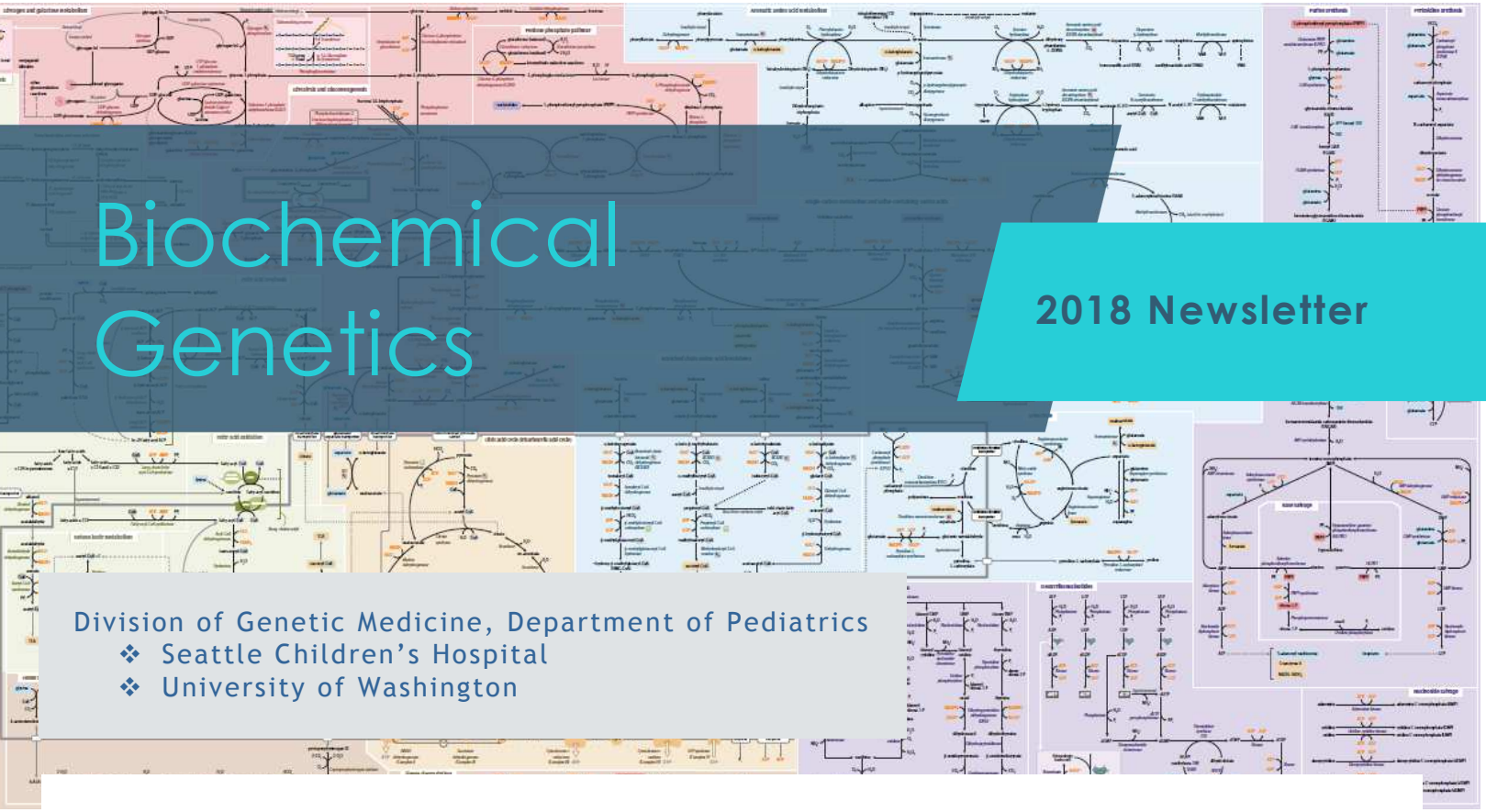

Biochemical Genetics

2018 Newsletter

Division of Genetic Medicine, Department of Pediatrics
- Seattle Children's Hospital
- University of Washington

2018 Highlights

Program Overview:

The Biochemical Genetics program at Seattle Children's Hospital (SCH) and the University of Washington (UW) provides diagnostic expertise and ongoing follow-up for patients with inborn errors of metabolism in the Washington, Wyoming, Alaska, Montana and Idaho (WWAMI) region.

Inborn errors of metabolism are inherited disorders that cause a disruption or abnormality in one of the biochemical pathways involved in the production or breakdown of proteins, fats, or carbohydrates.

Our Biochemical Genetics Program offers immediate resources for intervention by a specialized team of physicians and other specialized health care providers and is supported by a diagnostic laboratory that aids in diagnosis and management of children and adults. Serving the large population of Washington State and neighboring regions, the Biochemical Genetics program provides a comprehensive multidisciplinary evaluation, diagnosis and long-term management program for patients and their families.

Subspecialty clinics include the Cristine M Trahms Program for Phenylketonuria (PKU Clinic-UW), Biochemical/Metabolic Genetics clinics (SCH/UW), Lysosomal Disorders Clinic (UW/SCH), Urea Cycle Disorders Clinic (SCH/UW), Congenital Disorders of Glycosylation Clinic (SCH), and the Wilson Disease Clinic (SCH). Satellite clinics are held two times per year in Spokane.

The Biochemical Genetics Division is actively involved in clinical trials and research studies. Biochemical Genetics offers clinical trials working to benefit rare metabolic patients. We also provide extensive education for professionals and our patients.

Our team is growing!

In 2018, Kait Miller, MS, LCGC joined the Biochemical Genetics team at the University of Washington. Previously, she worked as a genetic counselor and research coordinator in the lysosomal storage disorder (LSD) clinic at Emory University and a cancer genetic counselor at Wellstar Medical Health Center in Atlanta, GA. At the UW, she works with Dr. Scott and Dr. Chanparasert in the care of LSD and other biochemical genetics patients.

Jeannie Parity, RN has 17 years of nursing experience and joined the Biochemical Genetics team at SCH in 2018. Prior to joining us, her experience and background was primarily in women's health including obstetrics, gynecology, high risk OB (including genetics) and reproductive health. Jeannie loves spending time with her family, camping, and traveling. She also claims to be an amateur wine connoisseur!

Aishleen O'Brien, RN, BSN, CPN also joined the Biochemical Genetics team at SCH in 2018. She is originally from Milwaukee, WI. She came to SCH as a CICU travel nurse. This ended up being her favorite travel assignment – so she decided to stay! Aishleen worked in the CICU/PICU at SCH for two years before joining our team. Outside of work Aishleen enjoys traveling, cooking, hiking, and hanging out with her cat, Freddie.

Hayden grew up in the Pacific Northwest and graduated from the University of Washington with a Bachelor's of Science in Cellular, Molecular, and Developmental Biology. He spent years conducting clinical research on Soft Tissue Sarcomas, Stem Cell Transplants, and Immunotherapies at Seattle Cancer Care Alliance and Fred Hutchinson Cancer Research Center. After arriving at Seattle Children's Hospital Biochemical Genetics Department in Spring of 2018, he began coordinating many of the research studies we offer to our patients. He is working to launch upcoming new therapeutic trials, establish a biochemical genetics bio-repository, and expand the research programs at Seattle Children's Hospital to help pave the way for Hope, Care, and Cures for our patients. In his free time, he enjoys Piña Coladas, long walks on the beach, and baking.

Fellowship in Medical Biochemical Genetics:

The University of Washington School Of Medicine's, Medical Biochemical Genetics Fellowship is based at Seattle Children's Hospital and provides care to children and adults at Seattle Children's Hospital and the University of Washington (Program Director: **Dr. J Lawrence Merritt, II**). Our program covers a diverse population from a large region covering five states in the Pacific Northwest. Fellows will have an opportunity to participate in clinical care and learn from patients from all areas of inborn errors of metabolism in clinic; will act as a member of the primary admitting in-patient service and hospital consultation service. Fellows will also have opportunities to participate in the vast clinical and basic science research programs at both institutions and in the clinical biochemical genetics laboratory to learn the complex interpretation of biochemical genetic testing.

During the year, fellows have an intensive exposure to inpatient and outpatient biochemical genetics and nutrition. Fellows are exposed to a wide variety of acute and chronic inborn errors of metabolism with exposure to treatment through nutritional manipulation, medications, enzyme replacement therapy, and solid organ or bone marrow transplantation. Through the year, fellows will have the opportunity to rotate in the Biochemical Genetics Laboratory. Fellows are encouraged and supported in presenting their research at national and international meetings. This training focuses on providing fellows the skills necessary to become independent academic medical biochemical geneticists.

We are experiencing steady interest from potential future candidates for this fellowship and we look forward to its ongoing success!

The Biochemical Genetics training program at UW is accredited by the American Board of Medical Genetics and leads to eligibility to sit for the Clinical Biochemical Genetics examination. The goal of the program is to provide medical genetics residents with a sound academic, clinical, and laboratory understanding of the diagnosis, treatment and management of patients with inborn errors of metabolism.

Pictured → Back row: Dr. Angela Sun, Jenny Thies, Kelly McKean, Matt Greever, Dr. J. Lawrence Merritt, II, Marie Norris, Dr. Sihoun Hahn, and Jacob Kelliher.
Front row: Andrea Barry-Smith, Dr. Irene Chang, Sarah Sullivan, Dr. Christina Lam, and Emily Burnham.

We are excited to announce our first Medical Biochemical Genetics Fellow, **Irene Chang, MD**, started her fellowship in July 2018. Irene is a diligent and caring physician who functions as an integral part of our team to provide excellent care to patients. She is taking full advantage of all the opportunities the training program offers to maximize her learning and growth.

Other Training:

In 2018, **Dr. Amanda Freed,** Medical Genetics Resident, spent a total of 4 months rotation with Biochemical Genetics at Seattle Children's. She was with us from April 2018 through June and the month of October 2018.

Biochemical Genetics also provides rotations for residents of other specialties to provide a greater knowledge of the complexities and range of many of the conditions and disorders referred here. There is emphasis on the need to maintain a coordinated collegial approach in the diagnosis and care of these patients, whose conditions cross the boundaries of many specialties. For instance, in June, **Dr. Ava Lin**, Neurology resident and **Dr. Voytek Slowik**, Hepatology resident spent a month on rotation with Biochemical Genetics.

In 2018, SCH and UW had over 2063 encounters encompassing outpatient visits and inpatient consultations with biochemical genetics. Major disorders seen in our clinic and hospital are summarized in **Table 1**. Some of the subspecialties of our program are highlighted below, but we see and welcome any patient with metabolic disorders or who needs evaluation regarding diagnosis, treatment or ongoing medical care.

Table 1. Major Disorders in 2018 at Seattle Children's & University of Washington Clinics
Lysosomal Storage Disorder
Phenylketonuria
Organic Acid Disorder
Amino Acid Disorder
Urea Cycle Disorder
Peroxisomal Disorder
Fatty Acid Oxidation Disorder
Cobalamin Metabolism Disorder
Mitochondrial Disorder
Congenital Disorders of Glycosylation
Wilson Disease
Developmental Delay
Failure to Thrive
Seizure Disorder
Carbohydrate Metabolism disorders
Biotinidase Deficiency
Biopterin Deficiency

"The provider was very thorough in answering all my questions and made me feel very comfortable in knowing that if I had any questions in the future, to call her or reschedule to come back and just really made me feel comfortable with where we were at with my child's prognosis. Was very impressed and that's just a very good feeling."

"My visit with Dr. Sun was wonderful. She was kind, caring, and compassionate. I'm grateful for her work!"

"Really good, patient centered, knowledgeable, good bedside manner. Definitely something someone who knows how to work with children. Office is timely, responsive, and communication is excellent both ways."

Faculty & Staff

Attending Physicians:
- C. Ronald Scott, MD
- Sihoun Hahn, MD, PhD
- J. Lawrence Merritt, II, MD
- Angela Sun, MD
- Christina Lam, MD
- Sirisak Chanprasert, MD
- Anne Leavitt, MD

Fellow:
- Irene Chang, MD

Registered Nurses (SCH):
- Emily Burnham, RN, BSN, CPN
- Jeannie Parity, RN
- Aishleen O'Brien, RN, BSN, CPN
- Andrea Hartgraves, RN, BSN, CPN

Metabolic Dietitians (SCH):
- Kelly McKean, MS, RDN, CD, CSP
- Sarah Sullivan, MS, RDN, CD
- Marie Norris, MS, RDN, CD, CNSC

Metabolic Dietitians (UW):
- Beth Ogata, MS, RDN, CD
- Janie Heffernan, MS, RDN, CD

Genetic Counselors:
- Jenny Thies, MS, LCGC (SCH)
- Kait Miller, MS, LCGC (UW)
- Jie Feng, MS, LCGC (UW)

Social Workers:
- Andrea Barry-Smith, MSW, LICSW, JD
- Janet Hamovitch, MSW

Clinical Research Associates:
- Hayden Vreugdenhil, BS
- James DeLappe, BS

Fellowship Coordinator:
- Jacob Kelliher, BS, MHA

Dietary Management Program

The Biochemical Genetics nutrition program at Seattle Children's Hospital provides medical nutrition therapy to a variety of inborn errors of metabolism (IEM). Nutrition therapy for these various IEM disorders is often the cornerstone of the medical treatment, so the dietitians work closely with the BCG physicians to ensure the most appropriate nutrition plan for each patient. Significant education and support is provided to the patient and their family to support their success. Each nutrition plan is tailored to each individual in order to achieve their normal growth and development while meeting nutrient requirements and modifying macronutrients (carbohydrates, proteins or fat) as needed for their disorder. Dietitians manage diets whether by mouth, through feeding tubes, or when specialized parenteral nutrition solutions are required during acute illness. They have in-depth knowledge of the numerous metabolic formulas available for patients and work with families to find a product that will be best tolerated and meet their needs.

All of the biochemical genetic dietitians at Seattle Children's are members of Genetic Metabolic Dietitians International (GMDI), which is an organization that works to provide standards of excellence and leadership in nutrition therapy for genetic metabolic disorders. **Sarah Sullivan** is co-chair of the GMDI technology committee and has worked to support MetabolicPro, an online tool that supports biochemical genetic dietitians with nutrition calculations. **Marie Norris** coauthored two peer-reviewed articles and was involved in a project to design and implement electronic parenteral nutrition ordering, which was successfully launched and subsequently nominated for Seattle Children's David Fisher Award for Excellence in Safety. **Kelly McKean** has been with our team since the start of Biochemical Genetics at Seattle Children's and is a leader in the nutrition department for patient education and website updates.

At University of Washington, the primary metabolic dietitian is **Beth Ogata.** She is also a member of GMDI and involved in workgroups for Nutrition Management Guidelines for MSUD and Nutrition Management Guidelines for PKU. **Janie Heffernan** is also at University of Washington as dietitian. Her focus is PKU nutrition.

Nursing Program

In 2018, our RN team led a quality improvement project aimed at standardizing emergency room letters our providers write for BCG patients. We also focused on ensuring all emergency room letters were uploaded into the patient's electronic medical record in the Seattle Children's Hospital System and to the statewide EDIE system. Our goal was to ensure that the information local providers need to give best care to our patients is widely and uniformly available. Getting the word out to community practitioners about our unique patient population and their unique needs is at the heart of what we do.

BCG RNs continue to be involved in various projects within the ambulatory nursing department including the EPIC transition project, Shared Governance Development of Nurses Council, Ambulatory RN New Graduate Residency Program Consultant Group, Specialty Care Coordination work group, and OMBC.

Additional projects our nurses have contributed to are the creation of telephone triage algorithms, escalation pathways for non-clinical staff, float/new hire RN orientation manual, and RN preceptor training.

The Center of Excellence for Wilson Disease

Our mission is to provide comprehensive best-quality care to our patients and families with Wilson disease. Our multidisciplinary approach ensures the best care for each individual with Wilson disease. Wilson disease program offers immediate resources for intervention by specialized physicians, nutritionists and genetic counselors and is supported by a diagnostic laboratory for confirmation; so we can provide a one-stop experience for patients and families. The molecular genetics laboratory at the hospital runs *ATP7B* gene sequencing testing as a clinical test with a quick turn-around time especially for those patients experiencing acute liver failure within 48 hours. **Drs**. **Hahn** (Biochemical Genetics), **Horslen** (Gastroenterology), **Weiss** (Ophthalmology), **Mingbunjerdsuk** (Neurology) and **de Lacy** (Psychiatry) are participating providers for care of Wilson disease patients.

The Lysosomal Storage Disease (LSD) Program at UW/SCH

The LSD program provides multidisciplinary care including consultation, examination, testing/ diagnosis, treatment, monitoring, and genetic counseling for patients with LSDs and their families. The patients' medical home is centered with the Biochemical Genetics team. The program is dedicated to the management of these rare diseases and provides care by UWMC and SCH specialists in many areas of medicine including ophthalmology, orthopedics, cardiology, neurology, nephrology, pulmonary, otolaryngology, neurodevelopmental, radiology and anesthesia. Our group also works with local hospitals to facilitate transition of treatment to centers closer to each patient's home or for infusions to be done in the patient's home. Long-term follow-up of patients with these rare diseases is essential.

There is much ongoing research in the field of lysosomal storage disorders. The UWMC and SCH teams currently have active patient registries for MPS I, MPS II, MPS IV, MPS VI, Pompe disease, Fabry disease, and Gaucher disease. The clinic team follows a large cohort of patients across the spectrum of LSDs and long-term follow-up of patients with these rare diseases is essential as is continuing to keep abreast of new developments in therapies and care. A clinical trial for Hunter syndrome is in progress at SCH under IRB approval to evaluate long-term safety and clinical outcomes of intrathecal Idursulfase enzyme replacement.

The Urea Cycle Disorders (UCD) Program at SCH

Provides multidisciplinary care including consultation, examination, testing, diagnosis, treatment, and genetic counseling for patients with urea cycle disorders and their families. Our goal is to provide patients and families with a comprehensive medical home. Our mission is to provide each patient with the knowledge, ability, and proper tools to allow them to manage their disorder. The biochemical genetics team is the core within a larger program dedicated to the management of these diseases and providing care by UWMC and SCH specialists in many areas of medicine including psychology, neurodevelopment, neurology, gastroenterology, and organ transplant. The clinic team follows a large group of children and adult patients across the spectrum of UCDs. Our group also works with local hospitals to coordinate treatment of care during acute emergencies and in routine follow-up closer to each patient's home.

We are actively providing our patients access to emerging research and clinical trials. We actively collaborate with industry partners with new clinical trials including recent studies with Aeglea Biotherapeutics, Inc, Kaleido Biosciences, and Translate Bio. We are a site of the Urea Cycle Disorders Consortium Longitudinal study, sponsored by the Rare Disease Clinical Research Network at the National Institute of Health along with the National Urea Cycle Disorders Foundation in order further improve treatment, quality of life, and our understanding of UCDs. We aim to encourage ongoing efforts to implement newborn screening for all UCDs – including ornithine transcarbamylase deficiency.

The Center of Excellence for Congenital Disorders of Glycosylation (CDG)

The CDG program at Seattle Children's was established in 2017, with patients scheduled into a quarterly clinic. It has been deemed a Center of Excellence by CDG Care, the US family group for congenital disorders of glycosylation. **Dr. Christina Lam** is currently the primary physician for these patients. In 2018, there were 8 patients seen here for this relatively new group of diagnoses and interest in the clinic remains high. An industry sponsored natural history study of PMM2-CDG began, and we have successfully enrolled 5 individuals. We hope to begin additional natural history and therapeutic studies for CDGs in 2019.

The Newborn Screening Follow-up Program

Since Washington State's Newborn Screening Program began in 1963 with PKU, the Biochemical Genetics Program has been providing confirmatory diagnostic testing, clinical treatment and care coordination for babies identified with metabolic diseases from infancy to adulthood. The Biochemical and Molecular Genetics Laboratory staff works very hard to prioritize and analyze these samples as quickly as possible. In 2018, Washington State screened for 6 amino acid disorders, 5 fatty acid oxidation disorders, 7 organic acid disorders, and 10 other congenital disorders.

We continue to be actively involved with the Western States Regional Genetics Network to study the outcomes of infants with abnormal newborns screens and, in particular, the long-term outcomes of infants identified with Very Long-Chain Acyl-CoA Dehydrogenase (VLCAD) Deficiency.

The Washington State Department of Health (DOH) continues to provide excellent Newborn Screening confirmation & follow-up. This program is made possible with contract funding for the consultative services and additional testing required to confirm or rule out presumptive diagnoses. This confirmatory diagnosis allows for the earliest possible treatment to begin, giving these children the best quality of life and in some cases a normal or nearly normal lifestyle that would not have been possible without this early care. DOH also continues to provide contract funding for metabolic dietitian services for the Newborn Screening Follow-up Program, as well as for outreach services for semi-annual outreach Biochemical Genetics Clinics in Spokane.

The Newborn Screening Program is partnering with researchers at the University of Washington to refine the lab method for detection of lysosomal storage diseases (LSDs) in infants through newborn screening. The data to-date indicates that the prevalence of Fabry, Pompe and Mucopolysaccharidosis Type 1 (MPS-1) is two to four times greater than the prevalence estimates by clinical diagnosis. It is apparent that the tandem mass spectrometry method can be expanded to detect additional LSDs from a single blood spot for which therapy exists or is being developed. Future plans include the addition of at least five more lysosomal storage diseases to the new assay: MPS Type II, MPS Type IV-A, MPS VI, neuronal ceroid lipofuscinosis (NCL-2), and lysosomal acid lipase (LAL) deficiency.

Table 3. 2018 Newborn Screening Totals of Confirmed Conditions

Condition	Severe	Mild
ASA/CIT		
BIO	3	
CUD	1	
GA I		
GALT	1	
HCY		
HMG/MCD		
IVA		
LCHAD	1	
MCAD	11	1
MMA	1	
MSUD		
PKU	7	4
TYR I	1	
VLCAD	1	
X-ALD	3	4
Total	**35**	**9**

Does not include 5 other non-panel conditions identified: one GA-2 case and 4 Zellweger cases

Washington State Department of Health

Biochemical Genetics Laboratory (SCH) & Molecular Genetics Laboratory (SCH)

For over 40 years, Seattle Children's has been providing comprehensive genetic testing and consultative services to healthcare providers and families in the Washington, Wyoming, Alaska, Montana and Idaho (WWAMI) region. Our genetics laboratories consist of biochemical genetics, molecular genetics, cytogenetics and a research and development laboratory dedicated to bringing the most current and specialized research tests into the clinical arena using tandem mass spectrometry and microarray technology.

The Biochemical Genetics Laboratories (SCH) are led by **Dr. Sihoun Hahn, Dr. Rhona Jack and Dr. Anna Scott**. Test volumes in the labs are summarized in **Table 5**.

The Biochemical and Molecular Genetics Laboratories serve as a key component of the Biochemical Genetics Program. The laboratories provide rapid, comprehensive diagnostic results and rapid monitoring results including interpretation and guidance for follow-up.

Our laboratory is committed to high quality results. To ensure accuracy, the laboratory is participating in a variety of external proficiency testing programs offered by various national and international agencies (ERNDIM; European network, CAP; College of American Pathologists, CDC; Center for Disease Control).

Research & Development (R&D) Laboratory

The Biochemical Genetics program's CLIA-certified R&D Laboratory is located at the Seattle Children's Research Institute (SCRI): Center for Integrative Brain Research (Center Director. Dr. Jan-Marino Ramirez). The facility is fully equipped with a LC-MS/MS and an Illumina Genome Analyzer IIx. Since 2007, the R&D team has continuously focused their efforts on refining current methodologies and developing new tests, with a fundamental goal to improve clinical practice through the implementation and integration of routine laboratory testing. In particular, the lab aims to develop and validate clinical tests to diagnose various metabolic and genetic disorders by utilizing tandem mass spectrometry.

At the heart of translational research, the R&D Laboratory's goal is to bridge basic research and the clinical applications of novel tests developed for effective patient diagnosis and treatment. Current staffs of the R&D team include **Dr. Christopher Collins, PhD, Dr. Fan Yi, PhD,** and **Remwilyn Dayuha, BS**, which is led by **Dr. Sihoun Hahn, MD, PhD.**

Table 5 A. High Volume Tests in 2018

Test	Analytic Method	# Analyses
Fragile X	Fragment Analysis, Southern Blot	317
Prader Willi /Angelman Syndrome	Methylation PCR	49
MCAD	Sequencing	23
Muscular Dystrophy	MLPA	8
POLG 1	Sequencing	16
Spinal Muscular Atrophy	PCR	23
Spinal Muscular Atrophy Carrier Testing	MLPA	9
VLCAD	Sequencing	45
Wilson Disease	Sequencing	12
GCK	Sequencing	5
HNF1A	Sequencing	9
HNF4A	Sequencing	9
MODY Panel	Sequencing	39
CHI panel	Sequencing	8
Neonatal Diabetes panel	Sequencing	2
Connexin	Sequencing	23
22q.11	MLPA	17
Lysosomal Acid Lipase	LIPA seq	2
Rett Panel	Sequencing/MLPA	3
Pompe Disease	GAA sequencing	7
Amino Acid Analysis	HPLC	1807
Phenylalanine / Tyrosine	HPLC	690
Organic Acid Analysis	GC/MS	1192
Acylcarnitine profile	MS/MS	993
Carnitine profile	MS/MS	581
Alpha aminoadipic semialdehyde	LC/MS/MS	245
Pipecolic acid	LC/MS/MS	39
Oligosaccharide	TLC	107
Very long chain fatty acids (peroxisomal)	GC/MS	119
MPS	Dye Binding	137
Succinylacetone QNT	GC-MS	21
MMA, plasma	LC-MS/MS	228

Table 5 B. High Volume Tests in 2018

Enzyme Testing	# Analyses
Lysosomal Acid Lipase	4162
Alpha-galactosidase	20
Alpha-glucosidase	86
Beta-galactosidase	1
Hexosaminidase	5
TPP Tripeptidyl peptidase (NCL2)	70
PPT Protein palmitoyl transferase (NCL1)	68
Arylsulfatase A	10
Beta-glucosidase	13
Biotinidase	12
Galactose 1 Phosphate	39
Galactose-1-PUT	12
Miscellaneous enzymes	18
Total number	11149

IEM Conference is held every first Wednesday of the month, with August hiatus. This Conference is open to any interested members of all specialties and provides a chance to hear and present interesting cases and diagnostic puzzles, as well as laboratory tests and process updates. Presentations are given by a variety of providers, fellows, and visiting experts from many specialties. This conference provides an interesting and open venue for the presentation of varied types of cases and histories.

This conference functions as a teaching event for fellows, residents, students and it also provides ongoing educational credit at CME Level II category.

2018 IEM Conference Schedule:

Topic	Presenter
"Diagnostic Utility of Next Generation Sequencing in Suspected Inborn Errors of Metabolism – 7 Years Experience on the Biochemical Genetics Service."	Jeongho Lee, MD, PhD Irene Chang, MD
"NBS policy 101: How to Add Conditions to the Mandatory Newborn Screening Panel."	John Thompson, PhD, MPH, MPA, Director, Office of Newborn Screening, DOH, WA.
"Metabolic Disease and Bone Marrow Transplant."	Kanwaldeep K Mallhi, MD
"An Update on the Biochemical Genetics Division's NGS Testing from 2010-2018." "Retrospective Pilot Study of Newborn Screening for Proximal Urea Cycle Disorders in Washington State."	Irene Chang, MD J Lawrence Merritt, II, MD
"C7 for treatment of cardiomyopathy in FAODs." "Revisiting 'An exceptional family with three consecutive generations affected by Wilson disease,' (published in 2012) through peptide analysis of ATP7B in dried blood spots by MSMS."	Amanda Freed, MD Sihoun Hahn, MD, PhD
"Differential diagnosis and evaluation of Hydrops Fetalis." "Brain Iron Accumulation Disorders."	Amanda Freed, MD Angela Sun, MD
"Practicum in Urea Cycle Disorders." "A Jab at CDG."	Tania Vasquez, MD Ava Lin, MD
"Initiating ERT in a Septuagenarian with Gaucher Disease."	Amanda Freed, MD
"ALDH18A1: Where Connective Tissue, Neuromuscular and the Urea Cycle Disorders Meet." "Diagnostic Quandaries from the BCG Lab."	Angela Sun, MD Irene Chang, MD Amanda Freed, MD
"Caveats of Newborn Screening."	Irene Chang, MD Jenny Thies, MS, LCGC

Funded Clinical Trials

Longitudinal Study of Urea Cycle Disorders, O'Malley Family Foundation. Children's Research Institute (Batshaw) (10/1/11 – 7/31/18) Site PI: J Lawrence Merritt, II

A Phase 1/2 Open-Label Study In Patients with Arginase I Deficiency to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of Intravenous AEB1102 (Protocol# CAEB1102-101A) Aeglea Biotherapeutics, Inc. (12/22/17 – present) Site PI: J Lawrence Merritt, II; Co-investigator: Angela Sun

A retrospective chart review study to assess the clinical outcome of triheptanoin treatment in patients with long-chain fatty acid oxidation disorders (LC-FAOD) treated under expanded access program. UX007-CL003 Ultragenyx Pharmaceutical; PI: J. Lawrence Merritt, II

An Open-label Long-Term Safety and Efficacy Extension Study in Subjects with Long-Chain Fatty Acid Oxidation Disorders (LC-FAOD) Previously Enrolled in UX007 or Triheptanoin Studies. UX007-CL202; Ultragenyx Pharmaceutical; PI: J. Lawrence Merritt, II

HGT-HIT-046 An Open-Label Extension Study of HGT-HIT-045 Evaluating Long-Term Safety and Clinical Outcomes of intrathecal idursulfase –IT Administered in Conjunction with Intravenous Elaprase® in Pediatric Patients with Hunter Syndrome and Cognitive Impairment; P.I.: Angela Sun; Co PI: Sihoun Hahn. Funding: Shire

A Four-Part, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Four-Arm, Discontinuation Study to Evaluate the Efficacy and Safety of Subcutaneous Injections of BMN 165 Self Administered by Adults with Phenylketonuria. 7/1/2015 – 12/31/2018, 165-302, BioMarin. Scott, C. Ronald (PI), Leavitt, Anne M. (Co-PI), Jie Feng (Coordinator)

Wilson Therapeutics 101-201. A multi-center study for the assessment of copper parameters in Wilson Disease subjects on standard of care treatment. P.I.: Sihoun Hahn, MD, PhD Period: 2016-present. Funding: Wilson Therapeutics Inc.

Wilson Therapeutics 101-301. A Phase 3, Randomised, Rater-Blinded, Multi-Centre Study to Evaluate the Efficacy and Safety of WTX101 Administered for 48 Weeks versus Standard of Care in Wilson Disease Subjects Aged 18 and Older with an Extension Phase of up to 60 Months. PI: Sihoun Hahn. Funding: Wilson Therapeutics Inc.

Clinical and Basic Investigations into Phosphomannomutase deficiency (PMM2-CDG). PI: Christina Lam. Funding: Glycomine, Inc.

Non-funded Clinical Trials & Research

Individual Patient, Non-Emergency FDA IND # 129399 Individual Patient, IND. Non-Emergency Single Patient Expanded Access Treatment of an individual patient with carnitine-acylcarnitine translocase (CACT) deficiency with UX007 (triheptanoin). PI: J. Lawrence Merritt, II

Individual Patient, Emergency FDA IND # 139430 Individual Patient, IND. Emergency Use Treatment of an Individual Patient with Carnitine-Acylcarnitine Translocase (CACT) Deficiency with UX007 (Triheptanoin) PI: J. Lawrence Merritt, II

Individual Patient, Emergency IND (FDA IND #140229 July 2018 to present) Individual Patient, Emergency IND. Emergency Single Patient Treatment of an Individual Patient with Very long-chain acyl-coenzyme A dehydrogenase deficiency (VLCADD) with UX007 (Triheptanoin). PI: Christina Lam

We enrolled over 100 patients into clinical trials and clinical disease registries in 2018!

Registries

Wilson Disease Registry. P.I. Sihoun Hahn. Funding: Yale University/Wilson Disease Association.

An open-label ascending dose cohort study to assess the safety, pharmacokinetics, and preliminary efficacy of neoGAA (GZ402666) in patients with infantile-onset Pompe disease treated with alglucosidase alfa who demonstrate clinical decline or sub-optimal clinical response. 2018-present. P.I.: Sihoun Hahn. Funding: Sanofi/Genzyme

The LSD Registry Program. Principal Investigators: Site PI, J Lawrence Merritt, II, MD; Co-PI, Angela Sun, MD. Funding: Genzyme Corporation. Four long-term natural history studies of treated and untreated patients with Gaucher, Fabry, MPS I and Pompe diseases. These four registries are also at UW with Principal Investigators C. Ronald Scott, and Jie Feng, MS, LCGC

Morquio A Registry Study (MARS), Angela Sun, PI. 2014 – present.

A Global Multi-Center, Long-Term, Observational Survey of Patients with Hunter Syndrome (Mucopolysaccharidosis II). **A long-term natural history disease registry of treated and untreated patients with MPS II.** Funding: Shire Human Genetic Therapeutics. Angela Sun,: PI; Sihoun Hahn, Christina Lam, Lawrence Merritt: Co-investigators

The MPS VI Clinical Surveillance Program. A long-term natural history disease registry of treated and untreated patients with MPS VI. Funding: BioMarin Pharmaceuticals. Angela Sun,: PI.

We enrolled over 150 patients in research studies in 2018!

Research Projects

Assay validation for MPS II, IIIA, and IIIB in a real-time newborn screening lab. MPS II/III Pilot Study, Shire Genetic Therapies. 5/8/2014 – 6/30/2019. C. Ronald Scott (PI); Michael H. Gelb (Co-PI); Jie Feng (Coordinator)

Clinical and Basic Investigations into Known and Suspected Congenital Disorders of Glycosylation NHGRI Intramural Protocol – 14-HG-0071 Christina Lam,Co-Investigator. (NCT02089789) (2014-2016 – PI; 2016-Current – CoI)

Multiplex Analysis of Inborn Errors of Metabolism to develop sensitive, reproducible assays for the measurement of lysosomal enzymes for the detection of lysosomal storage diseases in dried blood spots. R01 DK DK67859, NIDDK 4/1/2014 – 3/31/2018. Gelb, Michael H. (PI) Scott, Turecek, Frantisek (Co-PI) C. Ronald (Co-PI), Jie Feng (Coordinator)

MLD Studies. To field-test a novel assay in a working newborn screening lab to determine its effectiveness in identifying newborns with metachromatic leukodystrophy. 2/26/2016-2/25/2019. Michael H Gelb (PI), C. Ronald Scott (Co-PI), Jie Feng, MS, LCGC (Coordinator).

Assay validation for MPS-VII in a real-time newborn screening lab. Ultragenyx 2-18-2016 - 12 - 30-2019. Scott, C. Ronald, PI

Multiplexed immune-SRM screening for primary immunodeficiencies; Funding: NIH/National Institute of Allergy and Infectious Diseases. (2016-2020). PI: Sihoun Hahn.

Newborn screening for Cystinosis. Cystinosis Research Foundation. 2017-2019. Sihoun Hahn (PI)

Proteolytic quantification of GAA in dried blood spots by peptide immune-SRM as a potential screen for immunogenicity in Pompe disease. 2018-2020. PI: Sihoun Hahn. Funding: Sanofi/Genzyme

Targeted Proteomic Analysis of Extremely Low Abundance Signature Peptide Biomarkers for Potential Newborn Screening in Wilson's Disease. PI: Sihoun Hahn. Funding: NIH/National Institute of Child Health and Development (2018-2020).

Awards, Grants, Honors

Sihoun Hahn, MD, PhD: Chair, Department of Genome Medicine and Science, Gachon University School of Medicine, Incheon, Korea (2015 -2018)

Sihoun Hahn, MD, PhD: Director, Gachon Institute of Genome Medicine and Science, Gachon University School of Medicine, Incheon, Korea (2015 – 2018)

Extramural Invited Presentations

Sihoun Hahn: Newborn Screening for Cystinosis. International Research Symposium. Cystinosis Research Foundation. March 1-2, 2018 Irvine, CA, U.S.A.

Sihoun Hahn: Newborn Screening in the U.S.A. Korean Society for Newborn Screening. April 6, 2018, Seoul, Korea

Sihoun Hahn: Newborn Screening for Wilson Disease. Wilson Disease Association Annual Meeting, April 26, 2018, Houston, TX, U.S.A.

Sihoun Hahn: Rapid Multiplexed Proteomic Screening: Wilson Disease, Primary Immunodeficiencies, and Cystinosis. Pediatric Grand Round, Soonchunhyang University Hospital, September 18, 2018, Seoul Korea

Christina Lam: Genetics and CDGs / Doctor is in Session / Question and Answer Session; CDG-Care Family Conference; February 2018, San Diego, CA, U.S.A.

J. Lawrence Merritt, II: Improving Communication and Education in Newborn Screening Between Healthcare Professionals and Parents. 6th Asian Congress for Lysosomal Storage Disease Screening. Tokyo, Japan. August 2018

J. Lawrence Merritt, II: Implementation of Newborn Screening program- setting up the right clinical quality indicators. 6th Asian Congress for Lysosomal Storage Disease Screening. Tokyo, Japan. August 2018

J. Lawrence Merritt, II: Anticipating Challenges in Newborn Screening for LSDs. 6th Asian Congress for Lysosomal Storage Disease Screening. Tokyo, Japan. August 2018

Intramural Presentations

Angela Sun. 5/10/18 Research Update from the SCH Biochemical Genetics Group, Division of Genetic Medicine Research Day

MERRITT JL II, THOMPSON JD, RAGSDALE A. Retrospective Analysis of Newborn Screening Methods For Proximal Urea Cycle Disorders in Washington State. Seattle Children's Hospital, Center for Clinical And Translational Research Science Day, May 24, 2018.

Posters/Oral Presentations

Irene J. Chang, Jeongho Lee, **Christina Lam**, Sarah V. Clowes Candadai, **Jenny Thies**, J **Lawrence Merritt II, Angela Sun,** and **Sihoun Hahn**. Diagnostic utility of next generation sequencing in suspected inborn errors of metabolism- 7 years' experience on the biochemical genetics service. ACMGG annual conference, Charlotte, NC, April 10-14, 2018

Irene J. Chang, Remwilyn Dayuha, Jeongho Lee, Sunhee Jung, Rhona Jack, **Angela Sun, Christina Lam, John Lawrence Merritt II,** Regine Schoenherr, Jeffrey Whiteaker, Amanda G. Paulovich, **Sihoun Hahn.** Proteolytic immuno-SRM-MSMS in dried blood spots to determine immunogenicity in patients with infantile Pompe disease. World Symposium, San Diego, CA, Feb 5-9, 2018

Myers CM, Bennett JT, **Merritt II JL**, Tsuchiya KD, Vogel J, Rogge L, Thies JM, Foss K, Paschal CR. Expanding the clinical spectrum of KDM6A-associated Kabuki syndrome. Poster at American Society of Human Genetics, October 2018.

Zori RT, Diaz GA, **Merritt II JL**, Schulze A, Enns GM, McNutt MC, Teles EL, Patki KC, Wooldridge JE, Batzios SP. Improvements in arginase 1 deficiency-related disease manifestations following plasma arginine reduction with pegzilarginase: Early phase 2 results. American Society of Human Genetics, October 2018.

Diaz GA, Longo N, Schulze A, Bubb G, Eckert S, Patki KC, Wooldridge JE, **Merritt II JL**. Clinical features of arginase 1 deficiency: Review of literature case series. American Society of Human Genetics, San Diego, October 2018.

Zori RT, Diaz GA, **Merritt II JL**, Schulze A, Enns GM, McNutt MC, Teles EL, Patki KC, Alters SE, Wooldridge JE, Batzios SP. Improvements in arginase 1 deficiency-related disease manifestation following plasma arginine reduction with pegzilarginase. Society for the Study of Inborn Errors of Metabolism, September 2018.

Wooldridge JE, Diaz GA, Longo N, Schulze A, Bubb G, Eckert S, Patki KC, **Merritt II JL**. Clinical Features of Arginase 1 Deficiency: Review of Global Literature. Japanese Society for Inherited Metabolic Diseases, November 2018.

Chang IJ*, Lee J*, **Lam C, Merritt JL II, Sun A, Thies J, Hahn SH**. Diagnostic Utility of Next Generation Sequencing in Suspected Inborn Errors of Metabolism—7 Years' Experience on the Biochemical Genetics Service. ACMG Annual Clinical Genetics Meeting. Charlotte, North Carolina; poster, presenting author Chang IJ; (2018).

Lam C, Hall PL, Alexander JJ, Asif G, Berry GT, Ferreira C, Freeze HH, Gahl WA, Nickander KK, Sharer JD, Watson CM, Wolfe L, Raymond KM. Urine Oligosaccharide Screening by MALDI-TOF for the Identification of NGLY1-CDDG. Rare Disease Day. San Diego, CA; poster, presenting author Lam C; (2018).

Chapters & Educational

Chang IJ, Jung SH**, Hahn SH (2018). Population screening for Wilson disease (chapter 26, pages 287-296)).** In Nanda Kerkar and Eve A. Roberts eds. Clinical and Translational Perspectives on Wilson disease. Academic Press Elsevier, UK

Merritt, II, John Lawrence. Gaucher's Disease, Reference Module in Biomedical Sciences. Elsevier. 17-Jan-2018 doi:10.1016/B978-0-12-801238-3.65364-3.

Merritt, II, JL and Gallagher RC. Inborn Errors of Carbohydrate, Ammonia, Amino Acid, and Organic Acid Metabolism. In: Gleason CA and Juul SE, eds: Avery's Diseases of the Newborn. 10th ed, Philadelphia: Elsevier. 2018.

Merritt, II, JL and Vockley J. UpToDate. Specific fatty acid oxidation disorders. Updated January 9, 2018. https://www.uptodate.com/

Thomas JA, **Lam C,** Berry GT. Lysosomal Storage, Peroxisomal, and Glycosylation Disorders and Smith Lemli Opitz Syndrome in the Neonate. In Avery's Diseases of the Newborn 10th edition (CA Gleason, SU Devaskar, eds) Philadelphia, PA: Elsevier/Sauders (2018).

Lam C, Wolfe L, Need A, Shashi V, Enns G. "NGLY1-Related Congenital Disorder of Deglycosylation." GeneReviews. (2018).

Other Activities

Sihoun Hahn, MD, PhD
- Medical Advisory Committee, Wilson Disease Association International
- Genetics Section Editor for UpToDate, since 2011
- Advisory Committee for WA State Newborn Screening

J. Lawrence Merritt, II, MD
- Western States Regional Genetics Collaborative Representative for National Newborn Screening Translational Research Network
- Peer Reviewer for UpToDate, Inborn Errors of Metabolism topics
- American College of Medical Genetics, Mucopolysaccharidosis type II Evidence Based Medicine Delphi group

Angela Sun, MD
- Seattle Children's Hospital Clinical Exome Sequencing Committee Member
- Peer Reviewer for UpToDate, Inborn Errors of Metabolism topics
- Rotation coordinator for students, residents and fellows who rotate through Biochemical Genetics
- Chair of the Clinical Competency Committee for the MBCG Fellowship Program

Christina Lam, MD
- Program Evaluation Committee for Medical Biochemical Genetics Fellowship at Seattle Children's Hospital, Chair
- Interviewer for Pediatric Residency Candidates
- Rapid Exome Committee Member for Seattle Children's Hospital
- Medical Advisory Board Member for CDG Care (CDG Family Support Group), since 2015
- Medical Advisory Board Member for NGLY1.org (NGLY1-CDDG)
- Guest Researcher, NHGRI, NIH, Bethesda, MD
- Research Committee and Patient Information Network Committee CDG Care (Congenital Disorders of Glycosylation (CDG) Family Support Group)

Kelly McKean, MS, RD, CSP, CD
- Genetic Metabolic Dietitians International (GMDI) member

Sarah Sullivan, MS, RDN, CD
- Genetic Metabolic Dietitians International (GMDI) member
- Academy of Nutrition and Dietetics (AND) member

Marie Norris MS, RDN, CD, CNSC
- Genetic Metabolic Dietitians International (GMDI) member
- American Society for Parenteral and Enteral Nutrition (ASPEN) member
- NASPGHAN Council for Pediatric Nutrition Professionals (CPNP) member

Beth Ogata, MS, RD, CD
- Working Group Member of the NIH Phenylketonuria Review Conference (Diet Control & Management)
- Western Regional Genetics Collaborative member
- Grant Reviewer for the Galactosemia Foundation
- Genetic Metabolic Dietitians International (GMDI) Technology Committee and a member of the GMDI Nutrition Guidelines Work Groups for MSUD and PKU
- Co-Chair Scope and Standards Work Group, Academy of Nutrition and Dietetics

Jenny Thies, MS, LCGC
- Rapid Exome Committee (RIGhT Project) Member for Seattle Children's Hospital.
- ClinGen CCDS WorkGroup
- National Society of Genetic Counselors and the Metabolic/Lysosomal Storage Disease SIG member

Jie Feng, MS, LCGC - National Society of Genetic Counselors and the Metabolic/Lysosomal Storage Disease SIG member

Yi F, Hong X, Kumar AB, Zong C, Boons GJ, **Scott CR**, Turecek F, Robinson BH, Gelb MH. Detection of mucopolysaccharidosis III-A (Sanfilippo Syndrome-A) in dried blood spots (DBS) by tandem mass spectrometry. *Mol Genet Metab* 125:59-63, 2018. PMID: 30006231

Masi S, Chennamaneni N, Turecek F, **Scott CR**, Gelb MH. Specific Substrate for the Assay of Lysosomal Acid Lipase. *Clin Chem* 2018 64:690-696, 2018. PMID: 29339442

Hong X, Kumar AB, **Ronald Scott C**, Gelb MH, Multiplex tandem mass spectrometry assay for newborn screening of X-linked adrenoleukodystrophy, biotinidase deficiency, and galactosemia with flexibility to assay other enzyme assays and biomarkers. *Mol Genet Metab* 124:101-108, 2018. PMID: 30006231

Johannesen KM, Gardella E, Linnankivi T, Courage C, de Saint Martin A, Lehesjoki AE, Mignot C, Afenjar A, Lesca G, Abi-Warde MT, Chelly J, Piton A, **Merritt JL 2nd**, Rodan LH, Tan WH, Bird LM, Nespeca M, Gleeson JG, Yoo Y, Choi M, Chae JH, Czapansky-Beilman D, Reichert SC, Pendziwiat M, Verhoeven JS, Schelhaas HJ, Devinsky O, Christensen J, Specchio N, Trivisano M, Weber YG, Nava C, Keren B, Doummar D, Schaefer E, Hopkins S, Dubbs H, Shaw JE, Pisani L, Myers CT, Tang S, Tang S, Pal DK, Millichap JJ, Carvill GL, Helbig KL, Mecarelli O, Striano P, Helbig I, Rubboli G, Mefford HC, Møller RS. Defining the phenotypic spectrum of SLC6A1 mutations. Epilepsia. 2018 Feb;59(2):389-402. doi: 10.1111/epi.13986. Epub 2018 Jan 8. PMID: 29315614.

Merritt JL 2nd, Brody LL, Pino G, Rinaldo P. Newborn screening for proximal urea cycle disorders: Current evidence supporting recommendations for newborn screening. Mol Genet Metab. 2018 Jun;124(2):109-113. doi: 10.1016/j.ymgme.2018.04.006. Epub 2018 Apr 20. PMID: 29703588

Dines JN, Golden-Grant K, LaCroix A, Muir AM, Cintrón DL, McWalter K, Cho MT, **Sun A**, **Merritt JL**, **Thies J**, Niyazov D, Burton B, Kim K, Fleming L, Westman R, Karachunski P, Dalton J, Basinger A, Ficicioglu C, Helbig I, Pendziwiat M, Muhle H, Helbig KL, Caliebe A, Santer R, Becker K, Suchy S, Douglas G, Millan F, Begtrup A, Monaghan KG, Mefford HC. TANGO2: expanding the clinical phenotype and spectrum of pathogenic variants. Genet Med. 2018 Sep 24. doi: 10.1038/s41436-018-0137-y. [Epub ahead of print] Erratum in: Genet Med. 2018 Oct 15. PIMD 30245509.

Collins CJ, **Chang IJ**, Jung S, Dayuha R, Whiteaker JR, Segundo GRS, Torgerson TR, Ochs HD, Paulovich AG, **Hahn SH.** Rapid Multiplexed Proteomic Screening for Primary Immunodeficiency Disorders From Dried Blood Spots. Front Immunol. 2018 Dec 4;9:2756. PMID: 30564228

Hahn SH, Kronn D, Leslie ND, Pena LDM, Tanpaiboon P, Gambello MJ, Gibson JB, Hillman R, Stockton DW, Day JW, Wang RY, An Haack K, Shafi R, Sparks S, Zhao Y, Wilson C, Kishnani PS; Pompe ADVANCE Study Consortium. Efficacy, safety profile, and immunogenicity of alglucosidase alfa produced at the 4,000-liter scale in US children and adolescents with Pompe disease: ADVANCE, a phase IV, open-label, prospective study. Genet Med. 2018 Oct;20(10):1284-1294. PMID: 29565424

Kim SY, Kim WJ, Kim H, Choi SA, Lee JS, Cho A, Jang SS, Lim BC, Kim KJ, Kim JI, **Hahn SH,** Chae JH. Collagen VI-related myopathy: Expanding the clinical and genetic spectrum. Muscle Nerve. 2018 Sep;58(3):381-388. PMID: 29406609

Zarate YA, Ma, N, Smith W, **Sun A**, Wilson LC, Brain C, Jacobs B, Fish JL, Wakeling EL. Bone health and *SATB2*-associated syndrome. Clin Genet. 2018 Mar;93(3):588-594. PMID 28787087.

Bayart CB, Ishak GE, Finn LS, Lee A, Baran F, **Sun A**, Gupta D, Vitanza NA. Pilocytic Astrocytoma with Leptomeningeal Spread in a Patient with Incontinentia Pigmenti presenting with Unilateral Nystagmus. Pediatr Blood Cancer. 2018 Mar;65(3). PMID 29171168.

Zarate A et al. Natural history and Genotype-Phenotype correlations in 72 individuals with *SATB2*-Associated Syndrome. Am J Med Genet A. 2018 Apr;176(4):925-935. PMID 29436146.

Chang IJ, **Sun A**, Bouchard M, Kamps S, Hale S, Done S, Goldberg M, Glass I. Novel Phenotype of Achondroplasia due to Biallelic *FGFR3* Pathogenic Variants. Am J Med Genet A. 2018 Jul;176(7):1675-1679. PMID 30160829.

Sun A, Alshuaibi W, Petroni D, Skoda-Smith S, Goldberg M, Hale S. Immune Modulation in a Morquio A Patient Treated With Enzyme Replacement Therapy. J Allergy Clin Immunol Pract. 2018 Sep - Oct;6(5):1749-175. PMID 29426755.

Sun A. Lysosomal storage disease overview. Ann Transl Med 2018;6(24):476.

Starr MC*, **Chang IJ*,** Finn L, **Sun A,** Larson AA, Goebel J, Hanevold C, **Howell J**, Hingorani SR+, Van Hove JLK+, **Lam C**+. "COQ2 Nephropathy – A Treatable Cause of Nephrotic Syndrome." Pediatr Nephrol. 33(7): 1257-1261, 2018. PMCID 5990461. PMID 29637272.

Hall PL, **Lam C**, Alexander JJ, Asif G, Berry GT, Ferreira C, Freeze HH, Gahl WA, Nickander KK, Sharer JD, Watson CM, Wolfe L, Raymond KM. "Urine Oligosaccharide Screening by MALDI-TOF for the Identification of NGLY1 Deficiency." Mol Genet Metab. 124(1): 82-86, 2018. PMCID none. PMID 29550355.

Whitley B, **Lam C,** Cui H, Haude K, Bai R, Escobar L, Hamilton A, Brady L, Tarnopolsky MA, Dengle L, Snyder M, Picker J, Lincoln S, Lackner LL, Glass IA, Hoppins S. "Aberrant Drp1-mediated mitochondrial division presents in humans with variable outcomes." Hum Mol Gen. 27(21):3710-3719, 2018. PMCID none. PMID 30085106.

Chang IJ, Byers HM, Ng BG, **Merritt JL 2nd,** Gilmore R, Shrimal S, Wei W, Zhang Y, Blair AB, Freeze HH, Zhang B, **Lam C**. "Factor VIII and vWF deficiency in STT3A-CDG." J Inherit Metab Dis. 2018 Dec 27. Epub ahead of print. PMCID none. PMID 30701557.

Chang IJ, He M, **Lam CT.** "Congenital Disorders of Glycosylation." Ann Transl Med. 6(24):477, 2018. PMCID none. PMID 30740408.

Merritt JL 2nd, **Norris M,** Kanungo S**.** "Fatty acid oxidation disorders." Ann Transl Med. 6(24):473, 2018.

Ramsay J, Morton J, **Norris M,** Kanungo S**.** "Organic acid disorders." Ann Transl Med. 6(24):472, 2018.