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OVERVIEW:

The Biochemical Genetics program at Seattle Children’s Hospital (SCH) and the University of Washington (UW) continues to provide 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.

2014 BIOCHEMICAL GENETICS PROGRAM FACULTY AND STAFF

Attending Physicians
C. Ronald Scott, MD
Sihoun Hahn, MD, PhD
J. Lawrence Merritt, II, MD
Angela Sun, MD
Anne Leavitt, MD (PKU Clinic)

Nurse Practitioner
Susan Hale, MN, ARNP (SCH/UW)

Genetic Counselors
Jie Feng, MS, CGC (UW)

Metabolic Nutritionists
Beth Ogata, MS, RD, CD (UW)
Janie Heffernan, MS, RD, CD (UW)
Mari Obara, MS, RD, CD (UW)
Kelly McKean, MS, RD, CSP, CD (SCH)
Melissa Edwards, MS, RDN, CD (SCH)

Registered Nurse
Sarah Allen, RN, MSN, CPHON
Edie Anyieni, RNC, BSN
Michelle Wells, RN
Claire Burwash, RN
Faculty and Staff changes in 2014:

During 2014 we saw our wonderful nurse, Sarah Allen, move into different schedule and area of her career focus. In her place, we welcomed a team of RN’s to our service. Spending much of her time with us is Edie Anyieni, who came from NICU, making her well prepared for these fragile patients. Also helping to ensure the Biochemical Genetics patients always have an RN available are Michelle Wells and Claire Burwash. This new coverage arrangement for the RN group allows our nurses to rotate between the two specialty clinics and stay familiar with the processes unique to each service. This team approach for nursing also ensures full consistency and continuity of care in nursing. 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.

There were some transitions in our CRA Staff also this year. Krystle Benedict moved to a new position in Boston in order to be with her husband, whose fellowship began there in 2014. We couldn’t blame her, but did miss her! Julia Olsen came to the rescue and her diligence and hard work was most welcome.

Katie Golden-Grant, GC moved from Biochemical Genetics at UW to the Medical Genetics group at SCH. Stephanie Uhrich, GC moved from UW to private industry and we certainly wish her well. Jie Feng, GC came to UW and is a wonderful addition to their staff.

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

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

Social Work Staff Assigned
At SCH, we were able to formally incorporate a Social Work position into our clinic team in April of 2014. Andrea Barry-Smith, MSW, LICSW, JD is a social worker and former public interest attorney. Most recently, Andrea worked as part of a multi-disciplinary team in a research-based clinic at SCH for medically complex children. In addition to working with the BCG team, Andrea also works with the Dept. of Graduate Medical Education here at SCH providing support to the pediatric residents.

Medical social workers are licensed clinicians who provide the psychosocial perspective to the medical team, enhancing the multi-disciplinary team’s ability to treat patients and serve families. Many families of children with a chronic medical condition struggle with the emotional and financial toll that this condition takes on the family. Social workers assess families for support and cultural needs, potential barriers to medical treatment, and build on identified family strengths. For example, social workers provide emotional support and counseling for grief and adjustment to illness, and connect families with community resources (legal, financial, mental health) that will strengthen their ability to manage their child’s illness.

Andrea sees her role in BCG as twofold; helping families cope with their child’s illness in a variety of ways, and providing support to the rest of the BCG team as we work together to understand and navigate psychosocial issues that impact patient health.

2014 CLINICAL ACTIVITIES

In 2014, SCH and UW had over 1600 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:

- Seattle Children’s Hospital: Please visit the website [www.seattlechildrens.org](http://www.seattlechildrens.org) and follow instructions for Healthcare Professionals referral process. Alternatively, call 206-987-3012 for additional information.
- University of Washington: 206-598-1800

<table>
<thead>
<tr>
<th>Table 1. Major Disorders in 2014 at Seattle Children’s &amp; University of Washington Clinics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Disorders in 2014</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Lysosomal Storage Disorder</td>
</tr>
<tr>
<td>Phenylketonuria</td>
</tr>
<tr>
<td>Organic Acid Disorder</td>
</tr>
<tr>
<td>Amino Acid Disorder</td>
</tr>
<tr>
<td>Urea Cycle Disorder</td>
</tr>
<tr>
<td>Peroxisomal Disorder</td>
</tr>
<tr>
<td>Fatty Acid Oxidation Disorder</td>
</tr>
<tr>
<td>Cobalamin metabolism Disorder</td>
</tr>
<tr>
<td>Mitochondrial Disorder</td>
</tr>
<tr>
<td>Ketone Utilization Disorder</td>
</tr>
<tr>
<td>Wilson Disease</td>
</tr>
<tr>
<td>Developmental Delay</td>
</tr>
<tr>
<td>Failure to Thrive</td>
</tr>
<tr>
<td>Seizure Disorder</td>
</tr>
<tr>
<td>Carbohydrate metabolism disorders</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 7 other congenital disorders. Details of each disorder can be found at [www.doh.wa.gov/nbs](http://www.doh.wa.gov/nbs).

In 2014, 74 cases were referred for confirmation of possible biochemical disorders. Of those, 34 cases were true positive including 4 Medium Chain acyl CoA Dehydrogenase (MCAD) Deficiency, 4 Phenylketonuria (PKU), 3 Very Long Chain acyl CoA Dehydrogenase (VLCAD) Deficiency, 2 Methylmalonic Acidemia (MMA), 10 Galactosemia (GAL), 1 Isovaleric Acidemia (IVA), 1 Maple Syrup Urine Disease (MSUD), 1 Biotinidase Deficiency (BIO), 1 case of Argininosuccinic Aciduria, 2 cases of Long Chain L-3-Hydroxy acyl-CoA Dehydrogenase (LCHAD) Deficiency and 3 cases of conditions that are not on the required panel but share the same biochemical markers as one of the mandated conditions: three cases of 3-methylcrotonyl-CoA carboxylase (3-MCC) deficiency and one of maternal Glutaric Acidemia type I (GA-I). Of the remaining cases referred, 5 were found to be carriers and 21 were found to be false positives. In addition, 7 cases were due to carnitine deficiencies (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/](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 Mucopolysaccharidases 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, Ashleigh Fleischman, MPH, Amanda Kimura, MPH  
Quality Assurance: Gauri Gupta, MScPH; Heidi Lovejoy  
Laboratory Leadworkers: Tim Davis, Bill Hoffman, Greg Olin, Aihong Thai  
Laboratory Chemists & Microbiologists: Aaron Boyce, Andrew Haase, Sarah Hasselbalch, Luis Loyola, Benjamin Peprah, Aranjeet Singh, Arun Singh, Abbey Werebe, Gretchen Zych  
Support Staff: Bonnie Olsen, Relasha Sampson

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 2014, Seattle Children’s hosted a Fifth 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. This chance to learn and network among the families was well attended, and plans are in place for next year’s event. Camp Korey will also be holding its week long Metabolic Bone summer camp session in 2015 as it was also a great success.

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

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Table 3: 2014 Newborn Screening Totals of Abnormal Results requiring follow up testing

<table>
<thead>
<tr>
<th>Name</th>
<th>Severe</th>
<th>Mild</th>
<th>Carrier</th>
<th>FP</th>
<th>Other</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>MCAD</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
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<tr>
<td>PKU</td>
<td>4</td>
<td>1</td>
<td>1*</td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>VLCAD</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>MMA/PA</td>
<td>2</td>
<td>6</td>
<td>2**</td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>GAL</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>CUD</td>
<td>3</td>
<td>7***</td>
<td>(1)</td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>GA-1</td>
<td>1</td>
<td>1</td>
<td></td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>HCYS</td>
<td>5</td>
<td>5</td>
<td></td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>HMG/MCD</td>
<td>2</td>
<td>(3)</td>
<td>6****</td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>IVA</td>
<td>1</td>
<td>4</td>
<td></td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>MSUD</td>
<td>1</td>
<td>1</td>
<td></td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>BIO</td>
<td>1</td>
<td>1</td>
<td></td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>ASA</td>
<td>1</td>
<td>1</td>
<td></td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>LCHAD</td>
<td>2</td>
<td>1</td>
<td></td>
<td>FP</td>
<td>Other</td>
<td>Total</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>12</td>
<td>5</td>
<td>21</td>
<td>14</td>
<td>74</td>
</tr>
</tbody>
</table>

(n) counted as non-panel condition - one maternal glutaric acidemia type I (GA-I) deficiency and three 3-methylcrotonyl-CoA carboxylase (3-MCC) deficiencies

* Lost to follow-up, ** Vitamin B12 deficiency; *** Carnitine deficiency, **** Pending

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Table 4. Number of patients followed with Lysosomal Storage Disorders in 2014

<table>
<thead>
<tr>
<th>Lysosomal Storage Disorder</th>
<th># Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaucher Disease</td>
<td>31</td>
</tr>
<tr>
<td>Fabry Disease</td>
<td>58</td>
</tr>
<tr>
<td>Pompe Disease</td>
<td>19</td>
</tr>
<tr>
<td>MPS I (Hurler Syndrome)</td>
<td>6</td>
</tr>
<tr>
<td>MPS II (Hunter Syndrome)</td>
<td>2</td>
</tr>
<tr>
<td>MPS III (Sanfilippo Syndrome)</td>
<td>4</td>
</tr>
<tr>
<td>MPS IV (Morquio Syndrome)</td>
<td>8</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>Total number of patients:</td>
<td>126</td>
</tr>
</tbody>
</table>

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Seattle Children's Hospital Research Foundation
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.

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 75 tests and ran over 6,800 samples in 2014. 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).

Research and Development (R&D) Laboratory 2014

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. Skip Smith). The facility is fully equipped with a LC-MS/MS and an Illumina Genome Analyzer Ix. 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 2014, we developed targeted NGS tests for several other genetic conditions including microcephaly, lissencephaly and hereditary myopathies. In collaboration with Dr. William Dobyns of the Center for Integrative Brain Research at SCRI, we analyzed 90 patients affected by microcephaly/lissencephaly (manuscript in preparation) exploring ~250 nuclear genes associated with brain development. In collaboration with Dr Chae of Seoul National University College of Medicine, we analyzed 58 patients affected by myopathy of unknown origin by sequencing ~600 genes implicated in myopathies (Journal of Medical Genetics, 2015). 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). 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. We are developing methods for other proteins, such as Collagen VI to develop a test that could be applied to some forms of myopathy. Moreover, in our ongoing experiments (R56 AI106784-01A1), we have obtained preliminary data indicating that immuno-SRM can detect extremely low abundance marker proteins of congenital disorders, CD3Δ (for SCID), BTK (for XLA), WASP (for WAS), and ATP7B (for Wilson disease) in DBS.

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

The laboratory also continued to apply its expertise in small molecule detection by mass spectrometry for the diagnosis of genetic conditions, in particular, pyridoxine-dependent epilepsy. This opened up the possibility of newborn screening for this condition. The results of these studies were published in Mol Genet Metab. 2013 110(3):237-40 and Ann Neurol. 2014 75(1):22-32.

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 Valeria Vasta, PhD, 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 2014, Dr. Walaa Alshuaibi had a three month rotation in clinical biochemical genetics from July through September at Seattle. 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 residents Dr Stephanie Carapatian, Dr. Teresa Ko and Dr. John Carter, each with a one month rotation with Biochemical Genetics in 2014.

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.

We said farewell to Dr. So Hee Eun in 2014. She was here from Korea for over a year, having come to work with Dr. Hahn in the Research Institute and to observe in clinic as well. Her special interest is neurometabolic and neurogenetic disorders.

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 2014 was Gerard Vockley, MD, PhD, Chief, Division of Medical Genetics, Professor of Pediatrics, University of Pittsburgh School of Medicine, Professor of Human Genetics, University of Pittsburgh Graduate School of Public Health Pittsburgh, Pennsylvania.

Dr. Vockley’s talk was titled “Pushing the Boundaries of Academic Medicine: Translating metabolic analysis into clinical practice.”

We were honored to have Dr. Vockley with us in 2014 and look forward to Dr. Edward McCabe visiting with us in June of 2015 for the C. Ronald Scott Lecture Series.

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.

INBORN ERRORS OF METABOLISM CONFERENCE, HOSTED BY BIOCHEMICAL GENETICS AT SEATTLE CHILDREN’S HOSPITAL (CME Level II attached)

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.

2014 schedule of IEM Conference presentations:

<table>
<thead>
<tr>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Update on Lysosomal Storage Disease Clinical Research at Seattle Children’s Hospital.”</td>
<td>Susan Hale, ARNP</td>
</tr>
<tr>
<td>“Update on Lysosomal Storage Disease Clinical Research at University of Washington.”</td>
<td>Stefanie Uhrich, GC</td>
</tr>
<tr>
<td>“Population screening for late – onset Pompe disease: two case reports.”</td>
<td>Katie Golden-Grant, GC</td>
</tr>
<tr>
<td>“Case presentation – Metachromatic Leukodystrophy”</td>
<td>Ping-Ru Teresa Ko, MD</td>
</tr>
<tr>
<td>“Caring for Children with Medical Complexities: What Does the Future Look Like?”</td>
<td>Maggie Hood, MD</td>
</tr>
<tr>
<td>“Preliminary Analysis of Lysosomal Storage Disorders Within the Context of Newborn Screening in Washington State”</td>
<td>Megan Hawthorne</td>
</tr>
<tr>
<td>“Congenital adrenal hyperplasia”</td>
<td>Patricia Fechner, MD</td>
</tr>
<tr>
<td>Title</td>
<td>Authors</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>(CAH) Review, including non-21-OH deficiency type.</td>
<td>Sihoun Hahn, MD, PhD</td>
</tr>
<tr>
<td>“β-ureidopropionase deficiency in a patient with seizure and</td>
<td></td>
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<tr>
<td>microcephaly.”</td>
<td></td>
</tr>
<tr>
<td>“Newborn Screening observations in 3 cases of mild MSUD.”</td>
<td>Sheila Weiss, MD, Angela Sun, MD</td>
</tr>
<tr>
<td>“2 Case Presentations: Congenital Cataracts and Rhabdomyolysis.”</td>
<td>Amy Lawson Yuen, MD, Beth Ogata, RD</td>
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<tr>
<td>“One case of CPT II Deficiency and one case of Cystinosis.”</td>
<td>Julie Stewart, Med Student</td>
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<tr>
<td>“A case of Pyruvate Dehydrogenase Complex Deficiency.”</td>
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<tr>
<td>“Genetic testing for mitochondrial myopathies and exercise intolerance: Where we cast the net.”</td>
<td>Darci Sternen, GC, Anne Leavitt, MD, C. Ronald Scott, MD, Beth Ogata, RD</td>
</tr>
<tr>
<td>“Ongoing work, scope, progress within PKU clinics at UW.”</td>
<td>Fuki Hisama, MD, Cate Otten, MD</td>
</tr>
<tr>
<td>“Cirrhosis in a 58 year old woman.”</td>
<td></td>
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<tr>
<td>“Cerebral Folate Deficiency: A potential case and discussion.”</td>
<td></td>
</tr>
<tr>
<td>“The Utility of Next Generation Sequencing in Genetic Diagnosis of Early-Onset Hereditary Myopathy: The first experience in 43 patients.”</td>
<td>Sihoun Hahn, MD, PhD, Lawrence Merritt, MD</td>
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<td>“Whole Exome Sequencing vs. Mitochondrial Disease: NGLY1”</td>
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<td>“Discovery of genetic cause of epilepsy after 27 years using Epiplex: a new clinical next-gen sequencing test developed at UW/SCH.”</td>
<td>Fuki Hisama, MD, James Bennett, MD, Walaa Alshuaibi, MD</td>
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<td>“Lactic Acidosis in a newborn.”</td>
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<td>“Novel molecular insights into congenital microcephaly through targeted next generation sequencing.”</td>
<td>Ghayda Mirzaa, MD, Heather Mefford, MD</td>
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<td>“Gene discovery in the epileptic encephalopathies.”</td>
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**Funded Clinical Trials and Research Projects at Seattle Children’s and the University of Washington**

**Clinical Trials:**
Phase 2, Fixed-Sequence, Open-Label, Switch-Over Study of the Safety and Tolerability of HPN-100 Compared to Sodium Phenylbutyrate in Children 6–17 Years of Age with Urea Cycle Disorders, with a Long-Term Safety Extension (Hyperion Protocol HPN-100-005). Principal Investigator: Dr. J. Lawrence Merritt, II. Funding: Hyperion Therapeutics. This study compares the safety and efficacy of a new oral treatment for patients with urea cycle disorders.

**Long Term Use of HPN-100 in Urea Cycle Disorders.** (Hyperion Protocol HPN-100-011). Principal Investigator: Dr. J. Lawrence Merritt, II. Funding: Hyperion Therapeutics The major goal of this project is to study participants who have completed study HPN-100-005 or HPN-100-007. This study is an extension to assess long-term safety and provide continue access for individuals receiving the study medication. Open, prospective, case controlled, multi-center trial to evaluate the safety and efficacy of infusion of liver cell suspension (HHLivC) in children with urea cycle disorders. Phase II/III Clinical Study. Principal Investigator: Dr. J. Lawrence Merritt, II. Funding: Cytonet GmbH & Co. KG (Weinheim, Germany). This study will look at the safety an ability of liver cell infusion to in treating patients with Urea Cycle Disorders.

**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.: Sihoun Hahn, MD, PhD. Funding: Shire

**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.: Sihoun Hahn, MD, PhD, Angela Sun, MD. Funding: Shire

**A Phase 4, Open-Label, Prospective Study in Patients with Pompe Disease to Evaluate the Efficacy and Safety of Alglucosidase Alfa Produced at the 4000 L Scale.** P.I.: Sihoun Hahn, MD, PhD. Funding: Genzyme

**Disease Registries:**

The LSD Registry Program. Principal Investigators: Dr. Sihoun Hahn (co-investigator: Susan Hale, ARNP). 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 Sarah Ryan, MS, LCGC
A Global Multi-Center, Long-Term, Observational Survey of Patients with Hunter Syndrome (Mucopolysaccharidosis II). Principal Investigators: Dr. Sihoun Hahn (co-investigator: Susan Hale, ARNP). Funding: Shire Human Genetic Therapeutics. A long-term natural history disease registry of treated and untreated patients with MPS II.

MPS VI Clinical Surveillance Program. Principal Investigators: Dr. Sihoun Hahn (co-investigator: Susan Hale, ARNP). 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

RESEARCH PROJECTS:


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, C. Ronald (Co-PI)

Lysosomal Storage Disease Registries, Genzyme Corporation 01/01/2009 – 12/31/2015 Scott, C. Ronald, PI

A phase-IV clinical trial to study the outcomes of various forms of treatment on symptoms of Gaucher, Fabry, Pompe, and MPS-I diseases. Sponsored by Genzyme Corporation. Scott, C. Ronald, PI

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 – 6/30/2015 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

Clinical Follow-up of Children with Very-long Chain Acyl-CoA Dehydrogenase Deficiency (VLCAD) Identified through Newborn Screening. Principal Investigator: Dr. J. Lawrence Merritt, II. Western States Genetic Services Collaborative Project. Funding: Health Resources & Services Administration (HRSA) Genetic Services Branch. This study is being done to look at the clinical outcome of children with VLCAD deficiency in cooperation with the newborn screening centers in Alaska, California, Guam, Hawai‘i, Idaho, Nevada, Oregon, and Washington

Longitudinal Study of Urea Cycle Disorders Principal Investigator: Dr. J. Lawrence Merritt II. Funding: NIH, NICHD, ARRA Supplement. A long-term natural history study of patients with urea cycle disorders.


Multiplex Test for Primary Immunodeficiencies by Affinity Column coupled to MS/MS; National Institute of Health/National Institute of Allergy and Infectious Diseases, (R56 AI106784-01A1) Sihoun Hahn, MD, PhD (2014-2015)

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

2014 AWARDS, GRANTS, HONORS

Retrospective Hypophosphatasia (HPP) EMR Analysis. Sponsored by Alexion. The goal of this study is to develop the laboratory and ICD9 code diagnostic algorithm for the screening of hypophosphatasia. Sihoun Hahn (PI)

2014 EXTRAMURAL PRESENTATIONS
Invited presentations:

Hahn SH. Precision Medicine: Raising the bar for education, training and practice. Korea University Medical Center, April 16, 2014


Sun, A. Expansion of the Phenotype Associated with NAA10 Mutations, Pacific Northwest Genetics Exchange, 5/9/14


Poster/Oral Presentations:

Kelly Jones, Valeria Vasta, Sihoun Hahn, Ghayda Mirzaz, William B. Dobyns. Targeted sequencing in a large cohort of children with severe congenital microcephaly cohort yields important insights into the molecular pathogenesis. 35th Annual David W. Smith Workshop on Malformations and Morphogenesis July 25th - 30th, 2014 The Fluno Center, University of Wisconsin, Madison, WI


James T Bennett, MDPhD1, Min Zhang1, Jaya Narayanan1, Darci Stermen1 and Sihoun Hahn. Spectrum of mutations associated with maturity onset diabetes of the young and neonatal diabetes mellitus among 334 patients over 3 years. 2014 PAS/ASPR Joint Meeting, May1-6, 2014 Vancouver, Canada


2014 INTRAMURAL PRESENTATIONS

Hahn, SH. Pediatric Neurology Conference at Seattle Children’s. The utility of NGS for early onset muscular dystrophy; 12/19/14.

Hahn, SH. Mitochondria and Metabolism in the Pathogenesis of Human Disease at UW; Mitochondria Medicine; 10/16/14

Sun, A.: Gaucher Disease Overview, Seattle Children’s Hospital Hematopathology Conference, 2/6/14

Sun, A.: Overview of Inborn Errors of Metabolism, Rehabilitation Medicine lecture series, 2/25/14


2014 PUBLICATIONS

Chapters & Educational Publications:


Peer-Reviewed Journals:


Sun A. Glucose-6-phosphatase deficiency (glycogen storage disease I, von Gierke disease). UpToDate, revised 9/17/14.

Sun A, Merritt JL. Orphan drugs in development for long-chain fatty acid oxidation disorders: challenges and progress. Orphan Drugs: Research and Reviews, in press.

Other Activities:

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

Dr. Sihoun Hahn is a member of the Board of Advisors of MutaDATABASE

Dr. Sihoun Hahn is a member of the MSegDR Working group

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

Dr. Sihoun Hahn was an Organizer, UKC 2014 BMP Symposium Technical Session of Advances in Translational Research, San Francisco, CA

Dr. Sihoun Hahn was Co-organizer, Mitochondrial Biology Conference: The mitochondrial conundrum: Novel presentations and treatments of mitochondrial diseases, September 12, 2014, Bell Harbor International Conference Center

Dr. Sihoun Hahn is a Genetics Section Editor for UpToDate, since 2011
Dr. Sihoun Hahn is a Grant reviewer for Telethon Foundation, Italy

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. 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)

Susan Hale, ARNP, is WA State Chapter Treasurer of the National Association of Pediatric Nurse Practitioners.

Susan Hale, ARNP is on the Lysosomal Storage Disease Advisory Board (Shire HGT).

Susan Hale, ARNP is on the Planning Committee for the 37th Annual Pacific Northwest Conference for Advanced Practice in Primary and Acute Care in Seattle.

Susan Hale, ARNP was Co-Chair of Genzyme Regional Registry Meeting, San Francisco, CA.

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)