Research Use of Michigan's Residual Newborn Screening Blood Spots

Guidelines for Releasing Michigan's Residual Blood Spots

In 2009, the Michigan Department of Health and Human Services (MDHHS) created the Michigan BioTrust for Health. The BioTrust is a program that oversees the storage and research use of blood spots that are left over after newborn screening. For more information about the BioTrust, please visit www.michigan.gov/biotrust.

This report gives information about each research study that has been approved by MDHHS to use residual blood spots. Left over blood spots can only be in research if one of the following criteria is met:

- Consent was granted for use through the BioTrust (blood spots collected after April 30, 2010), *or*
- Waiver of informed consent was granted by MDHHS Institutional Review Board (blood spots collected between July 1984 and May 1, 2010) and no opt-out directive has been received, *or*
- Additional informed consent for use in a specific research study was obtained

2020 Approved Research

Steroid Panel to Identify Newborns with Congenital Adrenal Hyperplasia

Institution/Agency: Wisconsin State Laboratory of Hygiene- Newborn Screening Laboratory
Year Approved: 2020
Samples Requested: 30
Year Released: No samples released to date
Study Summary: Within the United States, all babies are screened at birth for congenital adrenal hyperplasia (CAH), due to 21-hydroxylase deficiency, to prevent a life threatening salt-wasting crisis in the newborn period. Reports have suggested that measurement of a single steroid, 17-hydroxyprogesterone, as an indicator of CAH may not be sufficient, leading to false negative (missed) cases. Wisconsin has developed a method for analyzing 8 steroids in dried blood spot specimens. Wisconsin wishes to assess the concentrations of these 8 steroids in residual newborn screening (dried blood spot) specimens collected from babies with CAH as well as the normal population. The goal is to develop a comprehensive data model for newborn screening programs to use to guide disease identification.

2019 Approved Research

Maternal Exposure to Vicarious Structural Racism and Newborn Health Disparities in Michigan: The Flint Water Crisis (Biomarkers)

Institution/Agency: University of Michigan
Year Approved: 2019
Samples Requested: 160
Year Released: No samples released to date
Study Summary: Residents of Flint, Michigan, a predominantly African American community, were directly harmed by exposure to lead-contaminated water after the state-appointed city manager switched the source of drinking water from the Detroit water system to the Flint River. However, the public health consequences of the Flint Water Crisis (FWC) may not be confined to Flint. Drawing on recent work that documents the health consequences of exposure to vicarious, or second-hand, racism, this study will use individual birth records linked to archived dried blood spots from the Michigan

Neonatal Biobank to examine changes in biomarkers of stress and aging (telomere length and DNA methylation in the glucocorticoid receptor gene) among infants born to non-Hispanic black and non-Hispanic white mothers in the Detroit metro area after the FWC. We expect to find that non-Hispanic black infants who were conceived in the eight months prior to widespread media coverage of the governor's declaration of a state of emergency in Flint (i.e., those who were conceived between May and December of 2015) had shorter telomere length and increased DNA methylation in the glucocorticoid receptor gene, when compared to non-Hispanic black infants who were conceived between May and December of 2014. We do not expect to find any changes for infants born to non-Hispanic white mothers.

SPOTCHECK® Neonatal IRT Screening Kit: Method Comparison

Institution/Agency: Astoria-Pacific, Inc.
Year Approved: 2019
Samples Requested: 15
Year Released: 2019
Study Summary: This study will evaluate the clinical efficacy of the SPOTCHECK® Neonatal IRT Screening Kit (in development) in screening newborn dried blood spot material for elevated immunoreactive trypsin (IRT) – an indicator of cystic fibrosis (CF) in neonates. Comparison of the new kit against a currently cleared kit will demonstrate safety and effectiveness for use in routine newborn screening for CF.

Pilot Test: Quality control of DNA extracted from residual dried newborn blood spots for Next-Generation Sequencing-based study

Institution/Agency: National Cancer Institute
Year Approved: 2019
Samples Requested: 40
Year Released: No samples released to date
Study Summary: This intramural-extramural-industry collaboration will evaluate germline DNA derived from neonatal blood spots collected by the MDHHS. Since the National Cancer Institute (NCI)-associated genomic facilities do not have an established protocol for DNA extraction of dried newborn blood spots, we propose a pilot test to evaluate the DNA quality generated by three external laboratories, headed by Dr. Carlos Saavedra-Matiz, Dr. Mei Baker, and Dr. Charlly Kao, with experience in performing this assay for different applications. These results will assess the feasibility of a subsequent Next Generation sequencing (NGS)-based project.

Socioeconomic Disadvantage, Adverse Birth Outcomes and Fetal Programming of Inflammation

Institution/Agency: University of Wisconsin- Milwaukee
Year Approved: 2019
Samples Requested: 1000
Year Released: 2019
Study Summary: This study examines whether maternal socioeconomic disadvantage at both the individual- and neighborhood-level experienced during pregnancy is associated with a pro-inflammatory

phenotype in children at birth, assess the role that adverse birth outcomes including preterm or small for gestational age birth play in explaining this association and assess whether these relationships differ by offspring sex.

Pesticide exposure and risk of childhood acute myeloid leukemia

Institution/Agency: University of Oklahoma Health Sciences Center
Year Approved: 2019
Samples Requested: 260
Year Released: No samples released to date
Study Summary: Acute myeloid leukemia (AML) is a rare malignancy which represents approximately 15-20% of all leukemia diagnoses among children. Maternal exposure to pesticides is suggestive of increased risk for childhood AML based on existing evidence. Pesticides, particularly organochlorines, may be carcinogenic, and although no longer used in the US, they have persisted in the environment. Exposure to other persistent organic pollutants (POP), including polychlorinated biphenyls (PCB) and polybrominated diphenyl ethers (PBDE) have been related to childhood leukemia in California. The primary source of exposure to these pesticides is through diet, mainly through dairy products and fish, and the fetus can be exposed through the placenta. Children and fetuses, due to their size and exposure potential, may have increased susceptibility to the effects of pesticides and other POPs. We propose to evaluate the relationship between organochlorine pesticide, PCBs, and polybrominated biphenyl (PBB) 153 exposure and childhood AML using newborn bloodspots from the Michigan BioTrust for Health.

2018 Approved Research

Neonatal protein markers and child neurodevelopment

Institution/Agency: Henry Ford Health System
Year Approved: 2018
Samples Requested: 10
Year Released: 2019
Study Summary: Neonatal dried blood spots offer a unique view into the early life health and metabolic state of children. As such, these dried blood spots may enable the investigation of angiogenic markers and their relevance to childhood health outcomes that are not identified until later in life (such as autism spectrum disorder). The work here seeks to demonstrate the feasibility and potential utility of measuring a panel of markers in neonatal dried blood spots. The proposed panel is cost effective and uses a minimal amount of dried blood spot. This data will serve as important and necessary preliminary data for future grant proposals that seek to understand how early life factors influence child health, especially ASD and other neurodevelopmental outcomes. **This study is done.**

A Comprehensive Newborn Screening Solution for Duchenne and Congenital Muscular Dystrophies

Institution/Agency: Baebies, Inc
Year Approved: 2018
Samples Requested: 450
Year Released: 2018 (partial), 2019 (partial)

Study Summary: Congenital genetic abnormalities are a leading cause of childhood mortality and morbidity. While routine newborn screening (NBS) has dramatically improved health outcomes, many congenital disorders such as Duchenne muscular dystrophy (DMD) and other congenital muscular dystrophies (CMD) are not currently detected by routine NBS. The goal of this project is to develop a complete testing solution for efficient newborn screening of DMD and CMDs from dried blood spot (DBS) specimens. The system will consist of automated, low volume biochemical assays for creatine kinase (CK) enzyme activity and CK isoform expression (CK-MM and CK-MB) followed by 2nd-tier targeted next generation sequencing (tNGS) in CK (+) individuals to detect common causal gene variants associated with DMD and CMDs.

Biosocial Impact on Black Births (BIBB) Study (NIH Title: Social Stressors and Inflammation: A mixed methods approach to preterm birth)

Institution/Agency: Wayne State University
Year Approved: 2018
Samples Requested: 2,800, additional study specific consent obtained
Year Released: No samples released to date
Study Summary: African American women have 1.5 times the rates of preterm birth (PTB) (<37 weeks completed gestation) compared with non-Hispanic white women. This disproportionately high PTB rate in African Americans is a persistent health inequity that leads to high child mortality, morbidity, and developmental delays. In the U.S. approximately $26 billion are spent annually on health care costs for infants and children that were born prematurely. Recent attempts to explain the high PTB rates in African American women have focused on social stressors, such as disadvantaged neighborhoods, racial discrimination, and stressful life events. These social stressors may lead to PTB by increasing women's emotional stress levels. Not surprisingly, emotional stress along with levels of the stress hormone cortisol and systemic inflammation - both physiological responses to stress - have all been related to higher risk of PTB. In contrast, one's psychosocial resources (e.g., social support) can lessen emotional stress and have protective effects on PTB. Little is yet known about the pathways by which social stressors affect inflammation, and ultimately PTB. The objective of the proposed study is to determine how social stressors alter inflammation during pregnancy and lead to PTB in African American women. We aim to: 1) determine the pathways by which social stressors affect PTB; and 2) describe social stressors, emotional stress and psychosocial resources; the associations among these concepts; and their impact on PTB from women's perspectives. We will conduct a variety of statistical, qualitative and mixed methods analyses using both quantitative and qualitative data to determine answers to the aims of our study. We will also consider the timing of pregnancy in our analyses, as the prenatal data are collected at three distinct time points. Insights gained from this mixed methods approach may lead to the development of an individualized PTB risk profile based on a woman's social stressors and biomarkers which will have potential use in clinical practice and be a target for culturally appropriate interventions to reduce PTB incidence in African American women, and will generate new perspectives for future research in other racial groups through our detailed focus on this high risk group. Examing maternal and infant DNA for methylation patterns and telomere length is a new avenue of research that will complement our other measures of biologic factors. Knowledge of the social context of African American women's lives will increase our understanding of why some women have poor pregnancy outcomes, generate new perspectives for future research, inform new lines of inquiry regarding the pathways through which stress affects preterm birth in other racial groups, contribute to the

development of culturally appropriate interventions to reduce racial disparities in preterm birth, and ultimately improve birth outcomes.

Fathers Matter (NIH Title: Paternal Role in Adverse Birth Outcomes in Black Families)

Institution/Agency: Wayne State University
Year Approved: 2018
Samples Requested: 500, additional study specific consent obtained
Year Released: No samples released to date
Study Summary: A wide range of factors have been examined as potential explanations for the high rates of adverse birth outcomes for Black women. Available research is limited in the extent to which it examines the role of babies' fathers in the lives of pregnant women. As we have reported, the few studies that have explored paternal effects on birth outcomes have generally excluded understanding the dynamic, complex, and often correlated maternal-paternal relationship. Given the significance placed on the father's role as a provider, studies have often been limited to an examination of paternal age, occupation, or socioeconomic status. The proposed study will assess whether and how fathers may have an impact on successful birth outcomes (birth weight, gestational age). Our study of Black fathers and birth outcomes builds on our previous studies and those of others although differing in several important ways. Innovative aspects of this study include direct collection of data from fathers, assessment of the mother-father relationship, and inclusion of measures rarely studied, particularly as related to fathers, such as discrimination, neighborhood environment, and telomere length across the life course. This study complements the recently funded NIH R01 Social stressors and Inflammation: A Mixed Methods Approach to Preterm Birth (Giurgescu PI, Misra, co-I) in that 400 fathers of the babies (to be born) of pregnant Black women in that study will be recruited for the proposed study. Both fathers and mothers will be interviewed during the prenatal period and within the first week after birth. Data on birth outcomes and additional maternal social, psychological, and biomedical data from BIBB will complement data from this study to address the aims. Thus, multiple sources of data will be available to provide a more comprehensive assessment of fathers as part of the social environment in which Black women experience pregnancies. We aim to: (1) Determine how the mother-father relationship (support, conflict) during pregnancy relates to maternal and/or paternal factors; and (2) Determine whether and how paternal factors relate to birth outcomes (birth weight, gestational age at birth). Complex processes are at work in the lives of pregnant Black parents. Understanding mechanisms through which these processes unfold is imperative for articulating risk and protective factors influencing birth outcomes. Although the literature has identified a number of risk factors associated with mothers, little attention has been given to understanding the role of fathers related to birth outcomes. Understanding their contributions to birth outcomes could expand service, intervention, and policy efforts beyond mothers.

Congenital cytomegalovirus infection, KIR genotypes, and acute lymphoblastic leukemia

Institution/Agency: University of Minnesota
Year Approved: 2018
Samples Requested: 6,250
Year Released: No samples released to date
Study Summary: Acute lymphoblastic leukemia (ALL) is cancer that affects cellular production in the bone marrow; it is the most common form of pediatric cancer and a leading cause of death in children.

Recent literature suggests that cytomegalovirus (CMV) could contribute to the development of ALL in the pediatric population. CMV affects people of all ages and is usually asymptomatic, but it can cause significant health outcomes for newborns and individuals with weakened immune systems. The body's internal immune response could be a contributing factor to the development of CMV. Interactions between specific cellular receptors and antigens leads to the formation of natural killer cells, a cell type that could increase susceptibility of infections, like CMV. Using blood spots to identify CMV and these cellular genotypes of ALL patients could detect possible modifiable viral and/or genetic risk factors that might lead to ALL.

Comparison study for NeoBase2 Non-derivatized MSMS kit on QSight Screening System

Institution/Agency: PerkinElmer/Michigan Department of Health and Human Services
Year Approved: 2018
Samples Requested: 4550
Year Released: 2019
Study Summary: De-identified blood spots from newborns diagnosed with certain metabolic conditions detected by newborn screening are used for a method comparison study. This type of study is done to determine if this company's testing technology performs on an additional MSMS instrument platform as well or better than on the current instrument platform. This could help improve current laboratory tests used to detect disorders through newborn screening

(Genetic Studies of Diabetes Mellitus) Newborn Screening for Earlier Diagnosis and Treatment of Congenital Diabetes

Institution/Agency: University of Chicago
Year Approved: 2018
Samples Requested: 11,500, Additional study specific consent obtained
Year Released: No samples released to date
Study Summary: Congenital diabetes is a rare but treatable form of diabetes diagnosed during the first days or months of life. Symptoms are often difficult to recognize in infants, causing a delay in diagnosis and possible adverse health outcomes; identifying congenital diabetes earlier could reduce morbidity and encourage proper treatments. According to the University of Chicago Monogenic Diabetes Registry, nearly half of the patients with congenital diabetes have mutations in the ATP-sensitive potassium (KATP) channel. Patients with these mutations normally have significant hyperglycemia within 24-72 hours of life, making it possible to be detected on dried blood spot samples. Identifying hyperglycemia through newborn screening also prompts the implementation of sulfonylurea drugs instead of insulin as an initial treatment measure. Sulfonylurea's functionality and lower price paired with recent evidence about it preventing possible neurological delays make it an ideal treatment option for individuals with congenital diabetes. Detecting congenital diabetes early through newborn screening could be an efficacious public health initiative. The goal of this study is to support the inclusion of congenital diabetes into newborn screening programs by demonstrating the feasibility to screen for congenital diabetes, highlighting the importance of preventing congenital diabetes morbidity by including it in newborn screening, and providing evidence on appropriate treatment directed toward improving long-term neurodevelopmental outcomes.

Aromatic L-Amino Acid Decarboxylase Deficiency (AADCD) Prevalence Study

Institution/Agency: RTI International
Year Approved: 2018
Samples Requested: 3,000
Year Released: No samples released to date
Study Summary: The purpose of this study is to determine the prevalence of aromatic L-amino acid decarboxylase deficiency (AADCD), a rare autosomal recessive condition resulting from mutations in the aromatic L-amino acid decarboxylase gene (DCC). AADCD results in both serotonin and catecholamine deficiency and clinical symptoms usually onset in infancy or childhood. Of 78 patients described in 2010, 6 had symptom onset in adolescence or later. Common symptoms include hypotonia (95%), oculogyric crisis (86%), and developmental delay (63%). Other frequently described symptom are temperature instability, movement disorders, feeding or speech difficulty, insomnia, and irritability. Many patients die before age 10 due to complications of seizures or feeding and breathing difficulties.The prevalence of AADCD is the United States is unknown. The best available estimate of prevalence of the disorder is 1:85,000. This estimate is derived from screening of random newborn blood spots in Taiwan, and the prevalence of elevated 3-OMD in CSF from patients with undiagnosed neurological disorders in the United States (unpublished data, Agilis Biotherapeutics) and Hong Kong. A gene therapy has been developed that uses adeno-associated viral vector–mediated gene transfer of functional DDC gene into the putamen of affected patients. Four patients received the treatment. Prior to treatment, the patients were bedridden, lacked head control or the ability to speak, and experienced frequent oculogyric crisis. After therapy (follow up, 15-24 months), the patients gained weight, had improved motor and cognitive function, fewer oculogyric crises, and increased emotional stability. The only major adverse effect of treatment observed in the study was transient dyskinesia. An accurate estimation of prevalence is needed for FDA approval of the therapy. We will sequence the DDC gene in a random sample of infants to estimate the allele frequency of pathologic mutations in the DDC gene among a US population. We will calculate the expected prevalence of AADCD as the total probability of all compound heterozygous or homozygous genotypes. **This study was closed with no work.**

2017 Approved Research

Looking back to look forward: Social Environment across the Lifecourse, Epigenetics, and Birth Outcomes in Black Families

Institution/Agency: Henry Ford Health System
Year Approved: Wayne State University
Samples Requested: 1700, Additional study specific consent obtained
Year Released: No samples released to date
Study Summary: We will investigate maternal environmental influences on neonatal epigenetic profiles; trajectories as well as critical periods will be assessed as the maternal social environment over the maternal life course may independently, cumulatively, and interactively impact offspring's epigenomic profile. Neighborhood level data will utilize both administrative and subjective measures of neighborhood. In addition to determining associations between the maternal social environment and her offspring's epigenomic profile, we will endeavor to explore potential biologic pathways linking the social environment across the maternal life course with the perinatal outcomes of her offspring. This will be accomplished by utilizing the newborn blood spots available for all of the offspring in this cohort as well as newborn blood spots for approximately half of their mothers. These will be assayed to determine the presence of epigenetic methylation changes. Researchers have recently begun to consider social

environmental factors and how they relate to epigenomic changes that are associated with adverse perinatal outcomes. Yet those populations disproportionately affected by these outcomes are grossly underrepresented in genomic studies. Our cohort of 1410 births to Black women in the Detroit metro area, with nearly half to women residing in Detroit, provides a rich source of data on the maternal social environment across the life course and a wide range of factors.

Archive for Research on Child Health Blood Spot Analyses

Institution/Agency: Michigan State University
Year Approved: 2017
Samples Requested: 1,550, Additional study specific consent obtained
Year Released: 2018 (partial), 2019 (partial)
Study Summary: The Archive for Research on Child Health (ARCH) is a pregnancy cohort in the Lansing area. Starting in 2008, the research team led by Dr. Nigel Paneth, began recruiting pregnant women in three different prenatal care clinics in the Lansing area. The project was designed to be as minimally invasive as possible and asks participants to complete a short in person survey and to allow the research team to store leftover biological samples, such as blood or urine, that they will provide to their doctor and would normally be thrown away. Following the birth of the baby, mothers are called annually to complete short telephone surveys that ask questions regarding the health and development of the mother and child. ARCH has recruited over 800 mother-infant pairs since 2008 and continues to study important factors that may affect pregnancy and child health such as environmental chemicals, infections, and diet.

Global Metabolomic Profiling in Metabolic Disease

Institution/Agency: Baylor College of Medicine
Year Approved: 2017
Samples Requested: 220
Year Released: 2018
Study Summary: Genetic defects that directly affect the creation or degradation of metabolites are termed inborn errors of metabolism and in many cases can be diagnosed by the accumulation or depletion of pathway intermediates. Beyond this, many other genetic disorders not directly associated with metabolic pathways also can be diagnosed by studying a patient's metabolic profile; examples include disorders relating to amino acid metabolism, fatty acid metabolism, organelle synthesis, and metal transport. Technological advances have now made possible the rapid and accurate detection of over 1,000 metabolites in human plasma samples. Insights afforded by such an analysis could prove crucial in the diagnosis of many genetic disorders. The goal of our study is to explore the ability of global untargeted metabolomics to identify and diagnose inborn errors of metabolism.

ARCH-Placenta

Institution/Agency: Michigan State University
Year Approved: 2017
Samples Requested: TBD, Additional study specific consent obtained
Year Released: No samples released to date
Study Summary: Since formulation of the "Barker Hypothesis" many studies have demonstrated associations between maternal/environmental factors and offspring pathologies. Maternal obesity and

associated metabolic disorders, smoking, and stress affect the in utero environment and have been associated with offspring disorders such as allergy and asthma, obesity, and neurologic disease. Despite these associations, we do not yet understand how these maternal factors affect the health of future offspring. It is our hypothesis that these environmental factors dysregulate placental function, which affects fetal development resulting in development of offspring disease. We know that maternal factors can affect the placenta, but we know very little about what changes in placental function affect development of offspring. In this study, instead of comparing placentas associated with the maternal environments, we will compare placentas associated with the health and pathologic offspring. Furthermore, we can retrospectively examine the maternal environment in association with both placental function and offspring phenotype, and with this design, begin to study a functional link between the environment, placental function and child health. **This study was closed with no work.**

2016 Approved Research

Development of Newborn Screen for Niemann-Pick C1 Disease

Institution/Agency: Washington University
Year Approved: 2016
Samples Requested: 20, Additional study specific consent obtained
Year Released: 2017
Study Summary: Niemann-Pick C (NPC) disease is a progressive, neurodegenerative disorder. NPC results in a buildup of cholesterol in cells, which, in turn, destroys neurons. Difficulty making the diagnosis (>5 years) leads to significant delays in treatment. NPC is an excellent candidate for newborn screening because therapies are available or entering into clinical trials that modify the disease. There is potential to reduce long-term morbidity and improve quality of life. These researchers have developed a fully-validated newborn screen for NPC. To further validate the screen, they will use blood spots from NPC patients from ~20 states including Michigan. **This study is done**. The results of the study demonstrate that newborn screening for npc1 disease is feasible using bile acid biomarkers. For more information see the article below:

1. *Jiang X, Sidhu R, Orsini JJ, Farhat NY, Porter FD, Berry-Kravis E, Schaffer JE, and Ory DS. Diagnosis of Niemann-Pick C1 by Measurement of Bile Acid Biomarkers in Archived Newborn Dried Blood Spots. Mol Genet Metab 2018, Mol Genet Metab. 2018 Aug 24. pii: S1096-7192(18)30400-1. doi: 10.1016/j.ymgme.2018.08.007. [Epub ahead of print]*

Determination of dried blood spot-derived DNA yield, quality, and next-generation sequencing capacity for applications in newborn screening

Institution/Agency: Veritas Genetics
Year Approved: 2016
Samples Requested: 42
Year Released: 2016
Study Summary: Targeted next-generation sequencing (NGS) of genes commonly associated with newborn illness promises to provide benefits to newborn screening by reducing costs and improving patient outcomes. The utility of blood spot-derived DNA must be validated for use in new genetic testing such as NGS. This study will use blood spots to test the suitability of blood spot-derived DNA for NGS.

They will test two different DNA extraction methods that vary in handling and age. DNA yield and quality will be measured and the extracted DNA assessed for suitability in NGS assays. **This study is done.**

WHEALS and CAS Metals Study

Institution/Agency: Henry Ford Health System
Year Approved: 2016
Samples Requested: 20, Additional study specific consent obtained
Year Released: No samples released to date
Study Summary: Data suggests that exposure to metals is associated with metabolic syndrome and dysregulated immune function in childhood. However, there is a lack of comprehensive longitudinal studies exploring prenatal metal exposures (and metal mixtures) with health across early childhood and into young adulthood. This project will examine the relationship between very early life exposure to metals (copper, zinc, lead, mercury, cadmium, calcium, iron and arsenic) and metabolic syndrome and immune function in childhood.

Genetic Susceptibility to Pediatric Rhabdomyosarcoma

Institution/Agency: Baylor College of Medicine
Year Approved: 2016
Samples Requested: 600
Year Released: 2017
Study Summary: Rhabdomyosarcoma (RMS), the most common soft-tissue sarcoma in children and adolescents, has one of the poorest 5-year survival rates (43% to 67%) among all childhood cancers and has few established risk factors. This highly malignant tumor is believed to arise from disrupted skeletal muscle cells (myoblasts) and can develop anywhere in the body. These tumors are frequent among children with genetic syndromes; however, recognized genetic syndromes account for only 5% of cases. Therefore, much work remains to be done to understand the causes of the other 95% that appear to be sporadic. Genome-wide association studies, in which hundreds of thousands of single-nucleotide polymorphisms (SNPs) are tested for association with a disease in hundreds or thousands of individuals, have revolutionized the search for genetic influences on complex traits. In spite of the importance of this unbiased approach to surveying the genome, to date, there has been no genome-wide association study (GWAS) of childhood RMS. This study will conduct the first GWAS of childhood RMS utilizing Michigan blood spots which will ensure a population-based approach in understanding this important childhood malignancy.

Gonadotropins and Retinopathy of Prematurity

Institution/Agency: Zietchick Research Institute
Year Approved: 2016
Samples Requested: 1,100
Year Released: 2016, 2018
Study Summary: Very premature babies are at risk for developing the potentially blinding disorder, retinopathy of prematurity (ROP). This project is aimed to demonstrate that there is an increased gonadotropin blood level in premature infants who develop ROP. The establishment of a gonadotropin-ROP association may lead to an ROP preventative agent. Dried blood spots (DBS) are an available source of neonatal biospecimens from premature babies. Hormone levels from the DBS will be measured and

statistical analyses correlating gonadotropin levels with ROP risk will be performed. For more information see the article below:

1. *Movsas T.Z., Paneth N., Gewolb I.H., Lu Q., Cavey G., Muthusamy A. The postnatal presence of human chorionic gonadotropin in preterm infants and its potential inverse association with retinopathy of prematurity. Pediatric Research. 2019 Sep 19; doi: 10.1038/s41390-019-0580-8.*

Early Life Risk, Resilience and Behavioral Outcomes (ELBO)

Institution/Agency: Wayne State University
Year Approved: 2016
Samples Requested: 160
Year Released: 2017

Study Summary: Decades of research have highlighted the damaging effects of prenatal exposure to common environmental toxicants (i.e., tobacco smoke, lead, persistent organic pollutants, and mercury) on later health outcomes. Fetuses and infants are particularly sensitive to such exposure, both because early disruptions in development can have long-lasting effects, but also because many neurotoxicants are readily transferred across the placenta and the fetal blood brain barrier. Children born in areas with high levels of pollutants (e.g., poor urban neighborhoods) suffer from notably higher rates of a number of adverse health outcomes, including child behavior problems such as aggression, antisocial behavior, and hyperactivity. Three studies within a single, well-characterized, longitudinal research cohort are proposed to improve mechanistic understanding of means by which prenatal environmental exposures influence long-term human health and well-being. We will thus be able to meaningfully evaluate whether and how prenatal toxicant exposures affect functional neurocircuitry of the developing fetal brain, and the long-term behavioral consequences of those associations. Such work would constitute a substantial advance in our understanding of not only the long-term effects of prenatal toxicant exposure, but also the mechanisms that drive these effects. For more information see the article below:

1. *Thomason M.E., Hect J.L., Rauh V.A., Trentacosta C., Wheelock M.D., Eggebrecht A.T., Espinoza-Heredia C., Burt A. Prenatal lead exposure impacts cross-hemispheric and long-range connectivity in the human fetal brain. NeuroImage. 2019 May 1; 191(186-192).*

Testing DNA Extraction Protocol on External Dried Blood Spot Samples of Neonates

Institution/Agency: Center for Applied Genomics
Year Approved: 2016
Samples Requested: 25
Year Released: 2017

Study Summary: The Center for Applied Genomics (CAG) operates and manages a pediatric biobank at the Children's Hospital of Philadelphia (CHOP), which is the largest biobank of its kind in the world for a pediatric population with ~100K unique subjects collected to date. The extant DNA collection are derived mostly from blood draws and saliva, however they are aiming to establish workflows from dried blood spots (DBS) as well, since many neonatal collections (both internal and external to CHOP) are stored in this form. The extracted DNA would be informative and useful for research into the genetic etiology of pediatric diseases. They have established a protocol to extract DNA from DBS in a high-throughput format, and are using DBS samples from external groups to test the robustness & reproducibility of their extraction process. Samples representing a diverse range of storage periods (1-20

years) and conditions (frozen vs. ambient temp vs. repeated freeze/thaws) are needed to assess quality of extracted DNA. **This study is done.**

2015 Approved Research

Genetic Analysis of Human First Trimester Trophoblast in Ongoing Pregnancies

Institution/Agency: Wayne State University
Year Approved: 2015
Samples Requested: 67, Additional study specific consent obtained
Year Released: 2015, 2018
Study Summary: This study is using blood spots to help determine if a new method of prenatal genetic diagnosis is informative. The method retrieves a type of cells, called trophoblasts, from a woman's cervix as early as 5 weeks gestation. Chromosomes in trophoblast cells from recruited patients are currently being evaluated. Patients recruited in the study have consented to allow extraction of DNA from their newborn's blood spots to compare with the DNA of the trophoblasts. For more information, see the article below:

1. *Jain C.V., Kadam L, van Dijk M, Kohan-Ghadr MR, Kilburn B, Hartman C, Mazzorana V, Visser A, Hertz M, Bolnick A, Fritz R, Armant D. R., Drewlo S. Fetal genome profiling at 5 weeks of gestation after noninvasive isolation of trophoblast cells from the endocervical canal. Science Translational Medicine. 2016 Nov 2; 8(363).*

Collection of Confirmed Positive Specimens for Evaluation in a Clinical Study to Establish Screening Performance of the PerkinElmer NeoBase2 Non-Derivatized MSMS Test System for Inborn Errors of Metabolism

Institution/Agency: Perkin Elmer
Year Approved: 2015
Samples Requested: 5
Year Released: 2016
Study Summary: De-identified blood spots from newborns diagnosed with certain metabolic conditions detected by newborn screening are used for a method comparison study. This type of study is done to determine if this company's new testing technology performs as well or better than the current testing. This could help improve current laboratory tests used to detect disorders through newborn screening.
This study was closed with no work.

The Impact of HepG2 Dnase I Hypersensitivity Site-Associated Variants on Risk of Hepatoblastoma

Institution/Agency: University of Minnesota
Year Approved: 2015
Samples Requested: 420
Year Released: 2016, 2019
Study Summary: Hepatoblastoma (HB) is a rare liver tumor that occurs most commonly in children under five years of age. Very little is known about the causes of HB, and genetic factors may play a role. Researchers will first use their existing bank of HB samples to identify genetic variants that increase risk of HB. They will then use Michigan's newborn blood spots to validate their initial findings.

Neonatal Dried Blood Spot Testing

Institution/Agency: Translational Genomics Research Institute
Year Approved: 2015
Samples Requested: 90
Year Released: 2016
Study Summary: The study will use blood spots for RNA extraction and analysis. The requested spots will be from 2014, 2010, 2008, 2005 and 1995. This time frame will encompass spots that have been stored at ambient temperature and in a -20° freezer. This study will investigate how storage conditions and age affect the amount and quality of the RNA. **This study is done.**

Enabling Fragile X Screening Using Blood Spot Cards

Institution/Agency: Asuragen
Year Approved: 2015
Samples Requested: 10,000
Year Released: 2016
Study Summary: This study is using blood spots to assess the accuracy of a rapid, high-throughput, and cost-effective newborn screening test for Fragile X syndrome. Fragile X syndrome (FXS) is the most common form of inherited intellectual disability and a known genetic cause of autism. Fragile X newborn screening (NBS) provides opportunities for behavioral therapies and other interventions at earlier ages when they may offer a greater benefit, and promises to reduce the "diagnostic odyssey" associated with FXS. In addition, multiple clinical trials are ongoing to assess therapeutics that impact molecular pathways that are disrupted in FXS. Finally, NBS has been favorably received by parents in prospective longitudinal studies. As a result, accurate and cost-effective screening technologies are needed in anticipation of emerging therapeutic options taken together with the existing benefits of early detection. This study has ended. Results: The newborn dried blood spot samples from the state of Michigan BioTrust enabled Asuragen to develop an accurate, high-preformance test to identify newborns at risk of fragile X syndrome, the leading inherited cause of intellectual disability. **This study is done**. *The results of study were presented at a national conference (ACMG Annual Clinical Genetics Meeting March 2017) and the work confirmed previously published results demonstrating a relatively high incidence of the fragile X gene disorder in the general population. The reagents and software that we developed are enabling the fragile X screening efforts of a large-scale research study (Early Check, https://earlycheck.org/) to identify newborns before symptoms appear.*

Genetic Overlap Between Anomalies and Cancer in Kids (GOBACK)

Institution/Agency: Baylor College of Medicine
Year Approved: 2015
Samples Requested: 300, Additional study specific consent obtained
Year Released: No samples released to date
Study Summary: One of the strongest risk factors for childhood cancer is being born with a congenital malformation. The underlying reasons for this association are unknown. This study uses blood spots to attempt to find new genetic mutations (mutations not inherited from the child's mother or father, also known as de novo mutations) that may explain the overlap of these conditions. We anticipate that the results of this study will ultimately lead to the identification of novel cancer predisposition syndromes

which could be used in cancer screening strategies for earlier detection of children at high risk for developing cancer. This study will be conducted through collaborative relationships among researchers in Texas, Arkansas, Michigan, North Carolina, Utah and Washington State.

2014 Approved Research

Maternal Social Environment and Telomere Length

Institution/Agency: University of Michigan
Year Approved: 2014
Samples Requested: 225
Year Released: 2015

Study Summary: This study assessed whether it is possible to use a common laboratory method, qPCR, to measure telomere length in blood spots. Telomeres are sections of DNA at the ends of chromosomes. The study also assesses whether telomere length is affected by the maternal social environment during pregnancy**. This study is done**. *Please see the following article for results:*

1. *Needham, Belinda L., Margaret T. Hicken, Ishtar O. Govia, Colter Mitchell, and Cleopatra M. Abdou. 2017. "Maternal Social Disadvantage and Newborn Telomere Length in Archived Dried Blood Spots from the Michigan Neonatal Biobank." Biodemography and Social Biology 63:221-235.*

Molecular Epidemiology of Pediatric Germ Cell Tumors

Institution/Agency: University of Minnesota
Year Approved: 2014
Samples Requested: 1,000
Year Released: 2015

Study Summary: Pediatric germ cell tumors (GCTs) are thought to result from events in utero. The incidence of GCTs has increased but the underlying causes are unknown. Given the early age of onset, a genetic cause seems likely. These researchers recently completed a large study to evaluate the genetic contribution to GCTs and will use Michigan blood spots to validate their initial findings. This research will be the largest genetic epidemiology study of pediatric GCTs to date, and will evaluate genetic susceptibility.

Genetic and Metabolic Associations with Congenital Hypothyroidism

Institution/Agency: University of Iowa
Year Approved: 2014
Samples Requested: 650
Year Released: 2014

Study Summary: Congenital hypothyroidism (CH) is partial or complete loss of thyroid function. If untreated, it results in damage to the brain and abnormal growth, but with treatment results in normal growth and development. Treatment must begin in the 1st months of life, so CH is part of newborn screening. This study assesses the risk for secondary problems like type 2 diabetes in people with CH. Results could improve follow-up screening for CH, help to better understand neonatal metabolism and later-life chronic conditions like type 2 diabetes.

Healthy Families

Institution/Agency: University of Michigan

Year Approved: 2014
Samples Requested: 140, Additional study specific consent obtained
Year Released: 2014, 2015, 2018

Study Summary: This study is part of a larger one exploring aspects of a child's biology, diet, physical activity, environment and family relationships to find factors that impact observable satiety cues (a child being full). Blood spots are used to study changes over time in epigenetic markers, genetic changes that influence whether and when certain genes are turned on or off. The study may reveal whether certain environments affect the expression of certain genes and contribute to obesity. Findings hope to support development of tailored interventions that can help parents better guide their children through healthy development and reduce childhood obesity. This study is ongoing but for more information, see the article below:

1. *Kochmanski J, Goodrich JM, Peterson KE, Lumeng JC, and Dolinoy DC. Neonatal bloodspot DNA methylation patterns are associated with childhood weight status in the Healthy Families Project. Pediatric Research 2018 Nov 13. doi: 10.1038/s41390-018-0227-1*

ARCH Study

Institution/Agency: Michigan State University
Year Approved: 2014
Samples Requested: TBD, Additional study specific consent obtained
Year Released: No samples released to date

Study Summary: The purpose of ARCH is to create an archive of health and biological data primarily for use in case control studies. Data is collected during pregnancy and then annually for five years to identify health conditions that develop in early childhood. ARCH is a resource for investigators. Blood spots may be used in future ARCH studies after IRB and Scientific Advisory Board review and approval of each study. *This study has been combined with a 2017 study titled "Archive for Research on Child Health Blood Spot Analyses".*

Measuring Orotic Acid in Newborn Screening Specimens as an Indicator for OTC Deficiency

Institution/Agency: Wisconsin Newborn Screening Program
Year Approved: 2014
Samples Requested: 6
Year Released: 2014

Study Summary: The purpose of this study is to determine if orotic acid can be measured in newborn screening blood spots and whether the amount of orotic acid in the blood spots is greater in patients with ornithine transcarbamylase (OTC) deficiency or carriers of the disease than the normal population. OTC deficiency is an inherited disorder that causes ammonia to build up in the blood. **This study is done.**

Neonatal Environmental Exposures and Epigenetics and Childhood Brain Tumor Risk

Institution/Agency: University of Michigan
Year Approved: 2014
Samples Requested: 200
Year Released: No samples released to date

Study Summary: This study will use blood spots to assess the association of prenatal heavy metal (cadmium, lead, mercury) exposure and prenatal gene-specific DNA methylation glioma risk. Known risk factors explain only 5-10% of childhood glioma, the most common malignant brain tumor in children.

Finding other risk factors may help better understand its cause and improve detection, treatment and prevention. The prenatal environment may play a role in childhood glioma development but prenatal risk factors have not been extensively studied. This project can advance childhood cancer research by establishing new methods for metal exposure assessment and measuring DNA methylation in neonatal blood spots. **This study was closed with no work.**

Development of an Improved Biotinidase Activity Assay

Institution/Agency: Future Diagnostics Solutions
Year Approved: 2014
Samples Requested: 100
Year Released: 2014

Study Summary: Biotinidase deficiency is an inherited disorder in which the body cannot recycle or reuse the vitamin biotin. Children found through newborn screening and treated can maintain normal health and development. This study will use blood spots to develop an improved assay to detect biotinidase deficiency through newborn screening. **This study is done**. The researchers have shared: *The biotinidase assay that we developed is easy to use, uses one dried-blood spot (DBS) and a four hours incubation at 37 °C. From the Michigan Neonatal Biobank we received discs from in total 100 subjects: 2 discs from 80 healthy subjects and 2 discs from 20 confirmed biotinidase deficient/intermediate subjects. At the end of the optimization phase, an evaluation batch has been prepared using draft manufacturing lot records and the DBS samples have been used for the evaluation. All samples reacted correctly in our assay and reference assay (the Spotcheck assay from Astoria Pacific). We concluded that a manual deficiency screening assay has been optimized to a user-friendly assay with a good stability, reproducibility and robustness.*

Frequency of 11p15.5 Gene Transcription Abnormalities in Newborns with Isolated Omphalocele

Institution/Agency: University Hospitals Case Medical Center
Year Approved: 2014
Samples Requested: 45
Year Released: No samples released to date

Study Summary: An omphalocele is a defect in the wall of the abdomen where the bowel and other organs are outside of the body. It is usually thought to be a sporadic birth defect, but an overgrowth condition known as Beckwith-Weidemann syndrome (BWS) is present in 20% of fetuses diagnosed with an apparently isolated omphalocele. Typical features of BWS include large size, asymmetry of the body, omphalocele and a large tongue. This study will assess blood spots from newborns with isolated omphalocele to determine the frequency of BWS-related genetic changes in these infants. **This study was closed with no work.**

Molecular Genetics of Acute Lymphoblastic Leukemia in Patients with Down Syndrome

Institution/Agency: Baylor College of Medicine
Year Approved: 2014
Samples Requested: 300
Year Released: 2015

Study Summary: Children with Down syndrome (DS) have a 10-20 fold increased risk of leukemia. While there is a clear genetic basis for the increased acute lymphoblastic leukemia (ALL) risk in DS, the exact gene(s) involved remain largely unknown. Recent studies have identified a number of genes that

influence ALL susceptibility in children. There are no published studies to date on susceptibility genes specific to children with DS. This study will assess whether there are unique genes that predispose ALL in combination with a genetic background of DS, which differ from those that predispose to ALL in the non-DS population. This could shed light on leukemia development in children with DS. This study is ongoing but for more information, see the article below:

1. *Brown AL et al.. Inherited genetic susceptibility to acute lymphoblastic leukemia in Down syndrome.. Blood 2019 Oct 10. doi: 10.1182/blood.2018890764.*

2013 Approved Research

ARCH Sub-Study: Effects of Maternal Physical Activity on Methylation Patterns in Offspring Blood Spots

Institution/Agency: Michigan State University
Year Approved: 2013
Samples Requested: 42, Additional study specific consent obtained
Year Released: 2014

Study Summary: More and more people are obese and suffer from chronic disease. Studies have shown that events during pregnancy and the state of the pregnancy may play a role. These factors may affect the way a newborn's cells work later in life. This study looks at whether a pregnant woman's physical activity has any effect on offspring's cells. The study also looks at the effect of maternal body mass index. **This study is done.** *Please see the article below for more information:*

1. Marshall, M., Paneth, N., Gerlach, J., Mudd, L., Biery, L., Ferguson, D., & Pivarnik, J. (2018). Differential methylation of insulin-like growth factor 2 in offspring of physically active pregnant women. *Journal of Developmental Origins of Health and Disease, 9*(3), 299-306. doi:10.1017/S2040174417001106

Blood Spot Environmental Epidemiology Project (BLEEP)

Institution/Agency: Michigan State University
Year Approved: 2013
Samples Requested: 35, Additional study specific consent obtained
Year Released: 2014

Study Summary: This study assesses twins and their siblings' behavior to see if there is a link between prenatal factors and mental health outcomes. The study uses blood spots to assess genetic and uterine factors that may have had an effect on the child's mental health. Neighborhood poverty levels are also assessed. **This study is done.**

Clinical Database of Children with Krabbe Disease: A World-Wide Registry

Institution/Agency: University of Buffalo/Hunter James Kelly Research Institute
Year Approved: 2013
Samples Requested: <20, Additional study specific consent/authorization was obtained
Year Released: 2014

Study Summary: Hunter's Hope Foundation helps support research and families of children with Krabbe which is an often fatal inherited nervous system disease. Hunter's Hope, with the University at Buffalo, created the Hunter James Kelly Research Institute to find better treatments and a cure for Krabbe and related diseases. This study develops a database of children with Krabbe. This will help doctors better understand signs and tests that can predict the type of Krabbe. Enrolled parents can ask for their child's blood spot, stored for their personal use, to do genetic testing for Krabbe. **This study has been closed.**

Research Use of Michigan's Residual Newborn Screening Blood Spots

Ecologic Stressors, PTSD and Drug Abuse in Detroit

Institution/Agency: University of Michigan
Year Approved: 2013
Samples Requested: 200, Additional study specific consent was obtained
Year Released: 2014
Study Summary: This project is part of a bigger study known as the Detroit Neighborhood Study (DNHS). DNHS is ongoing and began in 2007. Several DNHS projects have been done. The most recent asks subjects to grant consent for using part of their child's blood spots. The blood spots will be tested for markers of maternal immune response during pregnancy. Subjects also complete surveys about upsetting events during pregnancy and mental health outcomes. This project may help shed light on when steps can be taken to lower the chance of a child developing the same mental health challenges as their parent(s).

Gene-Environment Interplay and Young Children's Executive Functioning

Institution/Agency: Wayne State University
Year Approved: 2013
Samples Requested: 30, Additional study specific consent was obtained
Year Released: 2014
Study Summary: This study will use blood spots from twins to assess whether certain genes are active versus inactive. Parents are asked how twins perform tasks involving working memory and attention and differences are studied. Researchers are trying to see if there is a genetic role or other factors explaining any of the differences seen.

Identification of Genetic Causes of Tetralogy of Fallot Using Massively Parallel Sequencing

Institution/Agency: University of Michigan
Year Approved: 2013
Samples Requested: 490
Year Released: 2014, 2015
Study Summary: The high morbidity and mortality from severe congenital heart defects is prompting a search for their cause. This study uses blood spots from children with a severe heart defect (tetralogy of Fallot) to assess genes known or thought to be involved with heart development. These genes are not known to be implicated in cancer or other life-threatening conditions. **This study has been closed**.

Improving IRT/DNA Newborn Screening for Cystic Fibrosis to Reduce False Positive Results by a New Molecular Strategy

Institution/Agency: Wisconsin Newborn Screening Program
Year Approved: 2013
Samples Requested: 300
Year Released: 2013, 2014
Study Summary: A group of states is working to assess a new process for cystic fibrosis (CF) newborn screening. CF is an inherited chronic disease that affects the lungs and digestive system. Over 1800 changes in the CF gene can cause this disorder. Many states use a panel of about 40 of the most common CF gene changes to find babies with this disorder. This study will assess whether a panel of 157 CF gene changes improves the overall process. **This project is done.**

Lab-On-A-Chip for Multiplexed Newborn Screening of Metabolic Disorders-Assay Development

Institution/Agency: Advanced Liquid Logic
Year Approved: 2013
Samples Requested: 12
Year Released: 2013
Study Summary: Blood spots were used to assess a new method of newborn screening for metabolic disorders. Metabolic disorders affect the way the body gets or uses energy from the food we eat. Metabolic disorders on the newborn screening panels must be found shortly after birth. This allows treatment to prevent damage to the body. **This project is done.**

Neural and Genetic Factors Contributing to Variants of Pediatric Anxiety Disorder

Institution/Agency: Wayne State University
Year Approved: 2013
Samples Requested: 179, Additional study specific consent obtained
Year Released: No samples released to date
Study Summary: Changes that affect how a cell's gene activation and inactivation will be studied as well as the actual sequence of DNA in certain genes. Results will help link genes to behavior and develop better interventions for children at risk for adverse emotional development. **This study has been closed until funding becomes available**.

Newborns Conceived Through IVF Technology and the Incidence of Genetic Anomalies: A Pilot Study in Epigenetics

Institution/Agency: Wayne State University
Year Approved: 2013
Samples Requested: 150
Year Released: 2014
Study Summary: Genetic material in blood spots from children born to mothers aided by assisted reproductive technology is being assessed. Actual changes in the sequence of the DNA are not studied. Instead changes that affect the activation or inactivation of genes are studied to find out whether these changes affect children as they develop. These details could then be given to parents who are considering assisted reproductive technology. **This study is done.** *The researchers concluded that both infertility and ICSI alter DNA methylation at specific genomic loci, and the study identified additional genetic sites of interest for future investigations on IVF populations*. *For detailed results, please see the article:*

1. *Estill MS, Bolnick JM, Waterland RA, Bolnick AD, Diamond MP, Krawetz SA. Assisted reproductive technology alters deoxyribonucleic acid methylation profiles in bloodspots of newborn infants. Fertil Steril. 2016 Sep 1;106(3):629-639.*

Neurotoxin Exposure and Brain Development

Institution/Agency: University of Michigan
Year Approved: 2013
Samples Requested: 300
Year Released: No samples released to date
Study Summary: Early contact with toxins (lead and mercury) during development is associated with intellectual and memory impairment, developmental delays in language and attention deficit disorder. This study will assess the effects these neurotoxins have on neural function by assessing their levels at

different stages in development in people with typical development and those with Autism Spectrum Disorders. It will also expire the possible role of genetic processes and neurotoxin exposures to the impairments associated with such exposure and to the etiology of Autism Spectrum Disorders**. This study closed until funding becomes available**.

Next Generation Sequencing in the Newborn Period

Institution/Agency: University of Michigan
Year Approved: 2013
Samples Requested: 500
Year Released: No samples released to date
Study Summary: This study was closed with no work.

2012 Approved Research

Twins and Sibling Study

Institution/Agency: Michigan State University
Year Approved: 2012
Samples Requested: 200, Additional study specific consent obtained
Year Released: No samples released to date
Study Summary: This study will use blood spots from twins and their siblings to assess the level of androgen (a hormone) and whether androgen-related genes are activated. This work may show how prenatal and genetic factors impact acting out behaviors in children.

Astoria-Pacific, Inc.- Total Galactose Screening Method Comparison

Institution/Agency: Astoria-Pacific, Inc.
Year Approved: 2012
Samples Requested: 11
Year Released: 2012
Study Summary: This study aimed to show the Food and Drug Administration (FDA) that a new test could detect newborns with galactosemia as well as the current kit on the market. This would allow more newborn screening solutions that are safe and effective. Galactosemia is an inherited condition in which babies are not able to break down a sugar found in breast milk and most formulas. A special diet begun soon after birth will prevent damage to the body. ***This study is done.*** *The FDA approved Astoria-Pacific's kit. It is currently being used in one newborn screening lab and expected in others in the near future.*

2011 Approved Research

Dried Blood Spots to Determine the Effect of Pb on DNA Methylation in Children

Institution/Agency: Wayne State University
Year Approved: 2011
Samples Requested: 51
Year Released: 2013
Study Summary: Blood spots were tested for lead levels. The effect on gene expression (active versus inactive genes) was also compared between blood spots and current blood samples from the children. Results may provide data to help children exposed to lead. **This study is done.** *Results "suggest that lead exposure during pregnancy affects the DNA methylation status of the fetal germ cells, which leads to altered DNA methylation in grandchildren's neonatal dried blood spots. This is the first demonstration*

that an environmental exposure in pregnant mothers can have an epigenetic effect on the DNA methylation pattern in the grandchildren." For detailed results, please see the article:

1. D. Ruden, et al. Multigenerational epigenetic inheritance in humans: DNA methylation changes associated with maternal exposure to lead can be transmitted to the grandchildren. *Scientific Reports*. 2015 Sep; 14466

Newborn DNA Methylation and Biochemical Status in Autism, ADHD and Cerebral Palsy

Institution/Agency: Wayne State University
Year Approved: 2011
Samples Requested: 119, Additional study specific consent obtained
Year Released: 2012

Study Summary: DNA methylation is a biochemical process that affects the genetic activity within a cell. Factors such as diet, stress, drugs, toxins and aging may have an effect on which pieces of DNA in a cell are active. This study compares the degree of methylation in specific genes between persons with and without attention hyperactivity disorder (ADHD), autism and cerebral palsy. Biochemical testing combined with methylation studies soon after birth could help predict risk. **This study has been closed**.

Prenatal Alcohol Exposure: The Influence on Epigenetic Processes

Institution/Agency: Wayne State University
Year Approved: 2011
Samples Requested: 18, Additional study specific consent obtained
Year Released: 2011

Study Summary: Fetal Alcohol Spectrum Disorders are studied in this project. Epigenetic factors, resulting from inherited changes in gene expression (active versus inactive genes), are being assessed in the blood spots. Different epigenetic factors may help diagnose infants. They may also help explain why certain signs of fetal alcohol spectrum disorders develop in some children but not others. These epigenetic factors may also shed light on the risks from alcohol use just prior to and during pregnancy. **This study has been closed.**

Technology Enhancement and Implementation of Michigan Newborn Screening for Severe Combined Immunodeficiency (SCID) and Related Disorders

Institution/Agency: Michigan Department of Health and Human Services
Year Approved: 2011
Samples Requested: 2,500
Year Released: 2011, 2012

Study Summary: Severe Combined Immune Deficiency (SCID) is the most severe type of primary immunodeficiency. It is rare and can be lethal. Early treatment improves survival. The Michigan NBS laboratory used blood spots to validate its screen for SCID and related disorders. **This study is done**. *Resulted in addition of SCID to Michigan's newborn screening panel in 2011. After two years, over 230,000 MI newborns were screened for SCID and 34 newborns with immune deficiencies were detected. The study also resulted in improved methods for SCID screening which have been shared at a number of national events to help other newborn screening programs begin SCID screening.*

2010 Approved Research

Assessment of the SMN1 and 2 Genes in Spinal Muscular Atrophy Affected Patients and a Carrier Frequency Study

Institution/Agency: ARUP Laboratories
Year Approved: 2010
Samples Requested: 3,000
Year Released: 2011, 2012

Study Summary: Spinal muscular atrophy (SMA) is a group of inherited disorders that cause progressive weakness and wasting of muscles. Muscles of the limbs and trunk are affected. Feeding, swallowing and breathing can become impaired. This study used blood spots to develop a newborn SMA screening test. **The study is done.** *The screening test was able to identify all cases of SMA and did not incorrectly identify any normal samples as SMA cases. The researchers concluded the test had features that would make it suitable for newborn screening.* For detailed results, please see the article:

1. S. Dobrowolski, et al. Newborn Screening for Spinal Muscular Atrophy by Calibrated Short-Amplicon Melt Profiling. *Clinical Chemistry.* 2012; 58:1033-1039

DNA Methylation in Sudden Unexplained Infant Death Syndrome

Institution/Agency: Wayne State University/William Beaumont Hospital
Year Approved: 2010
Samples Requested: 24
Year Released: No samples released to date

Study Summary: Sudden Unexplained Infant Death Syndrome (SUIDS) is the sudden unexplained death of an infant or young child. SUIDS is a complex disorder with genetic, environmental, biochemical and social causes. There is strong evidence of a role played by prenatal factors such as maternal smoking and infection. A number of genes have also been linked to SUIDS. The aim of this study is to assess whether a difference exists in gene activation in blood spots from newborns who expired as a result of SUIDS. This could improve understanding of the causes of SUID including prenatal factors and potential risk factors. **This study has been closed.**

Methods Comparison of Luminex Multiplex Newborn Screening Assay to Delfia

Institution/Agency: Luminex Corporation
Year Approved: 2010 & 2012
Samples Requested: 2,210
Year Released: 2011, 2013

Study Summary: Hormone levels were assessed to determine accuracy of technology designed by Luminex Corporation to screen for congenital adrenal hyperplasia, congenital hypothyroidism and cystic fibrosis. **This study is done.** *Luminex discontinued their newborn screening program in 2013 after company restructuring. No results were provided from this study.*

High Throughput Methods to Measure Disparities in Childhood Exposure to Tobacco

Institution/Agency: University of Minnesota
Year Approved: 2010
Samples Requested: 350
Year Released: 2010

Study Summary: Children are exposed to tobacco in utero by maternal smoking and during childhood from second hand smoke (SHS). SHS is associated with health problems such as low birth weight, asthma, ear and lower respiratory infections and sudden infant death syndrome. SHS exposure and its

health effects vary by race, ethnicity and socio-economic status. Efforts to stop childhood exposure to SHS are critical for reducing health disparities. Blood spots enable thousands of samples to be assessed for exposure levels across a population. This project will use blood spots from several states to study differences in childhood exposure to SHS. Findings will provide estimates of the US population prevalence of in utero tobacco toxin exposure by race. **This study is done.** *Data from the study confirmed that parental reporting of smoking during pregnancy is an imperfect way to measure prenatal exposure to tobacco smoke. For detailed results, please see the article:*

1. LG Spector et al, Prenatal tobacco exposure and cotinine in newborn dried blood spots. *Pediatrics*. 2014 June; 133(6): e1632-8.

HLA Typing of Neonatal Blood Spots

Institution/Agency: Genomics USA
Year Approved: 2010
Samples Requested: 40
Year Released: 2010

Study Summary: A larger study is being done to develop a new technology to perform very-low-cost genetic testing. The testing targets the HLA locus, the set of genes responsible for person-to-person variation in the immune system, the basis for a tissue-match in organ transplants and possibly for personal variation in response to certain vaccines or infection. This study will not discover disease correlations with HLA-type. Instead the study will try to determine if a new approach to HLA-typing can be done using blood spots collected on a Guthrie card, the card used for newborn screening. Michigan's blood spots were used for a pilot study to show that HLA-typing data can be obtained from blood spots. **This study has been closed.**

DNA Methylation and Congenital Heart Defect (Metabolic Newborn Screening for Congenital Heart Defects)

Institution/Agency: Wayne State University/William Beaumont Hospital
Year Approved: 2010
Samples Requested: 312
Year Released: 2010

Study Summary: Prenatal risk factors such as maternal alcohol use, maternal fever, inflammation and diet are thought to play important roles in congenital heart defects (CHD). Recent studies report a link between certain classes of CHD in offspring and a deficiency in the vitamin, folic acid, in the mother. Folic acid deficiency could change essential gene functions and suppress important cardiac development leading to CHD. The aim of this study is to see if there is a relationship between changes in essential gene functions in blood spots of children with CHD. *For detailed results, please see the articles:*

1. RO Bahado-Singh et al, Genome-Wide DNA methylation analysis and epigenetic variations associated with congenital aortic valve stenosis (AVS). *PLoS One.* 2016; 11(5)
2. RO Bahado-Singh et al, Epigenetic markers for newborn congenital heart defect (CHD). *J Matern Fetal Neonatal Med*. 2016; 29(12): 1881-7.

2000-2009 Approved Research

Prior to the implementation of the Michigan BioTrust for Health

Microarray Analysis of Neonatal Blood Spots: Optimization and Application to Birth Outcomes

Institution/Agency: Van Andel Institute
Year Approved: 2009
Samples Requested: 20
Year Released: 2009
Study Summary: This was a pilot study to perform gene expression analysis of neonatal blood spot samples from 10 full-term neonates who subsequently developed neuroblastoma in the first year of life (randomly selected from the cancer registry and de-identified) and 10 full-term neonates who did not develop any malignancy. By correlating gene expression in blood spots with risk of disease (in this case, Neuroblastoma) we will gain new insights into the perinatal risk factors contributing to a wide range of neonatal and childhood conditions. **This study was closed with no work.**

Luminex Newborn Screening Multiplex Immunoassay

Institution/Agency: Luminex Corporation
Year Approved: 2009
Samples Requested: 1,500
Year Released: 2009
Study Summary: N/A. **This study is done.**

Mercury Levels in Blood from Newborns in the Lake Superior Basin

Institution/Agency: Minnesota Department of Health
Year Approved: 2009
Samples Requested: 200
Year Released: 2010
Study Summary: The level of methylmercury, the form of mercury found in fish, was assessed in the blood of newborns from mothers living along the Lake Superior Basin in Minnesota, Wisconsin and Michigan. **This study is done.** *Most newborns were found to have low or undetected total mercury levels. 8% of newborns had mercury levels about the U.S. EPA reference dose (none from Michigan). Babies born during the summer months were more likely to have an elevated mercury level. Minnesota's Department of Health increased outreach to health care providers and others to promote eating fish low in mercury. For detailed results please visit the Minnesota Department of Health's webpage with access to the full EPA report.*

CTA Catalytic Grant Proposal, Whole Genome DNA Amplification from Stored Dried Blood Spots

Institution/Agency: Wayne State University
Year Approved: 2008
Samples Requested: 99
Year Released: 2008
Study Summary: N/A. **This study is done.**

Novel Techniques for Neonatal Screening

Institution/Agency: Johns Hopkins
Year Approved: 2007
Samples Requested: 9
Year Released: 2008
Study Summary: N/A

Research Use of Michigan's Residual Newborn Screening Blood Spots

The Use of T Cell Receptor Excision Circles to Detect Missed Cases of Severe Combined Immunodeficiency

Institution/Agency: Wayne State University
Year Approved: 2007
Samples Requested: 160
Year Released: 2008
Study Summary: N/A

Analysis of Environmental Contaminants in Dried Blood Spots: A Pilot Study

Institution/Agency: Centers for Disease Control
Year Approved: 2007
Samples Requested: 15
Year Released: 2007
Study Summary: This study was a feasibility study done to determine if certain environmental contaminants could be measured in blood spots. **The study is done.** *The study was successfully carried out per investigator's feedback to MDHHS.*

ID of Genetic Markers in Blood Spots of Guthrie Newborn Screening Cards

Institution/Agency: Children's Hospital of Michigan
Year Approved: 2006
Samples Requested: 102
Year Released: 2007, 2008
Study Summary: This study screened blood spots of children who developed leukemia to determine if leukemic or "preleukemic" cells were present at birth and detectable in blood spots. **This study has been closed**. *Combining results from both studies listed below, preleukemic cells were detected in 63% of patients. For more detailed results, please see the articles:*

1. *Gruhn B, Taub JW, et al. Prenatal origin of childhood acute lymphoblastic leukemia, association with birth weight and hyperdiploidy. Leukemia. 2008 Sep; 22(9): 1692-7*
2. *Taub, JW., et al. High Frequency of leukemic clones in newborn screening blood samples of children with B-precursor acute lymphoblastic leukemia. Blood. 2002 Apr; 99(8)*

New Paradigms of Cerebral Palsy (CP)

Institution/Agency: Michigan State University
Year Approved: 2005
Samples Requested: 53, Additional study specific consent obtained
Year Released: 2009, 2010
Study Summary: Recruitment for this study has been discontinued although requests for blood spots from consented subjects may continue. Investigators are still analyzing molecular markers for cerebral palsy. Multiple articles have been published describing this work including findings from the first 53 matched pairs; two sub-studies comparing gene expression in umbilical cord and blood spots and in frozen vs unfrozen spots; and a paper on the effects of blood spot storage time on gene expression data. *For more detailed results, please see the articles:*

1. *N. T. Ho et al, Gene expression in archived newborn blood spots distinguishes infants who will later develop cerebral palsy from matched controls. Pediatric Research. 2013; 73: 450-456.*
2. *J. Resau et al, Evaluation of sex-specific gene expression in archived dried blood spots (DBS). Int J Mol Sci. 2012; 13(8): 9599-9608.*

3. *N. T. Ho et al, Effect of storage time on gene expression data acquired from unfrozen archived newborn blood spots. Mol Genet Metab. 2016 Nov; 119(3): 207-213.*
4. *J Slaughter et al, High correlations in gene expression between paired umbilical cord blood and neonatal blood of healthy newborns on Guthrie cards. Journal of Maternal-Fetal and Neonatal Medicine. 2013 Dec; 18: 1765-1767*
5. *P. Haak et al, Archived unfrozen neonatal blood spots are amenable to quantitative gene expression analysis. Neonatology. 2009 Mar; 95(3): 210-216.*
6. *C. Wei et al, Comparison of frozen and unfrozen blood spots for gene expression studies, The Journal of Pediatrics. 2014; 164(1): 189-191.*

Feasibility and Validity of Obtaining Guthrie Cards for Molecular Epidemiology Studies

Institution/Agency: University of Minnesota
Year Approved: 2005
Samples Requested: 100
Year Released: 2006
Study Summary: N/A

The Genetic Basis and Pathophysiology of Neonatal Persistent Pulmonary Hypertension.

Institution/Agency: Wayne State University
Year Approved: 2004
Samples Requested: 416
Year Released: 2009, 2010, 2016
Study Summary: Persistent pulmonary hypertension of the newborn (PPHN) is a clinical syndrome where blood is shunted away from the lungs. PPHN can be seen with neonatal diseases such as aspiration, infection or immature lungs. There are commonly seen risk factors for PPHN, but only a small number of patients with these risk factors develop it. It is likely there are inherited factors affecting development of PPHN. Limited studies have addressed the genetic basis of neonatal PPHN. The broad long term goal of this research is to find the genetic basis for neonatal PPHN.

Maternal Microchimerism and HLA Compatibility in Juvenile Diabetes and Autism

Institution/Agency: Children's Hospital of Michigan
Year Approved: 2001
Samples Requested: 17, Additional study specific consent obtained
Year Released: 2001
Study Summary: N/A

Prevalence of Three Hereditary Hemochromatosis Mutant Alleles in the Michigan Caucasian Population

Institution/Agency: Michigan State University
Year Approved: 2000-2002
Samples Requested: 3,532
Year Released: 2002
Study Summary: This study was done to find how common several mutations in the HFE gene associated with hereditary hemochromatosis, an iron overloading disease, are in the Michigan non-Hispanic Caucasian population. **This study is done.** *Results found one mutation more common than previously reported. For detailed results please see the article:*

1. E Barry et al, Prevalence of three hereditary hemochromatosis mutant alleles in the Michigan Caucasian population. *Community Genet.* 2005; 8(3): 173-9.