Abstracts for Presentation at the RDCRN Conference on Clinical Research for Rare Diseases

Poster Numbers will Correlate with the Abstract Number Listed Below

1. **Developmental outcomes of Aicardi Goutières Syndrome**
Laura Adang*[1], Francesco Gavazzi*[1, 2], Julia Kramer-Golinkoff[1], Elisa Fazzi[4, 7], Jessica Galli[4, 5], Jamie Koh[1], Kyle Peer[1], Simona Orcesi[3], Nicole Ulrick[1], Sarah Woidill[1], Justine Shults**, and Adeline Vanderver**[1]
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2. **Familial LCAT Deficiency: Searching for Biomarkers to Assess Treatment Efficacy**
Cecilia Vitali, PhD[1]*; Archna Bajaj, MD[1]*; Daniel J. Rader, MD[1]; Marina Cuchel, MD, PhD[1]
University of Pennsylvania, Philadelphia, PA, *Share first authorship

3. **Clinical, biochemical and genetic features of patients with mitochondrial diseases: Data from the North American Mitochondrial Disease Consortium (NAMDC) registry**
Emanuele Barca; Victoria Cooley; Robert Schoenaker; Valentina Emmanuele; Salvatore DiMauro; Long Yuelin; Bruce Cohen; Amel Karaa; Georgirene Vladutiu; Richard Haas; Johan Van Hove; Fernando Scaglia; Sumit Parikh; Jirair Bedoyan; Susanne DeBrosse; Ralitza Gavrilova; Russell Saneto; Gregory Enns; Peter Stacpoole; Jaya Ganesh; Austin Larson; Zarazuela Zolkipli-Cunningham; Marni Falk; Amy Goldstein; Mark Tarnopolsky ; Kathryn Camp, Danuta Krotoski; Kristin Engelstad; Xiomara Rosales, Joshua Kriger, Johnston Grier , Richard Buchsbaum, John Thompson, Michio Hirano.
Department of Neurology, Columbia University Medical Center, NY, Department of Biostatistics, Mailman School of Public Health, Columbia University, NY, Radboudumc, Nijmegen, The Netherlands, Department of Pediatrics, Northeast Ohio Medical University and Akron Children's Hospital, Akron, OH, Genetics Unit, Massachusetts General Hospital, Boston, MA, Department of Pediatrics, State University of New York at Buffalo, Buffalo, NY, Departments of Neurosciences and Pediatrics, University of California at San Diego, San Diego, CA, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, Department of Molecular and Human genetics, Baylor College of Medicine, Houston, TX, Department of Neurology, Cleveland Clinic, Cleveland, OH, Departments of Genetics and Genome Sciences and Pediatrics, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, OH, Departments of Neurology and Clinical Genomics, Mayo Clinic, Rochester, MN, Department of Neurology, University of Washington, Seattle Children's Hospital, Seattle, WA, Department of Pediatrics, Stanford University, Palo Alto, CA, Department of Medicine, University of Florida at Gainesville, Gainesville, FL, Department of Pediatrics, Cooper University Hospital, Camden, NJ, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, Department of Neurology, McMasters University, Toronto, ON, Office of Dietary Supplements, National Institutes of Health, Bethesda, MD, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD

4. **Emotional responses, stressors and coping strategies for parents of children with Zellweger spectrum disorder (ZSD).**
Mousumi Bose[1,2,3], Meena Mahadevan[1], Dana R. Schules[1], Rory K. Coleman[1], Kelly M. Gawron[1], Melissa B. Gamble[2], Jean-Baptiste Roullet[3], K. Michael Gibson[3], William B. Rizzo[3].
Montclair State University Department of Nutrition and Food Studies[1], Global Foundation for Peroxisomal Disorders[2], Rare Diseases Clinical Research Network: Sterol and Isoprenoid Research Consortium[3]

5. **Somatostatin Receptor-Targeted Imaging for Detection of Cardiac Sarcoidosis**
Paco E. Bravo, MD[1,2], Navkaranbir Bajaj, MD, MPH[1], Robert F. Padera, MD, PhD[1], Mi-Ae Park, PhD[1], Hyewon Hyun, MD,[1] Garrick C. Stewart, MD[1], Sharmila Dorbala, MD, MPH[1], Ron Blankstein, MD[1], Marcelo F. Di Carli, MD[1]
[1]Brigham and Women's Hospital, Boston, MA, USA; and [2]Hospital of the University of Pennsylvania, Philadelphia, PA, USA

6. **Enhancing Adult Education in Rare Disease Training with the Inclusion of Interactive Sessions within Standard Curriculum**
Nancy Cheng, Debra S. Regier
Children's National Rare Disease Institute, Children's National Health Systems, Washington, DC

7. **SLC26A3 (DRA) Inhibitor Identified in Small Molecule Screen Blocks Colonic Fluid Absorption and Treats Constipation in Cystic Fibrosis Mice**
Abstract selected for an oral presentation. There will be no poster.
Onur Cil[1,2], Peter M. Haggie[2], Sujin Lee[2], Joseph-Anthony Tan[2], Puay-Wah Phuan[2], Alan S. Verkman[2]
Departments of [1] Pediatrics and [2] Medicine, University of California, San Francisco

8. **Symptom Burden within One Year Differentiates Rapidly Progressive Multiple System Atrophy**
Elizabeth A. Coon M.D[1], David M. Sletten[1], Jay N. Mandrekar, Ph.D. [2], Mariana Suarez, J. Eric Ahlskog, Ph.D., M.D. [1], James H. Bower, M.D. [1], Paola Sandroni, M.D. [1], Eduardo E. Benarroch, M.D.[1], Philip A. Low M.D.[1], Wolfgang Singer, M.D.[1]
[1]Department of Neurology, Mayo Clinic, Rochester, MN, [2]Department of Biostatistics, Mayo Clinic, Rochester, MN

9. **Natural History Study of Succinic Semialdehyde Dehydrogenase (SSADH) Deficiency**
DiBacco M[1], Kapur K[2], Brown M[3] , Sideridis G[2], Roullet J-B[3], Gibson KM [3], Pearl PL[1]
[1] Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, [2] Biostatistics, Boston Children's Hospital, Harvard Medical School, Boston, MA, [3] Clin Pharmacology, Washington State University, Spokane, WA

10. **ApoM is downregulated in an experimental model of Alport syndrome and may contribute to the pathogenesis of proteinuria in glomerular diseases**
Yelena Drexler, Judith Molina, Alla Mitrofanova, Sandra Merscher, Alessia Fornoni
Katz Family Division of Nephrology and Hypertension and Peggy and Harold Katz Family Drug Discovery Center, Department of Medicine, University of Miami Miller School of Medicine, Miami, Florida

11. **Development of diagnostic criteria to facilitate research in mitochondrial disorders: A proposal from the North American Mitochondrial Disease Consortium**
Emmanuele Valentina, MD, PhD[1]; Jaya Ganesh, MD[2]; Georgirene Vladutiu, PhD[3]; Richard Haas, MD[4]; Charles Hoppel, MD[5]; Douglas Kerr, MD, PhD[6]; Russell Saneto, DO, PhD[7]; Bruce Cohen, MD[8]; Johan Van Hove, MD, PhD[9]; Fernando Scaglia, MD[10]; Xiomara Q. Rosales, MD[1]; Emanuele Barca, MD, PhD[1]; Richard Buchsbaum[11]; John L. Thompson, PhD[1,11]; Salvatore DiMauro, MD[1]; Michio Hirano, MD[1]; and the North American Mitochondrial Disease Consortium (NAMDC).
[1]Department of Neurology, Columbia University Medical Center, New York, NY, [2]Division of Genetics, Department of Pediatrics, Cooper Medical School at Rowan University, Camden, NJ, [3] Departments of Pediatrics, Neurology, and Pathology and Anatomical Sciences, Jacobs School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY, [4]Departments of Neurosciences and Pediatrics, University of California San Diego, La Jolla, CA, [5] Center for Mitochondrial Disease, School of Medicine, Case Western Reserve University, Cleveland, OH, [6] Department of Pediatrics, Case Western Reserve University, Cleveland, OH, [7]Department of Neurology, Seattle Children's Hospital/University of Washington, Seattle, WA, [8]Neurodevelopmental Science Center, Children's Hospital Medical Center of Akron, Akron, OH, [9] Department of Pediatrics, Section of Clinical Genetics and Metabolism, University of Colorado School of Medicine, Aurora, CO, [10]Department of Molecular and Human Genetics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, [11]Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, NY, United States

12. **Contribution of glycolate metabolism to endogenous synthesis of oxalate**
Sonia Fargue[1]
[1] University of Alabama at Birmingham. Department of Urology, Birmingham, Alabama.

13. **Modifiers of phenotypic severity in MECP2 duplication disorder**
Cary Fu, MD, Joern-Hendrik Weitkamp, MD, Mark Boothby, MD, PhD, Sarika Peters, PhD
Vanderbilt University Medical Center

14. **Utilization of healthcare administrative databases to accurately identify cases of ANCA associated vasculitis**
Garner, S. [1], Molnar, A. [1], Massicotte-Azarniouch, D. [2], Khalidi, N. [1], Walsh, M. [1]
[1]St. Josephs Healthcare Hamilton, Ontario, Canada; [2]The Ottawa Hospital, Ottawa, Ontario, Canada.

15. **Eosinophilic Esophagitis-Like Disease with Lack of Significant Esophageal Eosinophilia: Description of a New Disease Entity**
Abstract selected for an oral presentation. There will be no poster.
Thomas Greuter[1], Margaret H. Collins[2], Christian Bussmann[3], Mirna Chehade[4], Evan S. Dellon[5], Glenn T. Furuta[6], Nirmala Gonsalves[7], Ikuo Hirano[7], Fouad J. Moawad[8], Ekaterina Safroneeva[9], Alain M. Schoepfer[10], and Alex Straumann[11]

[1]Mayo Clinic, Rochester, MN and University Hospital Zurich, Switzerland, [2]Children`s Hospital Cincinnati, OH, [3]Pathology Viollier, Basel, Switzerland, [4]Icahn School of Medicine at Mount Sinai, New York, NY, [5]UNC Hospital, Chapel Hill, NC, [6]Children's Hospital Colorado, Aurora, CO, [7]Northwestern Hospital, Chicago, IL, [8]Scripps Clinic, La Jolla, CA, [9]University of Bern, [10]University Hospital Lausanne, [11]University Hospital Zurich, Switzerland

16. **Derivation and Validation of a Novel Angiographic Classification System in Takayasu's Arteritis**
Ruchika Goel[1], K. Bates Gribbons[2], Gary S. Hoffman[3], Peter A. Merkel[4], Debashish Danda[1], Peter C. Grayson[2]
for the Vasculitis Clinical Research Consortium
[1]Department of Clinical Immunology and Rheumatology, Christian Medical College, Vellore, India, [2]Systemic Autoimmunity Branch, NIAMS, National Institutes of Health, Bethesda, MD, USA, [3]Department of Rheumatic and Immunologic Diseases, Cleveland Clinic Foundation, Cleveland, Ohio, USA, [4]Division of Rheumatology, Boston University, Boston, MA, USA

17. **Population of urinary extracellular vesicles carrying biomarkers of calcification and inflammatory cells differentiate type 1 primary hyperoxaluria patients without and with nephrocalcinosis or kidney stones**
Muthuvel Jayachandran, Sanjay Kumar, Dawn S. Milliner, and John C. Lieske On behalf of the investigators of the Rare Kidney Stone Consortium
Department of Medicine; Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN

18. **Palovarotene reduces fibro/adipogenic progenitor driven heterotopic ossification but exhibits pronounced skeletal toxicity in juvenile FOP mice**
John B. Lees-Shepard, Sarah-Anne E. Nicholas, Sean J. Stoessel, Parvathi M. Devarakonda, Michael J. Schneider, Jr., and David J. Goldhamer
Department of Molecular & Cell Biology, University of Connecticut Stem Cell Institute, University of Connecticut, Storrs, CT

19. **Promoting patient engagement in the development of patient-reported outcome measures for rare diseases**
Iyar Mazar, Samantha L. Power, Kelsey A. Bruell, Leighann Litcher-Kelly
Adelphi Values

20. **Lentiviral-vector-mediated gene therapy for metachromatic leukodystrophy decreases sulfatide accumulation in the CNS**
Stephanie K. Newman, Jai Hui Lui, Cathy Regan, Tony Rupar
Bethany's Hope Research Laboratory, Children's Health Research Institute, LHSC Victoria Hospital, 800 Commissioners Rd. E. London, ON Canada

21. **Clinicopathological correlations of ALS by motor neuron degeneration predominancy**
Takuya Ohkubo[1], Shahram Saberi[1,2], Maria Rodriguez[1], John Ravits[1]
[1]Department of Neurosciences, ALS Clinical and Translational Research, School of Medicine, University of California, San Diego, La Jolla, CA, [2]Department of Pathology, Icahn School of Medicine at Mount Sinai, New York, NY

22. **Citrin Deficiency: Assessment of the Carrier Frequency for an Underdiagnosed Urea Cycle Disorder in the US and Identification a Novel Ashkenazi Jewish Founder Variant.**
Kimihiko Oishi[1], Eri Imagawa[1], Ashley H. Birch[1], Neal Cody[1], Ruth Kornreich[1], Lisa Edelmann[1], Laran T. Jensen[2], George A. Diaz[1]
[1]Departments of Genetics & Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, [2]Department of Biochemistry, Faculty of Science, Mahidol University, Bangkok, Thailand

23. **Expanding the genetic spectrum of rare hereditary sensory and autonomic neuropathies with whole exome sequencing**
Jose-Alberto Palma MD PhD[1], Dadi Gao PhD[2], Susan A. Slaugenhaupt PhD[2], Lucy Norcliffe-Kaufmann PhD[1], and Horacio Kaufmann MD[1]
[1] Department of Neurology, Dysautonomia Center, New York University School of Medicine, NY, [2] Brigham and Women's Research Institute, Harvard Medical School, Boston, MA

24. **Lessons learned from combined and comparative data analysis of over 1,000 patients with urea cycle disorders**
Posset R[1], Garbade SF[1], Boy N[1], Burlina AB[2], Dionisi-Vici C[3], Dobbelaere D[4], Garcia-Cazorla A[5], de Lonlay P[6], Leão Teles E[7], Vara R[8], Ah Mew N[9], Batshaw ML[9], Baumgartner MR[10], McCandless SE[11], Seminara J[9], Summar ML[12], Hoffmann GF[1], Kölker S[1], Burgard P[1]; on behalf of the UCDC and the E-IMD consortium.
[1]Centre for Pediatric and Adolescent Medicine, Heidelberg, Germany, [2]Azienda Ospedaliera di Padova, Padova, Italy

[3]Ospedale Pediatrico Bambino Gésu, Rome, Italy, [4]Jeanne de Flandre Hospital, CHRU Lille, and Faculty of Medicine, University Lille 2, Lille, France, [5]Hospital San Joan de Deu, Barcelona, Spain, [6]Hôpital Necker-Enfants Malades, Paris, France [7]Hospital de S. João, Porto, Portugal, [8] Evelina Children's Hospital, London, UK, [9]Children's National Health System and The George Washington School of Medicine, Washington, USA, [10]University Children's Hospital, Zurich, Switzerland, [11]Case Western Reserve University and University Hospitals Case Medical Center, Cleveland, USA, [12]Rare Disease Institute, Children's National Health System, Washington, USA

25. Expanding the clinical spectrum of EARS2 associated mitochondrial disease

Pankaj Prasun[1] Bryn Webb[1] Kimihiko Oishi[1] Cassie Mintz[1] Hong Li[2]
[1]Ichan School of Medicine at Mount Sinai, New York, NY, [2] Department of Human Genetics, Emory University School of Medicine

26. Subglottic Stenosis and Endobronchial Disease in Granulomatosis with Polyangiitis

Abstract selected for an oral presentation. There will be no poster.

Kaitlin Quinn[1,2], Cailin Sibley[3], Alexander Gelbard[4], Arlene Sirajuddin[5], Marcela A. Ferrada[2], Marcus Chen[6], David Cuthbertson[7], Simon Carette[8], Nader A. Khalidi[9], Curry L. Koening[10], Carol Langford[11], Carol A. McAlear[12], Paul A. Monach[13], Larry W. Moreland[14], Christian Pagnoux[15], Philip Seo[16], Ulrich Specks[17], Antoine G. Sreih[12], Steven R. Ytterberg[18], Peter A. Merkel[12] and Peter C. Grayson[2], for the Vasculitis Clinical Research Consortium
[1]Division of Rheumatology, Georgetown University Hospital, Washington, DC, [2]National Institute of Arthritis, Musculoskeletal and Skin Disease, National Institutes of Health, Bethesda, MD, [3]Oregon Health & Science University, Portland, OR, [4]Vanderbilt University Medical Center, Nashville, TN, [5]National Institutes of Health, Bethesda, MD, [6]NHLBI, National Institutes of Health, Bethesda, MD, [7]Biostatistics and Informatics, University of South Florida, Tampa, FL, [8]Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, Canada, [9]Rheumatology, McMaster University, Hamilton, ON, Canada, [10] Division of Rheumatology, University of Utah, Salt Lake City, UT, [11]Department of Rheumatic and Immunologic Diseases, Cleveland Clinic, Cleveland, OH, [12]Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [13]Section of Rheumatology, Boston University, Boston, MA, [14]Division of Rheumatology, University of Pittsburgh, Pittsburgh, PA, [15]Division of Rheumatology, Mount Sinai Hospital, Toronto, ON, Canada, [16]Division of Rheumatology, Johns Hopkins University, Baltimore, MD, [17]Mayo Clinic College of Medicine, Rochester, MN, [18]Division of Rheumatology, Mayo Clinic College of Medicine, Rochester, MN

27. Targeted Inhibition of Glutamate Dehydrogenase (GDH) by Alpha-tocopherol: A Potential Novel Treatment for Hyperinsulinism/Hyperammonemia (HI/HA) Syndrome

Elizabeth Rosenfeld[1], Changhong Li[1,2], Diva D. De Leon[1,2]
[1] Division of Endocrinology and Diabetes, The Children's Hospital of Philadelphia, Philadelphia, PA, [2] Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

28. Cystine Diamides as a Novel Therapy for Cystinuria

Amrik Sahota[1], David S. Goldfarb[2], Michael D. Ward[3], Jay A. Tischfield[1], Longqin Hu[4]
[1]Dept. Genetics, Rutgers University, Piscataway, NJ; [2]Nephrology Division, NYU Langone Medical Center, New York, NY; [3]Dept. Chemistry, New York University, New York, NY; [4]Dept. Medicinal Chemistry, Ernest Mario Sch. Pharmacy, Rutgers University, Piscataway, NJ

29. Experiences of parents of patients with Severe Combined Immunodeficiency Disease (SCID) identified by newborn screening: a qualitative study

Lauren A. Sanchez MD[1], Jennie Yoo BS[2], Carolyn Rennels BS[2], Megan Murnane MSc[1], Christian Mangurian MD, MAS[3], Meghan Halley PhD[4], MAS, Morton J. Cowan MD[1], Jennifer M. Puck MD[1], and Morna J. Dorsey MD[1]
[1]UCSF Division of Pediatric Allergy, Immunology and BMT; [2]UCSF School of Medicine; [3]UCSF Department of Psychiatry, [4]Palo Alto Medical Foundation Research Institute

30. Kinase inhibitors improve neurofilament distribution in CMT2E human motor neuron axons

Abstract selected for an oral presentation. There will be no poster.

Renata Maciel[1], Igor Prufer[1], Stephan Zuchner, Mario Saporta[1] (Miami, FL)
[1]Department of Neurology, [2]Department of Human Genetics, University of Miami, Miami, FL, 33136.
****Abstract selected for an oral presentation. There will be no poster.***

31. A multi-disciplinary clinic for patients with SCN8A-related epilepsy

John M. Schreiber, Adrian Bumbut, Laura Ball, Rapeepat Thewamit, Chelsea Black, Emanuel Boutzoukas, Eleanor Fanto, Madison Berl, William D. Gaillard. Neuroscience Institute, Children's National Health System

32. Combining Knowledge and Data Driven Insights to Facilitate the Differential Diagnosis of Rare Diseases
Feichen Shen, Ph.D., Hongfang Liu, Ph.D.
Department of Health Sciences Research, Mayo Clinic, Rochester, MN, USA

33. PI3K/Akt/mTOR is a Novel Therapeutic Target in Anti-IL-6 Refractory iMCD
Dustin Shilling[1], David Fajgenbaum[1], Helen Partridge[1], Sheila Pierson[1], Amrit Singh[2], Ruth-Anne Langan[1], Jason Ruth[3], Christopher Nabel[4], Katie Stone[5], Vandana Chaturvedi[6], Mariko Okumura[1], Anthony Schwarer[7], Fábio Freire Jose[8], Nelson Hamerschlak[8], Adam Cohen[1], Vera Krymskaya[1], Arthur Rubenstein[1], Taku Kambayashi[1], Michael Jordan[6], Frits van Rhee[5], Thomas Uldrick[9]
[1]University of Pennsylvania, [2]Prevention of Organ Failure Centre of Excellence, [3]Castleman Disease Collaborative Network, [4]Dana Farber Cancer Research Institute, [5]University of Arkansas for Medical Sciences, [6]Cincinnati Children's Hospital Medical Center, [7]Eastern Health Monash University, [8]Hospital Israelita Albert Einstein, [9]Fred Hutchinson Cancer Research Center

34. Repetitive Behavior Profile of Phelan-McDermid Syndrome
Siddharth Srivastava[1], Erin Carmody[1], Rajna Filip-Dhima [2], Kush Kapur[1], Jonathan A Bernstein[3], Elizabeth Berry-Kravis[4, 5, 6], Craig Powell[7, 8], Latha Soorya[9], Audrey Thurm[10], Joseph Buxbaum[11, 12, 13, 14], Alexander Kolevzon[11, 12], and Mustafa Sahin[1,2] on behalf of Developmental Synaptopathies Consortium
[1] Department of Neurology, Boston Children's Hospital, Harvard Medical School, [2] F.M. Kirby Neurobiology Center, Boston Children's Hospital, Harvard Medical School, [3] Department of Pediatrics, Stanford University School of Medicine, [4] Department of Pediatrics, Rush University Medical Center, [5] Department of Neurological Sciences, Rush University Medical Center, [6] Department of Biochemistry, Rush University Medical Center[7] Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center
[8] Department of Psychiatry and Neuroscience Graduate Program, University of Texas Southwestern Medical Center, [9] Department of Psychiatry, Rush University Medical Center, [10] Pediatrics and Developmental Neuroscience Branch, National Institute of Mental Health, National Institutes of Health, [11] Seaver Autism Center for Research and Treatment, Mount Sinai School of Medicine, [12] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, [13] Department of Genetics and Genomic Sciences, Mount Sinai School of Medicine, [14] Department of Neuroscience, Mount Sinai School of Medicine

35. Untargeted metabolomic profiling identifies potential clinical biomarkers that may inform management of urea cycle disorders
Bridget M. Stroup,[1] Lillian Ashmore[2], Qin Sun[1], Marcus Miller[1], Sandesh CS Nagamani[1,3] William Craigen[1,3], Fernando Scaglia[1,3,4], V. Reid. Sutton[1,3], Brett Graham[1,3], Adam Kennedy[5,], Members of the Urea Cycle Disorders Consortium, Aleksandar Milosavljevic[1,2], Brendan H. Lee[1,3], Sarah H. Elsea[1], Lindsay C. Burrage[1,3]
[1]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, [2]Program in Structural and Computational Biology and Molecular Biophysics, Baylor College of Medicine, Houston, TX, [3]Texas Children's Hospital, Houston, TX, [4]BCM-CUHK Center of Medical Genetics, Prince of Wales Hospital, ShaTin, Hong Kong SAR, [5]Metabolon, Inc. Durham, NC.

36. First-in-Human Study of the Efficacy, Safety, and Tolerability of Statin Therapy of Autoimmune Pulmonary Alveolar Proteinosis
Xinlun Tian, Cormac McCarthy, Brenna Carey, Leslie Korbee, Bruce C. Trapnell
Pulmonary Translational Science Center, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

37. A Multi-Center Study of Neonatal Chest X-ray Findings in Patients with Primary Ciliary Dyskinesia
Timothy J. Vece MD[1], Eric S. Takoushian[1], Adam J. Shapiro MD[2], Thomas W. Ferkol MD[3], William B. Wheeler MD[4], Anne G. Griffiths MD[4], Maimoona Zariwala Ph.D[1], Kelli M. Sullivan MPH[1], Michael R. Knowles MD[1], and Margaret W. Leigh MD[1]
[1]University of North Carolina, [2]McGill University Health Centre Research Institute, [3]Washington University, [4]Children's Minnesota

38. *In Vivo* Studies of MARS2 Deficiency (MIM #616430)
Webb BD[1], Swaroop A[1], Sherpa M[1], Argmann C[1], Schadt EE[1], Houten SM[1].
[1]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

39. A potential role for mast cells activation and phenotype in Eosinophilic Esophagitis
Lorena Ostilla, MD; Amanda Wenzel, MD, Gregory Harpring, BS, Scott Bolton, MD, Nina Garcia; Katie Keeley; Amir F. Kagalwalla, MBBS; Barry K Wershil, MD; Joshua B. Wechsler, MD

Division of Gastroenterology, Hepatology & Nutrition. Department of Pediatrics. Ann & Robert H. Lurie Children's Hospital of Chicago. Northwestern University Feinberg School of Medicine. Chicago, IL

40. **A cross-sectional quantitative analysis of the natural history of free sialic acid storage disease**
Matthias Zielonka[1,2,3], Sven F. Garbade[1,3], Stefan Kölker[1,3], Georg F. Hoffmann[1,3], Markus Ries[1,3]
[1] Division for Pediatric Neurology and Metabolic Medicine, Center for Pediatric and Adolescent Medicine, University Hospital Heidelberg, Heidelberg, Germany [2] Heidelberg Research Center for Molecular Medicine (HRCMM), Heidelberg, Germany
[3] Center for Rare Diseases, University Hospital Heidelberg, Heidelberg, Germany

Rare Diseases Clinical Research Network Summaries

41. **Data Management and Coordinating Center Summary**
Principal Investigator: Jeffrey Krischer, PhD

42. **Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) Clinical Research Consortium**
Principal Investigators: Adam L. Boxer, MD, PhD. and Howard J. Rosen, MD

43. **Autonomic Disorders Consortium**
Principal Investigator: Italo Biaggioni, MD

44. **Brain Vascular Malformation Consortium**
Principal Investigator: Michael T. Lawton, MD; Co-PI: Helen Kim, PhD

45. **Brittle Bone Disorders Consortium**
Principal Investigator: Brendan Lee, MD, PhD

46. **Consortium of Eosinophilic Gastrointestinal Disease Researchers**
Principal Investigator: Marc Rothenberg, MD, PhD

47. **Clinical Research in ALS and related disorders for Therapy development Consortium**
Principal Investigator: Michael Benatar, MD, PhD

48. **Developmental Synaptopathies Consortium**
Principal Investigator: Mustafa Sahin, MD, PhD

49. **Dystonia Coalition**
Principal Investigator: Hyder A. Jinnah, M.D., PhD

50. **Genetic Disorders of Mucociliary Clearance Consortium**
Principal Investigator: Michael R Knowles, MD

51. **Inherited Neuropathies Consortium**
Principal Investigator: Michael Shy, MD

52. **Lysosomal Disease Network (LDN)**
Principal Investigator: Chester Whitley, MD, PhD; James C. Cloyd, PharmD; Administrative Director

53. **Nephrotic Syndrome Study Network (NEPTUNE)**
Principal Investigator: Matthias Kretzler, MD

54. **North American Mitochondrial Disease Consortium (NAMDC)**
Principal Investigator: Dr. Michio Hirano, MD

55. **Porphyrias Consortium of the Rare Diseases Clinical Research Network**
Principal Investigator: Robert J. Desnick, PhD, MD

56. **Primary Immune Deficiency Treatment Consortium (PIDTC)**
    Principal Investigator: Jennifer Puck, M.D.

57. **Rare Kidney Stone Consortium (RKSC)**
    Principal Investigator: Dawn Milliner, MD, Co-P.I. John Lieske, MD

58. **Rare Lung Diseases Consortium**
    Principal Investigator: Bruce C. Trapnell, MD

59. **Rett Syndrome, MECP2 Duplication Disorder, and Rett-related Disorder Consortium**
    Principal Investigator: Alan Percy, MD – University of Alabama at Birmingham
    Study Administrator and Co-PI: Jeffrey Neul, MD, PhD – Vanderbilt University
    Project Manager: Jane Lane, RN BSN – University of Alabama at Birmingham

60. **Sterol and Isoprenoid Research Consortium** (**STAIR)**
    Principal Investigator: William B.Rizzo, M.D.

61. **Urea Cycle Disorders Consortium (UCDC)**
    Principal Investigator: Andrea Gropman, M.D

62. **Vasculitis Clinical Research Consortium (VCRC)**
    Principal Investigator: Peter A. Merkel, MD, MPH

1. Developmental outcomes of Aicardi Goutières Syndrome

Laura Adang*[1], Francesco Gavazzi*[1, 2], Julia Kramer-Golinkoff[1], Elisa Fazzi[4, 7], Jessica Galli[4, 5], Jamie Koh[1], Kyle Peer[1], Simona Orcesi[3], Nicole Ulrick[1], Sarah Woidill[1], Justine Shults**, and Adeline Vanderver**[1]

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Objective: A mimic of congenital infections and a rare genetic cause of interferon (IFN) overproduction, Aicardi Goutières Syndrome (AGS) results in significant neurologic disability. AGS is caused by pathogenic changes in the intracellular nucleic acid sensing machinery (*TREX1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, ADAR1,* and *IFIH1*). This triggers an endogenous IFN response that results in extensive end organ damage. While the systemic inflammation has variable effects throughout the body, all reported individuals exhibit some degree of motor and/or cognitive impairment. This can vary from mild spastic paraparesis to severe global developmental delay. We hypothesize that genotype influences the heterogeneous developmental trajectory found in AGS, but that even within a genotypic cohort, there will be significant variation.

Methods: To better characterize this spectrum, longitudinal developmental skill acquisition was collected from an international cohort of children (n=86) with genetically confirmed AGS.

Results: By creating Kaplan-Meier curves for developmental milestones, we were able to create genotype-based developmental trajectories for the children affected by the four most common genotypes, *TREX1, IFIH1, ADAR,* and *RNASEH2B*. While all individuals demonstrated delayed milestones, individuals with AGS secondary to *IFIH1* and *ADAR* pathogenic variants were less affected compared to *RNASEH2B* and *TREX1*.

Conclusions: Our results demonstrate the influence of genotype on early development, but also suggest other unidentified variables are important in overall course. These results underscore the importance of deep phenotyping to better characterize subcohorts within the AGS population. With a better understanding of the natural history of disease, we will be able to better counsel families and to design therapeutic trials with more appropriate clinical endpoints.

2. Familial LCAT Deficiency: Searching for Biomarkers to Assess Treatment Efficacy

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Objective. Familial LCAT Deficiency (FLD) is a rare disease caused by loss of function mutations in the gene for LCAT, an enzyme that esterifies free cholesterol in plasma. FLD patients experience high morbidity and mortality from renal complications. Fish Eye Disease (FED) is also caused by mutations in LCAT, but LCAT activity is not completely absent and patients typically do not develop renal disease. This suggests that partial restoration of LCAT activity may improve outcomes in FLD and an AAV-vector expressing LCAT has shown feasibility in mouse-models. However, current knowledge of LCAT deficiency is limited, hampering development of therapies in humans. The objectives of this study were to review existing literature to define the natural history of LCAT deficiency, and to identify prognostic biomarkers that can be used to monitor disease progression and assess efficacy of potential novel therapeutic strategies.

Methods. PubMed was searched for all reports describing LCAT deficiency published by mid-2017.

Results. There were 100 publications from 1978-2017 describing a total of 88 unique cases of FLD (69% male) and 33 of FED (61% male). Average age at publication was 39±15 years for FLD, and 49.3±17.7 years for FED. Corneal opacity was present in all FLD (n=41) and FED cases (n=14) when described. Anemia was present in 79/85 (93%) of FLD cases and 4/28 (14%) of FED cases. Proteinuria was present in 72/86 (84%) FLD cases and 2/32 (6%) FED cases. FLD and FED patients both had significantly lower HDL and apolipoprotein A-I levels compared to controls. Markers of cholesterol esterification were significantly more impaired in FLD compared to FED subjects. Mean LCAT activity in FLD patients was 2.28±4.74 nmol/mL/h compared to 25.2±21.5 nmol/mL/h in FED patients ($p<0.001$). The mean percentage of esterified cholesterol was 26.6±24.7% in FLD patients and 70.0±9.0% in FED patients ($p<0.001$).

Conclusions. Biomarkers of cholesterol esterification differ significantly between FLD and FED patients. Among the available biomarkers, the percentage of esterified cholesterol is easy to measure and directly correlated with LCAT activity thus representing a potentially suitable biomarker for monitoring disease progression and efficacy of treatment.

3. Clinical, biochemical and genetic features of patients with mitochondrial diseases: Data from the North American Mitochondrial Disease Consortium (NAMDC) registry

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Objective: Mitochondrial diseases are rare but devastating disorders. The North America Mitochondrial Disease Consortium (NAMDC) Registry provides data, which can help to improve standard of care and prepare for clinical trials. This work describe clinical, biochemical and genetic characteristics of patients with mitochondrial diseases enrolled in the NAMDC Registry.

Methods: This cross-sectional study evaluates the characteristics of patients enrolled in the NAMDC Registry from September 2011. Patient awere enrolled in 16 NAMDC sites in United States and Canada. To enroll in the Registry, patients had to visit an experienced clinician at a NAMDC site for a review of medical history, physical examination, laboratory tests, and provision of consent. Clinical, molecular and biochemical data were recorded. Clinical diagnosis used uniform diagnostic criteria across centers. Manifestations, laboratory results, and genetic data were collected for all patients.

Results: 995 out of 1029 participants had sufficient data for analysis. Age at onset ranged from infancy to adulthood. The majority of the patients had a non-canonical syndrome diagnosis; the most common diagnosis was multi-systemic disorder (200 subjects). The most frequent canonical syndromes diagnosed were mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) (60 patients); and Leigh Syndrome (99 patients). Five hundred and seventy-five subjects (56%) had a molecular diagnosis, with higher prevalence of pathogenic variants in mitochondrial DNA.

Conclusions: The NAMDC Registry data show the high variability of clinical, biochemical, and genetic features of patients with mitochondrial diseases. The application of uniform diagnostic criteria demonstrates that a large number of patients do not satisfy the diagnostic criteria for a canonical syndrome. This study provides the first description of mitochondrial disease patients in North America based upon consistent and current diagnostic criteria.

4. Emotional responses, stressors and coping strategies for parents of children with Zellweger spectrum disorder (ZSD).

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Objective: Zellweger spectrum disorders (ZSDs) are debilitating disorders of peroxisome biogenesis. The impact of ZSD on the caregiver is unknown. Our study sought to describe the overall emotional experience and coping strategies for ZSD caregivers.

Method: We conducted ZSD caregiver focus groups stratified for patient age. Focus group responses were collected via verbatim transcription and session notes, and data were analyzed qualitatively by tabulation of thematic responses.

Results: Thirty-seven ZSD caregivers (25 mothers and 12 fathers) participated in the study. Thirty-three participants had one affected child and 4 had two affected children. Three major themes emerged to describe the ZSD caregiver emotional experience: 1) range of emotions, 2) stressors contributing to emotions, and 3) coping strategies. Nearly a third of parents described their experience as a rollercoaster, referring to emotional responses changing rapidly throughout their caregiving experience. Feeling overwhelmed and devastated were the most frequently described emotions, as well as guilt and fear. The most common stressors included the burden of ZSD caregiver associated tasks, and negative interactions with health care providers. Typical coping strategies included acceptance of limitations of the disease and advocating on behalf of the ZSD patient community for optimal care.

Conclusion: This is the first study to characterize the impact of ZSD encompassing the whole family that demonstrates how different elements of the caregiver emotional experience were interrelated, while pinpointing potential intervention areas for caregivers that might improve their emotional experience and quality of life. For example, feelings of anger, frustration, and confusion (emotions) related to negative interactions with health care providers (stressors) were addressed by taking an active role in their child's care (coping strategy). Our findings echo studies among other rare pediatric disease caregivers, suggesting that the neglected rare disease caregiver experience is an important public health concern. Based on our findings, we urge clinicians, educators, and policymakers involved in rare pediatric diseases to better incorporate the experience of the caregiver in guiding care, budgeting for appropriate resources, and developing support networks.

5. Somatostatin Receptor-Targeted Imaging for Detection of Cardiac Sarcoidosis

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Objective: Gallium-68 Dotatate binds preferentially to somatostatin receptor subtype-2 (sstr-2) on neuroendocrine tumors and inflammatory cells. We aimed at investigating the potential clinical use of sstr-targeted imaging for the detection of myocardial inflammation in patients with suspected cardiac sarcoidosis (CS).

Methods: 13 patients with suspected CS based on clinical history and myocardial uptake on recent fluorine-18 fluorodeoxyglucose (FDG) PET, were prospectively enrolled to undergo Dotatate PET/CT after FDG (median time 37 days [IQR 25 – 55]). Additionally, we investigated ex-vivo the immunohistochemistry expression of sstr-2 in 6 explanted sarcoid hearts.

Results: All FDG scans showed cardiac uptake (focal/multifocal = 6, focal on diffuse/heterogeneous = 7), and 46% (n=6) extra-cardiac uptake (mediastinal/hilar). In comparison, Dotatate scans showed definite abnormal cardiac uptake (focal/multifocal) in 4 patients, equivocal (heterogenous/patchy) in 3, and negative uptake in 6 cases. Similarly, 6 patients had increased mediastinal/hilar Dotatate uptake. Overall concordance of FDG and Dotatate uptake was 54% in the heart and 100% for thoracic nodal activity. Quantitatively, FDG maximum standardized uptake value was 5.0 [3.8 – 7.1] higher in the heart, but only 2.25 [1.7 – 3.0; P=0.019] higher in thoracic nodes relative to Dotatate. Ex-vivo, sstr-2 immunostaining was seen within well-formed granulomas in all of the examined sarcoid heart specimens with no staining of normal myocardium.

Conclusion: Our data suggests that mechanisms other than inflammation may be contributing to FDG accumulation in the heart. Somatostatin receptor-targeted imaging may be an alternative approach to FDG imaging for the detection of myocardial inflammation.

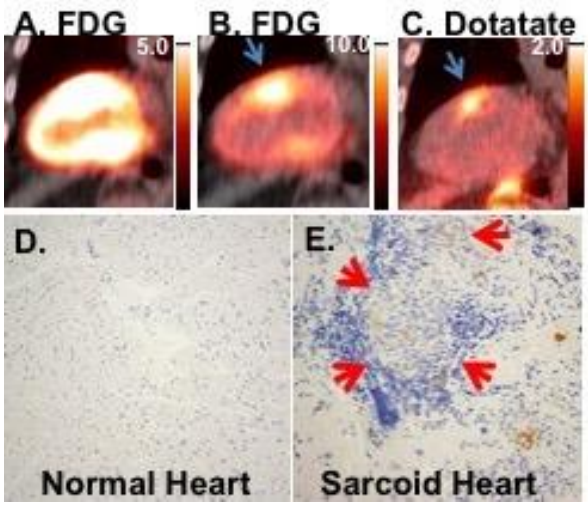

Figure. A-C. Case of focal on diffuse FDG activity matching LV Dotatate uptake on PET/CT. **A.** Intense FDG uptake is seen diffusely in the entire LV at the default SUV window threshold. **B.** However, a hint of focal FDG uptake in the anterior wall (arrow) is only evident when the PET window is widened. **C.** In contrast, Dotatate clearly shows focal uptake in the anterior wall (arrow). **D-E.** Expression of somatostatin receptor subtype-2 by immunohistochemistry. No staining is seen in normal myocardium (D), whereas, weak to moderate brown staining is seen within well-formed granulomas (arrows) in a sarcoid heart specimen (E). (Original magnification X100 for D, 200X for E)

6. Enhancing Adult Education in Rare Disease Training with the Inclusion of Interactive Sessions within Standard Curriculum

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Objective: Due to the enormous breadth of rare diseases, unique education strategies are essential to prepare clinicians, researchers, nurses, students, and other health care professionals on how to diagnose, treat, or manage patients with rare diseases. This is a tough goal for trainees who have only received little, informal training about rare diseases, especially if they are uninterested in the matter or believe they are unlikely to come in contact with patients with rare diseases. By introducing an interactive style of education, we propose that our teaching effectiveness increases and we are able to improve the abilities of students to be proactive learners.

Methods: For the 2017-18 year, 4 different learning styles were developed for residents and fellows to learn about genetic disease and techniques. The 4 learning styles are as follows: (1) The Money game (teaching genetic testing technologies and use for specific diagnosis (2) Genetic Pictionary (rare disease disorders taught through cases and creation of a picture memory tool) (3) Neonatal Body Parts (3 pictures of a unique rare disease findings in neonates and discussion of unique required clinical approaches) (4) Draw the Pathways: an interactive session with on-line reinforcement (i.e. real time and YouTube video follow-up resource). We collected feedback on each session to understand the effectiveness and how well received it was by the learners.

Results: Residents and fellows increased their confidence in diagnosing rare diseases, understanding the most cost effective genetic test to order in certain situations, and managing certain genetic or metabolic disorders in general. Learners reported increased engagement, interest, and knowledge retention based on feedback gathered from surveys given out after the sessions.

Conclusion: Overall, the introduction and inclusion of more interactive sessions within our curriculum has increased learners' confidence with rare diseases. Further studies are needed to determine if these introductions will improve learner's ability to communicate with others in the medical fields, encourage genetic and genomic research, and/or improve recruitment to the field of genetics.

7. SLC26A3 (DRA) Inhibitor Identified in Small Molecule Screen Blocks Colonic Fluid Absorption and Treats Constipation in Cystic Fibrosis Mice

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Objective: Gastrointestinal (GI) problems are common in Cystic Fibrosis (CF), including constipation, meconium ileus and distal intestinal obstruction syndrome. Impaired CFTR-mediated intestinal chloride secretion is thought to cause these problems. CF-associated constipation is often refractory to dietary modification and laxatives. Here, we report a novel target for drug therapy of GI problems in CF – SLC26A3 (down-regulated in adenoma, DRA), a chloride/anion (bicarbonate, oxalate) exchanger expressed in the luminal membrane of intestinal epithelial cells. *SLC26A3* loss of function in humans or mice causes chloride-losing diarrhea, and also reduces serum and urine oxalate levels, as DRA facilitates intestinal oxalate update. The objective of this study was to identify SLC26A3 inhibitors by high-throughput screening as novel tools to investigate intestinal fluid and oxalate absorption mechanisms, and as potential first-in-class drug candidates for anti-absorptive therapy of constipation and primary hyperoxalurias.

Methods: A screen of 50,000 synthetic small molecules was done in FRT cells co-expressing murine SLC26A3 and a yellow fluorescent protein halide sensor, followed by structure-activity studies on analogs of active compounds. After establishing pharmacokinetic profile, a potential lead compound was tested for efficacy in mouse models of intestinal fluid/oxalate absorption and loperamide-induced constipation.

Results: The 4,8-dimethylcoumarin DRA_{inh}-A250 fully and reversibly inhibited SLC26A3-mediated chloride / anion exchange with IC_{50} down to 150 nM. DRA_{inh}-A250 at 10 µM was selective for SLC26A3, as it did not inhibit the homologous anion exchangers SCL26A4 (pendrin), SLC26A6 (PAT-1) or SLC26A9, nor did it affect other chloride channels and intestinal ion transporters. Single dose oral administration of DRA_{inh}-A250 yielded predicted therapeutic serum levels for more than 6 hours. In mice, intraluminal DRA_{inh}-A250 fully blocked fluid absorption in closed distal colonic loops, and oral DRA_{inh}-A250 prevented loperamide-induced reductions in stool weight, number of pellets and stool water content in wild-type and CF mice. In preliminary experiments, DRA_{inh}-A250 prevented the elevation in serum oxalate levels in mice after an oral oxalate load.

Conclusions: These studies support a major role of SLC26A3 in gastrointestinal fluid and oxalate absorption, and suggest the therapeutic utility of SLC26A3 inhibition in CF-associated constipation, as well as primary hyperoxalurias.

8. Symptom Burden within One Year Differentiates Rapidly Progressive Multiple System Atrophy

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Objective: Median survival time in multiple system atrophy (MSA) is around 7.5 years however; some patients have a rapidly progressive course. Demographic and clinical features differentiating rapidly progressive MSA are uncertain. We sought to evaluate demographic and clinical features which may differentiate multiple system atrophy patients who have a rapidly progressive disease course.

Methods: We performed a retrospective review of all patients diagnosed with MSA between 1998 and 2012 with objective autonomic function testing. Living patients were called to assess development of symptoms. Survival data was obtained from the clinical record and social security data base. Short duration MSA patients were defined as those less than the 5th percentile of overall disease duration in the entire cohort. Patients lost to follow-up or with unknown death date were excluded.

Results: Of 669 MSA patients included in the survival analysis, 33 patients were short duration of disease patients with survival ranging from 1.13 to 3.21 years. When comparing short duration patients to the main cohort, there were no significant demographic or clinical differences at the time of assessment, when adjusting for multiple comparisons. However, when focusing on the first year of symptom onset, short duration patients were more likely to have motor symptoms ($p = 0.0002$), falls ($p = 0.0007$), orthostatic intolerance ($p = 0.0001$) and bladder symptoms ($p < 0.0001$). Odds ratios for short duration of MSA with development of specific symptoms within one year of onset were: bladder symptoms 5.41, orthostatic intolerance 4.04, and falls 3.42. Clinical features were often coexistent with short duration MSA patients having a median of 3 of the 4 factors compared to the main cohort exhibiting 2 of the 4 features ($p < 0.0001$).

Conclusions: Our data suggests that demographic and baseline clinical features do not readily differentiate MSA patients with short duration of disease; however, symptom burden within one year from the onset of symptoms may be indicative of rapid progression to death.

9. Natural History Study of Succinic Semialdehyde Dehydrogenase (SSADH) Deficiency

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Objective: SSADH deficiency has protean neurological manifestations but the natural history is unknown. Adult reports indicate worsening epilepsy and high SUDEP risk. We describe data from our registry, and preliminary data from a longitudinal study.

Methods: Patients from a REDCap SSADH registry are surveyed every six months. Measures are from the MACS (manual ability), GMFCS (gross motor), ABAS (adaptive behavior), and a QOL inventory that monitors patient and caregiver.

Results: There are 128 registered subjects (age range 8 wks – 63 yrs, median 7.75 yrs; 45%M); 48 have entered the longitudinal study. Motor impairments, speech delay, and intellectual disability are universal symptoms. Subjects in the 12+ group have a significantly higher proportion of compulsive behavior, sleep disturbances, and seizures. Conversely, a smaller proportion have hypotonia. Epilepsy affects half overall: ~70% (33/48) 12+ years vs 40% (31/80) <12 years (p=0.001). In the longitudinal cohort, active epilepsy (>2 seizures/yr) increases with age: 60% (16/28) 12+ years and 20% (4/20) <12 years (p=0.013). Nearly half (48%) have mild-to-moderate (level II) fine motor impairment. Nearly 1/5 of patients over 6y had moderate-severe gross motor impairment requiring a mobility device. Four adults experienced SUDEP, at ages 63, 33, mid-20s, and 19 yrs. The overwhelming majority of caregivers report considerable strain with 13% reporting depression.

Conclusions: A longitudinal study of SSADH deficiency discloses high levels of motor and QOL impairment across all age groups and worsening of epilepsy with apparent increased SUDEP with age. This natural history study will be augmented by neurophysiologic studies (EEG, TMS), imaging including GABA measurement, and metabolites. Burden of disease on patients and caregivers is high and will be followed. There appear to be age-related changes which may correlate with changes in GABA and GHB measurements over the life span.

10. ApoM is downregulated in an experimental model of Alport syndrome and may contribute to the pathogenesis of proteinuria in glomerular diseases

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Objective. Lipid-induced kidney injury has been observed in experimental models of non-metabolic glomerular diseases, including Alport syndrome (AS) and FSGS. Dysregulation of glomerular lipid metabolism is hypothesized to contribute to disease pathogenesis. Glomerular expression of ApoM, a protein thought to be a key modulator of lipid metabolism, has been found to be downregulated in an experimental model of AS and in patients with FSGS enrolled in the NEPTUNE study. We tested the hypothesis that decreased ApoM expression contributes to the pathogenesis of proteinuric glomerular diseases.

Methods. Glomerular Apom gene expression was determined by RT-PCR on isolated glomeruli of Col4a3 knockout (KO) mice (a mouse model of AS) at 8 weeks of age, when progression to renal failure had occurred. Col4a3 KO mice were treated with human recombinant APOM protein (rh-APOM) administered by weekly intraperitoneal injection starting at four weeks of age, when proteinuria and altered renal function start to manifest. Body weight and albuminuria were monitored weekly starting at 4 weeks of age. APOM protein concentrations in serum and urine were determined using ELISA at time of sacrifice.

Results. Glomerular Apom gene expression is markedly reduced ($p<0.01$) in Col4a3 KO mice when compared to wild type (WT). While glomerular APOM protein levels are decreased ($p<0.05$) in KO mice compared with WT, serum and urine levels of APOM are significantly increased ($p<0.05$ and $p<0.001$, respectively) compared with WT. Treatment with rh-APOM normalizes APOM protein levels in serum and urine. Treatment with rh-APOM results in a significant reduction in the urinary albumin/creatinine ratio, serum BUN, and serum creatinine levels ($p<0.01$ for all) compared with untreated AS mice. Rh-APOM also prevents weight loss ($p<0.01$) and protects from development of glomerulosclerosis and tubular atrophy and dilation.

Conclusions. Glomerular ApoM expression is reduced in experimental models of AS. Treatment with rh-APOM normalizes serum and urine APOM levels, results in improved clinical and pathologic parameters, and protects from renal failure. Further studies are needed to understand if decreased ApoM expression may represent a new biomarker and therapeutic target for proteinuric glomerular diseases.

11. Development of diagnostic criteria to facilitate research in mitochondrial disorders: A proposal from the North American Mitochondrial Disease Consortium

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Objective : To develop updated research diagnostic criteria for primary mitochondrial disorders.

Methods: The North American Mitochondrial Disease Consortium (NAMDC) established a Diagnostic Criteria Committee. Comprised of members with diverse expertise, the panel included: clinicians, researchers, diagnostic laboratory directors, statisticians and data managers. The committee conducted a comprehensive review of literature, evaluation of current clinical practices, diagnostic modalities, surveys, and teleconferences to reach a consensus in order to establish and validate diagnostic criteria for mitochondrial disease. Greater emphasis was placed on the molecular genetic criteria for the diagnosis of mitochondrial diseases. Refinement of the existing diagnostic criteria was achieved after manual application of the criteria to patients enrolled in the NAMDC registry.

Results: The Diagnostic Criteria Committee generated consensus criteria for the clinical definition of canonical and non-canonical mitochondrial syndromes and for achieving the level of certainty (definite, suspected, and unlikely) in the diagnosis of mitochondrial diseases.

Conclusions: Mitochondrial diseases are clinically, biochemically, and genetically heterogeneous and therefore challenging to classify and diagnose. Since the publication of the original mitochondrial disease diagnostic criteria more than 10 years ago, there has been an explosion of phenotypic and genotypic data including identification of numerous novel molecular genetic defects. To incorporate this new information, and to harmonize diagnostic criteria and terminology, NAMDC has generated updated research diagnostic criteria for mitochondrial diseases. The NAMDC Research Diagnostic criteria will be very helpful to confirm or exclude mitochondrial disease diagnoses, and improve enrollment in future natural history studies and clinical trials.

12. Contribution of glycolate metabolism to endogenous synthesis of oxalate

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Objective. Primary hyperoxalurias (PH) are rare inherited metabolic diseases causing excessive endogenous oxalate synthesis. PH manifest as severe recurrent calcium oxalate kidney stones leading to kidney failure with limited therapeutic options. The contribution of different precursors to endogenous oxalate synthesis has only been determined for 60-70% of urinary oxalate. Glycolate, a precursor of oxalate, is expected to play a major role in PH type 1, but the amount of its contribution to urinary oxalate remains to be established.

Methods. The stable isotope tracer $^{13}C_2$-glycolate was administered orally at 2 doses in a healthy subject in the fasted state, after 3 days of controlled diet. Serial urine and blood samples were taken over 24h. $^{13}C_2$- and $^{12}C_2$-oxalate and glycolate were measured using ion chromatography coupled with mass spectrometry.

Results. Glycolate was rapidly absorbed and metabolized. Urinary enrichment with $^{13}C_2$-glycolate and $^{13}C_2$-oxalate were detected until 8h post-load, plasma enrichment with $^{13}C_2$-glycolate until 6h post-load. The estimated contribution of glycolate to urinary oxalate was 13%.

Conclusion. The preliminary results demonstrate the feasability of the oral tracer dosing as a method to determine the contribution of glycolate to endogenous oxalate synthesis. This new approach will be evaluated against the gold-standard primed, steady state, infusion of $^{13}C_2$-glycolate tracer in a larger cohort of healthy subjects. Other metabolic pathways of oxalate synthesis remain be identified.

13. Modifiers of phenotypic severity in MECP2 duplication disorder

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Objective: MECP2 duplication disorder (MDD) is a rare, progressive neurodevelopmental disorder caused by interstitial chromosomal duplications at Xq28 encompassing the *MECP2* gene. Affecting primarily males, MDD is associated with hypotonia, cognitive and motor delays, epilepsy, and frequent respiratory infections. A significant proportion of affected children also experience developmental regression during childhood. There is much inter-patient variability in symptom severity, the causes of which are not well-defined. Clinical trials to test emerging disease-modifying therapies will require a better understanding of these symptom modifiers. Inter-patient differences in duplication breakpoints lead to differences in duplicated gene content that could alter phenotype. Additionally, reports of dysregulated immune function in MDD offer a potentially quantifiable predictor of severity and/or regression. *We aim to 1) determine the impact of duplication gene content on MDD phenotypic severity, and 2) identify immune biomarkers predictive of MDD severity and/or regression.*

Methods: 1) Retrospective, cross-sectional analysis of MDD clinical severity and duplication gene content: We assessed phenotypic severity based on the Clinical Severity Score (CSS), a standardized measure of severity in MDD and other Rett-related disorders. We determined gene content of duplications based on genomic boundaries reported on chromosomal microarray results. 2) Prospective analysis of MDD clinical and immunological phenotype: We isolated peripheral blood mononuclear cells from whole blood specimens from MDD patients and controls for immunophenotyping analysis by mass cytology and assessed for regression by telephone interviews at regular intervals.

Results: 32 individuals (27 male, 5 female) were included in the analysis of gene content. Independent of duplication length, presence of the *RAB39B* gene in the duplicated region was associated with higher CSS scores. 24 blood samples from 15 individuals (11 male, 4 female) have been immunophenotyped thus far. Preliminary immunophenotyping results extend published reports of lower memory and elevated naïve T-cells counts, and reveal increased production of pro-inflammatory T-cell subtypes in MDD compared to non-MDD controls.

Conclusions: Inclusion of *RAB39B* within the duplication boundaries of MDD is associated with worse overall disease severity as measured by the CSS. The independent contribution of *RAB39B* to MDD phenotype suggests additional disease mechanisms that will need to be considered when designing and testing therapies. The potential altered immunophenotype in MDD could impact disease severity as well as serve as an easily quantifiable biomarker of disease progression.

14. Utilization of healthcare administrative databases to accurately identify cases of ANCA associated vasculitis

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Objective: ANCA-associated vasculitis (AAV) is a group of diseases that include granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA). These rare multisystem autoimmune diseases are difficult to study. Large healthcare administrative databases provide a unique opportunity to study AAV. In Ontario, Canada there is a single provincial healthcare database that contains records of over ten million people. Local hospitals code patients using ICD10 and upload data to this provincial system. To date there has been no validation of the ICD10 coding that is done at the local level. Our objective was to validate local coding to determine if searching the provincial system by ICD10 code would result in patients being identified correctly.

Methods: Validation at hospital level was done by searching Hamilton Health Sciences and St. Joseph's Healthcare administrative databases from 2011 to 2017. The databases were searched using the following ICD 10 disease codes: AAV (GPA, MPA or eGPA), arteriitis, polyarthritis nodosa, giant cell arteritits, and nephritis. Chart review was completed to confirm or refute the diagnosis of AAV using the American College of Rheumatology classification criteria and/or the revised International Chapel Hill Consensus Conference criteria and/or the European classification system for ANCA Associated Vasculitis.

Results: A search of the two hospital databases led to 554 patients being identified. Of the 554, 207 patients were coded as having AAV (GPA n=176, MPA n=11, and eGPA n=20). The remainder were coded as arteritis unclassified (n=262), PAN (n=26), necrotizing vasculitis (n=2), nephritis (n=56). In the sample, 354 (64%) of patients had AAV. Patients who were incorrectly coded were most commonly coded as arteritis (39%). The sensitivity and specificity of the coding was found to be 53% and 94% respectively. When broken down by disease the results were as follows:

Disease	Sensitivity	Specificity	Positive Predictive Value
GPA	80.7% (CI 74.5-86.0%)	96.5% (CI 93.9-98.2%)	93.0% (CI 88.3-95.9%)
MPA	6.9% (CI 3.4-12.3%)	99.7% (CI 98.5-99.9%)	90.9% (CI 56.4-98.8%)
eGPA	91.7% (CI 61.5-99.8%)	98.5% (CI 97.0-99.3%)	57.9% (CI 40.4%-73.6)

When ANCA testing was added to the ICD coding, the sensitivity of the algorithm improved significantly.

Conclusions: Our results show that the specificity of the ICD10 coding for AAV is quite high. The sensitivity however is quite low, particular for identifying patients with MPA. Adding ANCA testing to the ICD10 coding improved this.

15. Eosinophilic Esophagitis-Like Disease with Lack of Significant Esophageal Eosinophilia: Description of a New Disease Entity

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Objectives: Observation of an eosinophilic esophagitis-like (EoE) disease with typical symptoms and endoscopic findings, but eosinophil-free biopsies has questioned the role of eosinophils (eos) in EoE pathogenesis. The purpose of this study was to determine the clinical, endoscopic and histological features of patients with chronic EoE symptoms, but less than 15 eos per hpf.

Methods: Patients with typical EoE-symptoms of esophageal dysfunction, but a peak eos count of <60/mm^2 (<15/hpf), from 6 tertiary EoE-centers were included. All biopsies were re-examined by 2 reference pathologists in a blind manner.

Results: We analyzed 61 patients (mean age at diagnosis 49.4y±19.9, median diagnostic delay 2.1y (IQR 1-6), 54.1% females). Median follow-up was 10.5 months (IQR 2.2-32.2) with 3 visits per patient (IQR 2-4). Family history for EoE was positive in 24.6% and 41% had atopic comorbidities. Esophageal biopsies were re-classified as EoE with low-grade eosinophilia (1-14 eos/hpf, 26 patients), EoE without eosinophilia (9 patients), lymphocytic esophagitis (11 patients), and non-specific esophagitis (15 patients). 60 patients reported dysphagia, while the only child (<12y) suffered from food refusal and failure to thrive. Endoscopic disease activity was seen in 52.5%. The leading endoscopic findings were: rings (37.7%), edema (32.8%), strictures (32.8%), white exudates (9.8%) and furrows (11.5%). In 27 patients, histological subtype changed over time (4 patients with >2 different subtypes). In 7 patients conventional EoE developed after 11.6 months (IQR 3.4-63.0). Presence of conventional EoE increased over time (10% after 1y, 15% after 3y and 45% after 6y). 39 patients were treated with swallowed topical corticosteroids resulting in symptom relief in 87.2%. Endoscopic dilation was needed in 24 patients (39.3%).

Conclusions: EoE-like disease, a condition that clinically resembles EoE, but lacks significant tissue eosinophilia, is a new entity regularly seen at major EoE-centers. Despite the absence of significant eosinophilia, considerable clinical and endoscopic activity can be observed. The condition may precede conventional EoE.

16. Derivation and Validation of a Novel Angiographic Classification System in Takayasu's Arteritis

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Objective: Takayasu's arteritis (TAK) is characterized by variable patterns of damage throughout the large arteries.

Methods: Data was used from patients with TAK from four independent cohorts: one in India and three in North America (NA). All patients underwent whole-body angiography of the aorta and branch vessels, with categorization of involvement (stenosis, occlusion, or aneurysm) in 13 arterial territories. K-means cluster analysis was performed to identify subgroups of patients based on pattern of angiographic involvement.

Results: 581 and 225 patients with TAK were included from the Indian and NA cohorts, respectively. Three distinct clusters were identified in the Indian cohort and validated in the NA cohorts. Patients in Cluster 1 had significantly more disease in the abdominal aorta, renal, and mesenteric arteries ($p<0.01$). Patients in Cluster 2 had significantly more bilateral disease in the carotid and subclavian arteries ($p<0.01$). Compared to Clusters 1 and 2, patients in Cluster 3 had asymmetric disease with fewer involved territories ($p<0.01$). In the Indian and the NA cohorts, patients in Clusters 1 and 2 compared to Cluster 3 were more likely to have a history of tuberculosis (8% vs 10% vs 3%; $p=0.03$). Disease onset in childhood (28% vs 16% vs 19%; $p<0.01$) and hypertension (71% vs 42% vs 39%; $p<0.01$) were more common in Cluster 1. Stroke (0% vs 22% vs 5%; $p=0.03$), carotidynia (3% vs 26% vs 9%; $p=0.01$) and persistent disease activity (46% vs 59% vs 44%; $p=0.02$) were significantly more prevalent in Cluster 2.

Conclusions: This large study in TAK identified and validated three novel subsets of patients based on patterns of arterial disease. Angiographic-based disease classification may help identify causal disease factors and enable stratified clinical decision making in this complex, clinically heterogeneous disease.

17. Population of urinary extracellular vesicles carrying biomarkers of calcification and inflammatory cells differentiate type 1 primary hyperoxaluria patients without and with nephrocalcinosis or kidney stones

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Objective: Renal cells involved in pathophysiological processes shed membrane sealed extracellular vesicles (EVs) into urine. Recent studies confirm that populations of urinary EVs can reflect kidney health and disease. This study was designed to determine whether urinary EVs carrying biomarkers of pathological calcification and inflammation differentiate type 1 primary hyperoxaluria (PH1) patients with nephrocalcinosis, kidney stones or neither disease.

Methods: Rare Kidney Stone Consortium bio-banked cell-free urine from PH1 patients without (n=10) and with nephrocalcinosis (n=6) or kidney stones (n=9) were studied. All selected patients had an eGFR > 40 ml/min/1.73m^2 and no prior kidney or liver transplantation. EVs expressing biomarkers for renal calcium and phosphate pathway regulators (phosphate transporter -1 (Pit-1)/Pit-2 , Klotho/fibroblast growth factor 23(FGF23)), vesicle generation (anoctamin-4 (ANO4) and Huntingtin interacting protein 1(HIP1)) and inflammatory cells (total leukocytes, neutrophils, monocytes, macrophages, T-/B-lymphocytes and plasma cells were all quantified by digital flow cytometry. Urinary EVs were normalized per mg creatinine. Statistical significance ($P<0.05$) was evaluated by the Wilcoxon rank sum test.

Results: The total number of EVs expressing Pit-1, klotho, FGF23, ANO4, and EVs derived from total leukocytes, macrophages, and lymphocytes were significantly ($P<0.05$) lower in PH1 patients with stones compared to PH1 patients without stones and nephrocalcinosis. EVs expressing ANO4, HIP-1, and EVs derived from total leukocytes, monocytes and macrophages were significantly ($P<0.05$) lower in PH1 with stones compared to PH1 patients with nephrocalcinosis. There was a trend toward an increase in EVs expressing ANO4, monocytes, macrophages, B-lymphocytes, and plasma cells biomarkers in PH1 patients with nephrocalcinosis compared to PH1 patients without nephrocalcinosis or stones.

Conclusion: EVs in the urine of PH1 patients expressing specific biomarkers of pathological calcification and from specific inflammatory cells reflect nephrocalcinosis and stone status. The mechanism(s) whereby EV-associated biomarkers influence kidney stone pathogenesis, or reflect underlying pathogenic events, warrants further study.

18. Palovarotene reduces fibro/adipogenic progenitor driven heterotopic ossification but exhibits pronounced skeletal toxicity in juvenile FOP mice

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Objective: Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disorder characterized by disabling heterotopic ossification (HO) of skeletal muscles, tendons, and ligaments. The vast majority of cases are caused by a single amino acid substitution in the type I bone morphogenetic protein receptor ACVR1[ACVR1(R206H)], which enables activation of canonical bone morphogenetic protein signaling by activin ligands. We have recently demonstrated that expression of ACVR1(R206H) in fibro/adipogenic progenitors (R206H-FAPs) is sufficient to replicate the full spectrum of HO pathogenesis in FOP mice. Although the retinoic acid receptor gamma (RARγ) agonist palovarotene and antibody-meditated sequestration of activin A have both entered clinical trials for FOP, how these drugs modulate R206H-FAP behavior is unclear.

Methods: Live-animal luminescence imaging was used to evaluate population growth of transplanted R206H-FAPs, and chondrogenesis was evaluated via 2D micromass culture. To evaluate the safety and efficacy of palovarotene, juvenile FOP mice received daily administration of palovarotene or vehicle alone from P14 to P41.

Results: R206H-FAPs undergo rapid expansion prior to differentiation and peak population growth is strongly correlated with final HO volume. Notably, activin inhibition restores wild-type population dynamics to transplanted R206H-FAPs. Palovarotene is less effective at blocking pathogenic population growth, and palovarotene pretreatment does not alter the skeletogenic potential of R206H-FAPs. In juvenile FOP mice, daily palovarotene administration reduces HO severity by 50% but results in previously unreported adverse effects, including aggressive synovial joint overgrowth and ablation of long bone growth plates.

Conclusions: Contrary to other RARγ agonists, palovarotene does not reprogram skeletogenic progenitors, indicating that chronic administration is required to inhibit HO formation in FOP. Ultimately, palovarotene was less efficacious than activin inhibition, and the potential for severe skeletal toxicity raises new safety concerns for chronic palovarotene administration in juveniles. These results highlight the challenge of inhibiting heterotopic bone formation prior to skeletal maturation.

19. Promoting patient engagement in the development of patient-reported outcome measures for rare diseases

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Adelphi Values

Objectives: Content-valid, disease-specific patient-reported outcome measures (PROMs), meaning questionnaires that measure symptom concepts relevant and understandable to target patient populations, are increasingly used to evaluate treatment benefit in clinical trials. Input from individuals with rare diseases is necessary when developing and evaluating PROMs to document evidence of content validity. Identifying and engaging individuals with rare conditions can be challenging given their small population, geographic dispersion, and possible physical limitations. The purpose of this abstract is to review methods for promoting patient engagement in PROM development studies.

Methods: A total of 18 PROM development/evaluation studies in rare disease populations completed between 2016 and 2018 by the authors' organization, a healthcare outcomes consultancy, were reviewed. Strategies were documented and evaluated for identifying and enrolling patients for non-interventional, qualitative (1) concept elicitation interviews (CEIs) to identify relevant signs, symptoms, and impacts associated with the specific condition, (2) cognitive debriefing interviews (CDIs) to collect patient feedback (e.g., relevance, readability) on disease-specific PROMs, and (3) hybrid CEI/CDIs.

Results: The therapeutic area categories represented in the rare disease studies evaluated were: hematology (n=5), lysosomal storage (n=2), mitochondrial diseases (n=2), gastroenterology (n=1), and autoimmune disorders (n=1). An average of 17 participants were included per study (range 9-33 participants), all of which included adult participants, and a subset (n=13 studies, 72.2%) also included pediatric and/or adolescent participants. Studies were CDIs (n=11, 61.1%), CEIs (n=5, 27.8%), or hybrid CEI/CDIs (n=2, 11.1%). Across studies, sources for identifying participants included patient advocacy groups (n=12, 66.7%), recruitment agencies (n=7, 38.9%), clinical sites (n=6, 33.3%), and/or disease-specific conferences (n=3, 16.7%). Seven studies utilized multiple recruitment methods to enroll participants. Interviews were conducted via telephone (n=16, 88.9%) and/or face-to-face (n=7, 38.9%). The majority of CDIs were conducted to evaluate newly developed, disease-specific, electronically administered PROMs.

Conclusions: Of the PROM development studies evaluated, most relied on advocacy groups for recruitment and used telephone interview methods to debrief new, electronically administered questionnaires with individuals across various age groups. Patient engagement in PROM development studies for rare diseases can be promoted by employing multiple recruitment and interview methods. Other considerations include facilitating enrollment through online consent, various diagnosis confirmation methods, thorough staff and researcher training, and disseminating findings to the community to build meaningful partnerships between researchers and individuals with rare diseases.

20. Lentiviral-vector-mediated gene therapy for metachromatic leukodystrophy decreases sulfatide accumulation in the CNS

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Objectives: Late-infantile Metachromatic Leukodystrophy (MLD) is an inherited lysosomal storage disease. It is characterized by deficient arylsulfatase A (ARSA) activity resulting in sulfatide accumulation in myelin producing cells. The most common clinical presentation of MLD is late infantile onset between 1-2 yr. with weakness, hypotonia, plateauing and loss of mental development, seizures, loss of vision and hearing and ultimately death within about 5 yr. The pathogenesis of MLD is based on the inability to metabolize the glycolipid sulfatide that is a prevalent lipid in myelin of both the central and peripheral nervous systems. Consequently, in MLD sulfatide accumulates in lysosomes and lysosome-derived vesicles resulting in cellular death and tissue dysfunction. Intravenous enzyme replacement therapies have been unsuccessful as treatment for MLD because of restricted transfer across the BBB. We propose the use of single intracerebral ventricular injection of lentiviral-vector codon-optimized human ARSA to decrease sulfatide accumulation and act as a therapeutic for MLD.

Methods: We designed a lentiviral vector incorporating codon-optimized human ARSA cDNA and green fluorescent protein (GFP) driven by the mammalian elongation factor 1 a (EF-1α) promoter. Stereotaxic injection to the lateral ventricle of the mouse was performed in ARSA deficient mouse models. Mice were transduced with ARSA (n=6) or GFP (n=6) vectors. 4-6 weeks post injection mice were sacrificed, and tissues were harvested to assess vector transduction and measure sulfatide concentration.

Results: Our data indicates that intracerebroventricular delivery of a lentiviral vector expressing ARSA (LV-ARSA) transduces the choroid plexus and ependymal cells that line the CSF compartment and expresses ARSA within about 4 days of delivery. The concentration of cerebellar sulfatide which is the principal endpoint is normalized in about 1 month.

Conclusion: We demonstrate correction of sulfatide accumulation in ARSA-deficient mice through lentiviral vector mediated gene transfer into the lateral ventricle providing proof of concept for gene therapy in MLD.

21. Clinicopathological correlations of ALS by motor neuron degeneration predominancy

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Objective: The 43kDa TAR DNA-binding protein (TDP-43) is one of the key proteins in most of the patients of both familial and sporadic ALS (Arai T, Biochem Biophys Res Commun 2006 / Neumann M, Science 2006). Phosphorylated TDP-43 (pTDP-43) was identified as the major component in their ubiquitin positive inclusions in 2006 (Hasegawa M, Ann Neurol 2008 / Neumann M, Acta Neuropathol 2009) and it must be the major pathological hallmarks of ALS. The progressive changes that start with normal nuclear TDP-43 and culminate in C-terminal truncated, phosphorylated and cytoplasmic aggregation remain unknown. Understanding the relation of these neuronal molecular changes to cell degeneration, and both to clinical phenotype is important in understanding pathogenesis.

Methods: We classified ALS nervous system by phenotype: the Upper Motor Neuron (UMN) dominant cases (n=5), and the Lower Motor Neuron (LMN) dominant cases (n=5). We performed morphometric analysis and also quantified pTDP-43 (S409/410) or TDP-43 stain of Betz cells in layer V and alpha motor neurons in the anterior horn of the spinal cord. pTDP-43 positive inclusions were classified four types; punctate, dot, skein and round. For analysis, we employed Mann-Whitney test and Tukey's multiple comparisons test using the GraphPad Prism 7 (GraphPad Software, La Jolla, CA).

Results: In the CNS of patients with the UMN predominant phenotype, neurons are more atrophic and more TDP-43 pathology in the motor cortex than in the spinal cord. In the LMN predominant cases, neurons are more atrophic in the lumbar spinal cord and have more pTDP-43 pathology in the spinal cord than in the motor cortex. Skein-like inclusions are most abundant in the UMN predominant cases, and round inclusions are identified only in the LMN predominant cases.

Conclusions: There are some trends of clinicopathological correlation in vulnerable site of neurons and pTDP-43 pathology by motor neuron predominancy.

22. Citrin Deficiency: Assessment of the Carrier Frequency for an Underdiagnosed Urea Cycle Disorder in the US and Identification a Novel Ashkenazi Jewish Founder Variant.

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Introduction: Citrin deficiency (CD) is an autosomal recessive urea cycle disorder caused by variants in the *SLC25A13* gene. CD can manifest as self-limited neonatal intrahepatic cholestasis (NICCD) during infancy, failure to thrive with aversion to carbohydrate-rich foods during childhood, or citrullinemia type II (CTLN2) characterized by a sudden onset of life-threatening hyperammonemia during adulthood. While it was previously thought that this condition was confined to East Asian populations, an increasing number of non-Asian CD cases have been identified. It is challenging to make early diagnosis of asymptomatic individuals with CD who are at-risk for life-threatening CTLN2 due to limited information of CD disease frequency and natural history in non-Asian populations.

Objective: To assess carrier frequency and the clinical/biochemical findings of CD in the US population.

Methods: We used NGS databases including the carrier screening tests done at the Mount Sinai Genetic Testing Laboratory and BioMe at Mount Sinai Medical Center to evaluate the frequency of pathogenic *SLC25A13* alleles. Retrospective chart review of patients with molecularly confirmed CD and *in vitro* functional assays using *Saccharomyces cerevisiae* were performed.

Results: The NGS carrier screening test identified an estimated CD carrier frequency of 1/199 in an unselected US population. Additionally, we identified an Ashkenazi Jewish CD variant, c.1336A>C, p.T446P. Newly identified adults with this variant had incidental hepatic steatosis and aversion to high-carbohydrate diet and to alcohol in a setting of normal biochemical profiles. Functional activity of the p.T446P variant was significantly reduced. African American sequencing data from BioMe detected only 7 variants including 6 novel presumed loss of function variants among 14,838 alleles with an estimated carrier frequency of 1/1,067.

Conclusions: CD may be more prevalent than previously thought and underdiagnosed in the US. We have identified a diverse spectrum of variants across ethnic groups and observed a low variant prevalence in the African American population. We have characterized a CD founder variant in the Ashkenazi Jewish population. Alcohol aversion and asymptomatic hepatosteatosis may be important clinical phenotypes for CD.

23. Expanding the genetic spectrum of rare hereditary sensory and autonomic neuropathies with whole exome sequencing

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Objective: Congenital impaired sensation to pain and temperature with autonomic dysfunction are characteristics of patients with familial dysautonomia (caused by a founder mutation in *IKPBAP*), congenital insensitivity to pain and anhidrosis (caused by mutations in the *NTRK1* gene), and the other hereditary sensory and autonomic neuropathies (HSAN). However, none of these mutations are identified in many patients presenting with congenital sensory and autonomic deficits. We aimed to examine the performance of whole exome sequencing in patients with congenital sensory and autonomic neuropathy who have undergone conventional genetic testing with negative results.

Methods: We enrolled 11 patients with impaired or absent sensation to pain and temperature sensation with onset at birth without a previously identified molecular diagnosis from a HSAN gene panel. We performed detailed phenotypic assessment including presentation, autonomic testing, and comprehensive neurological and ophthalmological examinations.

Results: Genetic variants were identified in 10 out of 11 patients (91%). We identified homozygous variants in *NGF* (n=2, siblings), *SMPDL3A* (n=2, siblings), *LIFR* (n=2, siblings), and *TECPR2* (n=1) never found in control populations and predicted to be likely pathogenic. We also identified heterozygous variants in *SCN10A* (n=1), *SCN9A* (n=1) predicted to be likely pathogenic. One patient had a homozygous variant in *SCN11A* of uncertain pathogenicity. Genetic testing was inconclusive in only one patient. Autonomic deficits included anhidrosis (*SCN9A, NGF*), hypohidrosis (*TECPR2),* hyperhidrosis (*SCN11A, SCN10A, TECPR2, LIFR),* alacrima/hypolacrima (*SMPDL3A, TECPR2, LIFR),* neurogenic dysphagia (*TECPR2, SMPDL3A, SCN11A),* gastroesophageal reflux *(SCN11A),* vomiting episodes (*LIFR),* central sleep apnea (*TECPR2),* and episodes of hypertension, tachycardia, hyperhidrosis and hypernatremia (*LIFR*).

Conclusions: Whole exome sequencing can improve molecular diagnosis of hereditary sensory and autonomic neuropathy and expand its genetic landscape. Further validation of some identified variants are required to confirm its definite pathogenicity.

24. Lessons learned from combined and comparative data analysis of over 1,000 patients with urea cycle disorders

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Objective: Patients with urea cycle disorders (UCDs) are followed by two international registries managed by the North American Urea Cycle Disorders Consortium (UCDC) and the European registry and network for intoxication type metabolic disease (E-IMD) aiming to study the natural history of UCDs.

Methods: Data from 1,095 individuals were retrieved from the two data bases that use remote data entry via electronic forms by comprising about 570 (UCDC) and 490 (E-IMD) variables with an overlap of approximately 250 variables describing the medical history. Patients are prospectively followed with protocols for regular follow-up and emergency visits.

Results: Case mixes were different between North America and Europe; however ages at first symptoms and ages at diagnosis showed similar patterns for specific UCDs. Ranking modes of diagnosis showed a dominant role for selective metabolic investigation, whereas the proportion of newborn screening increased continuously within recent decades. Furthermore, there is a clear shift from using enzymatic to mutation analysis on both continents.

Conclusions: It is demonstrated prototypically that combining databases is manageable and can enhance research of rare diseases by leading to increased sample sizes for natural history research, whereas comparative analysis can inform on various country-specific diagnostic and therapeutic peculiarities. Combined large data sets will enhance our understanding on phenotypic fingerprinting as well as long-term outcome studies and enable the establishment of parsimonious databases for rare diseases based on minimal core data sets.

25. Expanding the clinical spectrum of EARS2 associated mitochondrial disease

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Introduction: *EARS2* is associated neurological disorder characterized by leukoencephalopathy with thalamus and brain stem involvement and high lactate (LTBL). Presentation in all cases described so far had onset in infancy and characteristic MRI findings of diffuse white matter changes and symmetrical signal abnormalities in thalamus and brain stem. The presentation falls into two group- severe and mild. The patients in severe group present before 6 months of age with marked neuro-regression and then clinical stagnation. Patients in mild group present later in infancy with neuro-regression but they partially recover and regain some milestones. Here we describe 4 patients with atypical presentations.

Case studies: Patient 1 is a 6 month old girl who presented at 3 months of age with generalized tonic seizures. Her growth and development were appropriate. She had hepatomegaly, abnormal liver function tests (AST 237, ALT 146, GGT 356), and high lactate in blood (9.8), and CSF (9.4). Abdominal ultrasound showed diffusely echogenic enlarged liver and MRI of the brain showed restricted diffusion in white matter and corpus callosum. Basal ganglia and posterior fossa structures were normal. Two mutations in the EARS2 gene, c.322C>T (p.R108W) and c.328 G>A (p.G110S) were identified. At 6 months of age, her growth was normal. Mild motor delay but normal language and social development were noted. Both lactate and liver enzymes were trending down.

Patient 2 & 3 are female siblings (currently 2 and 5 years old), who were identified by newborn screening for low TREC values. They had persistent T cell lymphopenia, lactate elevation, and macrocytic anemia. In addition, failure to thrive and mild developmental delay was noted. Bi-allelic, novel, likely pathogenic variants, c.485+4090_511del5090 and c.667G>A, p.D223N in *EARS2* were detected in both patients.

Patient 4 is 3 year old boy with normal development until 12 months when he had fever episode. Rapid regression of milestones at that time was noted. Now he is slowly gaining skills. MRI of the brain at the onset of symptoms was normal. Plasma lactate was elevated to 3.5. WES identified two VUS in EARS2 gene.

Conclusion: Here we describe patients with *EARS2* mutations with developmental delay, liver abnormalities, macrocytic anemia, and lymphocytopenia without typical "LTBL" presentation. Thus, the clinical spectrum/phenotype of *EARS2* disease is wider than currently appreciated. EARS2 deficiency should also be considered with unexplained hepatopathy, anemia, lymphocytopenia, and developmental delay with high lactate even in the absence of characteristic neuroimaging findings. Moreover, *EARS2* related lymphocytopenia can trigger positive newborn screening for SCID.

26. Subglottic Stenosis and Endobronchial Disease in Granulomatosis with Polyangiitis

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Objective: Damage to the large airways is a devastating complication of granulomatosis with polyangiitis (GPA). Identification of patient subsets at particular risk for airway disease and development of non-invasive screening methods to detect tracheobronchial disease is an unmet need in GPA. This study aimed to characterize patients with subglottic stenosis (SGS) and bronchial disease and test whether dynamic expiratory-phase CT is useful to detect airway damage in patients with GPA.

Methods: i) A retrospective analysis of a multi-center cohort of patients with GPA identified demographic and clinical features associated with the presence of SGS or endobronchial involvement; ii) A subset of patients with GPA underwent a dynamic chest CT at a single center, assessed by a central reader blinded to clinical status. Differences were assessed by the chi square test and ANOVA with post-hoc Tukey test to account for multiple comparisons.

Results: Data from 962 patients with GPA from 9 centers were used for the initial phase analyses. SGS was identified in 95 (10%) patients with no differences in ANCA subtype in patients with SGS compared to the overall cohort. Patients with SGS were more likely to be female (72% vs 53%, $P < 0.01$), younger at time of diagnosis (36 vs 49 years, $p < 0.01$), and less likely to have constitutional, cardiovascular, renal, or nervous system involvement. Among 95 patients in the cohort with nasal septal perforation and saddle nose deformities, 28 (29%) and 27 (28%), respectively, also had SGS.

Endobronchial disease was seen in 59 (6%) patients. Compared to the full cohort, patients with endobronchial involvement were younger at time of diagnosis, more likely to have ENT involvement and be C-ANCA/anti-PR3 positive (85% vs 66%, $p<0.01$), but less likely to be ANCA-negative (0% vs 6%, $p = 0.04$) or have renal disease. There was no association between endobronchial involvement and sex. Concomitant SGS and endobronchial involvement (23 patients) was not associated with sex (60% vs 55% female, $p = 0.60$).

Seven of twenty-five patients screened by dynamic chest CT had large-airway pathology. Dynamic CT confirmed SGS in 4 patients with previously identified disease. Tracheobronchomalacia was discovered in 4 patients, including one male patient who was previously thought to have isolated SGS.

Conclusions: Both SGS and endobronchial disease are moderately common in GPA and each manifestation is associated with various other aspects of GPA. SGS is more commonly seen in female patients with GPA, whereas bronchial involvement is not associated with sex. There should be a low threshold to evaluate airway disease in GPA, especially in younger patients, and those with destructive sinonasal disease. Dynamic expiratory phase chest CT is a potential non-invasive screening test for tracheobronchial disease in GPA.

27. Targeted Inhibition of Glutamate Dehydrogenase (GDH) by Alpha-tocopherol: A Potential Novel Treatment for Hyperinsulinism/Hyperammonemia (HI/HA) Syndrome

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Objective: Congenital hyperinsulinism is a rare genetic disorder that causes severe hypoglycemia and can lead to permanent brain damage if inadequately controlled. Gain of function mutations in GDH result in hyperinsulinism hyperammonemia syndrome (HI/HA), the second most common cause of congenital hyperinsulinism. Current therapies inhibit insulin secretion but do not target GDH overactivity directly and thus fail to treat the spectrum of clinical manifestations observed, which in addition to hyperinsulinism and hyperammonemia, include seizures and developmental delays. The neurological symptoms are profound and occur independent of the hypoglycemia. We investigated the efficacy of alpha-tocopherol as a targeted GDH inhibitor in vitro and in vivo models of HI/HA syndrome.

Methods: Human embryonic kidney (HEK293T) cells were transduced with lentivirus to overexpress either wild-type GDH or H454Y GDH, a well-characterized disease-causing mutant. GDH enzyme kinetics were determined spectrophotometrically in cell homogenates perfused with escalating concentrations of alpha-tocopherol on a background of 10mM glutamine. To evaluate the inhibitory effect of alpha-tocopherol on GDH in vivo, wild-type (WT, n=10) and H454Y GDH transgenic (Tg, n=13) adult mice were treated with oral alpha-tocopherol (75µg/g body weight/dose) or vehicle twice daily for 3 doses and then fasted for 6 hours. Nadir fasting plasma glucoses were measured as a clinical correlate of GDH activity and compared between alpha-tocopherol and vehicle-treated wild-type and transgenic mice, respectively.

Results: Alpha-tocopherol effectively inhibited activity of wild-type and H454Y mutant GDH in HEK293T cells with 50% inhibitory concentration (IC_{50}) of 4.1 and 3.1 µM, respectively. In vivo, nadir fasting plasma glucose was significantly higher in alpha-tocopherol-treated versus vehicle-treated WT and Tg mice (WT: mean nadir plasma glucose 94.3 ± 9.6 mg/dl v. 80.1 ± 9.6 mg/dl, p=0.003; Tg: mean nadir plasma glucose 71.9± 11.3 mg/dl v. 57.2 ± 12.6 mg/dl, p=0.002).

Conclusions: Alpha-tocopherol effectively inhibits GDH in vitro and ameliorates fasting hypoglycemia in vivo in a mouse model of HI/HA syndrome. Based upon these findings, alpha-tocopherol is a promising potential treatment for HI/HA syndrome. Our next step will be to study the safety and efficacy of oral alpha-tocopherol supplementation in human subjects with HI/HA syndrome.

28. Cystine Diamides as a Novel Therapy for Cystinuria

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Objective: Cystinuria, caused by mutations in *Slc3a1* or *Slc7a9*, is characterized by excessive excretion of cystine in the urine and recurrent cystine stones in the urinary tract. We are developing a novel therapy for cystinuria, based on the inhibition of cystine crystal growth by cystine analogs. We synthesized cystine diamides as cystine crystal growth inhibitors that have greater stability and bioavailability compared with the previously tested cystine analog, cystine dimethyl ester (CDME). The most effective cystine diamide to date is cystine bis(N′-methylpiperazide) (LH708).

Methods: The concentration of LH708 required to double the solubility of cystine (EC_{2x}) was determined by fluorescence. The stability of LH708 in phosphate buffer was determined by LC-MS. Step velocities, as an indicator of cystine crystal growth rates, were determined by *in situ* atomic force microscopy. The concentrations of LH708 in plasma and urine from *Slc3a1* knockout male mice following intravenous or oral administration of LH708 (150 µmol/kg) were determined by LC-MS. To assess the efficacy of LH708, 3-months-old *Slc3a1* knockout male mice were screened by computed tomography (CT) and stone-negative mice were treated daily for 60 days with this analog (150 µmol/kg) or water alone. CT scans were repeated on days 30 and 60.

Results: The EC_{2x} for LH708 was 0.26 µM compared with 6.37 µM for CDME and the half-life of LH708 was 42.6 days compared with 2.7 hours for CDME. The step velocities in the presence and absence of CDME or LH708 (V/V_o) were in the range 0.21-0.48 at 45 µM for each analog, providing strong support for a common mechanism for cystine crystal growth inhibition. The bioavailability of LH708 after oral feeding was 18% and LH708 was detected in urine samples. Nineteen stone-free mice were treated with LH708 and five of them showed cystine stones at day 30 and the same five mice were stone-positive at day 60. Twenty-four stone-free mice were treated with water alone and 15 of them showed stones at day 30. Five of these mice died between the first 30 days, but three more mice were stone-positive at day 60.

Conclusion: These data strongly support the evaluation of LH708 as a potential therapy for cystinuria.

29. Experiences of parents of patients with Severe Combined Immunodeficiency Disease (SCID) identified by newborn screening: a qualitative study

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Objectives: Severe combined immunodeficiency (SCID) is a life-threatening immune deficiency. Newborn screening (NBS) for SCID has allowed for prompt identification and definitive treatment with hematopoietic cell transplant (HCT) or gene therapy (GT) before significant infections occur. At UCSF, newly diagnosed infants with SCID are hospitalized for treatment and remain in isolation until adequate immune reconstitution. Our group previously demonstrated nearly 60% of SCID parents at UCSF experience psychosocial trauma, including depression and post-traumatic stress disorder (PTSD). The specific challenges that contribute to depression and PTSD in these parents have not been described. This qualitative study sought to better understand these challenges to improve support for newly diagnosed SCID patients and their families.

Methods: Voluntary participation was elicited from parents of children with SCID who were status post HCT/GT for >1 year. Semi-structured, in-person interviews with 11 parents were recorded and transcribed. Parents were asked to discuss experiences from first notification of an abnormal screening result through hospital discharge. Emerging themes were identified from the transcribed interviews.

Results: We interviewed 6 mothers and 5 fathers of 7 infants with SCID. Commonly reported stressors included the first phone call regarding abnormal newborn screening results, preparing for HCT/GT, prolonged isolation, and preparing for discharge. Other challenges reflected the stress of caring for a newborn, including postpartum depression. Overall, themes identified included: loss of normalcy and control; prolonged waiting periods (especially the wait between diagnosis and HCT, and between HCT and T cell engraftment); and perceived lack of guidance on realistic expectations during the hospital stay. Parents reported that peer support from other SCID parents was important.

Conclusions: We identified psychosocial stressors uniquely faced by parents of infants with SCID diagnosed by NBS. Recognizing these challenges highlighted opportunities to improve both healthcare delivery to patients and institutional support for families affected by SCID. Emphasis should focus on provision of SCID-specific resources at time of diagnosis, connecting parents with SCID support networks, and facilitating access to psychosocial health services for caregivers.

30. Kinase inhibitors improve neurofilament distribution in CMT2E human motor neuron axons

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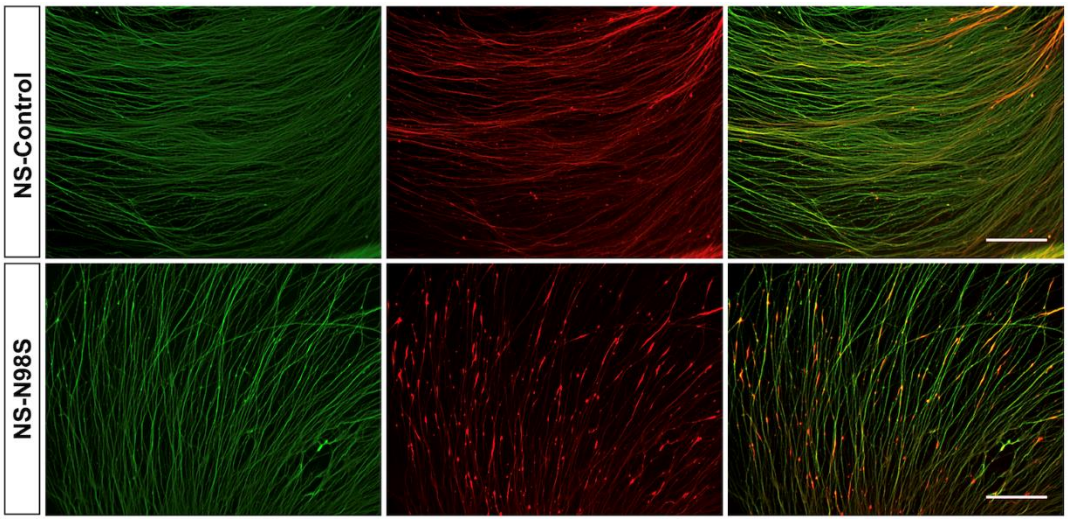
Objective: Mutations in neurofilament light chain (NEFL) gene cause autosomal dominant axonal Charcot-Marie-Tooth neuropathy (CMT2E), currently an untreatable disorder. The aim of this study was to develop a tridimensional human *in vitro* system to accelerate therapy development for axonopathies, including CMT2E.

Methods: Human motor neurospheres were formed by culturing induced pluripotent stem cell (iPSC)-derived motor neurons from CMT2E patients and unaffected controls in suspension and continuous agitation. When platted, neurospheres allow for robust centrifugal axonal growth, offering a tridimensional model to study axonopathies. Neurofilament axonal distribution was studied by immunostaining.

Results: Immunostaining of CMT2E neurospheres revealed numerous areas of NFL accumulation in motor axons from three different patients with N98S CMT2E, but not on four healthy controls (p=0.001) (Figure). Areas of NFL accumulation were also immunopositive for NFH, pNFH and NFM, demonstrating co-localization of the three neurofilament subtypes within the axonal deposits. In proof-of-concept experiments to evaluate the use of this platform to identify compounds that could reduce the number of axonal NFL deposits in N98S CMT2E motor neurons, we tested three different kinase inhibitors from the University of Miami Center for Therapeutic Innovation library and identify one kinase inhibitor that promoted a 50% reduction in the normalized number of neurofilament deposits at both 25 nM (2.262 ± 0.06 deposits/cm^2 of axon area) and 250 nM (2.99 ± 0.506 deposits/cm^2 of axon area) doses when compared to vehicle (5.192 ± 0.07 deposits/cm^2 of axon area)(p=0.0011).

Conclusion: We developed a human *in vitro* system to support drug screening for CMT2E and identified candidate kinase inhibitors with potential for development as therapies for CMT2E.



31. A multi-disciplinary clinic for patients with SCN8A-related epilepsy

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Objectives: The *SCN8A* gene encodes a voltage-gated sodium channel involved in action potential generation. Mutations may cause SCN8A Epileptic Encephalopathy (Early Infantile Epileptic Encephalopathy 13, or EIEE13) and autism spectrum disorder or developmental delay (Rauch et al., 2012). We endeavored to evaluate a cohort of patients diagnosed with epilepsy due to mutations in *SCN8A*in a multi-disciplinary clinic at Children's National Health System (CNHS).

Methods: We recruited patients with epilepsy due to mutations in *SCN8A* at CNHS, through family organizations, or SCN8A.net. Study procedures included medical record review, review of EEG and MRI data when available, clinical evaluation, and administration of the Vineland Adaptive Behavior Scales, Third Edition (Vineland-3) Comprehensive Parent/Caregiver Form.

Results: Twelve patients with epilepsy and known or suspected mutations in *SCN8A* completed the study. Median age was 6 years (range 2-19 years). Four subjects were female. Pathogenic mutations were present in eight; four had variants of unknown significance. Seizure onset was 1 day to 4 years old (median age 4 months). Current epilepsy type is variable: five generalized motor, four 4 focal or multifocal, two atypical absence, and one unknown. Neuroimaging was typically normal. Initial EEG was also reported as normal in the 5/10 in whom the report was available. One child had typical development, while developmental delay was evident in 11. Vineland-3 scores varied from the average to severely impaired range (Communication Standard Score (SS) range 20-98, mean SS=48; Daily Living Skills range 20-95, mean 56; Socialization range 23-101, mean 65; Motor Skills range 20-100, mean 58; Adaptive Behavior Composite range 21-97, mean 58). Two with a relatively mild epilepsy phenotype where seizures were controlled (one N1877S and one L257V) had the highest Vineland-3 scores. However, another with the N1877S mutation and controlled seizures had SS in the moderate to borderline deficient function.

Conclusions: This is the first report of a large series of patients with epilepsy due to *SCN8A* mutations evaluated in a single clinic. Epilepsy phenotypes are variable, with both focal/ multifocal and generalized epilepsies. Response to medication and development also vary widely, and may correspond to the specific mutation, to some degree. This study establishes the basis for a larger natural history study of epilepsy due to mutations in *SCN8A.*

32. Combining Knowledge and Data Driven Insights to Facilitate the Differential Diagnosis of Rare Diseases

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Abstract: Patients with rare diseases are typically left misdiagnosed or undiagnosed, which leads to a prolonged medical journey. In our previous study, we applied a collaborative filtering model on clinical data generated at Mayo Clinic to stratify patients into subgroups of rare diseases based on their phenotypic characterizations. Information mined from clinical data, however, usually contains a certain level of noise. In this study, therefore, we sought to incorporate a knowledge-driven approach into collaborative filtering to optimize results learned from clinical data.

Objective: A significant lack of knowledge and insufficient characterizations of the longitudinal and natural history of many rare diseases is the reason that diagnostic odyssey continues to exist. In our previous work, we built a rare disease recommendation framework leveraging a collaborative filtering algorithm and applied it on clinical data to stratify patients into subgroups based on phenotypic information[1]. A key drawback of clinical data, however, is that mined information usually contains a certain level of noise, such as comorbidities. In this study, we sought to incorporate a knowledge-driven approach with a collaborative filtering model to optimize predictions for differential diagnosis.

Methods: The proposed system is composed of a collaborative filtering recommendation component and a knowledge-driven optimization component. The prior component applies the Tanimoto coefficient and K-nearest neighbors (KNN) algorithm on patients' clinical data and produces initial prediction results ranked by Tanimoto score. The latter component used the Aber-OWL[2] as knowledge base then checked the phenotype-disease associations and compared recorded associations with patients' phenotypic set using probability-based similarity (PBS)[3]. As a result, the final rare disease prediction is selected as the top ranked disease by PBS score.

Results: Root-mean-square error for 10-fold cross validation reached its lowest value when k was equal to 5, therefore, we selected k=5 as the optimal number of neighbors for KNN. To evaluate the performance of differential diagnosis for rare diseases, we conducted experiments on 30,863 patients who only had diagnosis of rare diseases. We computed the micro-average of precision, recall, and F-measure for two experimental groups (collaborative filtering only (CFO) and collaborative filtering with knowledge (CFK)). In addition to evaluating the string matching strategy, we also used the SNOMED CT and DO to detect similar diseases if they contributed to a common ancestor node within 3 hierarchical generations. We observed that the CFK yielded higher F-measure than the CFO regardless of the selection of matching strategies, indicating that the CFK outperformed CFO in rare disease differential diagnosis.

Table 1. Performances comparison for rare disease differential diagnosis

	CFO	CFK (String)	CFO (DO)	CFK (DO)	CFO (SNOMED CT)	CFK (SNOMED
Precision	0.81	0.71	0.83	0.73	0.81	0.85
Recall	0.42	0.51	0.42	0.52	0.49	0.55
F-measure	0.55	0.59	0.56	0.61	0.61	0.67

Conclusion: We investigated the incorporation of the Aber-OWL knowledge resource into a collaborative filtering model to improve performance of rare disease differential diagnosis. Results demonstrated the feasibility of leveraging this approach to facilitate rare disease diagnosis in clinical practice.

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33. PI3K/Akt/mTOR is a Novel Therapeutic Target in Anti-IL-6 Refractory iMCD

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Objective: Idiopathic multicentric Castleman disease (iMCD) is a rare and deadly polyclonal lymphoproliferative disorder involving cytokine-induced multiple organ dysfunction. Management of interleukin(IL)-6-blockade refractory iMCD is challenging because the disease's molecular underpinnings remain unknown; identification of molecular and cellular abnormalities for therapeutic targeting is urgently needed.

Methods: All studies were approved by institutional review boards, compliant with HIPAA, and conducted following established protocols.

Results: Retrospective chart review of an index case (IC) of relapsing IL-6-blockade refractory iMCD revealed levels of soluble IL-2 receptor (sIL-2R), a marker of T-cell activation, and vascular endothelial growth factor (VEGF), an angiogenic factor, became abnormally elevated weeks before onset of the patient's fifth disease flare. Flow cytometry of peripheral blood mononuclear cells verified an increased proportion of activated $CD8^{+}$T-cells during flare. Pathway enrichment analysis of serum analytes with at least a two-fold change between flare and remission identified inhibition of PI3K/Akt/mTOR signaling as an actionable intervention linking sIL-2R and VEGF, and histological examination of lymph node tissue confirmed significantly elevated mTOR activity during flare. Based on these observations, we initiated treatment with the mTOR inhibitor sirolimus, which successfully maintained a complete, durable, and ongoing 56-month remission, 6.75-times longer than the average duration of IC's previous four remissions. Subsequently, two additional IL-6-blockade refractory iMCD patients, who were experiencing disease flare and exhibited significantly elevated mTOR activity, both demonstrated a clinical benefit response to sirolimus therapy.

Conclusions: Our precision medicine approach identifies the first novel therapeutic target, mTOR, for treatment of iMCD since 1994. Critically, we demonstrate efficacy of mTOR inhibition for prevention of iMCD relapse in one patient who experienced five disease relapses, as well as for amelioration of disease flare in two IL-6-blockade refractory patients. These data form the basis for a clinical trial of sirolimus in IL-6-blockade refractory iMCD that will begin enrollment in 2019.

34. Repetitive Behavior Profile of Phelan-McDermid Syndrome

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Objective: Phelan McDermid Syndrome (PMS), also known as 22q13 deletion syndrome, is a neurogenetic disorder associated with a high prevalence of autism. This study provides a more comprehensive profile of repetitive behaviors within the disorder.

Methods: Individuals with a confirmed PMS diagnosis participated in a multicenter observational study evaluating the genotype, and phenotype of the disorder. We evaluated data collected from this study pertaining to repetitive behaviors and adaptive functioning including the Aberrant Behavior Checklist (ABC), Repetitive Behavior Scales Revised (RBS-R), and Vineland Adaptive Behavior Scales 2nd edition (VABS-II),

Results: There were 45 individuals [mean age 8.08 (3.92) years] with PMS. Based on the ABC, stereotypies were slightly problematic with an average scaled score of 0.63 (0.70), and hyperactivity was slight to moderately serious with an average scaled score of 1.22 (0.80). The mean total number of items endorsed on the RBS-R was 10.11 (7.94) with a mean total overall score of 16.31 (17.76). The subscale with the highest scaled number of endorsed items (total number of endorsed items in the subscale divided by the number of *possible* endorsed items in the subscale) was the Stereotypy Subscale (0.42). The most prevalent items in the motor stereotypy subscale were hand/finger stereotypies (67%) and object usage (49%). RBS-R Stereotypic Behavior Score correlated with all VABS-II scores ($p \leq 0.0053$) as well as with ADOS-2 Overall Total scores ($p \leq 0.0052$).

Conclusions: Repetitive behaviors are common in PMS, even in those without ASD, and constitute a wide range of symptoms and severities. Poorer adaptive functioning is associated with increased severity of certain types of repetitive behaviors in PMS.

35. Untargeted metabolomic profiling identifies potential clinical biomarkers that may inform management of urea cycle disorders

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Objective: To test whether untargeted metabolomics profiling identifies plasma metabolites that could guide management of urea cycle disorders (UCDs).

Methods: Plasma samples for untargeted metabolomics were obtained during routine clinical visits from adults and children with ornithine transcarbamylase deficiency (OTCD, n=17), argininosuccinate lyase deficiency (ASLD, n=11), arginase deficiency (ARG1D, n=13), and argininosuccinate synthetase 1 deficiency (ASS1D, n=7). Specimens were analyzed using LC/MS/MS as previously described. Plasma concentrations of leucine, isoleucine, valine were obtained from adults and children with OTCD (n=257-325), ASLD (n=79-102), ARG1D (n=18-20) and ASS1D (n=59-78) who were enrolled in the Longitudinal Study of Urea Cycle Disorders (NCT00237315) conducted by the Urea Cycle Disorders Consortium of the NIH Rare Diseases Clinical Research Network.

Results: Our metabolomics analysis identified elevations in potentially neurotoxic guanidino compounds that are derived from arginine in ARG1D, such as argininate, 2-oxoarginine, N-acetylarginine and guanidinoacetate. Elevated guanidine compounds are implicated in multiple neuropathogenic mechanisms and may prove useful in monitoring treatment efficacy in ARG1D. We also detected biochemical perturbations in all UCDs that likely reflect clinical management, which may be secondary to nutritional and medication management. For instance, metabolomics analysis revealed decreased concentrations of branched-chain amino acids and their ketoacids. We confirmed this observation using data from subjects enrolled in the Longitudinal Study of Urea Cycle Disorders. This analysis suggested that the reduction in branched-chain amino acids concentrations may be associated with known off-target effects of nitrogen scavenging agents and dietary protein restriction.

Conclusions: Untargeted metabolomics analysis in plasma identified metabolites that may be useful for monitoring clinical management and off-target effects of medications in all UCDs. Use of untargeted metabolomics analysis in routine clinical management could have potential utility in the surveillance of UCDs and other inborn errors of metabolism.

36. First-in-Human Study of the Efficacy, Safety, and Tolerability of Statin Therapy of Autoimmune Pulmonary Alveolar Proteinosis

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Background: Autoimmune pulmonary alveolar proteinosis (aPAP) is a rare disease characterized by surfactant accumulation in pulmonary alveoli, hypoxemic respiratory failure, and innate immune deficiency. aPAP is mediated by neutralizing GM-CSF autoantibodies, which cause alveolar macrophage dysfunction. Recently, we determined that loss of cholesterol clearance results in intracellular cholesterol accumulation. Results from our previous study showed that statin therapy increased cholesterol clearance, was associated with clinical improvement in two aPAP patients, and reduced the severity of PAP in *Csf2rb*^{KO} mice. Based on these findings, we are now planning a human clinical trial.

Objective: This project will be the first-in-human study to evaluate the efficacy and the safety of oral rosuvastatin in patients with aPAP.

Methods: This trial will be a stratified, double blind, placebo controlled, multi-site study.

1. Randomization. Patients with unremitting or progressive aPAP will be stratified by disease severity to ensure equal representation of patients with severe or mild disease in the treatment and placebo group (**Figure 1**).
2. Grouping and intervention. During the blinded treatment administration period, participants will have one capsule of study drug (10 mg rosuvastatin or placebo) by daily oral administration for one year. All the participants will have oral rosuvastatin 10 mg daily during the open-label extension treatment period.
3. Sample size calculation. Based on our data, the mean density in aPAP ranges from 0.26 to 0.28 before treatment, and is 0.17 after statin treatment with common standard deviation of 0.06. The mean between group difference in change in density before and after treatment ranges from 0.09 to 0.11. Therefore the standardized mean difference in change ranges from 1.417 to 1.750. With the proposed sample size, 30 subjects (15 each group), we have 80% power to detect an effect size of 1.060 using a two group *t*-test with a 0.05 two-sided significance level.
4. Timeline. Four study periods included, an observation period, a double blind, placebo-control treatment period, an open label treatment period, and a follow-up period.
5. Measurements. We will evaluate the response to treatment as following measurements:
   (1) Primary endpoint will be change of quantitative CT analysis from Baseline to the End of Treatment.
   (2) Secondary endpoints will be change from Baseline in the following parameters, measured at the End of Treatment: DLCO, (A-a)DO_2, PO_2, minimum SpO_2 during 6MWT, 6MWD, questionnaire, need for rescue therapy, safety and tolerability.

Conclusions: Anticipated results will establish the efficacy, safety, and tolerability of statin therapy of autoimmune PAP.

37. A Multi-Center Study of Neonatal Chest X-ray Findings in Patients with Primary Ciliary Dyskinesia

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Objective: Primary ciliary dyskinesia (PCD) is a rare disorder of mucociliary clearance. Approximately 80% of PCD patients have a history of neonatal respiratory distress[1]. A recent single center study showed abnormal chest x-rays (CXR), specifically infiltrates and lobar collapse, were common seen in patients with PCD. The objective of this study was to confirm those findings in a multi-center study.

Methods: We identified children seen at the University of North Carolina, McGill University, Washington University, and Children's Minnesota that met the following criteria: PCD confirmed by presence of "hallmark" EM defect and/or two loss of function genetic mutations in a PCD gene; a history of neonatal respiratory distress; and a CXR within the first 28 days of life. Clinical information was extracted from the medical record. All CXRs were reviewed independently by two pediatric pulmonologists (TJV and MWL). The location of the findings was noted and description was of findings was placed into the following categories: lobar atelectasis, partial atelectasis, infiltrate/atelectasis, diffuse changes, and other.

Results: 72 subjects met inclusion criteria - 56 had at least 1 CXR available for review; the remainder had radiology reports. The mean age at diagnosis of PCD was 2.7 years. The mean length of oxygen therapy was 17.3 days, the mean hospitalization was 19.1 days. 81% of subjects had an abnormal CXR, with 58% having at least 1 CXR with lobar atelectasis. 50% had multi-lobar findings on at least 1 CXR and 36% had migrating findings on serial CXRs.

Conclusions: This study confirms that neonates with PCD and neonatal respiratory distress have abnormal CXRs. A new finding was the increased prevalence of multi-lobar and migrating atelectasis as this study included multiple CXRs per patient. PCD should be considered in the differential diagnosis of any neonate with neonatal respiratory distress and atelectasis or infiltrate on CVR.

Funding: This abstract was funded by 5U54HL096458-06 (NIH/ORDR/NHLBI), 5R01HL071798(NIH/NHLBI), and UL1 TR000083 (NIH/NCATS).

38. *In Vivo* Studies of MARS2 Deficiency (MIM #616430)

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Objective: To further characterize the pathophysiology of MARS2 deficiency using a newly generated knock-in mouse model.

Background: We recently identified by WES a novel mitochondrial disorder caused by recessive single nucleotide variants in mitochondrial methionyl amino-acyl tRNA synthetase (MARS2), which presents with clinical symptoms of developmental delay, poor growth, and sensorineural hearing loss. The MARS2 compound heterozygous mutations identified in the index family, c.550C>T;p.Gln184* and c.424C>T;p.Arg142Trp, led to: decreased MARS2 protein levels in patient lymphoblasts; decreased Complex I and IV enzyme activities in patient fibroblasts; and reduced protein levels of NDUFB8 and COXII, representing Complex I and IV respectively, in patient fibroblasts and lymphoblasts. Overexpression of wild-type MARS2 in patient fibroblasts rescued complex I and IV subunit deficiencies (Webb et al., 2015).

Methods: A knock-in mouse model was generated by CRISPR/Cas9 technologies on a C57BL/6 background. The Mars2 c.403C>T;p.Arg135Trp variant corresponding to the MARS2 p.Arg142Trp change was generated. Mice were bred to homozygosity, and littermates were sacrificed and tissues and organs harvested at different time points. Immunoblotting with a mitochondrial oxidative phosphorylation antibody cocktail was completed to assess for mitochondrial dysfunction. RNA-seq was completed with RNA generated from wild-type and homozygous mutant mice liver and gastrocnemius samples. Differentially expressed gene (DEG) signatures were identified using an in-house pipeline, which utilizes RNAStar, FeatureCounts, and Limma/Voom.

Results: Homozygous mutant mice are viable and survive to adulthood, but do not exhibit gross hypotonia or motor delay. However, immunoblotting studies revealed a biochemical phenotype of reduced protein levels of NDUFB8 in liver and kidney samples from homozygous mutant mice. RNA-seq analysis revealed 465 DEGs in liver and 99 DEGs in gastrocnemius (p-value <0.05). Gene ontology pathway analysis highlighted involvement of innate-immune response, regulation of glucose import, and phosphatidylinositol-3-kinase signaling pathways. We noted considerable overlap of our DEG lists with a previously identified innate antiviral immune response signature identified in Tfam+/- mice, which serve as a model for mitochondrial depletion.

Homozygous MARS2 Arg135Trp mice are a viable model to further study MARS2 deficiency. Additionally, study of this model highlights the connections between mitochondria and the innate immune system.

39. A potential role for mast cells activation and phenotype in Eosinophilic Esophagitis

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Objective: Eosinophilic Esophagitis (EoE) is a chronic inflammatory disorder involving mast cells. The pathogenic role of specific types of mast cells and their activation in EoE in the esophageal mucosa is unknown. Previous work from my laboratory identified elevated mast cell counts despite low eosinophils after treatment. These patients have persistence of endoscopic furrows and histologic epithelial reactivity (basal zone hyperplasia and dilated inter-cellular spaces). We hypothesize that specific types of mast cells along with their activation drives these abnormalities. We aimed to assess mast cell phenotype and activation during diet elimination in pediatric EoE along with the effect of mast cell activation on the esophageal epithelium.

Methods: Multicolor immunofluorescence is performed for tryptase, carboxypeptidase A3, and CD63 on slides with esophageal biopsies from EoE patients before and after diet elimination of dairy. Image capture is performed on a Nikon Ti2 and analysis using Nikon NIS Elements. In vitro 3-D air liquid interface cultures are generated using EPC2-hTERT immortalized esophageal epithelial cells, which are stimulated with mast cells mediators (histamine, tryptase, chymase). Co-cultures will be performed with CD34-derived Human Mast Cells (HuMCs). Trans-epithelial electric resistance and FITC-dextran permeability are assessed to determine barrier dysfunction, along with assessment of morphology by H&E, and change in junctional proteins via immunohistochemistry and RNA/protein analysis.

Results: Biopsies from 40 patients who prospectively underwent dairy elimination are currently being stained and imaged. We have completed 2/3 of the cohort. We have identified the presence of MC-T and MC-TC mast cells in the epithelium before and after treatment. Quantitative analysis will be performed once image capture is complete for the full cohort. Histamine and tryptase stimulation was assessed on ALI cultures. Preliminary experiments suggest histamine and tryptase may lower TEER, increase FITC-Dextran flux, and induce morphological changes consistent with dilated inter-cellular spaces. Further experiments to assess mast cell molecules and co-culture with HuMCs are ongoing.

Conclusion: Work is ongoing in the laboratory to the assess the phenotype and activation of mast cells during diet elimination by immunofluorescence. Ongoing experiments in the lab will be performed to further the mechanism by which mast cell activation may alter barrier function of the esophageal epithelium.

40. A cross-sectional quantitative analysis of the natural history of free sialic acid storage disease

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Objective: Free sialic acid storage disease (SASD, OMIM 604369) is an ultra-orphan progressive multisystemic neurodevelopmental lysosomal storage disorder caused by the deficiency of the proton-driven carrier SCL17A5. Hard clinical endpoints for future clinical trials remain to be elucidated. Therefore, the primary aim of the present study was to quantitatively define important disease characteristics such as disease onset, diagnostic delay and survival rates in SASD.
Methods: We quantitatively analyzed published cases with SASD (N=116). Main outcome variables were survival and diagnostic delay. As potential predictor of survival, the influence of the amount of free sialic acid storage was investigated. Moreover, major disease features and geographical patient distribution were explored. The analysis was performed in compliance with STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) criteria.
Results: Median age at disease onset was 0.17 years. Median age at diagnosis was 3 years with a median diagnostic delay of 2.5 years. Median survival was 11 years. The biochemical phenotype clearly predicted the disease course: Patients with an urinary free sialic acid excretion below 6.37-fold or an intracellular free sialic acid storage in fibroblasts below 7.37-fold of the mean of the reference range survived longer than patients with biochemical values above these thresholds. Cluster analysis of disease features suggests a continuous phenotypic spectrum rather than well-defined subtypes for SASD. Patient distribution was panethnic.
Conclusions: The combination of neurologic symptoms, visceromegaly and dysmorphic features and/or nonimmune hydrops fetalis should prompt specific tests for SASD, reducing diagnostic delay. The present quantitative data inform clinical studies and may stimulate and accelerate the development of specific therapies. Biomarker-phenotype associations are particularly important for counseling parents and study design.