Short Term Follow Up

Tandem Mass Spectrometry

Workshop Agenda

January 13-17, 2020

APHL Headquarters
8515 Georgia Ave
Silver Spring, MD 20910

NewSTEPs

A Program of the Association of Public Health Laboratories™

This meeting is sponsored by the

Association of Public Health Laboratories

About NewSTEPs

NewSTEPs (Newborn Screening Technical assistance and Evaluation Program) is a program of the Association of Public Health Laboratories in collaboration with the Colorado School of Public Health. It is a national newborn screening program designed to provide data, technical assistance, and training to newborn screening programs across the country and to assist states with quality improvement initiatives. NewSTEPs is a comprehensive resource center for state newborn screening programs and stakeholders.

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PURPOSE

This intensive five-day course assumes a basic understanding of newborn screening follow-up and metabolic biochemistry. Coursework will begin with a review of the principles of tandem mass spectrometry (MS/MS), diagnostic patterns in results, cut-offs, biochemical pathways, diagnostic follow-up and biochemical and clinical features of the metabolic disorders. Each day will cover interpretive skills and diagnostic follow up of certain disorders detectable through MS/MS screening including: amino acid disorders, urea cycle disorders, fatty acid oxidation disorders, and organic acid disorders. Interpretation homework assignments will be given along with daily examinations of information learned. Successful course performance will be recognized with a certificate of course completion and continuing education units will be available.

OBJECTIVES

- Interpret the results obtained from MS/MS analysis of dried blood spots for:
  - Amino Acidopathies and Urea Cycle Disorders.
  - Fatty acid oxidation disorders
  - Organic acid disorders.
- List appropriate expected ranges and cutoffs for MS/MS when applied to newborn screening disorders
- Describe the biochemical and clinical features of the metabolic disorders
- Recommend appropriate follow-up tests for confirmation of screening results and differential diagnosis

CONTACT

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DAY 1

AGENDA

Monday, January 13

8:00 – 9:15 am

Welcome
Scott Becker, MS
APHL Executive Director
Eric Blank, DrPH
Senior Director Public Health Systems
Jelili Ojodu, MPH
Director, Newborn Screening & Genetics

Overview, and Pre-Test
David Millington, PhD
- *Pre-test for participant knowledge of MS/MS in newborn screening (NBS).*

9:15 – 10:15 am

Brief History of MS/MS
David Millington, PhD
- *Understand MS/MS as related to clinical diagnostics and NBS.*

10:15 – 10:45 am

Break

10:45 – 12:15 am

Basic Theory of ESI and MS/MS
David Millington, PhD
- *Understand the basic theory of Electrospray Ionisation (ESI) and MS/MS, understand scan functions and how they are employed in NBS.*

12:15 – 1:15 pm

Lunch

1:15 – 2:30 pm

Amino Acid Disorders – I
Dwight Koeberl, MD, PhD
- *Understand the biochemistry and clinical manifestations of the amino acid disorders including the urea cycle, tyrosinemias, MSUD, etc.*

2:30 – 3:30 pm

Amino Acid Disorders - II
David Millington, PhD
- *Understand roles of personnel required for NBS expanded with MS/MS. Interpret amino acid MS/MS spectra, follow-up and diagnose amino acid disorders.*

3:30 – 3:45 pm

Break

3:45 – 5:00 pm

Disorders of Organic Acid Metabolism - I
Dwight Koeberl, MD, PhD
- *Understand the biochemistry and clinical manifestations of disorders of the catabolism of branched-chain amino acids and related disorders that comprise the organic acidurias.*

6:00 pm

Group Dinner *(optional)*
Matchbox
919 Ellsworth Dr, Silver Spring, MD 20910

DAY 2

AGENDA

Tuesday, January 14

8:00 – 9:30 am

Disorders of Fatty Acid Oxidation - I
Dwight Koeberl, MD, PhD

- *Understand the biochemistry and clinical manifestations of disorders of the catabolism of fatty acid oxidation disorders.*

9:30 – 10:30 am

Disorders of Organic Acid Metabolism - II
David Millington, PhD

- *Recognize disorders of amino acid catabolism by their acylcarnitine spectra and understand confirmatory test procedures.*

10:30 – 11:00 am

Break

11:00 – 12:30 am

Disorders of Fatty Acid Metabolism - II
David Millington, PhD

- *Recognize disorders of fatty acid oxidation by their acylcarnitine spectra and understand confirmatory test procedure.*

12:30 – 1:30 pm

Lunch

1:30 – 2:30 pm

Stable Isotopes
David Millington, PhD

- *Understand the historical relationship between stable isotopes and mass spectrometry, the principles of isotope-labelling, and how stable isotope-labeled analogs are used as internal standards to quantify analytes extracted from dried blood spots.*

2:30 – 3:30 pm

Summary of Results from the New York Program [teleconference]
Joseph Orsini, PhD

- *Understand the process and impact of expanded newborn screening in a highly populated state. Disorders detected, frequency.*

3:30 – 4:30 pm

Cutoff Decisions and Result Reporting
David Millington, PhD

- *Understand how cut-offs are established and affect result reporting.*

DAY 3

AGENDA

Wednesday, January 15

8:00 – 8:30 am	Homework Review
8:30 – 9:30 am	Region 4 Collaborative Program *David Millington, PhD* • *Discussion of post-analytical tools. Learn how to access the website and use the available tools to enhance interpretation*
9:30 – 10:00 am	Break
10:00 – 11:00 am	Overview of Laboratory Procedures- Artifacts and Sources of Potential Errors *David Millington, PhD* • *Recognize non-diagnostic MS/MS results and understand the causes*
11:00 – 12:00 pm	Summary of Results from "Early Check" Pilot Studies [Teleconference] *Lisa Gehtland, MD* • *Review recent pilot studies in North Carolina; Introduction of a new pilot program for conditions not yet on the Recommended Uniform Screening Panel.*
12:00 – 1:00 pm	Review of Cases Seen in Clinic Follow-Up {Teleconference] *Surekha Pendyal, MSc, MEd, RD*
1:00 pm	Free Afternoon

DAY 4

AGENDA

Thursday, January 16

8:00 – 8:30 am

Review Homework

8:30 – 9:30 am

Overview of the CDC QA/QC Program [Teleconference]
Joanne Mei, PhD

- *Appreciate the Centers for Disease Control and Prevention (CDC) Quality Assurance and Quality Control (QA/QC) program for expanded newborn screening.*

9:30 – 10:30 am

Theory and Application of GC/MS, Ion Exchange Chromatography, Tandem MS and Other Methods
David Millington, PhD

- *Understand response to abnormal NBS results and the role of the Biochemical Genetics Laboratories for first-tier follow-up testing for diagnosis – limitations and further steps.*

10:30 – 11:00 am

Break

11:00 – 12:00 pm

Discussion of ACMG NBS Recommendations- Birth of the RUSP
David Millington, PhD

- *Understand the process of linking analytes detected by MSMS with disorders – primary and secondary conditions. Learn how disorders are selected for the recommended uniform screening panel (RUSP).*

12:00 – 1:00 pm

Lunch

1:00 – 2:00 pm

Clinical Presentation and Treatment and Underlying Genetics of Pompe Disease [Teleconference]
Priya Kishnani, MD

- *Learn about the impact of NBS on the outcomes for patients with Pompe*

2:00 – 3:00 pm

Review of Cases Seen in Follow-Up [Teleconference]
Jennifer Sullivan

- *Understand the impact of expanded newborn screening from the genetic counselor's point of view.*

3:00 – 3:30 pm

Topics of concern or interest from the class

- *Discussion of issues specific to the participants*

3:30 – 4:30 pm

Origin and Role of T Cells in the Newborn [Teleconference]
Rebecca Buckley, MD

- *Understand the underlying cause of SCID and other T-cell lymphopenias, the TREC assay, treatment of SCID.*

DAY 5

AGENDA

Friday, January 17

7:30 – 8:00 am	Homework Review
8:00 – 9:00 am	Screening for Pompe and Other LSDs *David Millington, PhD* • *Review of methods for measurement of LSD enzyme activities in DBS samples, using benchtop microfluorometry, digital microfluidics and tandem mass spectrometry.*
9:00 – 10:00 am	Summary of Results from Recent Implementation of New Methods for LSDs [Teleconference] *Patrick Hopkins & Khaja Basheeruddin, PhD* • *Learn how digital microfluidics and tandem mass spectrometry have been implemented in a NBS program to screen for Pompe, MPS-I, ALD and other LSDs.*
10:00 – 10:30 am	Break
10:30 – 11:30 pm	Impact of expanded NBS: Results, Lessons Learned, Future Directions *David Millington, PhD* • *Understand the impact of MSMS on NBS. Results, lessons learned, future directions.*
11:30 – 12:30 pm	Review of Results from the NBS Lab *David Millington, PhD* • *Understand how to appreciate the significance of primary and secondary metabolites and analyte ratios in assessment of risk. Understand how to effectively interpret and respond to abnormal MS/MS screening results.*
12:30 – 1:00 pm	Lunch
1:00 – 2:30 pm	Written Final Exam
2:30 – 3:15 pm	Course Review and Discussion
3:15 – 4:00 pm	Course Certificates and Adjourn

SPEAKERS

Khaja Basheeruddin, PhD

Rebecca Hatcher Buckley, M.D. graduated with an A.B. degree from Duke University in 1954, an MD degree from the University of North Carolina School of Medicine in 1958 and received house staff training in Pediatrics at Duke. Dr. Buckley was a fellow in Allergy under Dr. Susan C. Dees and a fellow in Immunology under Dr. Richard S. Metzgar, all at Duke. She then became a faculty member in the Department of Pediatrics, served as Chief of the Division of Allergy and Immunology from 1974 to 2003 and has been the James Buren Sidbury Distinguished Professor of Pediatrics and Professor of Immunology at Duke since 1979. Dr. Buckley's research interests have been in the fundamental causes of genetically-determined immunodeficiency diseases. For the past 37 years her research has been on the syndrome of severe combined immunodeficiency (SCID) and the long-term clinical and immunologic outcomes of nonablative T cell-depleted haploidentical parental bone marrow transplants. For the past two decades she has advocated newborn screening for SCID, and the Secretary of HHS officially recommended that this be implemented in May of 2010. The North Carolina legislature and Governor approved this in 2015. Dr. Buckley is the author or co-author of 363 scientific publications. She trained more than 80 post-doctoral fellows during her 29 year tenure as Chief of the Division of Allergy and Immunology at Duke. Dr. Buckley has been a member of over 30 national committees and councils. She was president of The American Academy of Allergy, Asthma and Immunology (AAAAI) from 1979-80. She is an elected member of the Society for Pediatric Research, the American Pediatric Society (Council 1991-2001; President 1999-2000), American Association for the Advancement of Science, Fellow (2000); Chairman Section on Medical Sciences (2001-2003), American Association of Immunologists (Chairman, Clinical Immunology Committee 1984-87), and American Academy of Pediatrics (Section on Allergy & Immunology; Executive Committee 1981-84). She served two terms as a Director of the American Board of Allergy and Immunology. Dr. Buckley has also served on a number of editorial boards including the Journal of Immunology, the Journal of Allergy and Clinical Immunology and the Journal of Clinical Immunology, where she was Associate Editor. She chaired the NIH Immunological Sciences Study Section and was a member of NIAID's Board of Scientific Counselors. She is a member of Alpha Omega Alpha. In October of 2003 she was elected to the Institute of Medicine of the National Academy of Sciences. On September 30, 2007 she was appointed by the U.S. Secretary of HHS to a 4 year term as a member of the HRSA Advisory Committee on Heritable Disorders of Newborns and Children. In 2012 she was inducted into the National Academy of Sciences. In 2013, she was the recipient of the Thomas A. Waldmann Award from the Foundation for Primary Immunodeficiency Diseases, and she was the recipient of the March of Dimes Colonel Harlan Sanders Lifetime Achievement Award in Genetics from the American College of Medical Genetics. She was elected a member of the Association of American Physicians and was the recipient of the John Howland Award from the American Pediatric Society. In 2019 she received an Honorary Degree of Doctor of Science from the University of North Carolina and on she was selected as the 2019 Distinguished Fellow of the American Association of Immunologists. Dr. Buckley currently serves as Chairman of the Medical Advisory Committee of the Immune Deficiency Foundation. She remains actively involved in clinical and scientific research, teaching and patient care.

Lisa Gehtland, MD is a physician researcher with interests in newborn screening systems and maternal and child health. Dr. Gehtland is Project Director of the NCATS-funded Innovation Award entitled "Early Check: An Innovative Collaboration to Facilitate Pre-symptomatic Clinical Trials in Newborns." This statewide project offers voluntary newborn screening for a panel of conditions to all birthing parents in North Carolina and is a collaboration between three CTSAs (UNC, Duke, and Wake Forest) and the North Carolina State Laboratory of Public Health. Dr. Gehtland was also Associate Project Director for the North Carolina Newborn Screening Pilot Studies master task order contract and two associated task orders, one that performed newborn screening for mucopolysaccharidosis I for 80,000 babies in North Carolina and the second to perform newborn screening for X-linked adrenoleukodystrophy for 50,000 babies in North Carolina. She serves as the Program Manager for RTI's partnership with the North Carolina Translational and Clinical Sciences Institute (NC TraCS), the CTSA at UNC-Chapel Hill.

SPEAKERS

Patrick Hopkins is the retired Chief of the Missouri Newborn Screening Laboratory after working for the Missouri State Public Health Laboratory for over 33 years, with 27 years in the Newborn Screening Laboratory. Patrick serves on APHL's NBSGPH Committee and was a former Chair of the APHL QA/QC Subcommittee. He has made great contributions over the years in NBS emergency preparedness across the Heartland States and with the implementation of LSD screening in Missouri. Patrick continues to work part-time in the Missouri newborn screening laboratory as a Project Specialist leading Missouri's Peer Network Resource Center made possible by NewSTEPs to assist other state programs with their implementation efforts for Pompe and MPS I.

Dwight D. Koeberl, MD, PhD, is the medical director of the Mass Spectrometry Laboratory and the Glycogen Storage Disease Laboratory in the Department of Pediatrics, Division of Medical Genetics at Duke University. He is also an associate professor of pediatrics and an associate professor of molecular genetics and microbiology. Dr. Koeberl received his MD specializing in pediatrics and PhD in biochemistry from the Mayo Medical and Graduate Schools. Dr. Koeberl has generously supported research, and continues to give his support in ongoing research involving Pompe disease in newborn screening. He has published scientific reviews, contributed to journal articles and chapters in books. He has also released editorials, positions, and background papers and is an expert reviewer for a number of journals, including the Journal of Inherited Metabolic Disorders, Gene Therapy, Molecular Genetics and Metabolism, and the Journal of Gene Medicine. Dr. Koeberl has been recognized as being one of America's best doctors, and continues to provide his expertise as member of organizations such as the Society for the Study of Inborn Errors of Metabolism the Society of Inherited Metabolic Disorders, Association for Glycogen Storage Disease, and the North Carolina Medical Genetics Association.

Priya S. Kishnani, MD is Chief of the Division of Medical Genetics, Department of Pediatrics and Director of the YT and Alice Chen Center for Genomic Research which has a focus on developing new therapies for rare genetic disorders. She holds certification from the American Board of Medical Genetics and the American Board of Biochemical Genetics. She has a long-standing research and clinical interest in Pompe disease, and has been the Principle Investigator for several clinical trials involving Pompe disease. She is Chair of the North American Pompe Registry Board and is a member of the International Pompe Registry Board of Advisors. Dr. Kishnani is Chair of the Scientific Advisory Board for Association of Glycogen Storage Diseases, US. She is a task force member for PCORnet for the rare disease initiative.

Joanne Mei, PhD, Chief of the Newborn Screening Quality Assurance Program (NSQAP), received her BS in Chemistry and Master's and Ph.D in Entomology from the University of Massachusetts. Dr. Mei began her career at the Centers for Disease Control and Prevention, Division of Laboratory Sciences, by conducting radioimmunoassays and nephelometric assays for lipoprotein standardization. She then joined NSQAP in the Endocrinopathy laboratory group and as the quality control manager for the program. Shortly afterwards, she assumed supervisory functions over the manufacture and certification of dried-blood spot (DBS) quality control and proficiency testing materials for newborn screening assays for congenital hypothyroidism, congenital adrenal hyperplasia, hemoglobinopathy and cystic fibrosis phenotypic and molecular methods, HIV antibodies in DBS, Toxoplasma gondii antibodies in DBS, and the quality assurance for domestic serum/plasma-based tests for the estimation of population-based HIV incidence rates. Dr. Mei oversees all aspects of the program which includes the administration of 14 proficiency testing and 13 quality control programs for over 700 laboratories in 85 countries, web site database reporting, NSQAP participant logistics, and summary proficiency testing reports, participant evaluations, and quality control reports. Dr. Mei is a member of the Association of Public Health Laboratories' Quality Assurance/Quality Control Subcommittee and the Hemoglobinopathy Testing Work Group. Dr. Mei has been a member of the International Society for Neonatal Screening (ISNS) Council since 2009 and Secretary of ISNS since 2013. Dr. Mei's personal interests include playing recorders, capped reed instruments, and Renaissance flute with Lauda Musicam of Atlanta, a group dedicated to performing music written before 1750.

SPEAKERS

David S. Millington, Ph.D., is Emeritus Professor of Pediatrics, recently retired from Duke School of Medicine. He and his colleagues pioneered the application of tandem mass spectrometry for the targeted analysis of acylcarnitines that became a frontline diagnostic test for defects of fat oxidation and branched-chain amino acid catabolism. Subsequently, the method was modified to include several essential amino acids and applied to dried blood spots, paving the way for the expansion of newborn screening for from a handful to over 30 metabolic conditions. As the expanded newborn screening method has spread, Dr. Millington has developed educational material and taught many laboratorians and follow-up coordinators worldwide how to apply the technology and interpret results. More recently, he has collaborated with a North Carolina biotechnology company to bring digital microfluidics into biochemical diagnostics and newborn screening. He has also pioneered novel biomarker assays for numerous lysosomal storage conditions to facilitate patient diagnosis and monitoring. Dr. Millington has published over 200 research articles and book chapters and has served on the North Carolina Newborn Screening Program Advisory Board since 1990. He was honored jointly with Dr. Mohamed Rashed by the ISNS with the Robert Guthrie award for outstanding contributions to newborn screening in 1996. He was also honored by the MSACL in 2015 with their first Distinguished Contribution Award in recognition of achievements made in the field of clinical mass spectrometry that have furthered the advancement of knowledge and the implementation of science for the benefit of humanity.

Joseph Orsini has a Ph.D. in analytical chemistry from the University of Vermont. He oversees all method development and day to day operations of the Lysosomal Storage Disorders Screening Laboratory for the NYS Department of Health Newborn Screening Program (NSP). In addition, he has been the Director of Operations for the NYS Newborn Screening Program (NSP) since 2007. He has directly overseen the method development and implementation of universal screening for Krabbe disease. Most recently he implemented a first-tier tandem mass spectrometry screen for X-linked adrenoleukodystrophy (ALD).

Surekha Pendyal, MSc, MEd, RD, FANDhas been practicing as a registered dietitian for 25 yrs. For the last 20 years she is working in the area of pediatrics and inherited metabolic disorders. She has experience in the follow-up of MS/MS newborn screening and the dietary treatment of a wide variety of inborn errors of metabolism. She joined the Duke clinical genetics team in 2015 where she is now gaining valuable experience in providing medical nutrition therapy to individuals with glycogen storage diseases.

Jennifer Sullivan