Guidelines for Releasing Michigan’s Residual Blood Spots

- 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

2016 Approved Research

Development of Newborn Screen for Niemann-Pick C1 Disease

<table>
<thead>
<tr>
<th>Institution/Agency</th>
<th>Washington University</th>
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<tbody>
<tr>
<td>Year Approved</td>
<td>2016</td>
</tr>
<tr>
<td>Samples Requested</td>
<td>20, Additional study specific consent obtained</td>
</tr>
<tr>
<td>Year Released</td>
<td>2017</td>
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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.

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

<table>
<thead>
<tr>
<th>Institution/Agency</th>
<th>Veritas Genetics</th>
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<tr>
<td>Year Approved</td>
<td>2016</td>
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<tr>
<td>Samples Requested</td>
<td>42</td>
</tr>
<tr>
<td>Year Released</td>
<td>2016</td>
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</table>

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.

WHEALS and CAS Metals Study

<table>
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<tr>
<th>Institution/Agency</th>
<th>Henry Ford Health System</th>
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<tr>
<td>Year Approved</td>
<td>2016</td>
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<tr>
<td>Samples Requested</td>
<td>20</td>
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<tr>
<td>Year Released</td>
<td>No samples released to date.</td>
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</table>

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.
Research Use of Michigan’s Residual Newborn Screening Blood Spots

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

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.

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. 3 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
Research Use of Michigan’s Residual Newborn Screening Blood Spots

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.

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.

2015 Approved Research

Genetic Analysis of Human First Trimester Trophoblast in Ongoing Pregnancies

Institution/Agency: Washington State University
Year Approved: 2015
Samples Requested: 50, Additional study specific consent obtained
Year Released: 2015

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.

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: PerkinElmer
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 than the current testing. This could help improve current laboratory tests used to detect disorders through newborn screening.
Research Use of Michigan’s Residual Newborn Screening Blood Spots

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

Institutions/Agency: University of Minnesota
Year Approved: 2015
Samples Requested: 360
Year Released: 2016

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.

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.

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
Research Use of Michigan’s Residual Newborn Screening Blood Spots

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

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<tr>
<th>Institution/Agency</th>
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<tr>
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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.

Molecular Epidemiology of Pediatric Germ Cell Tumors

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<tr>
<th>Institution/Agency</th>
<th>University of Minnesota</th>
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<tr>
<td>Year Approved</td>
<td>2014</td>
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<tr>
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<td>1,000</td>
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<td>Year Released</td>
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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

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<th>Institution/Agency</th>
<th>University of Iowa</th>
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<tr>
<td>Year Approved</td>
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<tr>
<td>Samples Requested</td>
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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 and 2015

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.

ARCH Study

Institution/Agency: Michigan State University
Year Approved: 2014
Samples Requested: TBD
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.

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.

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
Research Use of Michigan’s Residual Newborn Screening Blood Spots

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.

**Development of an Improved Biotinidase Activity Assay**

<table>
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<tr>
<th>Institution/Agency</th>
<th>Future Diagnostics Solutions</th>
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<tr>
<td>Year Approved</td>
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<tr>
<td>Samples Requested</td>
<td>100</td>
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<td>Year Released</td>
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**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 closed.** 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**

<table>
<thead>
<tr>
<th>Institution/Agency</th>
<th>University Hospitals Case Medical Center</th>
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<tr>
<td>Year Approved</td>
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<td>45</td>
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<tr>
<td>Year Released</td>
<td>No samples released to date.</td>
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**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.

**Molecular Genetics of Acute Lymphoblastic Leukemia in Patients with Down Syndrome**

<table>
<thead>
<tr>
<th>Institution/Agency</th>
<th>Baylor College of Medicine</th>
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<tr>
<td>Year Approved</td>
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<td>300</td>
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<tr>
<td>Year Released</td>
<td>No samples released to date.</td>
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**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
Research Use of Michigan’s Residual Newborn Screening Blood Spots 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.

### 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.

**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.

**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.

**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**: No samples released to date

**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
Research Use of Michigan’s Residual Newborn Screening Blood Spots

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).

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Institution/Agency</th>
<th>Year Approved</th>
<th>Samples Requested</th>
<th>Year Released</th>
<th>Study Summary</th>
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<tbody>
<tr>
<td>Gene-Environment Interplay and Young Children’s Executive Functioning</td>
<td>Wayne State University</td>
<td>2013</td>
<td>30, Additional study specific consent was obtained</td>
<td>No samples released to date</td>
<td>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.</td>
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<tr>
<td>Identification of Genetic Causes of Tetralogy of Fallot Using Massively Parallel Sequencing</td>
<td>University of Michigan</td>
<td>2013</td>
<td>390</td>
<td>2014</td>
<td>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.</td>
</tr>
<tr>
<td>Improving IRT/DNA Newborn Screening for Cystic Fibrosis to Reduce False Positive Results by a New Molecular Strategy</td>
<td>Wisconsin Newborn Screening Program</td>
<td>2013</td>
<td>300</td>
<td>2013 and 2014</td>
<td>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.</td>
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</table>
Research Use of Michigan’s Residual Newborn Screening Blood Spots

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 study is complete. No results are available to date.

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. Study 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:


Neurotoxin Exposure and Brain Development

**Institution/Agency**: University of Michigan  
**Year Approved**: 2013  
**Samples Released**: 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. Study closed until funding becomes available.
Research Use of Michigan’s Residual Newborn Screening Blood Spots

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 informed consent obtained
Year Released: 2012
Research Use of Michigan’s Residual Newborn Screening Blood Spots

**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.

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 is done. No results have been made available to MDHHS.**

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 and 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 and 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:**
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.

Methods Comparison of Luminex Multiplex Newborn Screening Assay to Delfia

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


HLA Typing of Neonatal Blood Spots

**Institution/Agency**  Samples Requested  
**Year Approved**  Year Released
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.

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

Institution/Agency: Wayne State University/William Beaumont Hospital
Year Approved: 2008 and 2010
Samples Requested: 312
Year Released: 2010 (partial)

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. This study is on-going. For detailed results, please see the articles:


2000-2009 Approved Research
Prior to 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 is done.
Research Use of Michigan’s Residual Newborn Screening Blood Spots

Luminex Newborn Screening Multiplex Immunoassay

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<tr>
<th>Institution/Agency</th>
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**Study Summary:** This study is done. No results are available.

Mercury Levels in Blood from Newborns in the Lake Superior Basin

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**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

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**Study Summary:** This study is done. No results are available.

Novel Techniques for Neonatal Screening

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

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<th>Institution/Agency</th>
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<td>Year Approved</td>
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<td>Year Released</td>
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</table>
Research Use of Michigan’s Residual Newborn Screening Blood Spots

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.**

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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 is done.**  
**Combining results from both studies listed below, preleukemic cells were detected in 63% of patients.**

**For more detailed results, please see the articles:**


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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. This study is on-going. **For more detailed results, please see the articles:**

Research Use of Michigan’s Residual Newborn Screening Blood Spots

### Feasibility and Validity of Obtaining Guthrie Cards for Molecular Epidemiology Studies

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<tr>
<th>Institution/Agency</th>
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### The Genetic Basis and Pathophysiology of Neonatal Persistent Pulmonary Hypertension

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<td>Year Released</td>
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**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. This study is ongoing.

### Maternal Microchimerism and HLA Compatibility in Juvenile Diabetes and Autism

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<th>Institution/Agency</th>
<th>Children’s Hospital of Michigan</th>
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<td>Year Approved</td>
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### Prevalence of Three Hereditary Hemochromatosis Mutant Alleles in the Michigan Caucasian Population

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<th>Institution/Agency</th>
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<td>Year Released</td>
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**Study Summary:** This study was done to find how common several mutations in the HFE gene associated with hereditary hemochromatosis, an iron overloading disease, 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: