equity, and a Value Based-Care Institute. Prior symposia on precision health to local providers and enactment of institution-wide pharmacogenomic testing laid the early groundwork for this larger genomic screening program. Concurrent with the pharmacogenomic testing, Cone Health and the University of North Carolina – Greensboro (UNCG) began exploring a health equity-focused precision health translational research program involving healthcare, academia, and laboratory services. Through collaboration with a genetic testing laboratory, regional providers, academic institutions, public health, and community members, we initiated a genetic research study called GeneConnect. Our program aims to improve access to more personalized health care by providing no-cost, voluntary population health genomic screening of CDC tier 1 conditions for 100,000 individuals over 5 years. Patients identified with a pathogenic/likely pathogenic variant are offered no-cost genetic counseling through a novel student-supervised clinic, supported by the UNCG Genetic Counseling training program. GeneConnect will also target new discoveries for our community through various research endeavors. Current efforts are underway to optimize enrollment and the goals of the program to improve the health of our population now and in the future.

GAIN-OF-GLYCOSYLATION VARIANTS IN *IDUA* REPRESENT A MECHANISM OF DISEASE AMENABLE TO TREATMENT WITH NOVEL GLYCOSYLATION INHIBITORS

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We have developed a biochemical platform for the characterization of *IDUA* variants identified by newborn screening. To date, over fifty variants have been investigated using this expression-based platform, and new insights gained into how the different variants impact processing, maturation and lysosomal transport of iduronidase. In the course of these studies, we discovered one variant (p.Ala75Thr) that causes a gain-of-glycosylation phenotype, adding a single N-glycan to a new site in the protein. This leads to misfolding and very low activity of the resulting enzyme. We have now characterized five other variants deposited in ClinVar that are predicted to cause gain-of-glycosylation on human iduronidase, demonstrating variable effects on N-glycan occupancy and activity at the different sites. Those sites that add an extra N-glycan within the core of the enzyme tend to have a much stronger pathogenic outcome than those sites that add an N-glycan to the surface of the protein. We further demonstrated that selective N-glycosylation inhibitors being developed as novel cancer chemotherapeutics can increase the activity of cells expressing the p.Ala75Thr variant, suggesting that loss of the extra N-glycans that cause protein misfolding may be a promising treatment angle. This novel mode of small molecule therapy has potential for use when amenable genotypes are identified. As these inhibitors represent cell-permeable small molecules that can cross the blood-brain barrier, they could be used to address the neurological symptoms of disease across multiple MPS disorders in a variant-specific manner.

Prospective Characterization of Early Symptom Onset and Progression in Young Pediatric Patients with Variants in the GLA gene Across Five Years: Longitudinal Data from the Fabry MOPPet Study

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Purpose: This prospective, longitudinal study was designed to determine the natural history of Fabry disease (FD) in early pediatric patients across the disease spectrum. **Methods:** In this observational study of children under five years of age with variants in the *GLA* gene, prospective phenotypic and urinary biomarker data were collected annually over five years. **Results:** The study population included 40 subjects (35 male, 5 female) with *GLA* variants including: 15 with classic pathogenic variants (CFD), 6 with nonclassic pathogenic variants (NFD), and 19 with a variant of uncertain significance (VUS). The most common first symptoms reported were in subjects with CFD and included gastrointestinal symptoms (13/15), heat intolerance (13/15), reduced sweating after previously sweating normally (6/15), and neuropathic pain/uncomfortable feet/hands (3/15). Mapping symptom onset and progression reveals a consistent pattern of frequency and severity occurring in the first year of life and beginning at an average age of 22.9 months (range 8- 40 months) in subjects with CFD. Subjects with NFD and VUSs did not exhibit consistency in symptom onset or progression during the study period. **Conclusions:** This study highlights the onset and pattern of progression of the earliest Fabry related symptoms in children with CFD.

NEWBORN SCREENING FOR POMPE DISEASE IN GEORGIA: RESULTS AND FACTORS AFFECTING TIMELY RESOLUTION OF A POSITIVE SCREEN

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Pompe disease (PD) is a rare lysosomal storage disorder caused by biallelic pathogenic variants in the alpha-glucosidase gene, leading to glycogen accumulation in the heart, skeletal muscle, liver, and other organs. Early treatment with enzyme replacement therapy (ERT) reduces early morbidity and mortality, and is especially important for the most severe cases of PD. Consequently, PD was added to the Recommended Uniform Screening Panel for newborn screening and was implemented in Georgia in 2021. After a positive screen for PD in Georgia, diagnostic testing is required for case resolution. This project sought to examine the results and identify possible factors affecting case resolution. The medical charts of screen-positive individuals born between 9/1/2021 and 5/31/2024 were reviewed. Of approximately 250,000 infants screened in 2022 and 2023, 21 were resolved as late-onset PD (1/11,900). No infantile-onset PD cases were identified over the study window. Statistically significant delays in case resolution were found in association with carrier status outcome (p=0.008). Income, distance traveled, race, urbanicity, and NICU status did not significantly delay case resolution. The average time from birth to resolution was 60 days (STD=38 days, median=46 days). Further examination of records identified factors delaying resolution included incorrect testing ordered, primary care providers' unfamiliarity with the differential and appropriate testing for PD, patients undergoing multiple sample draws, and language barriers. These findings serve to identify areas in which case resolution may be delayed, which could serve as focal points for future improvement and overall reduction of time to case resolution.

BREAKING NEW GROUND: THE INTRODUCTION OF INPATIENT GENETIC COUNSELOR SERVICES IN SOUTH CAROLINA

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The integration of genetic counseling services into the inpatient setting has become increasingly crucial for improved genetic test coordination, increased communication with care teams, and more robust support for families through complex genetic diagnoses. This study evaluates the introduction of inpatient genetic counselor services, first of its kind in the state of South Carolina, tracking key metrics and experiences from June 1, 2024, to June 1, 2025. We share insight into the feasibility, immediate impact, and challenges faced when introducing this service into a high-acuity pediatric hospital setting. Preliminary data not only demonstrates improved time to completion of consults, consult notes and results disclosures, but also an increased number of trio tests ordered and completed. Remarkable patient cases demonstrate how updated phenotypes over time facilitated more accurate counseling, and increased availability contributed to more in-depth parent engagement. Educational efforts also play a significant role in improving communication and understanding of genetic counseling processes for inpatient teams. Genetic counselor involvement has resulted in improvement in tracking and turnaround of results after discharge, especially in setting of emotionally complex cases such as following patient death. Key lessons from the rollout include the importance of comprehensive inpatient genetic counseling for timely and appropriate consent and result review to guide inpatient management as crucial part of the genetics team. The experience has highlighted areas for improvement, such as continuing to streamline communication with the care team and ensuring timely sample collection despite logistical constraints.

PRENATAL PITFALLS: THE DIAGNOSTIC GAP BETWEEN PRENATAL SCREENING AND POSTNATAL REALITY

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Prenatal testing, including cell free DNA testing (non-invasive prenatal screening; NIPT) and expanded carrier screening (ECS), are screening tests routinely offered to people who are pregnant or trying to conceive. While testing technologies have advanced in the past decade leading to better detection of fetal aneuploidies, rare autosomal trisomies, and copy number variants, as well as detecting carrier status for more rare conditions, limitations of these screening tests still exist. Herein we present four cases that exemplify the limitations and gaps in prenatal testing technologies: (1) A child diagnosed with congenital myasthenic syndrome postnatally after carrier screening detected only one of his two parentally inherited variants, (2) A postnatally diagnosed isodicentric Trisomy 21 after two “no call” cfDNA results followed by a negative screen from a different laboratory, (3) A neonate found to have X-linked adrenoleukodystrophy via newborn screen in the setting of a known family history but felt to not be at risk due to inappropriate maternal prenatal testing, and (4) Two siblings affected with Schwartz-Jampel syndrome, for which inappropriate maternal carrier screening was ordered which did not include the gene associated with this condition. All four of these cases resulted from inappropriate prenatal testing, lack of reporting out variants of uncertain significance on prenatal screening and/or overconfident counseling. We share these cases to remind providers that prenatal screening is not always the best testing option, and that overconfident counseling can sometime be detrimental to the patient.

THE NEWBORN SCREEN: AN INVESTIGATION OF STRESS AND COPING AMONG CAREGIVERS

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The newborn screen (NBS) is a critical public health initiative aimed at the early detection and treatment of serious but treatable conditions. To minimize false negatives (FN), the NBS permits a certain level of false positives (FP). Despite efforts to reduce these FPs, they persist due to various factors including the prioritization of decreasing FNs (limiting “misses”) and the use of assay-based testing. Prior research indicates that abnormal screenings cause significant parental stress, though these studies are largely narrative-based and focus on common conditions (e.g. Cystic Fibrosis and Sickle Cell Disease). Recent quantitative data is lacking on how FP NBS rates impact caregiver stress across all screened conditions. Additionally, the coping mechanisms used by caregivers during follow-up testing have not been quantified. To address this gap, we aim to measure NBS- induced stress and caregiver coping using the validated Parental Stress Index 4 Short Form and the Brief Coping Orientation to Problems Experiences Inventory. Caregivers have been recruited since June 2024 at the initial appointment following a positive NBS at The University of Miami NBS Program, with recruitment ongoing and expected to conclude around June 2025. We have approximately 50 surveys responses and analysis will be completed by June 2025. Documenting caregiver experiences may underscore the importance of FP NBS reduction and inform strategies to improve parental coping during the NBS process. Future research should explore strategies to enhance caregiver support, healthcare systems communication, and FP rate reduction strategies, such as genetic testing and two-step initial NBS testing.

POSTER PRESENTATIONS
(Alphabetical By Presenting Author)

CLINICALLY IMPORTANT IMPROVEMENTS IN 6-MINUTE WALK DISTANCE AND FORCED VITAL CAPACITY IN ADULTS WITH LATE-ONSET POMPE DISEASE SWITCHING FROM ALGLUCOSIDASE ALFA TO CIPAGLUCOSIDASE ALFA PLUS MIGLUSTAT

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Introduction: When evaluating efficacy of interventions, change from baseline does not account for the meaningfulness of that change for patients. **Objective:** We used published minimal clinically important differences (MCIDs) for 6-minute walk distance (6MWD) and forced vital capacity (FVC) in late-onset Pompe disease (LOPD) to determine proportions of patients (%patients) with changes greater than these MCIDs. **Methods:** In the 52-week PROPEL study (NCT03729362), treatment-experienced patients were switched to cipaglucosidase alfa + miglustat (cipa+mig) or remained on alglucosidase alfa (alg). For 6MWD, we used anchor-based (change in 6MWD [meters] for patients improving in patient-rated overall physical wellbeing) and distribution-based (½ standard deviation of baseline 6MWD [% predicted]) MCIDs, stratified by baseline 6MWD. For FVC (% predicted), we used a prespecified ±3% threshold. **Results:** In 6MWD anchor-based analyses, %patients improving was higher with cipa+mig versus alg (29.2% vs 13.3%), and %patients worsening was lower (12.3% vs 26.7%). Distribution-based analyses of cipa+mig versus alg showed the same trend (%patients improving: 33.8% vs 13.3%; worsening: 7.7% vs 13.3%). For FVC, %patients improving was 27.7% versus 0.0%, and %patients worsening was 27.7% versus 53.3% for cipa+mig versus alg. Using distribution-based MCID for 6MWD and ±3% for FVC, %patients improving in 6MWD and/or FVC was 50.8% versus 13.3% for cipa+mig versus alg, while worsening occurred in 30.8% versus 56.7%, respectively. **Summary/conclusion:** These *post hoc* analyses suggest adults with LOPD switching from alg to cipa+mig have higher chances of experiencing clinically relevant motor and respiratory function improvements than those remaining on alg.

TOPLINE PRIMARY ANALYSIS OF THE SAFETY AND EFFICACY OF WEEKLY INTRAVENOUS TIVIDENOFUSP ALFA IN MUCOPOLYSACCHARIDOSIS TYPE II (MPS II): A PHASE 1/2 STUDY

Burton BK,[1] Muenzer J,[2] Harmatz P,[3] Rajan D,[4] Jones SA,[5] van den Hout JMP,[6] Mitchell JJ,[7] Troyer MD,[8] Engmann NJ,[8] Caprihan R,[8] Bhalla A,[8] Zubizarreta I,[8] Dong W,[8] Chin P,[8] Ho C[8] (Poster to be presented by **Bakker W**, Denali Theropeutics)

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Introduction: Tividenofusp alfa is an investigational iduronate-2-sulfatase fusion protein engineered to cross the blood–brain barrier and treat CNS and somatic MPS II manifestations. **Methods** A single-arm, 24-week, Phase 1/2 study (NCT04251026) with treatment extension enrolled males ≤18 years with MPS II. Participants received 15mg/kg tividenofusp alfa weekly intravenous infusion with/without dose escalation. Assessments included: safety; biomarkers (cerebrospinal fluid and urine heparan sulfate [CSF-HS/uHS], serum neurofilament light chain [sNfL]); hearing; liver volume; cognition (BSID-III); and adaptive behavior (Vineland-3). **Results:** Participants (N=47) had a median (range) age of 5.0 (0.3–12.6) years; 93.6% were neuronopathic and ~70% had prior enzyme replacement therapy. The most frequent TEAEs were infusion-related reactions (87.2% participants), which were manageable and decreased in frequency over time. Geometric mean fold change from baseline (GM-FCFB) in CSF-HS and uHS were −91.4% and −87.9% (W24), respectively, with normalization achieved in a majority and reductions maintained for both biomarkers. GM-FCFB in sNfL, a marker of neuronal damage, was −21.1% (W49) and −70.5% (W104). Mean CFB in pure tone average hearing thresholds improved from −8.8dB (W24) to −11.2dB (W104). All participants reached and maintained normal liver volume from W24. Mean CFB in BSID-III cognitive raw score and Vineland-3 adaptive behavior raw composite were +5.7 (W49) and +33.8 (W49), respectively; improvements were maintained at the latest follow-up. **Conclusions:** Tividenofusp alfa was generally well tolerated and resulted in maintained biomarker reductions; improvements in clinical outcomes were also observed. Tividenofusp alfa has potential to address CNS and somatic manifestations of MPS II.

EVALUATION OF THE FIRST TEN COHORTS OF THE GENETICS NUTRITION ECHO TRAINEESHIP USING THE MOORE MODEL

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Project ECHO uses videoconference to provide case-based education for clinicians in underserved areas from specialists in academic "hubs". We have adapted this methodology to a traineeship for genetic metabolic dietitians, consisting of twelve weekly one-hour Zoom-based sessions. Each session includes a 15-20 minute didactic component, a case presentation, and discussion. We evaluated the impact of the traineeship using the Moore model of evaluation of continuing medical education programs. In preliminary data from the first nine cohorts, 116 participants attended at least one session, and 105 completed the course. 86% of participants were dietitians, 11% were MDs/NPs, and 3% were genetic counselors. On average, participants attended 91% of sessions. 91% of participants agreed or strongly agreed that they would recommend the eGNA Genetic Nutrition ECHO Traineeship for a colleague. The average pre-session knowledge score was 62% and the average post-session knowledge score was 83%. The increase in score for the different topics ranged from 5% (for PPA/MMA) to 36% (for MSUD). Confidence in ability to perform job activities increased by 9% on a five-point Likert scale. Likert scale scores for reviewing publications on a monthly basis and utilizing SERN/GMDI nutrition management guidelines on a weekly basis increased by 8% and 11%, respectively. 80% agreed or strongly agreed that a case presented by another participant helped make clinical decisions for a patient. 60% believed that they made large or very large gains in the development of their network community. Data from the first ten cohorts of the traineeship will be presented.

LONG-TERM VATIQUINONE TREATMENT SLOWS FA DISEASE PROGRESSION RELATIVE TO FACOMS NATURAL HISTORY

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Background: Friedreich's Ataxia (FA) is a progressive neurological disease. We report long-term 36-month results of vatiquinone, a 15-lipoxygenase inhibitor, from the MOVE-FA extension and 24-month results from Study EPI-2010-006, compared to natural history data from FACOMS (Friedreich Ataxia Clinical Outcome Measures). **Methods:** MOVE-FA (NCT04577352), a global phase 3 study, evaluated the safety and efficacy of vatiquinone in FA patients aged ≥7 years (N=143; mean age, 18.7 years). Those who completed MOVE-FA were eligible to rollover into the long-term extension (NCT05515536). EPI-2010-006 (NCT01728064), a phase 2 study, examined the effects of vatiquinone on neurologic function in adult FA patients aged ≥18 years (N=63; mean age, 28.9 years). The pre-specified primary endpoint for both analyses was the change in modified Friedreich Ataxia Rating Scale (mFARS). **Results:** After 36 months in the MOVE-FA extension, vatiquinone-treated patients demonstrated a 3.75-point increase in mFARS, compared to a 7.48-points increase in the FACOMS cohort, resulting in a 3.7-point benefit ($p<0.0001$, N=70) for vatiquinone. This treatment difference represents a clinically meaningful 50% slowing of disease progression over 3 years. In EPI-2010-006, vatiquinone-treated patients demonstrated a 0.92-point decrease in mFARS while the FACOMS cohort progressed by 3.89-points, yielding a 4.8-point treatment benefit ($p<0.0001$, N=41), consistent with a 2-year delay in progression. **Conclusions:** Results of the extension studies provide further evidence of the potential benefit of vatiquinone for the treatment of FA. The pre-specified endpoints for two different long-term extension studies were met, demonstrating a significant and durable slowing of FA disease progression in both pediatric and adult patients.

NUTRITIONAL CHANGES AFTER AN AAV8-MEDIATED LIVER-DIRECTED GENE THERAPY IN PARTICIPANTS WITH GLYCOGEN STORAGE DISEASE TYPE IA (GSDIA): RESULTS FROM A PHASE 3 PIVOTAL TRIAL

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***Background*:** GSDIa is a rare, potentially life-threatening carbohydrate metabolism disorder caused by biallelic pathogenic *G6PC* gene variants, resulting in glucose-6-phosphatase deficiency. Exogenous glucose from cornstarch and/or enteral feedings and a restricted diet (including avoidance of non-utilizable sugars) is provided every 2-4 hours to avoid hypoglycemia. DTX401 is an investigational adeno-associated virus serotype 8 vector containing the human *G6PC* gene. ***Methods*:** DTX401-CL301 (NCT05139316) is an ongoing, pivotal, phase 3, double-blind, randomized, placebo-controlled trial of DTX401 in patients ≥8 years old with GSDIa. At Week 48, participants crossed over in a blinded manner (DTX401 at Day 1 received placebo and placebo at Day 1 received DTX401 [Crossover DTX401]) for an additional 48-week blinded period. Here we describe nutritional changes from the trial. ***Results*:** Following randomization, 21 participants received DTX401 and 25 received placebo. At Week 48, mean (standard error) reduction in daily cornstarch intake was 41% (4.2) after DTX401 (n=19) versus 10% (3.8) after placebo (n=23); $p<0.0001$. At baseline, mean percent total daily calories from cornstarch were 45.5/49.8 (Crossover DTX401/DTX401) versus 19.2/32.5 at 48 weeks after DTX401. At baseline, mean percent total daily calories from carbohydrate (diet and cornstarch) were 60.6/66.4 (Crossover DTX401/DTX401) versus 48.9/56.3 at 48 weeks after DTX401. Nutritional changes, impacts, and outcomes, including anthropometrics, macronutrients, and non-utilizable sugars will be presented. ***Conclusions*:** Treatment with DTX401 resulted in a statistically significant cornstarch intake reduction at Week 48 versus placebo. As cornstarch was titrated downward after DTX401, non-cornstarch calories were increased to maintain a balanced diet and avoid unintentional energy deficits.

LONG-TERM EFFICACY AND SAFETY EVALUATION OF ARIMOCLOMOL IN PATIENTS WITH NIEMANN-PICK DISEASE TYPE C: DATA FROM 48-MONTHS OPEN-LABEL TRIAL

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Niemann-Pick disease type C (NPC) is an ultra-rare, autosomal recessive, progressive neurodegenerative lysosomal disease with heterogeneous clinical presentation and declining neurological function. Arimoclomol, an orally available small molecule, is the first FDA-approved treatment for NPC when combined with miglustat. A 12-month double-blind (DB) randomized trial demonstrated a positive benefit-risk profile for arimoclomol in patients aged 2-19 years with NPC. This study presents long-term efficacy and safety data from up to 48 months of open-label extension (OLE) treatment with arimoclomol, using a rescored 4-domain severity scale (R4DNPCCSS: ambulation, speech, swallowing, and fine motor). Patients completing the DB phase were offered continuation into the OLE phase (NCT02612129), conducted at 15 sites in 9 countries (US and EU). Efficacy is reported as change from baseline at 12, 24, 36, and 48 months of treatment. Safety is described by frequencies and severity of adverse events (AEs). Of 41 patients entering the OLE phase, 29 completed it;12 withdrew (2 died). The mean age was 12.2 (4.8) years, 80% were treated with miglustat, and mean baseline R4DNPCCSS was 9.2 (6.5). Disease severity generally progressed slowly over 48 months with a stepwise pattern. The overall pattern of AEs remained stable, with the three most common being diarrhea, upper respiratory tract infections, and nasopharyngitis. The rate of disease progression in patients treated with arimoclomol was comparable between the DB and OLE phases. Arimoclomol was well tolerated with no new safety signals observed.

ARIMOCLOMOL FOR THE TREATMENT OF NIEMANN-PICK DISEASE TYPE C IN A REAL-WORLD SETTING: LONG-TERM DATA FROM AN EXPANDED ACCESS PROGRAM IN THE UNITED STATES

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Niemann-Pick disease type C (NPC) is a rare, progressive neurodegenerative disease. The US arimoclomol Expanded Access Program (EAP), initiated in June 2020 (NCT04316637), provides access to eligible NPC patients. This study presents effectiveness and safety data from pediatric and adult NPC patients treated in the US EAP with routine clinical care maintained. Physician-reported 5-domain NPC Clinical Severity Scale (5DNPCCSS) scores were analyzed at 1 year (<13 months), 2 years (≥13 to <25 months), and 3 years (≥25 to <37 months) post-treatment initiation for patients with a minimum of 1 year of follow-up. Adverse events were summarized. As of May 8, 2024, 56 (60% of 94 treated participants) from 14 US centers aged 2-41 years had at least 1 year of treatment experience. Fifty-five patients were included in the 1-year analysis, 45 in the 2-year analysis, and 28 in the 3-year analysis. Thirty-one patients (55%) were ≥18 years of age and 25 patients (45%) were under 18 at the time of arimoclomol initiation. Patients continued arimoclomol treatment for a period of 32.7 months (range: 12.3-45.0). Average (SD) 5DNPCCSS score prior to treatment initiation was 11.2 (6.2) (range: 1.0-25.0) with changes of -0.4, 0.5, and 0.3 in the first, second, and third treatment years respectively from baseline. Patients treated with arimoclomol in the US EAP experienced relatively stable disease through up to 3 years of follow-up. The US arimoclomol EAP for NPC has shown a safety profile consistent with the published clinical trial experience of arimoclomol in NPC.

ARIMOCLOMOL UPREGULATES EXPRESSION OF GENES IN THE COORDINATED LYSOSOMAL EXPRESSION AND REGULATION (CLEAR) NETWORK

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Niemann-Pick disease type C (NPC) is an ultra-rare, fatal neurodegenerative disease caused by mutations in the *NPC1* or *NPC2* gene, leading to lysosomal dysfunction due to impaired lipid transport. Arimoclomol, an orally available small molecule, is the first FDA-approved treatment for NPC when combined with miglustat. Transcription factors EB (TFEB) and E3 (TFE3) are master regulators of lysosomal biogenesis. The effect of arimoclomol on the nuclear translocation of TFEB and TFE3 was assessed in various cell types by immunofluorescence staining. Binding of TFE3/TFEB to promoter regions of coordinated lysosomal expression and regulation (CLEAR) genes was evaluated with chromatin immunoprecipitation and qPCR in wild-type (WT) fibroblasts treated with arimoclomol. The expression levels of seven selected CLEAR genes were examined by qPCR in WT and NPC1 fibroblasts. EndoH assays and Western blotting assessed NPC1 protein level and maturation. Filipin staining evaluated cholesterol clearance from lysosomes following arimoclomol treatment. Arimoclomol prolonged the activation of TFEB/TFE3, resulting in transcriptional upregulation of CLEAR genes, including *NPC1*. Arimoclomol increased the level of mature NPC1 protein and decreased unesterified cholesterol in NPC fibroblasts' lysosomes. CLEAR genes encode proteins involved in lysosomal and autophagosomal functions, suggesting arimoclomol may provide treatment effects through NPC1-dependent and NPC1-independent processes. The downstream effects of arimoclomol treatment included increased biosynthesis of NPC1, resulting in higher levels of mature protein and improved cholesterol clearance from lysosomes. Upregulation of other lysosomal genes suggests arimoclomol may generally enhance lysosomal function and autophagy flux to promote cell health.

THE LENGTHY AND BURDENSOME JOURNEY TO DIAGNOSIS FOR FEMALE PATIENTS WITH FABRY DISEASE

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Fabry disease (FD) is an X-linked lysosomal storage disorder with heterogeneous symptoms, causing delay in diagnosis. While traditionally considered more severe in males, significant symptoms have been reported in females. Understanding the varied disease manifestations in females is critical for diagnosis and treatment. This retrospective observational study used PicnicHealth data (2018–2021) consisting of de-identified medical records from consented patients. The dataset included 41 patients characterizing their experiences with FD from the first recorded symptom to diagnosis and treatment. This study included seven female patients who met the inclusion criteria (at least one healthcare visit prior to FD diagnosis). Swimmer plots illustrated individual patient journey marked by clinical events, medication use, and procedures across the timeline from the first observed symptom to treatment initiation. Time elapsed from the first recorded symptom to diagnosis ranged from 29 days to 39.6 years; time from diagnosis to treatment initiation ranged from 44 days to 12.6 years. Undiagnosed patients experienced significant disease burden, with 2/7 patients having neurological symptoms (cerebral infarction and cerebrovascular accident), 3/7 having cardiovascular symptoms (congestive heart failure and cardiomyopathy), and 4/7 having dermatological symptoms (angiokeratoma). Most frequently observed pre-diagnosis medications included antidepressants, cardiovascular medications, and analgesics. Monitoring before diagnosis often involved magnetic resonance imaging, computed tomography scans, electrocardiograms, and echocardiograms. This case series emphasizes the variability and severity of symptoms, such as heart failure and transient cerebral ischemia, in females with FD. Increased awareness and early recognition of these symptoms are crucial for timely diagnosis/management, potentially improving patient outcomes.

CALL FOR NEUROFIBROMATOSIS SPECIALTY CARE CLINICS IN SOUTH CAROLINA

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Purpose: Grounded in community input, this study assesses the perceived need for a dedicated multidisciplinary clinic for individuals and families with neurofibromatosis type 1 (NF1) in South Carolina, USA. Methods: A 62-question online cross-sectional survey, available in English and Spanish, was distributed to South Carolina residents over age 18 years who were either adults who do not have NF1 but have children with NF1, adults with NF1 who have children with NF1, and adults with NF1 who do not have children or may have children without NF1, to capture a wide range of experiences. Survey responses were analyzed using descriptive statistics to summarize key findings and chi-squared and Fisher's exact tests for categorical comparisons. Free-response data were examined by content analysis and evaluated by a second researcher. Results: Of a total of 52 survey responses analyzed in the study, 90.4% indicated agreement that a specialty clinic should exist in South Carolina. More than 70% of participants reported adherence to medical advice for NF1 and saw a doctor at least once per year with children and adults seeing several relevant specialists. Analysis of participant free text responses identified 4 clinical care gaps and 4 educational gaps in current care-seeking behaviors. Conclusion: Establishing a dedicated, multidisciplinary care center for individuals with NF1 in South Carolina can address 3 out of the 4 clinical care gaps and 1 out of the 4 education gaps identified by the content analysis and is highly supported by participant preference.

LIFESAVING REESE'S CUPS: AN UNEXPECTED AND IRONIC DIAGNOSIS OF CLASSIC GALACTOSEMIA

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Newborn screening for classic galactosemia began in 1963, with the last state adding it to their expanded panel in 2004. An expedited and accurate diagnosis of galactosemia allows for timely intervention. Without initiation of lactose free diet in infancy, serious complications including feeding difficulties, malnutrition, liver failure, bleeding, and *E. coli* sepsis can occur. Long term complications without treatment include developmental delays, extrapyramidal findings and liver failure. We report a 51-year-old male who presented with adult-onset tremors, ataxia and static encephalopathy. Whole genome sequencing (WGS) was recommended, which identified homozygous pathogenic variants in the *GALT* gene. At the age of 51, this patient was diagnosed with classic galactosemia. This patient was not identified on newborn screen, as this condition was not added to the South Carolina Newborn Screening Panel until 1992, nineteen years after this patient's birth. Inquiring further, his history was also notable for severe growth faltering, neonatal E-coli sepsis, and developmental delays. This history, alongside his presenting features, are all classic findings of untreated galactosemia. Despite years of multidisciplinary evaluation, no providers thought about the possibility of galactosemia. To this day, the patient's family attributes his survival to his favorite food, Reese's peanut butter cups, which is what ultimately led to weight gain at one year of age. Unfortunately, his favorite foods still include Reese's and other lactose-containing foods contraindicated with galactosemia. This has presented a challenge to optimizing his metabolic control. This case highlights the importance of newborn screening and early treatment initiation.

IMPROVEMENT IN UPRIGHT STABILITY SUBSCALE OF mFARS WITH VATIQUINONE TREATMENT IN MOVE-FA: A PHASE 3, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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Background: Friedreich's ataxia (FA) involves progressive neurological damage and ambulation loss. Safety and efficacy of vatiquinone, a 15-lipoxygenase inhibitor, was evaluated in the MOVE-FA (NCT04577352) global phase 3 trial. The upright stability subscale (USS) is a component of the modified FA Rating Scale (mFARS) that assesses functions related to balance, stance, and mobility. Natural history data shows that disease progression in ambulatory pediatric and adolescent FA patients is primarily driven by declines in the functions assessed in USS. **Methods:** MOVE-FA enrolled 143 FA patients aged ≥7 years (mFARS score 20–70, ability to ambulate ≥10 feet in 1 minute). The primary endpoint was placebo-corrected change from baseline in mFARS at 72-weeks. The modified ITT (mITT) population included 123 patients (mean age, 14.6 years; range, 7–21 years). **Results:** In placebo-treated patients, USS was the only mFARS subscale to demonstrate progression from baseline to week 72, consistent with natural history data. Significant treatment benefit was recorded in USS (−1.26 [p=0.021]) in the MOVE-FA mITT population. Vatiquinone treatment also delayed loss of functional milestones represented by individual items within USS, specifically items E2B (feet apart eyes closed) and E3A (feet together eyes open). Comparison of disease progression rates in USS predicted a 42% reduction in disease progression per year with vatiquinone versus placebo. **Conclusions:** Vatiquinone treatment resulted in clinically meaningful and statistically significant treatment effects on the USS, a sensitive and predictive endpoint for risk of loss of ambulation, prevention of which is a key goal for therapy in ambulatory FA patients.

RITONAVIR AS AN ANTICANCER THERAPY

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In recent years, researchers have looked to FDA-approved medications for chemotherapies because they may possess anti-tumor properties—such as the ability to inhibit angiogenesis and induce apoptosis—and because their safety and toxicity profiles are well known, providing a promising path to accelerated treatment. Ritonavir, a protease inhibitor (PI) used to treat viral diseases including HIV, HCV and COVID-19 has been shown to aid in the treatment of colorectal cancer (CRC) by reversing drug resistance to chemotherapies via efflux transporters and slowing metabolism of chemotherapeutics through the modulation of cytochrome P450 (CYP450) enzymes. Evidence suggests that ritonavir can act as an inducer, inhibitor and/or substrate of CYP450 and transporters in a dose-dependent manner. Hence, we hypothesize that at high doses of ritonavir, inhibition occurs leading to decreased drug catabolism and efflux, and increased sensitization of CRC cells to the chemo drug. This study aims to measure the effects of ritonavir on the activity of CYP3A4, CYP2C8, p-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Another aim is to measure the reversal of resistance to the chemo drugs SN-38 – the active metabolite of irinotecan, and paclitaxel. Mass spectrometry is utilized to determine whether active drug is retained in the cell, and drug resistance reversal is measured by MTT cell proliferation assay. The results of this study carry major implications for cancer research, including the potential to provide therapeutic benefit to late-stage chemo-resistant CRC patients with otherwise poor prognoses and the potential to repurpose viral PIs for advanced-stage cancer treatment.

REDUCED INCIDENCE OF STROKE IN PATIENTS WITH FABRY DISEASE TREATED WITH AGALSIDASE BETA: A MATCHED ANALYSIS FROM THE FABRY REGISTRY

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Fabry disease (FD), caused by α-galactosidase A deficiency, leads to lysosomal glycosphingolipid accumulation and progressive dysfunction of the kidneys, heart, and nervous system. We assessed stroke incidence among agalsidase-beta-treated (0.9–1.1 mg/kg biweekly) versus untreated patients, enrolled in the Fabry Registry (NCT00196742) as of May 2024. Agalsidase-beta-treated patients, stroke-free at treatment initiation, were 1:1 matched with untreated patients by sex, phenotype (classic, later-onset, or others), and age. Untreated patients were eligible for matching if they had FD symptoms and were stroke-free by the treatment initiation age of a treated patient. Patients were followed up until stroke occurrence, treatment switch (if treated), treatment initiation (if untreated), or the end of Registry follow-up, whichever occurred first. Cox proportional hazards regression models conditioned on matched pairs estimated hazard ratios (HRs) and 95% confidence intervals (CI) for stroke. The analysis included 1868 matched pairs of patients (52.4% males, 68.3% classic, 14.4% later-onset, 17.3% other/unclassified phenotype) with median age at FD diagnosis of 31.0 and 33.7 years for treated and untreated patients, respectively. After a median (25^{th}–75^{th} percentile) follow-up of 5.8 (3.5, 8.7) years for treated patients and 3.3 (1.9, 5.9) years for untreated patients, 70 treated (5.55 per 1000 person-years) and 102 untreated (11.18 per 1000 person-years) patients experienced stroke (72.7% ischemic). Treated patients had a significantly lower risk of stroke compared to untreated patients (HR=0.36; 95% CI: 0.23, 0.56). In conclusion, FD patients treated with agalsidase-beta may have significantly lower risk of developing stroke compared to untreated patients.

EPIDEMIOLOGICAL TRENDS IN SOUTH FLORIDA'S NEWBORN SCREENING PROGRAM: A RETROSPECTIVE STUDY OF INCIDENCE AND PREVALENCE

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Newborn screening, introduced in the United States in the 1960s, has become a critical public health initiative, significantly reducing infant mortality and improving quality of life. In Florida, approximately 220,000 infants are screened annually between 24 and 48 hours of life. While screening panels vary by state, Florida currently tests for 60 conditions. Alongside the expansion of tested conditions, technological advancements have improved diagnostic accuracy. This retrospective study aims to evaluate the incidence and prevalence of specific conditions included in Florida's newborn screening program, with a focus on Biotinidase Deficiency, Mucopolysaccharidosis Type I (MPS I), Galactosemia, Spinal Muscular Atrophy (SMA), Pompe disease, and X-linked Adrenoleukodystrophy (X-ALD) in the southern region of the state. Additionally, the study seeks to estimate the positive predictive value (PPV) of screening for these conditions. Data from 2017 to 2023, provided by the University of Miami's Genetics Department, will be analyzed to assess the effectiveness of early detection and diagnosis. In addition to statewide analysis, trends observed in South Florida will be compared to those seen across the state to identify any regional differences in outcomes or screening effectiveness. Findings from this study may help guide improvements in screening protocols and support the continued advancement of newborn screening practices, ultimately improving health outcomes for future generations.

REDEFINING CASCADE SCREENING AND UTILIZING MULTIPLE ENGAGEMENT METHODS TO ENCOURAGE CANCER GENETIC SCREENING IN HIGH-RISK POPULATIONS

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From 2020-2024, the JScreen program tested over 5,000 people for cancer genetic variants on a panel of up to 73 genes. Of these, 16.2% were positive for one or more actionable variants. The individuals potentially impacted by each positive result rises exponentially as we consider first-, second- and third-degree relatives who may be at risk, so screening through a cascade approach is imperative for managing hereditary cancer risk in a population. However, reaching and educating at-risk individuals is challenging. To maximize the impact of a cascade testing initiative, we propose an expansion of how we define cascade screening. If one positive result inspires other at-risk individuals to pursue testing, even if they are not biologically related, public health successes can be achieved. So, we implement a multi-pronged approach to cascade screening, utilizing a broader definition of the concept, with the goal of individual empowerment to identify hereditary risk through cancer genetic screening. We will present data from initiatives that utilized various educational and social media approaches and fostered relationships in order to reach at-risk individuals through personalized story-telling of patients' lived experiences. The data demonstrates that timely patient engagement coupled with professional clinical support motivates patients to take action as they recognize the value of personalized risk assessment through screening. We will also provide preliminary data on current collaborative approaches to leverage new technology platforms and develop targeted outreach campaigns within community partnerships. Finally, we will propose conceptual strategies to support cascade screening and expand its reach.

GENETIC DOUBLE TAKE: NAVIGATING THE OVERLAP OF JOUBERT SYNDROME AND NIEMANN-PICK DISEASE TYPE C

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Advances in next-generation sequencing have increased the identification of dual genetic diagnoses, particularly in patients with complex presentations. We present the case of a 31-year-old female with congenital oculomotor apraxia, suspected intellectual disability, hypothyroidism, iatrogenic adrenal insufficiency, bilateral carpal and cubital tunnel syndrome, unilateral L5 spondylolysis, and recent onset dysphagia and dysarthria. Whole exome sequencing revealed two pathogenic variants in *CSPP1* associated with autosomal recessive Joubert syndrome 21, and one pathogenic and one likely pathogenic variant in *NPC1* associated with Niemann-Pick Type disease C (NPC). Maternal testing for phasing confirmed inheritance of one variant in each gene. Biomarker testing (oxysterol profile and lyso-sphingomyelin) supported a diagnosis of NPC. Joubert syndrome is a neurodevelopmental disorder characterized by cerebellar and brain stem malformation (molar tooth sign), hypotonia, oculomotor apraxia, respiratory disturbance, ataxia and/or cognitive impairment. NPC is a progressive lysosomal disorder marked by neurologic manifestations such as developmental delay, ataxia, dysarthria, dysphagia, dystonia, and progressive dementia. The phenotypic overlap in this patient makes it challenging to delineate the contributions of each disorder; however, her lifelong congenital oculomotor apraxia and developmental delays are more consistent with Joubert syndrome, while her recent neurologic decline with progressive dysphagia and dysarthria reflects adult-onset NPC. The patient was initiated on Miglustat and the newly FDA-approved drug for NPC levacetylleucine (Aqneursa). This case highlights the utility of broad-based genomic testing in uncovering complex phenotypes and guiding diagnosis, management, and therapeutic intervention in rare neurogenetic disorders.

ADMINISTRATION OF A DUAL-COATED SODIUM PHENYLBUTYRATE (OLPRUVA) SUSPENSION VIA GASTROSTOMY TUBE

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Introduction: Urea cycle disorders (UCDs) are a group of inborn errors of metabolism characterized by hyperammonemia, which can lead to serious CNS toxicities. Treatment for UCDs often includes a protein-restricted diet, essential amino acid supplementation and nitrogen-scavenging therapy to reduce blood ammonia levels. Due to the complex treatment needs of UCD patients, gastrostomy tubes may be necessary to ensure sufficient energy and protein intake. Because gastric tubes play a critical part of the UCD management plan for some patients, gastrostomy tube administration studies were completed with OLPRUVA, a dual-coated formulation of sodium phenylbutyrate, to evaluate whether the medication can be effectively given via gastrostomy tubes. Methods: In-vitro administration studies were performed to assess the feasibility of administering OLPRUVA via gastrostomy tubes. In addition, hold studies of OLPRUVA were performed to evaluate in-use stability with OLPRUVA contacting gastrostomy tube materials for 30 minutes. 16-, 14- and 12-french gastrostomy tubes were evaluated. Results: The gastrostomy tube in-vitro administration studies demonstrated that the OLPRUVA dose recovered after administration through gastrostomy tubes met the label claim acceptance criteria in all studied gastrostomy tubes with the evaluated doses and administration volumes. The gastrostomy tube in-use stability study data found no significant changes in assay or impurities. Conclusion: This model of in-vitro analysis of passage of OLPRUVA through gastrostomy tubes may serve as a model for future studies to be conducted for other pharmacological and dietary supplementations to ensure safe administration via gastrostomy tubes, which is likely an understudied area in metabolic diseases.

SUBGROUP ANALYSIS BY PHENOTYPE IN A PHASE III, RANDOMIZED, PLACEBO-CONTROLLED CROSSOVER TRIAL WITH LEVACETYLLEUCINE (IB1001) FOR NIEMANN-PICK DISEASE TYPE C

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NPC is a rare, autosomal recessive neurodegenerative disorder where an earlier age at onset of neurological manifestations significantly correlates to more severe and rapid disease progression and prognosis. IB1001-301 was a Phase III, double-blind, randomized, placebo-controlled, crossover trial comparing levacetylleucine with placebo for the treatment of neurological signs and symptoms in NPC after 12 weeks. 60 genetically confirmed NPC patients aged 5 to 67 years were enrolled. The primary endpoint, Scale for Assessment at Rating of Ataxia (SARA) was -1.97 points with levacetylleucine and -0.60 for placebo ($p<0.001$). Methods: Subgroup analysis was conducted to evaluate levacetylleucine treatment across the 4 phenotypes of NPC, defined by age of neurological manifestation onset.; early infantile (onset <2 years), late infantile (2 - <6 years), juvenile (6 - <15 years), and adult/adolescent (≥ years). Results: Subgroup analysis was supportive of the primary endpoint findings in IB1001-301. Across all phenotypes, patients treated with levacetylleucine demonstrated improvements in the SARA compared to placebo: mean difference of -1.94 for early infantile onset patients, -1.61 for late infantile onset patients, -1.48 for juvenile onset patients, and -0.62 for adolescent/adult-onset patients. Consistent improvement was observed across for the secondary measures in levacetylleucine-treated patients. Adverse event frequency was comparable between subgroups. No treatment-related serious adverse events occurred. Conclusions: Levacetylleucine demonstrated improvement in neurological manifestations and status over placebo in all phenotypes of NPC, irrespective of the age of onset of neurological manifestations. Levacetylleucine was safe and well-tolerated, providing a favorable benefit-risk profile for the treatment patients with NPC.

ELEVATED TRANSAMINASES: DOES IT ALWAYS WARRANT A LIVER BIOPSY? LESSONS LEARNED FROM POMPE DISEASE

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Pompe disease (PD) is a neuromuscular disorder caused by pathogenic variants in the *GAA* gene, leading to acid alpha-glucosidase (GAA) deficiency and lysosomal glycogen accumulation in muscles. PD is classified into infantile-onset (IOPD), characterized by cardiomyopathy and death if untreated, and late-onset (LOPD), which presents from infancy to the sixth decade with a broad clinical spectrum ranging from muscle weakness to incidental laboratory findings. Although elevated transaminases are generally interpreted as liver dysfunction, in PD an elevated AST:ALT ratio with increased creatine kinase (CK) levels reflects underlying muscle damage. We describe two pediatric cases in which liver biopsy was performed before a LOPD diagnosis. Patient 1: A 23-year-old male had elevated transaminases and CK at age 7 years. Persistent elevation of transaminases prompted a liver biopsy at the age 15 years. The biopsy findings revealed glycogen accumulation without evidence of inflammation, fibrosis, or steatosis. Given the elevated levels of CK and the glycogen accumulation on biopsy, GAA activity was assessed and was deficient. Genetic testing of *GAA* confirmed a LOPD diagnosis. Patient 2: A 9-year-old female presented with poor weight gain, easy fatigability, elevated transaminases (AST>ALT) and CK at age 5 years. Due to the elevated transaminases, a liver biopsy was done and showed non-diagnostic findings. Given the elevated CK levels, a muscle biopsy was performed and revealed glycogen-laden fibers with decreased GAA activity, suggesting a LOPD diagnosis. These cases highlight the importance of careful phenotyping. Neuromuscular gene panels offer a non-invasive first step in the diagnosis of LOPD.

IMPROVED GROWTH IN YOUNG PATIENTS AGED 2-20 YEARS WITH CLASSIC FABRY DISEASE DURING AGALSIDASE BETA TREATMENT: A FABRY REGISTRY ANALYSIS

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Slow growth during adolescence, and delayed onset of puberty have been reported in males with Fabry disease (FD). We investigated the association between agalsidase-beta treatment (0.8-1.2 mg/kg/biweekly) and growth parameters in classic patients with FD aged 2-20 years, from the Fabry Registry (NCT00196742) as of October 2023. Height-for-age percentiles were calculated. Annual height-for-age percentile changes were analyzed using piecewise linear mixed models (≥1 record during natural history (NH) or agalsidase-beta periods). Models with the lowest Akaike information criterion were selected (knots at ages: males, 11 and 14 years; females, 11 years). Mean (SD) ages at last height measurement (agalsidase-beta vs NH) were 16.4 (3.6) vs 12.8 (4.9) years with an agalsidase-beta treatment duration of 4.0 (3.2) years in males, and 16.0 (3.9) years vs 14.7 (4.5) years with an agalsidase-beta duration of 3.3 (2.4) years in females. Height-for-age percentile slopes (percentile/year, 95% CI) among 399 males were (agalsidase-beta vs NH): age 3-11 years, 0.55 (-0.44, 1.54; p=0.276) vs -0.24 (-1.01, 0.52; p=0.528), p-difference=0.151; 11-14 years, -2.36 (-4.16, -0.56; p=0.011) vs -3.06 (-4.83, -1.30; p=0.001), p-difference=0.493; 14-20 years, 2.06 (0.85, 3.26; p=0.001) vs 0.51 (-0.84, 1.85; p=0.460), p-difference=0.016, and among 442 females (agalsidase-beta vs NH): 3-11 years, 2.52 (0.21, 4.83; p=0.032) vs -0.38 (-1.56, 0.79; p=0.519), p-difference=0.009; 11-20 years, -0.25 (-1.28, 0.78; p=0.631) vs 0.06 (-0.58, 0.69; p=0.861), p-difference=0.574. In conclusion, males with FD receiving agalsidase-beta treatment experienced improved growth during late adolescence/young adulthood moving into higher height percentiles. Females gained height percentiles only during the pre- and early adolescence periods.

PROSPECTIVE OBSERVATIONAL STUDY TO ASSESS THE LONG-TERM SAFETY OF OLIPUDASE ALFA EFFECT IN PEDIATRIC PATIENTS LESS THAN 2 YEARS OF AGE WITH ACID SPHINGOMYELINASE DEFICIENCY: STUDY DESIGN

Mendoza MR[1] presenting on behalf of: Bianculli P[2], Cil SU[3], Lewi D[4], Coolidge K[4], Gwadry-Sridhar F[4], Hull J[3], Oliveira-dos-Santos A[5]

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Acid sphingomyelinase deficiency (ASMD) is a rare genetic disorder characterized by deficient activity of the lysosomal enzyme acid sphingomyelinase, resulting in sphingomyelin accumulation and progressive disease. Olipudase alfa is indicated for treatment of non–central nervous system manifestations of ASMD patients. Low incidence of ASMD creates barriers to studying subpopulations within pivotal clinical studies, particularly children diagnosed early in life and needing treatment. The enrollment and follow-up of patients with ultra-rare diseases during clinical studies present challenges, necessitating to balance the demands of collecting necessary and sufficient data to address the study's objective while minimizing any incremental burden on patients and caregivers. Thus, the primary objective is to characterize long-term safety and immunogenicity of olipudase alfa in patients with ASMD <2 years of age at treatment initiation, and in patients with ASMD type A without age restriction, in real-world clinical practice in the United States (US). To minimize burden on patients of clinical visits for assessments and data collection, a decentralized study design was developed based on digital technologies for remote data collection. Such design contributes to overcoming the challenge of a short enrollment window and avoids the inefficiency of opening multiple study sites a priori and waiting for a new incident patient to be diagnosed or referred for medical care. Bringing the technology directly to families empowers them, allowing medical care at their facility of choice and preserving the real-world clinical practice observational nature of the data being collected. The study is currently enrolling in the US (ClinicalTrials.gov: NCT06192576).

EFFICACY AND SAFETY RESULTS FROM A PIVOTAL PHASE 3 TRIAL OF DTX401, AN AAV8-MEDIATED LIVER-DIRECTED GENE THERAPY, IN INDIVIDUALS WITH GLYCOGEN STORAGE DISEASE TYPE IA (GSDIA)

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***Background*:** GSDIa is a rare, potentially life-threatening carbohydrate metabolism disorder caused by biallelic pathogenic *G6PC* gene variants, resulting in glucose-6-phosphatase deficiency. DTX401 is an investigational adeno-associated virus serotype 8 vector containing the human *G6PC* gene. ***Methods*:** DTX401-CL301 (NCT05139316) is an ongoing, pivotal, phase 3, double-blind, randomized, placebo-controlled trial of DTX401 in patients ≥8 years old with GSDIa. At Week 48, participants crossed over in a blinded manner (DTX401 at Day 1 received placebo and placebo at Day 1 received DTX401) for an additional 48-week period. ***Results*:** The study met the primary endpoint: at Week 48, DTX401 treatment resulted in a mean (standard deviation [SD]) daily cornstarch intake reduction of 41.0% (18.4) versus a 10.1% (18.0) reduction with placebo; $p<0.0001$. In the Crossover Period, greater reductions in total daily cornstarch were observed in both the ongoing DTX401 group and the Crossover Placebo to DTX401 group. Patient experience data support cornstarch reduction clinical meaningfulness, with Week 48 Patient Global Impression of Change Moderately/Much Improved corresponding to a 34% mean reduction in daily cornstarch intake. Anticipated vector-induced liver enzyme elevations were manageable with prophylactic corticosteroids. Elevations in triglycerides were observed in individual participants, requiring adjustments of cornstarch and dietary intake. ***Conclusion*:** Treatment with DTX401 resulted in statistically significant and clinically meaningful reductions in cornstarch intake versus placebo at Week 48, with greater reductions in cornstarch in the Crossover Period. Confidence that all participants had been treated with DTX401 likely contributed to improvements in the Crossover Period. DTX401 had an acceptable safety profile.

ABSTRACT TITLE: INTERIM RESULTS FROM THE APHENITY OPEN-LABEL EXTENSION STUDY: SEPIAPTERIN REDUCES BLOOD PHE WITH IMPROVED DIETARY PHE TOLERANCE IN PARTICIPANTS WITH PKU

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Objectives: Sepiapterin is an oral, investigational treatment for phenylketonuria (PKU). The phase 3 APHENITY trial (NCT05099640) evaluated sepiapterin in a broad PKU population. Here, we describe results from the open-label extension (NCT05166161; June 30, 2024 data cut). **Design and Methods:** The extension study includes participants who completed the APHENITY trial (feeder participants) and participants who have not partaken in a PTC-sponsored phase 3 trial (non-feeder participants). Participants received sepiapterin once daily for ≥12 months. At month 2, day 1, participants with mean blood phenylalanine (Phe) <360 µmol/L underwent a dietary Phe tolerance assessment, evaluating mean blood Phe and dietary Phe consumption over 26 weeks. **Results:** Overall, 169 participants (median age, 14.0 [range: 0.2–55.0] years) received sepiapterin. Dietary Phe tolerance assessments were performed in 100 participants (non-feeder participants, n=27); median treatment exposure was 465.0 (range: 26–868) days. The least-squares mean change (95% CI) for change in dietary Phe consumption from baseline to week 26 was 38.0 (32.1–43.9) mg/kg/day (protein: 0.76 [0.64–0.88] g/kg/day). An approximately 2.3-fold increase from baseline in mean daily Phe consumption was achieved at week 26, while mean blood Phe remained within the recommended target (<360 µmol/L). The rate of discontinuations due to treatment-emergent adverse events (TEAEs) was low (1.8%) and there were no treatment-related serious TEAEs and no deaths during the study. **Conclusions:** Sepiapterin provides clinical benefits in children and adults with PKU and could potentially allow for liberalization of a highly Phe-restrictive diet. Sepiapterin was well tolerated; no long-term safety concerns were observed.

UX111 GENE THERAPY RAPIDLY REDUCED HEPARAN SULFATE (HS) EXPOSURE IN CEREBROSPINAL FLUID (CSF) AND IMPROVED COGNITIVE FUNCTION IN CHILDREN WITH MUCOPOLYSACCHARIDOSIS IIIA (MPS IIIA)

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Introduction: MPS IIIA is a progressive neurodegenerative lysosomal storage disease characterized by irreversible neurocognitive decline and early death. UX111 is an AAV9 viral vector encoding human *SGSH* being investigated for treatment of MPS IIIA. **Methods:** Data were combined across 2 open-label clinical trials (NCT02716246 and NCT04088734) and the ongoing long-term follow up (NCT04360265). Children received a single IV injection of UX111. The efficacy set included all children treated with the highest UX111 dose (3×10^{13} vg/kg). The mITT set included children treated with the highest UX111 dose and either ≤2 years old or >2 years old with a BSITD-III cognitive development quotient ≥60. Data cutoff was 01Aug2024. **Results:** In the efficacy set (n=27), UX111 led to a median 64.5% reduction in CSF HS exposure relative to baseline ($p<0.0001$), regardless of age or stage of disease. Reductions have been maintained (median follow up of 33.8 months). In the mITT set (n=17), model-estimated mean change in BSITD-III raw scores from 24-60 months of age significantly improved relative to natural history for cognitive (22.7 points, $p<0.0001$), receptive communication (7.4 points, $p=0.0212$), and expressive communication domains (15.9 points, $p=0.0011$). Fine and gross motor skill domains showed clear separation from natural history (7.3 points, $p=0.050$ and 2.0 points, $p=0.360$, respectively). Children who were older or had more advanced disease at treatment (n=10) retained key abilities of communication, self-feeding, and/or ambulation. No TEAEs led to death. Most UX111-related TEAEs were mild to moderate and resolved spontaneously. **Conclusions:** UX111 appears safe and effective in children with MPS IIIA.

UNDERSTANDING GENETIC TESTING COMPLETION IN A SOUTHEASTERN PEDIATRIC GENETICS CLINIC: INFLUENCING FACTORS AND OUTCOMES

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Genetic testing is crucial to the identification of rare genetic conditions. Access to genetics services has increased through the use of telehealth, the collaboration of geneticists and genetic counselors, and the advancement of genetic testing technology. However, barriers and limitations remain impeding the successful completion of genetic testing. This study aimed to understand how patient demographics and clinical factors of an appointment and the testing process affect a pediatric genetics clinic genetic testing completion rate. Through a retrospective chart review, 200 patient charts from the Medical University of South Carolina (MUSC) Children's Health Genetics Clinic were identified, reviewed, and analyzed. Patients who were seen within the outpatient general pediatrics genetics clinic from May 2023 to December 2023, were less than 18 years old, offered genetic testing, and elected to pursue genetic testing were included. Study factors of patient sex assigned at birth, race, ethnicity, age at evaluation, language, insurance type, referral source, appointment type, consenting provider, recommended genetic test, sample type, and sample collection method were assessed to understand their effect on testing completion rate. The study revealed that appointment type, sample type, and sample collection method had significant associations with genetic testing completion status. Patients who attended an in-person appointment and had a blood sample collected at the visit were most likely to complete genetic testing. Findings from this study provide insight into the delivery model of genetics services and support the effectiveness of a traditional model for patient care when genetic testing is recommended.

A STRUCTURAL STRATEGY FOR TYROSINEMIA MANAGEMENT: BLOCKING ACE2-B0AT1–MEDIATED TYROSINE UPTAKE AND ENGINEERING A TYROSINE-DEGRADING ENZYME

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Tyrosinemia is a metabolic disorder characterized by elevated plasma tyrosine levels, which can lead to severe liver and neurological complications if not properly managed. Current treatments, such as dietary restriction and use of nitisinone, are often insufficient in fully controlling tyrosine toxicity and preventing long-term sequela. The urgent need for novel interventions has sparked interest in targeting the molecular underpinnings of tyrosine homeostasis. The intestinal and renal co-transporter B0AT1 (SLC6A19), complexed with the angiotensin-converting enzyme 2 (ACE2), plays a critical role in the uptake of neutral amino acids, including tyrosine. By strategically blocking tyrosine absorption at its root, we may alleviate the metabolic burden associated with the disease. Simultaneously, computationally designed enzymes capable of selectively degrading circulating tyrosine offer a complementary, orthogonal approach to restoring metabolic balance. The proposed research leverages computational structural biology to address tyrosinemia at two distinct molecular fronts. We will utilize high-resolution modeling and docking simulations to identify compounds capable of binding and inhibiting the ACE2-B0AT1 complex and, in parallel, computationally optimize a phenylalanine ammonia lyase (PAL) variant to efficiently sequester and degrade excess tyrosine. Through advanced computational approaches such as molecular dynamics simulations, FEL analysis, and SMD evaluations, these aims are expected to deliver actionable targets and tools for controlling tyrosine levels more effectively than current standards of care.

INDEX OF SUSTAINED PHE RESPONSE AND IMPROVEMENTS IN PKU CLINICAL OUTCOME ASSESSMENTS IN PATIENTS RECEIVING PEGVALIASE

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Objective: The relationship between a sustained Phe response (SPR) and clinical outcomes assessments (COAs) is explored using the Attention Deficit Hyperactivity Disorder Rating Scale-IV Inattention (ADHD RS-IV IA) subscale and the PKU Profile of Mood States Total Mood Disturbance (PKU-POMS TMD) score. **Methods:** The longitudinal pattern of serial Phe measures for PRISM study participants, expressed as the expected value of Phe at time t, was estimated with a generalized additive model smoother function. SPR occurred when the upper 95% confidence interval of the longitudinally modeled pattern in estimated mean Phe_t remained below specific thresholds. A Bayesian multilevel ordinal regression model estimated the monotonic effects of SPR, fitted as a 4-level ordinal predictor (No SPR vs. SPR600, SPR360, and SPR120), on estimated COA scores. **Results:** Participants with baseline ADHD RS-IV IA score >9 (n=91), were included in a regression model with the ordinal predictor for SPR to estimate conditional outcomes. Estimated ADHD RS-IV IA score showed consistent improvement with lower SPR thresholds ("No SPR" was 9.6 vs. 7.3 for SPR600, 6.9 for SPR360, and 5.5 for SPR120). Models for PKU-POMS TMD score included patients with baseline scores greater than the median (>14; n=69) and similarly showed a consistent improvement with lower SPR thresholds ("No SPR" was 28.3 vs. 25.2 for SPR600, 24.6 for SPR360, and 22.1 for SPR120). **Conclusions:** COA scores improved with lower sustained blood Phe levels with those in SPR120 µmol/L being significantly better than SPR600 µmol/L or SPR360 µmol/L, suggesting that patients may benefit from normalizing Phe levels.

SEEING THE WHOLE PICTURE: THE ROLE OF CARE MAPPING AS A TOOL TO SUPPORT INDIVIDUALS WITH MEDICAL COMPLEXITIES

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For individuals with complex medical conditions, coordinating care across multiple providers and support systems is a significant challenge. Care mapping has emerged as a helpful tool to manage this complexity, providing a visual representation of an individual's entire care network. Emerging evidence suggests that care maps improve coordination and communication in these care networks, helping families and professionals identify care priorities and better understand the daily needs and burdens of complex conditions. Care maps also give patients and families new insight into their support networks, greater confidence in communicating their needs, and therapeutic relief by getting the complexity "out of their heads" and onto paper—helping to reduce stress and promote emotional clarity. Early studies have found that sharing a care map with healthcare providers fosters empathy and deeper understanding from the care team by illustrating the family's caregiving networks and challenges. Despite these benefits, care mapping is not yet widely adopted in practice. Challenges such as the effort required to create and update maps and the lack of integration into standard care processes have been identified. The current body of research is limited, relying mainly on qualitative findings, and further studies are needed to evaluate the long-term impact of care mapping and develop best practices for its implementation. We invited females with phenylketonuria or maple syrup urine disorder who attended Emory University's 2025 Metabolic Camp to create care maps. Selected examples will be presented to highlight key features and demonstrate the potential utility and benefits of this tool.

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

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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 the amino acid phenylalanine (PHE). Treatment involves lifelong PHE-restricted diets, posing significant challenges. Patients face additional challenges during the transition from pediatric to adult healthcare management. This study aims to explore caregivers' perspectives on transitioning their children affected by PAH deficiency from the pediatric to the adult healthcare system. Key study objectives include gaining an understanding of caregivers' perceptions of patient and family needs during the transition period. Purposive sampling was used to recruit participants from the National PKU Alliance patient registry. Email and social media recruitment was conducted. The recruitment materials included a web link to the study description, a prescreening form, and informed consent. All individuals who met the inclusion criteria were contacted. A total of 23 telephone interviews were completed. Following the interviews, the transcripts were analyzed using content analysis to identify essential themes and concepts associated with transitioning a child from pediatric to adult healthcare management. Data analysis is ongoing. Current identified themes include social determinants of health, such as lack of financial and psychosocial support, insufficient patient and parental education, and lack of standardized transition programs and guidelines. Gaining vital knowledge about caregivers' perceptions of transition care is crucial. By improving understanding of transition care needs, this study may lead to the identification of ways to optimize transition and enhance the quality of care for individuals affected by PAH deficiency.

SURVIVAL OUTCOMES IN PATIENTS WITH GAUCHER DISEASE TYPE III: A MULTINATIONAL CROSS-SECTIONAL STUDY

Mengel E[1], Stanescu S[2], Di Fonzo AB[3], Djatche L[4], Aragon MJ[5], Pulikottil-Jacob R[6], Santana IR[5], Perichon MG[7], Palli J[8], Ezgu FS[9] (To be presented by **Jennifer Stallworth** from Sanofi)
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Gaucher disease type 3 (GD3) is a rare genetic neurodegenerative disorder, characterized by heterogeneity in symptom burden, disease severity, and progression amongst patients. There is limited evidence on the burden of GD3. This study aimed to evaluate survival and causes of death in patients with GD3 treated by participating clinicians over the past decade. This retrospective, cross-sectional study collected data from clinicians (recruited via physician panel) in Germany, Italy, Spain, Turkey, UK and US in 2023–2024. Clinicians provided data on demographics, vital status, cause of death (if applicable), year of first GD3 symptoms, diagnosis and last consultation for patients they have treated over the past decade. Survival probability after the GD3 symptom onset and diagnosis was estimated using the Kaplan–Meier survival function for patients with non-missing data. This study included data from 440 patients, of which 96 (21.8%) died. Age of death was known in 53 cases with a mean (SD) of 12.81 (9.73) years. The most common causes of death were severe progressive neurodegeneration (21.9%), respiratory disease (21.9%), bleeding (20.8%) and severe neurological manifestations (19.8%). The 10-year survival from GD3 symptoms onset for 289 patients with available data was 78.7% [95% CI: 72.0%–84.0%] and from diagnosis for 377 patients with available data was 82.0% [95% CI:76.3%–86.5%]. Nearly a quarter of treated patients died within 10 years of GD3 symptom onset, the causes of death being driven by neurodegeneration, respiratory disease, and bleeding. These results underscore the remaining unmet need in this patient population.

EXPANDED NEWBORN SCREENING IN LOUISIANA 2005-2024: RESULTS AND CLINICAL OUTCOMES

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Background: Louisiana began screening for phenylketonuria (PKU) in 1964 and adopted tandem mass spectrometry (MS/MS) in 2004 to expand newborn screening (eNBS) for inborn errors of metabolism. This study evaluates the incidence of metabolic disorders detected from January 2005 to December 2024. *Methods*: Data were extracted from the state's newborn screening database and validated via confirmatory testing at Louisiana State University and Tulane University. Clinical outcomes were obtained from medical records. *Results:* Of approximately 1,230,000 infants screened, 472 were diagnosed with metabolic disorders, an incidence of 1 in 2,602 live births. The five most commonly identified conditions were biotinidase deficiency, PKU, medium-chain acyl-CoA dehydrogenase deficiency (MCADD), short-chain acyl-CoA dehydrogenase deficiency (SCADD), and very long-chain acyl-CoA dehydrogenase deficiency (VLCADD). At least 12 infants died. Their diagnoses included MCADD (3), VLCADD (1), LCHAD (1), CPT2 deficiency (2), CACT deficiency (1), PKU with maternal PKU (1), MADD (2), and holocarboxylase synthetase deficiency (1). *Conclusion:* The incidence rates of several disorders, including biotinidase deficiency and PKU, were similar to those reported in a previous U.S. cohort. Since 2005, eNBS in Louisiana has identified over 450 infants with inherited metabolic disorders. Early detection and intervention have led to normal or near-normal outcomes for most. However, some infants died despite early diagnosis and treatment, underscoring the severity and complexity of certain metabolic conditions.

IMPROVEMENTS IN BLOOD PHENYLALANINE AND HEALTH-RELATED QUALITY OF LIFE OUTCOMES AMONG ADULTS WITH PKU RECEIVING PEGVALIASE IN THE OPAL STUDY

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Objective: To report interim findings from the OPAL observational study, highlighting the impact of pegvaliase treatment on blood Phe levels and health-related quality of life (HRQoL) outcomes. **Methods:** Adults with PKU receiving or initiating pegvaliase, with blood Phe >600 µmol/L were enrolled. Blood Phe and HRQoL outcomes were assessed, including the PKU Quality of Life (PKU-QOL) Questionnaire and the Adult PKU Symptom Severity and Impacts Scale (PKU-SSIS). **Results:** By the second interim analysis (March 2024), 76 participants had enrolled, and the majority had completed ≥48 weeks in the study. We report on 51 participants with: baseline Phe, screening PKU-QOL & PKU-SSIS measurements, and ≥24 weeks of follow-up. Mean (SD) blood Phe level was 1029 (259) µmol/L at baseline and declined to 651 (391) µmol/L at week 24 (n=47), 569 (428) µmol/L at week 48 (n=39), and 293 (294) µmol/L at week 96 (n=16). Mean (SD) PKU-QOL overall impact scores showed improvement, declining from 29.0 (16.7) at baseline (n=47) to 23.2 (12.9) at week 24 (n=46), 23.2 (14.9) at week 48 (n=40), and 18.4 (14.0) at week 96 (n=31). Similarly, mean (SD) PKU-SSIS total scores improved, declining from 31.8 (16.4) at baseline (n=50) to 25.8 (13.5) at week 24 (n=46), 27.6 (14.5) at week 48 (n=40), and 23.4 (12.3) at week and 96 (n=31). **Conclusion:** Preliminary findings from OPAL demonstrate that blood Phe reductions observed with pegvaliase treatment in the real-world setting are consistent with findings from clinical trials. Moreover, improvements in HRQoL outcomes were observed in the study cohort.

INITIAL CLINICAL RESULTS FROM THE FIRST *IN VIVO*, LIVER DIRECTED, AAV-MEDIATED GENE INSERTION STUDY WITH ECUR-506 IN NEONATAL OTC DEFICIENCY: COMPLETE CLINICAL RESPONSE IN FIRST MALE INFANT TO COMPLETE 24-WEEK PHASE 1/2 STUDY

Baruteau J[1]; Cohn G[2]; Dhawan A[3]; Chakrapani A[1]; Grunewald S[1]; Abbott M[1]; Ashton H[1]; Foxall S[1]; Koh A-L[1]; Lazaridis C[1]; Navarro-Kennedy H[1]; Patel H[1]; Sivananthan S[1]; Tamvaki E[1]; Vecchiato K[1]; Hall M[2]; Kuhn K[2]; **White T**[2]; Pinho B[4]; Diaz GA[2]

[1]Great Ormond Street Hospital for Children, London, UK; [2]iECURE, Inc., Blue Bell, PA; [3]King's College Hospital, London, UK; [4]Fortrea, Inc., Princeton, NJ

Background: Ornithine transcarbamylase deficiency (OTCD) is a urea cycle disorder resulting in impaired ureagenesis and hyperammonemia. Males with severe neonatal onset OTCD typically become hyperammonemic within the first 48-72 hours and are commonly misdiagnosed. Despite aggressive medical management, repeat hyperammonemic events are common and mortality rates are high. **Methods:** ECUR-506 is an *in-vivo*, liver-directed, gene insertion, investigational product. OTC-HOPE (NCT06255782) is a 24-week, first in human, single arm, Phase 1/2, open-label, global, multi-center trial designed to assess safety and efficacy of ECUR-506 in males with neonatal onset OTCD who are <9 months of age. Study participants will be included in a 14.5-year follow-up study. Herein, initial clinical and biomarker data of the first study participant to complete the 6-month trial are described. **Results:** The participant experienced 2 hyperammonemic events by 3.5 months of age and underwent ECUR-506 (1.3×10^{13} GC/kg) infusion at 6.5 months of age. Transaminitis was observed, between weeks 4-8 post-infusion, which resolved with immunosuppression. Normal ammonia and reduced glutamine levels prompted nitrogen scavenger medication discontinuation and liberalization of protein intake by weeks 12 and 15, respectively. Subsequently, mean ammonia levels were normal. No hyperammonemic events and normal infant growth trajectory were observed over the remainder of the 6-month study. **Conclusion:** These data are from the first infant to receive ECUR-506 (the *in vivo* AAV-mediated gene editing therapy) and complete the OTC-HOPE study. The observed complete clinical response by study definition and safety profile support the continued evaluation of low dose ECUR-506 (1.3×10^{13} GC/kg) in the study.

DIAMOND EXHIBITORS

Amgen
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Representative Onsite: Matt German

Amgen's medicines treat serious illnesses and typically address diseases with a limited number of treatment options, with a presence in approximately 100 countries, we are proud to have reached millions of people with our products.

DIAMOND EXHIBITORS

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PTC is an established global biopharmaceutical company that delivers 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 patients.

PLATINUM EXHIBITORS

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BioMarin is a world leader in developing and commercializing innovative therapies for rare diseases driven by genetic causes. Visit www.biomarin.com to learn more.

Sanofi Rare Diseases
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Representatives Onsite: Kathryn Williams

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.

GOLD EXHIBITORS

Acadia Pharmaceuticals
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Guided by our mission to advance breakthroughs in neuroscience to elevate life, Acadia Pharmaceuticals is dedicated to creating a brighter future for people living with rare diseases. We launched the first and only FDA-approved treatment for Rett syndrome and are actively working to broaden access to this vital therapy worldwide. Our growing rare disease pipeline includes treatments for Rett syndrome, Prader-Willi syndrome and more.

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Representatives Onsite: Lisa Quirk, Sarah Knight
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Alexion's mission is to transform the lives of people affected by rare diseases and devastating conditions by continuously innovating and creating meaningful value in all that we do.

Amicus Therapeutics
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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.

GOLD EXHIBITORS

Chiesi Global Rare Diseases
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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
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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.

Fulgent Genetics
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Representatives Onsite: Chris Zerwas and Leslie Karras
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Fulgent is a full-service genomic testing company built around a foundational technology platform. Through our diverse testing menu, we're focused on transforming patient care across all clinical areas, including rare disease, oncology, and reproductive health.

GOLD EXHIBITORS

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Diagnostic Genetic Testing

Mirum Pharmaceuticals
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Mirum is dedicated to transforming scientific discoveries into therapies poised to change the trajectory of rare Inborn Errors of Metabolism. Our product is used to treat rare nutitional deficiencies, including Smilth Lemi Optiz Syndrom. Our medication is Cholbam

Soleno Therapeutics
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At Soleno, we are researching and developing medicines to treat rare geneti disorders, beginning with Prader-Willi syndrome (PWS). Vykat XR is the only FDA-approved treatment for hyperphagia in adults and pediatric patients 4 years of age and older with Prader-Willi syndrome (PWS).

GOLD EXHIBITORS

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Takeda is focused on creating better health for people and a brighter future for the world. We aim to discover and deliver life-transforming treatments in our core therapeutic and business areas, including gastrointestinal and inflammation, rare diseases, plasma-derived therapies, oncology, neuroscience and vaccines.

UCB, Inc
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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 severe diseases of the immune system or of the central nervous system. UCB is listed on Euronext Brussels (symbol: UCB).

GOLD EXHIBITORS

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Ultragenyx is a rare disease pharmaceutical company that promotes several products for Metabolic Genetic Diseases. We have supported the SERGG Conference for many years.

Variantyx, Inc
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Variantyx is a molecular diagnostics company. We provide genetic testing for rare genetic disorders, reproductive genetics and precision oncology – disrupting the traditional testing approach with our advanced proprietary technology.

SILVER EXHIBITORS

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For 45 years, Baylor Genetics has been the leading pioneer in genetic testing. Currently, we offer a full spectrum of cost-effective, genetic testing and provide clinically relevant solutions. Our team's unmatched knowledge and experience deliver a combination of advanced technology and deep patient data sets that lead to more accurate interpretations.

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Representative Onsite: Trevor Papkov

We have treatments for three different genetic rare neuromuscular diseases. We also offer sponsored genetic testing for free that HCPs can use to help diagnose patients.

BridgeBio, Inc
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Suite 250
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www.bridgebio.com
Representative Onsite: Luke Acre

Our mission is to discover, create, test, and deliver transformative medicines to treat patients who suffer from genetic diseases. Our focus is to capitalize on scientific advancements that deepen our understanding of genetic disease to develop breakthrough medicines for patients in need at an unprecedented scale.

SILVER EXHIBITORS

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Eton is an innovative pharmaceutical company focused on developing and commercializing treatments for rare diseases. The Company currently has five commercial rare disease product: ALKINDI SPRINKLE®, PKU GOLIKE®, Carglumic Acid, Betaine Anhydrous, and Nitisinone.

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3800 S Business Park Ave
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PreventionGenetics provides patients with sequencing and CNV tests for nearly all clinically relevant genes. These test include our powerful and comprehensive whole exome sequencing test, PGxomes®.

EXHIBITORS

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AiLife Diagnostics, an employee-owned company, is comprised of ABMGG certified geneticists, clinicians, PhD genome scientists, bioinformatics and IT experts. Our mission is to provide fast and accurate interpretation NGS services, including panels, WES, and WGS, RNA Seq and mtDNA.

AMBRY GENETICS
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Ambry Gentics 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.

DENALI THERAPEUTICS
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Denali is a biotechnology company developing drug candidates engineered to cross the blood-brain barrier (BBB) for neurodegenerative diseases. We are committed to advancing new potential treatments for lysosomal disorders that affect the brain, starting with tividenofusp alfa (DNL310), our investigational IV enzyme replacement therapy for Hunter syndrome (MPS II).

EMORY UNIVERSITY-MNT4P PROGRAM
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The MNT4P Program at Emory University is a unique initiative that combines academic expertise with key partnerships across Emory and beyond to create a robust platform for innovation in genetics metabolic nutrition, integrating research, education, and clinical community services.

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Evrysdi (risdiplam) is an oral medication approved for the treatment of spinal muscular atrophy (SMA) in newborns and older, proven to increase survival motor neuron protein levels and improve motor function in the most inclusive clinical trial program.

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The Greenwood Genetic Center is at the forefront of genetic discovery, research and clinical care. With a long history of providing genetics services, GGC is making bold advances in genetic and genomic medicine. We are committed to advancing the diagnosis, treatment, prevention, and cure of genetic disorders.

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jscreen® is a national non-profit genetic screening and education program offering access to comprehensive at-home testing and genetic counselling. Genetic screening with jscreen® provides important insights for hereditary health risks to help proactively manage your health and make informed decisions.

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Medunik USA is a pharmaceutical company seeking to improve the lives of patients with rare diseases by providing access to specialized treatments, including for urea cycle disorders. We are committed to addressing the unmet medical needs of the rare disease community through innovation, collaboration, and compassionate care.

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Novartis Gene Therapies is reimagining medicine to transform the lives of people living with rare genetic diseases. Utilizing cutting-edge technology, we are working to turn promising gene therapies into proven treatments. We are powered by an extensive manufacturing footprint, in capacity and expertise, enabling us to bring gene therapy to patients around the world at quality and scale.

REVVITY
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Revvity provides health science solutions, technologies, expertise, and services that deliver complete workflows from discovery to development, and diagnosis to cure. Revvity is pushing the limits of what's possible in healthcare.

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Zevra is a rare disease company combining science, data, and patient needs to create transformational therapies for diseases with limited or no treatment options. Our mission is to bring lifechanging therapeutics to people living with rare diseases.