MEETING LOCATIONS

DATE/TIME	FUNCTION	LOCATION
Wednesday, July 12		
6:00 p – 8:00 p	Registration	Crystal Promenade
7:00 p -	SERGG Board of Directors Dinner Meeting	Opal One
Thursday, July 13		
10:00 a – 12:00 p	Telegenetics Workgroup	Opal One
12:00 p – 5:00 p	Registration	Crystal Promenade
12:15 p – 1:15 p	ISS-Sanofi (with box lunch)	Topaz Room
1:30 p – 5:45 p	Platform Session 1	Crystal Ballroom ABC
3:25 p – 3:55 p	Break	Crystal Ballroom Promenade
6:00 p – 7:30 p	Reception and Poster Session	Crystal Ballroom DEF
7:00 p – 9:00 p	Dinner for IMD Providers (by invitation)	Opal One
Friday, July 14		
8:00 a – 9:00 a	ISS-Ultragenyx Pharm (with breakfast)	Emerald Three
8:00 a – 9:00 a	Continental Breakfast	Crystal Ballroom DEF
8:00 a – 3:00 p	Exhibits/Posters	Crystal Ballroom DEF
8:00 a – 3:00 p	Registration	Crystal Promenade
9:15 a – 10:45 a	Platform Session 2	Crystal Ballroom ABC
8:45 a – 1:30 p	Consumer Alliance	Yellow Topaz
10:45 a – 11:15 a	Break	Crystal Ballroom DEF
11:15 a – 12:00 p	Platform Session 3	Crystal Ballroom ABC
12:00 p – 1:30 p	Lunch	Crystal Ballroom DEF with overflow to Emerald Two
1:30 p – 3:15 p	Platform Session 4	Cystal Ballroom ABC
3:15 p – 3:30 p	Travel to Concurrent Industry Supported Symposia	
3:30 p – 4:30 p	ISS-Rhythm Pharma	Opal One
3:30 p – 4:30 p	ISS-Chiesi Global Rare Diseases	Opal Two
3:30 p – 4:30 p	ISS-Invitae	Blue Topaz
5:00 p – 6:00 p	ISS-Alexion	Opal Two
5:00 p – 6:00 p	ISS-Relief Therapeutics	Blue Topaz
Friday, July 15 - CONCURRENT SESSION – SERN CONSUMER ALLIANCE		
8:45 a – 10:15 a	Consumer Alliance Plenary	Yellow Topaz
10:15 a – 10:45 a	Break	Yellow Topaz
10:45 a – 12:00 p	Consumer Alliance Plenary	Yellow Topaz
12:00 p – 1:30 p	Lunch and State Updates	Yellow Topaz
Saturday, July 16		
8:00 a – 9:00 a	ISS – Rhythm Pharma Med (with breakfast)	Emerald Three
8:00 a – 9:00 a	Continental Breakfast	Crystal Ballroom DEF
8:00 a – 10:30 a	Exhibits and Posters	Crystal Ballroom DEF
8:00 a – 10:30 a	Registration Desk Open	Crystal Promenade
9:15 a – 10:45 a	Platform Session 5	Crystal Ballroom ABC
10:45 a – 11:15 a	Break	Crystal Ballroom DEF
11:15 a – 12:45 p	Platform Session 6	Crystal Ballroom DEF
12:45 p – 1:10 p	SERGG Business Meeting	Crystal Ballroom DEF

SOUTHEAST REGIONAL GENETICS NETWORK (SERN)
40th ANNUAL MEETING of the SOUTHEASTERN REGIONAL GENETICS GROUP (SERGG)
July 13-15, 2023
Charleston, South Carolina
This meeting is supported in part by a grant from the Maternal and Child Health Bureau (MCHB) (Title V, Social Security Act), Grant #UH7MC30772 Health Resources and Services Administration (HRSA), Department of Health and Human Services.

PRE-MEETING EVENTS

Wednesday, July 12, 2023

6:00 pm – 8:00 pm **Registration – Crystal Promenade**

7:00 pm - **SERGG Board of Directors Dinner Meeting – Opal One**

All Sessions and Workgroup Meetings are open to everyone!

Thursday, July 13, 2023

10:00 am – 12:00 pm **Telegenetics Workgroup -** Hans Andersson, MD, Chair – **Opal One**
This annual telegenetics meeting offers several presentations of diverse interests. Attendees do not need any experience in telegenetics. Plenty of time will be available for questions and discussion.
(CME Approved – must attend the entire session)

- **10:00 am** **Welcome**
  Rani H. Singh, PhD, RD, LD, Emory University, SERN Co-PI
- **10:00 am – 10:05 am** **Opening Remarks and Updates of Telegenetics Activities**
  Hans Andersson, MD, Tulane University, SERN Co-PI
- **10:05 am – 10:45 am** **What You Need to Know and Do to Bridge Digital Divide**
  Amy Sheon, Ph.D., MPH, Case Western Reserve University
- **10:45 am – 10:55 am** **Chatbots for Pre-Test Patient Education – Cleveland Clinic Experience**
  David Flannery, MD, Cleveland Clinic
- **10:55 am – 11:35 am** **Patient Perspectives on Telegenetics**
  Moderator: Rossana Sanchez Russo, MD, Emory University School of Medicine
- **11:35 am – 12:00 pm** **Telemedicine Workgroup Discussion**
  Michael Lyons, MD, Greenwood Genetics Center

12:15 pm – 1:15 pm **Industry Supported Symposium – "Biomarkers in Lysosomal Storage Diseases: Clear as Mud?" – Hosted by Sanofi** – **Topaz Room**
Laura Buch, MSPAS, PA-C and Laura Pollard, PhD, Greenwood Genetic Center
(Box Lunch provided for attendees) *(CME Not Provided)*

12:00 pm – 1:30 pm **Lunch On Your Own**

12:00 pm – 5:00 pm **Registration – Crystal Promenade**

SERN/SERGG ANNUAL MEETING

1:30 pm – 5:45 pm **Platform Session 1 –** *(CME Sessions marked with *)* – **Crystal Ballroom ABC**
Chair: Rani Singh, PhD, RD, LD, Emory University School of Medicine

- 1:30 pm – 1:40 pm **Introduction** – Rani Singh, PhD, RD, LD, Emory University School of Medicine
- 1:40 pm – 1:55 pm **Health Resources and Services Administration** (**HRSA) Update**
  Alisha Keehn, MPA, HRSA, Genetic Services Branch
  (CME Not Provided)
- 1:55 pm – 2:15 pm **National Coordinating Center (NCC) and Genetic Services Branch, MCHB Update**
  Megan Lyon, MPH, American College of Medical Genetics and Genomics
  (CME Not Provided)

2:15 pm –2:35 pm	**Updates from APHL and Expansion of Newborn Screening** Giusou Zarbalian, MS, MPH, Association of Public Health Laboratories (APHL) *(CME Not Provided)*
2:35 pm – 3:00 pm	***Blueprint for Change: A National Framework for a System of Services for Children and Youth with Special Health Care Needs** Loraine Swanson, MPH, Health Resources and Services Administration
3:00 pm – 3:25 pm	***Legislative Update: Genetic Counseling Licensure and Medicare Provider Status** John Richardson, National Society of Genetic Counseling
3:25 pm - 3:55 pm	**BREAK**
3:55 pm – 4:20 pm	***DNA Methylation Episignatures: Diagnostic Biomarkers for Rare Diseases and Beyond** Bekim Sadikovic, PhD, Western University
4:20 pm – 4:45 pm	***Mendelian Disorders of the Epigenetic Machinery: Clinical Insights and New Discoveries"** Jill Fahrner, MD, John Hopkins
4:45 pm – 5:25 pm	**PAUL M. FERNHOFF MEMORIAL LECTURE** ***Impact of New Treatment Strategies and Newborn Screening on Hunter Syndrome (MPS II)** Joseph Muenzer, MD, PhD, University of North Carolina at Chapel Hill
5:25 pm – 5:45 pm	Closing Remarks

* Indicates CME Approved

6:00 pm –7:30 pm	**Welcome Reception and Poster Session (Cash Bar) – Crystal Ballroom DEF** **Supported by all of the exhibitors.** *(CME Not Provided)* Be sure to visit each exhibit at some time during the meeting and get your card punched for the gift card drawing!
7:00 pm – 9:00 pm	**Dinner for IMD Providers & SERN Family Alliance Members –** **"A Taste of eGNA 2023: Long Chain Fatty Acid Oxidation Disorders and the Role of MCTs/Triheptanoin" – Opal One** ***Pre-registration required to attend this session*** *(CME Not Provided)*

Please place all phones on vibrate when in the meeting rooms.
There is no conference code for wi-fi in the meeting rooms.
Free wi-fi is available in the lobby areas and guest rooms.

There are currently no COVID mandates in the State of South Carolina. Please make your own decision whether to wear a mask in public areas.

CEUs are being offered for Genetic Counselors for this meeting. Apply for the credits at the registration desk during the meeting. You must provide your NSGC membership number and either cash or a check for $25. Please direct any questions to Amy Jonasson at argladstone@ufl.edu or in person during the meeting.

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

All Sessions and Workgroup Meetings are open to everyone!

Friday, July 14, 2023

8:00 am – 9:00 am **Industry Supported Symposium –– "Energy Metabolism of the Heart Under Physiological and Pathological Conditions" – Hosted by Ultragenyx – Emerald Salon Three**
(Continental Breakfast included for attendees) *(CME Not Provided)*

8:00 am – 9:00 am **Continental Breakfast – (for those not attending Symposium) – Crystal Ballroom DEF**

8:00 am – 3:00 pm **Registration – Crystal Promenade**

8:00 am – 3:00 pm **Vendor Exhibits and Posters – Crystal Ballroom DEF**

9:00 am – 9:15 am **Welcome/Announcements** Barbara DuPont, PhD, President, SERGG – **Crystal Ballroom ABC**

9:15 am – 10:45 am **Platform Session 2** *(CME Approved)* – **Crystal Ballroom ABC**
Moderator: Hans Andersson, MD, Tulane University

9:15 am – 10:00 am **Invited Speaker: Michael B. Bober, MD, PhD, Nemours Children's Health**
"Achondroplasia: A Clinical and Therapeutic Update"

10:00 am – 10:15 am ***"Evaluating CFSPID Phenotypes and Outcomes: A Retrospective Study from a Large UK CF Centre"***
Alison Mansfield, MBBS, Emory University

10:15 am – 10:30 am ***"Identification of Aromatic Amino Acid Decarboxylase (AADC) Deficiency via Retrospective Organic Acid Analysis"***
J. Dan Sharer, PhD, University of Alabama at Birmingham

10:30 am – 10:45 am ***"Biochemical and Molecular Characteristics Among Infants with Abnormal Newborn Screen for Very-long-chain Acyl-CoA Dehydrogenase Deficiency: A Single Center Experience"***
Jariya Upadia, MD, Tulane University

10:45 am – 11:15 am **Break with Exhibits and Posters – Crystal Ballroom DEF**

11:15 am – 12:00 pm **Platform Session 3** *(CME Approved)* – **Crystal Ballroom ABC**
Moderator: Dan Sharer, PhD, University of Alabama at Birmingham

11:15 am – 11:30 am ***"Qualitative Assessment of Primary Care Providers' Attitudes Towards Genetics Services and Genetics Education"***
Aileen Kenneson-Adams, PhD, Emory University

11:30am – 11:45 am ***"Successful Implementation of a Structured Healthcare Transition (HCT) Process for Sickle Cell Disease (SCD) Using Quality Improvement (QI): Final Results of a SCD HCT Learning Collaborative"***
Ifeyinwa Osunkwo, MD, MPH, Levine Cancer Institute, Atrium Health

11:45 am – 12:00 pm ***"The Financial Burden of Medical and Low-Protein-Modified Foods Warrants Increased Funding: A Pilot Study of Patients with Phenylketonuria"***
Serei Nath, MPH, Emory University

12:00 pm – 1:30 pm **Lunch – Crystal Ballroom DEF (Additional seating available in Emerald Two)**

12:00 pm – 1:30 pm **Genetic Counselors "Meet and Greet" – Licensure and Billing – Emerald Three**
(Please get your lunch from the buffet in the Promenade and take it with you to Emerald Three)

1:30 pm – 3:15 pm **Platform Session 4** *(CME Approved)* – **Crystal Ballroom ABC**
Moderator: Anna Hurst, MD, University of Alabama at Birmingham

1:30 pm – 2:15 pm **Invited Speaker: Bruce Korf, MD, University of Alabama at Birmingham**
"The SouthSeq Project"

2:15 pm – 2:30 pm ***"In Our DNA SC: Implementation and Interim Insights of Population Genomic Screening"***
Kimberly Foil, MS, Medical University of South Carolina

2:30 pm – 2:45 pm ***"Psychosine: A Powerful Tool for Second-tier Newborn Screening and Diagnosis of Krabbe Disease"***
Francyne Kubaski, PhD, Greenwood Genetic Center

2:45 pm – 3:00 pm ***"Variants of the LARP1 Gene are Associated with Autosomal Dominant Neurodevelopmental Delays and Autism"***
Olivia Larner BS, University of South Carolina School of Medicine - Greenville

3:00 pm – 3:15 pm ***"The Clinical Utility of Rapid Exome Sequencing in Critically Ill Patients"***
Shahad Salman, MBBS, University of Alabama at Birmingham

SERN Concurrent Family Alliance Session – Yellow Topaz
(Dietitians are invited to attend these sessions)

Moderators: Jim Eckman, MD and Amy Cunningham, MS, RD, LDN
(CME Not Provided)

8:45 am – 9:00 am	**Welcome and Introductions**
9:00 am – 9:15 am	**Update on HRSA Grant**, Rani Singh, PhD, RD, LD
9:15 am – 9:45 am	**Supports that Family Leaders Need to Make them Successful Partners** Molly Martzke, Expecting Health
9:45 am – 10:15 am	**Digital Divide for Families** Amy Sheon, PhD, MPH, Case Western Reserve University
10:15 am – 10:45 am	**Break**
10:45 am -11:15 am	**Genetic Testing for Families** Gwen Gunn, PhD, MS, Emory University
11:15 am – 12:00 pm	**State Updates/Begin Workgroup Discussions**
12:00 pm – 1:30 pm	**Working Lunch and Closing Remarks**

3:15 pm – 3:30 pm **Travel to Concurrent Industry-Supported Symposium**

CONCURRENT INDUSTRY-SUPPORTED SYMPOSIUM
(CME Not Provided)

TIME	Opal One	Opal Two	Blue Topaz
3:30 pm – 4:30 pm	**"Targeting Impairment in the MCAR Pathway: A Root Cause of Hyperphagia and Obesity in Bardet-Biedl Syndrome" – Hosted by Rhythm Pharmaceuticals**	**"A New Fabry Treatment Option" – Hosted by Chiesi Global Rare Diseases**	**"Aligning as Healthcare Partners to Harness the Value of Genomic Data and Optimize Patient Impace" – Hosted by Invitae**
4:30 pm – 5:00 pm	BREAK	BREAK	BREAK
5:00 pm – 6:00 pm		**"Disease State Hypophosphatasia (HPP)" – Hosted by Alexion**	**"Amino Acid Absorption and Utilization: The Importance of Nitrogen Balance in PKU" – Hosted by Relief Therapeutics**

6:00 pm **Adjournment for the Day** – Enjoy your evening in Charleston!

All Sessions and Workgroup Meetings are open to everyone!

Saturday, July 15, 2023

8:00 am – 9:00 am **Industry Supported Symposium – "Clinical Characteristics of Rare Genetic Diseases of Obesity" – Hosted by Rhythm Pharmaceutical Medical** – **Emerald Salon Three**
(Continental Breakfast included for attendees) *(CME Not Provided)*

8:00 am – 9:00 am **Continental Breakfast – (for those not attending Symposium) – Crystal Ballroom DEF**

8:00 am – 10:30 am **Vendor Exhibits and Posters – Crystal Ballroom DEF**

8:00 am – 10:30 am **Registration – Crystal Promenade**

9:00 am – 9:15 am **Announcements** – Barbara DuPont, PhD, President, SERGG – **Crystal Ballroom ABC**

9:15 am – 10:45 am **Platform Session 5** *(CME Approved)* – **Crystal Ballroom ABC**
Moderator: Laura Pollard, PhD, Greenwood Genetic Center

9:15 am – 10:00 am **Invited Speaker: Heather Flanagan-Steet, PhD, Greenwood Genetic Center**
"Bridging the Phenotype Gap: Variant Resolution to Therapy Development"

10:00 am – 10:15 am ***"Newborn Screening for Late-onset Pompe Disease: Longitudinal Follow Reveals Emerging Phenotype"***
Erin Huggins, MS, CGC, Duke University

10:15 am – 10:30 am ***"Long-term Efficacy and Safety of Cipaglucosidase Alfa/Miglustat in Ambulatory Patients with Pompe Disease: A Phase III Open-label Extension Study (ATB200-07)"***
Priya Kishnani, MD, Duke University

10:30 am – 10:45 am ***"A Path Forward for Patients with Glycogen Branching Enzyme Deficiency: Consensus on Diagnosing and Managing Glycogen Storage Disease Type IV"***
Rebecca Koch, PhD, Duke University

10:45 am – 11:15 am **Break with Exhibits and Posters – Crystal Ballroom DEF**

11:15 am – 12:45 pm **Platform Session 6** *(CME Approved)* – **Crystal Ballroom ABC**
Moderator: Jennifer Gass, PhD, Florida 'Cancer Specialists

11:15 am – 12:00 pm **Invited Speaker: Marilyn M Li, MD, Children's Hospital of Philadelphia**
"Using Multi-omics Approaches to Inform Precision Cancer Care"

12:00 pm – 12:15 pm ***"Managing Recommendations for PALB2 Carriers and Ovarian Cancer Risk with Consideration for Patient Re-contact"***
Mary Hurley, BS, Vanderbilt University

12:15 pm – 12:30 pm ***"Current Barriers in the Identification and Diagnosis of Patients with Hereditary Colon Cancer"***
Benjamin Usry, BS, Medical University of South Carolina

12:30 pm – 12:45 pm ***"Strategies for Genetic Counseling in APOE e4 Variants and Alzheimer's Disease"***
Camerun Washington, MS, CGC, Greenwood Genetic Center

12:45 pm – 1:15 pm **SERGG Business Meeting & Student Award Presentations –** Barbara DuPont, PhD, President

1:15 pm **Adjournment** – See you next year!

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

Self Regional Healthcare designates this live activity for a maximum of 11.75 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

SAVE THE DATES

SERN/SERGG ANNUAL MEETING

July 11-13, 2024

Renaissance Marriott Hotel
31 Woodfin Drive
Asheville, North Carolina

EVALUATING CFSPID PHENOTYPES AND OUTCOMES: A RETROSPECTIVE STUDY FROM A LARGE UK CF CENTRE

Mansfield A[1], Hine C[1], Nagakumar P[1], Davies B[1], Desai M[1]
[1]Birmingham Children's Hospital, Birmingham, United Kingdom

Cystic fibrosis screen positive inconclusive diagnosis (CFSPID) is a designation given following a positive newborn screen for cystic fibrosis (CF) when CF is not excluded but cannot be confirmed. This retrospective single centre study describes the phenotype and outcomes of a CFSPID cohort. 30 children were designated as CFSPID between 2007 and 2021. Mean immunoreactive trypsinogen was 82.8mmol/L. 13 different CFTR variants were identified, of which F508del and R117H, 7T/9T were the most common (seen in 25 and 20 children respectively). Mean initial sweat chloride was 34.5mmol/L (range 17.0-54.0mmol/L). Longitudinal assessment (n=27) occurred over a mean duration of 8.5 years. 5 children progressed to CF at a mean age of 9.5 years (range 6.4-12.3 years), of which 3 demonstrated mild bronchiectasis. All were pancreatic sufficient except one who progressed to CF. 4 isolated *Pseudomonas aeruginosa* (3 current CFSPID, 1 progressed to CF) and 12 isolated *Staphylococcus aureus* (10 current CFSPID, 2 progressed to CF). All recent z-scores were within ±2 for weight and >-2 for spirometry. Mean recent sweat chloride for current CFSPID children was 34.3mmol/L (range 20.0-49.0 mmol/L) and for those who progressed to CF was 61.8mmol/L (range 47.0-88.0mmol/L). Initial mean sweat chloride was higher in those who subsequently progressed to CF vs those who did not (38.4mmol/L vs 32.3mmol/L). Overall, most children with CFSPID in this study remained well with a low conversion rate to CF. Our results support a less intensive medical surveillance approach and highlight the importance of assessment in a dedicated CFSPID clinic during adolescence.

IDENTIFICATION OF AROMATIC AMINO ACID DECARBOXYLASE (AADC) DEFICIENCY VIA RETROSPECTIVE ORGANIC ACID ANALYSIS

Abdala Villa C[1], Moore JF[2], and Sharer J D[2]
[1]Department of Pediatrics, Nationwide Children's Hospital, Columbus, OH; [2]Department of Genetics, University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL

Aromatic L-amino acid decarboxylase (AADC) deficiency is an ultrarare recessive disorder of monoamine neurotransmitter metabolism characterized by hypotonia, oculogyric crises, and delayed motor development. This condition is associated with significant diagnostic delays (average age of onset: 2.7 months; average age of diagnosis: 3.5 yrs), but can be treated with several neurometabolic medications, and early clinical trials of a new AAV2-based gene therapy have been promising. However, as with many inherited metabolic disorders, early diagnosis and initiation of treatment is important for optimizing outcomes. Recent work has demonstrated that standard urinary organic acid analysis (performed in most biochemical genetics laboratories) can identify AADC-deficient patients via determination of the ratio between vanillactic acid (VLA) and vanilmandelic acid (VMA), two monoamine neurotransmitter metabolites. Utilizing this approach, we performed retrospective analysis of over 250 patient samples submitted for organic acid analysis. From this cohort, we identified 3 patients with significantly elevated VLA/VMA levels, two of whom were separately diagnosed with AADC deficiency. This study further demonstrates that measurement of VLA/VMA as part of standard urinary organic acid analysis may represent a noninvasive, widely available approach to identifying AADC deficiency, potentially facilitating early initiation of therapy.

BIOCHEMICAL AND MOLECULAR CHARACTERISTICS AMONG INFANTS WITH ABNORMAL NEWBORN SCREEN FOR VERY-LONG-CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY: A SINGLE CENTER EXPERIENCE

Upadia J[1,2], Lefante JJ[3], Noh G[1,2], Schiffman B[2], Andersson HC[1,2]
[1]Hayward Genetics Center, [2]Department of Pediatrics, Tulane University School of Medicine, New Orleans, LA; [3]Department of Biostatistics and Data Science, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA

Objective: To define the biochemical and molecular characteristics and diagnostic outcomes of a large US cohort of VLCAD positives cases as detected by newborn screening (NBS) with MS:MS. This relatively common disorder of fatty acid oxidation is screened for in every state in America and often results in extensive testing of multiple samples to arrive at a diagnostic conclusion. **Materials and methods:** We compare DBS C14, C14:1, C14:2, C14:1/C12:1 ratio and plasma C14, C14:1, C14:2, C14:1/C12:1, C14:1/C16 and C14:1/C2 ratio among 19 true-positive and 148 false-positive cases. Result of VLCAD enzyme analysis, molecular testing and fibroblast fatty acid oxidation oxidation probe assay were analyzed. **Results:** The presence of compound heterozygous or homozygous pathogenic variants along with elevation of C14, C14:1 and C14:1/C12:1 ratio identified 19 VLCAD deficiency cases. All are asymptomatic. The C14:1/C12:1 ratio in NBS dried blood spots and at follow-up acyl carnitine profile is the most useful value to differentiate among true and false positive group. However, this ratio needs to be utilized along with C14, C14:1 and C14:2. **Conclusion:** VLCAD NBS by MS:MS is highly effective at identifying asymptomatic affected infants. While molecular analysis is highly informative, elevation of C14:1/C12:1 was fully informative in discriminating affected from carrier individuals.

QUALITATIVE ASSSESSMENT OF PRIMARY CARE PROVIDERS' ATTITUDES TOWARDS GENETICS SERVICES AND GENETICS EDUCATION

Kenneson A[1], Thornton Y[1], Cole C[2], Singh RH[1]
[1]Emory University, School of Medicine, Department of Human Genetics, Atlanta, GA; [2]Emory University, Rollins School of Public Health, Atlanta, GA

Primary care providers (PCPs) are considered the "gatekeepers" of genetic services, as they are often responsible for recognizing the patient's need for referral to genetic services. Furthermore, because of the insufficient number of genetics professionals and the associated long appointment wait times, PCPs are increasingly involved in ordering genetic tests themselves. However, the evolving role of PCPs is unclear and unsupported, with PCPs commonly reporting a lack of knowledge about basic genetic concepts, about the availability of genetic services and testing, about interpreting genetic test results, and about how to refer to genetic services. PCPs in the Southeast region could benefit from education programs that meet these needs, and are designed to increase knowledge about genetics and genetic testing, when to refer to genetics, and how to refer to genetics. We conducted interviews with nine PCPs practicing in states in the Southeast Regional Genetics Network (SERN) region to collect qualitative data about their perceptions of the role of PCPs in genetics and the educational needs of PCPs regarding genetic referrals and genetic testing. Semi-structured interviews were conducted via Zoom. Two coders independently coded transcripts using MAXQDA software, and thematic analysis was conducted. The identified themes fell into the following topics: perceptions of genetics, PCPs' roles in genetics, common reasons for referrals to genetics, barriers to referrals to genetics services, genetic tests ordered by PCPs, and PCPs' educational needs regarding genetics. We will present the results of the qualitative analysis and discuss the implications for the development of an educational program for PCPs in the SERN region.

PLATFORM PRESENTATIONS IN ORDER PRESENTED

SUCCESSFUL IMPLEMENTATION OF A STRUCTURED HEALTH CARE TRANSITION (HCT) PROCESS FOR SICKLE CELL DISEASE (SCD) USING QUALITY IMPROVEMENT (QI): FINAL RESULTS OF A SCD HCT LEARNING COLLABORATIVE

Osunkwo I[1,6], J Cornette J[1], Courtlandt C[3], White PH[2], Noonan L[3], Patterson CG[4], McManus P[2], Desai P[1], Lawrence R[5], and all ST3P-UP Study Investigators and Study Coordinators

[1]The Levine Cancer Institute, Division of Hematological Oncology and Blood Disorders, Atrium Health, Charlotte NC; [2]The National Alliance to Advance Adolescent Health/Got Transition, Washington, DC; [3]Center for Advancing Pediatric Excellence, The Levine Children's Hospital, Atrium Health, Charlotte NC; [4]Department of Physical Therapy, University of Pittsburgh, Pittsburgh, PA; [5]Jiann-Ping Hsu College of Public Health; Georgia Southern University, Statesboro, GA; [6]Novo Nordisk A/S, Rare Disease Division, Zurich, Switzerland

A SCD HCT learning collaborative engaged 14 sites with (community participation) using QI. Monthly virtual meetings provided coaching on clinical recommendations, QI methods, and practical implementation of Six Core Elements of HCT (6CE). We report here the results of this 5-year multi-stakeholder collaborative effort. Implementation of 6CE was across 14 SCD clinical sites (each comprised pediatric and adult clinics with a local community-based organization); 12 urban, 2 rural; 12 academic, 2 non-academic; 6 small, 8 large. The HCT Process Measurement Tool (HCT-PMT) assessed implementation and adherence to the 6CE using iterative QI methods at baseline (2018) and every six months for 54 months. All sites made substantial progress towards implementing a structured HCT process over the study period. Overall HCT-PMT scores increased over time from 19.4 (SD 14.1) at baseline to 97.4 (SD 5.2) at 54-mo with pediatric site scores rising from 24 to 98.9 and adult site scores going from 15 to 95.8 at baseline and 54-mo respectively. Pediatric sites scored higher at each assessment interval compared to adult sites with similar gain in scores across large (21 to 97) and small sites (from 18 to 98) at baseline and 54-mo respectively. All but one adult clinic reached or exceeded the project goal of an HCT-PMT score of 90%. We demonstrate successful implementation of structured HCT process aligned with the 6CE across 28 SCD clinics using QI. This transition learning collaborative practice is applicable to improving transition programming for all genetic diseases and should be further explored.

THE FINANCIAL BURDEN OF MEDICAL AND LOW-PROTEIN-MODIFIED FOODS WARRANTS INCREASED FUNDING: A PILOT STUDY OF PATIENTS WITH PHENYLKETONURIA

Nath S. [1], Price E. [1], Gurung S. [1], Schoen M. [1], Narlow K. [1], Singh R. [1]

[1] Emory University, School of Medicine, Department of Human Genetics, Atlanta, GA

Background: Phenylketonuria (PKU) is an inherited metabolic disorder (IMD) that impairs the conversion of phenylalanine (Phe) into tyrosine, resulting in neurotoxic effects. To prevent cognitive impairment while meeting nutrient requirements, patients with PKU are subjected to lifelong expenses related to accessing Phe-free medical foods (MFs) and low-protein modified foods (LPMFs). **Methodology:** This is a secondary analysis of data collected by the Metabolic Nutrition Therapy for Prevention (MNT4P) program, which provides MFs and LPMFs as a bridge service to individuals with IMDs in Georgia. The costs of MFs and LPMFs were analyzed in a sample of 103 PKU patients across three age groups including adults, children/adolescents, and infants. These costs were then compared to the cost of a healthy diet for unaffected individuals estimated by the U.S. Department of Agriculture (USDA). **Findings:** The monthly cost of prescribed MF averaged $1,150 (±1,141) differed significantly across age groups *($p<0.001$)*, while the monthly cost of LPMF was $199 (±44) with no significant difference *($p=0.868$)*, and patients needing a combined MFs and LPMFs had an average monthly cost of $1,495 (±991) with significant difference *($p<0.001$)*. Adults incurred the highest expense, while infants had the lowest, and the differences were attributed to the variable cost of MF required to meet age-appropriate nutrient needs. The combined cost was approximately 3-fold the average cost of the liberal food plan of around $407 estimated by the USDA. With most IMD patients receiving little to no health insurance coverage for MFs and LPMFs, patients are faced with substantial financial burdens.

PLATFORM PRESENTATIONS IN ORDER PRESENTED

IN OUR DNA SC: IMPLEMENTATION AND INTERIM INSIGHTS OF POPULATION GENOMIC SCREENING

Foil K, Malphrus L, Harris C, Barker N, Allen C, Norman S, Johnson J, Bairel J, English S, King A, Champaigne N, Jackson A, MUSC In Our DNA SC Study Team; Judge D
Medical University of South Carolina

Background: In late 2021, MUSC partnered with Helix to provide population-level genomic screening and to power ongoing research. *In Our DNA SC* (*IODNASC*) participants receive CDC Tier 1 results: hereditary breast and ovarian cancer (HBOC), Lynch syndrome (LS), and familial hypercholesterolemia (FH), and a database of exome and phenotypic data will support new discoveries. Early results are presented. **Methods:**
MyChart users age ≥18 years (102,312) were invited; additional advertising occurred at events and via multimedia. Following consent, saliva samples underwent exome sequencing at Helix. MUSC research coordinator contact occurred with free genetic counseling (GC) offered for those with pathogenic/likely pathogenic (P/LP) variant(s) in CDC Tier-1 genes. Descriptive analyses were performed. **Results:** After 17 months (3/31/22), 24,088 enrolled: median age 50, 73% female and 85.4% Caucasian. Results on 10,511 of 13,931 samples demonstrate 1.67% positivity rate (0.68% HBOC, 0.45% LS, 0.54% FH). Sixty-four cancer and 20 FH-positive patients have completed GC; personal cancer history and hyperlipidemia were present in 22% and 90%, respectively; 50% with hyperlipidemia were on cholesterol-lowering therapy. Family histories were positive for hyperlipidemia in 90% with P/LP results for FH; none had prior genetic testing though 25% were aware of (probable) FH. Cancer family histories met NCCN criteria for testing for 64%, and 6.3% previously knew their positive result. **Discussion:** *IODNASC* demonstrates scalable genomic screening and identification of risk, which is often missed in routine care. Such initiatives are likely to improve outcomes for individuals, families and communities. Future efforts will capture downstream medical and psychosocial impacts.

PSYCHOSINE: A POWERFUL TOOL FOR SECOND-TIER NEWBORN SCREENING AND DIAGNOSIS OF KRABBE DISEASE

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Krabbe disease (KD) is caused by a deficiency of the galactocerebrosidase (GALC) enzyme, which degrades galactosylsphingosine (psychosine). Newborn screening for KD aims to identify asymptomatic patients to initiate treatment before neurodegeneration occurs. The screening was initially designed with enzyme analysis as first tier testing, followed by second tier molecular analysis. However, this approach can produce inconclusive cases due to variants of unknown significance. Because psychosine is a primary biomarker for KD, it can be used as the second tier test, with reflex to molecular analysis leading to a more definitive clinical interpretation. In addition, psychosine measurement can also be used for treatment monitoring and phenotype prediction. Psychosine levels were analyzed in 17 dried blood spots (DBS) from Krabbe patients and 103 healthy subjects. The average level of psychosine in controls was 0.28 nmol/L (range: 0.03-0.72 nmol/L), while the average level in Krabbe patients was 38.3 nmol/L (range: 2.1-94). Psychosine was not elevated in samples with GALC pseudodeficiency or in carriers. Psychosine was significantly elevated in a patient in whom only one pathogenic *GALC* variant was detected. We have also analyzed a sample identified with low GALC activity during the South Carolina newborn screening validation study and psychosine was mildly elevated, while molecular results were inconclusive. This infant is therefore undergoing additional evaluation due to concern for late-onset Krabbe disease or saposin A deficiency. Cases like these demonstrate the importance of psychosine measurement in patients being evaluated for Krabbe disease.

PLATFORM PRESENTATIONS IN ORDER PRESENTED

VARIANTS IN THE *LARP1* GENE ARE ASSOCIATED WITH AUTOSOMAL DOMINANT NEURODEVELOPMENTAL DELAYS AND AUTISM

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La-related protein 1 (LARP1) belongs to an evolutionarily ancient and highly conserved family of RNA binding proteins. It has been shown to bind and regulate the stability of approximately 3,000 mRNAs encoding cellular metabolism, cell survival and ribosomal biogenesis proteins. Studies have shown that the *Drosophila* equivalent of *LARP1* is important for embryogenesis, with mutations leading to embryonic mitotic defects. In humans, *de novo* mutations in the *LARP1* gene have been reported in large cohorts of individuals with neurodevelopmental disorders and autism. Currently, there is insufficient evidence to establish a causal gene-disease relationship for the *LARP1* gene. We report eight unrelated individuals with predominantly *de novo* variants in the *LARP1* gene. Patients within this cohort, collected through GeneMatcher, present with variable neurodevelopmental phenotypes including intellectual disability, hypotonia, motor delay, and/or autism spectrum disorder. Measurement of mitochondrial respiration studies, from the index patient with a *de novo* frameshift alteration, showed reduced glycolytic and oxygen consumption rates. Functional study results, constraint metrics that indicate intolerance to loss of function, and phenotypic patterns support *LARP1* haploinsufficiency as a novel autosomal dominant neurodevelopmental disorder.

THE CLINICAL UTILITY OF RAPID EXOME SEQUENCING IN CRITICALLY ILL PATIENTS

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Rapid whole exome sequencing (rWES) uses a technology that allows a rapid identification of genetic variations. It is an alternative to the standard exome sequencing with the potential to offer accurate and rapid results. Genetic disorders are a common cause of morbidity and mortality, particularly in patients admitted to the critical care units. Due to rapid progression of symptoms in those patients, it's crucial to rapidly identify genetic variations to allow for a timely therapeutic approach. In this study, we aim to investigate 30 patients who presented to our institute from September 2022 with features concerning for different genetic disorders. These patients were in critical need for a rapid diagnosis and management to improve outcome in acutely ill settings. Our patient population included both pediatric and adult patient, most of which were admitted to critical care units. Rapid exome sequencing has a comparable diagnostic yield to the standard exome sequencing. In our study, the average turnaround time was 7 days (range 6-10 days) compared to 30 days with the standard method. Hence, this exam has the potential to significantly increase the diagnostic efficiency and alter the management approach in critical settings. In conclusion, our study emphasizes the diagnostic utility and feasibility of rWES. The fast and precise diagnostic findings facilitates a better management approach for critically ill patients, redirects care, and avoids unnecessary tests and procedures. Eventually, rWES shortens the length of stay at the hospital and reduces overall cost.

PLATFORM PRESENTATIONS IN ORDER PRESENTED

NEWBORN SCREENING FOR LATE-ONSET POMPE DISEASE: LONGITUDINAL FOLLOW REVEALS EMERGING PHENOTYPE

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Newborn screening (NBS) allows for early diagnosis and life-saving treatment of infantile-onset Pompe disease (IOPD) with enzyme replacement therapy (ERT). However, the majority of confirmed NBS pickups are diagnosed with late-onset Pompe disease (LOPD), which does not have an apparent phenotype at birth and does not require immediate treatment with ERT. Clinical monitoring guidelines exist for children with LOPD, including recommendations to initiate ERT when symptomatic, yet there is a paucity of phenotypic data on these children. Clinicians are faced with the challenge of distinguishing symptomatic from asymptomatic children, and whether to begin treatment with ERT. We systematically evaluated 20 patients diagnosed with LOPD via NBS (age range 6-21 months). Patients were evaluated at baseline, 6 months, and 1 year with comprehensive physical therapy evaluation (kinematic assessment and standardized measures), biomarker testing, cardiac evaluation, and speech/feeding evaluation. All children had persistent musculoskeletal findings on exam, including hip extensor weakness, scapular winging, and abdominal oblique weakness. Three patients began treatment with ERT at some point during the study period and had improvements on kinematic and functional assessments along with normalization of serum CK. We present a detailed phenotype of these 20 patients and show that children can manifest musculoskeletal symptoms in early childhood, in some cases necessitating treatment with ERT. We present evidence of the wide phenotypic spectrum of LOPD in early childhood and highlight the importance of NBS and subsequent close monitoring and early intervention. This study was funded in part by Amicus Therapeutics.

LONG-TERM EFFICACY AND SAFETY OF CIPAGLUCOSIDASE ALFA/MIGLUSTAT IN AMBULATORY PATIENTS WITH POMPE DISEASE: A PHASE III OPEN-LABEL EXTENSION STUDY (ATB200-07)

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INTRODUCTION: The Phase III double-blind PROPEL study (NCT03729362) compared the investigational two-component enzyme replacement therapy (ERT) cipaglucosidase alfa plus miglustat (cipa+mig) with alglucosidase alfa plus placebo (alg+pbo) in ambulatory adults with late-onset Pompe disease (LOPD). This ongoing open-label extension (OLE) (NCT04138277) evaluates the long-term efficacy and safety of cipa+mig. **METHODS:** Outcomes include 6-minute walk distance (6MWD), forced vital capacity (FVC), creatine kinase (CK) and hexose tetrasaccharide (Hex4) levels and safety. Data are reported as change from the PROPEL baseline to OLE week 52 (104 weeks after the PROPEL baseline). **RESULTS:** Of 119 patients from PROPEL who enrolled to the OLE (91 ERT-experienced; 28 ERT-naïve), 82 continued cipa+mig (cipa+mig group) and 37 switched from alg+pbo to cipa+mig (switch group). Mean (standard deviation [SD]) change in % predicted 6MWD was +3.1(8.07) for the cipa+mig group and −0.5(7.76) for the switch group in ERT-experienced patients, and +8.6(8.57) and +8.9(11.65) in ERT-naïve patients, respectively. Mean (SD) change in % predicted FVC was −0.6(7.50) for the cipa+mig group and −3.8(6.23) for the switch group in ERT-experienced patients, and −4.8(6.48) and −3.1(6.66) in ERT-naïve patients, respectively. Biomarker levels (CK and Hex4) improved with cipa+mig treatment; both groups reached similar levels by OLE week 52. Three patients discontinued the OLE due to infusion-associated reactions (urticaria, urticaria and hypotension, and anaphylaxis). No new safety signals were identified. **CONCLUSIONS:** Data demonstrate treatment with cipa+mig up to 104 weeks was associated with a durable effect and was well tolerated, supporting long-term benefits of cipa+mig treatment for patients with LOPD.

PLATFORM PRESENTATIONS IN ORDER PRESENTED

A PATH FORWARD FOR PATIENTS WITH GLYCOGEN BRANCHING ENZYME DEFICIENCY: CONSENSUS ON DIAGNOSING AND MANAGING GLYCOGEN STORAGE DISEASE TYPE IV

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Glycogen storage disease type IV (GSD IV) is an ultra-rare autosomal recessive disorder caused by pathogenic variants in *GBE1*, resulting in deficient glycogen branching enzyme activity. Clinically, GSD IV is characterized by remarkable heterogenic presentations in the neonatal period, infancy, early childhood, adolescence, or adulthood. The clinical spectrum encompasses severe neurological and neuromuscular manifestations, myopathy, cardiomyopathy, and progressive liver fibrosis often requiring liver transplantation. The adult-onset form, Adult Polyglucosan Body Disease (APBD), is a neurodegenerative disorder that is particularly prevalent in the Ashkenazi Jewish population. In collaboration with the Association for GSD, the APBD Research Foundation, and patient advocates, a list of disciplines involved in the management of GSD IV was created. A national group of 19 experts assembled to form the "Consensus Development Panel" and created an educational resource that highlights the best practices for management of all GSD IV clinical phenotypes. We expect that this resource will support clinicians and caregivers who provide medical care for individuals with GSD IV, leading to improvements in patient outcomes by increasing awareness of this ultra-rare disease, reducing the misdiagnosis rate, shortening time to diagnosis, and standardizing the clinical care of individuals with GSD IV. New insights into the disease are detailed, providing a path forward for all patients with GSD IV, including patients whose phenotype and corresponding management remains unaddressed in the current literature. This model of collaboration between experts and patient advocacy groups provides a framework for future consensus development projects.

MANAGING RECOMMENDATIONS FOR PALB2 CARRIERS AND OVARIAN CANCER RISK WITH CONSIDERATION FOR PATIENT RE-CONTACT.

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Cancer risks and management guidelines for *PALB2* likely pathogenic/pathogenic variant (LP/PV) carriers have undergone refinement, illustrated by the updates to the National Comprehensive Cancer Network (NCCN) guidelines in the context of *PALB2*-associated ovarian cancer (OC). With evolving data, clinical genetics programs should weigh considerations for re-contact of patients when benefit of an intervention is known (i.e. bilateral salpingo-oophorectomy, BSO). In 2019 (v.1.2021), NCCN first quoted an absolute *PALB2*-OC risk (3-5%). In April 2021, an academic clinical cancer genetics program re-contacted *PALB2* LP/PV carriers via patient portal or letter and offered follow-up consultation (cohort 1). Chart review of *PALB2* LP/PV carriers ascertained post re-contact project was conducted for comparison (4/2021-3/2023) (cohort 2). We report on clinical follow-up and BSO in biological females, age ≥45. Nine of 22 patients in cohort 1 pursued consultation (41%), of whom, 4 had previous BSO unrelated to *PALB2*, 3 (33%) underwent and 2 (22%) were planning BSO, respectively, due to re-contact. For the 13 (59%) lost to follow-up, chart review revealed 7 had previous BSO (all > age 50) and 6 had ovaries intact, ranging in age 45-67. In the prospective cohort 2, the majority presented to care after publication of v.2.2021 NCCN ("consider BSO > age 45"). Higher rates of BSO, completed and intended with nuanced timing considerations, were observed, 10/19 (53%) and 9/19 (47%), respectively, due to *PALB2*. Data surrounding *PALB2* as well as others will continue to emerge. Programmatic re-contact and reciprocal patient check-ins are important to optimize shared provider-patient decision-making.

CURRENT BARRIERS IN THE IDENTIFICATION AND DIAGNOSIS OF PATIENTS WITH HEREDITARY COLON CANCER

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Background: The National Comprehnsive Cancer Network (NCCN) recommends screening for lynch syndrome (LS) in colorectal cancers (CRC) using mismatch repair (MMR) or microsatellite instability (MSI). Patients with MSI or MMR deficiency are referred for genetic testing. Despite guidelines, compliance with LS screening and genetic testing is low. The aim of this study was to evaluate compliance with LS screening and genetic testing in CRC. **Methods:** A single institution retrospective review of patients with CRC in 2018 and 2021 was performed. Patients were combined as a single cohort, representing pre and post-COVID periods, as demographics were similar. Compliance with LS screening was calculated. Patients meeting criteria for genetic testing were analyzed for compliance with genetic referral, genetic testing, and identification of pathogenic variants (PV). **Results:** 276 patients were reviewed. 71.2% Caucasian and 58% male. 146 (53%) had LS screening. 44 (16%) MSI, 19 (7%) MMR and 82 (30%) both. 78 patients met criteria for genetic testing; 47 age alone, 6 age and LS screening, and 25 screening alone. 35% (27/78) were referred to genetics, with 63% (17/27) following through, 63% (17/27) tested, and 37% (10/27) with PV. **Conclusions:**
Despite national guidelines, our institution was not compliant with LS screening. When screened, compliance with genetic referrals was poor, and 37% did not follow-through. Our findings support NCCN guidelines recommending genetic testing for CRCs despite age or MSI/MMR status, aiming to decrease a substantial barrier. Automatic referrals to genetics and point of care testing may increase our compliance and needs to be studied.

STRATEGIES FOR GENETIC COUNSELING IN *APOE* E4 VARIANTS AND ALZHEIMER'S DISEASE

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Alzheimer's disease is a devastating condition affecting millions of people worldwide. While there are many risk factors associated with the development of Alzheimer's, the most well-studied and validated genetic risk factor is the presence of one or two copies of the e4 variant found in the apolipoprotein E (APOE) gene. In light of the increasing availability of direct-to-consumer testing, media attention, and clinical trial data, it is essential to address the response to and use of this genetic risk information by both the lay population and healthcare professionals. In this talk, we will explore the implications of this genetic risk factor, and discuss strategies for genetic counseling used in four real-world examples of APOE e4 variants uncovered or referred for medical genetic evaluation. We will review the evidence linking APOE e4 variants to Alzheimer’s disease, and discuss the current challenges and opportunities in genetic counseling for patients and families with APOE variants and Alzheimer’s disease. By the end of this presentation, healthcare providers will be equipped with the knowledge and strategies needed to effectively respond to and use this genetic risk information.

DESIGN OF A GLOBAL, MULTICENTER STUDY TO ASSESS MATERNAL, FETAL, AND INFANT OUTCOMES OF PEGVALIASE EXPOSURE DURING PREGNANCY AND BREASTFEEDING

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Phenylketonuria (PKU) is an autosomal recessive disorder caused by deficiency of phenylalanine hydroxylase (PAH), which converts phenylalanine (Phe) to tyrosine. PAH deficiency leads to abnormally high levels of Phe that is toxic to the brain. Elevated Phe levels during pregnancy are associated with increased risk for pregnancy loss and major birth defects. Pegvaliase (Palynziq®) is a medicinal form of phenylalanine ammonia lyase that is administered subcutaneously to reduce Phe levels. There are no well-controlled studies on the effects of pegvaliase exposure during pregnancy and breastfeeding. PALomino (NCT05579548) is an observational, prospective, multicenter study of women with PKU exposed to pegvaliase during pregnancy. The objective of this study is to assess the frequency of pregnancy outcomes among women with PKU treated with pegvaliase during pregnancy and fetal/infant outcomes. This study will enroll pregnant women diagnosed with PKU who have been treated with pegvaliase from 2 weeks prior to last menstrual period (LMP) or at any time during pregnancy. Participants will be enrolled and followed for up to 21 months. Pegvaliase exposure will be collected for at least 3 months prior to LMP, during pregnancy and breastfeeding, and among participants with live-birth outcomes who initiate breastfeeding and breastfeed up to infant age 12 months. Fetal outcomes will be correlated to pegvaliase exposure and blood Phe levels. The study is currently open to enrollment in the US and is planned to open to enrollment in Europe in 2023. These results will increase knowledge about the safety of pegvaliase during pregnancy and breastfeeding.

EVALUATION OF A SERIES OF PATIENTS WITH LATE ONSET POMPE DISEASE WHO SWITCHED FROM ALGLUCOSIDASE ALFA TO AVALGLUCOSIDASE ALFA

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Pompe disease is an inherited, progressive neuromuscular disorder caused by deficiency of lysosomal acid α-glucosidase and accumulation of glycogen in tissues, resulting in cellular dysfunction, muscle damage, and functional disabilities. Enzyme replacement therapy with alglucosidase alfa (Myozyme/Lumizyme) has promoted better outcomes, but many patients have plateaued or declined despite treatment. The second-generation agent avalglucosidase alfa (Nexviazyme) was designed to have enhanced uptake into target cells via the conjugation of additional mannose-6-phosphate residues. There have been several trials comparing the efficacy of alglucosidase and avalglucosidase, but these used strict inclusion criteria and primarily focused on treatment-naïve patients. There is a need for more data on patients who switched from alglucosidase to avalglucosidase. A chart review was conducted on 16 patients with late-onset Pompe disease who switched from alglucosidase to avalglucosidase and continued for at least 6 months. There were statistically significant improvements in CK, Hex4, and AST with mean differences of -114.5 U/L, -3.0 mmol/molCr, and -14.6 U/L, respectively. 6-Minute Walk Test; Gait, Stairs, Gower, Chair; and Quick Motor Function Test scores improved or remained stable in most patients (n=8/12, n=13/13, n=7/11, respectively). Of n=8 patients with pulmonary function testing, n=5 had improved upright FVC, n=2 remained stable, and n=1 worsened. Patient-reported outcomes revealed improvements in dyspnea (n=4/4), physical function (n=3/4), fatigue (n=2/3), and lower back pain (n=3/3). In summary, significant improvements were seen across all outcome metrics in a majority of patients. This study presents additional evidence that switching to avalglucosidase is associated with better outcomes in patients with LOPD.

PHARMACOGENOMICS OF OPIOID CONSUMPTION AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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Background: As declared by the Centers for Disease Control and Prevention (CDC), the United States is in the midst of an opioid epidemic. There remains a paucity of research regarding how one's individual genetic composition may affect opioid consumption patterns. This study aims to further the field of personalized medicine by analyzing pharmacogenomics to predict patient's drug response in opioid consumption patterns post ACL reconstruction surgery. **Methods:** Patients aged 18-50 years old were divided in to cohorts based on opioid consumption patterns. Cohorts are defined as non-, low, average, high, and maximum opioid users stratified based on standard deviation of use. DNA was analyzed for the 100 total participants for genes relating to pharmacodynamics and pharmacokinetics such as CYP2D6, CYP3A5, OPRM1, and COMT. **Results:** The chi square analysis resulted in the association between the number of opioid pills taken and level of metabolization having the following p-values: CYP3A4 p=0.18, CYP2D6 p=0.63, CYP3A5 p=0.91, OPRM1 p=0.41, and COMT p=0.04. **Conclusions:** Further research is required to better understand the effect of a patient's individual genetic composition on opioid consumption patterns. At the present time we are unable to reject the null hypothesis that there is no association between CYP2D6, CYP3A5, and OPRM1 metabolization of opioids and the number of tablets taken post-ACL reconstruction surgery. COMT appears to be associated, and with larger sample size may find that others are associated too. We are recruiting additional patients to expand this study to further analyze consumption patterns.

A NEEDS ANALYSIS REGARDING PROVISION OF SERVICES FROM A DIVERSITY, EQUITY AND INCLUSION PERSPECTIVE IN A PEDIATRIC GENETICS CLINIC AT A SOUTHEASTERN ACADEMIC MEDICAL CENTER

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Barriers to genetics care experienced by patients documented in the medical literature include accessing and utilizing existing services, obtaining culturally informed care, geographical constraints, financial resources, and communication issues. This study aimed to identify diversity, equity and inclusion related barriers and needs pediatric patients and their caregivers experience during their genetics appointment through a survey. It focused on appointment scheduling, interactions with genetics providers and interpreter services, culturally sensitive care, and additional services that could be provided to patients by the clinic. All pediatric patients and their caregivers who received care through in person or telehealth appointments from September 2022 to February 2023, and were fluent in English or Spanish were eligible to participate in the study. A total of 25 participants completed the survey. Of these (n=16) had telehealth appointments and (n=23) were fluent in English. A majority of the patients were over 3 years (n=14), white (n=13) and did not report any Hispanic, Latinx or Spanish origin ethnicity (n=23). Data analysis revealed that 88% (n=22) of participants felt that care providers were respectful when providing sensitive information and 80% (n=20) agreed their needs were respected based on their race and ethnicity. Of the total, 4% (n=1) of participants reported discrimination from their provider. Additional services to improve access indicated as useful by participants include help navigating the school system, a voice message reminder prior to the appointment, and community resources. Limitations of this study included recruitment issues leading to small sample size and potentially biased results.

POSTER PRESENTATIONS
(Alphabetical by Presenting Author)

EARLY DETECTION OF DUCHENNE MUSCULAR DYSTROPHY AND 16P11.2 MICRODELETION FOLLOWING INFLUENZA INFECTION

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Duchenne Muscular Dystrophy (DMD) is an X-linked disorder characterized by progressive muscular weakness, starting with distal muscle groups and eventually affecting proximal groups. It often presents between the ages of 2-5 with an average age of diagnosis at 4.5 years. Patients with a family history of DMD can obtain a diagnosis much sooner, leading to earlier treatment. Several therapies are available to patients which can prolong lifespan significantly. However, delays in diagnosis can limit therapeutic benefit. We present a 1-year-old male admitted to the hospital with an influenza infection. Respiratory symptoms and fever were mild at presentation, but his weight was <1% and his neuro exam revealed hypotonia. He had a history of failure to thrive and transaminitis, neither of which had an underlying etiology. Pregnancy and birth were benign, but gross motor development was delayed as he was not yet sitting unaided or crawling. During admission, he was found to have a CK of 14,000, prompting the team to obtain a Neuromuscular gene panel which revealed his DMD diagnosis. A single nucleotide pathogenic variant (c.10171C>T, p.Arg3391*) within exon 70 was identified. An array CGH had been sent prior to CK level and revealed a 16p11.2 microdeletion which is associated with increased risk for neurodevelopmental disorders. He has been referred to a neuromuscular clinic and PT/OT services. We describe this case to review outcomes of early detection of DMD and how coinciding genetic diagnoses can complicate a patients' clinical picture.

QUALITATIVE STUDY: WOMEN WITH PHENYLKETONURIA REPORT HEALTH MANAGEMENT EDUCATION AND SOCIAL SUPPORT AT EMORY GENETICS' METABOLIC CAMP PREPARES FOR LATER PREGNANCY

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Background: Women with phenylketonuria (PKU) must maintain strict therapeutic diet and blood phenylalanine (phe) levels below 240 µmoles/L during pregnancy to minimize risk for neurological and physical defects in the newborn. **Hypothesis:** Adolescent and adult females with PKU, who attend a dietetic-supported camp focused on dietary self-management skills and reproductive outcomes, are better prepared to manage their PKU and maternal health during a future pregnancy. **Methods**: Study participants are recruited via IRB permitted email and phone contact of camp alumni, from the Emory Genetics Clinic, and study flyer distribution. Inclusion criteria are women (age 18 years+) with PKU who have attended one or more Emory Genetics Metabolic Camps, had at least one pregnancy regardless of pregnancy outcome, and given informed consent. Participants complete a REDCap distributed qualitative survey, with option of follow-up interview, asking whether metabolic camp influenced their pregnancy experience, and how so. Sample size goal is minimum of 20 camp alumni. Survey and interview responses will be analyzed with MAXQDA qualitative research software and descriptive statistics. **Results**: Preliminary data from 4 camp alumni demonstrate beneficial influence of Metabolic Camp on pregnancy experience with high reported value of 1) maternal PKU and dietary management education received 2) social support network developed at camp 3) knowledge of when, how, and who to contact when pregnancy happens. All participants report healthy birth outcomes. **Conclusion**: In preliminary data, camp alumni report how knowledge and social support attained during Metabolic Camp helped prepare them for future pregnancy. Larger sample size recruitment is ongoing.

POSTER PRESENTATIONS
(Alphabetical by Presenting Author)

PRECLINICAL EVALUATION OF A PROLONGED-RELEASE MEDICAL FOOD ON BLOOD PHENYLALANINE LEVELS WHEN COMBINED WITH DIETARY PROTEIN

Giarratana N[1], Giardino L[2], Cescatti M[3], Sannia M[3] and Giorgio Reiner G[1], presented by Draper K
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Background: Phenylketonuria (PKU) is an inborn error of phenylalanine (Phe) metabolism treated with a protein-restricted diet supplemented with Phe-free medical food. The large-neutral amino acids (LNAAs) in medical food are believed to influence the gastro-intestinal absorption of Phe by competitive inhibition of a shared transporter (LAT1). In this preclinical study, we seek to evaluate blood Phe levels in healthy rats following administration of a prolonged-release medical food along with a Phe-rich protein. **Methods:** Healthy Wistar rats were randomized into 2 groups: a prolonged release medical food (PKU GOLIKE) and its corresponding control. In each group, 11 rats were fasted and treated with the medical food (0.95 g of AA/kg) and a 3 mL bolus containing 0.45g/mL of an egg white mixture (0.3 g/kg of Phe). Phe measurements were obtained through blood sampling at baseline and repeated at intervals up to 300 minutes.
Results: The group treated with the prolonged release medical food had significantly reduced Phe levels ($p=0.0003$) compared to the control group. The Phe AUC and C_{max} were both significantly lower ($p=0.0137$; $p=0.0004$) for the rats treated with the prolonged release medical food vs the control. **Conclusion:** This preclinical study demonstrates the potential phe-lowering benefit of a prolonged release medical food. The prolonged release of LNAAs may have a competitive effect on Phe absorption at the gut level and could be used with a PKU diet to reduce blood Phe levels. Future studies will evaluate if providing a prolonged release medical food could reduce Phe levels in PKU patients and increase their protein tolerance.

CHARACTERIZING THE CLINICAL COURSE OF GLYCOGEN STORAGE DISEASE TYPE VI

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Glycogen storage disease type VI (GSD VI) is an autosomal recessive disorder occurring due to deficient glycogen phosphorylase activity in the liver, disrupting the rate limiting step of glycogen breakdown. Patients may present with hypoglycemia, hepatomegaly, delayed growth, and elevated transaminases. Of the hepatic disorders of glycogenolysis, GSD VI is considered to be less severe, but evidence from a recent literature review and liver histology study shows there is considerable clinical heterogeneity. To date, we do not have a complete understanding of the long-term outcomes of GSD VI. We enrolled 34 patients of different geographical backgrounds (Brazil, China, India, Iran, Israel, USA) in a GSD VI natural history study facilitated by international collaboration. For each, medical records were obtained and histology slides were reviewed when available. Age of diagnosis ranged from 6 months of age up to 7 years of age (median 2.2 years), with hepatomegaly (n=19/34) and elevated transaminases (n=15/34) being the most common presenting symptoms. We report on initial clinical presentation and clinical outcomes, including laboratory investigations and histological findings. Common features noted during review of 8 liver biopsies include glycogen accumulation, pauci-inflammation, delicate fibrosis, and central vacuolation suggesting steatosis. At last follow-up (range 6 months to 25 years), n=19/34 have elevated transaminases and n=18/34 have hepatomegaly. This is the first comprehensive, longitudinal review of GSD VI disease progression, providing insight to long-term patient outcomes.

MOLECULAR DIAGNOSIS FOR NEUROFIBROMATOSIS TYPE I: PAST, PRESENT, AND FUTURE

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Since the *NF1* gene was cloned in 1990, genetic testing has become increasingly important for diagnosis of NF1. However, identifying a mutation in *NF1* is complex due to the large size of the gene, the presence of many pseudogenes, and the lack of mutation hotspots. In the early 2000s, the Medical Genomics Laboratory (MGL) at UAB developed a comprehensive analysis approach, which comprises SNV and indel analysis by Sanger sequencing the entire *NF1* cDNA transcribed from cultured, puromycin-treated lymphocytic cells, and CNV analysis by MLPA. This approach has become a gold approach for NF1 molecular diagnosis with over 95% diagnostic yield. Beyond that, The MGL has also developed an assay to identify mosaic *NF1* variants from neural crest derived cells from affected lesions such as neurofibromas or cafe au' lait spots. Currently, the MGL employs a spectrum of methods including NGS, RNA-based Sanger sequencing, MLPA and FISH to provide the most comprehensive genetic testing approach for NF1 and has led to the MGL having the largest volume of NF1 genetic testing in the world. In line with the advances in genetic testing for NF1, the NF1 diagnostic criteria has been revised to incorporate the identification of a pathogenic variant in the NF1 as part of the established criteria. However, variant classification remains a challenge, particularly for missense variants and small in-frame indels. Developing high-throughput functional assays to determine the function of *NF1* variants could improve classification and facilitate clinical diagnosis.

CLINICALLY VALIDATED HETEROLOGOUS EXPRESSION AND FUNCTIONAL ANALYSIS SYSTEM FOR *GAA* EXONIC VARIANTS - A STEP TOWARDS CLASSIFICATION OF VARIANTS OF UNKNOWN SIGNIFICANCE IN POMPE DISEASE

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Pompe disease is an autosomal recessive metabolic disorder caused by pathogenic variations in *GAA* gene. The disease has wide clinical heterogeneity in severity, attributable to underlying *GAA* variants. Providers refer to curated *GAA* databases such as ClinVar to determine the significance of *GAA* variants especially in cases identified via newborn screening, and ~70% of *GAA* missense variants (689/934 in ClinVar) are classified as variants of uncertain significance (VUS). We have developed a HEK293 mammal cell-based functional expression system for analyzing *GAA* exonic VUS. We validated our expression system based on Clinical Genome Resource (ClinGen) guidance. Seven known pathogenic and six known benign variants were used to establish GAA enzyme activity ranges using the transient expression system. GAA activity for pathogenic/likely pathogenic and benign variants was <14% and >54% of normal respectively Eight *GAA* missense VUSes from 7 unrelated LOPD NBS patients with confirmed deficient GAA activity and no Pseudodeficiency were functionally analyzed. Seven of the 8 VUS showed reduced GAA activity (<14% of wild type) in our functional analysis. Following ClinGen *GAA* Variant Curation Expert Panel (VCEP) specifications and taking functional data as additional evidence, we were able to reclassify five VUSes : [c.316C>T(p.Arg106Cys); c.1048G>A(p.Val350Met); c.1103G>A(p.Gly368Asp); c.1123C>T(p.Arg375Cys); c.1721T>C(p.Leu574Pro)] as likely pathogenic, 3 remained as VUS due to conflicting or insufficient evidence. Expression of additional known *GAA* missense variants and VUS is underway to narrow the gap (14%-54% GAA activity).

POSTER PRESENTATIONS
(Alphabetical by Presenting Author)

RARE PRESENTATION OF SMALL BOWEL PSEUDO-OBSTRUCTION AND MEGACYSTIS IN A PATIENT WITH RECENTLY DESCRIBED PROTEIN-ELONGATING *MYH11* VARIANT: A CASE REPORT

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Background: MYH11 dimers are an essential component of smooth muscle myosin. Alterations in *MYH11* have previously been associated with disease, including ~1% of autosomal dominant familial thoracic aortic aneurysm and dissection (TAAD) and autosomal recessive megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS). Recently, heterozygous *MYH11* variants occurring near the c-terminus that extend the coding sequence resulting in protein elongation have been observed in patients with autosomal dominant gastrointestinal motility disorders and obstruction anomalies. **Case presentation:** Here we report a 17 y.o. female with chronic constipation, recurrent small bowel pseudo-obstruction, and megacystis. She is tall and thin with joint hypermobility and normal echocardiogram. There is a significant family history of gastrointestinal dysmotility including a maternal uncle that died at 17 years old from malrotation with perforated small bowel and sepsis. Whole exome sequencing identified a heterozygous *MYH11* variant c.5819del, which is predicted to result in a frameshift variant (p.Pro1940Hisfx*91) leading to extension of the coding region beyond the native stop codon. This variant segregated with disease in the patient's affected mother and unaffected sibling. **Conclusions:** The association between *MYH11* variants and gastrointestinal motility disorders is rare, and our study adds to this growing body of literature and expands the spectrum of phenotypic variations. For patients with an unexplained etiology of gastrointestinal dysmotility, particularly in the setting of positive family history, genetic causes should be considered, and a complete genetic evaluation should be performed. **Keywords:** Chronic intestinal pseudo-obstruction; Visceral myopathy; Megacystis-microcolon-intestinal hypoperistalsis syndrome; MYH11; Whole exome sequencing; Case report.

PATIENT AND PROVIDER VIRTUAL SUMMIT: THE CURRENT STATE OF MEDIUM CHAIN ACYL-COA DEHYDROGENASE DEFICIENCY MANAGEMENT

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PURPOSE: Medium chain acyl-coA dehydrogenase deficiency (MCADD) education summit brought together both patients/caregivers and health care providers to share perspectives and address unmet needs in the MCADD community by health promotion and poor health outcome prevention methodologies. **METHOD:** The virtual summit offered registration to health care providers, patients, and families managing MCADD worldwide. To understand current MCADD management and needs, 8-question survey was conducted via Qualtrics. Promotional materials were distributed to HRSA regional collaboratives, genetic metabolic nutrition listserv, parents organizations, and outpatient clinics. The program covered MCADD medical and nutritional management followed by patient panel. Polling was conducted around recommendations and usage of medical alert bracelets and glucose monitors. **RESULTS:** 240 participants registered for the event. 56% of survey respondents were health care providers and 44% were patients/caregivers. More than 90% of the cohort reported having either provided or received MCADD emergency letter. The treatment recommended most frequently by clinics and received by patients was limiting fasting time. 69% of providers reported having provided a sick day protocol, with only 33% of patients/caregivers reporting to have received one. Polling showed an overwhelming interest in usage of medical alert bracelets or necklaces (97%) among patients/caretakers as well as current usage of home glucose monitors by some patients (26%).
CONCLUSION: This summit highlighted gaps in best practices for care of patients with MCADD, including usage of medical alert bracelets. Additional topics emerged during the summit such as standard emergency letters, and resources available for pregnancy, exercise tolerance, weight loss will be presented.

POSTER PRESENTATIONS
(Alphabetical by Presenting Author)

REAL-WORLD MAJOR CLINICAL EVENTS AND HEALTHCARE RESOURCE USE AMONG PATIENTS WITH LONG-CHAIN FATTY ACID OXIDATION DISORDERS IN THE UNITED STATES

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Background: Major clinical events (MCEs) of long-chain fatty acid oxidation disorders (LC-FAOD) in triheptanoin clinical trials included inpatient or emergency room (ER) visits for 3 major clinical manifestations: rhabdomyolysis, hypoglycemia, and cardiomyopathy. Real-world LC-FAOD outcome data are limited. We quantify the real-world burden of LC-FAOD by management strategy as MCE rate and healthcare resource utilization (HRU).
Methods: This non-interventional cohort study uses data from the real-world LC-FAOD Odyssey program. Data were collected with the PicnicHealth digital record platform using a novel human-in-the-loop machine learning system to synthesize structured and unstructured data from US medical records and patient reported outcomes from August 2020-August 2022. MCEs included cardiomyopathy, hypoglycemia, and rhabdomyolysis in inpatient or ER settings. MCE-related and non-MCE-related HRU were assessed. Treatment periods (triheptanoin, medium-chain triglyceride [MCT]) were compared. Assessments used a cross-sectional design comparing periods of triheptanoin or MCT treatment of ≥6 months. **Results:** Annualized mean MCE rates on triheptanoin and MCT were 0.1 and 0.7, respectively (rhabdomyolysis: 0.07, 0.3; hypoglycemia: 0.05, 0.4; cardiomyopathy: 0, 0.02). Annualized disease-related inpatient and ER events of all reasons were lower on triheptanoin vs MCT (0.2, 1.2 for inpatient stays; 0.3, 1.0 for ER visits). Patients were managed more in an outpatient setting on triheptanoin (annualized visits: 8.9) than MCT (7.9). **Discussion:** Patients with LC-FAOD from Odyssey had fewer MCEs and HRU in inpatient and ER settings on triheptanoin vs MCT. The MCE rate was lower after triheptanoin initiation, consistent with clinical trials. Results should be interpreted with caution due to small sample size.

EXPANDING THE REACH OF MOLECULAR DIAGNOSTICS: THE BENEFITS OF ROUTINE GENOME SEQUENCING FOR PAN-DISEASE TESTING

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Variantyx, Inc

Despite a substantial decline in sequencing costs since the widespread adoption of NGS technology over a decade ago, exome (WES), rather than genome (WGS), is still the standard paradigm for genetic testing. Many patients incur additional expenses and delays in diagnosis when their genetic testing is limited to WES, as multiple additional technologies are required to assess genetic abnormalities undetectable by WES, such as intermediate-sized deletions/duplications (0.1-1kb) in nuclear DNA and mitochondrial DNA (mtDNA), most known repeat expansion loci, intronic variants, large deletions/duplications (>20kb), aneuploidy, inversions and uniparental disomy (UPD). Here, we highlight the advantages of routine genome sequencing for pan-disease diagnostics in a clinical laboratory setting, by reviewing previously undiagnosed WES cases that were subsequently resolved by our clinically validated, PCR-free WGS test. These cases involve an inversion breakpoint disrupting gene coding regions, deletions above WES detection limits yet below microarray resolution, large-scale mitochondrial DNA deletions, an intronic variant that induces a pseudoexon, and a repeat expansion in trans with a structural deletion. Moreover, we explore the validation and incorporation of 3rd generation ("long read") sequencing technology from Oxford Nanopore Technologies into our clinical testing workflow. The value of long read sequencing is exemplified by the diagnosis of an individual with Unverricht-Lundborg disease who harbored biallelic pathogenic expansions in the CSTB gene's dodecamer repeat region. Taken together, these cases emphasize the importance of WGS as first line diagnostic testing to accurately diagnose patients with complex genetic disorders and provide more effective treatment options.

PERCEPTIONS AND EXPERIENCES OF FAMILIES OF INFANTS DIAGNOSED WITH X-LINKED ADRENOLEUKODYSTROPHY VIA NEWBORN SCREENING IN THE SOUTHERN US

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Introduction: Newborn screening (NBS) for X-linked adrenoleukodystrophy (X-ALD) was added to the Recommended Uniform Screening Panel (RUSP) in 2016 to enable early diagnosis and treatment. We explored the experiences of parents/caregivers of children with X-ALD to improve the NBS process and referral to appropriate clinicians. Methods: Parents/caregivers were recruited in six states. Semi-structured interviews were conducted via Zoom. Two coders independently coded transcripts using MAXQDA software, and thematic analysis was conducted. Results: Four mothers and three fathers (for a total of four affected children) from two states were interviewed. Before NBS, some parents were unaware of the purpose of the heel prick test. During the screening process, parents expressed mixed emotions of confusion, anxiety, and fear. Most lacked understanding of X-ALD and disliked the way the information was disclosed. All were referred to genetics and had positive feedback on this interaction. All were followed by endocrinology and neurology. Barriers included lack of access to clinics during the COVID-19 pandemic and lack of primary care providers' knowledge about X-ALD. Participants made suggestions about how to improve the NBS screening, diagnosis, and referral process. Conclusion: Overall, parents were grateful for NBS but expressed concerns about the medicalization of their children's childhood. Parents had both positive and negative feedback at various points in the NBS screening, diagnosis, and referral process. Study results will help improve the NBS referral process in the Southern US and have implications for other locations that may choose to add X-ALD to their NBS programs in the future.

LIVER INVOLVEMENT IN GLYCOGEN STORAGE DISEASE TYPE IV: NEW INSIGHTS AND THERAPEUTIC IMPLICATIONS

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Glycogen storage disease type IV (GSD IV) is an autosomal recessive disorder resulting in glycogen branching enzyme deficiency. Hepatic GSD IV has been classified into discrete subtypes: (1) the “progressive” hepatic subtype, characterized by progressive liver fibrosis causing death by age 3-5 years without liver transplantation, and (2) the “non-progressive” hepatic subtype, retrospectively assigned to patients who survive without apparent disease progression. Due to lack of natural history data, there is no method to predict patient outcomes, leading to variability in management and practice of liver transplantation. Through international collaborations, 12 patients of different geographical backgrounds were enrolled in a GSD IV natural history study. We found that rate of liver disease in GSD IV varies, with patients exhibiting rapidly progressive (n=6, 1-33 years old), slowly progressive (n=2, 6 years old), or attenuated liver disease (n=4, 8-33 years old). Notably, all patients exhibited extensive liver fibrosis or cirrhosis on biopsy, suggesting that liver failure risk cannot be predicted from liver pathology alone in hepatic GSD IV. At the other end of the GSD IV clinical spectrum is a neurodegenerative disorder Adult Polyglucosan Body Disease (APBD) and there are reports of patients with “non-progressive” hepatic GSD IV in childhood that later developed APBD. We characterized the liver involvement in the *Gbe1$^{ys/ys}$* mouse model which harbors the most common variant observed in APBD (p.Y329S) and found that *Gbe1$^{ys/ys}$* mice recapitulate the attenuated liver disease observed in many patients. This study provides valuable insights into hepatic GSD IV and its connection with APBD.

POSTER PRESENTATIONS
(Alphabetical by Presenting Author)

FOLLOWME FABRY PATHFINDERS REGISTRY: MULTI-SYSTEMIC EFFECTIVENESS IN A MULTI-NATIONAL, MULTI-CENTRE COHORT OF PATIENTS ON MIGALASTAT TREATMENT FOR AT LEAST THREE YEARS

Hughes D,[1] Sunder-Plassmann G,[2] Jovanovic A,[3] Brand E,[4] West ML,[5] Bichet DG,[6] Pisani A,[7] Nowak A,[8] Torra R,[9] Khan A,[10] Azevedo O,[11] Lehman A,[12] Linhart A,[13] Rutecki J,[14] Giuliano JD,[14] Krusinska E,[14a] Nordbeck P,[15] Presented by Lawson, LA

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The followME Fabry Pathfinders registry (EUPAS20599) is evaluating safety, effectiveness, and patient-reported outcomes for current Fabry disease (FD) treatments. Patients ≥12 years old with a confirmed diagnosis of FD and estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2 were enrolled into one of three groups: migalastat-amenable *GLA* variants receiving migalastat; any *GLA* variant receiving enzyme replacement therapy; migalastat-amenable *GLA* variants not receiving FD-specific therapy (natural history cohort). We present clinical follow-up of patients who received ≥3 years of migalastat treatment; these patients represent a population with clinically significant FD in which to assess real-world migalastat use. As of August 2022, 125 patients (60.0% males; median age, 58.0 years) had a mean migalastat exposure of 3.9 years. At enrolment, median left ventricular mass index (g/m^2) was 115.1 (range: 23.9−289.0, n=61; males: 131.2 [43.0−289.0]; females: 98.0 [23.9−209.0]), median urine albumin creatinine ratio (mg/g) was 19.0 (range: 0−1124.0, n=40; males: 14.0 [0−312.0]; females: 26.6 [0−1124.0]) and mean±SD eGFR (mL/min/1.73 m^2) was 83.7±22.5 (n=122; males: 83.7±24.2; females: 83.8±20.1). Overall, 46 (36.8%) patients had an eGFR ≥90, 59 (47.2%) ≥60−90, and 17 (13.6%) <60 mL/min/1.73 m^2 at enrolment. Median eGFR Chronic Kidney Disease Epidemiology Collaboration annualized rate of change in all patients (n=116) was –1.2 (Q1 –3.7, Q3 1.0) mL/min/1.73 m^2/year (males: −1.4 [Q1 –3.7, Q3 1.1]; females: –1.1 [Q1 –3.4, Q3 1.0]). Overall, 76% of patients did not experience a cerebrovascular, cardiac or renal Fabry-associated clinical event. These data support sustained and multi-systemic migalastat effectiveness in an amenable Fabry population in real-world clinical practice.

A LONG-TERM FOLLOW-UP STUDY OF AAV GENE THERAPY FOR GLYCOGEN STORAGE DISEASE TYPE IX γ2

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Liver Glycogen Storage Disease type IX (GSD IX) is caused by a deficiency in phosphorylase kinase (PhK), a complex enzyme initiating the breakdown of glycogen to glucose comprised of four subunits, with α2, β, and δ regulating the activity of the catalytic γ2 domain. Mutations in the γ2 subunit are responsible for GSD IX γ2 (~25% of liver GSD IX). GSD IX γ2 patients present with hepatomegaly, fasting hypoglycemia, fasting ketosis, hypertriglyceridemia, and elevated serum AST/ALT levels. Over 95% of patients with GSD IX γ2 progress to liver fibrosis and cirrhosis with risks for liver failure and death. We recently characterized the GSD IX γ2 mouse model (Phkg2-/-), and this mouse model recapitulates human patients well. The *Phkg2-/-* mouse model presented progressive fibrosis from abundant subcapsular pericellular fibrosis at 6 months to cirrhosis at 18 months. *Phkg2*$^{-/-}$ mice were injected at 5E+12 vg/kg with the murine *Phkg2* transgene under the control of a liver-specific promoter in an AAV9 capsid at 6 months old. After 12 months of treatment, treated mice showed reduced liver size, restored PhK enzyme activity, and reduced liver glycogen and fibrosis similar to WT. Serum ALT and AST, and urine Hex_4 levels decreased comparable to WT levels. Both nonfasted and fasted blood glucose levels were normalized in treated mice. No sign of inflammation was detected in the treated liver. Results of our study suggest that AAV gene therapy may serve as the first definitive treatment for patients with GSD IX γ2.

POSTER PRESENTATIONS
(Alphabetical by Presenting Author)

HYPERMETHIONINEMIA AND DEVELOPMENTAL DELAY CAUSED BY GLYCINE-N-METHYLTRANSFERASE (GNMT) DEFICIENCY AND EXCESSIVE PROTEIN INTAKE

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Glycine-N-methyltransferase (GNMT) deficiency, a genetic disorder characterized by hypermethioninemia, is described in the literature with only five cases reported. Affected individuals are thought to be asymptomatic, the only clinical finding being hepatomegaly. Due to lack of literature describing individuals with GNMT deficiency, the clinical course of patients is not well defined and it is thought to be underdiagnosed. Treatment is not recommended unless methionine levels exceed 800 µmol/L due to the risk for neurological complications in individuals with methionine levels of >1000 µmol/L regardless of etiology. Here we describe a patient with GNMT deficiency exacerbated by excessive protein intake whose symptoms resolved with dietary restriction of protein. A 15-month-old male presented with developmental delay, macrocephaly, and abnormal brain MRI findings suggestive of a metabolic etiology. Laboratory testing revealed elevated transaminases and an elevated plasma methionine of 1424.94 µmoles/L (reference range 6-63). Next generation sequencing (NGS) identified two variants of uncertain significance in the *GNMT* gene, c.767T>C and c.467A>C. Further biochemical studies revealed a highly elevated plasma S-adenosylmethionine (SAM) and slightly elevated S-adenosylhomocysteine (SAH), consistent with a diagnosis of GNMT deficiency. NGS also identified one likely pathogenic variant in the *WDFY3* gene c.9496C>T associated variable intellectual disability and macrocephaly. Treatment included dietary restriction of protein, reducing intake from >5g/kg/day to 1-1.2g/kg/day. Within one year of initiating treatment, plasma methionine levels were within the normal range. Plasma SAM and SAH, and transaminases normalized. Developmental assessments revealed a significant acquisition of skills with most domains falling within the normal range for his age.

BENEFITS OF COLLABORATION WITH FAMILY-TO-FAMILY HEALTH INFORMATION CENTERS (F2FHICs)

Math L
Family Network on Disabilities

Healthcare professionals and providers working with families can experience many hurdles in the collaboration process that can impede the successful outcome of their services. The addition of genetic challenges adds to the burden felt by families, and by the providers who must help them successfully navigate systems, services, resources, and emotions. This is where Family-to-Family Health Information Centers (F2FHICs) become a meaningful and impactful resource to support the families throughout their journey with special needs. Family-to-Family Health Information Centers are part of a national network that promotes partnerships with state and federal agencies. Funded by the U.S. Dept. of Health, under the Health Resources Services Administration, and working in partnership with the Maternal and Child Health Bureau (MCHB), F2FHICs bridge the gap between systems and those receiving services, strengthen the voice of those being served, and collaborate with agencies to secure additional funding and resources. The values and goals of F2FHICs include inclusion and connection of underserved families by representing the cultural, linguistic and geographic diversity of the population; developing family and youth leaders particularly those from underserved and underrepresented populations; and creating and supporting policy positions for children and youth with special healthcare needs and disabilities to promote health equity. Staff of these organizations have personal lived experiences with special needs that bolster the families they serve and offer them compassion, empathy, and support through their loved one's journey.

POSTER PRESENTATIONS
(Alphabetical by Presenting Author)

QUANTIFYING LIVER FIBROSIS USING HISTOLOGIC IMAGE ANALYSIS AS A BIOMARKER FOR DISEASE SEVERITY IN GLYCOGEN STORAGE DISEASE TYPE IX Γ2

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Liver Glycogen Storage Disease Type IX (GSD IX) γ2 is a metabolic disease caused by the deficiency of hepatic phosphorylase kinase (PhK) enzyme. PhK deficiency prevents glycogen breakdown leading to increased glycogen accumulation in the liver. Most patients (>95%) with GSD IX γ2 develop liver fibrosis or cirrhosis attributed to increased glycogen concentration. A knockout *Phkg2*$^{-/-}$ mouse model has been described for GSD IX γ2 that demonstrates progressive liver fibrosis. Quantifying liver fibrosis development over time in *Phkg2*$^{-/-}$ mice can provide a baseline disease endpoint to inform the evaluation of novel therapeutics. Liver tissue from *Phkg2*$^{-/-}$ and wild-type (*Phkg2*$^{+/+}$) mice ages 3-24 months were fixed and embedded in paraffin. Histology slides were cut and stained with Masson's Trichrome to evaluate liver fibrosis and images of the histology slides were analyzed with ImageJ using colorimetric thresholding. We observed that *Phkg2*$^{-/-}$ mice develop fibrosis that increases exponentially with age: the average optical density slowly increased from the 3-month (3.966) to 6-month (4.479) age groups and then became more pronounced in the 9-month (7.149), 12-month (9.365), 18-month (11.044), and 24-month (31.330) age groups. Comparatively, wild-type mice demonstrated approximately 0% fibrotic area at all time points. These observations model what is seen in patients with GSD IX γ2 where liver fibrosis progresses to extensive bridging fibrosis and cirrhosis with age. Future characterizations will include segmentation (cellular size) and severity of fibrosis as metrics to determine the development of liver damage over time in the GSD IX γ2 mouse model.

ANALYSIS OF GLYCOSAMINOGLYCANS IN URINE AND AMNIOTIC FLUID REVEALS DIVERGING TRENDS IN HEPARAN SULFATE, DERMATAN SULFATE AND CHONDROITIN SULFATE CONCENTRATIONS WITH AGE

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Aim: To assess chondroitin sulfate (CS), dermatan sulfate (DS), and heparan sulfate (HS) in control AF and compare the relative concentrations of these species with those in urine. **Introduction:** Urinary glycosaminoglycans (GAGs) analysis is used for the diagnosis and monitoring of the mucopolysaccharidosis (MPS) disorders. GAG accumulation also occurs prenatally and amniotic fluid (AF) may be used for prenatal diagnosis and monitoring of in-utero therapies. **Method:** GAGs in control urine and AF were analyzed as methylated dimers by UPLC-MS/MS. Groups were compared using the Kruskal-Wallis test and Dunn's multiple comparison test. **Results:** A statistically significant decrease in CS, DS, and HS with age (0.0-83.9 years) was observed in control urine (n = 811). The mean relative amount of urinary CS decreased from 76% of total GAGs in group 0-6 months group to 52% in the 10 to 18-year-old group. The opposite trend was observed for DS. There was no clear trend for HS, which remained the minor component. GAGs in control AF (n = 28, 19.9-34.7 weeks gestational age, GA) were determined relative to volume. DS and CS had similar mean concentrations at 19 to 21 weeks GA, each accounting for 48% of total GAGs. The relative amount of DS decreased and CS increased with GA. The distribution of GAGs at 33-35 weeks was similar to that observed in the urine of young infants. **Summary:** Our data highlights the importance of having appropriate age-specific reference values for GAGs considering the variability in GAGs distribution across age-groups.

POSTER PRESENTATIONS
(Alphabetical by Presenting Author)

LONG-CHAIN FATTY ACID OXIDATION DISORDERS (LC-FAODS) DETECTED USING A SPONSORED GENE PANEL IN PATIENTS WHO HAD PRIOR NEWBORN SCREENING OR ACYLCARNITINE TESTING

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Objectives: Long-chain fatty acid oxidation disorders (LC-FAOD) are rare, life-threatening, conditions typically detected through newborn screening (NBS) or afterwards with plasma or dried blood spot acylcarnitine (AC) analysis. Signs and symptoms of LC-FAOD can include (but are not limited to) hypoglycemia, cardiomyopathy, cardiac arrhythmias, and rhabdomyolysis. **Methods**: Clinicians suspecting LC-FAOD were provided access to a 25-gene next-generation sequencing panel. Samples were submitted to Invitae as part of clinical testing sponsored by Ultragenyx (at no-charge to the patient) in the United States, Canada, and Mexico between July 2020 and October 2022. De-identified result data provided to Ultragenyx was used for this analysis. **Results**: There were 796 unique samples analyzed. There were 72 (9%) samples with a positive/potential positive (pathogenic, likely-pathogenic, or variant of uncertain significance) LC-FAOD genetic result for the following genes: *ACADVL (63%)*, *CPT2 (18%)*, *HADHA (10%)*, *HADHB (4%)*, *CPT1A (3%)*, *SLC25A20 (3%)*. A positive NBS was reported in 50/72 (69.4%) and a positive or inconclusive AC in 42/72 (58.3%). The age distribution of positive genetic results was: 10.5% < 1y, 4.3% 1y-12y, 10.5% 13y-20y, 12.5% 21y-40y, and 5.1% >40y. **Conclusions:** Our results demonstrate that this gene panel led to a genetic diagnosis additionally in patients who previously were not reported as diagnosed using NBS or AC testing, indicating that testing for LC-FAOD later in life should still be in consideration if a clinical suspicion exists. Further data may show whether molecular testing should be considered as an adjunct to biochemical profiling to look for LC-FAOD.

PTC PINPOINT CP SPECTRUM: A SPONSORED NO-CHARGE TO PATIENTS 265-GENE PANEL FOR PATIENTS WITH SYMPTOMS SUGGESTIVE OF CP AND ABSENCE OF RISK FACTORS FOR AN ACQUIRED BRAIN INJURY

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Objective: Cerebral palsy (CP) is one of the most common neurodevelopmental disorders affecting 2-3/1,000 livebirths. Studies find that 10-30% of cases have a genetic etiology. Diagnostic yield is suspected to be increased in patients without an environmental cause, such as an acquired brain injury. Identifying a genetic etiology has a significant impact on clinical management decisions. We report the utilization patterns and molecular diagnostic yield of a targeted, no-charge to patients sponsored gene panel program, PTC Pinpoint CP Spectrum. Methods: Eligibility criteria: (I) symptoms suggestive of CP, (II) absence of risk factors for an acquired brain injury. Gene curation focused on genes associated with clinical phenotypes consistent with cerebral palsy. Physician-reported clinical history was collected. Diagnostic yield was calculated from results of tests ordered for 1683 individuals between 9/15/2020 (program inception) and 12/15/21. Results: 166/1683 (10%) individuals had a definitive genetic cause of CP identified. There were causative variants identified in 59 different genes, with *SPAST* and *CTNNB1* being the most common cause in 19 patients and 18 patients, respectively. Providers from over 18 different specialties have utilized the panel. Age at testing varied greatly (ages 0-74) but the average age was 8 years. Conclusion: PTC Pinpoint CP Spectrum is a valuable tool utilized by a variety of providers that can identify the underlying genetic cause for patients with CP of unknown etiology. The diagnostic yield is expected to improve with continued gene curation. This no-charge to patients sponsored gene panel program can be part of a tiered diagnostic approach for patients with CP.

THE CASE FOR DOJOLVI® (TRIHEPTANOIN): OUTCOMES AND EXPEIRNECES OF TWO PATIENTS' TRANSITIONS FROM MCT-BASED FORMULA TO TRIHEPTANOIN

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Background: Very Long-Chain Acyl-CoA Dehydrogenase deficiency (VLCADD) is a long-chain fatty acid oxidation disorder (LC-FAOD) caused by a defect in an enzyme that metabolizes very long-chain fatty acids. Without intervention, affected individuals may experience hypoglycemia, rhabdomyolysis, cardiomyopathy, and even death. Diet intervention restricts long-chain triglycerides and supplements medium-chain triglycerides (MCT). Triheptanoin is a synthetic MCT that bypasses the defective very long-chain fatty acid enzyme, and is indicated for patients with VLCADD. However, there is limited literature on transitioning patients from MCT-based formulas to triheptanoin. **Methods**: We summarize two patients with molecularly-confirmed VLCADD who began triheptanoin as an alternative to MCT-based formula. Clinical history, anthropometrics, diet analyses, and laboratory data were reviewed. Metabolic dietitians provided nutrition education and patient follow-up throughout titration and transition. **Results**: Patient "A" initiated triheptanoin in September 2022. Throughout the observation period (September 2022 through March 2023), Patient A's creatinine kinase (CK) fluctuated, with no significant improvement noted. Patient A never completed the full transition to triheptanoin due to challenges weaning from MCT-based formula, and remains on a combination of both therapies. Patient "B" initiated triheptanoin in March 2021, and CK decreased from 345 to 226 U/L. Patient B experienced a smooth transition to triheptanoin, with the patient's caretaker noting an improvement in quality of life since switching treatments. **Conclusion**: Patients A and B transitioned from MCT-based formula to triheptanoin with variable results based on laboratory markers prior to, during, and after triheptanoin initiation. This underscores the need for personalized nutrition care plans for patients with LC-FAODs.

THE FUTURE OF NAVIGATING WORSENING AND EXISTING STAFFING SHORTAGES IN THE LABORATORY

Owens M
Allied Search Partners

Finding qualified clinical laboratory diagnosticians has always been a daunting task. There are multiple factors attributing to the declining availability of laboratory talent. Examples include an increase in retirement of laboratory professionals, increase in the demand for laboratory testing services, changes in the practice of the laboratory due to technology advances and vacancies exceeding the number of graduates in a laboratory education program. The shortage of laboratory professionals will continue at a rapid rate over the next several years like never before. The need for unique, affordable, and efficient ways to fill laboratory openings with qualified personnel is at an all-time high. The top ways in which laboratory leadership plans to mitigate this issue is lab automation, lab training programs, and increasing work/life balance offerings. Other ways include Temp/Travel workers, as this is on the rise for candidate preference in employment. There are major changes in what motivates a candidate to take on and seek out a new position. Our workforce is changing significantly, and this requires evolution of how we acquire talent in our laboratories.

POSTER PRESENTATIONS
(Alphabetical by Presenting Author)

THE LONG-TERM SAFETY AND EFFICACY OF PEGVALIASE 60 MG/DAY IN ADULTS WITH PHENYLKETONURIA

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Pegvaliase is a novel enzyme substitution therapy, to treat adults with PKU who have blood phenylalanine (Phe) levels >600 µmol/L on existing management. Use of pegvaliase up to 60 mg/day dose was approved in the US from the results of the phase 3 PRISM trials. Participants enrolled in PRISM-2 (165-302) Part-4, were able to receive >40 mg/day dosing and could continue treatment in 165-304, an open label extension study evaluating the long-term outcomes of >40 mg/day to 60 mg/day dosing. Herein we report results through the end of 165-304 for PRISM-2 patients on 60 mg/day for ≥4 weeks with ≥80% adherence (Stable 60 mg population, n=51), and safety for all participants receiving a 60 mg/day dose (n= 89). Total pegvaliase-exposure was 636 person-years; 137 person-years on 60 mg/day (n=89). Mean ± SD Phe was 1063 ± 372 µmol/L (n=51) on 40 mg/day; this decreased to 617 ± 528 µmol/L (n=23) following 8 weeks of treatment on 60 mg/day. On 60 mg/day stable dose 32/41 (78.0%) achieved Phe ≤600 µmol/L with 36/48 (75.0%) reaching Phe ≤360 µmol/L. Long-term sustained dose reductions to <60 mg/day occurred in the studies. Overall, adverse-event (AE) rates decreased with time and analysis by dose range showed that higher doses of pegvaliase were not associated with a higher AE rate or the development of AEs not reported at lower doses. The results of these studies support the use of 60 mg/day in patients who have not achieved a clinically meaningful Phe reduction on 40 mg/day.

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

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Objectives: Electronic Genetic Nutrition Academy (eGNA)'s Genetic Nutrition Extended Community Health Outcomes (ECHO) is a case-based learning program developed in 2020. Four patient cases of glutaric aciduria type 1 (GA-1) were shared within the first 6 cohorts of ECHO at Emory University. These cases prompted our team to explore the availability of nutritional guidelines of patients with GA-1 after a basal ganglia stroke. **Methods**: Participants include healthcare providers that enroll for a 12-week Genetic Nutrition ECHO cohort and a group of experienced providers from Emory University. Each week, cohort members present de-identified cases. Everyone on the call provides recommendations based on published literature and clinical experience, creating an "All Teach, All Learn" environment. **Results**: During cohorts 1-6, four case studies were presented that focused on patients with GA-1 after a basal ganglia stroke. Presenting symptoms complicated nutrition management including developmental regression, dystonia, feeding intolerance, and malnutrition. We were unable to identify published nutritional guidelines addressing the needs of these patients or answer the questions of the providers caring for them. **Discussion:** Given that there were four providers seeking guidance for similar cases, we conclude that there is a need for additional guidelines directing the management of patients with GA-1. **Conclusion**: eGNA's Genetic Nutrition ECHO has provided a forum for providers to spread best practice to help master complex cases and to identify unmet needs. The field of nutrition would benefit from consensus and research-based guidelines on the management of patients with GA-1 who have experienced a basal ganglia stroke.

POSTER PRESENTATIONS
(Alphabetical by Presenting Author)

RGX-121 GENE THERAPY FOR THE TREATMENT OF NEURONOPATHIC MUCOPOLYSACCHARIDOSIS TYPE II (MPS II): INTERIM ANALYSIS OF DATA FROM THE FIRST IN HUMAN STUDY

Harmatz P[1], Ficicioglu C[2], Giugliani R[3], Rajan D[4], Hagood J[5], Fiscella M[5], Yang L[5], Gilmor M[5], Cho Y[5], Phillips D[5], Pisani L[5], Falabella P[5]. Presented by Joseph Schneider[5]

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Background: MPS II is an x-linked lysosomal storage disease caused by deficiency of iduronate-2-sulfatase (I2S) leading to accumulation of glycosaminoglycans (GAGs). Neuronopathic MPS II (nMPS II) results in irreversible neurodevelopmental decline not addressed by intravenously administered enzyme replacement therapy. RGX-121, a recombinant adeno-associated virus serotype 9 capsid containing a human iduronate-2-sulfatase expression cassette (AAV9.CB7.hIDS), administered to the central nervous system (CNS) is designed to provide a permanent source of secreted I2S, potentially correcting neurologic and systemic disease manifestations. Methods: CAMPSIITE™ is a phase I/II/III, open-label, 104-week trial enrolling boys 4 months up to 5 years of age with nMPS II (NCT03566043) who receive one image-guided RGX-121 injection to the CNS. Assessments include safety and tolerability; CSF, plasma, and urine biomarkers; neurodevelopmental scales; and imaging. Participants are encouraged to enroll in a long-term follow-up study. Results: As of January 3, 2023, 15 participants were enrolled in the phase I/II portion of CAMPSIITE in 3 dose cohorts ($1.3x10^{10}$, $6.5x10^{10}$, and $2.9x10^{11}$ genome copies/gram brain mass). RGX-121 was reported to be well-tolerated with no drug-related serious adverse events. Longest post-administration follow-up was > 3 years. CSF GAGs showed dose-dependent reductions with D2S6 approaching normal levels in cohort 3 at 48 weeks. Interim neurodevelopmental assessments demonstrated CNS activity up to 3 years after RGX-121 administration. Evidence of systemic enzyme expression and biomarker activity was present after CNS RGX-121 administration. Updated interim results will be presented. Conclusions: RGX-121 has the potential to provide sustained CNS clinical outcomes and additional systemic effects in MPS II patients.

CHARACTERIZING THE CLINICAL COURSE OF PEDIATRIC-ONSET NEUROMUSCULAR GLYCOGEN STORAGE DISEASE IV

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Background: Glycogen storage disease type IV (GSD IV) is caused by deficiency of glycogen branching enzyme, leading to impaired glycogen synthesis and polyglucosan accumulation. GSD IV exhibits variability in onset, severity and manifestations. Historically, pediatric-onset neuromuscular GSD IV has been discretely categorized into perinatal, neonatal, and juvenile subtypes. While cases with features overlapping between subtypes have been recognized, long-term outcomes are unclear, warranting deeper study to understand the natural history of disease. Methods: Comprehensive retrospective evaluation of longitudinal clinical, laboratory, and histologic parameters of fourteen patients with neuromuscular presentations of GSD IV were included in this multicenter, international study following ethics approval and informed consent.

Results: The current median age was 7.8 years (range 0 - 41). Cases were categorized on the presence (n=7) or absence (n=7) of arthrogryposis. Of seven patients with arthrogryposis as an initial feature, six presented at birth and one at 1.8 years. Two patients experienced respiratory distress, leading to death within the first two months of life. Of five surviving patients (range 3.3 – 25.8 years), two experienced gross motor delays and one requires a mobility aid. In the patients with no arthrogryposis, gait abnormalities and muscle weakness (42.8%) were the most common symptoms, presenting at a median age of 2 years (range 0.75 – 12). Of those (range 6.2 – 41.8 years), two suffered gross motor delays with one utilizing a mobility aid. Muscle histology revealed similar histological features across all presentations. Discussion: Our study demonstrates the variable clinical features and outcomes in pediatric-onset neuromuscular GSD IV.

EXPANDING THE PHENOTYPIC SPECTRUM OF RERE-RELATED DISORDERS

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The arginine-glutamic acid dipeptide repeats (*RERE*) gene positively regulates retinoic acid signaling, which is critical in the development and differentiation of certain tissues, specifically in the brain, heart, eye, and kidney. Heterozygous pathogenic variants within this gene have been reported in 23 individuals with neurodevelopmental and congenital anomaly phenotypes. Within this limited cohort, a strong genotype-phenotype correlation has been established between missense alterations and an increased risk for structural anomalies when compared to loss of function alterations. Here we present a 14-month-old male who presented with a history of intrauterine growth restriction, mild hypertonicity (R>L), mild expressive speech delay, microcephaly (OFC 2nd centile), and short stature (length <1st centile). Brain MRI and early fine and gross motor milestones were normal. Family history was negative. Next generation sequencing revealed a heterozygous, *de novo* partial gene deletion of *RERE* encompassing exons 3-11. Additional cardiac, renal, and audiologic evaluations were normal. Ophthalmologic exam was structurally normal; however, strabismus was noted. IGF-1 was found to be low prompting initiation of growth hormone (GH) therapy at 16 months of age. Since starting GH therapy his growth rate has improved (length 5th centile), and his weight and OFC are now in the 3rd and 9th centiles, respectively. He continues to make steady developmental progress, particularly in his expressive speech with about 50 words at age 26 months. This case supports the previously reported genotype-phenotype correlation and adds to the literature regarding the wide spectrum of clinical manifestations of RERE-related disorders.

COVID-19 INFECTION IN A 2-YEAR-OLD FEMALE WITH NEONATAL-ONSET PROPRIONIC ACIDEMIA

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Background: Propionic acidemia (PA) is an organic acidemia caused by deficiency of propionyl-CoA carboxylase (PCC). The most common form of PA is neonatal onset, characterized by lethargy, poor feeding, hypotonia, and possible progression to encephalopathy, cardiorespiratory failure, seizures, and death if not promptly treated. Physiologic stressors causing catabolism can lead to severe metabolic decompensation. **Case Presentation**: A 2-year-old female with neonatal-onset PA presented to the hospital for lethargy, pancytopenia, and hyperammonemia due to an underlying UTI. She was treated with increased calories, IVFs, decreased protein diet, antibiotics and Carbaglu. On day of discharge, she experienced an acute decline with fever, irritability, and seizures. She was transferred to the PICU due to hypotension, status epilepticus and encephalopathy. She required endotracheal intubation and parenteral nutrition. She tested positive for SARS-CoV-2. A literature search did not reveal any data regarding use of remdesivir with organic acidemias, and guidelines suggest avoidance of steroids. It was decided that the potential benefits outweighed the risks. After a course of remdesivir and dexamethasone, along with continued management of her PA, her clinical condition improved, and she returned to her outpatient diet and medications. We observed significant hyperlactatemia during her treatment with steroids. Her ammonia remained within normal limits and her acylcarnitine profile revealed propionylcarnitine lower than her baseline. **Conclusion**: Our case demonstrates severe clinical presentation of COVID-19 infection in a patient with PA and describes novel use of remdesivir and steroids. Although she had a critical clinical course, she had a positive outcome with the treatment provided.

POSTER PRESENTATIONS
(Alphabetical by Presenting Author)

FUNCTIONAL CHARACTERIZATION OF IDUA VARIANTS IDENTIFIED BY NEWBORN SCREENING FOR MPS I

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With the expansion of newborn screening (NBS) efforts for MPS disorders across the U.S., the number of identified variants of uncertain significance (VUS) in *IDUA* and *IDS* continues to increase. In the absence of any clear clinical manifestations in these individuals with a positive NBS and ambiguous secondary GAG testing, decisions about medical management and early intervention are often delayed, leading to stress and uncertainty among families and caregivers. To offer the most comprehensive information about the variants that are associated with a positive NBS, we developed a HEK293-based expression platform for the functional characterization of *IDUA* variants that can be used to determine the specific activity of variant a-iduronidase enzymes relative to the wild-type enzyme. We have now used this platform to characterize over fifty different *IDUA* variants, including known benign, pseudodeficiency and pathogenic variants, multiple VUS, and several variant combinations that are present *in cis* on one allele in patients with a positive NBS. This analysis has allowed us to stratify the variant enzymes based on their relative specific activity, reclassify multiple VUS, and uncover distinct effects of the different variants on enzyme folding, processing and stability. We also present results demonstrating that certain *in cis* combinations of pseudodeficiency *IDUA* variants approach the pathogenic range, suggesting that such combinations may be contribute to disease. Strategies to complement the biochemical platform with cell-based functional assays that can monitor other parameters of enzyme function (trafficking, maturation, oligomerization, clearance of GAG storage) will be shared.

UNCOVERING RARE OBESITY GENETIC TESTING PROGRAM: UTILITY OF GENETIC TESTING IN PEDIATRIC AND ADULT PATIENTS WITH OBESITY

Kleyn P[1], Sleiman P[1], Bromberg E[2], Norton R[1]. Presented by Randy Ziss.
[1]Rhythm Pharmaceuticals, Inc., Boston, MA; [2]Beghou Consulting Inc., Rockville, MD

Introduction: Rare melanocortin-4 receptor (MC4R) pathway diseases associated with obesity can arise because of variants in one of multiple genes involved in the pathway, which regulates hunger and energy expenditure. Genetic testing can improve diagnosis and care in patients with rare genetic diseases of obesity. The Uncovering Rare Obesity® (URO) testing program aims to increase access to genetic testing and identify individuals with obesity caused by rare genetic variants. We compare the frequency of rare MC4R pathway variant outcomes in pediatric and adult patients. *Methods*: The proportion of patients with potentially pathogenic variants in 57 MC4R pathway genes including *POMC*, *PCSK1*, *LEPR*, *SH2B1, NCOA1*, and 22 genes associated with BBS were compared between age groups (≥18 years vs <18 years). *Results*: Variants and classification in adults with a history of childhood obesity and pediatric patients were generally consistent. Of 3,160 adult and 6,520 pediatric patients sequenced respectively, 39.73% and 38.33% carried a variant in ≥1 of the 57 genes analyzed,0.79% and 0.95% had pathogenic (P) or likely pathogenic (LP) variants associated with the MC4R pathway, and 0.34% and 0.31% had ≥1 P/LP heterozygous *POMC*, *PCSK1*, or *LEPR* variant. *Conclusions*: In this cohort, ~40% of adults and ~38% of pediatric patients had rare genetic MC4R pathway variants and, of those, ~2% and ~2.5% had P/PL variants, respectively. Genetic testing was more frequently done in pediatric patients vs adults, but the proportion of patients in each age category with variants (P/LP, uncertain significance, or uncertain significance suspected pathogenic) was similar.

VARIANTS IN OBESITY-RELATED GENES IN A POPULATION WITH EARLY-ONSET OBESITY

Kleyn P[1], Sleiman P[1], Bromberg E[2], Rick Norton R[1]. Presented by Randy Ziss.
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Introduction: Genetic testing can improve the diagnosis of rare genetic diseases of obesity and identify patients who may benefit from targeted therapy. Patients with genetic variants in the melanocortin-4 receptor (MC4R) pathway may present with early-onset, severe obesity and hyperphagia. The Uncovering Rare Obesity® (URO) testing program aims to enhance access to genetic testing for patients with suspected rare genetic diseases of obesity. We describe the frequency of select rare variants in these individuals. *Methods:* We sequenced 14,608 individuals with early-onset, severe obesity as part of the URO program. The panel included 79 genes and 1 chromosomal region with well-established associations with obesity and the MC4R pathway. *Results:* Overall, 4,949 sequenced individuals (34%) had genetic variants that are either indicated for treatment in the USA with the MC4R agonist setmelanotide or that are currently being investigated for setmelanotide efficacy in clinical trials. An additional 6,127 individuals (42%) had variants that might support a diagnosis of genetic obesity but are not currently indicated for setmelanotide treatment or being investigated for setmelanotide efficacy in clinical trials. The remaining 3,542 individuals (24%) did not carry pathogenic variants or variants of uncertain significance. *Conclusions:* In this cohort of individuals with early-onset, severe obesity, ~76% carried potentially actionable variants. Genetic testing of patients with severe obesity, particularly those with a history of early-onset obesity suggestive of a potential genetic origin, may be an important component of understanding the etiology of these patients' phenotypes and could potentially impact the course of care for these 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.

PLATINUM EXHIBITORS

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Horizon is a global biotechnology company focused on the discovery, development and commercialization of medicines that address critical needs for people impacted by rare, autoimmune and severe inflammatory diseases. We believe science and compassion must work together to transform lives.

PLATINUM EXHIBITORS

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Sanofi Genzyme focuses on developing specialty treatments for debilitating diseases that are often difficult to diagnose and treat, providing hope to patients and their families.

GOLD EXHIBITORS

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Allied Search Partners – An MRI Network Firm, specializes in the talent access solutions for medical and dental laboratories. Founded in 2008, a small-medium woman-owned Certified Healthcare Staffing Business.

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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. With extraordinary patient focus, Amicus Therapeutics is committed to advancing and expanding a robust pipeline of medicines for rare metabolic diseases.

GOLD EXHIBITORS

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Chiesi USA, Inc is a Certified "B" Corporation focusing on Global Rare Diseases.

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We're passionate about providing superior drug treatments and services to patients with rare metabolic conditions. We have two metabolic products: Nityr (Nitisinone) Tablets and Javygtor (sapropterin dihydrochloride) Tablets for Oral Use and Powder for Oral Solution. Learn more at www.cyclepharma.com.

GOLD EXHIBITORS

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Eton Pharmaceuticals is an innovative pharmaceutical company focused on developing and commercializing treatments for rare diseases, including Carglumic acid tablets and Betaine Anhydrous for oral solution.

Rhythm Pharmaceuticals, Inc
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Rhythm is committed to transforming the treatment paradigm for people living with rare genetic diseases of obesity. Early-onset severe obesity may result from genetic variants within MC4R pathway, that regulates hunger, caloric intake, and energy expenditure, consequently affecting body weight.

GOLD EXHIBITORS

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Variantyx is a technology-driven precision medicine company providing state-of-the-art diagnostic solutions for the rare genetic disorders and reproductive genetics markets and treatment optimization in oncology.

SILVER EXHIBITORS

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Alexion, AstraZeneca Rare Disease division's mission is to transform the lives of people affected by rare diseases and devasting conditions by continuously innovating and creating meaningful value in all that we do.

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

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GeneDX is focused on delivering personalized, actionable insights that improve health outcomes. We sit at the intersection of diagnostics and data science, pairing decades of genomic expertise with an unmatched ability to interpret clinical data at scale.

SILVER EXHIBITORS

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

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Novartis Gene Therapies offers a gene therapy for Spinal Muscular Atrophy.

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Nutricia has positively changed the lives of millions of people with specific nutritional needs from infancy to old age. We offer a broad range of products fo the nutritional management of a variety of conditions, including inherited metabolic disorders.

SILVER EXHIBITORS

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PreventionGenetics was founded in 2004 and acquired in 2022 by Exact Sciences. PreventionGenetics is an accredited laboratory, providing high-quality genetic testing for nearly all clinically relevant genes including whole exome and whole genome sequencing.

PTC Therapeutics
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PTC is a science-driven biopharmaceutical company. We combine strong clinical and scientific expertise with dedication to using ground-breaking science and new technologies to find innovative ways to treat diseases which give patients and their families more moments.

Relief Therapeutics
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Relief Therapeutics is a commercial-stage biopharmaceutical company committed to advancing treatment paradigms and delivering improvements in efficacy, safety, and convenience to benefit the lives of patients living with select specialty and rare diseases.

SILVER EXHIBITORS

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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.

Takeda Pharmaceuticals
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Takeda is a patient-focused, value-based, R&D-driven global biopharmaceutical company; our passion and pursuit of potentially life-changing treatments are rooted in our history. We know patients with rare diseases have spent their lives overcoming challenges. That's why for 70+ years we've been working to support them in their fight.

Travere Therapeutics
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Travere Therapeutics is a biopharmaceutical company dedicated to identifying, developing and delivering life-changing therapies to people living with rare disease.

SILVER EXHIBITORS

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Stop by our exhibit and learn about Dojolvi for treatment of LC-FAOD.

EXHIBITS

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PKU formula and low protein food.

BIONANO LABORATORIES
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At Bionano Laboratories, our mission is to advance the way you see the genome by offering a comprehensive testing portfolio including chromosomal microarray, panels, whole exome sequencing and optical genome mapping, Visit our booth to learn more about our services.

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

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At Marinus, our passionate team of experts are constantly innovating with the aim to drastically improve lives affected by seizure disorders.

MUSC: IN OUR DNA SC
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MUSC's In Our DNA SC aims to enroll 100,000 participants for genetic testing at no cost. Participants will receive confidential results about genetic risks for certain cancers and heart disease. The project will also develop a secure genetic research database.

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Nexus Patient Services offers a variety of innovative medical foods for use in the dietary management of metabolic disorders to make life easier for patients. Our benefits investigation team navigates insurance coverage to take the burden off your clinical team.

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REGENXBIO Inc is a leading clinical-stage biotechnology company seeking to improve lives through the curative potential of gene therapy using our NAV® Technology Platform. Our products are designed to deliver genes to produce therapeutic proteins of antibodies to impact disease.

SOUTHEAST REGIONAL GENETICS NETWORK (SERN)
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The Southeast Regional Genetics Network (SERN) is a HRSA supported program that focuses on improving health equity and health outcomes in individuals with genetic conditions.

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Thermo Fisher Scientific is the world leader in serving science. Customers worldwide trust our tools and solutions to help them accelerate innovation and enhance productivity. Together, we are making advancements that make a real difference.