OVERVIEW:

The Biochemical Genetics program at Seattle Children’s Hospital (SCH) and the University of Washington (UW) provides diagnostic expertise and ongoing follow-up of over 1600 patients with inborn errors of metabolism.

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), Mitochondrial Disorders Clinic (SCH), Urea Cycle Disorders Clinic (SCH/UW), and the Wilson Disease Clinic (SCH). Satellite clinics are held multiple times per year in Spokane.

Biochemical Genetics is actively involved in research studies funded by industry and government. Biochemical Genetics offers clinical trials working to benefit rare metabolic patients. We also provide extensive education for professionals and our patients.
Metabolic Nutritionists:
Beth Ogata, MS, RD, CD (UW)
Janie Heffernan, MS, RD, CD (UW)
Mari Mazin, MS, RD, CD (UW)
Melissa Edwards, MS, RDN, CD (SCH)
Sarah Sullivan, MS, RDN, CD (SCH)
Kelly McKean, MS, RD, CSP, CD (SCH)

Genetic Counselors:
Jie Feng, MS, LCGC (UW)
Christie Momohara, MS, LCGC (UW)

Social Workers
Andrea Barry-Smith, MSW, LICSW, JD (SCH)
Janet Garretson, MSW (UW)

Research Associates
Linnea Brody, MPH, CRA
Julia Olsen, CRA

Faculty and Staff changes in 2015:

We had some changes in the RN team in 2015. Edie Anyieni remains the primary Biochemical Genetics RN and we welcomed Andrea Hartgraves as one of the RNs rotating coverage with Medical Genetics. We were all sad to see the delightful Michelle Wells depart in 2015, but wish her well in her rearrangement of work/life balance! Claire Burwash also remains a strong part of the team. This team approach for nursing coverage of the two separate genetics specialties and initiated in 2014 by Clinical Operations Manager Tammy Fairbanks, has been a great success. It ensures full consistency and continuity of care in nursing for both patient groups. The nurses can and do work together and separately as members of the Biochemical Genetics team, handling a multitude of complex communication that often needs a lot of choreography, lab testing coordination and paperwork issues as well as the more traditional nursing roles connected directly to clinic.

Our Nurse Practitioner, Sue Hale, moved over to the specialty clinics of Orthopedics and we were sad to see her go. We miss her, and wish her the best!

We had a new dietitian join us in August of 2015. Sarah Sullivan moved here from Tennessee, where she was a metabolic dietitian at University of Tennessee. She also brings culinary experience with protein-restricted diets and is involved in the Genetic Metabolic Dietitians International group.

We are glad to report that Linnea Brody remains primary CRA in our group, though there were some transitions in our CRA Staff in 2015. Julia Olsen moved on to focus on other studies and recently accepted as a graduate student at Harvard TH Chan School of Public Health. She will be starting this fall, in the Global Population Health program. Congratulations Julia. Also assisting Dr. Hahn with new research studies is Jenny Skytta in CCTR.

Finally, 2015 saw much activity in recruitment for an additional MD to join the Biochemical Genetics staff at SCH. We are encouraged to welcome a new MD next year!

2015 Clinical Activities:

In 2015, SCH and UW had nearly 1800 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.

To refer a patient:
- University of Washington: 206-598-1800
**Dietary Management for Inborn Errors of Metabolism at SCH**

The Biochemical Genetic Nutrition (BCG) Program at Seattle Children’s Hospital provides the necessary 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 biochemical genetic physicians to ensure the most appropriate nutrition plan for each individual patient.

When an individual is diagnosed with an inborn error of metabolism the biochemical dietitians work diligently to initiate the most appropriate nutrition plan of care. 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 support normal growth and development, their specific nutrient requirements and appropriate modifications to macronutrients (such as carbohydrates, proteins or fat). As the patient grows and needs change, these nutrition plans are revised regularly to continue to provide the best therapy at each stage of development.

The Biochemical Genetics Nutrition Program at Seattle Children’s Hospital supports individuals who eat by mouth, as well as individuals that require feeding tubes to meet their nutrition needs. During acute inpatient admissions sometimes specialized parenteral nutrition solutions are required, which would be managed by the BCG dietitians.

With so many different inborn errors of metabolism there are many different specialized nutrition products available designed for each disorder. There are over 100 different metabolic formula and specialty products. The BCG dietitians have in depth knowledge of the available products and work with patients and their families to find a product that will be best tolerated.

All of the biochemical dietitians at Seattle Children’s Hospital are active members of Genetic Metabolic Dietitians International (GMDI) which is an organization that works to provide standards of excellence of and leadership in nutrition therapy for genetic metabolic disorders. **Melissa Edwards** worked on the Conference Planning Committee of GMDI to help plan the 2016 conference held in Scottsdale Arizona. **Sarah Sullivan** is the co-chair of the GMDI technology committee and has worked to support MetabolicPro, an online tool that supports biochemical genetic dietitians with nutrition calculations.

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<table>
<thead>
<tr>
<th>Major Disorders</th>
<th>2015 Encounters SCH &amp; UW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysosomal Storage Disorder</td>
<td>506</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>247</td>
</tr>
<tr>
<td>Organic Acid Disorder</td>
<td>20</td>
</tr>
<tr>
<td>Amino Acid Disorder</td>
<td>184</td>
</tr>
<tr>
<td>Urea Cycle Disorder</td>
<td>74</td>
</tr>
<tr>
<td>Peroxisomal Disorder</td>
<td>18</td>
</tr>
<tr>
<td>Fatty Acid Oxidation Disorder</td>
<td>201</td>
</tr>
<tr>
<td>Cobalamin metabolism Disorder</td>
<td>18</td>
</tr>
<tr>
<td>Mitochondrial Disorder</td>
<td>29</td>
</tr>
<tr>
<td>Ketone Utilization Disorder</td>
<td>2</td>
</tr>
<tr>
<td>Wilson Disease</td>
<td>13</td>
</tr>
<tr>
<td>Developmental Delay</td>
<td>33</td>
</tr>
<tr>
<td>Failure to Thrive</td>
<td>23</td>
</tr>
<tr>
<td>Seizure Disorder</td>
<td>34</td>
</tr>
<tr>
<td>Carbohydrate metabolism disorders</td>
<td>94</td>
</tr>
<tr>
<td>Biotinidase Deficiency</td>
<td>2</td>
</tr>
<tr>
<td>Biopterin Deficiency</td>
<td>4</td>
</tr>
<tr>
<td>Nephrogenic Diabetes Insipidus</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>288</td>
</tr>
<tr>
<td>Total</td>
<td>1795</td>
</tr>
</tbody>
</table>

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

The LSD program provides multidisciplinary care including consultation, examination, testing, diagnosis, treatment, and genetic counseling for patients with lysosomal diseases 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 orthopedics, cardiology, neurology, nephrology, pulmonary, otolaryngology, neurodevelopmental, radiology and anesthesia. Our group will also work 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.

Patient education and support meetings are held frequently, providing patients and their families an opportunity to mingle with other families and hear about recent advances in the field. As part of this support, in May 2015, Seattle Children’s hosted the Sixth Annual Family Day Meeting for MPS families at Camp Korey, including educational & clinical speakers as well as contributions from
family members. This event was jointly sponsored by Biomarin, Shire, and Genzyme, all of whom are involved in producing the medications needed for these disorders and whose representatives also attended.

Long term follow-up of patients with these rare diseases is essential. The UWMC and SCH team currently have active clinical trials for Pompe, MPS II, Fabry and Gaucher, and are participating in the LSD Disease Registry Program, as well as Hunter Outcome Study (HOS) and Biomarin’s MPS VI Registry. The clinic team follows a large cohort of patients across the spectrum of LSDs as illustrated in Table 4 below 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. Clinical trial on Hunter syndrome is in progress at SCH under IRB approval to evaluate long term safety and clinical outcomes of Intrathecal Idursulfase enzyme treatment. Another clinical trial on patients with Pompe disease to evaluate the efficacy and safety of Alglucosidase Alfa produced at the 4000L scale was successful and the medication was approved by the FDA.

**Table 4. Number of patients followed with Lysosomal Storage Disorders in 2015**

<table>
<thead>
<tr>
<th>Lysosomal Storage Disorder</th>
<th># Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaucher Disease</td>
<td>25</td>
</tr>
<tr>
<td>Fabry Disease</td>
<td>70</td>
</tr>
<tr>
<td>Pompe Disease</td>
<td>18</td>
</tr>
<tr>
<td>MPS I (Hurler Syndrome)</td>
<td>10</td>
</tr>
<tr>
<td>MPS II (Hunter Syndrome)</td>
<td>7</td>
</tr>
<tr>
<td>MPS III (Sanfilippo Syndrome)</td>
<td>9</td>
</tr>
<tr>
<td>MPS IV (Morquio Syndrome)</td>
<td>9</td>
</tr>
<tr>
<td>MPS VI (Maroteaux-Lamy Syndrome)</td>
<td>3</td>
</tr>
<tr>
<td>MPS VII (Sly Syndrome)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total number of patients:</strong></td>
<td><strong>153</strong></td>
</tr>
</tbody>
</table>

**The Newborn Screening 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. Currently Washington State is screening for 6 amino acid disorders, 5 fatty acid oxidation disorders, 7 organic acid disorders, and 10 other congenital disorders. Details of each disorder can be found at [www.doh.wa.gov/nbs](http://www.doh.wa.gov/nbs).

In 2015, 155 cases were referred for confirmation of possible biochemical disorders. Of those, 46
cases were true positive including 9 Medium Chain acyl CoA Dehydrogenase (MCAD) Deficiency, 10 Phenylketonuria (PKU), 3 Very Long Chain acyl CoA Dehydrogenase (VLCAD) Deficiency, 17 Galactosemia (GAL), 4 Isovaleric Acidemia (IVA), 1 Maple Syrup Urine Disease (MSUD), 1 Biotinidase Deficiency (BIO), 1 case of Trifunctional Protein Deficiency (TFP) and 7 cases of conditions that are not on the required panel but share the same biochemical markers as one of the mandated conditions: 3 cases of 3-methylcrotonyl-CoA carboxylase (3-MCC) deficiency, 3 cases of MAT deficiency and 1 case of biotinidin defect. Of the remaining cases referred, 15 were found to be carriers and 66 were found to be false positives. In addition, 5 cases were due to carnitine deficiencies, 6 cases had vitamin B12 deficiency, 1 case was maternal 3-MCC and 1 case was maternal MAT deficiency. Four cases are pending and 4 were unresolved because parents refused testing (see Table 3). All affected babies began treatment soon after birth and are doing well.

We continue to be actively involved with the Western States Genetic Services Collaborative (http://www.westernstatesgenetics.org/) 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 the Newborn Screening confirmation & follow-up program 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 working 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 Mucopolysaccharidoses 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.

**Newborn Screening Staff:**

**Office Director:** Lain Knowles, MBA  
**Laboratory Coordinator:** Santosh Shaunak, BS  
**Follow-up Manager:** John Thompson, MPH, PhD  
**Health Services Consultants:** Carol Nucup-Villaruz, MD, Amanda Kimura, MPH, Megan McCrillis, MPH  
**Quality Assurance Supervisor:** Ashleigh Fleischman, MPH  
**Quality Assurance:** Gauri Gupta, MScPH; Heidi Lovejoy  
**Laboratory Leadworkers:** Tim Davis, Bill Hoffman, Greg Olin, Aihong Thai  
**Laboratory Chemists & Microbiologists:** Aaron Boyce, Valerie Figueroa, Andrew Haase, Sarah Hasselbalch, Luis Loyola, Benjamin Peprah, Aranjeet Singh, Arun Singh, Abbey Werebe, Gretchen Zych  
**Support Staff:** Bonnie Olsen, Relasha Sampson

**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 that is centered on the patient and family. 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 the treatment of care during acute emergencies and in routine follow-up closer to each patient’s home.

We are active members of the Urea Cycle Disorders Consortium Longitudinal study,
sponsored by the Rare Disease Clinical Research Network at the NIH (http://rarediseasesnetwork.epi.usf.edu/ucdc/) along with the National Urea Cycle Disorders Foundation (www.nucdf.org) in order further improve treatment, quality of life, and our understanding of UCDs and to implement newborn screening for all UCDs – including ornithine transcarbamylase deficiency. We are also actively involved in multiple clinical research trials developing new novel drug and cell-based treatments of UCDs with industry.

LABORATORY UPDATE:

Biochemical Genetics Laboratory (SCH)
Molecular Genetics Laboratory (SCH) (http://www.seattlechildrens.org/geneticslab)
The Biochemical and Molecular Genetics Laboratories (SCH) are led by Dr. Sihoun Hahn and Dr. Rhona Jack. 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. Combined, the two labs offer 144 tests and ran over 11,000 samples in 2015. The lab activity is growing in conjunction with the expansion of newborn screening, local clinics and satellite/regional clinics. The laboratories provide rapid, comprehensive diagnostic and monitoring results along with 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).

The Molecular Development Laboratory (UW) (http://depts.washington.edu/moleclab)
The molecular development lab is directed by Dr. C. Ronald Scott, a pioneer in the area of research and development for diagnosis and treatment of metabolic disorders. Additional scientists, Jie-Yu Huang, PhD, Norman Buroker, PhD, and Zaining Wu, BS, each have 25 years research experience in molecular biology. The laboratory is in its tenth year and is a CLIA-certified clinical lab that offers DNA analysis for Gaucher, Congenital Sucrase-Isomaltase Deficiency (CSID), and Tyrosinemia.

Research and Development (R&D) Laboratory 2015
The Biochemical Genetics program’s CLIA-certified R&D Laboratory is located at the Seattle Children’s Research Institute (SCRI): Center for Developmental Therapeutics (Center Director: Dr.
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 high-throughput next generation sequencing (NGS) technology and tandem mass spectrometry.

In 2015, we developed a targeted NGS tests for hereditary myopathies in collaboration with Dr. JH Chae at Seoul National University College of Medicine. We analyzed 58 patients affected by myopathy of unknown origin by sequencing ~600 genes implicated in myopathies and published the result in the Journal of Medical Genetics. This article was Editor’s Choice paper for the March issue of Journal of Medical Genetics.

We are currently exploring the possibility to develop a Mass spectrometry based method for the detection of protein defects that could be amenable to screening, diagnosis and that could be used for rapid and large scale evaluation of potential therapeutic compounds.

The R&D Laboratory’s research efforts in the development of quantitative proteomic assays using tandem mass spectrometry recently demonstrated that Selected Reaction Monitoring (SRM) analysis of signature peptides can identify patients lacking specific protein markers of three life-threatening Primary Immunodeficiency Disorders (Proteomics Clin Appl, 2012). Currently, we are working to improve the sensitivity of our assay using peptide immunoaffinity enrichment coupled to SRM mass spectrometry and expand to other groups of congenital diseases such as Cystinosis and Wilson disease (NIH grant 1R21HD069890-01A1). In 2015, we received the grant from Cystinosis Research Foundation for Newborn Screening for Cystinosis. By using immunoenrichment coupled to mass spectrometry we have already been able to increase the signal of a peptide for the protein involved in Wilson disease by a factor of 60. Moreover, in our ongoing experiments (R56 Al106784-01A1), we have obtained preliminary data indicating that immuno-SRM can detect extremely low abundance marker proteins of congenital disorders, CD3 (for SCID), BTK (for XLA), WASP (for WAS), and ATP7B (for Wilson disease) in DBS. We received NIH grant (R01AI123135) to study multiplex immune-SRM screening for primary immunodeficiencies. In this study, we will develop the methodology to screen 11 different primary immunodeficient disorders as a multiplex analysis in DBS.

We believe that our proteomics based approach will provide an efficient and inexpensive screening for a broad range of genetic disorders.

At the heart of translational research, the R&D Laboratory’s approach is to bridge basic research and the clinical applications of novel tests developed for effective patient diagnosis and treatment. Current staffs include Sunhee Jung, PhD. The R&D Laboratory is led by Dr. Sihoun Hahn.

EDUCATION / TRAINING IN CLINICAL BIOCHEMICAL GENETICS

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. These residents are also exposed to and review the complexities and processes of the Newborn Screening program, a crucial tool in detecting these disorders as early as possible.

In 2015, Dr. Heather Byers had a three month rotation in clinical biochemical genetics from January through March at Seattle. May through July, Dr. Andrew Dervan was with us also. 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.

In 2015, Dr. Andrew Dervan was with us also. 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.

Neurology resident Jason Lockrow, MD was with us for a one month rotation with Biochemical Genetics in April, 2015.

The PKU and Biochemical Genetics Programs also provide ongoing training to residents, medical students, nutritionists, social workers, and others through didactic instruction and clinical experiences.
**C. RONALD SCOTT LECTURE SERIES**

**ANNUAL PRESENTATION**

This lecture series provides for presentations from world experts in different aspects of inborn errors of metabolism and has been made possible by a generous grant from the Yuhan Foundation. The lecture series was established to honor the over 40 years of contribution by Dr. C. Ronald Scott to the field of inherited metabolic diseases and his dedicated service to families and patients. The C. Ronald Scott Lecture is held the last Thursday in June, during Grand Rounds at Seattle Children’s Hospital.

The speaker for 2015 was **Edward R. B. McCabe, MD, PhD**. Dr. McCabe serves as the Senior Vice President and Chief Medical Officer of the March of Dimes. He is Distinguished Professor Emeritus, Department of Pediatrics, UCLA, Professor, Department of Pediatrics, University of Colorado School of Medicine, and Professor Adjunct of Pediatrics, Yale University School of Medicine.

Dr. McCabe’s talk was “Newborn Screening: The Future Is Here.”

We were honored to have Dr. Edward McCabe visiting with us in June of 2015 for the C. Ronald Scott Lecture Series.

Future speaker for 2016 has not been confirmed, but please refer to the Grand Rounds schedule on www.seattlechildrens.org web site for information on upcoming lectures. This is an annual event and if you are interested in attending, please call 206-987-3012 for further information.

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**INBORN ERRORS OF METABOLISM CONFERENCE, HOSTED MONTHLY BY BIOCHEMICAL GENETICS AT SEATTLE CHILDREN’S HOSPITAL**

Our IEM Conference is held every first Wednesday of the month, with the exception of the August hiatus. This Conference is open to any interested members of all specialties and provides a chance to hear and present new interesting cases and diagnostic puzzles, as well as laboratory tests and process updates. Presentations are made by a variety of providers, fellows, visiting experts from many specialties and topics can vary widely. This conference provides an interesting and open venue for the presentation of varied types of cases and histories, and it also provides ongoing educational credit at CME Level II category.

**2015 schedule of IEM Conference presentations:**

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>“A Clinical suspicion vs diagnostic testing in a mitochondrial disease.” “Neurometabolic Causes of Infantile Spasms.”</td>
<td>Walaa Alshuaibi, MD Stephanie Carapatian, MD</td>
</tr>
<tr>
<td>“Congenital Disorders of Glycosylation” “HHH – Not Just for Kids!”</td>
<td>Heather Byers, MD Lawrence Merritt, MD</td>
</tr>
<tr>
<td>“Burned by the Bili Lights – Congenital Erythropoietic Porphyria.” “FMR1 Deletion Presenting as Fragile X Syndrome.”</td>
<td>Heather Byers, MD John Carter, MD</td>
</tr>
<tr>
<td>“Dietary Treatment of Pyridoxine-Dependent Epilepsy.” “Seizure with CACNA1A mutation.”</td>
<td>Sidney Gospe, MD, PhD &amp; Angela Sun, MD Heather Byers, MD</td>
</tr>
<tr>
<td>“Understanding protein function: How pathogenic variants in REN can cause both autosomal dominant and autosomal recessive hyperuricemic kidney disease.” “Neurologic Sequelae of Cerebral Creatine Deficiency Syndrome”</td>
<td>Andrew Dervan, MD Jason Lockrow, MD</td>
</tr>
<tr>
<td>“A Unique Case of Morquio Syndrome.”</td>
<td>Walaa Alshuaibi, MD</td>
</tr>
<tr>
<td>“LPIN1 Related Rhabdomyolysis.” “An Ultra Rare but Diagnosable Metabolic Disorder.”</td>
<td>Cristian Ionita, MD Angela Sun, MD</td>
</tr>
<tr>
<td>“Cost-effectiveness of Liver Transplantation in Methylmalonic and Propionic Acidemias.” “A case of neurodegenerative disease”</td>
<td>Ryan Hansen, PhD Andrew Dervan, MD</td>
</tr>
</tbody>
</table>
in the Blackfoot tribe.”

| “Bioterin Deficiency: An Unusual Condition Detected by Newborn Screening.” | Jie Feng, GC |
| “Fabry Disease.” | Heather Byers, MD |
| “Congenital Disorders of Glycosylation and Deglycosylation: A Sweet Branch of Metabolism.” | Christina Lam, MD |

**Funded Clinical Trials and Research Projects at Seattle Children’s and the University of Washington**

**Clinical Trials:**

Longitudinal Study of Urea Cycle Disorders, O’Malley Family Foundation. The major goal of this project is the establishment of a rare disease clinical research center focused on the study of urea cycle disorders. Children’s Research Institute (Batshaw) (2008 – 2016)

Site PI: J Lawrence Merritt, II

An Open Label Study of the Safety, Efficacy and Pharmacokinetics of Glycerol Phenylbutyrate (GPB; RAVICTI®) in Pediatric Subjects under Two Years of Age with Urea Cycle Disorders (UCDs) (HPN-100-009) Horizon Therapeutics, Inc. (2015 - )

PI: J Lawrence Merritt, II

Horizon Therapeutics, Inc. Investigator Initiated Study 2/5/2015-2/4/2017 0.1 calendar months Development of a Long-term Outcome Study of Newborn Screening for Urea Cycle Disorders (NBS+UCD)

PI: J Lawrence Merritt, II

HGT-HIT-045: A Phase I/II Randomized Safety and Ascending Dose Ranging Study of Idursulfase (Intrathecal) Administration via an Intrathecal Drug Delivery Device in Pediatric Patients with Hunter Syndrome who Demonstrate Evidence of Central Nervous System Involvement and who are Receiving Treatment with Elaprase®. P.I.: Angela Sun, Funding: Shire


CCD05, Open, Prospective, Historic-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Infusion of Liver Cell Suspension (HiLiviC) in Children with Urea Cycle Disorders. The major goal of this project is to investigate the safety and efficacy of multiple human heterologous liver cell infusions in children with ornithine transcarbamylase deficiency, carbamoylphosphate synthetase I deficiency, and arginosuccinate synthetase deficiency. Lawrence Merritt, II, PI. Funding: Cytonet GmbH & Co. KG.

A Phase 3, Open-Label, Randomized, Multi-Center Study to Assess the Safety and Tolerability of an Induction, Titration, and Maintenance Dose Regimen of BMN 165 Self Administered by Adults With Phenylketonuria Not Previously Treated with BMN 165 10/25/2013 – 12/31/2015; 165-301, BioMarin BioMarin protocol to study the efficacy and safety of recombinant Anabaena variabilis phenylalanine ammonia lyase (rAvPAL) in lowering blood phenylalanine levels in patients affected with PKU.

Scott, C. Ronald (PI), Leavitt, Anne M. (Co-PI)

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 BioMarin protocol to study the long-term efficacy and safety of recombinant Anabaena variabilis phenylalanine ammonia lyase (rAvPAL) in lowering blood phenylalanine levels in patients affected with PKU.

Scott, C. Ronald (PI), Leavitt, Anne M. (Co-PI)

**Disease Registries:**

The LSD Registry Program. Principal Investigators: Dr. Sihoun Hahn. 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, Jie Feng, MS, LCGC and Christie Momohara, MS, LCGC

A Global Multi-Center, Long-Term, Observational Survey of Patients with Hunter Syndrome
(Mucopolysaccharidosis II). Principal Investigators: Dr. Sihoun Hahn. Funding: Shire Human Genetic Therapeutics. A long-term natural history disease registry of treated and untreated patients with MPS II.

The MPS VI Clinical Surveillance Program. Principal Investigators: Dr. Sihoun Hahn. Funding: BioMarin Pharmaceuticals. A long-term natural history disease registry of treated and untreated patients with MPS VI.

Morquio A Registry Study (MARS), Principal Investigator: Dr. Angela Sun on 2014 – present.

Lysosomal Storage Disease Registries, Genzyme Corporation 01/01/2009 – 12/31/2016
Scott, C. Ronald, PI
Lysosomal Storage Disease Registries, Genzyme Corporation 01/01/2009 – 12/31/2016
Scott, C. Ronald, PI

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 - 5/7/2018
Scott, C. Ronald, PI

Assay validation for Fabry, Pompe, Gaucher, MPS-I, in a real-time newborn screening lab. 6-Plex Reagents (PerkinElmer) 4/1/2014-3/31/2017, Scott, C. Ronald, PI

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)


Multiplex Test for Primary Immunodeficiencies by Affinity Column coupled to MS/MS; National Institute of Health/National Institute of Allergy and Infectious Diseases PI: Sihoun Hahn, (2014-2015)

Hypophosphatasia Prevalence Study; PI: Sihoun Hahn, Funding: Alexion (2015)

Newborn Screening for Cystinosis; PI: Sihoun Hahn, MD, PhD Funding: Cystinosis Research Foundation (CRF) (2015-2016)

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

FDA IND # 123292 July 2014 to present
Individual Patient, Emergency IND
Emergency Use of Triheptanoin (UX007) in Neonatal-Onset Very Long-Chain Acyl-CoA Dehydrogenase Deficiency
PI: Lawrence Merritt, II

2015 AWARDS, GRANTS, HONORS

Dr. C. Ronald Scott serves on the national North American Tyrosinemia Guidelines committee, hosted by Emory University, to develop national recommendations for the treatment of tyrosinemia.


S Hahn was appointed as visiting professor for the Department of Genome Medicine and Science at Gachon University School of Medicine in Korea in 2015. He also serves as a founding chair for the department to recruit the faculty and staff, and, develop planning and strategies.

2015 EXTRAMURAL PRESENTATIONS

Invited Presentations:

Hahn SH, Genomics in Medicine: Personal experience and prospect. Gachon University Gil Hospital. August 5, 2015, Incheon, Korea

Hahn SH, Genomics in Medicine: Personal experience and prospect. Korean University Medical Center, August 3, 2015, Seoul, Korea

Poster/Oral Presentations:


2015 INTRAMURAL PRESENTATIONS

Sun, A., Disorders of Carbohydrate Metabolism, Introduction to Human and Medical Genetics Lecture series, 2/27/15

Sun, A. Peroxisomal and Neurometabolic Disorders, Introduction to Human and Medical Genetics Lecture series, 2/27/15

Sun, A., Dietary Treatment of Pyridoxine-Dependent Epilepsy, Seattle Children’s Hospital Inborn Errors of Metabolism Conference, 4/1/15

Sun, A., Biallelic Acute Intermittent Porphyria, Seattle Children’s Hospital Inborn Errors of Metabolism Conference, 9/2/15

Sun, A., Overview of Inborn Errors of Metabolism, Rehabilitation Medicine lecture series, 11/25/15

2015 PUBLICATIONS

Chapters & Educational Publications:

Peer-Reviewed Journals:


Jong Hee Chae, Valeria Vasta, Anna Cho, Byung Chan Lim, Qimg Zhang, So Hee Eun, Si Houn Hahn. The Utility of Next Generation Sequencing in Genetic Diagnosis of Early-Onset Neuromuscular Disorders. Journal of Medical Genetics 2015:52:208-16 (Editor's choice paper for the March issue of JMG)


Sun A, **Merritt JL 2nd**. Orphan drugs in development for long-chain fatty acid oxidation disorders: challenges and progress. *Orphan Drugs: Research and Reviews*. 28 April 2015 Volume 2015:5 Pages 33—41. DOI http://dx.doi.org/10.2147/ODRR.S63061
Other Activities:

Dr. Sihoun Hahn is on the Medical Advisory Committee, Wilson Disease Association International

Dr. Sihoun Hahn is a member of the Hunter Outcome Survey (HOS) North American Board

Dr. Sihoun Hahn is a Reviewer, on-line NIH study section: ZRG1 MOSS-V (03)

Dr. Sihoun Hahn is a Genetics Section Editor for UpToDate, since 2011

Dr. Sihoun Hahn is a Grant reviewer for Telethon Foundation, Italy

Dr. Sihoun Hahn is on the Advisory Committee for WA State Newborn Screening

Dr. Sihoun Hahn is a Member of the IRB committee, Seattle Children’s Hospital

Dr. Sihoun Hahn is Chair, UW Korean Faculty Staff Meeting

Dr. Angela Sun is a member of the ACMG Therapeutics Committee.

Dr. Angela Sun is a Peer Reviewer for UpToDate, Inborn Errors of Metabolism topics.

Dr. Angela Sun is a Peer Reviewer for Genetics In Medicine.

Dr. Lawrence Merritt is on the American Academy of Pediatrics, Subcommittee on Apparent Life Threatening Events (ALTE). August 2013 to present. (Goal: to create an evidence-based guideline on the Management of Apparent Life Threatening Events)

Dr. Lawrence Merritt was a Member of Washington State Board of Health Newborn Screening Criteria Review Advisory Committee. March 6, 2015

Dr. Lawrence Merritt was a Member of Washington State Board of Health Newborn Screening Review Advisory Committee for X-Linked Adrenoleukodystrophy. October 28, 2015

Dr. Lawrence Merritt is ad hoc reviewer, JAMA Pediatrics

Dr. Lawrence Merritt is ad hoc reviewer, Molecular Genetics and Metabolism

Dr. Lawrence Merritt is on the American Academy of Pediatrics Subcommittee on Apparent Life Threatening Events (ALTE).

Ms. Beth Ogata is Chair of the Genetic Metabolic Dietitians International (GMDI) Technology Committee and a member of the GMDI Nutrition Guidelines Work Group

Ms. Kelly McKean is a member of the Genetic Metabolic Dietitians International (GMDI) organization.

Ms. Melissa Edwards is a member of the Genetic Metabolic Dietitians International (GMDI) organization.

Ms. Beth Ogata is a Working Group Member of the NIH Phenylketonuria Review Conference (Diet Control & Management)

Jie Feng, MS, LCGC is a member of the National Society of Genetic Counselors

Christie Momohara, MS, LCGC is a member of the National Society of Genetic Counselors.