

LINKING CANCER REGISTRIES AND BIRTH DEFECTS REGISTRIES FOR CLUES ON GENETIC CANCER RISK

NAACCR Annual Conference

Charlotte

2015

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Objectives



- Cancer risk in children with birth defects
- Review potential for investigating etiology
- Describe data/materials available
- Provide a sampling of ongoing research
- Outline ethical considerations

Cancer Risk among Children with Birth Defects

- Presence of a birth defect is the strongest risk factor for childhood cancer
- Associations with cancer and both major and minor malformations
- Examples of established associations include:
 - ▣ Down syndrome with leukemia
 - ▣ Beckwith-Wiedemann with Wilms tumor
 - ▣ Chromosome 13q14 deletion and retinoblastoma

Data Used to Assess this Association within Michigan

- Michigan Birth Defects Registry
 - ▣ Established in 1992
- Michigan Cancer Surveillance System
 - ▣ Established in 1985
- Selected 1992 through 2011 birth cohorts
 - ▣ 2,566,771 Michigan births in this period

MBDR -Some Key Facts

- Established by Act 236 of 1988
- Requires Reporting by Hospitals and Cytogenetics Laboratories
- Passive Reporting
- Defined List of Reportable Conditions
- Reporting Began State Wide in 1992

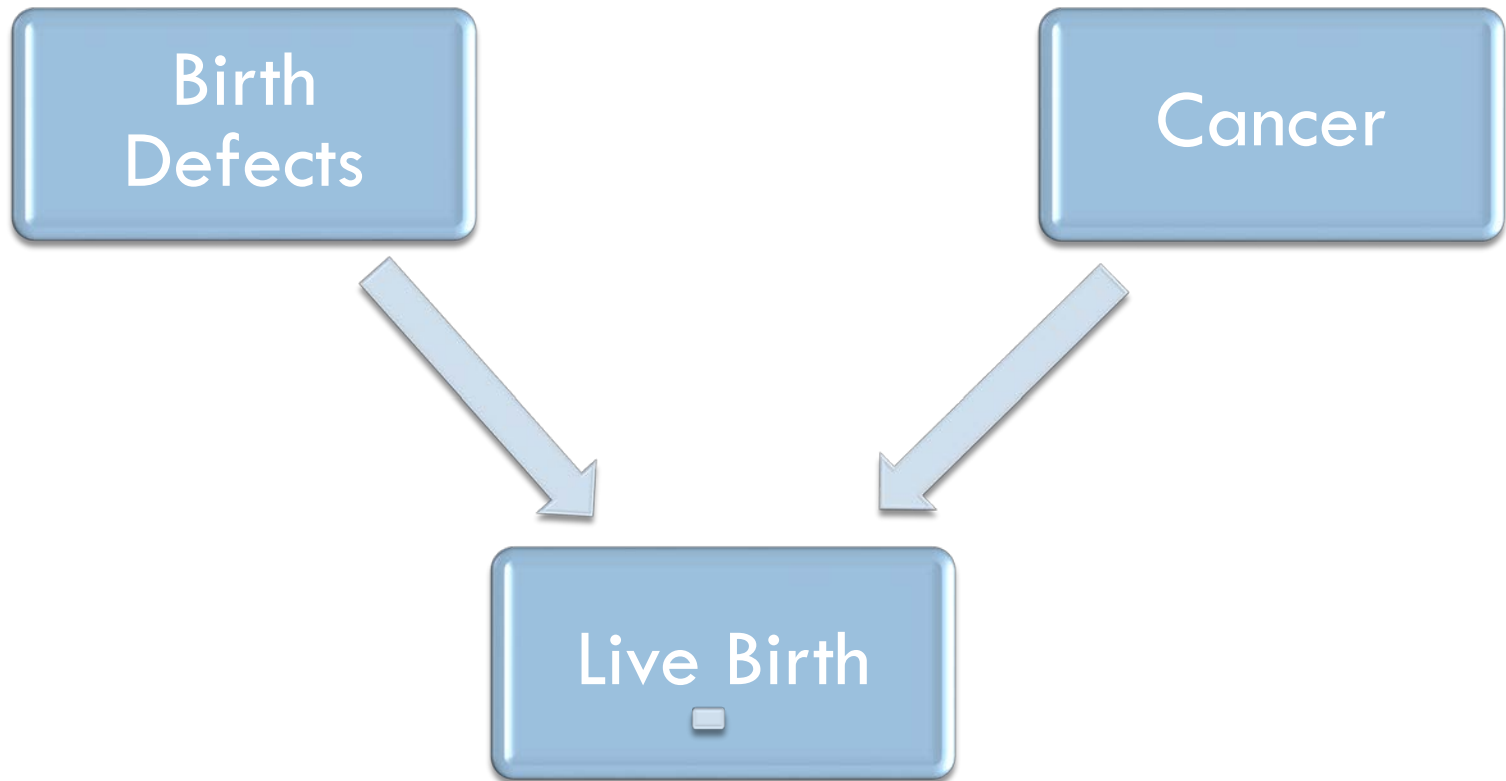
Reportable Conditions

- Congenital Anomalies
 - ▣ Excludes only minor conditions
- Other Conditions that Associate
 - ▣ Immune/Metabolic Deficiencies
 - ▣ Other Abnormalities
- Infectious Disease Exposures
 - ▣ Syphilis/Rubella/CMV/etc
- Maternal Exposures
 - ▣ Alcohol/Drugs/Toxic Agents

Current Status of the Registry

- Processed 638,000 reports
- Registry Contains 308,000 Cases
- Linked to Live Birth Registry
- Linked to Mortality Files

Measuring Relative Risk



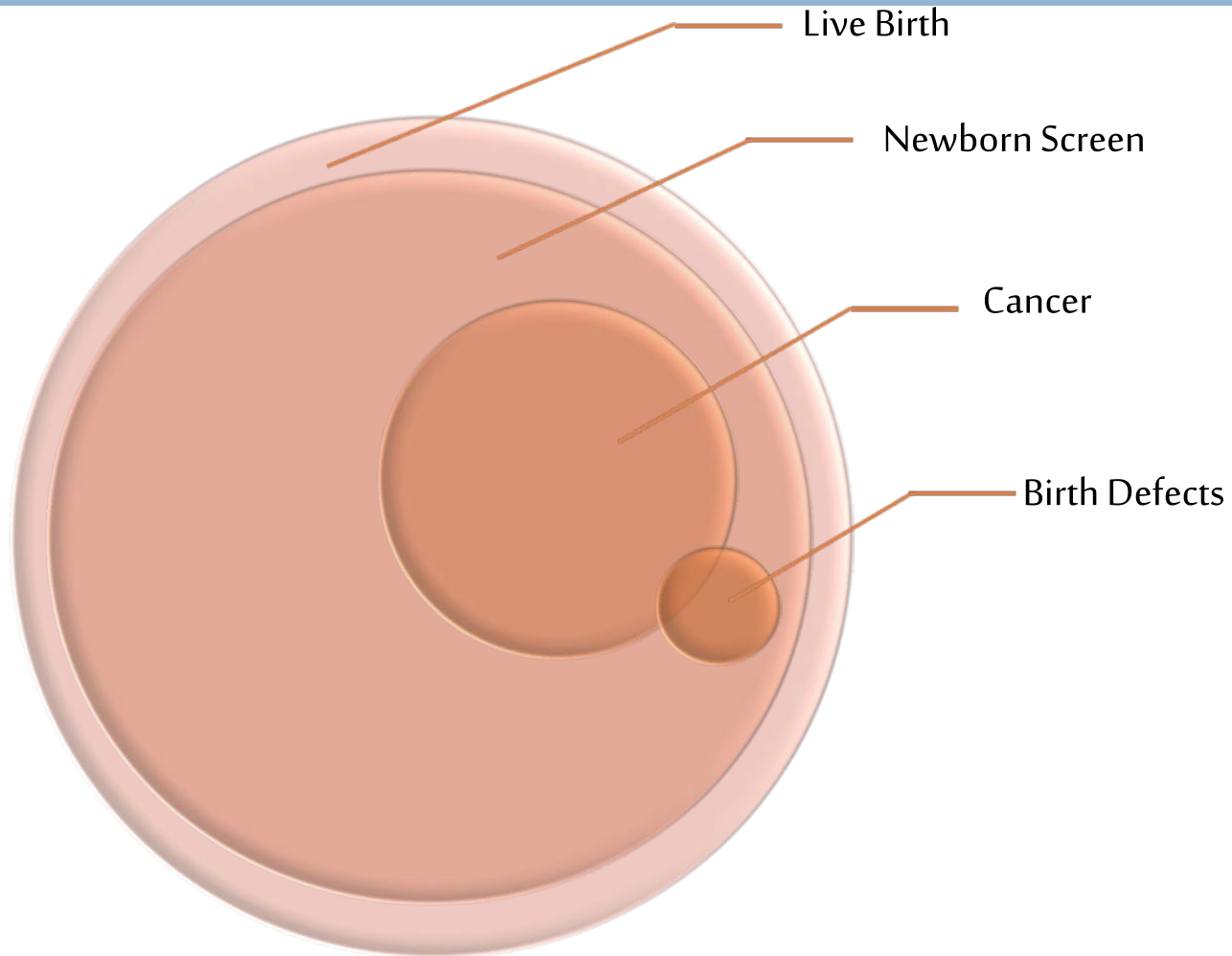
Defect group	BDs, N	BD-CC, N	RR (95% CI)
Central nervous system (CNS)	10,288	90	4.3 (3.5-5.3)
Neural tube	1,690	9	2.6 (1.3-5.0)
Eye and ear	12,960	54	2.0 (1.6-2.7)
Anophthalmia/microphthalmia	475	4	4.1 (1.5-10.8)
Cardiac and circulatory	44,466	200	2.2 (1.9-2.6)
Septal	26,402	120	2.2 (1.9-2.7)
Other heart	14,812	79	2.6 (2.1-3.3)
Other circulatory	22,941	104	2.2 (1.8-2.7)
Left ventricular outflow tract	4,681	18	1.9 (1.2-3.0)
Respiratory	10,826	58	2.6 (2.0-3.4)
Oral clefts	4,370	10	1.1 (0.6-2.1)
Gastrointestinal	14,258	89	3.1 (2.5-3.8)
Genitourinary	34,317	110	1.6 (1.3-1.9)
Musculoskeletal	45,522	162	1.9 (1.6-2.2)
Chromosomal	5,718	91	7.8 (6.4-9.6)

Cancer type	CCs, N	BD-CC, N	RR (95% CI)
Leukemia	1,182	273	3.1 (2.8-3.5)
Lymphoma	346	61	2.2 (1.7-2.9)
CNS tumor	824	277	5.3 (4.7-6.0)
Neuroblastoma	349	154	8.2 (6.9-9.7)
Retinoblastoma	147	32	2.9 (2.0-4.2)
Rhabdomyosarcoma	137	25	2.3 (1.5-3.5)
Wilm's tumor	233	58	3.5 (2.6-4.5)
Hepatic	89	51	14.0 (10.1-19.3)
Bone	127	22	2.2 (1.4-3.4)
Germ cell	126	47	6.2 (4.5-8.4)

Research Opportunities

- Etiology of most birth defects remains unknown
- Mechanisms that link birth defects and cancer are unknown
- Possible genetic/genomic factors in common are unknown
- Environment is ripe for exploration

Tools to enable molecular/genetic research



Environment

- Newborn screening in all states
 - ▣ Variations in availability to research
- Standardized live birth files in all states
 - ▣ Exceptions related to adoption of 2003 standard
- Standardized cancer registries in all states
- Birth defects registries in 42 states
 - ▣ Considerable variation in case definition/data set
- Standardized mortality data
 - ▣ Provides vital status



NBS Law MCL 333.5431

- Mandatory testing
 - Informed consent requirements not applicable
 - Violation is a misdemeanor
 - Parents can decline (Sign refusal for treatment form)
- Residual NBS DBS may be used for research during retention period



Michigan NBS Panel: 55 Disorders

www.michigan.gov/newbornscreening

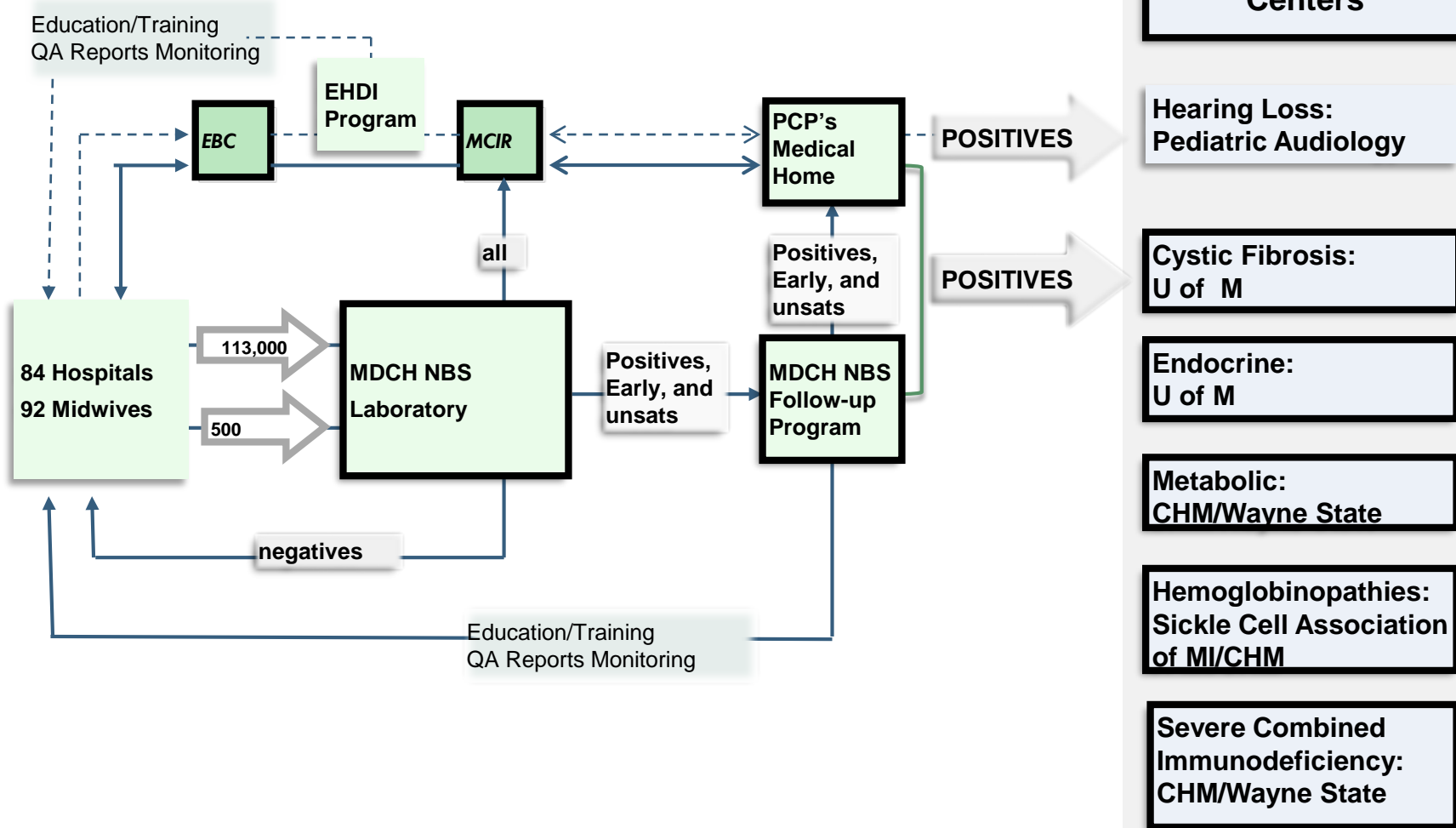
- 14 Amino Acid Disorders (1965)
- 13 Fatty Acid Oxidation Disorders (2003)
- 14 Organic Acid Disorders (2005)
- 2 Endocrine Disorders (CH: 1977, CAH: 1993)
- Hemoglobinopathies (1987), Biotinidase deficiency (1987), Galactosemia (1985), Cystic Fibrosis (2007), SCID (2011)



About 255 Michigan children diagnosed each year with
nearly 5,700 diagnosed since 1965.



Michigan Newborn Screening





After Newborn Screening

- Normally ~13 punches need from the 6 blood spots
- What happens to the residual sample?
- Does it matter how they are stored and used?
- Could storage and use policies impact perception of NBS?



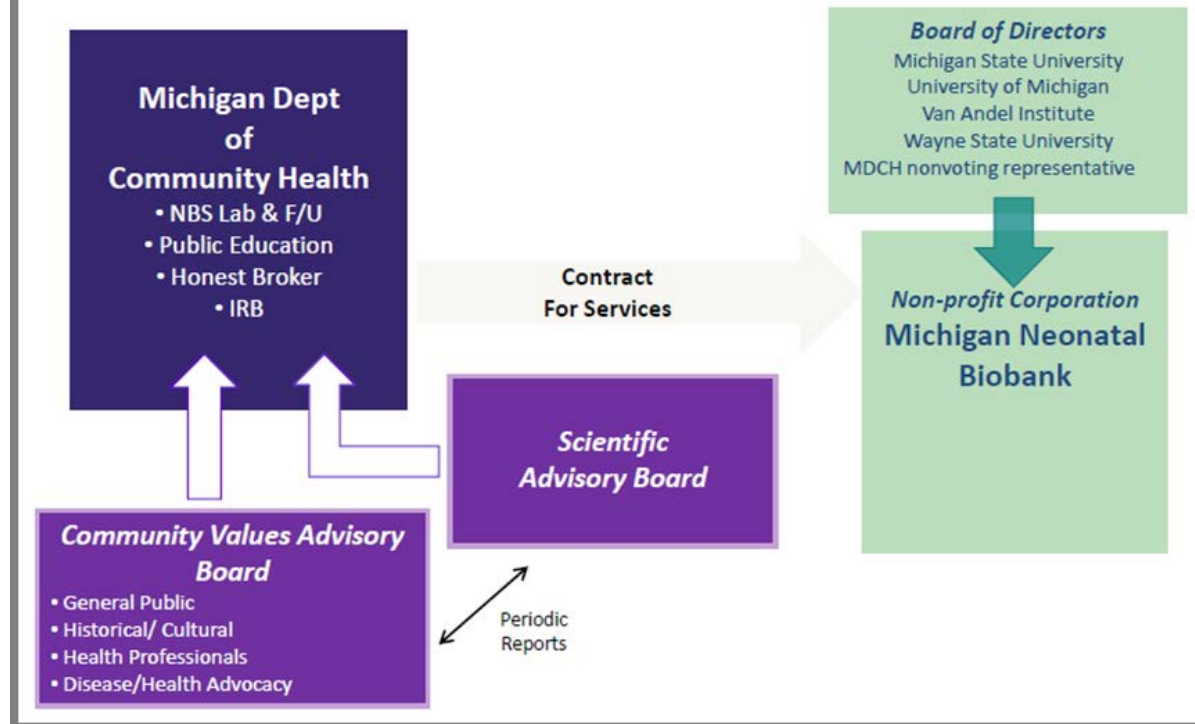
There are now added public health benefits from newborn screening.

- Population based sample
- Over 160 biomarkers
 - Proteins
 - Human DNA/mRNA
 - Viral/bacterial DNA
 - Metals



There is potential to reduce burden of disease in children.

BioTrust Governance Structure



- MDCH
- Community Values Advisory Board - CVAB
- Scientific Advisory Board- SAB
- MDCH IRB
- MNB BOD

Strict guidelines are in place to promote appropriate research use of dried blood spots.



- 2-step approval process
- 2-step de-identification process
- Scientific Advisory Board
- MDHHS Institutional Review Board
- Research guidelines

Potential Value of these Components



- *Near* population-based
- Generally available in all states
- Availability to research varies widely.
- Enables research into very rare conditions
- Near perfect source for control selection

Current Research using Biotrust

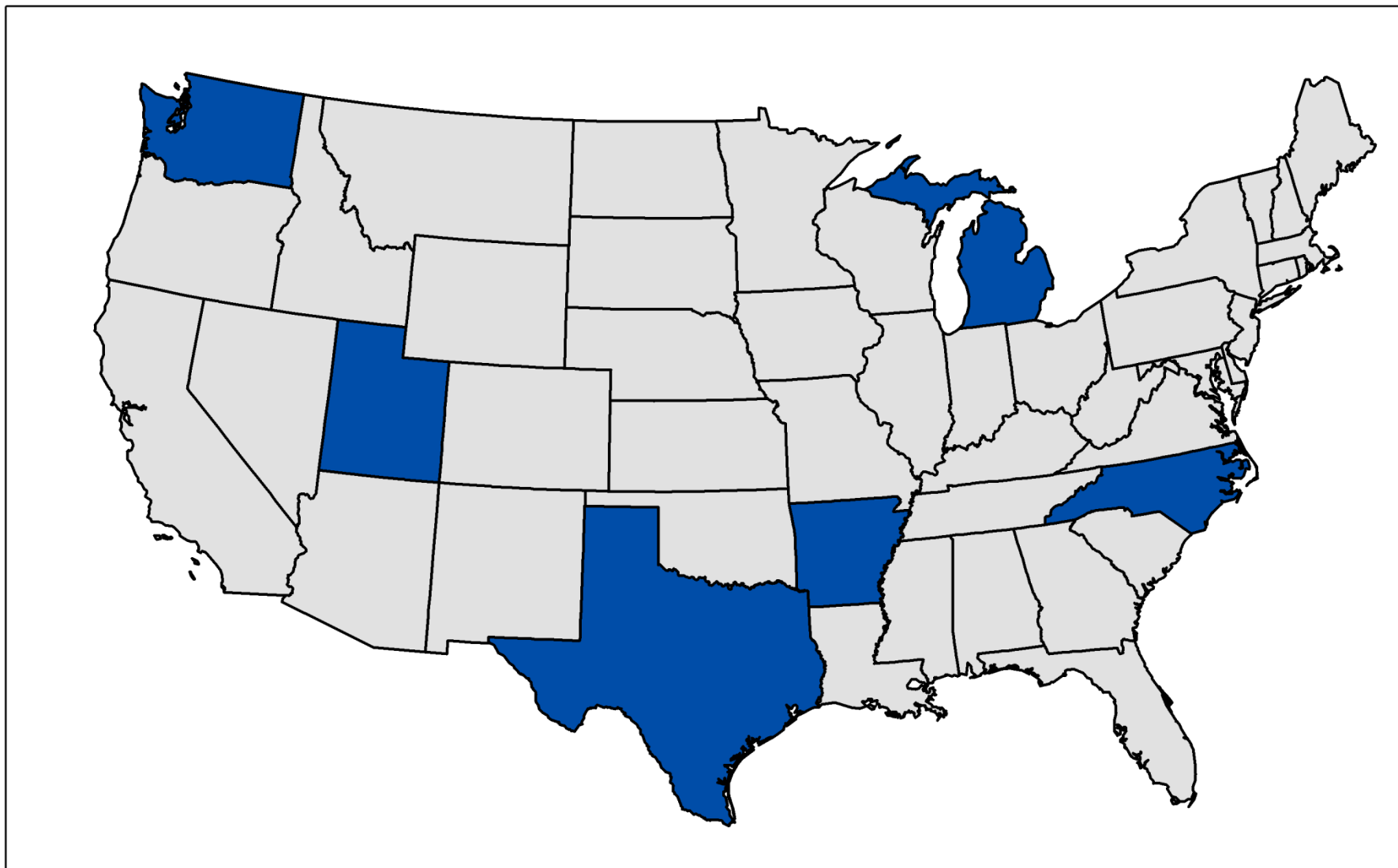
- Identification of genetic causes of tetralogy of Fallot using massively parallel sequencing – Mark Russell, U Michigan
- Evaluation of the Effects of Prenatal Exposure to Non-Essential Heavy Metals on Hearing - Richard Neitzel , U Michigan
- Maternal Social Environment and Newborn Telomere Length - Belinda Needham, U Michigan
- Newborn DNA Methylation Status in Autism and Cerebral Palsy - Ray Bahado Singh, WSU
- DNA Methylation and Congenital Heart Defects – Ray Bahado Singh, WSU
- Molecular Epidemiology of Pediatric Germ Cell Tumors – Jenny Poynter, U Minnesota

Plans for additional research



- Assemble a large population-based birth cohort
- Identify novel cancer predisposition syndromes by determining associations between birth defects and childhood cancer in a registry linkage study
- Develop a family-based cohort of children affected by both birth defects and childhood cancer to determine the molecular characteristics of susceptibility among these individuals
- Interrogate the genomes of children with cancer and birth defects

Genetic Overlap Between Anomalies and Cancer in Kids Study



Available NBS Biological Material

- Blood Spots from July 1984 through April 30, 2010
 - ▣ De-identified, available under waiver of informed consent
 - ▣ *Prior to implementing BioTrust informed consent process*
- May 1, 2010 through March 15, 2015
 - ▣ De-identified, available only with parental consent
 - ▣ *BioTrust parental consent requested at delivery*
- March 16, 2015 forward
 - ▣ NBS Saves Lives Reauthorization Act 2014
 - ▣ Pending HHS rules



States must address:

- Security, confidentiality and privacy concerns
- Appropriate research use
- Public awareness & trust
- Ability for informed parental decision making

It is critical to preserve primary newborn screening goal of detecting children with treatable disorders.



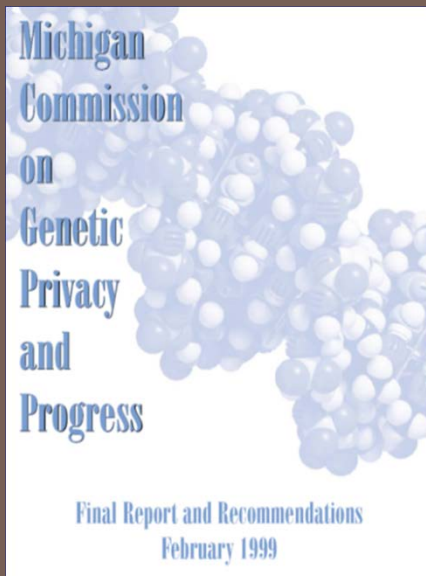
Protect Baby DNA



Citizens Council on Health
www.cchconline.org



www.cnn.com, February 4, 2010



Policies and best practices for DBS storage and use in Michigan have been re-examined and continue to evolve over time.

- 1987: Retention policy 21.5y
- 1999: Governor's Commission recommendations
- 2000: Public health code amended
- 2008: Retention policy -indefinite storage
- 2009: Implementation of BioTrust

NBS Saves Lives Reauthorization Act 2014

- Senate **Changes** (Amendment)
 - Section 12. Informed Consent for Newborn Screening Research
 - Research on newborn dried blood spots *shall be considered research carried out on human subjects* meeting the definition of section 46.102(f)(2) of title 45, Code of Federal Regulations, *for purposes of Federally funded research.*
 - Sections 46.116(c) and 46.116(d) of title 45, Code of Federal Regulations, *shall not apply.*
 - Shall apply only to newborn dried blood spots that were *collected not earlier than 90 days after the date of enactment* of this Act.

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