IMPACT OF PROTOCOL CHANGES IN MICHIGAN NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM ON SCREENING PERFORMANCE METRICS

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ABSTRACT

IMPACT OF PROTOCOL CHANGES IN MICHIGAN NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM ON SCREENING PERFORMANCE METRICS

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Objective: This study was conducted to evaluate changes in newborn screening for congenital hypothyroidism operations in Michigan.

Study Design & Participants: This population-based retrospective cohort analysis includes Michigan resident infants born and screened in Michigan from 1/1/1994 to 6/30/2010. Newborn screening laboratory and follow-up data managed by the Michigan Department of Community Health are used in this study.

Methods: The primary exposure is the method of dried blood spot testing: 1) thyroxine (T4) with backup thyrotropin (TSH) testing, 2) tandem T4 and TSH testing; 3) primary TSH testing without serial testing; and 4) primary TSH testing plus serial testing for births weighing <1,800g. Outcomes of interest include screening performance metrics: detection rate, positive predictive value, false positive rate, sensitivity, and specificity. The proportion of cases later determined to have transient disease is also investigated among those detected since 10/1/2003 that were followed-up after age three years and underwent diagnostic re-evaluation. Logistic regression analysis is used to investigate: a) whether the detection and false positive rates changed significantly as dried blood spot testing methods changed, and b) to investigate predictors of transient CH among cases followed-up and re-evaluated after age three years.

Results: T4 testing is as likely to detect CH as is primary TSH testing without serial testing. Primary TSH testing yields fewer false positive determinations. Primary TSH testing yields fewer false positive determinations. The addition of serial testing among infants born weighing < 1,800g to the

primary TSH testing protocol significantly increased the detection rate; in this period, 14% of detected cases were identified by retest and three of five cases weighing <1,800g were detected by retest. Primary TSH screening is more susceptible to false negative screening determinations and is incapable of detecting the 1-3 cases of central hypothyroidism expected annually in Michigan. Tandem T4 and TSH testing increased the detection rate by 80% and 20% relative to primary T4 backup TSH and primary TSH plus serial testing approaches respectively; however, this approach increased the number of false positives by eight fold relative to primary TSH plus serial testing. At three year follow-up, one of four cases was no longer receiving thyroid hormone medication. One of five cases re-evaluated had stopped treatment without medical supervision.

Discussion: Our results indicate that newborn screening programs should consider tandem T4 and TSH testing or primary TSH plus serial testing for infants at risk of later rising TSH for detecting congenital hypothyroidism; however, a benchmark balance between sensitivity and specificity is necessary to determine the optimal testing strategy. Further efforts are necessary to standardize the process of diagnosis and terminologies used to characterize cases across newborn screening programs to make comparisons between and within programs over time more meaningful; guidelines for newborn screening, pediatricians, and pediatric endocrinologists are necessary to support this effort. Our findings also indicate that long term follow-up should be conducted for all CH cases, not only those eligible for a trial off thyroid hormone supplements, to ensure treatment compliance in hopes of avoiding potential brain damage among cases. As diagnostics and the nomenclature of congenital hypothyroidism are standardized across newborn screening programs, cost-benefit analyses are necessary to support recommended program operations.

DEDICATION

This dissertation is dedicated to my lovely wife, Stephanie, for supporting me through many sleepless nights endured in finishing this work, teaching me every day the true meaning and feeling of love, and immeasurably brightening my existence. I also dedicate this work to my children, Akasha and Cassious, as well as our new baby due to arrive in September, for the endless inspiration they provide. Special thanks also goes to Jack and Lori Moore, my parents-in-law, for their interest in my work, the support they have given, the model they provide as parents, and most importantly the beautiful family they have raised, particularly their amazing daughter, the love of my life, Stephanie. Thanks also to my parents, Kathy Potter, Kim Korzeniewski and his wife also named Kim.

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He even helped me financially to avoid dropping out of school when I had fallen short of a semester's tuition several years ago. It is truly difficult to express how important his role has been and how honored and immeasurably grateful I am to have him as a mentor, role model and friend.

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LIST OF ACCRONYMS

AAP	American Academy of Pediatrics
CH	Congenital Hypothyroidism
CI	Confidence Interval
CLSI	Clinical and Laboratory Standards Institute
DIT	Diiodotyrosine
DOB	Date of Birth
FGR	Fetal Growth Ratio
FN	False Negative
FP	False Positive
g	Grams
HPT	Hypothalamic-Pituitary-Thyroid
IQ	Intelligence Quotient
LBW	Low Birth Weight
LIMS	Laboratory Information Management System
Lost to Follow-up	LTFU
MCIR	Michigan Care Improvement Registry
MDCH	Michigan Department of Community Health
MIT	Monoiodotyrosine
NBS	Newborn Screening
NBW	Normal Birth Weight
NICU	Neonatal Intensive Care Unit
OR	Odds Ratio
PEAC	Pediatric Endocrinology Advisory Committee
SCBU	Sick Child Birthing Unit
Se	Sensitivity
SGA	Small for Gestational Age
Sp	Specificity
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroxine-Binding Globulin
TN	True Negative
TP	True Positive
TPN	Total Parenteral Nutrition
TRH	Thyrotropin Releasing Hormone
TSH	Thyroid Stimulating Hormone
US	United States
VLBW	Very Low Birth Weight

KEY DEFINITIONS

Central Hypothyroidism	characterized by persistently low T4 concentrations and low or normal TSH concentrations, often associated with other pituitary hormone deficiencies
Classic or Primary Hypothyroidism	characterized by persistently low T4 concentrations and elevated TSH concentrations
Confirmed Transient CH rate	Proportion of cases exhibiting normal thyroid function[Number exhibiting normal thyroid function/total number followed-up]
Congenital Hypothyroidism	an umbrella term referring to congenital thyroid disorders often characterized by pathologically low concentrations of T4 that may or may not be accompanied by elevated concentrations of thyroid stimulating hormone (TSH), otherwise known as thyrotropin.
Detection Rate	Number of screens performed to yield 1 detected case [Total Number Screened/Total Number of Cases]
False Positive Rate (FPR)	Number of false positives divided by number absent disease [FP/(FP+TN), or 1-Specificity]
Hyperthyrotropinemia	characterized by normal T4 concentrations and persistently elevated TSH concentrations, often referred to as asymptomatic hypothyroidism
Hypothyroxinemia of Prematurity	characterized by low T4 concentrations and normal TSH concentrations, not associated with central hypothyroidism, common among premature infants, commonly resolves with maturity
Lost to follow-up	the proportion of children not followed-up among those eligible for follow-up[Number not Followed-up/Total Eligible for Follow-up]
Positive Predictive Value (PPV)	Proportion of infants with a positive screen that are confirmed as having CH[TP/(TP+FP)]
Proportion of False Positive Screens (PFP)	Proportion of screens having false positive determinations[FP/Total Screens]
Rate of self-cessation of therapy	Proportion of cases that stopped therapy of their own accord[Number stopped therapy/total number followed-up]
Rate of trial off therapy	Proportion of cases eligible for a trial off therapy that have undergone such a trial[Number trialed/Number followed-up eligible for trial]
Sensitivity (Se)	Proportion with disease that are correctly screened positive[TP/(TP+FN)]
Specificity (Sp)	Proportion absent disease that are correctly screened negative[TN/(FP+TN)]
Suspected Transient CH rate	Proportion of cases followed that are suspected to be transient[Number Untreated at Follow-up/total number followed-up]
Transient Hypothyroidism	characterized by having abnormal screening values (low T4 and elevated TSH) but normal serum T4 and TSH concentrations on a subsequent serum tests at 1 to 2 months of age or later among premature infants

CHAPTER 1: BACKGROUND

Introduction:

Newborn screening (NBS) for congenital hypothyroidism (CH) began in the mid 1970s following the development of a radioimmunoassay capable of measuring thyroxine (T4) in dried blood spotted on filter paper.[1-5] Based on findings from the first million infants screened, the NBS Committee of the American Thyroid Association recommended broad establishment and expansion of NBS programs for CH In 1977.[6] By 1992, it was estimated that 50 million infants were screened annually for CH worldwide.[7] While NBS for CH has been implemented in virtually all industrialized and in many developing nations over the past several decades, there has been a lack of emphasis on assessing and evaluating screening system components.[8] Accordingly, debates persist about the ideal CH screening algorithm, how best to screen for the disease in premature and sick newborns, and which children need particular attention and long term treatment based on the screening results. This study focuses on Michigan NBS for CH and investigates the impact of changes in program operations over time including alterations to dried blood spot testing protocols comprising four distinct screening periods and initiation of long term follow-up of detected cases.

Definition & Physiology of Congenital Hypothyroidism:

CH is often used as an umbrella term referring to congenital thyroid disorders often characterized by pathologically low concentrations of T4 that may or may not be accompanied by elevated concentrations of thyroid stimulating hormone (TSH), otherwise known as thyrotropin. The primary function of the thyroid gland is to combine iodine with the amino acid tyrosine to manufacture thyroid hormones, T4 and triiodothyronine (T3). Iodide is taken into the thyroid follicular cells by an active transport system and then oxidized to iodine by thyroid peroxidase. Next, organification occurs when iodine is attached to tyrosine molecules attached to thyroglobulin,

forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). The coupling of 2 molecules of DIT forms T4. The coupling of one molecule of MIT and one molecule of DIT forms T3. T3 is the metabolically active hormone that is produced primarily by cells when T4 is deiodinated by two deiodinase enzymes in the thyroid gland. While the thyroid gland produces all T4, approximately 80% of T3 is produced through conversion of T4 in various tissues of the body when more T3 is needed. Both T3 and T4 bind to thyroxine-binding globulin (TBG) for transport in the blood. Thyroglobulin, with T4 and T3 attached, is stored in the follicular lumen of the gland. TSH activates the enzymes needed to cleave T4 and T3 from thyroglobulin and also stimulates T4 production..

Thyroid hormones act on processes such as neuronal migration and differentiation, myelination and synaptogenesis which are essential for proper neurodevelopment and are also involved in maintenance of normal physiological function including bone maturation.[9, 10] Thyroid hormone concentrations are regulated by the hypothalamic-pituitary-thyroid (HPT) axis as portrayed in Figure 1.[10] The pituitary gland stimulates the thyroid to produce hormones by releasing TSH. The hypothalamus regulates the pituitary gland in response to low thyroid hormone concentrations (negative feedback) by stimulating it via production of thyrotropin releasing hormone (TRH) to produce TSH. Thus, when the levels of T4 and T3 are low, the hypothalamus secretes TRH which in turn stimulates the pituitary gland to release TSH which then stimulates the thyroid

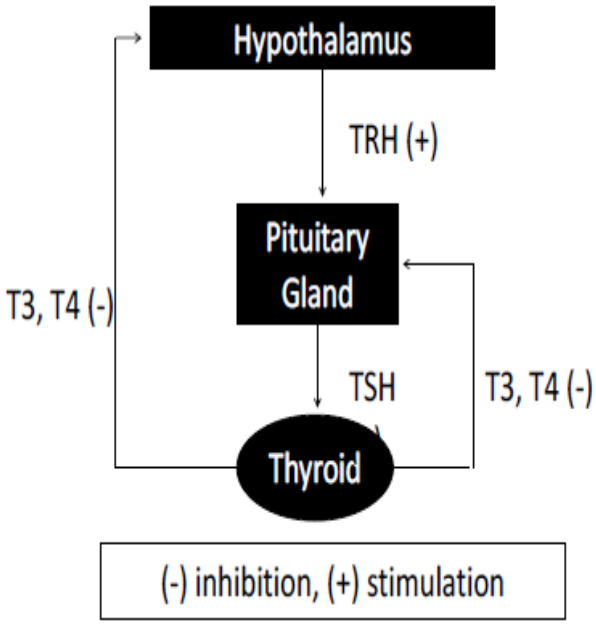

Figure 1: Hypothalamic-Pituitary-Axis

gland to increase secretion of T4.[11] TSH secretion is inhibited by dopamine, somatasotatin and high doses of corticosteroids.

The fetal thyroid is capable of producing thyroid hormone around 10-12 weeks of gestation and blood levels are thought to reach term concentrations by 18-20 weeks of gestation. Prior to 18-20 weeks of gestation, the fetus is dependent on transplacental passage of thyroid hormones; afterwards, in non-hypothyroid fetuses, the fetal HPT axis is believed to function independently of the maternal HPT axis.[12] Hypothyroid fetuses rely on transplacental passage of thyroid hormones throughout gestation.

At birth, full term (gestation $\geq$ 37 weeks) neonates experience a surge of TSH reaching greater than 50 mU/L during the first 24 hours of life as a physiological response to a cold environment followed by a decrease to below 10 mU/L during the first few postnatal weeks.[13] However, many preterm infants (gestation < 37 weeks) and/or sick newborns exhibit weak or no TSH surge at birth due to immaturity of the HPT axis.[14-19] Van Wassenaer et al. examined thyroid hormone concentrations during the first eight weeks of life among 100 infants born at less than 30 weeks gestation and reported that TSH increases from day three onward and from day seven onward in sick and healthy infants respectively and stabilizes after the 28th day life in both groups.[18] Estimates of the frequency of late rising TSH (occurring beyond the first 48 hours of life) range from 1:18,000 to 1:67,226 live births, 1:202 to 1:400 among very premature (gestation < 32 weeks) and/or very low birth weight infants (birth weight < 1,500g).[14, 16, 20-22]

Pathologically low concentrations of thyroid hormone are often associated with underlying structural abnormalities. In iodine sufficient nations, an estimated 85% of CH cases is characterized by thyroid dysgenesis (abnormality in thyroid gland development), the remaining 10%-15% are characterized by dyshormonogenesis (defects in the synthesis of T4) or, in rare cases, by defects in

peripheral thyroid hormone transport, metabolism or action.[23] Thyroid dysgenesis involves ectopia (abnormal formation of thyroid tissue) or aplasia/hypoplasia (full or partial absence of the thyroid gland). Defects involving thyroid hormone transport, metabolism or action most often involve hypopituitarism, the loss of function in an endocrine gland due to failure of the pituitary gland to secrete hormones which stimulate that gland's function; this is sometimes referred to as a 'peripheral' defect in that the problem originates outside of the thyroid.

CH is often sub-classified by distribution of thyroid hormones. Infants with persistently low T4 concentrations and elevated TSH concentrations are referred to as primary or classic CH. Central hypothyroidism refers to infants with persistently low T4 concentrations and low or normal TSH concentrations. Central CH is most often associated with other pituitary hormone deficiencies, particularly in the presence of features such as hypoglycemia or micropenis and undescended testes in males which are associated with growth hormone, ACTH and gonadotropin deficiencies.[24] When T4 concentrations are normal and TSH concentrations are persistently elevated, the disease is referred to as hyperthyrotropinemia or asymptomatic hypothyroidism.[25]

CH is classically defined as a permanent condition requiring lifelong treatment, although transient forms of the disease have also been identified. Yet they remain ill-defined, as recently reviewed by Parks et al.[26] The American Academy of Pediatrics (AAP) defines transient hypothyroidism as abnormal screening values (low T4 and elevated TSH) but normal serum T4 and TSH concentrations on a subsequent serum tests,, although NBS programs apply broad and varying definitions, and many fail to differentiate suspected transient from permanent types of CH.[27] When T4 concentrations are low, TSH concentrations are normal, and central hypothyroidism has been ruled out, the disease is referred to as hypothyroxinemia of prematurity, as it is commonly found among preterm infants and usually resolves with maturity.[28] Transient hypothyroxinemia

has also been reported in term infants and in rare cases the disorder may persist until approximately 10 years of age.[27]

Etiology of Congenital Hypothyroidism:

Globally, the most common cause of thyroid hormone insufficiency during gestation is lack of dietary iodine, referred to as endemic cretinism.[29] Unlike CH, brain damage associated with endemic cretinism likely occurs in utero due to maternal thyroid hormone deficiencies. Iodization of table salt has largely addressed the issue of iodine insufficiency among most developed nations, although recent data suggest dietary iodine intake has decreased in several countries including the US in recent years.[30] While many authors refer to underlying morphologies as etiologies of CH, structural defects lie in the causal pathway of the disease and are more appropriately referred to as mediators. The underlying causes of thyroid dysgenesis and dyshormonogenesis associated with primary permanent CH remain largely unknown; although an estimated 10%-20% of identified cases exhibit genetic etiologic factors including mutation in the TTF-2 gene and mutations in genes encoding transcription factors important in thyroid gland development.[24, 31] The etiology of central CH is similarly unknown, although on rare occasions, isolated genetic defects including mutations in the TSH β subunit or TRH receptor genes have been identified as etiologic factors.[24]

Better recognized are causes of transient CH including transplacental passage of thyrotropin receptor blocking antibodies or antithyroid drugs used to treat maternal hyperthyroidism, iodine deficiency, and iodine excess; on rare occasions transient dyshormonogenesis can also be caused by DUOX2 mutations.[26, 32] Hypothyroxinemia is thought to be caused by prematurity or delayed maturation of the HPT axis, increased TSH response to thyroid releasing hormone, presence of antithyroid antibodies or thyroperoxidase (an enzyme involved in the production of T4 or T3), or thyrotropin receptor gene sequence variations.[33, 34] Dopamine infusion and environmental

chemicals including certain polyhalogenated aromatic hydrocarbons have also been identified as potential causes of transient CH, although the role of environmental chemicals is less clear.[35-43]

Diagnosis of Congenital Hypothyroidism:

Globally, most CH cases are detected clinically, since only an estimated 25%-33% of the overall birth population is screened for the disease due to the lack of NBS programs in many developing nations.[24] Infants with CH usually appear unaffected at birth. Clinical signs associated with CH include gestation beyond 42 weeks, macrosomia, neonatal hyperbilirubinemia lasting more than three weeks, lethargy, feeding difficulties, constipation, umbilical hernia, macroglossia (large or muscular appearing tongue), and cold or mottled skin.[7, 44, 45] CH is also associated with other congenital anomalies including trisomy-21.[46-52] However, clinical signs of CH are not specific to the disease meaning that diagnosis absent NBS is often delayed beyond the first several weeks or months of life. Most industrialized nations use some form of NBS to detect and later diagnose CH.

NBS for CH began in Quebec, Canada in response to reports showing that while children treated within three months of birth developed normally intellectually, only one third of newborns were diagnosed during that period.[53-55] Dussault and Laberge developed a radioimmunoassay for measuring T4 from the eluate of filter paper blood spots in 1971 and early 1972, although initial reports of this work were not received well by the academic community.[56] The first report of their work was published in French in 1973, and in 1974 screening for CH was incorporated with NBS for phenylketonuria (PKU) and tyrosinemia in Quebec in 1974.[57] Dussault et al. soon developed radioimmunoassays to measure TSH and TBG from filter paper blood to reduce the number of false positive results.[58, 59] Initially, most NBS programs in North America, Australia, New Zealand and Israel and some in Europe conducted primary T4 and backup TSH testing among infants having T4 concentrations less than the 10^{th} centile.[5, 60] Most European and Japanese NBS programs

employed a primary TSH test strategy.[61-63] Most NBS make referrals for confirmatory testing based on TSH concentrations relative to age adjusted cutoffs.

While infants with significantly elevated dried blood spot TSH concentrations are expected to have permanent primary CH, confirmatory testing is usually based on serum tests of venipuncture blood samples combined with some measure of binding proteins (i.e., T3 resin uptake) used to differentiate free (active) from total T4.[24, 64] Blood samples for confirmatory testing are ideally obtained around 2-3 weeks of life when the upper range of TSH falls to approximately 10 mU/L. Reference ranges for free T4, total T4 and TSH concentrations measured in serum at 2-4 weeks of life are approximately 10-26 pmol/L, 90-206 nmol/L and less than 10 mU/L respectively.[22] Infants having two or more serum TSH concentrations >20 mU/L are expected to have permanent primary CH.[13] If a defect in thyroid hormone synthesis is suspected, perchlorate washout testing is sometimes performed to test the ability of the thyroid to transform iodine into organically bound iodine.[65] Other tests including scintigraphy and ultrasound are also useful during the process of diagnosing CH.

Evaluation of the thyroid gland via ultrasound imaging and radioisotope scanning is useful in identifying underlying morphologies and differentiating transient from permanent disease. Normal sized and anatomically positioned (eutopic) thyroid glands are more likely among transient conditions.[26] Newborns with permanent CH are most likely to have thyroid gland agenesis, an ectopic gland located along the path of embryonic descent of the thyroid, or a hypoplastic gland, although eutopic thyroid glands are also found among permanent cases of dyshormonogenesis.[26, 66] Isotope scanning is better able to detect ectopic tissue, whereas ultrasound is better able to portray abnormalities of thyroid volume and morphology including thyroid aplasia.[67] Ultrasonography can also identify large thyroid glands, suggestive of dyshormonogenesis.[24] Chang et al. recently compared ultrasound and scintigraphic findings and reported a significant correlation

($p<.001$) between measures of thyroid volume, concluding that use of both scintigraphy and ultrasound is preferable to either test individually. Results of thyroid imaging findings in CH are reported in Table 1.

Table 1: Radionuclide Image and Ultrasonography Findings in Congenital Hypothyroidism (Rastogi & LaFranchi, 2010)

Defect	Radionuclide image	Ultrasonography
Aplasia	No uptake	Absent gland
Hypoplasia	↓uptake	Small, eutopic
Ectopia	↓ uptake, ectopic	Ectopic gland (hypoplastic)
TSH β mutations	No uptake	Eutopic gland (hypoplastic)
TSH receptor inactivating mutation	↓ uptake	Eutopic gland
Trapping error	↓ or no uptake	Eutopic gland
Beyond trapping error	↑ uptake	Eutopic, large gland
Maternal TRB-Ab	↓ or no uptake	Eutopic gland

Imaging findings alone are unable to conclusively differentiate transient from permanent CH as eutopic thyroid glands are found in both scenarios. A trial off therapy consisting of a period during which thyroid hormone supplements are not provided or provided at a significantly lower dose and thyroid function is monitored by measuring TSH and T4 to determine if treatment remains necessary is recommended around age three years for all suspected cases other than those with thyroid aplasia to confirm the diagnosis of permanent CH.[27, 68-70] Infants having a low serum free T4 and elevated TSH concentration at the conclusion of the trial are confirmed as having permanent CH.[24] Some have also suggested that molecular analysis be conducted to identify genetic causes of CH during the process of medical management.[71]

While guidelines exist to assist clinicians in the management of CH, there is no consensus case definition or universal testing strategy applied in diagnosing the disorder.[69, 72] Many diagnosed infants do not undergo thyroid imaging or radioisotope scanning to identify the underlying thyroid morphology because the information gained is not required to manage CH. It is

unknown how many cases undergo therapy cessation around age three years to determine disease permanence due to the lack of long term follow-up in most NBS programs and the absence of pediatric endocrinology clinical guidelines.[26]

Outcomes of Congenital Hypothyroidism:

Pathologically low concentrations of thyroid hormone during critical stages of development can cause severe mental retardation and skeletal growth abnormalities and several studies have also associated CH with deaf-mutism, spastic diplegia and extrapyramidal rigidity.[9, 54, 73-80] Grosse and Van Vliet recently reviewed population based studies of the outcomes of CH prior to the NBS era and concluded that 8%-29% of cases detected clinically (~1:25,000 births) developed intellectual or learning disability as indicated by either low intelligence quotient (IQ) scores or requirement of special schooling.[81] The mean IQ scores observed among clinically detected cases of CH in studies included in their review ranged from 82 to 87, representing a 20-25 point loss in IQ relative to their potential assuming an expected score of 105-110. Gorsse and Van Vliet's review further reported that the percentage of clinically detected cases with height below the 10^{th} centile ranged from 19% to 31%.[81-83] Alternatively, normal development is expected in most CH cases detected by NBS and treated shortly after birth; deleterious outcomes in the context of NBS are associated with maternal thyroid disease, late onset and an inadequate dosage of thyroid hormone substitution, a poor social-economic environment and lack of treatment compliance.[46, 74, 81, 84-97]

Treatment of Congenital Hypothyroidism:

CH is treated by thyroid hormone supplementation with levothyroixne. The initial goal of treatment is to normalize T4 concentrations within two to three weeks and TSH concentrations within one month.[72, 98] Target values during the first year of life are 10-16 μg/dl for serum T4, 18-30 pmol/L for free T4 and less than 5 mU/L for TSH.[27, 99] Initial dosages of levothyroxine

reported in past studies range from 5 to 15 μg/kg/day, although the European Society for Paediatric Endocrinology and the AAP recommend a starting dose of 10-15 mcg/kg/day.[99-101]

Epidemiology of Congenital Hypothyroidism- All Birth Weights

Prior to NBS, the prevalence of CH was thought to range from 1:7,000 to 1:10,000 live births.[1] NBS programs around the world initially reported detection rates ranging from 1:3,000 to 1:4,000 infants screened [102-105], although unexplained international variation in the birth prevalence of CH has been observed. (Table 2)

Table 2: Geographic Variation in Birth prevalence of Congenital Hypothyroidism

First Author	Year	Location	Infants Screened (N)	Cases Detected (N)	Detection rate
Harris[106]	2002	United States	3,655,755	1,608	1: 2,274
Rendon-Macias[107]	2000-2004	Mexico	2,777,292	1,286	1:2,160
Deladoey[108]	1990-2005	Quebec	1,303,341	424	1:3,074
Mikelsaar[109]	1998	Estonia	20,021	7	1:2,860
Ray[110]	1979-1993	Scotland	1,513,600	344	1:4,400
Jones[66]	1994-2003	Scotland	54,473	17	1:3,084
AlJurayyan[111]	1989-1995	Saudi Arabia	1,007,350	306	1:3,292
AlJurayyan[112]	1990-1995	Saudi Arabia, Najran Province	30,810	22	1:1,400
Fernandeziglesias[113]	1995	Spain	91,529	27	1:3,400
Inoue[114]	1979-1990	Japan	270,597	46	1:5,900
Connelly[115]	1977-1997	Victoria, Australia	704,723	199	1:3,541
Skordis[116]	1990-200	Cypriot, Greece	109,800	61	1:1,800
Stranieri[117]	2003-2004	Brazil	66,337	7	1:9,448
Ordookhani[118]	1998-2002	Iran	35,067	25	1:1,403

Within the US, the birth prevalence of CH also varies considerably by state as depicted in Figure 2. NBS programs in the US have recently reported an increase in the birth prevalence of CH from 1:3,985 in 1987 to 1:2,274 in 2002 not fully explained by changes in laboratory methods or potential misclassification of transient disease.[26, 119-121] Analysis of US data from 1991-2000 revealed an increase in the birth prevalence of CH only among white infants, although state specific

differences by sex, race, ethnicity and birth weight have been reported.[122] California observed an increase in the birth prevalence of CH among Hispanic newborns from 2000-2007. Texas observed an increase among males that varied by race and ethnicity from 1992-2006. The increase in the birth prevalence of CH observed in Massachusetts was primarily among low birth weight newborns who had a delayed rise in TSH.

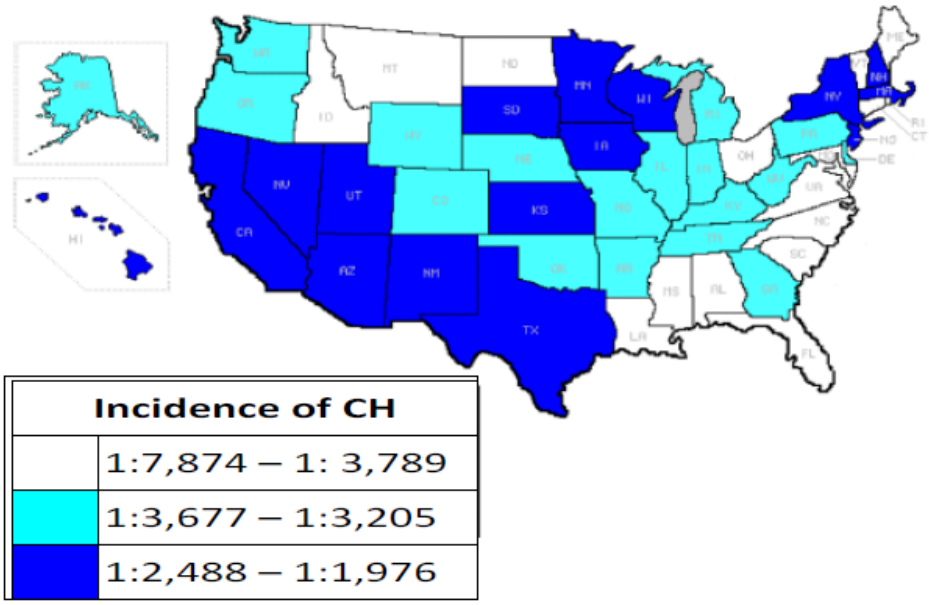

Figure 2: Birth Prevalence of Congenital Hypothyroidism in the United States, 1987-2002 (Harris et al., 2007) [For interpretation of the references to color in this and all other figures, the reader is referred to the electronic version of this dissertation]

Central CH is less common than primary CH; Dutch studies report a birth prevalence of central CH of 1:20,263 infants (95% CI: 1:12,976-1:33,654).[123, 124] The National Newborn Screening Information System reports an overall US birth prevalence of central CH of 1:158,268, although many NBS programs are either not designed to detect the disease or fail to differentiate it from primary CH making the estimate invalid.[125] It is similarly difficult to determine the birth prevalence of transient CH since definitions and estimates vary significantly by geographic location.

Kempers et al.'s analysis of Dutch NBS data revealed a birth prevalence of transient CH of 1:12,000.[126] Victorian NBS reports a transient CH detection rate of 1:23,750.[127] An earlier Canadian follow-up study of 56 CH cases estimated only 1%-2% of cases detected by NBS are transient.[128] Two Iranian studies reported the birth prevalence of transient CH to range from 1:1,114 to 1:5,845 infants screened.[129, 130] Gaudino et al.'s analysis of CH cases with gland in situ detected by a French NBS program revealed 38% were transient, amounting to a birth prevalence of 1:10,383.[131] However, if a case definition involving an initial positive test followed by a subsequent negative test result were used, the birth prevalence of transient CH would be significantly greater, particularly among premature infants screened by a primary T4 testing method given their high rate of false positive screening determinations.

The birth prevalence of transient CH in the US is less clear due to the lack of long-term follow-up. Kemper et al. analyzed MarketScan Commercial Claims and Encounters data and MarketScan Multi-State Medicaid data from 2001-2006 and revealed that 38% of more than 700 CH cases no longer exhibited claims for thyroid replacement therapy after 36 months and may have represented transient CH.[132] Texas NBS identified only four instances of a change from permanent to transient CH from 2004-2006, although their study relied on passive reporting by pediatric endocrinologists to determine transient etiology.[26] Eugster et al.'s clinic based follow-up study of 33 CH cases detected by Indiana NBS who either had anatomically normal thyroid glands on imaging, no thyroid imaging, or relatively mild T4 and TSH concentration abnormalities despite imaging results indicating thyroid agenesis revealed that 36% had a transient state.[68]

Similar follow-up studies conducted outside of the US that did not relate observed cases to a population base report varying estimates of the proportion of transient versus permanent CH detected by NBS. Three studies of children with CH having thyroid glands in situ conducted in Italy revealed varying distributions of transient disease. Corbetta et al.'s analysis of 59 CH cases revealed

22% were transient upon three year follow-up.[133] Costa et al.'s clinic based follow-up study of 23 infants revealed that nearly half were transient.[134] Weber et al's study determined only one of 31 CH cases evaluated were transient.[135] Nair et al.'s clinic based follow-up study of 36 CH cases with gland in situ detected by an Indian NBS program reported that half were transient.[136] Tamam et al.'s follow-up study of 182 cases detected by Turkish NBS revealed that 30% had transient CH.[137] In the largest follow-up study identified during comprehensive literature review, Panaoutsopoulos et al. reported that 24 of 413 cases detected by Greek NBS were determined to be transient at three year follow-up.[138] More recently, a Chinese study reviewed by Parks et al. followed up157 CH cases who required low maintenance levels of levothyroxine around age three years reported that 90% of the children's TSH concentrations eventually normalized.[139]

Demographic & Perinatal Differences in Birth Prevalence

Harris et al.'s report of New York state's NBS program findings indicates that CH is more common among white infants, those born earlier in gestation and/or at lower birth weights, multiparous infants, females and among infants born to older mothers relative to non-white infants, those born later in gestation and/or at greater birth weights, singleton infants, males and infants born to younger mothers respectively.[106] (Table 3) The birth prevalence is particularly elevated among LBW and/or premature infants. Historically, CH has been characterized by sexual dimorphism with the ratio of diagnosed females to males being 2:1; this ratio is greater among infants diagnosed specifically with thyroid aplasia or ectopy.[32, 46, 66, 108, 140, 141] An Italian NBS study reported female to male ratios of 2:1 and 0.5:1 among CH cases having thyroid dysgenesis and those diagnosed as having transient hypothyroidism respectively.[46] A Scottish NBS study also reported a female to male sex ratios of 2:1 and 1:1 among infants diagnosed with definite and transient hypothyroidism respectively.[66] Parks et al. recently analyzed US data from the National Newborn Screening and Genetics Resource Center for the period 1993-2000 and reported

a female to male ratio of 1.56:1, suggesting that misclassification of transient disease as permanent CH likely attenuated the ratio.[26] No US study has evaluated the sex ratio among transient relative to permanent CH cases identified by NBS due to the lack of long term follow-up.

Table 3: Congenital Hypothyroidism Detection by Selected Population Segment, New York State Newborn Screening, 2000-2003 (Harris & Pass, 2007)

Population Segment		Number of infants Screened (N)	Number of infants Diagnosed (N)	Detection Rate
Gender	Male	551,974	313	1: 1,763
	Female	520,271	325	1: 1,601
Race/Hispanic Ethnicity	Asian	59,987	59	1: 1,017
	Hispanic	204,293	131	1: 1,559
	White	551,701	304	1: 1,815
	Blacks	192,074	101	1: 1,902
Single vs. multiple births	Single	1,025,547	581	1: 1,765
	Twins	42,914	49	1: 876
	Triplets	4022	7	1: 575
Birth weight	<1500 g	39,086	28	1: 1,396
	1500 to <2500 g	78,225	92	1: 850
	P2500 g	954,454	518	1: 1,843
Mother's age	<20 years	80,251	45	1: 1,783
	20–29 years	481,213	285	1: 1,688
	30–39 years	464,420	277	1: 1,677
	>39 years	41,168	31	1: 1,328
Total		1,072,784	638	1: 1,681

Controversies in Newborn Screening for Congenital Hypothyroidism:

After more than 30 years of operation, a plethora of controversies persist about how to conduct many of the components of NBS for CH including screening, diagnosis, treatment/management, evaluation and long-term follow-up.[65, 142, 143] NBS programs employ

various screening methods and differ in their definitions of CH and its sub-classifications, as well as in the diagnosis and management of newborns with positive screening results (i.e., whether ultrasound or other tests are used). NBS programs also collect and report different types of information about diagnosed cases, varying by how long they follow identified cases and whether they play a role in confirming disease permanence.[26, 65, 121] This is in part due to the lack of quality assurance activities or comparative effectiveness evaluation involving other than NBS laboratory operations.[8, 144, 145] Guidelines have been published including those of the Council of Regional Networks for Genetic Services illustrating the need for cost-effectiveness evaluation and high quality NBS operations[65], although few studies demonstrating cost-effectiveness and/or quality have been published. Therrell et al. recently (2010) published the NBS Performance Evaluation Assessment Scheme to outline high quality indicators, although it is unknown whether any existing NBS program exemplifies high performance on each of the metrics.[8] Absent consistent evidence of ideal NBS operations, inter-program variation persists as do questions about how NBS should operate, particularly in regard to CH. Questions remain about dried blood spot testing methods including whether primary TSH, primary T4, or a combination of both is the ideal strategy. Controversy exists about whether serial testing is necessary to detect CH among infants at risk for later rising TSH concentrations. Questions also remain about which infants benefit from thyroid hormone treatment, how long some cases should be treated and what this means in regard to NBS program operations. Furthermore, specific pediatric endocrinology clinical guidelines are needed in addition to improvement in screening methods.

Dried blood spot testing for Congenital Hypothyroidism:

Initially, TSH testing methods were thought to be more specific and less sensitive in detecting CH relative to the primary T4 testing strategy.[56] While the sensitivity of TSH assays improved over time, their primary detractions are: a) an inability to detect rare cases of central CH

having low T4 and normal TSH concentrations, and b) an inability to detect infants having a late rise in TSH occurring beyond the time of initial NBS specimen collection. While T4 testing methods are capable of detecting some but not all cases of central CH and are not impacted by late rising TSH so long as referrals for confirmatory testing are made based on T4 alone, they also detect disorders other than primary CH including thyroid-binding-globulin deficiency and hypothyroxinemia of prematurity which inflates the number of false positive screening results. Further, in T4/TSH testing programs, 90% of infants do not receive a TSH screen meaning infants with normal T4 and elevated TSH concentrations are not referred for confirmatory testing. The primary detraction associated with tandem T4 and TSH testing for all infants is the additional associated costs of using two methods, although little evidence of cost-effectiveness, or lack thereof, has been published.[146]

The debate over whether T4 or TSH testing methods or a combination of both are preferable has persisted since the advent of NBS for CH. Shortly after developing the first TSH assay used in NBS for CH in Quebec, Canada, Dussault and Morissette simultaneously measured T4 and TSH concentrations from 93,000 consecutive filter paper blood samples over a six month period and reported that the T4 assay had greater precision and reproducibility than either of the two TSH kits commercially available at the time.[147] Their study reported similar frequencies of detected cases and false negative results for each method although one infant with secondary hypothyroidism was detected by the T4 and not the TSH testing method. Mandel et al. conducted a retrospective analysis of infants born in Massachusetts from 1993-1996 who underwent both T4 and TSH testing for CH and concluded that 13% of cases were not detected by the initial TSH screen due to delayed rise in TSH.[22] More recently, Zamboni et al. investigated detection of CH during a period of tandem TSH and T4 testing for all infants in northeast Italy from 1989-2001 (N= 745,258) and reported that an additional 21 CH cases detected (1:35,485 infants screened) via primary T4 testing would have been missed had primary TSH testing been the only method employed.[148]

Cases detected by the T4 method and missed by the TSH method included four cases of central CH and 17 diagnosed as primary CH with delayed rise in TSH within the second month of life. Zamboni et al. also noted that 10 cases of central CH were not detected by either T4 or primary TSH screening methods.

Alternatively, Wang et al. analyzed receiver operating characteristic (ROC) curves of primary T4 and primary TSH testing methods among 2,198 apparently healthy infant and 117 primary CH patient samples.[149] Their study reported a preferable area under the ROC curve for primary TSH testing relative to T4 backup TSH testing methods and estimated that approximately 8% of CH cases misclassified by T4 backup TSH testing strategy as 'normal' are appropriately detected by primary TSH testing. Wang et al. noted similar results from prior investigations in Oregon, Texas and Missouri in which 4%-10% of CH cases identified by the primary TSH screening method would have been missed by T4 backup TSH testing strategies.[150-152] Pass and Carmago report that 131 NBS programs worldwide employ a primary TSH testing strategy and 75 use the T4 backup TSH method.[31] However, in the US, most NBS programs employ a T4 backup TSH testing method, although several have recently switched to a primary TSH testing strategy or a combined T4 and TSH testing method for all infants screened to detect CH.[153]

The impact of serial testing protocols must also be considered in comparing dried blood spot testing protocols used in NBS for CH. Few NBS programs in the US make referrals for confirmatory testing based on low T4 concentrations alone, meaning most suffer from an inability to detect CH among newborns having late rising TSH in initial blood specimens collected during the first few days of life.[123] Serial testing protocols involve retesting selected infants later in life to account for difficulties in NBS among premature and/or sick newborns; however, there is no universally accepted method for serial NBS. In 2009, the Clinical and Laboratory Standards Institute (CLSI) published a guideline for NBS for preterm, LBW and sick newborns recommending a first

screen upon admission to a sick child birthing unit (SCBU), again at 48-72 hours of life, and once more at discharge or day 28 of life; the latter screen is indicated primarily for infants [I assume born] younger than 34 weeks and/or weighing <2,000g.[154] While the CLSI guideline states that their recommendations "..provide the most reliable screening for the infant requiring the fewest specimens possible..(pg.19)", there is little evidence supporting this statement. Prior studies of serial testing protocols have applied both varying inclusion criteria and different testing regiments and no study identified during comprehensive literature review objectively compared different serial testing protocols.

Mandel et al.'s study of tandem T4 and TSH testing among Massachusetts infants born in 1993-1996 retested those with low initial T4 concentrations at two weeks of life or at discharge. Their study identified 13% of all cases across all birth weights after the initial screen; of those detected, 4 were normal birth weight (NBW- ≥2,500g), 4 were low birth weight (LBW - <2,500g), and 10 were very low birth weight (VLBW- < 1,500g).[22] (Table 4) Larson et al. analyzed data from the New England combined T4 and TSH testing NBS program in which all infants born weighing less than 1,500g were retested at 2, 6 and 10 weeks of age or until reaching a weight of 1,500g; infants admitted to the neonatal intensive care unit (NICU) were also retested at two weeks of life.[21] Their study reported that 1:400 VLBW and 1:75,000 non-VLBW infants were diagnosed as CH with delayed TSH elevation. Similar results have been reported outside of the US.

Table 4: Birth Prevalence of Atypical Hypothyroidism (low T4 & late rising TSH) by Birth Weight, Massachusetts Newborn Screening, 1993-1996, (Mandel et al., 2000)

Birth Weight	Total Births	Atypical CH	Birth prevalence
NBW (>2,500g)	311,281	4	1: 77820
LBW (1,500-2,499g)	16,899	4	1: 4225
VLBW (<1,500g)	3,238	10	1: 324

Silva et al. recently analyzed data from a Brazilian NBS program that employed a primary TSH testing method and retested dried blood spot samples collected on the 5th, 10th and 30th days

of life from newborns born at gestational ages less than 32 weeks and/or those that were born VLBW from 2004-2006. Their study reported that 66% of TSH elevations were detected after the first screen and that only one of 11 cases was detected on the initial screen of blood samples conducted around the 5th day of life.[155] Tylek-Lemanska et al. evaluated data from a Polish NBS program employing a primary TSH testing method with repeat testing after four weeks for LBW infants and identified one case of elevated TSH (>10 mlU/L) per 202 LBW infants retested after four weeks of age; of those identified as having elevated TSH, 84% were treated.[16] Alternatively, Vincent et al. analyzed Quebec NBS data from 1993-1994 when tandem T4 and TSH screening methods were used and repeat NBS was conducted for all VLBW infants and concluded that serial testing was unnecessary based on their finding of a single case of late rising TSH later diagnosed as CH.[19] However, Vincent et al.'s study was under-powered (n=465) to detect CH among children having a late rise in TSH and their findings were likely impacted by delayed initiation of NBS.

Madison and LaFranchi reviewed the overall controversies regarding T4 versus TSH screening approaches and reported that while both methods detect 98%-100% of cases, the proportion of false positive screening results (calculated as the number of false positive results divided by the total number of screens and often referred to as the false positive rate in NBS) was significantly greater in T4 screening programs (1.44%) compared to TSH screening programs (0.45%).[156] Alternatively, Hertzberg et al. noted that during 1991-2000, US laboratories that used TSH assays reported a 24% greater birth prevalence of CH than those that used T4 assays suggesting greater sensitivity for primary TSH testing protocols.[121] Pass and Neto compared screening performance metrics among US NBS programs employing four separate protocols and noted significant variation in each, both between and within protocol groupings.[31] (Table 5) While it is relatively well understood that TSH testing for CH yields fewer false positive screening results than T4 testing strategies, the issue of sensitivity is less clear. Absent a clear and consistently

applied operational case definition, it is difficult to compare the birth prevalence of CH generated by different NBS programs or within the same program over time.

Early studies that observed equivalent sensitivity of T4 and TSH testing strategies reported detection rates ranging from 1:3,000 to 1:7,000, suggesting that they applied a classical CH case definition.[147, 148] Studies that report increased sensitivity via application of primary TSH testing, serial testing methods or reduced initial cutoff values have noted elevated detection rates (~1:2,000) suggesting that they likely include milder forms of CH, particularly HT or subclinical CH, although many NBS programs fail to differentiate HT from primary CH making it difficult to validate this assumption.[26, 133, 157-159] It remains controversial whether detection of HT or subclinical hypothyroidism is a useful application of NBS as it is unclear if these cases benefit from treatment. Thus, it is difficult to weigh the benefit of increased sensitivity associated with different dried blood spot testing protocols that identify mild cases of CH.

New methods of detecting CH in dried blood spots have also been developed and some are currently used in Europe. In 2009, Chace et al. reported a method of measuring T4 in dried blood spots using tandem mass spectrometry, an extremely cost-effective method of testing single blood spots for multiple conditions.[160] Similarly, Pass and Neto recently reported development of multiplex systems capable of simultaneously measuring T4, TSH, free T4 and TBG.[31] Some programs are also employing bioluminescence enzyme-linked immunosorbent assays to test TSH in dried blood spots.[161] Others have suggested that TRH be tested in NBS for CH; however, little evidence of the comparative effectiveness of new strategies relative to traditional testing methods has been reported.[162, 163]

Treatment for Congenital Hypothyroidism

The AAP currently recommends treating HT patients if the condition persists after six weeks of age, although little evidence exists about the cognitive outcomes of permanent or transient forms

of the disease.[27, 164, 165] A Swedish retrospective study identified six children with untreated subclinical CH by analyzing dried blood spots collected during the first week of life for NBS for PKU and tested them using the Griffiths test of developmental quotient at age five years.[166]

Table 5: Screening Performance Metrics, United States, 2006 (Pass & Neto, 2009)

Protocol/State	Infants Screened	Screened Positive		Dx Cases	PPV	Detection rate (1:)	FPR	
		N	%				N	%
T4 backup TSH								
Arizona	98,605	1141	1.2	0	N/A	N/A	1141	1.2
Colorado	69974	296	0.4	19	6.4	3683	277	0.4
Massachusetts	73156	981	1.3	36	3.7	2032	945	1.3
Indiana	89,888	1849	2	28	1.6	3210	1821	2.0
New York^	247,901	4539	1.8	217	5.3	1037	4300	1.7
Texas	394,629	7688	1.9	239	2.8	1819	7451	1.9
New Jersey	111,290	2648	2.3	79	2.9	1408	2569	2.3
TSH backup T4								
Missouri	44,621	123	0.3	16	13	2788	107	0.2
Oklahoma	51,126	39	0.07	15	38.5	3408	24	0.0
Oregon	46,881	990	2.1	23	2.3	2086	967	2.1
Virginia	104,475	2513	2.4	38	1.5	2749	2475	2.4
T4 and TSH								
West Virginia	21,356	883	1.3	24	2.7	889	465	2.2
Georgia	145,074	3326	2.3	26	0.8	5580	3300	2.3
Kansas	41,293	849	2.1	40	4.7	1032	309	0.7
Louisiana	61,456	524	0.8	16	3	3849	508	0.8
South Carolina	55,530	1529	2.8	27	1.8	2057	1502	2.7
TSH only								
Arizona	38,845	1546	3.9	13	0.8	2984	1533	3.9
Iowa	39,529	629	1.5	30	4.8	1318	588	1.5
New Mexico	28,538	196	0.6	15	7.6	1902	181	0.6
Minnesota	72,278	191	0.3	35	18.3	2605	159	0.2
California	656,090	789	0.1	301	38.2	1847	488	0.1

Note: PPV= Positive Predictive Value; Dx= Diagnosed; ^=2005 data reported; % represents proportion of total screens. Table modified from Pass & Neto, 2009 version.

None of the children with subclinical CH had an IQ below 70, nor did any require special education services; however, they had an average decrement of about 7 IQ points and also exhibited a greater frequency of behavioral problems compared to six euthyroid children. Similarly, Azizi et al.'s historical cohort study comparing global intelligence and psychomotor performance at age 9 years among 19 children having transient hyperthyrotropinemia relative to euthyroid children born at the same time reported an 8 point decrement in mean IQ among affected children.[167] Leonardi et al. followed-up 44 newborns transient hyperthyrotropinemia cases that did not receive treatment after approximately 5 years of age and reported that 31% had subclinical hypothyroidism.[168] McDermott and Ridgway's review of adult onset hyperthyrotropinemia concluded that treatment was both beneficial and cost-effective, yet these findings are not generalizable to newborns.[169]

Alternatively, several other small studies have reported normal mental and physical development among untreated HT cases.[170-173] Miki et al. reported normal mental and physical development among 16 cases of transient hyperthyrotropinemia, yet identified signs of mild pituitary-thyroid dysfunction in later childhood.[171] Cody et al. conducted a retrospective study of children with hyperthyrotropinemia attending a single clinic over a 20 year period; all of the children had normal growth and development yet only one child was treated at age one year, four had a transient form of the disease which resolved within 3-18 months, and three continued to have persistently elevated TSH concentrations at ages 5, 9 and 17 years.[172] Kohler et al. re-evaluated 61 children with transient neonatal elevations of TSH and reported that all had normal thyroid function and physical development at ages 6-14 years.[173] Several investigators have also reported potential harm associated with treatment of hyperthyrotropinemia patients. Zung et al. conducted a multicenter study of transient (n=18) and persistent (n=25) hyperthyrotropinemia patients and reported that 79% and 55% respectively experienced elevated concentrations of free T4 during treatment, concluding that iatrogenic hyperthyroidism was an issue of concern.[25] An earlier

follow-up study of 36 hyperthyrotropinemia cases similarly noted that treatment was stopped in three children due to iatrogenic hyperthyroidism.[174] Salerno et al.'s study of 30 young adults with CH detected by NBS also raised the issue of cardiovascular abnormalities potentially related to long-term levothyroxine therapy relative to age and sex matched controls, although further study is necessary.[175]

It is also unclear whether cases of hypothyroxinemia should be treated. While NBS programs have traditionally considered positive screening results associated with hypothyroxinemia of prematurity as false positives, evidence suggests poor outcomes and a potential benefit from treatment for such cases. Reuss et al. reported that after adjustment for gestational age and other perinatal and neonatal factors the odds of disabling cerebral palsy were more than fourfold greater (OR 4.4; CI: 1-18.6) and the mental-development scores were nearly 7 points less among children who had severe hypothyroxinemia, defined as blood T4 values greater than 2.6 standard deviations below the mean for New Jersey newborns, compared to those who did not have the disease.[176] Ongoing research is investigating whether premature infants suffering from hypothyroxinemia benefit from thyroid hormone supplementation.[70, 177] While further research is ongoing to assess the long-term neurodevelopmental effects of treatment, if the results determine benefit then hypothyroxinemia may warrant treatment and management in the context of NBS.

It is clear that primary CH requires lifelong treatment, although debate persists about the ideal initial dosage. Higher doses (10-15 μg/kg/day) of levothyroxine have been associated with a quicker time to normalize thyroid hormone concentrations (within 3 weeks) compared to 8 μg/kg/day (within 6-8weeks), although the association between higher initial dosage and cognitive outcome remains controversial.[178-180] Higher doses have also been associated with hyperactivity, delinquency, aggression and poorer attention in school aged children.[180, 181] Ng et al. recently published a Cochrane review of high versus low dose of initial thyroid hormone replacement for CH

and concluded that there is inadequate evidence to suggest that a high doses are more beneficial.[182] However, the single trial (published in two parts) that met Ng et al.'s inclusion criteria reported favorable outcomes associated with higher levothyroxine starting dose including earlier thyroid hormone normalization and improved full scale intelligence quotient, although adverse effects were not reported.[183, 184] Determination of whether certain types of CH should be treated or which dosages are ideal requires long term follow-up.

Long Term Follow-Up and Confirmation of Disease Permanence

While long term follow-up of cases detected by NBS has received progressively more attention over the past decade, few programs are designed to follow children beyond the first few months of life.[26, 143, 185] Accordingly, it is unknown whether many CH cases detected by NBS are permanent considering that few have documented therapy cessation trials as recommended. Texas NBS relies on passive reporting by pediatric endocrinologists to monitor changes in the diagnosis of CH from permanent to transient, although less than a quarter of cases are followed up to age three years.[26] Indiana NBS reports following up CH cases whom a permanent requirement for exogenous thyroid hormone has not been established and conducting trials of therapy cessation after age three years, although no information on the proportion of eligible cases followed has been published.[186] Three year follow-up and therapy cessation trials to confirm the diagnosis of permanent CH appear more common outside of the US, although few programs, if any, do so in a standardized manner and achieve follow-up of a majority of detected cases.[118, 129, 133, 134, 136]

There is no clear standard for conducting treatment cessation trials or interpreting their results to confirm permanence of CH. The duration of treatment cessation varies from 3-4 weeks to 10 months among the few published studies and the frequency and timing of follow-up thereafter among children whose thyroid function normalizes after cessation of thyroid hormone therapy also varies.[68, 128, 139] The AAP briefly reports that therapy cessation should be conducted for CH

cases after age three years for 30 days if no permanent etiology was found and no increase in TSH was observed after the newborn period, yet the guideline cites only a single study conducted by Eugster et al.[27] Eugster et al. advise a more rigorous protocol for confirming CH permanence including: a) a trial off therapy for four weeks after age three for cases without an identified permanent cause; b) after 4 weeks, re-measurement of thyroid hormone concentrations and conduct of thyroid ultrasounds; c) follow-up of abnormal ultrasound results with a Te-99m thyroid scan and follow-up of abnormal thyroid function tests with a perchlorate washout test; and follow-up of children with normal results for an additional 12 months.[68]

The concept of long term follow-up in the context of NBS is also expanding beyond the first few years of life. The US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children defines long term follow-up as providing assurance and provision of quality chronic disease management, condition-specific treatment, and age-appropriate preventive care throughout the lifespan of affected individuals through coordination of a medical home, evidence-based treatment, continuous quality improvement and new knowledge discovery.[143] However, a system demonstrating successful long term follow-up across the lifespan has yet to be realized and many physicians may be unprepared to assist in managing follow-up care for children with positive NBS results, suggesting an even greater need for NBS programs to coordinate such care.[187]

CHAPTER 2 METHODS

Study Design & Participants:

In this dissertation, a population-based retrospective cohort design is applied in studying outcomes and implications of changes in MI NBS for CH program operations from 1/1/1994-6/30/2010; the primary exposure of interest is the method of dried blood spot testing defined based on infant date of birth (DOB) as follows: 1) T4 backup TSH testing (DOB: 1/1/1994-12/31/1997), 2) tandem T4 & TSH testing for all infants, no serial testing (DOB: 1/1/1998-9/30/2003); 3) primary TSH testing, no serial testing (DOB: 10/1/2003-2/28/2007); 4) primary TSH testing, serial testing for births weighing <1,800g (DOB: 3/1/2007-6/30/2010). MI resident infants born and screened in MI are included in this study; out-of-state infants born within the state are followed-up and diagnosed elsewhere and are accordingly excluded from consideration. The period of observation is restricted to beyond 1994 due to inadequate availability of data capable of representing the period 1977-1993. Results of the overall comparative analysis are reported in chapter 3.

Two sub-cohorts are also studied. First, in sub-cohort 1, outcomes of serial testing for CH are investigated among children born weighing less than 1,800g during primary TSH testing periods (DOB: 10/1/2003- 6/30/2010); results are reported in chapter 4. Second, in sub-cohort 2, the proportion of cases later determined transient is investigated among those detected since 2004 and followed-up after age three years; this cohort includes followed cases whose clinician either engaged in diagnostic re-evaluation or reported why they had not or would not conduct a diagnostic re-evaluation (i.e., if thyroid imaging was indicative of permanent disease). Cases that were followed-up but did not undergo diagnostic re-evaluation for a specified reason were excluded from sub-cohort 2 because it was unable to be determined whether the case experienced transient or permanent CH.

Results of the sub-cohort 2 analysis are reported in chapter 5. Chapter 6 provides conclusions and details future directions focusing on the need for additional research and program changes based on our findings.

Research Questions & Hypotheses:

R.1 Do NBS for CH performance metrics (Detection Rate, False Positive Rate (FPR), False Negative Rate (FNR), Positive Predictive Value (PPV), Sensitivity, and Specificity) differ during four periods defined by method of dried blood spot testing as follows: T4 backup TSH testing (DOB: 1/1/1994-12/31/1997); tandem T4 & TSH testing for all infants, no serial testing (1/1/1998-9/30/2003); primary TSH testing, no serial testing (10/1/2003-2/28/2007); primary TSH testing, serial testing for births weighing <1,800g (3/1/2007-6/30/2010)?

H1.a: During tandem T4 and TSH testing, the T4 screen will have greater sensitivity and less specificity compared to the TSH screen.

H1.b: The majority of false positive screening determinations resulting from the initial T4 screen will be observed among LBW and/or premature infants.

H1.c: Tandem T4 and TSH testing will have greater sensitivity and less specificity than both primary TSH testing protocols.

H1.d: The FNR will be greater during primary TSH testing periods relative to the tandem TSH and T4 testing period.

H1.e: Sensitivity will be greater and specificity will be lesser during the primary TSH plus serial testing period compared to the primary TSH testing absent serial testing period among the overall population and among births weighing < 1,800g.

H1.f: Among primary TSH testing periods, fewer cases will be detected among births weighing 1,800g-2,499g after the addition of serial testing among births weighing < 1,800g.

R.2 Are more cases of central hypothyroidism detected in Michigan during primary T4 testing periods compared to the primary TSH testing absent T4 testing periods?

H2: T4 testing will detect a greater number of central hypothyroidism cases than primary TSH testing.

R.3 Do diagnostic re-evaluation methods differ by physician and do they adhere to guidelines published by the AAP?

H3: Child's age at time of diagnostic re-evaluation, duration of time off treatment, whether or not treatment is stopped or dosage reduced, and/or reason for not conducting a trial off medication during diagnostic re-evaluation will differ by physician.

R.4 At what rate to CH cases stop taking thyroid hormone medication without medical supervision?

H4: Greater the 10% of cases' treatment will be stopped absent medical supervision.

R.7 Do results of medication cessation (confirmed transient or permanent CH) differ by whether treatment was stopped with or without medical supervision?

H7: Cases whose treatment is stopped without medical supervision will be more likely to be determined transient CH compared to those whose treatment was stopped under medical supervision during diagnostic re-evaluation.

R.8 Among detected cases, how many are later determined to have had transient CH?

H8: Greater than 30% of cases whose diagnosis is re-evaluated will be determined to have had transient CH.

R.9 Do initial TSH and retest analyte concentrations and demographic/perinatal characteristics differ among cases determined to have transient CH compared to those considered to have permanent CH?

H9: Cases considered to have had transient CH will have lesser initial and retest analyte concentrations and will be more likely to be: black, born LBS and/or premature, small for gestational age (SGA), a twin birth and/or admitted to the NICU relative to cases initially detected by the first screen.

Newborn Screening for Congenital Hypothyroidism in Michigan:

NBS began in MI in 1965 shortly after Dr. Robert Guthrie developed a bacterial inhibition assay to detect PKU in newborn blood spotted on filter paper. The program expanded to include screening for CH in 1977 as recommended by the American Thyroid Association. NBS for CH and several other conditions was mandated in Michigan in 1987 by Public Act 14 which also designated the state laboratory as the sole testing facility and set a fee to fund the program along with additional components including follow-up, medical management and quality assurance. The program, conducted by the Michigan Department of Community Health (MDCH), includes the state laboratory and Follow-up Program which contracts four medical management centers located outside of the MDCH.

The state laboratory is housed in the Division of Chemistry and Toxicology within the Bureau of laboratories and is tasked with testing blood spots and establishing newborn reference ranges that maximize sensitivity and specificity in detecting 49 conditions now included in the NBS panel. The Follow-up Program, housed in the Division of Genomics, Perinatal Health and Chronic Disease Epidemiology within the Bureau of Epidemiology, coordinates follow-up and medical management of infants having positive screening determinations. The primary objective of the Follow-up Program is early initiation of treatment, although it is also responsible for education, training, quality assurance and data management. Medical management of infants screened positive for CH is performed under contract from the NBS Follow-up Program by the Endocrine Follow-up Program, located in the Department of Pediatrics at the University of Michigan. The Endocrine

Follow-up Program is responsible for ensuring appropriate diagnostic evaluation and treatment of infants having positive dried blood spot screening determinations for CH or congenital adrenal hyperplasia.

As indicated in table 6, MI NBS for CH initially used a T4/TSH testing strategy in which infants having T4 concentrations below the 10th centile underwent TSH testing; referrals for confirmatory testing were made based on the TSH concentration. In 1998, the dried blood spot testing protocol was changed to include TSH and T4 testing for all infants to improve sensitivity/specificity while retaining the ability to detect central CH; during this period, referrals for confirmatory testing were made if either T4 or TSH concentrations exceeded fixed cutoffs. Around 2000, interpretation of test results was modified to include a borderline positive determination. In 2003, T4 testing was removed from the NBS protocol due to an unacceptable number of false positive determinations (3%-5% of all screens), identification of few cases of central CH and experiences suggesting that central CH would likely be detected clinically in the process of hypopituitarism work-up. March 1st, 2007, a serial testing protocol was implemented as follows. Infants born weighing less than 1,800g are re-screened at two and four weeks of life; if the final specimen is consistent with continuous transfusions and/or total parenteral nutrition (TPN), testing is repeated after 72 hours from discontinuation of transfusion and/or TPN and again 90 days after the last transfusion if there is no documented negative screen for hemoglobinopathies.

[Insert Table 6 here]

Upwards of 99% of live births in Michigan undergo dried blood spot screening.[188] Infants having positive or strong-positive dried blood spot screening determinations are immediately referred for confirmatory testing. Borderline positive initial screening determinations undergo a repeat dried blood spot screen for CH; if the result of the re-test is other than negative, then the infant is referred for confirmatory testing. Confirmatory testing involves clinical evaluation by a

pediatric endocrinologist and one or more thyroid function tests consisting of serum TSH and usually free T4 measurement; tests including thyroid ultrasound or others useful in diagnosing CH may also be conducted, although this varies by physician. Pediatric endocrinologists involved in the NBS Pediatric Endocrinology Advisory Committee (PEAC) anecdotally report that if serum TSH concentrations do not fall below 10 mU/l after approximately four weeks of age then treatment is initiated. Treated infants are recorded as confirmed cases of CH by the NBS Follow-up Program. Thereafter, cases may be managed by pediatric endocrinologists involved in the NBS process, endocrinologists not involved with the NBS program or by primary care physicians.

In 2007, the NBS Follow-up Program initiated follow-up of CH cases detected by NBS after age three years to determine whether disease permanence had been confirmed and if so, the results. Initially, borderline cases, defined as those having pre-treatment serum TSH concentrations below the 15th centile calculated among all cases identified from 2004-2007, were targeted for three year follow-up. In 2008, follow-up was expanded to include all CH cases detected by Michigan NBS beginning with those born in 10/01/2003. Three year follow-up was initiated by mailing a brief survey to the endocrinologist recorded in NBS Follow-up Program data. The survey was developed by the author and the NBS Follow-up Program manager in collaboration with the PEAC and was pilot tested among several pediatric endocrinologists. Information collected during three year follow-up included whether the targeted physician was still providing care to the child; if so, whether the child was still being treated for CH and if not, the reason why; whether a trial off therapy had been or would be conducted and if not, the reason why. If the surveyed endocrinologist was not currently providing care to the child, they were asked to provide contact information for the last known care provider and another survey was mailed to that provider. If the child's current care provider was unknown or incorrectly identified, then NBS Follow-up Program staff extracted current physician contact information from the Michigan Care Improvement Registry (MCIR); if so,

the physician was contacted by phone by the NBS program manager and the survey was conducted by phone. MCIR, initially designed as a child immunization registry, is updated basically in accordance with the timing of immunizations and provided a near universal source of current provider contact information.

Data:

Data used to populate the analytic file used in this dissertation are portrayed in Figure X. Demographic and perinatal information collected on the NBS card and managed by the state laboratory were used to identify and characterize infants screened in 1/1/1994-6/30/2010. NBS Follow-up and medical management data were extracted from different sources before and after 10/1/2003, when the current laboratory information system (LIMS- PerkinElmer Life Sciences, Inc.) was implemented. Archived data managed by the NBS Follow-up Program were used to identify and characterize infants born in 1/1/1994-9/30/2003 who received a positive initial blood spot screen determination for CH; these data included screening analyte concentrations and determinations and other test results generated during the process of medical management. LIMS data including screening analyte concentrations and determinations and NBS Follow-up Program medical management data were used to characterize infants screened 10/1/2003-6/30/2010. Medical management data managed by the NBS Follow-up Program includes diagnostic and treatment information. LIMS data were linked to NBS Follow-up Program data by a unique patient identification number found in both laboratory and follow-up program data. Reports actively and passively ascertained from pediatric endocrinologists by the NBS Follow-up Program are used in this study to identify false negative screening results.

Results of three year follow-up of CH cases detected by Michigan NBS since 10/1/2003 that are recorded by the Michigan NBS Follow-up Program are also used in this study. Survey activities stopped temporarily while transitioning responsibilities from the NBS Follow-up Program to the

Endocrine Follow-up Program in 2009. Upon resuming three year follow-up survey activities, the decision was made to start with children born in 2007 meaning follow-up was attempted for only three cases born in 2006.

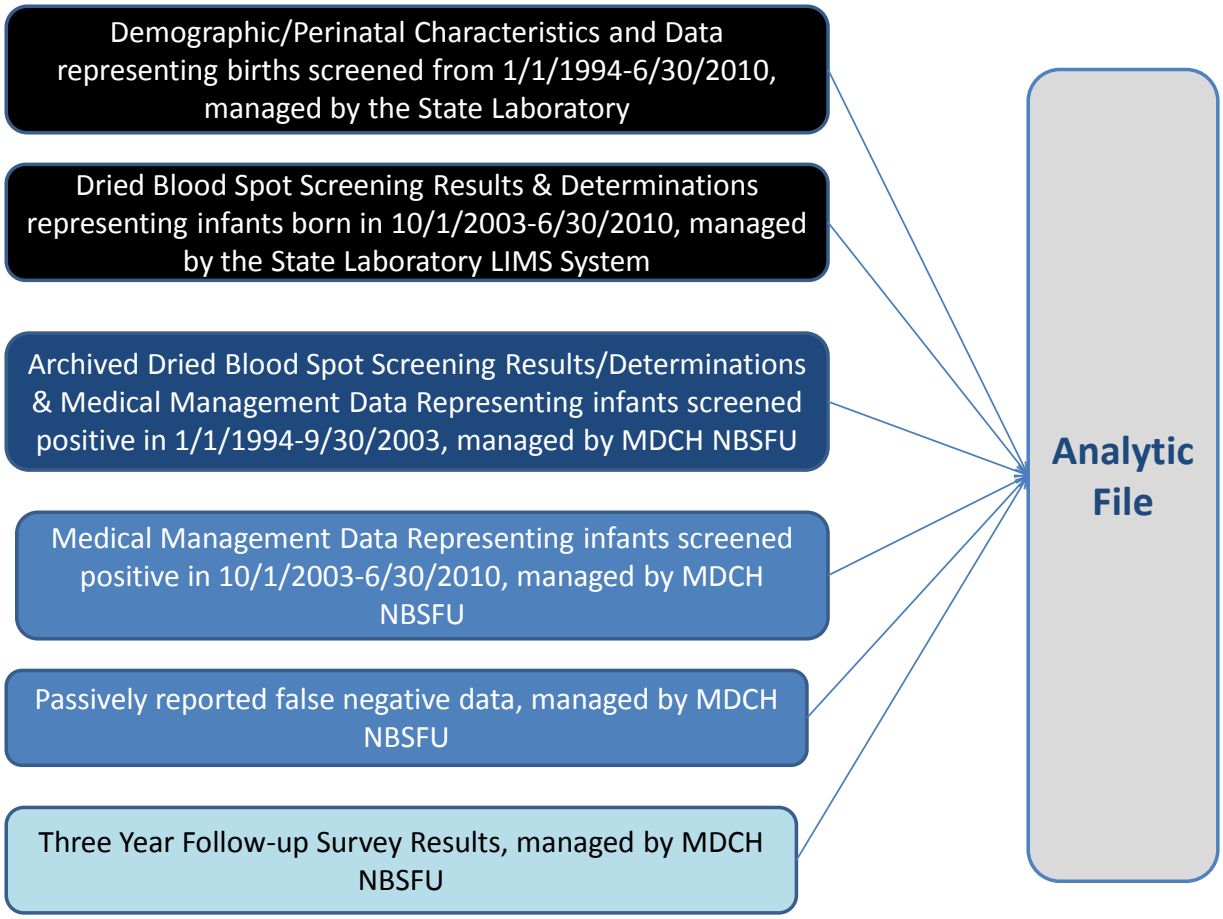

Figure 3: Data Sources Used to Populate the Final Analytic File

Demographic and perinatal information extracted to characterize infants included their sex, race, ethnicity (Hispanic), gestational age (weeks), birth weight (grams) and whether they were admitted to a NICU. Gestational age was categorized as <28 weeks, 28-31 weeks, 32-36 weeks and (≥37 weeks. Birth weight was categorized as <750g, 750g-1,499g), 1,500g-2,499g and ≥2,500g. Fetal growth ratio (FGR) was calculated by dividing the observed birth weight by mean birth weight for

gestational age based on percentile distributions published by Alexander et al.[189] Infants having FGRs at or below the 10th centile are categorized as small for gestational age (SGA); otherwise, infants are considered normal for gestational age (NGA). Prior to 1997, NICU admission and gestational age were not recorded on the NBS card and are accordingly not reported during this period.

NBS information extracted to characterize infants included specimen collection date, dried blood spot T4 and TSH concentrations, serum TSH and free T4 concentrations, ultrasound imaging and/or radioisotope scanning results, and treatment initiation date. Infants who received positive dried blood spot screening determinations and received treatment at the conclusion of confirmatory testing performed by the Endocrine Follow-up Program are considered as having CH by the Michigan NBS program. Treated infants are sub-classified by dried blood spot TSH concentration, ultrasound and/or radio isotope scan results (when available) and pre-treatment serum TSH and FT4 concentration to identify children most likely to have permanent CH. Prior literature indicates that newborns having initial dried blood spot TSH concentrations at or greater than 50 uIU/mL, imaging results indicating thyroid dysgenesis, a serum TSH concentration greater than or equal to 20 mU/L and/or a serum FT4 concentration less than 1ng/dL are considered at greater risk of permanent CH than infants having dried blood spot TSH concentrations < 50 uIU/mL, normal imaging results, a serum TSH concentration < 20 mU/L and/or a serum FT4 concentration greater than or equal to 1ng/dL.[13, 26, 64]

Results of three-year follow-up are used to differentiate transient from permanent CH cases among those followed-up. Cases that were not receiving thyroid hormone supplements at follow-up are considered transient; those whose clinician sent their normal lab values while not receiving thyroid hormone treatment to the MDCH NBS Follow-up Program are considered confirmed transient cases, those whose clinician indicated that their lab values were normal but did not yet

transmit those values to the MDCH NBS Follow-up Program are considered suspected transient cases.

Analysis:

Full Cohort

Descriptive and analytical techniques are used to investigate the impact of NBS protocol changes. Descriptive techniques include tabulation and trending of newborn characteristics by NBS outcomes of interest (reported in Table 7) during four periods defined by method of NBS based on their DOB as follows: T4 backup TSH testing (DOB: 1/1/1994-12/31/1997), tandem T4 & TSH testing for all infants, no serial testing (DOB: 1998-2003); primary TSH testing, no serial testing (DOB: 2004-2/28/2007); primary TSH testing, serial testing for births weighing <1,800g (DOB: 3/1/2007-6/30/2010).

Logistic regression analysis is used to investigate whether the detection rate and rate of false positive screening determinations changed significantly over time as NBS program operations changed after adjusting for differences in the distribution of selected newborn demographic and perinatal characteristics. Differences in the overall risk of CH as well as the risk of false positive determination are investigated.

Sub-Cohort 1: Infants Born Weighing < 1,800g (1/1/2004-6/30/2010)

Implications of serial testing are similarly investigated among infants born in 1/1/2004-6/30/2010 weighing less than 1,800g and characteristics of cases detected after having an initial negative screen are compared to those detected by an initial positive screen. Newborn characteristics are tabulated by NBS outcomes of interest during two periods again defined by dried blood spot testing method: 1) primary TSH testing, no serial testing (DOB: 2004-2/28/2007); primary TSH testing, plus serial testing for births weighing <1,800g (DOB: 3/1/2007-6/30/2010). Crude and adjusted Logistic regression models are used to investigate the association between serial testing and

overall detection of CH. Predictors of detection after having a negative first screen are also investigated during the serial testing period (3/1/2007-6/30/2010) using crude and adjusted logistic regression models.

Sub-Cohort 2: Cases Detected Since 10/1/2003 & Followed-up After Age 3 Years

Three-year follow-up findings are reported by selected newborn characteristics. Outcomes of interest of the three year follow-up project are as follows: whether the child was followed-up and if so, whether they were currently being treated; if treated at follow-up, the dosage used; if untreated at follow-up, the reason for absence of treatment including whether a trial off therapy had been conducted; if a trial off therapy had been conducted, how it was conducted and its results including those of thyroid function tests; if a trial off therapy had not been conducted, whether and when one would be conducted; if a trial off therapy had not been or would not be conducted, the reason why. Cases lost to follow-up are compared to those followed. Permanent cases are also compared to transient cases. Crude and adjusted logistic regression models are used to investigate predictors of transient CH among cases diagnosed and followed-up. Cases no longer receiving thyroid hormone medication at follow-up are considered transient CH in this study.

Table 6: Dried Blood Spot Testing Protocols, Cutoff Values and Associated Determinations Applied by Michigan Newborn Screening for Congenital Hypothyroidism, 1977-2010

Time Period	Test Method	T4 (mug/dl)	Age at Specimen Collection	TSH (uIU/mL)	Determination
1977-1997	T4 follow-up TSH	<10th Centile	All Ages	>20	Positive
1998-2003	Tandem T4 and TSH	< 5.0		>20	Positive
				23-49	Borderline Positive
				>49	Strong Positive
2004-2010	Primary TSH*	N/A	< 24 hours	≥ 50	Strong Positive
				< 50	Early specimen - needs repeat NBS
			24-36 hours	< 33	Negative
				33-49	Borderline Positive
				≥ 50	Strong Positive
			37hours-6days	< 25	Negative
				25-49	Borderline Positive
				≥ 50	Strong Positive
			7-31 days	< 13	Negative
				13-49	Borderline Positive
				≥ 50	Strong Positive
			> 31 days	≤ 10	Negative
				> 10	Refer for serum testing

Note: ^ Daily percentiles were used to refer children for confirmatory testing from 1977-1997. Serial testing was implemented for infants born weighing <1,800g March 1st, 2007. .

CHAPTER 3: COMPARISON OF DRIED BLOOD SPOT TESTING PROTOCOLS IN MICHIGAN NEWBORN SCREENING FOR CONGENITAL HYPOTHYROIDISM, 1/1/1994-6/30/2010

Results:

Descriptive Characteristics of Births Screened

Greater than two million infants are included in this population-based retrospective cohort study. Table 7 reports the distributions of demographic and perinatal characteristics across the four exposure periods defined by dried blood spot testing procedure. The population characteristics did not meaningfully differ among the periods; although, due to the large sample size, observed differences were statistically significant.

[Insert Table 7 Here]

Descriptive Characteristics of Births Screened Positive

The distribution of demographic and perinatal characteristics among infants screened positive for CH are reported by dried blood spot testing protocol in Table 8. White infants were proportionally more common among positive screens during the tandem T4 and TSH testing compared to other periods. While the sex distribution among infants screened positive differed statistically across periods, the actual differences were negligible. Twins were proportionally more common among infants screened positive during the T4 and backup TSH testing and Primary TSH plus serial testing relative to other periods of observation. Infants born SGA were proportionally more common among positive screens during the primary TSH plus serial testing period compared to both tandem T4 and TSH and primary TSH without serial testing periods. The proportion of infants having positive screens who were admitted to the NICU after birth was greater during the primary TSH plus serial testing period compared to prior protocols.

[Insert Table 8 Here]

Descriptive Characteristics of Detected Cases

As indicated in Table 9, among detected cases, the distributions of race, multiparous births, and those born SGA did not statistically differ by dried blood spot testing protocol. The expected sexual dimorphism of more female than male cases was reversed only during the tandem T4 and TSH testing period; otherwise, more females than males were diagnosed as having CH. Detection among LBW and/or premature infants as well as among those admitted to the NICU was increased in both primary TSH testing periods relative to the T4 and backup TSH and the tandem T4 and TSH testing periods. While CH detection increased among children born weighing less than 1,500g following the introduction of serial testing for children born weighing <1,800g, the detection rate among moderately LBW children (1,500g-2,499g) decreased.

[Insert Table 9 Here]

While pre-treatment serum TSH and free T4 concentrations varied substantially before and after 10/1/2003, these data are not comparable because the time to treatment was significantly shorter during primary TSH testing periods meaning cases would be expected to have greater serum TSH concentrations compared to those whose serum TSH concentrations were measured later.[Table 10] The median number of days from birth to treatment during each exposure period is as follows: in 1/1/1994-12/31/1997, 18 days; in 1/1/1998-9/28/2003, 22 days; in 10/1/2003-2/28/2007, 11 days; and in 3/1/2007-6/30/2010, 15 days. Across all exposure periods, few cases (~12-25%) underwent any form of thyroid imaging. In total, seven cases of central CH were detected; one by the primary T4 backup TSH testing protocol and the remaining six by the tandem T4 and TSH testing protocol.

[Insert Table 10 Here]

Screening Performance Metrics

Table 11 reports screening performance metrics by dried blood spot testing protocol. During the T4 backup TSH testing period the detection rate, positive predictive value, and specificity were each less than observed during primary TSH testing periods, both with and without serial testing; alternatively, the FPR was more than twofold greater during the primary T4 relative to primary TSH testing periods. The greatest rate of detection was observed during the tandem T4 and TSH testing period (1:1,271); however, the FPR (4.45%) was far greater than during other periods of observation. Accordingly, the PPV and specificity were significantly less during the tandem T4 and TSH testing period compared to others observed in this study. Primary TSH testing protocols were more specific, yielding greater PPVs; however, the detection rate observed during primary TSH testing periods is less than was observed during the tandem T4 and TSH testing period. Overall, primary TSH testing with serial testing for infants born weighing less than 1,800g yielded fewer false positive results, a greater PPV and greater overall detection than either primary TSH testing without serial testing or primary T4 backup TSH testing protocols. However, the two false negative results observed during this study occurred during the primary TSH plus serial testing period.

[Insert Table 11 Here]

Odds of Detection & False Positive Screen Determination

Overall, after adjusting for potentially confounding factors, Tandem T4 and TSH testing and primary TSH plus serial testing for infants born weighing <1,800g are associated with a 90% and 58% increase in the odds of detection respectively compared to primary T4 backup TSH testing. In comparing the two primary TSH testing periods to the primary T4 backup TSH testing period, the rate of detection was significantly increased only after introducing serial testing to the primary TSH screening protocol. While tandem T4 and TSH testing was associated with a near twofold increase in detection compared to primary T4 testing, it was also associated with a near threefold increase in the rate of false positives compared to primary T4 testing. Alternatively, the FPR was significantly

reduced during both primary TSH testing periods relative to the primary T4 backup TSH and tandem testing periods in both crude and adjusted models. The strongest predictor of detection and false positive screening determination observed in this study was birth weight which was inversely associated with both outcomes (detection and false positive determination).

[Insert Table 12 Here]

To compare the tradeoffs of tandem TSH and T4 testing verse primary TSH plus serial testing for infants born weighing <1,800g, we applied the detection rates and FPRs to a hypothetical birth population of 125,000 infants and estimated that an additional 297 false positive determinations would be incurred for each additional case detected if Michigan were go switch from primary TSH plus serial testing back to tandem T4 and TSH testing for all births.

Limitations:

This study is limited by missing data. While missing demographic and perinatal information appeared to occur at random meaning it is unlikely to have introduced differential misclassification, the lack of thyroid imaging results inhibited our ability to estimate whether cases more likely to have transient CH were more likely to be detected during any of the observed exposure periods. We were also unable to investigate ethnic, maternal age or gestational length related differences in screening performance metrics across protocols due to missing data.

Our findings are also negatively impacted by reliance on passive reporting to identify false negative screening results. It is possible that false negatives have occurred yet were not reported to the MDCH NBS Follow-up Program; accordingly, our results per false negative determinations should be interpreted with caution. However, the MDCH and the PEAC have a strong relationship and meet often to discuss cases with the greater community of pediatric endocrinologists. Thus, it is unlikely that any known false negatives have not been reported, although some may have escaped clinical detection.

It is also possible that observed differences in the rate of detection between protocols is confounded by unmeasured changes in diagnostic practice or changes in laboratory operations (including kit changes). Given that the greatest rate of detection was observed during the tandem T4 and TSH testing period and that this was the only period during which the number of male cases was greater than the number of female cases, it is possible that more cases that are likely to be transient CH were diagnosed.

This study is also limited by the lack of universal long term follow-up beyond age three years for infants diagnosed with CH by NBS given that we are unable to differentiate true permanent from transient CH for a majority of cases. However, long term follow-up for CH cases beyond age three years is now standard practice for infants born after 2007 (results of follow-up activities to date are reported in chapter 5).

Discussion:

This study finds that unless serial testing is conducted, the T4 testing strategy is equally as likely to detect CH as the primary TSH testing method in a population characterized by a high birth prevalence of CH relative to the historically known detection rate of approximately 1:4,000. However, primary TSH testing yields fewer false positive determinations making it preferable in terms of program operating efficiency.

The addition of serial testing among infants born weighing < 1,800g to the primary TSH testing protocol significantly increases the rate of detection relative to the primary T4 backup TSH testing approach. During the primary TSH plus serial testing period, 14% of all detected cases were identified by retest after having an initial negative screen which is comparable to Mandel et al.'s earlier findings, although their serial testing protocol was not restricted to infants born >1,800g.[22] It is potentially concerning that the detection rate decreased slightly among moderately LBW (1,500g-2,499g) children following the implementation of serial testing for births weighing <1,800g.

The decline may reflect that clinicians who previously used their clinical judgment to select infants for retesting now apply a fixed serial testing cutoff based on the MDCH serial testing protocol inclusion criteria (<1,800g) meaning marginally LBW cases exhibiting later rising TSH may remain undetected.

Prior literature supports the possibility of cases born weighing >1,800g remaining undetected due to later rising TSH and the lack of serial testing in Michigan. Four of the 18 infants detected by retest in Mandel et al.'s study had normal birth weights (>2,499g).[22] Hyman et al. reported that 6/13 infants identified in their study as having a late rise in TSH were born weighing greater than 1,500g and concluded that all infants admitted to the NICU should be subjected to serial NBS.[14] Larson et al. reported in their study of infants admitted to neonatal intensive care that for every 20 CH cases born weighing greater than 1,500g that had an elevated initial TSH screen, one additional case was detected with delayed TSH elevation.[21] In this study, the two false negative determinations occurred among NBW infants that were admitted to the NICU at birth. Thus, had serial testing been conducted among all births transferred to the NICU, the observed false negative determinations would have been screened positive by a later retest.

While serial testing significantly increased detection in our study, the downside is that primary TSH screening approaches appear more susceptible to false negative screening determinations and remain incapable of detecting the one to three cases of central CH expected in Michigan each year. Our findings indicate that testing T4 in tandem with TSH increases the CH detection rate by approximately 80% relative to the primary T4 backup TSH testing approach and by 20% relative to the primary TSH plus serial among infants born weighing <1,800g approach. Tandem testing is also capable of detecting the one to three cases of central CH expected in Michigan each year.

In this study, during the tandem testing period, 8% of cases correctly detected by primary T4 testing would have been missed by primary TSH testing; alternatively, a surprising 72% of cases detected by primary TSH testing would have been missed by primary T4 screening alone, a far greater proportion than previously estimated (4%-10%).[149-152] This finding suggests that many treated children had hyperthyrotropinemia yet were classified as CH and received treatment. The reversal of the expected sex ratio during the tandem T4 and TSH testing period further suggests that a greater number of cases unlikely to have permanent CH were diagnosed as CH during this period, perhaps explaining why the observed birth prevalence was among the greatest worldwide. Nearly 70% (n=16) of children detected by primary T4 testing alone weighed <750g at birth; alternatively, nearly 80% of children detected by TSH alone were NBW.

Our study also finds that while tandem testing identified the greatest number of cases, the FPR (4.5%) represents an eight fold increase in the number of false positive determinations relative to primary TSH plus serial testing. Operating costs associated with the additional laboratory resources as well as those necessary to manage confirmatory testing among the significantly increased number of false positive determinations deters many NBS programs from conducting tandem testing. Accordingly, our findings indicate that primary TSH plus serial testing is a preferable testing strategy for programs unwilling to bear the burden of additional laboratory costs and false positive determinations created by tandem testing.

Recently developed techniques capable of measuring T4 via tandem mass spectrometry (MS/MS) could sharply reduce the laboratory costs associated with tandem testing.[160] Our findings indicate that if Michigan added T4 to their MS/MS screening panel it would likely detect 1-3 additional cases per year, far more than many of the rarer conditions currently screened for using this technique. However, the additional false positives would be greater than yielded by other conditions screened for by MS/MS; but this too may soon no longer be an issue. Emerging evidence

suggests that many children having hypothyroxinemia of prematurity, now considered false positives in NBS for CH, may actually benefit from T4 supplementation.[70, 177] If ongoing trials of T4 supplementation continue to suggest a beneficial effect of treatment for cases of transient hypothyroxinemia, tandem T4 and TSH testing would clearly be preferable to primary TSH plus serial testing given that the number of treatable cases identified would increase significantly as many false positives would then be considered treatable cases.

Table 7: Newborns Screened by Selected Demographic & Perinatal Characteristics & by Dried Blood Spot Testing Method, Michigan Newborn Screening, 1/1/1994-6/30/2010

Population Segment		T4 backup TSH (1/1994-12/1997)		Tandem T4 and TSH (1/1998-9/2003)		TSH, No Serial Testing (10/2003-2/2007)		TSH, Plus Serial Testing (3/2007-6/2010)	
		N	%	N	%	N	%	N	%
Race	White	386459	73.37	511212	72.23	281854	71.9	253137	70.59
	Black	103361	19.62	129240	18.26	73688	18.8	70611	19.69
	Other	36929	7.01	67327	9.51	36474	9.3	34845	9.72
Sex	Female	260569	48.79	364919	48.75	211349	48.85	193165	48.85
	Male	273445	51.21	383625	51.25	221266	51.15	202298	51.15
Multiple Birth	No	526879	97.04	729276	96.63	417431	96.49	381470	96.46
	Yes	16066	2.96	25446	3.37	15184	3.51	13993	3.54
Birth Weight	<750	2249	0.43	4410	0.58	1199	0.28	144	0.29
	750-1499g	643.7	1.23	8293	1.1	4690	1.1	4352	1.12
	1500-2499g	35301	6.73	47864	6.35	28308	6.65	25778	6.62
	>2,500g	480752	91.62	693477	91.97	391351	91.96	358355	91.97
Gestational Age	<28 weeks					2327	0.57	2184	0.57
	28-37 weeks					40212	9.85	36115	9.42
	>37 weeks					365499	89.57	344903	90.01
SGA	No					318936	90.44	295320	90.23
	Yes					33698	9.56	31964	9.77
NICU Admission	No					387543	89.58	353966	89.51
	Yes					45072	10.42	41497	10.49
Total		*542945*	*100*	*754722*	*100*	*432615*	*100*	*395463*	*100*

Note: Missing data are as follows: race, n= 140,620; sex, n=22,140; birth weight, n=31,786; gestational age, n=36,843; NICU admission and gestational age data were not recorded on the NBS card prior to 10/1/2003. Percentages reported are column based.

Table 8: Newborns Screened Positive by Selected Demographic & Perinatal Characteristics & by Dried Blood Spot Testing Method, Michigan Newborn Screening, 1/1/1994-6/30/2010

Population Segment		T4 backup TSH (1/1994-12/1997)		Tandem T4 and TSH (1/1998-9/2003)		TSH, No Serial Testing (10/2003-2/2007)		TSH, Plus Serial Testing (3/2007-6/2010)		p-value
		N	%	N	%	N	%	N	%	
Race	White	6303	63.22	21678	67.76	2142	64.13	1356	61.72	<.0001
	Black	3131	31.4	7723	24.14	951	28.47	635	28.9	
	Other	536	5.38	2592	8.1	247	7.4	206	9.38	
Sex	Female	3734	40.71	14303	43.02	1622	45.04	1098	46.23	<.0001
	Male	5439	59.29	18947	56.98	1979	54.96	1277	53.77	
Multiple Birth	No	9139	87.5	32416	94.89	3466	96.25	2227	93.77	<.0001
	Yes	1306	12.5	94.89	5.11	135	3.75	148	6.23	
Birth Weight	<750	703	7.97	929	2.77	32	0.91	72	3.08	<.0001
	750-1,499g	1657	18.8	1429	4.26	95	2.7	182	7.79	
	1,500-2,499g	2110	23.93	3115	9.28	327	9.3	258	11.04	
	>2,500g	4346	49.3	28101	83.7	3061	87.08	1824	78.08	
Gestational Age	<28 weeks					49	1.47	117	5.14	<.0001
	28-37 weeks					437	13.1	421	18.49	
	>37 weeks					2851	85.44	1739	76.37	
SGA	No					2506	87.32	1630	83.98	0.0005
	Yes					364	12.68	311	16.02	
NICU Admission	No	8362	80.06	29770	87.15	2891	80.28	1611	67.83	<.0001
	Yes	2083	19.94	4390	12.85	710	19.72	764	32.17	
Total		*10445*	*20.65*	34160	67.54	3601	7.12	2375	4.7	

Note: Missing data are as follows: race, n= 3,092; sex, n=2,367; birth weight, n= 2,346; gestational age, n= 363. Gestational age data were not recorded on the NBS card prior to 10/1/2003. Percentages reported are column based. P-values represent the test for differences in the proportion of infants in each population segment by exposure period.

Table 9: Congenital Hypothyroidism Cases Detected by Selected Demographic & Perinatal Characteristics & by Dried Blood Spot Testing Method, Michigan Newborn Screening, 1/1/1994-6/30/2010

Population Segment		T4 backup TSH (1/1994-12/1997)		Tandem T4 and TSH (1/1998-9/2003)		TSH, No Serial Testing (10/2003-2/2007)		TSH, Plus Serial Testing (3/2007-6/2010)		p-value
		N	%	N	%	N	%	N	%	
Race	White	153	65.38	401	71.35	130	67.01	154	67.84	0.3515
	Black	52	22.22	84	14.95	36	18.56	41	18.06	
	Other	29	12.39	77	13.7	28	14.43	32	14.1	
Sex	Female	119	55.61	265	46.9	122	54.22	143	55.21	0.0399
	Male	95	44.39	300	53.1	103	45.78	116	44.79	
Multiple Birth	No	223	92.53	563	94.78	206	91.56	239	92.28	0.2777
	Yes	18	7.47	31	5.22	19	8.44	20	7.72	
Birth Weight	<750	6	2.94	23	4.04	5	2.28	10	3.89	0.001
	750-1,499g	15	7.35	18	3.16	8	3.65	26	10.12	
	1,500-2,499g	29	14.22	55	9.65	33	15.07	30	11.67	
	>2,500g	154	75.49	474	83.16	173	79	191	74.32	
Gestational Age	<28 weeks					5	2.34	16	6.43	<.0001
	28-37 weeks					40	18.69	51	20.48	
	>37 weeks					169	78.97	182	73.09	
SGA	No					142	82.56	159	79.1	0.43
	Yes					30	17.44	42	20.9	
NICU Admission	No	226	93.78	518	87.21	171	76	182	70.27	<.0001
	Yes	15	6.22	76	12.79	54	24	77	29.73	
Total		*241*	*18.27*	594	45.03	225	17.06	259	19.64	

Note: Missing data area as follows: race, n=111; sex, n= 68; birth weight, n= 70; gestational age, n= 303. Percentages reported are column based. P-values represent the test for differences in the proportion of infants in each population segment by exposure period. Fisher test used when ≥35% of cell counts were below 5.

Table 10: Congenital Hypothyroidism Cases Detected by Newborn Screening Result & by Dried Blood Spot Testing Method, Michigan Newborn Screening, 1/1/1994-6/30/2010

Population Segment	T4 backup TSH (1/1994-12/1997)		Tandem T4 and TSH (1/1998-9/2003)		TSH, No Serial Testing (10/2003-2/2007)		TSH, Plus Serial Testing (3/2007-6/2010)		p-value
	N	%	N	%	N	%	N	%	
Initial T4 Screen Result									
>5 mug/dl	149	63.14	437	74.32					0.0014
≤5 mug/d	87	36.86	151	25.68					
Initial TSH Screen Result									
≤50 uIU/mL	97	40.25	298	50.17	57	25.33	95	36.68	<.0001
>50 uIU/mL*	144	59.75	296	49.83	168	74.67	164	63.32	
Confirmatory Testing Results									
Serum TSH < 20 mU/L	125	77.64	375	80.47	47	22.27	72	29.15	<.0001
Serum TSH ≥ 20 mU/L	36	22.36	91	19.53	164	77.73	175	70.85	
Serum FT4 < 1pmol/L	22	14.47	82	17.98	108	54.55	108	54.55	<.0001
Serum FT4 ≥ 1 pmol/L	130	85.53	374	82.02	90	45.45	90	45	
Thyroid Imaging Result									
Abnormal	53	21.90	60	10.1	28	12.44	36	13.9	<.0001
Normal	11	4.50	9	1.52	5	2.22	2	0.77	
Not Imaged	177	73.40	525	88.38	192	85.33	221	85.33	
Central Hypothyroidism									
No	240	99.60	588	99.00	225	100	259	100	<.0001
Yes	1	0.40	6	1.00	0	0	0	0	
Total (row % reported)	*241*	*18.27*	594	45.03	225	17.06	259	19.64	

Note: missing data are as follows: tsh, n=11; t4, n=11; serum free T4, n=278; serum TSH, n=235. P-values represent the test for differences in the proportion of infants in each population segment by exposure period. Fisher test used when ≥35% of cell counts were below 5.

Table 11: Newborn Screening Results & Performance Metrics, Michigan, 1/1/1994-6/30/2010

Newborn Screening Results/ Performance Metrics	T4 backup TSH	Tandem T4 and TSH	TSH, No Serial Testing	TSH, Plus Serial Testing
True Positives (N)	241	594	225	259
False Positive (N)	10,213	33,578	3,376	2,116
True Negative (N)	532,491	720,550	429,014	393,088
False Negative (N)	0	0	0	2
Population Screened (N)	542,945	754,722	432,615	395,463
Detection Rate	1: 2253	1: 1271	1: 1923	1: 1527
Positive Predictive Value (%)	2.31	1.74	6.25	10.91
Sensitivity (%)	100	100	100	99.20
Specificity (%)	98.12	95.55	99.22	99.46
False Positive Rate (%)	1.88	4.45	0.78	0.54

Table 12: Likelihood of Congenital Hypothyroidism Detection and False Positive Screening Determination by Dried Blood Spot Testing Protocol, Michigan Newborn Screening, 1/1/1994-6/30/2010

Population Segment	CH Detection						False Positive Screen					
	Crude			Adjusted			Crude			Adjusted		
	OR	LCL	UCL	OR	LCL	UCL	OR	LCL	UCL	OR	LCL	UCL
Serial Testing T4 backup TSH												
Tandem T4 and TSH	1.77	1.53	2.06	1.89	1.61	2.22	2.43	2.38	2.48	2.85	2.78	2.92
TSH, No Serial Testing	1.17	0.98	1.41	1.19	0.98	1.46	0.41	0.40	0.43	0.48	0.46	0.50
TSH, Plus Serial Testing	1.48	1.24	1.76	1.58	1.30	1.91	0.28	0.27	0.29	0.33	0.32	0.35
Race White												
Black	0.97	0.83	1.12	0.86	0.73	1.00	1.54	1.50	1.57	1.37	1.34	1.40
Other	1.62	1.37	1.91	1.53	1.28	1.82	0.91	0.88	0.94	0.87	0.84	0.91
Sex Male												
Female	1.12	1.00	1.25	1.09	0.97	1.22	0.78	0.76	0.79	0.76	0.74	0.77
Multiple Birth No												
Yes	2.08	1.68	2.58	1.23	0.96	1.57	2.10	2.03	2.18	1.09	1.04	1.14
Birth Weight												
<750	9.52	7.04	12.89	5.81	6.33	12.26	12.04	11.41	12.70	10.47	9.87	11.11
750-1,499g	5.48	4.28	7.02	5.81	4.46	7.56	8.38	8.06	8.70	8.48	8.13	8.85
1,500-2,499g	2.08	1.75	2.47	2.08	1.72	2.52	2.24	2.17	2.30	2.17	2.10	2.24
>=2,500g												

Note: Missing data are as follows: race, n= 140,620; sex, n=22,140; birth weight, n=31,786.

CHAPTER 4: IMPACT OF SERIAL TESTING ON CONGENITAL HYPOTHYROIDISM NEWBORN SCREENING PERFORMANCE METRICS AMONG MICHIGAN RESIDENT BIRTHS WEIGHING <1,800g, 1/1/2004-6/30/2010

Results:

Slightly more than 17,000 infants born weighing <1,800g were screened by primary TSH testing for CH in Michigan during 1/1/2004-6/30/2010; half were exposed to a serial testing designed to detect CH among children characterized by later rising TSH concentrations. The distribution of selected demographic and perinatal characteristics did not statistically differ among the population of infants screened, those screened positive for CH, or among those diagnosed with CH following the implementation of the serial testing protocol. (Tables 13 & 14)

[Insert Tables 13 & 14]

While the characteristics of cases did not appreciably differ following the implementation of serial testing, the number of cases detected increased significantly, as did the number of false positive determinations. Table 16 reports the screening performance metrics before and after implementation of the serial testing protocol. [Table 15] Following implementation of serial testing, the detection rate nearly tripled and the FPR nearly doubled.

[Insert Table 15]

The proportions of children born weighing <1,500g and of those having gestational lengths <28 weeks were greater among cases detected by a retest compared to those detected on the first screen. [Table 16] The proportion of multiple births was also greater among cases detected by retest compared to those detected on the initial screen. Otherwise, cases detected by retest did not appreciably differ compared to those detected by the first screen.

[Insert Table 16]

Overall, the likelihood of CH detection increased nearly threefold (OR 2.77; CI 1.5-5.1) following the implementation of serial testing; the rate of detection by retest increased by 11 fold.[Table 17] Retest detection was significantly more likely among multiparous births. While, as expected, cases detected by retest had lesser initial TSH concentrations compared to those detected on the first screen, they did not differ in regard to pre-treatment serum TSH and free T4 concentrations. Female cases were less likely to be detected by retest, although the association was not statistically significant. The false positive rate increased by nearly 80% after the implementation of serial testing; LBW/premature infants and those born SGA were most likely to receive a false positive screening result compared to infants of normal growth or gestational length. The increase in false positive determinations accordingly resulted in reduced specificity during the serial testing period.

[Insert Table 17]

Limitations:

We suggest interpreting our findings per Hispanic ethnicity with caution as the data may have been under-recorded. Race may also be mis-recorded as it is often assigned rather than obtained by parental report. Due to the absence of thyroid scans via ultrasound or scintigraphy for all cases we are unable to report our results by type of thyroid abnormality. We observed an extreme rise in CH birth prevalence in the first half of 2010; we suggest this rise be interpreted with caution as it is unexplained and may not be comparable to birth prevalence estimates obtained over the course of an entire year. Gestational age may have been misclassified as few infants are expected to be born weighing less than 1,800g at gestational ages beyond 37 weeks. Our study is also impacted by missing race, sex and gestational age data; although missing data appears to occur at random.

Discussion:

Our findings indicate that serial NBS for CH increased detection by nearly threefold among Michigan resident infants born weighing <1800g. Overall, three of five cases were detected by retest during the serial testing period observed in this study. The detection rate observed among infants born weighing < 1,500g observed in this study (1:182) is nearly 80% greater than reported by Mandel et al (1:324) and more than twofold greater than reported by Larson et al. (1:400).[21, 22] Accordingly, our findings suggest that the impact of serial NBS on detection in a program characterized by earlier initial specimen collection (24-36hrs. of life) is greater than reported among programs characterized by later specimen collection (>36hrs. of life). While serial testing significantly increased detection, the FPR also increased by nearly 80%, although this amounted to only an additional 125 false positive screening determinations representing a negligible increase in NBS program operating costs.

While this and other studies support the necessity of serial testing for primary TSH testing programs, others have suggested that serial testing may be unnecessary. Vincent et al. analyzed data from the Province of Quebec from 1993-1994 when repeat NBS was conducted for all VLBW infants and concluded that serial testing was unnecessary based on their finding of a single case of late rising TSH identified in an infant that was not later diagnosed as CH.[19] However, Vincent et al.'s study was likely under-powered to detect CH among children having a late rise in TSH and their findings were impacted by delayed initiation of NBS. Korada et al. suggest that repeat NBS for CH may be unnecessary if the initial TSH cutoff value were reduced to 6mU/L; although their findings are impacted by later specimen collection and were also associated with a 126% increase in false positives.[190] Had Michigan employed a 6mU/L initial cutoff rather than serial testing, 30% of the cases detected by retest in this study would have been missed meaning our findings indicate that

serial testing is preferable to lowering of initial test cutoff values in NBS for CH among premature/LBW infants.

Table 13: Infants Screened, Screened Positive & Diagnosed by Selected Demographic Characteristics among Children Born Weighing <1,800g Before and After Implementation of Serial Testing, 1/1/2004-6/30/2010

Population Segment	Screened				p-value	Positives screens				p-value	Detected Cases				p-value
	Pre		Post			Pre		Post			Pre		Post		
	N	%	N	%		N	%	N	%		N	%	N	%	
Race															
White	4430	55.0	4459	54.7	0.89	86	58.9	157	55.5	0.37	10	66.7	28	65.1	0.50
Black	2933	36.4	3001	36.8		53	36.3	102	36.0		3	20.0	13	30.2	
Other	685	8.5	692	8.5		7	4.8	24	8.5		2	13.3	2	4.7	
Ethnicity															
Hispanic	450	5.3	431	5.0	0.52	7	4.4	14	4.6	0.94	1	5.9	0	0.0	0.28
Non-Hispanic	8119	94.8	8130	95.0		152	95.6	294	95.5		16	94.1	44	100.0	
Sex															
Female	4279	50.8	4259	50.3	0.54	80	51.0	141	46.8	0.40	9	52.9	20	46.5	0.65
Male	4148	49.2	4207	49.7		77	49.0	160	53.2		8	47.1	23	53.5	
Multiple Birth															
No	5962	69.6	6112	71.4	0.01	116	73.0	221	71.8	0.78	14	82.4	27	61.4	0.12
Yes	2607	30.4	2449	28.6		43	27.0	87	28.3		3	17.7	17	38.6	
Total	8569	100	8561	49.48		159	100	308	100.0		17	100	44	100	

Note: Missing data are as follows- race, n= 930; sex, n=237. . P-values represent the test for differences in the proportion of infants in each population segment by exposure period. Fisher test used when ≥35% of cell counts were below 5.

Table 14 (Table 14 continued): Infants Screened, Screened Positive & Diagnosed by Selected Demographic Characteristics among Children Born Weighing <1,800g Before and After Implementation of Serial Testing, 1/1/2004-6/30/2010

Population Segment	Screened				p-value	Positives screens				p-value	Detected Cases				p-value
	Pre		Post			Pre		Post			Pre		Post		
	N	%	N	%		N	%	N	%		N	%	N	%	
Birth Weight															
<750	1111	13.0	1137	13.3	0.67	32	20.1	72	23.4	0.58	5	29.4	10	22.7	0.439
750-1,499g	4313	50.3	4333	50.6		94	59.1	182	59.1		7	41.2	26	59.1	
1,500-1,799g	3145	36.7	3091	36.1		33	20.8	54	17.5		5	29.4	8	18.2	
Gestational Age															
<28 weeks	2057	25.2	2119	25.6	0.74	48	32.0	115	38.7	0.32	5	29.1	16	37.2	0.5806
28-36 weeks	5735	70.2	5752	65.6		98	65.3	172	57.9		11	64.7	26	60.5	
>37 weeks	383	4.7	394	4.8		4	2.7	10	3.4		1	5.9	1	2.3	
SGA															
No	5098	70.6	5165	70.8	0.78	83	62.4	159	61.9	0.92	10	71.4	23	59.0	0.41
Yes	2120	29.4	2126	29.2		50	37.6	98	38.1		4	28.6	16	41.0	
NICU															
No	545	6.4	478	5.6	0.03	11	6.9	13	4.2	0.21	0	0	1	2.3	0.53
Yes	8024	93.6	8083	94.4		148	93.1	295	95.8		17	100.0	43	97.7	
Total	8569	100	8561			159	100	308	100		17	100	44	100	

Note: Missing data are as follows- gestational age, n=690; SGA, n=2617. P-values represent the test for differences in the proportion of infants in each population segment by exposure period. Fisher test used when ≥35% of cell counts were below 5.

Table 15: Newborn Screening Performance Metrics Before & After Implementation of Serial Testing among Infants Born Weighing <1,800g, Michigan, 1/1/2004-6/30/2010

Exposure Period	Detection Rate	Positive Predictive Value	False Positive Rate	Sensitivity	Specificity
Pre- Serial Testing	1:571	9.68%	1.60%	100%	98.40%
Post-Serial Testing	1:203	13.64%	3.10%	100%	96.90%

Table 16: Characteristics of Congenital Hypothyroidism Cases Detected by Initial vs. Retest Dried Blood Spot Screen, Michigan Newborn Screening, 1/1/2004-6/30/2010

Population Segment	Detected by 1st Screen			Detected by 2nd Screen			p-value
	N	C%	R%	N	C%	R%	
Repeat NBS Protocol							
Pre	14	56.0	82.4	3	8.3	17.7	<.0001
Post	11	44.0	25.0	33	91.7	75.0	
Race							
White	17	70.8	44.7	21	61.8	55.3	0.6207
Black	5	20.8	31.3	11	32.4	68.8	
Other	2	8.3	50.0	2	5.9	50.0	
Sex							
Female	13	54.2	44.8	16	44.4	55.2	0.4603
Male*	11	45.8	35.5	20	55.6	64.5	
Multiple Birth							
No	21	84.0	51.2	20	55.6	48.8	0.0199
Yes	4	16.0	20.0	16	44.4	80.0	
Gestational Length							
<28 weeks	6	24.0	28.6	15	42.9	71.4	0.3104
28-37 weeks	18	72.0	48.7	19	54.3	51.4	
>37 weeks	1	4.0	50.0	1	2.9	50.0	
Birth Weight							
<750	6	24.0	40.0	9	25.0	60.0	0.5525
750-1,499g	12	48.0	36.4	21	58.3	63.6	
1,500-1,799g	7	28.0	53.9	6	16.7	46.2	
SGA							
No	14	66.7	42.4	19	59.4	57.6	0.5922
Yes	7	33.3	35.0	13	40.6	65.0	
NICU Admission							
No	1	4.0	100	0	0.0	0.0	0.4098
Yes	24	36.0	40.0	36	100.0	60.0	
Initial Screen							
TSH <50 uIU/mL	16	64.0	30.8	36	100.0	69.2	<.0001
TSH $\geq$50 uIU/mL	9	36.0	100	0	0.0	0.0	
Confirmatory Testing							
Serum TSH < 20 mU/L	11	50.0	44.0	14	38.9	56.0	0.407
Serum TSH $\geq$ 20 mU/L	11	50.0	33.3	22	61.1	66.7	
Serum FT4 < 1pmol/L	14	66.7	46.7	16	53.3	53.3	0.341
Serum FT4 $\geq$ 1 pmol/L	7	33.3	33.3	14	46.7	66.7	
Total	25	100	41.98	36	100	59.02	

Note: Missing=SGA, n=8; GA, n=1; sex, n=1; race, n=3; serum TSH, 3; serum free T4, n=10. P-values represent the test for differences in the proportions by first & retest detection.

Table 17: Likelihood of Overall Congenital Hypothyroidism Detection, Detection by Retest & False Positive Determination Following Implementation of Serial Testing, Michigan Newborn Screening, 1/1/2004-6/30/2010

Population Segment	Overall Detection			Retest Detection			False Positive		
	OR	**LCL**	**UCL**	**OR**	**LCL**	**UCL**	**OR**	**LCL**	**UCL**
Serial Testing									
No									
Yes	2.77	1.50	5.10	11.05	3.39	36.03	1.78	1.42	2.24
Race									
White									
Black	0.63	0.35	1.13	0.78	0.38	1.63	0.95	0.76	1.19
Other	0.68	0.24	1.90	0.61	0.14	2.62	0.64	0.16	2.60
Ethnicity									
Non-Hispanic									
Hispanic	0.31	0.04	2.22	0.53	0.07	3.84	0.98	0.46	2.08
Sex									
Male									
Female	0.92	0.55	1.52	0.78	0.41	1.51	0.97	0.78	1.21
Multiple Birth									
No									
Yes	1.17	0.68	1.99	1.91	0.99	3.69	0.81	0.63	1.04
Birth Weight									
<750	3.22	1.53	6.77	4.18	1.49	11.76	3.53	2.50	5.00
750-1,499g	1.83	0.97	3.49	2.53	1.02	6.27	2.41	1.80	3.24
1,500-1,799g									
Gestational Age									
<28 weeks	1.56	0.91	2.68	2.18	1.11	4.29	1.73	1.37	2.17
28-37 weeks									
>37 weeks	0.80	0.19	3.32	0.78	0.10	5.82	0.61	0.30	1.24
SGA									
No									
Yes	1.47	0.84	2.56	1.48	0.72	3.03	1.49	1.19	1.87

Note: Missing data are as follows: race, n= 930; sex, n=237; gestational age, n=690; SGA, n=2621.

CHAPTER 5: RESULTS OF FOLLOW-UP OF CONGENITAL HYPOTHYROIDISM CASES DETECTED BY MICHIGAN NEWBORN SCREENING AFTER AGE 3 YEARS

Results:

Follow-up after age three years was attempted for 152 CH cases detected by Michigan NBS in 10/1/2003-12/31/2007; follow-up was attempted for only 3 cases detected in 2006 because survey activities stopped temporarily while transitioning responsibilities from the NBS Follow-up Program to the Endocrine Follow-up Program. As indicated in Figure 4, 68 (44.7%) cases were LTFU, diagnostic re-evaluation was in process for 8 (5.3%), and diagnostic re-evaluation was not completed, in-process or planned for unknown reasons for 4 (2.6%) cases, leaving a final study population of 72 cases having undergone some degree of diagnostic re-evaluation to determine whether the child had transient or permanent CH.

Cases that were LTFU were marginally more likely to be born LBW or premature, admitted to the NICU at birth, and were more likely to have pre-treatment serum FT4 values < 1pmol/L; although none of the differences reached statistical significance given an alpha of 5%. (Tables 18 & 19) The majority of cases successfully followed-up were white (67%), singleton births (95%), born NBW (90%) and/or at full term (82%), were normal for gestational age at birth (90%), and were not admitted to the NICU at birth. Slightly more males (52%) were followed-up compared to females (48%). Few followed-up cases underwent thyroid imaging (13%); of those that underwent thyroid imaging (n=11), nine exhibited a thyroid abnormality. A minority of followed cases had initial TSH concentrations measured in dried blood spots <50 uIU/mL (27%), or pre-treatment serum TSH concentrations < 20 mU/L. Nearly half (47%) of the cases followed-up had pre-treatment serum FT4 concentrations < 1pmol/L.

[Insert Tables 18 & 19]

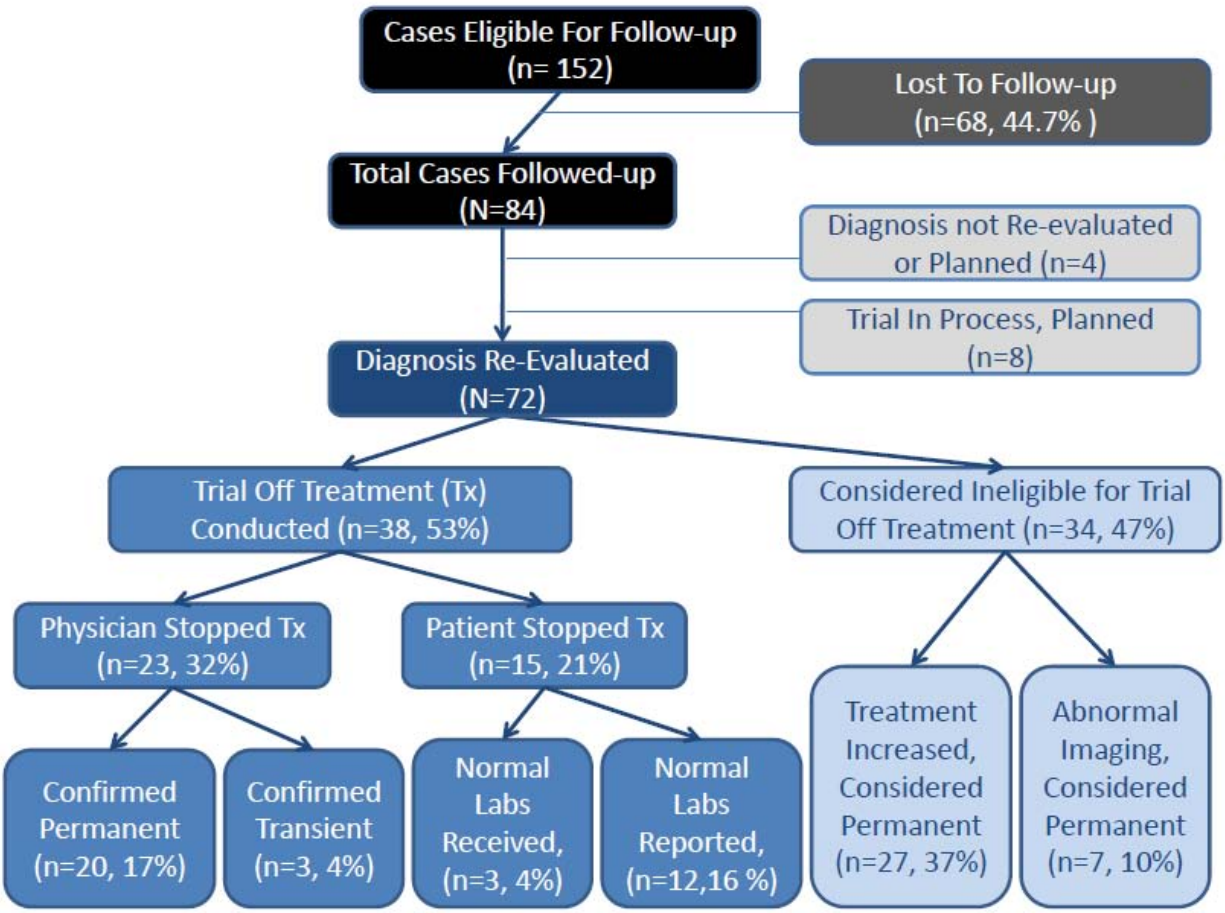

Figure 4: Three Year Follow-up Study Flow Diagram

As indicated in Figure 4, of the 72 cases followed-up and known to have undergone some form of diagnostic re-evaluation, 34 (47%) were deemed ineligible for a trial off thyroid hormone supplements and were considered to have permanent CH. Of the 34 cases deemed ineligible for a trial off thyroid hormone supplements, reasons for ineligibility reported by clinicians included that thyroid imaging depicted permanent CH (n=7, 21%) and that the child's thyroid hormone supplement dosage had increased over time (n=27, 79%) representing a permanent need for treatment. Of note, 3 of the 27 children whose diagnosis was considered permanent based on an increase in thyroid hormone supplement dosage had their dosages increased at ages 5 weeks, 6 and 9 months; age at time of thyroid hormone supplement dosage increase was not reported for the remaining 24 cases deemed permanent CH by this criterion. While the overall number of cases

confirmed permanent based on abnormal thyroid imagine results was small (n=7), they were more likely to be female (57%), whereas cases confirmed permanent CH based on a medication increase were more likely to be male (63%). (Table 20)

A trial during which patients were either not taking thyroid hormone supplements or taking them at a lower dosage was conducted among 38 (53%) cases. Of those having undergone a trial off therapy, nearly 40% (n=15) were conducted absent medical supervision when children's families decided to no longer provide treatment. Unsupervised cessation of thyroid hormone supplementation was more likely among racial minorities, cases born LBW, and cases admitted to the NICU at birth compared to the distribution of these characteristics in the overall population of cases re-evaluated.

[Insert Table 20]

While all cases whose family stopped medication of their own accord were reported to have normal lab values off treatment, thyroid hormone supplementation was re-instated for 20 of the 23 cases that underwent a trial off therapy under medical supervision.(Table 21) Normal lab values were transmitted to the NBS Follow-up Program confirming transient CH for 3 of 15 cases that underwent a trial off therapy absent medical supervision. Treatment was more likely to be resumed among white cases, those born LBW and/or premature, and those that were admitted to the NICU after birth compared to the distribution of these characteristics in the overall population of cases re-evaluated; the association between reinstatement of treatment and birth weight was the only to reach statistical significance. The rate of treatment reinstatement did not vary significantly by NBS results. (Table 22)

[Insert Tables 21 & 22]

Table 23 reports the odds of treatment cessation among all cases that underwent diagnostic re-evaluation, including those deemed ineligible for a trial off treatment based on medication dosage

increase or abnormal thyroid imaging results. The crude odds of treatment cessation at diagnostic re-evaluation was elevated among non-white cases, those born LBW, and those admitted to the NICU after birth relative to cases of white race, those born NBW, and those not admitted to the NICU respectively. After adjustment, the only factor significantly predictive of treatment cessation was black race (OR: 9.86; CI: 1.82*53.31) Clinically, the likelihood of treatment cessation was appreciably elevated among LBW cases and those admitted to the NICU at birth.

[Insert Table 23]

Limitations:

This study is limited by significant LTFU; approximately half of the cases for whom follow-up was attempted were unable to be located. Given the rarity of CH and the characteristically low response rate associated with physician surveys, this study represents a major success in public health programming considering that more than half of the targeted cases were successfully followed-up and that the final study population did not statistically differ from the population of cases LTFU. However, it is noteworthy that cases that were LTFU may have been more likely to stop treatment, thus creating a selection bias.

Our results are impacted by missing data. The dearth of thyroid imaging results particularly impacted our ability to predict transient CH among treated cases. Survey respondents were also unlikely to report exact dates and lab values or specify their method of diagnostic re-evaluation and/or follow-up regiment. Due to the survey design, our results are potentially subject to response bias. Race information was also missing for an appreciable number of records. However, missing information did not appear to be systematically distributed and thus should not have lead to differential misclassification. Results pertaining to Hispanic ethnicity should be interpreted with caution because this factor is often reported or collected incorrectly.

Discussion:

One of four CH cases detected by Michigan NBS that were followed-up and underwent any form of diagnostic re-evaluation is no longer receiving thyroid hormone medication, indicating that while the rate of treatment for CH is 1:1,527 births screened, the birth prevalence of CH maintaining a sustained need for treatment after age three years is closer to 1:2,035 births screened. However, our study may have underestimated the proportion of cases no longer requiring treatment after age three years for the following reasons. First, children that were LTFU may have been more likely to stop treatment. Second, children that underwent a trial off treatment under medical supervision may have had insufficient time for their thyroid hormones to normalize and thus could have been inappropriately categorized as permanent. Alternatively, discrepant results of trials off therapy conducted with and without medical supervision could be explained by the fact that cases more likely to have transient CH were also more likely to stop taking their medication without medical supervision in which case our estimate the proportion of cases having transient disease would be internally valid. Third and finally, 27 cases were considered as having permanent CH based on an increase in thyroid hormone medication dosage, at times occurring as early as 5 weeks to 6 months of age, some of which may not still require medication.

Our study also found that one of five cases re-evaluated had stopped treatment without medical supervision. While normal lab values were reported for children removed from treatment by their families, this represents a significant threat to public health given that poor treatment compliance is a predictor of brain damage. Cases that were removed from treatment by their families without medical supervision did not differ in terms of their NBS and confirmatory testing results; it is possible that some cases LTFU may have stopped treatment without medical supervision suffered poor outcomes not observed in this study.

Due to differences in study design, our findings are not directly comparable to prior investigations of CH medication cessation after age three years. Generally, we observed a smaller proportion of cases that no longer required treatment after age three years compared to Kemper et al.'s claims-based analysis and Eugster et al.'s clinic based follow-up study of 33 CH euthyroid cases which estimated that approximately 38% and 36% of CH cases are no longer treated after age three years respectively.[68, 191] However, among cases who underwent a trial off therapy in our study, nearly half did not resume treatment, greater than the rate observed among euthyroid cases included in Eugster et al.'s study.

Table 18: Proportion of Congenital Hypothyroidism Cases Detected by Michigan Newborn Screening from 10/1/2003-12/31/2007 Followed-up at or Beyond Age Three Years by Selected Demographic/Perinatal Characteristics

Population Segment	Lost to Follow-up		Followed-up		p-value
	N		N		
Race					
White	46	64.65	56	66.67	0.34
Black	9	13.24	17	20.24	
Other	13	19.12	11	13.10	
Sex					
Female	37	55.22	40	47.62	0.35
Male	30	44.78	44	52.38	
Multiple Birth					
No	66	97.06	80	95.24	0.69^
Yes	2	2.94	4	4.76	
Birth Weight					
<750	4	5.97	1	1.23	
750-1,499g	6	8.96	2	2.47	0.06^
1,500-2,499g	7	10.45	5	6.17	
≥2,500g	50	74.63	73	90.12	
Gestational Length					
<28 weeks	10	14.71	7	8.33	0.08
28-37 weeks	13	19.12	8	9.52	
>37 weeks	45	66.18	69	82.14	
Small for Gestational Age					
No	43	84.31	62	89.86	0.36
Yes	8	15.69	7	10.14	
NICU Admission					
No	48	70.59	70	83.33	0.06
Yes	20	29.41	14	16.67	
Total	68	100	84	100	

Note: ^Fisher Exact Test Used. Missing data are as follows: Sex (n=1), Birth Weight (n=4), Small for Gestational Age (n=32). P-values represent the test for differences in the proportion of infants in each population segment by follow-up.

Table 19: Proportion of Congenital Hypothyroidism Cases Detected by Michigan Newborn Screening from 2004-2007 Followed-up at or Beyond Age Three Years by Newborn Screening Result

Population Segment	LTFU		Followed		p-value
	N	%	N	%	
Dried Blood Spot TSH					
TSH <50 uIU/mL	24	35.29	23	27.38	0.29
TSH ≥50 uIU/mL	44	64.71	61	72.62	
Serum TSH					
Serum TSH < 20 mU/L	22	32.84	29	36	0.66
Serum TSH ≥ 20 mU/L	45	67.16	51	63.75	
Serum FT4					
< 1pmol/L	39	63.93	37	47.44	0.053
≥ 1 pmol/L	22	32.35	41	48.81	
Thyroid Image Result					
Normal	1	1.47	2	2.38	
Abnormal	12	17.65	9	10.71	0.47
No thyroid image	55	80.88	73	86.90	
Total	68	100	84	100.00	

Note: Missing data are as follows: TSH, n=3; Serum TSH, n=5; Serum FT4, n=13. P-values represent the test for differences in the proportion of infants in each population segment by follow-up.

Table 20: Method of Trial Off Thyroid Hormone Medication or Reason for Lack of Trial, Congenital Hypothyroidism Cases Followed-up after Age 3 Years, Michigan Newborn Screening

Population Segment	Diagnosis Re-Evaluated		Trial Off Medication				Reason for Lack of Trial			
			Patient Initiated		Physician Initiated		Abnormal Thyroid Scan		Medication Increase	
	N	%	N	%	N	%	N	%	N	%
Race										
White	48	66.7	5	33.3	17	73.9	3	42.9	23	85.2
Black	15	20.8	7	46.7	4	17.4	2	28.6	2	7.4
Other	9	12.5	3	20.0	2	8.7	2	28.6	2	7.4
Sex										
Female	38	52.8	10	66.7	14	60.9	4	57.1	10	37.0
Male	34	47.2	5	33.3	9	39.1	3	42.9	17	63.0
Twin										
No	69	95.8	14	93.3	22	95.7	7	100.0	26	96.3
Yes	3	4.2	1	6.7	1	4.3	0	0.0	1	3.7
Birth Weight										
<750	1	1.4	1	6.7	0	0.0	0	0.0	0	0.0
750-1,499g	1	1.4	1	6.7	0	0.0	0	0.0	0	0.0
1,500-2,499g	4	5.7	0	0.0	2	9.1	0	0.0	2	7.7
≥2,500g	64	91.4	13	86.7	20	90.9	7	100.0	24	92.3
Gest. Age										
<28 weeks	5	6.9	1	6.7	3	13.0	0	0.0	1	3.7
28-37 weeks	8	11.1	2	13.3	1	4.3	1	14.3	4	14.8
>37 weeks	59	81.9	12	80.0	19	82.6	6	85.7	22	81.5
SGA										
No	55	91.7	11	91.7	16	84.2	5	100.0	23	95.8
Yes	5	8.3	1	8.3	3	15.8	0	0.0	1	4.2
LBW										
No	64	88.9	13	86.7	20	90.9	7	100.0	24	92.3
Yes	6	8.3	2	13.3	2	9.1	0	0.0	2	7.7
NICU										
No	61	84.7	10	66.7	20	87.0	7	100.0	24	88.9
Yes	11	15.3	5	33.3	3	13.0	0	0.0	3	11.1
Total	72	100	15	100	23	100	7	100	27	100

Note: Missing data are as follows: Sex (n=8), Birth Weight (n=4), Small for Gestational Age (n=32).

Table 21: Results of Trial Off Thyroid Hormone Medication among Congenital Hypothyroidism Cases Followed-up After Age 3 Years by Selected Demographic & Perinatal Characteristics, Michigan Newborn Screening

Population Segment	Underwent Trial		Treatment Resumed		Treatment Not Resumed		P-value
	N	%	N	%	N	%	
Race							
White	22	57.9	15	75	7	38.9	0.10
Black	11	28.9	3	15	8	44.4	
Other	5	13.2	2	10	3	16.7	
Sex							
Female	24	63.2	12	60	12	66.7	0.67
Male	14	36.8	8	40	6	33.3	
Multiple Birth							
No	36	94.7	20	100	16	88.9	0.22
Yes	2	5.3	0	0	2	11.1	
Gestational Age							
<28 weeks	4	10.5	3	15	1	5.6	0.70
28-37 weeks	3	7.9	1	5	2	11.1	
>37 weeks	31	81.6	16	80	15	83.3	
SGA							
No	27	87.1	15	93.8	12	80	0.33
Yes	4	12.9	1	6.3	3	20	
LBW							
No	33	89.2	19	100	14	77.8	0.046
Yes	4	10.8	0	0	4	22.2	
NICU							
No	30	78.9	18	90	12	66.7	0.12
Yes	8	21.1	2	10	6	33.3	
Total	38	100	20	100	18	100	

Note: Missing data are as follows: Birth Weight (n=4), Small for Gestational Age (n=7). P-values represent the test for differences in the proportion of infants in each population segment by whether treatment was resumed.

Table 22: Results of Trial Off Thyroid Hormone Medication among Congenital Hypothyroidism Cases Followed-up After Age 3 Years by Newborn Screening & Confirmatory Testing Results, Michigan Newborn Screening

Population Segment	Underwent Trial		Treatment Resumed		Treatment Not Resumed		p-value
	N	%	N	%	N	%	
Dried Blood Spot Screen Result							
TSH <50 uIU/mL	13	34.2	5	38.46	8	61.54	0.21
TSH ≥50 uIU/mL	25	65.8	15	60.00	10	40.00	
Confirmatory Testing Results							
Serum TSH < 20 mU/L	19	51.4	10	52.63	9	47.37	0.88
Serum TSH ≥ 20 mU/L	18	48.6	9	50.00	9	50.00	
Serum FT4 < 1pmol/L	10	27.0	5	50.00	5	50.00	0.92
Serum FT4 > 1 pmol/L	27	73.0	14	51.85	13	48.15	
Image result- Eutopic Thyroid	1	2.6	1	100.00	0	0.00	0.63
Image result- Thyroid Dysgenesis	2	5.3	1	50.00	1	50.00	
No thyroid image	35	92.1	18	51.43	17	48.57	
Total	38	100	20	52.63	18	47.4	

Note: Missing data are as follows: TSH, n=3; Serum TSH, n=1; Serum FT4, n=1. P-values represent the test for differences in the proportion of infants in each population segment by whether treatment was resumed.

Table 23: Predictors of Transient Determination among Children Diagnosed with Congenital Hypothyroidism and Followed-up by Michigan Newborn Screening after Age 3 years, 2004-2007

Population Segment	Diagnosis Re-Evaluated		Transient CH					
			Crude			Adjusted		
	N	R%	OR	LCL	UCL	OR	LCL	UCL
Race								
White	48	85.71						
Black	15	88.24	6.69	1.84	24.39	9.86	1.82	53.31
Other	9	81.82	2.93	0.59	14.52	5.10	0.86	30.19
Sex								
Female	38	95.00	2.15	0.71	6.57			
Male	34	77.27						
Gestational Length								
<28 weeks	5	71.43	0.73	0.08	7.09			
28-37 weeks	8	100.00	0.98	0.18	5.38			
>37 weeks	59	85.51						
LBW								
No	64	88.90						
Yes	6	8.30	7.14	1.18	43.11	2.77	0.18	42.26
NICU Admission								
No	61	87.14						
Yes	11	78.57	4.70	1.22	18.05	5.20	0.78	34.71
Dried Blood Spot Screen Result								
TSH <50 uIU/mL	18	78.26	3.36	1.06	10.69	1.35	0.30	6.02
TSH ≥50 uIU/mL	54	88.52						
Confirmatory Testing Results								
Serum TSH < 20 mU/L	24	80.00	2.50	0.82	7.61			
Serum TSH ≥ 20 mU/L	45	88.24						
Serum FT4 < 1pmol/L	37	100.00						
Serum FT4 ≥ 1 pmol/L	37	90.24	2.60	0.80	8.48			
Total	72	85.71						

Note: Missing data are as follows: Sex (n=8), Birth Weight (n=4), Small for Gestational Age (n=32).

Chapter 6: Conclusions and Future Directions

Comparison of Dried Blood Spot Testing Methods

Our findings suggest that different cases are detected by primary T4 compared to primary TSH approaches to NBS for CH. While each test independently detected an equivalent number of cases, when they are combined they detect a significantly greater number of cases, many more by the TSH screen compared to the T4 screen. It appears that each test (T4 and TSH) falsely screens different infants positive based on the same evidence; while the FPR is comparable between each test method independently, when they are combined, the FPR increases significantly. To make a final conclusion about whether the additional false positive determinations generated by tandem T4 and TSH testing is acceptable in the context of increased detection, guidelines detailing a benchmark balance between sensitivity and specificity are needed. Alternatively, the overall mission of NBS may need to be revisited to determine the ideal approach to testing.

If the goal of NBS is to detect all cases and ensure prompt provision of treatment, then tandem T4 & TSH screening is the ideal approach; it detects a greater number of cases, including infants having central CH. If the mission of NBS is to detect the most cases as *efficiently* as possible in the context of financial resources, then primary TSH testing plus serial testing for infants at risk of later rising TSH may be the ideal approach. If the latter is true, then cost-benefit analyses are necessary to support NBS operational decisions. This research would need to determine the number of false positives acceptable to detect an additional case of CH; costs saved by early detection of potentially 'borderline' cases that would be picked up as sensitivity increases as well those related to early detection of central CH would need to be estimated. Regarding central CH, our findings do not support the contention that it is detected clinically absent NBS considering that no central CH cases were detected after T4 testing stopped and that the two false negative results observed in our study

were primary CH. Thus, the estimated costs savings per detection of central CH would likely be significant.

In determining the most cost-effective means of NBS for CH, it may be beneficial to also investigate a combined approach including aspects of tandem TSH and T4 in addition to serial testing to maximize detection while conserving the number of false positive determinations. Additionally, further efforts are necessary to identify the ideal target population for serial testing and similarly, the acceptable balance between false and true positives. Future studies should also determine whether serial testing increases detection among primary T4 or tandem T4 and TSH test programs.

Need for Standardization & Guidelines

To make future research more meaningful, further effort is necessary to standardize the process of diagnosing and classifying CH, similar to efforts done in developing cerebral palsy surveillance systems in Europe. Otherwise, absent a consistent and operational case definition, it is difficult to meaningfully compare screening performance metrics both between and within NBS programs over time. Guidelines are necessary to:

- illustrate the number and type of tests needed to make the initial CH diagnosis, particularly thyroid imaging by ultrasound and/or radioisotope scanning;
- recommend cutoffs for confirmatory analyte testing adjusted for the time of the test and other pertinent characteristics associated with potentially immature thyroid development or function;
- standardize the nomenclature used to describe CH, ensuring that treated cases are consistently sub-classified into primary CH, central CH, hyperthyrotropinemia, hypothyroxinemia of prematurity and/or potentially transient CH in accordance with specified ranges of thyroid hormone concentrations and thyroid imaging results;

- recommend follow-up regiments adjusted to the type of case identified including those focused towards potentially transient CH; and
- detail specifically when and how to confirm the diagnosis of CH after age three years.

Few cases in this study underwent any form of thyroid imaging. While it is true that thyroid imaging does not augment the course of treatment for CH, it does allow for more precision in predicting whether a child will have a transient or permanent need for treatment. If parents were informed that their child may or may not require lifelong treatment, it would perhaps reduce the possibility of them taking their children off treatment without medical supervision. Those informed that their child may be able to stop treatment later on under medical supervision would be more inclined to follow-up with their physician to determine when/how they should stop treatment. Those informed that their child would likely require lifelong treatment would better understand that they are not to stop treatment without medical supervision. In short, thyroid imaging would provide a better opportunity to discuss prognosis and emphasize the importance of treatment compliance and diagnostic re-evaluation after three years of age.

Greater clarity about other types of tests and how to interpret their results coupled with an improved nomenclature of CH would further allow for standardization between and within NBS programs, yet would preserve the opportunity of clinicians to initiate treatment based on clinical judgment alone if necessary. If classic primary CH were defined in operational terms and that diagnosis were applied consistently across programs, inter-program and intra-program variation over time would be minimized and more meaningful comparisons could be made. Improved classification would not preclude clinicians from rendering treatment based solely on clinical judgment; however, it would allow for such decisions to be monitored and evaluated apart from treatment of classic primary CH. For instance, it may be correct that children with marginal T4 concentrations and elevated TSH concentrations benefit from thyroid hormone treatment; although, if this is the case

then it should be demonstrated and such cases should be classified separate from classic CH as not to distort birth prevalence estimates. In short, the current process of treating infants for CH based primarily on clinical judgment has led to considerable and unexplained variation which precludes investigators from effectively learning from comparison of NBS performance data.

Greater specificity in CH typology would not only allow a better understanding of the tradeoffs of different approaches to screening and whether we're truly observing a rising birth prevalence as recently reported, it would also allow us to investigate different follow-up regiments for cases classified as more likely to be transient CH. Several of the cases determined transient at follow-up stopped treatment before age three. Accordingly, for particular cases, it may be possible to conduct diagnostic re-evaluation earlier. However, further research is also necessary to identify the optimal time for diagnostic re-evaluation, which cases should be re-evaluated using a trial off thyroid hormone supplements, and whether and when treatment should be resumed for cases undergoing a trial off thyroid hormone supplements.

While current AAP guidelines recommend therapy cessation after age three years if no permanent etiology was found and no increase in TSH was observed after the newborn period, the method of determining 'permanent etiology' and separately what constitutes important changes in TSH in terms of degree and timing need further clarification.[27] Similarly, when to reinstate treatment in conducting a trial off therapy should be operationally defined. There is no clear standard for conducting treatment cessation trials or interpreting their results to confirm permanence of CH. The duration of treatment cessation varies from 3-4 weeks to 10 months among the few published studies and the frequency and timing of follow-up thereafter among children whose thyroid function normalizes after cessation of thyroid hormone therapy also varies.[68, 128, 139] In our study, all children removed from treatment by their families were reported to have normal thyroid function off treatment, yet virtually all re-evaluated by a physician resumed treatment

suggesting that clinicians may prematurely reinstate treatment, although without a clear guideline detailing when to reinstate treatment the determination of permanent CH is again made solely based on clinical judgment which is subject to significant variation. Our findings also indicate that long term follow-up should be conducted for all CH cases, not only those eligible for a trial off therapy, given that one of five cases followed-up after age three years in our study had been removed from treatment absent medical supervision.

Conclusion

In sum, our results indicate that NBS programs should consider tandem T4 and TSH testing, or primary TSH plus serial testing for infants at risk of later rising TSH. A benchmark balance between sensitivity and specificity is necessary to make the decision between tandem TSH and T4 testing and primary TSH plus serial testing methods. Further efforts are necessary to standardize the process of diagnosis and terminologies used to characterize cases across NBS programs; guidelines are necessary to support this effort.

APPENDIX

APPENDIX- APPROVALS FOR REPRINTS

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Approval for Table 4:

From: Ballen, Karen [mailto:KBallen@liebertpub.com]
Sent: Monday, April 11, 2011 11:08 AM
To: Steven Korzeniewski
Subject: RE: reprint inquiry

Dear Steven:
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Sent: Friday, April 08, 2011 4:07 PM
To: Ballen, Karen
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Hello,

I would like to include a table from Mandel, S. J., R. J. Hermos, et al. (2000). "Atypical hypothyroidism and the very low birthweight infant." Thyroid. **10**(8): 693-695 in my dissertation and notice that there is no request option for inclusion in dissertations. May I use the table of interest at no charge, or does it actually cost $87?

I look forward to your reply, thank you.

Steven J. Korzeniewski, PhD-Candidate, MSc, MA,
Director, Statistical Analysis Resource Group (SARG),
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Approval for Table 5:

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