Cerebral Palsy Research: On the Cutting Edge

CP Research Consortium of Michigan
3rd Biennial Conference

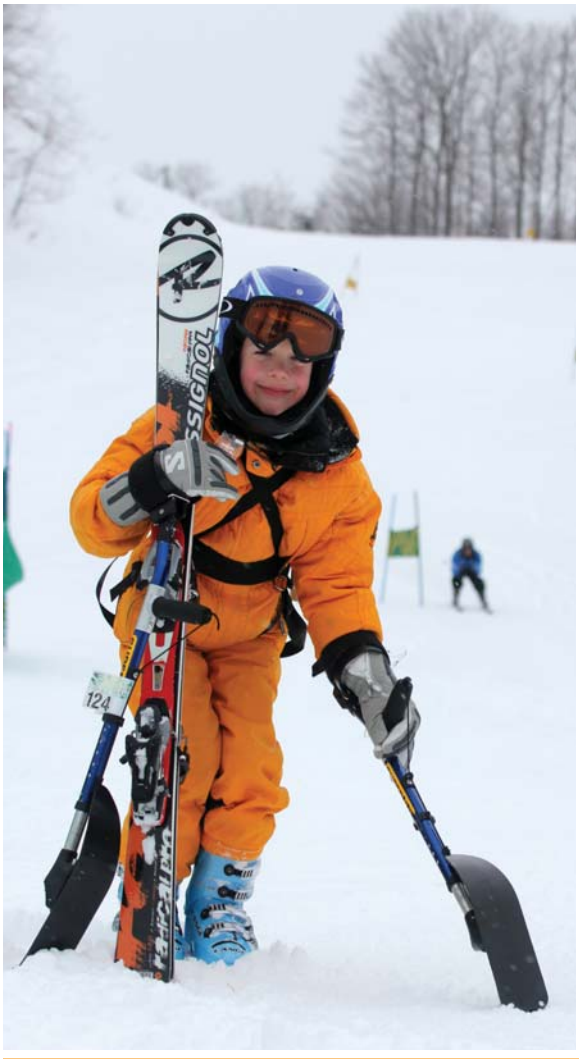
MARGHERIO CONFERENCE CENTER
Wayne State University School of Medicine
Gordon H. Scott Hall, 540 East Canfield, Detroit, MI 48201

Wednesday, January 30, 2013
8:00 a.m. – 5:00 p.m.

Sponsored by Cerebral Palsy Research Consortium of Michigan, and held in collaboration with Michigan State University, University of Michigan, and Wayne State University.

MISSION STATEMENT

The goal of the 3rd biennial conference is to present cutting edge research on cerebral palsy and kindle collaborations among Michigan's rich array of researchers interested in CP. This includes partners at our universities, Michigan Department of Community Health, UCP-Michigan, clinicians, therapists, and educators, as well as people with CP and their families. We also encourage population based and clinical research registries for CP to support and accelerate research. Registry activities will link Michigan area researchers who can collaboratively apply for funding, carry out studies, and provide joint training opportunities in research. Through an ongoing interactive network of researchers, providers, people with CP, and public health leaders, we can make progress on problems of vital concern to people with CP.



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CPRCoM

The Cerebral Palsy Research Consortium of Michigan was formed in 2007 by Drs. Edward Hurvitz and Seth Warschausky of the University of Michigan, Department of Physical Medicine and Rehabilitation, and Dr. Nigel Paneth of Michigan State University. The Consortium includes members from around the state, including Spectrum health system in Grand Rapids and Wayne State University in Detroit. The Consortium has developed a voluntary registry for individuals with cerebral palsy which will be a valuable tool for recruiting subjects for studies. Consortium members are working together on both multicenter research and training efforts, and sponsoring periodic conferences and workshops featuring current CP research in Michigan.

IN APPRECIATION

Keynote Speaker

Roberto Romero (NIH)

and all our speakers and panelists

Conference Organizers

Edward Hurvitz (UM)

Steven Korzeniewski (WSU)

Madeleine Lenski (MSU)

Nigel Paneth (MSU)

Seth Warschausky (UM)

Booklet and Program

Design by: Ann Cook, Michigan State University

Photos: Thanks to Daneel and his parents for the wonderful Cutting Edge Ski photos!

Financial, administrative, and collegial support

The CP Research Consortium of Michigan gratefully acknowledges

Wayne State University Perinatal Research Initiative*

Michigan State University, Department of Epidemiology and Biostatistics

University of Michigan, Department of Rehabilitation and Physical Medicine.

and many support personnel from Wayne State University

*The Perinatal Initiative was established in 2009 by the Wayne State University (WSU) Board of Governors to foster research in perinatal medicine. The mission of the WSU Perinatal Initiative is to foster and recruit faculty and collaborators within WSU, the School of Medicine, universities, and community and governmental organizations, with a specific focus on research in the area of maternal, perinatal and child health. The WSU Perinatal Initiative seeks to amplify the University's impressive record of innovative discoveries and achievements in this area.

CONFERENCE AGENDA

8:30 a.m. **Welcome and Introductions**
Steven Korzeniewski, PhD, Director, Perinatal Epidemiology Unit, Wayne State University

PLENARY Session I: Early Intervention and Prevention

8:35 a.m. **"Distinctive databases for etiologic investigations: MOBAND, OWL, NCPP, ELGAN, UM registry, and other databases"**
Steven Korzeniewski, PhD, Director, Perinatal Epidemiology Unit, Wayne State University

9:00 a.m. **"Hypothermia and Cerebral Palsy in term and near-term infants"**
Seetha Shankaran, MD, Director, Neonatal/Perinatal Medicine, Wayne State University

9:30 a.m. **Keynote Speech: "Fetal Infection and Inflammation in Cerebral Palsy: Insights from Molecular Imaging and Nanotechnology"**
Roberto Romero, MD, Chief, Perinatology Research Branch, NICHD, NIH

10:30 a.m. BREAK and POSTERS

PLENARY Session II: Etiology and Outcomes Research

11:00 a.m. **"CP case control study using newborn blood spots: latest results"**
Nigel Paneth, MD, University Distinguished Professor, Epidemiology and Biostatistics, Michigan State University

11:20 a.m. **"Cognition in CP: Adapted Cognitive Assessment Laboratory update"**
Seth Warschausky, PhD, Professor, Physical Medicine and Rehabilitation, University of Michigan

11:40 a.m. **"Communication and CP: what do CFCS scores tell us?"**
Mary Jo Cooley Hidecker, PhD, Assistant Professor, Speech-Language Pathology, University of Central Arkansas

12:00 noon **"The NIH PROMIS: Measuring Health Related Quality of Life in Children and Adults with CP"**
Anna Kratz, PhD, Assistant Professor, Physical Medicine and Rehabilitation, University of Michigan

12:20 p.m. **"Research in interventions and QOL: Introduction to breakout"**
Edward Hurvitz, MD, Chair, Physical Medicine and Rehabilitation, University of Michigan

12:40 p.m. LUNCH

1:00 p.m. Brief lunchtime presentations: Jacqueline Kaufman, Danielle Shapiro, Mark Peterson.

1:30 p.m. POSTERS

BREAKOUT Sessions: Learn, Contribute, Collaborate

2:00 p.m.
- **Using the CP databases: Collaborative opportunities.** Led by N. Paneth
- **Interventions: Issues in design and studying lifespan.** Led by E. Hurvitz
- **Research in social integration and quality of life.** Led by S. Warschausky and N. Lomerson Schickling

3:30 p.m. BREAK and POSTERS

PANEL Discussion:

Edward Hurvitz, Moderator. Panel participants: Nicole Lomerson Schickling, Kathleen Brockel, Steve Korzeniewski, Nigel Paneth, Seth Warschausky

4:00 p.m.
- Review of break sessions
- Future research
- Patient advocacy

5:00 p.m. Adjournment: Steven Korzeniewski

KEYNOTE SPEAKER - ROBERTO ROMERO, MD, D.MED.SCI.

Roberto Romero, MD, D.Med.Sci., has been Chief of the Perinatology Research Branch of the NICHD/NIH for 20 years. He trained in Obstetrics and Gynecology and Maternal-Fetal Medicine at Yale University, where he was Director of Perinatal Research, before joining NIH. Dr. Romero's team has made pioneering contributions to understanding the mechanisms responsible for preterm parturition and the role of subclinical infection in preterm birth, and discovered the role of cytokines in parturition. He has a particular interest in the role of the human fetus in the initiation of labor and other pregnancy complications. Dr. Romero has authored over 850 peer-reviewed publications, edited 9 books and is a member of the Institute of Medicine of the National Academies of the United States. He has been honored by national and international professional societies for his medical and scientific contributions, including the Erich Saling Award from the World Association of Perinatal Medicine, and most recently, the Maternité Prize in Obstetrics, awarded by the European Congress of Perinatal Medicine. Dr. Romero is the recipient of seven Doctorate Honoris Causa from Universities worldwide (Athens, Hungary, Spain, Chile, Peru, Venezuela, and Barcelona).

STEVEN J. KORZENIEWSKI, PHD, MS, MA

Dr. Korzeniewski is currently appointed as an Assistant Professor in the Division of Maternal-Fetal Medicine (MFM) within the Department of Obstetrics & Gynecology at the Wayne State University School of Medicine (WSU-SOM). This division, one of the oldest of its kind nationwide, is the central research partner for the Perinatology Research Branch (PRB) of the National Institute of Child Health and Human Development. With funding from the WSU Perinatal Research Initiative, Dr. Korzeniewski supports the PRB as founding director of the Perinatal Epidemiology Unit. This unit provides observational research support and training to investigators studying the prediction, etiologies and management of multiple obstetrical syndromes implicated in the pathogenesis of preterm birth and other adverse pregnancy outcomes. Dr. Korzeniewski's research interests focus on perinatal screening and the etiologies of both the 'Great Obstetrical Syndromes' and neurodevelopmental disorders with roots in pregnancy.

SEETHA SHANKARAN, MD

Seetha Shankaran, MD, is a Professor of Pediatrics and the Director of Neonatal Perinatal Medicine at Wayne State University. She has been in the NCHD Multi-Center Network of Neonatal Intensive Care Units since 1986. She is the principal investigator of the first US trial of neuroprotection with hypothermia for hypoxic ischemic encephalopathy in term infants, performed in the NCHD Neonatal Research Network and published in the New England Journal of Medicine. She has served on the study sections of NNDS and NCHD Maternal and Child Health Research subcommittee. Dr. Shankaran is currently involved in clinical trials in NCHD Research Network and in investigating gene targets for neonatal intracranial hemorrhage as site PI of an NINDS funded study. Currently, Dr. Shankaran is the PI of a large randomized controlled trial evaluating longer and deeper cooling for neonatal HIE. She is also PI of the study evaluating maternal lifestyle during pregnancy and childhood and adolescent outcome funded by NIDA and NIMH.

NIGEL PANETH, MD, MPH

Nigel Paneth is a pediatrician and perinatal and child health epidemiologist with a particular interest in the causes and prevention of childhood neurodevelopmental handicap, especially cerebral palsy. He was the founder of the Neonatal Brain Hemorrhage Study, a population-based longitudinal follow-up of cohort of more than a thousand infants who weighed < 2 kg at birth which has been followed, with NIH support, for more than 20 years. This study has produced a comprehensive overview of brain damage in premature infants, based on newborn cranial ultrasound imaging and brain pathological examination, and has shown the powerful relationship of ultrasound images indicating white matter injury to cerebral palsy and intellectual disability. Risk factors for CP in prematures uncovered in that study include hypocapnea from mechanical ventilation and low levels of thyroid hormone in the first days of life. He is principal investigator of the OWL study, a case-control study of CP in Michigan, which focuses especially on gene expression in newborn blood spots, the topic of today's talk.

SETH WARSCHAUSKY, PHD

Seth Warschausky, PhD, is an Associate Professor and Director of the Division of Rehabilitation Psychology and Neuropsychology in the Department of Physical Medicine and Rehabilitation at the University of Michigan. He founded the Adapted Cognitive Assessment Laboratory and has been principal investigator on grants from the NIH and US Dept. of Education to study the neuropsychology of cerebral palsy. He is on the Board of Directors of United Cerebral Palsy of Michigan.

MARY JO COOLEY HIDECKER, PHD, CCC-A/SLP

Mary Jo Cooley Hidecker, PhD, M.S., M.A., CCC-A/SLP is an assistant professor in Communication Sciences and Disorders at the University of Central Arkansas. Dr. Hidecker led the research team that developed the Communication Function Classification System (CFCS). Her research focus includes the epidemiology of communication disorders in cerebral palsy and the WHO ICF model.

ANNA KRATZ, PHD

Anna Kratz received her doctorate in Clinical Psychology from Arizona State University, where her research and clinical work focused on psychosocial adjustment to chronic pain. She completed an internship at the VA Puget Sound Health Care System – Seattle Division, and a postdoctoral fellowship at the University of Washington, Department of Rehabilitation Medicine; in both positions her training focused on rehabilitation psychology and clinical research in populations with cerebral palsy, amputation, spinal cord injury, and multiple sclerosis. In 2011, she joined the faculty at the University of Michigan, Department of Physical Medicine and Rehabilitation. There, she conducts research on outcomes measurement, and on the phenotypic nature and impact of chronic pain, cognitive dysfunction, and other symptoms on functioning and quality of life across medical conditions.

EDWARD A. HURVITZ, MD

Edward Hurvitz is Associate Professor and Chair, Department of Physical Medicine and Rehabilitation (PM&R) at the University of Michigan Medical School. He is the James W. Rae Collegiate Professor in Physical Medicine and Rehabilitation Dr. Hurvitz has been involved in the diagnosis and management of children with disabilities for over 20 years. His focus has been on individuals with cerebral palsy and other brain-related syndromes that start in the childhood years. His work covers such areas as spasticity management, motor control, and health and fitness. His current work focuses on body composition and fitness in children and adults with cerebral palsy, as well as overall health and function in adults with cerebral palsy. He also has worked to promote research in individuals with disability, serving as Co-Director of a National Institute of Health (NIH) sponsored rehabilitation research training program, and participating in panels and national courses related to this area.

NICOLE LOMERSON SCHICKLING, MPH

Nicole Lomerson Schickling, MPH is a health policy researcher with a specific interest in disability-related topics. She has conducted research on the specific needs of dually-eligible individuals on Massachusetts Medicare, and consumer satisfaction with the acquisition and use of high-end mobility equipment, among many other topics.

SHORT TALKS

Jacqueline Kaufman , PhD Assistant Professor, Physical Medicine & Rehabilitation

Danielle Shapiro, PhD, postdoctoral fellow in pediatric neuropsychology and rehabilitation psychology at the University of Michigan.

Mark Peterson, PhD, Research Assistant Professor. Dr. Peterson is currently a research fellow at the University of Michigan, in the Department of Physical Medicine and Rehabilitation.

DISTINCTIVE DATABASES FOR ETIOLOGIC INVESTIGATIONS: MOBAND, OWL, NCPP, ELGAN, UM REGISTRY, AND OTHER DATABASES

Steven Korzeniewski, PhD, Director, Perinatal Epidemiology Unit, Wayne State University

Dr. Korzeniewski's presentation will review distinctive databases for cerebral palsy etiologic investigations including the National Collaborative Perinatal Project (NCPP); University of Michigan Cerebral Palsy Registry; Extremely Low Gestational Age Newborn (ELGAN) study; Origins, Wellness and Life-History (OWL) case-control study; the combined Norwegian and Danish national birth cohort studies (collectively referred to as MOBAND)and others. The objective of this talk is to convey opportunities for new learning by describing existing data sources and introducing planned analyses aiming to examine the relation between methodological factors and whether or not estimated magnitudes of association are consistently replicated across independent study populations.

HYPOTHERMIA AND CEREBRAL PALSY IN TERM AND NEAR-TERM INFANTS

Seetha Shankaran, MD, Director, Neonatal/Perinatal Medicine, Wayne State University

Neonatal encephalopathy due to hypoxic ischemia (HI) occurs in 1.5 (95% confidence interval [CI], 1.3–1.7) per 1000 live full-term births. About 15% to 20% of affected newborns die in the postnatal period, and an additional 25% will sustain childhood disabilities. The presence of an abnormal neurologic examination in the first few days of life highly predicts a brain insult in the perinatal period. Neonates with mild encephalopathy usually do not have an increased risk of motor or cognitive deficits. Neonates with severe encephalopathy have a high risk of death (up to 85%) and an increased risk of cerebral palsy (CP) and mental retardation among survivors. Neonates with moderate encephalopathy have significant motor deficits, fine motor disability, memory impairment, visual or visuomotor dysfunction, increased hyperactivity and delayed school readiness. Hypothermia, in fetal and neonatal models of hypoxia-ischemia, is neuroprotective. The state of the art of hypothermia therapy in neonates with moderate or severe encephalopathy in reducing CP will be presented.

FETAL INFECTION AND INFLAMMATION IN CEREBRAL PALSY: INSIGHTS FROM MOLECULAR IMAGING AND NANOTECHNOLOGY

Roberto Romero, MD, Chief, Perinatology Research Branch, NICHD, NIH

Neuroinflammation, caused by activated microglia and astrocytes, plays a key role in the pathogenesis of CP. The peripheral benzodiazepine receptor expressed on the outer mitochondrial membrane of the activated microglia is a sensitive biomarker for the detection of this neuroinflammatory response to an insult. Injury to the central nervous system is characterized by localization of activated microglia at the site of injury. PK11195, an isoquinoline ligand that specifically binds peripheral benzodiazepine receptor, can be tagged with a positron emitter and used as a tracer for molecular imaging of this receptor in vivo by positron emission tomography (PET). [(11)C](R)PK11195 has been used in the imaging of various neuroinflammatory disorders, such as Alzheimer disease and multiple sclerosis. On the basis of our small-animal PET imaging studies using a neonatal rabbit model of maternal inflammation-induced cerebral palsy, we propose that PET imaging using [(11)C](R)PK11195 may be a valuable tool for detecting neuroinflammation in the brain of newborns born to mothers with chorioamnionitis. Using this same animal model, we also show that systemically administered polyamidoamine dendrimers localize in activated microglia and astrocytes in the brain of newborn rabbits with CP, but not healthy controls. We further demonstrate that dendrimer-based N-acetyl-l-cysteine (NAC) therapy for brain injury suppresses neuroinflammation and leads to a marked improvement in motor function in the CP kits. The well-known and safe clinical profile for NAC, when combined with dendrimer-based targeting, provides opportunities for clinical translation in the treatment of neuroinflammatory disorders in humans. The effectiveness of the dendrimer-NAC treatment, administered in the postnatal period for a prenatal insult, suggests a window of opportunity for treatment of CP in humans after birth.

CP CASE CONTROL STUDY USING NEWBORN BLOOD SPOTS: LATEST RESULTS

Nigel Paneth, MD, University Distinguished Professor, Epidemiology and Biostatistics, Michigan State

Background: Gene expression in archived newborn blood specimens remaining from newborn screening may reflect pathophysiological disturbances useful in understanding the etiology of cerebral palsy (CP). Methods: We examined the expression of gene sets representing four physiological pathways hypothesized to contribute to CP in archived unfrozen residual newborn blood spot specimens from 53 children with CP and 53 age, gender, and gestational-age matched controls. We selected four empirical and three canonical gene sets representing inflammatory, hypoxic, coagulative, and thyroidal pathways, and examined mRNA expression using an Agilent 8x60K oligonucleotide microarray. The log2 fold change of gene expression between matched cases and controls were analyzed using the Generally Applicable Gene Set Enrichment (GAGE) Method. Results: The empirical inflammatory and empirical hypoxic gene sets were significantly down regulated in term-born CP cases (N = 33) as compared to matched controls (P = 0.0007 and 0.0009, respectively), while both pathways were significantly up-regulated (P = 0.0055 and 0.0223, respectively) in preterm-born CP cases (N = 20). The empirical thyroidal gene set was significantly up-regulated in preterm-born CP (P = 0.0023). Conclusion: The newborn blood spot transcriptome can serve as a platform for investigating distinctive gene expression patterns in children who later develop CP.

COGNITION IN CP: ADAPTED COGNITIVE ASSESSMENT LABORATORY UPDATE

Seth Warschausky, PhD, Professor, Physical Medicine and Rehabilitation, University of Michigan

Studies of the neuropsychological risks associated with cerebral palsy typically utilize traditional clinical instruments that may not be accessible or valid for these purposes. The University of Michigan Adapted Cognitive Assessment Laboratory (UM-ACAL) was established in 2002 to conduct psychometric studies of modified and alternative neuropsychological instruments to demonstrate cognitive capabilities and needs in this population. This presentation briefly reviews recent UM-ACAL studies of inspection time and processing speed, as well as current work that examines event-related brain potentials as alternative cognitive test access for children with CP.

COMMUNICATION AND CP: WHAT DO CFCS SCORES TELL US?

Mary Jo Cooley Hidecker, PhD, Assistant Professor, Speech-Language Pathology, University of Central

The Communication Function Classification System (CFCS) consists of 5 levels that can be assigned to describe a person's usual communication. The CFCS can be downloaded from www.cfcs.us. This presentation will briefly describe the CFCS and present some preliminary findings on using the CFCS in research and clinical projects.

THE NIH PROMIS: MEASURING HEALTH RELATED QUALITY OF LIFE IN CHILDREN AND ADULTS WITH CP

Anna Kratz, PhD, Assistant Professor, Physical Medicine and Rehabilitation, University of Michigan

The Patient Reported Outcomes Measurement Information System (PROMIS) began in 2004 as a National Institutes of Health (NIH) Common Fund Initiative to improve outcomes measurement in clinical research. To date, the PROMIS contains measures of over 40 adult and 9 pediatric health-related quality of life (HRQOL) domains. This presentation will provide an overview of the PROMIS instruments, information on how to access and use PROMIS instruments, and specific information for clinicians and researchers who are interested in using PROMIS to measure HRQOL for those with CP.

RESEARCH IN INTERVENTIONS AND QOL: INTRODUCTION TO BREAKOUTS

Edward Hurvitz, MD, Chair, Physical Medicine and Rehabilitation, University of Michigan

There are many challenges in designing studies that evaluate interventions for cerebral palsy. Chief among them are heterogeny of sample, control group design, defining the intervention (especially for therapy interventions) and defining meaningful outcomes considering the ICF classification. In addition, lifespan research is important, as we need to know how our treatment of children affects adult lives.

EXHIBITS:

- CPRCoM registry: www.med.umich.edu/pmr/research/cprcom.htm
- Europeds: www.europeds.org/
- Mary Free Bed Rehabilitation Hospital: www.maryfreebed.com/
- Preemie Growth Project: www.preemiegrowthproject.org/
- United Cerebral Palsy of Michigan: www.ucpmichigan.org/

POSTERS:

- **Child Gender and Parental Nurturance in Children with and without neurodevelopmental congenital condition**
  Danielle Shapiro, Pamela Dixon-Thomas, Seth Warschausky (University of Michigan, Ann Arbor, MI)
- **Chronic Disease Risk among Adults with Cerebral Palsy: The Role of Premature Sarcopenia, Obesity, and Sedentary Behavior.**
  Mark Peterson (University of Michigan, Ann Arbor, MI)
- **Communication function (CFCS), gross motor function (GMFCS) and manual function (MACS) in children with cerebral palsy.**
  Hidecker, M.J.C*., Ho, N.T., Dodge, N., Hurvitz, E.A., Slaughter, J., Workinger, M.S., Kent, R., Lenski, M., DeRoos, S., Rosenbaum, P., Paneth, N. (*University of Central Arkansas)
- **Em-POWERing Children and Young Adults through Movement: Use of a Power Wheelchair Trainer to Enable Movement Exploration and Success.**
  Ripmaster Catherine, Farris John, Kenyon Lisa*, Peck John (*Grand Valley State University, Grand Rapids, MI)
- **Impact of the social and physical environment on the disability experience.**
  Piotr J Pasik, MSU (Rehabilitation Counseling)
- **Is the diagnosis of CP at age two stable over time? Assessment of a low birth weight cohort at ages two, six and nine.**
  Steven J. Korzeniewski, PhD[1,2], Jennifer A. Pinto-Martin3, Agnes H. Whitaker[4], Judith F. Feldman[4], John M. Lorenz[5], Susan Levy[6] and Nigel Paneth[7]
  [1]Perinatology Research Branch, NICHD/NIH/DHHS; [2]Wayne State University School of Medicine, Department of Obstetrics and Gynecology; [3]University of Pennsylvania School of Nursing and School of Medicine; [4]Division of Child and Adolescent Psychiatry, Department of Psychiatry, Columbia University Medical Center, New York State Psychiatric Institute; [5]Division of Neonatology, Department of Pediatrics, Columbia University Medical Center; [6]Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine; [7]Departments of Epidemiology and Biostatistics and Pediatrics, College of Human Medicine, Michigan State University
- **Labor complications, birth depression, and signs of brain injury in the path towards cerebral palsy: A matched case-control study in Michigan**
  Qing Li, Matt Francis, Nigel Paneth (Michigan State University, East Lansing, MI)
- **Sex-specific gene expression in archived dried blood spots.**
  J Resau, NT Ho, K Dykema, MS Faber, JV Busik, RZ Nickolov, KA Furge, N Paneth, S Jewell, SK Khoo (Van Andel Institutue, Grand Rapids, MI)

NOTES