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), Metabolic Bone Clinic (SCH), and the Wilson Disease Clinic (SCH). Satellite clinics are held multiple times per year in Spokane.

Our newborn screening follow-up program has rapidly grown since the summer of 2008 expansion of the Washington State Newborn Screening program from 10 to 25 conditions. We have developed a tightly coordinated partnership between the Department of Health Public Health Laboratory, the Biochemical and Molecular Genetics Laboratories (SCH) and our clinics at SCH and UW. Our program serves as the medical home for many of the patients with inherited metabolic disorders from Washington and neighboring states.

BIOCHEMICAL GENETICS PROGRAM STAFF

Attending Physicians
C. Ronald Scott, MD
Sihoun Hahn, MD, PhD
Michael Raff, MD
J. Lawrence Merritt, II, MD
Anne Leavitt, MD

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

Genetic Counselors
Lisa Sniderman-King, MSc, CGC (SCH)
Penny Schubert, MS, CGC (SCH)
Angela Fox, MS, CGC (UW)
Stefanie Uhrich, MS, CGC (UW)

Metabolic Nutritionists
Cristine M Trahms, MS, RD, CD, FADA (UW)
Beth Ogata, MS, RD, CD (UW)
Janie Heffernan, MS, RD, CD (UW)
Maura Sandrock, MS, RD, CD (SCH)
2009 CLINICAL ACTIVITIES

In 2009, SCH and UW had over 1400 encounters encompassing outpatient visits and inpatient consultations with biochemical genetics. Major disorders seen in our clinic and hospital are summarized in Table 1. Two 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>Major Diseases in 2009</th>
<th>Encounters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysosomal Storage Disorder</td>
<td>455</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>352</td>
</tr>
<tr>
<td>Organic Acid Disorder</td>
<td>34</td>
</tr>
<tr>
<td>Amino Acid Disorder</td>
<td>44</td>
</tr>
<tr>
<td>Urea Cycle Disorder</td>
<td>22</td>
</tr>
<tr>
<td>Peroxisomal Disorder</td>
<td>5</td>
</tr>
<tr>
<td>Fatty Acid Oxidation Disorder</td>
<td>88</td>
</tr>
<tr>
<td>Cobalamin metabolism Disorder</td>
<td>48</td>
</tr>
<tr>
<td>Mitochondrial Disorder</td>
<td>28</td>
</tr>
<tr>
<td>Ketone Utilization Disorder</td>
<td>27</td>
</tr>
<tr>
<td>Wilson Disease</td>
<td>24</td>
</tr>
<tr>
<td>Cystinosis</td>
<td>9</td>
</tr>
<tr>
<td>Muscle disease</td>
<td>3</td>
</tr>
<tr>
<td>Developmental Delay</td>
<td>153</td>
</tr>
<tr>
<td>Failure to Thrive</td>
<td>39</td>
</tr>
<tr>
<td>Seizure Disorder</td>
<td>62</td>
</tr>
<tr>
<td>Hyperinsulinemia</td>
<td>3</td>
</tr>
<tr>
<td>Nephrogenic Diabetes Insipidus</td>
<td>14</td>
</tr>
<tr>
<td>Biotinidase deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Carbohydrate metabolism disorders</td>
<td>22</td>
</tr>
</tbody>
</table>

**The Newborn Screening Follow-up Program**

Since newborn screening began in 1963 with PKU, the Biochemical Genetics program has been providing confirmatory diagnostic testing, clinical treatment and care coordination for babies 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 May 2008, the Washington State Board of Health unanimously approved adding 15 new disorders to the newborn screening panel. On July 21, 2008, screening for 14 new conditions officially started and then tyrosinemia type I (TYR-I) was added in September, 2008.

Washington State is now screening for 6 amino acid disorders, 5 fatty acid metabolic disorders, 7 organic acid disorders and 7 other inherited disorders. Details of each disorder can be found at [www.doh.wa.gov/nbs](http://www.doh.wa.gov/nbs). In 2009, 75 cases were referred for confirmation. Of those, 21 cases were true positive including 4 Medium Chain AcylCoA Dehydrogenase (MCAD) Deficiency, 6 PKU, 2 Very Long Chain AcylCoA Dehydrogenase (VLCAD) Deficiency, 2 Methylmalonic Acidemia, 1 Maple Syrup Urine Disease, 2 3-MethylcrotonylCoA carboxylase (MCC) deficiency, 3 Glutaric Acidemia (GA) type 1 and 1 Beta Ketothiolase deficiency were included. All babies began treatment soon after birth and are doing well. We are also 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 newborn screens and the long-term outcomes of infants identified with Very Long-Chain Acyl-CoA Dehydrogenase Deficiency.

**The Lysosomal Disease (LSD) Program at UW/SCH** 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 in 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 radiology and anesthesia. Our group will also work with local hospitals to facilitate transition of treatment to centers closer to each 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.

The clinic team follows a large cohort of patients across the spectrum of LSDs as illustrated in Table 2 below. Up to now, treatment has been limited to
bone marrow or stem cell transplantation for a few disorders and enzyme replacement for a few more. Many are still untreatable. A more recent approach is Substrate Reduction Therapy. This oral drug slows the production of the accumulating lipid and is able to enter the brain. It is FDA-approved for use in Gaucher disease. Recent advances in industry technology have led to the development of newer modes of delivery, currently available under research protocols, such as the intrathecal infusion of enzyme replacement therapy (ERT) for Hunter syndrome (MPS II), which allows the drug to reach the brain. Another new development is an oral pharmacological chaperone therapy, which stabilizes the misfolded enzyme protein, allowing it to function rather than be degraded and may ultimately be used alone or in conjunction with ERT. A clinical trial of chaperone therapy for Fabry disease is underway at our center. ERT using carrot cells rather than mammalian cells as a medium for production has been developed and is currently in clinical trials with some Gaucher patients at our center. Other clinical trials we are participating in include the Fabry FIELD study, which compares whether ERT infusions every 4 weeks are as effective as every 2 weeks. The Myozyme Temporary Access Program (MTAP) study for adults with Pompe disease has allowed them access to ERT while awaiting final FDA approval. Long term follow-up of patients with these rare diseases is essential. With IRB approval, we enter patient medical information into global disease-specific registries, contributing to the development and improvement of management guidelines and documenting the effects of new therapies on the natural histories of these disorders.

Table 2. Number of patients followed with Lysosomal Storage Disorders

<table>
<thead>
<tr>
<th>Lysosomal Storage Disorder</th>
<th># Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaucher Disease</td>
<td>30</td>
</tr>
<tr>
<td>Fabry Disease</td>
<td>64</td>
</tr>
<tr>
<td>Pompe Disease</td>
<td>11</td>
</tr>
<tr>
<td>MPS I (Hurler Syndrome)</td>
<td>4</td>
</tr>
<tr>
<td>MPS II (Hunter Syndrome)</td>
<td>7</td>
</tr>
<tr>
<td>MPS III (Sanfilippo Syndrome)</td>
<td>5</td>
</tr>
<tr>
<td>MPS IV (Morquio Syndrome)</td>
<td>3</td>
</tr>
<tr>
<td>MPS VI (Maroteaux-Lamy Syndrome)</td>
<td>2</td>
</tr>
</tbody>
</table>

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 cohort of 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 actively involved with that National Urea Cycle Disorders Foundation (www.nucdf.org) and in an international Longitudinal Urea Cycle Disorders Consortium study to further improve the treatment, improve the quality of life, and our understanding of UCDs (http://rarediseasesnetwork.epi.usf.edu/ucdc/). We are also actively involved in clinical research in developing new therapies for treatments of UCDs with industry and are investigating the long term effects and ethics of newborn screening for UCDs.

BIOCHEMICAL GENETICS 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 and supported by Lisa Sniderman-King, a board-certified genetic counselor. High volume tests in the lab are summarized in Table 3.

The Biochemical and Molecular Genetics Laboratories serve as a key component of the Biochemical Genetics Program. Combined, the two labs offer 70 tests and tested over 7,000 patients in 2009. 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). In 2009, the Biochemical and
Molecular genetics laboratories had 100% success rate for proficiency testing from CAP.

Table 3. High Volume Tests in 2009

<table>
<thead>
<tr>
<th>Test</th>
<th>Analytic Method</th>
<th># Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fragile X</td>
<td>Fragment Analysis, southern Blot</td>
<td>553</td>
</tr>
<tr>
<td>Factor V Leiden/PTV</td>
<td>Luminex (OLA)</td>
<td>285</td>
</tr>
<tr>
<td>Prader Willi/Angelman Syndrome</td>
<td>Methylation PCR</td>
<td>103</td>
</tr>
<tr>
<td>Amino Acid Analysis</td>
<td>HPLC</td>
<td>1456</td>
</tr>
<tr>
<td>Organic Acid Analysis</td>
<td>GCMS</td>
<td>1272</td>
</tr>
<tr>
<td>Acylcarnitine Analysis</td>
<td>MSMS</td>
<td>1120</td>
</tr>
<tr>
<td>Metabolic Screens</td>
<td>Colorometric</td>
<td>327</td>
</tr>
<tr>
<td>Lysosomal Enzymes</td>
<td>Fluorometric</td>
<td>912</td>
</tr>
</tbody>
</table>

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 and Norman Buroker, PhD, each have 25 years research experience in molecular biology. The laboratory is in its fourth year and is a CLIA certified clinical lab that offers DNA analysis for lysosomal storage diseases: including Gaucher, Pompe, and Fabry. In addition, the lab performs diagnostic mutation analysis and/or sequencing for several other disorders including Congenital Sucrase-Isomaltase Deficiency and Tyrosinemia.

Research and Development Laboratory

The Biochemical Genetics Program is unique in having a CLIA certified R&D laboratory. The center is fully equipped with high technology including LC-MS/MS (tandem mass spectrometry) and newly purchased Next Generation Genome Analyzer (Illumina). The lab is aiming at development of highly complex tests in metabolomics and genomics. This is truly translational research from bench to clinical practice. The laboratory works in collaboration with a large network of geneticists/scientists in order to develop and validate tests that are critical for patient diagnosis and management. The R&D Laboratory is located in the Seattle Children's Hospital Research Institute and includes three dedicated development scientists. Dr. Valeria Vasta is working on developing genetic testing by conventional sequencing and multiplex gene analysis by next generation sequencing. Dr. Xiulian Chen is working on a project to develop mitochondrial enzyme assays in muscle tissues. Dr. Sandra Kerfoot recently joined our team as a research scientist and is working on peptide analysis by tandem mass spectrometry for various genetic conditions. The ultimate goal for the laboratory is to serve as a bridge between basic research and clinical practice.

Table 4. Clinical Tests Implemented from R&D in 2009

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCHAD/TFP</td>
<td>HADHB DNA Sequencing</td>
</tr>
<tr>
<td>Spinal Muscular Atrophy Carrier Testing</td>
<td>Duplication/deletion (MLPA)</td>
</tr>
<tr>
<td>POLG1 related disorders</td>
<td>POLG1 DNA Sequencing</td>
</tr>
<tr>
<td>POLG 2 related disorders</td>
<td>POLG2 DNA Sequencing</td>
</tr>
<tr>
<td>Pompe Disease</td>
<td>GAA DNA Sequencing</td>
</tr>
<tr>
<td>Maturity onset diabetes of the young (MODY)</td>
<td>HNF4A, GCK and HNF1A DNA Sequencing</td>
</tr>
<tr>
<td>Neonatal Diabetes</td>
<td>KCNJ11, INS, ABCC8, GCK DNA Sequencing</td>
</tr>
</tbody>
</table>

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. Two genetic residents, Dr. Mitzi Murray and Dr. David Cobb had three month rotation in our biochemical genetics program in 2009.

Two neurology chief residents, Dr. Ann Hyslop and Dr. Alana Golden had one month rotation in biochemical genetics in 2009.

Dr. JH Byeon (October 23 – 31, 2009), pediatric resident from Korea University Medical Center was with us for a rotation with Biochemical Genetics at Seattle Children’s. She observed patients with our attending physicians at clinic and also participated in rounding for in house patients.
In partnership with the ABMG Fellowship program, Seattle Children’s Biochemical Genetics Laboratory will be sponsoring four Fellows in 2010 for rotations in the Biochemical Genetics Laboratory. 2010 will also see three fellows, each rotating in Biochemical Genetics for 3 months; David Cobb, MD (Jan. – March) and two others later in the year.

CLINICAL RESEARCH PROTOCOLS AT SEATTLE CHILDREN’S AND THE UNIVERSITY OF WASHINGTON

Clinical Trials:

An Open-label Expanded Access Trial of Plant Cell Expressed Recombinant Human Glucocerebrosidase (prGCD) in Patients with Gaucher Disease Who Require Enzyme Replacement Therapy. Principal Investigator: Dr. C. Ronald Scott. Funding: Protalix Biotherapeutics. This study provides access to an investigational new enzyme for derived from plant cells for patients with Gaucher disease.

A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy, Safety and Pharmacodynamics of AT1001 in Patients with Fabry Disease and AT1001-Responsive GLA Mutations. Principal Investigator: Dr. C. Ronald Scott. Funding: Amicus Therapeutics Inc. Investigation of a new oral chaperone therapy treatment for adults with Fabry disease.

A Randomized, Multicenter, Multinational, Phase 3B, Open-Label, Parallel-Group Study of Fabrazyme® (agalsidase beta) in Treatment-Naive Male Pediatric Patients with Fabry Disease Without Severe Symptoms. Principal Investigator: Dr. C. Ronald Scott. Funding: Genzyme Corporation. This study looks at effects of low dose enzyme replacement therapy in children with Fabry disease.

Aglucosidase Alfa Temporary Access Program. Principal Investigator: Dr. C. Ronald Scott. Funding: Genzyme Corporation. This study provides temporary access of enzyme replacement therapy to individuals with Pompe disease until the FDA approves the new manufacturing process and sufficient commercial supply is available.

A 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, III. Funding: Hyperion Therapeutics. This study compares the safety and efficacy of a new oral treatment for patients with urea cycle disorders.

Disease Registries:

The LSD Registry Program. Principal Investigators: Dr. Sihoun Hahn, Susan Hale, ARNP and Lisa Sniderman King, M.Sc. CGC. 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, Stefanie Uhrich, MS, and Angela Fox, MS.

A Global Multi-Center, Long-Term, Observational Survey of Patients with Hunter Syndrome (Mucopolysaccharidosis II). Principal Investigators: Dr. Sihoun Hahn, Susan Hale, ARNP and Lisa Sniderman King, M.Sc. CGC. 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, Susan Hale, ARNP and Lisa Sniderman King, M.Sc. CGC. Funding: BioMarin Pharmaceuticals. A long-term natural history disease registry of treated and untreated patients with MPS VI.

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

Laboratory Studies:

Validation of Next Generation Sequencing for Mitochondrial Disorders. Principal Investigator: Dr. Sihoun Hahn. Funding: The Mitochondrial Research Guild. This study aims to develop a rapid, minimally-invasive test to simultaneously sequence hundreds of genes involved in mitochondrial disease.


Newborn Screening for Lysosomal Storage Disorders by Tandem Mass Spectroscopy. Principal Investigator: Dr. C. Ronald Scott. Funding: NIH. A pilot protocol to evaluate the feasibility,
sensitivity and specificity of tandem mass spectroscopy to detect lysosomal storage disorders by newborn screening. Screening for Fabry disease currently underway.

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 Hunan Foundation. This 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 speaker this year was David Rosenblatt, MD, Professor & Chair of the Department of Human Genetics, McGill University, Montreal, Quebec, Canada. He gave a most interesting and informational presentation titled “Vitamin B12: Can You Teach an Old Vitamin New Tricks?” Dr. Rosenblatt is arguably the premier expert on vitamin B12 and his visit was a most memorable. The lectures were made at SCH and the following day at UW on the last Thursday and Friday of February. This schedule will hold for upcoming lectures and if you are interested in attending, please call 206-987-3012 for further information.

AWARDS, GRANTS, HONORS

J. Lawrence Merritt, II, MD

- Site Principal Investigator, Seattle. Longitudinal Study of Urea Cycle Disorders. Urea Cycle Disorders Consortium. Rare Diseases Clinical Research Network. $75,000/ year. June 1, 2008 – July 31, 2009. Study chairs Mark Batshaw, MD and Mendel Tuchman, M.D. Children’s National Medical Center (CNMC), Washington, DC.

- Longitudinal Study of Urea Cycle Disorders. 9/30/09-7/31/11. Study PI Mark Batshaw Children’s National Medical Center and O’Malley Family Foundation.

- Urea Cycle Disorders Training Grant. 9/30/09-7/31/11 To study the experiences and attitudes of families with children with urea cycle disorders identified through newborn screening and the impact of this diagnosis and follow-up care upon their quality of life.

- FDA Clinical Study. A 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. 8/6/09-8/5/10 Hyperion Inc.

- FDA IND Approval: Emergency Use of Sodium DL-3-Hydroxybutyrate for Treatment of Multiple Acyl-CoA Dehydrogenase Deficiency (Glutaric Acidemia type II).

Ron Scott, MD

- Validation of Lysosomal Storage Disease Enzymes for Newborn Screening, 9/30/06-6/30/2010

- Multiplex Analysis of Inborn Errors of Metabolism, 9/1/06-7/31/2013

- PKU 007 : A Phase 2, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of PhenoOptin™ in Subjects with Hyperphenylalaninemia Due to Primary BH4 Deficiency, 12/19/06-7/31/09

- Genetic Analysis of the Sucrase-Isomalase (SI) Gene, 3/1/08-9/30/2010


Sihoun Hahn, MD, PhD

- Mitochondrial Research Guild Fund for Development Scientist (10/1/07-9/30/09)


- Luminex/ACMGF Grant Award (2009-2010) for promotion of safe and effective genetic testing and services
• On March 20th C Trahms received the Duncan Award. This Seattle Children’s award is given annually to acknowledge groups or individuals who have demonstrated extraordinary positive social or scientific impact on the well-being of children with disabilities above and beyond usual career expectations.

• In February the University of Washington PKU Clinic was renamed The Cristine M Trahms Program for Phenylketonuria. This honor was awarded on recognition of Cris’ extraordinary vision, dedication, and service to the clinic.

Beth Ogata, MS, RD, CD

• Ogata received her specialty certification in pediatric nutrition from the Commission on Dietetic Registration.

Anne Leavitt, MD

• Leavitt MD received her subspecialty certification in Developmental and behavioral pediatrics.

EXTRAMURAL PRESENTATIONS

Scott CR. Newborn Screening for Fabry Disease. Fabry Registry Board of Advisers Meeting, Chicago, IL, June 27, 2009.


McKean, KN, Medical Nutrition Therapy for Metabolic Disorders, Seattle Pacific University, Seattle, WA, February 3, 2009.


Leavitt, A. prepared a Power Point presentation at the request of Mead Johnson Metabolics for the Chinese Ministry of Health on PKU diagnosis, management and the essential role of formula.


PUBLICATIONS


